New developments in the medical treatment of endometriosis

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Endometriosis affects 1 in 10 women of reproductive-age. The current treatments are surgical and hormonal but have limitations, including the risk of recurrence, side effects, contraceptive action for women who desire pregnancy, and cost. New treatments include gonadotropin-releasing hormone analogues, selective progesterone (or estrogen) receptor modulators, aromatase inhibitors, immunomodulators, and antiangiogenic agents. Further research is needed into central sensitization, local neurogenesis, and the genetics of endometriosis to identify additional treatment targets. A wider range of medical options allows for the possibility of precision health and a more personalized treatment approach for women with endometriosis. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)

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Endometriosis, a chronic and recurrent disease, represents a challenge to health-care providers and a burden on the health care system. The reported prevalence of endometriosis is between 2% and 10% in the general population, 50% in the infertile population (1, 2), and more than 60% in patients with chronic pelvic pain (CCP) (3). Several studies have reported a long delay in the diagnosis of endometriosis in various countries, which adds to the challenging nature of the disease (4).

Endometriosis, defined as the presence of endometrial-like tissue outside the uterus, is associated with a chronic inflammatory reaction. Cellular proliferation, invasion, and neoangiogenesis are key to the establishment, progression, and recurrence of the disease. In addition, sloughing of the estrogen-dependent ectopic endometrial tissue leads to a chronic inflammatory process mediated by the overproduction of inflammatory mediators such as cytokines and prostaglandins. That inflammation, with its resultant adhesions and scarring, mediates the patient's symptoms of pain and other morbidities such as infertility (5).

Understanding the pathogenesis and the endocrinology of endometriosis allows for the improvement of the currently existing treatment options and the introduction of new treatments. Currently, successful treatment of endometriosis-associated pain is based on suppressing estrogen production and inducing amenorrhea. This creates a relatively hypoestrogenic environment that inhibits ectopic endometrial growth and prevents disease progression (6). This treatment strategy, however, several limitations.

LIMITATIONS OF CURRENT ENDOMETRIOSIS TREATMENT MODALITIES

Suppressive Rather than Curative Therapy

Almost all currently available treatments of endometriosis are suppressive, not curative. They are associated with the temporary relief of symptoms during treatment. On treatment discontinuation, recurrence of the symptoms is the rule. For instance, endometriosis-associated pain can continue after medical treatment or conservative surgery. After medical treatment or surgical treatment, the recurrence of endometriosis was estimated to be 21.5% at 2 years and 40% to 50% at 5 years (7). After surgical treatment, the recurrence rate of clinically detectable endometriosis tends to be higher in older women with advanced stages of the disease and lower in women with infertility (8). In a 7-year follow-up study, the re-operation rate increased with increasing time since the initial surgery (9).

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Contraceptive Rather than Fertility-Promoting Therapy

The current treatment options for endometriosis-associated pain are contraceptive in nature. This is, in part, mediated by blocking the hypothalamopituitary-ovarian axis and inducing a suppression of ovulatory function. In addition, the associated endometrial atrophy with hormone therapy (HT) hinders embryo implantation. This represents a challenge for endometriosis patients with painful symptoms who wish to become pregnant.

Several randomized controlled trials (RCTs) have proven that there is no improvement in natural conception after a course of ovarian suppression by medical therapy (10, 11). In addition, a systematic review of 25 trials (12) found no evidence of benefit in the use of ovulation suppression in subfertile women with endometriosis who wished to conceive. Consequently, in women desirous of pregnancy who have painful endometriosis, nonsteroidal anti-inflammatory drugs (NSAIDs) appear to be the only medical option consistent with the maintenance of fertility. However, pretreatment with a gonadotropin-releasing hormone (GnRH) agonist before in vitro fertilization (IVF) has been shown in a systematic review of three clinical trials totaling 165 patients to improve clinical pregnancy four-fold compared with controls. However, the reported improvement in the live-birth rate was derived from only one study in this analysis (13) and could be secondary to enhancing endometrial receptivity (14).

Endometrioma: Lack of Effective Medical Treatment and Hazardous Surgical Options

The treatment goals for endometriomas include pain relief, avoiding rupture or torsion, excluding malignancy, and preventing symptomatic or expanding endometriomas. Several reports have indicated that current medical therapy does not resolve endometriomas (15–18). Hence, laparoscopic management is frequently implemented after medical therapy. However, surgical removal negatively affects ovarian reserve. In a systematic review to investigate the impact of surgery for endometriomas on ovarian reserve as determined by serum antimüllerian hormone (AMH) levels, a pooled analysis of 237 patients was performed. There was a statistically significant postoperative fall of AMH concentration (with a weighted mean difference of −1.13 ng/mL) (19). Given the poor response to medical treatment and the negative effect of surgery on the ovarian reserve, the search for an ideal treatment for symptomatic endometriomas continues.

Limited Medical Options for Deep Infiltrating Endometriosis and Extrapelvic Disease

Deep infiltrating endometriosis is a subtype of endometriosis involving the uterosacral ligaments, rectovaginal septum, bowel, ureters, or bladder. Patients with symptomatic urinary endometriosis are usually treated by medical therapy with variable response (20), but they may also require surgery. For patients with bowel endometriosis, surgery is indicated for women who fail medical management or develop obstructive symptoms (21). For hormone suppression, GnRH agonists are usually the first-line agents because they are highly effective at suppressing ovarian hormone production and inhibiting the growth of the extrapelvic endometrial tissue (22).

Failure of medical treatment is frequently encountered with these aggressive disease phenotypes. Consequently, a large proportion of these patients will require extensive multidisciplinary surgeries. There is a need for more high quality studies to evaluate the efficacy of the different treatment options for deep infiltrating endometriosis (or extrapelvic disease), and the search continues for alternatives.

Central Sensitization

Central sensitization is being increasingly recognized as a key factor in the pathogenesis of endometriosis-associated pain in addition to the peripheral nociceptive effect of endometriotic lesions (23). Central sensitization amplifies pain signaling from the periphery (24). It is associated with myofascial trigger points (25) and psychological comorbidities (26). Therefore, treatments to reduce central sensitization are required in some patients, although there is little research in this area for women with endometriosis. Clinically, tricyclics and antiepileptics can be used, although there is an absence of clinical trials for endometriosis. There is also a RCT that suggested a multidisciplinary approach (physiotherapy and psychological therapy) may offer additional benefits (27), although further research to confirm this initial finding is needed.

To date there is no optimal medical treatment for endometriosis and its associated symptoms. This is, in part, due to lack of understanding of the pathogenesis and natural history of the disease. In addition, all currently available options have limitations as previously detailed. Consequently, the search continues for a medical treatment based on a more accurate understanding of the different disease mechanisms that is efficacious in treating endometriosis-associated comorbidities. The limitations of the currently available options pose a challenge and present an opportunity to seek novel therapies for endometriosis.

Ideally, medications for endometriosis should be curative rather than suppressive. In addition, they should effectively treat pain and have an acceptable side-effect profile. Long-term use should be safe and affordable. Moreover, they should not be contraceptive and not interfere with spontaneous ovulation and normal implantation of the endometrium to enhance spontaneous conception. Furthermore, they should have no teratogenic potential in case of inadvertent use during the first trimester of a pregnancy. They should suppress the growth of already existing lesions and prevent the development of new ones to limit the need for repeat surgery and prevent the complications associated with advanced endometriosis. Finally, they should be efficacious for all disease phenotypes, including superficial disease, endometriomas, deep infiltrating endometriosis, extrapelvic disease, and adenomyosis (Table 1).