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MEDICAL MANAGEMENT OF ENDOMETRIOSIS

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Abstract

Endometriosis is a chronic medical condition that affects around 6–10 % of reproductive age women. Pelvic pain, dysmenorrhea and infertility are the most common presenting symptoms. The disease is characterized by estrogen dependent growth of the endometrial glands and stroma outside the endometrial cavity. The diagnosis requires a high degree of suspicion and can be only confirmed on histopathology. Treatment includes medical and surgical options. Both hormonal and non-hormonal medical options are available and are tried at first with a goal to control pain and stop the growth of the endometriotic lesions. NSAIDs, oral contraceptive pills, GnRH agonists, aromatase inhibitors are some of the commonly used medications. With more research on the molecular and biochemical aspects of endometriosis, newer targets of therapy are being developed like selective progesterone receptor modulators, anti-angiogenic factors and immunomodulators. In women who do not respond to medical therapy or have severe symptoms, surgical excision of the endometrial lesions and adhesions is often helpful and offers confirmatory diagnosis by histopathology.

Keywords

Endometriosis; medical management; pelvic pain

INTRODUCTION

Endometriosis is a chronic medical condition characterized by the presence of endometrial glands and stroma outside the endometrial cavity. It affects approximately 6-10% of reproductive age women, however, the reported prevalence is 20–50% in women with infertility and 30–80% in women with pelvic pain.[1, 2] Endometriosis is a challenging medical condition with debilitating effects on the life of patients. It is also a diagnostic dilemma for physicians with majority of patients being asymptomatic or presenting with atypical symptoms. The final diagnosis requires surgery and histopathology of the lesions, which further delays the management. Suspicion is higher in women presenting with the classical triad of dysmenorrhea, dyschezia (pain during defecation) and dyspareunia.

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Although the exact pathogenesis is still a subject of research, the most predominant theory is of retrograde menstruation. It is proposed that with retrograde menstruation the endometrial glands and stroma are attached and implanted in peritoneal cavity. Other popular theories include celomic metaplasia, stem cell origin and lymphatic and hematogenous spread. Genetic predisposition, hormones and immunological status is also proposed to have an effect along with new research suggesting a role of environmental exposure to certain agents.[3]

The most common site of endometriosis is the ovaries with spread to anterior and posterior cul-de sac, broad ligament, fallopian tube, uterosacral ligaments, uterus, fallopian tubes, sigmoid colon, appendix and round ligament. Other areas, which are less commonly involved, include the vagina, cervix, recto-vaginal septum, cecum, ileum, inguinal canal, perineal scars, urinary bladder, ureter and the umbilicus. Rare cases of endometriosis of gastrointestinal tract, bones, vertebra, central nervous system and lungs have been reported. These lesions are hormonally active and respond to the cyclical changes in estrogen and progesterone and may have a different appearance in various phases of the menstrual cycle. Grossly they can range from red, brown, black, white, yellow, pink, clear or red vesicle. There could be degree of hemorrhage, fibrosis and inflammation depending on the duration of the lesions.

Clinically approximately one third of women are asymptomatic. When symptomatic, pelvic pain is the most common presenting symptom.[4] Other symptoms include dysmenorrhea, dyspareunia, dyschezia, irregular bleeding, low back pain, hematuria and dysuria.[5] In rare cases, endometriosis of the lungs and brain may present with hemoptysis and seizures. Endometriosis related pain is attributed to the increase in inflammatory mediators, neurological dysfunction and estrogen mediated neuromodulation of the peripheral sensory neurons.[6] Studies have found increased number of inflammatory cells like macrophages and pro-inflammatory cytokines like interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF) in the endometrial lesions.[7] Increased production of prostaglandins (PGs) along with chronic inflammation leads to pain.

Infertility in endometriosis is proposed to be due to multiple mechanisms including underlying adhesions, ovarian cysts and change in tubal anatomy. Excess production of inflammatory mediators can also result in suboptimal function and damage to oocyte and sperm along with decreased endometrial receptivity.[8] Studies have also shown that women with endometriosis have a decreased ovarian reserve predicted by low levels of anti-mullerian hormone.[9]

The definitive diagnosis of endometriosis can only be made by histopathology showing endometrial glands and stroma with varying degree of inflammation and fibrosis. No serum markers are currently available that can diagnoses endometriosis. CA −125 levels can be elevated, however, it has limited clinical utility as the levels can be elevated in other conditions as well. Imaging studies like ultrasonography, CT and MRI are helpful in cases of ovarian cysts or adnexal masses.[10]

Endometriosis related pain leading to dysmenorrhea, pelvic pain, dyspareunia, dyschezia is often the most common presenting complaint and can seriously effect the quality of life of women and their mental and emotional health.[11] As the endometriotic lesions are hormonally active, modifying the hormonal milieu of the body helps in suppression of the lesions and suppress the inflammatory mediators leading to pain. The management of endometriosis includes medical and surgical treatment options. Often the medical management is offered first, reserving surgery for resistant or recurrent cases. The focus of this chapter is on the medical management of endometriosis and in the next section we will discuss the various available therapeutic options in detail.

MEDICAL MANAGEMENT OF ENDOMETRIOSIS

In recent years, a lot of research has been done to develop new therapies for the treatment of endometriosis. To understand how the currently available therapies work, it is crucial to understand the underlying biochemical abnormalities and the therapeutic targets. Exaggerated inflammatory responses, along with excess production of estrogen, and progesterone resistance are some of the critical underlying mechanisms that lead to the symptoms of endometriosis.[6] Studies have shown that the endometriotic implants have impaired molecular and immunological functions. This leads to increased production of estrogen, pro-inflammatory cytokines, prostaglandins and metalloproteinases and a failure of immune cells to suppress and clear the inflammatory response.

Constant supply of estrogen is crucial for the growth and persistence of the endometriotic implants, which comes from multiple sources. First, the endometrial implants have intrinsic aromatase activity, which leads to the conversion of cholesterol to estradiol.[12] The endometrium is rich in PG-E2 receptors and activation of the PG receptor subtype EP-2 leads to activation of cyclic AMP, which increases the expression of key steroidogenic genes, and aromatase activity eventually leading to increased estradiol production. Along with intrinsic aromatase activity estradiol produced from ovary and peripheral fat also reaches the sites of endometriosis. This continuous supply of estrogen is important for the continuous growth and survival of endometriotic implants.

Pelvic pain in endometriosis is secondary to increased concentrations of PGs, especially of the subtype E2 and F2α.[13] Cyclooxygenase catalyzes the conversion of arachidonic acid to PGH2 which is converted to PGE2 and F2α via the action of PG synthetase.[14] COX 2 is expressed in higher concentrations in the endometrial implants as compared to the normal endometrial cells.[15] Again, as discussed previously, the increased concentration of PGE2 also provides a stimulus for estrogen production. Along with estradiol and PGE2, studies have shown a role of cytokines, especially IL-1β and angiogenic factors like vascular endothelial growth factor (VEGF) in inducing COX-2 expression and increased PG production in endometriotic implants.

Growing evidence also suggests a role of progesterone resistance in women with endometriosis. Studies have shown that the endometriotic lesions have a low progesterone receptor level.[16] Progesterone is important for the activation of key enzyme 17-beta-hydroxy-steroid-dehydrogenase 2, which helps in converting estradiol to estrone, which is

less biologically active. Thus, increased production of estradiol and decreased clearance leads to the growth of the endometriotic tissue.[17](Table 1)

ENDOMETRIOSIS AND MEDICATIONS

The medical management of endometriosis is targeted towards controlling pain and suppression of the hormonally active endometriotic tissue. Over years, several therapeutic options have been developed and successfully used to achieve these aims and newer targets are being developed at a fast pace. A trial of non-steroidal anti-inflammatory drugs (NSAIDs) initially can be helpful in controlling the pain associated with dysmenorrhea. Hormonal therapies that rely on suppression of the endometriotic tissues include combined oral contraceptives, progesterone only contraceptives, gonadotropin releasing hormone (GnRH) agonists, aromatase inhibitors and danazol. Although quite successful, they have unwanted side effects secondary to hormonal suppression and need to be closely monitored. (Table 2)

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

NSAIDs are the most commonly used first line agents in the management of endometriosis related pain and dysmenorrhea.[18] The pain in endometriosis is mostly secondary to elevated levels of PGs, interleukins and cytokines. NSAIDs work by blocking the enzyme COX that is crucial for the production of the inflammatory mediators. Although, both COX1 and COX2 receptors are present, studies have shown that the ectopic endometrial tissues have a higher concentration of COX 2 receptors. Both selective and non-selective COX inhibitors are widely used for symptomatic relief. Along with pain control, new studies have shown that selective COX 2 inhibitors like rofecoxib can also inhibit the growth of the endometrial tissue.[19] Despite inconclusive evidence regarding effectiveness of NSAIDs in controlling endometriosis related pain and negative gastrointestinal side effect profile, a trial of NSAIDs is the most common first intervention in patients with pelvic pain.

COMBINED HORMONAL CONTRACEPTIVES

The suppression of ovaries and disease activity forms the basis of the use of hormonal contraceptives in endometriosis and they are the most commonly used first line hormonal therapy. Estrogen and progesterone combinations or progesterone alone lead to decidualization of the endometriotic tissue and is proposed to slow the progression of the disease. They have been used with varying degree of success in women with endometriosis. Cost, ease of administration and tolerability are some of the key features that have made their use popular. As compared to cyclic administration, continuous therapy with COC has been shown to have better pain control.[20] However the limiting factors include long-term administration, risk of thromboembolism, high rates of recurrence after discontinuation and impaired fertility due to contraceptive action. Combinations containing lower dose of ethinyl estradiol (20 micrograms) as compared to high dose (30 micrograms) have a lower risk of venous thromboembolism and are currently recommended.[21]

GONADOTROPIN RELEASING HORMONE AGONISTS (GnRH AGONISTS)

The successful use of GnRH agonists is based on the fact that it leads to profound hypoestrogenism by blocking ovarian estrogen production and hence regression of endometriotic implants. During the first few days of administration, GnRH agonists stimulate the pituitary releasing FSH and LH, however, chronic administration leads to downregulation of pituitary GnRH receptors that results in suppression of the hypothalamic pituitary ovarian axis leading to anovulation. This eventually leads to hypoestrogenism, amenorrhea and regression of the endometriotic implants by depriving the implants of estrogen that is crucial for their survival. They are a great option for women who have failed initial therapy with OCPs or are not candidates for OCPs due to their medical history. GnRH agonists are available in both nasal and injectable forms and offer high rates of pain relief and longer symptom free period for up to 12 months.[22] Leuprolide acetate 3.75 mg monthly injection or 11.25 mg used three monthly, Goserelin and Nafarelin are the most commonly used preparation. Studies have shown that GnRH agonists cause significant reduction in pelvic pain in women with endometriosis, however they are approved for continuous use for only up to six months due to concerns of side effects secondary to hypoestrogenism like bone loss, vaginal atrophy and dryness, hot flashes and abnormalities in lipid profile.[23] The addition of add- back therapy provides symptomatic relief and decreases the rate of bone loss. Norethindrone acetate, a progestrin is the only FDA approved add-back therapy, but low dose estrogen and a combination of estrogen and progesterone have also been used.[24] The combination of GnRH agonists and norethindrone acetate are only approved for use for duration of 12 months, as the data beyond that duration is not available. Another limitation of the use of GnRH agonists is that they suppress ovulation and cannot be used in women desiring fertility.

GONADOTROPIN RELEASING HORMONE ANTAGONISTS (GnRH ANTAGONISTS)

These are another group of drugs that have shown promising results in the treatment of endometriosis. Compared to GnRH agonists they do not cause the initial flare and have lower degree of hypoestrogenism and a better side effect profile with equivalent symptomatic improvement. In their study, Kupker et al showed that administration of GnRH antagonist Cetrorelix provided symptomatic relief and regression of the endometriotic implants as visualized on laparoscopy.[25] With a lower degree of hypoestrogenemia and better tolerance than the GnRH agonists they offer a great potential in the treatment of endometriosis.

PROGESTERONE CONTAINING CONTRACEPTIVES

Progesterone has multiple mechanisms of action that form the pathophysiologic basis of its use in endometriosis. It induces decidualization of the endometrium, inhibits estrogen induced mitosis, alters estrogen receptors, inhibits angiogenesis and expression of matrix metalloproteinase needed for the growth of the endometriotic implants.[26,27] Available in different forms oral, injectable or intra-uterine device, they have gained popularity and are a great option for women with contraindications to estrogens. Some of the progestins that have

been studies and used in the treatment of endometriosis include cyproterone acetate, dienogest, dydrogesterone, gestrinone, lynesterole, medroxyprogesterone acetate, megesterol acetate, and norethindrone acetate.

Medroxyprogesterone is available as oral and injectable preparation and can be administered 150 mg intramuscularly every three months. Although there is no standardized oral dose, studies using different doses of oral medroxyprogesterone from 10 to 100 mg per day for 3–6 months have reported varying degree of improvement in endometriosis related pain.[28, 29] Injectable progesterone offers the added advantage of better compliance by avoiding daily administration and erratic gastrointestinal absorption.

Northethisterone acetate is a 19-nortesterone derivative and has been proven effective in control of dyspareunia, dysmenorrhea, pelvic pain and dyschezia with better tolerability and less side effects in lower doses. Vercellini et al in their study used Norethindrone acetate at a dose of 2.5 mg per day for 12 months and achieved similar pain control when compared to combined oral contraceptive and cyproterone acetate and suggested that it could be a good alternative to COC.[30]

Dienogest, a 19- nortestosterone derivative is another progestin that has been studied in the treatment of endometriosis. It has high specificity for progesterone receptors and less anti-androgenic side effects. Continuous administration leads to decidualization and atrophy of the endometrial lesions. It also has anti- inflammatory, anti-angiogenic and anti-proliferative effects. In a dose of 2mg or 4mg per day, dienogest has been shown to have a favorable profile for safety and efficacy, patients reported improvement in the endometriosis related symptoms and an overall improvement in quality of life.[31, 32] It is in general well tolerated and side effects included irregular bleeding, which improves with time.

LEVONORGESTREL CONTAINING INTRA-UTERINE SYSTEMS (LNG-IUS)

While oral progesterones have a better side effect profile than combined hormonal contraceptives, daily administration and variable serum concentrations are some of the limitations associated with them. LNG- IUS is a T shaped device that contains 52 mg of Levonorgestrel, which releases 20 micrograms of hormone per day over a five-year period. Multiple studies have shown the efficacy of LNG-IUS, which delivers progesterone locally and avoids the systemic side effects. A longer duration of activity further improves compliance. The theory behind their success in women with endometriosis is progesterone induced atrophy of the endometrium, hypomenorrhea with possible decreased retrograde menstruation and higher concentration of progesterone in the peritoneal cavity suppressing the activity of ectopic endometrium by anti-inflammatory and immunomodulatory functions.[33] In their study, Vercellini et al showed LNG IUS to successfully control endometriosis related pelvic pain and improve patient satisfactions.[34] There are also reports of successful use in patients with adenomyosis and deep rectovaginal endometriosis.[35] In another study comparing LNG–IUS to depot administration of GnRH analogues, similar efficacy was reported with lower incidence of hypo estrogenic side effects in women using the intrauterine device.[36] It has also been shown to decrease the rates of recurrence of dysmenorrhea in women after laparoscopic surgery for symptomatic dysmenorrhea. With its

long term use and better side effect profile LNG-IUS offers a great option in women who are do not desire to conceive.[37] More research is underway to understand the long-term efficacy in women with endometriosis.

ETONOGESTREL IMPLANT

Another route of progesterone delivery that has been studied is the subdermal implant also commonly marketed as Implanon and Nexplanon. Inserted intradermally in the arm, it contains progestin etonogestril and offers contraceptive benefits for three years. Reported rates of improvement in dysmenorrhea in women using it for birth control prompted research for its use in endometriosis. Walch et al in their study compared the therapeutic efficacy of depot medroxyprogesterone acetate and implanon in 41 women with endometriosis and reported that both groups had similar incidence of pain relief and both groups had similar side effect profile and degree of satisfaction.[38] Commonly reported side effects include irregular menstrual bleeding, weight gain, nausea, headache, breast tenderness, acne that are similar to depot medroxyprogesterone acetate. In carefully selected women who do not desire fertility etonogestrel implant could be another option for symptomatic endometriosis, however, larger studies are needed in this direction.

SELECTIVE PROGESTERONE RECEPTOR MODULATORS (SPRMs)

SPRMs are a relatively new class of agents that have tissue effect ranging from pure agonists to agonist/antagonist to antagonist. Mifepristone and ulipristal acetate are the two SPRMs that are commonly used. Mifepristone, which has a predominant progesterone antagonist effect, has been used for medical abortions and ulipristal acetate for emergency contraception. Selective inhibition of endometrial growth without the side effects of hypoestrogenism, decreased menstrual bleeding via effect on the endometrial blood supply and suppression of endometrial blood supply are some of the mechanisms that have provoked interest in their use in endometriosis. In animal models, treatment with antiprogestin onapristone and ulipristal acetate has shown to result in atrophy of the endometrium and suppression of estrogen dependent endometrial growth.[39, 40] Decreased expression of COX-2 has also been shown in rat models treated with mifepristone and ulipristil acetate.[41] Studies in humans are however limited. In one study, Kettel et al studied nine women with endometriosis. Women were treated with mifepristone 50 mg/day for six months and all nine women reported an improvement in pelvic pain without significant side effects of hypoestrogenism.[42]

AROMATASE INHIBITORS

Aromatase enzyme helps in the conversion of the steroid precursors into estrogen. Although the ovaries and the fat are the predominant source of the enzyme, other sources include skin, placenta and the brain. Studies have shown that aromatase activity is absent in normal endometrium, but is over expressed in endometriosis.[43] Aromatase induced estrogen synthesis leads to the growth of the endometrial implants, COX expression, prostaglandin secretion, which further induces aromatase activity. Unlike GnRH agonists, aromatase inhibitors block estrogen synthesis both in the periphery and the ovaries. This mechanism is

particularly helpful in postmenopausal women with endometriosis where peripheral fat is the predominant source of estrogen. Anastrazole, letrozole and exemestane are third generation aromatase inhibitors that can be administered orally. They are reversible, more potent and have faster onset of action. Used in combination with combined oral contraceptives, GnRH agonists or progesterone, they significantly decrease the endometriosis-associated pain, improve quality of life and have shown to decrease the size of the lesion. However their side effects include ovarian follicular cyst and bone loss with long-term use.[44] Combination with GnRH agonists and birth control pills can help prevent follicular development and add back oral contraceptives and progestins can decrease the bone loss.

DANAZOL

Danazol, a derivative of 17 alpha-ethinyl–testosterone, is an androgenic agent that inhibits LH surge and decreases ovarian steroidogenesis by direct inhibition of the ovarian enzymes. Although it has been effective in controlling endometriosis-associated pain, its use has fallen over the years due to its side effects. Usually given in divided doses of 400–800 mg per day for six months. Side effects include acne, hirsutism, deepening of voice, weight gain, muscle cramps, liver dysfunction and an abnormal lipid profile. A meta- analysis by Selak et al, showed that when treated with danazol, patients had improved laparoscopic scores and decreased pain symptoms as compared to placebo or no treatment.[45] However, adverse effects related to hyperandrogenism limit their use. As the side effects are mostly associated with oral administration, alternative routes of like danazol vaginal ring and intrauterine devices are currently in research and studies have shown improvement in pain symptoms with better tolerability.[46, 47]

NEWER THERAPIES

Endometriosis is a chronic medical condition and requires long duration of therapy. Currently available treatment options have varying degrees of success in symptom control but are limited by long-term use, side effects of prolonged hypoestrogenism and high rates of recurrence after therapy is discontinued. Also, endometriosis predominantly is a disease of young reproductive age women and most of the commonly available therapeutic agents interfere with fertility. With these drawbacks there is a constant search for newer therapies that could offer cure and be safely used with fewer side effects. (Table 3)

ANTI-ANGIOGENESIS FACTORS

A network of capillaries surrounds endometriotic lesions and angiogenesis is a crucial event in the growth and survival of the lesions. Studies have also shown that these lesions secrete angiogenic factors like vascular endothelial growth factor (VEGF) and the peritoneal fluid is rich in angiogenic factors. In theory, halting the growth of new blood vessels could stop the growth of new lesions and regress older ones. With this thought a lot of research is being done in understanding the role of anti–angiogenic factors in the treatment of endometriosis. These agents are still in early development with most of the research on animal models. Agents like TNP-470 (an analog of antibiotic fumagilin), endostatin (a proteolytic fragment of collagen with endogenous anti-angiogenic activity), anginex (a synthetic peptide that

stops the growth of blood vessels and induces apoptosis) and anti-VEGF antibody (Avastin) have been successful in decreasing the size of endometriotic lesions in animal models, however, no data is available in humans.

Dopamine receptor 2 agonists, cabergoline and quinagolide have been shown to reduce angiogenesis by dephosphorylation of VEGF2. They have been used safely in humans for the treatment of hyper-prolactinemia and lactation suppression. In mouse model, treatment with ergot derived dopamine agonist (cabergoline) and non-ergot dopamine agonist (quinagolide) were effective in inhibiting angiogenesis and reducing the size of endometriotic lesions.[48] In a human study, Gomez et al studied 9 women with endometriosis-associated hyperprolactinemia, women first had a surgical procedure where half of the endometriotic lesions were excised and the other half were marked. This was followed by treatment with quinagolide for 18–20 weeks followed by a second laparoscopy. They showed a significant reduction in the size of the lesion and down regulation of VEGF/VEGF2, pro-angiogenic cytokines and plasminogen activator inhibitor (PAI-1).[49]

STATINS

Typically used in the treatment of hypercholesterolemia, statins are a group of drugs that lower cholesterol levels by blocking the conversion of 3-hydroxy-3 methylglutaryl-coenzyme A into mevalonate, which is a precursor for cholesterol. Their anti-inflammatory, antiangiogenic and antioxidant properties have provoked interest in their use in endometriosis.[50] Atorvastatin, simvastatin, mevastatin and lovastatin have been tested in in-vitro tissue cultures and animal models of endometriosis. In their study Sharma et al reported an increased inhibition of inflammatory and angiogenic genes (COX-2, VEGF, RAGE and EN-RAGE) in atorvastatin treated endometrial- endometriotic cells. They also reported increased expression of anti-inflammatory genes (PPAR-γ and LXRα and IGFBP-1).[51] In another study, simvastatin induced a dose dependent decrease in MMP-3 (matrix metalloproteinase) and the number and size of the endometriotic lesions in a mouse model.[52] They proposed that inhibition of MMP-3 could be a mechanism of action of simvastatin. Statins offer another potential therapeutic agent, which could be used the treatment of endometriosis.

TNFα BLOCKERS

TNFα is a pro-inflammatory cytokine and its levels have been found to be elevated in the peritoneal fluid of women with endometriosis with a direct correlation with the stage of the disease. Agents targeting TNFα have been successfully used in the treatment of inflammatory conditions like rheumatoid arthritis and Crohn's disease. Infliximab, a monoclonal antibody against TNFα and Etanercept, a fusion protein with the ability to neutralize TNFα are being actively studied in the treatment of endometriosis. In animal models, treatment with these agents has shown to reduce the size and number of the endometriotic implants along with a decrease in the levels of inflammatory cytokines.[53] However, there is paucity of evidence in humans regarding the efficacy of these agents. One study studied the effect of treatment of infliximab versus placebo in women with endometriosis, however no improvement was reported in the severity of pain.[54] More studies

are needed to fully understand the scope of these agents in the management of endometriosis.

PEROXISOME PROLIFERATOR- ACTIVATED RECEPTOR GAMMA LIGANDS (PPAR-γ)

PPARs are ligand activated nuclear receptors with a suggested role in inflammation and lipid and glucose metabolism. PPAR- **γ** ligands have anti-inflammatory properties and reduce estrogen biosynthesis by inhibiting aromatase enzyme. In experimental models they have been shown to inhibit cell proliferation, increase apoptosis and inhibit the growth of the endometriotic lesions by an affect on the angiogenic factor VEGF. In animal models rosiglitazone and pioglitazone reduce the volume, weight and size of the endometriotic lesions. Human studies are underway, however there are concerns about the possible risk of myocardial infarction and cardiovascular side effects of rosiglitazone.

PENTOXIFYLLINE

Another agent that has been lately studied in the treatment of endometriosis is pentoxifylline. Currently used in the treatment of intermittent claudication, it helps in improving the vascular supply in stenotic arteries by inhibiting the phosphodiesterase enzyme. It also has TNFα blocking properties, suppressing the release of inflammatory mediators. In mouse models of endometriosis pentoxifylline has been successful in improving fertility and reducing the size of the lesions.[55] Human studies are limited and a recent meta-analysis showed that there was no significant improvement in pelvic pain or clinical pregnancy rates in women treated with pentoxifylline.[56] Therefore, current evidence does not support the routine use of pentoxifylline in endometriosis related pain or infertility and more research is needed.

CONCLUSION

In summary, endometriosis is a chronic medical condition that not only negatively affects a woman's quality of life but has a huge economic impact often due to delay in diagnosis, need for ongoing treatment and high recurrence rates. Currently, several therapeutic options both hormonal and non-hormonal are available to provide symptomatic relief and control the progression of the disease. All the options discussed above have been fairy successful in controlling pelvic pain in women with endometriosis. In carefully selected women these medications can be used either alone or in combination with surgery. However, they are limited by their side effects and negative impact on fertility. Currently there is no evidence that the medical therapy alone or a combination of medical therapy with surgery improves fertility.[57] Management of infertility in women with endometriosis is a complex issue and needs to take into account the age, duration of infertility, severity of symptoms and stage of the disease. Studies have also shown that women with endometriosis have higher rates of pregnancy complications like pre-term delivery, pre–ecclampsia, antepartum bleeding, placental complications and cesarean section rates.[58] Women desiring fertility often require assisted reproductive techniques. With more understanding of the pathophysiology of

endometriosis, newer targets are being developed with the hope of avoiding unwanted side effects and specifically targeting the lesions without affecting the ovarian function.

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TABLE 1

PATHOPHYSIOLOGY OF ENDOMETRIOSIS

• Increases production of estradiol
• Increased intrinsic aromatase activity
• Increased production of inflammatory markers
• Progesterone resistance

TABLE 2

MEDICATIONS USED IN ENDOMETRIOSIS

Hormonal

- Combined oral contraceptives
- Progesterone containing contraceptives
  - ➢ Oral or injectable
  - ➢ Implant
  - ➢ Levonorgestrel containing intrauterine system (LNG- IUS)
- Selective progesterone receptor modulators
  - ➢ Mifepristone
  - ➢ Ulipristal acetate
  - ➢ Onapristone
- Gonadotrophin releasing hormone agonists
  - ➢Leuprolide acetate
  - ➢ Nafarelin
  - ➢ Goserelin
- Gonadotrophin releasing hormone antagonists
  - ➢ Cetrorelix

Non-Hormonal

- NSAIDS
- Aromatase inhibitors
- Danazol

TABLE 3

FUTURE THERAPIES

• Anti- angiogenesis factors
• Statins
• TNF-α blockers
• Peroxisome proliferator activated- receptor gamma ligand (PPAR-γ)
• Pentoxifylline