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Endometriosis: Where are We and Where are We Going?

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Abstract

Endometriosis currently affects ~5.5 million reproductive-aged women in the U.S. with symptoms such as painful periods (dysmenorrhea), chronic pelvic pain, pain with intercourse (dyspareunia), and infertility. It is defined as the presence of endometrial tissue outside the uterine cavity and is found predominately attached to sites within the peritoneal cavity. Diagnosis for endometriosis is solely made through surgery as no consistent biomarkers for disease diagnosis exist. There is no cure for endometriosis and treatments only target symptoms and not the underlying mechanism(s) of disease. The nature of individual predisposing factors or inherent defects in the endometrium, immune system, and/or peritoneal cavity of women with endometriosis remains unclear. The literature over the last 5 years (2010-2015) has advanced our critical knowledge related to hormones, hormone receptors, immune dysregulation, hormonal treatments, and the transformation of endometriosis to ovarian cancer. In this review, we cover the aforementioned topics with the goal of providing the reader an overview and related references for further study to highlight the progress made in endometriosis research, while concluding with critical areas of endometriosis research that are urgently needed.

Introduction

Endometriosis is an estrogen-dependent gynecological condition characterized by the presence and growth of ectopic endometrial tissue, often associated with inflammation, severe and chronic pain, and infertility (Hickey *et al.* 2014). Lesions identified during laparoscopy are categorized as superficial peritoneal lesions, endometriomas, or deep infiltrating nodules, with high degree of individual variability in lesion color, size, and morphology. Histopathological analysis requires the presence of at least two features for a

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diagnosis of endometriosis, the features being endometrial epithelium, endometrial glands, endometrial stroma, and hemosiderin-filled macrophages (Hsu *et al.* 2010). Retrograde menstruation, in which uterine epithelial and stromal cells are disseminated and implanted into the peritoneal cavity via the fallopian tubes, is the most accepted mechanism for the pathogenesis of endometriosis (Sampson 1927b, Ahn *et al.* 2015a). Greater than 90% of women undergo retrograde menstruation; however, the prevalence of endometriosis in the general population is 6-10% (Sampson 1927a, Syrop & Halme 1987). Such a discrepancy between these two values suggests women who develop endometriosis are likely to have other genetic, biochemical, and pathophysiological factors contributing to development of the disease (Ahn *et al.* 2015a).

The goal of this review is to provide a broad overview of the advancements in endometriosis research over the last 5 years (2010-2015). First, we delve into animal models often used in endometriosis research. After which, we cover critical areas of endometriosis study, including basic and clinical research, and the transformation of endometriosis into ovarian cancer. Within basic research, we focus on angiogenesis, cytokine/chemokine expression, and hormones and their receptors, and the significance they may play in the pathogenesis of endometriosis. This review is a synopsis of important findings for researchers to quickly find relevant sources of interest to his/her studies.

Animal Research Models

The use of animal models in the study of endometriosis allows for the control of numerous variables related to pathogenesis and disease progression, including angiogenesis, inflammation, and hormonal response. Non-human primate and rodent models are the most common animal models used, while the chicken chorioallantoic membrane model has limited use.

Non-human Primate Models

Non-human primates (baboons and rhesus macaques) are often used to study pathogenesis, progression, and treatment of endometriosis. While primates can spontaneously develop endometriosis at a low prevalence (D'hooghe *et al.* 1996, Zondervan *et al.* 2004, King *et al.* 2015), techniques have been developed to increase disease incidence. Cervical occlusion to promote retrograde menstruation (Scott *et al.* 1953, D'Hooghe *et al.* 1994) and a homologous model, in which endometrial tissue is excised from a donor primate and surgically transplanted or injected into a recipient primate, are used (Te Linde & Scott 1950, D'Hooghe *et al.* 1995, Sillem *et al.* 1996). Primate models, including advantages and disadvantages, have been previously described (Tirado-Gonzalez *et al.* 2010, Grummer 2012, King *et al.* 2015).

Rodent Models

Rodents are often used in endometriosis research due to quick generation time, ability for genetic manipulation, and relatively low cost, especially in comparison to non-human primate models. Rodent models of endometriosis are divided into two main groups: heterologous or homologous/autologous models. Heterologous models use human tissue

transplanted into immunocompromised mice, while homologous models involve transferring endometrial tissue from one animal to a syngeneic animal (Tirado-Gonzalez *et al.* 2010, King *et al.* 2015).

Heterologous models involve the transfer of human endometrial tissue into an immunocompromised rodent, such as athymic nude, severe combined immunodeficient (SCID), or Rag2γ(c) mice, to prevent the rodent immune system from attacking the foreign tissue (Zamah *et al.* 1984, Aoki *et al.* 1994, Greenberg & Slayden 2004). Once human tissue is collected, it is disseminated via intraperitoneal or subcutaneous injection into the immunocompromised rodent. Heterologous rodent models with associated advantages and disadvantages have been described (Tirado-Gonzalez *et al.* 2010, Bruner-Tran *et al.* 2012, Grummer 2012, King *et al.* 2015).

Several homologous rodent models are utilized in endometriosis research, and the generation of these models involves several important considerations regarding the reproductive status of the donor and recipient, transplantation method, and potential genetic manipulation (King *et al.* 2015). Often, the recipient rodents are ovariectomized and treated with estrogens to promote lesion growth (Cummings & Metcalf 1995, Somigliana *et al.* 1999, Styer *et al.* 2008, Burns *et al.* 2012). Critically valuable for the study of endometriosis is that the homologous model maintains an intact immune system. A large difference between homologous models is the method of transplantation and tissue dissemination. Various models exist for the development of ectopic lesions, including: 1) suturing uterine tissue into the peritoneal wall or intestinal mesentery, 2) injecting minced uterine tissue intraperitoneally to disperse freely and attach at sites within the peritoneal cavity, 3) using entire uterine tissue or endometrial tissue, and 4) using minced “menstruated” tissue for intraperitoneal injection (Vernon & Wilson 1985, Somigliana *et al.* 1999, Burns *et al.* 2012, Greaves *et al.* 2014). For models used to study endometriosis, it is critically important to remember the definition of and requirements for an endometriotic lesion. Discouragingly, some models inherently do not fulfill these criteria and are suboptimal for the study of endometriosis, ultimately occluding comprehensive comparison and interpretation of data in the scientific literature.

Chicken Chorioallantoic Membrane Model

The chicken chorioallantoic membrane (CAM) assay is used to study molecular processes involved in adhesion, invasion, and angiogenesis of developing endometriotic lesions. This assay involves culturing human endometrial tissue on the CAM of fertilized chicken embryos (Maas *et al.* 2001). The CAM has a dense microvasculature, useful for examining angiogenesis and for experimentation with anti-angiogenic agents (Nap *et al.* 2005). This method has been used to study the impact of matrix metalloproteinase (MMP) expression and activity on adhesion and invasion (Nap *et al.* 2004, Juhasz-Boss *et al.* 2010). However, it is not suited for studying immunological or inflammatory aspects of lesion development or for potential effects of systemic treatments.

Pathogenesis and Progression of Endometriosis

Animal models and human samples are paramount in the study of pathogenesis and progression of endometriosis. They allow for in-depth analysis of factors involved in this disease, including inflammation, angiogenesis, cytokine/chemokine expression, and endocrine alterations such as steroid and steroid receptor expression. These components also form a complex, interacting system greatly impacting the development of endometriosis. While we understand that several other factors are involved in the pathogenesis and progression of this disease, including genetics and epigenetics, and significant advances in these components have been made, covering them in depth is beyond the scope of this review. For researchers interested in these topics, an elegant and comprehensive review by Bulun *et al.* (2015) recently addresses the molecular biology, genetics, and epigenetics of endometriosis and covers 25 years of research (1990-2015).

Inflammation - Angiogenesis

Angiogenesis is the formation of new blood vessels, and subsequently, is a key process to form functional blood vessels to ectopic menstrual tissue for the establishment/maintenance of endometriotic lesions. Theorized is that women with endometriosis respond to retrograde menstrual tissue as a “wound” that must be healed and not as “self” that must be removed (Herington *et al.* 2011). Examining key players involved in angiogenesis, both in women with endometriosis and in animal models, similarities between angiogenesis in endometriotic lesions and angiogenesis in wound healing exist. A variety of growth factors and genes related to angiogenesis have been studied in endometriosis.

The VEGF protein family is well known for roles in angiogenesis, vasculogenesis, and lymphangiogenesis. Human peritoneal fluid (PF) from women with endometriosis show inconsistent protein levels of VEGF, but this may be due to sample size, dilution of PF, or true variability among women. For example, some studies show increased VEGF levels in the PF (Bourlev *et al.* 2010, Xu *et al.* 2013, Szubert *et al.* 2014); however, other studies show no increase in VEGF levels in women with endometriosis compared to healthy women (Barcz *et al.* 2012, Bersinger *et al.* 2012, Rathore *et al.* 2014). Interestingly, more consistency is found in animal models of endometriosis, most likely because of controlled onset of experimental conditions. A variety of rodent models of endometriosis show VEGF levels increase in endometriosis-like lesions (Machado *et al.* 2010, Ricci *et al.* 2011, Kumar *et al.* 2014, Lu *et al.* 2014a, Machado *et al.* 2014, Zhao *et al.* 2015). Data are inconsistent when attempting to target VEGF in the mouse to treat endometriosis (Xu *et al.* 2011, Novella-Maestre *et al.* 2012, Virani *et al.* 2013, Kumar *et al.* 2014); however, the data suggest VEGF drives angiogenesis in endometriosis. Furthermore, these results from human and animal models demonstrate challenges of clearly deciphering VEGF as an appropriate marker for endometriosis.

Other angiogenic factors play important roles in the adhesion and maintenance of endometriosis lesions, including hypoxia factors (ie. HIF1A), MMPs (ie. MMP9), and microRNAs (miRNA). As mentioned, the peritoneal microenvironment of women with endometriosis is often different from healthy women. In a heterologous mouse model, hypoxic conditions promote angiogenesis and proliferation of endometriosis demonstrated

by larger lesions, higher levels of VEGF, HIF1A, Ki67, and PECAM1 (Lu *et al.* 2014b). Concomitantly, the same group shows lesion location affects adhesion and angiogenesis when comparing intraperitoneal versus subcutaneous endometriotic tissue injection (Lu *et al.* 2014a), suggesting the microenvironment of the peritoneal cavity plays a crucial role in lesion adhesion and angiogenesis. MMPs are proteases required for reorganizing existing blood vessels during budding angiogenesis (Page-McCaw *et al.* 2007). Recently, the role of MMPs in endometriosis were not studied in-depth; but MMPs play a known role in endometriosis (Machado *et al.* 2010). For example, *Mmp9*$^{-/-}$ uterine tissue does not grow in a mouse suture endometriosis model (Han *et al.* 2012); however, this model does not account for actual tissue attachment. An emerging field in endometriosis is the function of miRNA in angiogenesis. Primary eutopic and ectopic endometrial stromal cells exposed to PF from women with endometriosis have downregulated miRNAs known to regulate VEGF expression compared to cells exposed to PF from control women (Braza-Boils *et al.* 2013, Braza-Boils *et al.* 2014, Braza-Boils *et al.* 2015). Future in-depth analysis of the interplay between inflammation and angiogenesis in the early stages of endometriosis development is needed to determine which molecules could potentially be targeted therapeutically.

Inflammation - Cytokine and Chemokine Expression

Cytokines and chemokines are emerging as key players in endometriosis pathobiology. Cytokines are a broad group of secreted proteins important in cell signaling, while chemokines are a family of cytokines important in inducing chemotaxis in nearby cells. A complete overview of chemokines and cytokines in endometriosis is too exhaustive; however, these proteins are altered in PF, ectopic lesions, eutopic endometrium, and serum. To demonstrate the growing role of cytokine research in the study of endometriosis, Table 1 lists cytokines and chemokines that appear in > two endometriosis research papers between 2010-2015. Additional to the dysregulation of cytokines/chemokines, altered levels of a large number of cytokines/chemokines are found in cyst fluid removed from endometriomas/chocolate cysts (Chen *et al.* 2013b). Before the interplay and implications of chemokines and cytokines can be elucidated in endometriosis, large scale controlled human studies or meta-analyses will need to be conducted to fully encompass cytokine dysregulation. Most likely, with the signaling complexity of the immune system and endometriosis as a disease, a single chemokine/cytokine will not diagnose disease, but instead, a disease profile of altered cytokines may be used to establish disease diagnosis. Furthermore, as nicely outlined in Fassbender et al., international standardized methods for BioBanking endometriosis samples needs to be implemented (Fassbender *et al.* 2013).

Hormones and Hormone Receptors

Endometriosis is intimately associated with steroid metabolism and associated pathways, corresponding to the paramount roles estrogen receptors (ESRs) and progesterone receptors (PGRs) play in uterine biology. Both human and animal model studies show endometriosis is estrogen (E2) dependent and is regulated through the ESRs alpha and beta (*ESR1* and *ESR2*) (Burns *et al.* 2012, Pellegrini *et al.* 2012, Wu *et al.* 2012, Han *et al.* 2015, Zhao *et al.* 2015). An increased ratio of *ESR2* to *ESR1* mRNA is observed in endometriomas compared with endometriosis implants and eutopic endometrium (Bukulmez *et al.* 2008). Knockout studies in mice show lesion attachment, size, and proliferation are closely associated with

the presence or absence of *Esr1* and *Esr2* (Burns *et al.* 2012). The Bulun Laboratory have focused efforts on ESR2 and demonstrate ESR2 expression is highly increased in endometriotic tissue due to hypomethylation of the promoter region (Dyson *et al.* 2014). They also identify RAS-like estrogen-regulated growth inhibitor (RERG) as a key enzymatic target of estradiol signaling through ESR2. This enzyme regulates numerous factors involved in the progression of endometriosis, including cell proliferation and apoptotic resistance (Monsivais *et al.* 2014). Additionally, they have nicely detailed multiple studies on the role of ESR2 in endometriosis in a comprehensive review (Bulun *et al.* 2012). Use of estrogen receptor ligands, inhibitors, and agonists also support the role of ESRs in endometriosis (Colette *et al.* 2011, Kulak *et al.* 2011, Han *et al.* 2012, Chen *et al.* 2014, Naqvi *et al.* 2014, Palmer *et al.* 2015, Zhao *et al.* 2015). Specifically, selective estrogen receptor modulators (SERMs) are synthetic molecules which bind to ESRs and act either as antagonists or agonists. Two compounds, chloroindazole (CLI) and oxabicycloheptene sulfonate (OBHS), have strong ER-dependent anti-inflammatory effects on endometriosis lesions *in vivo* in a suture mouse model of endometriosis and *in vitro,* with primary human endometriotic stromal cells (Zhao *et al.* 2015). Their data suggests that both CLI and OBHS inhibit the establishment of new lesions and reduce the size of already established lesions; however, important next studies using these inhibitors will be to examine lesion attachment without a suture endometriosis model, as suturing alone creates an unnecessary inflammatory response similar to any reaction towards a foreign body, (Carr *et al.* 2009) and, in some respects, negates the use of homologous tissue.

Progesterone (P4) and its receptor isoforms, PGR-A and –B, also have established roles in endometriosis. The endometrium of women with endometriosis demonstrates an attenuated response to P4 because PGR responsive genes are not suppressed in the eutopic endometrium of women with endometriosis compared to healthy women in the early secretory phase of the menstrual cycle, suggesting the presence of a progesterone resistance phenotype in these women (Burney *et al.* 2007). A more recent study to discriminate between the PGR isoforms finds elevated levels of PGR-A in endometriosis lesions and eutopic endometrium from women with endometriosis and shows a PGR-A-dominant state, regardless of menstrual phase (Bedaiwy *et al.* 2015). While the data is from a small cohort of women, their findings suggest a PGR-A-dominant menstrual efflux in the peritoneal cavity may mirror the growth and invasive properties known about cancers overexpressing PGR-A.

Aromatase is the enzyme responsible for the aromatization of androgens into estrogens. Aromatase protein level is increased in vaginal septum lesions and decreased in intestinal lesions in women with endometriosis (Goncalves *et al.* 2015). Ovarian endometriomas express higher levels of aromatase and peroxisome proliferator-activated receptor gamma co-activator 1 alpha (PPARGC1A) than associated ectopic lesions and eutopic endometrium (Suganuma *et al.* 2014). Activation of peroxisome proliferator-activated receptor gamma (PPARG) inhibits the growth and survival of human endometriotic cells by suppressing E2 biosynthesis and prostaglandin E2 (PGE2) signaling (Lebovic *et al.* 2013). The use of AIs for the treatment of endometriosis is becoming more common and is discussed below.

The last 5 years have expanded our knowledge of hormones, hormone receptors (HRs), and associated co-regulators. These studies are important for integrating dysregulation found in

ectopic lesions, but also have allowed for the design of more targeted areas to be studied. More in-depth studies with targeted HR uterine knockouts, co-regulator knockouts, and/or with the recently synthesized SERMS will lead to greater understanding of the role of HR in disease. The results of these future experiments will allow for even more targeted experiments and hopefully development and use of more targeted therapeutic paradigms.

Interactions between Inflammation and the Endocrine System

Cross-talk between the immune/inflammatory and endocrine systems can significantly impact pathogenesis and progression of endometriosis. The sex hormone receptors can markedly alter the immune response in ectopic tissue. Both *ESR1* and *ESR2* have distinct roles in regulating the immune response, as discovered through the use of multiple animal models. Signaling of E2 through ESR1 appears to have both an anti- and pro-inflammatory role, as observed by increased mitogenesis and decreased *IFNG*, *TNF*, and *IL12* transcript expression (Burns *et al.* 2012). Overexpression of *ESR2* activates the inflammasome and modulates TNF-induced apoptosis, as observed with increases in IL1B and cleaved caspase-1 levels and decreases in cleaved caspase-8 levels in ectopic lesions (Han *et al.* 2015).

Hormones themselves also directly alter the immune system. Monocyte chemotactic factor-1 (MCP1/CCL2) is an example of a chemokine significantly affected by sex hormones. In human endometrial endothelial cells from women with endometriosis, both E2 and P4 increase *MCP1* mRNA and protein expression; this effect is not observed in cells from healthy women (Luk *et al.* 2010). After treating monocytes with control peritoneal fluid (cPF) or endometriotic peritoneal fluid (ePF), the addition of E2 to the culture suppresses MCP1 release from cPF-treated monocytes. However, E2 does not suppress MCP1 release from ePF-treated monocytes (Lee *et al.* 2012). E2 promotes a pro-inflammatory environment by increasing secretion of IL6 and TNF from peritoneal macrophages from women with endometriosis compared to control women. This effect is further enhanced by co-treatment with lipopolysaccharide (Khan *et al.* 2015). Other chemokines, CXCR4 and CXCL12, are downregulated by sex hormones in human epithelial endometrial cells and human endometrial stromal cells respectively (Ruiz *et al.* 2010). All of these findings provide evidence that the immune environment and its response to sex hormones is altered in women with endometriosis; however, a definitive mechanism for these differences is largely unknown and is a major area that future research needs to address.

A third aspect to the endocrine-immune crosstalk involves aromatase expression. Macrophage migration inhibitory factor (MIF) increases aromatase mRNA and protein expression in ectopic endometrial stromal cells via posttranscriptional stabilization (Veillat *et al.* 2012). Interestingly though, E2 treatment in the same cells increases *MIF* mRNA and protein expression, suggesting a positive feedback loop between the endocrine and immune systems in women with endometriosis (Veillat *et al.* 2012). Potential for a continuous positive feedback loop between these systems is an area for further exploration to understand the dynamic and altered environment in women with endometriosis.

Clinical Symptoms and Diagnosis of Endometriosis

Endometriosis is often characterized by pelvic pain that manifests in a variety of ways; most commonly, patients present with dysmenorrhea, noncyclical pelvic pain, and dyspareunia, but other common symptoms are dyschezia, dysuria, and infertility (Fritz MA 2011, Practice Committee of the American Society for Reproductive 2014). Definitive diagnosis of endometriosis is by visualization or excision of lesions via laparoscopy. The American Society for Reproductive Medicine (ASRM) grading system for endometriosis guides surgeons in determining the severity of disease (1997) and was created to help predict pregnancy with fertility treatment. The grading system does not correlate with pain level, and has limited reproducibility to predict pregnancy; however; it remains the best objective way to communicate disease severity between physicians and surgeons.

Accuracy of visual diagnosis increases with disease severity (Fernando *et al.* 2013). While the European Society of Human Reproduction and Embryology (ESHRE) requirements suggest surgical diagnosis by visualization alone is appropriate, ASRM stresses that biopsies be taken when diagnosis is unclear (Fernando *et al.* 2013). Importantly, poor correlation exists between clinical symptoms and disease burden (Dunselman *et al.* 2014, Practice Committee of the American Society for Reproductive 2014). Diagnosing endometriosis by pelvic pain alone is not sufficient, as pelvic pain is also a symptom of many other diseases, including pelvic adhesions, adenomyosis, and gastrointestinal urologic disorders (Bulun 2009, Practice Committee of the American Society for Reproductive 2014). This vast differential diagnosis for pelvic pain can complicate the diagnosis of endometriosis.

Treatments

Several different treatment modalities, including medical, surgical, and alternative, exist for endometriosis. First-line medical management includes options that have a favorable safety and cost profile, are well tolerated by the patient, and are effective in treatment (Zito *et al.* 2014). If medical therapy fails, surgical therapy to remove endometriotic lesions and endometriomas is performed. Finally, alternative therapies are being used to supplement conventional treatments.

Medical Therapy

Combined oral contraceptive pills (OCPs), which include ethinyl estradiol (EE) and various progestins, are used to treat endometriosis, particularly in women not trying to conceive (Practice Committee of the American Society for Reproductive 2014, Zito *et al.* 2014). Historically, OCPs have been first-line therapy, but most studies are decades old and the pills contained higher doses of EE. Based on a more recent randomized control trial (RCT) in 100 patients, low dose OCPs decrease pain more significantly than placebo on the Visual Analog Scale (VAS) (Harada *et al.* 2008). Continuous OCPs decrease recurrence rates of dysmenorrhea after surgical therapy when compared to cyclic OCPs (Muzii *et al.* 2015, Zorbas *et al.* 2015). Of the progestins, the 19-nortestosterone derivatives are less androgenic and offer better side effect profiles (Angioni *et al.* 2014). In a RCT, dienogest significantly decreases endometriosis-related pain similar to gonadotropin releasing hormone agonists (GnRHa), both as initial and post-operative therapy, without the negative side effect profile

of GnRHa (Angioni *et al.* 2014, Andres Mde *et al.* 2015, Granese *et al.* 2015, Strowitzki *et al.* 2015). Levonorgestrel, delivered through an intrauterine system after conservative surgery, significantly decreases dysmenorrhea, dyspareunia, and non-cyclic pelvic pain compared to expectant management in a RCT of 55 patients (Tanmahasamut *et al.* 2012, Imai *et al.* 2014).

Several therapies aim to create a hypoestrogenic state in women with endometriosis. Examples of these treatments include GnRHa, GnRH antagonists (GnRH-ant), synthetic androgens, and AIs. GnRHa therapy downregulates gonadotropin receptors and desensitizes the body to gonadotropins. It decreases pain and endometriotic nodules in comparison to placebo (Leone Roberti Maggiore *et al.* 2014, Brown & Farquhar 2015). A multi-center RCT comparing GnRHa to OCPs as post-surgical therapy reports both groups increase quality of life scores (Granese *et al.* 2015). Although GnRHa is proven effective, a severe side effect is decreased bone mineral density (BMD); therefore, estrogens or progestins are given for bone protection (Leone Roberti Maggiore *et al.* 2014, Zito *et al.* 2014). In contrast, GnRH-ant inhibit gonadotropin receptors. Elagolix improves dysmenorrhea and dyspareunia compared to placebo in a phase 2 RCT (Ezzati & Carr 2015, Munoz-Hernando *et al.* 2015) and, comparing BMD profiles of elagolix with depot medroxyprogesterone acetate, both minimally impact BMD (Carr *et al.* 2014, Ezzati & Carr 2015).

Danazol, a synthetic androgen, inhibits the luteinizing hormone (LH) surge; however, it also increases free testosterone, causing undesired side effects including hirsutism, deepening of voice, weight gain, and acne. Danazol effectively decreases pelvic pain compared to placebo, and is as effective as other hormonal therapies, but the numerous side effects limit use (Practice Committee of the American Society for Reproductive 2014, Zito *et al.* 2014). AIs are currently a second line treatment in women refractory to first line treatments (Abu Hashim 2014). AIs such as letrozole decrease estrogen stimulation of endometriosis and, when used in combination with GnRHa, improve pelvic pain more than GnRHa alone. Additionally, letrozole with norethindrone acetate add-back has improved endometriosis symptoms, and high dose aromatase inhibition reduces ovarian endometrioma size (Agarwal *et al.* 2015). In contrast, a small RCT investigating post-surgical endometriosis pain comparing OCPs alone and in combination with letrozole reports similar pain scores, suggesting no benefit with letrozole addition (Almassinokiani *et al.* 2014).

Surgical Therapy

Surgical therapy for endometriosis is typically necessary for intractable pelvic pain despite medical therapy. Several different surgical techniques are performed (Table 2), including excision/removal of endometriosis, uterosacral nerve ablation, presacral neurectomy, and hysterectomy with bilateral salpingo-oophorectomy (BSO) (Daniels *et al.* 2010, Healey *et al.* 2014, Posadzka *et al.* 2015), and some techniques provide better symptomatic control than others. For symptom improvement and preventing disease recurrence, endometrioma removal is superior to drainage (Duffy *et al.* 2014, Practice Committee of the American Society for Reproductive 2014). Hysterectomy without BSO is less effective because of continued hormonal stimulation of microscopic endometriotic lesions. Hysterectomy with BSO leads to surgical menopause, which negatively impacts bone and cardiac health.

Extreme surgical management is reserved for patients who fail conservative management (Duffy *et al.* 2014, Practice Committee of the American Society for Reproductive 2014).

Alternative Therapy

Given that endometriosis is such a difficult disease to treat, alternative therapies are welcomed in addition to conventional therapy. Comparing Chinese medicine (CM) to GnRHa as post-surgical treatment for endometriosis found no differences in recurrence rates on follow-up (Weng *et al.* 2015). In contrast, Chinese herbal enemas decrease dysmenorrhea comparable to danazol (Kong *et al.* 2014), and CM and herbal enema combination is superior to danazol in decreasing pain symptoms (Flower *et al.* 2012). An acupuncture study in addition to conventional medical therapy significantly decreases pelvic pain by 5 to 6 points on the 10-point VAS (Rubi-Klein *et al.* 2010). Pelvic physical therapy includes internal manual treatment to stretch pelvic floor muscles, myofascial release, biofeedback, and trigger point release. In those with myofascial chronic pelvic pain, 63% report significant pain improvement after at least 6 sessions (Bedaiwy *et al.* 2013). Exercise can provide pain relief, based on questionnaire studies composed of 50-2730 women with endometriosis and 400-4000 control women; however, other survey studies correlate exercise with increased pelvic pain. Unfortunately, not all of these studies are controlled and all are from self-reporting (Bonocher *et al.* 2014). Large prospective cohort or case-control studies demonstrate increased risk of endometriosis with diets high in trans-fatty acids and decreased risk with diets containing high levels of long-chain omega 3 fatty acids (Hansen & Knudsen 2013). More high quality studies are needed in these areas and importantly, a positive publication selection bias likely exists with alternative therapies, exaggerating true effectiveness (Kong *et al.* 2014).

Association between Endometriosis and Cancer

The potential association between endometriosis and cancer has been theorized for decades. This association is based upon observational case-control and cohort studies that propose malignant transformation occurs within endometriotic lesions, giving rise to cancer. Our molecular-genetic understanding of both endometriosis and ovarian cancer continues to rapidly evolve; yet, a definitive mechanism for malignant transformation remains elusive.

Risk and Prognosis

The 10% prevalence of endometriosis and an even higher prevalence for women with infertility or chronic pelvic pain, makes the establishment of an absolute “cause-and-effect” relationship problematic. Lifetime risk of developing ovarian cancer in the general population is ∼1.4%, with a median age of onset in the early 60s (Schorge *et al.* 2010). Epithelial ovarian cancer is no longer seen as a single disease, but rather a constellation of multiple diseases based upon histologic subtypes and unique molecular signatures (Galic *et al.* 2013). The risk of ovarian cancer increases for women who incur fewer pregnancies and/or suffer from infertility. The possibility of confounding when assessing associative risk between these two entities must be considered because infertility is related to both conditions.

Nonetheless, a number of epidemiologic and clinical features lead investigators to propose an association between endometriosis and cancer. The establishment of an association was reported 90 years ago (Sampson 1925) and was refined in 1953, proposing that benign endometriosis should be observed in close anatomic proximity to the arising endometriosis-associated cancer (Scott 1953). Chief among the observations are that both entities produce tissues that can metastasize, invade, and destroy normal surrounding tissues. Furthermore, cancers often are identified in endometriotic lesions or in tissues that are contiguous with endometriosis, and there are often findings of candidate precursor lesions exhibiting histologic atypia in these surrounding tissues (Wei *et al.* 2011). Finally, endometriosis in younger women, which persists into older age, creates a long window for malignant transformation.

Several retrospective studies initially document the increased rate of endometriosis in women with ovarian cancer. A Swedish study containing over 20,000 patients that cross-matched inpatient endometriosis diagnosis and any cancer diagnosis (Brinton *et al.* 1997) found a small increased risk of any cancer, but the risks were not confirmed upon longer-term follow up (Brinton *et al.* 1997). The risk of ovarian cancer, however, is significantly increased in both the initial and long-term analyses. In patients with a history of prolonged endometriosis, the statistical risk for the development of ovarian cancer is even higher.

A linkage analysis of over 99,000 women from Denmark shows an endometriosis-related increase in ovarian cancer occurs in two histologic subtypes, clear cell and endometrioid (summarized in Table 3) (Brinton *et al.* 2005). Recent evidence also suggests a correlation between endometriosis and high-grade serous histologic type ovarian cancer (Lee *et al.* 2016). A large case-control study confirms an approximate 3-fold increased risk of clear cell or endometrioid ovarian cancer in association with endometriosis (Rossing *et al.* 2008). Malignant transformation risk to ovarian cancer from ovarian endometriosis is reportedly 0.2-2.5% (Gadducci *et al.* 2014). Recent studies also show the association between endometriosis and different forms of ovarian cancer: serous, mucinous, clear-cell, and endometrioid, with the predominant cell types being clear cell and endometrioid (Table 4).

A meta-analysis conducted by Kim *et al.* (2014) evaluates the risk and prognosis of ovarian cancer in ∼445,000 women with or without endometriosis. Based on 35 studies, women with endometriosis are significantly at risk of developing ovarian cancer; however, stage is more likely to be early and low-grade, suggesting the cancer is slow growing and less invasive. Endometrioid and clear cell are common in women with endometriosis, with the serous subtype occurring less frequently and the mucinous subtype displaying no differences between control women and women with endometriosis (Kim *et al.* 2014). Endometriosis does not affect prognosis, and overall survival in women with endometriosis-associated ovarian cancer (EAOC) and in women with non-EAOC are similar when accounting for histology, disease status, assessment of endometriosis, and potential confounding factors. Unfortunately, the effect of endometriosis on a successful debulking surgery is not analyzed (Kim *et al.* 2014), so it is unknown if there is a benefit in survival in women with EAOC.

Proposed Mechanisms of Malignant Transformation

Complex hormonal, genetic, and immunologic interactions must be considered when assessing the interplay between endometriosis in the development of epithelial primary peritoneal or ovarian carcinomas. Chronic inflammation, autocrine and paracrine effects, hormonal interactions, and micro-environmental alterations caused by endometriosis in the pelvic region could be relevant mechanisms for malignant transformation. Aberrant immune function, stimulated by estrogens, may create a positive feed-forward loop, enhancing growth and invasiveness of endometriosis and promoting malignant transformation (Ness 2003). Zanetta et al. report a role for a hyper-estrogenic state in stimulating endometriosis and promoting malignant transformation (Zanetta *et al.* 2000).

A permissive microenvironment and accumulation of genetic mutations is suggested to cause malignant change of endometriosis (Wei *et al.* 2011). Distinct molecular events may occur in early stages of tumorigenesis of endometriosis-associated carcinoma. Recent studies focus on genetic alterations such as phosphatase and tensin homolog (*PTEN*), tumor protein p53 (*TP53*), and B-cell lymphoma (*BCL*) gene mutations that lead to malignant changes of endometriosis (Nezhat *et al.* 2008, Munksgaard & Blaakaer 2012, Lai *et al.* 2013, McConechy *et al.* 2014). An interplay of genetics and oxidative stress, with decreased expression of interleukin 1 receptor type 2 (*IL1R2*), is a common signature between endometrioid ovarian cancer and endometriosis (Kobayashi *et al.* 2009, Keita *et al.* 2010, Keita *et al.* 2011). IL1 ligands are expressed by all endometriosis-associated ovarian cancer subtypes and endometrial cells. A decrease in IL1R1 levels, a protector against the tumorigenic effects of IL1, occurs in endometrioid carcinoma (Keita *et al.* 2010, Keita *et al.* 2011).

Multiple tumor-associated somatic mutations, detected by examining single gene or by whole genome sequencing, have revealed a signature of mutations. Mutations in catenin beta 1 (*CTNNB1*) are seen in 60% of ovarian endometrioid carcinomas (Matsumoto *et al.* 2015). Mutations in AT Rich Interactive Domain 1A (*ARID1A*) and phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (*PIK3CA*) appear most consistently in clear cell ovarian carcinomas (Gadducci *et al.* 2014, Anglesio *et al.* 2015, Matsumoto *et al.* 2015). Mutations in *ARID1A*, involved in chromatin remodeling, are present in both clear cell (15-75%) and endometrioid carcinomas (30-55%) (Wiegand *et al.* 2010, Gadducci *et al.* 2014). Associated with malignant transformation, mutations in *ARID1A* lead to the loss of its product, BAF250a, which correlates strongly with ovarian clear-cell carcinoma and endometrioid carcinoma subtypes, as well as with high-grade endometrial carcinomas (Wiegand *et al.* 2010, Wiegand *et al.* 2011, Ayhan *et al.* 2012, Lowery *et al.* 2012, Samartzis *et al.* 2012, Chene *et al.* 2015). *ARID1A* mutations and BAF250a loss are also observed in tumors and contiguous atypical endometriosis, but not in distant endometriotic lesions. The loss of *ARID1A* expression usually coexists with PI3K-Akt pathway activation and/or zinc finger protein 217 (ZNF217) amplification in ovarian clear cell cancers and may indicate an early event in the malignant transformation of endometriosis into the various histotypes of ovarian cancer (Ayhan *et al.* 2012, Huang *et al.* 2014).

Loss of *PTEN* is observed in clear cell-associated endometriosis and cancers, including a significant increase in expression levels of X-ray repair cross-complementing protein 5

(XRCC5), patched 2 (PTCH2), elongation factor 1-alpha 2 (EEF1A2) and protein phosphatase 1 regulatory subunit 14B (PPP1R14B). However, these changes are not observed in benign endometriosis (Worley *et al.* 2015). *PTEN* loss is proposed as an early and permissive event in endometriosis development, while loss of *ESR1* and polycomb-mediated transcriptional factor cause ultimate malignant transformation (Worley *et al.* 2015).

Future research will clarify the likely complex interaction between genetic alterations, estrogen exposure, inflammatory cytokines, and the immunologic microenvironment in the transformation of endometriosis to endometrioid and clear cell ovarian and primary peritoneal cancers. Treatment of these cancers will hopefully improve with use of targeted and immunologic therapies that address underlying causes of malignant transformation.

Concluding Remarks: Where are we going?

While the studies reviewed from the last 5 years demonstrate a deeper understanding of endometriosis as dysregulations pertain to hormones, hormone receptors, immune function, and transformation to ovarian cancer, endometriosis still remains mysterious from many facets. Critically needed for this enigmatic disease are mechanistic understandings of disease initiation and perturbation that will hopefully lead to the development of non-invasive disease diagnosis and the development of treatments that do not negate hormonal cyclicity or have other undesired side effect profiles and decrease the need for surgical extirpation. To allow for this to happen, the following areas of need are identified:

- Establish clear limits to animal models and clarify what the model may and may not reveal
- Establish international standards for collection of patient information and samples as outlined by (Fassbender *et al.* 2013)
- Establish disease profile through clearer understanding of cytokines and the potential association with autoimmune disorders
- Characterization of interplay between the hormonal milieu and immune system
- Focus on lifetime exposures, acute and chronic, to endocrine disrupting chemicals that may interfere with uterine development, immune system regulation, and ultimately endometriosis development
- Full recognition that this disease is truly multifaceted with pain, psychology, infertility, immunity, etc.
- Transformation of endometriosis to ovarian cancer through characterization of the lag between endometriosis found on the ovary to an ovarian cancer diagnosis
- Determine if age, parity, weight, hormonal regulators (oral contraceptives) contribute to transformation to cancer diagnosis

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References

Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril. 1997; 67:817–821. [PubMed: 9130884]

Abu Hashim H. Potential role of aromatase inhibitors in the treatment of endometriosis. Int J Womens Health. 2014; 6:671–680. [PubMed: 25092998]

Acien P, Velasco I, Acien M, Capello C, Vela P. Epithelial ovarian cancers and endometriosis. Gynecol Obstet Invest. 2015; 79:126–135. [PubMed: 25634648]

Agarwal S, Fraser MA, Chen I, Singh SS. Dienogest for the treatment of deep endometriosis: case report and literature review. J Obstet Gynaecol Res. 2015; 41:309–313. [PubMed: 25303112]

Ahn S, Monsanto S, Miller C, Singh S, Thomas R, Tayade C. Pathophysiology and Immune Dysfunction in Endometriosis. Biomed Res Int. 2015a; 2015:795976. [PubMed: 26247027]

Ahn SH, Edwards AK, Singh SS, Young SL, Lessey BA, Tayade C. IL-17A Contributes to the Pathogenesis of Endometriosis by Triggering Proinflammatory Cytokines and Angiogenic Growth Factors. J Immunol. 2015b; 195:2591–2600. [PubMed: 26259585]

Akbarzadeh-Jahromi M, Shekarkhar G, Sari Aslani F, Azarpira N, Heidari Esfahani M, Momtahan M. Prevalence of Endometriosis in Malignant Epithelial Ovarian Tumor. Arch Iran Med. 2015; 18:844–848. [PubMed: 26621017]

Almassinokiani F, Almasi A, Akbari P, Saberifard M. Effect of Letrozole on endometriosis-related pelvic pain. Med J Islam Repub Iran. 2014; 28:107. [PubMed: 25664308]

Andreoli CG, Genro VK, Souza CA, Michelon T, Bilibio JP, Scheffel C, Cunha-Filho JS. T helper (Th)1, Th2, and Th17 interleukin pathways in infertile patients with minimal/mild endometriosis. Fertil Steril. 2011; 95:2477–2480. [PubMed: 21392744]

Andres Mde P, Lopes LA, Baracat EC, Podgaec S. Dienogest in the treatment of endometriosis: systematic review. Arch Gynecol Obstet. 2015; 292:523–529. [PubMed: 25749349]

Angioni S, Cofelice V, Pontis A, Tinelli R, Socolov R. New trends of progestins treatment of endometriosis. Gynecol Endocrinol. 2014; 30:769–773. [PubMed: 25144122]

Anglesio MS, Bashashati A, Wang YK, Senz J, Ha G, Yang W, Aniba MR, Prentice LM, Farahani H, Li Chang H, Karnezis AN, Marra MA, Yong PJ, Hirst M, Gilks B, Shah SP, Huntsman DG. Multifocal endometriotic lesions associated with cancer are clonal and carry a high mutation burden. J Pathol. 2015; 236:201–209. [PubMed: 25692284]

Aoki D, Katsuki Y, Shimizu A, Kakinuma C, Nozawa S. Successful heterotransplantation of human endometrium in SCID mice. Obstet Gynecol. 1994; 83:220–228. [PubMed: 8290184]

Aris A. Endometriosis-associated ovarian cancer: A ten-year cohort study of women living in the Estrie Region of Quebec, Canada. J Ovarian Res. 2010; 3:2. [PubMed: 20205767]

Ayhan A, Mao TL, Seckin T, Wu CH, Guan B, Ogawa H, Futagami M, Mizukami H, Yokoyama Y, Kurman RJ, Shih Ie M. Loss of ARID1A expression is an early molecular event in tumor progression from ovarian endometriotic cyst to clear cell and endometrioid carcinoma. Int J Gynecol Cancer. 2012; 22:1310–1315. [PubMed: 22976498]

Barcz E, Milewski L, Dziunycz P, Kaminski P, Ploski R, Malejczyk J. Peritoneal cytokines and adhesion formation in endometriosis: an inverse association with vascular endothelial growth factor concentration. Fertil Steril. 2012; 97:1380–1386 e1381. [PubMed: 22542989]

Bedaiwy MA, Dahoud W, Skomorovska-Prokvolit Y, Yi L, Liu JH, Falcone T, Hurd WW, Mesiano S. Abundance and Localization of Progesterone Receptor Isoforms in Endometrium in Women With and Without Endometriosis and in Peritoneal and Ovarian Endometriotic Implants. Reprod Sci. 2015; 22:1153–1161. [PubMed: 26037298]

Bedaiwy MA, Patterson B, Mahajan S. Prevalence of myofascial chronic pelvic pain and the effectiveness of pelvic floor physical therapy. J Reprod Med. 2013; 58:504–510. [PubMed: 24568045]

Bellelis P, Barbeiro DF, Rizzo LV, Baracat EC, Abrao MS, Podgaec S. Transcriptional changes in the expression of chemokines related to natural killer and T-regulatory cells in patients with deep infiltrative endometriosis. Fertil Steril. 2013; 99:1987–1993. [PubMed: 23517860]

Bersinger NA, Dechaud H, McKinnon B, Mueller MD. Analysis of cytokines in the peritoneal fluid of endometriosis patients as a function of the menstrual cycle stage using the Bio-Plex(R) platform. Arch Physiol Biochem. 2012; 118:210–218. [PubMed: 22632541]

Beste MT, Pfaffle-Doyle N, Prentice EA, Morris SN, Lauffenburger DA, Isaacson KB, Griffith LG. Molecular network analysis of endometriosis reveals a role for c-Jun-regulated macrophage activation. Sci Transl Med. 2014; 6:222ra216.

Bonocher CM, Montenegro ML, Rosa ESJC, Ferriani RA, Meola J. Endometriosis and physical exercises: a systematic review. Reprod Biol Endocrinol. 2014; 12:4. [PubMed: 24393293]

Bourlev V, Iljasova N, Adamyan L, Larsson A, Olovsson M. Signs of reduced angiogenic activity after surgical removal of deeply infiltrating endometriosis. Fertil Steril. 2010; 94:52–57. [PubMed: 19324337]

Boyraz G, Selcuk I, Yazicioglu A, Tuncer ZS. Ovarian carcinoma associated with endometriosis. Eur J Obstet Gynecol Reprod Biol. 2013; 170:211–213. [PubMed: 23849309]

Braza-Boils A, Gilabert-Estelles J, Ramon LA, Gilabert J, Mari-Alexandre J, Chirivella M, Espana F, Estelles A. Peritoneal fluid reduces angiogenesis-related microRNA expression in cell cultures of endometrial and endometriotic tissues from women with endometriosis. PLoS One. 2013; 8:e62370. [PubMed: 23620826]

Braza-Boils A, Mari-Alexandre J, Gilabert J, Sanchez-Izquierdo D, Espana F, Estelles A, Gilabert-Estelles J. MicroRNA expression profile in endometriosis: its relation to angiogenesis and fibrinolytic factors. Hum Reprod. 2014; 29:978–988. [PubMed: 24608518]

Braza-Boils A, Salloum-Asfar S, Mari-Alexandre J, Arroyo AB, Gonzalez-Conejero R, Barcelo-Molina M, Garcia-Oms J, Vicente V, Estelles A, Gilabert-Estelles J, Martinez C. Peritoneal fluid modifies the microRNA expression profile in endometrial and endometriotic cells from women with endometriosis. Hum Reprod. 2015; 30:2292–2302. [PubMed: 26307093]

Brinton LA, Gridley G, Persson I, Baron J, Bergqvist A. Cancer risk after a hospital discharge diagnosis of endometriosis. Am J Obstet Gynecol. 1997; 176:572–579. [PubMed: 9077609]

Brinton LA, Sakoda LC, Sherman ME, Frederiksen K, Kjaer SK, Graubard BI, Olsen JH, Mellemkjaer L. Relationship of benign gynecologic diseases to subsequent risk of ovarian and uterine tumors. Cancer Epidemiol Biomarkers Prev. 2005; 14:2929–2935. [PubMed: 16365012]

Brown J, Farquhar C. An overview of treatments for endometriosis. JAMA. 2015; 313:296–297. [PubMed: 25603001]

Bruner-Tran K, McConaha M, Osteen K. Models of Endometriosis: Animal Models I - Rodent-based Chimeric Models. Endometriosis: Science and Practice. 2012

Bukulmez O, Hardy DB, Carr BR, Word RA, Mendelson CR. Inflammatory status influences aromatase and steroid receptor expression in endometriosis. Endocrinology. 2008; 149:1190–1204. [PubMed: 18048499]

Bulun SE. Endometriosis. N Engl J Med. 2009; 360:268–279. [PubMed: 19144942]

Bulun SE, Monsavais D, Pavone ME, Dyson M, Xue Q, Attar E, Tokunaga H, Su EJ. Role of estrogen receptor-beta in endometriosis. Semin Reprod Med. 2012; 30:39–45. [PubMed: 22271293]

Bulun SE, Monsivais D, Kakinuma T, Furukawa Y, Bernardi L, Pavone ME, Dyson M. Molecular biology of endometriosis: from aromatase to genomic abnormalities. Semin Reprod Med. 2015; 33:220–224. [PubMed: 26036904]

Burney RO, Talbi S, Hamilton AE, Vo KC, Nyegaard M, Nezhat CR, Lessey BA, Giudice LC. Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. Endocrinology. 2007; 148:3814–3826. [PubMed: 17510236]

Burns KA, Rodriguez KF, Hewitt SC, Janardhan KS, Young SL, Korach KS. Role of estrogen receptor signaling required for endometriosis-like lesion establishment in a mouse model. Endocrinology. 2012; 153:3960–3971. [PubMed: 22700766]

Carmona F, Chapron C, Martinez-Zamora MA, Santulli P, Rabanal A, Martinez-Florensa M, Lozano F, Balasch J. Ovarian endometrioma but not deep infiltrating endometriosis is associated with

increased serum levels of interleukin-8 and interleukin-6. J Reprod Immunol. 2012; 95:80–86. [PubMed: 22819248]

Carr B, Dmowski WP, O'Brien C, Jiang P, Burke J, Jimenez R, Garner E, Chwalisz K. Elagolix, an oral GnRH antagonist, versus subcutaneous depot medroxyprogesterone acetate for the treatment of endometriosis: effects on bone mineral density. Reprod Sci. 2014; 21:1341–1351. [PubMed: 25249568]

Carr BJ, Ochoa L, Rankin D, Owens BD. Biologic response to orthopedic sutures: a histologic study in a rabbit model. Orthopedics. 2009; 32:828. [PubMed: 19902886]

Chen S, Wu RF, Su L, Zhou WD, Zhu MB, Chen QH. Lipoxin A4 regulates expression of the estrogen receptor and inhibits 17beta-estradiol induced p38 mitogen-activated protein kinase phosphorylation in human endometriotic stromal cells. Fertil Steril. 2014; 102:264–271. [PubMed: 24835059]

Chen SQ, Li JB, Jiang HY, Yuan L, Niu G, Yao SZ. Expression of human beta-defensin-2 in the eutopic and ectopic endometrial tissues in patients with endometriosis. Arch Gynecol Obstet. 2013a; 287:1151–1157. [PubMed: 23269356]

Chen YJ, Wu HH, Liau WT, Tsai CY, Tsai HW, Chao KC, Sung YJ, Li HY. A tumor necrosis factor-alpha inhibitor reduces the embryotoxic effects of endometriotic peritoneal fluid. Fertil Steril. 2013b; 100:1476–1485. [PubMed: 24012198]

Chene G, Ouellet V, Rahimi K, Barres V, Provencher D, Mes-Masson AM. The ARID1A pathway in ovarian clear cell and endometrioid carcinoma, contiguous endometriosis, and benign endometriosis. Int J Gynaecol Obstet. 2015; 130:27–30. [PubMed: 25912412]

Colette S, Defrere S, Lousse JC, Van Langendonckt A, Gotteland JP, Loumaye E, Donnez J. Inhibition of steroid sulfatase decreases endometriosis in an in vivo murine model. Hum Reprod. 2011; 26:1362–1370. [PubMed: 21441545]

Cummings A, Metcalf J. Induction of Endometriosis in Mice: A New Model Sensitive to Estrogen. Repro Toxicol. 1995; 9:233–238.

D'hooghe T, Bambra C, De Jonge I, Lauweryns J, Koninckx P. The prevalence of spontaneous endometriosis in the baboon (*Papio anubis, Papio cynocephalus*) increases with the duration of captivity. Acta Obstet Gynecol Scand. 1996; 75:98–101. [PubMed: 8604618]

D'Hooghe T, Bambra C, Raeymaekers B, De Jonge I, Lauweryns J, Koninckx P. Intrapelvic injection of menstrual endometrium causes endometriosis in baboons (*Papio cynocephalus* and *Papio anubis*). Am J Obstet Gynecol. 1995; 173:125–134. [PubMed: 7631669]

D'Hooghe T, Bambra C, Suleman M, Dunselman G, Evers H, Koninckx P. Development of a model of retrograde menstruation in baboons (*Papio anubis*). Fertil Steril. 1994; 62:635–638. [PubMed: 8062962]

Daniels JP, Middleton L, Xiong T, Champaneria R, Johnson NP, Lichten EM, Sutton C, Vercellini P, Gray R, Hills RK, Jones KD, Aimi G, Khan KS. International LIPDM-aCG. Individual patient data meta-analysis of randomized evidence to assess the effectiveness of laparoscopic uterosacral nerve ablation in chronic pelvic pain. Hum Reprod Update. 2010; 16:568–576. [PubMed: 20634210]

Davis M, Rauh-Hain JA, Andrade C, Boruta DM 2nd, Schorge JO, Horowitz NS, May T, del Carmen MG. Comparison of clinical outcomes of patients with clear cell and endometrioid ovarian cancer associated with endometriosis to papillary serous carcinoma of the ovary. Gynecol Oncol. 2014; 132:760–766. [PubMed: 24440832]

Delbandi AA, Mahmoudi M, Shervin A, Akbari E, Jeddi-Tehrani M, Sankian M, Kazemnejad S, Zarnani AH. Eutopic and ectopic stromal cells from patients with endometriosis exhibit differential invasive, adhesive, and proliferative behavior. Fertil Steril. 2013; 100:761–769. [PubMed: 23721717]

Duffy JM, Arambage K, Correa FJ, Olive D, Farquhar C, Garry R, Barlow DH, Jacobson TZ. Laparoscopic surgery for endometriosis. Cochrane Database Syst Rev. 2014; 4:CD011031. [PubMed: 24696265]

Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap A, Prentice A, Saridogan E, Soriano D, Nelen W. European Society of

Human R & Embryology. ESHRE guideline: management of women with endometriosis. Hum Reprod. 2014; 29:400–412. [PubMed: 24435778]

Dyson MT, Roqueiro D, Monsivais D, Ercan CM, Pavone ME, Brooks DC, Kakinuma T, Ono M, Jafari N, Dai Y, Bulun SE. Genome-wide DNA methylation analysis predicts an epigenetic switch for GATA factor expression in endometriosis. PLoS Genet. 2014; 10:e1004158. [PubMed: 24603652]

Dzatic-Smiljkovic O, Vasiljevic M, Djukic M, Vugdelic R, Vugdelic J. Frequency of ovarian endometriosis in epithelial ovarian cancer patients. Clin Exp Obstet Gynecol. 2011; 38:394–398. [PubMed: 22268283]

Elgafor, El; Sharkwy, IA. Combination of non-invasive and semi-invasive tests for diagnosis of minimal to mild endometriosis. Arch Gynecol Obstet. 2013; 288:793–797. [PubMed: 23545836]

Ezzati M, Carr BR. Elagolix, a novel, orally bioavailable GnRH antagonist under investigation for the treatment of endometriosis-related pain. Womens Health (Lond Engl). 2015; 11:19–28. [PubMed: 25581052]

Fassbender A, Vodolazkaia A, Saunders P, Lebovic D, Waelkens E, De Moor B, D'Hooghe T. Biomarkers of endometriosis. Fertil Steril. 2013; 99:1135–1145. [PubMed: 23414923]

Fernando S, Soh PQ, Cooper M, Evans S, Reid G, Tsaltas J, Rombauts L. Reliability of visual diagnosis of endometriosis. J Minim Invasive Gynecol. 2013; 20:783–789. [PubMed: 24183270]

Flower A, Liu JP, Lewith G, Little P, Li Q. Chinese herbal medicine for endometriosis. Cochrane Database Syst Rev. 2012; 5:CD006568. [PubMed: 22592712]

Fritz MA, S L. Clinical Gynecologic Endocrinology and Infertility. 2011

Funamizu A, Fukui A, Kamoi M, Fuchinoue K, Yokota M, Fukuhara R, Mizunuma H. Expression of natural cytotoxicity receptors on peritoneal fluid natural killer cell and cytokine production by peritoneal fluid natural killer cell in women with endometriosis. Am J Reprod Immunol. 2014; 71:359–367. [PubMed: 24495049]

Gadducci A, Lanfredini N, Tana R. Novel insights on the malignant transformation of endometriosis into ovarian carcinoma. Gynecol Endocrinol. 2014; 30:612–617. [PubMed: 24905724]

Galic V, Coleman RL, Herzog TJ. Unmet needs in ovarian cancer: dividing histologic subtypes to exploit novel targets and pathways. Curr Cancer Drug Targets. 2013; 13:698–707. [PubMed: 23675882]

Goncalves HF, Zendron C, Cavalcante FS, Aiceles V, Oliveira MA, Manaia JH, Babinski MA, Ramos CF. Leptin, its receptor and aromatase expression in deep infiltrating endometriosis. J Ovarian Res. 2015; 8:53. [PubMed: 26242176]

Granese R, Perino A, Calagna G, Saitta S, De Franciscis P, Colacurci N, Triolo O, Cucinella G. Gonadotrophin-releasing hormone analogue or dienogest plus estradiol valerate to prevent pain recurrence after laparoscopic surgery for endometriosis: a multi-center randomized trial. Acta Obstet Gynecol Scand. 2015; 94:637–645. [PubMed: 25761587]

Greaves E, Cousins FL, Murray A, Esnal-Zufiaurre A, Fassbender A, Horne AW, Saunders PT. A novel mouse model of endometriosis mimics human phenotype and reveals insights into the inflammatory contribution of shed endometrium. Am J Pathol. 2014; 184:1930–1939. [PubMed: 24910298]

Greenberg LH, Slayden OD. Human endometriotic xenografts in immunodeficient RAG-2/gamma(c)KO mice. Am J Obstet Gynecol. 2004; 190:1788–1795. discussion 1795-1786. [PubMed: 15284801]

Grummer R. Models of Endometriosis: *In vitro* and *In vivo* Models. Endometriosis: Science and Practice. 2012

Guo Y, Chen Y, Liu LB, Chang KK, Li H, Li MQ, Shao J. IL-22 in the endometriotic milieu promotes the proliferation of endometrial stromal cells via stimulating the secretion of CCL2 and IL-8. Int J Clin Exp Pathol. 2013; 6:2011–2020. [PubMed: 24133578]

Han SJ, Hawkins SM, Begum K, Jung SY, Kovanci E, Qin J, Lydon JP, DeMayo FJ, O'Malley BW. A new isoform of steroid receptor coactivator-1 is crucial for pathogenic progression of endometriosis. Nat Med. 2012; 18:1102–1111. [PubMed: 22660634]

Han SJ, Jung SY, Wu SP, Hawkins SM, Park MJ, Kyo S, Qin J, Lydon JP, Tsai SY, Tsai MJ, DeMayo FJ, O'Malley BW. Estrogen Receptor beta Modulates Apoptosis Complexes and the

Inflammasome to Drive the Pathogenesis of Endometriosis. Cell. 2015; 163:960–974. [PubMed: 26544941]

Hansen SO, Knudsen UB. Endometriosis, dysmenorrhoea and diet. Eur J Obstet Gynecol Reprod Biol. 2013; 169:162–171. [PubMed: 23642910]

Harada T, Momoeda M, Taketani Y, Hoshiai H, Terakawa N. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. Fertil Steril. 2008; 90:1583–1588. [PubMed: 18164001]

Healey M, Cheng C, Kaur H. To excise or ablate endometriosis? A prospective randomized double-blinded trial after 5-year follow-up. J Minim Invasive Gynecol. 2014; 21:999–1004. [PubMed: 24768960]

Herington JL, Crispens MA, Carvalho-Macedo AC, Camargos AF, Lebovic DI, Bruner-Tran KL, Osteen KG. Development and prevention of postsurgical adhesions in a chimeric mouse model of experimental endometriosis. Fertil Steril. 2011; 95:1295–1301 e1291. [PubMed: 20934690]

Hickey M, Ballard K, Farquhar C. Endometriosis. BMJ. 2014; 348:g1752. [PubMed: 24647161]

Hsu AL, Khachikyan I, Stratton P. Invasive and noninvasive methods for the diagnosis of endometriosis. Clin Obstet Gynecol. 2010; 53:413–419. [PubMed: 20436318]

Huang HN, Lin MC, Huang WC, Chiang YC, Kuo KT. Loss of ARID1A expression and its relationship with PI3K-Akt pathway alterations and ZNF217 amplification in ovarian clear cell carcinoma. Mod Pathol. 2014; 27:983–990. [PubMed: 24336158]

Hull ML, Johan MZ, Hodge WL, Robertson SA, Ingman WV. Host-derived TGFB1 deficiency suppresses lesion development in a mouse model of endometriosis. Am J Pathol. 2012; 180:880–887. [PubMed: 22210480]

Ilad RS, Fleming SD, Murphy CR, Fazleabas AT. Immunohistochemical study of the ubiquitin-nuclear factor-kB pathway in the endometrium of the baboon (Papio anubis) with and without endometriosis. Reprod Fertil Dev. 2010; 22:1118–1130. [PubMed: 20797350]

Imai A, Matsunami K, Takagi H, Ichigo S. Levonorgestrel-releasing intrauterine device used for dysmenorrhea: five-year literature review. Clin Exp Obstet Gynecol. 2014; 41:495–498. [PubMed: 25864246]

Juhasz-Boss I, Hofele A, Lattrich C, Buchholz S, Ortmann O, Malik E. Matrix metalloproteinase messenger RNA expression in human endometriosis grafts cultured on a chicken chorioallantoic membrane. Fertil Steril. 2010; 94:40–45. [PubMed: 19345347]

Kang YJ, Jeung IC, Park A, Park YJ, Jung H, Kim TD, Lee HG, Choi I, Yoon SR. An increased level of IL-6 suppresses NK cell activity in peritoneal fluid of patients with endometriosis via regulation of SHP-2 expression. Hum Reprod. 2014; 29:2176–2189. [PubMed: 25035432]

Keita M, AinMelk Y, Pelmus M, Bessette P, Aris A. Endometrioid ovarian cancer and endometriotic cells exhibit the same alteration in the expression of interleukin-1 receptor II: to a link between endometriosis and endometrioid ovarian cancer. J Obstet Gynaecol Res. 2011; 37:99–107. [PubMed: 21083841]

Keita M, Bessette P, Pelmus M, Ainmelk Y, Aris A. Expression of interleukin-1 (IL-1) ligands system in the most common endometriosis-associated ovarian cancer subtypes. J Ovarian Res. 2010; 3:3. [PubMed: 20181040]

Khan KN, Kitajima M, Inoue T, Fujishita A, Nakashima M, Masuzaki H. 17beta-estradiol and lipopolysaccharide additively promote pelvic inflammation and growth of endometriosis. Reprod Sci. 2015; 22:585–594. [PubMed: 25355803]

Kim HS, Kim TH, Chung HH, Song YS. Risk and prognosis of ovarian cancer in women with endometriosis: a meta-analysis. Br J Cancer. 2014; 110:1878–1890. [PubMed: 24518590]

King C, Barbara C, Prentice A, Brenton J, Charnock-Jones D. Models of endometriosis and their utility in studying progression to ovarian clear cell carcinoma. J Pathol. 2015

Kinugasa S, Shinohara K, Wakatsuki A. Increased asymmetric dimethylarginine and enhanced inflammation are associated with impaired vascular reactivity in women with endometriosis. Atherosclerosis. 2011; 219:784–788. [PubMed: 21880316]

Kobayashi H, Yamada Y, Kanayama S, Furukawa N, Noguchi T, Haruta S, Yoshida S, Sakata M, Sado T, Oi H. The role of hepatocyte nuclear factor-1beta in the pathogenesis of clear cell carcinoma of the ovary. Int J Gynecol Cancer. 2009; 19:471–479. [PubMed: 19407577]

Kondi-Pafiti A, Papakonstantinou E, Iavazzo C, Grigoriadis C, Salakos N, Gregoriou O. Clinicopathological characteristics of ovarian carcinomas associated with endometriosis. Arch Gynecol Obstet. 2012; 285:479–483. [PubMed: 21717140]

Kong S, Zhang YH, Liu CF, Tsui I, Guo Y, Ai BB, Han FJ. The complementary and alternative medicine for endometriosis: a review of utilization and mechanism. Evid Based Complement Alternat Med. 2014; 2014:146383. [PubMed: 24701237]

Kulak J Jr, Fischer C, Komm B, Taylor HS. Treatment with bazedoxifene, a selective estrogen receptor modulator, causes regression of endometriosis in a mouse model. Endocrinology. 2011; 152:3226–3232. [PubMed: 21586552]

Kumar R, Clerc AC, Gori I, Russell R, Pellegrini C, Govender L, Wyss JC, Golshayan D, Canny GO. Lipoxin A(4) prevents the progression of de novo and established endometriosis in a mouse model by attenuating prostaglandin E(2) production and estrogen signaling. PLoS One. 2014; 9:e89742. [PubMed: 24587003]

Kumar S, Munkarah A, Arabi H, Bandyopadhyay S, Semaan A, Hayek K, Garg G, Morris R, Ali-Fehmi R. Prognostic analysis of ovarian cancer associated with endometriosis. Am J Obstet Gynecol. 2011; 204:63 e61–67. [PubMed: 21074136]

Lai CR, Hsu CY, Chen YJ, Yen MS, Chao KC, Li AF. Ovarian cancers arising from endometriosis: a microenvironmental biomarker study including ER, HNF1ss, p53, PTEN, BAF250a, and COX-2. J Chin Med Assoc. 2013; 76:629–634. [PubMed: 23962610]

Lebovic DI, Kavoussi SK, Lee J, Banu SK, Arosh JA. PPARgamma activation inhibits growth and survival of human endometriotic cells by suppressing estrogen biosynthesis and PGE2 signaling. Endocrinology. 2013; 154:4803–4813. [PubMed: 24064359]

Leconte M, Chouzenoux S, Nicco C, Chereau C, Arkwright S, Santulli P, Weill B, Chapron C, Dousset B, Batteux F. Role of the CXCL12-CXCR4 axis in the development of deep rectal endometriosis. J Reprod Immunol. 2014; 103:45–52. [PubMed: 24534089]

Lee AW, Templeman C, Stram DA, Beesley J, Tyrer J, Berchuck A, Pharoah PP, Chenevix-Trench G, Pearce CL. Ovarian Cancer Association C. Evidence of a genetic link between endometriosis and ovarian cancer. Fertil Steril. 2016; 105:35–43 e10. [PubMed: 26477498]

Lee DH, Kim SC, Joo JK, Kim HG, Na YJ, Kwak JY, Lee KS. Effects of 17beta-estradiol on the release of monocyte chemotactic protein-1 and MAPK activity in monocytes stimulated with peritoneal fluid from endometriosis patients. J Obstet Gynaecol Res. 2012; 38:516–525. [PubMed: 22381103]

Leone Roberti Maggiore U, Scala C, Remorgida V, Venturini PL, Del Deo F, Torella M, Colacurci N, Salvatore S, Ferrari S, Papaleo E, Candiani M, Ferrero S. Triptorelin for the treatment of endometriosis. Expert Opin Pharmacother. 2014; 15:1153–1179. [PubMed: 24832495]

Lin W, Chen S, Li M, Wang B, Qu X, Zhang Y. Expression of macrophage migration inhibitory factor in human endometriosis: relation to disease stage, menstrual cycle and infertility. J Obstet Gynaecol Res. 2010; 36:344–351. [PubMed: 20492386]

Lowery WJ, Schildkraut JM, Akushevich L, Bentley R, Marks JR, Huntsman D, Berchuck A. Loss of ARID1A-associated protein expression is a frequent event in clear cell and endometrioid ovarian cancers. Int J Gynecol Cancer. 2012; 22:9–14. [PubMed: 22193641]

Lu Z, Zhang W, Jiang S, Zou J, Li Y. Effect of lesion location on endometriotic adhesion and angiogenesis in SCID mice. Arch Gynecol Obstet. 2014a; 289:823–830. [PubMed: 24150520]

Lu Z, Zhang W, Jiang S, Zou J, Li Y. Effect of oxygen tensions on the proliferation and angiogenesis of endometriosis heterograft in severe combined immunodeficiency mice. Fertil Steril. 2014b; 101:568–576. [PubMed: 24290003]

Luk J, Seval Y, Ulukus M, Ulukus EC, Arici A, Kayisli UA. Regulation of monocyte chemotactic protein-1 expression in human endometrial endothelial cells by sex steroids: a potential mechanism for leukocyte recruitment in endometriosis. Reprod Sci. 2010; 17:278–287. [PubMed: 19933497]

Maas J, Groothuis P, Dunselman G, de Goeij A, Struijker-Boudier H, Evers J. Development of endometriosis-like lesions after transplantation of human endometrial fragments onto the chick embryo chorioallantoic membrane. Hum Reprod. 2001; 16:627–631. [PubMed: 11278208]

Machado DE, Berardo PT, Palmero CY, Nasciutti LE. Higher expression of vascular endothelial growth factor (VEGF) and its receptor VEGFR-2 (Flk-1) and metalloproteinase-9 (MMP-9) in a rat model of peritoneal endometriosis is similar to cancer diseases. J Exp Clin Cancer Res. 2010; 29:4. [PubMed: 20085636]

Machado DE, Palumbo A Jr, Santos JM, Mattos RM, dos Santos TA, Seabra SH, Boldrini Lda C, Perini JA, Nasciutti LE. A GFP endometriosis model reveals important morphological characteristics of the angiogenic process that govern benign and malignant diseases. Histol Histopathol. 2014; 29:903–912. [PubMed: 24385307]

Malhotra N, Karmakar D, Tripathi V, Luthra K, Kumar S. Correlation of angiogenic cytokines-leptin and IL-8 in stage, type and presentation of endometriosis. Gynecol Endocrinol. 2012; 28:224–227. [PubMed: 21848410]

Margari KM, Zafiropoulos A, Hatzidaki E, Giannakopoulou C, Arici A, Matalliotakis I. Peritoneal fluid concentrations of beta-chemokines in endometriosis. Eur J Obstet Gynecol Reprod Biol. 2013; 169:103–107. [PubMed: 23474119]

Matsumoto T, Yamazaki M, Takahashi H, Kajita S, Suzuki E, Tsuruta T, Saegusa M. Distinct beta-catenin and PIK3CA mutation profiles in endometriosis-associated ovarian endometrioid and clear cell carcinomas. Am J Clin Pathol. 2015; 144:452–463. [PubMed: 26276776]

McConechy MK, Ding J, Senz J, Yang W, Melnyk N, Tone AA, Prentice LM, Wiegand KC, McAlpine JN, Shah SP, Lee CH, Goodfellow PJ, Gilks CB, Huntsman DG. Ovarian and endometrial endometrioid carcinomas have distinct CTNNB1 and PTEN mutation profiles. Mod Pathol. 2014; 27:128–134. [PubMed: 23765252]

Mier-Cabrera J, Jimenez-Zamudio L, Garcia-Latorre E, Cruz-Orozco O, Hernandez-Guerrero C. Quantitative and qualitative peritoneal immune profiles, T-cell apoptosis and oxidative stress-associated characteristics in women with minimal and mild endometriosis. BJOG. 2011; 118:6–16. [PubMed: 21083865]

Milewski L, Dziunycz P, Barcz E, Radomski D, Roszkowski PI, Korczak-Kowalska G, Kaminski P, Malejczyk J. Increased levels of human neutrophil peptides 1, 2, and 3 in peritoneal fluid of patients with endometriosis: association with neutrophils, T cells and IL-8. J Reprod Immunol. 2011; 91:64–70. [PubMed: 21831449]

Monsivais D, Dyson MT, Yin P, Coon JS, Navarro A, Feng G, Malpani SS, Ono M, Ercan CM, Wei JJ, Pavone ME, Su E, Bulun SE. ERbeta- and prostaglandin E2-regulated pathways integrate cell proliferation via Ras-like and estrogen-regulated growth inhibitor in endometriosis. Mol Endocrinol. 2014; 28:1304–1315. [PubMed: 24992181]

Munksgaard PS, Blaakaer J. The association between endometriosis and ovarian cancer: a review of histological, genetic and molecular alterations. Gynecol Oncol. 2012; 124:164–169. [PubMed: 22032835]

Munoz-Hernando L, Munoz-Gonzalez JL, Marqueta-Marques L, Alvarez-Conejo C, Tejerizo-Garcia A, Lopez-Gonzalez G, Villegas-Munoz E, Martin-Jimenez A, Jimenez-Lopez JS. Endometriosis: alternative methods of medical treatment. Int J Womens Health. 2015; 7:595–603. [PubMed: 26089705]

Muzii L, Di Tucci C, Achilli C, Di Donato V, Musella A, Palaia I, Panici PB. Continuous versus cyclic oral contraceptives after laparoscopic excision of ovarian endometriomas: a systematic review and metaanalysis. Am J Obstet Gynecol. 2015

Nap AW, Dunselman GA, de Goeij AF, Evers JL, Groothuis PG. Inhibiting MMP activity prevents the development of endometriosis in the chicken chorioallantoic membrane model. Hum Reprod. 2004; 19:2180–2187. [PubMed: 15242997]

Nap AW, Dunselman GA, Griffioen AW, Mayo KH, Evers JL, Groothuis PG. Angiostatic agents prevent the development of endometriosis-like lesions in the chicken chorioallantoic membrane. Fertil Steril. 2005; 83:793–795. [PubMed: 15749522]

Naqvi H, Sakr S, Presti T, Krikun G, Komm B, Taylor HS. Treatment with bazedoxifene and conjugated estrogens results in regression of endometriosis in a murine model. Biol Reprod. 2014; 90:121. [PubMed: 24740602]

Ness RB. Endometriosis and ovarian cancer: thoughts on shared pathophysiology. Am J Obstet Gynecol. 2003; 189:280–294. [PubMed: 12861175]

Nezhat F, Datta MS, Hanson V, Pejovic T, Nezhat C, Nezhat C. The relationship of endometriosis and ovarian malignancy: a review. Fertil Steril. 2008; 90:1559–1570. [PubMed: 18993168]

Novella-Maestre E, Herraiz S, Vila-Vives JM, Carda C, Ruiz-Sauri A, Pellicer A. Effect of antiangiogenic treatment on peritoneal endometriosis-associated nerve fibers. Fertil Steril. 2012; 98:1209–1217. [PubMed: 22921078]

Page-McCaw A, Ewald AJ, Werb Z. Matrix metalloproteinases and the regulation of tissue remodelling. Nat Rev Mol Cell Biol. 2007; 8:221–233. [PubMed: 17318226]

Palmer SS, Altan M, Denis D, Tos EG, Gotteland JP, Osteen KG, Bruner-Tran KL, Nataraja SG. Bentamapimod (JNK Inhibitor AS602801) Induces Regression of Endometriotic Lesions in Animal Models. Reprod Sci. 2015

Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, Nagle CM, Doherty JA, Cushing-Haugen KL, Wicklund KG, Chang-Claude J, Hein R, Lurie G, Wilkens LR, Carney ME, Goodman MT, Moysich K, Kjaer SK, Hogdall E, Jensen A, Goode EL, Fridley BL, Larson MC, Schildkraut JM, Palmieri RT, Cramer DW, Terry KL, Vitonis AF, Titus LJ, Ziogas A, Brewster W, Anton-Culver H, Gentry-Maharaj A, Ramus SJ, Anderson AR, Brueggmann D, Fasching PA, Gayther SA, Huntsman DG, Menon U, Ness RB, Pike MC, Risch H, Wu AH, Berchuck A. Ovarian Cancer Association C. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. Lancet Oncol. 2012; 13:385–394. [PubMed: 22361336]

Pellegrini C, Gori I, Achtari C, Hornung D, Chardonnens E, Wunder D, Fiche M, Canny GO. The expression of estrogen receptors as well as GREB1, c-MYC, and cyclin D1, estrogen-regulated genes implicated in proliferation, is increased in peritoneal endometriosis. Fertil Steril. 2012; 98:1200–1208. [PubMed: 22884659]

Podgaec S, Rizzo LV, Fernandes LF, Baracat EC, Abrao MS. CD4(+) CD25(high) Foxp3(+) cells increased in the peritoneal fluid of patients with endometriosis. Am J Reprod Immunol. 2012; 68:301–308. [PubMed: 22817851]

Posadzka E, Jach R, Pitynski K, Jablonski MJ. Treatment efficacy for pain complaints in women with endometriosis of the lesser pelvis after laparoscopic electroablation vs. CO2 laser ablation. Lasers Med Sci. 2015; 30:147–152. [PubMed: 25053520]

Practice Committee of the American Society for Reproductive M. Treatment of pelvic pain associated with endometriosis: a committee opinion. Fertil Steril. 2014; 101:927–935. [PubMed: 24630080]

Rathore N, Kriplani A, Yadav RK, Jaiswal U, Netam R. Distinct peritoneal fluid ghrelin and leptin in infertile women with endometriosis and their correlation with interleukin-6 and vascular endothelial growth factor. Gynecol Endocrinol. 2014; 30:671–675. [PubMed: 24845415]

Ricci AG, Olivares CN, Bilotas MA, Meresman GF, Baranao RI. Effect of vascular endothelial growth factor inhibition on endometrial implant development in a murine model of endometriosis. Reprod Sci. 2011; 18:614–622. [PubMed: 21266664]

Rossing MA, Cushing-Haugen KL, Wicklund KG, Doherty JA, Weiss NS. Risk of epithelial ovarian cancer in relation to benign ovarian conditions and ovarian surgery. Cancer Causes Control. 2008; 19:1357–1364. [PubMed: 18704718]

Rubi-Klein K, Kucera-Sliutz E, Nissel H, Bijak M, Stockenhuber D, Fink M, Wolkenstein E. Is acupuncture in addition to conventional medicine effective as pain treatment for endometriosis? A randomised controlled cross-over trial. Eur J Obstet Gynecol Reprod Biol. 2010; 153:90–93. [PubMed: 20728977]

Ruiz A, Salvo VA, Ruiz LA, Baez P, Garcia M, Flores I. Basal and steroid hormone-regulated expression of CXCR4 in human endometrium and endometriosis. Reprod Sci. 2010; 17:894–903. [PubMed: 20720261]

Sabbaghi M, Aram R, Roustaei H, Fadavi Islam M, Daneshvar M, Castano AR, Haghparast A. IL-17A concentration of seminal plasma and follicular fluid in infertile men and women with various clinical diagnoses. Immunol Invest. 2014; 43:617–626. [PubMed: 24927491]

Samartzis EP, Samartzis N, Noske A, Fedier A, Caduff R, Dedes KJ, Fink D, Imesch P. Loss of ARID1A/BAF250a-expression in endometriosis: a biomarker for risk of carcinogenic transformation? Mod Pathol. 2012; 25:885–892. [PubMed: 22301703]

Sampson J. Metastatic or Embolic Endometriosis, due to the Menstrual Dissemination of Endometrial Tissue into the Venous Circulation. Am J Pathol. 1927a; 3:93–110.143. [PubMed: 19969738]

Sampson J. Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. Am J Obstet Gynecol. 1927b; 14:422–469.

Sampson JA. Endometrial carcinoma of the ovary, arising in endometrial tissue in that organ. Archives of Surgery. 1925; 10:1–72.

Santulli P, Borghese B, Chouzenoux S, Streuli I, Borderie D, de Ziegler D, Weill B, Chapron C, Batteux F. Interleukin-19 and interleukin-22 serum levels are decreased in patients with ovarian endometrioma. Fertil Steril. 2013; 99:219–226. [PubMed: 23025883]

Scarfone G, Bergamini A, Noli S, Villa A, Cipriani S, Taccagni G, Vigano P, Candiani M, Parazzini F, Mangili G. Characteristics of clear cell ovarian cancer arising from endometriosis: a two center cohort study. Gynecol Oncol. 2014; 133:480–484. [PubMed: 24642093]

Schorge JO, Modesitt SC, Coleman RL, Cohn DE, Kauff ND, Duska LR, Herzog TJ. SGO White Paper on ovarian cancer: etiology, screening and surveillance. Gynecol Oncol. 2010; 119:7–17. [PubMed: 20692025]

Scott R, Te Linde R, Wharton L. Further studies on experimental endometriosis. Am J Obstet Gynecol. 1953; 66:1082–1103. [PubMed: 13104506]

Scott RB. Malignant changes in endometriosis. Obstet Gynecol. 1953; 2:283–289. [PubMed: 13087921]

Sikora J, Mielczarek-Palacz A, Kondera-Anasz Z. Imbalance in cytokines from interleukin-1 family - role in pathogenesis of endometriosis. Am J Reprod Immunol. 2012; 68:138–145. [PubMed: 22537218]

Sillem M, Hahn U, Coddington C, Gordon K, Runnebaum B, Hodgen G. Ectopic growth of endometrium depends on its structural integrity and proteolytic activity in the cynomolgus monkey (*Macaca fascicularis*) model of endometriosis. Fertil Steril. 1996; 66:468–473. [PubMed: 8751750]

Somigliana E, Vigano P, Rossi G, Carinelli S, Vignali M, Panina-Bordignon P. Endometrial ability to implant in ectopic sites can be prevented by interleukin-12 in a murine model of endometriosis. Hum Reprod. 1999; 14:2944–2950. [PubMed: 10601076]

Strowitzki T, Faustmann T, Gerlinger C, Schumacher U, Ahlers C, Seitz C. Safety and tolerability of dienogest in endometriosis: pooled analysis from the European clinical study program. Int J Womens Health. 2015; 7:393–401. [PubMed: 25926759]

Styer AK, Sullivan BT, Puder M, Arsenault D, Petrozza JC, Serikawa T, Chang S, Hasan T, Gonzalez RR, Rueda BR. Ablation of leptin signaling disrupts the establishment, development, and maintenance of endometriosis-like lesions in a murine model. Endocrinology. 2008; 149:506–514. [PubMed: 17962343]

Suganuma I, Mori T, Ito F, Tanaka Y, Sasaki A, Matsuo S, Kusuki I, Kitawaki J. Peroxisome proliferator-activated receptor gamma, coactivator 1alpha enhances local estrogen biosynthesis by stimulating aromatase activity in endometriosis. J Clin Endocrinol Metab. 2014; 99:E1191–1198. [PubMed: 24654751]

Syrop CH, Halme J. Peritoneal fluid environment and infertility. Fertil Steril. 1987; 48:1–9. [PubMed: 3109960]

Szubert M, Suzin J, Duechler M, Szulawska A, Czyz M, Kowalczyk-Amico K. Evaluation of selected angiogenic and inflammatory markers in endometriosis before and after danazol treatment. Reprod Fertil Dev. 2014; 26:414–420. [PubMed: 23544741]

Tanmahasamut P, Rattanachaiyanont M, Angsuwathana S, Techatraisak K, Indhavivadhana S, Leerasiri P. Postoperative levonorgestrel-releasing intrauterine system for pelvic endometriosis-related pain: a randomized controlled trial. Obstet Gynecol. 2012; 119:519–526. [PubMed: 22314873]

Tao Y, Zhang Q, Huang W, Zhu H, Zhang D, Luo W. The peritoneal leptin, MCP-1 and TNF-alpha in the pathogenesis of endometriosis-associated infertility. Am J Reprod Immunol. 2011; 65:403–406. [PubMed: 20825374]

Te Linde R, Scott R. Experimental endometriosis. Am J Obstet Gynecol. 1950; 60:1147–1173. [PubMed: 14789879]

Tirado-Gonzalez I, Barrientos G, Tariverdian N, Arck P, Garcia M, Klapp B, Blois S. Endometriosis research: animal models for the study of a complex disease. J Reprod Immunol. 2010; 86:141–147. [PubMed: 20594597]

Veillat V, Sengers V, Metz CN, Roger T, Leboeuf M, Mailloux J, Akoum A. Macrophage migration inhibitory factor is involved in a positive feedback loop increasing aromatase expression in endometriosis. Am J Pathol. 2012; 181:917–927. [PubMed: 22759564]

Velasco I, Acien P, Campos A, Acien MI, Ruiz-Macia E. Interleukin-6 and other soluble factors in peritoneal fluid and endometriomas and their relation to pain and aromatase expression. J Reprod Immunol. 2010; 84:199–205. [PubMed: 20074813]

Vernon M, Wilson E. Studies on the surgical induction of endometriosis in the rat. Fertil Steril. 1985; 44:684–694. [PubMed: 4054348]

Virani S, Edwards AK, Thomas R, Childs T, Tayade C. Blocking of stromal cell-derived factor-1 reduces neoangiogenesis in human endometriosis lesions in a mouse model. Am J Reprod Immunol. 2013; 70:386–397. [PubMed: 23650939]

Wang XQ, Yu J, Luo XZ, Shi YL, Wang Y, Wang L, Li DJ. The high level of RANTES in the ectopic milieu recruits macrophages and induces their tolerance in progression of endometriosis. J Mol Endocrinol. 2010; 45:291–299. [PubMed: 20732991]

Wei JJ, William J, Bulun S. Endometriosis and ovarian cancer: a review of clinical, pathologic, and molecular aspects. Int J Gynecol Pathol. 2011; 30:553–568. [PubMed: 21979592]

Weng Q, Ding ZM, Lv XL, Yang DX, Song YZ, Wang FF, Ye YH, Qu F. Chinese medicinal plants for advanced endometriosis after conservative surgery: a prospective, multi-center and controlled trial. Int J Clin Exp Med. 2015; 8:11307–11311. [PubMed: 26379940]

Wickiewicz D, Chrobak A, Gmyrek GB, Halbersztadt A, Gabrys MS, Goluda M, Chelmonska-Soyta A. Diagnostic accuracy of interleukin-6 levels in peritoneal fluid for detection of endometriosis. Arch Gynecol Obstet. 2013; 288:805–814. [PubMed: 23553197]

Wiegand KC, Lee AF, Al-Agha OM, Chow C, Kalloger SE, Scott DW, Steidl C, Wiseman SM, Gascoyne RD, Gilks B, Huntsman DG. Loss of BAF250a (ARID1A) is frequent in high-grade endometrial carcinomas. J Pathol. 2011; 224:328–333. [PubMed: 21590771]

Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T, Senz J, McConechy MK, Anglesio MS, Kalloger SE, Yang W, Heravi-Moussavi A, Giuliany R, Chow C, Fee J, Zayed A, Prentice L, Melnyk N, Turashvili G, Delaney AD, Madore J, Yip S, McPherson AW, Ha G, Bell L, Fereday S, Tam A, Galletta L, Tonin PN, Provencher D, Miller D, Jones SJ, Moore RA, Morin GB, Oloumi A, Boyd N, Aparicio SA, Shih Ie M, Mes-Masson AM, Bowtell DD, Hirst M, Gilks B, Marra MA, Huntsman DG. ARID1A mutations in endometriosis-associated ovarian carcinomas. N Engl J Med. 2010; 363:1532–1543. [PubMed: 20942669]

Worley MJ Jr, Liu S, Hua Y, Kwok JS, Samuel A, Hou L, Shoni M, Lu S, Sandberg EM, Keryan A, Wu D, Ng SK, Kuo WP, Parra-Herran CE, Tsui SK, Welch W, Crum C, Berkowitz RS, Ng SW. Molecular changes in endometriosis-associated ovarian clear cell carcinoma. Eur J Cancer. 2015; 51:1831–1842. [PubMed: 26059197]

Wu MH, Lu CW, Chang FM, Tsai SJ. Estrogen receptor expression affected by hypoxia inducible factor-1alpha in stromal cells from patients with endometriosis. Taiwan J Obstet Gynecol. 2012; 51:50–54. [PubMed: 22482968]

Xu H, Becker CM, Lui WT, Chu CY, Davis TN, Kung AL, Birsner AE, D'Amato RJ, Wai Man GC, Wang CC. Green tea epigallocatechin-3-gallate inhibits angiogenesis and suppresses vascular endothelial growth factor C/vascular endothelial growth factor receptor 2 expression and signaling in experimental endometriosis in vivo. Fertil Steril. 2011; 96:1021–1028. [PubMed: 21821246]

Xu H, Zhang T, Man GC, May KE, Becker CM, Davis TN, Kung AL, Birsner AE, D'Amato RJ, Wong AW, Wang CC. Vascular endothelial growth factor C is increased in endometrium and promotes endothelial functions, vascular permeability and angiogenesis and growth of endometriosis. Angiogenesis. 2013; 16:541–551. [PubMed: 23334337]

Yang Y, Zhang X, Zhou C, Huang X, Lin J, Xu H. Elevated immunoreactivity of RANTES and CCR1 correlate with the severity of stages and dysmenorrhea in women with deep infiltrating endometriosis. Acta Histochem. 2013; 115:434–439. [PubMed: 23219091]

Yeo SG, Won YS, Lee HY, Kim YI, Lee JW, Park DC. Increased expression of pattern recognition receptors and nitric oxide synthase in patients with endometriosis. Int J Med Sci. 2013; 10:1199–1208. [PubMed: 23935397]

Young VJ, Brown JK, Maybin J, Saunders PT, Duncan WC, Horne AW. Transforming growth factor-beta induced Warburg-like metabolic reprogramming may underpin the development of peritoneal endometriosis. J Clin Endocrinol Metab. 2014a; 99:3450–3459. [PubMed: 24796928]

Young VJ, Brown JK, Saunders PT, Duncan WC, Horne AW. The peritoneum is both a source and target of TGF-beta in women with endometriosis. PLoS One. 2014b; 9:e106773. [PubMed: 25207642]

Zamah N, Dodson M, Stephens L, Buttram V, Besch P, Kaufman R. Transplantation of normal and ectopic human endometrial tissue into athymic nude mice. Am J Obstet Gynecol. 1984; 149:591–597. [PubMed: 6742039]

Zanetta GM, Webb MJ, Li H, Keeney GL. Hyperestrogenism: a relevant risk factor for the development of cancer from endometriosis. Gynecol Oncol. 2000; 79:18–22. [PubMed: 11006024]

Zhao Y, Gong P, Chen Y, Nwachukwu JC, Srinivasan S, Ko C, Bagchi MK, Taylor RN, Korach KS, Nettles KW, Katzenellenbogen JA, Katzenellenbogen BS. Dual suppression of estrogenic and inflammatory activities for targeting of endometriosis. Sci Transl Med. 2015; 7:271ra279.

Zito G, Luppi S, Giolo E, Martinelli M, Venturin I, Di Lorenzo G, Ricci G. Medical treatments for endometriosis-associated pelvic pain. Biomed Res Int. 2014; 2014:191967. [PubMed: 25165691]

Zondervan K, Weeks D, Colman R, Cardon L, Hadfield R, Schleffler J, Goudy Trainor A, Coe C, Kemnitz J, Kennedy S. Familial aggregation of endometriosis in a large pedigree of rhesus macaques. Hum Reprod. 2004; 19:448–455. [PubMed: 14747196]

Zorbas KA, Economopoulos KP, Vlahos NF. Continuous versus cyclic oral contraceptives for the treatment of endometriosis: a systematic review. Arch Gynecol Obstet. 2015; 292:37–43. [PubMed: 25644508]

Table 1
Cytokine or Chemokine Alterations in Endometriosis

Cytokine/chemokine	Model	Results	Reference
CCL2 (MCP-1)	hPF	+, ++, +++	(Mier-Cabrera *et al.* 2011, Margari *et al.* 2013), (Tao *et al.* 2011),(Bersinger *et al.* 2012)
CCL5 (RANTES)	hPF	NS, +, ++	(Bersinger *et al.* 2012, Margari *et al.* 2013), (Mier-Cabrera *et al.* 2011),(Beste *et al.* 2014)
	hEctopic	qualitative +, ++	(Wang *et al.* 2010),(Yang *et al.* 2013)
CCL11 (Eotaxin)	hPF	++, +	(Bersinger *et al.* 2012), (Mier-Cabrera *et al.* 2011)
CXCL1 (GROa)	hPF	Nearing	(Bersinger *et al.* 2012)
CXCL8 (IL8)	hPF	NS, +, ++	(Velasco *et al.* 2010, Bersinger *et al.* 2012), (Mier-Cabrera *et al.* 2011, Beste *et al.* 2014), (Milewski *et al.* 2011, Malhotra *et al.* 2012)
	hSerum	++	(Carmona *et al.* 2012)
	hEESCs	++	(Delbandi *et al.* 2013)
	hPF mRNA Cells	NS	(Yeo *et al.* 2013)
CXCL10 (IP-10)	hLesion	NS trend –	(Bellelis *et al.* 2013)
	hPF	++	(Bersinger *et al.* 2012)
CXCL12 (SDF1)	hEctopic	+	(Bellelis *et al.* 2013)
	hPF	+	(Leconte *et al.* 2014)
IL1B	hPF	+, +++	(Mier-Cabrera *et al.* 2011, Beste *et al.* 2014), (Sikora *et al.* 2012)
	hEctopic	+	(Chen *et al.* 2013)
	hPF cells	NS	(Yeo *et al.* 2013)
IL4	hPF	NS, ++	(Mier-Cabrera *et al.* 2011, Wickiewicz *et al.* 2013), (Beste *et al.* 2014)
IL6	hPF	NS, +, ++, +++	(Rathore *et al.* 2014), (Mier-Cabrera *et al.* 2011, Khan *et al.* 2015), (Velasco *et al.* 2010, Kang *et al.* 2014), (Milewski *et al.* 2011, Bersinger *et al.* 2012, Podgaec *et al.* 2012, Wickiewicz *et al.* 2013)
	hSerum	+, ++, +++	(Kinugasa *et al.* 2011), (Carmona *et al.* 2012), (Elgafor El Sharkwy 2013)
	hEESC	++	(Delbandi *et al.* 2013)
	hPF mRNA Cells	NS	(Yeo *et al.* 2013)
	hSerum/PF	NS/NS	(Andreoli *et al.* 2011)
IL10	hPF	NS, +	(Bersinger *et al.* 2012, Podgaec *et al.* 2012), (Mier-Cabrera *et al.* 2011, Wickiewicz *et al.* 2013)
	hPF mRNA Cells	NS	(Yeo *et al.* 2013)
	hSerum/PF	NS/NS	(Andreoli *et al.* 2011)
IL12	hPF	NS	(Mier-Cabrera *et al.* 2011)
	hPF mRNA Cells	NS	(Yeo *et al.* 2013)
IL17A	hEndo, Serum	**/+	(Ahn *et al.* 2015)
	hSerum/PF	NS/NS	(Andreoli *et al.* 2011)
	hPF	NS	(Podgaec *et al.* 2012)
	hFF/Serum	+++/+++	(Sabbaghi *et al.* 2014)
IL18	hPF	+, ---	(Bersinger *et al.* 2012), (Sikora *et al.* 2012)
IL22	hEctopic	**	(Guo *et al.* 2013)
	hSerum	--	(Santulli *et al.* 2013)
IFNG	hPF	NS, +	(Wickiewicz *et al.* 2013),(Mier-Cabrera *et al.* 2011)

Cytokine/chemokine	Model	Results	Reference
MIF	hPF mRNA Cells	NS	(Yeo *et al.* 2013)
	hPF	*++*	(Beste *et al.* 2014)
	hEctopic	*++*	(Lin *et al.* 2010)
TGFB	hPF	*+++*	(Podgaec *et al.* 2012)
	mKO w/human	- size	(Hull *et al.* 2012)
	hPF	NS, *+*, *++*	(Tao *et al.* 2011, Wickiewicz *et al.* 2013),(Mier-Cabrera *et al.* 2011, Beste *et al.* 2014, Young *et al.* 2014a, Young *et al.* 2014b), (Khan *et al.* 2015)
TNFA	hEctopic cd56^{+}	*+*	(Chen *et al.* 2013)
	pfNKcell	*+*	(Funamizu *et al.* 2014)
	bEctopic	NS	(Ilad *et al.* 2010)
	hPF mRNA Cells	NS	(Yeo *et al.* 2013)

Increased levels:

+ = p<0.05,

++ = p<0.01,

+++ = p<0.001,

**** = qualitative IHC,

Decreased levels: - = p<0.05; NS = non-significant

h=human, b=baboon, Ectopic=ectopic endometriosis lesion, PF=peritoneal fluid, FF=follicular fluid, EESC=ectopic endometrial stromal cells

Table 2
Endometriosis Surgical Treatments and Associated Efficacy

Surgical Treatment	Surgical Technique	Compared Treatment	Efficacy
Laparoscopic Ablation	Ablate, or apply heat, to lesion	CO_2 laser vs. electric cautery	Decreased pain with ablation (NRS 3) vs. CO_2 laser (NRS) (Posadzka *et al.* 2015)
		Diagnostic Laparoscopy	Decreased overall pain OR 5.63 (Duffy *et al.* 2014)
Laparoscopic Excision	Remove lesion with scissor or laser	Ablation	No difference in overall pain, dyspareunia, or dyschezia at 1 year (Bulun 2009, Duffy *et al.* 2014)
			Excision decreased dyspareunia (VAS 3.2) vs. ablation (VAS 6.0) at 5 years (Healey *et al.* 2014)
			Ablation required more medical treatment (31%) vs. excision (20%) (Healey *et al.* 2014)
Conservative Laparoscopy	Ablate or excise lesions, restore anatomy, adhesiolysis	Diagnostic Laparoscopy	Decreased overall pain OR 6.58 (Duffy *et al.* 2014)
Laparoscopic Uterosacral Nerve Ablation	Ablate nerve fibers responsible for pain pathway	Conservative Laparoscopy	No difference in pain level (Daniels *et al.* 2010)
Endometrioma Removal	Separate cyst wall from ovary and excise cyst	Cyst drainage	Decreased recurrence of cyst (Dunselman *et al.* 2014)
			Decreased recurrence of dysmenorrhea (OR 0.15) (Brown & Farquhar 2015)
Presacral Neurectomy	Disrupts sympathetic innervation of uterus at level of superior hypogastric plexus	Conservative Laparoscopy	1 RCT: decrease midline dysmenorrheal (Practice Committee of the American Society for Reproductive 2014) (Dunselman *et al.* 2014)
			1 RCT: no additional benefit (Practice Committee of the American Society for Reproductive 2014)
Hysterectomy + BSO	Debulking to place in surgical menopause	Hysterectomy without BSO	Improved symptoms (Practice Committee of the American Society for Reproductive 2014)(Dunselman *et al.* 2014)(Duffy *et al.* 2014)

BSO = bilateral salpingo-oophorectomy, VAS = Visual Analog Scale, NRS = Numeric Rating Scale, OR = Odds Ratio

Table 3

Summary of Risks Associated with Endometriosis and Cancer from Registry Studies by Brinton et. al. (Brinton *et al.* 1997, Brinton *et al.* 2005)

Population	Risk	SIR* or RR	95% CI
History of endometriosis admission (HEA)	Any cancer	1.2*	1.1-1.3*
HEA	Ovarian Cancer	1.9*	1.3-2.8*
HEA & Prolonged endometriosis	Ovarian cancer	4.2*	2.0-7.7*
HEA	Endometrial cancer	1.1*	0.6-1.9*
HEA Long term F/U	Any cancer		
HEA Long term F/U	Ovarian Cancer	1.43*	1.19-1.71*
Long term F/U & Prolonged endometriosis	Ovarian Cancer	2.23*	1.36-3.44*
HEA Denmark cohort	Clear cell Ovarian Cancer	3.37	1.24-9.14
HEA Denmark cohort	Endometrioid Ovarian Cancer	2.53	1.19-5.38

HEA-History of endometriosis admission, SIR- Standardized incidence ratio, RR-Relative Risk, CI – Confidence interval, F/U- Follow up

Table 4
Ovarian Cancer Types Arising from Endometriosis Transformation

Population (# Patients EAOC/Total in Study)	Ovarian Cancer Type in EAOC	Age (Mean ± SD) years	Reference
Quebec, BC (41/2854)	Serous 19.51% Mucinous NR Clear-Cell 21.9% Endometrioid 24.4%	OC 53.9 ± 11.4 EAOC 48.3 ± 10.8	(Aris 2010)
Belegrade, Serbia (23/210)	Serous 3.5% Mucinous NR Clear-Cell 36.8% Endometrioid 31.6%	NR	(Dzatic-Smiljkovic *et al.* 2011)
Michigan, USA (42/184)	Serous 55% Mucinous 10% Clear-Cell 21% Endometrioid 14%	OC 59 EAOC 52	(Kumar *et al.* 2011)
Athens, Greece (17)	Serous 5.9% Mucinous NRClear-Cell 58.8% Endometrioid 35.3%	EAOC 58 (27-76)	(Kondi-Pafiti *et al.* 2012)
Ovarian Cancer Association Consortium (738/7911)	Serous 7.1% Mucinous 6.0% Clear-Cell 20.2% Endometrioid 13.9%	OC 56.1 EAOC 56.3	(Pearce *et al.* 2012)
Ankara, Turkey (45/1086)	Serous 13.3% Mucinous 8.9% Clear-Cell 37.8% Endometrioid 33.3%	EAOC 55 (35-77)	(Boyraz *et al.* 2013)
Massachusetts, USA (67/134)	Serous 0% Mucinous NR Clear-Cell 38.8% Endometrioid 61.2%	OC 56.6 EAOC 51.7	(Davis *et al.* 2014)
Milano, Italy (27/73)	Serous NR Mucinous NRClear-Cell 76.1%Endometrioid NR	OC 58.4 ± 11.2 EAOC 51.4 ±10	(Scarfone *et al.* 2014)
San Juan, Puerto Rico (20/192)	Serous 2.2% Mucinous 2.7% Clear-Cell 23% Endometrioid 50%	OC 56.1 ± 14.9 EAOC 48.8 ± 11.6	(Acien *et al.* 2015)
Shiraz, Iran (28/110)	Serous 14.5% Mucinous 0% Clear-Cell 14.5% Endometrioid 39%	OC 50.18 ± 12.8 EAOC 49.93 ±9.36	(Akbarzadeh-Jahromi *et al.* 2015)

OC=Ovarian Cancer, EAOC=Endometriosis Associated Ovarian Cancer, NR=not reported