

Review Article

The Biochemical Role Of Environmental Pollution In The Etiology Of Endometriosis

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Abstract

Endometriosis is an estrogen dependent inflammatory disorder plays a pivotal role in the reproductive system of the females which regarded as one of the most important gynecological disorders due to it is a key cause of infertility for women and also it has a remarkable impact on the women's life quality. Indeed, environmental pollution have an extremely importance in the etiology of endometriosis. Hence, the present article submits an abbreviated literature review to the biochemical role of environmental pollutants in the etiology and development of endometriosis. Anyway, this review article represented the major environmental pollutants: the organic pollutants of air, heavy metals, gaseous pollutants and the particulate matter. The aim of the present review article is to highlight the biochemical role of the environmental pollutants as risk factors for endometriosis by focusing on different information from researches and articles within this field by linking between the data and conclusions resulted from previous and recent studies. From the literature review , the present theoretical paper highlighted the biochemical role of the different of environmental pollution in the etiology and development of endometriosis : the organic compounds that influence the female reproductive system , heavy metals which accumulate in water , soil and food , the gaseous pollutants

which trigger the oxidative stress , particulate matters that linked with the higher level of prolactin hormone and any pollutant factor in the life style may contribute to the etiology and development of endometriosis. Every type of environmental pollutants has a specific impact in this context but in Iraq , the heavy metals and gaseous pollutants play the key role because they directly linked with the Wars results and the waste products of the electrical private generators.

Keywords : Endometriosis , heavy metals , organic pollutants , gaseous pollutants.

1. Introduction:

Endometriosis is an inflammatory estrogen dependent disease, [1] characterized by the presence of resembling functional endometrial tissues and stroma residing in other sites than the uterine cavity. [2,3,4] Generally , endometriosis occurs in women with reproduction age (8-10) % although it could be developed after menopause in a rare cases. [4] Endometrial tissues encompass lesions respond to exogenous and endogenous hormones. [5] Interestingly, estrogen has been implicated as a major factor in endometriosis , its level is higher in endometriosis patients compared with healthy women because of excessive activation of local biosynthesis of estrogen in the ectopic tissue . [6] The most common features of endometriosis include pelvic pain, dysmenorrhea , dyspareunia , infertility and dysuria. [7] Although retrograde menstruation of the endometrial cells into the peritoneum is the most accepted theory, other factors may contribute to the etiology of endometriosis, specifically the environmental pollutants. [1] Anyway, differences in geographic location and urbanization may affect endometriosis due to the diet and lifestyle which have a key action on the estrogen activity and menstrual cycle. [8] Remarkably, environmental deterioration may be resulted from the exposure to heavy metals which subsequently cause health complications including disorders in the reproductive system. [9] The air pollution is regarded as a risk factor for endometriosis by promoting the chronic inflammation, oxidative stress and hormonal imbalance. [10] Generally, any profile of female infertility can not only regarded as a health problem related to the uterus but have many sides including majorly environmental factors. In particular, during Iraqi wars (1980-1988) , 1991 and 2003 thousands tons of weapons were spread out and negatively influence the fertile status of females more than males because the female reproductive or hormonal system is more sensitive than males. [11]

Indeed, sand particles in Iraq contain toxic materials due to the pollution caused by military actions and wars through the last four decades. Remarkably, metal contamination was heavily detected in several Iraqi cities particularly Basra and Falluja while very low quantities of environmental pollutants found in the north of Iraq because these cities not involved in the conflicts followed by the the Iraq-Iran war (1980-1988). Regarding Baghdad and other cities, the air (gaseous) pollutants resulted from private electrical generators and loaded traffics and roads play a great role in this field. [12] Additionally, the change in water quality of Tigris, Euphrates and the Shatt Al-Arab river caused by the effects of upstream damming can rise the scale of water pollution. [13] Endometriosis has a bad impact on life quality as it affects the most important aspects of women's life including social life, mental health and working capacity. [7]

2. The role of organic compounds in the etiology of endometriosis

The female reproductive system has been reported to be affected by hormonal disrupting chemicals. Hence, a large category of organic compounds have an impact in the development of endometriosis, these compounds including: dioxins and dioxins like compounds, persistent organic pollutants (POPs) [14, 15] and other compounds like biphenols and phthalates. [16] Interestingly, dioxins are chemical contaminants found in water, these compounds are able to disrupt the hormonal system and consequently contribute to the development of endometriosis. [10] Remarkably, dioxins appear to be one of the strongest environmental pollutants among the others in the development of endometriosis. [1]

• Dioxins and dioxins like compounds

Dioxin is a general name applied to a category of by – product compounds of anthropogenic activities like incineration, combustion, industrial and manufacturing operations. [17] Structurally, dioxins are polycyclic aromatic hydrocarbons substituted by chlorine atoms which are assigned to different branches due to the position of halogens. [14] dioxins and dioxins like compounds include polychlorinated dibenzo-p-dioxins (PCDDs) , 2,3,7,8- Tetrachlorodibenzo- p – dioxin (TCDD) , polychlorinated dibenzofurans (PCDFs) , 2,3,7,8-tetrachlorodibenzofuran (TCDF), [17] polychlorinated biphenyls (PCBs). [14] TCDD exposure is a definite risk factor for infertility and

weak fecundability through binding with the aryl hydrocarbon receptor (AHR) that metabolize TCDD , affect steroidogenesis and subsequently disrupt AHR-mediated regulation of the female reproductive system including the uterus , the ovaries , placenta and reproductive senescence. [18] Interestingly , exposure to dioxin at levels equal to ten times the level of normal human exposure cause endometriosis in rhesus monkeys , this toxicity is determined by the number of chlorine atoms it posses and their configuration. [17]

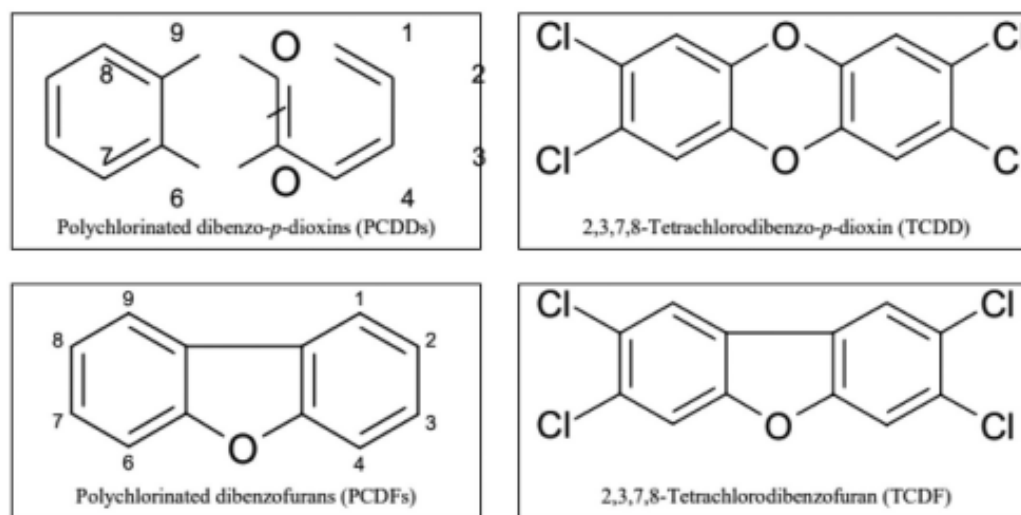


Figure 1: Chemical structures of some dioxins. [14]

• Persistent organic pollutants (POPs)

Another group of organic pollutants includes persistent organic pollutants (POPs) which characterized by long half life in air , soil and sediments , these compounds have strong hydrophobic and lipophilic properties , organo-chlorine pesticides (OCPs) represent an example of POPs that strongly linked with endometriosis. Remarkably, OCPs have a negative impact on the reproductive and immune systems , some of theses reactive compounds and their derivatives can trigger proliferation of endometrial tissue or affect promoting for the uterine tissue. [14]

• Bisphenol A and Phthalates

Other compounds such as bisphenol A and Phthalates may be linked with endometriosis caused by their impact on the reproductive system , in particular with female fertility. In this regard , bisphenol A posses a binding affinity to estrogen receptors , the result is dysregulation of these receptors. Anyway, bisphenol A and phthalates are widely used in many daily consumer products, bisphenol A is a major monomer used in the production of epoxy resins and some polycarbonate in unbreakable materials . Phthalates are short and long chains used as plasticizers in polyvinyl chloride products by esterification with different substituents of phthalic anhydride. [16]

3. The role of heavy metals in the etiology of endometriosis

Heavy metals constitute health problem caused by their accumulation in soil, water and food. Remarkably, not all heavy metals are obligatory toxic because some of them like zinc and iron are essential at very low levels but toxic at higher. In contrast, nickel , cadimium , mercury and lead do not characterized by any metabolic roles , so they are regarded as toxic at even lower levels. [16] Since heavy metals accumulate in soil and water , their influence become more substational in Iraq. In particular lead (Pb) and mercury (Hg) were detected in several places accompanied by uranium as a result from the military actions of the wars.[12] Anyway, the major heavy metals linked with infertility and particularly endometriosis are:

• Iron (Fe)

Iron is found in the environment with concentrations depending on the geology of the region. Iron plays a crucial role in the formation of highly functional biochemical compounds like hemoglobin, ferritin and transferrin and some iron containing enzymes [19] In particular which involved in oxidation / reduction reactions. [20] Naturally, iron is found in both of animal and plant sources such as beef, chicken liver, salmon, brand , almonds and broccoli. [21] Anyway, endometriosis is accompanied by retrograde menstruation; the last is the backflow of menstrual blood into the peritoneal cavity through the fallopian tubes. [1] Retrograde menstruation seems to be associated with highly prooxidant factors including heme and iron within the peritoneal cavity. Anyway, the free or catalytic iron induces reactive oxygen species production and subsequently induction oxidative stress. [20] On the other hand , iron release is resulted from the metabolism of hemoglobin and heme by macrophages . In this regard, iron overload in various components of the peritoneal cavity affects

endometriotic lesions , cosequently a distrupction in iron homeostasis is happened within the peritoneal cavity [22] A previous study has linked among endometriosis , erythrocytes , macrophages and iron. Endometriosis resulted from erythrocytes carried into the pelvic cavity predominantly by retrograde menstruation, subsequently peritoneal macrophages play a key role in the degradation of those erythrocytes and in subsequent peritoneal iron metabolism, excess iron accumulation resulted from this degradation could be one of the risk factors contributing to endometriosis development. [23] Broadly, the volume and the content of the peritoneal cavity vary in different phases of the menstrual cycle because the vascular permeability increases with estrogen concentration. Peritoneal fluid contains ovarian steroidal hormones including estrogen, electrolytes and urea besides cellular components involving endometrial cells, erythrocytes, lymphocytes and macrophages. [2]

• **Zinc (Zn)**

Zinc is a major essential heavy metal required by the human system. [19] It is necessary for the activity of different types of enzymes like dehydrogenases, aldolases and transphosphorylases. [20] The main food sources of Zinc are vegetables, meat, rice , and also it is found in low percent in fish. Zinc plays several functions in the human body just like blood clotting, wound healing, proper thyroid function, maintenance of eye vision, protein synthesis, bone mineralization , cell growth and development. [19] Zinc could be altered by different environmental, dietary or lifestyle factors. [24] In accordance with endometriosis, the dysfunctional immune system and the inflammatory status in addition to the oxidative stress associated with endometriosis cause Zinc deficiency, Zinc controls the function of immune system and stimulates lymphocytes production. Consequently, Zinc level in women with endometriosis is decreased and also seem to affect endometriosis pathogenesis. [25]

• **Nickel (Ni)**

Nickel (Ni) is a silvery-white metal used mainly as an alloy with other metals also it is used for jewelry , plating , coins , eyeglasses , batteries and heat exchangers. A nickel level in the whole blood in endometriotic patients was significantly increased compared with healthy control subjects. Anyway , similar to other heavy metals enters the blood via injection or inhalation. Moreover, nickel is commonly found in accessories used by women and it's absorption by the intact or damaged skin must be considered. [26] Remarkably, nickel allergy has a prevalence ranged from (10-23)% among

women. Otherwise has been suggested that nickel allergy is a risk factor for endometriosis, this effect mostly due to the estrogenic characteristics of nickel. Interestingly, nickel can bind the metal binding sites on the estrogen receptor in vitro. The mechanism of nickel allergy is delayed cell mediated hypersensitivity. At this point, endometriosis is related to an increase T-helper 1 response, which plays a key role in cell mediated hypersensitivity. [27] Nevertheless, whether nickel could be considered as an etiological risk factor for endometriosis remains inconclusive. [26]

• Cadmium (Cd)

Cadmium is a non - essential heavy metal associated with refining of other metals in production of other metals in production of cadmium containing soil fertilizers, plastic stabilizers, nickel - cadmium battery and pigment production. [27] Cadmium retention can affect both genders, but its toxic effect is commonly higher in females than in males. [16] It has been recently shown that cadmium affects the reproduction system for female by acting as an endocrine disrupter. [28] Cadmium acts to decrease the expression of enzymes responsible for steroidogenesis like P450 cholesterol side-chain cleavage and 3 β - hydroxy steroid dehydrogenase in placental cells. [16] A significant increase in endometrial Cadmium concentration was found in women with unexplained infertility compared with fertile women. [29] Cadmium has been suggested to play a key role in modification of female hormone levels, specifically its association with high level of estrogen. [27] Moreover, Cadmium is considered to be metalloid - estrogen or estrogen - mimetic compound. Surprisingly, Cadmium can join both alpha and beta estrogen receptors and stimulates their binding with the membrane, resulting in enhancing estrogen activity. [24,28,30] Cadmium has a direct effect on uterine volume by increasing it via the induction of estrogen regulated genes. [30] According to endometriosis, Cadmium is a potential key agent of estrogen - dependent diseases like endometriosis and endometrial cancer, endometriosis was reported to be strongly associated with Cadmium exposures because it is accumulated in human endometrial tissue. [24] Furthermore, an association between high level of Cadmium and smokers endometriotic women was found. [26]

• Mercury (Hg)

The majority of Hg emission occurred since 1800 A.D, it's increasing is related to industrial revolution. [31] This heavy metal also has a key relationship with endometriosis by exhibiting estrogen - mimetic changes. [30] Recently, it has been reported that Hg affects both level and function of estrogen and its exposure is associated with the etiology of endometriosis. [16] Anyway, contaminated food with fish and aquatic invertebrates are the main source of Hg exposure. Moreover, Hg may contact with the life style through the dental amalgam (an alloy of Mercury with various other metals used for dental fillings). Women exposed to Mercury have the most chance to abnormalities with menstrual cycle which is a major feature for endometriosis. [31,32] Another study has suggested that mercury is a risk factor for endometriosis even if in low concentrations because it induces poor immune function and damages enzyme activity in cell membranes and DNA. [8]

• **Lead (Pb)**

Female are exposed to lead from the air and food in equal percentage. [31] Air pollutants of Pb resulting mainly from fossil fuels combustion and certain special industrial process change the endometrial homeostasis. [33] Similar to Cadmium and Mercury, lead can mimic estrogen effects (metalloid - estrogen). [30] In particular, lead is highly toxic even if at low doses, it's concentration is higher in smoking female than healthy subjects. [9] A recent study has reported that endometrial tissue collected from women from Urban areas are characterized by high levels of lead due to increased atmospheric lead emission in those locations , lead can be absorbed on the surface of the endometrial tissue and consequently it's concentration will be significantly elevated in Urban compared with rural regions. [24]

4. The role of gaseous pollutants in the etiology of endometriosis

Gaseous pollutants including sulfur dioxide (SO₂), nitrate oxide (NO₂) and carbon monoxide (CO) play a key role in female infertility including endometriosis. [16] Ozone (O₃) is also associated with reproductive diseases. [32] SO₂, NO₂ and CO may enhance miscarriage and stillbirths. [30] A recent study has indicated that gaseous pollutants trigger oxidative stress. [34] In this regard, as reported by [35] oxidative stress is a key risk factor for endometriosis. Generally, the air pollutants have a great influence in Iraq because these pollutants are waste products resulted from the private electrical generators. [12]

5. The role of particulate matter in the etiology of endometriosis

Fine particulate matter (PM) is a chemical mixture of multiple particles including organic compounds, toxic metals and crystal elements from many sources like wood burning and dusty roads particularly in the developed countries. [36] A recent study has reported that the adverse effect of particulate matter on human health in general is confirmed but focused on the infertility and the endometrium functions. [37] Indeed, fine particulate matter as air pollutant [38] have a small diameter but a large surface area, consequently these physical properties are responsible for toxic effects and damage for many tissues of human bodies, these particles are directly detected in the female reproductive organs: the uterus and the ovaries and subsequently affect the pregnancy rate, in other words can lead to infertility. [36] Regarding endometriosis, a previous study has reported that PM is responsible for the change in the level of prolactin hormone which plays a key role in the reproductive system including which related to endometriosis. [39] Hence, PM affects the cell proliferation and inflammation of the endometrium tissues by modifying the cell signaling molecules. Interestingly, it can increase the endometrium proliferation and inflammation and also reduce the apoptosis; consequently gynecological disorders like endometriosis may strongly be occurred. [37] Moreover, PM is associated with endometriosis by promoting oxidative stress, chronic inflammation and hormonal imbalances. [10] PM exposure remarkably inhibits different bioactive functions of the endometrial stem cells like self renewal trans-differentiation and migratory capacities in vivo and in vitro. [36]

6. The role of general life style factors in the etiology of endometriosis

The other studied risk factors for endometriosis are sun exposure, radiation, phthalates, Bisphenol A and nanomaterials. Also, smoking, coffee intake, soy eating and alcohol consumption are reported by [1]

7. Conclusions

This review article has demonstrated the systemic role of the environmental pollution in the etiology of endometriosis which reported and highlighted as one of the most gynecological disorders linked with the reproductive system and infertility. Firstly, the organic compounds (in particular dioxins and dioxins like compounds) have a key impact in the etiology of endometriosis because these

compounds influence the hormonal system for females which play the major role in the development of endometriosis. Secondly, the heavy metals play a key role in the etiology of endometriosis due to these pollutants accumulates in water, soil and food. Thirdly, gaseous pollutants constitute an essential risk factor in the etiology of endometriosis caused by the relationship with oxidative stress which triggers the development of endometriosis. Fourthly, particulate matters have a role in this regard because these particles promote the increasing of prolactin level which linked with the development of endometriosis. Finally, any pollutant linked with the lifestyle (sun exposure, radiation, alcohol consumption) may be a risk factor for endometriosis. Honestly, all types of pollution cited above (without exception) are dangerous because everyone has a different role and specific biochemical action directly linked with the etiology and the development of endometriosis, but in Iraq both the heavy metals and the gaseous pollutants have the most impact caused by heavy metals accumulated in water and soil due to pollution resulted from the wars and gaseous pollutants are waste products resulted from the private electrical generators. Environmental pollution affects the quality of human population health. Therefore, the investigation regarding the environmental pollutants as a major risk factor for endometriosis must be continued and fully understood.

CONFLICT OF INTEREST

Regarding this review article, We confirm that there are no conflicts of interest.

8. References

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