

## **Perspective study**

### **Are Dioxins the Causative Agent of Polycystic Ovaries Syndrome?**

Mosab Nouraldein Mohammed Hamad

Head of Parasitology Department, College of Health and Allied Sciences, St. Joseph University In Tanzania, Dar Es Salaam, Tanzania

#### **Abstract**

Stein-Leventhal syndrome (Polycystic ovaries syndrome) , represent one of the major obstacles facing reproductive medicine researchers , because there is no information about the etiology of it, and that made them fail to draw smile on faces of millions of women around the world, who are suffering from it. Scientists said that it is attributed to genetic and environmental factors , and we hypothesized that it was caused by environmental pollution by dioxins ( specifically heavy metals) , which disturb aryl hydrocarbon receptor and that lead to disturbing of nuclear receptors and then express genes which lead to hormonal , metabolic and immunological abnormalities appear in PCOS patients. And fortunately this hypothesis supports our hypothesis about the etiology of COVID-19 and its variants , clinically and epidemiologically. PCOS can be transmitted transmammary , sexually from Dixon exposed male partners , and due to direct exposure to Dixon either via explosion or by excessive use of makeup .Experimental studies are required to test our hypothesis.

**Keywords:** Stein –Leventhal syndrome etiology , Dioxins , COVID-19 , PCOS, Environmental pollution

## **Introduction:**

Stein-Leventhal syndrome ( polycystic ovaries syndrome), affects 5–20% of females of reproductive age worldwide. It is recognized by hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology (PCOM) — with severe androgen production by the ovaries being a chief sign of it [1].

Dioxins are a set of chemically-related compounds that are persistent environmental pollutants. They are found throughout the globe in the environment and they build up in the food chain, chiefly in the fatty tissue of animals. More than 90% of human exposure is by food, mostly meat and dairy products, fish and shellfish. They are extremely toxic and can cause reproductive and developmental disorders, harm the immune system and interfere with hormones [2].

Polycystic ovarian syndrome can also be accompanied with metabolic concerns counting obesity, insulin resistance , hyperinsulinemia, and type 2 diabetes mellitus (T2DM). PCOS is accompanied with cardiovascular problems, neurological and psychological influences on quality of life (counting anxiety and depression), and breast and endometrial cancers. 20% of women with infertility disorders (counting fecundability and early pregnancy loss) have been diagnosed with polycystic ovaries syndrome. In spite of augmented interest to PCOS, one of the most critical features of this syndrome is still highly doubtful upon - the diagnosis. The aetiology of PCOS has not been well understood [3].

Study done by et al [4] , showed that there are no racial or ethnic influences on the prevalence of PCOS.

Study done by et al [5], showed that PCOS is a result of androgenization as well as modification of the encoding of target tissue differentiation throughout foetal development, metabolic disorders, exposure to endocrine disturbing substances through pre and postnatal development, along with way of life and food factors in later life are accompanied with development of polycystic ovaries syndrome phenotypic symptoms.

recent proof suggests that the Stein Leventhal syndrome (PCOS) results from a genetic predisposition interacting with developmental events through foetal or perinatal life that together increase susceptibility in some people. This implies that

environmental factors manipulate the initiation of PCOS in the foetus or infant, either directly or via the mother. Polycystic ovaries syndrome is often considered to be an earliest disorder but there is no direct evidence of this in the medical or historic documentation [6].

In spite of studies that have analysed the influences of air pollution on fertility and hormonal levels, the connection between PCOS and air pollution has rarely been investigated .

Study done by et al [7] , showed that raised exposure to fine air pollutant particles and pollutant gases was accompanied with increased PCOS risk.

The highest raises in the PCOS age-standard incidence and DALYs rates from 2007 to 2017 were observed in the middle-SDI quintile, high-middle-SDI quintiles, tropical Latin America and countries such as Ethiopia, Brazil, and China [8] .

Study done by et al[9], showed that women and girls in resource poor countries ( Ethiopia and Uganda) experience much greater exposure to household air pollutants than men. youthful females had exposures approximately two-thirds of the adult female cluster.

Pollution may play a role in population tendencies observed in declining semen quality and regional differences in time to pregnancy (TTP)in industrialized societies. One class of environmental compounds assumed to impact population fertility is endocrine disruptors which include dioxins.

Study done by et al [10], showed that dose-related raises in TTP and infertility accompanied with individual serum TCDD levels in the women from Seveso, Italy. This owing to event In July 1976, a chemical plant explosion near Seveso, Italy exposed locals to the highest known concentrations of 2,3,7,8-tetracholorodibenzo-*p*-dioxin (TCDD ) exposure to a inhabited people [11].

Study done by et al [12], showed that TCDD exposure may be accompanied with low fertility in Seveso mothers and potentially in their daughters exposed *in utero*. But I hypothesized that genetic defect in daughters also attributed to male factor , because both males and females exposed to that explosion in 1976 , furthermore it influence

semen quality and in case of successive pregnancy , female daughter are at risk of fertility disorders.

Study done by et al [13], showed that in utero and lactational dioxin exposure of male mice may alter placental epigenome ensuing in placental dysfunction and poor pregnancy outcomes in unexposed mating partners. significantly, these adverse outcomes may be inherited transgenerationally to unexposed generations.

Experimental studies have shown that environmentally provoked epigenetic alteration of gametes may result in modifications in fertility, embryonic development, and health of the next generations.

TCDD treatment of sperm in vitro results in low viability of Y-spermatozoa leading to low proportion of Y-spermatozoa. As well, Y-spermatozoa have further a lower capability to fertilize oocytes than X-spermatozoa, and these alterations are probably contribute to the decreased male/female sex ratio after paternal dioxin exposure [13].

Study done by[14] et al found clear proof of an adverse influence of *in utero* TCDD exposure on epididymal sperm count but do not support the conclusion that spermatogenesis is adversely affected. I hypothesized that this owing to damage of aryl hydrocarbon receptor by dioxin and this supported by study done by [15] et al showed that the in vitro fertilization rate was significantly lower with Ahr(-/-) sperm as compared to wild-type sperm, and there were morphologic abnormalities of the Ahr(-/-) sperm head and tail, indicate that AHR plays an important role in normal sperm development.

Study done by[16] et al showed that the highest risk of PCOS was noticed in females with blood group 'O' positive followed by 'B' positive who were on mixed food & used to drink alcohol.

It is now well established that the incidence of cardiovascular disease is lower in premenopausal women than in men, but it is augmented for women after menopause, signifying cardioprotective influences of estrogens. Estrogen- and androgen-responsive genes, such as nitric oxide synthase and superoxide dismutase are present in megakaryocytes and in platelets. In vitro, human platelet aggregation induced by arachidonic acid was improved by androgens.

Platelet production was also confirmed to be altered by hormonal treatment in mice, where castration reduces thrombocytopoiesis and testosterone restores platelet production [17].

The markedly increased incidence of diabetes seen in those with both higher AhR ligand bioactivity and amplified mitochondrial inhibition [18].

Xenobiotics exert their biological activity by binding to transcription factors called nuclear receptors. Nuclear receptors represent a family of proteins that, in response to ligand binding, directly adjust the expression of their target genes. The activity of the nuclear receptor (NR) depends on a conformational change initiated by specific small molecules binding to the protein moiety, which in turn results in coactivator or corepressor linking and, as a consequence, the stimulation or repression of regulated genes. And The aryl hydrocarbon receptor (AhR) is ligand-dependent and mediates nuclear receptors that react with heterologous substances, I hypothesized that Dixon induce polycystic ovary syndrome by affecting aryl hydrocarbon receptors and that reflected on nuclear receptors led to expression of genes responsible for clinical features of Stein-Leventhal syndrome.

Nuclear receptors are implicated in processes of development, differentiation and homeostasis and are linked to a wide range of human diseases, including diabetes, autoimmune disorders and atherosclerosis and are drug targets for the treatment of these diseases [19]. They are key regulators of innate immune responses and tissue homeostasis [20].

A study done by [21] et al, showed that dioxins promoted epigenetic transgenerational inheritance of disease and DNA methylation epimutations in sperm and caused polycystic ovaries to the third generation.

Study done by et al [22], showed that Women with PCOS are at an increased risk of COVID-19 infection. And that supported the hypothesis said that COVID-19 is mutated influenza virus due to synergistic actions of cadmium and lead [23].

Study done by [24] et al, showed that cadmium was associated with endocrine features central to PCOS, but not with metabolic markers.

A study done by [25] et al, found high levels of serum arsenic, cadmium, lead and mercury in polycystic ovaries patients. And according to the hypothesis said that alpha and beta COVID-19 variants contain these heavy metals [26], I hypothesized that polycystic ovaries will be more common among beta variants of COVID-19 infected women.

The beta variant of COVID-19 was first discovered in South Africa , where polycystic ovaries account for up to 35 - 40% of the female factor causes of infertility [26,27].

The above supports the hypothesis about role the of dioxins in polycystic ovarian syndrome by disturbing aryl hydrocarbon receptor and explaining the relationship between COVID-19 variants and polycystic ovary syndrome.

### **Discussion :**

We suggest that polycystic ovary syndrome attributed exposure to dioxin before pregnancy from father's sperm , during lactation , and due to exposure to dioxin during childhood ( up to 18 years old). It binds to aryl hydrocarbon receptors and leads to hormonal abnormalities, certainly estrogen and androgens , immune system dysregulation , obesity , diabetes and other clinical signs of Stein Leventhal syndrome. So we hypothesized that environmental gene-toxicity (dioxins ) is the only cause of polycystic ovary syndrome. Furthermore, we suggest an intimate relationship between COVID-19 and Polycystic ovaries and we regard PCOS as one of the main risk factors for getting infection with COVID-19 or its variants due to sharing of etiology. We hypothesized that COVID-19 Positive males , certainly those infected with beta and alpha variants, can transmit genes responsible for PCOS to their off-springs , and Stein -Leventhal syndrome , besides sexual transmission from male partners, can be transmitted via transmammary and by exposure to direct dioxin pollution in explosions, or due to excessive use of cosmetics.

### **Conclusion :**

We conclude Stein -Leventhal Syndrome is a consequence of direct or indirect exposure to dioxins ,and males who are exposed to dioxins put the fertility of their female off-springs at great risk . Experimental research is required.

### **References:**

1. Azziz R, Carmina E, Chen Z, Dunaif A, Laven JS, Legro RS, Lizneva D, Natterson-Horowitz B, Teede HJ, Yildiz BO. Polycystic ovary syndrome. Nature reviews Disease primers. 2016 Aug 11;2(1):1-8.
2. <https://www.who.int/news-room/fact-sheets/detail/dioxins-and-their-effects-on-human-health#:~:text=Dioxins%20are%20a%20group%20of,persistent%20environm>

ental%20pollutants%20(POPs).&text=Dioxins%20are%20highly%20toxic%20and,hormones%20and%20also%20cause%20cancer.

3. Barthelmess EK, Naz RK. Polycystic ovary syndrome: current status and future perspective. *Front Biosci (Elite Ed)*. 2014 Jan 1;6:104-19. doi: 10.2741/e695. PMID: 24389146; PMCID: PMC4341818.
4. Wolf WM, Wattick RA, Kinkade ON, Olfert MD. Geographical Prevalence of Polycystic Ovary Syndrome as Determined by Region and Race/Ethnicity. *Int J Environ Res Public Health*. 2018 Nov 20;15(11):2589. doi: 10.3390/ijerph15112589. PMID: 30463276; PMCID: PMC6266413.
5. Kshetrimayum C, Sharma A, Mishra VV, Kumar S. Polycystic ovarian syndrome: Environmental/occupational, lifestyle factors; an overview. *J Turk Ger Gynecol Assoc*. 2019 Nov 28;20(4):255-263. doi: 10.4274/jtgga.galenos.2019.2018.0142. Epub 2019 Mar 1. PMID: 30821135; PMCID: PMC6883751.
6. Rodgers RJ, Suturina L, Lizneva D, Davies MJ, Hummitzsch K, Irving-Rodgers HF, Robertson SA. Is polycystic ovary syndrome a 20th Century phenomenon?. *Medical hypotheses*. 2019 Mar 1;124:31-4.
7. Lin SY, Yang YC, Chang CY, Lin CC, Hsu WH, Ju SW, Hsu CY, Kao CH. Risk of Polycystic Ovary Syndrome in Women Exposed to Fine Air Pollutants and Acidic Gases: A Nationwide Cohort Analysis. *Int J Environ Res Public Health*. 2019 Nov 30;16(23):4816. doi: 10.3390/ijerph16234816. PMID: 31801197; PMCID: PMC6926786.
8. Jingjing Liu, Qunhong Wu, Yanhua Hao, Mingli Jiao, Xing Wang, Shengchao Jiang, Liyuan Han, Measuring the global disease burden of polycystic ovary syndrome in 194 countries: Global Burden of Disease Study 2017, *Human Reproduction*, Volume 36, Issue 4, April 2021, Pages 1108–1119, <https://doi.org/10.1093/humrep/deaa371>.
9. Okello G, Devereux G, Semple S. Women and girls in resource poor countries experience much greater exposure to household air pollutants than men: Results from Uganda and Ethiopia. *Environment international*. 2018 Oct 1;119:429-37.
10. Eskenazi B, Warner M, Marks AR, Samuels S, Needham L, Brambilla P, Mocarelli P. Serum dioxin concentrations and time to pregnancy.

- Epidemiology. 2010 Mar;21(2):224-31. doi: 10.1097/EDE.0b013e3181cb8b95. PMID: 20124903; PMCID: PMC6267871.
11. Eskenazi B, Warner M, Brambilla P, Signorini S, Ames J, Mocarelli P. The Seveso accident: A look at 40 years of health research and beyond. *Environ Int.* 2018 Dec;121(Pt 1):71-84. doi: 10.1016/j.envint.2018.08.051. Epub 2018 Sep 1. PMID: 30179766; PMCID: PMC6221983.
  12. Brenda Eskenazi, Jennifer Ames, Stephen Rauch, Stefano Signorini, Paolo Brambilla, Paolo Mocarelli, Claudia Siracusa, Nina Holland, Marcella Warner, Dioxin exposure associated with fecundability and infertility in mothers and daughters of Seveso, Italy, *Human Reproduction*, Volume 36, Issue 3, March 2021, Pages 794–807, <https://doi.org/10.1093/humrep/deaa324>
  13. Viluksela M, Pohjanvirta R. Multigenerational and Transgenerational Effects of Dioxins. *Int J Mol Sci.* 2019 Jun 17;20(12):2947. doi: 10.3390/ijms20122947. PMID: 31212893; PMCID: PMC6627869.
  14. Foster WG, Maharaj-Briceño S, Cyr DG. Dioxin-induced changes in epididymal sperm count and spermatogenesis. *Environ Health Perspect.* 2010 Apr;118(4):458-64. doi: 10.1289/ehp.0901084. PMID: 20368131; PMCID: PMC2854720.
  15. Hansen DA, Esakky P, Drury A, Lamb L, Moley KH. The aryl hydrocarbon receptor is important for proper seminiferous tubule architecture and sperm development in mice. *Biol Reprod.* 2014 Jan 16;90(1):8. doi: 10.1095/biolreprod.113.108845. PMID: 24174576.
  16. Pal R, Chatterjee PK, Chatterjee P, Vinodini NA, Mithra P, Banerjee S, Suman VB, Pai SR. Polycystic Ovary syndrome, blood group & diet: a correlative study in South Indian females. *International Journal of Medical Research & Health Sciences.* 2014;3(3):604-9.
  17. Farré AL, Modrego J, Zamorano-León JJ. Effects of hormones on platelet aggregation. *Hormone molecular biology and clinical investigation.* 2014 Apr 1;18(1):27-36.
  18. Duncan BB, Castilhos CD, Bracco PA, Schmidt MI, Kang S, Im S, Lee HK, Vigo Á, Pak YK. Aryl-hydrocarbon receptor binding and the incidence of type 2 diabetes: the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Environmental Health.* 2020 Dec;19(1):1-8.



19. Karaś K, Sałkowska A, Dastyh J, Bachorz RA, Ratajewski M. Cardiac glycosides with target at direct and indirect interactions with nuclear receptors. *Biomedicine & Pharmacotherapy*. 2020 Jul 1;127:110106.
20. Lamorte S, Shinde R, McGaha TL. Nuclear receptors, the aryl hydrocarbon receptor, and macrophage function. *Mol Aspects Med*. 2021 Apr;78:100942. doi: 10.1016/j.mam.2021.100942. Epub 2021 Jan 12. PMID: 33451803; PMCID: PMC7987878.
21. Manikkam M, Tracey R, Guerrero-Bosagna C, Skinner MK. Dioxin (TCDD) induces epigenetic transgenerational inheritance of adult onset disease and sperm epimutations.
22. Subramanian A, Anand A, Adderley NJ, Okoth K, Toulis KA, Gokhale K, Sainsbury C, O'Reilly MW, Arlt W, Nirantharakumar K. Increased COVID-19 infections in women with polycystic ovary syndrome: a population-based study. *Eur J Endocrinol*. 2021 May;184(5):637-645. doi: 10.1530/EJE-20-1163. PMID: 33635829; PMCID: PMC8052516.
23. Hamad MN. COVID. 19: Man Made Pandemic: Lead and Cadmium Mutate Influenza Virus Produce: SARS COV-2.
24. Kim K, Pollack AZ, Nobles CJ, Sjaarda LA, Zolton JR, Radoc JG, Schisterman EF, Mumford SL. Associations between blood cadmium and endocrine features related to PCOS-phenotypes in healthy women of reproductive age: a prospective cohort study. *Environ Health*. 2021 May 22;20(1):64. doi: 10.1186/s12940-021-00749-4. PMID: 34022900; PMCID: PMC8141255.
25. Abudawood M, Tabassum H, Alanazi AH, Almusallam F, Aljaser F, Ali MN, Alenzi ND, Alanazi ST, Alghamdi MA, Altoum GH, Alzeer MA. Antioxidant status in relation to heavy metals induced oxidative stress in patients with polycystic ovarian syndrome (PCOS). *Scientific reports*. 2021 Nov 25;11(1):1-8.
26. Mosab Nouraldein Mohammed Hamad. COVID-19 The Roots and Branches, <http://dx.doi.org/10.13140/RG.2.2.20174.54085>.
27. Siebert TI, Kruger TF, Grieve CL, Steyn DW. Is the use of a GnRH antagonist effective in patients with polycystic ovarian syndrome? A South African perspective. *South African Journal of Obstetrics and Gynaecology*. 2012 Mar 12;18(1).

