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Szamatowicz Marian & Kinga Hermanowicz-Szamatowicz

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REVIEW

Endometriosis – a decade later – still an enigmatic disease. What is the new in the diagnosis and treatment?

Szamatowicz Marian[a] and Kinga Hermanowicz-Szamatowicz[b]

[a]Faculty of Health Services PWSIiP in Lomża, Department of Reproductive and Gynecological Endocrinology, Medical University, Bialystok, Poland; [b]Department of Clinical Oncology, Comprehensive Cancer Center in Bialystok, Bialystok, Poland

ABSTRACT

Endometriosis is a common disease in women of reproduction age. It causes pain and difficulty in getting pregnant. However the exact causes of infertility associated with endometriosis still remain controversial. The treatment of endometriosis consists of medical treatment of pain as well as medical and surgical treatment of infertility caused by endometriosis and assisted reproduction techniques. Since the treatment of endometriosis is often connected with diminishing ovarian reserve, the techniques for ovarian tissue preservation and oocyte and embryo freezing are used to maintain the ability for childbearing.

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Introduction

In 2008 a mini review entitled "Endometriosis- still an enigmatic disease. What are the causes, how to diagnose it and how to treat successfully?" was published in the Gynecological Endocrinology. More than a decade later, it seems to be the right time to ask the question whether there is anything new concerning the diagnosis and treatment of this enigmatic disease, and what has changed? Endometriosis is a disease affecting women of reproductive age. Histologically it is characterized by the presence of endometrial glands and stroma outside the uterine cavity. The real presence of endometriosis remains unknown due to lack of noninvasive diagnostic tests for endometriosis. It is calculated that it affects from 0.8% to 6% women in general population, and up to 50% of infertile patients [1]. Typical symptoms of endometriosis are abdominal pain and/or infertility. Although the possible mechanisms of causing infertility are various, it was shown that, generally, fecundity of women with endometriosis decreases ten times [2]. It can be stated that endometriosis is a common cause of infertility either alone or with other infertility factors. It was also demonstrated by several studies that endometriosis has a negative impact on mental health and since it is a multidimensional disease it may affect quality of life in different ways [3]. Women with endometriosis show higher occurrence of psychiatric disorders, especially those related to pain severity [4].

This is a review article of literature based on the content of Medline and other browsers, resulting from the following search words: endometriosis, pathogenesis, treatment and infertility. The ESHRE and ASRM guidelines for diagnosis and treatment of infertility were also included.

The etiology and pathogenesis of endometriosis

Endometriosis is commonly defined as the presence of endometrium-like tissue outside the uterus which leads to an inflammatory process. Despite many studies and investigations the etiology and pathogenesis of this enigmatic disease remains poorly understood. There are many theories which present the role of different pathogenic factors involved in the development of endometriosis: retrograde menstruation, metaplasia, hormones, oxidative stress and inflammation, immune dysfunction, apoptosis suppression, genetic and stem cells [5].

These various theories try to explain the mechanisms involved in the development and progression of endometriosis but since there is no single theory that can explain all aspects of this disease many hypotheses can be found in the literature [6].

The most popular and commonly accepted is the theory of retrograde menstrual flow from the uterus into the peritoneal cavity. However the cases of Mayer–Rokitansky–Kuster–Hauser/MRKH/syndrome with endometriosis present the proof for the role of celomic metaplasia [7,8].

In many publications the pelvic endometriosis is described as the complex syndrome characterized by an estrogen-dependent chronic inflammatory process and there are rather convincing suggestions that sex steroid hormones impact the pathophysiology of this disease [9].

Recently, the study of oxidative stress (OS) has become increasingly popular showing that the extensive production of reactive oxygen is responsible for a number of female reproductive diseases including endometriosis [10].

A lot of immunological factors are known to contribute significantly to the pathogenesis and pathophysiology of endometriosis. Although the auto-immune etiology in endometriosis remains controversial it seems that a better understanding of the link between autoimmunity and endometriosis might lead to future developing an immunomodulatory therapy of endometriosis [11,12].

Endometriosis is characterized by the presence of endometrial cells with capacity to avoid apoptosis outside the uterus, hence

CONTACT Szamatowicz Marian szamatow@umb.edu.pl Department of Reproductive Medicine and Gynecological Endocrinology, Medical University, Sklodowskiej 24A, Bialystok 15-276, Poland

that, the apoptosis is added to the factors playing a fundamental role in the pathogenesis of endometriosis [13].

As the steroid receptor coactivator {SRC)-1 isoform/estrogen receptor (ER)- beta axis plays an essential role in endometriosis progression, the bufalin-induced disruption of this axis might induce apoptosis and could be employed as an medical approach for endometriosis treatment [14].

A great number of studies have been recently elucidating the role of genetic polymorphism as a possible factor contributing to the development of endometriosis [15,16]. This is closely related to the data showing that environmental influences on the complex etiology of endometriosis cannot be neglected [17]. By the application of the genome-wide association analysis (GWAS) the new insight into novel biological pathways associated with endometriosis has been possible [18]. Other authors, using SNP-array (type of DNA microarray) detected almost 50-ty copy number variation (CNV) which can be associated with endometriosis [19].

The endometriosis needs new drug therapy which will target directly endometrial stem/progenitor cells and the application of adult stem cells brings some hope [20].

Looking for the new perspectives for the future clinical implications in the diagnosis and treatment of endometriosis the role of anti-inflammatory cytokines has been raised [21].

The new concept concerning endometriosis development has been called "the bacterial contamination hypothesis" and the authors suggest that it might have effective therapeutic potential [22].

Several studies have shown that endometriosis may have negative impact on *in vitro* fertilization outcomes via its influence on the quality of embryos and oocytes. However, evidence in this field is still far from being conclusive [23]. In the recent study oocyte quality was examined by transmission electron microscopy (TEM). The oocytes obtained from the patients with minimal or mild endometriosis showed abnormal mitochondria and reduced mitochondria mass when compared with oocytes obtained from women with other infertility factors. This suggests that oocyte quality is affected by endometriosis. However, it was pointed out that these findings could not be generalized and more studies using quality assessment methods and patients with different stages of endometriosis are necessary [24].

In discussion of the pathogenesis of endometriosis the role of vitamin D should not be omitted. Since the receptors of vitamin D are expressed in endometrium, the link between vitamin D metabolism and the development of endometriosis might be suspected [25].

Finally, the risk of cancer connected to endometriosis ought be considered. The data from the literature show that there is significant correlation between endometriosis and clear-cell carcinoma and endometroid ovarian cancer [26]. This idea has been supported by the investigation of the immunohistochemical expression pattern of metastasis suppressors (KAI1 and KISS1) [27] and confirmed by others [28].

Classification

There are several forms of endometriosis. The peritoneal endometriosis is the most common, other are: ovarian endometriosis and deep infiltrating endometriosis. In 1979 American Fertility Society proposed classification of endometriosis that was widely accepted. This system was then revised twice. In 1996 American Society for Reproductive Medicine proposed revised classification based on the localization, size of implants, ovarian endometriosis and extent of adhesions. The points scored on a rating-scale obtained during laparoscopic examination define endometriosis as minimal, mild, moderate or severe [29]. The ASRM classification of endometriosis now is introduced as the standard procedure which allows for comparing the results of different treatments of particular stages of the disease, however it does not have any prognostic significance regarding the prognosis of female fertility potential. Moreover, the ASRM classification of endometriosis ignores the presence of deep infiltrating disease (DIE). This is why Enzian classification of DIE was proposed as a complement to r-ASRM [30]. In 2011 another proposal that included adenomyosis, peritoneal pocket lesions and subtle endometriosis combined with three traditionally recorded lesions was presented. It considers the size of each lesion and includes a pain score. Nevertheless, this classification has not been validated so far [31]. The Endometriosis Fertility Index (EFI) is a new classification proposed for prediction of woman's fertility potential. EFI consists of two factors. The first one is historical, i.e. the age of woman, duration of infertility and occurrence of prior pregnancy. The second factor is a so called 'least function score' and can be considered after the surgery, as a description of function of ovaries, fallopian tubes and fimbria. This system is then combined with the ASRM score and gives EFI index from zero to then points and predicts results from subsequent non-IVF treatments. It has been shown that after 3 years, those individuals with the score 0 to 3 had only 10% probability of becoming pregnant and on contraindicate women with score 9–10 points of EFI had approximately 75% success rate [32]. Results of other studies, including external validation of French and Belgian population, have showed similar results. Endometriosis Fertility Index/EFI/is a valuable tool for the predicting success rate of non-IVF treatments, and then can be used for the proper counseling of infertility couples in terms of need for IVF treatment [33,34]. In 2014 World Endometriosis Society reached a consensus on the Classification of Endometriosis at XII World Congress on Endometriosis in Sao Paulo, Brazil. Since the surgery is a decisive moment in establishing the severity of the disease, the recommendation states that all women should have the r-ASRM classification completed, women with DIE should additionally have Enzian, and women with infertility and endometriosis should additionally have EFI [35].

Treatment

There is no perfect treatment of endometriosis, however the optimal treatment should include specific goals and the answers to the following questions: Is it a treatment focused solely on pain? Is it a treatment of subfertility? Or is it a treatment of infertility caused by endometriosis? As much as possible the positive results should be obtained at the shortest time and at minimal costs, possibly with no side effects and with the longest duration of remission. Such a strategy is in accordance with the ESHRE guideline for the management of women with endometriosis [36]. As the cause of endometriosis, despite hundreds publications, is not fully established, there is no cause treatment of symptoms related to endometriosis. Therefore, we can only choose the way of treatment from the limited possibilities, based on their expected or proofed effectiveness. Depending on the diagnosis of endometriosis (superficial, endometrioma or deep infiltrating) there are three modalities available: medical treatment [37], surgery [38], and medically assisted reproduction [39].

In coping with the pain associated with endometriosis the strategy of medical treatment generally involves suppression of follicle growth, including amenorrhea and suppression of endometric foci on peritoneum. To achieve this goal many treatments have been proposed but oral combined contraceptives/OCC/play the first line role, although their application has certain negative effects [40]. An alternative to OCC are progestogens alone or anti-progestogens which are less expensive and have better side effect profile [41]. There are many clinical attempts but the data about the pain treatment with the use of dienogest are the subject of the great interest [42]. It has been shown that dienogest can influence the inflammatory response of the endometriotic cells [43], cause down-regulation of the midkine and eliminate bleeding irregularities. The addition of a 3,3' di-indolymethane (DIM) to the therapy significantly reduces the pain and ameliorates the bleeding pattern [44].

In looking for the promising compounds for treatment of endometriosis the attention has been brought to resveratrol, a plant-derived polyphenolic phytoalexin which demonstrates broad spectrum health beneficial effects [45]. However, in spite of some positive effects [46], in randomized clinical trial, the resveratrol has not been superior to placebo in treatment of pain in endometriosis [47]. On the other hand, a desert plant, *Calligolum comosum (Escambil)* targets multiple fundamental processes in the pathogenesis of endometriosis which might be beneficial for treatment [48].

Apart from the medical treatments for endometriosis mentioned above the new class of medications anti-gonadotropic oral agents. III phase clinical trials on elagolix an oral GnRH antagonist were conducted. In result on 24th July 2018, FDA approved elagolix for management of moderate to severe pain relayed to endometriosis [49].

As it has been shown above, the majority of currently available forms of medical treatment of endometriosis are suppressive, not curative, hence there is a permanent need for new developments in this field [50,51].

Another strategy in endometriosis treatment is surgery, and most frequently it is laparoscopy. Surgical and laparoscopic interventions aim to remove visible areas of endometriosis and to restore the anatomy as much as possible [52]. From the clinical point of view there are three different situations: superficial endometriosis, endometriomas of the ovary and a deep infiltrating endometriosis therefore there are several surgical options available, such as coagulation or vaporization of visible lesions, excision of endometriotic nodules, excision of adhesions. Special attention should be paid during surgery of ovarian endometriomas due to the risk of potential harm to the future fertility [53,54]. In the literature there are a lot of proposals of the laparoscopic techniques used in the treatment of endometriosis. For instance, a single-port access laparoscopy should not be recommended to patients undergoing endometrioma excision who want to preserve their fertility [55]. It has been shown that women with endometriosis-related infertility have similar cycle outcomes with other patients going through ART and the risk of surgical intervention put on the ovarian reserve should not be neglected. Having in mind the detrimental role of surgical treatment of endometrioma on fertility it is vital that clinicians should asses such risks prior to initiating therapy [53,56,57].

Recently the laparoscopic technique has been enriched with robot-assisted laparoscopy as the innovation in the treatment of endometriosis [58], however it has been shown that robotic-assisted laparoscopy is "money for nothing" for endometriotic purposes [59].

The right choice of the deep endometriosis treatment is a difficult issue. The medical treatment can reduce the symptoms but does not cure the disease There is no consensus regarding the choice of technique or the timing of surgery [60,61].

The results of the catheter-directed sclerotherapy for ovarian endometrioma using 95% ethanol have been recently published and short-term outcomes are promising [62].

The first meta-analysis that compared outcomes of *in vitro* fertilization treatment revealed that women with endometriosis had substantially lower success rate than those with tubal infertility, which is probably due to the poor oocyte and embryos quality and resulting in reduced implantation rate. Further investigations showed only marginally higher cancelation rate due to a poor response but with the similar birth rate in women with endometriosis when compared with patients with a tubal factor. ASRM registry of outcome of IVF reveals that women with endometriosis had a live birth rate similar or even slightly higher compared with patients with other infertility factors [63,64].

In the treatment of infertility of women with endometriosis the option of fertility preservation should not be omitted. This is why endometriosis may be recognized as an indication for fertility preservation. The technology of ovarian preservation in women at high risk of premature ovarian failure is widely used in the cancer treatment. The possibilities include embryo and oocyte freezing and ovarian tissue cryopreservation. The advantages of embryo and oocyte freezing include documented effectiveness of the procedures and no need for invasive techniques when collecting cells. The disadvantages are the decreased quality of oocytes and embryos, however data on that subject is controversial. However, ovarian tissue cryopreservation is a highly effective technique which can be easily performed, but this technique *per se* decreases ovarian reserve and requires laparoscopy procedure. It is also pointed out that women with endometriosis, who undergo fertility preservation, may unwisely delay childbearing [65,66]

Conclusion

Although each year approximately 300 new scientific papers concerning endometriosis are published, the disease remains an enigma. The etiopathogenesis is unknown. There are findings which suggest a strong genetic influence on phenotypic manifestation of endometriosis, there is also data showing a close link between infertility and endometriosis. However it is unknown whether they have a common genetic origin. Despite many attempts there are no biochemical markers of the disease. In the surgical treatment of endometriosis the goal is to remove all visible lesions and endometriotic cyst. It is vital to remember about patient's fertility and ovarian reserve, as well as to eliminate deep nodules with a careful restoration of the lower pelvis anatomy. There are clinical trials devoted to finding new medical agents for coping with pain and with infertility in cases of endometriosis and the results might be known relatively soon.

Disclosure statement

The authors report no conflict of interest

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