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MANAGEMENT OF ENDOMETRIOSIS: AN ENIGMATIC DISEASE

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ABSTRACT

Endometriosis is an enigmatic disease that could start at birth which affects women of reproductive age. It is associated with hormonal imbalance, including increased estrogen synthesis, metabolism and progesterone resistance. These changes in hormones cause increased proliferation, inflammation, pain and infertility. The current treatments are surgical and hormonal but have limitations including risk of recurrence, side effects, contraceptive action for women who desire pregnancy and cost. New treatments include gonadotropin releasing hormone (GnRH) analogues, selective progesterone (or estrogen) receptor modulators, aromatase inhibitors, immunomodulators and antiangiogenic agents. More research is needed into central sensitization, local neurogenics and the genetics of endometriosis to identify additional treatment targets. Despite a range of symptoms, diagnosis of endometriosis is often delayed due to lack of non-invasive, definite and consistent biomarkers for diagnosis of endometriosis. The future trend will be to define new drugs to use for prolonged period of time and with poor side effects considering endometriosis a chronic disease. Aim of this review article is to understand and study the new molecules and conventional treatment that are effective for the management of endometriosis associated pain.

Keywords: Endometriosis, Dienogest, GnRH.

Abbreviations: GnRH: Gonadotropin Releasing Hormone, COC: Combined Oral Contraceptive, VEGF: Vascular Endothelial Growth Factor, VEGF: Vascular Endothelial Growth Factor (VEGF) and Its Receptor (VEGFR), QOL: Quality Of Life, ART: Assisted Reproductive Technology, CPP: Chronic Pelvic Pain

INTRODUCTION

Endometriosis is a chronic disease which occurs recurrently and thereby is a challenge to the health care professionals and also a burden on the health care system [1]. Despite of being a factor of high burden on health and high prevalence, several aspects related to endometriosis still remain unclear which includes the risk factors and underlying biological mechanisms. It is believed that exposures during early life play important role in subsequent onset of the condition [2]. The prevalence of endometriosis reported ranges between 2% and 10% among the general population, 50% prevalent in the infertile population and beyond 60% of patients which are suffering from chronic pelvic pain [1]. Unfortunately reduced quality of life and suffering in these women is due to delay in diagnosis of endometriosis. This is as a result of high cost of diagnosis and treatment in adolescent patients and certain confounding factors like cyclic and acyclic pain [2]. Endometriosis is a medical condition in which endometrial-like tissue grows on the outer side of the uterus or sometimes on other parts including ovaries, fallopian tubes, rarely and bowel as well which results in severe pelvic pain and inflammation [3]. The risk of endometriosis is higher for individuals with early age of menarche, shorter menstrual length and taller heights whereas smoking, parity and elevated body mass index (BMI) are associated with decreased risk [2].There are several mechanism regarding how endometriosis occurs one of it being the retrograde menstruation in which the endometrial lining flows through the fallopian tubes into the pelvic space. This fashion of menstrual flow along with hematogenous and lymphatic circulation can result in growth of endometrial tissues in the ectopic sites [2].The symptoms can include pelvic pain prior to menstruation, painful intercourse, severe cramps during intercourse, pain during urination and bowel movement, pain during pelvic examinations and infertility. Intensity of symptoms depends on the position and density of implants. Other symptoms like lower abdominal pain, lower back pain,

bloody urine mainly during menstruation, diarrhea, chronic fatigue and heavy menstruation can also be observed [4]. Laparoscopy is the gold standard which is used for diagnosing endometriosis which shows the presence of disease and its extension [5]. Altered expression of estrogen and progesterone receptors in the endometriotic tissue is the basic recognized event in endometriosis. Thus, the treatment basically targets estrogen and progesterone receptors. Endometriosis has a strong influence on patient's mental health causing high levels of depression, anxiety and alexithymia which leads to understanding the necessity of finding new therapeutic strategies for this condition [6]. There is unclear explanation regarding the association between smoking and endometriosis, although it is dangerous and is associated with many aspects of health but decreased risk is observed as per some studies of endometriosis also associating to 80% reduction in the risk whereas passive smoking increases risk. The consumption of alcohol and caffeine depends on fertility status for their role in endometriosis. Dietary and other lifestyle factors influence the risk for endometriosis based on their ability to cause inflammation. In Spite of many recent advances for identification of risk factors causing endometriosis, this topic still requires a lot of research [2]. Aim of this review article is to understand and study the new molecules and conventional treatment that are effective for the management of endometriosis associated pain.

Management of endometriosis

A multidisciplinary approach is needed for the management of endometriosis which includes (i) surgical diagnosis for reducing the disease bulk, (ii) hormonal therapy to suppress and prolong the reoccurrence and progress of the disease, (iii) pain management plan to reduce pain associated with the condition [2]. Different drugs used are given in Figure 1. Ideally, drugs used for endometriosis must be curative rather than suppressive, they should treat pain efficiently, should be effectively treating pain, and have acceptable side effects, long term use must be safe and affordable, should not be contraceptive in nature or interfere with spontaneous ovulation and normal implantation, should be non-teratogenic, should be able to suppress the growth of existing lesions and prevent the development on new ones and should be efficacious for all disease phenotypes including superficial disease, endometriomas, deep infiltrating endometriosis, extrapelvic disease and adenomyosis [1].

Pain management

Pain can be managed by using either painkillers, certain hormonal therapies and surgical excision using the laparoscopic approach. There is considerable proportion of financial and emotional cost for patients and society. In Canada the total direct cost ranged between $1, 109 to $12, 118 in USA per patient per year. Whereas the indirect cost for endometriosis per patient per year ranged from $3, 314 in Austria to $15, 737 in USA [7]. Several drugs can be used in terms of pain relief with magnitude of effect. They can be classified based on cost as low cost drugs (Oral contraceptives and most progestogens) and high cost drugs (dienogest, GnRH agonist and the recently introduced elagolix). It is recommended to initiate the treatment with low cost drugs in a stepwise approach and later choose high cost drugs in case of inefficacy or intolerance. The traditional management of pain includes various approaches and pathways. Non-steroidal anti-inflammatory agents (NSAIDs) like cyclooxygenase inhibitors can be used to relief pain. They have a favourable effect on primary dysmenorrhea and are used are first line agents for pain associated with endometriosis [5]. The hormonal management for endometriosis is depicted in Figure 2.

Danazol

Back in the late 1970s danazol was the drug to relieve pain associated with post diagnostic laparoscopy or conventional ovarian cystectomy. It is synthetic androgen 2, 3 isoxazole which is a derivative of 17α-ethynyl testosterone with a mild androgenic and strong antiestrogenic activity. It stops the gonadotropin release, regulates the immunological function, reduces the cell proliferation and pain symptoms associated with endometriosis [5,6]. The major drawback of oral danazol is its poor tolerability. The side effects of danazol include weight gain, growth of beard, elevated hepatic enzymes, oily hair, seborrhea, changes in serum lipoprotein, endometrial changes, vaginal atrophy, interference with the regularity of menstrual cycles. Due to these side effects of oral danazol, other routes of administration were discovered like danazol-loaded intrauterine systems and danazol loaded vaginal rings which decrease dysmenorrheal, dyspareunia and pelvic pain in women with deep infiltrating and rectovaginal endometriosis. Liver function and lipid parameters were reported to be unaltered whereas systemic and gynecological side effects are very rare. The dose of danazol 200 mg daily through vaginal administration for 12 months used postoperatively showed a significant decrease of painful symptoms within 3 months with an efficacy that lasts for all treatment time with less side effects. The same also reduced dyspareunia and vaginal bleeding in adenomyosis [6]. Danazol is a drug which was used in the past [5]. A study by Taymor et al. in 1988 discussed about the clinical efficacy of danazol in infertile women. It was a prospective randomized study which has shown danazol to be ineffective in improving the pregnancy rates by doing nothing in patients with minimal endometriosis. In the later years the world consensus for the current management of endometriosis has recommended the use of danazol only before IVF in severe cases of endometriosis [5]. However, it should be taken into account that danazol has a possibility to increase the risk for ovarian cancer in patients with endometriosis as per certain studies [7]. Newer medications have been introduced since then which will be discussed further.

Depot Medroxyprogesterone acetate (DMPA)

Oral progestins have been demonstrated for their use in endometriosis for over 50 years from now [8]. MPA is a 17-hydroxy derivative of progestin with moderate androgenic activity which has minor adverse effects on lipoprotein metabolism. Oral route of MPA is used for long term treatment of endometriosis which acts by reducing pain and improves the health related quality of life. Its effectiveness is almost similar to that of GnRH analogs. The optimal dose is not yet defined. Common side effects for MPA include localized pain, acne and vasodilation. Single intramuscular injection of dose 150 mg administered every 3 months is most common [6]. This progestin was studied in comparison to monophasic oral contraceptive with low dose of danazol, which has shown good results with respect to women's satisfaction and reduction in pain symptoms despite of DMPA group having high incidence of adverse effects. DMPA at a dose of 104 mg given subcutaneously for the treatment of endometriosis has been studied comparing with leuprolide acetate of dose 11.25 mg and has proved statistical equivalence in reducing pain symptoms. DMPA is associated with few hypoestrogenic symptoms and more of irregular bleeding. Therefore is used as an effective alternative for treatment of endometriosis, specifically in USA [6]. A Cochrane review has shown the use of MPA at a dose of 100 mg/day is more effective than placebo in

controlling pain. On the other hand it had burdened by several side effects like menstrual irregularities, amenorrhea, and weight gain and breast tenderness. The authors have therefore concluded that the use of progesterone, both oral and depot form do not appear to be more effective that other treatment options (e. g, low dose estro progestin or leuprolide acetate) for controlling symptoms [9].

Dienogest

Dienogest is a newer progesterone which is used in the treatment of endometriosis. It is a 19-nortestosterone derivative which has properties of 19-nortestosterone and natural progesterone derivatives. Presence of cyanomethyl group in place of ethinyl group at 17-a position makes it different from other 19-norprogestins. It has strong progestogenic activity on endometrium and has antiandrogenic properties like other progesterones and leads to minimal changes in lipid and carbohydrate metabolism. It has anti-inflammatory activity by modification of pro inflammatory markers. Dienogest causes suppression of ovulation by inhibiting endometrial cell proliferation, increasing apoptosis of eutopic endometrium and induces decidualization.

It has shown good efficacy in treatment of endometriosis when compared with placebo and other drugs [10]. Currently, the oral route is approved for endometriosis treatment in Europe, Japan and Australia. There are no clinical trials which could prove the contraceptive efficacy of drug as monotherapy. In European randomized controlled trials, the authors have proven that 2 mg/day of drug is the optimal dose as it is well tolerated with minimal side effects like abnormal uterine bleeding and little influence on bone mineral density. An open label long term study of 53 weeks has shown favourable efficacy and safety profile of drug with progress in decrease of pain and bleeding irregularities [9]. Long term studies on dienogest have shown that dienogest 2 mg/day may represent a safe and effective long term treatment option for women with endometriosis. Graph has been shown in Figure 3 [11].

Although Dienogest is near of being an ideal candidate for endometriosis treatment it is not completely free of side effects. There are certain cases of severe depression with dienogest which requires careful monitoring. Active venous thromboembolism, past or present cardiovascular disease, diabetes with cardiovascular involvement, past or present severe hepatic diseases/tumours, hormone dependent malignancy and undiagnosed vaginal bleeding are contraindicated for dienogest [10]. In an open labelled, double blinded study, the responder rates were markedly increased in prior placebo group at the end of open label treatment when compared to the end of double blinded study, obtaining rates alike the prior dienogest group. Majority of prior dienogest group were responders by the end of open label treatment. Graph is given in Figure 4 [12].

Norethisterone acetate (NETA)

It is a 19-nortestosterone derivative which causes hypoestrogenism by suppression of gonadotropins, inhibiting ovulation and developing amenorrhea eventually causing decidualization and atrophy of endometrium. Previous studies have shown that NETA was effective in reducing chronic pain in women for whom endometriosis was confirmed laparoscopically [6]. It offers various advantages in the treatment of long term endometriosis and has good control for uterine bleeding with a positive effect on calcium metabolism and no negative effects on lipoprotein metabolism when administered at low doses [9]. It has been proven to be effective for dysmenorrheal, deep dyspareunia, non-menstrual pelvic pain and dyschezia like OCs. In patients with colorectal endometriosis it improves the gastrointestinal symptoms which conclude that low dose NETA can be considered as an effective tolerable, inexpensive first choice alternative to OCs for patients who do not seek conception [6]. A prospective study conducted on 82 women who had pain symptoms caused by rertovaginal endometriosis has proven that NETA combined with Letrozole has been more effective to reduce pain and dyspareunia than NETA alone but high incidence of side effects without patient satisfaction have been observed with this combined regimen. (Table 1) [13]. Norethisterone acetate is approved by U. S. Food and Drug Administration as well as by the Italian ministry of health for the treatment of endometriosis [6].

Gestrinone

It is a synthetic trienic 19-nor-steroid, which inhibits the pituitary gland and thereby releases gonadotropins [14]. The resulting suppression of ovary determines the atrophy of endometrium and endometriosis lesions. The drug also exhibits antiprogestinic, antiestrogenic and androgenic action. There are several studies which show the effect of gestrinone in reducing pain associated with endometriosis [15]. The use of gestrinone is limited due to high percentage of anabolic and androgenic effects [9].

Intrauterine device loaded with levonorgestrel (IUD-LNG)

Levonorgestrel is the levorotatory form of norgestrel and a synthetic progestogen which possesses progestational and androgenic activity. It binds to the progesterone receptor in the target cells thereby stimulates the resulting hormone-receptor complex initiating transcription and increases the synthesis of certain proteins [16]. Luukkainen has developed a device which could deliver progesterone continuously into the uterus in low doses over years which was the birth of LNG-IUD [17]. In the recent years, the use of IUD-LNG has triggered interest in treatment of endometriosis of the rectovaginal septum which provides a significant reduction in dysmenorrheal, pelvic pain, deep dyspareunia and size of endometriotic implants, thereby showing levels of efficacy comparable to GnRH analogues [18]. Furthermore, it seems to be effective in preventing the reoccurance of endometriosis after surgical treatment is done [19]. A study conducted by Petta et al. has suggested that its use could be favourable for treatment of chronic pelvic pain as it determines a long state of hypoestrogenism requiring just a single medical intervention for its introduction every 5 years. In the second laparoscopy, observed reduction in pelvic endometriotic lesions was 60% in patients treated with LNG-IUD and 37. 5% in patients treated with GnRH agonist. However this difference was not very significant probably as the sample size under evaluation was small. Certain clinical trials which compared the use of LNG-IUD and DMPA administered for 3 years have shown better compliance in patients who were on IUD. Moreover, bone gain was noticed with LNG-IUD use whereas bone loss was reported with DMPA use [9]. Biopsy samples of endometriotic tissue of women who were treated with LNG-IUD for 6 months has shown reduction in expression of glandular and stromal ER-

α, ER-β and progesterone receptor and reduced cell proliferation index. Side effects frequently related to LNG-IUD were bleeding and pain. However, with use of LNG the symptoms of hypoestrogenic state were avoided and better lipid profile was observed when compared to GnRH analogs [6]. It is ideal for most cases of excess estrogen and is comfortable for patients who want contraception but wish to return to her fertility soon after removal. It has been used effectively in ART patients with abnormal endometrium before going for IVF [17].

INVESTIGATIONAL TREATMENTS

Over the past 2 decades a wide variety of medical treatment options for endometriosis have been tested which aim at specific targets that contribute to the pathogenesis of the disease.

Hormonal treatments

Gonadotropin Releasing Hormone (GnRH) analogues

GnRH analogs (goserelin, leuprolide, nafarelin, buserelin and triptorelin are effective in treatment of endometriosis associated pain and has been considered as gold standard for two decades, currently considered as second line treatment option when first line treatment fails, is contraindicated or intolerated. Administration of these was initially limited to 6 months which can now be prolonged upto 2 years. Common regimens are low dose combined with estro-progestin, estrogen or progestins alone, bisphosphonates, tibolone or raloxifene [6]. They suppress estrogen ovarian production through downregulation of GnRH receptors at pituitary level which causes hypoestrogenism and consequently amenorrhea and hypertrophic regression of heterotopic endometrium. This effect is reversible when administration of GnRH-analogue is stopped. Limitations of their use includes high rate of recurrence of pelvic pain (5 years after withdrawal of therapy is 75%) and side effects like deterioration in lipid profile, depression, hot flashes, urogenital atrophy, loss of libido and reduction in bone mass [9].

Gonadotropin Releasing Hormone (GnRH) antagonist

The use of GnRH antagonist for many reproductive indications has immensely evolved over the past decade. The injectables in this class are Ganirelix and Cetrorelix and the oral non peptide forms include Elagolix, Abarelix, Ozarelix, TAK-385. These oral forms produce a dose dependent hypoestrogenic environment by directly suppressing the pituitary gonadotropin which thereby inhibits endometriotic cell proliferation and invasion meanwhile maintaining sufficient estradiol levels to avoid the vasomotor symptoms, vaginal atrophy and bone demineralization [1]. Cetrorelix shows reduction in symptoms and improvement in disease stages (from stage III-stage II) [6].

On July 24 2018, FDA has approved the use of elagolix for the management of moderate to severe pain associated with endometriosis [5]. This elagolix caused dose dependent pituitary and gonadal suppression in healthy post-menopausal women within 24 hours in subjects which were administered a dose of ≥ 50 mg/d [6]. The safety and efficacy of elagolix in endometriosis associated pain was examined in phase 2 randomized trial which was conducted in 155 women who were confirmed for endometriosis laparoscopically [20]. This drug demonstrated an acceptable efficacy and safety profile women who suffered from pain associated with endometriosis with minimum bone mineral density changes observed during the treatment. Information about the safe duration of GnRH antagonist treatment is currently unclear [21]. Elagolix was found to have minimal impact on bone mineral density over a period of 24 weeks and it has demonstrated its efficacy which was similar to subcutaneous DMPA used for pain related with endometriosis [22]. Phase III clinical trial of elagolix has introduced a promising treatment of endometriosis and when it was compared with placebo it has shown a significant decrease from the baseline in the mean pain score. This significant result was observed in months 3 and 6 of the treatment. The current protocol for similar drugs includes an addback hormonal therapy to minimize the effect of bone density which is one side effect of elagolix [5]. Other antagonist such as cetrorelix has been tested in vitro and the effects on endometrial cells obtained from patients and controls have been evaluated. Treatment with GnRH agonist or antagonist reduces the cell proliferation which is induced by tumor necrosis factor-α (TNF-α) in the endometrial stromal cells, whereas the endometriotic stromal cells did not respond to this treatment. Also these drugs did not repress TNF-α induced interleukin-8 production in endometriotic stromal cells which concludes that both GnRH agonists and antagonists have little effect in slowing down the growth of endometriotic stromal cells [23]. Both oral and injectable forms of GnRH antagonist are effective in reducing pain associated with endometriosis. However, certain more non inferiority studies are required to compare them with other treatment options.

Aromatase inhibitors

Aromatase inhibitors (AIs) act by inhibiting the local estrogen production in endometriotic implants, the ovary, the brain and the adipose tissue. They convert testosterone and androstenedione to estradiol and estrone respectively. Early clinical experience with AIs have suggested the possibility of their use in the treatment of endometriosis [1]. The third generation AI (anastrozole, letrozole, exemestane and vorozole) are more potent and more specific for the aromatase enzyme and are associated with certain side effects like headache, nausea and diarrhea [24]. Normally AIs are administered in various doses such as 2.5 mg daily for letrozole and 1 mg daily for anastrozole. The effect of Letrozole is comparable to oral contraceptive pills in management of pelvic pain associated with endometriosis [1]. Aromatase inhibitors are usually reserved for the treatment of severe, intractable endometriosis associated pain in combination with oral contraceptive pills, progestins and GnRH analogues [25]. Monotherapy with AIs when given to reproductive age women will cause increased follicle-stimulating hormone (FSH) and subsequent pre ovulation, which results in the ovarian cyst development due to the initial FSH rise. Other concerns about prolonged AI therapy are bone loss secondary to hypoestrogenism. Hence, they are combined with FSH-suppression agent like COCs, progestins or GnRH agonists [1]. In one study, letrozole with an add back of progestin led to 75% of reduction of endometrioma volume and has improved pain symptoms after 3 months of treatment [26]. In another study, letrozole alone has caused statistically significant reduction in endometriomas and had better reduction in endometriotic cysts with given in combination with NETA [26]. In studies where AIs were used alone or in combination the side effects reported were irregular bleeding, joint pain and weight gain [6]. In another prospective randomized study, letrozole plus norethisterone acetate versus letrozole plus triptorelin were compared and both group of patients showed a similar reduction in pain symptoms during treatment, endometriotic nodules were more reduced in group who received GnRH agonist but they experienced arthralgia, decreased libido, hot flashes and depression. [13].

Selective Estrogen Receptor Modulators (SERM)

Selective estrogen receptor modulator's tissue selective activity qualifies certain molecules that have mostly antagonism in breast and uterus and ER agonism in skeleton. Raloxifene, commercially available SERM was approved for the management of postmenopausal osteoporosis [27]. Raloxifene was tested in rat models at various doses for endometriosis and was proven to have an estrogen-antagonist effect in uterine tissue, Raloxifene at dose 10 mg/kg has only produced statistically significant implant regression [1]. The decrease in size of experimental endometriotic implants was similar to the

results that were achieved by aromatase inhibitor, anastrazole [28]. Bazedoxifene (BZA), a third generation SERM antagonizes estrogen- induced uterine endometrial stimulation effectively without countering estrogenic effects in bone or the central nervous system. Testing in rat models with BZA alone has reduced the size of endometriotic lesions with an evidence of antiproliferative effects [29]. Additionally, BZA was shown to decrease proliferating cell nuclear antigen and estrogen receptor expression in the endometrium of the animals who were treated with drug compared with controls. As a result, BZA induced regression of endometriosis is likely involved in decreasing estrogen mediated cell proliferation [27]. When BZA was combined with conjugated estrogen in a tissue-selective estrogen complex, similar kind of results were obtained [22]. This novel therapy has partnered SERM with one or more estrogens which aims towards better tolerability and minimal side effect profile. The effectiveness on endometriosis in humans with BZA alone or in a tissue-selective estrogen complex still needs evaluation. In a double blind prospective study, patients who had endometriosis related pelvic pain after surgical treatment were randomly allocated to daily dose of raloxifene or placebo for 6 months which was halted because raloxifene group had statistically significant earlier pain and had a necessity for second surgery [6]. The future trend will be to explore new SERMs which can act in the modulation of lesions and chronic pelvic pain like as ER antagonists.

Selective Progesterone Receptor Modulators (SPRM)

Selective progesterone receptor modulators are a class of drugs with progesterone antagonist activity that may have therapeutic benefit for reproductive disorders in premenopausal women. Endometrial structure which is dynamically controlled by the circulating sex hormones is likelt to be disturbed by progesterone receptor modulators through their progesterone antagonist activity [5]. SPRMs can have variable effects on progesterone receptors from various tissues ranging from being a pure agonist or a mixed agonist/antagonist to a pure antagonist [1].

In human cell lines, a variety of SPRMs, including mifepristone, asoprisnil, ulipristal acetate, lonaprisan and telapristone acetate suppress the endometrial proliferation which consequently results in endometrial atrophy. Further studies on animal models show that mifepristone, onapristone and ZK136799 suppress endometrial growths along with reducing the production of prostaglandins with possible beneficial effects on pain [30]. The modulators which have potent progesterone antagonist activity, comprising the progesterone antagonist, mifepristone and asoprisnil have also been suggested as therapeutic agents for endometriosis [6].

Mifepristone (RU486), the most clinically studied SPRM, has been used majorly for the induction of medical abortions. In a study, mifepristone was shown to have positive effects on pain symptoms. It also induced amenorrhea without causing hypoestrogenism in 16 patients with endometriosis [1]. Only two small open trials have been published using treatment with mifepristone in the treatment of endometriosis. A dose of 50 mg daily has shown to improve pain and cause regression of endometriosis implants. But, at a lower dose it is unable to control the growth of endometriosis lesions. Mifepristone-loaded subcutaneous implants can also offer an effective treatment for endometriosis [6].

Ulipristal acetate and asoprisnil are other members of the same family. Ulipristal acetate is approved for the use as an emergency contraceptive in the United States and for the management of fibroids in Europe and Canada. A treatment with Ulipristal reduces the cellular proliferation, as indicated by a decrease in Ki-67 expression, and possesses an anti-inflammatory effect by a decrease in cyclo-oxygenase 2 expression [31]. The feasibility of ulipristal acetate for the management of endometriosis is yet to be evaluated [1] Reports on a possible relationship with endometrial malignancy and severe liver damage has excluded it from currently available endometriosis drugs, The FDA in August 2018 has refused again to authorize Esmya (brand name of ulipristal acetate) for human use. It has been preliminary approved by the EMA in 2015. In May 2018, the EMA issued a warning regarding the rare occurrence of liver complications. In June 2018, the agency has approved its use in the pre-operative treatment of fibroids. Hence, there could be a possible role of ulipristal acetate in the management of endometriosis:a surgical pretreatment [5]. Endometriosis is a benign condition and care has to be taken when prescribing medications with dangerous side effects if rare and infrequent.

Asoprisnil, another SPRM was shown to statistically significantly reduce non menstrual pelvic pain/dysmenorrheal scores at various doses of 5, 10 and 25 mg [1]. A randomized placebo-control clinical trial using asoprisnil in the treatment of endometriosis associated pain significantly reduced the average daily combined non menstrual pain scores compared to placebo along with a favourable safety and tolerability profile during a 3 month treatment period. The trials were stopped due to some cases of endometrial hyperplasia. Common side effects of SPRMs are headache, abdominal pain and tenderness [6].

Resveratrol

It is a natural drug derived from grape wine which induces apoptosis in endometrial stromal cells by the suppression of surviving expression. Ines Barano and her group at IBYME-CONICET (Buenos Aires, Argentina) are working in animal experimentation with endometriosis surgical implants in rats. They have demonstrated the suppressive effect of this drug in the process of disease progression [5]. Makabe et al. [32] has described the process of enhancement of apoptosis in endometrial stromal cells. There is a lot to be studied and to be accomplished but these preliminary results are promising [33].

Non hormonal treatments

Immunomodulators

Tumor necrosis factor-α which is a proinflammatory cytokine is able to initiate cascades of inflammation which is increased in peritoneal fluid and serum of women with endometriosis. In a RCT using a baboon model, a TNF- α inhibitor (etanercept) was examined. Results led to statistically significant reduction in red lesion surface in the treatment group with decrease in the absolute number of red lesions [1]. Long term treatment conducted in rat model with human interferon- α2b (INF- α2b) has resulted in more decrease in surgically induced endometriosis implant size when compared with placebo [34]. Loxoribine is another immunomodulator which reduces the natural killer cells and endometriotic lesions in rat model. Similar results were observed with other immunomodulators like lipoxin, rapamycin and pentoxifylline. A RCT on infliximab which is another TNF- α inhibitor has shown to have no effect in the treatment of endometriosis associated pain [1]. Many reviewers have concluded that there is insufficient evidence to support the use of anti-TNF –α drugs in the treatment of pelvic pain related to endometriosis [1]. Pentoxifylline, a competitive non selective phosphodiesterase inhibitor is known to have immunomodulatory properties which can be used for the management of endometriosis associated pain. Although, a Cochrane review has evaluated four clinical trials of 334

infertile endometriosis patients, there is lack of evidence to recommend pentoxifylline for management of pain or to improve the chances of spontaneous pregnancies [1].

Antiangiogenic agents

Neoangiogenesis is important for the initiation, growth, invasion and recurrence of endometriosis. A plethora of antiangiogenic agents have been tested in vitro as effective treatments for endometriosis which includes growth factor inhibitors, endogenous angiogenesis inhibitors, fumagillin analogues, statins, cyclooxygenase-2 inhibitors, phytochemical compounds, immunomodulators, dopamine agonists, peroxisome proliferator-activated receptor agonist, progestins, danazol and GnRh agonists. However, evidences for safety and efficacy for most of them are still deficient [35]. An angiogenesis inhibitor lodamin which is an oral nontoxic formulation of TNP-470 has statistically significantly reduced endothelial progenitor cell levels meanwhile suppressing lesion growth [36].

Romidepsin is a histone deacetylase (HDAC) inhibitor which targets at VEGF at the transcriptional level which leads to a reduction of secreted active form of VEGF from human immortalized epithelial cells. Thereby, it may be a potential therapeutic drug against angiogenesis in endometriosis [37]. The immunoconjugate (Icon) molecule of romidepsin binds with high affinity and specificity to the endothelial tissue factors. Unlike the other antiangiogenic treatments that can only target developing angiogenesis, Icon romidepsin can set out as a novel, non-toxic, fertility preserving and effective candidate for the management of endometriosis [1]. Cabergoline, a dopaminergic agonist was shown to reduce VEGF and VEGFR-2 protein expression in cabergoline treated mice. Additionally, cabergoline and quinagolide have an equivalent effect in reducing endometriotic lesions as angiogenic agents [1]. Moreover, cabergoline and bromocriptine were almost comparable to GnRH agonist in decreasing endometriotic lesion size in one human study [38]. Peroxisome proliferator receptor γ (PPAR γ)ligands have been shown to hamper 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 them have shown a lower volume of endometriotic lesions when compared with placebo. Rosiglitazone is associated with increased risk for myocardial infarction and death from cardiovascular causes. This led to the premature termination of all clinical trials for testing its effectiveness in pain associated with endometriosis [1]. Bentamapimod is a c-Jun NH-2 terminal kinase inhibitor (JNKI) which was evaluated for its feasibility in treated of endometriosis. It resulted in lower total lesion size when given alone or in combination with MPA or cetrorelix. It has less side effects and less effect on cycle length or serum reproductive hormones [14].

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine), a secretory product of pineal gland, is a scavenger of free radical and a broad spectrum antioxidant. It has immunomodulatory and anti-inflammatory effects. Endometriosis was induced in 25 rats surgically and a subgroup of n=11 were treated with melatonin and other subgroup n=11 was given no treatment. Four weeks later regression and atrophy of endometriotic lesions were noted in melatonin treated group [9].

Alternative treatments

The Montpellier Consensus includes acupuncture and high frequency transcutaneous electrical nerve stimulation. Others are Chinese herbal medicines, Vitamin B1 and B6, magnesium, tropical heat, spinal manipulation and behavioral interventions. There are no strong studies which can support these therapies. When they cause no damage or delay specific treatment, they can be considered at supporting therapies. Cannabis has been shown to be effective moderately for relief of chronic pain and has potential serious side effects [5].

Lifestyle: Diet and exercise

There are no interventions demonstrated on lifestyle, exercise or diet with acceptable evidence that they can be used to improve the QOL. However, most patients find them useful and the favourites are cognitive therapies and yoga. Certain small retrospective studies suggest that they might be useful in reducing dysmenorrhea. There is a consensus that says gluten- free diets improve symptoms in some women who suffer from endometriosis and gastrointestinal complaints [5].

Fertility

The opportunity, extension and quality of the first surgery are determinant when fertility is the main issue. Hence, Milani and Cesana et al. [39] recently evaluated the reproductive prognosis during the first three years after the surgery. They surveyed 140 patients who were operated for endometriosis. Without any infertility factors, the pregnancy rate in group of patients who were previously infertile was 53%. Those patients who had not sought pregnancy before surgery were also followed and 71% of them became pregnant. Only 3 among the group of 31 required ART. An algorithm has been proposed in cases where laparoscopy is indicated for endometriosis-associated infertility. Many patients who were suspected with endometriosis had benefits directly from ART without a prior laparoscopy. Algorithm is given in Figure 5 [5].

CONCLUSION

In the last decades, large plentiful pharmacological agents have been evaluated for treatment of endometriosis associated pelvic pain. Few resulted ineffective; others proved unfit for clinical use, while few seemed to be very promising but must be investigated in RCT. Among them, very few have been introduced into the clinical practice. Although, current medical treatments are helpful for many women with endometriosis but they include side effects in some women and contraceptive action for women who desire to conceive. Further research should be directed in helping to shorten the delay in diagnosis of endometriosis, involving primary and secondary care. Lifestyle measures such as diet and exercise for CPP must be examined in RCT prospectively. Progress is being made in creating better awareness of endometriosis, identifying methods to diagnose earlier, and enabling women to access effective treatment. As all women with CPP with or without endometriosis will not benefit from surgery, a multi-disciplinary patient-centred approach is needed. Future strategy for endometriosis treatment will include use of non-hormonal drugs associated with hormonal treatments which can target multiple sites of action.

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