CHAPTER

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The Role of Oxidative Stress in Endometriosis

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INTRODUCTION

Endometriosis is a disease that affects women of reproductive age primarily and is characterized by the presence of endometrial glands and stroma outside the endometrial lining and uterine muscle. This complex disease primarily affects 10% of all women, and is linked to infertility and chronic pelvic pain [1]. In the pathological state, the endometrial tissue is known to implant in other locations in the body, most commonly in the ovaries, peritoneal cavity, and even in the bladder, liver, kidneys, pleural cavity, and the gluteal muscles (Fig. 25.1) [2]. The etiology of endometriosis, though currently unclear, can be ascribed to one of five origins. Endometriosis is a common gynecological disorder, affecting 10–15% of women in their reproductive years. Because surgical confirmation is necessary for the diagnosis, the true prevalence of the disease is underestimated [3]. Specifically, 10–70% of women presenting with pelvic pain have been found to have endometriosis and it has been shown to be the causal factor in 35–50% of those women diagnosed with infertility [4].

BACKGROUND OF DISEASE

Risk Factors

Women with first-degree relatives with the disease have an increased propensity (seven times more likely) to display symptoms of endometriosis [3]. One out of every 10 women with endometriosis has a first-degree relative with this disease [5]. Specifically, a new genetic linkage for the disease has been noted on chromosome 10q26 and chromosome 20p13, further showing that endometriosis has a familial relationship [6]. Endometriosis also shares a relationship with autoimmune disorders such as lupus.

Symptoms of Endometriosis

The classic presentation of endometriosis is cyclic pelvic pain, or dysmenorrhea, that peaks 1–2 days prior to the onset of menses, and then diminishing at the onset of flow. Symptoms of endometriosis vary depending on the area involved. Dysmenorrhea usually should be considered in women who develop pain after years of normal, pain-free cycles. Other symptoms associated with endometriosis include dysmenorrhea, dyspareunia, abnormal bleeding, and infertility. On physical examination, typically nodularity is felt on the uterosacral ligament, and on bimanual examination of the reproductive structures, the uterus is typically in fixed, retroverted position [3].

Diagnosis of Endometriosis

Unfortunately, diagnostic tools to detect endometriosis are few, invasive, and not ideal. The only way to diagnose endometriosis is through direct visualization of endometrial implants through laparoscopy or laparotomy [3]. These implants may appear as rust-colored or dark-brown powder burns or blue-colored raspberry lesions. Unfortunately, this is an invasive procedure that does not function ideally to detect subtle endometriosis and early preventive diagnosis. It is thereby essential to develop nonsurgical methods for early detection that would provide a more appealing option for women. Aside from laparoscopy, the most recent noninvasive alternatives for the diagnosis of endometriosis are via the
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Analysis of serum and peritoneal markers. Such indirect markers include those that are indicated when levels of oxidative stress increase, and may be less accurate.

In this review, we will discuss the current markers of this disorder, which are mainly concentrated on oxidative stress elevation, and the various roles of different types of reactive oxygen species (ROS) such as nitric oxide, iron, and mediators of inflammation in endometriosis.

THE ORIGIN OF ENDOMETRIOSIS

The origin of endometriosis is yet unknown. However, multiple theories exist as to the causes and pathophysiology of the disease.

Sampson’s Implantation Theory

Sampson’s implantation theory is the most widely accepted theory for the cause of endometriosis. Sampson suggests that endometrial tissue gets transported back through the fallopian tubes during retrograde menstruation, leading to intra-abdominal pelvic implants [3]. This theory of retrograde reflux followed by peritoneal implantation is supported by the location of endometriotic lesions. The four main places that endometriotic lesions have been found include the pouch of Douglas at the rectosigmoid level, the cecum and ileocecal junction, the superior portion of the sigmoid mesocolon, and the right paracolic gutter [7]. These regions are those that experience increased contact with peritoneal fluid, as well as repetitive fluid flow [7].

Sampson’s theory also has three requirements for occurrence. These include retrograde menstruation through the fallopian tubes, which is present in 76–90% of women, the presence of viable refluxed cells in the peritoneal cavity, and the adherence of refluxed cells to the peritoneal cavity surface where they then implant and multiply [8].

Coelomic Metaplasia Theory

The coelomic metaplasia theory proposes that endometriosis comes from reversible changes of the epithelial lining in the peritoneal cavity. Specifically, coelomic epithelium is a derivative of endometrial and peritoneal cells and thus, this theory hypothesizes that transformation from one type of cell to the other in the form of metaplasia is perhaps triggered by inflammation seen in endometriosis. The idea that substances in menstrual fluid can induce peritoneal tissues to form endometrial cells suggests that there is a factor found in menstrual fluid that is possibly a precursor for the disease [8].

Embryonic Rest Theory

The embryonic rest theory implies that rest cells of müllerian origin differentiate into endometrium from certain stimuli [8]. Specifically, during the embryonic stage of development, certain endometrial cells that should grow in the uterus develop in the abdomen,
which in turn, are activated during puberty under the influence of estrogen and progesterone and result in the vaginal bleeding and pelvic pain of endometriosis [9].

**Vascular and Lymphatic Metastasis**

Finally, the vascular and lymphatic metastasis theory states that endometrial cells spread through the body much like cancer, via the body’s blood and lymphatic systems [8]. Moreover, approximately one third of the microvascular endothelium of ectopic endometrial tissue is derived from endothelial progenitor cells, which results in de novo formation of microvessels by the process of vasculogenesis seen in endometriosis [10].

**RELATIONSHIP BETWEEN OXIDATIVE STRESS AND ENDOMETRIOSIS**

Oxidative stress results from an imbalance of free radicals and antioxidant defense mechanisms in the body. Normally, antioxidants, enzymatic and nonenzymatic, scavenge free-radical species and protect the body from overexposure to oxidative stress [11]. An imbalance in the ratio of the antioxidants to ROS can result in a variety of pathological processes within the body. One such form of oxidative stress includes ROS. Specifically, ROS comprise a class of radical and nonradical oxygen derivatives that play a significant role in reproductive biology. Because they have an unpaired electron in their outer orbit, ROS are highly reactive and interact with a variety of lipids, proteins, and nucleic acids in the body [11]. Abnormal levels of ROS are not only harmful for reproductive potential, but they also generate more free radicals, thereby perpetuating a chain of reactions and creating high amounts of oxidative stress [12].

Present in the oviductal fluid, ROS has shown to affect a variety of female reproductive processes such as ovulation, fertilization, embryo development, and implantation. Specifically, this fluid has been found to contain cellular debris that act as a substrate for oxidative stress reactions in women with endometriosis. ROS are produced by activated neutrophils and macrophages, which are elevated in proinflammatory conditions such as endometriosis [13]. Despite the lack of substantial evidence of a causal relationship, multiple studies have shown a direct association between ROS and endometriosis, [14,15] while others have provided evidence to suggest the absence of the link between ROS and endometriosis [16,17].

Huge strides have been made to prove the detrimental effect of ROS to the reproductive potential, in general, but the purpose of this review is to address the impact of oxidative stress on endometriosis. A consolidation of the available information on this topic will allow the development of potential antioxidant treatments for conditions associated with this condition.

**OXIDATIVE STRESS MARKERS IN ENDOMETRIOSIS**

Oxidative stress markers present potential therapeutic targets for the treatment of endometriosis. By expanding and researching these markers, the diagnostics of endometriosis may progress from requiring surgery to a much less invasive method. The following sections will discuss the most relevant markers of ROS in endometriosis (Fig. 25.2).
Heat Shock Protein 70

The normal function of heat shock proteins (HSP) is to regulate and guide protein synthesis and protect the proteins from undue stress. Previous studies have found that heat shock protein 70B' is increased in endometriosis [18]. Another study stated that HSP-70 stimulated vascular endothelial cell growth factor, interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) by macrophages in women with endometriosis when compared with healthy women [19]. Khan and colleagues also suspect that HSP-70 is implicated in the toll-like receptor 4 (TLR4) mediated growth of endometrial cells [19].

Macrophages

In endometriosis patients, macrophage number has been noted to increase in peritoneal fluid. This increase of phagocytic cells results in a higher amount of phagocytosis, which in turn releases more ROS [20]. Endometriosis results in the inflammation of the peritoneal cavity and other sites of implantation due to irritation from the refluxed blood, and results in the activation of neutrophils and macrophages – known producers of ROS [20].

Transcription Factor NF-kB

Nuclear factor kappa B (NF-kB) is a transcription factor that normally functions to control the transcription of DNA. It also plays a vital role in the regulation of immune factors during infection [21]. NF-kB is normally responsible for the expression of proinflammatory cytokines, growth factor, angiogenic factor, adhesion molecules, and inducible enzymes iNOS and COX-2 [22]. These products contribute to the development of endometriosis through the increase of endometrial fragment adhesion, proliferation, and neovascularization [23,24].

Matrix Metalloproteinases

The pathogenesis of endometriosis involves many different enzymes including matrix metalloproteinases (MMPs) that are produced in the endometrial stroma and function to degrade the extracellular matrix in the peritoneal mesothelium in order for ectopic cells to implant [25]. These MMPs may be necessary for the formation of endometriotic lesions [25].

Vascular Endothelial Growth Factor

Just as with metastatic tumors, endometriosis involves neovascularization for lesions to proliferate. Vascular endothelial growth factor (VEGF) is a known participant in endometriosis. It is hypothesized to be a participant in the angiogenesis that occurs in endometriotic lesions. Particularly, a study by Kim and colleagues determined that the VEGF polymorphism +405 C/G was associated with the increased risk of endometriosis in Korean women [26]. Additionally, a recent meta-analysis determined that certain VEGF polymorphisms are associated with an increased risk of endometriosis while others may be protective [27]. These studies indicate that VEGF has a strong role in the development of endometriosis, and potentially can function as a diagnostic factor or therapeutic target.

Destruction of Mesothelial Cells

During endometriosis and oxidative stress, the peritoneal mesothelium is particularly susceptible to damage [16,28]. In a healthy individual, the mesothelium serves as a protective barrier to ward off endometrial implants. However, in an individual with endometriosis, the mesothelium is fragile and susceptible to damage from oxidative stress. These damaged mesothelial cells function as adhesion sites for endometrial cells, which leads to progression of the disease [11,29].

Nitric Oxide and Endometriosis

ROS not only includes oxygen radicals, such as the hydroxyl radical, superoxide radical, and hydrogen peroxide, but also a subclass of nitrogen-containing compounds collectively known as reactive nitrogen species (RNS). Examples of RNS include peroxynitrite anion, nitroxyl ion, nitrosyl-containing compounds, and nitric oxide [12]. All of these forms of RNS have been shown to play physiologic and pathologic roles in the female reproductive system; however, the role of nitric oxide in endometriosis has been most extensively reviewed in the literature.

Production of Nitric Oxide

Nitric oxide (NO) is produced from L-arginine via nitric oxide synthase (NOS). It requires oxygen and a number of cofactors, such as nicotinamide adenine dinucleotide phosphate (NADPH), flavin mononucleotide (FMN), flavin adenine dinucleotide (FAD), calmodulin, and calcium, resulting in the production of NO as well as a byproduct known as L-citrulline [30,31]. There are three forms of NOS that exert their effect through protein–protein interactions and catalyze the aforementioned reaction: (1) endothelial NOS (eNOS), (2) inducible NOS (iNOS), and (3) neuronal NOS (nNOS). Each isoform has a reductase domain that contains a compound known as tetrahydrobiopterin (BH4), which is essential for the efficient
production of NO [32,33]. Pertinent to endometriosis, studies show that the peritoneal fluid in women with this condition contain increased concentrations of eNOS and iNOS, making the peritoneal fluid one of the richest sources of nitric oxide within the female reproductive tract. With regard to eNOS, it is located mainly in the endometrial glandular epithelium and elevated during the midluteal phase of the menstrual cycle. Moreover, studies report that the expression pattern of eNOS has an inverse relationship with an adhesive marker for uterine receptivity known as integrin alpha V beta 3. As levels of eNOS increase during the second half of the menstrual cycle, there is a respective decrease in integrin alpha V beta 3, potentially contributing to the implantation difficulties seen in endometriosis [13].

Aside from NOS, there are a variety of other compounds and biochemical reactions that produce NO in the body. Namely, studies have linked the generation of NO to the rate-limiting enzyme glucose-6-phosphate dehydrogenase as well as the NADPH-producing pentose phosphate pathway [34].

Additional pathways of nitric oxide transport can be generated via binding of NO to iron–sulfur clusters, formation of nitrotyrosines, and binding of NO to heme-containing proteins of the respiratory chain [35].

Furthermore, glucose has been shown to indirectly produce NO by stimulating the pentose phosphate pathway, as well as the conversion of L-arginine to L-citrulline. Other studies have indicated that NO can regulate its own activity via a feedback inhibition mechanism [32,33]. In particular, the reaction of NO with the superoxide anion results in the formation of a more noxious oxidant – peroxynitrite [36,37]. Specifically, the formation of peroxynitrite occurs only when NO has reached toxic levels and begins to compete with superoxide dismutase for the scavenging of superoxide [38]. While excessive levels of NO undoubtedly damage reproductive organs, it is nevertheless one of the least potent of the RNS [12].

Physiologic Actions of Nitric Oxide

Nitric oxide plays an important physiologic role within the female reproductive system. NO is known to regulate the endometrial microvasculature and is produced by eNOS, which is distributed in the glandular surface of epithelial cells of the endometrium.

Moreover, it regulates endometrial stromal edema production, which is an important step for endometrial growth during the menstrual cycle, embryo implantation, and uterine contraction. Furthermore, in healthy fertile women, NO promotes contractions in the subendometrial myometrium, necessary for a normal menstrual cycle [13].

Detrimental Actions of Nitric Oxide

In endometriosis, ROS and RNS are produced via the interaction of interferon-alpha and interferon-gamma with lipopolysaccharide (LPS). This reaction activates peritoneal fluid mononuclear cells and macrophages to produce nitric oxide [5,13]. Moreover, these peritoneal macrophages have the capacity to move from the peritoneal cavity to other parts of the female reproductive system including the fallopian tubes where fertilization takes place [11]. When the migration of these macrophages is left unchecked, such as in endometriosis, pathological concentrations of NO can accumulate within the fluid of the peritoneal cavity and inhibit fertility by altering the following reproductive processes: ovulation, gamete transport, sperm–oocyte interaction, peritoneal fluid environment, fertilization, and early embryonic development [39]. Moreover, increased NO production has been shown to inhibit tubal motility and uterine contractions, causing uterine dysperistalsis. Consequently, this impairs implantation, and in turn leads to compromised fecundity [5,13].

Reproductive Hormones and Nitric Oxide Production

The levels of NOS and NO are also associated with the levels of the reproductive hormones estrogen and progesterone. In a study on endometriosis-related infertility, fasting blood samples procured from women with this condition demonstrated a positive correlation between the levels of estrogen and progesterone and eNOS protein levels [40]. Specifically, NO activates cyclooxygenase-2 (COX-2), which in turn increases the levels of prostaglandin E2, thereby causing the levels of aromatase, an enzyme necessary for estrogen production. The resultant estrogen elevation stimulates further eNOS gene expression in a positive feedback loop [41].

ROLE OF IRON

Retrograde menstruation includes red blood cells, which contain the factors of hemoglobin and heme. These factors are also proinflammatory and generate iron – a redox-generating molecule [42]. An overload of iron from these erythrocytes can result in damage mediated by the molecule, inflammation, and ultimately, oxidative stress. When women have endometriosis, the overload of iron facilitates the lysis of erythrocytes in the pelvic cavity. Normally, women have mechanisms to protect themselves from such lysis; however, two theories contribute to the lack of these protective mechanisms in women with endometriosis. These hypotheses include...
an abundance of reflux and defective auto-oxidative capacity [5]. Furthermore, as mentioned previously, the state of endometriosis contributes to high numbers of activated macrophages. As iron is continually delivered to these macrophages, ferritin is unable to store and sequester iron. This ultimately leads to iron’s production of free radicals, and finally an imbalance between ROS and the body’s natural antioxidant defense mechanisms. Furthermore, as iron is a generator of free radicals, it causes macromolecular oxidative stress and cellular damage to the normally protective mesothelial cells from the iron binding Hb protein, a factor prevalent in menstrual fluid [43].

Bilirubin is another antioxidant that is produced by heme oxidase, whose decrease further contributes to the formation of oxidative stress [44]. While heme oxygenase levels are elevated in the peritoneal fluid, macrophages, the main cells present in cases of endometriosis, do not express it [45]. Therefore, bilirubin cannot form and its antioxidant capacity is not present in women with endometriosis.

With iron playing such a fundamental role in endometriosis, it becomes a strong therapeutic target.

ROLE OF CYTOKINES

As cytokines get released into the peritoneal fluid, they begin to play a role in endometriosis. These cytokines contribute to tissue remodeling and implantation of cells or tissue within the endometrium [46].

Interleukin 1 (IL-1) is involved with the activation of T-cells and differentiation of B-cells; it has been implicated in the implantation of ectopic endometrium in the disease process of endometriosis [47].

Interleukin 6 (IL-6) is a regulator of other cytokines. Among other duties, it activates B-cells and is important in the folliculogenesis, steroid hormone synthesis, implantation, and growth of endometrial cells [48]. IL-6 was demonstrated to increase in the peritoneal fluid along with the increased severity of endometriosis, and levels of IL-6 were shown to be higher in women with minimal-moderate endometriosis when compared to controls [49,50]. Further studies have shown IL-6 to be upregulated in women with endometriosis, facilitating its use as a marker of the disease [51,52,53].

Interleukin 8 (IL-8) is an important factor involved in chemotaxis and angiogenesis. This cytokine was found to be elevated in the peritoneal fluid of women with endometriosis, and its levels appeared to increase as the disease progressed. The levels of IL-8 were also increased in women with endometriosis when compared to normal women during the proliferative phase of menarche [54,55].

TNF-α is crucial in the body, produced by multiple immunologic cells, and functions as a proinflammatory cytokine. TNF-α will disrupt glutathione, decreasing the protective mechanisms available in women. It has been found that with the addition of TNF-α in a time- and dose-dependent manner, spermatozoa quality decreased [56]. The levels of TNF-α in peritoneal fluid were found to be increased in patients with endometriosis [57,58,59].

TREATMENT OF ENDOMETRIOSIS

Current treatment for endometriosis involves symptomatic therapy and potentially curative therapy. Symptomatically, health care providers may give patients pain control, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids. These may accompany “watchful waiting” by the clinician, who will periodically examine the patient’s symptoms and adjust the pain management regimen accordingly. Furthermore, the symptoms of endometriosis can be relieved by hormone therapy, which are aimed at inhibiting the production of estrogen and thus, prevent ovulation. Consequently, this inhibition helps to slow the growth and local activity of both the endometrium and the endometrial lesions. Treatment via hormone therapy also prevents the growth of new areas of endometriosis, but it will not make existing lesions go away [60]. Examples of such treatments includes gonadotropin-releasing hormone (GnRH) analogs, which have been found to diminish elevated levels of NO, and thus endometriosis-associated infertility. Specifically, this occurs via the reduction of eNOS by these analogs in the early and middle secretory and early proliferative stages of the menstrual cycle [40]. Peroxynitrate was also found to be diminished in eutopic and ectopic endometrium once treated with GnRH agonist [60]. Moreover, studies have also shown benefit in adding specific inhibitors of eNOS to the GnRH analog in order to diminish the positive feedback loop of estrogen and progesterone on eNOS, and in turn, reduce endometriotic implantation and improved pregnancy outcomes [11]. Danazol is another form of hormone therapy that prevents ovulation by suppressing the increase of luteinizing hormone during the middle of the menstrual cycle. Specifically, it promotes hypoestrogenic- and hyperandrogenic-like effects, causing atrophy of the endometrium, which in turn helps to alleviate the symptoms of endometriosis. Moreover, Danazol suppresses the production of interleukin-1 beta and tumor necrosis factor by human monocytes, which are key cytokines that contribute to ectopic implantation of the stromal and glandular endometrial tissue throughout the body [61].

Finally, surgical treatments can provide significant, albeit short-term, relief from the pain of endometriosis through laparoscopy, laparotomy, or surgery to sever pelvic nerves [62]. Although studies show improved pregnancy rates following this type of surgery, the success rate is not clear. Therefore, if pregnancy does not
occur after laparoscopic treatment, in vitro fertilization (IVF) may be the best option to improve fertility [63]. Although treatments aimed at mitigating the symptoms and improving fertility outcomes caused by endometriosis are important, therapies that aid in the prevention of oxidative damage involved in this condition, such as antioxidants, have also proven to be beneficial.

**Antioxidants**

Antioxidants are a defense mechanism produced by the body to neutralize the effects of ROS. They can be enzymatic and nonenzymatic. Nonenzymatic sources of antioxidants include vitamin C, vitamin E, selenium, zinc, beta carotene, carotene, taurine, hypotaurine, and glutathione. Enzymatic antioxidants include SOD, catalase, glutaredoxin, and glutathione reductase [64]. However, as the body ages, antioxidant levels decline, resulting in a disruption in the balance between antioxidants and prooxidant molecules. This results in the generation of oxidative stress and in turn, overrides the scavenging capacity by antioxidants either due to the diminished availability of antioxidants or excessive generation of ROS. Therefore, supplementation with oral oxidants may help to alleviate oxidative stress and its contribution to the pathogenesis of obstetrical disease such as endometriosis [65]. Only the most relevant antioxidants beneficial to endometriosis will be discussed.

**Vitamin E and Vitamin C**

Two dietary vitamins, vitamin C (ascorbic acid) and E (α-tocopherol), can be used to thwart the oxidative damage caused by endometriosis via their ability to scavenge free radicals and neutralize oxidative stress [66]. In a study of infertile women, those with endometriosis were shown to have lower levels of vitamin C in their follicular fluid, compared to women who did not have endometriosis, implicating the important role antioxidants play in mitigating bodily harm. Moreover, in a randomized, placebo-controlled trial of antioxidant vitamins E and C in women with pelvic pain and endometriosis, patients in the treatment group were found to have decreased levels of oxidative stress cytokines, interleukin-6 in the peritoneal fluid, and improvement in the symptoms of dysmenorrhea and dyspareunia when compared to the placebo group [67]. Other studies report that lower intake of antioxidants, including vitamins E and C, in women with endometriosis correspond with increased disease severity [68]. Additionally, data have shown that women with endometriosis have lower levels of the endogenous antioxidant superoxide dismutase in their plasma, thereby suggesting the need for supplementation in these women. It is important to note, however, that at high doses, vitamin C and E have deleterious effects on the body. Specifically, large quantities of vitamin C (>2000 mg/day) have been suggested to cause diarrhea, abdominal cramps, bloating, nausea, vomiting, and kidney stones [69]. Furthermore, high doses of vitamin E (>1000 mg/day) may increase the risk of bleeding by having an anticoagulant-like effect on the body and may also increase the risk of birth defects. Thus, when using vitamin C and E to quell the adverse effects of endometriosis, it is important that appropriate dosages be used [70].

**Glutathione Peroxidase**

Glutathione peroxidase is an antioxidant enzyme class with the capacity to scavenge free radicals. This is in turn helps to prevent lipid peroxidation and maintain intracellular homeostasis as well as redox balance [71]. Glutathione peroxidase is localized in the glandular epithelium of normal human endometrium and reaches a maximum level in the late proliferative and early secretory phases of the menstrual cycle [72]. A study on endometriosis-associated infertility demonstrated a lower mean activity of glutathione peroxidase and increased lipid peroxidation in infertile women with endometriosis compared to women without this disease. This suggests that low level of antioxidant enzymes in the peritoneal fluid plays an integral role in the development of endometrial pathology [73]. Furthermore, in women with endometriosis, abnormal expression of glutathione peroxidase in eutopic and ectopic endometrium has been reported [13]. Overall, this aberrant change in antioxidant enzyme level can be one of the many contributors of the oxidative damage seen in endometriosis.

**CONCLUSIONS**

Despite the lack of evidence of a causal relationship between the excess free-radical molecules and pathophysiology of endometriosis, it is clear that an association between oxidative stress and the pathogenesis of this condition exists. Therefore, investigation on the various oxidative markers implicated in endometriosis, such as iron, cytokines, nitric oxide, and other immune modulators, needs to be continued. Furthermore, measurement of these markers in the peritoneal fluid could possibly be used as noninvasive alternatives to diagnose endometriosis, but this remains to be investigated. Additionally, continued research on the role of antioxidant agents should be performed due to the proven benefit in both the prevention and treatment of endometriosis via the alleviation of endometriotic lesions and severity of symptoms. Overall, by understanding the role of oxidative stress in endometriosis, we can potentially stem the increasing rates of female infertility and improve the quality of life in women hindered by this condition.

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References


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REFERENCES


