Medical treatment of endometriosis

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UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

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Medical treatment of endometriosis

GRADUATION THESIS

Zagreb 2016

This graduation paper was made at the University Hospital Centre Zagreb, Department of Obstetrics and Gynecology, mentored by dr. sc. Lana Škrgatić Lana and was submitted for evaluation in the academic year 2015 / 2016.

ABBREVIATIONS

BMI - Body Mass Index
COC - Combined oral contraceptives
EFI - Endometriosis Fertility Index
ESHRE - European Society of Human Reproduction and Embryology
FDA - Food and Drug Administration
GDG - Guideline Development Group
GnRH - Gonadotropin Releasing Hormone
MPA - medroxyprogesterone acetate
MRI - Magnetic resonance imaging
NSAIL Non steroidal ant-inflammatory drugs
SERM - Selective Estrogen Receptor Modulator
SPRM - Selective Progesterone Receptor Modulator
TENS Transcutaneous electrical nerve stimulator
TVUS - transvaginal ultrasound
QoL - Quality of Life

SUMMARY

Title: Medical treatment of endometriosis

Name: Leslie Chelon

This paper is about medical treatment of endometriosis. The main medical treatment is hormonal therapy in order to suppress endometrial tissue inflammation. Pain is managed through non steroidal anti-inflammatory drugs and opioids. Alternative treatment is also helpful.

Keywords: endometriosis, treatment.

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INTRODUCTION

Endometriosis is defined as the presence of endometrial tissue outside the uterus. It is qualified as a benign disease, even though it is one of the most important cause of abdominal pain and infertility[1]. The pathophysiology is poorly understood, in consequence diagnostic and treatment are a long way of being improved.

Available medical treatment include hormonal drugs (combined oral hormonal contraceptives, progestins, gonadotropin releasing hormone agonists, danazol, aromatase inhibitors), and alternative treatment (acupuncture, diet, ….)

This paper will provide an overview of the current medical treatments used for symptomatic endometriosis.

1. HISTORY

Symptoms of Endometriosis have been described since the 1800's century, but we could presume that this disease was around since a longer time[2]. During the Hippocrates time, young women were described with chronic abdominal pain. In the Middles Ages, these women were thought to be punished by God by having done unacceptable behaviour, resulting in this pain. Unfortunately these are only speculations since the only way to get proof of ectopic endometrial tissue is through surgery and precisely by getting histological parameter of the tissue sampled.

The first (published) person that notified endometriotic tissue on the ovary was W.W Russell, in 1898: "on the microscopic study of the ovary, we were astonished to find areas which were an exact prototype of the uterine glands and interglandular connective tissue."[3]

Sampson, a gynecologist at The Albany Medical Hospital (New York State), became fascinated by this disease and gave the name "chocolate cyst" of the endometrioma. At that time, he estimated the prevalence of being 10 % of the reproductive women population[5].

2. EPIDEMIOLOGY

Sampson's estimated prevalence of endometriosis was not far from today's actual numbers. Surgery being the diagnosis apparatus, true prevalence is unknown, but we estimate that around 5 to 10% of women get affected by endometriosis in their reproductive years (from 15 to 49 years old)[5]. Hundred and seventy-six Millions of women are diagnosed, leaving millions of other undiagnosed women, (approximately 1 billion of reproductive women population).

Many different studies detected several risk factors for endometriosis[2,6]:

- early menarche,
- polymenorrhea (menstruation cycle less than 27 days),
- menorhagia (duration of menses more than seven days),
- increases with the number of years since last childbirth ,
- heavy consumption of alcohol and caffein,
- prenatal exposure to diethylstilbestrol,
- inverse relationship to parity,
- hypoxia and iron deficiency may contribute to early onset,

Several protective factors are also detected:

- increased body mass,
- pregnancy,
- parity,
- prolonged period of lactation,
- regular exercises,
- smoking[2,6.]

Women in their reproductive age are the principal group affected. Mean age for diagnosis is between 25 to 35 years old (27 being the average)[2]. This supports the fact that endometriosis is related to hormones. Cases of endometriosis in pre-menarcheal girls or post-menopausal women have also been reported with frequency around 12% among pre-menarchal and 2-5% in postmenopausal women. In girls under

17 years endometriosis is frequently associated with Mullerian anomalies following cervical and/or vaginal obstruction, while in post-menopausal women with oestrogen therapy[2]

The reported prevalence of endometriosis among asymptomatic patients seeking elective sterilisation is between 3 and 45 %[7].

2. PATHOPHYSIOLOGY

THEORIES

The search for underlying mechanism behind development of endometriosis took years. Back in the days, Sampson was surprised by the histologic nature of the cyst he discovered. He found that this tissue was similar to the one of uterine endothelium. Those similarities made him "create" one of the etiological theory of endometriosis: the retrograde theory.[4]

In a 5 years period, he collected 293 cases of women with endometriosis . During surgery he visualised menstrual blood retrogradely passing through the fallopian tubes and lining in to the peritoneal cavity[4]. It has been proposed that endometriosis is caused by the seeding or implantation of endometrial cells.

Retrograde menstruation is observed in 75 to 90 % of the laparoscopy performed on women having there menses and those numbers are higher among women with endometriosis[2]. Endometrial cells can be grown *in vitro* in cell culture, and even *in vivo* after being implanted beneath abdominal skin of chimpanzee.[2].

Transplantation theory can not explain existence of endometriotic tissue outside the peritoneal cavity (lungs, pleura..), neither why pre-menarcheal girls can be affected and why cases of men were observed[2].

The other theory states that foci of peritoneal endometriosis might be "due to some specific irritant present in the cyst contents which stimulates the peritoneal endothelium to a metaplasia with the development of endometrial tissue typical both in structure and function"[2]. The idea behind metaplastic (coelomic) theory it is that metaplasia may occur in coelomic

epithelium (derived from Mullerian ducts cells, ovarian mesenchymal stroll cells, gonad somatic cells and testicular interstitial cells). Metaplasic process is induced by activation of an oncogenic K ras allele[8]. Metaplastic theory can explain situations that are not supported by the transplantation theory. It explains endometriosis in sites like thumb, knee, tights, that had disintegrated coelomic epithelium adjacent to the mesenchymal limb buds during early embryogenesis[2]. There are also reports of men treated with very high dose of oestrogen to treat andropause who developed endometrial cells in their abdominal walls or urinary bladder[2]. This has been also shown in vitro by cultivating ovarian surface epithelium, stromal cells and oestradiol in a collagen gel lattice form endometrial glands and stroma[2].

Another theory implies that vascular and lymphatic dissemination of endometrial cells may occur as well as direct seeding during invasive procedures like Cesarean section, pelvic surgery or episiotomy [2]

GENETIC FACTORS

A genetic basis for the disorder has been suggested by familial clustering cases. There is a 6 to 9 times fold increase risk of endometriosis in 1st degree relative compared with general population. A relative risk of 7,2 is observed between mothers and sisters[2].

IMMUNOLOGIC FACTORS AND INFLAMMATION

When looking for autoantibody, we see a high prevalence of antinuclear antibodies directed against endometrial antigen, more specifically against transferrin and laminin[2]. Those findings support the idea that there is some local chronic inflammatory process going on in the peritoneal cavity of these patients. This impaired immune functions have many actors. Progesterone has the capacity of balancing the endocrine/ immune physiology of the endometrium tissue. In endometriotic tissue, there is a failure of the progesterone to act appropriately. Indeed, these women seem to secrete normal progesterone level but their endometrium's respond is reduced. It does not display the changes in specific gene and protein expression normally expressed during the pregesterone-dominated secretory phase of the menstrual cycle[9]. Macrophages and monocytes in peritoneal fluid are numerous. Instead of gatekeepers

protectors, they seem to promote the disease by secreting growth factors and cytokines that stimulate proliferation of ectopic endometrium[2]. Interleukin-8 seems to correlate with the severity of the disease. It is elevated in women with severe disease condition[2]. Some studies pointed out the impaired function of retinoid activity in women affected by endometriosis. The effect relationship is still unknown but in model system, retinoid activity decreases pro-inflammatory cytokines while increasing anti-inflammatory proteins like IL-10[10].

MOLECULAR MECHANISMS

Mechanism of pain

Pain is the most common symptom in endometriosis. Aside with infertility, relieving pain is the gold standard of endometriosis treatment.

Mechanism of pain associated with endometriosis is very complex. It is proposed to occur through 3 mechanisms:

- directly and indirectly form focal bleeding of endometriotic epithelium
- local inflammation
- irritation or infiltration of pelvic nerves[2].

All three mechanisms oftenly exist in synergy The local inflammation and the bleeding will make adhesion formation, resulting in fibrotic thickening which results in painful traction of physiologic tissue[1].In patients with pain endometriosis stage is oftenly not related to pain symptoms. Some women with advanced endometriosis have little pain or in contrary mild disease presents with excruciating pain. Pain stays a subjective and inter personal symptoms.

Mechanism of infertility: Long term consequence

An association between endometriosis and infertility is generally accepted and prevalence ranges from 20 to 40 % in those women[2]. Studies reported a lower spontaneous monthly fecundity rate (total number of pregnancies by the number of month of pregnancy exposure). It is oftenly associated with tuboovarian adhesions and disturbed anatomy. Also, excess production of prostaglandin, metalloproteinase, cytokines and chemokines is probably part of the process, through a

chronic inflammation that can impair the physiologic functions of folliculogenesis, fertilisation and implantation[1]. Even in the field of in vivo fertilisation process, a meta analysis revealed lower implantations and pregnancy rates among women with endometriosis[2]. It could be a reflection of poor oocyte quality. Indeed, experiences with oocyte donation from women with Endometriosis shows higher incidence of arrested and abnormal development of the embryos[2].

3. SYMPTOMS

The two most common symptoms of endometriosis are chronic pelvic pain and infertility. Thirty to forty-four percent of infertile women are diagnosed with endometriosis. Pain mainly depends on the area affected. Dysmenorrhea, irregular or heavy bleeding, pelvic pain, power back pain, dyspareunia (worsened in the premenstrual phase), are the most representative one[2].

Bladder and colon can be affected resulting in dyschezia, inguinal pain, dysuria, hematuria.. Pulmonary involvement can be presented with hemoptysis. Diaphragm lesions can cause reflected pain in the right shoulder. Brain lesions can cause catamenial seizures. Umbilicus implant display with umbilical bleeding. Approximately one third of them remain asymptomatic[6].

4. DIAGNOSIS

It is well recognised that a delay from symptoms to the diagnosis of endometriosis exists. Studies report an overall diagnostic delay of 10 years in Germany and Austria, 8 years in the UK and Spain, 7 years in Norway, 7-10 years in Italy and 4-5 years in Ireland and Belgium[7]. However since endometriosis highly affects QoL the patients awareness on diagnosis is rising[7].

CLINICAL

The severity of the disease does not correlate with the number and severity of the symptoms[2]. Clinical informations are not sufficient for diagnosis. Bases on studies and expert opinion, the Guideline Development Group (GDG) recommends clinicians to consider the diagnosis of endometriosis:

- in the presence of gynaecological symptoms such as: dysmenorrhoea, non-cyclical pelvic pain, deep dyspareunia, infertility and fatigue in the presence of any of the above;
- in women of reproductive age with non-gynaecological cyclical symptoms (dyschezia, dysuria, haematuria and rectal bleeding, shoulder pain)[7].

Clinical exam also guides you toward endometriosis. Again, the GDG recommends clinicians to consider following:

- the diagnosis of deep endometriosis in women with painful induration and/ or nodules of the rectovaginal wall found during clinical examination or visible vaginal nodules in the posterior vaginal fornix;
- the diagnosis of ovarian endometrioma in women with adnexal masses detected during clinical examination;
- the diagnosis of endometriosis in women with positive history for symptoms mentioned above, even if the clinical examination is normal[7].

CA-125

CA-125 is a cell surface antigen expressed by derivatives of coelomic epithelium. CA-125 marker has a good specificity but low sensitivity in detecting endometriosis. A meta analysis that tested sensitivity and specificity of this marker using surgery based diagnosis of endometriosis concluded a 90 % specificity, but a 30 % sensitivity. It cannot be used as a screening/diagnostic test, but could help differentiating an ovarian endometrioma from a benign cyst. Also a sustained level of CA-125 after endometriosis surgery is a factor of bad prognosis[2].

IMAGING

Transvaginal ultrasonography (TVUS) is first line of imaging method as it can detect ovarian endometriomas with a 90 % specificity and almost a 100 % sensitivity. However,TVUS is not a good tool in distinguishing pelvic adhesions from superficial disease. Another barrier is that it is highly operator dependent[7]. Transrectal ultrasonography ameliorates discovering a deep infiltrating structures (endometriotic lesions of the bladder, uterosacral ligament, recto-vaginal septum). MRI has 70 % sensitivity and 75 % specificity. MRI is useful in distinguishing between acute hemorrage (isointense T1 and hypo intense T2) and blood products (hypointense T1 and T2). It could detect only 30-40% of lesions observed in surgery[2].

SURGICAL DIAGNOSIS BY LAPAROSCOPY IS THE GOLD STANDARD TOOL

Surgical diagnosis by laparoscopy represents the gold standard for diagnosis. Examination should include a careful and complete inspection and palpation in a clockwise or counterclockwise fashion with a blunt probe of the bowel, bladder, uterus, tubes, ovaries, cul-de sac and broad ligament[1]. To avoid any under diagnosis, this procedures should not be performed during 3 months of hormonal treatment[2]. The classical image looks like blue black “powder burn” in the middle of fibrotic plaque. However those are the less frequent findings. Implants can have various aspects. Red lesions would represent an early stage being vascularised and proliferative. Advanced disease’s lesions are characterised being pigments. Both types are metabolically active in comparison with the less vascularised white lesions which are often asymptomatic and of fortuite findings. White lesions represent lower activity and metabolism, which is not correlated to symptom severity. Differential diagnosis of those lesions are endosapingiosis, mesothelial hyperplasisia, hemosiderin deposition, hemangiomas, adrenal rests, inflammatory changes or splenosis[1,2]. Biopsies of any lesion found on laparoscopy are performed for differential diagnosis. Histologic criterias (mitotic activity, vascularisation…) confirm approximatively 60% of endometriosis[2]. Ovarian puncture and aspiration

can be helpful when no specific macroscopic characteristics are found in endometrioma.

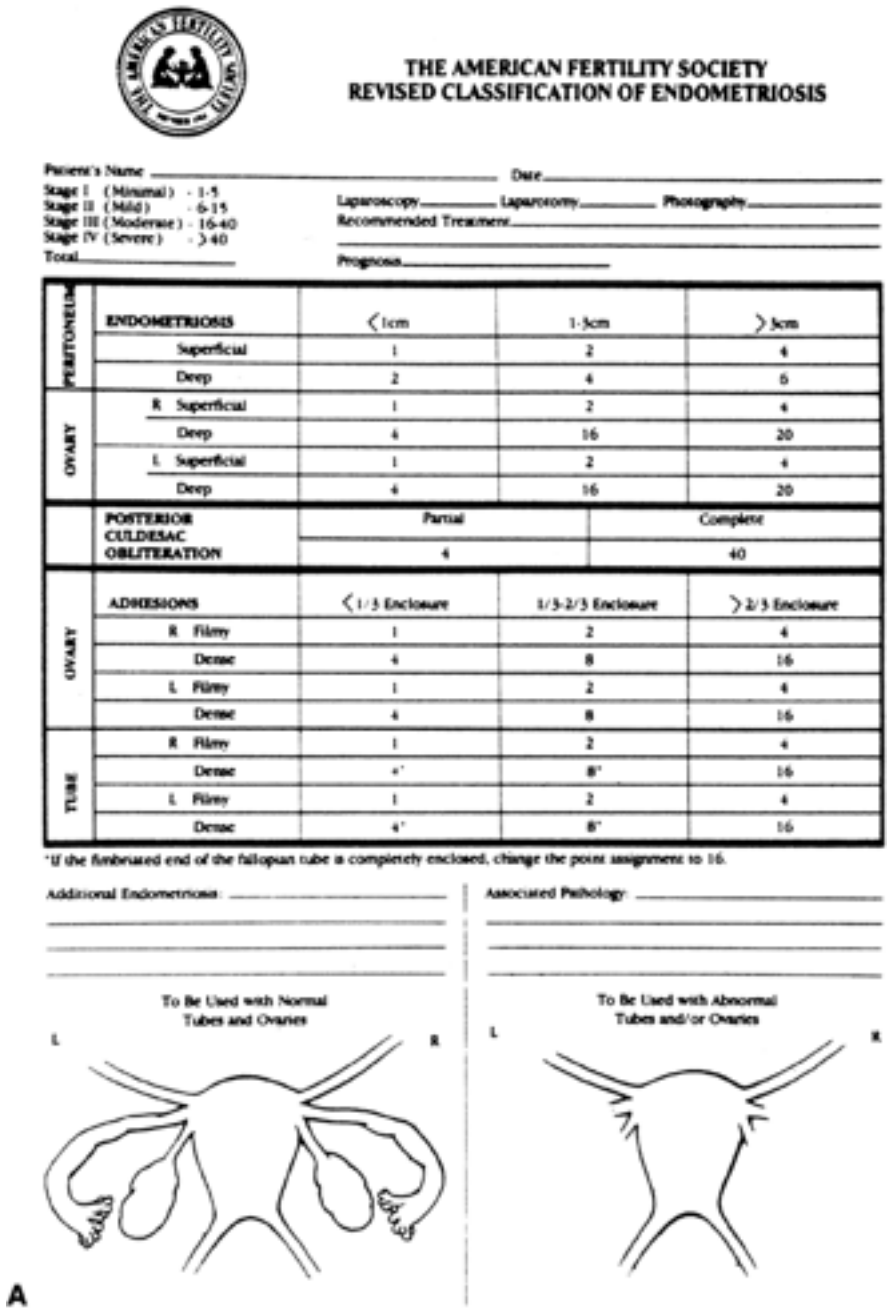
A negative diagnostic laparoscopy seems to be highly accurate for excluding endometriosis[7].

The GDG recommends that clinicians:

- perform a laparoscopy to diagnose endometriosis, although evidence is laking that a positive laparoscopy “without histology” proves the presence of disease;
- confirm a positive laparoscopy by histology, since positive histology confirms the diagnosis of endometriosis even though negative histology does not exclude it[7].

CLASSIFICATION

Classification criteria and staging is crucial for improvement of the management of endometriosis and predicting the outcome. The most widely used is the classification by the American Society of Reproductive Medicine, in 1996. This classification includes appearance, size, depth of peritoneal and ovarian implants; the presence, extent, type of adnexal adhesions, the degree of cul de sac obliterations, morphology of the implants (red, white, black)[1,2]. Only the women who have undergone surgery can be evaluated by this classification. Stages are graded from I to IV, respectively from minimal to severe affectation[2].



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 _____

PERITONEUM	ENDOMETRIOSIS	<1cm	1-3cm	>3cm
	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

A

Figure 1: The American Fertility Society revised classification of endometriosis [2]

Annexe A

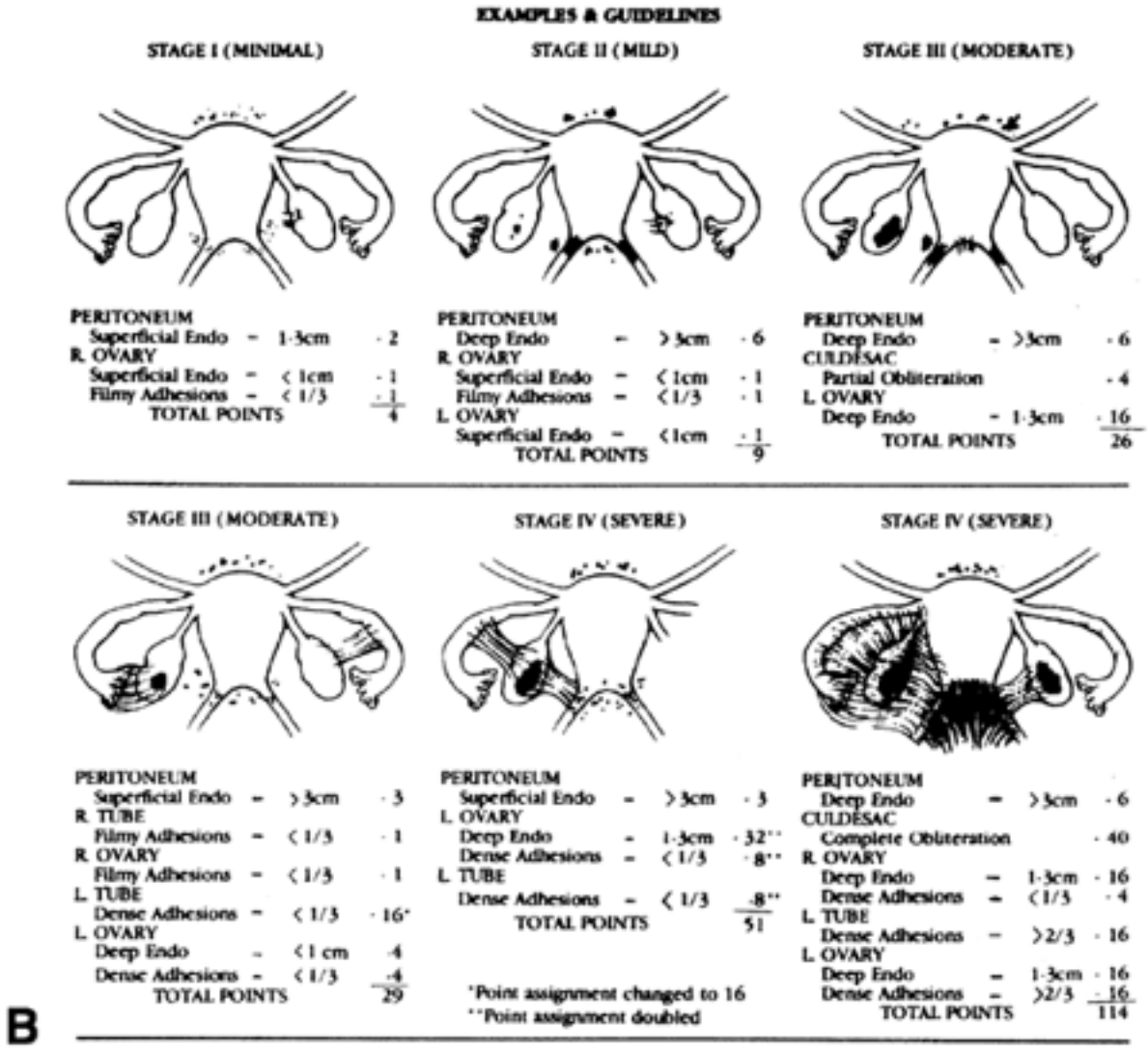


Figure 2: The American Fertility Society revised classification of endometriosis[2]

Annexe B

In 2010, Adamson and Pasta, (two specialist fertilization doctors), created another surgical classification resulting from a retrospective cohort study, which is the Endometriosis Fertility Index (EFI). It adds the historical score (factors as age, number of infertility year and previous pregnancies), and the surgical score (functions of fallopian tubes, fimbriae and ovaries). The final EFI score is placed in a graph with the time in month in the x axis and the percentage of being pregnant in y axis. The EFI score predicts predicts cumulative pregnancy rates over 3 years, going from 0 to 10, 0 representing the poorest and 10 the best prognosis. For example, if a woman has a EFI score of 6, she has 20 % chance of being pregnant in 6 months. This form is used as a tool for developing treatment plans in infertile patients[2].

ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score		Description
4	=	Normal
3	=	Mild Dysfunction
2	=	Moderate Dysfunction
1	=	Severe Dysfunction
0	=	Absent or Nonfunctional

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

	Left		Right		
Fallopian Tube	☐		☐		
Fimbria	☐		☐		
Ovary	☐		☐		
Lowest Score	☐	+	☐	=	☐
	Left		Right		LF Score

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	Description	Points	Factor	Description	Points
Age			LF Score	☐	
	If age is ≤ 35 years	2		If LF Score = 7 to 8 (high score)	3
	If age is 36 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF Score = 1 to 3 (low score)	0
Years Infertile			AFS Endometriosis Score		
	If years infertile is ≤ 3	2		If AFS Endometriosis Lesion Score is < 16	1
	If years infertile is > 3	0		If AFS Endometriosis Lesion Score is ≥ 16	0
Prior Pregnancy			AFS Total Score		
	If there is a history of a prior pregnancy	1		If AFS total score is < 71	1
	If there is no history of prior pregnancy	0		If AFS total score is ≥ 71	0
Total Historical Factors		☐	Total Surgical Factors		☐

EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS: ☐ (Historical) + ☐ (Surgical) = ☐ (EFI Score)

ESTIMATED PERCENT PREGNANT BY EFI SCORE

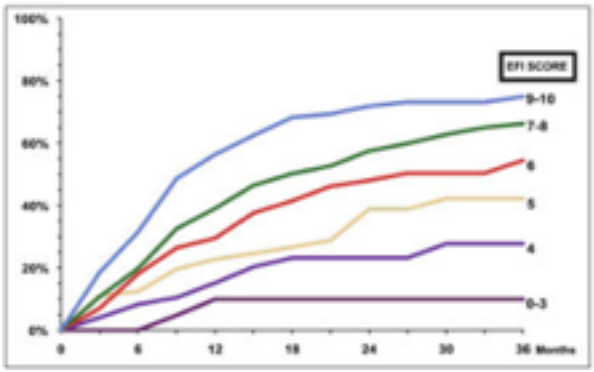


Figure 3: Endometriosis Fertility Index (EFI) surgery form

TREATMENT

Classifications used for diagnosis of endometriosis in women have a main goal to help improve treatment plans for patients with endometriosis. Endometriosis treatment is patient dependant. It is administrated according to the pain and to the infertility which impede the most on quality of life[2]. Of course, before starting medical treatment, other causes of pelvic pain symptoms should be considered[7]. Also, if a patient doesn't respond well to medical treatment, a la-parascopy is performed to find further signs[7]. In more than 50 % of patients, endometriosis will progress through their life. Early treatment, even with mild symptoms, might be beneficial. Surgical treatment should be reserved for severe stages, but even in minimal to mild endometriosis, it offers a little improvement in the fertility outcome.

Focusing more on the medical treatment, the population we are interested in are patients desiring pain relief with or without definitive surgical diagnosis. Medical treatment does not seem to improve fertility, and it is not effective for endometriomas and pelvic adhesions[2]. Knowing what we know about the pathophysiology of this disease, the goal of the treatment is to reduce or eliminate menstruations, which will, not only help with the acute situation, but also will decrease the chance of getting new endometrial implants[2]. Therefore, hormonal treatment acts directly by treating the aetiology, and consequently the pain. Pure analgesic drugs will help as treating the symptomatic patients with pain as leading symptom. Pain relief is managed through pure analgesic drugs and through drugs decreasing the endometrial tissue, as we said above, that is responsible for inflammation and pain.

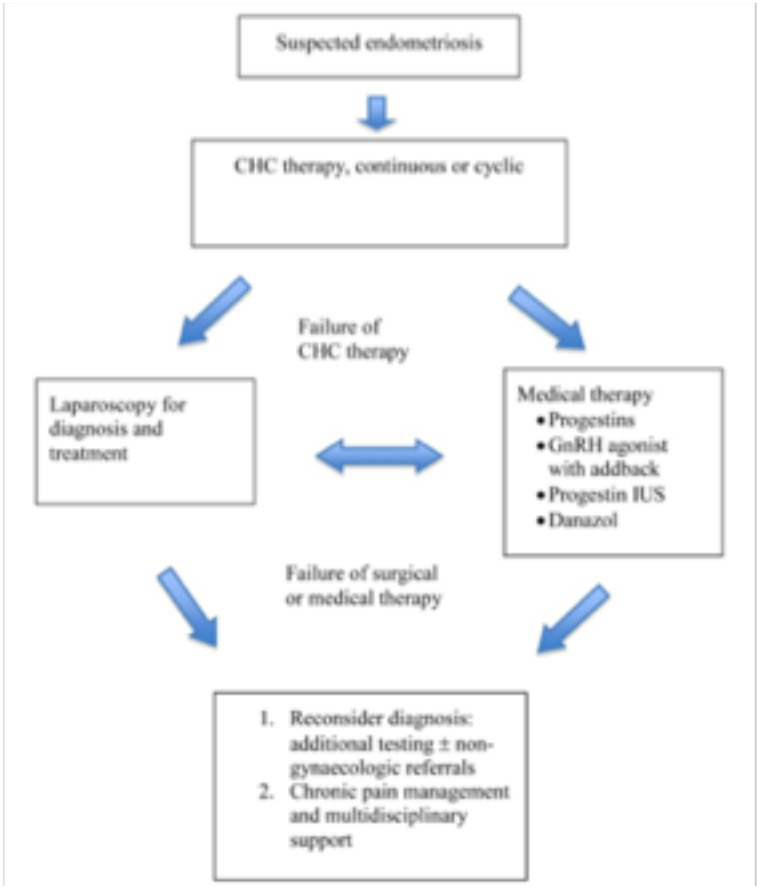


Figure 4: Management of pain associated with suspected endometriosis

According to: Leyland N et al (2010) S10.

1. COMBINED HORMONAL CONTRACEPTIVES

Combined hormonal contraceptives (COC) are the cornerstones of medical endometriosis treatment. The debate still exist between taking COCs continuously or cyclic. Studies have been conducted without proving superiority of one over another[1]. This concept of suppressing the physiologic hormonal rhythm was introduced by Robert Kistner, an American gynaecologist who specialised in the treatment of endometriosis[1].

A continuous administration (1 pill per day), for 6 to 12 months will induce a state of “pseudopregnancy”. The oestrogen component can potentially stimulates endometrial tissue growth with increasing symptoms for the first weeks[1]. Amenorrhea and decidualization of endometrial tissue (some evidence of inducting apoptosis of the tissue) are effective in reducing the pain[2].

As much as 75 to 90 % of women experience pain relief [2]. It also reduce retrograde flow, thus limiting spreading of the disease[1]. The lower effective dose should be 30 microgram of ethinyl oestradiol[1]. Unfortunately this treatment only seems to silence the condition. A recurrence rate of 17% is observed during the first year after stoping the COCs[1]. COCs should remain the first line in treatment of woman with mild pain symptoms without plans for pregnancy at that moment. Most common sides effects associated with oestrogen or progestin include: premenstrual syndrome, migraine, breast tenderness, menstrual irregularities, abdominal discomfort, mood lability. Most serious complication of COC use are thromboembolitic events that can be avoided by determining potential risk in each patient[6]. A variety of biological parameters have to be checked within three months of treatment. Glycemia on fasting, complete blood count, triglyceridemia and cholesterol level[6]. Contra-indications are: personal history of thromboembolytic events (arterial or veinous), migraine with aura, hormone dependant cancer (breast, endometrial), tobacco use more than 15 cigarettes per day if over 35 years old, non treated hypertension (systole > 160 mmHg and/or diastole > 100 mmHg), thrombophilia,

hypercholesterolemia > 8 mmol/l, morbid obesity (BMI > 39), pregnancy, breast feeding < 6 weeks post partum, ischemic cardiomyopathy, valvular cardiomyopathie with complications, stroke, active viral hepatitis, severe hepatitis insufficiency[12].

The GDG advise clinicians to[7]

- consider prescribing a combined hormonal contraceptive, as it reduces endometriosis-associated dyspareunia, dysmenorrhoea and non-menstrual pain;
- consider the continuous us of combined oral contraceptive pill in women suffering from endometriosis-associated dysmenorrhea;
- consider the use of vaginal contraceptive ring or a transdermal (oestrogen/ progestin) patch to reduce endometriosis-associated dysmenorrhoea, dyspareunia and pelvic pain

2. PROGESTINS

Progestins have been used for treating endometriosis since the 1950[1]. Oral progestins are effective and cheap in treating endometriosis and their efficacy has been proven by many studies[1]. A randomized controlled study compared a cylic 21days contraception (20 microgram ethynil estradiol and with desogestrel 0.15mg), combined with danazol (50mg per day), versus medroxypogesterone acetate (MPA 150mg every 3 months) observed superiority of MPA for the relief of dysmenorrhea: 72,5% versus 57,5%[12].

This superiority is due to the power of inhibiting the pituitary gland when high dose is administered, leading to an ovulation and thus amenorrhea. High dose of progestins also shows suppression of endometrial matrix metalloproteinase[2].

A single randomised controlled trial comparing high doses of MPA (100mg/day for 6 months) and placebo found that fifty percent of the progestins group presented with complete remission of the visible endometrial tissue versus 12% in the placebo group[13]. Side effects are nausea, weight gain,fluid retention, breast tenderness, irregular bleeding (up to 40 % but easily controlled by estradiol 2 mg / day for 7 to 10 days),

depression (5%. One of the main reason to discontinuous medication)[2]. Progestins can also decrease HDL level (which is risk factor for cardiovascular diseases)[2]. At the dose needed to suppress the hypothalamo-pituiatry-ovarian axis, four percent of the spinal bone mineralisation is depleted after 6-12months treatment but without any pathological fractured observed and a rapid recover is seen after discontinuing the treatment[2].

A variety of progestins are available. There is no particular clinical trials evidence showing that one progestin is more suitable than another[1].

MPA can be given intramuscularly every 3 months. At a dose of 150 mg, it also decreases pain. This progestin induce a profound amenorrhea and anovulation with which the body has trouble recreating a physiologic cycle, and thus needing a long recovery period if the patient desires a pregnancy[1].

NETA (2.5 mg/day) is effective in reducing the intensity of pain in women with deep infilitrating endometriosis (Surgical versus low-dose progestin treatment for endometriosis-associated severe deep dyspareunia II: effect on sexual functioning, psychological status and health-related quality of life[14].

Other form, like the 52mg levonorgestrel-releasing intra uterine device, is of great use regarding deep infiltrating recto-vaginal endometriosis, reducing its volume as well as reducing dysmenorrhea, dyspaneuria and pelvic pain. This intra-uterine device can stay in place for up to 5 years[1,2].

Gestrinome is a 19 nortestosterone derivative with androgenic, antiprogestagenic, antiestrogenic, and antigonadotropic properties. The androgenic effect acts centrally and peripherally. It leads to an increase of free testosterone and also reduces sex hormone binding globulin levels. The anti-estrogenic effect reduces estradiol levels as down as in the early follicular phase. The anti-gonadotropic effect reduces LH . Those overall effects cause cellular inactivation and degradation of the endometric implants. As we can assume, amenorrhea appears, but is dose dependent. This drug has a 28 hours long half life when orally taken. The standard posology is 2,5 mg twice a week. In a multi-centered, double blind study, comparing Gestrinone and GnRH, with reducing pelvic pain

as the primary goal, showed non significant difference. Side effects of Gestrinone include nausea, muscle cramps, weight gain, acne, seborrhoea and oily skin and hair. One of the main precaution using this drug is contraception to avoid pregnancy which can have effect on the masculinisation of the foetus[1].

Dienogest is an oral progestin that has been investigated extensively in the treatment of endometriosis in two clinical programs performed in Europe and Japan, including dose-ranging, placebo-controlled, active comparator-controlled, and long-term (up to 65 weeks) studies. These studies demonstrated that dienogest 2 mg daily effectively alleviates the painful symptoms of endometriosis, reduces endometriotic lesions, and improves indices of quality of life. Dienogest showed a favorable safety and tolerability profile in these studies, with predictable adverse effects, high rates of patient compliance, and low withdrawal rates[15].

The GDG advise the use of progestagins to reduce endometriosis-associated pain[7].

3. GnRH AGONIST

Gonadotropin releasing hormones agonists are a modified version of native GnRH. Chemically, a switch of the L-amino acid to the D-amino acid makes this drug resistant to degradation, thus increasing its half life (3 to 8 hours) and time of receptor occupancy in the pituitary gland. This constant stimulation of GnRH receptors causes, after initial “flare up”, a down regulation of receptors concentration[2]. Down regulation of receptors creates a ‘pseudo menopausal” state. Deprivation of oestrogen results in amenorrhea, preventing new peritoneal seeding[2]. Furthermore, GnRH receptors are present in ectopic endometrium. Direct inhibition was shown in in-vitro models. Another potential action decreases adhesion formation (causing pain). This effect was proven in in-vivo rat models, through a decrease of plasminogen activators and matrix MMPs[1].

A variety of GnRH agonists are available: leuprolide, buserelin, nafarelin, histrelin, goserelin, deslorelin, and triptorelin. An inconvenient fact about those drugs is that they are ineffective orally and must be taken

either intramuscularly, subcutaneously or intra-nasally[1]. After two months of treatment, almost 100 % of women are in a pseudo-menopausal state with pain release[2]. There are several side effects associated with GnRH treatment: hot flashes, vaginal dryness, decrease libido, depression, irritability, fatigue, head ache, change in skin texture changes associated with hypogonadism. Hypogonadal state rises a risk for bone mineral depletion especially after 6 months of treatment mostly in the lumbar spine and the femoral neck. It can be up to 1% per month. Although, mineralisation slowly recovers after treatment discontinuation in most women, it is not the case for all women. In order to prevent bone loss “add-back” therapy is used adding a progestins or a combination of progestin/oestrogen. A minimum of 30 to 45 pg / mL of serum oestrogen should be maintained. Ones can wonder why adding oestrogen when we know that it is causing endometriosis symptoms. The “oestrogen treash-hold hypothesis’, sustains that the oestrogen level needed to counter back vasomotor state and mineral bone loss in the hypo-oestrogenic state associated with GnRH use is much lower than the level causing endometriosis signs. Nevertheless, adding only oestrogen to the GnHR agonist therapy showed increase in pelvic pain. Combinations of oestrogen and progestin are available. A 0,625 mg conjugated oestrogen's with 2,5 mg medroxyprogesterone acetate; or with norethindrone acetate, 5mg ; or oestradiol, 2 mg, with norethisterone acetate 1mg. Progestine only can reduce the side effect of bone loss, using noresthisterone with a higher posology from 1,2 mg to 5 mg, tibolone 2,5 mg, bisphosphonate (cyclic etidronate using 400 mg daily for 2 weeks every 2 months, or alendronate 10 mg daily), also option of the selective oestrogen receptor modulator: raloxifene, 60 mg per day. Other progestins do not prevent bone loss[1,2].

After cessation of GnHR agonist + add back therapy or GnHR agonist alone, pain relapses is 10 to 20 % per year, with a cumulative recurrence rate after 5 years of 55 %[2]. In another report, mineral bone density if not fully recovered even after 6 years or terminating the therapy, and the add back regime did not reverse this process. In this way, GnHR agonists should not be prescribed to women that had not reach there full bone density[1].

Opposite to this “add- back” therapy, the “draw back” therapy consists of a single GnHR Agonist: the nafarelin for a 6 months treatment at 400 micro gram/ day. It has shown to be equally competent with lower bone loss[1].

Clinicians are recommended to use GnRH agonists as one of the options, although evidence is limited regarding dosage or duration of treatment and with careful considerations in young women and adolescents[7].

4. GnRH ANTAGONIST

Recently introduced, GnRH antagonists induce a competitive inhibition of the GnRH receptors on the cell membrane of the gonadotropic cell. It suppress FSH, LH and consequently oestrogen secretion without inducing the flare effect[16]. Cetrorelix is administered subcutaneously at the dosage of 3 mg within 8 weeks. In this study, 100 % of the patients were symptoms free during the treatment, but the power of the study can be questioned, only 15 persons were studied. Adverse effects are headache and urterine bleeding[3].

A relatively new agent elagolix was studied in a study consisting of 3 groups of 252 women with surgical diagnosis of endometriosis that were treated with 150 mg elagolix (GnRH antagonist), 75 mg elagolix or an active control: DMPA-SC (depot medroxyprogesterone acetate). After 6 and 12 months of treatment the pain was reduced in up to 86 % of the women treated with elagolix compared to DMPA-SC[17].

Do to there peptide structure, potential adverse effects are histamine related. Thus, allergic reaction symptoms and hypersensitivity states could be fatal[18].

5. DANAZOL

This drug was the first one approved by the FDA of the United State for the treatment of endometriosis in 1970[19]. Chemically, it is an isoxazole

derivative of ethinyltestosterone and has a profound growth-inhibitory effect on an established human endometrial adenocarcinoma cell line, with isolated weak androgenic activity and no oestrogen or progestin effect[2,20]. This causes a high androgenic and low oestrogen environment, by directly inhibiting the mid-cycle urinary LH surge, causing an anovulatory state[2]. The amenorrhea side effect prevents more peritoneal seeding of Endometriosis and the low oestrogen state prevents growth of already present lesions[1,2].

Other immunological effects of this drug include, decrease of serum immunoglobulin, decrease C3 complement, rise C4, decrease level of auto antibodies against phospholipids antigen, and decrease serum level of CA125. It also decrease IL-1 and TNF, (inflammatory cytokines), by production of monocytes , and suppresses macrophages and monocytes mediated cytotoxicity of target cells in women with mild disease[1]. This explains the use of danazol in inflammatory diseases such as fibrocystic breast disease, immune thrombocytopenic purport and hereditary angioedema[1]. The starting dose is 400 mg per day 2 times orally, with increasing doses until pain release and amenorrhea develops (amenorrhea being the best indicator of the treatment effectiveness)[1]. In a 6 months treatment period, pain relief is present in 90 % of patients[2]. Maximum dose reaches 800 mg per day in North America[1]. This limit is due to side effects of androgenic and hypo-oestrogenic state[1]. Negative side effects of this treatment include weight gain, fluid retention, hot flashes, fatigue, nausea, muscle cramps, emotional lability, acne, oily skin, which are all due to the hypo-oestrogenic state. Androgenic effects are hirsutism, acne, deepening of the voice which is non reversible[1,2]. The blood profile is also modified. Increase cholesterol and LDL and decreases HDL[1,2]. It is, therefore, contra-indicated in patients with hypertension, congestive heart failure and renal impairment functions (adding fluid retention effect). Patients with liver diseases also cannot benefit from this drug, as it is metabolised by this organ[1]. For long term treatment, liver enzymes have to be monitored repetitively. A potent contraception has to be used because Danazol causes masculinisation on the foetus[1,2]. Other routes of administration are in progress. A vaginal

danazol ring (1,5 mg) presented pain release in deep infiltrative endometriosis without the typical side effects of oral Danazol[1].

6. AROMATASE INHIBITOR

Aromatase is an enzyme that converts testosterone to estradiol and androstenedione to estrone[21]. Inhibition of this enzyme results in hypo-oestrogenic state. Aromatase activity is not detectable in normal endometrium and it has been shown to be expressed incorrectly in the biopsies of endometrium of women suffering from endometriosis[22]. In case reports, 1 mg per day of anastrozole or 2.5 mg per day of letrozole, reduce pelvic pain[2].

A randomised trial evaluated the pain reduction in post operative women that underwent endometrial reduction, comparing GnHR agonist alone with GHR agonist joined with anastrozole[2]. Anastrozole, letrozole and triazole are the third generation of aromatase inhibitors. They are more selective, reversible and potent inhibitors with less sides effects than the first or second generation[22]. Aromatase inhibitors are also associated with several side effects associated with hypogonadal state like: -bone loss, a possible increased incidence of coronary heart disease and changes in cognitive function[23]. Most frequent side effects of third generation are hypoestrogenic symptoms (vaginal dryness, hot flushes, headache, back pain and leg cramps)[22]. In case of deep infiltrating rectovaginal endometriosis, refractory to other medical or surgical treatment, clinicians can consider aromatase inhibitor in combination with oral contraceptive pills, progestagens or GnRH agonists[7]. But as for the treatment of non-profond endometriosis, aromatase inhibitors should be considered after prescribing all other medical options are exhausted[24].

In addition, adding progestins or oral contraceptive pills will act as add-back therapy to prevent reduction of bone demineralisation, thence, osteoporosis[22].

7. SELECTIVE ESTROGEN RECEPTOR MODULATORS

Regression of endometriosis tissue has been shown in vivo , in rat models, with a SERM called Raloxifene[1]. This SERM mimic oestrogen in decreasing bone resorption and increasing its density. It also decreases LDL[6]. It is, thus, prescribed to women suffering from osteoporosis[6]. They can be targeted towards the alpha or beta subunits of oestrogen. Alpha receptors are SERMs target in bone, mammary and endometrium, whereas beta receptors are SERMs target for expressing anti-inflammatory action. One study conducted on endometriotic mice showed 40 to 75 % of mice treated with beta-SERMs[5]. SERMs are also associated with side effect caused by depletion of oestrogen[7]. Warning is mandatory and usage of this drug is contra-indicated in pregnant women, during lactation and with history of an active thromboembolic disorder (cancer, thrombophilia)[25]

8. SELECTIVE PROGESTERONE RECEPTOR MODULATORS

This class of drug shows agonist and antagonist progesterone activities. If progesterone is present, they act like weak progestins and if progesterone is absent, they show weak anti-progestagenic activity[26]. The SPRM potentially induce reversible amenorrhea through selective inhibition of endometrial proliferation, a direct effect on endometrial vessels and suppression of prostaglandin production without the systemic effects of oestrogen deprivation[25]. One clinical trial composed of 130 women experiences reduction of pelvic pain and dysmenorrhoea. No serious adverse effects were reported[6]. Common reported side effects include: headache, abdominal pain and tenderness[26]

Other use of SPRM, in development, are endometrial cancer Cushing’s disease, Alzheimer disease and long-term contraception[28]

9. IMMUNOMODULATORS

As we explained in the pathogenesis part, altered immune functions play a role in endometriosis. A promising study on rodent and baboon model using a TNF-alpha inhibitor showed inhibition of the development of endometriosis[6]

A study compared a new drug: bentamapimod against GnRH antagonist on rat to evaluate the regression of endometrial tissue. Bentamapimod is a c-Jun N-terminal Kinases inhibitor. This kinase has its place in immune reactions. The result of the study showed 48% regression the lesions with bentamapimod compared to 84% regression with the GnRH antagonist [29].

PAIN MANAGEMENT

Severe pain associated with endometriosis can frequently be managed by medical treatment while pain associated with deep infiltrative endometriosis could only be resolved by a surgical approach. Management of pain associated with endometriosis with targeted medical therapies may require one cycle for pain relief[30]

1. NON STEROIDAL ANTI-INFLAMMATORY DRUGS

Non steroidal ant-inflammatory drugs (NSAIDs) are first line treatment of pain associated with endometriosis. A small doubled blind cross over study compared naproxen versus placebo for the relief of pelvic pain. Ablation of pain was in 83% of the NSAIDs group compared to 41 % in the placebo group[31]. NSAIDs inhibit a specific enzyme called cyclooxygenase (COX) which catalyse the formation of prostaglandin and thromboxane from a common precursor: arachidonic acid. By blocking this enzyme, less prostaglandin are produced and that is the goal we want to achieve. Two COXs enzymes are known. The second one is believed to be induced during an inflammatory state[32]. Selectively inhibiting COX, we will decrease gastro-intestinal side effect but studies did not prove any superiority of these drugs compared to one another. Since the main mechanism releasing pain is by blocking prostaglandin's formation, the drug must be taken before activation of this enzyme. Hence, NSAIDS are usually taken one to tow days before the menstrual cycle. Ibuprofen, one tablet every four to six hours. Naproxen sodium, one tablet every six to height hours[33]

Side effects associated with NSAID are gastric ulcers, nausea, vomiting, diarrhoea and possible inhibition of ovulation. If the pain is not relieved by NSAIDs only, one’s can add paracetamol, or paracetamol+ codeine[34.]

2. OPOIDS

Opioids related drugs bind on four different types of receptors in central and also on peripheral nerves: mu, kappa, delta and sigma. These receptors are the binding sites of many endogenous peptides which regulates pain, stress, temperature, respiration, endocrine activity, gastrointestinal activity, mood and motivation. The opioid drug can either act as an agonists or antagonists of the receptors. Using a full mu receptor agonist will cause pain relief, mood alteration, respiratory depression, decrease gastrointestinal motility, cough suppression, suppression of corticotrophin-releasing factor and adenocorticotropin hormone and myosis. Using a partial agonist, like buprenorphine, will cause less mood alteration. Sigma receptors mediate dysphoria, hallucinations, and psychosis; delta receptor agonism results in euphoria, analgesia, and seizures. Pain release effect differs depending on the administration routes. Intra venous action takes few minutes, intra-nasally 10-15 minutes, intramuscularly 30-45 minutes, orally 90 minutes and two to four hours after dermal patches. Most common side-effects are: constipation, urinary retention, nausea, sedation, confusion, hallucination, sweating, xerostomia. The use of opioids may be associated with serious side effects that include: respiratory depression, seizures, hyperalgesia, myoclonus, delirium[35].

ALTERNATIVE TREATMENT

1. NATUROPATHY

The naturopathic approach is mainly to provide a good liver function.

A study made by the Institut of Perinatalogy in Mexico demonstrated the association between anti-oxydant and the pathology intensity. A group with anti-oxidant intake made from Vitamin C, E, Selenium and Zinc, was compared to a placebo group of women. No statistical difference was shown between those two groups, but when the data were stratified according to the pathology severity, it increases among lower anti-oxidant intake[36].

Chastberry increases progesterone effect from the ovaries. 1000 mg is recommended, taking daily in morning. It should not be added to the oral contraceptive pills, and is contra indicated during pregnancy.

Vitamin E may alleviate with dysmenorrhea. It can also decrease the menstrual flow. Dosage is 400 - 500 unit daily, two days before menstruation and continuing the first three days of bleeding.

Zinc tablet is common in Australia. It decreases pain but has many side effects (poor wound healing, poor appetite, lower immunity, acne, nausea, fatigue, it prevents body absorption of copper, manganese and molybdenum in food). Natural zinc is found in oyster, fish, nuts, dried peas and beans. Forty milligrams is used daily for the first month, for then being decreased to twenty milligrams.

Magnesium tablet, naturally present in green vegetables, whole grain food, nuts and seeds, also decreases pelvic pain. In tablet, 100 mg is taken every two hours for less than two days. Side effects include: diarrhoea and bowel cramps[37].

2. PHYSIOTHERAPY

There is a psychological component of pain that may create a negative circle. Pain leading to anxiety and depression, leads to

aggravating pain. Relaxation techniques and strengthening of pelvic floors muscles had shown positive feed back in women. Yoga will reduce dysmenorrhea by helping regulating the gate control pain mechanising in central nervous system by liberating endorphins. Reinforcing your pelvic floor will also help reducing dyspareunia[33].

3. TRANSCUTANEOUS ELECTRICAL NERVE STIMULATOR

Transcutaneous electrical nerve stimulator (TENS) is designed to send slow voltage electrical current trough electrodes placed on the skin. The current stimulates the myelinated fibers which inhibit the unmyelinated C fibers. This prevents delivery of the “pain message” to the T cell present in the dorsal horn of the spinal, which will not trigger the pain area in the thalamus. The dorsal horn of the spinal cord is presynaptically inhibited. They also stimulate the body to produce more endorphins, enkephalin and dynorphins, that are natural pain antagonist. The use of this machine can be ambulatory. Each patient will try different intensities and frequencies to best suppress the pain. Each patient should also try different electrodes positions. There are three standards settings. The conventional, the acupuncture and the pulsed. Each of them has different frequency, intensity and discharge moment. It is up to the patient to decide which treatment provides with best results. The conventional way can be used all day long but the pain will generally recur when the current is turned off. The acupuncture way can be more effective than the conventional in inhibiting the pain despite turning off the voltage but the tolerance is debatable. The most frequent adverse effect if skin irritation. Contraindications to TENS usage include: pacemaker and pregnancy. The overall pain relief is recorded to be up to 80 %, all indications mixed. This number drops to 20 % after few months of service making us believe that continuous nerve stimulation has a threshold[38].

4. ACUPUNCTURE

Acupuncture acts in many different ways. It activates endogenous descending pain inhibitory systems, deactivates brain areas that transmit pain related sensation, interacts between nociceptive impulses and somato-visceral reflexes, and induced the expectation of symptoms relief. We can it has physiological and psychological components. A meta-analysis that included three studies of 99 women diagnosed with endometriosis explored the positive effect of acupuncture in endometriosis related pain. Similar approach was used in all studies by: 7 to 12 needle insertions per subject/ session, and 15 to 25 minutes of needle retention time. The needles were placed in the lower back/ pelvic-abdominal area, in the shank, feet, and hands. The number of sessions varied from 9 to 16 with one to two treatments per week. In all three studies, patients rated their pain lower after acupuncture treatment[39].

5. DIET

Deficiencies in nutrients can cause lipid metabolism disorders, oxidative stress and epigenetic abnormalities. The big picture is to avoid processed food and promote organic food. In processed food, we do not no what substance might be present (pesticides, colorants, preservatives, acidulants, stabilisers), and most of them are inflammatory. Red meat contains estradiol and estrange sulcate. Those contributes to high level of steroid in the blood. Food rich in omega 3 has anti-inflammatory effects. Only few studies concern the nutritional aspect related to endometriosis, but diet education seems to be a promising tool against it[40]

6. HERBAL

Herbal medication is described to be useful in the relief of endometriotic pain. It is also difficult to apply outside the Traditional Chinese Medicine[41]. Even though, phytotherapy is one of the most

popular form of complementary and alternative medication in the United States[42].

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BIOGRAPHY

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After high school in Fontainebleau, she completed two years of medicine in Paris La Pitié Salpetrière, France. She was enrolled into University of Zagreb School of Medicine complete her curriculum.