International Journal of Science and Healthcare Research
Vol. 8; Issue: 3; July-Sept. 2023
Website: ijshr.com
Review Article *ISSN: 2455-7587*

Relugolix, Estradiol, Norethindrone Acetate (40mg+1.0mg+0.5mg), Oral Combination Therapy for Uterine Fibroids (Relugolix) in Premenstrual Women: A Quality Life Perspective

Aparna Arora[1], Dr. P.R. Kamble[2], Dr. Chetan Singh Chauhan[3], Dr. R. Kamble[4]

[1]Department of Quality Assurance, [2]Department of Chemistry,
Bhupal Nobles' College of Pharmacy, Bhupal Nobles' University, Udaipur (Raj.), India

Corresponding Author: Aparna Arora

DOI: https://doi.org/10.52403/ijshr.20230350

ABSTRACT

The following article elucidates the role of oral therapy for uterine fibroids in increasing the quality of life and a better treatment option as compared to the conventional methods, which are operative and may result in infertility.

Uterine fibroids are non-cancerous growths (myomas or leiomyomas) also known as Uterine Leiomyomas or Fibromyomas appear in or around the uterus. They can shrink after menopause, exist in adults of reproductive age, and have been connected to oestrogen, however the specific origin is unknown. Uterine fibroids affect about 1 in 3 women, and their prevalence rises with age until menopause, peaking in the forties. In general, symptoms can be categorized as heavy and protracted menstrual bleeding, pelvic pain, and reproductive dysfunction.

The triple combination drug is given orally to the patients (once daily as early as possible after menstrual cycle but no later than seven days after menstrual cycle begins) and it can be given for the period of 24 months which is longer duration than its other alternatives like leuprolide (6-12 months) and it effectively resolves Abnormal Uterine Bleeding – Leiomyomata (AUB-L). It will resolve the imbalance of estrogen and progesterone in female body and reduces the side effects such as bone loss due to estrogen imbalance.

Being an oral tablet gives it an advantage over other surgical procedures and parenteral dosage forms as it is non-invasive and easy to administer, in small dose, once daily.

Keywords: Uterine Fibroids, Health Related Quality of Life, Gonadotropin Releasing Hormone Receptor Antagonist, Combination Therapy, Relugolix.

INTRODUCTION

The most frequent uterine tumours of smooth muscle origin are leiomyomas or fibromyomas, sometimes known as fibroids by gynecologists. They are frequently mixed with different amounts of fibrous tissue component. 20% of women over the age of 30 have uterine myomas, which can range in size. A large percentage of them are benign and exhibit no symptoms.

Less than 0.5% of leiomyomas develop malignant transformation. Infertility, irregular uterine bleeding, discomfort, and symptoms brought on by compression of nearby structures are all possible in symptomatic situations.

The uterus is where leiomyomas most usually develop, where they can be found in the myometrium (intramural or interstitial), the serosa (subserosal), or directly below the endometrium (submucosal). Leiomyomas that are subserosal and submucosal may grow pedicles and protrude as pedunculated myomas. The wide ligament or cervix may be affected by leiomyomas.

Although it may superficially resemble leiomyosarcoma and predominately consist of smooth muscle parts, cellular leiomyoma

can be recognised from it by the lack of mitoses.

Secondary alterations in the leiomyomas, such as hyaline degeneration, cystic degeneration, infarction, calcification, infection and suppuration, necrosis, fatty change, and infrequently sarcomatous change, may affect the pathologic appearance. [1]

Morphological features, Symptoms, Diagnosis and Treatment.

On a gross level, the tumour may take the appearance of a polypoid mass protruding into lumen or a diffuse, bulky, soft, and fleshy mass.

The number of mitoses per high power field (HPF), albeit there are typically certain areas indicating whorled arrangement of spindle-shaped smooth muscle cells with big and hyperchromatic nuclei, is the defining characteristic of diagnosis and prognosis. More than 10 mitoses per 10 HPF, with or without cellular atypia, or 5–10 mitoses per 10 HPF, with cellular atypia, are the crucial diagnostic requirements. The prognosis is worse if there are more mitoses per 10 HPF. [1]

Symptomatology

The main signs of UL are intense pelvic pressure and heavy menstrual bleeding. [2] Infertility, increased urination or incontinence, constipation, stomach bloating, dyspareunia, and weariness (caused by anaemia from heavy bleeding) are some other symptoms. [3, 4] The range and severity of symptoms frequently vary on the number, size, and location of uterine tumours.

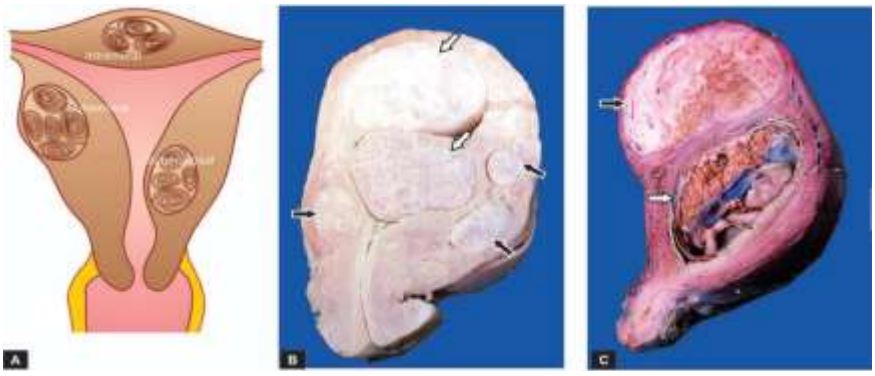

Figure 1. Leiomyomas.

A. *Diagrammatic appearance of common locations and characteristic whorled appearance on cut section.*

B. *Sectioned surface of the uterus shows multiple circumscribed, firm nodular masses of variable sizes—submucosal (white arrows) and intramural (black arrows) in location having characteristic whorling.*

C. *The opened up uterine cavity shows an intrauterine gestation sac with placenta (white arrow) and a single circumscribed, enlarged, firm nodular mass in intramural location (black arrow) having grey white whorled pattern.*

Diagnosis

Studies using ultrasound for screening are becoming more prevalent. Ultrasound can help with Uterine leiomyomata (UL) diagnosis confirmation and reduce misdiagnosis in controls that may have asymptomatic UL. These studies offer the most reliable data on the frequency of UL. [13]

In especially for bigger uteri or multiple UL, magnetic resonance imaging (MRI) is more expensive but more accurate than ultrasound

for UL mapping. Epidemiologic studies can lessen the impact of bias if systematic pelvic imaging is not feasible by include cases that have only recently been diagnosed by ultrasound (or MRI) in addition to those that have been confirmed histologically, albeit this strategy will still misclassify controls. [5]

Treatment for Uterine Fibroids

Combinational Oral Contraceptives

The use of oral contraceptives to lessen menstrual bleeding in women with fibroids is supported by observational data. Through their suppressive effects on endometrial growth, COCs can be used to reduce excessive monthly bleeding brought on by fibroids in the short term, but they have no overall impact on reducing uterine fibroid volume or uterine size. [6, 7]

Progestin

In cases of non-organic abnormal uterine bleeding, such as premenopausal bleeding and endometrial hyperplasia-related bleeding, progestin has been used in cycles to control bleeding. As with earlier COCs, uterine fibroids are frequently treated with progestin, but some people believe that progestin should not be used to treat uterine fibroids' symptoms. [8]

The FDA authorised the LNG-IUS in 2009 to treat heavy menstrual bleeding in women who choose to use an intrauterine device for contraception. Its application for treating uterine fibroid-related bleeding was quickly examined because it was well-known as a successful treatment for non-organic irregular uterine haemorrhage. [9]

Given that the LNG-IUS can be implanted and remain functional for up to five years, it may provide women a long-term therapy option. There are little side effects recorded because it is not given systemically, and since daily or monthly injections are not necessary, no additional patient compliance is needed after the device has been inserted. It is likely a successful alternative in some symptomatic women without endometrial distortion, despite the elevated risk of expulsion. [10]

Gonadotropin Releasing Hormone (GnRH) Agonists

The hypothalamus produces and releases native GnRH, a decapeptide, in a pulsatile manner. Synthetic peptides that are structurally similar to the natural GnRH molecule are known as GnRH agonists; however, they are more potent and have a longer half-life than native GnRH. [11, 12] They have a flare effect, which increases the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) immediately after administration. After that, they trigger receptor down-regulation and, 1-3 weeks later, a hypogonadotropic hypogonadal condition that is frequently referred to as "pseudomenopause". Given that oestrogen stimulates the formation of leiomyomas, this hypoestrogenic state aid in the pharmacologic effectiveness of GnRH agonists. Numerous investigations have revealed that the fraction of oestrogen receptor (ER)-positive cells in a tumour is inversely correlated with tumour size. [13]

Selective Progesterone Receptor Modulators (SPRMs)

Synthetic steroids with agonistic and/or antagonistic actions on progesterone receptors (PR) are known as SPRMs. They can be picked up by progesterone receptors because of their structural similarities, and depending on the change in receptor conformation brought on by the bond, co-repressors or co-activators (co-regulators) are accumulated in the corresponding binding domain. Depending on the SPRM's structure, the progesterone receptor's altered conformation, and the availability of coregulators (ratio of coactivators to corepressors in a certain cell type), an SPRM may have a stronger agonistic or antagonistic effect. The type of tissue, the type of cell, and the physiological milieu all have an impact on an SPRM's activity. [14, 15] The pituitary gland, the fibroid, and the endometrium are all directly impacted by

SPRMs. through preventing ovulation (in around 80% of patients) and keeping estrogen levels in the mid-follicular range, amenorrhea is brought on through a direct action on the pituitary gland. The cessation of uterine bleeding, benign reversible alterations to the endometrium (PAEC: Progesterone Receptor Modulator Associated Endometrial alterations), and reversible endometrial thickness are all signs of the direct influence on the endometrium. Additionally, SPRMs result in a decrease in fibroids by preventing cell growth and promoting apoptosis. [16]

Selective Progesterone Receptor Modulators (SERMs)

Numerous experimental findings and indirect evidence point to estrogen's potential role in uterine fibroids' proliferation via ER-. In order for tissue to respond to progesterone by promoting the production of PR, oestrogen and ER- play key permissive roles in myoma development. [17]

Selective oestrogen receptor modulators (SERMs) are nonsteroidal oestrogen receptor (ER) ligands that exhibit tissue-specific changes in gene expression through ER agonist and/or antagonist estrogenic effects. ER-positive breast cancer was the first indication for the use of these drugs. Tamoxifen and raloxifene are two of the SERMs used to treat uterine fibroids that are most often researched. [18]

Aromatase Inhibitors (AI)

Within a day of starting medication, aromatase inhibitors (AIs) drastically reduce ovarian and peripheral oestrogen production. Letrozole reduced the production of oestrogens by 76-79% relative to baseline levels, especially estrone and estrogen. The enzyme aromatase, which catalyses the conversion of androgenic chemicals into oestrogens, is what is responsible for the underlying mechanism.

In order to protect their potential fertility, short-term use of aromatase inhibitors might be considered in women with fibroids or in those who prefer to forgo surgical intervention. [18, 19]

Gonadotropin Releasing Hormone Receptor Antagonist (GnRH Receptor Antagonist)

Gonadotropin releasing hormone (GnRH) is a decapeptide produced in the hypothalamus that acts on GnRH receptors on the surface of pituitary gonadotropin cells, stimulating the release of luteinizing hormone (LH) and follicular stimulating hormone (FSH), which stimulate the production and release of testosterone by the male testes and oestrogen by the female ovaries and placenta. GnRH is normally synthesised in a pulsatile manner, and its synthesis is influenced by testosterone levels in males and oestrogen levels in women. GnRH agonists provide a transitory surge in sex hormones, but with continuous non-pulsatile stimulation, LH and FSH synthesis is suppressed, and oestrogen and testosterone levels fall. GnRH analogues have been shown to be far more effective and long-lasting than the original decapeptide and have been widely used in the control of sex hormone production. The GnRH analogue degarelix works in a somewhat different way in that it is an antagonist of the pituitary gonadotropin receptors, inhibiting LH and FSH production and release directly and without the first spike seen with GnRH agonists. The end effects and efficacy of GnRH agonists and antagonists are similar, with the pure antagonist having a faster onset and without an initial increase in sex hormone release.

The following GnRH agonists and antagonists have commercial names and years of approval in the United States: leuprolide (Lupron: 1985), goserelin (Zoladex: 1989), histrelin (Supprelin, Vantas: 1991 and 2004), triptorelin (Trelstar: 2000), degarelix (Firmagon: 2008), and relugolix (Orgovyk: 2021). Many of these agents are now also available in generic form. [20]

By inhibiting pituitary GnRH receptors, GnRH antagonists instantly reduce the

production of FSH and LH. As early as 3 weeks following the start of treatment, improved bleeding patterns and a decrease in uterine fibroid size are brought on by the subsequent fall in Estradiol levels. Patients enjoy quicker symptom relief due to its quick onset of action and avoidance of a gonadotropin flare effect. [21]

Mechanism of Action

Relugolix is a non-peptide GnRH receptor antagonist that competitively binds to pituitary GnRH receptors, reducing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), resulting in lower serum concentrations of the ovarian sex hormones estrogen and progesterone, as well as reduced bleeding from uterine fibroids and pain from endometriosis.

Estradiol works by attaching to nuclear receptors found in estrogen-responsive tissues. The addition of exogenous Estradiol as a component of RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE may prevent the increase in bone resorption and subsequent bone loss that can occur owing to a drop in circulating oestrogen concentrations caused by Relugolix alone.

Progestins like Norethindrone Acetate work by attaching to nuclear receptors found in progesterone-responsive tissues. Norethindrone Acetate, a component of RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE, may protect the uterus from the potentially harmful endometrial consequences of unopposed oestrogen.

Pharmacodynamics

- Estradiol and Norethindrone Acetate (RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE components) may have the following effects:

Increased levels of thyroxin-binding globulin, resulting in:

I. Elevated circulation total thyroid hormone concentrations as determined by protein-bound iodine (PBI), thyroxine (T4) levels (through column or radioimmunoassay), or triiodothyronine (T3) concentrations via radioimmunoassay.

II. Reduced T3 resin uptake

III. Unaltered free T4 and free T3 levels in women with normal thyroid function.

- Elevated levels of **corticosteroid-binding globulin (CBG) and sex hormone-binding globulin (SHBG)** cause a rise in total circulating corticosteroid and sex hormone concentrations, respectively.
- Possible reduction in free testosterone concentrations.
- Possible elevations in other plasma proteins (angiotensinogen/renin substrate, alpha1 antitrypsin, ceruloplasmin).
- Increased plasma HDL and HDL_2 cholesterol subfraction concentrations, decreased low-density lipoprotein concentrations, and increased triglyceride concentrations.
- Increased platelet count; increased factors II, VII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, and beta-thromboglobulin; decreased concentrations of anti-factor Xa and antithrombin III, decreased antithrombin III activity, increased fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Pharmacokinetics

Absorption

Relugolix has a mean (%CV) absolute bioavailability of 12 (62%).

The Influence of Food

The $AUC_{0\text{-}inf}$ and C_{max} of Relugolix were reduced by 38% and 55%, respectively, after administration of RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE following consumption of a high-fat, high-calorie meal (i.e., 800-1000 calorie meal with 50% of calories derived from fat) compared to the fasted state; however, the decrease in exposure to

Relugolix is not considered clinically meaningful. Food had no clinically significant effects on Estradiol or Norethindrone Acetate exposure.

Distribution

Relugolix binds to plasma proteins with a rate of 68% to 71%, mostly to albumin and to a lesser amount to 1-acid glycoprotein. The average blood-plasma ratio is 0.78. Estradiol circulates in the blood attached to SHBG (36% to 37%) and albumin (61%), with just 1% to 2% remaining unbound. Norethindrone Acetate also binds to SHBG (36%), as well as albumin (61%).

Elimination

The mean (SD) terminal phase elimination half-life (t1/2) of Relugolix, Estradiol, and Norethindrone Acetate after a single dose of RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE is 61.5 (13.2) hours, 16.6 (7.7) hours, and 10.9 (3.1) hours, respectively.

Metabolism

In vitro, Relugolix is largely metabolised by CYP3A and to a lesser amount by CYP2C8.

Table 3. Pharmacokinetics of Relugolix, Estradiol and Norethindrone Acetate

	Relugolix	**Estradiol**	**Norethindrone Acetate**
$AUC_{0\text{-}inf}$ (ng·hr/mL or pg·hr/mL), mean (SD)	198.1 (111.6)	818.7 (334.4)	17.5 (8.5)
C_{max} (ng/mL or pg/mL), mean (SD)	26.0 (18.2)	28.0 (19.2)	3.6 (1.4)
T_{max} (hr), median (min, max)	2.00 (0.25, 5.00)	7.00 (0.25, 24.00)	1.0 (0.50, 4.00)

Abbreviations: AUC = area under the concentration-time curve; $AUC_{0\text{-}inf}$ = AUC from time 0 extrapolated to infinity; C_{max} = maximum observed concentration; T_{max} = time to maximum observed concentration. Notes: AUC0-inf is presented in ng·hr/mL for Relugolix, Norethindrone Acetate and in pg·hr/mL for unconjugated E2. Cmax is presented in ng/mL for Relugolix, Norethindrone Acetate and in pg/mL for unconjugated Estradiol.

Estradiol is reversibly transformed to estrone, and both can be turned to estriol, a significant urine metabolite. Oestrogens are also recirculated through the liver due to sulphate and glucuronide conjugation, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption.

Norethindrone Acetate is biotransformed extensively, mostly via reduction, as well as sulfation, glucuronidation, and oxidation by sulfotransferases (SULTs), glucuronosyltransferases (UGTs), and CYP enzymes, notably CYP3A4. Sulphates account for the bulk of metabolites in circulation, with glucuronides accounting for the majority of urine metabolites.

After a single 80 mg radiolabeled dose of Relugolix was administered orally, roughly 81% of the radioactivity was recovered in faeces (4.2% as unchanged) and 4.1% in urine (2.2% as unaffected).

Estradiol is eliminated as glucuronide and sulphate conjugates in the urine. Norethindrone Acetate is mostly eliminated in the urine as polar metabolites.

INDICATIONS AND APPLICATIONS

1. Uterine Leiomyomas and Heavy Menstrual Bleeding

RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE is used to treat heavy menstrual bleeding caused by uterine leiomyomas (fibroids) in premenopausal women.

2. Pain Associated with Endometriosis

RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE is indicated in premenopausal women for the treatment of moderate to severe pain associated with endometriosis.

3. Use Restrictions

RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE should be used for no more than 24 months due to the possibility of irreversible bone loss.

Precautions

Thromboembolic Disorders and Vascular Events

Oestrogen and progestin combinations, such as the Estradiol/Norethindrone Acetate component of RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE increase the risk of thrombotic or thromboembolic disorders such as pulmonary embolism, deep vein thrombosis, stroke, and myocardial infarction, particularly in women who are predisposed to these events. Women over 35 who smoke and women with uncontrolled hypertension, dyslipidemia, vascular disease, or obesity are at highest risk.

Bone Loss

RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE is not recommended for women who have osteoporosis. Consider the benefits and risks of RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE treatment in patients who have a history of a low-trauma fracture or who have risk factors for osteoporosis or bone loss, such as taking medications that may lower bone mineral density (BMD) (e.g., systemic or chronic inhaled corticosteroids, anticonvulsants, or chronic use of proton pump inhibitors).

Hormone-Sensitive Malignancies

RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE is not recommended for women who have a history of hormone-sensitive cancers (e.g., breast cancer) or who are at high risk of developing hormone-sensitive cancers. If a hormone-sensitive cancer is diagnosed, stop taking RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE.

Suicidal Ideation and Mood Disorders (Including Depression)

Before beginning treatment, evaluate patients who have a history of suicide ideation, depression, or mood disorders. Monitor patients for mood changes and depressive symptoms, even right after starting treatment, to see if the hazards of continuing RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE medication exceed the benefits. Patients experiencing new or worsening sadness, anxiety, or other mood problems should be directed to a mental health specialist as needed. In the event of suicide ideation or behaviour, advise patients to seek emergency medical assistance. If such events occur, reassess the advantages and hazards of continuing RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE.

Hepatic Impairment and Transaminase Elevations

Contraindication in Hepatic Impairment Patients

RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE is not recommended for those who have known hepatic impairment or illness. In people with reduced liver function, steroid hormones may be inadequately metabolised.

Elevated transaminase levels

Instruct women to seek medical assistance immediately if they experience symptoms or signs of liver injury, such as jaundice or right upper abdominal pain. Acute liver test abnormalities may need RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE withdrawal until the liver tests revert to normal and RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE aetiology is ruled out.

Gallbladder Disease or History of Cholestatic Jaundice

If you have gallbladder problems or jaundice, stop taking RELUGOLIX+ ESTRADIOL+NORETHINDRONE ACETATE. Evaluate the risk-benefit of continuing medication for women who have a history of cholestatic jaundice caused by previous oestrogen usage or pregnancy. According to research, oestrogen users had a slightly increased relative chance of acquiring gallbladder illness.

Elevated Blood Pressure

RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE is not recommended for women who have uncontrolled hypertension. Continue to monitor blood pressure in women with well-controlled hypertension and discontinue RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE if blood pressure rises considerably.

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

Before starting RELUGOLIX+ ESTRADIOL+ NORETHINDRONE ACETATE, rule out pregnancy. Start RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE as soon as possible following the start of menstruation, but no later than 7 days. If MYFEMBREE is started later in the menstrual cycle, it may cause irregular and/or severe bleeding at first.

RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE may cause amenorrhea, or a reduction in the volume, intensity, or duration of monthly bleeding, which may delay the ability to detect pregnancy. If pregnancy is suspected, pregnancy testing should be performed, and RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE should be discontinued if pregnancy is confirmed.

Women of reproductive potential should utilise effective non-hormonal contraception during RELUGOLIX+ESTRADIOL+ NORETHINDRONE ACETATE treatment and for one week following the final dosage. RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE should not be used in conjunction with hormonal contraception.

Risk of Early Pregnancy Loss

RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE is not recommended for usage during pregnancy. RELUGOLIX+ ESTRADIOL+NORETHINDRONE ACETATE can cause early pregnancy loss, according to animal studies and its mechanism of action. However, no foetal abnormalities were observed in either rabbits or rats at any dose level evaluated, which were associated with Relugolix exposures around half and nearly 300 times that of women at the approved human dose.

Uterine Fibroid Prolapse or Expulsion

Inform women with known or suspected submucosal uterine fibroids about the likelihood of fibroid prolapse or expulsion and encourage them to call their doctor if they experience severe bleeding and/or cramps while taking RELUGOLIX+ ESTRADIOL+NORETHINDRONE ACETATE.

Alopecia

The treatment is discontinued if there is persistent hair loss.

Effects on Carbohydrate and Lipid Metabolism

More frequent monitoring may be required in RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE -treated women with prediabetes and diabetes. RELUGOLIX+ ESTRADIOL+NORETHINDRONE ACETATE may reduce glucose tolerance, resulting in higher blood glucose levels.

Keep an eye on your lipid levels and consider stopping RELUGOLIX+ ESTRADIOL+NORETHINDRONE ACETATE if your hypercholesterolemia or hypertriglyceridemia worsens. Oestrogen therapy may be related with triglyceride increases leading to pancreatitis in women who already have hypertriglyceridemia. RELUGOLIX+ESTRADIOL+NORETHINDRONE ACETATE use has been linked to an increase in total cholesterol and low-density lipoprotein cholesterol. [22, 23]

Defining a Quality Life Perspective

In the two phase 3 LIBERTY studies, a total of 509 women were enrolled and received treatment between April 2017 and July 2019 in the relugolix-CT (n=4253) and placebo

(n=256) groups in the modified intent-to-treat population. [35]

The LIBERTY program thoroughly evaluated the Uterine Fibroid (UF) symptoms experienced by women with symptomatic Uterine Fibroids, including Uterine Fibroids-related pain, overall Uterine Fibroids symptom severity, and distress related to important Uterine Fibroids symptoms (HMB, passing blood clots, and pelvic tightness or pressure), as well as *Health Related Quality of Life* (HRQoL). [24, 26]

Relugolix has been demonstrated to be useful in lowering pain brought on by Heavy Menstrual Bleeding (HMB) & Uterine Fibroid (UF) and in enhancing anemia. The patient-reported outcome findings that are given here offer more proof of the positive effects of relugolix on UF-associated symptom load, distress related to important UF symptoms, and Health Related Quality of Life (HRQoL). Notably, relugolix treatment significantly improved UF-related concern, activity energy and mood, control, self-consciousness, and sexual function in women compared to placebo treatment. Relugolix-CT significantly outperformed the placebo in terms of the percentage of women who experienced a clinically significant decline in the validated BPD subscale scores, which measure pelvic pressure, distress from heavy bleeding, and passing blood clots, as well as a clinically significant improvement in the RA subscale scores, which measure physical and social activities. [27]

The UFS-QoL questionnaire was also used in recent clinical studies of elagolix, a GnRH antagonist that is sold with estradiol and NETA. The results showed that, similar to relugolix-CT, elagolix reduced the burden of UF-related symptoms and enhanced HRQoL when compared to placebo treatment. However, because of its short half-life, elagolix needs to be administered twice daily; relugolix-CT is only needed once daily, which should make it easier to use and may aid with treatment adherence. [28, 29]

Relugolix-CT had important patient-relevant impacts on UF-related symptoms and quality of life while limiting hypoestrogenic side effects, such as vasomotor symptoms and bone loss.

The current analyses' findings show that relugolix-CT lowers UF-related symptom load and distress while enhancing HRQoL, which adds to the body of evidence already available. [30]

When patients and healthcare professionals consider treatment choices, the capacity of relugolix-CT to address the most distressing symptoms related to UFs has therapeutic implications.

Notably, the majority of women who received relugolix-CT treatment had reductions in their BPD subscale scores that were clinically significant, suggesting that the lessened distress had a real effect on their day-to-day activities.

Relugolix-CT has a significant positive impact on women's daily lives, as evidenced by increased feelings of wellbeing, decreased worry, increased participation in activities, and improved sexual function, as measured by the UFS-QoL, according to the results reflecting various aspects of HRQoL. When compared to 34.0% of women who received the placebo, the improvement in physical and social activities as measured by the RA subscale was clinically significant for 61.7% of women treated with relugolix-CT. We noticed improvements in symptom severity and HRQoL that were equivalent to those women experienced following surgical and procedural procedures. [31-34]

CONCLUSION

The chosen compound Relugolix is a new molecular entity and the combination (Relugolix + Estradiol + Norethindrone acetate) is a fixed dose combination which is a very effective approach towards treating heavy menstrual bleeding during uterine leiomyomas without using invasive surgical procedures. The oral tablet design will open doors and windows for further developments in oral treatments for such diseases. It is a well-tolerated treatment

which will ultimately result in better patient compliance and will increase quality of life of patients. This is also a pocket friendly alternative as it is less expensive than other traditional alternatives. Oral therapy will reduce the chances of infertility in women, which is a major disadvantage of surgical procedures. There are other oral alternatives for Uterine fibroids but they also have disadvantages of being single drug moiety that does not balance the decrease in essential hormones or hormonal imbalance in body. The (Relugolix + Estradiol + Norethindrone acetate) combination is add-back therapy which reduces hypo estrogenic effects. Most women suffering from uterine fibroids are asymptomatic, however if there are symptoms like heavy menstrual bleeding which may cause anemia and weakness, focus should be on symptom management.

Declaration by Authors

Ethical Approval: Not Applicable
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Mohan H. The female genital tract. Textbook of pathology. 6th edition. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd.;2010 737-738.
2. Wegienka G, Baird DD, Hertz-Picciotto I, Harlow SD, Steege JF, Hill MD, et al. Self-reported heavy bleeding associated with uterine leiomyomata. Obstetrics & Gynecology [Internet]. 2003 Mar 1;101(3):431–7. Available from: https://doi.org/10.1016/s0029-7844(02)03121-6
3. Kjerulff KH, Langenberg P, Seidman JD, Stolley PD, Guzinski GM. Uterine leiomyomas. Racial differences in severity, symptoms and age at diagnosis. J Reprod Med. 1996 Jul;41(7):483-90. PMID: 8829060.
4. Lippman SA, Warner M, Samuels SJ, Olive DL, Vercellini P, Eskenazi B. Uterine fibroids and gynecologic pain symptoms in a population-based study. Fertility and Sterility [Internet]. 2003 Dec 1;80(6):1488–94. Available from: https://doi.org/10.1016/s0015-0282(03)02207-6
5. Dueholm M, Lundorf E, Hansen ES, Ledertoug S, Olesen F. Accuracy of magnetic resonance imaging and transvaginal ultrasonography in the diagnosis, mapping, and measurement of uterine myomas. American Journal of Obstetrics and Gynecology [Internet]. 2002 Mar 1;186(3):409–15. Available from: https://doi.org/10.1067/mob.2002.121725
6. Marret H, Fritel X, Ouldamer L, Bendifallah S, Brun JL, De Jesus I, et al. Therapeutic management of uterine fibroid tumors: updated French guidelines. European Journal of Obstetrics & Gynecology and Reproductive Biology [Internet]. 2012 Dec 1;165(2):156–64. Available from: https://doi.org/10.1016/j.ejogrb.2012.07.030
7. Qin J, Yang T, Kong FJ, Zhou Q. Oral contraceptive use and uterine leiomyoma risk: a meta-analysis based on cohort and case–control studies. Archives of Gynecology and Obstetrics [Internet]. 2013 Apr 4;288(1):139–48. Available from: https://doi.org/10.1007/s00404-013-2797-9
8. Hoffman B, Schorge J, Schaffer J, Halvorson L, Bradshaw K, Cunningham F. Williams Gynecology, Second Edition. McGraw Hill Professional; 2012.
9. Sayed GH, Zakherah MS, El-Nashar SA, Shaaban MM. A randomized clinical trial of a levonorgestrel-releasing intrauterine system and a low-dose combined oral contraceptive for fibroid-related menorrhagia. International Journal of Gynaecology and Obstetrics [Internet]. 2010 Nov 19;112(2):126–30. Available from: https://doi.org/10.1016/j.ijgo.2010.08.009
10. Sohn GS, Cho S, Kim YJ, Cho CH, Kim MK, Lee SR. Current medical treatment of uterine fibroids. Obstetrics & Gynecology Science [Internet]. 2018 Jan 1;61(2):192. Available from: https://doi.org/10.5468/ogs.2018.61.2.192
11. Islam S, Protic O, Giannubilo SR, Toti P, Tranquilli AL, Petraglia F, et al. Uterine Leiomyoma: Available medical treatments and new possible therapeutic options. The Journal of Clinical Endocrinology and Metabolism [Internet]. 2013 Mar 1;98(3):921–34. Available from: https://doi.org/10.1210/jc.2012-3237

12. De Leo V, Morgante G, La Marca A, Musacchio MT, Sorace M, Cavicchioli C, et al. A benefit-risk assessment of medical treatment for Uterine leiomyomas. Drug Safety [Internet]. 2002 Jan 1;25(11):759–79. Available from: https://doi.org/10.2165/00002018-200225110-00002
13. Singh S, Belland L. Contemporary management of uterine fibroids: focus on emerging medical treatments. Current Medical Research and Opinion [Internet]. 2014 Nov 12;31(1):1–12. Available from: https://doi.org/10.1185/03007995.2014.982246
14. Vannuccini S, Luisi S, Tosti C, Sorbi F, Petraglia F. Role of medical therapy in the management of uterine adenomyosis. Fertility and Sterility [Internet]. 2018 Mar 1;109(3):398–405. Available from: https://doi.org/10.1016/j.fertnstert.2018.01.013
15. Rabe T, Saenger N, Ebert AD, Roemer T, Tinneberg HR, De Wilde RL, et al. Selective Progesterone Receptor Modulators for the Medical Treatment of Uterine Fibroids with a Focus on Ulipristal Acetate. BioMed Research International [Internet]. 2018 Jun 24; 2018:1–12. Available from: https://doi.org/10.1155/2018/1374821
16. Donnez J, Dolmans MM. Uterine fibroid management: from the present to the future. Human Reproduction Update [Internet]. 2016 Jul 27;22(6):665–86. Available from: https://doi.org/10.1093/humupd/dmw023
17. Sohn GS, Cho S, Kim YJ, Cho CH, Kim MK, Lee SR. Current medical treatment of uterine fibroids. Obstetrics & Gynecology Science [Internet]. 2018 Jan 1;61(2):192. Available from: https://doi.org/10.5468/ogs.2018.61.2.192
18. Sabry M, Al-Hendy A. Innovative oral treatments of uterine leiomyoma. Obstetrics and Gynecology International [Internet]. 2012 Jan 1; 2012:1–10. Available from: https://doi.org/10.1155/2012/943635
19. Laughlin-Tommaso SK, Stewart EA. Moving Toward Individualized Medicine for Uterine Leiomyomas. Obstetrics & Gynecology [Internet]. 2018 Oct 1;132(4):961–71. Available from: https://doi.org/10.1097/aog.0000000000002785
20. National Institute of Diabetes and Digestive and Kidney Diseases. Gonadotropin Releasing Hormone (GNRH) Analogues [Internet]. LiverTox - NCBI Bookshelf. 2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547863/
21. Kettel LM, Murphy AA, Morales AJ, Rivier J, Vale W, Yen SSC. Rapid regression of uterine leiomyomas in response to daily administration of gonadotropin-releasing hormone antagonist. Fertility and Sterility [Internet]. 1993 Oct 1;60(4):642–6. Available from: https://doi.org/10.1016/s0015-0282(16)56214-1
22. Myovant Sciences Inc. MyfembreeR (relugolix, estradiol, and norethindrone acetate) tablets, for oral use: US prescribing information. 2021. https:// www. acces sdata. fda. gov/ drugs atfda_ docs/label/ 2021/ 21484 6s000 lbl. pdf. Accessed 21 Sept 2023.
23. Patient Package Insert, U.S. Food and Drug Administration, Approved on 08/2022 Reference ID: 5025703, pg:12 <https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214846s002lbl >
24. Coyne KS, Margolis MK, Murphy J, Spies J. Validation of the UFS-QoL-hysterectomy questionnaire: modifying an existing measure for comparative effectiveness research. Value Health 2012; 15:674–9.
25. Schlaff WD, Ackerman RT, Al-Hendy A, et al. Elagolix for heavy menstrual bleeding in women with uterine fibroids. N Engl J Med 2020; 382:328–40.
26. Lukes AS, Soper D, Harrington A, et al. Health-related quality of life with ulipristal acetate for treatment of uterine leiomyomas: a randomized controlled trial. Obstet Gynecol 2019; 133:869–78.
27. Hudgens S, Gauthier M, Hunsche E, et al. Development of the Bleeding and Pelvic Discomfort Scale for use in women with heavy menstrual bleeding associated with uterine fibroids. Value Health 2022; 25:1986–94.
28. Simon JA, Al-Hendy A, Archer DF, et al. Elagolix treatment for up to 12 months in women with heavy menstrual bleeding and uterine leiomyomas. Obstet Gynecol 2020; 135:1313–26.
29. Ng J, Chwalisz K, Carter DC, Klein CE. Dose-dependent suppression of gonadotropins and ovarian hormones by

elagolix in healthy premenopausal women. J Clin Endocrinol Metab 2017; 102:1683–91.
30. Al-Hendy A, Lukes AS, Poindexter AN 3rd, et al. Treatment of uterine fibroid symptoms with relugolix combination therapy. N Engl J Med 2021; 384:630–42.
31. Wallace K, Zhang S, Thomas L, et al. Comparative effectiveness of hysterectomy versus myomectomy on one-year health-related quality of life in women with uterine fibroids. Fertil Steril 2020; 113:618–26.
32. Laughlin-Tommaso SK, Lu D, Thomas L, et al. Short-term quality of life after myomectomy for uterine fibroids from the COMPARE-UF fibroid registry. Am J Obstet Gynecol 2020; 222:345. e1–22.
33. Go VAA, Thomas MC, Singh B, et al. A systematic review of the psychosocial impact of fibroids before and after treatment. Am J Obstet Gynecol 2020; 223:674–708.e8.
34. Daniels J, Middleton LJ, Cheed V, et al. Uterine artery embolisation versus myomectomy for premenopausal women with uterine fibroids wishing to avoid hysterectomy: the FEMME RCT. Health Technol Assess 2022;26:1–74.
35. Stewart EA, Lukes AS, Venturella R, Li Y, Hunsche E, Wagman RB, et al. Quality of life with relugolix combination therapy for uterine fibroids: LIBERTY randomized trials. American Journal of Obstetrics and Gynecology. 2022 Nov.

How to cite this article: Aparna Arora, P.R. Kamble, Chetan Singh Chauhan, R. Kamble. Relugolix, Estradiol, norethindrone acetate (40mg+1.0mg+0.5mg), oral combination therapy for uterine fibroids (Relugolix) in premenstrual women: a quality life perspective. *International Journal of Science & Healthcare Research.* 2023; 8(3): 359-370. DOI: *https://doi.org/10.52403/ijshr.20230350*

******