

Association of Endometriosis and Oxidative Stress

I Gusti Ngurah Bagus Surya Udayana, Ida Bagus Putra Praja Adnyana,
Made Angga Diningrat, and William Alexander Setiawan

ABSTRACT

Endometriosis is a gynecologic illness that affects women of reproductive age. The presence of endometrial tissue outside the uterine cavity distinguishes it. Pelvic discomfort and infertility plague the women who are affected. Retrograde menstruation, coelomic metaplasia, and induction theory are three main ideas that have been proposed to explain the complex etiology. Endometriosis development is also influenced by genetics and epigenetics. Recent research has focused on the role of oxidative stress, an imbalance between reactive oxygen species (ROS) and antioxidants, in the pathophysiology of endometriosis, which results in a peritoneal cavity inflammatory response. Reactive oxygen species (ROS) are inflammatory mediators that control cell growth and have harmful effects. They are formed by normal oxygen metabolism. A systematic review was conducted to understand better the many roles of oxidative stress and its role in the development of endometriosis. Iron metabolism, oxidative stress markers (in the serum, peritoneal fluid, follicular fluid, peritoneal environment, ovarian cortex, and ectopic and endometrial tissue), oxidative stress genes, endometriosis-associated infertility, and cancer development have all been studied.

Keywords: Endometriosis, reactive oxygen species, oxidative stress.

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I. G. N. B. Surya Udayana

Obstetric and Gynecology Department,
Fertility and Reproductive
Endocrinology Division, Hasan Sadikin
Hospital, Bandung, West Java,
Indonesia.

I. B. P. Praja Adnyan

Obstetric and Gynecology Department,
Bali Royal Hospital, Denpasar, Bali,
Indonesia.

M. A. Diningrat

Obstetric and Gynecology Department,
Bali Royal Hospital, Denpasar, Bali,
Indonesia.

W. A. Setiawan*

Obstetric and Gynecology Department,
Sanglah Hospital, Denpasar, Bali,
Indonesia
(e-mail:
william.alexanders11@gmail.com)

**Corresponding Author*

I. INTRODUCTION

Endometriosis is an estrogen-dependent pelvic inflammatory disease characterized by endometrial tissue (glands and stroma) implantation and growth outside the uterine cavity. It affects 10%–15% of reproductive-age women. Pelvic discomfort and infertility are the most common signs of this condition [1]. Endometriosis affects 30 to 45 percent of infertile women with pelvic pain. On the other hand, endometriosis might be asymptomatic or present with symptoms including dysmenorrhea and dyspareunia. The etiology of endometriosis is still unknown: Sampson's implantation theory, Mayer's coelomic metaplasia theory, and the induction theory are three classic ideas that have tried but failed to identify the definitive pathogenetic mechanism of endometriosis. Other factors, including familial propensity and genetic predisposition, have recently been studied concerning the development of endometriotic lesions. It is now commonly known that oxidative stress, defined as an imbalance between reactive oxygen species (ROS) and antioxidants, plays a role in the pathophysiology of endometriosis, resulting in a peritoneal inflammatory response. Reactive oxygen species (ROS) are inflammatory mediators that control cell growth and have harmful effects [2]. They are formed as a byproduct of regular oxygen metabolism. Cells have evolved a variety of antioxidant

systems, including superoxide dismutase, catalase, and glutathione peroxidase, as well as vitamin E and vitamin C, to limit ROS production, inactivate them, and repair cell damage; however, oxidative stress can occur when the balance between ROS production and antioxidant defense is disrupted. Because macrophages, erythrocytes, and apoptotic endometrial tissue that transplant into the peritoneal cavity by retrograde menstruation are known inducers of oxidative stress and the peritoneal generation of ROS may play a role in endometriosis. Indeed, activated macrophages play a vital role in the breakdown of erythrocytes, which produce prooxidant and proinflammatory components such as heme and iron, which have been linked to the generation of harmful ROS [3].

II. MATERIALS AND METHODS

The most relevant research reported in the English language was identified through a literature study. We looked through the PubMed MEDLINE electronic database, which was updated until March 2022. "Endometriosis," "oxidative stress," "oxidative stress indicators," "reactive oxygen species," "inflammation," and "iron" were among the keywords utilized. The terms were combined in various ways. In addition, references in each article were combed for any studies that might have been overlooked.

III. RESULTS AND DISCUSSION

A. Role of Iron

Recent research has focused on the role of altered iron metabolism in developing endometriosis. The existence of iron overload in many components of endometriosis patients' peritoneal cavity has been extensively researched; nonetheless, it remains strongly isolated in the pelvic cavity and has little effect on body iron content [4].

In the peritoneal fluid of affected women, higher levels of iron, ferritin, and hemoglobin were observed than in controls. Iron conglomerates were found in the stroma of endometriotic lesions and the peritoneum. Peritoneal iron overload can occur due to increased influx produced by erythrocyte breakdown, which can occur as a result of more frequent menstrual reflux or bleeding lesions or as a result of a peritoneal iron metabolism system deficiency [5].

In endometriosis, macrophage iron metabolism appears to be elevated. Inside the pelvic cavity, siderophages, or iron-storing macrophages, are densely packed with hemosiderin. Furthermore, macrophages have more transferrin receptors and are more haptoglobin-saturated than neutrophils. Overwhelming iron can act as a catalyst in the Fenton reaction ($\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH} + \text{OH}$) to amplify oxygen and nitrogen toxicity by producing a wide range of ROS, resulting in oxidative damage to cells. The peritoneal mesothelium is destroyed locally by oxidative stress, resulting in ectopic endometrial cell adhesions. Haemoglobin, an iron-binding protein, has been identified as one of the menstrual effluent factors that may be detrimental to the mesothelium and cause adhesion development [5].

Reference [6] found that epithelial cells in endometriotic lesions enhance proliferative activity after erythrocyte injection in a mouse model. In contrast, desferrioxamine, an iron chelator, suppresses this process, suggesting that iron may play a role in endometriotic lesion progression.

B. Oxidative Stress Markers

Endometriosis development is linked to oxidative stress. The link between endometriosis and reactive oxygen species (ROS) generation is well-known and well-studied. Increased ROS production in endometriotic and tumor cells is linked to an increase in proliferation rate. Researchers have studied oxidative stress markers in endometriotic illness for over two decades. These markers were acquired from a variety of samples, which can be grouped into five categories: 1) Serum, 2) Peritoneal fluid, 3) Follicular fluid, and 4) Ovarian cortex and endometrial tissue (ectopic and eutopic) [7].

• Serum

Endometriosis patients had greater levels of oxidative stress indicators than non-affected women. Heat shock proteins (HSPs) are intracellular proteins produced in response to infection or inflammation to protect cells from numerous stressors. HSP70 is a member of the HSP family that is activated by stress. HSP70 is a chaperone protein that inhibits aberrant protein production interactions. Women with endometriosis have a higher serum level of HSP70, according to [8] the increase in expression is also seen in the eutopic endometrium of women diagnosed.

The relationship between lipid metabolism and inflammatory variables may play a role in the development of

oxidative stress. Women with endometriosis had their lipid levels checked, and it was discovered that they had higher amounts of triglycerides, total cholesterol, and low-density lipoprotein (LDL) in their blood. On the other hand, low amounts of high-density lipoprotein (HDL) have been found [8].

An increase in lipid peroxides can be used as an indicator of oxidative stress. Malondialdehyde (MDA) has been used as a lipid peroxides index. Reference [9] discovered that women with endometriosis have a higher level of MDA in their blood than healthy women. Lipid hydroperoxides are formed as a result of lipid peroxidation (LOOHs). Unsaturated phospholipids, glycolipids, and cholesterol are the sources of these molecules. Endometriosis patients have more LOOHs than healthy women [9].

Vitamin E, a natural antioxidant, is found in higher concentrations in endometriosis women's serum, although this discovery has not been fully explained. Catalase is an intracellular antioxidant enzyme involved in hepatic pathophysiology, and its concentration in endometriosis patients is higher than in healthy controls [10].

PON-1 is an HDL-associated antioxidant enzyme thought to be a good predictor of coronary artery disease (CAD). PON-1 activity is significantly reduced in the serum of endometriosis patients. Even though its activity has diminished, there is no link between PON-1 and the illness stage [11].

Superoxide dismutase is another enzyme implicated in oxidative stress (SOD). The antioxidant system SOD is very significant. The dismutation of superoxide into hydrogen peroxide and oxygen is catalyzed by it. SDO activity is lower in endometriosis-affected women's plasma, implying a lower antioxidant capacity in these individuals [12].

8F2-isoprostane is another oxidative stress marker that appears to be reduced in the serum of women with endometriosis. Thiols are chemicals that can create reversible disulfide bonds when they combine with oxidizing substances. Turkyilmaz et al. investigated the antioxidant system in endometriosis patients. They discovered that the total antioxidant system (TAS) and native thiol levels in the blood of endometriosis patients are significantly lower than in controls. They also observed increased levels of copper and ceruloplasmin in the serum of endometriosis patients, though [10] found lower levels, which contradicted the prior finding.

Reference [13] looked into the role of carbonic anhydrase activation in response to oxidative stress in the red blood cells of endometriosis patients. Compared to control serum, they discovered enhanced enzyme activity, an increase in glutathionylated protein on the membrane, and a decrease in glutathione levels in the cytoplasm. The glutathione concentration in red blood cells of women with endometriosis is also positively linked with oxidation-induced activation of carbonic anhydrase [13]. Most of this research is observational or case-control studies, and biomarker measurement is vulnerable to interlaboratory and interobserver differences. So that the results may be compared across investigations, a consistent procedure should be followed.

• Peritoneal Fluid

Peritoneal oxidative stress is now considered a crucial

component of endometriosis-related inflammation. Multiple factors based on immunological and inflammatory etiology have a role in the development of peritoneal endometriotic lesions. Several genes encoding immunoregulators, cytokines, and cell adhesion molecules are regulated by peritoneal oxidative stress.

Women with endometriosis have a greater peritoneal macrophage concentration, which may release prostaglandins, cytokines, growth factors, and other enzymes. Macrophages are thought to play a vital role at the beginning, maintenance, and progression of endometriotic illness [14].

Reference [15] investigated the oxidative state of the peritoneal fluid protein in endometriosis patients. Compared to controls, they discovered more significant amounts of advanced oxidation protein products (AOPP). Similarly, nitrate and nitrite concentrations are higher in affected patients than in controls. Furthermore, patients with deep infiltrating endometriosis, particularly those with intestinal involvement, had greater AOPP and nitrates/nitrites. Women with endometriosis discovered a strong association between pelvic pain symptom scores and peritoneal protein oxidative stress markers [15]. Women with endometriosis have more oxidative processes involving LDL. It involves the oxidation of lipoprotein lipids that include polyunsaturated fatty acids. Reference [16] found higher amounts of oxidized LDL (ox-LDL) in peritoneal fluid than in controls.

Women with endometriosis had increased peritoneal levels of MDA and LOOHs. After supplementing women with endometriosis with vitamins C and E, natural antioxidants, whose levels are low in affected women, [17] noticed a decrease in the amounts of MDA and LOOHs in both blood and peritoneal fluid. 8-hydroxy-2-deoxyguanosine, 8-isoprostane, 8-iso prostaglandin F₂, and 25-hydroxycholesterol were also increased in the peritoneal fluid of women with endometriosis.

- Follicular Fluid

Follicular fluid (FF) is essential for the oocyte's reproductive function. An imbalance in the FF's ROS and antioxidant systems could lead to aberrant oocyte development, resulting in DNA, cytoskeleton, and cell membrane damage, as well as decreased egg quality and endometriosis-related infertility. Endometriosis patients had higher levels of lipid peroxide (LPO) and lower total antioxidant capacity (TAC) than healthy women. The FF oxidative stress of women with endometriosis was extensively studied by Várnagy et al. The affected women's FF had more excellent ROS, MDA, and NO levels. High levels of ROS and NO were discovered to be associated with immature oocytes and poor-quality embryos. In women with endometriosis, the antioxidant system is less active. SOD, catalase, glutathione peroxidase, and glutathione reductase activity were reduced in the examined FF. The concentrations of vitamins A, C, and E in endometriosis women's FF are significantly lower than in controls. However, in individuals with unilateral endometrioma, the oxidative stress and antioxidant system in FF are similar to those who do not have endometrioma [18].

- Ovarian Cortex and Endometrial Tissue

Ovarian damage is caused by oxidative stress.

Endometriosis patients' granulosa cells show more evidence of oxidative DNA damage than controls. Women with endometriosis have more apoptotic bodies and nitrotyrosine in their granulosa cells than healthy women. Oxidative stress damages the ovarian cortex of women who are affected. Women with endometriosis have higher levels of 8-hydroxy-2-deoxyguanosine in their ovarian cortex than women with dermoid and serous cysts, according to [19].

In endometriosis, oxidative stress activity and ROS levels are high, and their main effects on cells are cell destruction and proliferation. Biopsies of eutopic endometrium and endometriotic lesions were used by [20] to assess oxidative stress levels. In both samples, superoxide anions were higher, while hydrogen peroxide was higher in endometriotic cells than in controls and endometrial cells. The detoxification of hydrogen peroxide is accomplished by two enzyme systems: glutathione peroxidase and catalase. Endometriotic cells express more glutathione peroxidase than controls, while catalase concentration is lower in endometriotic cells than in controls. In endometriotic lesions, SDO activity appears to be higher than in healthy individuals [20]. These findings demonstrate the importance of oxidative stress in endometriotic cell growth control.

Through the expression and activation of c-Fos and c-Jun, oxidative stress has a role in the survival and proliferation of endometriotic lesions via the mitogen-activated protein (MAP) kinase/extracellular signal-regulated kinase (ERK) pathway. The ERK signaling pathway is involved in the endogenous ROS-induced proliferative response. A particular inhibitor of phosphorylation of the protein tyrosine kinase ERK is used to activate the ERK pathway and link it to deep infiltrating endometriosis (DIE). The development of DIE is further aided by endogenous activation of the mammalian target of rapamycin (mTOR)/AKT pathways. 8-hydroxy-2-deoxyguanosine and MDA are oxidative stress markers that are greater in endometriotic lesions than in healthy subjects. In ectopic endometrioma, MDA levels are also strongly associated with plasma 17-estradiol (E2) concentrations. Endometrial cells from endometriosis patients that have been exposed to both E2 and hydrogen peroxide had enhanced phosphorylation of ERK. These findings reveal a link between E2 and apoptosis resistance and the evolution of endometriotic lesions [21].

Toll-like receptors (TLR) are endometrial endogenous ligands. TLR3 and TLR 4 are primarily expressed in healthy endometrium and endometriotic tissue; TLR 4 appears to enhance endometriosis cell proliferation [22].

C. Oxidative Stress and Endometriosis-Associated Infertility

The link between endometriosis and infertility has been thoroughly documented in the literature. Infertile women with endometriosis have a monthly fecundity rate of 2 to 10%, whereas healthy women have a monthly fecundity rate of 15 to 20%. The impact of ROS on a range of physiologic functions such as oocyte maturation, ovarian steroidogenesis, ovulation, implantation, blastocyst development, luteolysis, and luteal maintenance in pregnancy has been thoroughly documented in the literature. In either natural or aided conception, oxidative stress affects fertility in women with endometriosis. The oxidative stress status in the peritoneal

environment, follicular fluid, and ovary surround are caused by an imbalance between ROS and antioxidant processes, which can partially explain the infertility status associated with endometriosis [23].

D. Oxidative Stress and Genes

The significance of molecular changes such as genomic instability and cell survival in the etiology of endometriosis is hotly contested. Recent genetic investigations have focused on cell cycle checkpoint sensors, hepatocyte nuclear factor (HNF), forkhead transcription factor (FOX), and microRNAs, all of which have been linked to oxidative stress [24].

ROS, iron, and superoxide may play a role in epigenetic regulation. Superoxide regulates the key epigenetic processes of DNA methylation, histone methylation, and histone acetylation and plays an essential role in epigenetic processes in physiologic and pathologic settings. Histone alterations in the promoter regions of cell cycle checkpoint kinase genes are abnormal in recent investigations. As a result, oxidative stress promotes cell cycle progression and cellular transformation. Iron, heme, and hemoglobin buildup causes oxidative stress, which causes DNA hypermethylation and histone alterations. In endometriosis patients, DNA hypermethylation has been associated with abnormal endometrial growth [25].

ROS-induced posttranslational changes regulate FOX activity. FOX deficiency prevents cells from arresting at the checkpoint, allowing lesion growth to proceed more quickly. FOX levels in endometriosis patients are lower than in healthy women. MicroRNAs are small non-coding RNA regulating hundreds of genes by inhibiting posttranslational mRNA synthesis and degrading mRNA. Development, differentiation, apoptosis, proliferation, and cell survival are all controlled by microRNAs. MicroRNAs have been researched in endometriosis, and their levels have been up and downregulated in women with the disease. Immune changes and inflammatory cytokine production are caused by microRNA disruption [26].

Furthermore, microRNAs targeting nociceptive and inflammatory molecules are downregulated in women with endometriosis, possibly contributing to the etiology of endometriotic pain [27].

Reference [28] studied the expression of numerous genes implicated in estrogen oxidative metabolism. Endometriosis was found to have higher levels of CYP1A1, CYP3A7, and COMT expression. SULT1E1, SULT2B1, UGT2B7, NQO1, and GSTP1 expressions were reduced. In endometriosis, the balance between phase I and phase II metabolizing enzymes is disrupted, resulting in increased hydroxy-estrogen and altered ROS production and encouragement of ectopic endometrial proliferation [28].

E. Oxidative Stress and Endometriosis-Associated Cancer Development

Endometriosis' oxidative stress is thought to have a role in its malignant evolution. Literature data suggest that at least a two-step explanation could lead to cancer. Here is how to get started: Increased cell apoptosis and survival in endometriotic cells are triggered by oxidative stress-induced DNA damage. The following is the next step: Long-term antioxidant production that favors a protumoral microenvironment has

been linked to cancer progression. The antioxidant/antioxidant balance role is a two-edged sword that can promote cell death or tumorigenesis. Endometriosis's upregulation of antioxidant activities can lead to cell survival and subsequent malignant transformation [29].

IV. CONCLUSION

Reactive oxygen species (ROS) have a crucial role in modifying numerous physiological functions in reproduction and disorders like endometriosis and infertility; in the female reproductive process, a delicate balance between ROS and antioxidants maintains redox equilibrium. When the equilibrium between ROS production and antioxidant defense is upset, oxidative stress arises, which can be caused by either insufficient antioxidant protection or excessive ROS production.

Several lines of evidence support oxidative stress's significance in the genesis and progression of endometriosis. This finding could pave the way for testing treatment options targeting oxidative imbalance: oxidative stress status could be the key to treating and preventing endometriosis. Clinical research will assist in better defining the usefulness of antioxidants as prospective endometriosis therapy in the future.

CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

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