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A Comprehensive Review on Nanoparticulate System Through Intravaginal Drug Delivery for Endometriosis

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ABSTRACT

This review intends to offer the reader with a comprehensive summary of the available information on new research directions in nanoparticulate system through intravaginal drug delivery and alternate and unique drug delivery techniques for endometriosis treatment with drugs. Use of drugs is essential in the treatment of endometriosis. However, a sizable minority of patients only receive occasional or limited benefits. In this context, alternative and novel drug delivery systems are critical for improving the efficacy and compliance of existing treatments and developing new medical approaches. Progestins and estroprogestins, the first-line medication, are already available in several forms and are used for contraception. Nonetheless, evidence on their uptake for various medication delivery techniques, such as vaginal rings, patches, and subcutaneous implants, is still scarce. More research is needed to properly determine their clinical value in endometriosis patients. Nanotechnologies have been studied as innovative drug delivery systems capable of delivering drugs at the disease level. However, the data is restricted and preliminary, and more research is required before considering a possible clinical application in endometriosis.

Keywords: Endometriosis, Intravaginal drug delivery system, Estroprogestins, Nanoparticle, Aromataze Inhibitor

INTRODUCTION

Endometriosis is a chronic hormone-dependent inflammatory disease that primarily affects premenopausal women, with a prevalence of 5–10% [1–3]. The condition is defined by the presence of ectopic endometrial tissue, and the clinical presentation is varied, with pain sensations, infertility, and anatomic disturbance being the most common symptoms [4]. This illness poses a significant therapeutic challenge, particularly in the case of deep endometriosis, where lesion penetration can approach 5 mm; deep endometriosis affects up to 12% of patients [5-10]. Ectopic endometrium causes pelvic discomfort and infertility by forming lesions. It affects 10% of women of reproductive age and 20–50% of women who are not pregnant.Deep endometriosis, an estrogen-dependent condition, is treated with hormone suppression in the clinic. However, the outcomes of this treatment are unsatisfactory because severe side effects, such as climacteric symptoms, decreased bone mineral density, and irregular menstrual cycles, are common; treatment is ineffective in reducing endometriotic nodules; and symptoms frequently recur after treatment discontinuation [11-13]. Surgical treatment for severe endometriosis is

thus considered the gold standard, although surgical complications such as fistulas, bleeding, infection, intestinal sub blockage, bladder dysfunction, or intestinal dysfunction can be dangerous and even fatal. Furthermore, surgery's effectiveness is limited, with up to 20% lesion recurrence rates and common postsurgical endometriotic foci persistence [14-21]. Despite recent breakthroughs in medical therapy for endometriosis-related pelvic discomfort, there is still no medical cure. New endometriosis treatment options are required in this situation, but the many therapeutic approaches presented to date have been shown to be unsuccessful or have not yet been evaluated in women [22-24]. As a result, there is a need for novel endometriosis treatment options that can improve efficacy.

Nanoparticulate drug delivery through intravaginal drug delivery

For a variety of drugs, including hormones for contraceptive and replacement therapy, vaginal administration has been shown to be an effective drug delivery approach [25]. Vaginal rings come in a variety of sizes, structures, polymer compositions, and hormone delivery options, but they all offer similar benefits over oral treatment [26]. Vaginal rings release hormones that are successfully absorbed by the vaginal mucosa on a regular basis. This mode of delivery avoids the first hepatic passage and delivers a systemic exposure comparable to oral contraceptives with a nearly 50% reduced total exposure [27]. Reduced steroid exposure minimises adverse effects and their impact on hemostatic function, preserving ovulation inhibition [28,29]. Furthermore, the use of vaginal rings for contraception has been linked to increased compliance, consistency, and acceptability [30,31]. Based on this experience, vaginal rings have been studied as an alternative to oral delivery for the treatment of endometriosis [32]. The argument for using vaginal rings as a medication delivery technique in endometriosis is based mostly on two factors:1) take advantage of the "uterine first-pass" effect, which could provide direct action on deep infiltrating endometriosis; 2) take advantage of the local administration of the drug with the "uterine first-pass" impact, which could provide direct action on deep infiltrating endometriosis [32,33]. (Fig 1 and 2)

Estroprogestins

Vercellini et al. [34] conducted a patient preference trial comparing estroprogestins administered continuously for 12 months using a vaginal ring (ethinylestradiol (EE) 15 g + etonogestrel (ENG) 120 g) vs a transdermal patch (EE 20 g + norelgestromin 150 g) in women who had endometriosis surgery. Withdrawal was high in both groups, although it was higher in the transdermal patch group (36 percent versus 61 percent).AEs were the most common cause for discontinuation, followed by a desire to utilise a combination oral contraceptive (COC). Although both groups had inadequate bleeding control and better pain symptoms, patients who utilised the vaginal ring had less dysmenorrhea, less profound dyspareunia, fewer AEs, and higher satisfaction, especially when rectovaginal implants were present [34]. Despite these promising outcomes, only a second experiment looked into the vaginal route as a drug delivery technique for endometriosis estroprogestins. For symptomatic rectovaginal endometriosis, a combined contraceptive vaginal ring was compared to a desogestrel alone pill (75 mcg/day) taken continuously for 12 months.Women who took the desogestrel alone pill reported higher satisfaction (61.7 percent vs. 36.1 percent) and better improvement in gastrointestinal symptoms, chronic pelvic pain, and dyspareunia in this patient preference experiment. However, there were no differences in the rate of cessation or the reduction of rectovaginal nodules [35]. On this premise, while the vaginal route is effective and offers several benefits when estroprogestins are used for contraception, data on endometriosis treatment is lacking. As a result, we can't guarantee that all of the benefits of contraception, such as compliance, are present when vaginal rings releasing estrogestins are utilised. Every new clinical indication necessitates a separate evaluation of each medication delivery technique.

Danazol

In endometriosis, the vaginal route has been examined as an alternate delivery mechanism for many medications, with the goal of taking advantage of both local administration and lower systemic levels.

The majority of evidence focuses on the use of danazol, a 17-ethynyl-testosterone derivate that suppresses gonadotropin production, inhibits aromatase activity, and reduces inflammation, resulting in endometriotic implant atrophy [36]. Oral administration of danazol has been linked to adverse effects due to its modest androgenic activity, preventing a long-term use. Several studies looked into the use of danazol vaginally to preserve efficacy and reduce AEs. The doses studied ranged from 95 to 200 mg per day for 6–12 months [37-42]. In all studies, pain symptoms were reported to have improved, especially in patients with deep infiltrating endometriosis. It's worth noting that all of the trials showed a decrease in rectovaginal nodules but no effect on the amount of endometriomas. In contrast to oral delivery, serum levels of danazol were observed to be reduced or undetectable, with essentially no AEs associated with the androgenic effect. The concentrations of danazol in the ovaries and uterus were comparable to those obtained following oral treatment, but only 1/2 of the dose was administered. The release of danazol by vaginal rings in the vicinity of deep endometriotic implants provides large local concentrations, lowering systemic levels and associated adverse events. Low systemic levels, for example, have no contraceptive effect. If danazol is not discontinued after conception, persistent ovulation provides a danger of female foetal virilization; consequently, concomitant contraceptive treatments are suggested [43].

Aromatase inhibitors

Inhibitors of aromatase Letrozole and anastrozole (ATZ), third-generation AIs, are reversible inhibitors that compete with androgens for aromatase binding sites. They've been studied in endometriosis because they block aromatase, which suppresses oestrogen production more effectively than ovarian function inhibition. AIs have been shown to inhibit oestrogen synthesis in the ovaries, periphery tissues, and endometriotic implants [44]. In this regard, vaginal rings have recently been investigated to take advantage of the local administration and lower systemic levels provided by this route, based on the local presence and activity of aromatase in endometriotic lesions and the significant AEs after systemic administration.

Endometriosis drug delivery methods

Contraceptive hormones (oestrogen and progestin-based) have long been used to treat endometriosis symptoms (particularly pain). The usage of combination oral contraceptives has been the focus of a lot of research. Due of issues with once-daily contraception doses, a variety of contraceptive devices based on drug delivery ideas have been developed [45]. As a result, it's not unexpected that endometriosis is treated with drug delivery devices designed for contraception. Intravaginal rings (IVRs), transdermal patches, intrauterine systems, long-acting implants, and injectable medicines are just a few of the delivery modalities available. Both as a contraceptive delivery device and for hormone replacement, IVRs have found utility in female health [46]. Contraceptive hormones have been delivered by transdermal patch technology from a one-week delivery system. In order to manage pain associated with endometriosis, IVRs and transdermal patches have been compared [47]. NuvaRing® (Merck, Inc.) was used as an IVR product, while Ortho Evra® was used as a transdermal patch (Janssen Pharmaceuticals, Inc.). Ethinylestradiol (EE) is the same oestrogen delivered by both products.However, the progestins they deliver are different. The progestin in NuvaRing is etonogestrel, while the patch releases norelgestromin. A contraceptive study compared these two products before [48]. Both the ring and the patch reduced pain complaints, although the ring was more effective than the patch in patients with rectovaginal lesions. In comparison to ring users, more patch users dropped out of the study (61 vs. 36 percent, respectively). Both delivery methods have been linked to poor bleeding control. The levonorgestrel-releasing intrauterine system (LNG-IUS; e.g., Mirena®, Bayer Healthcare Pharmaceuticals) is another contraceptive-based delivery system that is also a medical device. The LNG-IUS has long been known to provide additional health benefits in addition to very effective contraception [49]. Treatment of endometriosis symptoms is one of these additional benefits [50-54]. Studies proving the efficacy of LNG-IUS in the treatment of endometriosis have not resulted in a particular indication for these products to date. Implanon® (Merck & Co.) is a three-year subdermal implant that delivers the progestin etonogestrel[55]. Implanon's ability to cure pelvic endometriosis has

been studied in a small number of women [56]. The women (a total of five) were generally pleased with the product's effect. This outcome was identical to Depo-Provera® (Pfizer, Inc.) [57], a much older in product. In a rabbit model, an experimental method along these lines was investigated utilising LNG microspheres [58]. Other endometriosis medications have been developed into long-acting delivery methods (e.g., GnRH agonists). These medications are typically used to treat pain caused by endometriosis. Initially, GnRH was manufactured into long-acting injectable and implanted systems for the treatment of various indications. These products were not designed to treat endometriosis at first, but they are currently used to manage endometrial pain. Leuprolide, manufactured as a 1- and 3-month long-acting injectable medication Lupron Depot®, is an example of a GnRH agonist (Abbvie, Inc.). Although it was an early example of a long-acting injectable (it was originally released in 1989), its primary prescription was for advanced prostate cancer treatment. The requirement of daily add-back norethindrone acetate 5 mg daily during early management complicates its usage in the treatment of endometriosis, and leuprolide medication should be stopped after 6 months [59]. Goserelin is a long-acting GnRH agonist that is used in a medication delivery system to reduce pain associated with endometriosis (Zoladex LA). SPRMs (selective progesterone receptor modulators) are a type of drug that could be used to treat endometriosis. The effects of these drugs on progesterone receptors, especially those in endometrial tissue, can vary. Mifepristone (RU486) has been linked to lowering discomfort and uterine cramps in women with endometriosis [60] and has been examined extensively in women (originally for induced medical abortions). Endometriosis could potentially be treated with newer SPRMs. For example, ulipristal acetate (UA) is being studied in a 3-month IVR formulation for contraception [61,62]. A ring like this could be useful in the treatment of endometriosis. UA has been developed as an IUS in addition to an IVR. The UA-loaded IUS was capable of inhibiting the endometrium in rhesus macaques, resulting in endometrial atrophy and amenorrhea [63]. Little is known regarding SPRM exposure after 3 months because the principal use in women is a single dose for emergency contraception. Danazol is a synthetic androgen that blocks luteinizing hormone surge and was developed primarily to alleviate endometriosis pain [64]. Danazol causes a hypoestrogenic-hyperandrogenic condition, which inhibits endometrial tissue formation [65]. However, because of its systemic adverse effects, particularly its androgenic effects [66], its usage has been limited. Danazol has been formed as an intravaginal ring to reduce these negative effects. The study of danazol-loaded hyaluronic acid hydrogels to locally treat endometriosis in a rat model served as the foundation for investigating an intravaginal ring formulation of danazol[67]. These researchers examined a danazol vaginal ring as well as a danazol intrauterine device at roughly the same time. In 35 infertile women, a vaginal danazol ring containing 2 g to 3.5 g danazol improved both dysmenorrhea and the amount of pelvic endometriosis [68]. A comparable ring tested in women some years later gave additional evidence that local delivery of danazol could be efficacious while significantly decreasing systemic exposure [69]. It's worth noting that danazol has been developed as an IUS for local delivery in the uterus. Danazol was combined into silicone gel, which was then coated onto a polyvinyl chloride rod. Danazol was released from the cured silicone elastomer element in vitro during a 10- to 60-day period, depending on drug loading [70]. The devices were tested in vivo in a mouse model of adenomyosis (a disorder comparable to endometriosis). The findings suggested that an IUS delivering danazol could be used to treat uterine inflammation. To avoid the necessity for frequent insertion and removal, a danazol IUS would need to release medicine for significantly longer periods of time. A unique vaginal ring formulation has recently been studied for the treatment of endometriosis symptoms. The ring, like many others, is made of silicone elastomers and can provide prolonged release once implanted in the vagina. This ring is special in that it releases the chemical anastrozole (ATZ). ATZ is an aromatase inhibitor that was initially developed to treat postmenopausal women with hormone-sensitive breast cancer [71]. The medicine causes oestrogen deficiency, which has been shown to alleviate endometriosis. Following a PK/PD trial with ATZ-releasing vaginal rings in cynomolgus macaques [72], a study in female volunteers was undertaken with rings releasing combinations of ATZ (500, 1000, or 1500 g/d) and LNG (20, 30, or 40 g/d) [73,74]. The use of a contraceptive hormone in conjunction with

ATZ is based on previous research in which contraceptives are used to prevent pituitary counter-regulation caused by aromatase inhibitors, resulting in an increase in gonadotropin levels and stimulation of follicular development, which can lead to the formation of ovarian cysts [75-77]. The findings of this ring study largely supported the use of an ATZ/LNG vaginal ring combination to create a Phase 2b trial design (EudraCT 2013-005090-53).

The above-mentioned delivery techniques are based on long-known approaches linked with contraceptive or extended-release systems (table 1). However, more sophisticated delivery techniques are being researched for the treatment of endometriosis (table 2). There are various examples of drug-loaded nanoparticles that are meant to overcome delivery obstacles, and in many cases, they are intended to treat the causes rather than the symptoms (such as pain). Oxidative stress [78], angiogenesis [79], and matrix breakdown [80] are all symptoms of endometriosis. As a result, pharmacological therapy targeting at these targets may improve therapeutic outcomes when compared to currently used approaches.

Nanoparticle technology is being used to increase the distribution of antioxidant chemicals as well as other compounds such as matrix metalloproteinases (MMPs) and MMP tissue inhibitors (TIMPs). Two medicines, epigallocatechingallate (antioxidant and antiangiogenic) and doxycycline (MMP inhibitor), have been combined into nanoparticles to tackle three distinct targets [81]. Dual drug-loaded poly(lactic-co-glycolic) acid (PLGA) nanoparticles were created and described. Various oxidative stress, MMP, and angiogenesis markers were evaluated in endometriosis-induced mice [82] before and after drug-loaded nanoparticle delivery. Following nanoparticle medication treatment, there was a significant reduction in oxidative stress, MMP activity, and angiogenesis.

While the study was intriguing, it lacked controls (e.g., medication administered unformulated in nanoparticles, administration of each drug individually, etc.) to properly establish the viability of the proposed strategy. Immunomodulators have the potential to be effective in the treatment of endometriosis since immunological systems are involved in the pathophysiology of endometriosis [83]. Endometrial lesions develop and increase in the presence of decreased peritoneal macrophage function [84]. Muramyl dipeptide (MDP) is a Gram-negative and Gram-positive bacterial cell wall component that has immunomodulatory effects on phagocytes [85]. MDP derivatives have been researched and synthesised to improve its effectiveness. GMDP (N-acetylglucosaminyl-Nacetylmuramyl-L-alanyl-D-isoglutamine) has been shown to strongly enhance adaptive and innate immune responses [86]. GMDP was adsorbed onto aminopropyl modified and unmodified mesoporous silica nanoparticles (AMNPs) to inhibit the expression of peritoneal macrophage scavenger receptors. Both types of nanoparticles were found to be harmful in the majority of cases. The researchers discovered that GMDP immobilised on various AMNP preparations outperformed free GMDP in terms of preventing undesirable hyperactivation of peritoneal macrophages [87]. As previously stated, oxidative stress is a feature of endometriosis and has been linked to disease progression and development. Endometriosis is associated with increased levels of reactive oxygen species and lipid peroxide indicators, but decreased levels of antioxidants such as superoxide dismutase, glutathione peroxidase, and vitamin E in blood and peritoneal fluids [88,89]. Cerium oxide (CeO2) nanoparticles have antioxidant capabilities due to catalytic reactions with superoxide and hydrogen peroxide. The antioxidant characteristics of CeO2 are generated from a percentage of Ce3+ ions.

Redox cycles between Ce3+ and Ce4+ oxidation states are involved in the reactions, allowing CeO2 nanoparticles (also known as nanoceria) to react catalytically with superoxide and hydrogen peroxide. The use of CeO2 nanoparticles to target endometrial oxidative stress is a possible therapeutic method [90,91]. Nanoceria, in particular, have been studied to see how they affect mice with induced endometriosis. Several outcomes were used to indicate that cerium oxide nanoparticles reduced endometrial lesions by reducing oxidative stress and inhibited angiogenesis.

Another attempt to improve endometriosis treatment with nanoparticles is based on copaiba oleoresin (CPO). CPO is a natural substance with a variety of possible therapeutic activity [92], including endometriosis therapy [93]. PLGA nanoparticles have been created to potentially boost the therapeutic

potential of CPO. After 48 hours of treatment, LGA nanoparticles containing CPO reduced the cell viability of endometrial stromal cells from ectopic endometrium. Nanoparticles devoid of CPO had no effect on cell viability, corroborating the notion that CPO is to blame for lower cell viability. Overall, these findings imply that CPO nanoparticles may be a viable therapy option for endometriosis [94,95].

CONCLUSION

Drug delivery and endometriosis treatment are an intriguing combination of existing goods and new ones. Approaches to experimentation that rely heavily on nanotechnology. Nanotechnology research has only recently begun animal models in preclinical stages. The gap between present preclinical evidence and clinical efficacy and safety demonstration. The importance of these formulations cannot be overstated. More traditional drug delivery methods utilising older medications (i.e., IVRs for delivery of ATZ paired with a contraceptive) are more likely to contribute to improvements in treatment of these two common disorders in the near future. It is also hoped that due to the vast number of women who suffer from these illnesses, the medical community will pay more attention to them.

CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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96.

Table 1: List of drug therapy for the management of endometriosis

Drug Category	Drugs	Mechanism of Action in Endometriosis	Dosing	Toxicity
NSAIDs	Ibuprofen, naproxen	Reversibly inhibits COX-1 and COX-2, resulting in decreased prostaglandin formation	May be prescribed at maximal doses. Ibuprofen: 400 mg po q4-6h prn. Naproxen: 500 mg po q12h prn	Epigastric pain/bleeding, edema, cross-sensitivity with aspirin-containing products, renal impairment
Combined estrogen-progestin contraceptives	Ethinyl estradiol combined with norethindrone, norgestrel, levonorgestrel, or desogestrel	Inhibits FSH and LH. Decreases cell proliferation and enhances endometrial apoptosis	Prescribed in monthly cycles for up to 3 mo or more	Thromboembolism, MI (age-dependent; highest in female smokers), increased risk of estrogen-dependent cancers
Progestin-only preparations	Norethindrone, medroxyprogesterone, levonorgestrel	Inhibits FSH and LH and stimulates atrophy or regression of endometrial lesions. Appropriate for patients with reported estrogen contraindications or those who are breastfeeding	Medroxyprogesterone acetate: initially 10 mg/day po; may increase up to 50 mg/day, depending on tolerance. Norethindrone acetate: initially 2.5 mg/day po; may increase to 30 mg/day	Weight gain, acne, breast tenderness, increase in LDL levels
Androgen	Danazol	Antiestrogen; inhibits enzymes involved in steroid formation. Decreases the release of gonadotropin	Mild disease: initially 200-400 mg/day in 2 divided doses; continue for 3-9 mo. Moderate-to-severe disease: initially 800 mg/day in 2 doses; continue for 3-9 mo	Teratogenic; hepatic injury, pseudotumor cerebri (rare; black box warning)
GnRH agonists	Leuprolide, goserelin	Chronic administration inhibits steroidogenesis due to reduced LH and FSH levels. The initial hormone flare is characteristic of GnRH agonists	Leuprolide: 3.75 mg IM q4w or 11.25 mg IM q12w. Goserelin: 3.6 mg SC every 28 days for 6 mo. Add-back therapy: norethindrone 5 mg/day	Hot flashes, vaginal atrophy, bone loss
Aromatase inhibitors	Letrozole, anastrozole	Blocks conversion of androgens to estrogen, which decreases endometrial proliferation	Letrozole: 2.5 mg/day. Anastrozole: 1 mg/day	Hot flashes, bone loss

COX: cyclooxygenase; FSH: follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; LH: luteinizing hormone; MI: myocardial infarction; NSAID: nonsteroidal anti-inflammatory drug. Source: Reference 28.

Table 2: Alternative drug delivery methods for the treatment of endometriosis

Delivery method		Drug	Level of investigation	Main results
Vaginal ring				
		Estroprogestins	Clinical	Conflicting results when compared with oral or transdermal routes. Limited investigation.
		Danazol	Clinical	Effective with lower serum level and AEs, not contraceptive.
		Aromatase inhibitors	Clinical	Ongoing investigation in patients with endometriosis.
Transdermal				
		Estroprogestins	Clinical	Compared only with vaginal ring. Limited investigation.
Intrauterine system				
		Levonorgestrel	Clinical	Effective, higher or comparable satisfaction, contraceptive, not prevention of endometrioma
		Danazol	Clinical	Effective with lower serum level and AEs. Limited investigation.
Depot and long-acting formulations				
	Injectable	Depot Medroxyprogesterone acetate	Clinical	Effective, from higher to lower satisfaction based on comparison, irregular bleeding, concern on BMD loss.
	Implants	Etonogestrel	Clinical	Effective, comparable to DMPA in terms of satisfaction, efficacy, and AEs
		GnRH analogs	Clinical	Multiple drug delivery option equally effective, 3 months depot formulation
Nanotechnologies				
	PLGA nanoparticles	Epigallocatechin gallate + doxycycline	Mouse model	Antioxidant and antiangiogenic + inhibition of metalloproteases. Reduction of endometriosic implants
		Copaiba Oleoresin	In vitro	Antioxidant, anti-inflammatory, and antinociceptive. Reduced cell viability.
		Anti-CTLA-4 antibody	Mouse model	Inhibition of CD4+/CD25+/Tregs. Sustained release of antibodies. Inhibition of proliferation and invasion of endometriosic cells.
		anti-CCR5 antibodies	Mouse model	Reduce anti-inflammatory and pro-fibrotic activity of macrophages. Reduced proliferation and invasion ability of ectopic endometrial cells.
	AMNPs	GMDP	In vitro	Increased stability and action of GMDP. Enhanced expression of scavenger receptors and macrophages activity
	Lipid nanoparticles	//	Clinical	lipid nanoparticles are up taken by the endometriotic implants, adjacent healthy peritoneum, and eutopic endometrium.
	TNYL peptide	HAuNS	Mouse model	Accumulation in and photothermal ablation of endometriosic implants without AEs
	nanoparticles	silicon naphthalocyanine	Rhesus macaques	Accumulation in, visualization of, and photothermal ablation of endometriosic implants without AEs
	nanofibers	curcumin	Mouse model	Continuous release of curcumin up to 30 days. Reduction of endometriosic implants and inflammatory infiltrate.

PLGA, Poly(lactic-co-glycolic) acid; AMNPs, Aminopropyl mesoporous silica nanoparticles; GMDP, N-acetylglucosaminyl-N-acetylmuramyl-L-alanyl-D-isoglutamine; HAuNS, hollow gold nanospheres; AEs, adverse effects; BMD, bone mineral density.

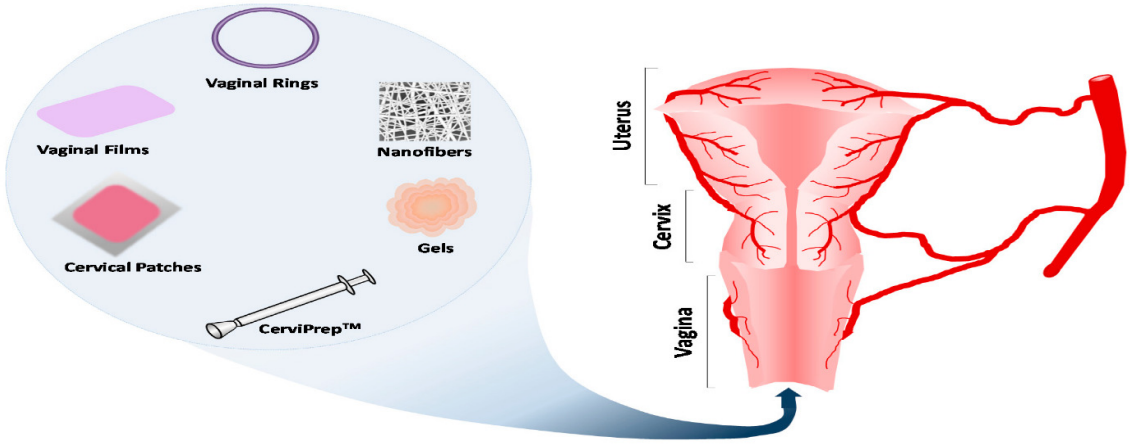

Fig 1: Vaginal drug delivery system.

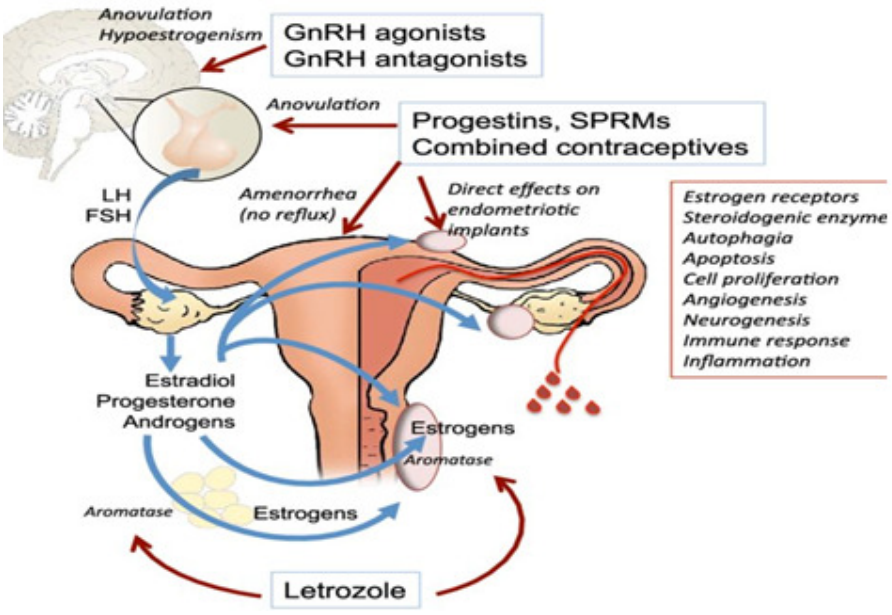

Fig 2: Endometriosis treatment

