UNIVERSITY OF NAPLES "FEDERICO II"

FACULTY OF MEDICINE

DEPARTMENT OF NEUROSCIENCE, REPRODUCTIVE SCIENCES AND DENTISTRY

"NEUROSCIENZE"

PhD THESIS XXXIII CICLO

Course coordinator : Prof. Maurizio Taglialatela

Tutor: Prof. Giuseppe Bifulco

"ENDOMETRIOSIS AND MULTIPLE SCLEROSIS: DIFFERENT PHENOTYPES WITH COMMON AUTOIMMUNE BACKGROUND?"

Candidate

Brunella Zizolfi

Academic course 2017- 2020

INDEX

CHAPTER I

1.1 ENDOMETRIOSIS

1.1.1 Introduction

Endometriosis is an enigmatic disease of yet-unknown origin and pathogenesis. Since the description of endometriosis by John Sampson in 1921 (1), numerous studies have failed to produce a consensus regarding the pathogenesis, mechanism of morbidity, and management of this condition. The complexity of this disease and the shortcomings in our knowledge base conspire to make our approach to the patient more difficult. Although endometriosis is not considered a life-threatening disease, it is a life-altering disease that requires timely diagnosis and treatment to minimize the clinical sequelae.

Endometriosis is defined as a pathologic condition in which the endometrium, consisting of endometrial glands and stroma, is found in locations outside the endometrial cavity and uterine musculature. The usual location of endometriosis is in the pelvis. However, endometriosis has been described in extrapelvic sites, including anterior abdominal wall, surgical scars, diaphragm, omentum, small intestine, appendix, lung, urinary tract, musculoskeletal, and neural systems.(2–8)

The prevalence of endometriosis in the general population has been difficult to determine primarily because of the selection bias of the populations used to make this estimate. Because the definitive diagnosis of endometriosis is surgical, the observed prevalence may be biased by the selection of patients for surgery and by which patients elect to proceed with surgery. Moreover, endometriosis is present in some women who are asymptomatic and do not have surgery. The observed prevalence may also depend on the skill and experience of the surgeon in identifying endometriosis. The population of women being studied has a significant effect on the prevalence estimates of endometriosis. The estimates range from 1% to 50%, depending on the surgical series.(9) A population of symptomatic women undergoing surgery has a higher prevalence estimate than the general population. In contrast, asymptomatic women undergoing tubal ligations probably have a lower prevalence estimate. In a compilation of several studies categorized by indication for surgery, the prevalence of endometriosis in women with pelvic pain was 24.5%, compared with 19.6% in women with infertility.(10) In women undergoing tubal ligation, the prevalence of endometriosis was 4.1%.

In large studies reviewing hospital discharge or surgical records, estimates of the prevalence of endometriosis have varied from 6% to 11% of reproductive-age women.(11–13) Because of the medical, social, and cultural influences on the selection of patients for surgery, attempts have been

made to estimate the prevalence of endometriosis in the general population. In one such study, the study population was extended to include surgical patients and women with symptoms and physical findings on examination suggestive of endometriosis.(14)

Endometriosis is a disease of reproductive-age women. The typical age at diagnosis is between 25 and 29 years,(15) but endometriosis occurring in premenarchal girls and postmenopausal women has been reported.(16–18) Among adolescents, the occurrence of endometriosis is not uncommon. A disproportionate number of adolescents with endometriosis have associated müllerian anomalies and outflow tract obstruction.(19,20)

Attempts by several studies have been made to identify the risk factors for the development of endometriosis.(10) The various factors that have been examined include age, race, socioeconomic status, marital status, education, contraceptive use, menstrual cycle characteristics, reproductive history, physical characteristics, and personal habits. Results from these studies have been inconsistent with respect to the significance of the risk factor examined. This inconsistency probably stems from differences in the population groups used, differences in the criteria for diagnosis, lack of a well-defined comparison group in some studies, or not controlling for potential confounding variables. Among the demographic factors, only age had a consistent relationship. In general, increasing age correlated positively with endometriosis.(21,22) A racial tendency for higher rates of endometriosis in white women originally was believed to exist. (23) The differences observed, however, were caused by socioeconomic factors such as access to health care and contraception. When these confounding variables are controlled, similar rates of endometriosis are observed among women of different races. (24–26) In women affected by endometriosis, an increased frequency of certain personality traits (e.g. intelligent, perfectionist, overachiever, anxious) has been reported, presumably because of the assumption that women with these traits are more likely to delay marriage and childbearing. These observations, however, have not been validated. (27) Other factors that may affect the risk of endometriosis relate to menstrual characteristics. In three case-control studies, greater exposure to menstruation because of longer flows, shorter cycles, or lower parity appears to increase the risk of endometriosis.(28–30) Greater peripheral body fat is associated with a greater risk of endometriosis, possibly because of elevated endogenous estrogen levels. (31) Direct measurement of body fat, however, was not determined. This hypothesis is also inconsistent with the observation that anovulatory women with persistently elevated estrogen levels do not have a higher reported incidence of endometriosis. Factors such as smoking that reduce endogenous estrogen levels may have an inverse association with the risk of endometriosis. (28,29) Other studies have reported no association between smoking and

endometriosis. (21,22) The data are inconclusive regarding the association of lifestyle factors and physical characteristics with endometriosis.

The use of oral contraceptives appears to reduce the risk of endometriosis in current or recent users. (21,22) In another study, however, no association with current oral contraceptive use and endometriosis risk was observed. (32) All three studies did not find an association between duration of oral contraceptive use and endometriosis.

A genetic susceptibility for endometriosis appears probable in light of the familial tendency that has been described in several studies. Early reports of familial clustering suggested a possible genetic basis for endometriosis. (26,33–35) Stronger evidence for a genetic basis is seen in two small studies of monozygotic twins. Concordance for endometriosis was found in 6 of 8 twins in one study (36) and 14 of 16 twins in the other. (37) Perhaps the strongest evidence in support of the involvement of genetic factors is the increased prevalence of endometriosis among relatives compared with the general population. (38–40) The risk of endometriosis was increased six to seven fold for relatives of an affected person compared with controls, which is similar to that seen for other multifactorial diseases. The Oxford Endometriosis Gene (OXEGENE) Study, a worldwide collaborative project, is studying affected sib pairs with linkage analysis and attempting to identify susceptibility loci and genes for endometriosis.

1.1.2 Pathogenesis

According to a recent review (41), there is growing evidence that hormonal and immune factors create a pro-inflammatory microenvironment that facilitates the persistence of endometriosis. This relates to the disease's two main symptoms: pain and infertility. New drugs on the market (and in research) have pharmacological effects on the endocrine and inflammatory functions implicated in the pathogenesis of the disease. This will lead to new investigative pathways in the pathogenesis of endometriosis.

Several theories have attempted to explain the pathogenesis of endometriosis: the most accredited are:

A. Implantation theory

In 1927, Sampson (1) proposed a retrograde flow of the menstrual mix of blood and full endometrial tissue through the Fallopian tubes into the peritoneal cavity as the first step in the development of the disease. Brosens and Benagiano (42) suggest that the first retrograde bleeding occurs at birth, when the newborn girl has drastic hormonal deprivation. Tight internal uterine cervix os, thick cervical mucus, or malformations impede the normal external drainage of that

mixture, which Brosens and Benagiano consider a source of stem cells. This results in the passage of that content into the abdominal cavity. These first implants will remain dormant because of the lack of estrogens in childhood. They shall grow rapidly after puberty, when the ovaries start to produce sexual hormones.

B. Celomic theory

According to Burney and Giudice, celomic metaplasia involves the transformation of normal peritoneal tissue to ectopic endometrial tissue. Endocrine-disrupting chemicals might play an important role in such transformation. Addressing the theory of Müllerian rests, the authors state that residual cells from the embryonic Müllerian duct migration maintain the capacity to develop into endometriotic lesions under the influence of estrogens. Endocrine, immune, and stem/progenitor cells and epigenetic modifications must be considered in the context of genetic background as well as stimulus driven reprogramming of the female reproductive tract (43). Even extrauterine stem/progenitor cells derived from bone marrow are suggested to be possible sources of ectopic endometriotic tissue (44).

C. Inflammatory disease

Other research suggests that there is evidence that endometriosis is, in fact, a pelvic inflammatory condition. A “peritonitis without germs”? The peritoneal fluid has an increased concentration of activated macrophages and an inflammatory profile in the cytokine/chemokine axis. Zimmer, in the review by Burney and Giudice, is reported to link a haptoglobin-like protein (that binds macrophages and reduces their phagocytic capacity) to the genesis of endometriosis. Increased production of interleukin-6 (IL-6), macrophage migration inhibitory factor, tumor necrosis factor-alpha, IL-1b, IL-6, and IL-8 alterations is also described. Gargett et al. (45) propose that human endometrium regenerates cyclically every month mediated by endometrial stem/progenitor cells such as CD140b+, CD146+, or SUSD2+ endometrial mesenchymal stem cells (eMSCs). N-cadherin+ endometrial epithelial progenitor cells and side population cells would also contribute to the pathogenesis of the disease. They are planted retrogradely at the time of birth or at puberty. The authors propose that the eMSCs may have a role in the generation of progesterone-resistant phenotype endometrial stromal fibroblasts. Stem/progenitor cell differences between healthy women and those with endometriosis have been proven.

D. Epigenetic modulators

In a recent “master review”, Gordts, Koninckx, and Brosens elaborate two different pathogenic hypotheses (46):

Hypothesis I: pathogenesis of early-onset endometriosis by neonatal uterine bleeding with the cyclic menstruation is the driving mechanism for adenomyotic nodule formation.

Hypothesis II: deep endometriosis (DIE) is a specific type of abnormal endometrium-like cell benign tumor. As proof of this, the authors show that DIE is a specific disease, as reflected by the distribution of deep lesions in all stages of the Revised American Fertility Society classification. It might share with peritoneal or cystic endometriosis the same cellular origin, but genetic and epigenetic modulators induce distinct presentations of the disease. In some cases, peritoneal endometriosis will prevail. With other epigenetic modulators, DIE will grow. They have common structures when analyzed by the pathologist. These authors propose that uterine adenomyosis and DIE have common origins, as in both cases glands are seen infiltrating muscle tissue.

1.1.3 Diagnosis

A. Anamnesis

Listen to the patient. Carry on a detailed anamnesis in a very slow fashion. This simple action gives us the best approach to the disease. She has so much to tell, to show with her face and expression. In most cases, the disease can be understood just by listening. The omnipresent symptom is pain: cyclic pelvic pain, dysmenorrhea, periovulatory pain, chronic non-cyclic pelvic pain, dyspareunia (positional or permanent), dyschezia, and dysuria. There are many other pain presentations that nobody even thinks of until confronted with an endometriosis patient who, incidentally, has exactly “that type of pain”.

Involuntary infertility, even when not the cause for consultation, should also be regarded as one of the frequent symptoms of endometriosis. Less frequently, cyclic nasal bleeding, umbilical bleeding, cyclic hemoptysis, cyclic constipation, and urinary urgency are reported by patients with endometriosis.

B. Pelvic examination

Even today, with the advancement of imaging diagnosis, pelvic examination (in expert hands) continues to be praised as an effective clinical tool for the diagnosis of endometriosis. It should be done with care, slowly, beginning with abdominal palpation. Only after no pain is registered, proceed to pelvic examination. This should be done with extreme delicacy and respect. Bimanual palpation of the uterine/bladder pouch, the Douglas pouch, and adnexa can reveal exquisitely painful sites typical of endometriosis. Fixed uterine retroversion is frequently due to uterosacral ligament compromise or adhesions at the Douglas pouch. Painful uterine mobilization is another typical sign of endometriosis. Compression of the uterine fundus is frequently painful when adenomyosis is present. Dyspareunia frequently corresponds with extremely painful palpation of the uterine-sacral ligaments. It will tell you exactly where the pain is more intense,

helping to clinically determine the extent of the disease. Careful and expert pelvic examination provides a lot of information at a very low cost.

C. Biomarkers

As of today, of the many biomarkers for endometriosis proposed in peripheral blood and endometrium, not one has been validated for endometriosis (47). This could be due to patient selection, sample collection, or analytical procedures. There is a current need to develop a non-invasive test for patients with symptomatic endometriosis.

Ca 125, considered a marker for endometriosis, is helpful only in postoperative follow-up. It usually decreases after surgery and rises when the disease recurs or progresses.

Signs, symptoms, and markers do not correlate well with the extent of disease, as stated by Taylor et al. (48). In 58 consecutive cases of endometriosis, Hirsch et al. (49)found increased values of Ca 125. This group concluded that Ca 125 of at least 30 units per milliliter is "highly predictive of endometriosis" in symptomatic patients. The authors propose it as mandatory but consider it "unable to rule out endometriosis".

In 2016, after a systematic search of the literature, Neil Johnson, Cyndy Farquhar, and the Cochrane Library group found only two biomarkers—PGP 9.5 (neural fiber marker) and CYP19 (hormonal marker)—that showed enough accuracy to replace surgical diagnosis. Even so, the authors state that "we could not statistically evaluate most of the biomarkers assessed in this review in a meaningful way. In view of the low quality of most of the included studies, the findings of this review should be interpreted with caution. Although PGP 9.5 met the criteria for a replacement test, it demonstrated considerable inter study heterogeneity in diagnostic estimates, the source of which could not be determined". Laparoscopy remains the gold standard for the diagnosis of endometriosis and using any non-invasive tests should only be undertaken in a research setting (29).

D. Genetics

For many years, there has been a search for genetic testing that could identify a population prone to develop endometriosis. A simple literature search identifies more than 3000 publications from 2018 linking genetics to endometriosis. Recently, an Australian group presented a summary of 17,045 cases included in a meta-analysis (50). In them, 14 genomic regions were identified, supported by results from multiple studies. The group found that "no independent associations were identified from direct genotyping of common and low-frequency protein-coding variants". According to them, the most common genetic factors related to endometriosis risk are located in regulatory DNA sequences. This, they say, alters the regulation of gene transcription. They

conclude that the target genes are present in three chromosome regions: “LINC00339 and CDC42 on chromosome 1, CDKN2A-AS1 on chromosome 9, and VEZT on chromosome 12”.

Using single-nucleotide polymorphism (SNP) array technology, a 2017 publication (51) describes genomic aberrations linked to the development of endometriosis. These investigators performed SNP array genotyping of pooled DNA samples from 100 patients with endometriosis and 50 controls. The authors detected 49 copy number variation (CNV) loci that were present in patients with endometriosis but that were absent in the control group. Six novel CNV loci in the subtelomeric regions representing gains and losses were identified. An intergenic locus on chromosome 19q12.1 showed a strong association with endometriosis. As with other biomarkers, we still lack a reliable genetic marker for endometriosis, and none of the proposed genes or gene alterations can be used to make a precise diagnosis.

E. Imaging

Ultrasound. Today, transvaginal ultrasound (TVS) is the first-line investigative tool in patients with symptoms of endometriosis, because of its high accurate, low cost and feasibility (52-53).

The International Deep Endometriosis Analysis group, confronting the wide variety of terms and descriptions used to identify endometriosis at TVS, proposes some basic steps that should be followed at the time of examination:

1. Routine evaluation of uterus and adnexa (search for adenomyosis and presence, or absence, of endometriomas)
2. Evaluation of transvaginal sonographic soft markers such as specific tenderness and ovarian mobility
3. Assessment of the Douglas pouch status (sliding sign)
4. Assessment for DIE nodules at the anterior and posterior compartments.

All steps should be performed, though not necessarily in this order, with a small liquid content in the bladder. A dynamic examination assessing the real-time mobility of the pelvic organs is mandatory in these cases. The prediction of the pouch of Douglas obliteration is very accurate. They give most importance to the sliding sign since it allows clinicians to predict the severity of the deep pelvic disease. It helps to organize multidisciplinary surgical teams in the most severe cases. One possible drawback is the issue of experience: only those who have performed more than 2500 scans can achieve real proficiency in the sliding maneuver, after about 40 examinations. Any trained staff can manage this non-invasive diagnostic method for other locations of DIE.

Computerized axial tomography. Computed tomography has no role in the routine evaluation of endometriosis except in very few particular scenarios (54). An inguinal endometriotic nodule and a case of round ligament endometriosis that looked like a hernia were published. Contrast studies

might be of use for the diagnosis of ureteral stops, stenosis, or deviations in the case of lateral pelvic side-wall DIE. CAT virtual colonoscopy can also be of help.

Magnetic resonance imaging. In 1999, a pioneer article described the use of MRI for the preoperative diagnosis of endometriosis (55). Diagnosis was accurate except when contrast was not used. Using a high-resolution technique (1-mm slices), intravenous contrast (for bladder visualization), and vaginal and rectal gel contrast (for better visualization of the rectovaginal septum), MRI able to stage the disease before laparoscopy, thanks to the special ability of this method to visualize superficial implants, adhesions, uterosacral ligament infiltration, rectovaginal septum infiltration (including the depth of rectal invasion), bladder wall infiltration, and ovarian disease. Images of ureteral compromise were also obtained (unpublished). Whenever possible, MRI would be mandatory before laparoscopy.

In 2009, the PRISMA (Preferred Reporting Items of Systematic reviews and Meta-Analyses) group proposed an evidence-based minimum set of items required for reporting in systematic reviews (http://www.prisma-statement.org). A recent publication evaluated the use of TVS and MRI for the diagnosis of adenomyosis, reviewing evidence in accordance with PRISMA requirements and suggested that MRI is more useful than TVS for the diagnosis of adenomyosis. (56)

MRI currently represents a second choice investigation for the diagnosis of endometriosis, used in more particular cases or when TVR remains inconclusive.

F. Laparoscopy

Laparoscopy is the “gold standard” for the diagnosis of endometriosis. It certifies the presence of the disease and its extension. By means of tissue biopsies and its pathological analysis, the aggressiveness of the lesions can be determined. It is also the opportunity to perform the initial treatment of endometriosis.

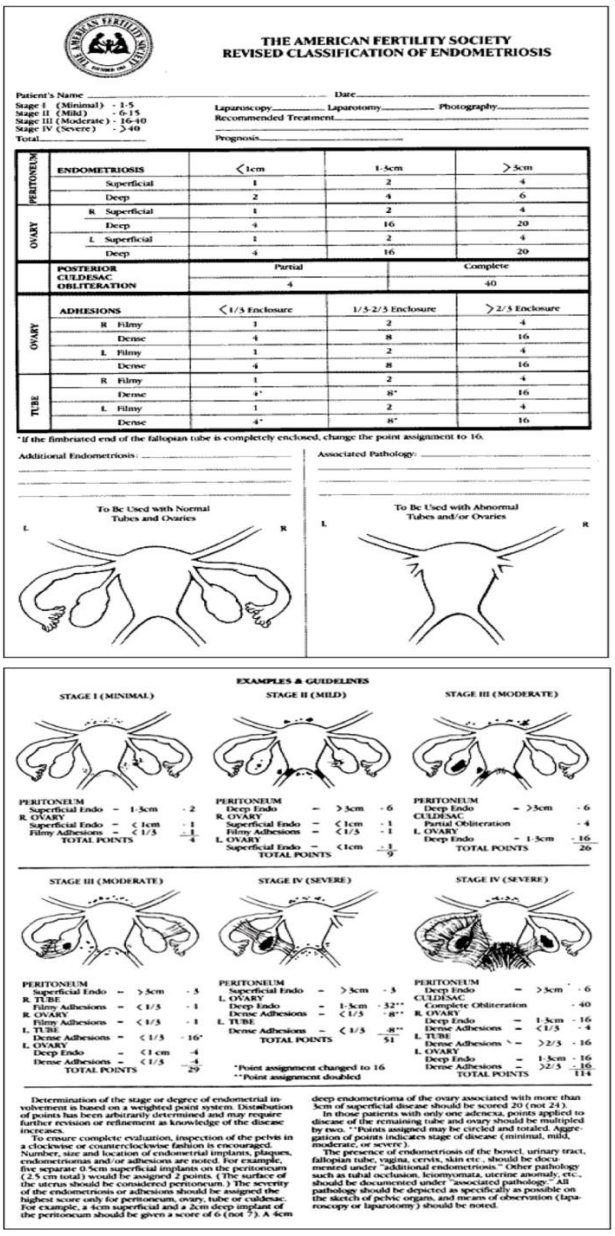
1.1.4 Classifications

The most used staging system is the rASRM classification (1997), which ignores DIE (Figure 1). Kecktein in 2003 and Haas in 2013 proposed the Enzian classification for DIE as a complement to rASRM, shown in Figure 2. Clear drawings help the surgeon to better stage the disease. This classification addresses the issues of the posterior compartment DIE and bladder (anterior) and ureteral (lateral) compartments (57-59).

In 2010, Adamson and Pasta introduced the EFI, although it is strictly related to endometriosis-associated infertility. Validated by several other authors, such as Hobo et al.(60),

this index includes not only the laparoscopic findings (least functional score at the end of surgery) but also other issues that affect fertility, such as the length of infertility, patient's age, and previous pregnancies.

However, the classification systems in current use continue to attract criticism from women with endometriosis and those providing care for them because of the poor correlation with disease symptoms as well as a lack of predictive prognosis and, to date, unclear pathways of treating pelvic pain and infertility based on them (61).



THE AMERICAN FERTILITY SOCIETY
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date _____

Stage I (Minimal) - 1-5
Stage II (Mild) - 6-15
Stage III (Moderate) - 16-40
Stage IV (Severe) - >40
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
Prognosis _____

		<1cm	1-5cm	>5cm
PERITONEUM	ENDOMETRIOSIS			
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
	POSTERIOR CULDESAC OBLITERATION	Partial	Complete	
		4	40	
OVARY	ADHESIONS	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Additional Endometriosis: _____

Associated Pathology: _____

To Be Used with Normal Tubes and Ovaries

To Be Used with Abnormal Tubes and/or Ovaries

EXAMPLES & GUIDELINES

STAGE I (MINIMAL)
PERITONEUM
Superficial Endo – 1-5cm · 2
R. OVARY
Superficial Endo – <1cm · 1
Filmy Adhesions – <1/3 · 1
TOTAL POINTS 4

STAGE II (MILD)
PERITONEUM
Deep Endo – >5cm · 6
R. OVARY
Superficial Endo – <1cm · 1
Filmy Adhesions – <1/3 · 1
L. OVARY
Superficial Endo – <1cm · 1
TOTAL POINTS 9

STAGE III (MODERATE)
PERITONEUM
Deep Endo – >5cm · 6
CULDESAC
Partial Obliteration · 4
L. OVARY
Deep Endo – 1-5cm · 16
TOTAL POINTS 26

STAGE III (MODERATE)
PERITONEUM
Superficial Endo – >5cm · 3
R. TUBE
Filmy Adhesions – <1/3 · 1
R. OVARY
Filmy Adhesions – <1/3 · 1
L. TUBE
Dense Adhesions – <1/3 · 16*
L. OVARY
Deep Endo – <1 cm · 4
Dense Adhesions – <1/3 · 4
TOTAL POINTS 29

STAGE IV (SEVERE)
PERITONEUM
Superficial Endo – >5cm · 3
L. OVARY
Deep Endo – 1-5cm · 32**
Dense Adhesions – <1/3 · 8**
L. TUBE
Dense Adhesions – <1/3 · 8**
TOTAL POINTS 51

*Point assignment changed to 16
**Point assignment doubled

STAGE IV (SEVERE)
PERITONEUM
Deep Endo – >5cm · 6
CULDESAC
Complete Obliteration · 40
R. OVARY
Deep Endo – 1-5cm · 16
Dense Adhesions – <1/3 · 4
L. TUBE
Dense Adhesions – >2/3 · 16
L. OVARY
Deep Endo – 1-5cm · 16
Dense Adhesions – >2/3 · 16
TOTAL POINTS 114

Determination of the stage or degree of endometrial involvement is based on a weighted point system. Distribution of points has been arbitrarily determined and may require further revision or refinement as knowledge of the disease increases.

To ensure complete evaluation, inspection of the pelvis in a clockwise or counterclockwise fashion is encouraged. Number, size and location of endometrial implants, plaques, endometriomas and/or adhesions are noted. For example, five separate 0.5cm superficial implants on the peritoneum (2.5 cm total) would be assigned 2 points. (The surface of the uterus should be considered peritoneum.) The severity of the endometriosis or adhesions should be assigned the highest score only for peritoneum, ovary, tube or culdesac. For example, a 4cm superficial and a 2cm deep implant of the peritoneum should be given a score of 6 (not 7). A 4cm deep endometrioma of the ovary associated with more than 5cm of superficial disease should be scored 20 (not 24).

In those patients with only one adnexa, points applied to disease of the remaining tube and ovary should be multiplied by two. **Points assigned may be circled and totaled. Aggregation of points indicates stage of disease (minimal, mild, moderate, or severe).

The presence of endometriosis of the bowel, urinary tract, fallopian tube, vagina, cervix, skin etc., should be documented under "additional endometriosis." Other pathology such as tubal occlusion, leiomyomata, uterine anomaly, etc., should be documented under "associated pathology." All pathology should be depicted as specifically as possible on the sketch of pelvic organs, and means of observation (laparoscopy or laparotomy) should be noted.

Figure 1. American Society for Reproductive Medicine revised classification.

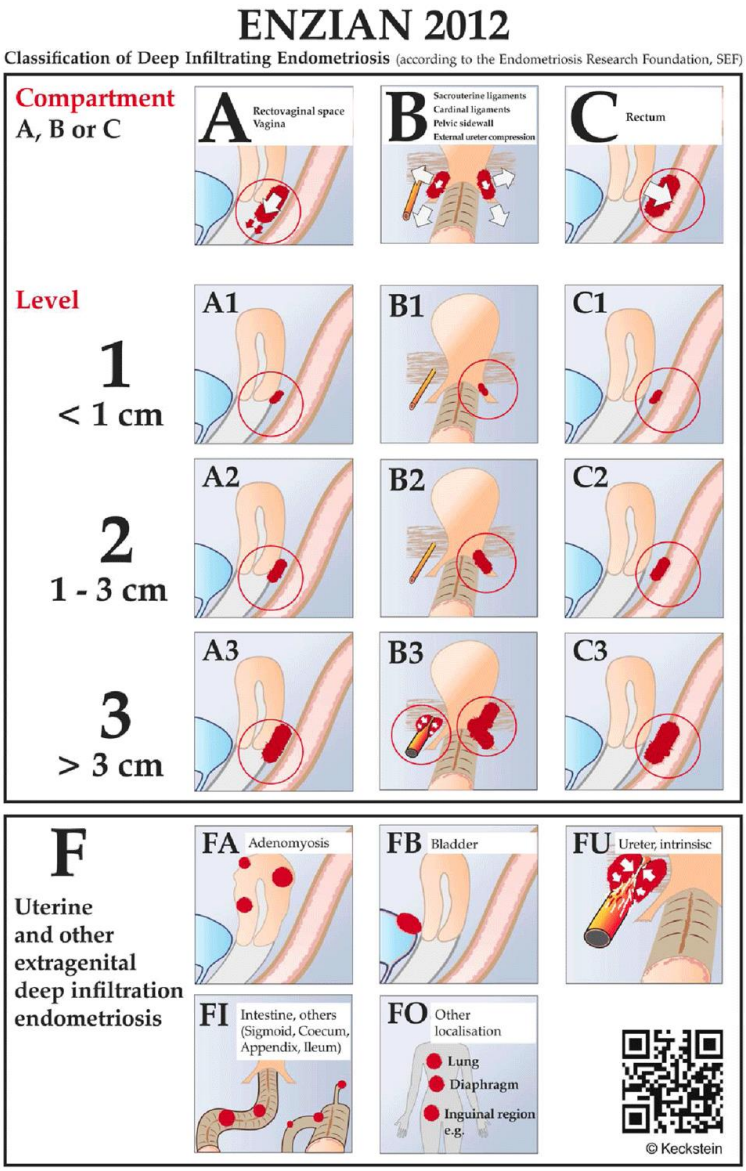


Figure 2. The Enzian classification for deep infiltrating endometriosis

A major drawback of all existing classifications is that no one of them links the severity of the pain with the findings. Some patients who would be classified as "severe" by ASRM revised charts experience little pain but do not get pregnant. Others, with only superficial red and blue lesions and minor adhesions, experience severe pain and a poor QOL.

1.1.5 Therapy

The choice of therapy is based on several factors: size, location and extension of endometriotic lesions, symptoms, age of the patient, desire of pregnancy. In some cases of mild endometriosis, with poor symptoms, waiting, without any therapy, may be help, simply performing regular periodic checks. Pain, if present, can be controlled with several analgesics. An important

concept to keep in mind is that, since the cause of endometriosis is not yet known, whatever therapy is practiced, it cannot to resolve the disease definitively, but it can be useful to reduce symptoms or promote fertility.

Current available medical treatments for symptomatic endometriosis act by inhibiting ovulation, reducing serum estradiol levels, and diminishing uterine blood flow. Several drugs can be used with a similar magnitude of effect, in terms of pain relief. Danazol is a drug of the past. OCs, progestogens, GnRH agonists, and lately GnRH antagonists (elagolix) and (to some extent) hormonal receptor modulators (such as ulipristal) are current specific medications. The role of antiestrogens is not clear, nor is that of natural origin substances (such as resveratrol), anti-aromatases, anti-angiogenic molecules, and immunomodulators. They can be categorized by price, as low-cost drugs (OCs and most progestogens) or high-cost drugs (dienogest, GnRH agonists, and the newly introduced elagolix). It is recommend starting treatment with low-cost drugs and step up to high-cost ones only in case of "inefficacy or intolerance".(62)

The guideline recommends prescribing hormonal treatment—combined OCs, progestagens, anti-progestogens, or GnRH agonists—as one of the options, as it reduces endometriosis-associated pain and clinicians have to take patient preferences, side effects, efficacy, costs and availability into consideration when choosing hormonal treatment for endometriosis-associated pain.

Combined estrogen and progestin OCs are recommended, as they reduce endometriosis-associated dyspareunia, dysmenorrhea, and non-menstrual pain, in a continuous protocol. Also, vaginal contraceptive rings or transdermal estrogen/progestin patches are suggested.

Recommended progestogens are medroxyprogesterone acetate (oral or depot), dienogest, cyproterone acetate, and noretisterone acetate. The different side effect profiles of each one of those drugs, especially thrombosis and androgenism, should be regarded. Aside from difficult cycle control in some users, dienogest in doses of 2 mg per day results in very effective pain reduction and control of the disease progression. It can be used over prolonged periods of time provided that no recurrent bleeding occurs. This is the main cause of discontinuation.

The guidelines recommend giving careful consideration to the use of GnRH agonists in young women and adolescents, since these women may not have reached maximum bone density. Aromatase inhibitors are considered for those who have pain from rectovaginal endometriosis, refractory to other medical or surgical treatment. They should be prescribed in combination with OC pills, progestagens, or GnRH analogs.(63)

Certainty, surgery can be achieved staging and biopsy (for histological confirmation of the disease) to make a better prognosis. Laparoscopy gives the opportunity to excise all disease present, including adhesions, peritoneal lesions of all types, endometriomas, and deep infiltrating

lesions. Surgery should be provided by experts on the disease. Much of the recurrence (or persistence) of endometriosis is related to poor first surgery quality, incomplete removal of all lesions, or wrong attitude at the time of laparoscopy. Indeed, the treatment of endometriosis requires a delicate and experienced surgeon and, if it is the case, an interdisciplinary team, including gastrointestinal surgeons or urologists (or both), in selected patients. Multidisciplinary pelvic surgeons may be available at some institutions, where a reduced number of gynecologists operate a large number of patients.

Although RCTs have failed to demonstrate benefit of excision over ablation, excising peritoneal lesions where possible is recommended, especially where pain is present.

Although this might be disputed by many, destruction by electrocoagulation or laser does not allow histological study of the lesions, a reliable diagnosis, or the evaluation of the degree of functionality of the disease. In some cases, extensive "peritonectomies" must be performed in order to correctly remove all disease present.

Surgery for endometriomas is an issue that needs attention. Laparoscopy is the best surgical approach. Stripping and removing the cysts, whenever possible, are considered the best options because they allow lower recurrence rates (64) and, in the case of infertility, better pregnancy rates.

Lower levels of anti-Müllerian hormone—considering it a marker of ovarian reserve—precede surgery, suggesting that the ovarian damage is due at least in part to the endometrioma itself and not only the surgical procedure.

DIE remains the most complex surgical procedure in the domain of endometriosis.

The controversy on DIE and the need (or not) for surgery before seeking pregnancy should come to an end, and patients should be counselled on the risks of pregnancy prior to the resection of DIE nodules. Surgery is mandatory as a first step in the treatment of endometriosis-associated infertility in the presence of DIE.

1.2 MULTIPLE SCLEROSIS

1.2.1 Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS), demyelinating and degenerative, with a highly variable course. It preferentially affects young people and is the first cause of disability in young adults, after craniomedullary trauma (65) (66). The disease in its course has a significant impact on the quality of life of patients, their families and their socio-working life.

MS is considered a complex disease with autoimmune pathogenesis and multifactorial etiology that involves the interaction of still poorly defined genetic and environmental factors. Like all autoimmune diseases, MS is believed to be characterized by a dysregulation of the immune system with the formation of self-reactive cells against components of the CNS. These cells are able to adhere to the vessel walls, cross them and migrate into the nervous tissue where they attack the myelin sheath that covers the axonal fibers. The main feature of the disease is the presence of an inflammatory process responsible for the loss of the myelin sheath and the consequent axonal degeneration with the appearance of signs and symptoms of focal CNS damage. The demyelinating process primarily involves the periventricular white matter (SB), the optic nerve, the spinal cord, the brain stem, and the cerebellum. Acute clinical episodes, defined as relapses (both in the case of the first and subsequent episodes), can spontaneously regress (especially in the initial phase of the disease) or cause permanent neurological deficits. Relapses are due to the appearance of focal inflammatory lesions, also called plaques.

1.2.2 Epidemiology

MS is more common in females, with the female/male ratio being approximately 2: 1 (ranging from 1.9 to 3.1). Onset is rare before puberty and after 65 years, usually occurring between 20 and 45 years, with a peak of incidence for age around 30 years, even if there are cases in childhood or late (67).

The highest prevalence of MS is found in the United States and Northern Europe, where it is around 100 cases / 100,000 population (68).

The thesis that Italy represents a relatively low-risk area compared to Northern Europe has been revised by accurate epidemiological studies carried out in recent years which have made it possible to highlight rates of about 50-80 cases per 100,000 inhabitants, thus placing our countries with high disease risk (69-71).

Most epidemiological studies have shown a relationship between MS and latitude: the disease is very rare around the tropics (from the 23rd parallel north to the 23rd parallel south) and increases in frequency with increasing latitude until it becomes common among the 50th and 60th parallel north and to a lesser extent between the 50th and 60th parallel south, and then decreases again. (72) These data seem to suggest the existence of environmental factors linked in a particular way to the "Western world", with a frequency gradient in relation to the variation of latitude (Fig. 3).

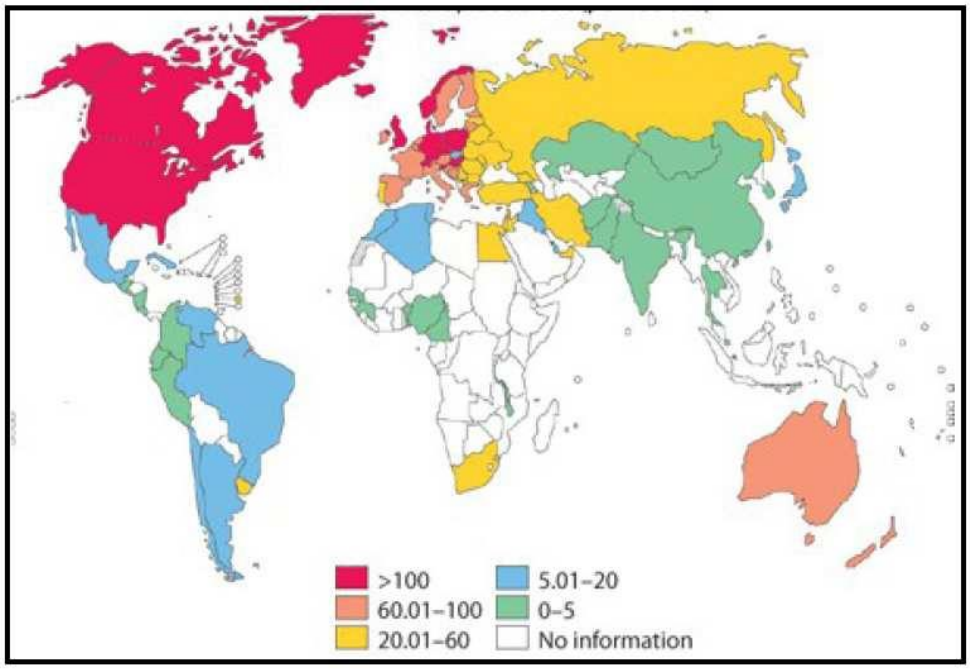


Figure 3. Prevalence of MS worldwide.

However, this hypothesis is accompanied by the possibility that genetics influences the geographic distribution of MS. For example, genetics studies have shown an association between geographic distribution and population genetic factors. In Sardinia, a high prevalence of the disease (over 100 cases / 100,000 inhabitants) is associated with a particular haplotype of the major histocompatibility system (DR4) (73). In this sense, the data of a low incidence of disease in populations such as the Japanese, the Asians living in Great Britain, the Gypsies of Hungary, the African Americans of the USA, the Maori of New Zealand or the Africans of South Africa, groups racial people living in geographically defined high risk areas. Furthermore, migration studies have shown that migrant populations tend to retain the risk of the area of origin when migration occurs after the 15th year of life, while they acquire the risk of the new country of residence when migration occurs before the 15th year. of life (74).

These latest data would therefore suggest the existence of environmental factors that would act in childhood or early adolescence.

1.2.3 Etiology

MS can be considered the result of a complex multifactorial interaction between environmental and genetic influences (75).

In MS, the genetic component is defined by the action of several allelic variants of different loci, located along the genome, still largely unknown. Numerous studies carried out on the heredity of

the disease, conducted on the twins and siblings of affected individuals, have highlighted the importance of the role of genetic factors in the predisposition to the disease. Genes play an important role in the development of MS, but they cannot fully explain its etiology. In fact, the risk of getting sick with MS increases with the increase in parental relationships (76), but monozygotic twins agree for the disease only for about 30% (77). This clearly highlights incomplete penetrance and the importance of genetics in the development of MS, but underlines the need for permissive environmental factors, as well as the modulation of post-transcriptional and epigenetic factors (processes that cause hereditary changes in the functioning of genes without variations in the DNA sequence), equally important for the overall risk of developing MS. (78)

The field of genetics and the identification of disease genes could also provide important help in indicating the environmental factors that play a role in the risk of developing the disease. In fact, the disease genes, related proteins and mechanisms of action could suggest various environmental factors involved in the etiopathogenesis of MS, which are difficult to highlight with prospective studies. However, even the search for genetic factors has represented for many years, and still represents today, an arduous challenge.

In the early 1970s, the association of some haplotypes of the Major Histocyte Compatibility (MHC) / Human Leukocyte Antigen (HLA) region, in 6q31, with MS was illustrated (79), but the primary effects still remain to be clarified. The HLA / MHC region currently represents the locus that exerts the greatest genetic risk effect of MS.

The explanation for this phenomenon is to be found in the physiological function that the human leukocyte antigen plays in the various immunological processes, such as antigen binding, presentation, and the determination of the T cell repertoire.

Today we are aware of a vast series of polymorphisms of the genes of the immune system (especially genes involved in the differentiation pathway of T helper cells) which are positively correlated to the disease, once again confirming the autoimmune character of the disease. The most accredited polymorphisms concern: cytokines, co-stimulatory molecules, molecules involved in signal transduction, molecules related to the metabolism of Vitamin D, membrane receptors (which were then used as pharmacological targets for therapies for MS, such as Natalizumab (VCAM1) and Daclizumab (IL2RA)), and only two genes with a role in axonal neurodegeneration.

With regard to the environmental factors involved in the development of MS, the evidence of the considerable variability of the prevalence of the disease depending on the geographical areas considered, has led to indicate as predisposing factors elements such as pollution (80), the foods present in the diet , daily habits (81), and exposure to UV radiation (and consequently the levels of Vitamin D) (82).

Indeed, geographic areas with higher sunlight exposures show a lower prevalence of MS and vice versa. Furthermore, low circulating levels of the major metabolites of the vitamin would be associated with a higher incidence of MS. These metabolites have demonstrated immunomodulating effects, capable of shifting the immune response towards the "anti-inflammatory pool", enhancing regulatory T lymphocytes (83).

Exposure to viral agents, among the various candidates, has attracted the attention of the scientific world in recent years (84).

Attention has focused in particular on those viruses that are capable of inducing a chronic-latent infection in humans, and among these above all on the neurotrophic virus Human herpesvirus 6 (HHV6) (85) and the Epstein-Barr lymphotrophic virus (EBV) (86).

In particular, there are numerous studies that have sought a possible etiological role of EBV in the development of MS, with often conflicting results.

Some studies have shown that the prevalence of seropositivity to the virus is significantly higher in patients with MS than in the general population (87) and above all they have shown a constant intracerebral accumulation of B cells infected with the EBV virus in patients with MS, and a link between virus reactivation in the brain and episodes of acute inflammation and relapse (88).

On the contrary, other studies have tended to considerably reduce the possible role of EBV in the development of MS, even going so far as to hypothesize a possible neuroprotective role played by the virus, in particular by one of its proteins, called BARF 1 (89).

1.2.4 Pathogenesis

MS is traditionally considered to be an idiopathic demyelinating disease of the CNS of an inflammatory character with autoimmune pathogenesis.

However, since the first neuropathological studies it has been shown that axonal damage and loss are an essential element of the typical anatomopathological finding of the disease, the “sclerotic plaque” (90-91).

Furthermore, it has been shown that axonal damage directly correlates with the degree of inflammation (92-94) and that it represents the main substrate of permanent disability, typical of advanced states of the disease (95).

Although it is now recognized as an essential pathogenetic element in the late stages of the disease, the role of axonal loss in the early stages of MS remains uncertain, as well as the relationships that link inflammation, demyelination and neurodegeneration.

1.2.4.1 The role of inflammation in MS

The CNS has long been considered an "immunological sanctuary" due to the presence of a small resident lymphocyte population, in the absence of latent or ongoing infection. However, numerous studies have shown that a small number of T lymphocytes circulate physiologically throughout the CNS, preserving it from possible infectious or traumatic attacks and that T lymphocytes activated in the periphery can cross the blood-brain barrier (BEE) and thus penetrate the CNS. (96-97).

In addition, within the immune system there is the presence of a pool of T and B lymphocytes defined as "self-reactive", because it is sensitized to autologous antigens. It has been shown that some of these autoreactive cells can be stimulated, in healthy individuals, by myelinated components, but do not appear to have a pathogenic action without prior activation and concomitant loss of normal immunological tolerance (34).

It has been hypothesized that different mechanisms, such as molecular mimicry, bystander activation and epitope expansion, contribute to the induction of autoimmune reactions to myelinated components in the CNS (98-99).

Once activated, myelin-specific T lymphocytes can cross the BEE where by proliferating and secreting pro-inflammatory cytokines, they would stimulate microglia, macrophages and astrocytes, and by recruiting B lymphocytes, they would ultimately cause the destruction of the myelin sheath and the contextual damage of oligodendrocytes and axons (100).

1.2.4.2 Demyelination in MS

Myelin is an insulating substance with a lamellar structure, consisting mainly of lipids and proteins, which externally covers the axons of neurons; this coating can be monolayered or composed of various concentric layers, which give rise to a sort of sheath or sleeve. The main function of myelin is to allow the correct conduction of nerve impulses, amplifying the speed of transmission through the so-called "saltatory conduction". In myelinated fibers, in fact, the coating of the axons does not occur in a uniform and continuous way, but at intervals, forming the Ranvier nodes (101).

In MS, the demyelination of the fibers alters saltatory conduction: the nerve impulse will be forced to travel along the fiber for its entire length, causing a reduction of the conduction speed (102). While the clinical manifestations of MS can be changeable, reflecting the fact that the disease can affect any site of the CNS, the pathogenesis of most acute symptoms (relapses) can be traced back to the delayed axonal conduction in SB following acute inflammatory demyelination. (103-104).

Furthermore, demyelinated axons become sensitive to environmental factors such as the increase in temperature that worsens nerve conduction (Utothoff's phenomenon), metabolic changes in the

extra-cellular "milieu" and mechanical stimuli, with the appearance of sudden action potentials due to , for example, with head flexion, as in Lhermitte's phenomenon, or with tonic spasms secondary to movement.

Demyelination can also generate ectopic impulses, at the origin of the phenomenon of hepaptic transmission between contiguous demyelinated axons. These anomalous conduction mechanisms underlie paroxysmal sensory or motor phenomena, such as trigeminal neuralgia, paresthesia, prolonged tonic muscle contractions.

1.2.5 Neuropathological aspects

The disease is characterized by the presence of numerous areas of demyelination in the SB, called plaques or lesions, preferentially distributed around the lateral ventricles, the floor of the Silvio aqueduct and the fourth ventricle, in the corpus callosum, in the optic nerve and in the spinal cord. (105). Nevertheless, plaques can also form in the gray matter (SG) of the cerebral cortex (especially in the subpial region), in the deep nuclei and in the spinal cord. Plaques can be classified according to their location, shape and above all according to the degree of activity.

According to this last criterion, the plaques can be classified as acute, chronic active, inactive and, shadow plaques. A histological feature is the presence of macrophage-microglia infiltrates, CD4 and CD8 lymphocytes, responsible for myelin damage, resulting in an astroglial reaction, more or less effective repair of damaged nervous tissue (106) and progressive reduction of inflammatory activity over time. The activity is determined by the presence of foamy macrophages containing fragments of myelin with variable inflammatory perivascular infiltrate mainly composed of T lymphocytes, reactive astrocytosis, and a variable degree of activation of microglial cells. Axons appear swollen and sometimes interrupted with the formation of spheroids (107)

MS is also characterized by other pathogenetic aspects of particular relevance such as:

- Axonal damage: technically demonstrable from the accumulation of APP (amyloid precusor protein) within the axon, already present in the early stages of the disease, but which becomes quantitatively relevant in the medium-advanced ones. Nitrogen monoxide (NO), glutamate, numerous inflammatory cytokines, T lymphocytes, in particular CD4 + are involved in the genesis of axonal damage (108). In recent years, with the advancement of knowledge, it has become increasingly evident that axonal damage represents the main substrate of the progressive and irreversible disability observed in patients with MS.
- Lesions of the SG, cortical and deep; It is interesting to note that, unlike what happens in SB, the demyelination areas of the SG (in particular at the cortical level) are not affected by an equally

evident lymphocytic infiltrate, which could suggest a different pathogenetic mechanism (109) or in any case to the presence of extraparenchymal lymphocytic infiltrates. The regions most affected are: the insular, temporal-basal and gyrus cortex (110-111).

- Apparently normal SB (SBAN): small inflammatory foci with mild but widespread axonal alterations, are found in areas of SB without lesions visible on conventional MRI, even in the early stages of the disease (112). Furthermore, alterations in the permeability of the BEE occur not only in correspondence with the demyelination plaques, but also in the absence of the latter, indicating cerebral impairment that extends beyond the boundaries of macroscopically evident SB lesions (113). Inflammatory abnormalities of SBAN, such as perivascular infiltration of lymphocytes, microglial activation and meningeal inflammation, are constant especially in the progressive phases of the disease.
- Cerebral atrophy: it is another evident feature in MS patients and has also been proposed as a potential tool for monitoring the disease. Often the relationship between lesion load and clinical disability is poor, probably because the lesion load does not reflect the entire extent of the clinically relevant pathology (114). In fact, if it is true that relapses are characterized by the presence of inflammatory demyelinating lesions of the SB, the chronic progression of the disease would be more related to the widespread damage of the SBAN and to cortical and deep nuclei atrophy (115-116). Although SG involvement is usually related to axonal damage secondary to SB lesions, Wallerian degeneration and neuronal loss, a recent histopathological study has suggested a dissociation between inflammatory demyelination and neurodegeneration (117); this interpretation is supported by other studies that suggest that cortical atrophy appears early in the disease process and could occur independently of the SB pathology and relapses (118-119). These observations support the hypothesis that the first pathological events in MS could be concentrated, in some cases, in the cortical SG. The studies published so far have therefore established that: a) the involvement of the SG can occur independently of the lesions of the SB; b) the involvement of the SG may be among the first manifestations of MS and may be related to physical disability, fatigue and cognitive impairment; c) the involvement of the SG may explain the dissociation observed between inflammatory demyelination markers and disease progression. Although the extent of brain atrophy appears to be greater in patients with progressive forms than in patients with relapsing-remitting MS (RRMS) (120-121), studies have shown that significant tissue loss also occurs in patients with RRMS at onset (122-123), and in patients with clinically isolated syndrome (CIS) (124-125). Furthermore, cross-sectional and longitudinal studies have shown that measures of cerebral atrophy are better correlated with clinical disability (126) and with neuropsychological deficit (127-128) than with lesional load.

1.2.6 Clinical aspects

Because demyelination and neurodegeneration can affect any area of the CNS, the resulting symptoms are extremely variable depending on the lesion site, but some symptoms recur more frequently, as the areas of demyelination are distributed in preferential sites.

In most cases, the initial symptom is weakness in one or more limbs (40%), optic neuritis (22%), a subjective sensitivity disorder (21%, such as paraesthesia and dysesthesia), diplopia, vertigo or urination disorders (10%).

These symptoms may appear alone (monosymptomatic onset) or in association (polysymptomatic onset). Few diseases are as variable as unpredictable as MS, and the age of onset, the initial symptom, the frequency of relapses, the course of the disease, the disability and its progression will differ for each individual case (Fig. 4).

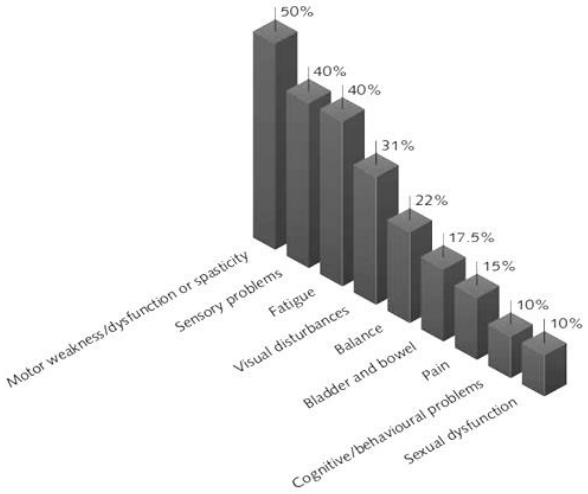


Figure 4. Percentage of symptoms presented by people with MS in the course of illness (WHO 2008).

1. Pyramidal disorders

The involvement of the pyramidal system with consequent weakness and spasticity, localized to one or more limbs, is a constant event and represents an important cause of disability (65).

2. Fatigue

Fatigue, a very common symptom among MS patients (80%), is defined as a "lack of physical and / or mental energy that the patient feels is interfering with desired and usual activities (129-130-132).

3. Sensitivity disorders

   These disorders are due to lesions of the posterior cords, the spino-thalamic tracts or the entrance areas of the posterior roots, and are described by patients as a feeling of numbness, tingling, bandaging, swelling, etc. (65).

4. Cerebellar disorders

   They are not a frequent symptom at onset, but they become common later. Intention tremor and limb discrepancy are particularly disabling, poorly sensitive to symptomatic therapies, and cause severe disability and significant limitation of autonomy (65).

5. Cranial nerve involvement

   The optic nerve is particularly vulnerable, so much so that optic neuritis is the presenting symptom in 22% of cases. Oculomotor nerves can also be involved. A lesion of the VI, III or, more rarely, the IV cranial nerve can be responsible for the onset of diplopia, often with a favorable course. Other manifestations related to the involvement of the cranial nerves are trigeminal neuralgia, peripheral facial paralysis, subjective dizziness, hearing loss and nystagmus (65).

6. Affective and cognitive disorders

   Depression is one of the most common manifestations in MS patients and is partly secondary to the awareness of being affected by a progressively disabling disease, uncertainty about the future, and the fear of having to depend on others (133).

7. Sphincter and sexual disorders (65).

1.2.7 Course

The course of the disease is variable and often unpredictable. In 80% of cases the disease presents relapses, with acute and subacute onset of a clinical symptom that reaches its peak in days or weeks, and then partially or completely regress. Conventionally, the minimum period of a relapse is 24 hours, and fluctuations in pre-existing symptoms or the appearance of new symptoms with a shorter period have no clinical relevance (134).

The anamnestic presence of a single attack suggestive of MS, in the absence of the accessory criteria necessary for the diagnosis of clinically defined MS (CDM), leads to the diagnosis of "clinically isolated syndrome" (CIS) (135).

The second episode of neurological deficit can occur within one a very variable period of time which generally is around 2 years but which in 10-15% of cases can last for many years configuring

a form of disease with a benign course with modest or no disability even after 15 years from the first symptom. The frequency of relapses is variable but generally less than one per year; however they tend to be more frequent in the first years of the disease and then decrease. The free interval between one relapse and another can be a few weeks or many years. Relapses can heal completely or leave outcomes that add up over time.

At least four forms are clinically accepted today:

- Relapsing-Remitting (RRMS) (relapses and remissions): in which acute episodes of neurological dysfunction (relapses) are followed by total or partial recovery, and are interspersed with periods characterized by the absence of disease progression (remissions).
- Secondary-Progressive (SMSP) (secondary progressive): the disease initially has a relapsing-remitting course, followed by a progression that may or may not be associated with relapses, mild remissions and plateaux.
- Primary-Progressive (SMPP) (primary progressive): in which a progressive course of the disease is observed from the clinical onset, with or without occasional plateaus and temporary slight improvements, but without acute relapses or sudden worsening.
- Progressive-Relapsing (SMPR) (progressive with relapses): the disease has a progressive course from onset but with evident acute episodes, followed or not by complete recovery.

About 50% of patients affected by RRMS enter the "secondarily progressive" form within 10 years of diagnosis; 90% of patients reach this stage within 25 years of onset. In some individuals, the secondary progressive course is still associated with relapses (secondarily progressive MS with relapses). About 10-15% of cases the disease is progressive from the beginning, without sudden deterioration (Primary Progressive or PP) (136).

Although it is particularly difficult in such an unpredictable disease to formulate a correct prognosis, some factors can be taken into consideration: the course appears more favorable in the female sex than in the male sex, the early onset is associated with a better prognosis, while the late onset is often followed by a progressive course with rapid onset of disability. Onset symptoms of the sensory type and involvement of the cranial nerves, such as the optic nerve, are associated with a more favorable course than in cases in which pyramidal or cerebellar symptoms mark the onset of the disease.

About 80% of patients have an acute monosymptomatic onset, called CIS, a condition in which there is a single neurological event, lasting more than 24 hours, compatible with a demyelinating disease, in which, however, it is impossible to prove the DIT. To date, CIS is considered a full-fledged MS phenotype (137) and, therefore, requires follow-up over time. If it is evaluated as "active", it falls

within the SMRR forms, according to the new diagnostic criteria.

Less defined is the concept of "radiologically isolated syndrome" (RIS) which identifies cases of patients who perform an MRI for reasons not related to MS (eg headache, head trauma, confusional state), with characteristic findings of a disease demyelinating, albeit in the absence of symptoms (138). RIS is not considered a distinct MS phenotype, nevertheless it is preferable to follow up over time a patient whose MRI one or more lesions suggestive of MS have been found, in the absence of symptoms or clinical signs (139-141) .

1.2.8 Clinical rating scales

The great inter and intra-individual variability that characterizes MS has prompted the scientific community to develop over time numerous clinical evaluation scales that could quantify the degree of disability achieved by the patient and monitor it over time.

Among these, the one currently most used in the assessment of MS patients is the "Expanded Disability Status Scale" (EDSS). The EDSS, the result of the re-elaboration over time of the original "Disability Severity Scale" proposed by Kurtzke in 1955, assigns a severity score to the patient's clinical status ranging from 0 (absence of neurological deficits) to 10 (death of patient due to MS), evaluating the dysfunction in the following functional systems (SF): pyramidal, cerebellar, brainstem, sensory, sphincter, visual, mental, other neurological functions (Figure 5).

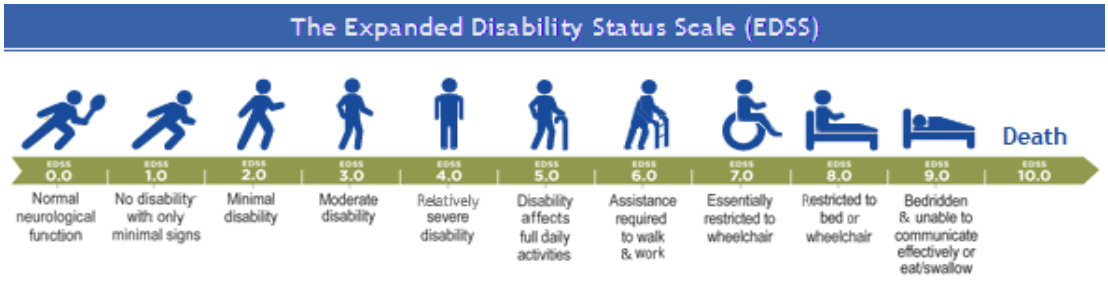


Figure 5. Degree of disability achieved according to EDSS.

The advantages offered by EDSS are constituted by the fact that it is widely accepted and used in the clinic, easy to manage and does not require special equipment.

However, its limitations are also noteworthy: EDSS is in fact strongly dependent on patient mobility; makes use of some subjective symptoms in the evaluation of certain SF (for example in the sphincter function); it is insensitive to minimal clinical variations and finally is unable to provide a precise picture of the patient's cognitive abilities and functional abilities in carrying out

the activities of daily life.

Beyond the problem of objectively quantifying the patient's disability, an important goal to ensure the best possible care is to quantify the impact that subjective and therefore unobjectionable symptoms have on their quality of life.

In particular, the problem of quantifying fatigue, due to the considerable discomfort it causes to patients with MS, has been addressed by numerous studies and has led to the formulation of various evaluation scales. Among these the most used, especially in clinical studies, is the "Fatigue Severity Scale" (FSS) (142). Initially developed by Krupp to identify common features in the fatigue of patients with MS and Systemic Lupus Erythematosus, the FSS evaluates the impact of fatigue and on multiple aspects of patients' daily life.

1.2.9 Diagnosis

There are three fundamental elements on which the diagnostic process of MS is based:

1. The demonstration of the "spatial dissemination" of inflammatory brain lesions.

2. The demonstration of the “temporal dissemination” of the lesions.

3. The lack of elements suggestive of other pathology which, at the clinical onset, can mimic the disease.

Briefly, "spatial dissemination" implies the need to highlight on neurological examination "signs of multifocal CNS involvement", in other words the clinical signs observed cannot be explained by a single CNS lesion, while "temporal dissemination" refers to the need to document two or more episodes of neurological deficit spaced over time, as an expression of the characteristic relapsing-remitting or progressive course of the disease.

The extensive use of MRI, the dizzying growth of research on MS, together with the improvement of methodologies for the analysis of liquor and a more correct use of PE, have led to the need to further review the Diagnostic Criteria for MS. In 2001, new criteria were therefore proposed, called McDonald's criteria, which place the demonstration of spatial and temporal dissemination of lesions by MRI at the center of the early diagnosis of MS.

McDonald's criteria allow for the diagnosis of MS at an earlier stage of the disease, with a high rate of both sensitivity and specificity, allowing for better patient care and earlier treatment.

Since the first revision of the McDonald's Criteria in 2005, new data and fora have stressed the

need for their simplification, to improve their comprehensibility and usefulness and to assess their appropriateness in populations that differ from the adult Caucasian population, on which they were processed.

In May 2010, in Dublin, the "Interanational Panel on Diagnosis of MS" met for the third time to review these criteria, focusing on the possibility of applying the McDonald's Criteria to the pediatric population and to the Asian and American populations. Latina. At the end of 2017, the new updated McDonald's criteria were published (143) (Figure 6). The aim of the work is to facilitate the early diagnosis of MS and to preserve the specificity of the 2010 criteria by reducing the frequency of misdiagnosis.

The most important changes that are introduced with the new criteria are 3:

• the presence of oligoclonal bands when examining the cephalorchidian liquor allows for the diagnosis of MS in the presence of DIS, allowing the replacement of the DIT;

• there is no longer a distinction between symptomatic and asymptomatic Gd + lesion to satisfy the criteria of DIS and DIT;

• Cortical lesion can be used in conjunction with subcortical lesion to support DIS

The group that formulated the new criteria decided not to include optic nerve injury as a typical fifth area at the moment, pending new studies.

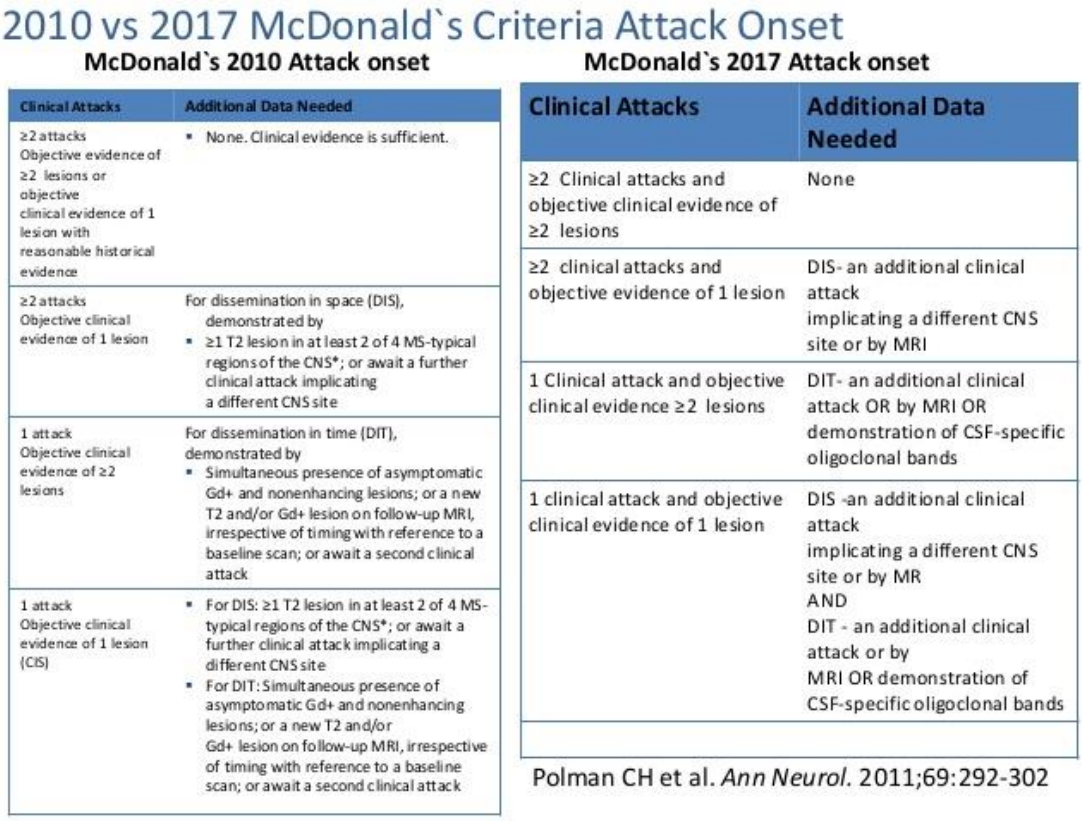


Figure 6. Mc Donald's criteria

1.2.9.1 Magnetic Resonance Imaging in Multiple Sclerosis

MRI is currently the gold standard imaging exam for diagnosis and follow up (FU) of MS (144).

MRI shows brain abnormalities in nearly all patients with multiple sclerosis and up to 75% of spinal cord injury (145). In the clinical setting, the MRI protocol for the diagnosis and FU of MS patients involves the acquisition of images weighted in fluid-attenuated inversion recovery (FLAIR), DP, T2-weighted and T1-weighted sequences after paramagnetic contrast medium. (gadolinium). Thanks to these sequences it is possible to identify important pathological findings of MS, such as foci of active inflammation, and to discern the various stages of the typical lesions of the disease. (146,147).

Although the diagnosis of MS can be made on the basis of clinical criteria alone, MRI is frequently used to demonstrate the spread over time (DIT) or space (DIS) of lesions in patients presenting with CIS or to obtain early information. prognostics on the course of the disease, as established by the latest revision of the McDonald's diagnostic criteria.

1.2.10 Therapy

Effective management of patients with MS involves addressing symptoms, treating acute exacerbations, and reducing long-term disability through disease modification. Treatment of the person with MS should begin as soon as possible after diagnosis and continue indefinitely unless there is a suboptimal treatment response or the individual develops intolerable side effects or fails to adhere to the treatment regimen. Decreased adherence is associated with poorer outcomes including higher rates of relapse and disease progression.(148)

The treatment of multiple sclerosis (MS) falls into 3 categories: treatment of exacerbations, slowing disease progression with disease-modifying therapies (DMTs), and symptomatic therapies. The management of MS is becoming increasingly complex with the development of additional DMTs that, like the older DMTs, reduce the frequency and severity of relapses, and the accumulation of lesions detected by magnetic resonance imaging. Initiating treatment to slow or reverse inflammatory lesion formation early in the course of the disease is advocated as a way to prevent accumulation of disability. Nevertheless, there is a lack of comparative efficacy data and few clinical guidelines to aid healthcare providers in the optimal selection of DMTs. Given that some of the newer agents are associated with potentially serious, but rare, adverse events, careful consideration of the risk-benefit profile is necessary to minimize the risk to patients.

Treatment of acute relapses aims to: (1) speed functional recovery from the neurologic deficits sustained as a result of inflammatory demyelination, (2) alleviate the severity of the attack, and (3) lessen or eliminate potentially persistent residual deficits. The treatment of MS exacerbations with short-term courses of anti-inflammatory agents, such as high-dose intravenous or oral corticosteroids, represents an established practice among neurologists. Although steroids do not affect the course of MS, over time, they have been shown to reduce symptoms, improve motor function, and shorten time to recovery from acute attacks.

The mechanism of action of disease-modifying therapies (DMTs) is linked to the pathophysiology of MS, which is a central nervous system (CNS) disease that consists of damage to the myelin sheath and axonial destruction. The damage is associated with inflammation caused by a perivenular infiltrate consisting of T and B lymphocytes, macrophages, antibodies, and complement. Until recently, it was largely thought that the autoimmune disease was primarily mediated by T cells; however, it is now understood that B cells within the immune system also play a pivotal role in MS disease pathology. It is this new understanding that has led to the advent of new

DMTs targeting B-cell involvement within the disease. DMTs are a component of the long-term management of patients with MS. The goal of disease modification is to reduce the early clinical and subclinical disease activity that is thought to contribute to long-term disability. Treatment is highly variable and differs based on disease severity, cost, adverse effect (AE) profiles, and patient and prescriber preference.

Self-Injected DMTs: Interferon Beta-1a, Interferon Beta-1b, Peginterferon Beta-1a, and Glatiramer Acetate.

Oral DMTs: Dimethyl Fumarate, Fingolimod, and Teriflunomide Dimethyl fumarate is a second-generation fumaric acid ester.

Intravenous Agents: Alemtuzumab, Natalizumab, and Mitoxantrone The monoclonal antibodies alemtuzumab and natalizumab are the most effective DMTs currently available for the treatment of MS.

An additional component of the comprehensive treatment of patients with MS is management of MS-related symptoms. MS is associated with a wide range of symptoms that can affect an individual's ability to carry out routine activities of daily living. Symptomatic management is based on the individual needs of the person with MS and begins with the identification of issues and symptoms that are affecting the patients functionally, emotionally, socially, and vocationally.

1.3 CORRELATION BETWEEN ENDOMETRIOSIS AND MULTIPLE SCLEROSIS

For the first time, in 1987, Gleicher introduced the hypothesis that endometriosis may be considered an autoimmune disease [149], starting from the evidence that it satisfied most of classification criteria including polyclonal B cell activation, immunological abnormalities in T and B cell functions, increased apoptosis, tissue damage and multi-organ involvement.

A possible genetic susceptibility, familial occurence and a female preponderance is also described [150-152]. Indeed, autoimmune diseases are commonly associated with certain HLA alleles and, in the last decade, several studies have addressed this issue in relation to endometriosis (150;153]; earlier studies in the 1980s, did not find any deviations in HLA class I or class II allele distribution among Caucasian endometriosis patients compared to controls [154-156].

Probably the ability of endometrial implants to survive in ectopic sites may be related to an inadequate immune response [157-158]. Several mechanisms have been suggested to explain how endometriotic cells evade leukocyte recognition and immune surveillance:

- an aberrant cellular mediated immune response could facilitate ectopic implantation of the endometrial cells [159]; Natural Killer cells (NK) may play a role in the clearance of this ectopic tissue from the peritoneal cavity. In patients affected by endometriosis, a decreased local NK-mediated cytotoxicity to both autologous and heterologous endometrium in the peripheral and peritoneal fluid was demonstrated [160]. The peritoneal fluid from women with endometriosis contains significantly greater NK cell suppressive activity than the serum [161] and peritoneal fluid from fertile controls patients [162-163]. This decreased activity is more evident in the moderate and severe stages of the disorder.

- Activated macrophages, through the liberation of cytokines and growth factors, can simultaneously contribute to early establishment and progression of endometriosis at several foci [150].

- Several pro-inflammatory chemo-attractant cytokines for monocytes, macrophages and granulocytes in the peritoneal fluid of women with endometriosis have been identified. Interleukin-1 (specifically IL-1β) may play a role in promoting angiogenesis in endometriotic lesions by inducing angiogenic factors (vascular endothelial growth factor and IL-6) in endometriotic stromal cells but not in normal endometrial stromal cells [164].

- Modified B-cell activity and increased incidence of autoantibodies in women with endometriosis have been shown; [165-169]. Is possible that, during retrogade mestruation, an excess of endometrial proteins in extra-uterine localizations, may cause an autoimmune response. The alterate immune response, as immunological tolerance can result in development and /or manteinance of endometriosis [170].

So, evidence of a potential link between endometriosis and other autoimmune disease has been found in several studies, reporting common clinical elements or serologic factors; some authors have reported significantly higher rates of hypothyroidism, rheumatoid arthritis, SLE, Sjögren syndrome, multiple sclerosis (MS), allergies and asthma, but not hyperthyroidism or diabetes in women with endometriosis. Morover, it seems that a history of endometriosis makes patients more susceptible to developing autoimmune diseases and a history of autoimmune diseases more susceptible to endometriosis [171]. However, determining whether women with endometriosis

are at risk of one or more autoimmune diseases must need clarification in future large-scale prospective studies.

In particular, in 2002, Sinaii showed that women with endometriosis were at higher risk of other autoimmune diseases, particularly (7-24 fold) of MS in comparison to the general population [172].

Although MS and endometriosis are clearly different in their phenotype, they seem to be characterized by a common autoimmune background resulting both in the establishment of endometriosis and in the possible increased risk of women with endometriosis to develop MS. [173]. In particular, as underlined above, the specific immune cell type called macrophage has a well-known role in the onset and progression of endometriosis, due to a misperception about ectopic endometrial tissue: instead of removing the endometrial cells, activated macrophages promote their repair and survival. Similar to endometriosis, macrophages also play an essential role in the development of MS, in which were found to be directly involved in the pathogenesis by attacking myelin sheath and oligodendrocytes [174]. Furthermore, the evidence that both endometriosis and MS are characterized by systemic inflammation and immune system dysregulation with an increased ratio of inflammatory th1 to anti-inflammatory th2 cells, as well as a prominent role of interferon-gamma, potentially suggests a pathogenetic link between these two entities [175]. However, there is still limited evidence explaining the molecular, immunological or defense mechanisms shared by these two diseases and the evaluation of common molecular pathways and their components may help clarify the association between endometriosis and MS [176].

In the future researches, the common molecular signatures can be explored as therapeutic targets and disease biomarkers for simultaneous treatment of both diseases.

CHAPTER II

OBJECTIVES

The first objective of this study is to perform an epidemiological analysis to evaluate the prevalence of MS in a cohort of patients with endometriosis; The second aim of this study is clinical: to analyze any clinical correlations in patients with both endometriosis and MS; the third step of our study consists in a laboratory analysis to examine the immune profile of the enrolled patients and the possible correlation to other autoimmune diseases.

CHAPTER III

METHODS

Patients were retrospectively recruited from database of reference center for the diagnosis and treatment of endometriosis of our gynecological department of the University of Naples "Federico II".

Patients with following inclusion criteria were enrolled: age between 15 and 50 years old; diagnosis of MS; treated or untreated for MS; all patients who meet following criteria were excluded: age <15 years and> 50 years; BMI >30; malignancy; presence of other severe intercurrent conditions; previous gynecological surgery (i.e. hystero-annessiectomy); premature ovarian failure (POF).

All patients enrolled with these criteria were invited to participate to a prospective study to evaluate the characteristics of both diseases and to examine their autoimmune serological profile. The study was conducted following the Declaration of Helsinki (1975) and Good Clinical Practice guidelines. Before enrolment, the purpose of the study was clearly explained, and all patients received detailed information about the study, to which they gave their consent. The information obtained were anonymized before analysis.

All data of history of endometriosis (clinical symptoms, stage, obstetric and gynecological history) and MS (onset, degree of clinical expression (EDSS), MRI) at the time enrollment and after one year were collected to evaluate any clinical correlation and to understand how their personal therapy can control the pathologies. Furthermore, a pharmacological anamnesis was made. These recruited patients were screened by ultrasound for the confirmation and staging of endometriosis by experienced operator at gynecological department of the University of Naples "Federico II" at the time enrollment and after one year. Finally, a peripheral blood sample (4ml) was performed to analyze the presence of autoantibody in the serum to exclude other immunological disorders (ANA, AMA, AGA, EMA, dsDNA, ASMA, APCA, ATA, anti-TG, anti-TPO) and to evaluate the immune profile of enrolled patients (CD4-CD8 ratio, percentage of B lymphocytes, percentage of NK and iNKT lymphocytes). FITC, PE, Pecy5 and Pecy7 labelled mAb against CD3, CD4, CD8, CD56, CD19, Va24, CD54 and isotype-matched controls were purchased from BD PharMingen (San Jose, CA).

All phenotypes referred to flow cytometry analysis of the lymphocyte population gated by using forward scatter (FSC) and Side Scatter (SSC) parameters. Flow cytometry and data analysis were

performed by using a ATTUNE NxT acoustic focusing cytometer (life technologies) and the analysis was performed by ATTUNE NxT Software.

The analysis of the immune profile required the enrollment of negative control group: patients with diagnosis of endometriosis, patients with diagnosis of MS and negative patients for endometriosis and MS.

Statistical analysis

Statistical evaluation of data, by *InStat 3.0* software (GraphPad Software Inc., San Diego, California, USA), has been performed by means of the Mann-Whitney test. Two-sided p values of less than 0.05 were considered to indicate statistical significance.

CHAPTER IV

RESULTS

We report for the first time an italian epidemiological analysis of the prevalence of MS in patient with endometriosis.

All the patients of the endometriosis reference center of our gynecological department of the University of Naples "Federico II" (n patients = 1652) were evaluated retrospectively to select those who had a history of MS. It was found that 9 out of 1652 patients had co-diagnosis of endometriosis and MS (9/1652 = 0.005%).

The general characteristics of these patients were summarized in table 1.

PATIENT	ACTUAL AGE	BMI	PREGNANCY
1	43	27	NOT DESIRED
2	28	26	1 SD
3	28	28	NOT DESIRED
4	46	26	1 SD
5	36	28	1 TC
6	48	25	NOT DESIRED
7	47	26	NOT DESIRED
8	42	25	NOT DESIRED
9	35	26	NOT DESIRED

Table 1. General characteristics of patients

Subsequently, as determined by the second objective of the study, a clinical evaluation was carried out on the state of the pathology and ongoing therapy of the recruited patients. The recruited patients have mild forms of both pathologies: in relation to endometriosis, one patient has

undergone drug treatment (ended in 2018), but no one has undergone surgery; at one year ultrasound of follow up, no significant progression was evidenced; moreover, 3 of the 9 patients obtained pregnancy spontaneously, 1 is undergoing an assisted reproduction technique, while the other 5 did not seek pregnancy. In consideration of the neurological aspect, all patients have a relapsing remitting form of MS, with an average EDSS of 3.

Table 2 (endometriosis) and Table 3 (multiple sclerosis) summarize the characteristics described.

PATIENT	AGE AT DIAGNOSIS	DYSMENORREA	MENSES	USG	STAGE (AFS)	SURGERY	THERAPY
1	28	YES	REGULAR	ENDOMETRIOMA	3	NO	NO
2	22	YES	REGULAR	ENDOMETRIOMA	3	NO	NO
3	20	YES	REGULAR	ENDOMETRIOMA	3	NO	DIENOGEST (2016-2018)
4	27	YES	REGULAR	ENDOMETRIOMA	3	NO	NO
5	21	NO	REGULAR	ENDOMETRIOMA	3	NO	NO
6	35	NO	OLIGOMENORRHEA	ENDOMETRIOMA	3	NO	NO
7	42	NO	REGULAR	RETROCERVICAL NODULE	4	NO	NO
8	30	NO	REGULAR	ENDOMETRIOMA+ LUS	4	NO	NO
9	19	YES	OLIGOMENORRHEA	ENDOMETRIOMA+ LUS	4	NO	NO
AVARAGE	27.1	55%	22%	STABLE AT ONE YEAR FOLLOW-UP	67% :3 33% : 4	100%	1/9

Table 2. Clinical and therapeutic characteristics of endometriosis

PATIENT	ONSET AGE	EDSS	TYPE	THERAPY
1	27	4.5	RR	OCRELIZUMAB
2	24	3.5	RR	NATALIZUMAB
3	21	1.5	RR	FINGOLIMOD
4	25	2.5	RR	INFERFERON BETA
5	23	3	RR	GLATIRAMER
6	31	2	RR	GLATIRAMER
7	23	6	RR	DIMETHYL FUMARATE
8	26	2.5	RR	GLATIRAMER
9	32	1.5	RR	GLATIRAMER
AVARAGE	25.7	3	100%	

Table 3. Clinical and therapeutic characteristics of Multiple Sclerosis

The diagnosis of endometriosis was found to follow that of multiple sclerosis in the whole patient group and in most cases, the diagnosis of endometriosis was fortuitous (Table 4).

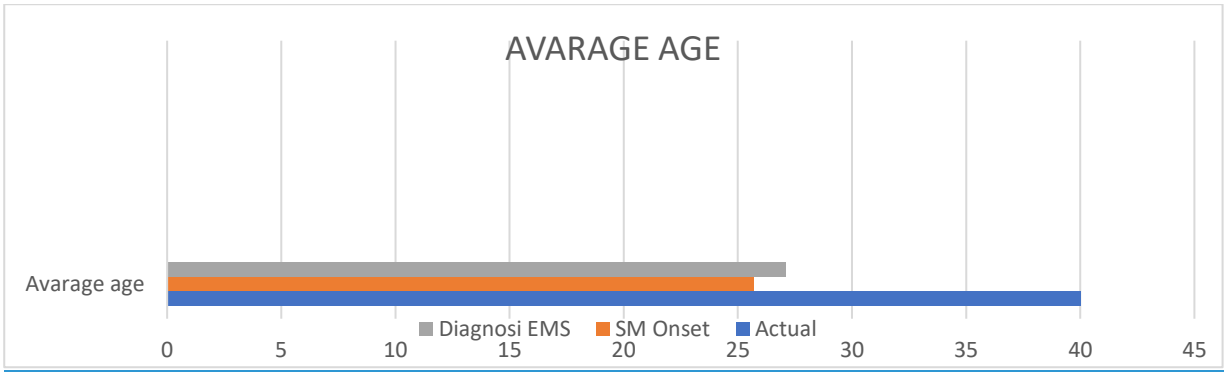


Table 4. The onset diagnosis of MS anticipates on average that of endometriosis.

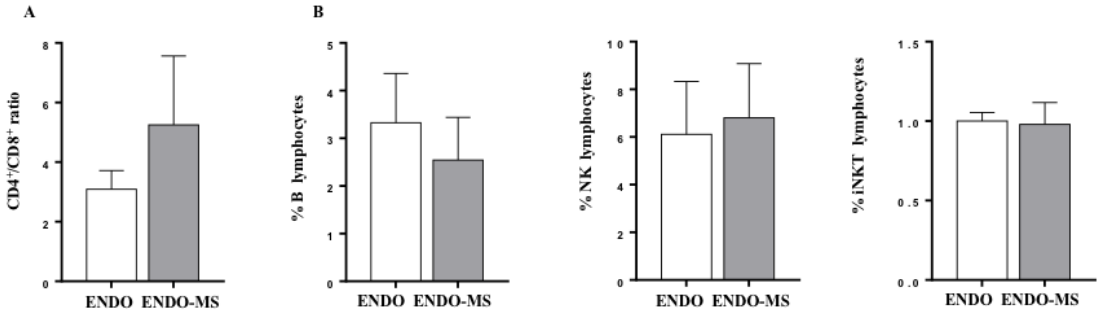
In accordance with the third objective of the study, an evaluation of the main autoantibodies involved in the most frequent autoimmune diseases was carried out.

In this regard, 1 of the 9 patients refused peripheral blood sampling.

Out of the 8 patients screened, in 2 patients anti-thyroperoxidase (AbTPO) were found and a diagnosis of Hashimoto's thyroiditis was performed .

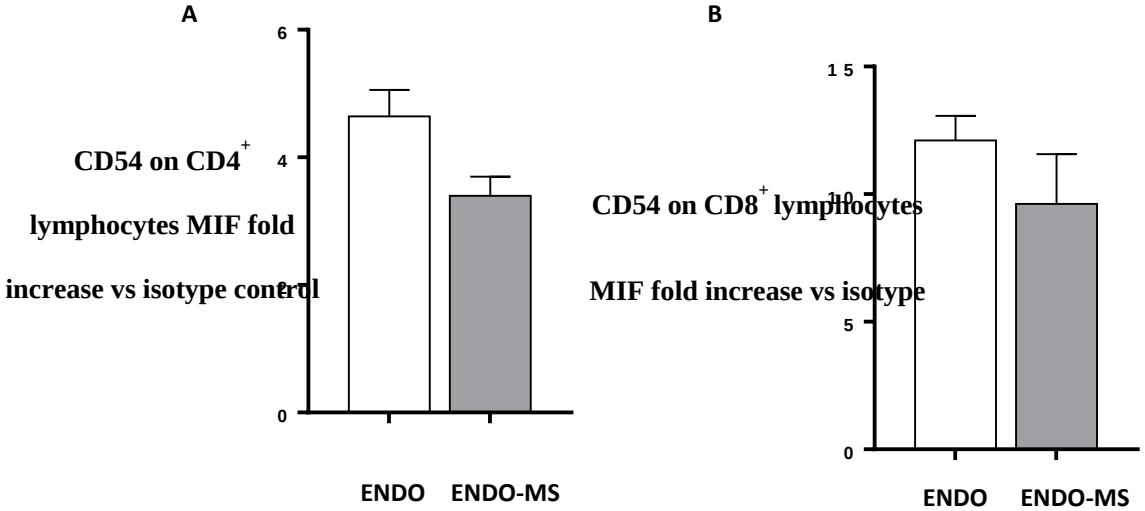
For the analysis of the immune profile, 8 patients with only diagnosis of endometriosis and 8 patients not suffering from endometriosis and multiple sclerosis were recruited as control group. At the moment, the data in our possession is lacking in the healty controls group (i.e. patients not suffering from endometriosis and MS, and patients affected by only MS).

So, in consideration of the immunological data, an evaluation of the subpopulations of the immune system protagonists (CD4-CD8 ratio, percentage of B lymphocytes, percentage of NK lymphocytes and iNKT) was carried out in the two groups, patients with endometriosis and patients with endometriosis and multiple sclerosis.

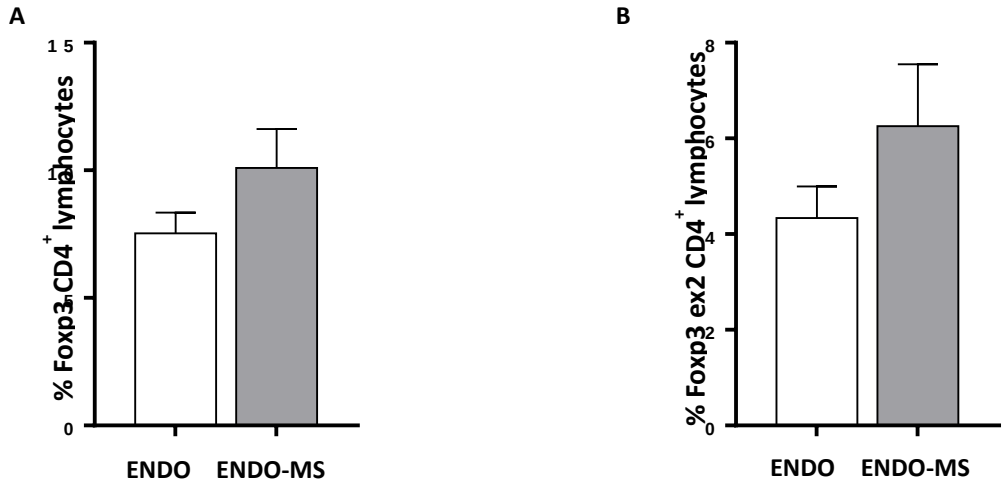


Immune profile of patients with endometriosis (group 1, white column; N=7) or affected by endometriosis associated with multiple sclerosis

Preliminary data confirm an increased ratio of CD4 T versus CD8 T lymphocytes and decreased level of B cells. Similar percentage of NK effectors and of iNKT lymphocytes have been also detected.



The activation level of the adaptive immunity effectors (CD4+ and CD8+ T lymphocytes) has been evaluated through CD54 molecule expression. As shown, CD54 level is increased in both helper (Panel A) and cytotoxic (Panel B) T cells in the group of women with endometriosis, not affected by MS (white column).



Patients affected by endometriosis with MS (Group 2) show increased level of Treg subset with an higher expression of exon 2 Foxp3 transcription factor, largely associated with effective immune modulating properties of the Treg population. As shown, (A) Treg subset percentage was basically higher in Group 2 individuals, as compared with Group 1 subjects. Foxp3 Exon2 expression analysis confirmed such observation (B).

CHAPTER V

DISCUSSION

Although multiple sclerosis and endometriosis are clearly different in their phenotype, more and more studies in the literature seem to highlight a common pathogenetic background. In this regard, our study aims to define, for the first time, epidemiological data relating to the association of the two diseases and to evaluate the immune characteristics. In fact, this is a first Italian attempt of an epidemiological study not only a report of sporadic clinical cases, as reported in the introduction.

In consideration of the epidemiological objective, our study ranks as the first Italian study to highlight the prevalence of MS in women with endometriosis. In accordance with our selection criteria, 9 out of 1652 patients presented co-diagnosis of endometriosis and multiple sclerosis (9/1652 = 0.005%). Considering that in the general female population, the prevalence of women with MS is 70: 100,000, detecting a prevalence of women with MS in the population with endometriosis equal to 500 per 100,000, he suggests, in agreement with international data (Sinai et al) a greater likelihood of MS being diagnosed in patients who have endometriosis than in the general population. As described in the literature, this data may be motivated by the possible greater association of pathologies that share an autoimmune alteration.

From the analysis of the clinical data of the progress of the two pathologies, both were found to present themselves in a mild form: none of the patients has a high degree of neurological disability and none of the patients need surgical-pharmacological intervention for endometriosis. The diagnosis of endometriosis was found to follow that of multiple sclerosis in the whole patient group and in most cases, the diagnosis of endometriosis was fortuitous.

This evidence could be justified by the fact that, as described in the literature, the simultaneous appearance of multiple pathologies involving the immune system, make the severity and age of onset of symptoms milder. From a purely speculation perspective, this finding leaves ample room for the hypothesis that the therapy for MS has in some way also modulated the inflammatory activity of endometriosis. Given the heterogeneity of MS therapies it is not possible to establish whether one of these has a better impact on endometriosis than another, but it can be asserted that, being all immunosuppressive and / or immunomodulating drugs, these have a positive effect on the clinic and evolution of endometriosis.

Moreover, in view of the high fertility rate, it seems to suggest that fertility is not compromised in these women with both diseases.

In relation to the autoimmune pattern, the diagnosis of Hashimoto's Thyroiditis was carried out in two patients, demonstrating how the coexistence of multiple autoimmune diseases can be a distinctive element in this selected population.

Preliminary data confirm an involvement of the immune system in the two pathologies with possible diversification of the protagonists. In particular, if the statistically significant difference observed between the two groups in relation to the CD4-CD8 ratio and the percentage of CD20 lymphocytes, may suggest the involvement of immunity in both pathologies even if with different protagonists, the absence of the difference statistically significant for iNKT- and NK-mediated suppression, could suggest dysfunction in both pathologies of iNKT suppression.

Although, at the moment there is no processing of all data relating to the control group that can strengthen the concept, we can still speculate from the preliminary data that, as in MS, even in endometriosis, proper control of immunity may be lacking. Indeed, at the moment, the investigation is still ongoing: due to the covid-19 emergency, the recruitment of negative patients for endometriosis and MS and patients affected by only MS has been blocked and the data in our possession are currently related only to the first two groups of patients (endometriosis only and MS + endometriosis), therefore, it will be necessary to wait for the processing of the data of the control group to highlight the truthfulness of the result and optimize its interpretation.

This circumstance has caused the following consequences: prohibition of students from attending the polyclinic's care settings; extreme reduction of care services by all operating units not involved in assisting COVID patients; consequent impossibility of proceeding with blood sampling from patients already recruited as well as performing further recruitments; postponement of all laboratory services of our study, due to the focus on investigations on patients with suspected COVID.

This data may be also the basis for possible future multicentre studies, not only Italians, and to extend the knowledge and discussion about two diseases with important social impact.

CHAPTER VI

CONCLUSION

According to the current data of the literature, a higher risk of MS is found in women with endometriosis in comparison to the general population, confirming that a history of endometriosis makes the patients more susceptible to develop autoimmune disease as well as a history of autoimmune disease more susceptible to endometriosis. So, the evidence of these results can be taken as a warning for clinicians, caring for adolescent with MS should be aware that it could be associated with endometriosis, especially if they complaints for pelvic pain or infertility and at the sometime, patients with endometriosis should be monitored closely to ensure early detection of MS.

Moreover, considering the possible common immunological element, future research studies are needed to open up possibilities for the implementation of new strategies for immunomodulatory intervention therapy in order to treat or even prevent both endometriosis and MS and new possible therapeutic targets (e.g., mast cells) considering that even if the “triggers” for activation of MS versus endometriosis may be different, they do share common elements including mast cell involvement.

REFERENCES

1. Sampson JA: Perforating haemorrhagic (chocolate) cysts of the ovary: their importance and especially their relation to pelvic adenomas of endometrial type. Arch Surg 3: 245, 1921

2. Cowart CL, London SN: Extrapelvic endometriosis. Infertil Reprod Med Clin North Am 3: 731, 1992

3. Schenken RS: Pathogenesis. In Schenken RS (ed): Endometriosis: Contemporary Concepts in Clinical Management, p 1. Philadelphia: JB Lippincott, 1989

4. Koger KE, Shatney CH, Hodge K, McClenathan JH: Surgical scar endometrioma. Surg Gynecol Obstet 177: 243, 1993

5. Mitchell GW: Extrapelvic endometriosis. In Schenken RS (ed): Endometriosis: Contemporary Concepts in Clinical Management, p 307. Philadelphia: JB Lippincott, 1989

6. Markham SM: Extrapelvic endometriosis. In Thomas E, Rock J (eds): Modern Approaches to Endometriosis, p 151. Boston: Kluwer Academic, 1991

7. Carta F, Guiducci G, Fulcheri E et al: Radicular compression by extradural spinal endometriosis: case report. Acta Neurochir 114: 68, 1992

8. Nunley WC, Kitchin JD: Endometriosis. In Sciarra JJ (ed): Gynecology and Obstetrics, vol 1. Philadelphia: Lippincott-Raven, 1992

9. Wheeler JM: Epidemiology and prevalence of endometriosis. Infertil Reprod Med Clin North Am 3: 545, 1992

10. Eskenazi B, Warner ML: Epidemiology of endometriosis. Obstet Gynecol Clin North Am 24: 235, 1997

11. Boling RO, Abbasi R, Ackerman G et al: Disability from endometriosis in the United States Army. J Reprod Med 33: 49, 1988

12. Wheeler JM: Epidemiology of endometriosis-associated infertility. J Reprod Med 34: 41, 1989

13. Velebil P, Wingo PH, Xia Z et al: Rate of hospitalization for gynecologic disorders among reproductive-age women in the United States. Obstet Gynecol 86: 764, 1995

14. Houston DE, Noller KL, Melton LJ et al: Incidence of pelvic endometriosis in Rochester, Minnesota, 1970-1979. Am J Epidemiol 125: 959, 1987

15. Olive DL, Schwartz LB: Endometriosis. N Engl J Med 328: 1759, 1993

16. Clark AH: Endometriosis in a young girl. JAMA 136: 690, 1948

17. Kempers RD, Dockerty MB, Hunt AB, Symmonds RE: Significant postmenopausal endometriosis. Surg Gynecol Obstet 111: 348, 1960

18. Punnonen R, Klemi PJ, Nikkanen V: Postmenopausal endometriosis. Eur J Obstet Gynecol Reprod Biol 11: 195, 1980

19. Schifrin BS, Erez S, Moore JG: Teenage endometriosis. Am J Obstet Gynecol 116: 973, 1973

20. Huffman JW: Endometriosis in young teen-age girls. Pediatr Ann 10: 44, 1981

21. Vessey MP, Villard-Mackintosh L, Painter R: Epidemiology of endometriosis in women attending family planning clinics. Br Med J 306: 182, 1993

22. Sangi-Haghpeykar H, Poindexter AN: Epidemiology of endometriosis among parous women. Obstet Gynecol 85: 983, 1995

23. Meigs JV: Medical treatment of endometriosis and significance of endometriosis. Surg Gynecol Obstet 89: 317, 1949

24. Scott RB, Te Linde RW: External endometriosis-the scourge of the private patient. Ann Surg 131: 697, 1950

25. Lloyd FP: Endometriosis in the Negro woman. Am J Obstet Gynecol 89: 468, 1964

26. Ridley JH: The histogenesis of endometriosis. Obstet Gynecol Surv 23: 1, 1968

27. Darrow SL, Selman S, Batt RE et al: Sexual activity, contraception, and reproductive factors in predicting endometriosis. Am J Epidemiol 140: 500, 1994

28. Cramer DW, Wilson E, Stillman RJ et al: The relation of endometriosis to menstrual characteristics, smoking, and exercise. JAMA 255: 1904, 1986

29. Darrow SL, Vena JE, Batt RE et al: Menstrual cycle characteristics and the risk of endometriosis. Epidemiology 4: 135, 1993

30. Candiani GB, Danesino V, Gastaldi A et al: Reproductive and menstrual factors and risk of peritoneal and ovarian endometriosis. Fertil Steril 56: 230, 1991

31. McCann SE, Freudenheim JL, Darrow SL et al: Endometriosis and body fat distribution. Obstet Gynecol 82: 545, 1993

32. Parazzini F, Ferraroni M, Bocciolone L et al: Contraceptive methods and risk of pelvic endometriosis. Contraception 94: 47, 1994

33. Frey GH: The familial occurrence of endometriosis: report of five instances and review of the literature. Am J Obstet Gynecol 73: 418, 1957

34. Ranney B: Endometriosis. IV. Hereditary tendency. Obstet Gynecol 37: 734, 1971

35. Lamb K, Hoffmann RG, Nichols TR: Family trait analysis: a case-control study of 43 women with endometriosis and their best friends. Am J Obstet Gynecol 154: 596, 1986

36. Moen MH: Endometriosis in monozygotic twins. Acta Obstet Gynecol Scand 73: 59, 1994

37. Hadfield RM, Mardon HJ, Barlow DH, Kennedy SH: Endometriosis in monozygotic twins. Fertil Steril 68: 941, 1997

38. Simpson JL, Elias S, Malinak LR et al: Heritable aspects of endometriosis. I. Genetic studies. Am J Obstet Gynecol 137: 327, 1980

39. Coxhead D, Thomas EJ: Familial inheritance of endometriosis in a British population. A case control study. J Obstet Gynaecol 13: 42, 1993

40. Moen MH, Magnus P: The familial risk of endometriosis. Acta Obstet Gynecol Scand 72: 560, 1993

41. Patel BG, Lenk EE, Lebovic DI, et al.: Pathogenesis of endometriosis: Interaction between Endocrine and inflammatory pathways. Best Pract Res Clin Obstet Gynaecol. 2018; 50: 50–60. PubMed Abstract | Publisher Full Text | F1000 Recommendation

42. Brosens I, Benagiano G: Is neonatal uterine bleeding involved in the pathogenesis of endometriosis as a source of stem cells? Fertil Steril. 2013; 100(3): 622–3. PubMed Abstract | Publisher Full Text

43. Burney RO, Giudice LC: Pathogenesis and pathophysiology of endometriosis. Fertil Steril. 2012; 98(3): 511–9. PubMed Abstract | Publisher Full Text | Free Full Text

44. Sasson IE, Taylor HS: Stem cells and the pathogenesis of endometriosis. Ann N Y Acad Sci. 2008; 1127(1): 106–15. PubMed Abstract | Publisher Full Text | Free Full Text

45. Cousins FL, O DF, Gargett CE: Endometrial stem/progenitor cells and their role in the pathogenesis of endometriosis. Best Pract Res Clin Obstet Gynaecol. 2018; 50: 27–38. PubMed Abstract | Publisher Full Text | F1000 Recommendation

46. Gordts S, Koninckx P, Brosens I: Pathogenesis of deep endometriosis. Fertil Steril. 2017; 108(6): 872–885.e1. PubMed Abstract | Publisher Full Text | F1000 Recommendation

47. Singh SS, Taylor H, Giudice L, et al.: O-GYN-MD-126 Primary Efficacy and Safety Results from Two Double-Blind, Randomized, Placebo-Controlled Studies Of Elagolix, an Oral Gonadotropin-Releasing Hormone Antagonist, in Women With Endometriosis-Associated Pain. J Obstet Gynaecol Can. 2017; 39(5): 401. Publisher Full Text

48. Taylor HS, Johnson N, Carr B, et al.: Maintenance of endometriosis-associated pain reduction and quality of life improvement in phase 3 extension studies with elagolix. Fertil Steril. 2017; 108(3): e96–e97. Publisher Full Text

49. Hirsch M, Duffy JMN, Deguara CS, et al.: Diagnostic accuracy of Cancer Antigen 125 (CA125) for endometriosis in symptomatic women: A multi-center study. Eur J Obstet Gynecol Reprod Biol. 2017; 210: 102–7. PubMed Abstract | Publisher Full Text | F1000 Recommendation

50. Fung JN, Montgomery GW: Genetics of endometriosis: State of the art on genetic risk factors for endometriosis. Best Pract Res Clin Obstet Gynaecol. 2018; 50: 61–71. PubMed Abstract | Publisher Full Text

51. Mafra F, Mazzotti D, Pellegrino R, et al.: Copy number variation analysis reveals additional variants contributing to endometriosis development. J Assist Reprod Genet. 2017; 34(1): 117–24. PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

52. Rodriguez R, Lopez-Carrasco A, Antolin E, et al.: EP26.02: Ultrasound accuracy of transvaginal ultrasound compared with magnetic resonance image in deep infiltrating endometriosis. Ultrasound Obstet Gynecol. 2017; 50(S1): 381. Publisher Full Text

53. Guerriero S, Condous G, van den Bosch T, et al.: Systematic approach to sonographic evaluation of the pelvis in women with suspected endometriosis, including terms, definitions and measurements: a consensus opinion from the International Deep Endometriosis Analysis (IDEA) group. Ultrasound Obstet Gynecol. 2016; 48(3): 318–32. PubMed Abstract | Publisher Full Text

54. Hoyos LR, Johnson S, Puscheck E: Endometriosis and Imaging. Clinical Obstetrics and Gynecology. 2017; 60(3): 503–16. PubMed Abstract | Publisher Full Text

55. Kinkel K, Chapron C, Balleyguier C, et al.: Magnetic resonance imaging characteristics of deep endometriosis. Hum Reprod. 1999; 14(4): 1080–6. PubMed Abstract | Publisher Full Text

56. Bazot M, Daraï E: Role of transvaginal sonography and magnetic resonance imaging in the diagnosis of uterine adenomyosis. Fertil Steril. 2018; 109(3): 389–97. PubMed Abstract | Publisher Full Text | F1000 Recommend

57. http://www.endometriose-sef.de/dateien/ENZIAN_2013_web.pdf. Reference Source

58. Keckstein J, Ulrich U, Possover M, et al.: ENZIAN-Klassifikation der tief infiltrierenden Endometriose. Zentralbl Gynäkol. 2003; 125: 291.

59. Tuttlies F, Keckstein J, Ulrich U, et al.: ENZIAN-score, a classification of deep infiltrating endometriosis. Zentralbl Gynakol. 2005; 127(5): 275–281. PubMed Abstract | Publisher Full Text

60. Hobo R, Nakagawa K, Usui C, et al.: The Endometriosis Fertility Index Is Useful for Predicting the Ability to Conceive without Assisted Reproductive Technology Treatment after Laparoscopic Surgery, Regardless of Endometriosis. Gynecol Obstet Invest. 2018; 83(5): 493–8. PubMed Abstract | Publisher Full Text

61. Johnson NP, Hummelshoj L, Adamson GD, et al.: World Endometriosis Society consensus on the classification of endometriosis. Hum Reprod. 2017; 32(2): 315–24. PubMed Abstract | Publisher Full Text ation

62. Dunselman GA, Vermeulen N, Becker C, et al.: ESHRE guideline: management of women with endometriosis. Hum Reprod. 2014; 29(3): 400–12. PubMed Abstract | Publisher Full Text | F1000 Recommendation

63. Practice Committee of the American Society for Reproductive Medicine: Treatment of pelvic pain associated with endometriosis: a committee opinion. Fertil Steril. 2014; 101(4): 927–35. PubMed Abstract | Publisher Full Text | F1000 Recommendation

64. Somigliana E: Ovarian reserve, endometriomas, and surgery: Research must go on. Fertil Steril. 2018; 110(5): 856–7. PubMed Abstract | Publisher Full Text | F1000 Recommendation

65.Bradley, G.D., BR; Fenichel, GM; Jankovic, J. Neurology in Clinical Practice, (2008)

66.Adams, D:V:, Ropper, A.H. Adam's & Victor's Principles of Neurology, (1997).

67.Pugliatti M et al. The epidemiology of multiple sclerosis in Europe. Eur J Neurol 2006;13:700-722.

68.Pugliatti M et al. The worldwide prevalence of multiple sclerosis. Clin Neurol Neurosurg. 2002 Jul;104(3):182-91.

69.Granieri E et al. Multiple sclerosis in Italy. A reappraisal of incidence and prevalence in Ferrara. Arch Neurol. 1996 Aug;53(8):793-8.

70.Ranzato F et al. Increasing frequency of multiple sclerosis in Padova, Italy: a 30 year epidemiological survey. Mult Scler. 2003 Aug;9(4):387-92.

71.Millefiorini E er al. The prevalence of multiple sclerosis in central Italy. Mult Scler. 2010 Dec;16(12):1432-6

72.Simpson S Jr et al. Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. J Neurol Neurosurg Psychiatry. 82(10): 1132(2011).

73.Granieri E et al. The increasing incidence and prevalence of MS in a Sardinian province. Neurology 55:842-848 (2000).Dalmay F et al. Multiple sclerosis and solar exposure before the age of 15 years: case-control study in Cuba, Martinique and Sicily. 2010 Aug;16(8):899-908

74.Dalmay 1, D Bhalla, A Nicoletti, J A Cabrera-Gomez, P Cabre, F Ruiz, M Druet-Cabanac, M Dumas, P M Preux Multiple Sclerosis and Solar Exposure Before the Age of 15 Years: Case-Control Study in Cuba, Martinique and Sicily Multicenter Study Mult Scler. 2010 Aug;16(8):899-908.

75.Bernard CC et al. Multiple sclerosis: an autoimmune disease of multifactorial etiology. Curr Opin Immunol. 1992 Dec;4(6):760-5.

76.Fisher R.A.. The Correletion between relatives on the supposition of mendelian inheritance. Transactions of the Royal Society of Edinburgh 52:399-433 (1918).

77.Ebers, G.C. et al. A genetic basis for familial aggregation in multiple sclerosis. Canadian Collaborative Study Group. Nature 377:150-151 (1995).

78.Sospedra, M., and R. Martin. Immunology of multiple sclerosis. Annu Rev Immunol 23:683-747 (2005).

79.Jersild, C. et al. HL-A antigens and multiple sclerosis. Lancet 1:1240-1241 (1972).

80.Schiffer RB et al. Exposure to environmental tobacco smoke is associated with increased risk for multiple sclerosis. Mult Scler. 2011 Jul;17(7):788-93.

81.Schwarz S et al. Multiple sclerosis and nutrition. Mult Scler. 2005 Feb;11(1):24-32.

82. Handunnetthi L et al. UV radiation, vitamin D, and multiple sclerosis. Proc Natl Acad Sci U S A. 2010 Aug 17;107(33).

83.Smolders J, Menheere P, Kessels A, Damoiseaux J, Hupperts R. Association of vitamin D metabolite levels with relapse rate and disability in multiple sclerosis. Mult Scler. 2008 Nov;14(9):1220-4. doi: 10.1177/1352458508094399. Epub 2008 Jul 24

84.Tselis A. Evidence for viral etiology of multiple sclerosis. Semin Neurol. 2011 Jul;31(3):307-16.

85.Christensen T et al. Gene-environment interactions in multiple sclerosis: innate and adaptive immune responses to human endogenous retrovirus and herpesvirus antigens and the lectin complement activation pathway. J Neuroimmunol. Feb;183(1-2):175-88 (2007).

86.Pohl D. Epstein-Barr virus and multiple sclerosis. J Neurol Sci. 2009 Nov 15;286(1-2):62-4.

87.Ascherio A et al. Review Environmental risk factors for multiple sclerosis. Part I: the role of infection. Ann Neurol. 2007 Apr; 61(4):288-99.

88.Wandinger KP et al. Association between clinical disease activity and Epstein-Barr virus reactivation in multiple sclerosis. Neurology 2000.

89.Simon N. Willis et al. Epstein–Barr virus infection is not a characteristic feature of multiple sclerosis. Brain. 2009 December; 132(12): 3318–3328.

90.Charcot M. Histology of sclerotic plaques. Gazette Hôpitaux. 1868;141:554–558.30.Bjartmar C et al. Neurological disability correlates with spinal cord axonal loss and reduced N-acetyl aspartate in chronic multiple sclerosis patients. Ann Neurol. 2000 Dec; 48(6):893-901.

91.Kornek B et al. Axonal pathology in multiple sclerosis. A historical note. Brain Pathol. 1999 Oct;9(4):651-6.

92.Ferguson B et al. Axonal damage in acute multiple sclerosis lesions. Brain. 1997 Mar;120 (Pt 3):393-9.

93.Kuhlmann T et al. Acute axonal damage in multiple sclerosis is most extensive in early disease stages and decreases over time. Brain. 2002 Oct; 125(Pt 10):2202-12.

94.Trapp BD et al. Axonal transection in the lesions of multiple sclerosis. N Engl J Med. 1998 Jan 29; 338(5):278-85.

95.C Bjartmar 1, G Kidd, S Mörk, R Rudick, B D Trapp Neurological Disability Correlates With Spinal Cord Axonal Loss and Reduced N-acetyl Aspartate in Chronic Multiple Sclerosis Patients Ann Neurol. 2000 Dec;48(6):893-901.

96.Hickey WF et al. T-lymphocyte entry into the central nervous system. J Neurosci Res. 1991 Feb; 28(2):254-60.

97.Wekerle H et al. Review Immune reactivity in the nervous system: modulation of T-lymphocyte activation by glial cells. J Exp Biol. 1987 Sep; 132():43-57.

98.Diaz-Villoslada P et al. Autoreactivity to myelin antigens: myelin/oligodendrocyte glycoprotein is a prevalent autoantigen. J Neuroimmunol.1999 Sep 1; 99(1):36-43.

99.Vanderlugt CL et al. Review Epitope spreading in immune-mediated diseases: implications for immunotherapy. Nat Rev Immunol. 2002 Feb; 2(2):85-95.

100.Von Herrath MG et al. Review Microorganisms and autoimmunity: making the barren field fertile? Nat Rev Microbiol. 2003 Nov; 1(2):151-7.

101.Frohman EM, Racke MK and Raine CS. Multiple sclerosis—the plaque and its pathogenesis. N Engl J Med 2006; 354: 942–955.

102.Wang C, Paling D, Chen L, Hatton SN, Lagopoulos J, Aw ST, Kiernan MC, Barnett MH. Axonal conduction in multiple sclerosis: A combined magnetic resonance imaging and electrophysiological study of the medial longitudinal fasciculus. Mult Scler. 2015 Jun;21(7):905-15.

103.Compston A and Coles A. Multiple sclerosis. Lancet 2008; 372: 1502–1517.

104.Smith KJ. Sodium channels and multiple sclerosis: Roles in symptom production, damage and therapy. Brain Pathol 2007; 17: 230–242.

105.Loeb, C., Favale, E. Neurologia du Fazio Loeb, Società Editrice Universo, (2003).

106.Patrikios P, Stadelmann C, Kutzelnigg A, Rauschka H, Schmidbauer M, Laursen H, Sorensen PS, Brück W, Lucchinetti C, Lassmann H. Remyelination is extensive in a subset of multiple sclerosis patients. Brain. 2006 Dec;129(Pt 12):3165-72. Epub 2006 Aug 18. Erratum in: Brain. 2007 Mar;130(Pt 3):879.

107.Lassmann H. Recent neuropathological findings in MS--implications for diagnosis and therapy. J Neurol. 2004 Sep;251 Suppl 4:IV2-5. Review.

108.Coman I, Aigrot MS, Seilhean D, Reynolds R, Girault JA, Zalc B, Lubetzki C. Nodal, paranodal and juxtaparanodal axonal proteins during demyelination and remyelination in multiple sclerosis. Brain. 2006 Dec;129(Pt 12):3186-3195. Epub 2006 Jun.

109.Bø L, Vedeler CA, Nyland H, Trapp BD, Mørk SJ. Intracortical multiple sclerosis lesions are not associated with increased lymphocyte infiltration. Mult Scler. 2003 Aug;9(4):323-331.

110.Kutzelnigg A, Lassmann H. Cortical demyelination in multiple sclerosis: a substrate for cognitive deficits? J Neurol Sci. 2006 Jun 15;245(1-2):123-6. Epub 2006 May 2.

111.Kutzelnigg A, Lucchinetti CF, Stadelmann C, Brück W, Rauschka H, Bergmann M, Schmidbauer M, Parisi JE, Lassmann H. Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain. 2005 Nov;128(Pt 11):2705 12. Epub 2005 Oct 17.

112.De Stefano N, Narayanan S, Francis SJ, Smith S, Mortilla M, Tartaglia MC, Bartolozzi ML, Guidi L, Federico A, Arnold DL. Diffuse axonal and tissue injury in

patients with multiple sclerosis with low cerebral lesion load and no disability. Arch Neurol. 2002 Oct;59(10):1565-1571.

113.Hochmeister S, Grundtner R, Bauer J, Engelhardt B, Lyck R, Gordon G, Korosec T, Kutzelnigg A, Berger JJ, Bradl M, Bittner RE, Lassmann H. Dysferlin is a new marker for leaky brain blood vessels in multiple sclerosis. J Neuropathol Exp Neurol. 2006 Sep;65(9):855-65.

114.Bakshi, R., Minagar, A., Jaisani, Z., Wolinsky, J.S. Imaging of multiple sclerosis; role in neurutherapeutics. NeuroRx; 2: 277-303 (2005).

115.Cifelli, A., Arridge, M., Jezzard, P. et al. Thalamic neurodegeneration in multiple sclerosis. Ann Neurol; 52: 650-653 (2002).

116.Roemer, S., Stadelmann, C., Bruck, W. Et al. Cortical demyelination is present in early multiple sclerosis. Neurology; 66 (suppl 2): A93- A94 (2006).

117.Dalton CM, Chard DT, Davies GR, Miszkiel KA, Altmann DR, Fernando K, Plant GT, Thompson AJ, Miller DH. Early development of multiple sclerosis is associated with progressive grey matter atrophy in patients presenting with clinically isolated syndromes. Brain. 2004 May;127(Pt 5):1101-1107. Epub 2004 Mar 3.

118.De Stefano N, Matthews PM, Filippi M, Agosta F, De Luca M, Bartolozzi ML, Guidi L, Ghezzi A, Montanari E, Cifelli A, Federico A, Smith SM. Evidence of early cortical atrophy in MS: relevance to white matter changes and disability. Neurology. 2003 Apr 8;60(7):1157-1162.

119.Tiberio M, Chard DT, Altmann DR, Davies G, Griffin CM, Rashid W 56.Losseff NA, Wang L, Lai HM, Yoo DS, Gawne-Cain ML, McDonald WI, Miller DH, Thompson AJ. Progressive cerebral atrophy in multiple sclerosis. A serial MRI study. Brain. 1996 Dec;119 (Pt 6):2009-19

120.N. A. Losseff, S. L. Webb, J. I. O'Riordan, R. Page, L. Wang, G. J. Barker, P. S. Tofts,W. I. McDonald, D. H. Miller and A. J. Thompson Brain (1996), 119, 701-708 Spinal cord atrophy and disability in multiple sclerosis A new reproducible and sensitive MRI method with potential to monitor disease progression

121.Kalkers NF, Bergers E, Castelijns JA, van Walderveen MA, Bot JC, Adèr HJ, Polman CH, Barkhof F. Optimizing the association between disability and biological markers in MS. Neurology. 2001 Oct 9;57(7):1253-1258.

122.De Stefano N, Narayanan S, Francis GS, Arnaoutelis R, Tartaglia MC, Antel JP, Matthews PM, Arnold DL. Evidence of axonal damage in the early stages of multiple sclerosis and its relevance to disability. Arch Neurol. 2001 Jan;58(1):65-70.

123.Chard DT, Griffin CM, Parker GJ, Kapoor R, Thompson AJ, Miller DH. Brain atrophy in clinically early relapsing-remitting multiple sclerosis. Brain. 2002 Feb;125(Pt 2):327-337.

124.Dalton CM, Brex PA, Jenkins R, Fox NC, Miszkiel KA, Crum WR, O'Riordan JI, Plant GT, Thompson AJ, Miller DH. Progressive ventricular enlargement in patients with clinically isolated syndromes is associated with the early development of multiple sclerosis. J Neurol Neurosurg Psychiatry. 2002 Aug;73(2):141-147.

125.Filippi M, Bozzali M, Rovaris M, Gonen O, Kesavadas C, Ghezzi A, Martinelli V, Grossman RI, Scotti G, Comi G, Falini A. Evidence for widespread axonal damage at the earliest clinical stage of multiple sclerosis. Brain. 2003 Feb;126(Pt2):433-7.

126.Fisher E, Rudick RA, Cutter G, Baier M, Miller D, Weinstock-Guttman B, Mass MK, Dougherty DS, Simonian NA. Relationship between brain atrophy and disability: an 8-year follow-up study of multiple sclerosis patients. Mult Scler. 2000 Dec;6(6):373-377.

127.Zivadinov R, Sepcic J, Nasuelli D, De Masi R, Bragadin LM, Tommasi MA, Zambito-Marsala S, Moretti R, Bratina A, Ukmar M, Pozzi-Mucelli RS, Grop A, Cazzato G, Zorzon M. A longitudinal study of brain atrophy and cognitive disturbances in the early phase of relapsing-remitting multiple sclerosis. J Neurol Neurosurg Psychiatry. 2001 Jun;70(6):773-80

128.Benedict RH, Bakshi R, Simon JH, Priore R, Miller C, Munschauer F. Frontal cortex atrophy predicts cognitive impairment in multiple sclerosis. J Neuropsychiatry Clin Neurosci. 2002 Winter;14(1):44-51.

129.Chaudhuri A, Peter O Behan Fatigue in Neurological Disorders Lancet. 2004 Mar 20;363(9413):978-88. doi: 10.1016/S0140-6736(04)15794-2.

130.Iriarte J, Subirá ML, Castro P. Modalities of fatigue in multiple sclerosis: correlation with clinical and biological factors. Mult Scler. 2000 Apr;6(2):124-30.

131.L B Krupp 1, L A Alvarez, N G LaRocca, L C Scheinberg Fatigue in Multiple Sclerosis Arch Neurol. 1988 Apr;45(4):435-7. doi: 10.1001/archneur.1988.00520280085020

132.Letizia Leocani 1, Bruno Colombo, Giancarlo Comi Physiopathology of Fatigue in Multiple Sclerosis Neurol Sci. 2008 Sep;29 Suppl 2:S241-3.

133.Kantorová E, Poláček H, Bittšanský M, Baranovičová E, Hnilicová P, Čierny D, Sivák Š, Nosáľ V, Zeleňák K, Kurča E. Hypothalamic damage in multiple sclerosis correlates with disease activity, disability, depression, and fatigue. Neurol Res. 2017 Apr;39(4):323-330.

134.Polman CH et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006 Mar 2;354(9):899-910.

135.Langer-Gould A et al. Progressice multifocal leukeoencephalopathy in a patient treated with natalizumab. N Engl J Med, 2005.

136.Yousry TA et al. Evaluation af patients treated with natalizumab for progrssive multifocal leukoencelopathy. N Engl J Med, 2006.

137.Miller D H, B G Weinshenker, M Filippi, B L Banwell, J A Cohen, M S Freedman, S L Galetta, M Hutchinson, R T Johnson, L Kappos, J Kira, F D Lublin, H F McFarland, X Montalban, H Panitch, J R Richert, S C Reingold, C H Polman Differential Diagnosis of Suspected Multiple Sclerosis: A Consensus Approach Mult Scler. 2008 Nov;14(9):1157-74.

138.Granberg Tobias, Juha Martola, Maria Kristoffersen-Wiberg, Peter Aspelin, Sten Fredrikson

Radiologically Isolated Syndrome--Incidental Magnetic Resonance Imaging Findings Suggestive of Multiple Sclerosis, a Systematic Review Mult Scler . 2013 Mar;19(3):271-80.

139.Christine Lebrun 1, Caroline Bensa, Marc Debouverie, Sandrine Wiertlevski, David Brassat, Jerome de Seze, Lucien Rumbach, Jean Pelletier, Pierre Labauge, Bruno Brochet, Ayman Tourbah, Pierre Clavelou, Club Francophone de la Sclérose en PlaquesAssociation

Between Clinical Conversion to Multiple Sclerosis in Radiologically Isolated Syndrome and Magnetic Resonance Imaging, Cerebrospinal Fluid, and Visual Evoked Potential: Follow-Up of 70 Patients Arch Neurol. 2009 Jul;66(7):841-6.

140. A Siva 1, S Saip, A Altintas, A Jacob, B M Keegan, O H KantarciMultiple Sclerosis Risk in Radiologically Uncovered Asymptomatic Possible Inflammatory-Demyelinating Disease Mult Scler. 2009 Aug;15(8):918-27.

141. D T Okuda 1, E M Mowry, A Beheshtian, E Waubant, S E Baranzini, D S Goodin, S L Hauser, D Pelletier Incidental MRI Anomalies Suggestive of Multiple Sclerosis: The Radiologically Isolated Syndrome Neurology. 2009 Mar 3;72(9):800-5.

142.Gold R et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012 Sep 20;367(12):1098-107.

143.Alan J Thompson 1, Brenda L Banwell 2, Frederik Barkhof 3, William M Carroll 4, Timothy Coetzee 5, Giancarlo Comi 6, Jorge Correale 7, Franz Fazekas 8, Massimo Filippi 9, Mark S Freedman 10, Kazuo Fujihara 11, Steven L Galetta 12, Hans Peter Hartung 13, Ludwig Kappos 14, Fred D Lublin 15, Ruth Ann Marrie 16, Aaron E Miller 15, David H Miller 17, Xavier Montalban 18, Ellen M Mowry 19, Per Soelberg Sorensen 20, Mar Tintoré 21, Anthony L Traboulsee 22, Maria Trojano 23, Bernard M J Uitdehaag 24, Sandra Vukusic 25, Emmanuelle Waubant 26, Brian G Weinshenker 27, Stephen C Reingold 28, Jeffrey A Cohen 29 Diagnosis of Multiple Sclerosis: 2017 Revisions of the McDonald Criteria Lancet Neurol. 2018 Feb;17(2):162-173.

144.Napoli SQ et al. Magnetic resonance imaging in multiple sclerosis. Rev Neurol Dis. 2005 Summer;2(3):109-16.

145.Rovira A et al.MR in the diagnosis and monitoring of multiple sclerosis: an overview. Eur J Radiol. 2008 Sep;67(3):409-14. Epub 2008 Apr 22.

146.Lovblad KO et al. MR imaging in multiple sclerosis: review and recommendations for current practice. AJNR Am J Neuroradiol 2010;31:983–989.

147.O'Riordan JI, Losseff NA, Phatouros C, et al. Asymptomatic spinal cord lesions in clinically isolated optic nerve, brain stem, and spinal cord syndromes suggestive of demyelination. J Neurol Neurosurg Psychiatry 1998;64:353–357.

148. Lekha Pandit and J. M. K. Murthy. Treatment of multiple sclerosis. Ann Indian Acad Neurol. 2011 Jul; 14(Suppl1): S65–S69.

149. Gleicher N, el-Roeiy A, Confino E, Friberg J. Is endometriosis an autoimmune disease? Obstet Gynecol 1987;70:115–22.

150. Nothnick WB. Treating endometriosis as an autoimmune disease. Fertil Steril 2001;76:223–31.

151. Matarese G, De Placido G, Nikas Y, Alviggi C. Pathogenesis of endometriosis: natural immunity dysfunction or autoimmune disease? Trends Mol Med2003;9:223–8.

152. Sundqvist J, Falconer H, Seddighzadeh M. Endometriosis and autoimmune disease: association of susceptibility to moderate/severe endometriosis withCCL21 and HLA-DRB1. Fertil Steril 2011;95:437–40.

153. Witz CA. Pathogenesis of endometriosis. Gynecol Obstet Invest 2002;53:52–62.

154. Moen M, Bratlie A, Moen T. Distribution of HLA-antigens among patients with endometriosis. Acta Obstet Gynecol Scand Suppl 1984;123:25–7.

155.Simpson JL, Malinak LR, Elias S, Carson SA, Radvany RA. HLA associations in endometriosis. Am J Obstet Gynecol 1984;148:395–7.

156. Maxwell C, Kilpatrick DC, Haining R, Smith SK. No HLA-DR specificity is associated

with endometriosis. Tissue Antigens 1989;34:145–7.

157. Bulun SE. Endometriosis. N Engl J Med 2009;360:268–79.

158. Bulun SE. Physiology and pathology of the female reproductive axis. In: MelmedS, Polonsky KS, Larsen PR, Kronenberg HM, editors. Williams textbook of endocrinology. 12 ed. Philadelphia, PA: Elsevier; 2011. p. 638–41. Chapter 17.

159. Berkkanoglu M, Arici A. Immunology and endometriosis. AJRI 2003;50:48–59.

160. Wilson TJ, Hertzog PJ, Angus D, Munnery L, Wood EC, Kola I. Decreased natural killer cell activity in endometriosis patients: relationship to disease pathogenesis. Fertil Steril 1994;62:1086–8

161.Kanzaki H, Wang HS, Kariya M, Mori T. Suppression of natural killer cell activity by sera from patients with endometriosis. Am J Obstet Gynecol 1992;167: 257–61.

162. Oosterlynck DJ, Meuleman C, Waer M, Koninckx PR, Vandeputte M. Immunosuppressive activity of peritoneal fluid in women with endometriosis. Obstet Gynecol 1993;82:206–12.

163.Ho HN, Wu MY, Yang YS. Peritoneal cellular immunity and endometriosis. Am J Reprod Immunol 1997;38:400–12.

164. Lebovic DI, Bentzien F, Chao VA, Garett EN, Meng YG, Taylor RN. Induction of an angiogenic phenotype in endometriotic stromal cell cultures by interleukine-1β. Mol Hum Reprod 2000;6:269–75.

165.Gleicher N, el-Roeiy A, Confino E, Friberg J. Is endometriosis an autoimmune disease? Obstet Gynecol 1987;70:115–22.

166. Kennedy SH, Sargent IL, Starkey PM, Hicks BR, Barlow DH. Localization of anti-endometrial antibody binding in women with endometriosis using a double-labeling immunohistochemical method. Br J Obstet Gynaecol 1990;97: 671–4.

167. Confino E, Harlow L, Gleicher N. Peritoneal fluid and serum autoantibody levels in patients with endometriosis. Fertil Steril 1990;53:242–5.

168. Taylor PV, Maloney MD, Campbell JM, et al. Autoreactivity in women with endometriosis. Br J Obstet Gynaecol 1991;98:680–4.

169. Mathur S, Peress MR, Williamson HO, et al. Autoimmunity to endometrium and ovary in endometriosis. Clin Exp Immunol 1982;50:259–66.

170. Mathur SP. Autoimmunity in endometriosis: relevance to infertility. AJRI 2000;44:89–95.

171.Katiyar A, Sharma S, Singh TP et al. Identification of Shared Molecular Signatures Indicate the Susceptibility of Endometriosis to Multiple Sclerosis. Front Genet. 2018 Feb 16;9:42.

172.Sinaii N, Cleary SD, Ballweg ML et al. High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis. Hum Reprod. 2002 Oct;17(10):2715-24.

173.Mormile R, Vittori G. Endometriosis and susceptibility to multiple sclerosis: is there any absolute truth? Eur J Obstet Gynecol Reprod Biol. 2014 Aug;179:253.

174.Hart DA.Curbing Inflammation in Multiple Sclerosis and Endometriosis: Should Mast Cells Be Targeted? .Int J Inflam. 2015;2015:452095.

175.Shigesi N, Kvaskoff M, Kirtley S et al. The association between endometriosis and autoimmune diseases: a systematic review and meta-analysis. Hum Reprod Update. 2019 Jul 1;25(4):486-503.

176.Katiyar A, Sharma S, Singh TP et al. Identification of Shared Molecular Signatures Indicate the Susceptibility of Endometriosis to Multiple Sclerosis. Front Genet. 2018 Feb 16;9:42.