

**Univerzita Karlova v Praze
1. lékařská fakulta**

Autoreferát disertační práce



MUDr. Luděk Fiala MBA

Role endometriózy v rozvoji dyspareunie a algopareunie

The role of endometriosis in the development of
dyspareunia and algopareunia

2019

Doktorský studijní program psychologie
Univerzita Karlova v Praze

Obor: Lékařská psychologie a psychopatologie

Předseda oborové rady: Prof. MUDr. Jiří Raboch, DrSc.

Školící pracoviště: Sexuologický ústav 1.LF a VFN Praha

Školitel: Doc. MUDr. Zvěřina Jaroslav CSc.

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Summary

Endometriosis 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.

There are many theories regarding the cause of the disease, however, none of them affects 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. Likewise, there is no unambiguous 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 11 years from the discovery of the first, often indefinite symptoms, to the unequivocal confirmation of the diagnosis.

This 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.

Women with endometriosis were evaluated for general anamnestic data, and in addition, hormone levels (FSH, LH, PRL, oestradiol, progesterone, TSH, DHEA-S, cortisol) and oncomarkers (CA-125 and CA-19-9) were

measured. The statistical results show significant Spearman correlations of CA-125 and CA-19-9 with dehydroepiandrosterone sulphate (DHEA-S). This finding, according to the literature, represents the first recorded evidence documenting elevated androgen levels as significant markers of endometrial pathology in endometriosis. 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 had 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 conservative and surgical treatment of endometriosis.

In conclusion, the studies presented in the dissertation 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.

Souhrn

Endometrióza je definována 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.

Teorií zabývajících se vznikem onemocnění je mnoho, žádná ale nepostihuje komplexní stav tohoto onemocnění, které 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 jejich partnerské vztahy. Onemocnění tak nabývá na významu nejen z čistě medicínského hlediska, ale i z hlediska psychosociálního.

V současné době neznáme žádný specifický laboratorní marker, který by endometriózu jednoznačně diagnostikoval. Významnou skutečností je 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, shrnují všechny dostupné možnosti vyplývající z imunologického pohledu na endometriózu, její vznik, šíření, diagnostiku a případnou léčbu.

Ženy s endometriózou byly nejprve vyhodnoceny z hlediska obecných anamnestických údajů, a dále byly 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.

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

Poslední část disertační práce je zaměřena na konzervativní a chirurgickou léčbu endometriózy. Závěrem lze říci, že studie uvedené v disertační práci prokázaly nejen možnosti časně diagnostiky endometriózy, ale především vliv tohoto onemocnění na dyspareunii a algopareunii u žen s endometriózou.

Introduction

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, however, 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 also 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.

Recently there is no direct evidence about a role of stress and disturbed partnerships in the endometrium pathophysiology although various neuroendocrine and immune changes are significantly stress related and may play a role in endometrial diseases (Kralickova and Vetvicka, 2015; Cloke and Christian, 2011; Simitsidellis et al., 2017). In addition, there is evidence that neuroendocrine disturbances might play an important role in endometrium related

pathology and some findings indicate that they may play a role in hormone-dependent endometrial cancer (Gibson et al., 2018; Barry et al., 2014; Ito et al., 2016; Simitsidellis et al., 2017). For example, 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). Nevertheless, according to the recent literature there is no evidence about relationship of stress and dissociative symptoms with CA-125 and CA 19-9 as indicators of endometrial and cancer pathology.

Hypotheses and aims of the study

Etiology and pathogenesis are not yet known, therefore there is no causal therapy. The underlying symptom is pain, 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.

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.

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).

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 (Barry et al., 2014; Ito et al., 2017; Gibson et al., 2018; Simitsidellis et al., 2017).

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 CA19-9 molecules represent important markers of endometrial and cancer pathology (Socolov et al., 2017, Hirsch et al., 2017). Nevertheless, according to the recent literature there is no evidence about relationships of DHEA-S with CA-125 and CA19-9 as indicators of endometrial and cancer pathology.

With respect to these findings we have tested this hypothesis and assessed 50 female outpatients with endometriosis and the clinical investigations were focused on biochemical serum analysis of DHEA-S, oncological markers CA-125 and CA19-9, oestradiol, thyrotrophic hormone, and prolactin.

Methods

For all patients, age, year of first menstrual period, menstrual cycle, eventual painful menstruation, smoking and alcohol use were reported. The clinical investigations were focused on biochemical serum analysis of dehydroepiandrosterone sulphate (DHEA-S), oncological markers CA-125 and CA 19-9, cortisol, oestradiol, thyrotrophic hormone and prolactin.

To test the above hypothesis, in the first study were included 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.

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.

In the second study, we have assessed 55 female outpatients mean age (32.78 ± 4.36), age range (26-44) with endometriosis. The 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.

Results

The results show significant Spearman correlations of CA-125 and CA-19-9 with dehydroepiandrosterone sulphate ($R=0.52$ resp. $R=0.49$). This is the 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). Nevertheless, according to the recent literature, there is no evidence about relationship of DHEA-S with CA-125 and CA 19-9 as indicators of endometrial and cancer pathology.

Results of the second study had shown significant Spearman correlations of TSC-40 with CA-125 and CA-19-9 ($R=0.52$, resp. $R=0.30$) and correlations of SDQ-20 with CA-125 and CA-19-9 ($R=0.53$, resp. $R=0.31$). 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.

Discussion

The results of the first study are in agreement with the tested hypothesis focused on the relationship of DHEA-S with oncological markers CA-125 and CA 19-9. These results are in accordance with recent findings indicating that CA-125 and CA 19-9 molecules represent important markers of endometrial and cancer pathology (Socolov et al., 2017, Hirsch et al., 2017). According to current literature, there is no evidence of DHEA-S relationship with CA-125 and CA 19-9 as endometrial pathology, thus we can suppose that potential biomarkers could have clinical importance with respect to timely diagnosis, because diagnosis of endometriosis is generally delayed by 8-10 years due to misinterpretation of symptoms in juveniles and young women (Ahn et al., 2017). The search for new biomarkers and validation of predicted biomarkers continues to be a priority of endometriosis research to shorten the time between diagnosis and treatment initiation.

The results of the second study are in agreement with the tested hypothesis focused on the relationship of stress and dissociative symptoms with CA-125 and CA 19-9 as indicators of endometrial and cancer pathology. In addition, the results indicate relationships of stress and somatoform symptoms with CA-125 and CA 19-9, which suggests that chronic stress symptoms likely influence endometrial pathology. According to current literature, there is no evidence of stress and somatoform dissociative symptom in their relationship with CA-125 and CA 19-9 as indicators of endometrial pathology. Therefore, we assume that C-125 and CA 19-9 as well as chronic stress assessment within this psychosomatic approach could have clinical importance with respect to prevention and timely diagnosis.

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. Current knowledge still does not lead to a clear identification of the causes that lead to the disease.

Another 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, in case we suspect this disease, we can use a simple patient's blood test for these two markers and DHEA-S, and, as a result, we can confirm or disprove the suspicion of this serious civilization illness.

The second part of our research confirmed that 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 dissociation which significantly affects not only the lives of sick women but also impacts their partnerships and sexual life. We have been successful in this part of the research task because we have found 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, and also correlations of SDQ-20 with CA-125 and CA-19-9. 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.

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.

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List of original 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., & Vetricka, 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)