

Review Article

Endometriosis a brief review: evaluation of crucial risk factors and current treatment regimes

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ABSTRACT

Endometriosis is an estrogen-dependent chronic inflammatory disease associated with substantial morbidity, including dyspareunia, dysmenorrhea, pelvic pain, multiple surgery, and infertility. This disease has a high impact on both woman's physical and mental wellbeing. The etiology of endometriosis is complex and multifactorial. The risk factors associated with the development of endometriosis include family history, menstrual and reproductive cycle, low body mass index (BMI), diet, alcohol uses, smoking, environmental factors, immune system, genetic factors and intrinsic abnormalities in the endometrium. There exist many theories on the initiation and propagation of different types of endometriotic lesions and consequent biological disturbances, of which the most common is the Sampson's theory according to which the retrograde flow of menstrual blood is linked to the development of endometriosis. Endometriosis affected women have a higher risk than the general female population, for ovarian cancer, coronary heart disease (CHD), and other long-term disease risks as well for autoimmune and atopic disorders. Therefore it becomes a necessity for the clinician not only to attain right diagnosis but also follow up for the other associated disorders. In this review, we have considered the crucial risk factors and biomarkers of the endometriosis as well as the possible pathogenesis towards the development of endometriosis and its prevention strategies. The currently available therapies for the control and treatment of endometriosis have also been elaborated.

Keywords: Endometriosis, Epidemiology, Infertility, Risk factors, Biomarkers, Genetic risk factor

INTRODUCTION

Endometriosis is an estrogen-dependent chronic inflammatory disease condition in women in which tissue resembling the endometrium, usually stromal or glandular in structure. The definition of endometriosis is determined histologically and requires its identification of the presence outside (ectopic) the uterus. These ectopic lesions may commonly be located on the pelvic organs and peritoneum. They may occasionally be, present in other parts of the body such as bladder, lungs kidney, and even in the brain.¹

It is a disease that results in significant morbidity, including multiple operations, pelvic pain, adnexal mass, and further infertility in the suffering women. Many studies have defined the risk factors associated with the disease, and it has shown to be multifactorial; age, race, alcohol usage, body mass index (BMI), cigarette smoking, and menstrual characters (such as the early age menarche, menstrual length, regularity of cycle, dysmenorrhea, and intensity of menstrual flow).² Lately, the genetic factors, the environment and dietary elements, immune system cytokines, and intrinsic abnormalities in the endometrium also have been attributed to its etiology.³ Most of the causative elements for it are mainly related to the

steroidogenic pathway, adenosine 3', 5'-cyclic monophosphate (cAMP) pathway, or hypothalamic-pituitary-gonadal axis. The regulatory genes of all these pathways together lead to endometriosis. Insights into the pathogenesis of endometriosis have served as the background for new treatments of endometriosis as well as associated symptoms; like abnormal or heavy periods (menorrhagia), cyclic urinary symptoms/gastrointestinal, dysmenorrhea (menstrual cramps), dyspareunia (painful intercourse), dyschezia (obstructed defecation), dysuria (discomfort urinating), and pelvic pain and infertility.⁴ Beside the allopathic treatment with medicines, yoga, lifestyle changes, and Ayurveda has also pronouncing effect on endometriosis treatment.⁵ The purpose of this study was to review the current literature regarding risk factors, etiopathogenesis, and subsequent treatment modalities adopted. Further, we also explore the importance of eutopic endometrium as a source of impending diagnostic biomarker by looking at the expression levels of noncoding ribonucleic acid (RNA) in tissue as well as in blood.

METHODS

Search strategy

The initial literature searches were conducted on the comprehensive online electronic database, including English literature, research articles were searched till July 2019. This research was conducted using scopus, PubMed, MEDLINE, EMBASE, web of sciences, and cochrane library. The following keywords and text: “endometriosis”, “confounding factors”, “risk factors”, “retrograde menstrual”, “endometriosis and diet”, “endometriosis and BMI”, and “endometriosis and infertility” were used. Expanding these search terms on PubMed, relevant articles were selected for a comprehensive review, and investigation of literature was further supplemented by searching the reference articles created by the original investigators. A total of 34 studies were included in this systematic review (PRISMA guidelines; Moher, 2009), outlined in Figure 1.

ENDOMETRIOSIS AND EPIDEMIOLOGY

Epidemiology

The accurate assessment of endometriosis burden requires detailed information related to its occurrence and incidences in the general population, but it is not known because diagnosis is often overlooked by clinicians.⁶ Due to miss treatments, it takes an average of 7-10 years to get diagnosed in most of the women, and a general lack of awareness about the illness itself contributes. It is estimated that 1 out of 10 women, during their reproductive years (between puberty to menopause), have endometriosis, that is 176 million worldwide suffering to endometriosis, with more recent research proposing up to 30-50% women with infertility. In the general female population, to assess the rates of endometriosis is

immensely challenging to quantify because the definitive diagnosis requires surgical visualization.⁷

Accordingly, for its estimate, one has to access many different population samples and modes of disease diagnosis - all influenced by presenting symptoms and access to care. Despite this limitation, in a study of large group of women in their first laparoscopic investigation in 10 countries, across five countries showed that endometriosis is a common global problem, with an incidence ranging from 35% to 100% in symptomatic women. Although the lack of reliable data confirms that the prevalence of this disease varies among different ethnic groups as any experimental variations cannot be extricated from differential access to health care.⁸

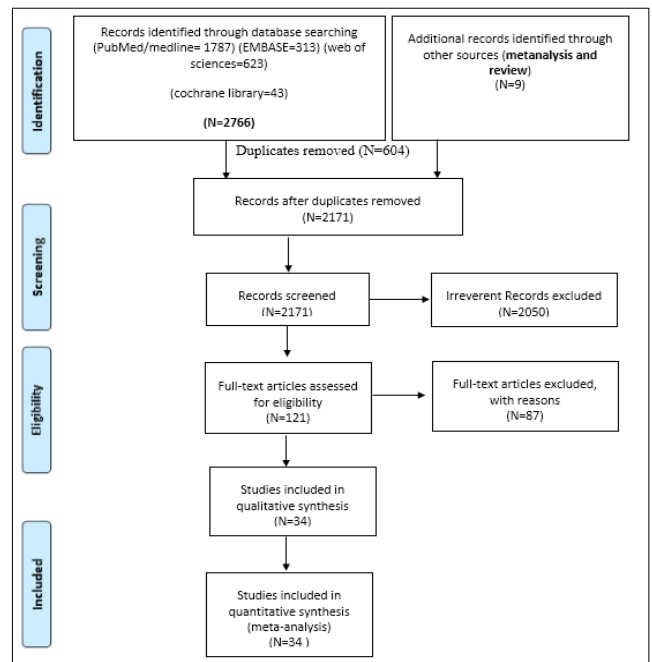


Figure 1: Expanding the relevant search terms related articles were selected, for a comprehensive systematic review (PRISMA protocol 2009).

The symptoms of endometriosis includes painful ovulation and periods, dyspareunia, chronic pelvic pain, heavy menstrual flow, infertility, fatigue, and it impacts severely on general physical, mental, and social wellbeing of a women. The disease has increased rate of recurrence after bilateral oophorectomy (removal of the ovaries) or in postmenopausal women, particularly in those who have undergone hormonal replacement therapy. In spite of the existing data as well as the case reports, accurate prevalence is not known because of the lack of reliable data. The incidence of clinically diagnosed endometriosis in Rochester, Minnesota, was 187 per 100,000 person-from years 1987 to 1999. In a similar study, in 1989, among whom the 10-year incidence of laparoscopically confirmed significant cases with endometriosis were 298 per 100,000 person. The endometriosis society of India

estimate of 25 million cases of endometriosis is prevalent in India.⁹

Classification systems of endometriosis

Numerous proposed systems to classify endometriosis exist at present. These include those by American society for reproductive medicine (rASRM 1979). The number, size, location of peritoneal endometrial implants, plaques, endometriomas, and adhesions imposed ASRM to revise and chart their classification into a point system with a scoring system to translate the disease into differential stages.¹⁰ The classification has been revised, modified, and renamed as revised rASRM for classification of endometriosis. Mainly, all of these classifications divide endometriosis disease into four stages related to increasing severity of the ovarian lesions, particularly the number of endometrial implants and their depth and adhesion formation. The main objective of this classification system is to predict disease severity, based on a numerical scale and the chance for conception after treatment. It had shown to provide a higher reproducible tool in staging of endometriosis during (stage I) 1-5 point's score indicates minimal disease (few superficial implants). A score of stage II (6-15 points) higher may indicate mild (more and deeper implants) disease. A score of stage III (16-40 points) higher may indicate moderate (many deep implants small cysts) on one or both ovaries disease. A score of stage IV (>40 points) severe with many deep implants large cysts on one or both ovaries with dense adhesions (Figure 2).¹¹ Limitation of the ASRM staging system is that the scoring includes only intraperitoneal endometriosis, and it under-represents other manifestations of endometriosis such as extraperitoneal lesions in the bowel or bladder.¹² Therefore, ASRM classification and scoring is currently under investigation to reflect the multifaceted aspects of endometriosis and its impact on fertility. On the other hand, fertility index (EFI) is another tool that predicts pregnancy rates (PRs) after endometriosis surgical staging. The EFI takes into account reproductive potential by scoring the involvement of the fallopian tubes, fimbria, and ovaries while omitting uterine abnormalities. It is used to create the EFI least function score. Its revisions simplified the scoring system and enhanced its benefits for staging deep infiltrating retroperitoneal endometriosis, but still, it lacks poor international acceptance (Figure 3).¹³ A case of bilateral endometrioma in young women, suffering with chronic pain and infertility. Written informed consent was obtained from the individual for the publication of this image.

RISK FACTORS FOR ENDOMETRIOSIS

Family history

The risk of the hereditary aspects of endometriosis demonstrates a seven-fold higher risk in first-degree relatives of the patients has been elucidated in the early seventies 1981, Simpson et al suggested that the risk for

endometriosis in first-degree relatives of endometriosis patients was seven-fold in comparison to normal population.¹⁴ In 1986, only a four-fold increased risk for developing endometriosis was estimated for mothers and sister. A study conducted in twins demonstrated that the incidence of endometriosis in monozygotic twins was twice that in dizygotic twins In addition, it has been shown that the severity of endometriosis is higher among patients with a positive family history.¹⁵ Study by dos Reis et al also showed an increased prevalence of endometriosis in the family, including sisters, mothers, aunts, and cousins, and a higher risk in first-, second-, and third-degree relatives. A study by Nouri et al from 2010, suggested that endometriosis showed an increased trend in the family, but definitive risk in relatives were not relevant. In a population-based study by Stefansson et al using a genealogy data for the last eleven centuries in Iceland including genealogy manuscripts, censuses and church books reports of familial clustering and increased prevalence among first-degree relatives, found a raised risk for endometriosis among close and distant relatives. In the study, all the reported sisters and cousins of patients were diagnosed with endometriosis from 1981 to 1993. Patent sisters were found to have a 5.20 percent higher risk of disease than those without a sibling with endometriosis. First cousins, on the mother or father's side, were found to have a 1.56% higher risk than those while not a case history of the endometriosis those while not a case history of the endometriosis.¹⁶

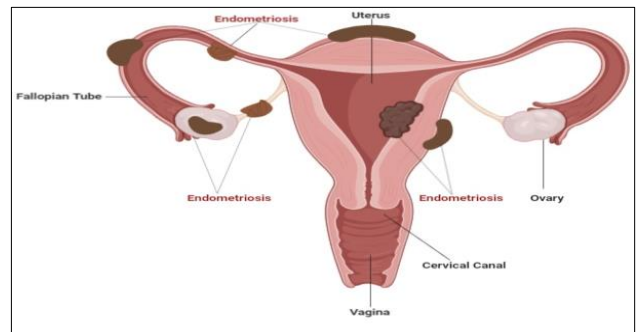


Figure 2: A theoretical model of possible site of endometriosis; eutopic and ectopic lesion.

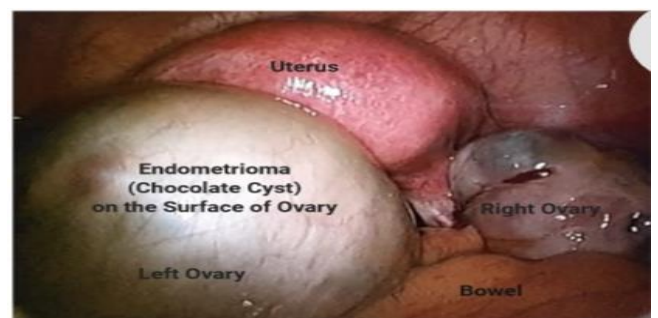


Figure 3: A case of bilateral endometrioma in young women, suffering with chronic pain and infertility. Written informed consent was obtained from the individual for the publication of this image.

Genetics risk factors of endometriosis

Genome-wide association studies on endometriosis (GWAS)

Developments in high throughput genotyping technology have driven the discovery of genomic regions linked to a contributing factor of endometriosis. Many scientists agreed that there is a genetic component to the cause of endometriosis. Studies have attempted to define the roles genes play in the development of endometriosis in one or more populations. A recent meta-analysis, including 17,045 endometriosis cases, identified 16 genomic regions, they suggested that most common genetic risk factors contributing to endometriosis risk are in regulatory

deoxyribonucleic acid (DNA) sequences that changes the regulation of gene transcription.¹⁷ A comparative meta-analysis of genes in the Chinese population showed treatment of endometriosis with traditional Chinese medicine (TCM) danazol. An analysis of multiple genes studies, reported in clinical gynecology in the field of reproductive health, determined endometriosis candidate gene run in families while researchers speculated that numerous genes, as well as environmental factors, may play a role in disease occurrence. A genome-wide association study in Japanese population showed identification of a significant association of endometriosis with rs10965235, the CDKN2BAS gene located on chromosome 9p21, encoding the cyclin-dependent kinase inhibitor 2B antisense RNA.¹⁸

Table 1: Genome-wide relevant loci reported in genome-wide association studies of endometriosis.

Gene and chromosome	Locus	Position (nearest gene)	Risk/non-risk nucleotide	Effect size from most extensive study Or (95% CI); P value		Significant or non-significant/ancestry	References
				All endometriosis	Stage iii/iv		
WNT1p36.12	rs7521902	22490724 (intrinsic)	C>A	1.37 (0.89-2.11) 0.16	1.55 (0.93-2.57) 0.11	Significant/European	20
VEZT12q22	rs10859871	95711876	A>C	0.82 (0.6-1.13) 0.25	0.79 (0.54-1.17) 0.26	Significant/European	20
FSHB11p14.1	rs11031006	30226528 (intron)	G>A	0.55 (0.32-0.95) 0.0316	0.74 (0.39-1.40) 0.44	Significant/European	20
NGF1p13.2	rs12030576	115817221	G>T	1.07 (1.05-1.09) 5.2×10-13	1.09 (1.00-1.18) 0.03	Significant/European	40
CD1096q13	rs1595344	74611632	G >A	1.05 (1.03-1.0) 1.2×10-8	1.04 (0.96-1.13) 0.32	Significant/European	40
HEY26q22.31	rs2226158	125995467 (intron)	G>A	1.05 (1.03-1.07) 2.6×10-8	0.95 (0.90-1.01) 0.16	Significant/European	40
WT111p13	rs7924571	32350027	C > A	1.06 (1.041.08) 3.5×10-8	0.99 (0.92-1.08) 0.90	Significant/European	40
GREB12p25.1	rs11674184	11721535 (intrinsic)	T>G	1.13 (1.10-1.15) 2.7×10-17	1.18 (1.10-1.24) 1.9×10-6	Significant/Japanese	41, 42
SYNE16q25.2	rs71575922	152554014 (intrinsic)	G>C	1.11 (1.07-1.15) 2.0×10-8	1.35 (1.24-1.43) 2.9×10-12	Significant/Japanese	42
CCDC1706q25.1	rs1971256	151816011 (intrinsic)	C>T	1.09 (1.06-1.13) 3.7×10-8	1.28 (1.19-1.36) 1.5×10-10	Significant/Japanese	42

The Hox/HOX genes encode highly conserved transcription factors responsible for imparting functional identity to specific body segments. Human, Hoxa10/HOXA10 has a role in cell proliferation and implantation, hematopoiesis, differentiation, and embryogenesis.¹⁹ These genetic findings of Hoxa10/HOXA10 in endometriosis may help to describe the mechanism and can identify genetic and non-genetic factors potentially contributing to the high progression of endometriosis. Many candidate gene link studies have been conducted, concentrating on putative genes of

interest, but generally, these do not produce a replicable result. A study in Greek population was conducted for polymorphism with three SNPs, rs7521902, rs10859871, and rs11031006, mapping to WNT4, VEZT and FSHB genetic loci Figure 4.²⁰ A largest study on European ancestry with (37,183 cases and 251,258 controls) endometriosis genome-wide association study (GWAS). GWAS study replicated at genome-wide significance; seven loci were reported in endometriosis, further identified new candidate loci with genome-wide significance (NGF, ATP1B1-F5, CD109, HEY2, OSR2-VPS13B, WT1, and TEX11-SLC7A3) (Table 1).

Table 2: Potential diagnostic biomarkers for endometriosis.

Biological groups	Biomarkers	References
Proinflammatory markers-cytokines	IL-1 β , IL-5, IL-6, IL-8, IL-12, IL-17, IL-21, RANTES*, TNF- α , hypoxia inducible factor (HIF)-1 α signaling pathways, IFN- γ , MCP-1, MIF, CRP	43
Steroids and hormones	Sulfatase, sulfotransferase, ERs, 17 β HSD, aromatase, estrogens, progesterone	44
Growth factors	IGF, activin, TGF β 1, HGF, annexin-1	45
Cell-matrix adhesion	Integrins, vimentin, E-cadherin, immunoglobulin (Ig CAMs), osteopontin, ICAM-1 (CD54), β -catenin, FAK, alpha 2, 3, 6 (collagen/laminin receptors)	46
Angiogenesis	Anti-VEGFA siRNA, VEGF, NGF, FGF-2, leptin, IGFBP-3, glycodelin, endoglin, and thrombospondin-1M-CSF, angiopoietin-1 and -2, MVD	47
Apoptosis and cell cycle control	GSK3- β / β -catenin pathway, telomerase activity, Pak-1, cyclin D1, survivin, Bcl-2, MCL-1, Bax, BclxL, Bcl-xS	48
Stem cell markers	Notch-1 and Numb, CD9, CD34, CD73, CD90, CD105, CD166, and HLA-ABC Oct-4, FGFR2 (+)	49
Genetics and genomics	HOXA10 clusters, TP53, ESRI, CYP17A1, CYP1A, CYP19CYP1B1, CYP2C19, IL-16, IL-1A, IL-10, IL12B, COX-2, HLA-G, LILRB1, LILRB2, MUC2, MUC4, VEGF, FAS, TYK2, PLGF, HIF-1 α , MAP3K4, KAZN, LAMA5, WNT4RND3-RBM43, NFE2L3-, GREB, VEZT, PTPRD	50

Menstrual cycle and reproductive history

The more exposure to menstruation cycle, have a more chances of developing endometriosis. Thus, several observational studies and a meta-analysis have provided some evidence that early age at menarche increases the risk of endometriosis.²¹ Earlier age (<12 years) at menarche and shorter menstrual cycles (<26 days) have been consistently associated with endometriosis, perhaps through the higher frequency of retrograde menstruation or hormonal context. Endometriotic tissues prompts the formation of new nerve fibers. The retrograde menstrual cycles causes flow of sloughed endometrial cells/debris via the fallopian tubes into the pelvic cavity during menstruation. Bleeding triggers inflammation, while inflammatory cells and mediators stimulate the nerves, which cause pain. A recent meta-analysis of 10 case-control studies calculated that endometriosis cases were 0.15 standard deviations of age (in years) younger at the time of first menstrual period than controls.⁴⁴ Similar findings have been reported in the ENDO study. Among parous NHSII cohort, shorter menstrual cycles (<26 days) during late adolescence (18-22 years) were associated with a greater rate of endometriosis compared to 26 to 31-day menstrual cycles.²²

However, the interpretation to link between endometriosis and parity is mostly complicated given temporality issues (endometriosis may have been present before pregnancy or endometriosis is identified. Only once the patient is diagnosed with female infertility). Sangi-Haghpeykar's study showed that women with long cycle lengths were 1.8 times more likely to develop endometriosis than those with

short cycle lengths but some studies did not find any significant correlation between short menstrual cycle length and endometriosis at all.²¹

Therefore, the association between menstrual cycle length and endometriosis needs further confirmed.

Cigarette smoking

The association between endometriosis and cigarette smoking factor is still unknown and might differ by female infertility status. Many meta-analysis studies (Missmer et al) have shown an inverse association of the endometriosis with smoking, whereas other studies have no link. Although women who smoke have lower estrogen levels and increases progesterone receptor and homeobox A10 expression in human endometrium and endometrial cells. They are also exposed to higher levels of estrogenic endocrine disruptors in the form of dioxin that exerts aryl hydrocarbon receptor-mediated oestrogenic activity through interactions with the estrogen receptor (ER). Across-sectional study with smoking habits of 411 proven endometriosis and 567 unaffected women result shown that smoking does not stand as an independent risk factor for endometriosis in a population. The meta-analysis provided no evidence for an association between tobacco smoking and the risk of endometriosis.²³

Endometriosis and BMI

An association between adult BMI and endometriosis has regularly been observed. BMI is an important measure which is easily obtained at the time of clinical questioning.

Significant relationships between endometriosis and BMI are still controversial. In a study for BMI of 366 women with laparoscopy, confirmed endometriosis were compared to that of 248 controls. BMI was significantly lower in endometriosis than controls and was restricted to subjects with normal BMI.²⁴ A relationship was established between endometriosis and body fat distribution waist-to-hip ratio; genetic studies have further reinforced this association. A meta-analysis of 11 studies (two cohort studies and nine case-control studies), the pooled relative risk (RR) of endometriosis was statistical significance for each case 5 kg/m² increase in the BMI. Compared with normal-weight women, the pooled risk for obese women was less than that for overweight women, wherein it was suggested that higher body mass index may be associated with a lower risk of endometriosis. The research now need to focus on exploring the underlying biologic mechanism that contributes to the initiation of endometriosis.

Endometriosis and diet

The current scientific evidence suggests that diet and lifestyle may influence the presence of inflammation in the body activity, estrogen, menstrual cycle, and prostaglandin metabolism.²⁵ An endometriosis-associated positive influence of specific diet interventions, recommend dietary interventions to lessen, and also prevent the disease. Few studies have investigated the association between diet and endometriosis indicators. Many previous studies suggested that women who take fruits and vegetables during a week, the risk of developing endometriosis is less and are more protected from symptoms of endometriosis, while those who consumed trans fats, coffee and red meat consumption may have experienced the opposite effect or increased risk of endometriosis.²⁶ In a case-control study the disease was significantly decreased in women who ate large amounts of green vegetables and fresh fruits. Literature published in Brazil suggested that eating a healthful diet can prevent endometriosis from developing and even worsening. Women with diet that includes palmitic acid unsaturated fats with consumption of omega-3 and omega-6 polyunsaturated fatty acids as compared to other women have decreased endometriosis risk.²⁷

Endometriosis and autoimmune diseases

Immunological factors play a pivotal role in genesis and expansion of the disease, with importance on inflammatory cytokines, growth, and adhesion factors. Sampson's theory proposes that the menstrual debris carries sloughed-off tissue from the endometrium. The viable endometrial tissue spreads into the peritoneal cavities through the fallopian tubes during menstruation, eliciting an inflammatory response.²⁸ Retrograde menstruation is a phenomenon in endometriosis disease women of reproductive age, but not all women with retrograde menstruation develop endometriosis. It seems to be associated with several factors, including quantity

and quality of endometrial cells in the peritoneal fluid (PF), increased endometrial-peritoneal adhesion and angiogenesis, increased inflammatory activity in PF, compacted immune surveillance and clearance of endometrial cells, and the increased production of autoantibodies against endometrial cells.²⁹ Retrograde menstruation triggers a local inflammatory response in the endometrium involving infiltration of monocyte, leukocytes, cytokine release, edema, and activation of matrix metalloproteinase (MMPs).³⁰ Inflammatory biomarkers like autoantibodies and cytokines get upregulated during the disease development and are considered as non-surgical diagnostic tool.³¹ Tumor necrosis factor (TNF- α), a pro-inflammatory cytokine, initiates inflammatory response, its level can be correlated with the severity of the disease by activating a cascade of other cytokines, such as interleukin-1 (IL-1), IL-6, and vascular endothelial growth factor (VEGF) (Figure 4).³²

Recent studies have shown association between PTPN22 and autoimmune diseases, including systemic lupus erythematosus (SLE), autoimmune thyroiditis, and rheumatoid arthritis (RA) highly. Few results have suggested a common pathway in the genetic etiology of endometriosis and autoimmune diseases such as RA.³³ The most extensive cohort study to date, with >37,000 patients with endometriosis in Denmark, showed a significantly higher risk of SLE, Sjögren syndrome, and multiple sclerosis.³⁴ A study among 59 laparoscopically staged endometriosis patients, 28.8% were tested positive for the antinuclear antibody, and out of 44 patients, 45.5% were lupus anticoagulant positive (greater than 1.3), and 20.5% were within a borderline range (1.2-1.3).³⁵

BIOMARKER AND ENDOMETRIOSIS

Endometriosis can be treated by surgery or hormonal treatment, in combination with anti-inflammatory drugs; however, there is no cure for this disease. The world endometriosis and research foundation (WERF) endocost study has shown that the economic burden of endometriosis is comparable to that of diabetes mellitus and Crohn's disease, a biomarker research defined for clinical and research priority by the WERF and endometriosis society (WES). A study of (Horne et al) United Kingdom and Ireland women with endometriosis, cleansing, and researchers in the United Kingdom and Ireland have ranked finding a non-invasive diagnosis number four in the top ten of research priorities for endometriosis.³⁶ Despite decades of research, now biomarkers have been validated for the diagnosis of endometriosis. Thus, accurate diagnosis and proper treatment of endometriosis patients can spend year's impact on their quality of life.

Potential diagnostic biomarkers for endometriosis

Widening the panel of biomarkers correlated with diagnosis and prognosis in endometriosis, a noninvasive test for endometriosis would be easier for the early

detection of the disease in the symptomatic women. Women who have pelvic pain and infertility with average ultrasound results include nearly all cases of peritoneal or rectovaginal endometriosis, without a visible ovarian endometrioma. And the cases with pelvic adhesions and other pelvic pathology might benefit from surgery to improve pain and infertility. At present, the ‘gold standard’ for diagnosis of endometriosis is laparoscopic inspection with histological confirmation, but it is an invasive technique. In this field, many biomarkers or panels of biomarkers were tested up to now: tumor marker (CA125), cytokines: IL-1, IL 6, IL 8 (IL-1, 6, 8), TNF- α , interferon-gamma (IFN-g), angiogenic and growth factors (annexin V), VEGF. Soluble intercellular adhesion molecule-1 (s-ICAM-1) and glycodelin, show altered levels in peripheral

blood (serum or plasma) of women with endometriosis when compared with controls, but not with a sufficient sensitivity or specificity to be validated in current practice other new biomarkers are now discovered by proteomics neural transmitters such: vasoactive intestinal polypeptide (VIP), substance P (SP), neural proteins such as protein gene product 9.5 (PGP 9.5), neurofilament (NF), neuropeptide Y (NPY), and calcitonin gene-related protein (CGRP). These show different levels in patients with endometriosis when compared with controls, while micro RNAs such as miR135b are dysregulated in patients versus controls.³⁷ The different morphologic, histologic, and biochemical properties of endometriotic lesions require future studies to compare samples of peritoneal fluid, ovarian, and/or rectovaginal septum endometriosis tissues.

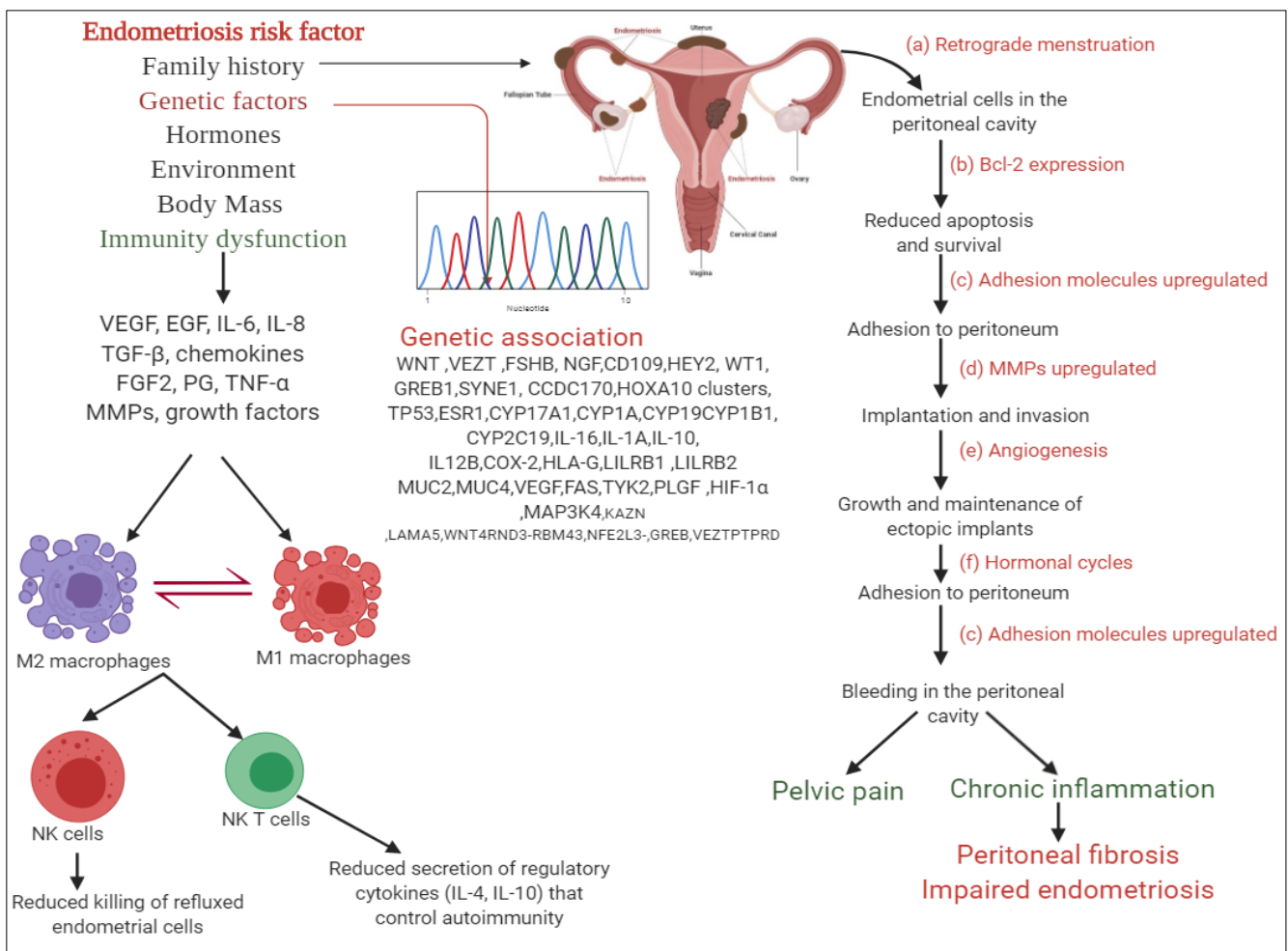


Figure 4: A schematic view of the different risk factors that account for the pathogenesis of eutopic and ectopic endometriosis, with particular emphasis on the role of macrophages, natural killer (NK) cell subsets, and genetic polymorphism.

Treatment regimes

Endometriosis is mainly treated with medications or surgery. These treatments can help to manage symptoms, though there's no cure for endometriosis. Generally, the clinicians recommend conservative drug treatments first. Many clinicians might also suggest conventional surgery

(laparoscopy) to take a biopsy earlier, as that's the only way for a clinician to know for sure whether one has endometriosis or not. But repeated or more-significant surgeries are usually saved as a last resort, that's because all surgeries come with risks, and the disease and pain sometimes persist even after surgery.

Initial treatment

Initial endometriosis treatment via medications or hormone therapies aims to control pain and improve fertility by preventing the progression of endometrial tissue growth outside the uterus (endometrial implants).

Medications

The primary therapy initially recommended for the pain of endometriosis disease is nonsteroidal anti-inflammatory drug (NSAID) such as, such as ibuprofen (advil, motrin IB, others) or naproxen sodium (aleve), that may ease painful menstrual cramps. If the maximum dose of these medications doesn't provide full relief, patients further underwent other treatments.

Hormone therapy

Supplemental hormones sometimes help to reduce or eliminate endometriosis pain. These hormonal medications slow the existing painful endometriosis tissue growth and further prevent the new endometriosis implants to form. Hormone therapy is not a permanent fix, but it can be used for extended period of time. But a long-term therapy is needed for it as endometriosis can continue to cause symptoms until menopause.

Endometriosis hormone therapies

Endometriosis hormone therapies include birth control pills (OCPs), patches, and vaginal rings. It helps to control the hormones responsible for the monthly buildup of both healthy endometrial tissues inside the uterus and abnormal endometrial tissue implants outside the uterus. Antagonists and Gonadotropin-releasing hormone (Gn-RH) agonists; the drugs to block the production of lowering estrogen levels, ovarian-stimulating hormones, and it prevents menstruation by causing endometrial tissue to shrink. These drugs create an artificial menopause, by taking a low dose of estrogen or progestin along with Gn-RH agonists and antagonists may decrease menopausal side effects, such as hot flashes, vaginal dryness, and bone loss. The periods and the ability to get pregnant return when one stops taking these medications. Progestin therapy, a progestin-only contraceptive, such as an intrauterine device (mirena) or contraceptive implant or a contraceptive injection (depo-provera), can halt menstrual periods and the growth of endometrial tissue implants, which may relieve endometriosis symptoms.³⁸

Conservative surgery

While endometriosis, if women wants to be pregnant, a surgery to remove as much endometriosis as possible while leaving your uterus and ovaries intact (called as conservative surgery) may increase your chances of success. Conservative surgery might also help if you have severe pain from endometriosis. However, disease and pain can return.³⁹ This procedure is done using small

instruments inserted through incisions in the abdomen (laparoscopically) or through traditional abdominal surgery in more advanced cases. If one is trying to get pregnant, assisted reproductive technologies such as in-vitro fertilization, are sometimes preferred over conservative surgery. In severe stages of endometriosis, surgery to remove the uterus and cervix (hysterectomy), as well as to both ovaries, preferred to be the best treatment. A hysterectomy alone is not adequate- as estrogen that ovaries produce can stimulate any remaining endometrial tissue implants and cause pain to persist.

CONCLUSION

Endometriosis is a leading cause of pain, menstrual irregularities, infertility in reproductive women, and its incidences are rising globally. It has a substantial contribution towards the escalating costs of health care, generating a high socio-economic burden in general population because of its underlying pathogenesis and progression risk factors. It's one of the most severe gynaecological diseases, with little knowledge about its distribution, prevalence, risk factors and multiple pathogenic associations. Some risk factors have confounding influences, and are involved in as a consequence of this disease instead of its cause. The risk factors leading to the onset of infertility are now well recognized that includes familial history, irregular menstrual cycle, smoking, BMI, diet, environmental and genetic exposures, comorbidities, long long-term disease risks, autoimmune diseases, cardiovascular conditions and lack of physical activities. Aberrant changes in cellular immune response and cytokines are found to be related to the pathophysiology of the disease (immune escape, adhesion, invasion, angiogenesis, and proliferation), causing decreased fecundity or sometimes infertility. However studies shown 25-50% of infertile women have endometriosis, while 30-50% of women suffering with endometriosis are infertile. So the identification and prevention of these underlying risk factors can significantly reduce the global epidemic risks of endometriosis. Many centers need to collaborate together to include as many patient samples as possible, from an established biobank with the same standardized operating procedures, to discuss the research approach in a collaborative manner. In conclusion, searching for a noninvasive diagnostic test to detect symptomatic endometriosis is still under research. Primary regimes for the anticipation and treatment of endometriosis are use of hormonal contraceptives, GnRH agonists or antagonists, aromatase inhibitors, and progestin therapy. Intake of green vegetables and fruit reduces, whereas beef and other red meat increases the risk of the disease, the fiber contents in fruits and vegetables increases estrogen excretion. It remains essential to take these epidemiologic studies together into consideration when dealing with diseases risks in women suffering with endometriosis. For the search of broad and wide-reaching influences, there always be possibilities of great discoveries and

applications in the clinical realm of gynecologic care of women.

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