PHARMACOLOGY OF ENDOMETRIOSIS

Edgardo D. Rolla MD

docrolla@gmail.com

San Isidro Medicina

Av. Libertador 16483, San Isidro, 1642, Bs. As., Argentina

Medical Director

Founding Member, World Endometriosis Society

Ambassador

Founding Member, Sociedad Argentina de Endometriosis

Past President

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Abstract

Pharmacology of endometriosis is the science of drugs prescribed for endometriosis, and their effects on *the disease* and the *patient.* This is a clinician's essay on the pharmacology of the disease. A brief mention of the pathogenesis of the disease is included. Available treatment options for endometriosis associated pain are included, and those for infertility associated to endometriosis briefly described. Mechanism of action of drugs, and description of hormonal receptors are discussed. Treatments are introduced beginning with progesterone and progestogens, followed by hormonal contraceptives, GnRH agonists, GnRH antagonists, a brief historical review of past treatments (including antiprogestogens and androgens), hormone releasing intrauterine devices and implants, estrogen antagonists and aromatase inhibitors. Formulas are shown for all compounds, and comments on efficacy and side effects are included. The purpose of this article is to describe current treatments and help the clinician to make decisions when confronted with a patient complaining of pain and low quality of life due to endometriosis.

Introduction

According to the British Pharmacological Society, the definition of "pharmacology" is: "the science of drugs and their effects on living systems". (1)

Pharmacology of endometriosis then should be considered the science of drugs and their effects on *the disease* and the *patient.*

This is a clinician's essay, not a pharmacologic digest. The exclusive aim of the present article is to guide practitioners in the medical treatment of the disease. Long time dilated personal experience is expressed only after reassuring its validity by an extensive review of available bibliography. Literature review is not systematic: it was oriented exclusively to reaffirm my concepts on how to treat endometriosis.

Endometriosis is an enigmatic disease. Of yet unknown origin and confirmed pathogenesis, we still treat this disease as a syndrome, with different (but generally confounding) signs and symptoms.

As such, we must first decide if all types of endometriosis are the same disease: superficial peritoneal lesions, deep infiltrating endometriosis, ovarian endometriomas, adenomyosis, and extra pelvic disease. Extended bibliography, clinical practice and personal experience allows me to state that progesterone resistance is a key in the pathogenesis of this disease. The different proportions of glandular and fibrotic tissue found in peritoneal disease, versus deep infiltrating nodules, could explain the different efficacy of hormonal treatments at different sites or clinical expressions of the disease.

Pathogenesis

Updated information considers that it is probably a newborn's disease, still during childhood, and evolutive as soon as the ovaries start producing estrogens and progestogens (2).

New theories propose that the altered progesterone receptivity found in endometriotic lesions, might be acquired after migration of eutopic endometrial cells. The progesterone resistance and the changes in the progesterone target gene expression could occur only in ectopic endometrial tissue (3).

Even more, the regulation of progesterone receptors expression by epigenetics, is suggested as a critical factor for the development of the disease (4). Petraglia proposes that some classic epigenetic mechanisms, such as DNW methylation and histone modification, as well as some routes – miRNAs and IncRNA – participate in the epigenetic regulation of estrogen and progesterone receptors expressions in endometriotic lesions. This group of investigators propose, as well, that those findings could be useful in the development of new diagnostic tests and therapeutic agents for endometriosis.

Endometriosis is a disease that not only is related to altered hormonal receptivity, but also to significant immunologic and inflammatory pathological pathways and responses. According to Zhow Liu (5), inflammatory processes are crucial in the pathogenesis of endometriosis. Key cytokines involved could be TNF-alpha, as well as altered neutrophil and macrophage activity (associated to estrogens), RANTES, and T cell activity.

Available treatment options

Laparoscopic surgery and the excision of all visible lesions, including deep infiltrating ones, is the first step in the treatment of endometriosis associated pain. Still considered the "Gold Standard", be it by conventional or robotic laparoscopy, the removal of adhesions and as much as possible amount of diseased tissue, allows for an immediate relief and better efficacy of all possible medical treatments.

If the disease is linked to altered response to ovarian hormones, mainly progesterone resistance, and inflammatory components (also probably related to hormonal disruption), a basic pharmacological treatment should target either hormonal suppression (endometriosis is not present, or at least not symptomatic either in childhood or menopause) or try to "overpass" bad progesterone receptivity. Anti-inflammatory agents (SERMS and others) with painkilling

activity should also be considered. New findings in genetics and epigenetics suggest that gene therapy, still unknown, could be the future of pharmacological treatment of this disease.

Pain and quality of life

A classic Cochrane review from 2012 (6), that found only 13 RCTs published that could be included in this study, concluded that "there is only limited evidence to support the use of progestogens and anti-progestogens for pain associated with endometriosis". This contrasts with the widespread use of both therapeutic strategies for the treatment of this disease.

According to this review, a low-cost progestogen, medroxyprogesterone acetate, in a dose of 100 mg/day, was better than placebo for the treatment of endometriosis associated pain. Pain, and quality of life, are without doubt, the main objectives of the medical treatment of endometriosis. Infertility frequently requires not only pharmacological interventions, but also surgery and assisted reproduction procedures.

If fertility is desired, all treatments available for endometriosis associated pain – aside SERMS, other painkillers and psychotropic agents – are ruled out: basically, all hormonal or antihormonal therapies have a contraceptive effect.

In the Cochrane publication, dydrogesterone (Duphaston NR), a 3-oxo-Delta(4) steroid and a 20-oxo steroid, with a light progestine activity (that does not inhibit ovulation), was not effective vs. placebo. A depot progestogen group experienced significantly more adverse effects (medroxyprogesterone 150mg depot injections every three months).

Surprisingly, this review found no benefit of oral progestogens over other medical treatments after six months. The progestogen users presented more frequently either amenorrhea or irregular bleeding.

The use of anti-progestogens, such as gestrinone, rendered no benefits compared to danazole (an isoxazolic synthetic drug chemically related to 17-ethinil testosterone that creates a high androgenic environment, low in estrogens)(7).

In contrast, Leuprorelin (a GnRH analogue) significantly improved dysmenorrhea, although it was associated with increase post-menopausal symptoms. Leuprolide Acetate, Triptorelin, Goserelin, Buserelin and other GnRH agonists have demonstrated efficacy in the treatment of endometriosis associated pain. Usually, depot preparations are preferred. Long term use is limited by side effects, especially bone density damage.

Recently, Elagolix, a GnRH oral antagonist, and Relugolix a similar drug, have rendered excellent results in the industry based clinical trials (8) (9).

Infertility

Traditionally, laparoscopic surgery was considered the first step for the treatment of endometriosis associated infertility. In lower grade cases (minimal or mild) pregnancy is

achieved at reasonable rates after a correct surgical procedure (10): “cumulative Pregnancy Rate at 36 months after surgery was 53.6% for stage I and 36.0% for stage II”. Even in the worst scenarios, pregnancy can be naturally achieved if by surgery a complete anatomical restoration of the pelvis is possible, and tubes are patent.

When assisted reproduction is needed to achieve a pregnancy, low and high complexity treatments require the use of ovulation induction.

Intrauterine insemination is performed regularly with the help of low-cost medication (Clomiphene Citrate), or an association of this drug with gonadotropins, usually HMG (Human Menopausal Gonadotropins). For in vitro fertilization, a combination of different gonadotropins and other drugs is frequently used: recombinant FSH, HMG, purified FSH, synthetic LH, GnRH antagonists, natural or synthetic HCG and different types of progestogens after oocyte pick up to improve endometrial receptivity.

Mechanism of action

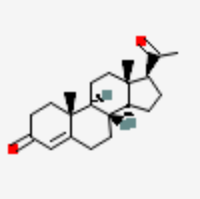
As said, endometriosis is a disease that grows and spreads endometrial like tissue that has altered progesterone receptors. There are two protein isoforms: progesterone receptor A (PR-A) and B (PR-B). The “B” type is a heavier protein that has 164 additional amino acids. During the proliferative phase of the menstrual cycle, estrogens induce the presence of both types of PRs. During the secretory phase, increasing levels of progesterone reduce the number of PRs. Type “A” PR is responsible for most of the progesterone dependent endometrial functions. Endometriosis progesterone resistance could be linked to an altered ration of PR-A to PR-B. Progesterone target genes, such as HOXA 10, are downregulated in patients with endometriosis (11).

1.1. Progesterone

For some authors (12) as Vercellini, hormonal treatment of endometriosis aims at a “similar end-result”. They interfere pituitary gonadal function, produce anovulation, induce steady hormonal levels (associated to reduction or suppression of menstrual flow).

A therapeutic pathway for progestogens probably includes the continuous reduction of PRs in the eutopic and ectopic endometrium, that at large results in the transient atrophy of those tissues (the effect of hormonal therapies is maintained only during the treatment periods and the disease, sooner or later, recurs after its discontinuation).

Simultaneously, another pathway includes the hypothalamus/hypophysis axis. Consistent levels of exogenous progestogens block this circuit, downregulating gonadotropin production, reducing estrogen secretion and inducing anovulation. With less circulating estrogens, eutopic and ectopic endometrial tissue will reduce the availability of PRs, contributing to tissue atrophy.



PROGESTERONE

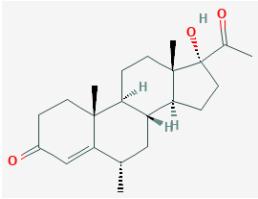
Micronized progesterone has not been routinely used for the treatment of endometriosis, although supposedly at a daily dose of 300 mg it should induce endometrial atrophy in the long run. A revision of literature has not found any clinical trial, or any type of publication related to the use of progesterone for endometriosis.

On the contrary, several progestogens have a widespread prescription for the treatment of this disease.

1.2 Medroxyprogesterone:

The 17-medroxyprogesterone acetate has been widely used for the treatment of pain associated to endometriosis. Discovered in 1956, it still is in use, mainly in third world countries, in a depot intramuscular injection, that also gives strong contraceptive safety.

Frequent side effects include irregular bleeding, headaches, weight gain, liquid retention, emotional distress, gastrointestinal discomfort, and vertigo.



MEDROXIPROGESTERONE

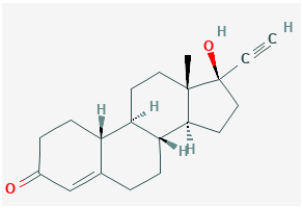
Back in 1988 Luciano (13) presented excellent results with oral medroxyprogesterone acetate. Given at a daily dose of 50 mg, after a four-month trial, the treatment was efficacious for controlling pain. Ovulation inhibition was proven, as well as decidualization and atrophy of both eutopic and ectopic endometrium. Total LH and Estradiol levels were significantly reduced.

Today this drug is available in 2.5, 5 or 10 mg tablets, and no other recent studies are found either for its use in high doses as referred before, or specifically the treatment of endometriosis.

1.3 Norethisterone acetate (NETA):

This drug was introduced in the year 1951. In 2010 Ferrero (14) used NETA to treat 40 patients with gastrointestinal symptoms and pain due to colorectal

endometriosis, at a daily dose of 2.5 mg (that in some cases was doubled due to persistent irregular bleeding). After 12 months, in a prospective study, he found regression of pain and diarrhea, but persistence of constipation and bloating. A strong progestin derived from 19 nor-testosterone (second generation progestin), some time before, in 2005, Vercellini (15) had tried this drug for rectal endometriosis postoperative persistent pain, at a similar dose, versus and estrogen/progestogen combination. Results were similar but in and "intention to treat" analysis, 73% of the NETA treated patients were satisfied vs. 63% in the estrogen/progestogen combination. NETA, also known as norethindrone, is a low-cost progestogen that has some negative side effects such as irregular bleeding, changes in vaginal secretions, edema, weight gain, cholestatic jaundice, rare allergic rashes, melasma, chloasma and depression.

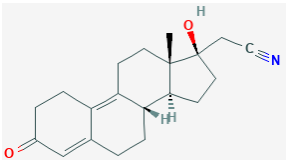


NORETISTERONE

It binds to progesterone receptors, activating them and interacting with DNE specific sites, altering protein synthesis. It inhibits LH pike producing anovulation.

1.4 Dienogest:
A fourth-generation progestin(16), it has a low inhibitory effect on FSH and LH, and at therapeutic doses it inhibits ovulation. It has a proven efficacy for the treatment of endometriosis associated pain. It decreases, with time, expression of estrogen receptors. It reduces the production of estradiol.

It is orally active and has an antiandrogenic, anti-inflammatory and antiangiogenic activity. It binds to progesterone receptors modifying target genes. It has proven action reducing the growth of endometrial epithelial cells.



DIENOGEST

This compound has been widely investigated for the treatment of this disease (17), "in dose-ranging, placebo-controlled, active comparator-controlled, and long-term trials". It combines the potency of 19-norprogestins and the safety of progesterone derivates.

It has a high oral bioavailability, and a short half life that allows for rapid return to non-treatment previous status after discontinuation. It affects endometriotic lesions inhibiting gonadotropin secretion, lowering estradiol levels, and on the other hand, it provokes an elevated progestogenic milieu that decidualizes and atrophies endometriotic tissue.

By far, where available, it is the first choice for hormonal treatment of endometriosis. Recently, Römer (18) assessed retrospectively 60 months of treatment for endometriosis associated pain in 37 women, using a daily dose of 2 mg per os. Using an 1-100 analogue scale, measured yearly, they concluded that it was effective to treat pain and avoid recurrence of the disease. Adverse events included bleeding abnormalities and depression (that were medically controlled when needed).

2.1 Oral Combined Contraceptives, transdermal patches, and vaginal rings

In a 2018 systematic review, The Cochrane Library included three randomized clinical trials (n:404) that studied the efficacy of combined oral contraceptives (COC) for the treatment of endometriosis (19).

Treatment with COC was associated with an improvement in self-reported pain at the end of treatment as evidenced in a randomized controlled trial (RCT) that included 96 women. A lower score on the Dysmenorrhoea verbal rating scale (scale 0 to 3) compared with placebo was seen (mean difference (MD) -1.30 points, 95% CI -1.84 to -0.76; very low-quality evidence).

Two RCTs including 327 women, showed a lower score on the Dysmenorrhoea visual analogue scale (no details of scale) compared with placebo (MD -23.68 points, 95% CI -28.75 to -18.62, very low-quality evidence).

Another RCT with an “n” of 169 women, revealed a reduction in menstrual pain from baseline to the end of treatment (MD 2.10 points, 95% CI 1.38 to 2.82; very low-quality evidence).

There exists a long list of different oral contraceptive hormonal combinations, including different estrogens, and a wide range of progestogens. We lack studies that could show better results using one or other combination. In each case, incidence and severity of side effects varies (please refer to combined hormonal oral contraceptives extended bibliography).

The advantage of COCs is mainly their low costs and ample availability. In many regions, they are provided free of charge, in contrast to high priced tailored progestogens.

Their mechanism of action is widely known (inhibition of the secretion of gonadotropins via hypothalamus/hypophysis blockage). On endometriosis they act inducing a low estrogenic environment, and decidualizing endometrial tissues. Continuous administration, with no

hormonal free intervals, allow for a rapid improvement of menstrual associated pain, as amenorrhea is the rule.

From a pharmacological point of view, transdermal patches and vaginal rings have similar mechanism of actions and effects on endometriosis, although experience is limited and publications scarce.

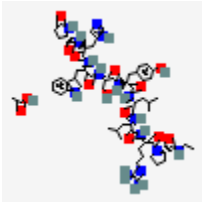
3.1 GnRh agonists

Different pharmacological products downregulate gonadotropin production depleting and later blocking the hypophysis. Initially a “flare up” effect induces ovarian hyperfunction and estrogen secretion, but rapidly, the hypophysis ceases the production of gonadotropins, essentially Follicle Stimulating Hormone (FSH), leading follicular growth to a stop, resembling a “post-menopausal” like status. GnRH agonists bind pituitary gonadotropin receptors and antagonize the link-receptor of endogenous GnRH, inhibiting the mechanism of GnRH pulsatility (20). Estrogens are not produced, and endometrial tissue is not any more stimulated leading to the atrophy of both eutopic and ectopic tissue.

Side effects of complete ovarian suppression (lack of estrogens) are frequent: hot flushes, skin, and vaginal dryness, etc. The most important of all is the damage to bone density. Sudden “menopause” impedes bone rechange and growth and induces osteopenia. This limits the use of GnRH agonists for short periods of time. Estro/progestogen addback could counteract, but there is lack of sufficient evidence in the published literature to allow me to recommend those drugs for long periods of time.

Most used GnRH agonists are (21):

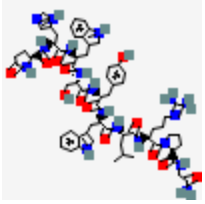
3.1.1 Leuprolide acetate



LEUPROLIDE

Introduced in 1973m it is mainly used for the treatment of prostate cancer in the man. For endometriosis it is prescribed in depo presentations containing 3.75 mg for intramuscular injection, once monthly.

3.1.2 Triptorelin



TRIPTORELIN

Triptorelin is also a synthetic decapeptide GnRH analogue. It is similarly administered via intramuscular injection at a monthly dose of 3.75 mg.

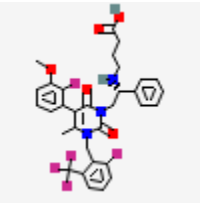
3.1.3 Other compounds

Naftarelin, Goserelin and Buserelin have not been so widely used for the treatment of endometriosis associated pain, except for Goserelin. This drug can also be administered monthly via subcutaneous implants. The other two require frequent daily nasal spray usage, and thus have not been popular in endometriosis.

3.2 GnRH antagonists

Recent publications of industry sponsored clinical trials with new drugs that directly block the hypophysis (without the initial GnRH agonist induced flare up) have demonstrated the efficacy of these new drugs, orally administered, in the treatment of endometriosis associated pain. Elagolix NR is the first of a series of "new" GnRH antagonists, that in contrast to the "old generation", do not require subcutaneous injections or implants. They act immediately and have a rapid reversibility (22). In contrast to peptidic GnRH agonists, antagonists are non peptidic preparations, and as such induce no histamine like reactions. They are well tolerated in long term treatments.

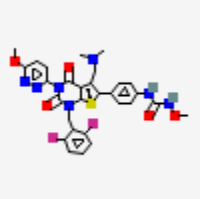
Elagolix clinical trial (of which I was Principal Investigator at Fertilab, Buenos Aires, Argentina) did not include an estro/progestogen addback arm, and as such, osteopenia and risk of bone fracture was present, as discussed by Watts (20).



ELAGOLIX

A later product, Relugolix - PubChem CID: 10348973 (of which I am Principal Investigator in a current clinical trial at San Isidro Medicina, San Isidro, Buenos Aires, Argentina), on the contrary, included add back therapy in all cases after week 12. The Relugolix 40 mg daily dose was supplemented with 1mg of estradiol and 0.5 mg of norethindrone acetate. Results of the Spirit trial were presented this year at ASRM 2020, including 24 weeks of treatment.

Additionally, all enrolled patients were offered and extension period of 80 weeks, extending the total treatment time to 104 weeks, the longer known menopause like medically induced status. Conclusions will be available at the end of the year, but in the short 24 weeks study, the drug met the endpoints ($p < 0.0001$) with 74.5% and 75.2% meaningful reductions in dysmenorrhea. Relugolix combination therapy was generally well-tolerated with minimal bone mineral density loss (data presented at the 2020 ASRM Scientific Congress and Meeting).



RELUGOLIX

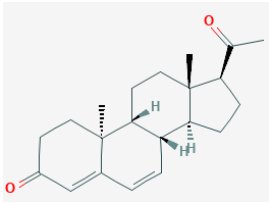
Other similar products are currently under study in other clinical trials. As so, GnRH oral antagonists are arising as the new treatment for endometriosis. And as all other treatments, it only controls symptoms, possibly regressing lesions, but by no means cure the disease.

4.1 A little bit of history

As mentioned before, other treatments have been used in the past – some are still in the market – that have been left aside because of poor activity against the disease, frequent adverse effects, or a combination of both.

4.1.1 Duphaston:

It is a progestogen (dydrogesterone) introduced in the fifties and used after 1961. Discontinued in many countries, it is still available in many others. It does not inhibit ovulation and has a weak antimineralocorticoid activity (23). In 10mg tablets, infrequent side effects are headaches, nauseas, menstrual disorders, and weight gain. Efficacy was rated average (a total of 21.1% of the patients were considered cured and 66.7% showed improvement)(24).

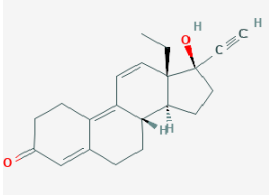


DUPHASTON

4.1.2 Gestrinone:

Introduced in 1986, it was popular in Europe, but is now marketed in very few places. Its main drawback: anabolic effects. It has antiestrogen and antiprogesterone effects. It exerts an agonist/antagonist action on progesterone receptors and acts as an agonist on

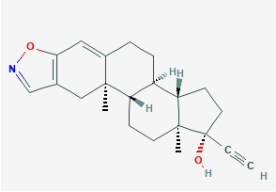
androgen receptors. Used in a dose of 2.5 mg twice a week, it induces endometrial atrophy. Adverse effects include acne, hirsutism, weight gain and voice masculinization. It inhibits ovulation but due to its embryotoxic effects, additional barrier contraception was required (25).



GESTRINONE

4.1.3 Danazol:

Presented in1963, it reached the marketplace in 1971. It has considerable adverse effects: acne, hirsutism, and voice masculinization, among others. It has androgenic activity, anabolic effects. It presents a lean progestogen action, as well as antiestrogen, antigonadotropin and anti-steroidogenesis activity. It binds directly to hormone carrier proteins. It inhibits steroidogenesis enzymes (26).

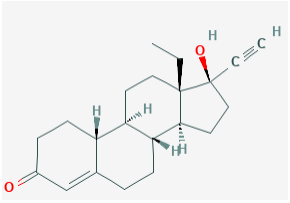


DANAZOLE

Danazole was for many years the preferred drug for the initial post-surgical treatment of endometriosis. Its heavy side effects and the irruption of GnRH agonists provoked a steady cessation of its frequent use. It is still available in many countries, but nor chosen as a regular treatment of endometriosis.

5.1 Intrauterine devices

The levonorgestrel (LNG) liberating intrauterine system (IUS) has been proposed for the treatment of endometriosis (and adenomyosis) associated pain. LNG is the levorotatory form of norgestrel, a synthetic progestine with pregestational and androgenic activity (27).



LEVONOGESTREL

Introduced first in Finland in 1990, it is widely used for contraception. Bahamondes (28) reviewed the literature on the use of LNG IUS in women with endometriosis, adenomyosis, cyclic pelvic pain and dysmenorrhea. They identified nine studies, only two of which were RCTs. One compared this device after surgery vs. expectant conduct, and the other compared it with a GnRH agonist. In both cases, an improvement of pelvic pain and dysmenorrhea was reported. As a rule, LNG IUS induce amenorrhea, so it is not surprising that dysmenorrhea diminished. Women were followed for up to 3 years with no severe side effects. For use as a contraceptive, the LNG IUS is recommended for up to five years after insertion.

This same author (29) recently presented the results of a RCT comparing the efficacy of an etonogestrel releasing implant vs. an LNG IUS. Quality of life improvement was evaluated using the Endometriosis Health Profile – 30 Questionnaire comparing baseline and six months controls. A Visual Analogue Scale (VAS) measuring 0/10 centimeter was used to evaluate changes in endometriosis associated chronic pelvic pain and dysmenorrhea at baseline and 6th month.

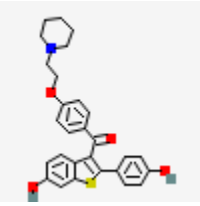
Fifty-two women received the implant and 51 the LNG IUS. At the 180-day final evaluation, symptoms decreased significantly ($p<0.0001$ in both groups. This reassures the efficacy of both methods for the treatment of endometriosis associated pain, allowing at the same time a safe contraception. Bias of this study is the small number of subjects included.

5.2 Implants

Etonogestrel implants have limited use in regular treatment of pain due to endometriosis. As shown in the previous section dedicated to LNG IUS, a small clinical trial revealed it could be an alternative for other progestin preparations.

6.1 Estrogen antagonists and aromatase inhibitors

In 2003 Vigano (31) introduced the news: estrogen antagonists and aromatase inhibitors could have a place for the treatment of endometriosis. The high aromatase expression found in endometriotic implants and ovarian cysts made suggested this drug could regress endometriosis. Raloxifene, was proposed at that time, but a later clinical trial had to be early terminated because of recurrence of postoperative pain in women treated with this compound (32).



RALOXIFENE

Raloxifene is a selective estrogen receptor modulator (SERM). It has mixed agonist–antagonist actions on estrogen receptors. It has estrogenic effects in bone and antiestrogenic effects in the breasts and uterus.

Aromatase inhibitors have limited efficacy suppressing estrogen availability in premenopausal women. But they have been proposed for the treatment of the infrequent cases of postmenopausal disease (2/3%). A renown group of investigators (33) have recently discussed the use of these antiestrogens. There is lack of sufficient information, and the use of those agents in the menopause could be linked to bone density damage.

Discussion

In an extensive systematic review of the literature, including 58 articles that met acceptance criteria, know medical treatments for endometriosis were analyzed (34). Of those, 29 publications presented data demonstrating the efficacy of treatment to reduce endometriosis associated pain. In those studies, 11 to 19% of women showed no pain reduction at all. At the end of the treatment, in a widespread result collection, 5 to 59% of patients had remaining pain. After follow up, 17 to 34% of the subjects experienced recurring pain. In a median range of 2 to 24 moths of duration, discontinuation rates due to adverse events were of 5 to 16%.

This interesting review clearly demonstrates that not all treatments are equal in efficacy and tolerance. The authors conclude that many women gain only “limited or intermittent benefits” from medical treatments.

I coincide, in some way, with these authors considering that laparoscopic surgery is an ideal basic treatment. Laparoscopy has the advantage to certify the disease by biopsy and evaluate the superficial extension of the lesions (deep infiltrating endometriosis -DIE is better appraised by pelvic examination, ultrasound and/or MRI). Surgery must be performed only after a complete and detailed clinical diagnosis, by experienced surgeons. In some way, the oncologic criteria of “mass reduction” must be achieved at surgery, plus adhesiolisis and any other procedure that can help to restore anatomy. Medical therapies will be more efficacious in best surgically treated patients.

Some drugs are more effective than others. Some present more intense, frequent, or severe adverse events. Some are inexpensive – or even given free in some regions, while other are awfully expensive.

Endometriosis is a special disease, that needs individualized diagnosis and treatment. The principal aim is quality of life. Associated psychosocial therapies are almost always required. Availability of the professional team at all times is the key for patient compliance. They need to be cared for.

Personal experience allows me to say that with time, all different medical treatments will be used by the same patient. Probably GnRH agonists or antagonists (preferably with estro/progestogen addback) will be used after surgery for advanced cases; later progestogens

for long periods of time, replaced by combined hormonal contraceptives (by any route of administration) when irregular bleeding occurs, hormone liberating IUS (specially for pain associated to adenomyosis), and anti-aromatases in the menopause rare cases.

Ovarian stimulation with clomiphene or gonadotropins (not described in the present article) will be used at the time of pregnancy desire, if not spontaneously achieved, together with different low and high complexity assisted reproduction techniques.

Formulas

All formula images were taken from NIH - National Library of Medicine, National Center for Biotechnology Information – PubChem

Bibliography

1) https://www.bps.ac.uk/about/about-pharmacology/what-is-pharmacology
2) I Brosens, J Brosens, G Benagiano. Neonatal uterine bleeding as antecedent of pelvic endometriosis. Human Reproduction, Volume 28, Issue 11, November 2013, P. 2893–2897.
3) B McKinnon, M Mueller, G Montgomery. Progesterone Resistance in Endometriosis: An acquired property? Trends in Endocrinology & Metabolism. Volume 29, Issue 8, August 2018, Pages 535-548.
4) H Chen, F Malentacchi, M Fambrini, A Halim Harrath, H Huang & F Petraglia . Epigenetics of Estrogen and Progesterone Receptors in Endometriosis. Reproductive Sciences volume 27, pages1967–1974(2020).
5) L Jiang , Y Yan , Z Liu, Y Wang. Inflammation and endometriosis. Frontiers in Bioscience, Landmark, 21, 941-948, June 1, 2016.
6) Brown J, Kives S, Akhtar M. Progestogens and anti-progestogens for pain associated with endometriosis. The Cochrane Database of Systematic Reviews, 13 Mar 2012.
7) Ke Lq, Yang K, Li C-M, Li J. Danazol para el tratamiento de las mujeres con síntomas provocados por los fibromas uterinos. Cochrane Library, July 8, 2009
8) . H S Taylor, M.D., L C Giudice, M.D., Ph.D., B A Lessey, M.D., Ph.D., M S Abrao, M.D., J Kotarski, M.D., Ph.D., D F Archer, M.D., M P Diamond, M.D., E Surrey, M.D., N P. Johnson, M.D., N B Watts, M.D., J. C Gallagher, M.D., J A Simon, M.D., et al. Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist July 6, 2017 N Engl J Med 2017; 377:28-40.
9) Y OsugaM.D., Ph.D., Y Seki M.Sc.b, M Tanimoto B.Pharm.b., T Kusumoto M.Sc.b., K Kudou M.Sc.b., N TerakawaM.D., Ph.D.c. Relugolix, an oral gonadotropin-releasing hormone receptor antagonist, reduces endometriosis-

associated pain in a dose–response manner: a randomized, double-blind, placebo-controlled study. Presented at the 13th World Congress on Endometriosis, May 17–20, 2017, Vancouver, British Columbia, Canada. Fertility and Sterility, Available online 7 September 2020.

10) Zeng C.a · Xu J.a · Zhou Y.a · Zhou Y.a · Zhu S.b · Xue Q.a. Value of the Revised American Fertility Society Classification and the Endometriosis Fertility Index. Gynecol Obstet Invest 2014;77:180-185.
11) . H Cakmak, M.D. and H S Taylor, M.D. Monitoring Editor: Serdar E. Bulun, M.D. Molecular Mechanisms of Treatment Resistance in Endometriosis: The Role of Progesterone–Hox Gene Interactions Semin Reprod Med. 2010 Jan; 28(1): 69–74. Published online 2010 Jan 26.
12) Vercellini P, Buggio L, Frattaruolo MP, Borghi A, Dridi D, Somigliana E,Medical treatment of endometriosis related pain, Best Practice & Research Clinical Obstetrics & Gynaecology (2018), doi: 10.1016/j.bpobgyn.2018.01.015.
13) Luciano AA1, Turksoy RN, Carleo J. Evaluation of oral medroxyprogesterone acetate in the treatment of endometriosis. Obstetrics and Gynecology, 31 Aug 1988, 72(3 Pt 1):323-327.
14) S. Ferrero, G. Camerini, N. Ragni, P.L. Venturini, E. Biscaldi, V. Remorgida. Norethisterone acetate in the treatment of colorectal endometriosis: a pilot study. Human Reproduction, Volume 25, Issue 1, January 2010, Pages 94–100.
15) PVercelliniM.D.,GPietropaoloM.D.,ODeGiorgiM.D.,RPasinM.D.,AChiodiniM.D., PGCrosignaniM.D. Treatment of symptomatic rectovaginal endometriosis with an estrogen–progestogen combination versus low-dose norethindrone acetate. Fertility and Sterility, Volume 84, Issue 5, November 2005, Pages 1375-1387
16) National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 68861, Dienogest. *https://pubchem.ncbi.nlm.nih.gov/compound/Dienogest*.
17) Adolf E Schindler. Dienogest in long-term treatment of endometriosis. Int J Women's Health. 2011; 3: 175–184.
18) Römer, T. Long-term treatment of endometriosis with dienogest: retrospective analysis of efficacy and safety in clinical practice. Arch Gynecol Obstet 298, 747–753 (2018).
19) J BrownTineke, J Chree Datta, A Prentice. Oral contraceptives for pain associated with endometriosis. Cochrane Database of Systematic Reviews Intervention. Version published: 22 May 2, 2018.
20) Watts, N.B. Adverse bone effects of medications used to treat non-skeletal disorders. Osteoporos Int 28, 2741–2746 (2017).
21) National Center for Biotechnology Information. PubChem Compound Summary.

22) }G B Melis, M Neri, V Corda, M E Malune, B Piras, S Pirarba, S Guerriero, M Orrù, M N D'Alterio, S Angioni & A M Paoletti (2016). Overview of elagolix for the treatment of endometriosis, Expert Opinion on Drug Metabolism & Toxicology, 12:5, 581-588.
23) Tausk MA (1972). "Pharmacology of the Endocrine System and Related Drugs: Progesterone, Progestational Drugs and Antifertility Drugs". International Encyclopaedia of Pharmacology and Therapeutics. 48: 19, 220, 278, 285, 481
24) P Trivedi , K Selvaraj, P Das Mahapatra, S Srivastava, S Malik. Effective post-laparoscopic treatment of endometriosis with dydrogesterone. Gynaecol Endocrinol. 2007 Oct;23 Suppl 1:73-6.
25) M A Bedaiwy, T Falcone. Endometriosis and Adenomyosis .General Gynecology2007, Pages 321-345.
26) E J Thomas; J Rock (6 December 2012). Modern Approaches to Endometriosis. Springer Science & Business Media. pp. 239–256.
27) National Center for Biotechnology Information. "PubChem Compound Summary for CID 13109, Levonorgestrel" PubChem, https://pubchem.ncbi.nlm.nih.gov/compound/Levonorgestrel.
28) L Bahamondes , C A Petta, A Fernandes, I Monteiro. Use of the levonorgestrel-releasing intrauterine system in women with endometriosis, chronic pelvic pain and dysmenorrhea. Contraception,2007 Jun;75(6 Suppl):S134-9. doi: 10.1016/j.contraception.2006.12.008. Epub 2007 Feb 16.
29) Amdan, D; Bignardi, T; Hardas, G; Merkur, H; Condous, G. Mirena Intra-Uterine System: Does it Improve Long Term Symptoms in Women with Chronic Pelvic Pain and/or Endometriosis after Laparoscopy? A Multicentre Randomized Controlled Trial. Reviews on Recent Clinical Trials, Volume 5, Number 3, 2010, pp. 143-146(4).
30) N Carvalho, M.D., Ph.D., D Margatho, M.D., K Cursino, M.D., Ph.D., C L Benetti-Pinto, M.D., Ph.D., L Bahamondes, M.D., Ph.D. Control of endometriosis-associated pain with etonogestrel-releasing contraceptive implant and 52-mg levonorgestrel-releasing intrauterine system: randomized clinical trial. Fertility and Sterility,VOLUME 110, ISSUE 6, P1129-1136, NOVEMBER 01, 2018.
31) Viganò P, Mangioni S, Odorizzi MP, Chiodini A, Rocca S, Chiodo I. Use of estrogen antagonists and aromatase inhibitors in endometriosis. Curr Opin Investig Drugs. 2003 Oct;4(10):1209-12. PMID: 14649213.
32) P Stratton; N Sinaii; J Segars; D Koziol; R Wesley. Return of chronic pelvic pain from endometriosis after raloxifene treatment: a randomized controlled trial. Obstetrics and gynecology. PMID: 18165396, 2008-01-01 .
33) N P Polyzos, H M Fatemi, A Zavos, G Grimbizis, D Kyrou, J Garcia Velasco, P Devroey, B Tarlatzis, and E G Papanikolaou. Aromatase inhibitors in post-menopausal endometriosis. Reprod Biol Endocrinol. 2011; 9: 90. Published online 2011 Jun 21.

34) C M Becker, M.D., W T Gattrell, Ph.D., K Gude, M.D., Ph.D., S S Singh, M.D. Reevaluating response and failure of medical treatment of endometriosis: a systematic review. Fertility and Sterility, VOLUME 108, ISSUE 1, P125-136, JULY 01, 2017.

Disclosures

Principal Investigator, Elagoliz, AbbVie

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Key Words

Androgens

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