

## Review Article

# Environmental cadmium exposure: a possible factor in the pathogenesis of preeclampsia

Nnenna L. Nwobi<sup>1\*</sup>, Joshua O. Owolabi<sup>2</sup>, John O. Sotunsa<sup>3</sup>, Joseph C. Nwobi<sup>4</sup>,  
Razaq A. Abiodun<sup>5</sup>, John I. Anetor<sup>5</sup>

<sup>1</sup>Department of Chemical Pathology, <sup>2</sup>Department of Anatomy, Ben Carson School of Medicine, Babcock University, Ilishan Remo, Ogun State, Nigeria

<sup>3</sup>Department of Gynaecology and Obstetrics, Babcock University Teaching Hospital, Ilishan Remo, Ogun State, Nigeria

<sup>4</sup>Department of Biochemistry, Ben Carson School of Medicine, Babcock University, Ilishan Remo, Ogun State, Nigeria

<sup>5</sup>Department of Chemical Pathology, College of Medicine, University of Ibadan, Ibadan, Oyo State, Nigeria

**Received:** 27 June 2019

**Revised:** 01 October 2019

**Accepted:** 07 October 2019

### \*Correspondence:

Dr. Nnenna L. Nwobi,

E-mail: [lindanwobi@yahoo.ca](mailto:lindanwobi@yahoo.ca)

**Copyright:** © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

## ABSTRACT

Cadmium is a toxic metal, an environmental contaminant and a multi-organ poison which has been implicated in the derangement of a number of biological and molecular systems. Exposure to cadmium is a serious global health threat particularly in developing countries and pregnant women are at great risk, This is because they have increased gastrointestinal absorption and retention of cadmium and the tendency for increased risk of complications owing to its toxic effects. Preeclampsia is a pregnancy complication characterized by the development of onset of hypertension and significant proteinuria after 20 weeks of gestation or during labour and/or within 48 hours of delivery. This pregnancy-specific syndrome is a leading cause of maternal death particularly in developing countries. Several reports have provided evidence of remote association between preeclampsia and cadmium but the mechanism of the involvement of this toxic metal in this disease is still surrounded with uncertainty. Some possible mechanistic pathways such as induction of oxidative stress, acting as an antimetabolite to zinc and deregulation of epigenetic mechanisms have been elucidated in this article may be interconnected, work synergistically or act independently. However, pertinent to understand them in a bid to possibly prevent the disease or forestall its devastating consequences. Environmental cadmium exposure may be considered a factor that merits further serious attention in the continuous search for the precise an etiology of preeclampsia particularly in developing countries that experience uncontrolled cadmium release into the environment.

**Key words:** Cadmium exposure, Environmental contaminant, Preeclampsia, Pregnancy complication, Toxic metal

## INTRODUCTION

Preeclampsia (PE), is a pregnancy-specific syndrome that is characterized by the development of hypertension and significant proteinuria ( $\geq 0.3$  g/L) after 20 weeks of

gestation or during labour and/or within 48 hours of delivery.<sup>1</sup> Although this life-threatening multisystem disorder is a significant global health threat that contributes to maternal mortality and morbidity, its prevalence is higher in developing countries where a

pregnant woman is about seven times more likely to develop the disorder than a pregnant woman in a developed country.<sup>2</sup>

The etiology of PE still remains unclear. However, risk factors such as nulliparity, maternal age, subclinical infections, genetic predisposition and exposure to environmental contaminants have been linked to its development.<sup>3,4</sup> Several reports have provided evidence of remote association between PE and Cadmium (Cd), a well-known environmental contaminant and multi-organ poison, which has been implicated in the derangement of a number of biological and molecular systems.<sup>5,6</sup> However, there still exists paucity of information on the mechanism of the involvement of Cd in PE. This article, therefore, attempts to elucidate some of these mechanistic pathways such as; induction of oxidative stress, acting as antimetabolite to zinc and deregulation of epigenetic mechanisms.

## REVIEW OF LITERATURE

### *Cadmium*

Cadmium is a toxic metal that occupies the 7<sup>th</sup> position out of 275 top priority hazardous substances listed by the US Agency for Toxic Substances Disease Registry in 2017.<sup>6</sup> This heavy metal has atomic number 48, atomic mass 112, melting point 321°C, boiling point 765°C and occurs as an earth's crust natural mineral element in combination with other elements such as oxygen, chloride and sulphur.<sup>6</sup> However, for more than 50 years now, increased anthropogenic, industrial and domestic activities such as the use of fossil fuels, metal ore combustion, waste burning and cigarette smoking among others, have led to increased release of Cd into the environment with great negative impacts particularly on developing countries with poor environmental pollution laws and control.<sup>7</sup>

It is worthy of note that Cd is not bio-degradable, as such, every new release into the environment adds to the pre-existing environmental deposits leading to increased environmental Cd pollution, subsequent human exposure and increased human bioavailability and bioaccumulation.<sup>8</sup> The population of particular concern are the pregnant women who have been reported to be at increased risk of Cd exposure owing to increased gastrointestinal absorption, retention and accumulation of Cd in the placenta which inadvertently increases mother and foetal mortality and morbidity.<sup>9</sup>

### *Cadmium and oxidative stress*

Cadmium exposure leads to the production of Reactive Oxygen Species (ROS) such as superoxide ion (O<sub>2</sub><sup>-</sup>), Hydrogen Peroxide (H<sub>2</sub>O<sub>2</sub>) and Hydroxyl radicals (OH<sup>•</sup>).<sup>10</sup> An imbalance between the production of ROS and the ability of the body to counteract their harmful effects through neutralization by antioxidants results to oxidative stress.<sup>10</sup> Oxidative stress can lead to disruption of cellular

macromolecules which might result in physiological damage to organs such as the placenta and impact negatively on main antioxidant enzymes in the placenta such as Superoxide Dismutase (SOD), Catalases (CAT) and Glutathione Peroxidases (GSH-PX).<sup>11</sup> Superoxide dismutase catalyzes the dismutation of O<sub>2</sub><sup>-</sup> to H<sub>2</sub>O<sub>2</sub> and works together with other enzymes such as CAT and GSH-PX to remove excess H<sub>2</sub>O<sub>2</sub>. These antioxidant enzymes have been reported to have decreased activity in women with preeclampsia.<sup>11</sup>

The metabolites of these antioxidant enzymes also possess antioxidant properties and are also essential for diverse metabolic processes. These metabolites may be classified as hydrophilic metabolites such as Glutathione (GSH) and vitamin C and hydrophobic metabolites such as vitamin E. Glutathione is a tripeptide made up of three amino acids (cysteine, glutamic acid, and glycine) that plays a predominant role as a substrate for GSH-transferase and it is maintained in the reduced form by glutathione reductase. In Cd-induced cellular responses, GSH and vitamin C have dual role of neutralizing ROS and also detoxifying Cd directly.<sup>13</sup> The plasma levels of GSH and vitamin C have been reported to be low in preeclamptic women.<sup>14,15</sup> Vitamin E, is another essential vitamin that protects cell membranes from lipid peroxidation caused by Cd-induced oxidative damage which is low in women with preeclampsia.<sup>16,17</sup> Plasma malondialdehyde, a major metabolite of lipid peroxidation, increased in preeclampsia.<sup>17</sup> Amino acid side-chains of proteins have also been reported to be modified by direct oxidative attack or by lipid peroxidation products, resulting in the formation of additional carbonyl groups.<sup>18</sup> Higher placental levels of markers of lipid peroxidation, oxidative protein damage or oxidizing potential when compared with placentas from normal pregnancies have also been reported.<sup>19,20</sup>

### *Cadmium as antimetabolite to zinc*

In contrast to Cd that is a non-essential metal, Zinc (Zn), is an essential metal.<sup>21</sup> The interaction between these two metals are mostly antagonistic owing to their similar physicochemical properties such as similar electronic configuration, oxidation state of +2 and equal affinities for Sulphur, nitrogen and oxygen ligands.<sup>21</sup>

Hence, Cd can displace Zn in several biological systems by competing with Zn for its transporters, displacing it in proteins such as p53 and decreasing the activities of Zn-dependent enzymes such as Copper-Zn SOD resulting to increased risk of preeclampsia.<sup>22,23</sup> Also, exposure to Cd in pregnant women has been associated with functional loss and compromised p53-mediated DNA damage repair resulting to increased risk of preeclampsia.<sup>24,25</sup>

### *Cadmium and epigenetics*

Epigenetics involves heritable alteration in gene expression and chromatin without accompanying changes

in DNA sequence.<sup>26</sup> These alterations may arise from DNA methylation which often modifies the function of the genes and affects gene expression. DNA methylation is controlled at different levels in cells and is carried out by DNA methyltransferases which are enzymes required for establishment and maintenance of DNA methylation patterns.<sup>27</sup> Reports have shown that Cd exposure can modulate the activity of this enzyme. While acute exposure to Cd induces DNA hypomethylation and decreases DNA methyltransferase activity, prolonged exposure results in DNA hypermethylation and increases DNA methyltransferase activity, thereby disrupting DNA methylation and subsequently, predisposing a pregnant woman to preeclampsia.<sup>28,29</sup>

## DISCUSSION

Preeclampsia, a public health issue of global significance, appears to be a serious concern particularly in developing countries. In Nigeria this disorder is a serious concern contributing about 36.9% of all maternal deaths in pregnant women.<sup>30</sup> The causes of preeclampsia are largely unknown but more recently, Cd, a ubiquitous toxic metal has been added to the list of risk factors. Cadmium is a ubiquitous, toxic metal and multi-organ poison which has been implicated in the derangement of a number of biological and molecular systems such as membrane lipids, enzymes in endothelial cells and placental tissues.<sup>4-6</sup> As such, established features of preeclampsia such as maternal vascular endothelial dysfunction and impaired placental function, which are surrounded by molecular events, may be secondary to Cd pollution, exposure and toxicity.

Given the current rate of increased release of Cd particularly in developing countries and the fact that it is not bio-degradable, relevant new policies on improved environmental emission control might be required to control Cd release into the environment. For instance, the government should have its own vehicle inspection and maintenance facilities in order to ensure the roadworthiness of vehicles since growing number of vehicles and poor road conditions are major causes for high environmental Cd pollution particularly in developing countries.<sup>7,31</sup> In addition, efforts should be made to phase-out Cd in products and get appropriate replacements for applications for which Cd is still being used.

Furthermore, there is the need for continuous extensive awareness campaign on the adverse effect of Cd pollution on the environment and the populace. Pregnant women should be highly concerned about staying in endemic areas of Cd contamination to protect their reproductive health and the development of the foetus. However, considering the relevance of micronutrients such as Zn in mitigating Cd toxicity, supplementation with micronutrients should be encouraged particularly in poor resource developing nations where pregnant women are prone to micronutrient malnutrition.<sup>32</sup>

## CONCLUSION

Environmental cadmium exposure is a factor that merits further consideration in the continuous search for the precise etiology of preeclampsia. Hence, it is pertinent to understand the mechanism of involvement of cadmium in this disorder in a bid to possibly prevent the disease or forestall its devastating consequences. Some of the suggested mechanistic pathways such as induction of oxidative stress, acting as an antimetabolite to zinc and deregulation of epigenetic mechanisms may be interconnected, have synergistic effects or act independently. Exposure to cadmium may be considered a serious threat to pregnancy since it may at least in part, contribute to preeclampsia.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: Not Required*

## REFERENCES

1. Dolea C, AbouZahr C. Global Burden of hypertensive disorders of pregnancy in the year 2000 Evidence and information for policy World Health Organization. *Global Burden Dis.* 2000 2003:1-11.
2. Wagneu M, Dessalegn M, Worku A, Nyagero J. Trends of preeclampsia/eclampsia and maternal and neonatal outcomes among women delivering in addis ababa selected government hospitals, Ethiopia: a retrospective cross-sectional study. *Pan Afri Med J.* 2016;25(2):9716.
3. Chaiworapongsa T, Chaemsaitong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. *Nat Rev Nephrol.* 2014;10(8):466.
4. Rosen EM, Muñoz MI, McElrath T, Cantonwine DE, Ferguson KK. Environmental contaminants and preeclampsia: a systematic literature review. *J Toxicol Env Health.* 2018;21(5):291-319.
5. Laine JE, Ray P, Bodnar W, Cable PH, Boggess K, Offenbacher S, et al. Placental cadmium levels are associated with increased preeclampsia risk. *PLoS One.* 2015;10(9):0139341.
6. Agency for Toxic Substance and Disease Registry. CERCLA Priority List of Hazardous Substances. U.S. Department of Health and Humans Services, Public Health Service, CDC; Atlanta, GA 2017 Retrieved on 21/12/18. Available at: <https://www.watsdr.cdc.gov/spl/previous/07list.html>. 2017.
7. Anetor JI. Rising environmental cadmium levels in developing countries: threat to genome stability and health. *Niger J Physiol Sci.* 2012;27(2):103-15.
8. Moulis JM, Thévenod F. New perspectives in cadmium toxicity: an introduction. *Bio Metals.* 2010;23(5):763-8.
9. Kippler M, Hoque AW, Raqib R, Öhrvik H, Ekström E-C, Vahter M. Accumulation of cadmium in human placenta interacts with the transport of

- micronutrients to the fetus. *Toxicol Lett.* 2010;192(2):162-8.
10. Oh SH, Lim SC. A rapid and transient ROS generation by cadmium triggers apoptosis via caspase-dependent pathway in HepG2 cells and this is inhibited through N-acetylcysteine-mediated catalase upregulation. *Toxicol Appl Pharma.* 2006;212(3):212-23.
  11. De Lucca L, Gallarreta FM, de Lima Gonçalves T. Oxidative stress markers in pregnant women with preeclampsia. *Am J Med Biolog Res.* 2015;3(3):68-73.
  12. Dickinson DA, Forman HJ. Cellular glutathione and thiols metabolism. *Biochem pharmacol.* 2002;64(5-6):1019-26.
  13. Sies H, Stahl W, Sundquist AR. Antioxidant Functions of Vitamins: Vitamins E and C, Beta-Carotene, and Other Carotenoids a. *Annals of the N Y Acad Sci.* 1992;669(1):7-20.
  14. Chappell LC, Seed PT, Briley A, Kelly FJ, Hunt BJ, Charnock-Jones DS, et al. A longitudinal study of biochemical variables in women at risk of preeclampsia. *Am J Obstet Gynecol.* 2002;187(1):127-36.
  15. Sağol S, Özkinay E, Özşener S. Impaired antioxidant activity in women with pre-eclampsia. *Intern J Gynecol Obstet.* 1999;64(2):121-7.
  16. Kharb S. Vitamin E and C in preeclampsia. *Eur J Obstet Gynecol Reproduct Biol.* 2000;93(1):37-9.
  17. Chan AC. Partners in defense, vitamin E and vitamin C. *Canad J Physiol Pharmacol.* 1993;71(9):725-31.
  18. Zusterzeel PL, Mulder TP, Peters WH, Wiseman SA, Steegers EA. Plasma protein carbonyls in nonpregnant, healthy pregnant and preeclamptic women. *Free Radic Res.* 2000;33(5):471-6.
  19. Walsh SW, Vaughan JE, Wang Y, Roberts LJ. Placental isoprostane is significantly increased in preeclampsia. *The FASEB J.* 2000;14(10):1289-96.
  20. Zusterzeel PL, Rütten H, Roelofs HM, Peters WH, Steegers EA. Protein carbonyls in decidua and placenta of pre-eclamptic women as markers for oxidative stress. *Placenta.* 2001;22(2-3):213-9.
  21. Brzówska MM, Moniuszko-Jakoniuk J. Interactions between cadmium and zinc in the organism. *Food Chem Toxicol.* 2001;39(10):967-80.
  22. Berg JM. Zinc fingers and other metal-binding domains. Elements for interactions between macromolecules. *J Biol Chem.* 1990;265(12):6513-6.
  23. Farzin L, Sajadi F. Comparison of serum trace element levels in patients with or without preeclampsia. *J Res Med Sci.* 2012;17(10):938.
  24. Loh SN. The missing zinc: p53 misfolding and cancer. *Metallo.* 2010;2(7):442-9.
  25. Urani C, Melchiorretto P, Fabbri M, Bowe G, Maserati E, Gribaldo L. Cadmium impairs p53 activity in HepG2 cells. *ISRN Toxicol.* 2014;2014:976428.
  26. Reik W. Stability and flexibility of epigenetic gene regulation in mammalian development. *Nat.* 2007;447:425-32.
  27. Takiguchi M, Achanzar WE, Qu W, Li G, Waalkes MP. Effects of cadmium on DNA-(Cytosine-5) methyltransferase activity and DNA methylation status during cadmium-induced cellular transformation. *Exp Cell Res.* 2003;286(2):355-65.
  28. Huang D, Zhang Y, Qi Y, Chen C, Ji W. Global DNA hypomethylation, rather than reactive oxygen species (ROS), a potential facilitator of cadmium stimulated K562 cell proliferation. *Toxicol Lette.* 2008;179(1):43-7.
  29. Martin E, Ray PD, Smeester L, Grace MR, Boggess K, Fry RC. Epigenetics and preeclampsia: defining functional epimutations in the preeclamptic placenta related to the TGF- $\beta$  pathway. *PLoS One.* 2015;10(10):0141294.
  30. Sageer R, Kongnyuy E, Adebimpe WO, Omosehin O, Ogunsola EA, Sanni B. Causes and contributory factors of maternal mortality: evidence from maternal and perinatal death surveillance and response in Ogun state, Southwest Nigeria. *BMC Preg Childbir.* 2019;19(1):63.
  31. Adedeji OH, Olayinka OO, Oyebanji FF. Assessment of Traffic Related Heavy Metals Pollution of Roadside Soils in Emerging Urban Centres in Ijebu-North Area of Ogun State, Nigeria. *J Appl Sci Environ Manag.* 2013;17(4):509-14.
  32. Neggers Y. Epidemiology of Malnutrition: Maternal and Child Malnutrition. *J Gynecol Neonat Biol.* 2016;2(2):33-37.

**Cite this article as:** Nwobi NL, Owolabi JO, Sotunsa JO, Nwobi JC, Abiodun RA, Anetor JI. Environmental cadmium exposure: a possible factor in the pathogenesis of preeclampsia *Int J Res Med Sci* 2019;7:4818-21.