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;107:555–65. ©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).

TABLE 1

Criteria for the ideal medication for endometriosis.

Curative rather than suppressive
Treats pain and fertility at the same time
Acceptable side effect profile
Long-term use should be safe and affordable
Noncontraceptive nature
No interference with spontaneous ovulations and normal implantation
Enhances spontaneous conception
No teratogenic potential and safe to use periconceptionally
Inhibits the growth of already existing lesions
Aborts the development of new lesions
Efficacious for all endometriosis phenotypes including superficial disease, endometriomas, deep infiltrating endometriosis, and extrapelvic endometriosis and adenomyosis

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INVESTIGATIONAL TREATMENTS

Over the past 2 decades a wide variety of medical options has been tested. All are aimed at a specific target that contributes the pathogenesis of the disease. A summary is provided in Table 2.

Hormonal

GnRH antagonists. The use of GnRH antagonists for a variety of reproductive indications has greatly increased over the past decade. Gonadotropin-releasing hormone antagonists are available as injectables (Ganirelix, Cetrorelix) and increasingly as oral nonpeptide forms (Elagolix, Abarelix, Ozarelix, TAK-385). Oral GnRH antagonists produce a dose-dependent hypoestrogenic environment by direct pituitary gonadotropin suppression. This inhibits endometriotic cell proliferation and invasion while maintaining sufficient circulating estradiol levels to avoid vasomotor symptoms, vaginal atrophy, and bone demineralization. Several studies have evaluated the use of elagolix for the management of endometriosis-associated pain with this partially suppressed estrogen paradigm in mind.

In a phase 2 RCT, Diamond et al. (28) showed that elagolix has acceptable efficacy and safety. Further, its efficacy, safety, and tolerability have been demonstrated in phase 1 and 2 trials (86). A randomized double-blind study with 24-week treatment and 24-week post-treatment periods compared the effects of elagolix to subcutaneous depot medroxyprogesterone acetate in 252 patients with endometriosis-associated pain. Elagolix was found to have minimal impact on bone mineral density over a 24-week period and demonstrated efficacy similar to subcutaneous depot medroxyprogesterone acetate for endometriosis-associated pain (87).

Other antagonists such as cetrorelix have been evaluated in vitro. The effects of cetrorelix on endometrial stromal cells obtained from ovarian chocolate cyst linings and the eutopic endometria of endometriosis patients and controls have been evaluated. Treatment with a GnRH agonist or antagonist attenuated the cell proliferation induced by tumor necrosis factor-α (TNF-α) in endometrial stromal cells, whereas endometriotic stromal cells did not respond to treatment. Also, GnRH agonists or antagonists did not repress TNF-α–induced interleukin-8 production in endometriotic stromal cells. This study concluded that both GnRH agonists and antagonists have little effect for slowing the growth of endometriotic stromal cells (29). Additionally, in a rat model, leuprolide and cetrorelix were found to have similar efficacy in the regression of both the size and the histologic structure of experimental endometriotic implants (30).

In a feasibility study to evaluate cetrorelix in the treatment of endometriosis, all patients (15 of 15; 100%) reported a pain-free period during GnRH antagonist treatment, although mood changes, hot flushes, loss of libido, vaginal dryness, and other symptoms occurred. Serum estradiol oscillated around a mean concentration of 50 pg/mL during therapy. A second-look laparoscopy showed regression of endometriotic lesions occurred in 60% of cases (9 of 15) and the degree of endometriosis declined from stage III to stage II. Sequential weekly administration of cetrorelix in a 3-mg dosage once a week over 8 weeks could be a feasible medical treatment for endometriosis-associated pain. The main advantage is reserving basic estrogen production, thereby limiting the side effects associated with profound hypoestrogenism (31). Both oral and injectable forms of GnRH antagonists are effective in reducing endometriosis-associated pain. However, more noninferiority studies to compare them with other treatment options are required.

Selective progesterone receptor modulators. Selective progesterone receptor modulators (SPRM) can have variable effects on progesterone receptors from different tissues, ranging from being a pure agonist or a mixed agonist/antagonist to a pure antagonist. Mifepristone-loaded implants have been shown to have dose-dependent inhibitory effects on the growth of endometrial explants in Wister rats (33).

Mifepristone (RU486), the most clinically studied SPRM, has been used mostly for the induction of medical abortions. Mifepristone was shown by the same group to have a positive effect on pain symptoms; it is interesting that it induced amenorrhea without causing hypoestrogenism in 16 patients with endometriosis (88, 89). However, these findings have not been substantiated in an RCT compared with placebo or other hormone alternatives.

Ulipristal acetate and asoprisnil are other members of the same family. Ulipristal acetate is approved for clinical use as an emergency contraceptive in the United States and for the treatment of fibroids in Europe and Canada. It was shown that it contributed to the regression and atrophy of endometriotic lesions in rats through its proapoptotic effects. In addition, treatment with ulipristal reduced cellular proliferation, as indicated by a decrease in Ki-67 expression, and has an anti-inflammatory effect, as shown by a decrease in cyclooxygenase-2 expression (36). The feasibility of ulipristal acetate for the treatment of endometriosis has yet to be determined. Asoprisnil, another SPRM, was shown to statistically significantly reduce non-menstrual pelvic

TABLE 2

Common medications used for the management of endometriosis-associated pain.

Compound	Study	Species	Comment
Hormonal			
GnRH antagonists[a]			
Elagolix	Diamond et al., 2014 (28)	Humans	Acceptable efficacy and safety in phase 2 RCT.
Cetrorelix	Taniguchi et al., 2013 (29)	Human cell culture	No effect on TNF-α induces IL-8 production in endometriotic stromal cells.
	Altintas et al., 2008 (30)	Rats	Similar to leuprolide effect in implants regression.
	Küpker et al., 2002 (31)	Humans	Weekly administration of 3 mg offers safe and efficient treatment option.
SPRM[b]			
Mifepristone	Zhang YX, 2016 (32)	Humans	Reduction of endometrial thickness and alleviation of symptoms during 6 mo of treatment.
	Mei et al., 2010 (33)	Rats	Subcutaneous implanted capsules an effective means for long-term treatment of chronic endometriosis.
Asoprisnil	Chawlisz et al., 2005 (35)	Humans	At dose of 5, 10, 25 mg significantly reduces non-menstrual pelvic pain/dysmenorrhea scores.
Ulipristal acetate	Hunaidi et al., 2013 (36)	Rats	Decreases COX-2 experation.
Tanaproget	Bruner-Tran et al., 2006 (37)	Humans/mice	Decreases MMP expression and endometriotic lesions.
SERM[c]			
Raloxifine	Stratton et al., 2008 (38)	Humans	CCP return sooner in raloxifene-treated women compared with placebo after surgical excitation of endometriosis (led to study termination).
	Atlintas et al., 2010 (39)	Rats	Statistically significant reduction of implanted endometrial tissue comparable to anastrozole.
	Yao et al., 2005 (40)	Rats	At 10.0 mg/kg caused statistically significant regression of implant ($P < .05$).
	Yavuz et al., 2007 (41)	Rats	Similar to anastrazole in significant reduction of the endometriotic implants.
Bazedoxifene	Lyu et al., 2015 (42)	Rats	Statistical significant reduction in volume of implants.
	Naqvi et al., 2014 (43)	Mice	Treatment with bazedoxifene alone or with conjugated estrogen caused decrease endometriotic lesion compared with control.
	Kulak et al., 2011 (44)	Mice	Statistically significant regression of endometriosis.
Chloroindazole Oxabicycloheptene	Zhao et al., 2015 (45)	Mice	ER-dependent antiproliferative effect causes regression of endometriotic lesion and prevents new lesion formation.
Aromatase inhibitors[d]			
Letrozole	Agarwal et al., 2015 (46)	Humans	With progestin add-back led to 75% reduction of endometrioma volume and improved pain symptoms after 3 mo of treatment.
	Almassinokiani et al., 2014 (47)	Humans	Effect comparable with OCP in endometriosis-related pelvic pain.
	Ferrero et al., 2011 (48)	Humans	Letrozole causes reduction in endometriosis related pain.
Anastrazole	Bilotas et al., 2010 (49)	Mice	Letrozole reduced VEGF and PGE in peritoneal fluid; anastrazole reduced VEGF with no effect on PGE level.
	Verma and Konje, 2009 (50)	Humans	Aromatase inhibitors (letrozole and anastrazole) effective in treating endometriosis-associated CCP without compromising fertility.
Nonhormonal			
Imunomodulaters[e]			
Etanercept	Barrier et al., 2004 (51)	Baboons	Statistically significant decreases endometriotic lesion surface area.
IFN-2b	Badawy et al., 2001 (52)	Human cell culture	Caused statistically significant suppression of endometrioma.
	Ingelmo et al., 2013 (53)	Rats	Caused greater reduction in implant size compared with placebo.
Loxoribine	Keenan et al., 1999 (54)	Rats	Reduced NK cells and endometriotic lesions.
Lipoxin	Xu et al., 2012 (55)	Mice	Inhibited endometriotic lesion development, suppressed MMP-9, and decreased VEGF.
	Kumar et al., 2014 (56)	Mice	A4 compound decreased PGE2 production, aromatase expression, and estrogen signaling.
Rapamycin	Ren et al., 2016 (57)	Mice	Reduced VEGF serum level and MVD, led to decreased endometriotic lesions in SCID mice.
	Laschke et al., 2006 (58)	Hamsters	Decreased VEGF and MVD, led to inhibition of endometriotic cell proliferation.
Infliximab	Koninckx et al., 2008 (59)	Humans	No effect in endometriosis-related pain.

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TABLE 2

Continued.

Compound	Study	Species	Comment
Pentoxifylline	Kamencic and Thiel, 2008 (60)	Humans	Patients with better VAS score after 2 and 3 mo from surgery compared with controls.
	Vlahos et al., 2010 (61)	Rats	Caused reduction in VEGF-C, decreased volume and no. of endometriotic implants.
Antiantiangiogenics[f]			
Caplostatin	Backer et al., 2006 (62)	Mice	Suppression of VEGF.
Endostatin	Jiang et al., 2007 (63)	Mice	VEGF in peritoneal fluid after treatment statistically significantly lower than in control group.
	Zhang et al., 2012 (64)	Rats	Gene therapy resulted in lower VEGF, MMP-2, and MVD compared to control.
	Ma and He, 2014 (65)	Mice	Significant decrease in endometriosis volume and MVD.
Angiostatin	Dabrosin et al., 2002 (66)	Mice	Gene transfer therapy caused eradication of endometriosis in all treated mice, decreased estradiol and progesterone production.
Lovastatin	Esfandiari et al., 2007 (67)	In vitro human tissue	Inhibited angiogenesis and cell proliferation.
Atorvastatin	Oktem et al., 2007 (68)	Rats	Decreased VEGF level and area of implants.
	Sharma et al., 2010 (69)	Human cell culture	Inhibited gene expression of COX-2, VEGF, RAGE, and EN-RAGE in endometrial and endometriotic cell culture.
Simvastatin	Bruner-Tran et al., 2009 (70)	Mice	Decreased endometrial implants and MMP-3.
	Almassinokiani et al., 2013 (71)	Humans	Comparable to GnRH-a in the management of endometriosis-related pelvic pain.
Lodamin	Becker et al., 2011 (72)	Mice	Caused reduction of endothelial progenitor cells, resulting in suppression of endometriotic tissue growth.
Romidepsin	Imesch et al., 2011 (73)	Human cell culture	Decreased VEGF secretion.
Icon	Krikun et al., 2010 (74)	Mice	Destroyed endometriotic implants through vascular disruption without toxicity, effect on fertility, or teratogenicity.
Cabergoline Bromocriptine	Novella-Maestre et al., 2009 (75)	Mice/human cell culture	Cabergoline, decreased VEGF and VEGFR-2 protein expression.
Quinagolide	Delgado-Rosas et al., 2011 (76)	Mice	Cabergoline and quinagolide, equal effect in reducing endometriotic lesions as antiangiogenic agents.
	Ercan et al., 2015 (77)	Rats	Cabergoline and bromocriptine, comparable to GnRH agonist in reducing endometriotic lesion.
	Hamid et al., 2014 (78)	Humans	Cabergoline, better result in reducing endometrioma size compared with triptorelin acetate.
Fenofibrate	Onalan et al., 2009 (79)	Rats	Reduction of endometriotic lesion and VEGF.
	Herington et al., 2011 (80)	Mice	Decrease in endometriosis-related postsurgical adhesion in immunocompromised mice.
Rosiglitazone	Lebovic et al., 2007 (81)	Baboons	Statistically significant reduction of endometriotic lesion compared with placebo.
	Chang et al., 2013 (82)	Human cell culture	Inhibited aromatase and COX-2 expression, led to decreased PGE2 production.
Ciglitazone	Lebovic et al., 2004 (83)	Rats	Statistically significantly decreased explant size and weight compared with control.
	Lebovic et al., 2013 (84)	Human cell culture	Decreases PGE2 and aromatase expression.
Bentamapimod	Hussein et al., 2016 (85)	Baboons	Alone or combined with medroxyprogesterone acetate led to lower surface area and volume of lesions.

Note: CCP = chronic pelvic pain; COX-2 = cyclooxygenase-2; ER = estrogen receptor; GnRH = gonadotropin-releasing hormone; IFN = interferon; IL = interleukin; MMP = matrix metalloproteinases; MVD = microvessel density; NK = natural killer; OCP = oral contraceptive pills; PGE = prostaglandin; PGE2 = prostaglandin E2; RAGE = receptor for advanced glycation end products; RCT = randomized controlled trial; SPRM = selective progesterone receptor modulators; TNF = tumor necrosis factor; VAS = visual analogue score; VEGF = vascular endometrial growth factor.

[a] GnRH antagonists suppress gonadotropin and gonadal steroids for a hypoestrogenic environment.

[b] SPRM provide selective suppression of endometrial proliferation and PGE2 production.

[c] SERM provide selective estrogen antagonism in uterine and endometriotic tissue.

[d] Aromatase inhibitors inhibit ovarian and endometriotic tissue estrogen production.

[e] Imunomodulaters enhance, regulate, or suppress the immune response.

[f] Antiantiangiogenics reduce MVD, leading to atrophy of established lesions and prevention of new lesion development.

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pain/dysmenorrhea scores at dose of 5, 10, and 25 mg (35). In 2005, however, phase 3 trials were discontinued due to endometrial changes in patients.

One study has evaluated the ability of another newly developed SPRM, tanaproget, to down-regulate endometrial matrix metalloproteinase expression in vitro and regress experimental endometriosis in vivo. Tanaproget effectively down-regulated matrix metalloproteinase expression in vitro and induced a statistically significant reduction of lesions in mice with disease established by tissues from endometriosis patients (37). The feasibility of using tanaproget in humans has yet to be evaluated.

Selective estrogen receptor modulators. Raloxifene, a commercially available selective estrogen receptor modulator (SERM), has been used for the treatment of postmenopausal osteoporosis. Raloxifene was tested at various doses in a rat model of endometriosis and was shown to have an estrogen-antagonist effect in rat uterine tissue. Raloxifene at only one dose (10.0 mg/kg) produced statistically significant implant regression (40). The reduction in size of the experimental endometriotic implants was similar to that achieved by the aromatase inhibitor anastrazole (39, 41). In a randomized clinical trial, 93 women with biopsy-proven endometriosis and CCP received 6 months of raloxifene treatment compared with placebo. The Data Safety Monitoring Committee terminated the study early when the raloxifene group experienced significant pain and had second surgery statistically significantly sooner than the placebo group. This truncated trial concluded that raloxifene statistically significantly shortened the time to return of CCP (38).

Bazedoxifene (BZA), a third-generation SERM, effectively antagonizes estrogen-induced uterine endometrial stimulation without countering estrogenic effects in bone or the central nervous system. In a rat model, BZA alone reduced the size of endometriosis lesions, with experimental evidence of an antiproliferative effect (42). In addition, BZA was shown to decrease proliferating cell nuclear antigen and estrogen receptor expression in the endometrium of treated animals compared with controls. Consequently, BZA-induced regression of endometriosis likely involves decreased estrogen-mediated cell proliferation (44). A similar effect was observed when BZA was combined with conjugated estrogen in a tissue-selective estrogen complex (TSEC) (43). This novel TSEC therapy partners a SERM with one or more estrogens. This pairing aims toward better tolerability and a reduced side-effect profile. The effectiveness on endometriosis in humans of BZA alone or in a TSEC has yet to be evaluated.

Aromatase inhibitors. Aromatase inhibitors (AIs) inhibit local estrogen production in endometriotic implants, the ovary, the brain, and adipose tissue (90). The aromatase enzyme converts testosterone and androstenedione to estradiol and estrone, respectively. Endometriotic implants express aromatase and consequently generate their own estrogen, which can maintain their viability and growth. Animal studies have shown that AIs can effectively eradicate endometriotic implants and affect peritoneal fluid vascular endothelial growth factor (VEGF) (49). Early clinical experience with AIs suggested the possibility of their use in the treatment of endometriosis (91, 92). Generally AIs are administered in various doses, such as 2.5 mg daily for letrozole and 1 mg daily for anastrazole (50). Letrozole's effect is comparable to oral contraceptive pills in endometriosis-related pelvic pain (47).

Aromatase inhibitors are a treatment option that usually is reserved for managing severe, intractable endometriosis-associated pain in combination therapy with oral contraceptive pills, progestins, and GnRH analogues (93). A systematic review of eight studies that included a total of 137 patients showed that AIs combined with progestogens, oral contraceptive pills, or GnRH agonists had reduced mean pain scores and lesion size and improved quality of life (94). Monotherapy with AI given to reproductive-age women will cause increased follicle-stimulating hormone (FSH) levels and subsequent superovulation, resulting in ovarian cyst development due to the initial FSH rise. Other concerns about prolonged AI therapy are associated bone loss secondary to hypoestrogenism. For this reason, AIs are combined with an FSH-suppression agent such as COCs, progestins, or GnRH agonists.

In one study, letrozole with progestin add-back led to a 75% reduction of endometrioma volume and improved pain symptoms after 3 months of treatment (46). In another study, letrozole alone caused a statistically significant reduction in endometriomas with better reduction in endometriotic cysts when combined with NETA (46). However, the sustainability of this size reduction was not evaluated. Patients should be counseled about the off-label nature of its use for endometriosis-associated pain.

Nonhormone Treatments

Immunnomodulators. Tumor necrosis factor-α, a proinflammatory cytokine able to initiate inflammatory cascades, is increased in the peritoneal fluid and serum of women with endometriosis. It has been implicated in the pathogenesis of endometriosis (95). In a RCT using a baboon model, a TNF-α blocker (etanercept) was evaluated. It led to a statistically significant decrease in red lesion surface area in the treatment group with a trend toward a decrease in the absolute number of red lesions (51). In a rat model, long-term treatment with human interferon-α2b (IFN-α2b) resulted in more reduction in surgically induced endometriosis implant size compared with placebo (53). Another immunomodulator (loxoribine) caused a reduction in natural killer cells and endometriotic lesions in a rat model (54). A similar reduction of endometriotic lesions was observed with other immunomodulators such as lipoxin (55, 56), rapamycin (58), and pentoxifylline (61).

Clinically, a small RCT of infliximab, another TNF-α blocker, was shown to have no effect on endometriosis-related pain (59). In a systematic review, the effectiveness and safety of anti-TNF-α treatment in the management of endometriosis in premenopausal women was evaluated. Only the one trial of 21 patients was included where infliximab (a monoclonal anti-TNF-a antibody) was compared with placebo. The reviewer concluded that there is not enough evidence to support the use of anti-TNF-α drugs in the management of women with endometriosis for the relief of pelvic pain (97).

Pentoxifylline is a competitive nonselective phosphodiesterase inhibitor that is known to have immunomodulatory properties that could be used for endometriosis-associated pain (60). A Cochrane review evaluated four clinical trials, including a total of 334 infertile endometriosis patients. There is lack of evidence to recommend pentoxifylline for pain relief or to improve the chances of spontaneous pregnancies (98).

Antiangiogenic agents. Neoangiogenesis is essential for the initiation, growth, invasion, and recurrence of endometriosis. A wide variety of antiangiogenic agents has been evaluated in vitro as potential treatments for endometriosis. These include growth factor inhibitors, endogenous angiogenesis inhibitors, fumagillin analogues, statins, cyclooxygenase-2 inhibitors, phytochemical compounds, immunomodulators, dopamine agonists, peroxisome proliferator-activated receptor agonists, progestins, danazol, and gonadotropin-releasing hormone (GnRH) agonists. However, clinical evidence for the efficacy and safety of most of them is still lacking (99).

Different members of the statin family have been shown to be effective in vitro in reducing angiogenesis and endometriotic implant size in mice (47, 62, 63, 66, 70), rats (68), and human cells in vitro (67, 69, 71). The angiogenesis inhibitor lodamin, an oral nontoxic formulation of TNP-470, statistically significantly decreased endothelial progenitor cell levels while suppressing lesion growth (72).

Romidepsin is a histone deacetylase (HDAC) inhibitor. It targets VEGF at the transcriptional level, which subsequently leads to the reduction of the secreted active form of VEGF from human immortalized epithelial cells. Thus, romidepsin may be a potential therapeutic candidate against angiogenesis in endometriosis (73). The immunoconjugate (Icon) molecule of romidepsin binds with high affinity and specificity to aberrant endothelial tissue factors. It has been shown to induce a cytolytic immune response that eradicates tumors and choroidal blood vessels. In a nude mouse model of endometriosis, Icon romidepsin destroyed endometriotic implants by vascular disruption without apparent toxicity, reduced fertility, or subsequent teratogenic effects. Unlike other antiangiogenic treatments that can only target developing angiogenesis, Icon romidepsin eliminates preexisting pathologic vessels. Consequently, Icon romidepsin could serve as a novel nontoxic, fertility-preserving, and effective treatment for endometriosis (74).

Multiple dopaminergic agonists also exhibit antiangiogenic activities. Cabergoline was shown to decrease VEGF and VEGFR-2 protein expression in cabergoline-treated mice (75). In addition, cabergoline and quinagolide have an equal effect in reducing endometriotic lesions as antiangiogenic agents (76). Moreover, cabergoline and bromocriptine were comparable to GnRH agonist in reducing endometriotic lesion size in one human study (77). Cabergoline induced a similar reduction of endometrioma size compared with triptorelin acetate (78). Another dopaminergic agonist, quinagolide, led to the down-regulation of VEGF and VEGFR-2, and also had anti-inflammatory effects in endometriotic lesions in hyperprolactinemia patients (76).

Peroxisome proliferator receptor γ (PPARγ) ligands have been shown to inhibit the proliferation and reduce the vascularization of endometriotic lesions by affecting the expression of the angiogenic factor VEGF. Rosiglitazone and pioglitazone are members of this family. Baboons treated with rosiglitazone and pioglitazone showed a lower volume of endometriotic lesions compared with placebo (80, 81). Rosiglitazone is associated with an increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes. This led to the premature termination of all clinical trials for evaluating its effectiveness on endometriosis-related pain (100, 101).

Bentamapimod is a c-Jun NH2-terminal kinase inhibitor (JNKI). A prospective randomized, placebo-controlled study in baboons was conducted to evaluate its feasibility in treating induced endometriosis. Compared with placebo or treatment with JNKI alone, JNKI + medroxyprogesterone (MPA) or cetrorelix resulted in a lower total lesion size. Treatment with JNKI alone was as effective as JNKI + MPA or JNKI + cetrorelix in reducing induced endometriosis in baboons, with a lower surface area and volume of endometriotic lesions compared with placebo. It also has fewer side effects and less effect on cycle length or serum reproductive hormones (85).

FUTURE DIRECTIONS

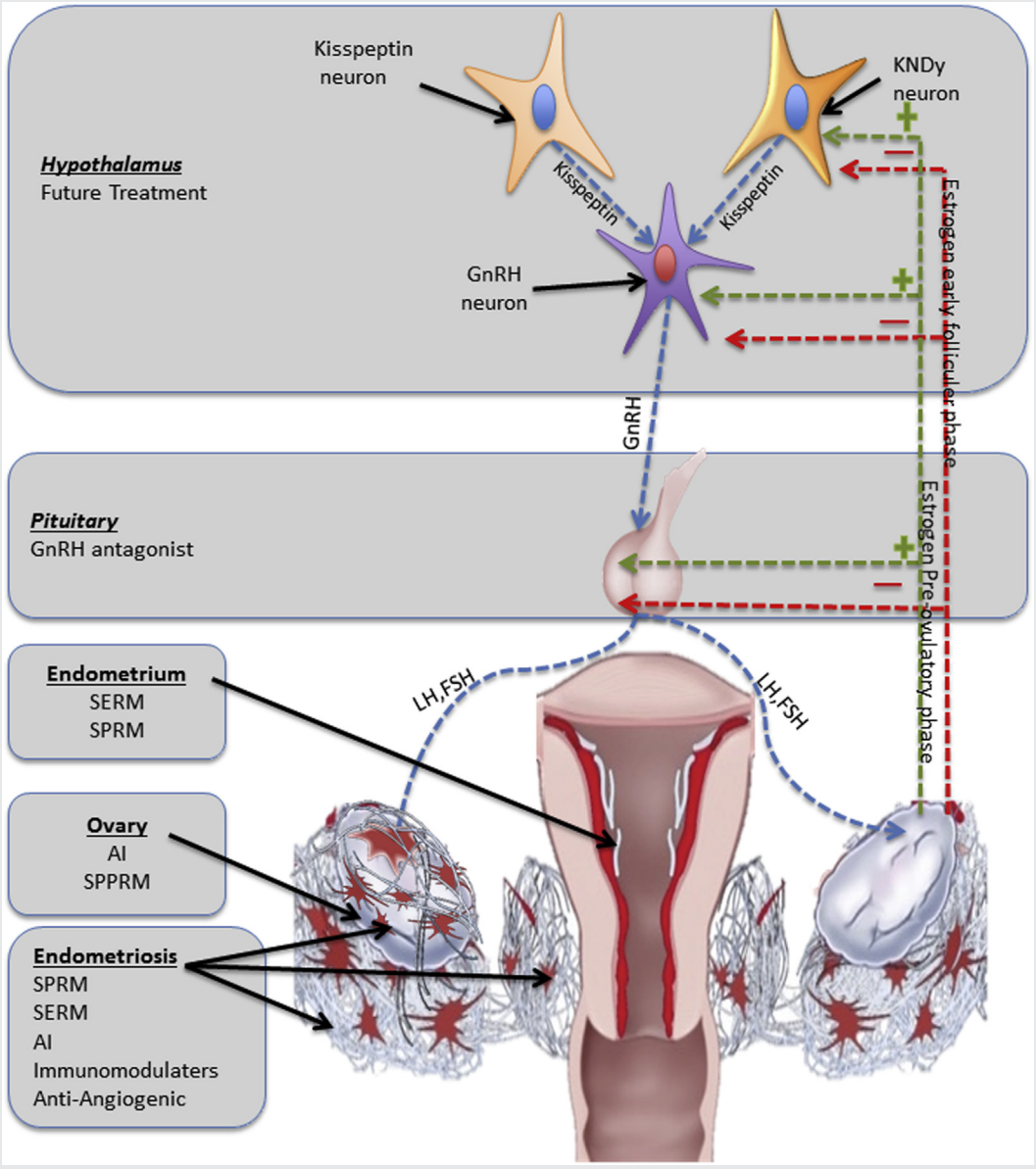
Currently, the treatment choices for symptomatic endometriosis are based on patient preferences, treatment goals, the side-effect profile, and the efficacy, costs, associated comorbidities, and availability (18). Recent discoveries in neuroendocrinology, endocrinology, tumorigenesis, neurogenesis, and genomics will greatly transform the current management approaches for endometriosis. A few related recent reports are noteworthy.

First, a group of hypothalamic neurons colocalized in the arcuate nucleus involving three neuropeptides—kisspeptin, neurokinin B (NKB), and dynorphin—have been collectively termed KNDy neurons. There is accumulating evidence to suggest they interact to affect pulsatile GnRH release, where kisspeptin stimulates, NKB modulates, and the opioid dynorphin inhibits the pulsatile release of GnRH (102). This has led to the establishment of the kisspeptin/neurokinin B/dynorphin (KNDy) hypothesis, which suggests that KNDy neurons in the arcuate nucleus may interact to control the release and pulsatility of GnRH (103). In a very recent study and for the first time in humans, LH was used as a surrogate marker to elucidate the interactions of KNDy signaling in regulating GnRH release and pulsatility (104).

It is interesting that we have shown that kisspeptin is differentially expressed at the level of the endometrium in patients with and without endometriosis. In addition, kisspeptin expression was statistically significantly lower in deep infiltrating endometriosis compared with superficial peritoneal disease (96). This has important implications not only for improving our understanding of the pathogenesis of endometriosis but also for optimizing novel hormonal agents to treat different disease phenotypes (Fig. 1).

Second, endometriosis as a major cause of CPP acts as a cyclic source of peripheral nociceptive input. Recent data support the hypothesis that changes in the central pain system also play an important role in the development of chronic

FIGURE 1



Schematic representation of the different experimental treatments for endometriosis with their target sites. Kisspeptin/neurokinin B/dynorphin (KNDy) neurons with their hypothalamic connections were also identified as a potential target.

Bedaiwy. Future of endometriosis medical therapy. Fertil Steril 2017.

pain, regardless of the presence of endometriosis. Women with endometriosis-associated CPP displayed decreased gray matter volume in brain regions involved in pain perception. Women with CPP without endometriosis also showed decreases in gray matter. These changes were not observed in patients with endometriosis who had no CPP (34). Consequently, the presence or absence of central nervous system changes should be taken into consideration when thinking about CPP. In the endometriosis patient with central sensitization, other treatment strategies could be offered such as neuromodulators or myofascial trigger point injections. Multidisciplinary approaches to the sensitized patient should also be considered, such as physiotherapy (105) and cognitive treatment (106), although more clinical trials specifically in endometriosis are required.

In addition, endometriosis has been associated with local neurogenesis, which in combination with central sensitization would further amplify pain signaling. Using highly phenotyped patients with cul-de-sac/uterosacral endometriosis, with or without deep dyspareunia, we found that the local nerve bundle density was statistically significantly higher in women with deep dyspareunia (107). Nerve growth factor

has been shown to be a major neurotrophic factor in endometriosis (108) and may be implicated in this increase in local nerve density. Further research into the signaling underlying local neurogenesis in endometriosis is needed to identify potential treatment targets.

Furthermore, treatments targeted to genes associated with endometriosis remain a future hope. Genomewide association studies have demonstrated several reproducible loci associated with endometriosis, particularly for moderate-to-severe disease (109). Before these findings translate to clinical practice, additional work will be required to identify the genes adjacent to the loci that are of pathophysiologic importance for endometriosis and the signaling pathways associated with these genes.

CONCLUSION

In conclusion, although current medical treatments are helpful for many women with endometriosis, these treatments have limitations that include side effects in some women and contraceptive action for women desiring to conceive. Emerging medical treatments range from GnRH antagonists, SPRM/SERM, aromatase inhibitors, immunomodulators, and antiangiogenic drugs. More research into local neurogenesis, central sensitization, and the genetics of endometriosis may provide future targets. Endometriosis has a highly variable phenotype, and thus a wide variety of medical treatments targeting different pathways is likely to be important to move toward precision health (personalized medicine) in endometriosis.

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