Univerzita Karlova

1. lékařská fakulta

Studijní program: Psychologie

Studijní obor: Lékařská psychologie a psychopatologie

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Role endometriózy v rozvoji dyspareunie a algopareunie

The role of endometriosis in the development of dyspareunia and algopareunia

Typ závěrečné práce

Disertační

Vedoucí závěrečné práce/Školitel: Doc. MUDr. Jaroslav Zvěřina, CSc.

Praha, 2019

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Endometriosis is a very serious disease that affects up to 10-15% of women, according to statistics. The prevalence of fertility disorders is described in up to 40 % of cases, and in 50 % of cases, some form of dyspareunia or algopareunia is described. A very important factor is also the fact that from the onset of pain or the first difficulties to the diagnosis it usually takes 8 to 12 years, as was shown in some Anglo-Saxon studies (Moradi, 2014).

Endometriosis was first described almost 160 years ago (Von Rokytansky, 1860) and has been intensively studied ever since. However, despite being the most studied gynaecological disorder, the causes of endometriosis which is most commonly defined as a presence of endometrial tissue outside the uterus remain unsolved. Numerous hypotheses exist: embryonic stem cell origin, retrograde menstruation, implantation, genetic influences (Song and Lee, 2014), or coelomic metaplasia. None of these hypotheses have been fully confirmed (Kralickova et al., 2014), presenting the likelihood that endometriosis might be a result of some or even all these possibilities. Endometriosis is the leading cause of morbidity among premenopausal women (Baldi et al., 2008). This disease negatively affects 10–15 % of women in their reproductive age. Despite several available treatment options, no real cure exists (Kralickova et al., 2018).

Endometriosis is defined as the presence of endometrial cells outside the uterine cavity. (Kučera et al., 2011). Although reliable data on the incidence of the disease are not available; for comparison we can use data from DGGG (Deutsche Gesellschaft für Gynäkologie und Geburtshilfe, German Society for Gynecology and Genetics) which may be socio-demographically responsive to our circumstances. For example, only 40,000 new cases per year are estimated in neighbouring Germany (Chvátal and Fiala, 2016).

The average time from the first symptoms to the correct diagnosis usually takes about 11 years, which is alarming. The

incidence is growing steeply due to laparoscopy as a major diagnostic tool for endometriosis. However, we observe, even based on indirect evidence, an increase in heavy, infiltrative forms and the adenomyosis pandemic of young people. We can only speculate about the reasons. It is plausible to block uterine peristalsis by hormonal anticonceptions, the iatrogenic induction of dysperistalsis between archimetra and neometra, as was described previously in Leyendecker's theory (Leyendecker et al. 1998), and also the iatrogenic disturbance of the continuity of these layers by diagnostic and therapeutic operations, the increase of the number of caesarean sections, the constant shift of pregnancy to a higher age and, last but not least, the change of the social assignment of a woman in the western society (abandonment of the female archetype), characterized by cyclic hormonal secretion in favour of powerful, masculine, tonic one. In this spirit, it would be a civilization disorder that destroys the procreation ability of a person and thus threatens its existence.

The epidemiology of the disease, especially the rate of propagation, is not explained by standard linear reasoning in the sense of the cause and the result, and therefore we must admit also other theories, such as morphic resonance (Chvátal and Fiala, 2016).

In the case of endometriosis, it is a benign disease that can have a biological nature of malignancy because it metastasizes and infiltrates, furthermore, it is also pre-cancerous for ovarian and endometrial cancer.

Etiology and pathogenesis are not yet known, therefore there is no causal therapy. The underlying symptom is pain, however, endometriosis is often associated with primary or secondary sterility, and it plays a significant role in the development of female dyspareunia and algopareunia in sexology. It is an oestrogen-dependent disease which affects women of reproductive age. Exceptionally, it also occurs postmenopausal. In the body of a woman with endometriosis there are three sources of oestrogen production: ovarian, adipose tissue and skin, and also endometriosis itself. In addition to oestrogen overproduction, a woman with endometriosis has multiple oestrogen receptors. The relationship

between inflammation and oestrogen production was confirmed by a positive linkage where overexpression of COX-2 aromatase enzyme causes the local overproduction of oestradiol and prostaglandin E2 in endometrial tissue (Hrušková, 2011). In anamnesis, we concentrate on the three DYS, namely dysmenorrhoea, dyspareunia, and dyschezia.

Early menarche, shorter menstrual periods, and higher height are associated with a higher risk of endometriosis, while higher body mass index (BMI), and smoking are associated with a reduced risk. We often observe the cyclicality of issues related to menses, in some cases also pain in scars, or the presence of fresh blood in urine and faeces. Some patients have problems with sexual dysfunction, dyspareunia or algopareunia, sometimes accompanied by anorgasmia, in other cases with infertility. These difficulties have a social overlap; many partnerships are falling apart, although the pain in sex or the failure of orgasm are no longer a taboo topic as before.

Preliminary diagnosis of endometriosis is usually performed based on a clinical history. Most women show normal physical examination results. For gynaecologic examination, we usually find sensitivity in the palpation of the back fornix. Since pelvic pain is a symptom of other illnesses such as pelvic adenomas, adenomyosis and urological or digestive problems, a differential diagnosis is required in which these diagnoses should be excluded by performing appropriate diagnostic tests. Transvaginal ultrasound is used to better visualize the endometrium and uterine cavity and to detect endometrial ovarian cysts, however, it cannot exclude peritoneal endometriosis, small pelvis adherence, and deep infiltrating endometriosis.

From the viewpoint of investigation methods, it has to be noted that so far no specific laboratory marker has been identified to help to diagnose endometriosis. From the imaging methods, the sovereign method is vaginal or rectal ultrasound where their reading value is higher than CT or MRI (Fiala et al., 2018). We should not forget also the sonography of kidneys to eliminate hydronephrosis. Therefore

laparoscopy, which has also a high potential in rehabilitation, remains the basic diagnostic tool.

1.2 FSD - Female sexual disorders

1.2.1 FSD – Classification

Female sexual disorders include a variety of sexual difficulties affecting women of all ages, a persistent or recurring disorder of sexual interest/desire, insufficient subjective or genital arousal, difficulty in achieving orgasm, or pain and other sexual issues during the intercourse (Lue, 2004; Fisher, 2016). These issues bring reproductive, relational and interpersonal problems. Their exact etiopathogenesis is not usually obvious. Dyspareunia, or algopareunia, is defined as the persistent or recurring pain that occurs during or during vaginal penetration attempts.

Painful sexual intercourse affects the sexual intimacy within the partnership and interferes with emotional life of the partners. In most cases, it has its own biological base and may become an illness on its own. Pain is perceived as a complex experience, which involves both psychological and relational component. Chronic pain causes even more intense issues. Sexual pain should be seen as a multifactorial, multisystemic, and complex disorder.

In terms of the classification of female sexual disorders, it should be noted that in May 2013, the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) was presented, which significantly changed the original definition of female sexual disorders and significantly differed from older diagnostic criteria. DSM-5 is the US National Classification of Mental Disorders used by the American Psychiatric Society (APA) which is more detailed and specific than the International Classification of Diseases (ICD) (Fiala and Chvátal, 2017). It was originally developed for the needs of the

US Army when comparing psychiatric diagnoses and statistics. The World Health Organization (WHO) in 1992, in its 10th revision of the International Classification of Diseases (ICD-10), defined sexual disorders as several different problems in which individuals are unable to act sexually as they wish.

Categories included lack and loss of desire, sexual aversion, and lack of sexual enjoyment, also genital mutilation, orgasm dysfunction, non-organic vaginism, inorganic dyspareunia and excessive sexual appetite. In 1998, a group of experts from various medical disciplines agreed on the modifications and the previous classification was extended by the psychogenic and organic etiology of the disorders.

Changes in definitions and criteria of individual diagnoses have also been made. Emphasis was placed on the personal nature of the problems. The category of non-sexual sexual pain was also added.

This trend, which was a change from the linear to circular model, appeared in the DSM-5 version (2013). Disorders of sexual desire and excitement have been included in one category: Female sexual interest / arousal disorders. Sexual aversion has been excluded in the face of rare use and inadequate support within scientific research. Vaginism and dyspareunia have been grouped into the pain / discomfort category in the penile-genital pelvis area. All categories now require duration of issues for at least 6 months and set stricter criteria for distinguishing between temporary and persistent difficulties (Fiala and Chvátal, 2017).

1.2.2 FSFI - Rosen's questionnaire

The necessary part of the endometriosis test must be a qualified and internationally recognized questionnaire. One of the most well-known and most frequently used questionnaires is the Female Sexual Function Index (FSFI), a questionnaire for the evaluation of female sexual function (Rosen et al., 2000) that contains questions about excitement, desire, lubrication, orgasm, satisfaction and pain (Fiala and Chvátal, 2017).

The Rosen's questionnaire was confirmed on a clinically diagnosed sample of women originally with sexual arousal disorders, however, later was expanded to other symptoms. FSFI (Rosen et al., 2000) is a short, nineteen item self-regulatory measure of female sexual function that provides scores in the area of six domains of sexual function as well as the overall score. Scientists have established domains that are subsequently evaluated by individual patients using factor analysis. These include: desire (2 items), excitement (4 items), lubrication (4 items), orgasm (3 items), satisfaction (3 items) and pain (3 items). This questionnaire has expanded FSFI validation to include women with primary clinical diagnosis of female orgasmic disorder (FOD; n = 71) and hypoactive sexual desire disorder (HSDD; n = 44). The internal consistency and the different validity of the FSFI are considered within an acceptable range for these female populations. Significant differences among women with FOD and among women with HSDD, both with controls, were subsequently recorded for each FSFI domain and for overall score (Meston, 2003).

1.3 Immunological part of the study

In attempt to understand the nature of the onset and behaviour of endometriosis, a thorough analysis of the immune system was needed. Basic immunological functions, particularly nonspecific immunity, usually do not change in patients with endometriosis. On the other hand, other parts of immune reactions are known to be altered (Steele et al., 1984). In addition, direct damage of the immune system by irradiation resulted in increased prevalence of endometriosis and increased severity of the disease (Wood et al., 1983). This suggests that the normal immune system plays a significant role in blocking the development of endometriosis. Cells in the peritoneal cavity can initiate inflammatory response, helping vasodilation and increased permeability of blood vessels. The persistent nature of inflammation may contribute to initial endometrial growth and also to other medical problems that patients with endometriosis commonly suffer (Králíčková et al., 2018).

1.3.1 Macrophages

Macrophages represent the primary defence cells in our body. As they reside in the peritoneal cavity, their defensive role is manifested mainly via phagocytosis and support of cytokine secretion. Phagocytosis evolved from feeding to eliminating pathogen invasion and cellular debris. Phagocytosis is, among other factors, regulated through activation of matrix metalloproteinases and expression of CD36 receptors. Expression of these components is reduced in endometriosis (De Villiers et al., 1994; Wu et al., 2005), most likely by changes in prostaglandin E2 levels (Wu et al., 2005).

1.3.2 Lymphocytes

Lymphocytes localized inside the ectopic tissue significantly contribute to lesion growth, mostly by low ratios of Th1 to Th2 cells (Takamura et al., 2015) and by absence of natural killer (NK) cells (Jones et al., 1998). The Th1-Th2 ratio depends on stage. Once the endometriotic foci are established, the strict interaction between endometriotic and immune cells addresses toward a prevalence of Th1 cytokines in the peritoneal fluid at minimal and mild stages, whereas Th2 cytokines prevailed in severe stages (Andreoli et al., 2011; Kralickova and Vetvicka, 2015). Determination of various T and B lymphocyte subpopulations in blood and peritoneal fluid found no differences between control group and patients (Hassa et al., 2009).

1.3.3 Granular lymphocytes

NK cells are large granular lymphocytes representing approximately 10% of peripheral blood lymphocytes and represent an important component of innate immunity. As endometrial cells mimic cancer cells in their ability to adhere, infiltrate, and proliferate at ectopic locations, NK cells are often suggested to be involved. Increased KIR+ NK cells in peripheral blood may represent a risk factor for endometriosis (Maeda et al., 2002). An increased number and activation of peritoneal macrophages, and decreased T cell and NK cell cytotoxic effects observed in endometriosis (Herington et al., 2011) represent significant changes in cellular immunity. This might result in inadequate removal of ectopic endometrial cells from the peritoneal cavity. Some studies even suggest that NK cells are key

players in endometriosis; for review, see Thiruchelvam et al. (2015). Activated NK cells can migrate and infiltrate endometriotic lesions, suggesting the potential use in treatment of this disease (Montenegro et al., 2015).

1.3.4 Cytokines

Cytokines represent the key mediators of intracellular communication in both healthy and unhealthy individuals. Cytokines are important for cooperation between immune and endocrine systems. Peritoneal cytokines, which are produced by mesothelial cells, leukocytes, and ectopic endometrial cells, interwork locally and systemically in women with endometriosis (Wu et al., 2003). Increased levels of several cytokines which are secreted by immune or endometrial cells and growth factors seem to promote implantation and growth of ectopic endometrium via induction of proliferation and angiogenesis. It is known that COX-2 and IL-1β can regulate the invasion of ectopic EN-MSCs. In the future, these effects might be utilized in developing a new therapeutic strategy for endometriosis. Better characterization of EN-MSCs will need an ex vivo invasion model (Kao et al., 2011).

1.3.5 Florid inflammation

Following the florid inflammation associated with menstruation, endometrium shows strong regenerative capacity. For details on inflammatory processes possibly influencing development of endometriosis, see Maybin et al. (2011). Endometriosis is usually

characterized by a chronic inflammatory state, which leads to the release of several cytokines. Initial inflammatory response occurs via increased influx of cells. The subsequent acute inflammation involves local vasculature, somatic cells, and immunocytes. Numerous studies document an increased level of inflammatory cytokines in peritoneum. Similarly, with many changes of immune parameters in endometriosis, even now we are not sure whether these inflammatory conditions represent cause or consequence. Mouse studies reveal that induction of endometriosis in an already inflamed peritoneum decreased endometriosis, suggesting that the second option is more probable (Nowak et al., 2008). Anti-inflammatory drugs helped ameliorate numerous symptoms (Vignali et al., 2002) connected with endometriosis probably via growth inhibition of endometriotic implants. This suggests the involvement of inflammatory activity. However, no mechanisms or direct proof was described (Olovsson, 2011).

1.3.6 Autoimmunity

Some studies showed increased levels of autoantibodies in endometriosis (Taylor et al., 1991; Eisenberg et al., 2012). Some of these antibodies are organ-specific, probably a result of an excess of endometrial antigens triggering immunological tolerance. Most of these autoantibodies were directed against endometrial antigens, so they might be the result and not the cause of the disease.

A detailed study showed that most of these autoantibodies are directed against carbohydrate epitopes, which led to several hypotheses about the involvement of autoantibodies in endometriosis (Osuga et al., 2011), mostly by aberrant matrix metalloproteinase function or genetic defects in glycosylation (Dmowski et al., 1981).

Based on these results, a link between endometriosis and autoimmunity has been suggested. One of the first observations was the similarity in symptoms between patients with systemic lupus erythematosus and endometriosis (Pasoto et al., 2005). A subsequent study of over 37,000 women with endometriosis found an increased risk for lupus, scleroderma, and multiple sclerosis (Nielsen et al., 2011).

In theory, endometriosis fulfils most of the criteria commonly used for definition of autoimmune diseases: immunologically abnormal functions of T and B lymphocytes, polyclonal activation of B lymphocytes, elevated apoptosis, and multi-organ involvement. Numerous studies trying to find an association with HLA antigen described interesting results without reaching any definitive conclusions (Eisenberg et al., 2012).

Several methods used for the treatment of autoimmune diseases were also suggested for the treatment of endometriosis; so far, the results are disappointing. In addition, some later findings did not confirm this option (Matorras et al., 2007).

1.3.7 Other parts of the immune system

Relatively less studied parts of the defence reactions that can participate in endometriosis is the lymphatic system. Lymphangiogenic growth factor and receptor expression along with vascular density is changed in endometriosis (Takehara et al., 2004), a support for the entry of endometrial tissue. The presence of endometriotic lesions in some pelvic lymph nodes indicated insufficient clearance of endometrial cells. It is therefore possible that specific inhibition of lymphangiogenesis in endometriotic lesions may provide a new approach to treatment (Kralíčková et al., 2018).

A compelling approach studied immune gene expression in patients with benign endometriosis, atypical endometriosis, and

endometriosis-associated ovarian cancer. The first group showed mixed profile but the second group showed over 85% of patients having a cancer-like immune environment. Surprisingly, the most changed expression was of complement (Edwards et al., 2015). This study suggested that the link between endometriosis and ovarian cancer might be stronger than originally expected. Some experiments suggested potential involvement of mast cells. Mast cells are an important, albeit rather overlooked part of defence reactions. Mast cell progenitors are recruited upon start of inflammation and after differentiation, thus further initiating and shaping inflammation via their response to the different stimuli by the IgG-dependent pathway. These events result in secretion of Th2 cytokines such as IL-4, IL-5, and IL-13, some of which were found to be elevated in patients with endometriosis. Individual mast cells, however, are rather scarce in the endometrium. Animal models showed infiltration of peritoneal stromal tissue by mast cells (Uchiide et al., 2002).

1.4 Conclusions

Endometriosis is a serious disease with unclear causes. Lately, numerous studies suggest the significant role of both endocrine and immune dysregulations, which further underlines the complexity of this gynaecologic disorder. Despite intensive research and interesting advances, it is still unclear if the changes in various immune parameters found in women suffering from endometriosis are the cause of the disease or body's reaction to the disease. Data presented in our review showed changes in leukocyte numbers and activities within the endometrium and peritoneal cavity without allowing us to reach a clear conclusion.

As endometriosis is an oestrogen-dependent inflammatory disease, immune-endocrine interactions might be involved; for review see Cakmak et al. (2009). Oestrogens are known to influence numerous signalling pathways (including MAPK and NF-B) which are involved in endometrial cell properties and behaviour. Clearly, further research into a possible role of the endocrine-immunologic axis is necessary (Králíčková et al., 2018).

2 EMPIRICAL RESEARCH

2.1 Initial examination of patients

During our first part of the research, 50 outpatient patients (Mean age = 32.78; SD = 4.36; age range: 26-44) with diagnosed endometriosis cooperated with the Institute of Sexology, First Faculty of Medicine of the Charles University in Prague and with the General University Hospital in Prague, Czech Republic (Fiala et al., 2018).

For all patients, age, year of first menstrual period, menstrual cycle, eventual painful menstruation, smoking, and alcohol use were reported (Figure 1).

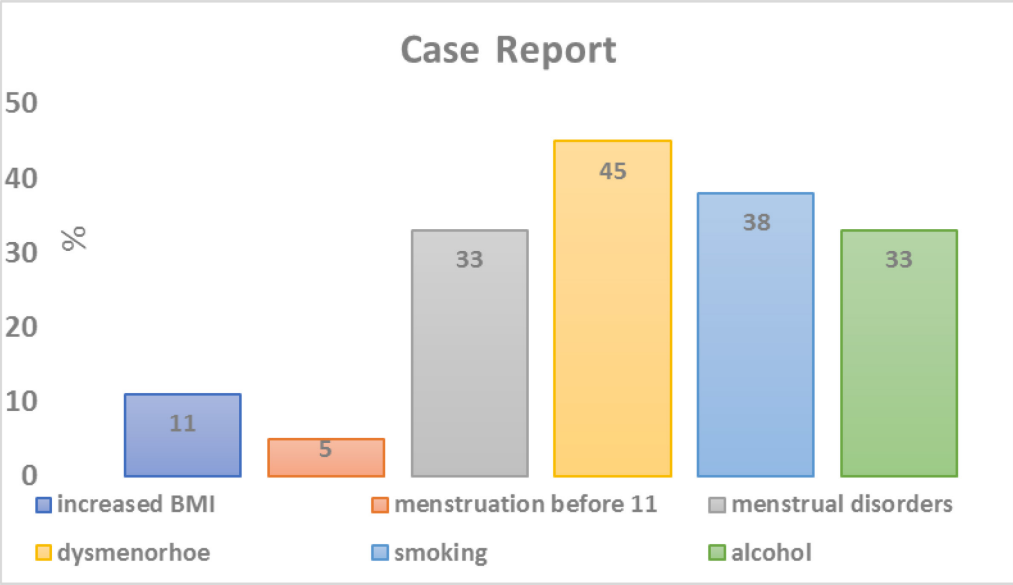

Figure 1. Case Report

In addition, women underwent complete gynaecological examination – cultures, two samples from a cervix in oncological cytology were taken, and the colposcopy was performed. All patients had, sometimes repeated, sonographic examination of the small pelvis or abdominal cavity, and 35 of them had one or more

laparoscopic procedures, as will be discussed in the next part of this paper. Subsequent examinations in patients were focused on the hormonal profile. From the second to third day of the cycle were taken also FSH, LH, and prolactin, and oestradiol in the follicular phase, residual progesterone, DHEA-S, morning cortisol and TSH. The on-line markers CA-125 and CA-19-9 were taken simultaneously. All values, both within range and outside of the physiological ranges for laboratory tests, were statistically processed, which will be discussed later in following chapters.

2.2 Oncomarkers and hormones used for diagnosis of endometriosis

The endometrium is a mucosal tissue comprising epithelial lined glands and a substantial vascularised supporting stroma which is functionally androgen related and plays an important role in regulation of women's fertility and menstrual cycle (Cloke and Christian, 2011; Simitsidellis et al., 2017). The endometrial tissue creates the uterine lining and its pathology may lead to endometriosis when the tissue is present in other parts of the body mainly within the peritoneal cavity at lower abdomen or pelvis (Cloke and Christian, 2011; Simitsidellis et al., 2017). Recent findings suggest that androgens might play an important role in endometrium related pathology which is closely linked to disrupted androgen biosynthesis and associated regulatory functions (Simitsidellis et al., 2017). These findings also indicate that androgens may play a role in hormone-dependent cancer pathology and these studies suggest a link between risk of endometrial cancer and androgen functions (Gibson et al., 2014; Barry et al., 2014; Ito et al., 2017; Simitsidellis et al., 2017).

The clinical investigations were focused on biochemical serum analysis of dehydroepiandrosterone sulphate (DHEA-S), oncological markers CA-125 and CA 19-9, oestradiol, thyrotrophic hormone and prolactin.

2.2.1 Dehydroepiandrosterone sulphate (DHEA-S)

DHEA-S is an androgenic hormone that plays a very important role in male development but is present in both men and women. DHEA-S can be metabolized in the body to other androgens such as testosterone and androstenedione or can be converted into female hormones oestrogen. DHEA-S is produced mainly from the adrenal cortex reticular zone, partially is produced in male testicles, and in the pathophysiological conditions also in female ovaries. Hormone values are high after birth and in childhood rapidly decrease until the age of 30 years (Rizner, 2016).

2.2.2 CA-125

CA- 125 is a glycoprotein with a high carbohydrate component and its molecular weight is at about 200 kDa. CA-125 is produced in the foetal period by epithelial tissues and in adulthood it may occur in the normal epithelium of the fallopian tubes, cervix or bronchus. CA-125 is particularly important as a marker of serosa membrane carcinomas and undifferentiated ovarian carcinomas and its serum concentrations may reflect tumour size (Hirsch et al., 2017).

2.2.3 CA-19-9

CA 19-9 is a penta-saccharide with carbohydrate component containing fructose components and it belongs to a group of oncofoetal antigens. In the foetal period, it is synthesized in the epithelial structures of the stomach and in adulthood its production is significantly decreased. In addition, recent findings show that CA 19-9 may be produced in glandular structures of the gall bladder, pancreas, bronchus and some gynaecological tumours. Some studies show that CA-19-9 may be demonstrably elevated in endometriosis and exhibit the same or decreased sensitivity as CA – 125 (Fassbender, et al., 2015).

2.2.4 Prolactin

Prolactin is a non-steroidal hormone of adenohypophysis whose production is primarily inhibited by dopamine, which acts as a CNS transmitter; however, the dopamine receptors are also present on the periphery. Dopamine released from the neuron may encounter different types of dopamine receptors, all of which are associated with G-proteins. We can distinguish a group of D1 receptors, with subtypes D1 and D5, and a group of D2 receptors with D2, D3 and D4 subtypes. Different subtypes activate different signal transduction paths. Stimulation of PRL in the CNS is mainly related to the production of thyroliberin and vasoactive intestinal peptide. Its secretion is pulse but with longer intervals than, for example, FSH or LH (Fiala, 2018). The main function of prolactin is the preparation, progress and termination of lactation in women. The onset of lactation depends on the decrease in placental steroid hormones

during the third stage of labour, with the result that only prolactin elevation is insufficient to induce lactation (Fölsch, et al., 2000).

2.2.5 Thyrotrophic hormone (TSH)

Thyrotrophic hormone, also called thyrotropin (TSH), is a glycoprotein composed of 201 amino acids. It stimulates the synthesis and release of thyroid hormone thyroid hormones and triiodothyronine by increasing circulation and metabolism of the thyroid gland. It is produced by thyrotrophic cells of adenohypophysis.

2.2.6 Oestradiol

Oestradiol, together with oestriol and oestrone, is another of the female sex hormones of oestrogens. Oestradiol is synthesized from testosterone by enzymes. It is a process of steroidogenesis in the yellow body of the ovaries. During pregnancy it is produced by a placenta. A small amount is also produced by the liver and adrenal glands, which is especially important in postmenopausal women. Oestradiol is the predominant oestrogen in women from the first menstruation to the menopause. After this period, the oestrone, which has weaker effects, predominates.

2.2.7 Progesterone

Progesterone is a steroid female sex hormone that is ranked among the progestins. It is a 21-carbon steroid hormone that is made mainly in the yellow body of the ovaries. During pregnancy, progesterone is also produced by the placenta; it is also produced in a small amount in the adrenal cortex, in men also in the testicles. In the climacteric period, the progesterone production decreases. Progesterone induces the secretory phase of the menstrual cycle, supporting growth of the uterine mucosa after ovulation. If there is no fertilization of the egg, hormone production will cease, and menstrual bleeding will occur. When a woman becomes pregnant, progesterone stops the menstrual cycle, induces the development of the mammary gland, increases the amount of mucus in the uterine throat and decreases premature contractions of the uterus. Unlike oestrogen, it does not affect the creation of sex during the foetal development.

2.2.8 Cortisol

Cortisol is the most effective hormone in the group of glucocorticoids produced by the adrenal cortex. Cortisol production is strongly stimulated by adrenocorticotropic hormone (ACTH), which is derived from adenohypophysis. In addition, ACTH also has pronounced trophic effects on the adrenal cortex, most notably on the zona fasciculata. Cortisol increases the overall alertness of the organism in stressful situations such as stress, infection, physical exertion or long-term starvation. Its effect on metabolism can be described as catabolic, anti-anabolic and diabetogenic. In the liver,

however, the effect is anabolic. Cortisol is involved in the conversion of all essential nutrients.

2.3 Clinical application

There are some controversial findings suggesting that dehydroepiandrosterone sulphate (DHEA-S) is associated (Audet-Walsh et al., 2011) or not associated (Allen et al., 2008) with increased risk of the endometrial cancer. Recent data indicate that CA-125 and CA 19-9 molecules represent important markers of endometrial and cancer pathology (Socolov et al., 2017; Hirsch et al., 2017).

To test the above hypothesis, we have assessed 50 female outpatients mean age (32.78±4.36), age range (26-44) with endometriosis that were treated at the Institute of Sexology of the Charles University Hospital in Prague. All women included in this study had dyspareunia, pelvic pain, orgasm disorders, lubrication disorders and irregular and painful bleeding. Most women had pains during the menstrual and non-menstrual stages; other reported symptoms were fatigue, difficulty sleeping, painful sex, and partner relationship disturbances. All participants provided written informed consent and the study was approved by University Hospital ethical committee. Exclusion criteria were gravidity, oncological diseases, urological disorders, intestinal diseases and metabolic disorders.

2.3.1.1 Statistical methods

Statistical evaluation of the individual hormones, namely prolactin, TSH, cortisol, DHEA-S, oestradiol and CA-125, CA-19-9, included descriptive statistics and Spearman's correlation coefficients, which were subsequently confirmed by the Mann-Whitney test. All methods of statistical evaluation were performed using the statistical software Statistica, version 6.

2.3.2 Results

Nevertheless, according to the recent literature there is no evidence about relationships of DHEA-S with CA-125 and CA 19-9 as indicators of endometrial and cancer pathology.

The clinical investigations were focused on biochemical serum analysis of dehydroepiandrosterone sulphate, oncological markers CA-125 and CA 19-9, oestradiol, thyrotrophic hormone and prolactin (Fiala, 2018).

The results show significant Spearman correlations of CA-125 and CA-19-9 with dehydroepiandrosterone sulphate (R=0.52 resp. R=0.49, Figure 2). This finding represents first reported evidence documenting increased androgen levels as significant markers of endometrium pathology. Results of the Mann-Whitney test for the subgroups lower or higher than median DHEA-S are in agreement with these correlations (Z=-2.259, p=0.024 for CA-125 and Z=-2.529, p=0.011 for CA-19-9).

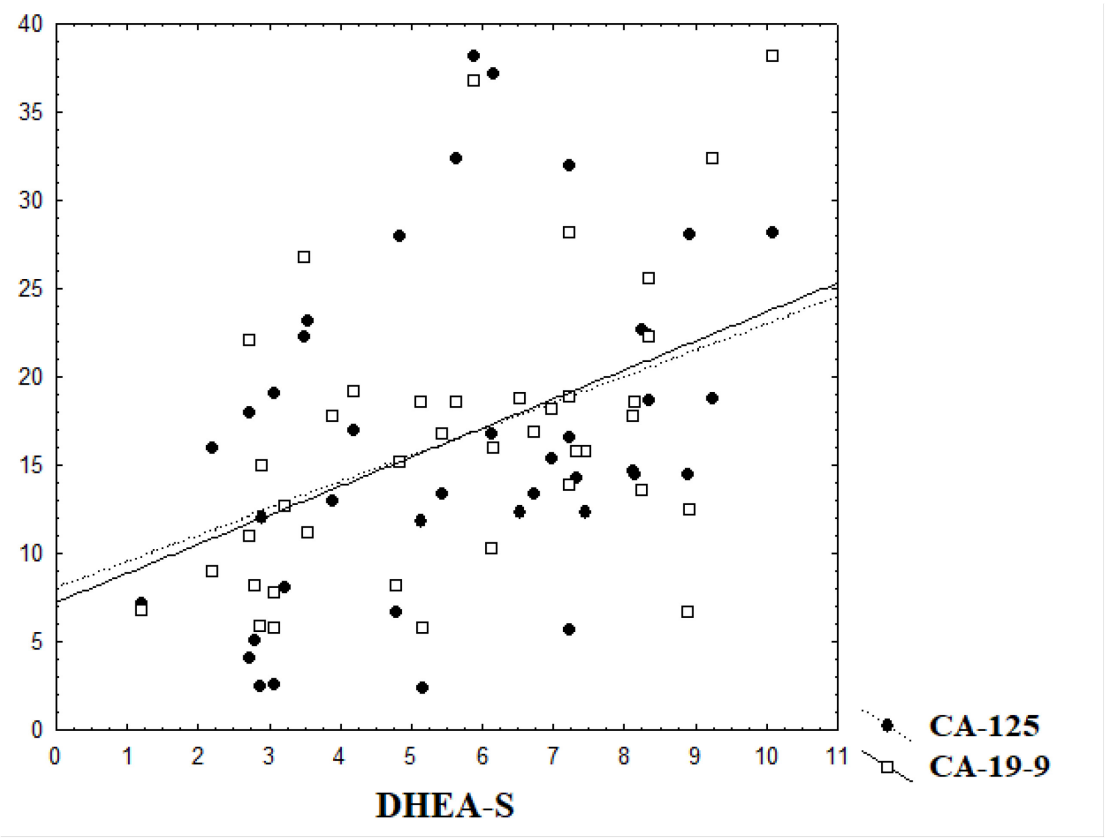

Figure 2. Dependence of DHEA-S, CA- 125, and CA-19-9

2.4 Endometriosis and stress and somatoform disorders

In contrast to Rosen's questionnaire which focuses solely on individual symptoms and perception of dyspareunia and algopareunia, such as disturbance of excitement, desire, lubrication, orgasm, satisfaction, and pain, in aim to prove the deeper connection between endometriosis and the impact of this disease on the woman's own sexual experience, with subsequent impact on the partnership relationship, other questionnaires should be used. For further research, standardized TSC-40 and SDQ-20 questionnaires focused on stress, trauma and somatoform symptoms were used (Fiala and Bob, accepted). Painful sexual intercourse and also other

symptoms and negative experiences that can accompany it, affect the sexual intimacy of the partnership and interfere with the emotional life of the partners. And because painful intercourse can very often have its own biological basis, it often becomes a disease itself. Pain is then perceived as a complex experience, which includes the psychological and relational component. In the context of chronicity, it becomes even more intensive and disturbing (Fiala and Chvátal, 2017).

2.4.1 TSC-40 - Trauma Symptoms Checklist

Symptoms of traumatic stress in endometriosis were evaluated using Trauma Symptom Checklist (Briere, 1996). The TSC-40 is a questionnaire with 40 questions that are recorded on the Likert 4-point scale - the total score is from 0 to 120. Using the TSC-40 we evaluate the symptoms of adult stress associated with traumatic experiences and aspects of post-traumatic stress found in some traumatized individuals. The list of questions includes subgroups for depression, anxiety, dissociation, sexual abuse trauma index (SATI), difficulty sleeping and sexual problems. The TSC-40 in the Czech version is a highly reliable test.

2.4.2 SDQ-20 - Somatoform Dissociation Questionnaire

Somatoform dissociative symptoms in patients with endometriosis were measured using 20 questions in the Somatoform Dissociation Questionnaire (SDQ-20) (Nijenhuis, 1996). Somatoform dissociative symptoms are changes in attitude to feelings of pain, changes in

perception, loss of control, gastrointestinal symptoms, etc. Normative weight score defines a significant incidence of somatoform dissociative symptoms for a score higher than 30. The subjects that fill in the questionnaire indicate the level of their experience with the Likert 5-point scale.

2.4.3 Participants and methods

To test the above hypothesis, we have assessed 55 female outpatients mean age (32.78±4.36), age range (26-44) with endometriosis that were treated at the Institute of Sexology of the Charles University Hospital in Prague. All women included in this study had dyspareunia, pelvic pain, orgasm disorders, lubrication disorders, and irregular and painful bleeding. Most women had pain during the menstrual and non-menstrual stages; other reported symptoms were fatigue, difficulty sleeping, painful sex, and partner relationship disturbances. All participants provided written informed consent and the study was approved by University Hospital ethical committee. Exclusion criteria were gravidity, oncological diseases, urological disorders, intestinal diseases, and metabolic disorders.

The clinical investigations focused on biochemical serum analyses on biochemical serum analyses of oncological markers CA-125 and CA 19-9, oestradiol, prolactin and cortisol. CA 125 is a glycoprotein with a high carbohydrate component and its molecular weight is at about 200 kDa. CA 125 is produced in the foetal period by epithelial tissues and in adulthood it may occur in the normal epithelium of the fallopian tubes, cervix or bronchus. CA 125 is particularly important as a marker of serosa membrane carcinomas and undifferentiated ovarian carcinomas and its serum concentrations may reflect tumour size (Hirsch et al., 2017). CA 19-9 is a penta-saccharide with carbohydrate component containing

fructose components and it belongs to a group of oncofoetal antigens. In the foetal period, it is synthesized in the epithelial structures of the stomach and in adulthood its production is significantly decreased. In addition, recent findings show that CA 19-9 may be produced in glandular structures of the gall bladder, pancreas, bronchus and some gynaecological tumours (Fassbender et al., 2015). Some studies show that CA-19-9 may be prominently elevated in endometriosis and exhibit the same or decreased sensitivity as CA – 125 (Fassbender et al., 2015).

2.4.3.1 Statistical methods

In this study, oncomarkers (CA-125 and CA-19-9), hormones (prolactin, oestradiol, and cortisol), and questionnaires (Rosen, TSC-40 and SDQ-20) were statistically processed and the results included descriptive statistics and Spearman's correlation coefficients. All methods of statistical evaluation were done using the software Statistica, version 6.

2.4.4 Results

The results had shown significant Spearman correlations of TSC-40 with CA-125 and CA-19-9 (R=0.52, resp. R=0.30, Figure 3) and correlations of SDQ-20 with CA-125 and CA-19-9 (R=0.53, resp. R=0.31, Figure 4). Other correlations, with exception of correlation between CA-125 and CA-19-9 (R=0.60), were not statistically significant.

These results represent findings documenting relationship of CA-125 and CA-19-9 with stress related psychopathological symptoms suggesting influence of stress on endometrium pathology.

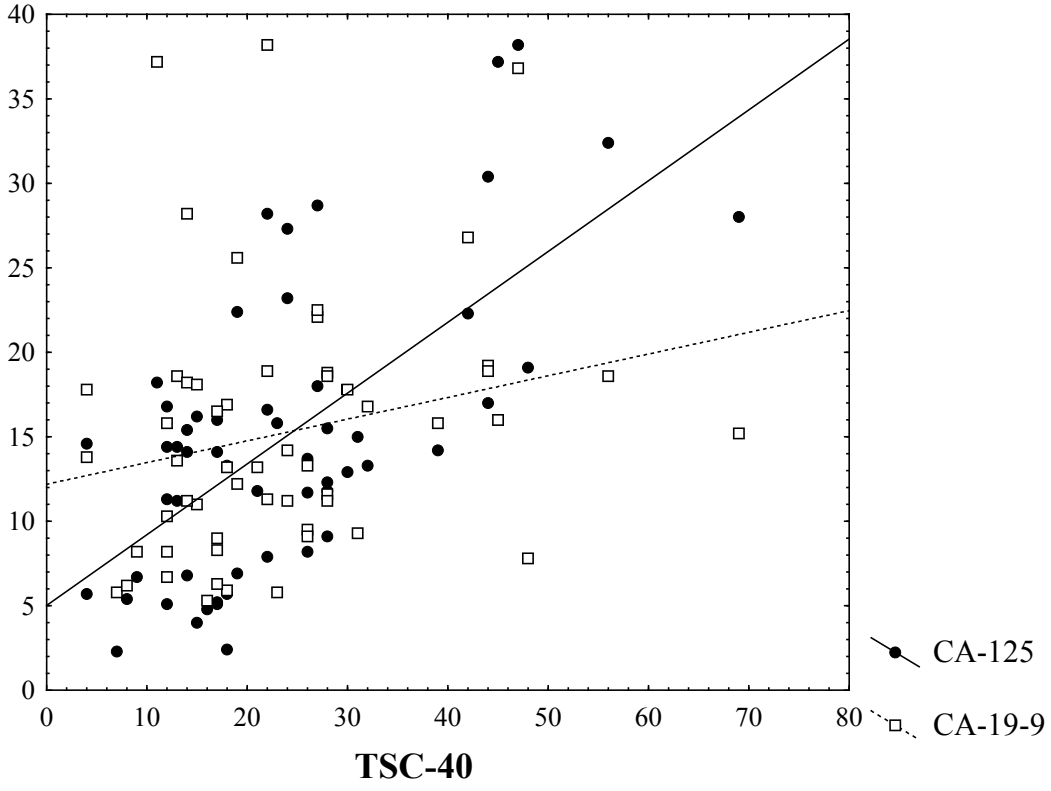

Figure 3. Relationship of TSC-40 with CA- 125 and CA-19-9

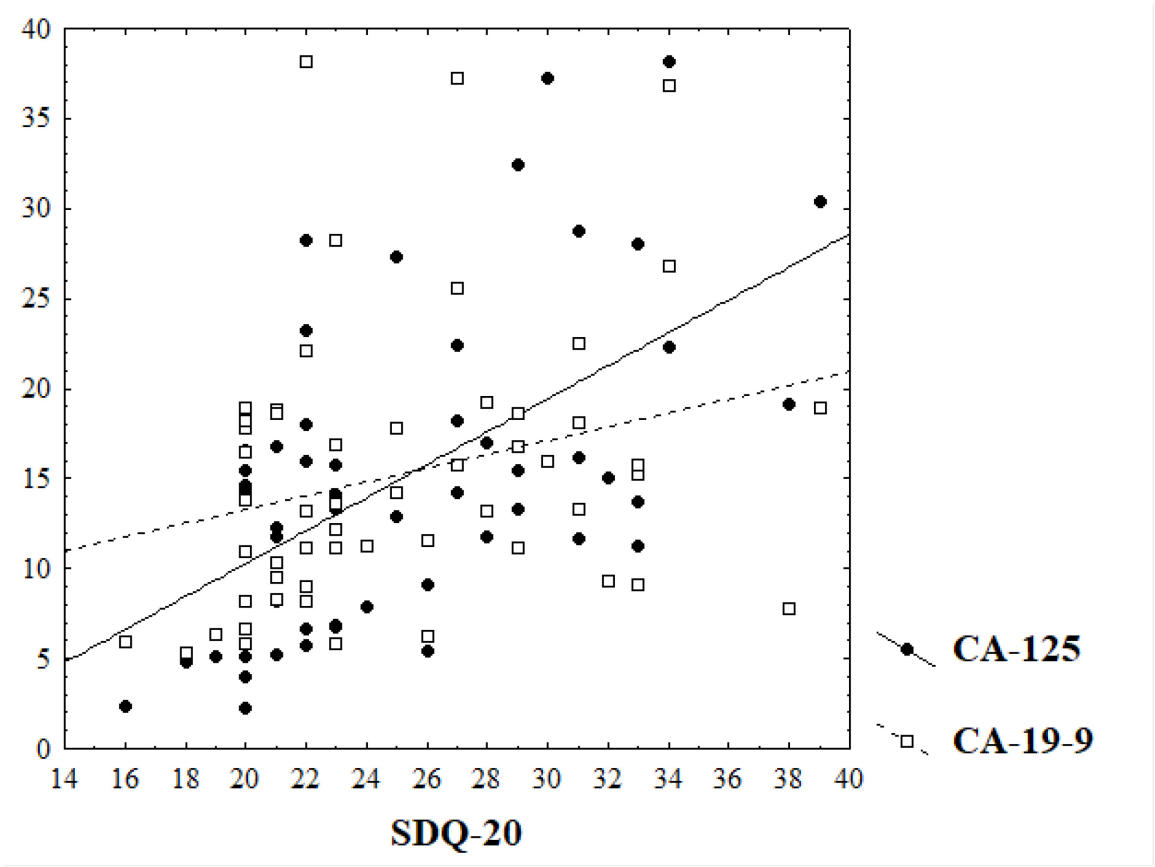

Figure 4. Relationship of SDQ-20 with CA- 125 and CA-19-9

2.5 Endometriosis therapy

Early diagnosis of endometriosis, as well as the impact of this disease on the individual psyche and on the psyche of the partnership, is very important from a medical point of view. Equally important is also the treatment of women experiencing this disease.

2.5.1 Options of conservative treatment

1) In general, a doctor usually recommends a conservative treatment approach first (Chvátal and Fiala, 2016). If we find that painkillers (such as non-steroidal anti-inflammatory drugs) are not effective, some of the hormonal therapies begin. Ectopic endometrium increases the production of prostaglandins which has to be suppressed. Nonsteroidal anti-rheumatic drugs (COX-2 inhibitors, coxibs) reduce and suppress pain in endometriosis; therefore, they are often the primary, but usually temporary, treatment for endometriosis.

2) Hormonal contraception can reduce or eliminate pain especially during menstruation (dysmenorrhoea) – it is best for continuous treatment with conventional contraceptives, possibly with contraception plasters or with the NuvaRing vaginal ring, but some preparations do not always fully meet the criteria for endometriosis treatment.

3) GnRH (antagonist hormone releasing gonadotropin) – suppression of subjective problems, reduction of endometriosis deposits (climacteric disorder, acne, weight gain, unusual bleeding, etc.) – e.g. ganirelix acetate.

4) Gonadoliberin agonist - suppression of subjective problems, reduction of endometriosis deposits (side effects - depression,

migraine, climacteric disorder, loss of bone mass) - Zoladex (goserelin acetate).

5) Gestagen therapy is based on one-component hormonal treatment. The first-choice medicine is Visanne (2 mg dienogestum), however, there is no reported experience with treatment longer than 15 months. Other commonly used preparations are Mirena (levonorgestrel) or Depo-Provera (medroxyprogesterone acetate). Stopping the menstrual cycle is part of therapy; the main effect of treatment is the elimination of pain during menstruation.

6) Synthetic androgens - originally first-line drugs in the 1970s, despite several unpleasant side effects, however, their use was significantly reduced in the 80s and 90s with simultaneous increase of the use of GnRH (Shaw, 2005).

7) Selective oestrogen receptor modulators (SERM), so-called synthetic non-steroidal anti-oestrogens – e.g., Nolvadex (tamoxifen citrate).

8) Aromatase inhibitors - pilot project (2004) which was based on the oral use of letrozole (2.5 mg / day for 6 months), there was a significant reduction in painful symptoms and regression of the deposits in second-look laparoscopy. The undesirable effects of the drug are mild headache, nausea, and diarrhoea.

9) Selective progesterone receptor modulators (SPRMs) including antagonists - the synthetic steroid mifepristone (known as the chemoreceptor abortive), is a progesterone antagonist that occupies progesterone receptors.

10) At the stage of experimental treatment, the use of angiostatins to affect vascular supply in the endometrium is primarily used in oncology treatment (Javaherian, 2011).

11) Similarly, inhibitors of matrix metalloproteinases are used experimentally. It is a group of enzymes capable of cleaving most of the intercellular matrix components. They are regulated at the level of transcription, translation, or the presence of natural inhibitors (Franková et al., 2000).

2.5.1.1 *Results of conservative treatment*

Scores for FSFI domains shown that after the six months treatment of Visanne, the domain scores for all domains increased compare to the scores obtained prior the treatment (Fiala et al., 2018). Comparison of results before and after six months treatment is shown in Figure 5 and Figure 6, respectively. Despite the six months of treatment, there is still a lower level in the domain of orgasm, and also persistent pain (Figure 6). Therefore, it is necessary to consider (in some cases) also the surgical solution of dyspareunia, caused by endometriosis.

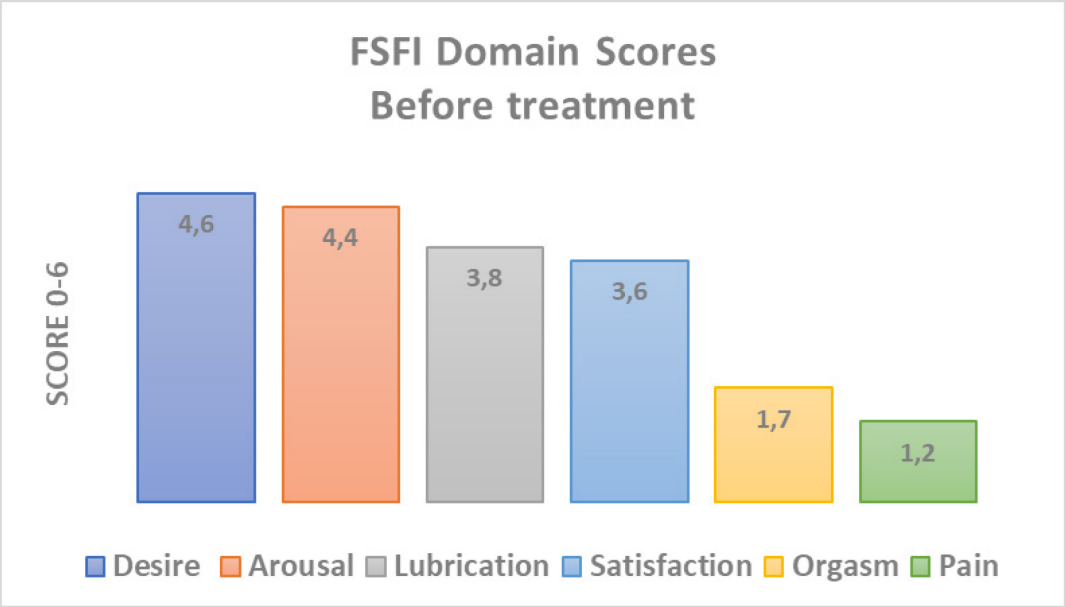

Figure 5. FSFI Domain Scores before treatment

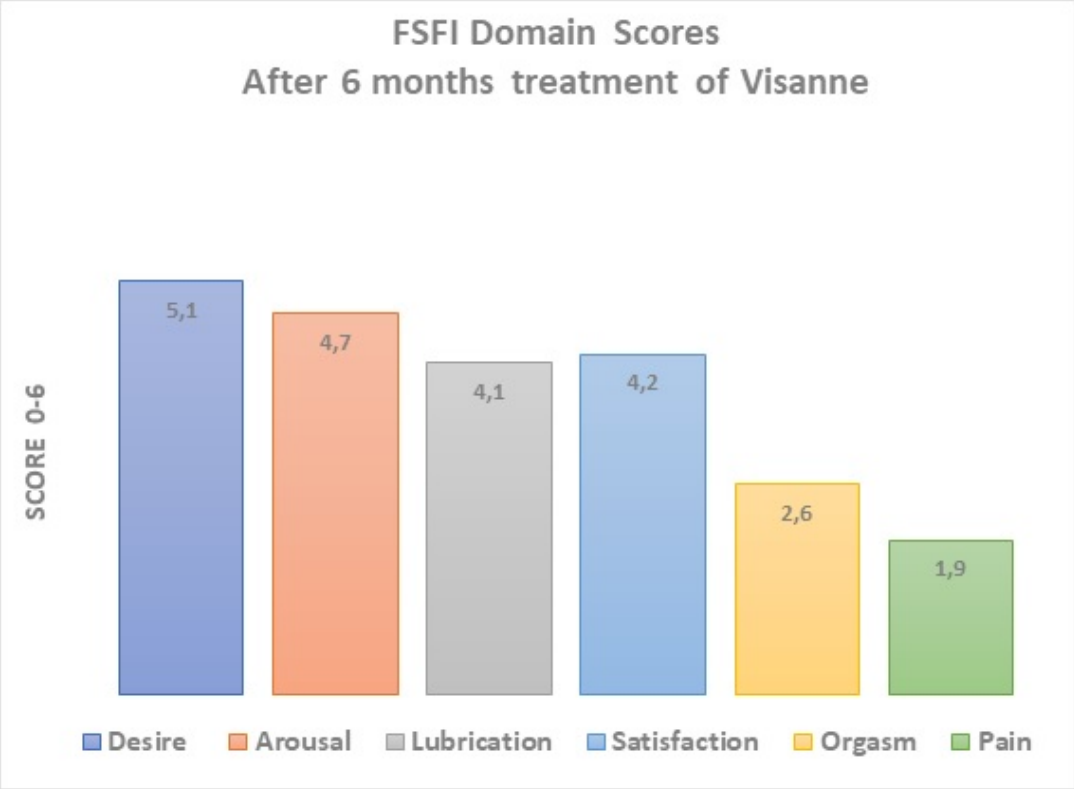

Figure 6. FSFI Domain Scores – After 6 months treatment of Visanne

2.5.2 Possibilities of surgical treatment

Surgical treatment (Figure 7) is of the resection type, so that we can reach a compromise on the degree of resection and organ preservation, fertility. The surgical procedures are defined, and the goal is a certain unification of procedures, again analogous to oncological surgery. In peritoneal forms, we do not suffice with the destruction of the deposits by coagulation; the correct procedure is deperitonealisation with free margin.

Ovarian deep endometriosis is treated only from a certain size that has been exhaustively determined to 5 cm. This border is free, it is pseudocysts, invagination, we choose an adequate technique of "cold" resection, e.g., enucleation with minimal use of coagulation tools, especially avoiding monopolar coagulation. With each surgery on the ovary, its follicular capacity decreases.

Endometriomas can be resected with respect to their anatomical localization. These are very demanding surgical procedures, where we always try to preserve the utmost nerve structure, ureter, and rectum.

Rectosigmoid excision is the only extreme variant in the case of obstructive penetrating endometriosis. This also applies to the back wall of the vaginal bladder. However, if we have clear evidence of a penetrating, destructive illness, then we do not hesitate to resect because it is the only way to get rid of the difficulties. Detection of penetrating disease of the rectosigmoid is often not easy, proctoscopy is not a suitable tool because colonoscopy may be false negative or impossible for adhesion.

It is not necessary to emphasize that these are multidisciplinary surgical procedures where the cooperation of gynaecologist, surgeon and urologist is the only way to success. It is good to send patients to centres where they have experience with such surgery; there is nothing more frustrating for the patient than the announcement that the surgery of endometriosis of the rectovaginal septum is

dangerous and therefore was not performed. Each surgical procedure is subject to acute and chronic post-operative morbidity.

Very unpleasant are partial denervation of urinary bladder or rectum, especially in cases where the required resection does not respect the organ contour, then we try to limit it to one side only if the anatomical pathological situation allows it. The rate of recidivism is about 20%, the age factor and, of course, the biological nature, which we cannot yet judge, is relevant.

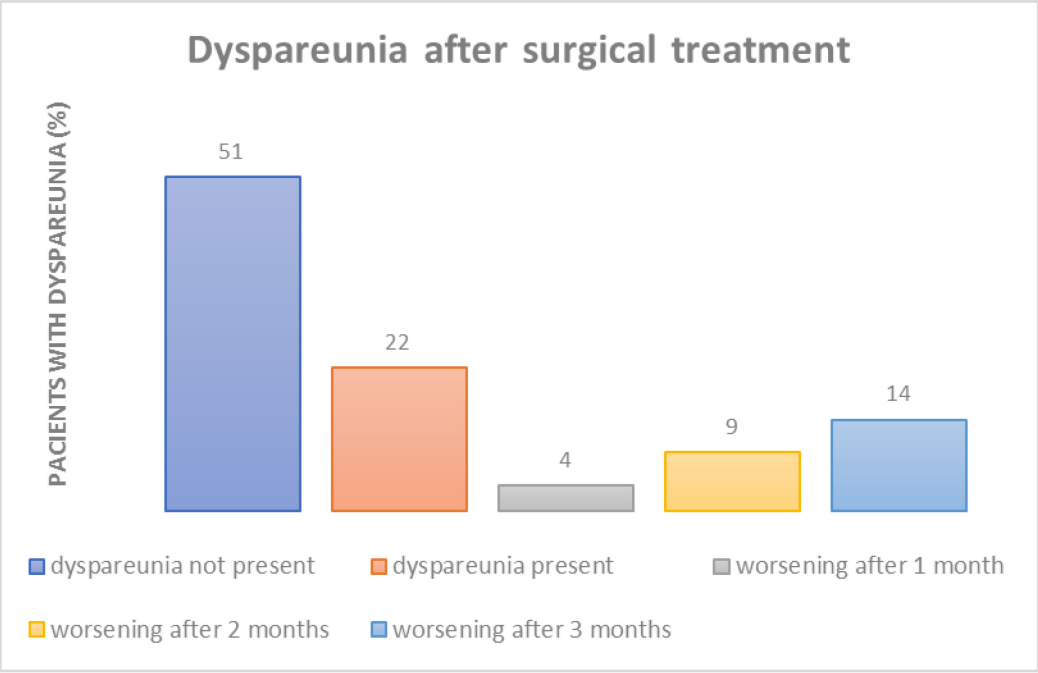

Figure 7. Dyspareunia after surgical treatment

Very specific is the problem of adenomyosis which may not be homogeneous, so the use of punch biopsy does not make sense. Therefore, the only surgical method is the Osada's reduction of archimetra and the reconstruction of the uterus (Osada, 2010). In centres involved in surgical treatment of endometriosis, histological results should be correlated to 80% with clinical findings. Hysterectomy is the ultimate method when all other eventualities

have previously been excluded. It must always be performed within complex endometriosis rehabilitation, not as a separate surgery.

The problem of accompanying sterility, whether primary or secondary is evidence that independent conservative therapy does not improve fertility; this can be reached only a combination of surgical performance and subsequent therapy in the IVF centre. Each patient should be presented with an individual therapy plan according to the therapy goals. The surgical operations should be carried out in centres that deal with these complex tasks, where the cooperation of these specialists with the IVF centre is ensured.

Finally, there is a necessary to provide a psychological support and also a sexological consultation. Endometriosis is a disease that does not only directly affect the life of the patient but also affects the physical and social health of society. Although we do not have a causal therapy, we are able to relieve pain, reduce the number of relapses, and improve the fertility of affected women (Chvátal and Fiala, 2016).

2.5.2.1 Case report

How serious endometriosis can be, is documented in the case report of a twenty-year-old childless woman suffering from more than two years of atypical abdominal pain treated for psychiatry as a form of somatoform disorder (Lenz et al., in print). The intestinal involvement by endometriosis occurs in 3 % to 37 % of patients. Up to 73 % of cases affect the lower rectosigmoid colon followed by the rectovaginal septum, terminal ileum, caecum, and the appendix (Douglas, 2004). Superficial intestinal diseases in the form of serosal implants usual do not cause any symptoms, but bulky, deeply invasive diseases can cause real problems. Spontaneous perforation of intestinal endometriosis is a very rare complication but occurs most frequently during pregnancy (Garg, 2009; Schweitzer, 2006). Intestinal endometriosis typically involves areas where the

peritoneum is irregularly folded, such as the rectovaginal septum, rectum, and sigmoid colon (Witz, 1999). Most cases occur during surgical intervention or are revealed incidentally by pathological examination of tissues removed for different surgical indications (Bossotti, 2000).

The symptoms of gastrointestinal tract involvement by endometriosis are nonspecific and depend on a) the severity and b) the location of the disease. Superficial intestinal endometriosis may be asymptomatic or cause cyclical spastic pain (Fu, 2007). When endometriosis deeply invades the bowel wall, it causes a scarring and retraction and can form a mass lesion which partially obstructs the bowel wall (Pereira, 2010). In such cases symptoms may include constipation, diarrhoea, melena, rectal bleeding, meteorism and tenesmus. It is very rare that the colon is perforated by endometriosis. When searching the literature, 12 cases of perforation of the small bowel, 16 cases of perforation of the large bowel and 3 cases of perforation of the appendix, due to intestinal endometriosis were found (a total of 31 cases). From a histopathological point of view, it is necessary to differentiate between colorectal adenocarcinoma and endometriosis. Chen et al. (2015) described a case report of 39-year-old women with rectal mucosal endometriosis primarily misinterpreted as adenocarcinoma. Initial colonoscopy showed a rectal mass with ulceration and circum wall involvement. Laparoscopy and laparotomy, often considered as the gold standards for diagnosing pelvic endometriosis, may be insufficient in case of an inactive endometriosis. As in the work published by Galazis et al. (2014), no active endometriosis of the bowel wall was seen during laparoscopy and laparotomy. It is the histological examination that provides the definitive diagnosis.

3 CONCLUSIONS

This research work on endometriosis and its influence on the female organism which is associated not only with the occurrence of infertility but mainly with dyspareunia and algopareunia, was based on current information which is known about endometriosis, especially in the field of immunological research, concerning the possible origin and subsequent spread of this disease in the organism. However, current knowledge still does not lead to a clear identification of the causes that lead to the disease.

Another remaining significant fact is the relatively long time from the onset of the disease, which is often tied to the age of about 11 years, until the illness is diagnosed. This period is often reported to range from 8 to 12 years. This reason led us to find a marker or a combination of markers that would allow the endometriosis to be confirmed even earlier in the age before the disease is fully developed. We have been successful in this part of the research project because we have demonstrated a statistically significant relationship among CA-125 and CA-19-9 oncomarkers with DHEA-S in patients. Statistical significance has also been confirmed by the Mann-Whitney test. In practice, this means that in the future, if we suspect this disease, we can use a simple patient's blood test for these two markers and DHEA-S and, as a result, confirm or disprove the suspicion of this serious civilization illness.

The second part of our research was to confirm whether endometriosis is a disease that also (in addition to female dysfunction, investigated according to Rosen's standardized questionnaire) involves or is associated with stress and somatoform dissociations which significantly affects not only the life of sick women but also affects their partnerships and sexual life. Also, we have been successful in this part of the research task and we have demonstrated significant Spearman correlations of TSC-40 with CA using standardized questionnaires SDQ-20 and TSC-40, together

with examination of female hormonal profile and marker CA-125 and CA 19-9 (R = 0.52 or R = 0.30, respectively) and correlations of SDQ-20 with CA-125 and CA-19-9 (R = 0.53 or R = 0.31, respectively). Based on our results, endometriosis is a significant stress factor and contributes to the formation of a somatoform disorder, which was the basic assignment of the research task.

The last part of the research was focused on the treatment of endometriosis and its evaluation after six months of hormonal therapy. Comparing the results of Rosen's pre-treatment questionnaire and after six months of treatment, we see a slight improvement which, however, cannot be regarded as a solution to the problem called endometriosis. In some cases, we also decide for to surgical resolution of the disease, especially in severe, possibly life-threatening situations, as is shown in the last part of the research, which contains a published case report.

Considering the severity of the disease, we assume that we will continue to research endometriosis, especially in the search for the factors that lead to its development.

4 QUESTIONNAIRES

4.1 Rosen - Female Sexual Function Index (FSFI)

Instructions:

These questions ask about your sexual feelings and responses during the past 4 weeks. Please answer the following questions as honestly and clearly as possible. Your responses will be kept completely confidential.

In answering these questions, the following definitions apply:

Sexual activity can include caressing, foreplay, masturbation, and vaginal intercourse. Sexual intercourse is defined as penile penetration (entry) of the vagina. Sexual stimulation includes situations like foreplay with a partner, self-stimulation (masturbation), or sexual fantasy.

Check only one box per question

Sexual desire or interest is a feeling that includes wanting to have a sexual experience, feeling receptive to a partner's sexual initiation, and thinking or fantasizing about having sex.

1. Over the past 4 weeks, how often did you feel sexual desire or interest?

☐ 5 = Almost always or always

☐ 4 = Most times (more than half the time)

☐ 3 = Sometimes (about half the time)

☐ 2 = A few times (less than half the time)

☐ 1 = Almost never or never

2. Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?

☐ 5 = Very high

☐ 4 = High

☐ 3 = Moderate

☐ 2 = Low

☐ 1 = Very low or none at all

Sexual arousal is a feeling that includes both physical and mental aspects of sexual excitement. It may include feelings of warmth or tingling in the genitals, lubrication (wetness), or muscle contractions.

3. Over the past 4 weeks, how often did you feel sexually aroused ("turned on") during sexual activity or intercourse?

☐ 0 = No sexual activity

☐ 5 = Almost always or always

☐ 4 = Most times (more than half the time)

☐ 3 = Sometimes (about half the time)

☐ 2 = A few times (less than half the time)

☐ 1 = Almost never or never

4. Over the past 4 weeks, how would you rate your level of sexual arousal ("turn on") during sexual activity or intercourse?

☐ 0 = No sexual activity

☐ 5 = Very high

☐ 4 = High

☐ 3 = Moderate

☐ 2 = Low

☐ 1 = Very low or none at all

5. Over the past 4 weeks, how confident were you about becoming sexually aroused during sexual activity or intercourse?

☐ 0 = No sexual activity

☐ 5 = Very high confidence

☐ 4 = High confidence

☐ 3 = Moderate confidence

☐ 2 = Low confidence

☐ 1 = Very low or no confidence

6. Over the past 4 weeks, how often have you been satisfied with your arousal (excitement) during sexual activity or intercourse?

☐ 0 = No sexual activity

☐ 5 = Almost always or always

☐ 4 = Most times (more than half the time)

☐ 3 = Sometimes (about half the time)

☐ 2 = A few times (less than half the time)

☐ 1 = Almost never or never

7. Over the past 4 weeks, how often did you become lubricated ("wet") during sexual activity or intercourse?

☐ 0 = No sexual activity

☐ 5 = Almost always or always

☐ 4 = Most times (more than half the time)

☐ 3 = Sometimes (about half the time)

☐ 2 = A few times (less than half the time)

☐ 1 = Almost never or never

8. Over the past 4 weeks, how difficult was it to become lubricated ("wet") during sexual activity or intercourse?

☐ 0 = No sexual activity

☐ 1 = Extremely difficult or impossible

☐ 2 = Very difficult

☐ 3 = Difficult

☐ 4 = Slightly difficult

☐ 5 = Not difficult

9. Over the past 4 weeks, how often did you maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

☐ 0 = No sexual activity

☐ 5 = Almost always or always

☐ 4 = Most times (more than half the time)

☐ 3 = Sometimes (about half the time)

☐ 2 = A few times (less than half the time)

☐ 1 = Almost never or never

10. Over the past 4 weeks, how difficult was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?

☐ 0 = No sexual activity

☐ 1 = Extremely difficult or impossible

☐ 2 = Very difficult

☐ 3 = Difficult

☐ 4 = Slightly difficult

☐ 5 = Not difficult

11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how often did you reach orgasm (climax)?

☐ 0 = No sexual activity

☐ 5 = Almost always or always

☐ 4 = Most times (more than half the time)

☐ 3 = Sometimes (about half the time)

☐ 2 = A few times (less than half the time)

☐ 1 = Almost never or never

12. Over the past 4 weeks, when you had sexual stimulation or intercourse, how difficult was it for you to reach orgasm (climax)?

☐ 0 = No sexual activity

☐ 1 = Extremely difficult or impossible

☐ 2 = Very difficult

☐ 3 = Difficult

☐ 4 = Slightly difficult

☐ 5 = Not difficult

13. Over the past 4 weeks, how satisfied were you with your ability to reach orgasm (climax) during sexual activity or intercourse?

☐ 0 = No sexual activity

☐ 5 = Very satisfied

☐ 4 = Moderately satisfied

☐ 3 = About equally satisfied and dissatisfied

☐ 2 = Moderately dissatisfied

☐ 1 = Very dissatisfied

14. Over the past 4 weeks, how satisfied have you been with the amount of emotional closeness during sexual activity between you and your partner?

☐ 0 = No sexual activity

☐ 5 = Very satisfied

☐ 4 = Moderately satisfied

☐ 3 = About equally satisfied and dissatisfied

☐ 2 = Moderately dissatisfied

☐ 1 = Very dissatisfied

15. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?

☐ 5 = Very satisfied

☐ 4 = Moderately satisfied

☐ 3 = About equally satisfied and dissatisfied

☐ 2 = Moderately dissatisfied

☐ 1 = Very dissatisfied

16. Over the past 4 weeks, how satisfied have you been with your overall sexual life?

☐ 5 = Very satisfied

☐ 4 = Moderately satisfied

☐ 3 = About equally satisfied and dissatisfied

☐ 2 = Moderately dissatisfied

☐ 1 = Very dissatisfied

17. Over the past 4 weeks, how often did you experience discomfort or pain during vaginal penetration?

☐ 0 = Did not attempt intercourse

☐ 1 = Almost always or always

☐ 2 = Most times (more than half the time)

☐ 3 = Sometimes (about half the time)

☐ 4 = A few times (less than half the time)

☐ 5 = Almost never or never

18. Over the past 4 weeks, how often did you experience discomfort or pain following vaginal penetration?

☐ 0 = Did not attempt intercourse

☐ 1 = Almost always or always

☐ 2 = Most times (more than half the time)

☐ 3 = Sometimes (about half the time)

☐ 4 = A few times (less than half the time)

☐ 5 = Almost never or never

19. Over the past 4 weeks, how would you rate your level (degree) of discomfort or pain during or following vaginal penetration?

☐ 0 = Did not attempt intercourse

☐ 1 = Very high

☐ 2 = High

☐ 3 = Moderate

☐ 4 = Low

☐ 5 = Very low or none at all

4.1.1 FSFI Domain Scores and Full-Scale Score

A score ≤ 26.55 is classified as FSD.

Domain	Questions	Score range	Factor	Minimum score	Maximum score	Score
Desire	1,2	1 – 5	0,6	1,2	6,0	
Arousal	3,4,5,6	0 – 5	0,3	0	6,0	
Lubrication	7,8,9,10	0 – 5	0,3	0	6,0	
Orgasm	11,12,13	0 – 5	0,4	0	6,0	
Satisfaction	14,15,16	0 – 5	0,4	0,8	6,0	
Pain	17,18,19	0 – 5	0,4	0	6,0	

4.2 TSC-40

How often have you experienced each of the following in the last two months?

0 = Never 3 = Often

1. Headaches	0	1	2	3
2. Insomnia (trouble getting to sleep)	0	1	2	3
3. Weight loss (without dieting)	0	1	2	3
4. Stomach problems	0	1	2	3
5. Sexual problems	0	1	2	3
6. Feeling isolated from others	0	1	2	3
7. "Flashbacks" (sudden, vivid, distracting memories)	0	1	2	3
8. Restless sleep	0	1	2	3
9. Low sex drive	0	1	2	3
10. Anxiety attacks	0	1	2	3

11. Sexual overactivity	0	1	2	3
12. Loneliness	0	1	2	3
13. Nightmares	0	1	2	3
14. "Spacing out" (going away in your mind)	0	1	2	3
15. Sadness	0	1	2	3
16. Dizziness	0	1	2	3
17. Not feeling satisfied with your sex life	0	1	2	3
18. Trouble controlling your temper	0	1	2	3
19. Waking up early in the morning and can't get back to sleep	0	1	2	3
20. Uncontrollable crying	0	1	2	3
21. Fear of men	0	1	2	3
22. Not feeling rested in the morning	0	1	2	3
23. Having sex that you didn't enjoy	0	1	2	3

24. Trouble getting along with others	0	1	2	3
25. Memory problems	0	1	2	3
26. Desire to physically hurt yourself	0	1	2	3
27. Fear of women	0	1	2	3
28. Waking up in the middle of the night	0	1	2	3
29. Bad thoughts or feelings during sex	0	1	2	3
30. Passing out	0	1	2	3
31. Feeling that things are "unreal"	0	1	2	3
32. Unnecessary or over-frequent washing	0	1	2	3
33. Feelings of inferiority	0	1	2	3
34. Feeling tense all the time	0	1	2	3
35. Being confused about your sexual feelings	0	1	2	3
36. Desire to physically hurt others	0	1	2	3

37. Feelings of guilt	0	1	2	3
38. Feelings that you are not always in your body	0	1	2	3
39. Having trouble breathing	0	1	2	3
40. Sexual feelings when you shouldn't have them	0	1	2	3

6.3.1. Subscale composition and scoring for the TSC-40

The score for each subscale is the sum of the relevant items, listed below.

The TSC-40 total score contains several items not included in subscales.

Dissociation: 7, 14, 16, 25, 31, 38

Anxiety: 1, 4, 10, 16, 21, 27, 32, 34, 39

Depression: 2, 3, 9, 15, 19, 20, 26, 33, 37

SATI (Sexual Abuse Trauma Index): 5,7,13,21,25,29,31

Sleep Disturbance: 2, 8, 13, 19, 22, 28

Sexual Problems: 5, 9, 11, 17, 23, 29, 35, 40

TSC-40 total score: 1-40

4.3 SDQ-20

This questionnaire asks about different physical symptoms or body experiences, which you may have had either briefly or for a longer time. Please indicate to what extent these experiences apply to you in the past year. For each statement, please circle the number in the first column that best applies to YOU.

The possibilities are:

1 = this applies to me NOT AT ALL
2 = this applies to me A LITTLE
3 = this applies to me MODERATELY
4 = this applies to me QUITE A BIT

Sometimes:

1. I have trouble urinating 1 2 3 4 5 No Yes, namely .....

2. I dislike tastes that I usually like 1 2 3 4 5 No Yes, namely .....

3. I hear sounds from nearby as if they were coming from far away 1 2 3 4 5 No Yes, namely .....

4. I have pain while urinating 1 2 3 4 5 No Yes, namely .....

5. My body, or a part of it, feels numb	1 2 3 4 5	No Yes, namely .....
6.People and things look bigger than usual	1 2 3 4 5	No Yes, namely .....
7. I have an attack that resembles an epileptic seizure	1 2 3 4 5	No Yes, namely .....
8. My body, or a part of it, is insensitive to pain	1 2 3 4 5	No Yes, namely .....
9. I dislike smells that I usually like	1 2 3 4 5	No Yes, namely .....
10. I feel pain in my genitals	1 2 3 4 5	No Yes, namely .....
11. I cannot hear for a while (as if I am deaf)	1 2 3 4 5	No Yes, namely .....
12. I cannot see for a while (as if I am blind)	1 2 3 4 5	No Yes, namely .....

13. I see things around me differently
than usual (for example as if looking
through a tunnel, or seeing merely
a part of an object) 1 2 3 4 5 No Yes, namely .....

14. I am able to smell much BETTER
or WORSE than I usually do
(even though I do not have a cold) 1 2 3 4 5 No Yes, namely .....

15. It is as if my body, or a part of it,
has disappeared 1 2 3 4 5 No Yes, namely .....

16. I cannot swallow, or can
swallow only with great effort 1 2 3 4 5 No Yes, namely .....

17. I cannot sleep for nights on end,
but remain very active during
daytime 1 2 3 4 5 No Yes, namely .....

18. I cannot speak (or only with
great effort) or I can only whisper 1 2 3 4 5 No Yes, namely .....

19. I am paralysed for a while	1 2 3 4 5	No Yes, namely .....
20. I grow stiff for a while	1 2 3 4 5	No Yes, namely .....

5 SOUHRN

Endometrióza je významné onemocnění, které bylo poprvé popsáno Von Rokytanskym před více jak 160 lety. Onemocnění je definováno jako přítomnost endometriálních buněk mimo dutinu děložní. Základním symptomem je bolest, velmi často je endometrióza spojena s primární nebo sekundární sterilitou, předpokládá se, že se také podílí na vzniku a rozvoji ženské dyspareunie a algopareunie.

Jde o onemocnění vázané na estrogen, které postihuje především ženy v reprodukčním věku, ale může se vyskytnout i postmenopausálně. V těle ženy s endometriózou existují tři zdroje tvorby estrogenů, ovaria, tuková tkáň a kůže a samotná ložiska endometriózy. Kromě nadprodukce estrogenů nacházíme u těchto žen také více receptorů pro estrogen. Teorií zabývajících se vznikem onemocnění je mnoho, žádná ale nepostihuje komplexní stav tohoto onemocnění, které se se vyskytuje v populaci dle statistik u 10-15 % žen. U žen s diagnózou sterility a infertility je výskyt endometriózy popisován u více jak 40 % a více jak 50% žen popisuje nejrůznější formy dyspareunie a algopareunie, které mají dopad nejen na vlastní život žen, ale i na partnerské vztahy. Onemocnění tak nabývá na významu nejen z čistě medicínského hlediska, ale i z hlediska psychosociálního.

Je třeba konstatovat, že v současné době neznáme žádný specifický laboratorní marker, který by endometriózu jednoznačně diagnostikovat. Stejně tak neexistuje jednoznačné řešení v rámci terapie, ať již jde o léčbu konzervativní, chirurgickou nebo kombinovanou. Významnou skutečností je také ten fakt, že endometrióza bývá diagnostikována se značnou časovou prodlevou, statistiky hovoří až o jedenácti letech mezi objevením prvních, mnohdy neurčitých příznaků, do jednoznačného potvrzení diagnózy.

Studie, které jsou podkladem této disertační práce, nejprve shrnuly prakticky všechny dostupné možnosti vyplývající z imunologického pohledu na endometriózu, její vznik, šíření, diagnostiku a případnou léčbu.

Následně byly soubory žen s endometriózou vyhodnoceny z hlediska obecných anamnestických údajů jako je výskyt první menstruace, poruchy menstruačního cyklu, snížený BMI, kouření a alkohol. Dále byly u žen s endometriózou zjišťovány krevní hodnoty jednotlivých hormonů (FSH, LH, PRL, estradiol, progesteron, TSH, DHEA-S, kortizol) a onkomarkerů (CA-125 a CA-19-9). Statisticky zpracované výsledky ukazují významné Spearmanovy korelace mezi onkomarkery CA-125, CA-19-9 spolu s dehydroepiandrosteron-sulfátem (DHEA-S). Toto zjištění představuje v odborné literatuře první zaznamenaný důkaz dokumentující zvýšené hladiny androgenů jako významných markerů patologie endometria u endometriózy. Výsledky byly potvrzeny také Mann-Whitneyho testem.

Následný soubor pacientek s endometriózou byl vyhodnocen z hlediska Rosenova dotazníku určeného pro vyšetření ženské sexuální dysfunkce, dále dotazníkem TSC-40, který hodnotí symptomy traumatického tresu a somatoformní disociativní příznaky u pacientů s endometriózou byly měřeny pomocí dvaceti otázek dotazníkem SDQ-20. Výsledky této studie potvrzují významnou korelaci podle Spearmana, potvrzenou Mann-Whitneyho testem mezi traumatickým stresem a patologií endometria.

Poslední část disertační práce je zaměřena na léčbu endometriózy a její hodnocení po šesti měsících hormonální léčby. Porovnáním výsledků Rosenova dotazníku před léčbou a po šesti měsících léčby vidíme pouze mírné zlepšení, které však nelze považovat za řešení problému nazývaného endometrióza. Proto se v některých případech, zvláště těch závažných a život ohrožujících, přikláníme k chirurgickému vyřešení, jak ukazuje poslední část výzkumu, obsahující publikovanou kazuistiku.

Závěrem lze říci, že studie uvedené v disertační práci prokázaly nejen možnosti časné diagnostiky endometriózy, ale především vliv tohoto onemocnění na dyspareunii a algopareunii u žen s endometriózou.

6 SUMMARY

Endometriosis is a serious illness that was first described by Von Rokytansky over 160 years ago. The disease is defined as the presence of endometrial cells outside the uterine cavity. The underlying symptom is pain, endometriosis is often associated with primary or secondary sterility, and it is assumed to be involved in the development of female dyspareunia and algopareunia.

Endometriosis is an oestrogen-dependent disease that affects mainly women of reproductive age but can also occur during postmenopausal age. There are three sources of oestrogen production in the woman body, ovaries, adipose tissue and skin, and endometriosis itself. In addition to oestrogen overproduction, we also find more oestrogen receptors in these women. There are many theories regarding the cause of the disease, however, none of them affect the complex state of the disease, which occurs in the population according to statistics in 10-15 % of women. In women with a diagnosis of sterility and infertility, the incidence of endometriosis is described in more than 40 %. Also, more than 50 % of women describe the most diverse forms of dyspareunia and algopareunia that affect not only women's own lives but also their relationships. The illness thus becomes important not only from a purely medical point of view but also from a psychosocial point of view.

It should be noted that there is currently no known specific laboratory marker to diagnose endometriosis. Similarly, there is no universal approach and solution within the therapy, whether it is conservative, surgical, or combined. An important fact is that endometriosis is diagnosed with a considerable delay, according to statistics; it takes up to eleven years from the discovery of the first, often indefinite symptoms, to the unequivocal confirmation of the diagnosis.

The thesis is based on several studies where we summed up practically all the available options resulting from the immunological view of endometriosis, its origin, spread, diagnosis and possible treatment.

Subsequently, women with endometriosis were evaluated for general anamnestic data such as first menstrual periods, menstrual cycle disorders, reduced BMI, smoking and alcohol. In addition, hormone levels (FSH, LH, PRL, oestradiol, progesterone, TSH, DHEA-S, cortisol) and oncomarkers (CA-125 and CA-19-9) were measured in women with endometriosis. The statistical results show significant Spearman correlations of CA-125 and CA-19-9 with dehydroepiandrosterone sulphate (DHEA-S). This finding represents in the literature the first recorded evidence documenting elevated androgen levels as significant markers of endometrial pathology in endometriosis. The results were also confirmed by the Mann-Whitney test.

Set of patients with endometriosis was evaluated using Rosen's questionnaire for female sexual dysfunction, a TSC-40 questionnaire evaluating the symptoms of traumatic stress, and somatoform dissociative symptoms in endometriosis patients were measured using twenty questions in the SDQ-20 questionnaire. The results of this study have shown a significant correlation according to Spearman, which was also confirmed by the Mann-Whitney test, between traumatic stress and endometrial pathology.

The last part of the dissertation thesis is focused on the treatment of endometriosis and its evaluation after six months of hormonal treatment. By comparing the results of Rosen's questionnaire before and after six months of treatment, we see only a slight improvement which cannot be considered as a solution to a problem called endometriosis. Therefore, in some cases, especially those of a serious and life-threatening nature, we are inclined to surgical therapy, as is shown in the last part of the thesis, which contains a case report.

In conclusion, the studies presented in the dissertation thesis proved not only the possibility of early diagnosis of endometriosis but also the influence of this disease on dyspareunia and algopareunia in women with endometriosis.

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8 LIST OF ABBREVIATIONS

1) BMI – Body Mass Index
2) MRI – Magnetic resonance Imagining
3) TSC-40 - Trauma Symptom Checklist
4) SDQ-20 - Somatoform Dissociation Questionnaire
5) DHEA-S - Dehydroepiandrosterone sulphate
6) FSFI - Female Sexual Function Index
7) TSH - Thyrotrophic hormone
8) FSD - Female sexual disorders

9 LIST OF PUBLICATIONS

1) Chvátal, R. & **Fiala, L.** (2016). Endometrióza. *Gynekolog 4*, 174.
2) **Fiala, L**., & Chvátal, R. (2017). Ženské sexuální dysfunkce a endometrióza II. *Gynekolog* 4, 142.
3) **Fiala, L**., Bob P., Tomeš P. (2018). Ženské sexuální dysfunkce a endometrióza III. *Gynekolog 4*, 6.
4) Králíčková, M., **Fiala, L.**, Losan, P., Tomes, P., & Vetvicka, V. (2018). Altered Immunity in Endometriosis: What Came First? *Immunological investigations*, 1-14. (IF= 2.588)
5) **Fiala, L**., Bob P., Raboch J. (2018). Oncological markers CA-125, CA-19-9 and endometriosis. *Medicine (Baltimore),* 97. (IF= 2.028)
6) **Fiala, L.**, & Bob P., (accepted). Traumatic stress, oncoproteins CA-125, CA 19-9 and endometriosis. *Journal of Psychosomatic Research.* (IF= 2.947)
7) Lenz J., **Fiala L.**, Chvátal R., Tihon J., Uncapher L., Kavka M., Čížek P. (in print). Rectal perforation caused by deep infiltrating endometriosis in nonpregnant woman: case report and short review of the literature. *Annali Italiani Di Chirurgia.* (IF= 0.708)

10 PUBLISHED ARTICLES