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REVIEW

Endometriosis: Current and Emerging Therapies

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Abstract: Endometriosis remains a cause of significant morbidity in reproductive-aged women resulting in pelvic pain, pelvic masses and infertility. Endometriosis is defined as the presence of endometrial glands and stroma outside of their normal intrauterine location, most commonly in the dependent portions of the pelvis. Endometriosis can be treated with medical therapies or surgery, both conservative and radical. The medical therapies include oral contraceptive pills, progestins, gonadotropin releasing hormone analogues and danazol. All of these medical therapies induce a hormonal steady state that results in an environment not conducive to the growth of endometriosis. Surgical therapies for endometriosis-associated pain include conservative treatments which include removal of endometriotic implants and adhesions with restoration of normal anatomy. Radical surgery involves removal of the uterus with or without removal of the ovaries in patients who have completed childbearing. Basic science discoveries about endometriosis hold the promise for less invasive diagnostic tests and improved therapies.

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Introduction

Endometriosis is a significant cause of morbidity in reproductive aged women, resulting in pelvic pain, pelvic masses and infertility. Endometriosis is defined by the presence of endometrial glands and stroma outside of the normal intrauterine location, most commonly in the dependant portions of the pelvis.[1]

The etiology of endometriosis remains enigmatic and an area of ongoing research. Retrograde menstruation with survival of viable endometrial implants remains a probable cause of most cases of endometriosis. However, atypical or extragenital endometriosis can not always be explained by retrograde menstruation. Other theories have been developed to explain these unusual presentations of endometriosis, including lymphatic and vascular spread, coelomic metaplasia or direct inoculation. Immunologic and genetic differences may also explain why one patient develops the disease while others remain unaffected.[2]

The gold standard for the diagnosis of endometriosis depends upon surgical evaluation with histopathologic confirmation of endometrial glands and stroma outside of the uterine cavity. A noninvasive, precise method of diagnosing endometriosis is needed.[3]

The treatment of endometriosis depends on the presenting symptoms as well as the patient's future fertility desires. Treatment modalities include both surgical, conservative or radical, and medical therapies.

Medical Therapies

All current medical therapies for endometriosis function by interrupting the cyclic changes in estrogen and progesterone normally seen during the menstrual cycle, resulting in a steady state. This lack of cyclic hormonal changes results in a suboptimal state for endometriotic lesion growth. A Cochrane review demonstrated no significant difference between oral contraceptive pills (OCPs), Danazol, progestins and GnRH agonists in the treatment of endometriosis-related pain. Continuous OCPs have a better response for dysmenorrhea than cyclic OCPs.[4]

Gonadotropin Releasing Hormone Analogues

Gonadotropin releasing hormone (GnRH) is a decapeptide produced in the preoptic area of the hypothalamus. GnRH is released from the hypothalamus in a pulsatile fashion and it functions by binding to its receptor located on the pituitary gonadotropes. In response, the gonadotropes released luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH and FSH then stimulate the gonads to produce sex hormones and gametes. If GnRH is absent or continuously administered it results in a hypogonadotropic hypogonadal state.

GnRH Agonists

The native GnRH molecule has a short half-life of 2 to 4 minutes. GnRH agonists have substitutions at amino acid position 6, which protects against proteolysis, and the c-terminus which enhances binding to the receptor. These modifications of the native molecule result in a prolonged half-life and enhanced activity. The GnRH agonists function by binding to the GnRH receptor and de-sensitizing and down-regulating the receptor.

Initially after the GnRH agonist binds to its receptor on the gonadotrope there is an increase in gonadotropin release. This initial increase in luteinizing hormone (LH) and follicle simulating hormone (FSH) levels can increase sex hormone production by the ovary. This increase in ovarian hormone production, also known as the flare, usually lasts 7 to 10 days and can increase symptoms of endometriosis and other estrogen dependant diseases. Following the flare there is a decrease in LH and FSH resulting in a hypogonadotropic hypogonadal state. In endometriosis, this hypogonadotropic hypogonadal state results in atrophy of the eutopic endometrium and of ectopic endometrial implants which results in amenorrhea and alleviation of symptoms.[5]

The achievement of the hypogonadal state with GnRH agonists results in a number of symptoms similar to those of the menopause including vasomotor symptoms, vaginal dryness, dyspareunia and loss of bone. This loss of bone is similar to the initial loss seen when a woman goes through natural menopause. When the GnRH agonist is discontinued the bone recovers. These menopausal signs and symptoms prompted the US Food and Drug Administration (FDA) to recommend only using a GnRH agonist by itself for up to 6 months.

In the hypogonadotropic hypogonadal patient, add-back therapy with estrogen, progestins or the

combination of estrogen and progestins may improve symptoms and bone loss related to the low estrogen environment. The estrogen threshold hypothesis supports a differential sensitivity to estrogen in different estrogen responsive tissues. According to the estrogen threshold hypothesis add back therapy works because bone will respond favorably to lower estrogen levels that will not stimulate the endometrium or endometriosis. With add-back therapy adverse effects are minimized and one is no longer constrained to 6 months of therapy with GnRH analogues for endometriosis.[6]

GnRH Antagonists

GnRH antagonists are decapeptides which are competitive antagonists for the GnRH receptor. When they bind to the receptor they result in an immediate decrease in LH and FSH production, which results in an immediate hypogonadotropic hypogonadal state. This is a clear advantage for the GnRH antagonists in that they do not elicit a flare response and hence will not exacerbate endometriosis-associated symptoms. There are three GnRH antagonists currently available for clinical use; Ganirelix, cetrorelix, and degarelix. Ganirelix and cetrorelix have short half lives and are usually given subcutaneously daily. Cetrorelix in a 3 milligram dose can suppress gonadotropins for four days or 96 hours.[7]

The GnRH antagonists have similar side effects as the GnRH agonists. With the advent of the hypogonadal state the patient may have vasomotor symptoms, vaginal dryness and bone loss.

Danazol

Danazol is an isoxazole derivative of 17 α-ethinyltestosterone. It functions by binding to the androgen, progesterone and glucocorticoid receptors and inhibits key enzymes in steroid biosynthesis. Danazol has been demonstrated to stem the midcycle and menopausal increase in gonadotropins, however, it does not suppress baseline gonadotropin levels. The half-life of danazol is approximately 15 hours so it can be given twice daily and achieve stable levels. The customary dose of danazol for the treatment of endometriosis is 400 mg twice daily. The side effects at this dose are usually mild and are primarily related to androgenic activity, weight gain, edema, oily skin, acne, hirsutism, decreased breast size, lowering of the voice, increased muscle mass and increased libido. Other potential side effects include headaches and hot flushes. The severity of these side effects can be reduced by lowering the dose of danazol. However, lowering the dose may allow for ovulation which could result in pregnancy. Danazol is a non-aromatizable androgen and hence it can cross the placenta unchanged and result in virilizing affects on the developing female fetus. The GnRH analogues have significantly reduced the use of danazol as a treatment for endometriosis.[8]

Oral Contraceptive Pills (OCPs)

Combined oral contraceptive agents are combinations of a progestin and estrogen. There are currently monophasic, multiphasic and progestin only regimens. The customary method of taking OCPs is to take the hormonally active pill for 21 days followed by 7 days of placebo. This allows for withdrawal bleeding during the 7 days of placebo. There are new methods that focus on the continuous administration of the hormonally active pill for a prolonged period of time, including one method where an active pill is taken every day of the year. The purpose of the continuous administration is to suppress withdrawal bleeding, which can assist in the relief of dysmenorrhea. Recent pharmacologic developments allow the delivery of estrogen and progestin, with similar reproductive effects as OCPs, via a patch or a vaginal ring.[9]

In OCPs the progestin component inhibits luteinizing hormone (LH) secretion and inhibits ovulation, thereby supplying the contraceptive action of the pill. The progestin also results in thickening of the cervical mucus as well as decidualization and atrophy of the uterine endometrium. The progestin also has a similar effect of decidualization and atrophy on endometriotic lesions. The estrogen component suppresses FSH and reduces withdrawal bleeding. The treatment of endometriosis with the combination of estrogen and progesterone is felt to induce a "pseudo-pregnant" state.[10]

Progestins

Progesterone is an important hormone in the human serving a role in reproduction as well as a precursor to a number of steroid hormones including androgens, estrogens, mineralocorticoids and glucocorticoids. Progesterone exerts its physiological effects by binding

to the progesterone receptor, which then dimerizes and binds to the progesterone response element initiating DNA transcription. The progesterone receptor has both an A and B isoform. Progesterone has a number of different physiologic effects depending on the distribution of receptors, progesterone concentration and involved tissue. In terms of the endometrium, progesterone is primarily secreted after ovulation by the corpus luteum which converts the proliferative endometrium into its secretory state. The conversion and maintenance of the endometrium in a secretory state with ultimate decidualization is important in initiating and maintaining a pregnancy.

Endometriotic lesions tend to be more resistant to progesterone. High doses of progesterone induce decidualization and atrophy of endometriotic implants as well as induce a hypogonadotropic hypogonadal state.[11]

There are a number of progestins or compounds that have progesterone-like activity. These agents include the 19 alpha-acetoxyprogesterone derivatives (pregnanes), 19-nortestosterone derivatives (estranes), norgestrel compounds (gonanes) and the C21 steroids medroxyprogesterone acetate and megestrol acetate. These compounds can be given orally, subcutaneously, intramuscularly, and intrauterine.

Endometriosis-Associated Pain Treatment

Non-steroidal anti-inflammatory drugs (NSAIDs) are reasonable first line agents in the treatment of pain associated with endometriosis. By decreasing prostaglandin levels and central analgesic effects the NSAIDs may result in sufficient pain relief in many subjects.[12]

Current medical therapy for women with endometriosis-associated pain primarily functions by interrupting the normal monthly cycle of hormones in reproductive age women. The goal of this interruption of reproductive hormones is to cause a suboptimal environment for the development and growth of endometriosis. A Cochrane review demonstrated that all of the current medical therapies for endometriosis including GnRH analogues, oral contraceptive pills, medroxyprogesterone acetate, gestrinone and danazol similarly reduce endometriosis-associated pain over a 6-month period of time.[13] This suggests that appropriate therapy can be selected based on fewest side effects, improved compliance and cost of the specific medication.

In the patient with presumed endometriosis-associated pain, dysmenorrhea and dysparuenia, the use of oral contraceptive pills (OCPs) have been demonstrated to improve pain. Previous studies have demonstrated improvements in dysmenorrhea with OCPs which is equivalent to the relief afforded by GnRH analogues.[14] If patients have continued dysmenorrhea despite cyclic OCP use, one may use continuous OCPs which have been demonstrated to improve cyclic pain by inducing amenorrhea and improved pain.[15]

Progestins have been used in a number of studies evaluating pain relief in patients with endometriosis and in most studies have shown a 70%–90% improvement. Schlaff et al in a recent, prospective, double-blind trial demonstrated that Depot-medroxyprogesterone acetate had similar efficacy in the treatment of endometriosis-associated pain as leuprolide acetate, with fewer vasomotor symptoms.[16] The levonorgestrel intrauterine system has also been demonstrated to improve symptoms. In a prospective trial the levonorgestrel intrauterine system had a statistically significant reduction in endometriosis-associated chronic pelvic pain over 6 months. This reduction in pain with the levonorgestrel intrauterine system compared favorably to the pain relief afforded by the gonadotropin-releasing hormone agonist in this trial.[17]

In patients with endometriosis-associated pain, a reasonable initial approach is to begin OCPs or progestins in a continuous fashion. Similar to GnRH agonists, continuous use of OCPs and continuous progestins should result in amenorrhea with reduced retrograde menstruation. Continuous OCPs, continuous progestins, and GnRH agonists with add-back therapy can be successfully and safely used for a number of years in endometriosis-associated pain. Patients will often wonder if they need to have a "monthly menstrual cycle"; the lack of a monthly menstrual cycle in treated patients is not necessary and does not increase their risk of later complications.

If the initial medical therapy fails to improve the patient's pain it is important to rule out other potential causes and sources of pain. If after a thorough evaluation endometriosis remains high on the differential diagnosis list a trial of a GnRH agonist

for 3 months is a reasonable option versus performing a diagnostic laparoscopy. This 3 month regimen has been demonstrated to improve pain in this group of patients suspected of having endometriosis.[18]

Surgery, both conservative and radical, remains an effective method of improving pain secondary to endometriosis. Surgery with excision or destruction of endometriotic implants is as effective as medical therapies in alleviating pain from endometriosis.[19] In randomized controlled trials, conservative surgery has been shown to improve pain by 62.5%–80% in patients with endometriosis as compared to 22.6%–32% for controls.[20,21]

Recurrence of pain following conservative surgery, especially immediately after surgery, should alert one to the possibility of co-existence of adenomyosis, interstitial cystitis, or other potential causes of pain. In patients with adenomyosis associated with endometriosis, conservative removal of the endometriosis will not usually completely alleviate their pain. Adenomyosis often results in an enlarged boggy uterus, with menorrhagia and dysmenorrhea. Pelvic magnetic resonance imaging (MRI) has revolutionized the diagnosis of adenomyosis, allowing one to reproducibly and accurately determine the presence of this condition. However, due to the cost of MRI most would not suggest obtaining a pre-operative pelvic MRI, unless the physician has a high-index of suspicion for the presence of adenomyosis in their patient. The use of post-operative medical therapies such as continuous OCPs or progestins can significantly enhance pain relief in this group of patients.

Endometriomas can be associated with pain and infertility. It is suggested that endometriomas be removed if there is no history of proven endometriosis since one needs to histologically document that the ovarian mass is an endometrioma. Another reason to remove an endometrioma is if it is large (>3 centimeters in diameter). One concern with an endometrioma is the possibility of co-existent malignancy. Recent studies have demonstrated an increased risk of of malignant transformation in patients with endometriosis.[22] A cystectomy is associated with a lower risk of pain recurrence than simple drainage or coagulation of the endometrioma. It is also important to note that removal of an endometrioma can reduce ovarian reserve by excising normal ovarian cortex at the time of cystectomy.[23]

In the patient who has completed child-bearing, hysterectomy with bilateral salpingo-oophorectomy accompanied by removal of endometriotic lesions is considered definitive therapy. In subjects in whom the ovaries are not removed the patient has a higher incidence, about 60%, of recurrence of pain and about half of these patients require further surgery.[24] Another study evaluated re-operation rates at 2, 5 and 7 years in women with endometriosis-associated pain who had a hysterectomy with or without oophorectomy. In those patients who had a hysterectomy and bilateral oophorectomy the rate of re-operation was 4%, 8.3% and 8.3% compared to 4.3%, 13.4% and 23% in those with ovarian preservation, at 2, 5 and 7 years respectively. In younger patients there was no significant difference between preserving or removing the ovaries and rate of re-operation.[25] These new results are reassuring and suggest that it is reasonable in a reproductive-aged patient with endometriosis to preserve a normal appearing ovary at the time of hysterectomy.

The peri-operative use of medical therapy may have some benefits in patients with endometriosis-associated pain. Pre-operative use of medical therapy has not been shown to improve the operative outcome,[26] however, postoperative medical treatment may be beneficial.[26,27] Postoperative GnRH agonists, OCPs and the levonorgestrel intrauterine system have been demonstrated to delay the return of endometriosis-associated symptoms in a number of patients.

The recurrence of pelvic pain following conservative and radical surgery for endometriosis is a cause of significant morbidity for patients. Following conservative surgery 36%–55% of patients require further surgery for recurrence of their symptoms, and the need for further surgery increases with time from the initial surgery. Following definitive hysterectomy patients may also have a recurrence of symptoms regardless of postoperative hormone replacement therapy.[28]

Endometriosis-Associated Infertility

The treatment of endometriosis-associated infertility with medical therapies has not been demonstrated to improve fertility. In fact, most medical therapies have been demonstrated to delay pregnancy.[29]

In patients with minimal to mild endometriosis, previous studies have demonstrated improvement

in fertility following conservative surgery. Two randomized controlled trials have been conducted in this group of women with subfertility and minimal to mild endometriosis. In the first trial the authors demonstrated an improvement in fertility (odds ratio 2.06, 95% CI 1.28, 3.33) in women with endometriosis who had ablation of peritoneal implants.[30] In a second RCT there was no difference in fertility rates between the diagnostic and operative groups.[31] A meta-analysis of these two trials demonstrated an improvement in fertility with an odds ratio of 1.65 (95% CI, 1.06, 2.58).[32]

There have been no randomized controlled trials of the improvement of fertility following conservative surgery in those patients with more severe disease. However, most surgeons who operate on patients with endometriosis have had severe cases with conception following conservative surgery.

In patients with endometriosis, especially those with moderate and severe disease, in vitro fertilization remains a mainstay of therapy. Studies have demonstrated that endometriosis does not have a detrimental affect on the success rate with in vitro fertilization.[33] In patients preparing for in vitro fertilization, the removal or ablation of endometriomas has not been demonstrated to improve pregnancy rates. In fact, the removal of endometriomas may reduce the number of eggs retrieved from the surgically manipulated ovary. Some patients with endometriosis may benefit from prolonged down-regulation with GnRH agonists prior to beginning stimulation. One must be aware that these patients with prolonged down-regulation may require longer or higher doses of gonadotropin stimulation. In patients with endometriosis who are preparing to proceed with in vitro fertilization, especially if they have failed to become pregnant with previous IVF cycles, one needs to discuss the option of prolonged down regulation prior to starting therapy.[34]

Other Medical Therapies

Endometriosis is an area of emerging treatments based on basic biologic and genetic research. A number of innovative, transitional therapies are currently being evaluated for therapy of endometriosis. These medical treatments include aromatase inhibitors, antiprogestins, selective estrogen receptor modulators, immunomodulators and inhibitors of angiogenesis as well as inhibitors of metalloproteinase enzymes.

Previous basic science studies have demonstrated increased aromatase activity in endometriotic implants. It has also been demonstrated that endometriosis is an estrogen-dependent neoplasm. These observations have stimulated interest in using aromatase inhibition as a possible treatment for endometriosis-associated symptoms.

Case studies and series have shown improvement in endometriosis-symptoms with the use of aromatase inhibitors and progestins.[35–37] In reproductive-age women, aromatase inhibitors can stimulate folliculogenesis with its concomitant rise in estrogen levels. Because these rising estrogen levels could stimulate endometriotic lesion growth, aromatase inhibitors when used to treat endometriosis are combined with progestins, OCPs, or GnRH agonists to halt folliculogenesis. Further study is needed to explore this exciting class of compounds as therapy for endometriosis.

There are over 400 progestin analogues which have been developed and may play a role as a future treatment of endometriosis-related symptoms. Selective Progesterone Receptor Modulators (SPRMs) are molecules with an agonistic, antagonistic, or both agonistic-antagonistic affect depending on the hormonal environment. RU486 is a pure antagonist which been investigated in the treatment of a number of diseases including endometriosis. In trials RU486 in doses up to 100 mg/day have been shown to improve pain and result in regression of lesions in endometriosis.[38] Other SPRMs are currently being investigated for the treatment of endometriosis.[39]

Another area of active research is using immunomodulating agents in patients with endometriosis. Hopefully by altering the abnormal immune response in endometriosis one can relieve their symptoms. Some of the agents used in initial studies include pentoxifylline, tumor necrosis factor-alpha blockers and peroxisome proliferator-activated receptor gamma ligands. While some of the studies have showed promise others have been disappointing.[40–43]

Endometriosis is an enigmatic disease which continues to cause significant morbidity for reproductive-aged women. Basic science research directed at endometriosis continues to identify new potential targets for therapeutic agents. Recent examples

include the use of agents which target angiogenesis or metalloproteinase enzymes. The metalloproteinase enzymes and angiogenic factors are important components of the basic pathophysiology of endometriosis. New advances in our understanding of the fundamental mechanism of this disease should ultimately identify therapies which alleviate the pain and infertility of endometriosis.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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