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Review Article

What Does Diagnosis of Endometriosis Mean? The Patient's Perspective

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Abstract

Endometriosis is a gynecological disease, which causes significant physiological pain but also psychological distress leading to decreased quality of life for those afflicted with the disease. Though researchers have investigated this disease for over 90 years, there is still much information unknown about its pathophysiology, hence impeding the development of effective treatment options. In addition, the difficulty to diagnose the disease using non-invasive measures increases the prevalence of this disease among reproductive aged women. This review discusses the challenges that the scientific and medical communities endure combating endometriosis along with the social and financial burdens of patients whom suffer from endometriosis. Finally this review highlights the positive and negative side effects of current treatment options, discusses some alternative treatment and new potential treatment options that have shown variable success in reducing the symptoms associated with endometriosis.

Keywords: Endometriosis; Diagnosis; Quality of life; Treatment

Endometriosis-What Is It?

Endometriosis is a benign gynecological disease that globally affects an estimated 10-15% of reproductively aged women [1]. In women experiencing sub- or infertility, the prevalence of endometriosis increases to 50% [2]. Endometriosis is pathologically defined as the development of endometrial glands and stromal cells outside of the uterus, but this definition has broadened to include the development of any endometrial cell type (glands or stroma) outside of the uterus [3]. The development of endometriotic lesions induces a wide variety of symptoms with the most reported being that of chronic pelvic pain [4,5] and infertility [6]. Endometriotic lesions develop primarily in the pelvic region on the outer lining of abdominal organs, but have also been associated with pulmonary conditions [7].

Pathogenic origination of endometriosis has many different theories, including; coelomic metaplasia (metaplastic change in the coelomic epithelium covering peritoneum and reproductive organs) and Mullerian remnant abnormalities (aberrant differentiation and migration of Mullerian originated cells). The most widely accepted theory for pathogenic origination of endometriosis is that of retrograde menstruation (ejection of endometrial fragments from the Fallopian tubal openings during menstruation) followed by implantation of endometrial stem cell niches contained within the shed endometrial fragments (reviewed in [8,9]). However, retrograde menstruation occurs in nearly 70 percent of all reproductively active women and the prevalence of symptomatic endometriosis is only 10-15%. Therefore, pathogenesis of endometriosis must also involve hereditary genetic traits and/or also immune dysfunction leading to improper clearance of menstrual tissue within the abdominal cavity (reviewed in [8]). Identification of factors involved with the pathogenesis of endometriosis is currently the topic of several research investigations. Discovery of pathogenic factors could lead to the development of robust screening tools for diagnosis and novel therapeutic interventions for treatment of endometriosis.

Economic Impact

There is a huge impact of the diagnosis and treatment of endometriosis on the medical economy in both US and Canada and these rates continue to rise even though surgical technologies are improving. The average in-patient medical cost for laparoscopic intervention in 2004 was $3,721 vs $4,300 in 2007 [10,11]. This cost increased dramatically for patients whom had hysterectomies, which are performed on almost 20% of patients who have endometriosis, to $11,400 in 2007. The medical costs associated with pharmaceutical intervention of gonadotropin releasing hormone (GnRH) therapies are similar to costs associated with surgical intervention, approximately $4,400 for a 6-month course of GnRH treatment [12]. This study also reported that reoccurrence of disease was >50% in patients receiving GnRH therapy vs surgical intervention. There is a critical need to develop more effective diagnostic tests and treatment options for patients who have endometriosis to alleviate this financial burden on our medical economy.

How to Diagnose?

Although there have been considerable advancements in imaging technology utilized in pathophysiology of several disease states, there is no current non-invasive imaging technology that can definitively detect the growth of endometriotic lesions. Rather imaging technology has been effective for providing aid in surgical visualization of suspected lesions and adhesions [13,14]. One reason for the insufficiency of imaging technology to detect endometriotic lesions is due to the ability of the lesions to activate wound-healing mechanisms immediately following the attachment of the endometrial tissue fragments to the peritoneal surface of abdominal organs [15,16]. This "cloaking" mechanism nearly renders it impossible for imaging technology to discern normal tissue or scar tissue from an endometriotic lesion. Therefore, laparoscopic evaluation and excision followed by histological confirmation is the gold standard for diagnosis of endometriosis. The accuracy of histological confirmation of the presence of endometriotic lesions is highly dependent upon surgical determination and excision of suspected endometriotic lesions and pathological expertise in

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confirmation of the diagnosis [3]. At the time of laparoscopic evaluation the surgeon is able to categorize the patient's severity of disease into one of four different stages (rASRM guidelines) [17]. Briefly, Stage 1 (minimal) classification entails superficial peritoneal and ovarian lesions with minor peritoneal adhesions, Stage 2 (mild): deep peritoneal lesions and superficial ovarian lesions on both ovaries, Stage 3 (Moderate): deep peritoneal and ovarian lesions with lesions found in the culdesac region or involvement of the fallopian tubes, and Stage 4 (Severe): dense adhesions involving fallopian tubes, deep peritoneal and ovarian lesions with adhesions and involvement of adhesions/lesions in the culdesac. Factors that influence disease staging are lesion location, number and depth of invasion. Other factors that influence staging assignment are the amount of scar tissue and/or adhesions that have formed in the pelvic cavity and if the patient has ovarian endometriosis, or endometriomas. Because the rASRM guidelines do not distinguish different types of disease pathologies (i.e., Deeply infiltrating endometriosis or retroperitoneal endometriosis) another classification system ENZIAN has been developed to be used in conjunction with the rASRM guidelines for proper classification of disease [18]. This revised system classifies lesion size and presence in 3 different regions (rectovaginal space/vagina), (sacrouterine/cardinal ligaments, pelvic sidewall and external ureter compression) and (lower bowel, rectum/sigmoid). But the ENZIAN classification does not consider ovarian disease. While the utilization of these two classification guidelines help differentiate surgical intervention strategies utilized for treatment of endometriosis, these guidelines do not help with understanding the chronic pelvic pain and subfertility induced by presence of minimal and moderate (Stage 2 and 3, respectively) endometriotic lesions [19]. Therefore recently another classification system called EFI, which builds open the rASRM guidelines but takes into account fertility success, has been utilized to guide clinical treatment for patients suffering from endometriosis associated infertility [20]. The most important factor for treatment success is overcoming the delay from origination of disease to diagnosis.

Delay to Diagnosis

The responsibility of the delay in proper diagnosis of endometriosis can be shared between both the patient and the clinician. Most women will wait an average of 2.1 years before seeking medical attention for endometriosis [21]. On the other hand clinicians will contribute to this delay period by almost 3.4 years before a conclusive diagnosis of endometriosis is made [21]. What is the reason behind this prolonged delay in diagnosis? One reason is that the development of endometriotic lesions impacts a multitude of physiological systems (gastrointestinal, urology, neuronal, and pulmonary), and making an accurate and early diagnosis of endometriosis is unlikely with typical clinical workups. There is no biomarker, routine blood test, genetic test or imaging technology that can diagnose endometriosis. The second problem is getting patients who have endometriosis treated by the "appropriate" clinician. Finding the appropriate physician is difficult because of the clinical presentation of disease symptoms. Clinical presentations of patients who have endometriosis typically are complaints of chronic pelvic pain, painful urination, pain during menstruation, painful bowel movements and pain during sexual intercourse. In routine medical care, patients usually would present these symptoms to a family or general medicine practitioner instead of a gynecologist. A general medicine practitioner's differential work up would include: possible gastrointestinal disorder, possible urinary tract infection and possible psychological disorder (i.e., depression). Upon further evaluation and results from imaging or laboratory tests, the patient may be referred to a gynecologist or may simply be advised to begin non-steroidal anti-inflammatory drugs (NSAIDS) or oral contraception pills (OCPs). The diagnostic work up and decision of treatment options differs depending if a patient who has endometriosis is under the medical care of a general practitioner or a gynecologist [11]. Patients under the medical care of a gynecologist are more likely to undergo exploratory laparoscopic surgery and excisional removal of lesions followed by endocrine disruptors such as GnRH antagonists than those patients seen by a general practitioner. The decision of medical care is therefore critical to early diagnosis and treatment of disease and shortening the time from onset to acute symptoms associated with endometriosis.

Impact on Quality of Life

Symptoms associated with endometriosis negatively impact the patient's quality of life both personally and professionally. As stated previously, reoccurrence of disease in patients receiving treatment for endometriosis can be as high as 50% in as little as one year after stopping treatment or surgical intervention [12]. The regrowth of endometriotic lesions is coupled with a resurgence of the chronic pelvic pain and multitude of other negative symptoms associated with disease and once again the patient is forced with the decision on what therapeutic option to endure. This "roller coaster" effect of treatment strategies and chronic pelvic pain, not to mention fertility complications, renders patients to increasing levels of anxiety, depression and exhaustion [4,22,23]. The hopelessness of an effective treatment and the ongoing duration of chronic pelvic pain impact not only the patient's personal life and social relationships, but also frequently spill over into a patient's professional life. Understanding endometriosis from the psychological aspect has intrigued both clinicians and researchers because of how we now know "stress" positively impacts the pathophysiology of endometriosis by decreasing a patient's immune clearance of endometrial lesions [24].

The vicious circle between chronic pain and the development of psychological disorders in patients with endometriosis results in decreased quality of life self-assessments. Recently it was reported that almost 50% of women studied with endometriosis had decreased social relationships than women without endometriosis [21,25]. How does endometriosis have such a negative impact on a woman's' quality of life? Several factors contribute to decreased quality of life in women with endometriosis, making the impact of endometriosis multi-factorial.

First, women with endometriosis can have severe chronic pelvic pain, which results in missed social interactions due to bed-rest and restricted mobility. Nnoaham et al. [4] reported in a multi-center study across ten countries, that women affected with endometriosis had reduced physical activity and limitation in both physical and mental health. This reduction of physical and mental health and reduced sexual satisfaction supports findings that 34% of women with endometriosis have impaired social and intimate relationships and 19% of these women attribute their disease with the reason for their marital divorce [4,21]. Although it has not been reported, it is logical to predict that women with endometriosis would also have impaired care-giving relationships (i.e., parenting or caring for an elderly relative) due to their own physical and emotional battle with depression and anxiety.

Second, women with endometriosis also have a significant decrease in work productivity due to both work absences and also reduced function in the workplace. Nearly one out of every two women with endometriosis has reported decreased work productivity because of the severity of symptoms from endometriosis [6]. Of these women whom have reduced work productivity, over one third of them attribute this reduction to loss in efficiency and impaired work activity [6]. This decreased work productivity results in a loss of approximately 10.8 hours per week at a cost of $250 per week for the employer [4].

Compounding this problem is that women with endometriosis also feel or perceive themselves as having a decreased sense of "worth" due to their decreased work productivity. They may feel guilty for missing work or not being able to fulfill career goals and they perceive themselves as a "weak" co-worker thus creating a negative impression on workplace relationships. These perceptions ultimately result in an overall increase in frustration and add to the already mounting anxiety in women with endometriosis.

Third, nearly 45% of women with endometriosis also suffer from sub-or infertility [2]. The direct cause for sub- or infertility in women with endometriosis is very complex. Women with endometriosis have disrupted folliculogenesis, decreased follicles and altered steroidogenesis (reviewed in [26,27]). Endometriosis that forms directly on the epithelial surface of the ovary (endometriomas) can also cause a reduction in oocyte quality, ovulation dysfunction and ultimately impact the ovarian oocyte reserve, thus limiting number of successful ovulations (reviewed in [28]). Adhesion formation in the pelvic cavity as a result of the growth of endometriotic lesions results in a physical distortion of the reproductive organs and oocyte pick-up and transfer from the ovary through the oviduct (fallopian tube) is compromised. Women with endometriosis also have impaired embryo development and improper endometrial receptivity, which result in lower implantation rates and higher early pregnancy loss [29]. Medical intervention strategies commonly utilized for the treatment of endometriosis-associated infertility is the surgical excision of endometriotic lesions. Surgical intervention has been shown to improve fecundity rates [30,31] and *in-vitro* fertilization (IVF) success rates [32]. Women who are not successful in conception or carrying a pregnancy to term after exhausting all treatment options have an enormous burden of personal and social pressure and many suffer from increased anxiety and other psychological disorders [33,34]. Internationally, women whom suffer from infertility have even greater social pressures and can be seen as an outcast or have less societal valued [35].

Finally, treatment options for endometriosis are stressful and cause very negative side effects. Women with endometriosis undergo more surgeries compared to women without endometriosis, approximately 60% of all women with endometriosis will undergo laparoscopic surgery and 7% will undergo laparotomy [21]. Surgical intervention elevates patient stress levels because of risks associated with the surgical procedure, fear of anesthesia and anticipation of painful recoveries. However, quality of life scores are significantly higher for almost 5 years post-surgical intervention [36,37], indicating that although a patient's need for repetitive surgical therapies has a negative impact, the relief from chronic pelvic pain that surgical excision of endometriotic lesions provides results in a positive prolonged impact.

Coping with High Levels of Stress

What does it mean that women with endometriosis are living every day with such high levels of anxiety and perceived stress? Normally, the stress response (activation of the hypothalamus pituitary adrenal cortex, HPA) is to stimulate production of the adrenal hormone cortisol over short periods of time (hours or 1-2 days). Cortisol secretion then helps physiological functions, such as digestion, pulmonary, cardiac and skeletal muscle to function efficiently while a person is stressed (i.e., getting ready for a speech). Cortisol also has an important immune function in that, under normal secretory patterns, aids the immune system to fight off infection and allow for immune suppression. However, elevated levels of perceived stress do not always trigger an elevation in adrenal cortisol levels. In fact, several, medical conditions that are difficult to diagnose (chronic pelvic pain, fibromyalgia, lower back pain and chronic fatigue syndrome) have been associated with lower levels of cortisol [5,38-40]. Women with endometriosis whom experience chronic pelvic pain have overall decreased cortisol levels but also have a decreased cortisol morning spike, known as the cortisol awakening response [5]. Decreased adrenal cortisol production promotes inflammatory processes and triggers pain responses, which may contribute to the pathophysiology of the disease. Additionally, some common endocrine targets used to treat endometriosis may negatively affect cortisol levels, thus exacerbating the inflammatory condition [39].

Treatment Options

Even after decades of research and millions of dollars invested by pharmaceutical companies, there still is no cure for endometriosis. Patients with endometriosis face the continuing battle of which treatment options they want to pursue and many patients will endure a variety of treatment options and end up with the same result: reoccurrence of disease. An additional clinical complication is the fact that, while rare, endometriosis can reoccur even after ovarian senescence (menopause) [41-44] and treatment of endometriosis in post-menopausal women infers of risk of malignant transformation [44]. Therefore patients with endometriosis are faced with life long management of disease and need to be very critical in selecting their treatment plan. Treatment options should be chosen based on the severity and location of disease, patient symptoms and ultimate reproductive end goals (pregnancy or hysterectomy). Prior to a patient's decision on treatment strategy, they need to have a very systematic discussion with their clinician, preferably a clinician that is trained in reproductive endocrinology. In this patient/clinician discussion, not only is there a critical need for the clinician to fully disclose the advantages or side effects of each treatment option but to also understand why the patient is seeking treatment, 1) to become pregnant, 2) to alleviate chronic pain or 3) both. It is also pertinent for successful treatment that patients empower themselves by increasing their understanding of the disease and emerging novel treatment options, which should be facilitated by their clinician. Currently, treatment strategies can be divided into conventional and complimentary alternative medicines. The overall goal for any treatment of endometriosis is to reduce symptoms, decrease presence of endometriotic lesions and improve fertility and quality of life.

Conventional treatment options for women suffering from endometriosis are grouped into two different categories pharmacological and surgical. Pharmacological treatment strategies are commonly the first line of treatment and are many times used in conjunction with surgical intervention. There are two primary targets for pharmaceutical intervention, blocking endometriotic lesion growth through altering endocrinology and/or decreasing the inflammatory environment created by the presence of lesions.

Endometriotic lesion growth is dependent upon estrogen secretion. Common endocrine targets to reduce the estrogenic environment in patients with endometriosis are hypothalamic secretion of gonadotropin releasing hormone (which stimulates ovarian estrogen production via the hypothalamic pituitary gonadal axis) [45-51], aromatase inhibitors (block conversion of testosterone to biologically active estrogen) [52,53], danazol (testosterone derivative that suppresses estrogen secretion) [54] and progestins (negative feedback at the hypothalamic and pituitary level to suppress estrogen secretion) [45,55,56]. Each of these endocrine targets has been shown to be effective at reducing endometriotic lesion growth but each is associated with negative side effects and once treatment stops there is a reoccurrence of symptoms.

Inadequate immune clearance of endometriotic lesions also

contributes to the establishment and pathological progression of endometriosis. Disruption of immune suppression and ineffective immune surveillance has been attributed to the pelvic inflammatory conditions that have been reported in women with endometriosis (reviewed in [57]). Elevated peritoneal fluid levels of TNF-alpha, impaired NK cell activity, increased secretion of inflammatory cytokines and chemokines [58] and a shift in regulatory T cell and Th17 inflammatory cell ratios have all been reported in women and animal models with endometriosis [59,60]. Immune targets have hence been identified as possible therapeutic treatment options for suppression of endometriosis associated inflammation. Anti-TNF-alpha therapies have been developed and found to be ineffective at reduction of pain or improvement of conception rates in both women and animal models of endometriosis [61,62]. Statins are another class of compounds that have been used to target the immune disruption due to the presence of endometriosis. Recently it has been reported that simvastatin does reduce endometriotic lesion growth through up-regulation of endometrial cell apoptosis and activation of retinoic acid [63,64], however these studies have only been performed in immune compromised mouse models and through in vitro studies on human endometrial cell lines, so should be taken with caution. To date, there is not a "good" immune based therapeutic approach to alleviate symptoms associated with endometriosis.

Surgical intervention performed by a highly skilled surgeon is the most effective interventional strategy for the temporary relief of symptoms associated with endometriosis. Laparoscopic evaluation of the peritoneal cavity can be used for initial diagnosis of disease, but then subsequently for treatment of disease through excisional or ablation removal of endometriotic lesions. Although surgical costs are higher than pharmacological treatment strategies, the utilization of more minimally invasive surgical technology has lowered surgical costs and improved post-surgical recovery times [65-67]. In addition, surgical intervention provides immediate improvements for fertility and successful achievement of spontaneous pregnancy within months of surgical intervention [68].

Complementary and Alternative Therapeutic Strategies

For several decades women have sought for alternative treatment options, instead of surgery or pharmacological use, for relief from the pain and infertility that is a result of having endometriosis. Their decision on which complimentary and alternative medicines (CAM) to use comes primarily from the historic use of several decoctions or biophysical practices in Eastern countries for the treatment of numerous conditions [69,70]. Patients typically approach CAM strategies only after exhaustion of all conventional medical therapies and their frustration with their continuing "battle with endometriosis" is at its climax [71]. Alleviation of symptoms associated with endometriosis has been explored with CAM strategies such as: herbal decoctions, herbal extracts, herbal patents, acupuncture, aromatherapy, yoga and exercise. While clinical and research studies of effectiveness are significantly lacking in the United States, there has been a number of studies reported of CAM use in Asian countries for the treatment of pain and infertility in patients with endometriosis [71]. Although the specific herbal therapies are too plentiful to fully describe in this manuscript, it is important to mention that the majority of these herbal therapies help to reduce inflammation and angiogenesis, impairing development of endometriotic lesions. Utilization of yoga, acupuncture, massage and aromatherapy techniques are poorly correlated with a reduction in pain associated with endometriosis [72]. Interestingly, women who exercise daily have reduced pain scores than women who do not exercise and was weakly associated with higher quality of life scores [73]. This association may be due to the benefit of exercise on mental capacity and the positive reduction of stress levels and not directly through reduction of disease status. Overall, the employment of complimentary and alternative therapies should be encouraged for their positive effects but closely monitored by the patient's clinician to ensure that they do not cause any potential negative associations.

Future Directions of Research in Endometriosis

The prevalence of endometriosis, its impact on the medical economy and more importantly, a patient's quality of life, substantiates the need for continued research for an effective treatment and furthermore a thorough understanding of the etiology of the disease. Advancements in research related to endometriosis need to focus on three key areas: the immune system, therapeutic interventional strategies and biomarker development. Endometriosis is highly regarded as an inflammatory disease and therefore investigations that elucidate how the immune system is involved with the etiology of endometriosis or what impact the presence of endometriotic lesions has on immune function are greatly beneficial for both increasing our understanding of disease pathogenesis and for development of immune-based therapeutic targets. This leads in to the second area of focus for endometriosis research, therapeutic strategies. Improvement of the effectiveness of medical intervention for women with endometriosis begins with systematic clinical approaches, beginning with getting the patient with the appropriate clinical specialist to shorten the time from onset of disease symptoms with clinical diagnosis. There needs to be an overall awareness in the medical community that the symptoms associated with endometriosis should not be discounted and aggressive treatment options (other than NSAIDs and OCP's) should be considered at the initial onset of symptoms. An accurate diagnosis and early interventional treatment would curtail disease progression and hopefully provide some relief to the chronic pain and infertility complications, which currently plague women with disease. Additionally, the presence of ovarian endometriomas is currently being investigated as a risk factor for the development of ovarian cancer [74,75]. The transformation of typical endometriomas to ovarian cancer involves the activation of oncogenic KRAS and PI3K pathways and inactivation of tumor suppressor pathways (PTEN and ARID1A) [76]. While there is no consensus on instituting risk reducing procedures for patients with endometriomas the association of ovarian endometriosis and ovarian cancer emphasizes the need for a prompt and accurate diagnosis of endometriosis for patients [77]. Concurrently there also needs to be exploration into novel molecular targets (in addition to endocrine) that can increase the quality of life scores and also improve fertility rates. For this to occur it is critical those patients with endometriosis are seen as individuals and individualized approaches to their medical care for treatment are explored. Aiding individualized health care would be the discovery of a reliable biomarker(s) that can profile a patient's unique signature of disease. To date, the discovery of a reliable biomarker has been a frustration for the research community. Although many systems, (urine, blood, endometrial) and many candidates (CA-125, Il-6, CCR1/HPRT and nerve fiber) have been explored, none have been found to be accurate for the heterogeneity of this disease [78]. Currently, the only clinically useful marker is CA-125, which is the most marker for endometriosis, but with low specificity. Progression on all three of these fronts (immune, clinical intervention and biomarker discovery) is imperative for significant advancements in the medical care for patients with endometriosis.

References

1. Eskenazi B, Warner ML (1997) Epidemiology of endometriosis. Obstet Gynecol Clin North Am 24: 235-258.

2. Meuleman C, Vandenabeele B, Fieuws S, Spiessens C, Timmerman D, et

al. (2009) High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. Fertil Steril 92: 68-74.

3. Clement PB (2007) The pathology of endometriosis: a survey of the many faces of a common disease emphasizing diagnostic pitfalls and unusual and newly appreciated aspects. Adv Anat Pathol 14: 241-260.
4. Nnoaham KE, Hummelshoj L, Webster P, d'Hooghe T, de Cicco Nardone F, et al. (2011) Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril 96: 366-373 e368.
5. Petrelluzzi KF, Garcia MC, Petta CA, Grassi-Kassisse DM, Spadari-Bratfisch RC (2008) Salivary cortisol concentrations, stress and quality of life in women with endometriosis and chronic pelvic pain. Stress 11: 390-397.
6. Fourquet J, Báez L, Figueroa M, Iriarte RI, Flores I (2011) Quantification of the impact of endometriosis symptoms on health-related quality of life and work productivity. Fertil Steril 96: 107-112.
7. Nezhat C, Nicoll LM, Bhagan L, Huang JQ, Bosev D, et al. (2009) Endometriosis of the diaphragm: four cases treated with a combination of laparoscopy and thoracoscopy. J Minim Invasive Gynecol 16: 573-580.
8. Ahn SH, Monsanto SP, Miller C, Singh SS, Thomas R, et al. (2015) Pathophysiology and Immune Dysfunction in Endometriosis. Biomed Res Int 2015: 795976.
9. Vercellini P, Viganò P, Somigliana E, Fedele L1 (2014) Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol 10: 261-275.
10. Fuldeore M, Chwalisz K, Marx S, Wu N, Boulanger L, et al. (2011) Surgical procedures and their cost estimates among women with newly diagnosed endometriosis: a US database study. J Med Econ 14: 115-123.
11. Levy AR, Osenenko KM, Lozano-Ortega G, Sambrook R, Jeddi M, et al. (2011) Economic burden of surgically confirmed endometriosis in Canada. J Obstet Gynaecol Can 33: 830-837.
12. Surrey E1 (1997) An economically rational method of managing early-stage endometriosis. Med Interface 10: 119-124.
13. Exacoustos C, Manganaro L, Zupi E3 (2014) Imaging for the evaluation of endometriosis and adenomyosis. Best Pract Res Clin Obstet Gynaecol 28: 655-681.
14. Lo Monte G, Wenger JM, Petignat P, Marci R3 (2014) Role of imaging in endometriosis. Cleve Clin J Med 81: 361-366.
15. Nair AS, Nair HB, Lucidi RS, Kirchner AJ, Schenken RS, et al. (2008) Modeling the early endometriotic lesion: mesothelium-endometrial cell co-culture increases endometrial invasion and alters mesothelial and endometrial gene transcription. Fertil Steril 90: 1487-1495.
16. Bartley J, Julicher A, Hotz B, Mechsner S, Hotz H (2014) Epithelial to mesenchymal transition (EMT) seems to be regulated differently in endometriosis and the endometrium. Arch Gynecol Obstet 289: 871-881.
17. [No authors listed] (1997) Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril 67: 817-821.
18. Haas D, Shebl O, Shamiyeh A, Oppelt P (2013) The rASRM score and the Enzian classification for endometriosis: their strengths and weaknesses. Acta Obstet Gynecol Scand 92: 3-7.
19. Haas D, Oppelt P, Shebl O, Shamiyeh A, Schimetta W, et al. (2013) Enzian classification: does it correlate with clinical symptoms and the rASRM score? Acta Obstet Gynecol Scand 92: 562-566.
20. Adamson GD (2013) Endometriosis Fertility Index: is it better than the present staging systems? Curr Opin Obstet Gynecol 25: 186-192.
21. De Graaff AA, D'Hooghe TM, Dunselman GA, Dirksen CD, Hummelshoj L; WERF EndoCost Consortium, et al. (2013) The significant effect of endometriosis on physical, mental and social wellbeing: results from an international cross-sectional survey. Hum Reprod 28: 2677-2685.
22. Sepulcri Rde P, do Amaral VF (2009) Depressive symptoms, anxiety, and quality of life in women with pelvic endometriosis. Eur J Obstet Gynecol Reprod Biol 142: 53-56.
23. Jia SZ, Leng JH, Shi JH, Sun PR, Lang JH (2012) Health-related quality of life in women with endometriosis: a systematic review. J Ovarian Res 5: 29.
24. Lorencatto C, Vieira MJ, Pinto CL, Petta CA (2002) [Evaluation of the frequency of depression in patients with endometriosis and pelvic pain]. Rev Assoc Med Bras 48: 217-221.
25. Klein S, D'Hooghe T, Meuleman C, Dirksen C, Dunselman G, et al. (2014) What is the societal burden of endometriosis-associated symptoms? a prospective Belgian study. Reprod Biomed Online 28: 116-124.
26. Stilley JA, Birt JA, Sharpe-Timms KL (2012) Cellular and molecular basis for endometriosis-associated infertility. Cell Tissue Res 349: 849-862.
27. Macer ML, Taylor HS (2012) Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. Obstet Gynecol Clin North Am 39: 535-549.
28. Holoch KJ, Lessey BA (2010) Endometriosis and infertility. Clin Obstet Gynecol 53: 429-438.
29. Donaghay M, Lessey BA (2007) Uterine receptivity: alterations associated with benign gynecological disease. Semin Reprod Med 25: 461-475.
30. 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.
31. Jacobson TZ, Barlow DH, Koninckx PR, Olive D, Farquhar C (2002) Laparoscopic surgery for subfertility associated with endometriosis. Cochrane Database Syst Rev : CD001398.
32. Littman E, Giudice L, Lathi R, Berker B, Milki A, et al. (2005) Role of laparoscopic treatment of endometriosis in patients with failed in vitro fertilization cycles. Fertil Steril 84: 1574-1578.
33. Cousineau TM, Domar AD (2007) Psychological impact of infertility. Best Pract Res Clin Obstet Gynaecol 21: 293-308.
34. Burns LH (2007) Psychiatric aspects of infertility and infertility treatments. Psychiatr Clin North Am 30: 689-716.
35. Evens EM (2004) A global perspective on infertility: an under recognized public health issue. The University of North Carolina at Chapel Hill.
36. Abbott JA, Hawe J, Clayton RD, Garry R (2003) The effects and effectiveness of laparoscopic excision of endometriosis: a prospective study with 2-5 year follow-up. Hum Reprod 18: 1922-1927.
37. Tan BK, Maillou K, Mathur RS, Prentice A (2013) A retrospective review of patient-reported outcomes on the impact on quality of life in patients undergoing total abdominal hysterectomy and bilateral salpingo-oophorectomy for endometriosis. Eur J Obstet Gynecol Reprod Biol 170: 533-538.
38. Fries E, Hesse J, Hellhammer J, Hellhammer DH (2005) A new view on hypocortisolism. Psychoneuroendocrinology 30: 1010-1016.
39. Heim C, Ehlert U, Hellhammer DH (2000) The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. Psychoneuroendocrinology 25: 1-35.
40. Jerjes WK, Peters TJ, Taylor NF, Wood PJ, Wessely S, et al. (2006) Diurnal excretion of urinary cortisol, cortisone, and cortisol metabolites in chronic fatigue syndrome. J Psychosom Res 60: 145-153.
41. Bendon CL, Becker CM (2012) Potential mechanisms of postmenopausal endometriosis. Maturitas 72: 214-219.
42. Simpson PD, McLaren JS, Rymer J, Morris EP (2015) Minimising menopausal side effects whilst treating endometriosis and fibroids. Post Reprod Health 21: 16-23.
43. Palep-Singh M, Gupta S (2009) Endometriosis: associations with menopause, hormone replacement therapy and cancer. Menopause Int 15: 169-174.
44. Oxholm D, Knudsen UB, Kryger-Baggesen N, Ravn P (2007) Postmenopausal endometriosis. Acta Obstet Gynecol Scand 86: 1158-1164.
45. Brown J, Kives S, Akhtar M (2012) Progestagens and anti-progestagens for pain associated with endometriosis. Cochrane Database Syst Rev 3: CD002122.
46. Fatima P, Hossain MM, Rahman D, Suman GM (2011) Outcome of pregnancies after inadvertent exposure to GnRH agonist in early pregnancy. Mymensingh Med J 20: 303-307.
47. Kim NY, Ryoo U, Lee DY, Kim MJ, Yoon BK, et al. (2011) The efficacy and tolerability of short-term low-dose estrogen-only add-back therapy during post-operative GnRH agonist treatment for endometriosis. Eur J Obstet Gynecol Reprod Biol 154: 85-89.
48. Lee SL, Chang CY, Chen PH, Lu CH, Chang CC (2011) A cumulative strategy of GnRH agonist, clomiphene citrate, and GnRH antagonist in a patient with recurrent endometriosis and repeated aspiration. Taiwan J Obstet Gynecol 50: 366-369.

49. Magon N (2011) Gonadotropin releasing hormone agonists: Expanding vistas. Indian J Endocrinol Metab 15: 261-267.

50. Yang XH, Ji F, AiLi A, TuerXun H, He Y, et al. (2014) Effects of laparoscopic ovarian endometriosis cystectomy combined with postoperative GnRH-a therapy on ovarian reserve, pregnancy, and outcome recurrence. Clin Exp Obstet Gynecol 41: 272-275.

51. Leone Roberti Maggiore U, Scala C, Remorgida V, Venturini PL, Del Deo F, et al. (2014) Triptorelin for the treatment of endometriosis. Expert Opin Pharmacother 15: 1153-1179.

52. Alborzi S, Hamedi B, Omidvar A, Dehbashi S, Alborzi S, et al. (2011) A comparison of the effect of short-term aromatase inhibitor (letrozole) and GnRH agonist (triptorelin) versus case control on pregnancy rate and symptom and sign recurrence after laparoscopic treatment of endometriosis. Arch Gynecol Obstet 284: 105-110.

53. Langoi D, Pavone ME, Gurates B, Chai D, Fazleabas A, et al. (2013) Aromatase inhibitor treatment limits progression of peritoneal endometriosis in baboons. Fertil Steril 99: 656-662.

54. Chatterjee S, Dey S, Chowdhury RG, Ganguly DD (2012) Pregnancy outcome in pre-operative danazol treatment followed by laparoscopic correction in infertility associated with endometriosis. J Indian Med Assoc 110: 694-699.

55. Jeng CJ, Chuang L, Shen J (2014) A comparison of progestogens or oral contraceptives and gonadotropin-releasing hormone agonists for the treatment of endometriosis: a systematic review. Expert Opin Pharmacother 15: 767-773.

56. Kitawaki J, Kusuki I, Yamanaka K, Suganuma I (2011) Maintenance therapy with dienogest following gonadotropin-releasing hormone agonist treatment for endometriosis-associated pelvic pain. Eur J Obstet Gynecol Reprod Biol 157: 212-216.

57. Bruner-Tran KL, Herington JL, Duleba AJ, Taylor HS, Osteen KG (2013) Medical management of endometriosis: emerging evidence linking inflammation to disease pathophysiology. Minerva Ginecol 65: 199-213.

58. Kokcu A (2013) Possible effects of endometriosis-related immune events on reproductive function. Arch Gynecol Obstet 287: 1225-1233.

59. Chen S, Zhang J, Huang C, Lu W, Liang Y, et al. (2012) Expression of the T regulatory cell transcription factor FoxP3 in peri-implantation phase endometrium in infertile women with endometriosis. Reprod Biol Endocrinol 10: 34.

60. Braundmeier A, Jackson K, Hastings J, Koehler J, Nowak R, et al. (2012) Induction of endometriosis alters the peripheral and endometrial regulatory T cell population in the non-human primate. Hum Reprod 27: 1712-1722.

61. Lu D, Song H, Shi G (2013) Anti-TNF-alpha treatment for pelvic pain associated with endometriosis. Cochrane Database Syst Rev 3: CD008088.

62. Koninckx PR, Craessaerts M, Timmerman D, Cornillie F, Kennedy S (2008) Anti-TNF-alpha treatment for deep endometriosis-associated pain: a randomized placebo-controlled trial. Hum Reprod 23: 2017-2023.

63. Sokalska A, Anderson M, Villanueva J, Ortega I, Bruner-Tran KL, et al. (2013) Effects of simvastatin on retinoic acid system in primary human endometrial stromal cells and in a chimeric model of human endometriosis. J Clin Endocrinol Metab 98: E463-471.

64. Villanueva JA, Sokalska A, Cress AB, Ortega I, Bruner-Tran KL, et al. (2013) Resveratrol potentiates effect of simvastatin on inhibition of mevalonate pathway in human endometrial stromal cells. J Clin Endocrinol Metab 98: E455-462.

65. Healey M, Cheng C, Kaur H (2014) To excise or ablate endometriosis? A prospective randomized double blinded trial after 5 years follow-up. J Minim Invasive Gynecol 21: 999-1004.

66. Sirota I, Nezhat F (2014) Robotic compared with conventional laparoscopy for treatment of severe endometriosis: comparison of outcomes. Obstet Gynecol 123 Suppl 1: 129S-130S.

67. Duffy JM, Arambage K, Correa FJ, Olive D, Farquhar C, et al. (2014) Laparoscopic surgery for endometriosis. Cochrane Database Syst Rev 4: CD011031.

68. Cirpan T, Akman L, Yucebilgin MS, Terek MC, Kazandi M (2013) Reproductive outcome after surgical treatment of endometriosis--retrospective analytical study. Ginekol Pol 84: 1041-1044.

69. Pujol LA, Monti DA (2007) Managing cancer pain with nonpharmacologic and complementary therapies. J Am Osteopath Assoc 107: ES15-21.

70. Coulter ID, Willis EM (2004) The rise and rise of complementary and alternative medicine: a sociological perspective. Med J Aust 180: 587-589.

71. Kong S, Zhang YH, Liu CF, Tsui I, Guo Y, et al. (2014) The complementary and alternative medicine for endometriosis: a review of utilization and mechanism. Evid Based Complement Alternat Med 2014: 146383.

72. Osayande AS, Mehulic S (2014) Diagnosis and initial management of dysmenorrhea. Am Fam Physician 89: 341-346.

73. Marques A, Bahamondes L, Aldrighi JM, Petta CA (2004) Quality of life in Brazilian women with endometriosis assessed through a medical outcome questionnaire. J Reprod Med 49: 115-120.

74. Nezhat F, Datta MS, Hanson V, Pejovic T, Nezhat C, et al. (2008) The relationship of endometriosis and ovarian malignancy: a review. Fertil Steril 90: 1559-1570.

75. Boruban MC, Jaishuen A, Sirisabya N, Li Y, Zheng HG, et al. (2008) Ovarian endometriosis associated with carcinoma and sarcoma: case report. Eur J Gynaecol Oncol 29: 393-396.

76. Grandi G, Toss A, Cortesi L, Botticelli L, Volpe A, et al. (2015) The Association between Endometriomas and Ovarian Cancer: Preventive Effect of Inhibiting Ovulation and Menstruation during Reproductive Life. Biomed Res Int 2015: 751571.

77. Guo SW (2015) Endometriosis and ovarian cancer: potential benefits and harms of screening and risk-reducing surgery. Fertil Steril 104: 813-830.

78. Burney RO (2014) Biomarker development in endometriosis. Scand J Clin Lab Invest Suppl 244: 75-81.

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