HJOG
An Obstetrics and Gynecology
International Journal

Review

Toxicological impact of heavy metals on the placenta: A literature review

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Abstract

The purpose of this study is the review of the literature regarding the placental damage after exposure to heavy metals. The role of the feto-placental unit is particularly important during pregnancy and replaces the function of the not fully formed organs of the fetus, like the lungs, kidneys, the gastrointestinal and the endocrine system. Moreover, it protects the fetus from infections, toxins, pharmaceutical agents, drugs as well as chemical substances. The examination of the placenta provides relevant information for the endometrium as well as it contributes significantly in the investigations of the perinatal deaths, the intrauterine growth retardation, the malformations, the infections and the maternal diseases effects on the fetal development. The size of the clinical problem associates with the development of the placenta function so intensely, that the histological aspect of the human placenta should be taken a lot into consideration. A thorough examination is often underestimated, although it can yield invaluable role regarding the fetal development. Most people during their lifetime are exposed to a large number of chemical substances which may be hazardous to the reproduction system. Many chemicals have been identified in laboratory studies to create reproductive problems, but also problems in the function of placenta, the fetal development and even cause perinatal death.

Key words: placenta, heavy metals, toxicity, complications

The placenta examination provides important information on the state of the endometrium and the investigations of the perinatal death, the intrauterine growth restriction, the malformations, the maternal infectious diseases and their effects on fetal development[1].

The magnitude of the clinical problems associated with the development of placental function requires proper action to be taken towards the histological investigation of the human placenta in several occasions. A thorough examination, though often underestimated, can yield invaluable role regarding fetal development[2]. The histopathologic examination of the placenta postnatally, in cases of maternal or fetal complications, abortion or neonatal death, may provide an explanation regarding the aforementioned complications as well as relevant information on the management of future pregnancies[3].

The placenta has two main functions, exchange of nutrients and protection of the embryo[4]. It may

adapt continuously to maximize maternal and fetal nutrient offer and export, without compromising the integrity of the circulatory system of participants, meaning the mother and the fetus. Furthermore, the placenta performs a protective role against innumerous inflammatory conditions[5]. A normal placenta is 22cm in diameter and from 2.0 to 2.5cm thick, and, generally, it weighs about 470gr[6]. However, these values may vary. The maternal surface of the placenta is dark brown and shows lobules or cotyledons, which are complete. The fetal surface of the placenta is usually gray and transparent. The placental membranes are characterized by a metallic smell. Additionally, the umbilical cord belongs in the feto - placental unit and connects the fetus to the placenta. In full - term pregnancies, the umbilical cord is about 55 - 60cm with a diameter 2.0 - 2.5cm[7]. The placenta contains a viscous substance, the so-called Wharton's jelly crossed by the umbilical vein and the two umbilical arteries[8].

Generally, the placenta is sufficiently impermeable to chemical or pharmaceutical substances with a molecular weight of 1,000Da or more[9,10]. Most pharmaceutical agents have a molecular weight of 500Da or less. Therefore, the molecular size rarely represents a risk factor for pharmaceutical agents in correlation with the placenta and the fetus/neonate. The permeability of the placenta to chemicals reflects the characteristics of the agent, the thickness of the surface, and the concentration of lipid-protein membranes[11]. The intrinsic characteristics of the chemical substance, like the degree of ionization, the solubility of the lipids, the protein binding and the molecular weight also affect the substance's transport through the placenta[12]. Of note, gases, vitamins, amino acids, sugars, ions, viruses, and fat soluble chemicals have easier access to the fetus[13,14]. Unionized lipo - soluble substances readily penetrate from ionized water soluble materials. Furthermore, the passage of the fetal membranes is not dependent on the number of placental layers formed as the fetus matures[15]. Although more than 80 known metals are crucial for the human physiological processes, other metals are known for their toxicity to the human body. Many metals are considered essential for normal cellular activity, while prolonged exposure to them can cause toxic reactions. The metals are also used in medicine as in diagnostic and therapeutic procedures[16]. The major heavy metals are: antimony, aluminium, silver, arsenic, vanadium, barium, bismuth, tungsten, gallium, zirconium, thallium, indium, iridium, cadmium, tin, lanthanum, platinum, manganese, lead, nickel, niobium, palladium, rhodium, ruthenium, scandium, strontium, tantalum, mercury, yttrium, copper, hafnium, gold, chrome. Most metals appear in the natural environment at relatively low levels. However, with regards to human exposure and toxicological significance, human activities are increasing the levels of metals in several regions.

Common toxic mechanisms and side effects

Enzyme inhibition/activation. An important point of the toxic actions of metals is the enzyme interaction, resulting in either enzyme inhibition or activation. Two mechanisms are particularly important: Inhibition may occur as a result of interaction between the metal and the sulfhydryl groups (sulfhydryl, SH) on the enzyme, or the metal may displace an essential cofactor of the enzyme[17].

Intracellular organelles. Toxic metals can disrupt the structure and function of a significant number of organelles. For example, enzymes associated with the endoplasmic reticulum may be suspended, the metals can accumulate in the lysosomes, the respiratory enzymes in mitochondria can be suspended and the metallic inclusion can be formed in the core[18].

Carcinogenesis. A number of metals have been shown to be carcinogenic in humans or animals. Arsenic, certain chromium compounds, and nickel metals are known carcinogens in humans. Beryllium, cadmium and cisplatin are probably toxic carcinogens. The carcinogenic action, in certain instances, is believed to result from the interaction of metal ions with DNA[19].

Kidney. As kidney is the main excretory organ of the body, it is also a main target organ for metal tox-

icity. Cadmium and mercury, in particular, are key toxic substances that affect the kidneys[20].

Nervous system. The nervous system is also affected by particular toxic metals, which are derived from organic metal compounds. For example, methylmercury, due to lipid solubility, enters the nervous system by crossing the bloodstream. In contrast, inorganic mercury compounds, which are more water soluble, are less likely to enter the nervous system, particularly affecting the kidneys. Similarly, organic lead compounds are especially neurotoxic substances[21].

Endocrine and reproductive system. Since the male and the female reproductive organs are characterized by complexity in terms of hormones, any toxic substance, altering some of the hormonal processes, can have an impact on the reproductive system. Moreover, metals may act directly on the reproductive organs. Cadmium, for example, is known to cause damage to the testicles after acute exposure and binds to testicular degeneration, inhibition of spermatogenesis and Leydig cell atrophy[22].

Respiratory system. Occupational exposure to metals in metallic powder form makes respiratory system a potential target. Acute exposure may cause irritation and inflammation of the respiratory tract, while chronic exposure can result in fibrosis (aluminium) or carcinogenesis (arsenic, chrome, nickel)[23].

Heavy metals are considered one of the most important groups of environmental pollutants, which may well in small quantities be essential nutrients protecting health, but in greater quantities they can become toxic and dangerous. Heavy metals such as arsenic, mercury, copper, lead and cadmium have adverse effects in pregnancy. An overview of the current knowledge of the toxic effect of metals during pregnancy is very important. Arsenic, for example, can be harmful in pregnancy. Exposure to this substance can come from food, brought from agricultural areas where fertilizers containing arsenic have been used. It can also come from water wells near mines or manufacturing plants. Arsenic affects pregnant women who are at an increased risk for gestational diabetes. Chronic arsenic exposure through drinking water can increase fetal morbidity and mortality. There are reported higher proportions of infants with mental retardation and developmental disabilities due to maternal exposure. Exposure to lead during pregnancy can cause miscarriage or premature birth with low birth - weight, and is often associated with brain developmental defects and mental retardation[24]. Infants and fetuses exposed to lead, can develop behavioral and learning disabilities. Regarding the exposure to copper, estrogens promote its conservation and enhance its toxic effects on fertility rates[25]. Mercury is transferred from the mother to the fetus via the placenta and to the infant through the breastfeeding. In the United States, it is estimated that one in ten fetuses are born annually with increased risk of neurological disorders due to mercury exposure during pregnancy. The mercury toxicity can damage the fetal developing nervous system causing learning difficulties and can affect the reproductive system, involving in problems such as infertility, miscarriage and premature birth. Mercury reduces zinc levels, which can cross the placental barrier and the blood-brain barrier. It is also associated with reduced libido and premenstrual syndrome. Mercury is also transmitted through breast milk and is affecting the learning ability of the newborn[26]. Association of cadmium exposure in pregnancy with low birth - weight and premature birth is also often reported[27]. Various heavy metals such as lead, mercury and cadmium are known to alter the delicate balance of mother - fetus, potentially causing long - term damage in newborns. The thickness of placental layers is one of the major determining factors which affect the ability and interactive substance transport from the mother to the fetus[28]. Lead is known to be easily crossing the placental barrier by passive diffusion. This certifies a positive correlation. Similarly, a positive correlation was observed in the majority of studies on its levels in placental and cord blood. According to toxicodynamics, lead can alter the associated with calcium cellular processes in syncytiotrophoblasts

and appears to be associated with reduced oxidation activity on cytochrome[29]. The role of the placenta as a mercury barrier is not completely clear: the cellular uptake of this heavy metal appears to be related to its chemical structure. It has been observed that the mercury and methylmercury fumes can cross the placenta, using passive transfer and amino acid transporters. On the contrary, inorganic mercury often accumulates in the placenta, limiting the amount that reaches the fetus[30]. The mercury - induced toxicity to the placenta has an impact on the hormone secretion deregulation, the amino acid transport, the oxygen consumption and the membrane fluidity.

Conclusion

Heavy metals have a negative impact on the placenta formation and further pregnancy development. Multiple biochemical procedures interact and exert toxic effects on the fetus formation. Multidisciplinary cooperation is necessary in order to ensure a healthy gestation.

Conflict of interest

All authors declare no conflict of interest.

References

1. Gong JS, Kim GJ. The role of autophagy in the placenta as a regulator of cell death. Clin Exp Reprod Med 2014;41:97-107.
2. Huppertz B. Maternal - fetal interactions, predictive markers for preeclampsia, and programming. J Reprod Immunol 2014 (Epub ahead of print).
3. Tomas SZ, Roje D, Prusac IK, Tadin I, Capkun V. Morphological characteristics of placentas associated with idiopathic intrauterine growth retardation: a clinicopathologic study. Eur J Obstet Gynecol Reprod Biol 2010;152:39-43.
4. Bustamante J, Ramírez - Vélez R, Czerniczyniec A, Cicerchia D, Aguilar de Plata AC, Lores - Arnaiz S. Oxygen metabolism in human placenta mitochondria. J Bioenerg Biomembr 2014;46:459-69.
5. Yui J, Garcia - Lloret M, Wegmann TG, Guilbert LJ. Cytotoxicity of tumour necrosis factor - alpha and gamma - interferon against primary human placental trophoblasts. Placenta 1994;15:819-35.
6. De Paepe ME, Shapiro S, Young LE, Luks FI. Placental weight, birth weight and fetal: placental weight ratio in dichorionic and monochorionic twin gestations in function of gestational age, cord insertion type and placental partition. Placenta 2015;36:213-20.
7. Schmid A, Jacquemyn Y, Loor JD. Intrauterine growth restriction associated with excessively long umbilical cord. Clin Pract 2013;3:e23.
8. Gervaso F, Boschetti F, Pennati G. Evaluation of the Wharton's jelly poroelastic parameters through compressive tests on placental and foetal ends of human umbilical cords. J Mech Behav Biomed Mater 2014;35:51-8.
9. Huppertz B, Gauster M. Trophoblast fusion. Adv Exp Med Biol 2011;713:81-95.
10. Rudge CV, Röllin HB, Nogueira CM, Thomassen Y, Rudge MC, Odland JØ. The placenta as a barrier for toxic and essential elements in paired maternal and cord blood samples of South African delivering women. J Environ Monit 2009;11:1322-30.
11. Wick P, Malek A, Manser P, et al. Barrier capacity of human placenta for nanosized materials. Environ Health Perspect 2010;118:432-6.
12. Shintaku K, Hori S, Tsujimoto M, et al. Transplacental pharmacokinetics of diclofenac in perfused human placenta. Drug Metab Dispos 2009;37:962-8.
13. Desforges M, Sibley CP. Placental nutrient supply and fetal growth. Int J Dev Biol 2010;54:377-90.
14. Brownbill P, McKeeman GC, Brockelsby JC, Crocker IP, Sibley CP. Vasoactive and permeability effects of vascular endothelial growth factor - 165 in the term in vitro dually perfused human placental lobule. Endocrinology 2007;148:4734-44.
15. Battaglia FC. Placental transport: a function of permeability and perfusion. Am J Clin Nutr 2007;85:591S-597S.
16. Ozdemir U, Gulturk S, Aker A, Guvenal T, Imir G, Erselcan T. Correlation between birth weight, leptin, zinc and copper levels in maternal and cord blood. J Physiol Biochem 2007;63:121-8.
17. Guo Y, Chen L, Yang L, Wang Q. Counting sulfhydryls

and disulfide bonds in peptides and proteins using mercurial ions as an MS - tag. J Am Soc Mass Spectrom 2008;19:1108-13.
18. Chatterjee S, Sarkar S, Bhattacharya S. Toxic metals and autophagy. Chem Res Toxicol 2014;27:1887-900.
19. Luevano J, Damodaran C. A review of molecular events of cadmium - induced carcinogenesis. J Environ Pathol Toxicol Oncol 2014;33:183-94.
20. Miller S, Pallan S, Gangji AS, Lukic D, Clase CM. Mercury - associated nephrotic syndrome: a case report and systematic review of the literature. Am J Kidney Dis 2013;62:135-8.
21. Colquhoun A, Eibl JK, Krol KM, Chan HM, Ross GM. Conformational analysis of the effects of methylmercury on nerve growth factor and brain derived neurotrophic factor. Environ Toxicol Pharmacol 2009;27:298-302.
22. Apostoli P, Catalani S. Metal ions affecting reproduction and development. Met Ions Life Sci 2011;8:263-303.
23. Xie H, Huang S, Martin S, Wise JP Sr. Arsenic is cytotoxic and genotoxic to primary human lung cells. Mutat Res Genet Toxicol Environ Mutagen 2014;760:33-41.
24. Neeti K and Prakash T, Effects of heavy metal poison during pregnancy. Int Res J Environment Sci 2013;2:88-92.
25. Williams P, James R, Roberts S. Principles of Toxicology. Environmental and Industrial Applications. 2nd Edition. New York:John Wiley & Sons Inc;2000.
26. Eccles CU, Annau Z. Prenatal methyl mercury exposure: II. Alterations in learning and psychotropic drug sensitivity in adult offspring. Neurobehav Toxicol Teratol 1982;4:377-82.
27. Sun H, Chen W, Wang D, Jin Y, Chen X, Xu Y. The effects of prenatal exposure to low - level cadmium, lead and selenium on birth outcomes. Chemosphere 2014;108:33-9.
28. Thévenod F, Lee WK. Cadmium and cellular signaling cascades: interactions between cell death and survival pathways. Arch Toxicol 2013;87:1743-86.
29. Srivastava RK, Pandey P, Rajpoot R, Rani A, Dubey RS. Cadmium and lead interactive effects on oxidative stress and antioxidative responses in rice seedlings. Protoplasma 2014;251:1047-65.
30. Urbach J, Boadi W, Brandes JM, Kerner H, Yannai S. Effect of inorganic mercury on in vitro placental nutrient transfer and oxygen consumption. Reprod Toxicol 1992;6:69-75.