Combined Surgical and Hormonal Approach as a Treatment Option for Deep Endometriosis

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Abstract

Background: Deep endometriosis represents a chronic, progressive disease, frequently characterized by pelvic pain and infertility. Although laparoscopic surgery is the mainstay of treatment for severe endometriosis-associated pain or failed medical therapy, post-surgical management of the disease still remains a subject of discussion. As for infertility treatment, the effectiveness of surgical intervention remains controversial due to the lack of robust trials. Few existing studies suggest that the use of selective progestin–dienogest may have a positive effect on improving endometriosis-associated pain, fertility rate and in-vitro outcomes. A possible improvement in the prognosis may be attributed to the positive effect of dienogest on the eutopic endometrium, which is structurally altered in endometriosis. Therefore, it has become reasonable to include hormonal therapy for the effective management of endometriosis after surgical intervention.

Aim: We aimed to observe the available literature data to weigh prospects of combined surgical and medical therapy for more effective management of endometriosis. To bring more insights into better understanding the challenges associated with endometriosis treatment, epidemiology, classification systems, pathogenesis along with current treatment options were reviewed.

Methods: For this purpose, the following electronic databases were searched: PubMed, Medline, Scopus, Cochrane Library, Web of Science, WES, Science Direct, NCBI, National Library of Medicine, Springer.

Results: Overall, 120 articles, expert recommendations and practice committee options were reviewed, 59 of them displayed certain degree of statistical significance. They were analyzed and discussed in our article.

Conclusion: After literature review, it has become more obvious that existing research data are mostly heterogeneous and inconclusive; therefore, the majority of study findings can't be generalized. Research data is limited to accurately analyze and determine the timing and duration of optimal hormonal therapy after surgery for deep endometriosis. Further studies are needed to address the challenges of effective management of endometriosis.**(TCM-GMJ June 2024; 9 (1):P24-P28)**

Keywords: Deep endometriosis; infertility; pelvic pain; dienogest.

Introduction

Endometiosis is a chronic, progressive disease mainly affecting the women of reproductive age. It's frequently associated with pelvic pain and infertility accounting for decreased quality of life (1). Endometriosis is a benign, chronic condition characterized by the presence of endometriotic glands and stroma outside the uterine cavity, predominantly involving the pelvis and, less commonly, distant extra-pelvic sites. Pain symptoms associated with endometriosis have a wide variety of clinical manifestations encompassing non-menstrual pelvic pain, dysmenorrhea, dyspareunia, dysuria or dyschezia, which have negative impact on women's functional capacities (2, 3). Deep endometriosis (also previously known as deep infiltrative endometriosis) is the most aggressive and advanced types of the three distinct entities of the disease. Peritoneal endometriosis and ovarian endometriotic cysts (endometrioma) constitute the remaining two phenotypes (4). It is associated with severe pelvic pain in more than 95% of cases. Deep endometriosis largely compromises the female reproductive function by distorting normal pelvic anatomy as a result of excessive adhesion formation (5, 6).

In order to contribute to the improved management of deep endometriosis, it has recently become reasonable to consider other factors that may play significant role in the pathogenesis of the disease. Some few existing studies

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suggest that the use of selective progestin–dienogest may have a positive effect on improving endometriosis-associated pain, fertility rate and in-vitro outcomes (7, 8). A possible improvement in the prognosis may be attributed to the positive effect of dienogest on the eutopic endometrium, which is structurally altered in endometriosis.

Although endometriosis belongs to common types of gynecologic conditions, estimating its prevalence using existing epidemiologic data can be very difficult. This can be explained by the fact that diagnosing endometriosis, as generally accepted, requires endoscopic visualization and histologic confirmation of endometriotic lesions. Hence, the available data are mostly from hospital records on women who sought medical attention for the treatment of endometriosis-associated pain symptoms and/or infertility (9, 10). According to the World Health Organization and other available studies, the prevalence of endometriosis among women of reproductive age is about 10%, which makes up about 176 million women worldwide (11). Based on the data from certain countries, endometriosis is the second most common benign gynecologic disease; however, it should be noted that its prevalence also varies between different populations. It can be partially attributed to the differences between investigated groups as well as to the use of different criteria for establishing the diagnosis (12, 13, 14). Among women who complain of chronic pelvic pain will have endometriosis in about 20% of cases (15). Approximately 30-50% women with infertility have endometriosis (16). About 40% of adolescents who were diagnosed with genital tract anomalies had significantly higher incidence of endometrial disease (17). Though the pain is the main symptom of endometriosis, about 20-25% of patients may be fully asymptomatic, which makes it hard to recognize (16).

Furthermore, according to research, it's estimated that 20% of patients suffering from endometriosis have been found to have deep disease. Deep endometriosis is defined as a presence of endometriotic nodules deeper than 5mm beyond peritoneal surface (17). It is associated with severe pelvic pain in more than 95% of cases (5). The estimated prevalence of deep endometriosis in the general population constitutes about 1% (18). Main anatomic sites of involvement of deep endometriosis include uterosacral and cardinal ligaments, pouch of Douglas, posterior vaginal fornix, vesicouterine pouch, bladder, bowel and rectovaginal septum (19). Rectovaginal lesions account for 90% of cases of deep endometriosis and may also involve organs such as the colon, ureters, and bladder (20). Since multiple sites may be affected by the deep disease, it's ultimately becoming a common practice to include multidisciplinary team, comprising gynecologists, surgeons and urologists, to ensure complex and comprehensive surgical care.

Though the existing classifications of endometriosis are still far from perfect, the World Endometriosis Society encourages clinicians to use the given systems before developing improved ones. They include mainly the revised American Society for Reproductive Medicine (rASRM) classification, the revised Enzian classification (ENZIAN), and the Endometriosis Fertility Index (EFI) (21). These classification systems fall short in terms of linking the extent of the disease to the surgical treatment strategy and its outcome. Also, they do not fully provide a description of the complex phenotypic manifestations of the disease (22). It is also well established that the disease stage doesn't not necessarily correlate with the pain symptoms, the risk of recurrence, the effectiveness of treatment and fertility, limiting the effective use of proposed classifications in endometriosis management (23, 24).

The revised American Society for Reproductive Medicine (rASRM) classification is currently the most recognized system that has been used for a long time for staging endometriosis. It is a relatively simple system to use to explain the patient the extent of the disease. Its main disadvantage is that the disease severity doesn't always relate to pain intensity and infertility. It ignores the spread of deep endometriosis in anatomical structures located in the retroperitoneal and subperitoneal spaces. In order to describe the spread of endometriosis in deeper structures, revised Enzian classification (ENZIAN) was developed (22).

The main advathage of revised Enzian classification is that it is the most perfect among the existing systems for determining the stage of deep endometriosis. Before the update, Enzian classification didn't not allow for the full assessment of other forms of endometriosis and synechiae, which became possible after introducing it. Its use is based on anatomical principles and therefore ensures to map all endometriotic lesions. They are evaluated both preoperatively, using diagnostic modalities (MRI, TVU), and during surgical intervention. Despite the progress, more research is needed to fully validate and internationally recognize the aforementioned classification (25). As for the Endometriosis Fertility Index (EFI), it is used as a means of predicting pregnancy outcomes after surgery for endometriosis (22).

Aim of the Study

Though endometriosis belongs to common gynecologic conditions, its multifactorial etiology and chronically progressive nature pose challenges to effective treatment of the disease. In many cases, only medical or surgical treatment is not sufficient to achieve a long-term and desired therapeutic effect. Despite the fact that laparoscopic surgery has become a treatment of choice for severe endometriosis-associated pain or failed medical therapy, post-surgical management of the disease still remains a subject of discussion. As for infertility associated with deep endometriosis, the role of surgery still remains controversial. Some existing studies suggest that the use of selective progestin–dienogest may have a positive effect on improving endometriosis-associated pain, fertility rate and in-vitro outcomes. Thus, is it has become more reasonable to include hormonal therapy after surgery for the effective treatment of endometriosis.

We aimed to observe the available literature data to weigh prospects of combined surgical and medical therapy for more effective management of endometriosis. To bring more insights into better understanding the challenges as-

sociated with endometriosis treatment, epidemiology, classification systems, pathogenesis along with current treatment options were reviewed.

Methods

For the purpose of literature review, the following electronic databases were searched: PubMed, Medline, Scopus, Cochrane Library, Web of Science, WES, Science Direct, NCBI, National Library of Medicine, Springer. Overall, 120 articles, expert recommendations and practice committee options were reviewed, 59 of them displayed certain degree of statistical significance. They were analyzed and discussed in our article.

Results and discussion

Although endometriosis belongs to common gynecologic conditions, its multifactorial etiology and chronically progressive nature pose challenges to effective treatment of the disease. In many cases, only medical or surgical treatment is not sufficient to achieve a long-term and desired therapeutic effect (26). Although laparoscopic surgery has become a treatment of choice for severe endometriosis-associated pain or failed medical therapy, post-surgical management of the disease still remains a subject of discussion (27, 28). Laparoscopic surgical treatment of deep endometriosis-associated infertility remains still controversial since the mechanism by which it results in infertility hasn't yet been identified (29). However, surgery can improve pregnancy rate in the case of superficial endometriosis (30). The outcomes of surgical intervention oftentimes also depend on other coexisting conditions such as uterine fibroids, adenomyosis, pelvic adhesions and etc., and surgery may not always insure the best treatment outcome. Successful management of endometriosis is also complicated by the fact that regardless of surgical treatment, the probability of recurrence still remains high. According to one retrospective study based on data from Great Britain, patients required repeat surgery after laparoscopic treatment in 20% of these cases (31).

Along with surgical intervention, it has become reasonable to include hormonal therapy for the effective management of endometriosis, which is aimed at the pathogenesis of the disease. In this regard, the selective progestagen - dienogest is an effective means of treating endometriosis according to many studies, meta-analyses and expert opinion (32, 33, 34). Dienogest is 19-nortestosterone and differs from other gestagens in that it combines the pharmacological properties of both 19-nortestosterone group and progesterone derivatives. The uniqueness of its properties is determined by the presence of a cyanomethyl group instead of an ethynyl group in its molecule (35).

According to available research data, dienogest is an effective treatment for endometriosis-related pain (36, 37, 38, 39, 40, 41, 42). Accordioning to one study, which evaluated medical treatment for endometriosis-associated pain, dienogest turned out to be the most effective treatment option for pelvic pain in contrast to other hormone medicines such as medroxyprogesterone, goserelin, and danazol (43). Administration of progestogens in the postoperative period significantly lowers both menstrual and non-menstrual pelvic pain, which, in its turn, improves the quality of life in patients affected by endometriosis (44, 45).

It should also be taken into consideration that dienogest has a positive effect on improving fertility, which can be explained by its positive effect on the endometrium. According to scientific evidence, there might be alterations in eutopic endometrium in patients with endometriosis, including abnormalities in endometrial structure, proliferation and gene expression. Abnormalities in enometrium may eventuate endometriosis-related infertility (46).

Dienogest significantly down-regulates expression of genes that are present in eutopic endometrium of patients with endometriosis. As a result, the amount of PTPRR (protein tyrosine phosphatase receptor type R) and AKAP13 (A-kinase anchor protein 13) decreases in the endometrium. As it is known, PTPRR belongs to protein tyrosine phosphatase group, which is a signaling molecule regulating a variety of cellular processes such as cell growth, differentiation and mitosis. When it comes to AKAP13-ს, it binds to estrogen receptor ∝ (ERα) that's present in endometrium and along with PTPRR takes part in the pathogenesis of endometriosis. Similar effect was not observed in the case of levonorgestrel (47). It is also worth noting that according to one of the studies dienogest inhibits 17β-hydroxysteroid dehydrogenase and aromatase, which significantly reduces the amount of excess estrogen and therefore increases its therapeutic effectiveness (48).

Also, studies have documented that ednometriosis may be the main cause of impaired receptivity of the endometrium. This opinion derives from the fact that ednometriosis is a chronic, inflammatory disease that disrupts the progesterone response in the reproductive system and thus causes resistance to progesterone (49). Changes in the ratio of progesterone and estrogen receptor isoforms may cause endometriotic tissue resistance to progesterone Dienogest may improve the sensitivity of endometriotic tissue to progesterone by increasing the expression ratio of progesterone-B and progesterone-A receptors and decreasing the ratio of estrogen-β and estrogen-α receptors (50).

Dienogest has high selectivity for progesterone receptors. It has only a minimal effect on ovarian function, has the antiproliferative effect on endometrium, increases the expression of progesterone receptors and reduces the synthesis of inflammatory cytokines (51, 52, 53). Also, according to one retrospective study, the administration of dienogest 3 months before in vitro fertilization improves fertility in patients with endometriosis, which may be explained by its anti-inflammatory and anti-angiogenic activity (54). There is a limited evidence that post-operative medical therapy increases pregnancy rates in patients compared with patients treated with surgery alone (8).

Laparoscopic excision of deep endometriotic infiltrates is an effective method of disease treatment (55). Although surgical treatment significantly reduces disease-related symptoms, surgery alone is not always successful due to

heterogeneous nature of endometriosis (10). Hence, the treatment of both infertility and pain syndrome, along with surgery, should also include consideration of currently known pathogenic and genetic factors involved in pathogenesis of endometriosis. The management of deep endometriosis requires a personalized approach that should take into account the woman's age, desire to have children, the presence of pain syndrome, comorbid conditions and patient's personal decision (19).

The main indications for surgical treatment include ineffectiveness or contraindication of hormonal treatment, infertility and the presence of severe pain (18). According to one the of recent reviews, the majority of current guidelines recommend surgical treatment of deep endometriosis in endometriosis-related pain syndrome. As for infertility treatment, according to the available data, the effectiveness of surgical intervention remains controversial due to the lack of robust studies (56). Long-term medical treatment is mainly indicated for those patients who do not desire pregnancy (57). Treatment duration depends on patient's individual the reproductive plans.

There is moderate-quality evidence showing that pregnancy rates are increased with the use of post-operative hormone therapy. In particular, the pregnancy rate was relatively higher in the group where hormonal treatment (other than dienogest) was used after surgery compared to the group where only surgery was performed (35-48% vs, 34%) (8). According to the same systematic review, which included only a few studies in the data analysis process, only one study looked at the effect of progestogen - medroxyprogesterone acetate. Thus, the results of the study can't be generalized. Also, the research data is limited to accurately analyze and determine the timing and duration of hormone therapy to optimize the effectiveness of postoperative treatment. Further studies are needed to address the challenges of effective management of endometriosis since the existing data is heterogeneous and inconclusive. There is no definitive evidence that postsurgical hormone therapy improves pregnancy rates. Therefore, it is necessary to conduct further studies in order to develop appropriate recommendations in this regard.

As for the use of dienogest in the postoperative period to reduce the pain syndrome, it significantly reduces the intensity of pain associated with deep endometriosis and improves the quality of life (58) Also, based on multiple studies, dienogest significantly reduces the risk of recurrence of endometriosis and is therefore recommended for its use as maintenance therapy in the postoperative period (59).

Conclusion

After analyzing the results of multiple scientific studies it is reasonable to assume that combined surgical and hormonal therapy for deep endometriosis may be more effective than surgical or therapeutic treatment alone. A possible improvement of the reproductive prognosis may be related to the positive effect of dienogest on the eutopic endometrium, which is structurally altered in endometriosis. Since the existing research data are mostly heterogeneous and inconclusive it's hard to generalize study findings. Further studies are needed to address the challenges of more effective management of endometriosis.

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