Chapter 9
Endometriosis and Oxidative Stress

Lucky H. Sekhon and Ashok Agarwal

Abstract Endometriosis is a chronic gynecologic disease process with multifactorial etiology. Increased oxidative stress, a result of increased production of free radicals or depletion of the body's endogenous antioxidant defense, has been implicated in its pathogenesis. Oxidative stress is thought to promote angiogenesis and the growth and proliferation of endometriotic implants. Oxidative stress in the reproductive tract microenvironment is known to negatively affect sperm count and quality and may also arrest fertilized egg division leading to embryo death. Increased DNA damage in sperm, oocytes, and resultant embryos may account for the increase in miscarriages and fertilization and implantation failures seen in patients with endometriosis. The evidence linking endometriosis and infertility to endogenous pro-oxidant imbalance provides a rationale for the empiric use of antioxidant therapy. Vitamin C and E deficiency has been demonstrated in women with endometriosis. Observational and randomized controlled studies have shown vitamin C and E combination therapy to decrease markers of oxidative stress.

Keywords Endometriosis · Oxidative stress · OS induced infertility · Antioxidant treatment · Curcumin · Melatonin · Pentoxifylline

L. H. Sekhon
Department of Obstetrics and Gynecology, Mount Sinai School of Medicine,
1176 5th Ave Klingenstein Pavilion, 9th Floor, New York, NY 10029, USA
e-mail: sekhon@hotmail.com; lucky.sekhon@mountsinai.org

A. Agarwal (✉)
Center for Reproductive Medicine, Lerner College of Medicine, Cleveland Clinic,
9500 Euclid Avenue, Cleveland, OH 44195, USA
e-mail: agarwaa@ccf.org

A. Agarwal et al. (eds.), *Studies on Women's Health*, Oxidative Stress in Applied Basic Research and Clinical Practice, DOI: 10.1007/978-1-62703-041-0_9,

9.1 Introduction

Endometriosis is defined by the development of endometrial tissue, including both glandular epithelium and stroma, outside the uterine cavity, in the pelvic peritoneum, ovaries and the recto-vaginal septum and rarely in remote locations such as the pericardium, pleura, and brain [1–3]. It is a benign, chronic gynecologic disease and is clinically associated with dysmenorrhea, dyspareunia, pelvic pain, and subfertility. It affects 10–15 % of all women of reproductive age and 30 % of infertile women [4, 5].

Despite a large number of studies on endometriosis, its etiology has yet to be clearly defined as the disease is known to have multifactorial characteristics. There is a growing body of evidence suggests that a combination of genetic, hormonal, environmental, immunological, and anatomical factors play a role in the pathogenesis of this disorder [6–8].

The widely accepted Sampson's theory asserts that endometriosis originates from the implantation and invasion of cells from retrograde menstruation to particularly the pelvic peritoneal cavity (Fig. 9.1). This reflux of menstrual endometrial tissue through the fallopian tubes into the peritoneal cavity is a common physiologic event which results in red blood cells being present in the peritoneal fluid of most women [9]. Recent findings indicate that the influence of the local environment is crucial in the development of endometriosis [10]. Iron overload, from lysis of pelvic red blood cells has been identified in different components of the peritoneal cavity of endometriosis patients, including peritoneal fluid, ectopic endometrial tissue and peritoneum adjacent to lesions, and macrophages. It is hypothesized that the peritoneal protective mechanisms of patients with endometriosis might be overwhelmed by menstrual reflux, either because of the abundance of reflux or because of defective scavenging systems [11]. Bleeding from endometriotic lesions may further contribute to the accumulation of iron in peritoneal fluid. Iron can act as a catalyst which generates free radicals. Peritoneal iron overload encountered in lesions, peritoneal fluid and peritoneal macrophages of endometriosis patients may contribute to oxidative stress (OS) which impairs the functionality of protective immune cells, thereby contributing to the development of the disease. In a study by Yamaguchi et al. abundant free iron in the contents of endometriotic cysts was found to strongly associated with OS and frequent DNA mutations [12]. Therefore, the iron-rich environment within endometriotic cysts during may also play a crucial role in carcinogenesis through the iron-induced persistent oxidative stress.

Metaplasia of celomic epithelial cells lining the pelvic peritoneum is one of several theories regarding the pathogenesis of endometriosis. This may explain the mechanism by which endometriosis occurs in the ovary. Endometriotic implants proliferate on the ovarian surface epithelium, as a single cell layer on the surface of ovaries, which invaginates to form cortical inclusion cysts [13]. Both theories of implantation and celomic metaplasia are possible mechanisms of endometriotic lesion initiation. Both estrogen production and progesterone dysregulation may

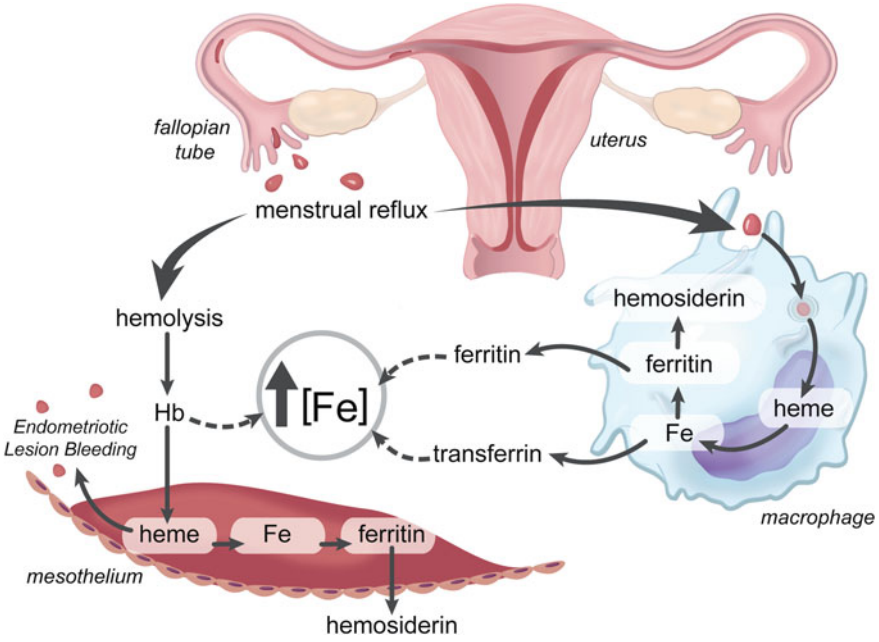

Fig. 9.1 The reflux of menstrual endometrial tissue through the fallopian tubes into the peritoneal cavity results in red blood cells being present in the peritoneal fluid. Iron overload, from lysis of pelvic red blood cells has been identified in different components of the peritoneal cavity of endometriosis patients, including peritoneal fluid, ectopic endometrial tissue and peritoneum adjacent to lesions, and macrophages. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2011. All Rights Reserved)

also play a major role in the initiation and promotion of endometriosis [13]. The initial development of endometriosis occurs as a result of induction of attachment, invasion angiogenesis, cell growth, and survival. Additional factors contributing to the establishment and persistence of these endometriotic lesions involve hormonal imbalance, genetic predisposition, and altered immune surveillance.

Mediators of fibrosis and inflammatory changes in the follicular fluid and peritoneal fluid environments are likely involved in the development of the symptoms associated with endometriosis. An increased percentage of B lymphocytes, natural killer cells, and monocyte-macrophages in the follicular fluid have been noted in a case-controlled study of patients with endometriosis compared to patients with other causes of infertility, providing evidence of altered immunologic function in the follicular fluid of patients with endometriosis [14]. Impaired natural killer cell activity may result in inadequate removal of refluxed menstrual debris leading to the development of endometriotic implants. Although the peritoneal fluid of women with endometriosis contains increased numbers of immune cells, these seem to facilitate rather than inhibit the development of endometriosis [15]. Macrophages,

that would be expected to clear the peritoneal cavity from endometrial cells, appear to enhance their proliferation by secreting growth factors and cytokines.

Increased concentrations of interleukins IL-6, IL-1b, IL-10, and tumor necrosis factor-a (TNF-a), as well as decreased vascular endothelial growth factor (VEGF) have been documented in the follicular fluid of endometriosis patients [16–18].

As current evidence suggests that endometriosis induces local inflammatory processes, many studies have focused on markers of inflammation and OS in an effort to find less invasive methods of diagnosis [19–21]. OS has been implicated in the pathogenesis of endometriosis. Moreover, evidence is emerging that women with endometriosis experience a greater degree of OS than healthy fertile women.

9.2 Oxidative Stress

Oxidative stress has been implicated in endometriosis and develops when there is an imbalance between the generation of free radicals and the scavenging capacity of antioxidants in the reproductive tract. Free radicals are defined as any species with one or more unpaired electrons in the outer orbit [22]. There are two types of free radicals: reactive oxygen species (ROS) and reactive nitrogen species (RNS). The main free radicals are the superoxide radical, hydrogen peroxide, hydroxyl, and singlet oxygen radicals. ROS are intermediate products of normal oxygen metabolism. Oxygen is required to support life, but its metabolites can modify cell functions, endanger cell survival, or both [23]. Almost all major classes of biomolecules, including lipids, proteins, and nucleic acids, are potential targets for ROS. Hydroxyl radicals are the most reactive free radical species known and have the ability to react with a wide range of cellular constituents, including amino-acid residues, and purine and pyrimidine bases of DNA, as well as attacking membrane lipids to initiate a free radical chain reaction known as lipid peroxidation. Therefore, ROS must be continuously inactivated to keep only a small amount necessary to maintain normal cell function. Both enzymatic and non-enzymatic antioxidant systems scavenge and deactivate excessive free radicals, helping to prevent cell damage. The body's complex antioxidant system is influenced by dietary intake of nonenzymatic antioxidants such as manganese, copper, selenium and zinc, beta-carotenes, vitamin C, vitamin E, taurine, hypotaurine, and B vitamins [24]. On the other hand, the body produces several antioxidant enzymes such as catalase, superoxide dismutase, glutathione reductase, glutathione peroxidase, and molecules like glutathione and NADH. Glutathione is produced by the cell and plays a crucial role in maintaining the normal balance between oxidation and antioxidation. NADH is considered as an antioxidant in biological systems due to its high reactivity with some free radicals, its high intracellular concentrations and the fact that it has the highest reduction power of all biologically active

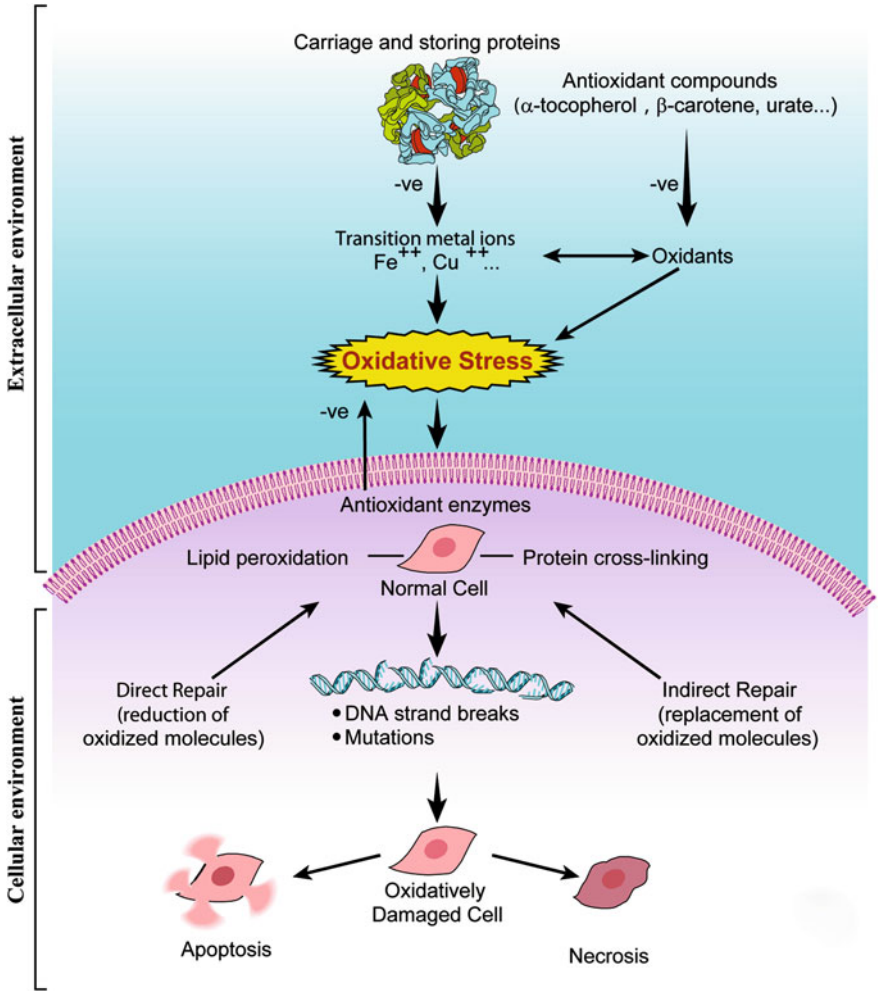

Fig. 9.2 Peritoneal fluid containing ROS-generating iron, macrophages, and environmental contaminants such as polychlorinated biphenyls may disrupt the balance between ROS and antioxidants, resulting in increased proliferation of tissue and adhesions, direct cytotoxic actions, and higher rates of apoptosis. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2004–2011. All Rights Reserved)

compounds [25]. When the balance between ROS production and antioxidant defense is disrupted, higher levels of ROS are generated and OS may occur, leading to harmful effects (Fig. 9.2). OS is implicated as a major factor involved in the pathophysiology of endometriosis.

9.3 Oxidative Stress and Endometriosis

Peritoneal fluid containing ROS-generating iron, macrophages, and environmental contaminants such as polychlorinated biphenyls may disrupt the balance between ROS and antioxidants, resulting in increased proliferation of tissue and adhesions [26–29]. OS is thought to have a biphasic dose-response, where only moderate doses of ROS induce endometriotic growth and proliferation, whereas higher doses do not, due to its direct cytotoxic actions and higher rates of apoptosis [30]. OS may have a role in promoting angiogenesis in ectopic endometrial implants by increasing VEGF production [31]. This effect is partly mediated by glycodelin, a glycoprotein whose expression is stimulated by OS. Glycodelin may act as an autocrine factor within ectopic endometrial tissue by augmenting VEGF expression [31].

Altered molecular genetic pathways may also contribute to the effects of OS in the pathogenesis of endometriosis and endometriosis-associated infertility. Differential gene expression of ectopic and normal endometrial tissue has been identified, including differential gene expression of glutathione-S-transferase, an enzyme in the metabolism of the potent antioxidant glutathione [32]. Thioredoxin (TRX), an endogenous redox regulator that protects cells against OS, and TRX-binding protein-2 play a crucial role in the homeostasis of eutopic endometrium. A study by Seo et al. showed that altered TRX and TRX-binding protein-2 mRNA expression in the endometrium is associated with the endometriosis. Therefore, altered molecular genetic pathways may determine the development of OS and its ability to induce cellular proliferation and angiogenesis in women with endometriosis [33].

The peritoneal fluid of women with endometriosis has been reported to exhibit increased ROS generation by activated peritoneal macrophages [34]. Increased macrophage activity is accompanied by the release of cytokines and other immune mediator. After adjusting for confounding factors such as age, BMI, gravidity, serum vitamin E, and serum lipid levels, Jackson et al. found a weak trend involving elevated levels of thiobarbituric acid reactive substances (TBARS), an overall measure of OS, in women with endometriosis [29]. Ota et al. demonstrated that there was a consistently high expression of xanthine oxidase, an enzyme producing ROS, in the endometrium of women with endometriosis, in contrast to the cyclic variations seen in normal subjects. Similarly, they showed that enzymes associated with free radicals are present in the glandular epithelium of endometrium, at levels which are pronounced in endometriosis [35]. These findings suggest that free radical metabolism is abnormal, overall, in endometriosis. Levels of the OS marker, 8-hydroxy 1-deoxyguanosine, were seen to be higher in patients with endometriosis than in patients with tubal, male factor, or idiopathic infertility. A 6-fold increase in the levels of 8-hydroxy 1- deoxyguanosine and lipid peroxide was demonstrated in ovarian endometriomas compared with normal endometrial tissue [36]. Increased NItric oxide (NO) production and lipid peroxidation have been reported in the endometrium of women with endometriosis [37, 38]. NO is a

pro-inflammatory free radical that decreases fertility by increasing the amount of OS in the peritoneal fluid, an environment that hosts processes such as ovulation, gamete transportation, sperm–oocyte interaction, fertilization, and early embryonic development
[37, 39, 40]. However, several studies failed to find significant differences in the peritoneal fluid levels of NO, lipid peroxide and ROS in women with, and without endometriosis associated infertility. The failure of some studies to confirm alterations in peritoneal fluid NO, lipid peroxide and antioxidant status in women with endometriosis may be explained by the fact that OS may occur locally, without affecting total peritoneal fluid ROS concentration. Also, markers of OS may be transient and not detected at the time endometriosis is diagnosed. In a study by Lambinoudaki et al. stable stress-induced heat shock proteins were used as serum markers of systemic oxidative stress. Women with endometriosis demonstrated increased systemic OS expressed by higher levels of heat shock protein 70bo, which indicated that OS may not be confined to the peritoneal cavity in women with endometriosis [41]. Many of the studies which failed to show increased OS in the peritoneal fluid or systemically [39, 42, 43] often measured ROS or total antioxidant capacity (TAC), parameters that can be affected by handling, whereas heat shock proteins are considered more stable and easily detected.

Increased OS may be due to increased production of ROS or due to depletion of antioxidant reserve. Many recent studies in women with endometriosis have shown altered expression of enzymes involved in defence against OS [35, 44]. Murphy et al. showed that vitamin E levels are significantly lower in the peritoneal fluid of women with endometriosis, possibly due to a local decrease of antioxidants caused by excessive OS [45]. Enzymes associated with free radicals are present in the glandular epithelium of the endometrium and these levels vary dynamically throughout the menstrual cycle. In healthy women, levels of superoxide dismutase (SOD) and nitric oxide synthase (NOS) in the endometrium are low during the proliferative phase and increase during the early and midsecretory phase. However, in women with endometriosis, this variation is lost and the levels of SOD and NOS are seen to remain constant throughout the menstrual cycle [46]. Furthermore, expression of glutathione peroxidase also ceases to vary during the menstural cycle in endometriosis [47]. Women with endometriosis have been shown to have significantly lower levels of antioxidants than women without endometriosis and significantly higher levels of lipid peroxides [48]. Szczepanska et al. reported that women with endometriosis have significantly lower levels of SOD and glutathione peroxidase in peritoneal fluid compared with fertile control women [37]. Excessive OS is thought to contribute to formation of endometriosis-related adhesions. Portz et al. found that injection of antioxidant enzymes, such as SOD and catalase, into the peritoneal cavity prevented the formation of intraperitoneal adhesions at endometriosis sites in rabbits [49]. Therefore, there is evidence to suggest that antioxidants oppose the processes involved in the pathogenesis of endometriosis by controlling OS in the female reproductive tract and peritoneal cavity.

9.4 OS Induced Infertility in Endometriosis

An association between endometriosis and infertility has been often reported in the literature, but a direct causal relationship has yet to be confirmed [50–52]. Severe cases of endometriosis are thought to render a woman infertile by mechanical hindrance of the sperm–egg encounter due to adhesions, endometriomata, and pelvic anatomy disruption. However, in less severe cases where there is no pelvic anatomical distortion, the mechanism by which their fertility is reduced is poorly understood. Numerous mechanisms have been proposed to account for fertility impairment. Endometriosis can cause ovulatory dysfunction, poor oocyte quality [53], luteal phase defects [54], and abnormal embryogenesis [55] which may lead to poor fertilization [56]. Peritoneal macrophages from women with endometriosis associated infertility expressed higher levels of NOS2, had higher NOS enzyme activity and produced more NO in response to immune stimulation in vitro [57]. Peritoneal fluid from women with endometriosis, with high concentrations of cytokines, growth factors, and activated macrophages, has been shown to have levels of ROS that are toxic to the sperm plasma and acrosomal membranes, resulting in a loss of motility and decreased spermatozoal ability to bind, and penetrate the oocyte [58, 59]. Increased iron in the peritoneal fluid results in OS in the reproductive tract microenvironment which negatively affects sperm motility and may also arrest division of the fertilized egg leading to embryo death. Spermatozoa have been shown to exhibit increased DNA fragmentation when incubated with peritoneal fluid from endometriosis patients, with the extent of fragmentation correlating with the stage of endometriosis and duration of infertility [60]. Oocytes exhibited increased DNA damage as they were incubated in peritoneal fluid of endometriosis patients, and the extent of the damage was dependent on the duration of peritoneal fluid exposure [61]. Embryos incubated in the peritoneal fluid of endometriosis patients also exhibited DNA fragmentation as indicated by increased apoptosis [62]. It has been proposed that IVF may improve the conception rate in women with endometriosis as it avoids contact between the gametes and embryos with potentially toxic peritoneal and oviductal factors [57].

Several studies on assisted reproduction have suggested lower than normal rates of pregnancy among women with endometriosis. A meta-analysis of most of these studies showed that the pregnancy rate in women with endometriosis was about half of that in women with tubal-factor infertility, after controlling for confounding factors. Excessive ROS can also interfere with IVF by decreasing the likelihood of fertilization, inducing embryonic fragmentation when intracytoplasmic sperm injection is used, and hampering the in vitro development of blastocysts [63]. The results of studies focusing on IVF treatment suggest poor ovarian reserve in more advanced endometriosis, low oocyte and embryo quality, and poor implantation [64]. Changes in granulosa cell cycle kinetics may be responsible for impaired follicle growth and oocyte maturation in endometriosis patients [36]. Flow cytometric analysis was used to determine the cell cycle of granulosa cells in endometriosis and nonendometriosis patients. A decreased number of granulosa

cells in the G2/M phase and an increase in both the S phase and apoptotic cells were documented in women with endometriosis [36, 65]. Oocyte quality may be influenced by granulosa cell apoptosis as well. Granulosa cell apoptosis increased proportionally with the severity of disease and resulted in poor oocyte quality and a reduction in fertilization and pregnancy rates [66]. A higher percentage of granulosa cell apoptosis was associated with significantly reduced pregnancy rates in patients with endometriosis or tubal-factor infertility undergoing IVF [67]. In an observational IVF study using natural cycles, the follicular phase was significantly longer and the fertilization rate was lower in patients with minimal to mild endometriosis compared with women with tubal factor and unexplained infertility [68]. Women with endometriosis were noted to have a slower follicular growth rate [53] and reduced dominant follicle size compared with women with unexplained infertility [69]. Trinder and Cahill also concluded that endometriosis patients have abnormal follicle development, ovulation, and luteal function [70]. Conversely, Mahmood et al. found that women with endometriosis did not experience significant differences in the duration of their follicular phase, and that dominant follicle development was not effected by the disease [71].

The increased DNA damage in sperm, oocytes, and the resultant embryos is proposed to be accountable for increased miscarriages and fertilization and implantation failures among endometriosis patients [60].

Amelioration of infertility associated with endometriosis has been investigated with medical and surgical therapeutic modalities, individually, and in combination. Medical treatments have uniformly been unsuccessful and the outcomes of surgical trials have been inconsistent. Two randomized controlled trials investigating the effects of surgical treatment of mild endometriosis yielded conflicting results [72, 73]. Studies on the surgical management of ovarian endometriomas before assisted reproduction also produced contradictory outcomes [74, 75]. The excessive ROS implicated in the pathogenesis of endometriosis-induced infertility may be a potential target for medical treatment of these patients.

9.5 Antioxidant Treatment of Endometriosis

Several studies have shown that the peritoneal fluid of women with endometriosis-associated infertility have insufficient antioxidant defense, with lower TAC and significantly reduced SOD levels [37, 39]. An early study used a simple rabbit model to demonstrate the beneficial effect of antioxidant therapy in halting progression of the disease [49]. SOD and catalase were instilled in the rabbit peritoneal cavity and were shown to significantly reduce the formation of intraperitoneal adhesions at endometriosis sites by blocking the toxic effects of the superoxide anion and hydrogen peroxide radicals [49]. An in vitro study by Foyouzi et al. was conducted to compare the effects of culturing endometrial stromal cells with antioxidants or with agents inducing oxidative stress. OS induced by hypoxanthine and xanthine oxidase was seen to stimulate endometrial

stromal proliferation and DNA synthesis. However, culture with antioxidants such as vitamin E, ebselen, and N-acetylcysteine was shown to inhibit proliferation of endometrial stromal cells in a dose-dependent manner [30].

Lifestyle factors such as inadequate dietary intake of antioxidants may contribute to the OS seen in women with endometriosis. Parazzini et al. reported a significant reduction in risk of endometriosis in women with a greater intake of green vegetables and fresh fruit [76]. Mier-Cabrera et al. conducted a study which reported that women with endometriosis have lower vitamin A, C, E, zinc, and copper intake compared to women without endometriosis. The application of a high antioxidant diet in women with endometriosis increased the peripheral concentration of vitamins A, C, and E after 3 months of intervention in comparison to the control diet group. The antioxidant diet also increased the peripheral enzymatic SOD and glutathione peroxidase activity after 3 months of intervention while decreasing the peripheral concentration of malondialdehyde and lipid hydroperoxides in women with endometriosis [77]. Westphal et al. studied the impact of a nutritional supplementation formula called FertilityBlend on the reproductive health of women who had unsuccessfully attempted to become pregnant for 6–36 months. After 5 months, 33 % of the women in the supplementation group were pregnant compared to 0 % in the placebo group. Therefore, dietary supplementation with antioxidants to alleviate OS may be an effective alternative to conventional fertility therapy [78].

Women with endometriosis are likely to be prescribed a number of empirical therapies. There is a rationale to support the use of antioxidants in these patients. The low cost and relatively low risk of toxicity of these compounds is appealing to both patients and clinicians. Several studies have examined the potential use of antioxidant supplementation to treat OS associated symptoms and complications in endometriosis.

9.5.1 Vitamin E and Vitamin C

The daily requirement of vitamin E varies from 50 to 800 mg, depending on the intake of fruits, vegetables, tea, or wine [79]. Vitamin E (a-tocopherol) is an important lipid-soluble antioxidant molecule in the cell membrane. It is thought to interrupt lipid peroxidation and enhance the activity of various antioxidants that scavenge free radicals generated during the univalent reduction of molecular oxygen and during the normal activity of oxidative enzymes [80, 81]. Vitamin E works synergistically with selenium as an antiperoxidant [82]. Compared with healthy fertile women, women with endometriosis have been shown to have a lower overall intake of vitamin E [83] as well as lower levels of vitamin E within their peritoneal fluid [45]. Afamin, a specific carrier protein of vitamin E in extravascular fluids, was found to be lower in women with endometriosis [84, 85]. A possible explanation of vitamin E deficient intake observed in women with endometriosis could be attributed to nutritional customs and behavioral habits,

such as decreased dietary consumption of nuts, wheat germ, sunflower seeds, and extra virgin olive oil [86]. Previous studies done in the US population have shown that only 8–11 % of men and 2–8 % of women meet the new estimated average requirement for vitamin E [87]. Given the strong association between vitamin E deficiency and endometriosis, its use as a supplement may be beneficial to patients with uncontrolled levels of oxidative stress. It is important to mention, however, that vitamin E should be used cautiously in women who are on anticoagulants, because it can have antiplatelet properties and daily intake should be limited to 400 IU or less [88, 89].

Vitamin C (ascorbic acid) is a water-soluble ROS scavenger with high potency. It protects the reproductive microenvironment against endogenous oxidative damage by neutralizing hydroxyl, alkolyl, peroxyl and superoxide anions, hydroperoxyl radicals, and reactive nitrogen radicals such as NO and peroxinitrite. Vitamin C and vitamin E are often prescribed in combination as they act synergistically, with vitamin C exerting its antioxidant function in the aqueous phase, scavenging radicals and regenerating the tocopheroxyl radical [24], whereas Vitamin E scavenges peroxide radicals in the hydrophobic phase of cellular lipid membranes and lipoproteins, protecting them from lipoperoxidation. In addition, Bruno et al. found that supplementation with vitamin C decreased plasma α-tocopherol disappearance rates in smokers [90].

However, this concept must be verified by further prospective controlled clinical studies in selected patients with endometriosis with identified raised markers of oxidative stress.

9.5.2 Pentoxifylline

Another drug being investigated for its potential use in the treatment of endometriosis-associated infertility is pentoxifylline, a 3′,5′-nucleotide phosphodiesterase inhibitor that raises intracellular cAMP and reduces inflammation by inhibiting TNF-a and leukotriene synthesis. Pentoxifylline has potent immunomodulatory properties and has been shown to significantly reduce the embryotoxic effects of hydrogen peroxide [91]. Zhang et al., conducted a recent randomized control trial in which pentoxifylline treatment failed to demonstrate significant reduction in endometriosis-associated symptoms such as pain. Furthermore, there was no evidence of an increase in the clinical pregnancy rates in the pentoxifylline group compared with placebo [92]. Currently, there is not enough evidence to warrant the use of pentoxifylline in the management of premenopausal women with endometriosis-associated pain and infertility.

9.5.3 Curcumin

Curcumin is a polyphenol derived from turmeric (Curcuma longa) with antioxidant, anti-inflammatory and antiproliferative properties. This compound has been shown to have an anti-endometriotic effect by targeting aberrant matrix remodeling in a mouse model. Matrix metalloproteinase-9 (MMP-9) levels are thought to positively correlate with the severity of endometriosis. In randomized controlled trials, curcumin treatment was seen to reverse MMP-9 activity in endometriotic implants near to control values. Furthermore, the anti-inflammatory property of curcumin was demonstrated by the fact that the attenuation of MMP-9 was accompanied by a reduction in cytokine release. Decreased expression of TNF-a was demonstrated during regression and healing of endometriotic lesions within the mouse model. Pretreatment of endometriotic lesions with curcumin has been shown to prevent lipid peroxidation and protein oxidation within the experimental tissue, attesting to its therapeutic potential to provide antioxidant defense against OS-mediated infertility in endometriosis [93].

9.5.4 Melatonin

MMP-9 also was identified as a therapeutic target for melatonin in the treatment of OS-mediated endometriosis in another study evaluating the effectiveness of melatonin in treating experimental endometriosis in a mouse model [94]. Melatonin is a major secretory product of the pineal gland with anti-oxidant properties that has been shown to arrest lipid peroxidation and protein oxidation, while downregulating MMP-9 activity and expression in a time and dose dependent manner. Tissue inhibitors of metalloproteinase (TIMP)-1 were found to be elevated in response to melatonin treatment. Regression of peritoneal endometriotic lesions was seen to accompany the alteration in metalloproteinase expression [94]. Guney et al. confirmed these findings in that treatment with melatonin was seen to cause regression and atrophy of endometriotic lesions in an experimental rat model [95]. Endometrial lesions treated with melatonin demonstrated lower MDA levels and significantly increased SOD and catalase activity [95], further substantiating the usefulness of this hormone to neutralizing endometriosis associated OS.

9.5.5 Green Tea

As previously mentioned, OS stimulates factors that increase VEGF expression and promote angiogenesis of endometriotic lesions. The green tea-containing compound, epigallocatechin gallate (EGCG) has been evaluated as a treatment for

endometriosis due to its powerful antioxidant and anti-angiogenic properties. Xu et al. conducted a study in which eutopic endometrium transplanted subcutaneously into a mouse model was used to compare the effects of EGCG treatment on endometriotic implants to the effects seen with vitamin E treatment or untreated controls [96]. Lesions treated with EGCG were seen to have significantly downregulated levels of VEGF-A mRNA. While the control endometrial implants exhibited newly developed blood vessels with proliferating glandular epithelium, the EGCG group demonstrated significantly smaller endometriotic lesions and smaller and more eccentrically distributed glandular epithelium. Despite its widely studied benefits as a potent antioxidant in the treatment of female infertility, vitamin E was not shown to control or decrease angiogenesis compared with baseline controls [96]. As EGCG was shown to significantly inhibit the development of experimental endometriotic lesions in a mouse model, its effectiveness as an oral therapy in female patients to limit progression and induce remission of their endometriosis should be further investigated.

9.5.6 Other

Treatment with an iron chelator could be beneficial in the case of endometriosis to prevent iron overload in the pelvic cavity [97], thereby diminishing the deleterious effects of the resulting OS. However, in women suffering from endometriosis, menstrual periods are often longer and heavier [98]. Sanfilippo et al. and cycles tend to be shorter [99]. Therefore, iron overload observed in these patients is generally localized in the pelvic cavity, whereas body iron content may actually be decreased due to abundant menstruation. For this reason, iron chelator treatment may only be helpful if applied locally, within the peritoneal cavity, by means of intrapelvic implants that release deferoxamine over several months or years.

Guney et al. evaluated caffeic acid phenethyl ester (CAPE), an active component of propolis from honeybee hives that is known to have antimitogenic, anticarcinogenic, antiinflammatory, and immunomodulatory properties. The effect of this compound on experimental endometriosis in a rat model, and the levels of peritoneal SOD and catalase activity, and MDA [100]. Treatment with CAPE was seen to decrease peritoneal MDA levels and antioxidant enzyme activity in rats. Endometriotic lesions treated with CAPE were histologically demonstrated to undergo atrophy and regression, compared with untreated controls [100].

Medical treatments which modulate the hormonal imbalances associated with endometriosis may also have an antioxidant mechanism of action. More recently, mifepristone (RU486)- a potent antiprogestational agent with antioxidant activity, was shown to effectively decrease the proliferation of epithelial and stromal cells in endometriosis [101].

9.6 Conclusion

ROS have been shown to have an important role in the normal functioning of the reproductive system and in the pathogenesis of infertility in females and is thought to play a role in the pathogenesis of endometriosis. Although many studies have investigated the factors that might be involved in the development of different stages of endometriosis, the precise mechanism by which this disease is established remains unclear. Decreased antioxidant protection within the peritoneal fluid of patients with endometriosis may render the reproductive tract more susceptible to damage by OS. The identification of highly sensitive and specific markers of oxidative stress in peritoneal fluid, serum, and tissue biopsies may facilitate the development of reliable non-invasive techniques for endometriosis diagnosis and prognosis. At present, there are many medical or surgical interventions for treating endometriosis. A multidisciplinary and integrative approach may offer expanded therapeutic solutions for this disorder. Endometriosis is associated with hormonal, chemical, and immunologic that may affect ovulation and oocyte quality, tubal function, sperm function, fertilization, and implantation. A greater understanding of these mechanisms is necessary to develop noninvasive methods of detection and diagnosis and to shift from surgical management of disease to medical treatment options.

Further studies to evaluate the effects of ROS and antioxidants on endometrial implants and on endometrial epithelial cells both in vitro and in vivo may provide a basis for clinical use of antioxidants in the treatment of endometriosis. However, the current data evaluating antioxidant supplements is derived from randomised controlled trials that often differ in terms of the selection of the control population, eligibility criteria, markers of OS and antioxidant status and the biological medium in which OS markers were measured, making it difficult to come to a definitive conclusion. Dietary supplements with antioxidants may be a potential strategy in the long-term treatment of endometriosis that is better accepted by patients due to increased cost-effectiveness and lower risk of toxicity. Future research should be directed towards implementing robust, large scale, randomized controlled trials in order to determine the efficacy, safety profiles, and effective doses of specific therapeutic regimens.

References

1. Snesky TE, Liu DT (1980) Endometriosis: associations with menorrhagia, infertility, and oral contraceptives. Int J Gynaecol Obstet 17:573–576
2. Cramer DW (1987) Epidemiology of endometriosis in adolescents. In: Wilson EA (ed) Endometriosis, vol 1. Alan Liss, New York, pp 5–8
3. Giudice L, Kao L (2004) Endometriosis. Lancet 364:1789–1799
4. Koninckx PR (1999) The physiopathology of endometriosis: pollution and dioxin. Gynecol Obstet Invest 47:47–49

5. Donnez J, Chantraine F, Nisolle M (2002) The efficacy of medical and surgical treatment of endometriosis-associated infertility: arguments in favour of a medico-surgical approach. Hum Reprod Update 8:89–94
6. Nisolle M, Donnez J (1997) Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. Fertil Steril 68:585–596
7. Van Langendonckt A, Casanas-Roux F, Dolmans MM, Donnez J (2002) Potential involvement of hemoglobin and heme in the pathogenesis of peritoneal endometriosis. Fertil Steril 77:561–570
8. Heilier JF, Donnez J, Lison D (2008) Organochlorines and endometriosis: a mini-review. Chemosphere 71:203–210
9. Halme J, Hammond MG, Hulka JF, Raj SG, Talbert LM (1984) Retrograde menstruation in healthy women and in patients with endometriosis. Obstet Gynecol 64:151–154
10. Nap AW, Groothuis PG, Demir AY, Evers JL, Dunselman GA (2004) Pathogenesis of endometriosis. Best Pract Res Clin Obstet Gynaecol 18:233–244
11. Van Langendonckt A, Casanas-Roux F, Donnez J (2002) Iron overload in the peritoneal cavity of women with pelvic endometriosis. Fertil Steril 78:712–718
12. Yamaguchi K, Mandai M, Toyokuni S, Hamanishi J, Higuchi T, Takakura K, Fujii S (2008) Contents of endometriotic cysts, especially the high concentration of free iron, are a possible cause of carcinogenesis in the cysts through the iron-induced persistent oxidative stress. Hum Cancer Biol 14(1):32–40
13. Templeton DM, Liu Y (2003) Genetic regulation of cell function in response to iron overload or chelation. Biochim Biophys Acta 1619:113–124
14. Lachapelle MH, Hemmings R, Roy DC, Falcone T, Miron P (1996) Flow cytometric evaluation of leukocyte subpopulations in the follicular fluids of infertile patients. Fertil Steril 65:1135–1140
15. Seli E, Arici A (2003) Endometriosis: interaction of immune and endocrine systems. Semin Reprod Med 21:135–144
16. Pellicer A, Albert C, Mercader A, Bonilla-Musoles F, Remohi J, Simon C (1998) The follicular and endocrine environment in women with endometriosis: local and systemic cytokine production. Fertil Steril 70:425–431
17. Garrido N, Navarro J, Remohi J, Simon C, Pellicer A (2000) Follicular hormonal environment and embryo quality in women with endometriosis. Hum Reprod Update 6:67–74
18. Wunder DM, Mueller MD, Birkhauser MH, Bersinger NA (2006) Increased ENA-78 in the follicular fluid of patients with endometriosis. Acta Obstet Gynecol Scand 85:336–342
19. Bedaiwy MA, Falcone T, Sharma RK, Goldberg JM, Attaran M, Nelson DR, Agarwal A (2002) Prediction of endometriosis with serum and peritoneal fluid markers: a prospective controlled trial. Hum Reprod 17:426–431
20. Darai E, Detchev R, Hugol D, Quang NT (2003) Serum and cyst fluid levels of interleukin (IL) -6, IL-8 and tumour necrosis factor-alpha in women with endometriomas and benign and malignant cystic ovarian tumours. Hum Reprod 18:1681–1685
21. Ulukus M, Ulukus EC, Seval Y, Zheng W, Arici A (2005) Expression of interleukin-8 receptors in endometriosis. Hum Reprod 20:794–801
22. Agarwal A, Gupta S (2005) Role of reactive oxygen species in female reproduction. Part I. Oxidative stress: a general overview. Women Health 1:21–25
23. de Lamirande E, Gagnon C (1995) Impact of reactive oxygen species on spermatozoa: a balancing act between beneficial and detrimental effects. Hum Reprod 10:15–21
24. Alul RH, Wood M, Longo J, Marcotte AL, Campione AL, Moore MK, Lynch SM (2003) Vitamin C protects low-density lipoproteins from homocysteine-mediated oxidation. Free Radic Biol Med 34(7):881–891
25. Olek RA, Ziolkowski W, Kaczor JJ, Greci L, Popinigis J, Antosiewicz J (2004) Antioxidant activity of NADH and its analogue—an in vivo study. J Biochem Mol Biol 37:416–421

26. Reubinoff BE, Har-El R, Kitrossky N, Friedler S, Levi R, Lewin A, Chevion M (1996) Increased levels of redox-active iron in follicular fluid: a possible cause of free radical mediated infertility in beta-thalassemia major. Am J Obstet Gynecol 174(3):914–918
27. Arumugam K, Yip YC (1995) De novo formation of adhesions in endometriosis: the role of iron and free radical reactions. Fertil Steril 64(1):62–64
28. Murphy AA, Palinski W, Rankin S, Morales AJ, Parthasarathy S (1998) Evidence for oxidatively modified lipid-protein complexes in endometrium and endometriosis. Fertil Steril 69(6):1092–1094
29. Donnez J, Van Langendonckt A, Casanas-Roux F et al (2002) Current thinking on the pathogenesis of endometriosis. Gynecol Obstet Invest 54(Suppl 1):52–58. Discussion 9–62
30. Foyouzi N, Berkkanoglu M, Arici A, Kwintkiewicz J, Izquierdo D, Duleba AJ (2004) Effects of oxidants and antioxidants on proliferation of endometrial stromal cells. Fertil Steril 82(3):1019–1022
31. Park JK, Song M, Dominguez CE, Walter MF, Santanam N, Parthasarathy S, Murphy AA (2006) Glycodelin mediates the increase in vascular endothelial growth factor in response to oxidative stress in the endometrium. Am J Obstet Gynecol 195(6):1772–1777
32. Wu Y, Kajdacsy-Balla A, Strawn E, Basir Z, Halverson G, Jailwala P, Wang Y, Wang X, Ghosh S, Guo SW (2006) Transcriptional characterizations of differences between eutopic and ectopic endometrium. Endocrinology 147(1):232–246
33. Seo SK, Yang HI, Lee KE, Kim HY, Cho S, Choi YS, Lee BS (2010) The roles of thioredoxin and thioredoxin-binding protein-2 in endometriosis. Hum Reprod 25(5):1251–1258
34. Zeller JM, Henig I, Radwanska E, Dmowski WP (1987) Enhancement of human monocyte and peritoneal macrophage chemiluminescence activities in women with endometriosis. Am J Reprod Immunol Microbiol 13:78–82
35. Ota H, Igarashi S, Tanaka T (2001) Xanthine oxidase in eutopic and ectopic endometrium in endometriosis and adenomyosis. Fertil Steril 75:785–790
36. Saito H, Seino T, Kaneko T, Nakahara K, Toya M, Kurachi H (2002) Endometriosis and oocyte quality. Gynecol Obstet Invest 53(1):46–51
37. Szczepanska M, Kozlik J, Skrzypczak J, Mikolajczyk M (2003) Oxidative stress may be a piece in the endometriosis puzzle. Fertil Steril 79:1288–1293
38. Gupta S, Agarwal A, Krajcir N, Alvarez JG (2006) Role of oxidative stress in endometriosis. Reprod Biomed Online 13(1):126–134
39. Polak G, Koziol-Montewka M, Gogacz M, Blaszkowska I, Kotarski J (2001) Total antioxidant status of peritoneal fluid in infertile women. Eur J Obstet Gynecol Reprod Biol 94(2):261–263
40. Dong M, Shi Y, Cheng Q, Hao M (2001) Increased nitric oxide in peritoneal fluid from women with idiopathic infertility and endometriosis. J Reprod Med 46:887–891
41. Lambrinoudaki IV, Augoulea A, Christodoulakos GE, Economou EV, Kaparos G, Kontoravdis A, Papadias C, Creatsas G (2009) Measurable serum markers of oxidative stress response in women with endometriosis. Fertil Steril 91(1):46–50
42. Wang Y, Sharma RK, Falcone T, Goldberg J, Agarwal A (1997) Importance of reactive oxygen species in the peritoneal fluid of women with endometriosis or idiopathic infertility. Fertil Steril 68:826–830
43. Ho HN, Wu MY, Chen SU, Chao KH, Chen CD, Yang YS (1997) Total antioxidant status and nitric oxide do not increase in peritoneal fluids from women with endometriosis. Hum Reprod 12:2810–2815
44. Ota H, Igarashi S, Hatazawa J, Tanaka T (1999) Endometriosis and free radicals. Gynecol Obstet Invest 48:29–35
45. Murphy AA, Santanam N, Morales AJ, Parthasarathy S (1998) Lysophosphatidyl choline, a chemotactic factor for monocytes/T-lymphocytes is elevated in endometriosis. J Clin Endocrinol Metabol 83:2110–2113

46. Ota H, Igarashi S, Hatazawa J, Tanaka T (1999) Immunohistochemical assessment of superoxide dismutase expression in the endometrium in endometriosis and adenomyosis. Fertil Steril 72:129–134
47. Ota H, Igarashi S, Kato N, Tanaka T (2000) Aberrant expression of glutathione peroxidase in eutopic and ectopic endometrium in endometriosis and adenomyosis. Fertil Steril 74:313–318
48. Jackson L, Schisterman E, Day-Rao R, Browne R, Armstrong D (2005) Oxidative stress and endometriosis. Hum Reprod 20:2014–2020
49. Portz DM, Elkins TE, White R, Warren J, Adadevoh S, Randolph J (1991) Oxygen free radicals and pelvic adhesion formation: I. Blocking oxygen free radical toxicity to prevent adhesion formation in an endometriosis model. Int J Fertil 36:39–42
50. ASRM (2004) Endometriosis and infertility. Fertil Steril 82(1):S40–S45
51. Mahutte NG, Arici A (2002) New advances in the understanding of endometriosis related infertility. J Reprod Immunol 55:73–83
52. Alpay Z, Saed GM, Diamond MP (2006) Female infertility and free radicals: potential role in adhesions and endometriosis. J Soc Gynecol Investig 13(6):390–398
53. Doody MC, Gibbons WE, Buttram VC Jr (1988) Linear regression analysis of ultrasound follicular growth series: evidence for an abnormality of follicular growth in endometriosis patients. Fertil Steril 49:47–51
54. Grant A (1966) Additional sterility factors in endometriosis. Fertil Steril 17:514–519
55. Wardle PG, Mitchell JD, McLaughlin EA, Ray BD, McDermott A, Hull MG (1985) Endometriosis and ovulatory disorder: reduced fertilisation in vitro compared with tubal and unexplained infertility. Lancet 2:236–239
56. Garrido N, Navarro J, Garcia-Velasco J, Remoh J, Pellice A, Simon C (2002) The endometrium versus embryonic quality in endometriosis-related infertility. Hum Reprod Update 8:95–103
57. Osborn B, Haney AF, Misukonis M, Weinberg JB (2002) Inducible nitric oxide synthase expression by peritoneal macrophages in endometriosis-associated infertility. Fertil Steril 77:46–51
58. Curtis P, Lindsay P, Jackson AE, Shaw RW (1993) Adverse effects on sperm movement characteristic in women with minimal and mild endometriosis. Br J Obstet Gynaecol 100:165–169
59. Oak MK, Chantler EN, Wiliams CA, Elstein M (1985) Sperm survival studies in peritoneal fluid from infertile women with endometriosis and unexplained infertility. Clin Reprod Fertil 3:297–303
60. Mansour G, Aziz N, Sharma R, Falcone T, Goldberg J, Agarwal A (2009) The impact of peritoneal fluid from healthy women and from women with endometriosis on sperm DNA and its relationship to the sperm deformity index. Fertil Steril 92:61–67
61. Mansour G, Agarwal A, Radwan E, Sharma R, Goldberg J, Falcone T (2007) DNA damage in metaphase II oocytes is induced by peritoneal fluid from endometriosis patients. ASRM 63rd annual meeting
62. Mansour G, Radwan E, Sharma R, Agarwal A, Falcone T, Goldberg J (2007) DNA damage to embryos incubated in the peritoneal fluid of patients with endometriosis: role in infertility. ASRM 63rd annual meeting
63. Agarwal A, Gupta S, Sikka S (2006) The role of free radicals and antioxidants in reproduction. Curr Opin Obstet Gynecol 18:325–332
64. Polak G, Rola R, Gogacz M, Koziol-Montewka M, Kotarski J (1999) Malonyldialdehyde and total antioxidant status in the peritoneal fluid of infertile women. Ginecol PII 70:135–140
65. Toya M, Saito H, Ohta N, Saito T, Kaneko T, Hiroi M (2000) Moderate and severe endometriosis is associated with alterations in the cell cycle of granulosa cells in patients undergoing in vitro fertilization and embryo transfer. Fertil Steril 73:344–350
66. Nakahara K, Saito H, Saito T, Ito M, Ohta N, Sakai N et al (1997) Incidence of apoptotic bodies in membrana granulosa of the patients participating in an in vitro fertilization program. Fertil Steril 67:302–308

67. Sifer C, Benifla JL, Bringuier AF, Porcher R, Blanc-Layrac G, Madelenat P, Feldman G (2002) Could induced apoptosis of human granulosa cells predict in vitro fertilization-embryo transfer outcome? A preliminary study of 25 women. Eur J Obstet Gynecol Reprod Biol 103:150–153
68. Cahill DJ, Wardle PG, Maile LA, Harlow CR, Hull MG (1997) Ovarian dysfunction in endometriosis-associated and unexplained infertility. J Assist Reprod Genet 14:554–557
69. Tummon IS, Maclin VM, Radwanska E, Binor Z, Dmowski WP (1988) Occult ovulatory dysfunction in women with minimal endometriosis or unexplained infertility. Fertil Steril 50:716–720
70. Trinder J, Cahill DJ (2002) Endometriosis and infertility: the debate continues. Hum Fertil 5:S21–S27
71. Mahmood TA, Templeton A (1991) Folliculogenesis and ovulation in infertile women with mild endometriosis. Hum Reprod 6:227–231
72. Marcoux S, Maheux R, Berube S (1997) Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian collaborative group on endometriosis. N Engl J Med 337:217–222
73. Parazzini F (1999) Ablation of lesions or no treatment in minimal–mild endometriosis in infertile women: a randomized trial. Gruppo Italiano per lo Studio dell'Endometriosi. Hum Reprod 14:1332–1334
74. Garcia-Velasco JA, Arici A (2004) Surgery for the removal of endometriomas before in vitro fertilization does not increase implantation and pregnancy rates. Fertil Steril 81:1206
75. Suzuki T, Izumi S, Matsubayashi H, Awaji H, Yoshikata K, Makino T (2005) Impact of ovarian endometrioma on oocytes and pregnancy outcome in in vitro fertilization. Fertil Steril 83:908–913
76. Parazzini F, Chiaffarino F, Surace M, Chatenoud L, Cipriani S, Chiantera V et al (2004) Selected food intake and risk of endometriosis. Hum Reprod 19:1755–1759
77. Mier-Cabrera J, Genera-Garcia M, De la Jara-Diaz J, Perichart-Perera O, Vadillo-Ortega F, Hernandez-Guerrero C (2008) Effect of vitamins C and E supplementation on peripherals oxidative stress markers and pregnancy rate in women with endometriosis. Int J Gynecol Obstet 100:252–256
78. Westphal LM, Polan ML, Trant AS, Mooney SB (2004) A nutritional supplement for improving fertility in women: a pilot study. J Reprod Med 49:289–293
79. National Academy of Sciences (1989) Recommended dietary allowances. 10th edn. National Academy Press, Washington
80. Ehrenkranz R (1980) Vitamin E and the neonate. Am J Dis Child 134:1157–1168
81. Palamanda JR, Kehrer JR (1993) Involvement of vitamin E and protein thiols in the inhibition of microsomal lipid peroxidation by glutathione. Lipids 28:427–431
82. Burton GW, Traber MG (1990) Vitamin E: antioxidant activity, biokinetics, and bioavailability. Annu Rev Nutr 10:357–382
83. Hernandez-Guerrero CA, Bujalil-Montenegro L, De la Jara-Diaz J, Mier-Cabrera J, Bouchan-Valencia P (2006) Endometriosis and deficient intake of antioxidant molecules related to peripherals and peritoneal oxidative stress. Ginecol Obstet Mex 74:20–28
84. Jackson D, Craven RA, Hutson RC, Graze I, Lueth P, Tonge RP, Hartley JL, Nickson JA, Rayner SJ, Johnston C, Dieplinger B, Hubalek M, Wilkinson N, Perren TJ, Kehoe S, Hall GD, Daxenbichler G, Dieplinger H, Selby PJ, Banks RE (2007) Proteomic profiling identifies afamin as a potential biomarker for ovarian cancer. Clin Cancer Res 13:7370–7379
85. Dieplinger H, Ankerst DP, Burges A, Lenhard M, Lingenhel A, Fineder L, Buchner H, Stieber P (2009) Afamin and apolipoprotein A-IV: novel protein markers for ovarian cancer. Cancer Epidemiol Biomarkers Prev 18:1127–1133
86. de Muñoz CM, Antonio RJ, Angel LJ, Eduardo M, Adolfo C, Fernando P-G, Sonia H, Alejandra C (1996) Tablas de valor nutritivo de los alimentos. Editorial Pax México, México D.F.

87. Gao X, Martin A, Lin H, Bermudez OI, Tucker KL (2006) α-tocopherol intake and plasma concentrations of hispanic and non-hispanic white elders is associated with dietary intake patters. J Nutr 136:2574–2579
88. Dennehy CE (2006) The use of herbs and dietary supplements in gynecology: an evidence-based review. J Midwifery Womens Health 51:402–409
89. Ziaei S, Faghihzadeh S, Sohrabvand F, Lamyian M, Emamgholy T (2001) A randomised placebo-controlled trial to determine the effect of vitamin E in treatment of primary dysmenorrhoea. Br J Obstet Gynecol 108:1181–1183
90. Bruno RS, Leonard SW, Atkinson J, Montine TJ, Ramakrishnan R, Bray TM, Traber MG (2006) Faster plasma vitamin E disappearance in smokers is normalized by vitamin C supplementation. Free Radic Biol Med 40:689–697
91. Zhang X, Sharma RK, Agarwal A, Falcone T (2005) Effect of pentoxifylline in reducing oxidative stress-induced embryotoxicity. J Assist Reprod Genet 22(11–12):415–417
92. Lv D, Song H, Clarke J, Shi G (2009) Pentoxifylline versus medical therapies for subfertile women with endometriosis. Cochrane Database Syst Rev 8(3):CD007677
93. Swarnaker S, Paul S (2009) Curcumin arrests endometriosis by downregulation of matrix metalloproteinase-9 activity. Indian J Biochem Biophys 46(1):59–65
94. Paul S, Sharma AV, Mahapatra PS, Bhattacharya P, Reiter RJ, Swarnakar S (2008) Role of melatonin in regulating matrix metalloproteinase-9 via tissue inhibitors of metalloproteinase-1 during protection against endometriosis. J Pineal Res 44(4):439–449
95. Guney M, Oral B, Karahan N, Mungan T (2008) Regression of endometrial explants in a rat model of endometriosis treated with melatonin. Fertil Steril 89(4):934–942
96. Xu H, Liu WT, Chu CY, Ng PS, Wang CC, Rogers MS (2009) Antiangiogenic effects of green tea catechin on an experimental endometriosis mouse model. Hum Reprod 24(3):608–618
97. Defre're S, Van Langendonckt A, Vaesen S, Jouret M, Gonza′lez Ramos R, Gonzalez D, Donnez J (2006) Iron overload enhances epithelial cell proliferation in endometriotic lesions induced in a murine model. Hum Reprod 21:2810–2816
98. Sanfilippo JS, Wakim NG, Schikler KN, Yussman MA (1986) Endometriosis in association with uterine anomaly. Am J Obstet Gynecol 154:39–43
99. Arumugam K, Lim JM (1997) Menstrual characteristics associated with endometriosis. Br J Obstet Gynaecol 104:948–950
100. Guney M, Nasir S, Oral B, Karahan N, Mungan T (2007) Effect of caffeic acid phenethyl ester on the regression of endometrial explants in an experimental rat model. Reprod Sci 14(3):270–279
101. Murphy AA, Zhou MH, Malkapuram S, Santanam N, Parthasarathy S, Sidell N (2000) RU486-induced growth inhibition of human endometrial cells. Fertil Steril 71:1014–1019