

Teratogenic Effect of Cadmium: From The Developing Embryo To The Fetus

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ABSTRACT. Cadmium is recognized as a toxic metal recognized by the United Nations Organization list, and also a potential teratogen in humans. The levels of ingestion varies by country, being seafood and tobacco smoke the principal reported sources. This metal has a long half-life, ranging from 75 days to 26 years, and is associated in humans to many cancers. The teratogenic impact of cadmium in each stage of the developing embryo is clear in animal models, but not in humans. In the pre-implantation phase it affects the progression from the two-cell stages to morula; in the implantation phase it affects the trophoblastic invasion; in post-implantation phase it affects organogenesis; in the placenta it decrease Zinc levels in the fetus. The objective of this study was to review the teratogenic effects of Cd in the human embryonic development from pre implantation, implantation and post implantation, and impact on the placenta and fetus.

Keywords: Cadmium, teratogenesis, carcinogenesis, embryonic development.

EFFECTO TERATOGÉNICO DE CADMIO: DESDE EL EMBRIÓN EN DESARROLLO HASTA EL FETO. RESUMEN. El cadmio ha sido reconocido como un metal tóxico en la lista de la Organización de las Naciones Unidas. También como teratógeno en animales y potencial teratógeno en humanos, además por su extensa vida media que va entre 75 días a 26 años se ha asociado con varios tipos de cáncer. Los niveles de cadmio séricos en humanos varían según el país, siendo los mariscos y tabaco las principales fuentes de ingestión. El impacto teratogénico de cadmio en cada etapa del embrión en desarrollo ha sido demostrado en varios modelos animales, pero los estudios no sean del todo concluyentes en humanos. Se ha observado que el cadmio durante la fase de preimplantación afecta el progreso desde los estadios de dos células a de mórula; en la fase de implantación afecta la invasión del trofoblasto; en la fase de post-implantación afecta la organogénesis; y en la placenta afecta el paso de zinc al feto. El objetivo de este estudio es realizar una revisión de la literatura publicada a la fecha sobre los efectos teratogénicos del cadmio en el desarrollo embrionario humano, como también el impacto en la placenta y el feto.

Palabras clave: Cadmio, teratogénesis, carcinogénesis, desarrollo embrionario.

INTRODUCTION

Cadmium (atomic number 46, atomic weight 112.40, IIb group) is recognized as a toxic metal recognized by the United Nations Organization list and also a potential teratogen in humans¹, with a wide distribution in the environment².

The World Health Organization has set around 500 ug/week of Cd intake as a secure ingestion level²⁻⁴, but in some European studies it has been reported that many cities in Europe the secure level doubles, having as a principal route of ingestion the seafood and the rice, where in the others where the food was not the principal, the tobacco smoke was the principal route of ingestion,

followed by pollution and breast milk or powdered formula in the newborns^{2,4-18}.

For each cigarette smoked 0.2-1.0 mg of Cd are assimilated, where 10% is deposited in the lung tissue, 30 - 40% circulates in the blood and the other half is eliminated¹⁹⁻²⁴. It is important to know that this metal has a long half-life ranging from 75 days to 26 years^{23,25-27} with an additional decrease in renal clearance then affecting not only the renal system, and also considerate a teratogenic agent in animals and a carcinogenic agent in humans by the IARC²⁸⁻³¹. Additionally recent studies in which multiple heavy metals were measured in blood found that the presence of Cd in the blood is a marker of co-exposition to others toxics as lead³².

Occupational exposure to Cd is also important because there are a wide ranges of occupational exposures in which workers can get exposed³³⁻³⁵. Characteristically jobs in which there is manipulation of paints, metals, plastics, alkaline batteries, ceramics, welding operations, construction, manufacturing, and minery are those related to exposition to Cd^{33,36-38}; to Colombia this can be important because all of these are occupations in which a Colombian worker can get involve. Available data from the Occupational Safety and Health Administration (OSHA) estimates that around 500,000 workers in the USA face exposure to Cd each year, with very adverse long-term complications as chronic kidney disease, lung cancer, and prostate cancer³³.

Although the teratogenic effect of Cd in humans it is not proved yet, several studies in animals have found Cd as an important teratogen, affecting the embryo from the implantation to the organogenesis. The objective of this work is to review the teratogenic effects of Cd exposure in the embryonic development and make a brief summary of the purposed mechanisms of cell damage.

METHODOLOGY

It was performed a systematic review of clinical studies, clinical assays, topic reviews and controlled clinical trials related with the relationship of exposition or presence of Cd in maternal/fetal blood and teratogenic effects published in mostly in English language.

Bibliographic review was done using the following databases: EMBASE, MEDLINE, pubmed, SciELO, Lilacs, using the keywords "cadmium toxicity", "cadmium teratogenic AND embryo", "Cadmium AND embryo", "Cadmium AND pregnancy", "Cadmium AND placenta". The review was completed searching in the references of the principals articles of this topic.

The included articles were analyzed by quality using as

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reference a protocol created for this study composed with 13 inclusion criteria and 5 exclusion criteria. This instrument is a modified version of the instrument originally created by Stalenhoef et al³⁹, to which we had added some criteria to identify systematic bias of observational studies^{40,41}.

EFFECTS OF CD ON THE DEVELOPING EMBRYO

PRE-IMPLANTATION

Failure of developmental progression in the pre-implanted embryo is documented from the two-, four-, and eight-cell stages to morula^{42,43}. The effects are observed in a dose-related effect, whereas higher the exposure the higher is the risk of cell failure to progression to the follow stage⁴⁴.

The mechanisms by which Cd affects the progression at those are principally related to inhibition of several cellular mechanisms of connection. For example Cd affects phosphorylation of connexins, which are the forming molecules of the gap junctions by induction of β -catenin to translocate to the nucleus, where it alters gene expression of connexin 43, which is a key molecule for the gap junctions⁴⁵⁻⁴⁷.

Others mechanism purposed are the disruption of tight junctions and direct oxidative stress, where even when the dose of exposure is not high, low doses of Cd can stop the embryonic development^{11,48-50}.

IMPLANTATION

Occasionally when Cd does not affect embryonic development, it has been reported that it affects the implantation process, from the trophoblastic invasion to detach it. The molecules related to adhesion are those affected by Cd, such as connexins, cadherins and zonula occludens, and also activation of the Ca-Calmodulin complex which related to the detachment of the trophoblast. Goyer et al. exemplified the in vitro effect of Cd exposure using the JAR choriocarcinoma line, in which they found that Cd exposure to trophoblastic cells induces calcium release causing activation of the calmodulin activation that brings the cell to an apoptotic state that is responsible for the detachment of the embryo when is implanted⁵¹⁻⁵⁴.

POST-IMPLANTATION

The effects of Cd exposure in the post-implantation depend to many factors such as dose, stage of organogenesis and kind of animal in which the metal was used⁵⁵.

Exposure during the gastrulation phase results in widespread damage to the embryo, with multiple malformations, especially structural. In several species

such as Zebrafish, Xenopus, Rodents (hamster, rat, mouse) the kind of alterations range from growth retardation, craniofacial and ocular defects, notochord/somite abnormalities, gut and cardiovascular malformations, to hypopigmentation and skeletal deformities⁵⁵.

Chick, xenopus, rodents are species involved in others studies in which they found dose and time related exposure effects on the neurulation phase. The teratogenic effects observed in this phase were abnormal body axis, ventral body wall defect, upper and lower extremities abnormalities, diaphragmatic hernia, facial clefting; and most of these findings were very consistent in all the three studied species⁵⁵⁻⁵⁷.

In the ectoderm, neural tube, lateral plate mesoderm and somites are the structure that suffers from apoptotic changes; just after 4-6 hours after Cd has contact with them. The β -catenin also has a role here, where it activates the nuclear Wnt pathway, which alters the gene expression in the somites, causing an imbalance of genes that are required to the normal development of the embryo⁵⁵⁻⁵⁷.

High doses of Cd can also affect neural tissue after neurulation, when the neural tube is closed and most of the structures are developed. The effects on the neural tissues are re-opening of the neural tube, exencephaly, limb reduction defect, urogenital abnormalities and umbilical hernia; all those described especially in rodents^{55,56}.

The purposed mechanism by which Cd can cause re-opening of the neural tube is the inhibition of the Carbonic Anhydrase, and enzyme responsible for pH control. This mechanism of teratogenesis was purposed because the indistinguishable lesions that causes acetazolamide, an Carbonic Anhydrase inhibitor⁵⁵.

Other enzymes that could be implicated in this process are described by Messerle et al. in a study in which they found that Cd causes also inhibition of alcohol dehydrogenase, alkaline phosphatase, carboxypeptidase, and DNA binding proteins that controls gene expression during neurulation, all of this bringing to anencephaly and abnormalities related to the closure of the neural tube⁵⁸⁻⁶⁹.

EFFECTS OF CD ON THE PLACENTA AND FETUS

PLACENTA

Without the placenta the levels of Cd in the fetus will be much higher, the exact percentage of Cd that is stopped is around 30-40%, so the maternal blood analysis will have three times more Cd than the fetus⁷⁰⁻⁷⁶, and recent studies has shown three times the concentration of

MT in mothers who were exposed to Cd, making an induction of MT in placenta tissue^{3,77}.

But this protection also has a negative side, because it has been associated high placental levels of Cd with low levels of Zn in the fetus and negatives outcomes of pregnancy^{55,70-72,78}.

The Metallothionein (MT), which is a membrane protein in the Golgi apparatus of the placental cells has the capacity to bind Zn, Cu, Se to transport to the fetal circulation, but also is responsible for the protection against heavy metals such as Cd, Hg, Ar, Ag to pass through placental circulation⁷⁹. So, when any of these xenobiotics have contact with MT it alters its function decreasing the levels of Zn, Cu, and Se to pass to the fetal circulation⁸⁰.

Also MT is has anti-oxidative properties because it captures oxidant radicals like superoxide and hydroxyl radicals produced by Cd metabolism⁸¹⁻⁸⁶. This role was purposed after an experiment with knockout mutants mice for MT gene, in which was seen extensive placental cell necrosis^{55,84,87}.

Studies using rats also has shown a protective effect of Zn preventing anatomic abnormalities induced by Cd⁸⁸⁻⁹⁰. Ashraf et al. using four groups of rats in pregnancy and exposing to Cd and different levels of Zn showed a positive relationship between Zn exposure and less anatomic abnormalities as exencephaly⁸⁸.

Piasek et al. found in his study using 56 placentas of smokers and non-smokers mothers in a city of Croatia an association between high levels of heavy metals such as iron, lead, copper, zinc and cadmium with lower levels of hCG and progesterone compared to placentas from non-smoking mothers^{70,71}. The levels of human gonadotropin hormone (HCG) and associated progesterone are important for the maintenance of the pregnancy⁹¹, and lead to recurrent abortion⁹².

Another important finding in the placentas found in smoking mothers is related to hypoxic states in the fetus⁹³. The characteristics of those placentas were an increased villous membrane thickness, and increased hematocrit in the placenta blood, are comparative changes than rather than assist, compromise transplacental oxygen transfer^{70,93}.

Nitric Oxide (NO) is other molecule found to be protective when there is exposition of Cd in the placenta, something not seen with folic acid or vitamin C⁹⁴⁻⁹⁶. Cd induces superoxide and lipid peroxidation mediated activation of pro-apoptotic markers p21 and p53, but subsequence addition of exogenous NO via NO donor negated Cd mediated effects and protect the developing chick embryo⁹⁴.

FETUS

The pharmacokinetics of Cd in the fetuses are different from the normal adult, with more avid absorption, less efficient excretion and with blood-brain barrier less effective, that gives an extra risk for teratogenic effects from Cd¹⁰.

There are some studies that show that premature labor can be induced by Cd exposure leading to premature newborns⁹⁷⁻⁹⁹. The mechanism responsible of that preterm delivery is usually diagnosed as idiopathic, but the Cd induces on Calcium and oxytocin positive effects for contraction myometrial cells, but inhibitory response at higher doses¹⁰⁰.

One of the most impacting outcomes in Cd exposures in the newborn are low weights and small for gestational status when they were exposed to Cd during the pregnancy, whether or not there is a smoking status^{7,97,101-107}. Kipler et al. in a prospective study in humans found that maternal urinary Cd is negatively associate with low birthweight and head circumference, but in the regression analysis this impact affect more to woman than man¹⁰⁸. Pachajoa et al. found in a cohort study that Cd exposure from smoking during the pregnancy was associated with an OR of 2.07 (IC95% 7-5.78) compared to mothers with no exposition from smoking to develop vascular disruption that was expressed as hypoxia or tissues³².

Cord blood cadmium concentrations that are relatively low (0,29 ug/L) are associated with worse adaptation of the fetus^{10,99,109-113}. That was measure by the Apgar score that evaluates the fetus adaptation in the first 1-5-10 minutes after delivery; Those fetuses with higher concentrations of Cd had 15 and 22% lower Apgar scores than those with less Cd concentrations¹¹⁰.

CONCLUSIONS

Cadmium is a worldwide pollutant with direct and indirect ways of exposition and ingestion, from the air in the contaminated cities to the colostrum in the mothers. Exposition to this heavy metal starts early, from the embryonic stage that is aggravated by his high bioavailability that produces almost a life presence to this metal in the organism. It has been proved that Cd affects many organs in the mature organism, but also as early in the developing embryo and the placenta (See Table 1).

The impact of this problem has not been addressed globally, but it would be important to determine the extent in the health impact of this metal; Meanwhile it would be useful to test the presence of heavy metals in pregnant woman at risk to detect the presence of heavy metals, and to start an early intervention. An example of a protective measure would be the administration of antioxidants as was studied with Zinc and MT, but it is

needed more studies that shows the association between Zinc and MT with the reduction of the teratogenic effects induced by heavy metals.

Stages	Proposed Effect	References
Pre implantation	Failure to progress in the cellular stages	11, 39-44
Implantation	Embryonic Detachment	36, 37, 39, 40, 45, 46-50
Post implantation	Disruption in organogenesis (Teratogen?)	51-65
Placenta	Diminish Zn and progesterone in placental circulation	3, 66-72, 75-77, 87-89
Birth	Prematurity, low birth weight	10, 93-95, 97, 103-106

Cadmium has been declared as a carcinogenic agent in both humans and animals; in animals also Cd has been declared as a proved teratogenic agent, in humans this role has not been established yet, but the information that we reviewed here tends to prove Cd as a serious agent that can cause deleterious effects in the developing embryo and also in the mother, however more studies are needed to establish this relationship.

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