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Endocrine Disruptors-caused Faulty Hormonal Imprinting: Focus on Women

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Abstract

Hormonal imprinting is a physiological process, when hormone receptors and the target hormone meet in the first occasion, perinatally. This process is needed for the normal function of the receptor-hormone complex and valid for life. However, hormone-like molecules also can bind to the developing receptor causing faulty imprinting and its consequences: altered binding of hormones, inclination to diseases, manifestation of diseases, disturbing the physiological hormonal regulation. The faulty imprinting also has a lifelong effect. Industrial, communal, nutritional and medical endocrine disruptors are faulty imprinters and their variables as well, as amounts are enormously growing in the human environment. The faulty imprinting influences also the microsomal enzyme system. Numerous diseases, manifested at adult age can be deduced to perinatal faulty hormonal imprinting and the higher sensitivity of women to drugs (more adverse reactions) could be explained by perinatal events. The extremely growing variants and amount of endocrine disruptors could rearrange the whole endocrine system, which could be disastrous or useful alike in the future.

Keywords: *Bisphenol A, DOHaD, Endocrine Regulation, Steroid Hormones, Perinatal Period, Functional Teratogens*

Introduction

During fertilization the genom of the women's egg contain the maternal informations and the paternal informations are brought by the sperm. After the fusion of two germ cells the zygote is existing, which is able to develop further to the complete organism (individuum), controlled by the fused genome (ontogeny). The zygote is totipotent which means that it is able for developing to any organs (cells) of the organism however, during the ontogenetic development there is a continuous loss of potencies, to pluripotent (multipotent) and at last to unipotent cells, which are able to produce cells (by cell division) similar to the mother-cell, or are unable to divide (e.g. nerve cells) at all. This means that during the ontogenetic development a continuous narrowing of potencies happens which is resulted in diffent types of cells, with different structure and function. Therefore, in different cell types of the organism different genes are manifested (are working, giving information for function), while others are closed by methylation of the cytosin nucleotids of DNA. The organization of these different units is the duty of the neuroendocríne system in which the direct transmitter humoral components are the hormones. However, the neuroendocrine system can regulate only such functions, which are permitted by the genes, which are open for giving information to the given functions.

The Physiological and Faulty Hormonal Imprinting

The hormones are present in the blood circulation, where any cells of the organism can meet them. However, only such cells can decipher the message contained by the hormone, which have cell membrane or nuclear receptors for the given hormone, which can bind the hormone and after that can transmit the coded information into the cytoplasm or into the nucleus. These receptors are specific for a given hormone, nevertheless this specificity also develops gradually during the ontogenetic development. During the embryonal and early fetal period of human life maternal hormones (passed across the placenta) are dominating however, at the end of the fetal and during the perinatal period (prenatally, at birth and early postnatally) the „homegrown" hormones appear and hormonal imprinting is taking place, conforming the receptors for themselves. This imprinting is necessary, without it the fitting of receptor-hormone system is not working well [1]. The setting is valid for life and inherits to cell to cell inside the cell line as well as to the progenies of the individuum, as it is an epigenetic process, which alters the methylation pattern of a given gene (the expression of the gene), without disturbing the nucleotid sequences [2]. However in this critical perinatal period the receptors' specificity is weak, what means that other members of a hormone family or synthetic hormones, hormone-like molecules also can be bound by them and the amount of imprinter is also very important. In this case a faulty hormonal imprinting can develop, which is also have a lifelong validity and causes disturbed functions, with abnormal binding of hormones in adult age [3]. Consequently, disturbed functions appear in behavior [4–6], sexuality [6–8], body composition [9], in bone development [10]; the neurotransmitter production of brain is also altered and immune functions are changed (e.g. autoimmunity develops). One single encounter with very low doses of hormone-like molecules in the critical perinatal period is enough for the provocation of faulty imprinting and for the manifestation

of their consequences in adult age. The hormonal imprinting which was observed, described and experimentally justified by us (at first in 1980) [11] was the first in the series of new theories which lead to metabolic imprinting [12], immunological imprinting [13] and to the developmental origin of health and disease (DOHaD) [14]. As hormonal imprinting is an epigenetic process, the alterations happened in the perinatal period can be manifested at any time of life and also can be manifested in the progenies and by this, epigenetic alterations of the future generations are settled on the already changed genetic arrangements. This is important as the response of a faulty imprinted cell or organism would be different from which is observed in the present time.

The Endocrine Disruptors

Endocrine disruptors are molecules similar to (first of all, steroid) hormones, which are present in our environment and can enter into our organism by air, water, food, drug consumption and can be bound by hormone receptors influencing cell functions, stimulating or hindering them. Endocrine disruptors has been always present during the evolution of men in our environment as e.g. aromatic hydrocarbons produced by volcanic eruptions, food components (phytoestrogens, present in soy and other vegetables), smoke etc. However, they were not named to „endocrine disruptors" as their such effects were not known and their amount was insignificant. At present, in our modern (industrial) age their variety is high, their amount is large and both are enormously growing. They causes a crisis in the endocrine system as well in the systems, which are seriously influenced by the distorted endocrine system.

Endocrine disruptor exposures are believed harmful in adult age and this is demonstrated by many research data and statistics. However, they are more harmful in the critical periods of development, mainly in the time of hormonal imprinting. In this case they are causing faulty hormonal imprinting with lifelong consequences. In animal experiments single treatment with aromatic hydrocarbons (benzpyrene or dioxin) are decreasing the binding capacity of glucocorticoid receptor as well as estrogen receptor. Vitamin D3 (which is not a vitamin in reality, but a steroid-like hormone having receptors in the cytoplasmic-nuclear steroid receptor family [15], lifelong decreases the sexual activity (libido) of female and male rats, similar to industrial or communal endocrine disruptors [16].

Faulty Hormonal Imprinting and Functional Teratogenicity of Endocrine Disruptors

Teratogen materials, which evoke morphological alterations which are visible at birth are known from immemorial time and these are most effective during the embryonal period and their effects gradually decreases whith the time passed and vanishes after birth. Faulty hormonal imprinting does not provoke morphologically observable important alterations, but changes in functions of cells organs or systems which are manifested in diseases. They are not diagnosed at birth however, manifested later, mostly in adults. This is a functional teratogenity, without organic changes. An other difference to the morphological (real) teratogens that the possibility for exposure is longer: the perinatal period is the late phase of intrauterine development for morphological teratogens however, faulty imprinting can be provoked at any time e.g. also postnatally, few days or weeks after birth and other critical periods of life. The absolute need for taking place is the multiplication and differentiation of the touched cells.

Faulty hormonal imprinting inclines to diseases, alters behaviors, influences cell-responses to attacks, etc. In the scientific literature there are extreme amount of experimental data and also human observations can be found however, in the frame of a short review paper only a selection of them can be shown. Nevertheless they are represantatively demonstrate the importance and amount of the problems caused by it in the present modern age.

Sexual and Behavioral Problems Caused by Faulty Hormonal Imprinting

Perinnatal exposure to TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) an environmental contaminant (originated from volcanic eruptions as well as from exhaust gas of cars) and industrial or agricultural imprinters (bisphenol A, vinclozolin) pushes the boy-adventageous sex-ratio (more boys are delivered than girls) for the adventage of girls after paternal exposure (in human [16] and also to maternal exposure [17]) (in rats and mice). Bisphenol A (the well known plasticizer and representative of endogen disruptors) by prenatal and lactational exposure, changes the behavior of adults. Prenatal bisphenol A exposure provokes externalizing behavior in 2 years old children, especially in females [18] and abolishes the differences between male and female sexual behavior [19] and also modifies sexual behavior in female mice. It also alters sex difference in affective disorders. There is such opinion which calls attention to the future problems with school age. Some experiments and observations point to the possible association between early bisphenol A exposures (perinatal imprinting) and autism spectrum disorders) [19,20]. Pubertal bisphenol A exposures caused long term alterations in microglia of the prefrontal cortex when this was lower in males and higher in females [21]. There were also alterations in body weight and composition. Perinatal treatment and adolescent reexposure exacerbated adverse effects in females and reduce differences in males. Symptoms of sex dependent anxíety/depression appeared in 7–9 years girls without expression in boys after gestational bisphenol A exposures [22]. Altered sociosexual and mood disorders were observed in animal models and children after developmental exposure by bisphenol A [23].

Other Problems Caused by Faulty Hormonal Imprinting

Reproductive organs and puberty

First in the US and later in Europe an alteration in the timing of puberty (decline) was observed and also the growing number of obesity for which environmental factors, mainly endocrine disruptors was believed as responsible, by influencing genetic factors [24] These problems were observed after imprinting with polychlorinated biphenyls, polibrominated biphenyls, DDT and phtalate esters [25]. Both puberty age and menarche age were influenced [26, 27]. The

perinatal endocrine exposures can provoke central precocious puberty or isolated breast development in 2 months to 4 year old girls [28].

Growing number of human (male and femele) infertility and decreased fertility were observed [29]. In the case of perinatal exposure by bisphenol A decreased methylation of DNA and increased histone H3 acetylation were observed in the cerebral cortex and hippocampus, affecting the liver, gut, adipose tissue endocrine pancreas, mammary gland and reproductive tract functions [30]. Maternal programming was also altered [31]. Neonatal exposure to diethylstilbestrol (DES) caused early or delayed puberty, depending on the dose [32] by affecting hypothalamus and hippocampus. This is supported by rodent and human data [33]. Exposure in people is a result of contamination of foods or inhalation (e.g.house or occupational dust). Endocrine disruptors (bisphenol A and phtalates) negatively influence the function of the immune system, altering T cell subsets, B cell functions, dendritic cell and macrophage biology, and provoking autoimmune diseases [34,35]. They have a controversial role in influencing longevity [36]. The developing immune system, the cells of which have steroid (estrogen) hormone receptors is very sensitive to the presence of endocrine disruptors [35]. Faulty imprinting by endocrine disruptors could be responsible for pathological development of bones as well, as for changes in bone mineralization and osteoporotic fractures or other bone problems [37–41].

Gender differences in adverse drug reactions between men and women

It is very difficult to compare data of gender differences in the past-time adverse reaction to drugs, with relatively fresh (which were won in the time of endocrine disruptors) data as earlier always mens'data were studied and dosages of drugs were also prescribed exclusively for men [42–44]. However, new data show that women have 1.5 to 1.7-fold greater risk for adverse drug reactions than men [43]. For example, anti-bacterial and anti-inflammatory drugs cause more adverse reactions in females, as compared to males [42]. Cardiovascular diseases are the first case in mortality and disability of women [44]. There is a similar situation in case of addictions: considering alcohol intoxication compared to men, women metabolize alcohol less than men, it become intoxicated drinking half as much, develop cirrhosis more rapidly and have a greater risk of dying from alcohol-related accidents [45]. Drug abuse and dependence are not identical in males and females and females are less successful in quitting of alcoholism and nicotinism.

Conclusion

As most of the known endocrine disruptors are steroid hormone-like molecules, the functions [46], which are regulated by physiological steroid hormones are disturbed by them. The palette of these functions is broad, from sexuality to immunity and the period in which their effects are manifested is also very broad. They already disturb the sexual (male-female) ratio at birth, pushing it to the adventage of females, cause malformations of sexual organs (micropenis, cryptorchidism and hypospadias), provoke, as functional teratogens, faulty hormonal imprinting. However there are other critical periods of life (development) at weaning, during adolescence and for continuously dividing cells, during the whole life. In these cases endocrine disruptors are also able to provoke hormonal imprinting, which can modify the perinatal setting however, the effect of them less serious, than the perinatal one.

The difference between males and females in adverse drug reactions can be explained by sex differences in pharmacokinetics and pharmacodynamics, in which the liver microsomal enzyme system has an important role. The hormonal imprinting touches not only the hormonal system but also the (microsomal) enzyme system [47,48] and this interferes into the different adverse drug reactions by males and females. There is a gender-dependent metabolism which is influenced by microsomal enzymes which are different in the two sexes [49]. This influences pharmacokinetics and consequently toxicity. As was mentioned, this factor can give some explanation to the differences in adverse reactions by males and females, and faulty hormonal imprinting can disturb this process. This means that in contrast to the real (morphological) teratogens faulty hormonal imprinting does not causes morphological alterations, which are visible to the naked eye, however alterations in the hormonal or receptorial system as well, as in the enzyme system, durably changing the function of the cells, which are regulated by hormones. This renders likely (though the animal and human data are modest) that women (females) are more sensitive to faulty imprinters and some of their adverse reactions (and the overweight of women in adverse reactions) can be wrote to the expense of faulty perinatal hormonal imprinting.

It was mentioned that a single low dose of an endocrine disruptor seems to be enough for the provocation of faulty hormonal imprinting if it arrives in the optimal time for doing it (e.g.perinatal critical period). It is not surprizing if somebody consider that during the differentiation of the brain, when the direction of sexual development is determined, a part per billion of testosterone and about twenty parts per trillion of estradiol (endogeneous estrogen) actually predict entirely different brain structures, behavioral traits, enzyme levels and receptor levels in tissues [50]. It must be consider that the brain is basically female and it must be exposed to testosterone and related hormones for transforming to male . This means, that the receptorial system is ready to accept the imprinters, the developmental window is open for setting by single minimal doses of hormone-like materials (endocrine disruptors) and this is „exploited" by them (faulty imprinters). The gender differences in sensitivity and its epidemiological importance should be considered.

The late manifestation of alterations after the faulty hormonal imprinting makes more difficult to recognize the participation of faulty imprinting in the manifestation of a disease, or in the changes of behavior. It is supposed, that prenatal exposure to bisphenol A may be related to increased behavioral problems in school age boys, but not girls. However, although serious problems are expectable very difficult to forecast their quality and quantity. At any rate, thorough observations would be needed, for avoiding the problems. However, it seems to be difficult really to avoid, as the variants and amount of different endocrine disruptors are enormously growing because of the claims of the industry, which wants to earn a lot of money, and the people, who want to live more comfortable. In additon,

when a new molecule justifies its usefulness in the industry or as a medicament, it is not known (however sometimes could be guessed, but the expected pleasant effects suppresses anxiety), that it will be an endocrine disruptor. Fortunately, it is known that during pregnancy new exogeneous molecules must be avoided however, it is not known by lay medical practitioners and laywomen, that this regulation -in the light of faulty imprinting- must be extended to the whole period of pregnancy and also postnatally.

The task of medicine is to help people in the avoidance of illnesses or to heal ill people. This is done by giving advices or after diagnosing a disease, giving therapy for healing, which is mostly done by prescribing drugs. However, some drugs are endocrine disruptors themselves, for example anticoncipients and some vitamins. Anticoncipients are used for avoiding pregnacy, consequently they do not cause faulty imprinting in the person (women), who intakes it. However, the wast products of metabolized anticoncipients are present in the urine and contaminates drinking water, which is drinked by other, (pregnant) women. If we know, that minute amounts of an endocrine disruptor is able to provoke faulty imprinting, this could be done by the communal water. This is obvious, however can not be declared without exact measurements. Other medicaments are not tested for imprintership before running to circulation and can also contaminate the waters, or influence the endocrine system of developing fetus, directly. Drugs entering into breastmilk also can be faulty imprinters [51] and it is also known that most of baby foods are soy-based, consequently contain phytoestrogens (coumestrol, genistein and daidzein), which are known faulty imprinters [52–54]. Lipid soluble vitamins are prescribed by doctors and can be bought in pharmacies however, also can be purchased without prescription in self-service shops [55]. This shows that mankind is not prepared for the invasion and effects of faulty imprinters.

Afterwords

Pessimistically grasping, the growing of disruptor-inventar and the amount of disruptors, the future of mankind seems to be dangerous and threatening, as -endocrine disruptors -by faulty hormonal imprinting- can attack the whole endocrine system and the desorganization of the gene-level determined well- functioning system could cause hitherto unknown diseases or proliferation of known malignancies. In addition, the alterations are inherited to the progenies, epigenetically. However, there is -optimistically- an other version [55]: some of the endocrine disruptors internalized into the present endocrine system and new (better) functions will be manifested, which will be better suited to the continuously transformed world. Some examples had been observed to such transformation in the past, e.g. the infiltration of lipid soluble vitamins (e.g.vitamin A and D -hormones) and their prominent function in animal (human) life [56] . As can not be known what scenario will be the winner, the protection of women (as mothers) from endocrine disruptor effects is a very important mission of the present day mankind.

References

1. Csaba G, Nagy SU (1985) Influence of the neonatal suppression of TSH productiion (neonatal hyperthyroidism) on response of TSH production in adulthood. *J Endocrinol Invest* 8: 557–559. [crossref]
2. Csaba G (2011) The biological basis and clinical significance of hormonal imprinting, an epigenetic process. *Clin Epigenetics* 2: 187–196. [crossref]
3. Csaba G (1984) The present state in the phylogeny and ontogeny of hormone receptors. *Horm Metab Res* 16: 329–335. [crossref]
4. Nakamura K, Itoh K, Dai H, Han L, Wang X, et al. (2012) Prenatal and lactational exposure to low-doses of bisphenol A alters adult mice behavior. *Brain Dev* 34: 57–63. [crossref]
5. Wolstenholme JT, Taylor JA, Shetty SR, Edwards M, Connelly JJ, et al. (2011) Gestational exposure to low dose bisphenol A alters social behavior in juvenile mice. *PLoS One* 6: e25448. [crossref]
6. Chen F, Zhou L, Bai Y, Zhou R, Chen L (2014) Sex differences in the adult HPA axis and affective behaviors are altered by perinatal exposure to a low dose of bisphenol A. *Brain Res* 1571: 12–24. [crossref]
7. Evans SE, Kobrosly RW, Barrett ES, Thurston SW, Calafat AM, et al. (2014) Prenatal bisphenol A exposure, maternally reported behavior in boys and girls. *Neurotoxicology* 45, 91–99.
8. Csaba G (2017) The Present and Future of Human Sexuality: Impact of Faulty Perinatal Hormonal Imprinting. *Sex Med Rev* 5: 163–169. [crossref]
9. Rubin BS, Paranjpe M, DaFonte T, Schaeberle C, Soto AM, et al. (2017) Perinatal BPA exposure alters body weight and composition in a dose specific and sex specific manner: The addition of peripubertal exposure exacerbates adverse effects in female mice. *Reprod Toxicol* 68: 130–144.
10. Csaba G (2018) Bone manifestation of faulty perinatal hormonal imprinting: a review. *Curr Pediatr Rev* 25. [crossref]
11. Csaba G (1980) Phylogeny and ontogeny of hormone receptors: the selection theory of receptor development and hormonal imprinting. *Biol Rev Camb Philos Soc* 55: 47–63.
12. Hanley B, Dijane J, Fewtrell M, Grynberg A, Hummel S, et al. (2010) Metabolic imprinting, programming and epigenetics – a review of present priorities and future opportunities. *Br J Nutr* 104: 1–25.
13. Lemke H, Tanasa RI, Trad A, Lange H (2009) Benefits and burden of the maternally-mediated immunological imprinting. *Autoimmun Rev* 8: 394–399.
14. Barker DJ (2007) The origins of the developmental origins theory. *J Intern Med* 261: 412–417. [crossref]
15. Lorenzen M, Boisen IM, Mortensen LJ, Lanske B, Juul A, et al. (2017) Reproductive endocrinology of vitamin D. *Mol Cell Endocrinol* 453: 103–112. [crossref]
16. Ishihara K, Warita K, Tanida T, Sugawara T, Kitagawa H, et al. (2007) Does paternal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) affect the sex ratio of offspring? *J Vet Med Sci* 69: 347–352. [crossref]
17. Yonemoto J, Ichiki T, Takei T, Tohyama C (2005) Maternal exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin and the body burden in offspring of long-evans rats. *Environ Health Prev Med* 10: 21–32. [crossref]
18. Kubo K, Arai O, Omura M, Watanabe R, Ogata R, et al. (2003) Low dose effects of bisphenol A on sexual differentiation of the brain and behavior in rats. *Neurosci Res* 45: 345–356. [crossref]
19. Hashemi F, Tekes K, Laufer R, Szegi P, Tóthfalusi L, et al. (2013) Effect of a single neonatal oxytocin treatment (hormonal imprinting) on the biogenic amine level of the adult rat brain: could oxytocin-induced labor cause pervasive developmental diseases? *Reprod Sci* 20: 1255–1263.
20. Stein TP, Schluter MD, Steer RA, Guo L (2015) Bisphenol A Exposure in Children With Autism Spectrum Disorders. *Autism Res* 8: 272–283. [crossref]
21. Wise, LM, Sadowski RM, Kim T, Willing J, Juraska JM (2016) Long-term effects of adolescent exposure to bisphenol A on neuron and and glia number in the rat prefrontal cortex: Differences between the sexes and cell type. *Neurotoxicology* 53: 186–192.
22. Perera F, Nolte ELR, Wang Y, Margolis AE, Calafat AM, et al. (2016) Bisphenol A exposure and symptoms of anxiety and depression among inner city children at 10–12 years of age. *Environ Res* 151: 195–202. [crossref]
23. Hicks HD, Sullivan AV, Cao J, Sluzas E, Rebuli M, et al. (2016) Interaction of bisphenol A (BPA) and soy phytoestrogens on sexually dimorphic sociosexual behaviors in male and female rats. *Horm Behav* 84: 121–126.
24. Parent AS, Franssen D, Fudvoye J, Pinson A, Bourgignon JP (2016) Current changes in pubertal timing: Revised vision in relation with environmental factors including endocine disruptors. *Endocr Dev* 29: 174–184.
25. Den Hond E, Schoeters G (2006) Endocrine disrupters and human puberty. *Int J Androl* 29: 264–271. [crossref]
26. Massart F, Parrino R, Seppia P, Federico G, Saggese G (2006) How do environmental estrogen disruptors induce precocious puberty? *Minerva Pediatr* 58: 247–254.
27. Schoeters G, Den Hond E, Dhoge W, van Larebeke N, Leijs M (2008) Endocrine disruptors and abnormalities of pubertal development. *Basic Clin Pharmacol Toxicol* 102: 168–175.
28. Leonardi A, Cofini M, Rigante D, Lucchetti L, Cipolla C, et al. (2017) The effect of bisphenol A on puberty: a critical review of the medical literature. *Int J Environ Res Public Health* 14.

29. Tomza-Marciniak A, StÄ™pkowska P, Kuba J, Pilarczyk B (2018) Effect of bisphenol A on reproductive processes: A review of in vitro, in vivo and epidemiological studies. *J Appl Toxicol* 38: 51–80. [crossref]
30. Kumar D, Thakur MK (2017) Effect of perinatal exposure to Bisphenol-A on DNA methylation and histone acetylation in cerebral cortex and hippocampus of postnatal male mice. *J Toxicol Sci* 42: 281–289. [crossref]
31. Schneider, JE, Brozek JM, Keen-Rhinehart E (2014) Our stolen figures: the interface of sexual differentiation, endocrine disruptors, maternal programming, and energy balance. *Horm Behav* 66: 104–119.
32. Bourguignon JP, Franssen D, Gerard A, Jannsen S, Pinson A, et al. (2103) Early neuroendocrine disruption in hypothalamus and hippocampus: developmental effects including female sexual maturation and implications for endocrine disrupting chemical screening. *J Neuroendocrinol* 25: 1079–1087.
33. Rasier G, Toppari J, Parent AS, Bourgignon JP (2006) Female sexual maturation and reproduction after prepubertal exposure to estrogens and endocrine disrupting chemicals: a review of rodent and human data. *Mol Cell Endocrinol* 25: 254–255.
34. Rogers JA, Metz L, Yong VW (2013) Review: Endocrine disrupting chemicals and immune responses: a focus on bisphenol A and its potential mechanisms. *Mol Immunol* 53: 421–430.
35. Csaba G (2014) Immunoendocrinology: faulty hormonal imprinting in the immune system. *Acta Microbiol Immunol Hung* 61: 89–106. [crossref]
36. Csaba G (2018) Immunity and longevity. *Acta Microbiol Immunol Hung* 65: 1–17.
37. Karabélyos C, Horváth C, Holló I, Csaba G (1999) Effect of perinatal synthetic steroid hormone (allylestrenol, diethylstilbestrol) treatment (hormonal imprinting) on the bone mineralization of the adult male and female rat. *Life Sci* 64: 105–110.
38. Karabélyos C, Horváth C, Holló I, Csaba G (1998) Effect of neonatal glucocorticoid treatment on bone mineralizaton of adult non-treated, dexamethasone-treated or vitamin D3-treated rats. *Gen Pharmacol* 31: 789–791.
39. Karabélyos C, Horváth C, Holló I, Csaba G (1998) Effect of neonatal vitamin D3 treatment (hormonal imprinting) on the bone mineralization of adult non-treated and dexamethason-treated rats. *Hum Exp Toxicol* 17: 424–429.
40. Karabélyos C, Horváth C, Holló I, Csaba G (1999) Effect of perinatal synthetic steroid hormone (allylestrenol, diethylstilbestrol) treatment (hormonal imprinting) on the bone mineralization of the adult male and female rat. *Life Sci* 64: 105–110.
41. Curtis EM, Krstic N, Cook E, D'Angelo S, Crozier SR, et al. (2018) Gestational vitamin D supplementation leads to reduced perinatal RXRA DNA methylation: Results from the MAVIDOS trial. *J Bone Miner Res* 2018 Oct 15. [crossref]
42. Zopf Y, Rabe C, Neubert A, Janson C, Btune K, et al. (2009) Gender-based differences in drug prescription: relation to adverse drug reactions. *Pharmacology* 84: 333–339.
43. Rademaker M (2001) Do women have more adverse drug reactions? *Am J Clin Dermatol* 2: 349–351. [crossref]
44. Baggio G, Corsini A, Floreani A, Giannini S, Zagonel V (2013) Gender medicine: a task for the third millennium. *Clin Chem Lab Med* 51: 713–727. [crossref]
45. Greenfield SF (2002) Women and alcohol use disorders. *Harv Rev Psychiatry* 10: 76–85. [crossref]
46. Lymperi S, Giwercman A (2018) Endocrine disruptors and testicular function. *Metabolism* 86: 79–90. [crossref]
47. Csaba G, Dobozy O, Szeberényi S (1987) A single neonatal treatment with methylcholanthrene or benzo(a)pyrene alters microsomal enzyme activity for life. *Acta Physiol Hung* 70: 87–91. [crossref]
48. Csaba G, Szeberényi S, Dobozy O (1986) Influence of single neonatal treatment with allylestrenol or diethylstilbestrol on microsomal enzyme activity of rat liver in adulthood. *Med Biol* 64: 197–200. [crossref]
49. Waxman DJ (1984) Rat hepatic cytochrome P-450 isoenzyme 2c. Identification as a male-specific, developmentally induced steroid 16 alpha hydroxylase and comparison to a female-specific cytochrome P-450 isoenzyme. *J Biol Chem* 25: 15481–15490.
50. Hood E (2005) Are EDCs blurring issues of gender? *Environ Health Perspect* 113: 670–677. [crossref]
51. Csaba G (2018) Lifelong impact of breastmilk transmitted hormones and endocrine disruptors. *J Clin Endocrinol Res* In Press 2018.
52. Bar-El DS, Reifen R (2010) Soy as an endocrine disruptor: cause for caution? *J Pediatr Endocrinol Metab* 23: 855–861. [crossref]
53. Csaba G (2018) Effect of endocrine disruptor phytoestrogens on the immune system: Present and future. *Acta Microbiol Immunol Hung* 65: 1–14. [crossref]
54. Bennetau-Pelissero C (2016) Risks and benefits of phytoestrogens: where are we now? *Curr Opin Clin Nutr Metab Care* 19: 477–483. [crossref]
55. Csaba G (2018) The role of endocrine disruptors in future human endocrine evolution: The ED-exohormone system. *Current Trends Endocrinol* under publication.
56. Csaba G (2017) Vitamin-caused faulty perinatal hormonal imprinting and its consequences in adult age. *Physiol Int* 104: 217–225. [crossref]

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