GNRH ANTAGONISTS

A NEW ALTERNATIVE IN THE MANAGEMENT OF ENDOMETRIOSIS?

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- **Since clinical evidence shows that estrogens play a critical role in the pathogenesis of the disease, lowering their levels with oral GnRH antagonists may well prove effective, especially in women who fail to respond to progestogens.**
- **There is a need for reliable long-term oral treatment capable of managing endometriosis symptoms, taking into consideration both the main symptoms and phenotype of the disease.**
- **There is a place for GnRH antagonists in the management of symptomatic endometriosis.**

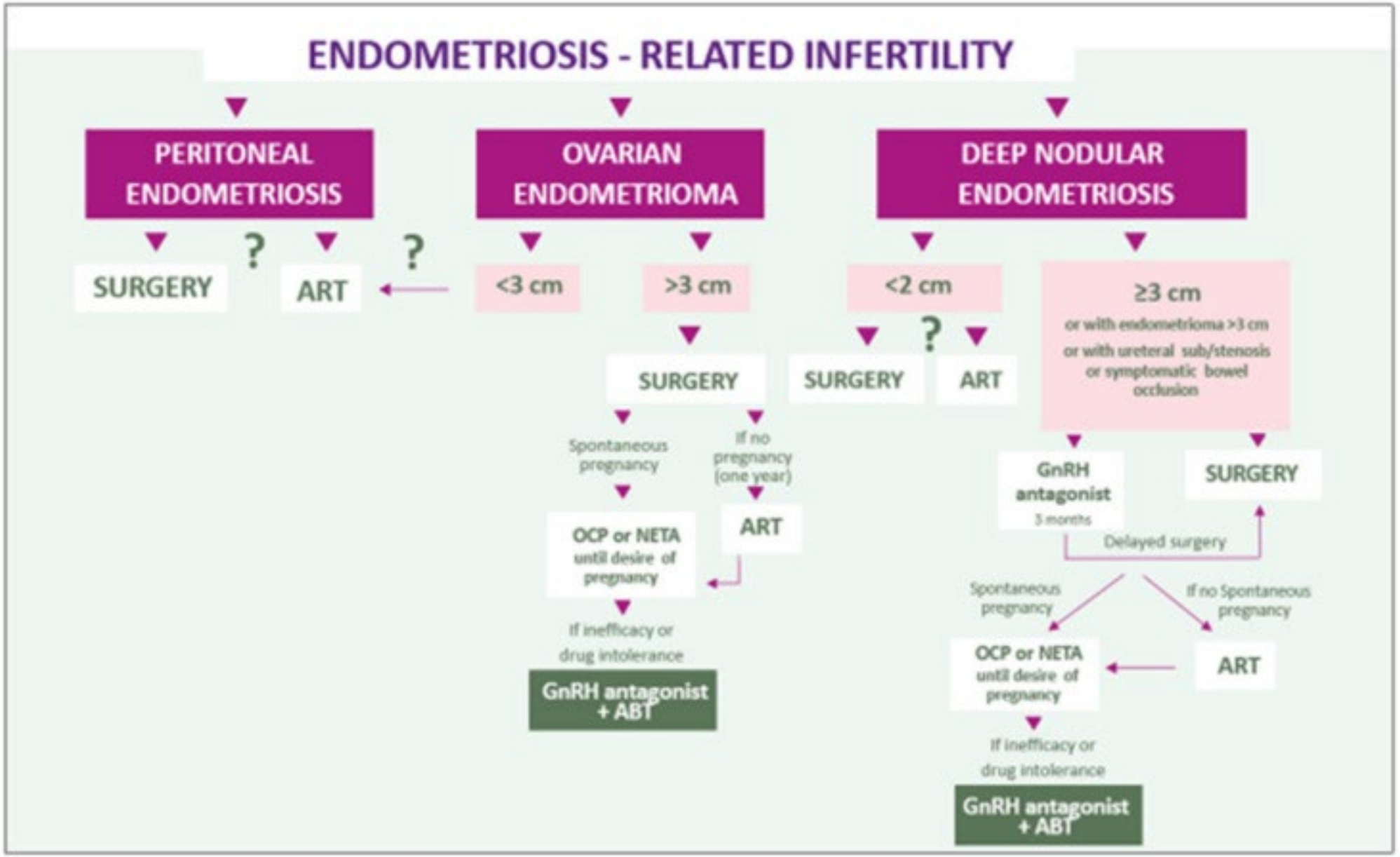
Endometriosis, the Problem

Endometriosis is a chronic inflammatory estrogen dependent disorder that is defined by the presence of endometrial-like tissue outside the uterine cavity.

- The disease affects 2–10% of women in their reproductive years.- Endometriosis is associated with subfertility and debilitating painful symptoms including dysmenorrhea, dyspareunia, dysuria, dyschezia,and chronic pelvic pain.- Other associated comorbidities include chronic pain syndromes, fatigability, anxiety/depression, autoimmune diseases, and an increased risk of certain types of cancers.

- Assisted reproductive technologies are often used to treat endometriosis related infertility because of the associated tubal dysfunction, diminished ovarian reserve or inability to have sexual intercourse.
- Although it is traditionally believed that pregnancy has a favorable influence on endometriosis, its negative impact on pregnancy is currently a growing area of concern as well.
- Since a cure for endometriosis is not available, treatment should be adjusted in line with changing life goals, needs and expectations during the reproductive lifespan and beyond.

Therefore, not only a multidisciplinary but also a life course approach in endometriosis is currently recommended.


ENDOMETRIOSIS - RELATED INFERTILITY
PERITONEAL ENDOMETRIOSIS
OVARIAN ENDOMETRIOMA
DEEP NODULAR ENDOMETRIOSIS
SURGERY
?
ART
?
<3 cm
>3 cm
<2 cm
?
≥3 cm
or with endometrioma >3 cm
or with ureteral sub/stenosis
or symptomatic bowel occlusion
SURGERY
SURGERY
ART
Spontaneous pregnancy
If no pregnancy (one year)
OCP or NETA until desire of pregnancy
ART
If inefficacy or drug intolerance
GnRH antagonist + ABT
GnRH antagonist
3 months
SURGERY
Delayed surgery
Spontaneous pregnancy
If no Spontaneous pregnancy
OCP or NETA until desire of pregnancy
ART
If inefficacy or drug intolerance
GnRH antagonist + ABT

AVAILABLE MEDICAL TREATMENTS OF ENDOMETRIOSIS

- **The ideal medication for endometriosis should meet the following criteria: it should be curative rather than suppressive, it treats pain and infertility at the same time, it has an acceptable side effect profile and long-term use is safe and affordable. Unfortunately, such a medication still does not exist for women with endometriosis.**
- **Current medical treatment options of endometriosis includes analgesics and anti-inflammatory drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), which reduce endometriosis related pain and associated inflammation. However, there is limited evidence supporting their effectiveness.- First line hormonal therapy includes oral contraceptive pills and progestins (oral, IM, or LNG-IUS) which are relatively cheap and usually well tolerated. They affect endometriosis by reducing circulating estrogen, achieving atrophy of the endometriosis implants and reducing the inflammatory reaction. The use of NSAIDs enhances this effect on the inflammatory response.**

- One fourth to one third of patients are non-responsive to these hormonal agents because of progesterone resistance or they experience intolerable side effects (breakthrough bleeding, depressive symptoms, breast tenderness, bloating, loss of libido, weight gain and headaches).- For such patients second line hormonal treatment including gonadotropin-releasing hormone (GnRH) agonists, which induce a profound hypoestrogenic milieu, could be used.- GnRH agonists can cause substantial bone mineral density loss with long-term use, hot flushes, dry vagina, and mood swings. Because of their side effect profile, GnRH agonist use should be limited to 6 months if used alone and to one year if used with hormonal add-back therapy to avoid clinically relevant reductions in bone mineral density.- Aromatase inhibitors represent another second line treatment option to treat endometriosis related pain.

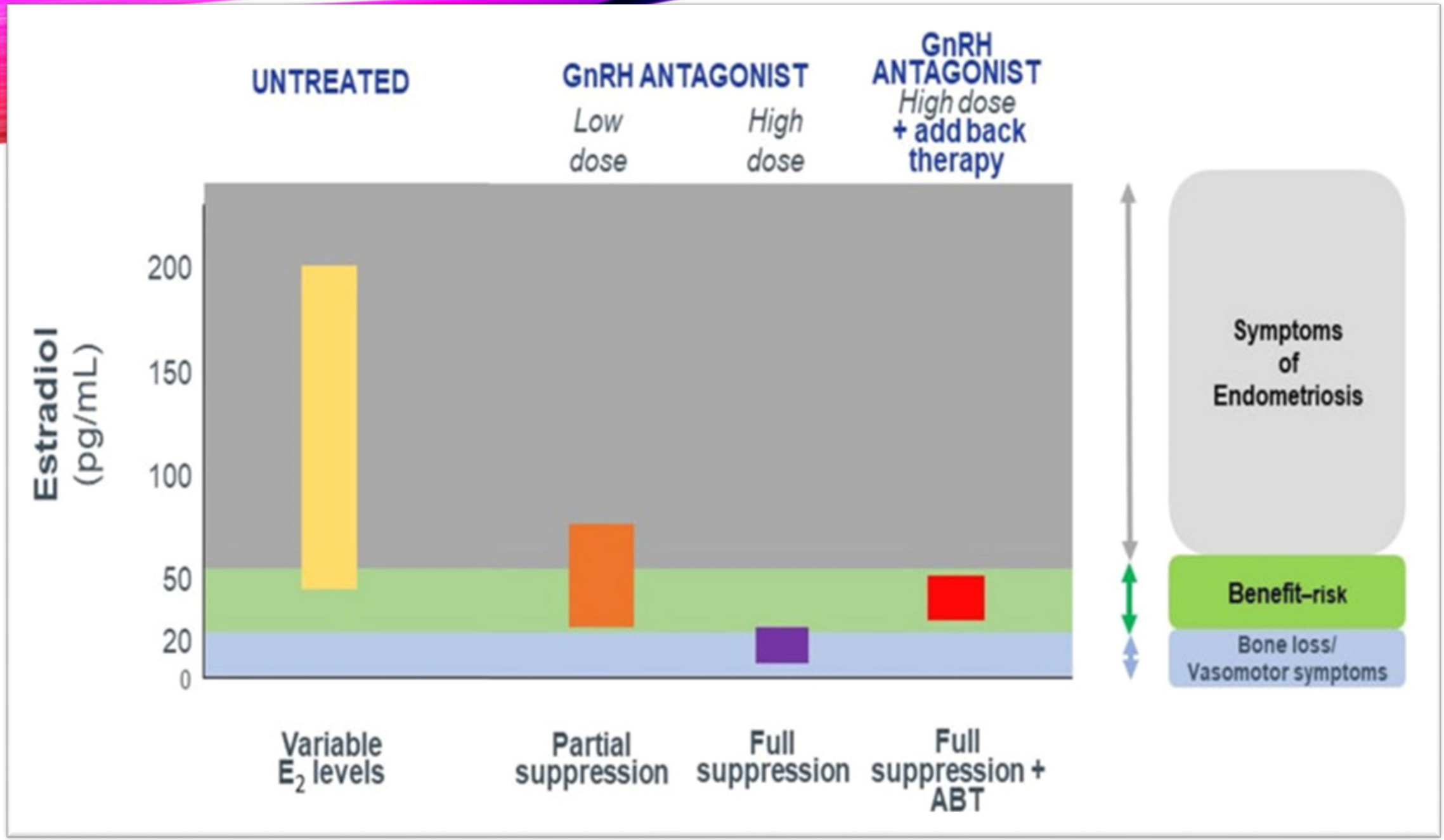
- **Off-label for this indication, the use of aromatase inhibitors (usually in combination with oral contraceptives, progestogens, GnRH agonists or GnRH antagonists) is currently recommended to prescribe to women with endometriosis-associated pain refractory to medical or surgical therapy.**
- **Their prolonged use is limited because of their hypoestrogenic side effects including bone mineral density loss, vaginal dryness, and the occurrence of vasomotor symptoms.**

ORAL GNRH ANTAGONISTS: A NEW CLASS OF AGENTS TO TREAT ENDOMETRIOSIS ASSOCIATED PAIN

- Oral GnRH antagonists are the newest addition to the armamentarium of medications indicated for treatment of endometriosis associated pains. They are orally active, non-peptide antagonists of the gonadotropin-releasing hormone (GnRH) receptors on the pituitary gland. Oral GnRH antagonists block the secretion of pituitary gonadotropins within hours, leading to a drop in ovarian production of estrogen, progesterone, and testosterone.

- **Several appealing advantages are provided by these novel medications in the treatment of endometriosis associated pain. Firstly, GnRH antagonists are orally administered instead of a depot injection, and therefore are easy to use. Secondly, they do not cause an initial flare-up of gonadotropin secretions like GnRH agonists do, which might lead to the exacerbation of endometriosis symptoms in the first 1–2 weeks of use.**

- **Thirdly, unlike GnRH agonists, which induce a complete block of the hypothalamic-pituitary-ovarian axis, with profound hypoestrogenic effect, GnRH antagonists can allow dose dependent lowering of estradiol level, which can adjust a balance between efficacy in treating endometriosis associated pain while avoiding major hypoestrogenic side effects. Fourthly, shortly after discontinuation of the oral GnRH antagonist, the recovery of the menstrual cycle occurs with estrogen levels returning to their normal premenopausal levels.- Oral GnRH antagonists have been identified as effective second line treatment of endometriosis associated pain.**


UNTREATED
GnRH ANTAGONIST
Low dose
High dose
GnRH ANTAGONIST
High dose
+ add back therapy
Estradiol (pg/mL)
200
150
100
50
20
0
Symptoms of Endometriosis
Benefit–risk
Bone loss/ Vasomotor symptoms
Variable E_2 levels
Partial suppression
Full suppression
Full suppression + ABT

ELAGOLIX, THE FIRST ORAL GNRH ANTAGONIST

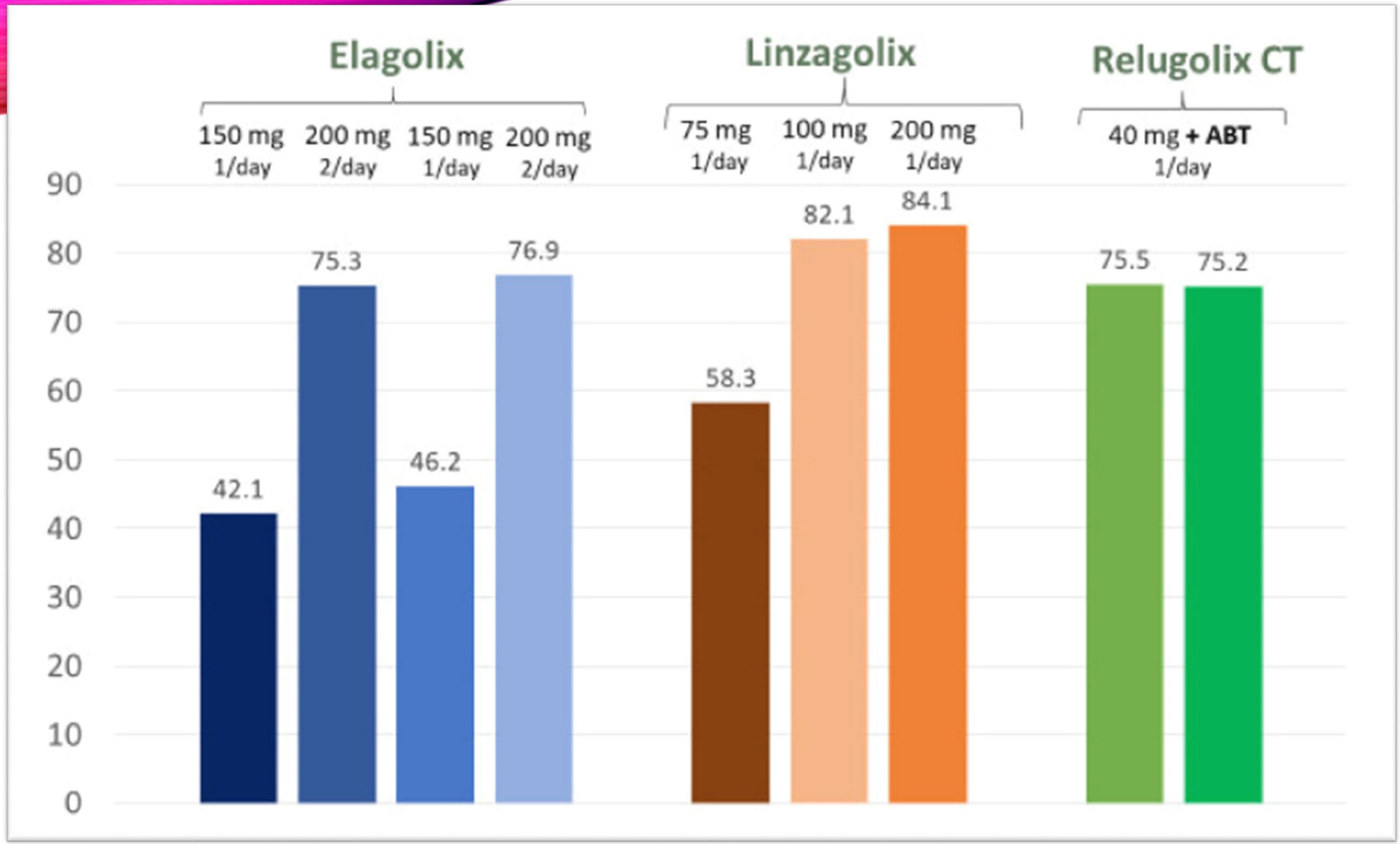
- It was approved by the US FDA on the 23rd of July 2018 for the management of moderate to severe pain associated with endometriosis. Elagolix has been labelled as a second-generation GnRH modulator due to its non-peptide and small-molecular nature which allows oral use. Its half-life after oral administration is 2.4–3.6 hours and it is metabolized mainly by the liver and excreted in feces.- Carr et al, in a phase 2 randomized clinical trial, evaluated two regimens of elagolix (elagolix 150 mg once daily, and elagolix 75 mg twice daily) versus depot medroxyprogesterone acetate (DMPA) for the treatment of endometriosis associated pain over a 24 week treatment period. Similar to DMPA, both doses of elagolix had a minimal effect on bone mineral density and had similar efficacy to DMPA in treating endometriosis associated pain.

RELUGOLIX, A NEW ORAL GNRH ANTAGONIST FOR TREATMENT OF ENDOMETRIOSIS- RELATED PAIN

- Relugolix is an orally active non-peptide GnRH antagonist. It competitively binds to GnRH receptors of the anterior pituitary, preventing the native GnRH molecule from binding to its receptor. Phase I clinical studies showed that multiple doses ≤40 mg can suppress pituitary gonadotropins and sustainably decrease gonadal steroid production.- The drug was well tolerated without adverse effects of concern. In a phase 2 multicenter trial conducted across 108 clinical sites in Japan, Osuga et al randomized premenopausal women with moderate/severe endometriosis associated dysmenorrhea or pelvic pain to receive daily oral dose of relugolix (10 mg, 20 mg, or 40 mg), or a daily oral dose of placebo, or monthly injection of leuprolin.

LINZAGOLIX, THE THIRD ORAL GNRH ANTAGONIST IN THE TREATMENT OF ENDOMETRIOSIS ASSOCIATED PAIN

- Linzagolix is another oral GnRH antagonist with a high bioavailability and a half-life of 15–18 hours.- In the EDELWEISS trial, investigators randomized 328 women complaining of pelvic pain associated with surgically diagnosed endometriosis to receive one of four different doses of oral linzagolix (50, 75, 100 and 200 mg/day) versus placebo for a total duration of 24 weeks. The study was conducted in 61 centers in Europe and US in the period 2016–2017. The proportion of women achieving ≥30% reduction of dysmenorrhea and non-menstrual pelvic pain was significantly higher in all linzagolix doses compared to placebo


Elagolix
Linzagolix
Relugolix CT
150 mg 1/day
200 mg 2/day
150 mg 1/day
200 mg 2/day
75 mg 1/day
100 mg 1/day
200 mg 1/day
40 mg + ABT 1/day
90
80
70
60
50
40
30
20
10
0
42.1
75.3
46.2
76.9
58.3
82.1
84.1
75.5
75.2

THE END

Thank you for your attention