یادواره دکتر کاظمی آشتیانی

وبینار میوم و ناباروری

درمان طبی میوم در ناباروری

دکتر اشرف معینی

جراح و متخصص زنان و زایمان، فلوشیپ ناباروری

استاد، عضو هیئت علمی دانشگاه تهران

In The Name Of GOD

Medical Treatment of Uterine Leiomyoma

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- **Uterine leiomyomas** →most common benign pelvic tumors →A monoclonal tumors of the smooth muscle cells of the myometrium.

- When they enlarge →significant distortion of the uterine surface or cavity.

- They commonly result in severe symptoms, such as **heavy, irregular**, and **prolonged menstrual bleeding** as well as **anemia** & also been associated with numerous other medical disorders, such as **infertility, recurrent abortion, and preterm labor.**

- Uterine leiomyomas are the most cited indication for more than 600 000 hysterectomies performed in the United States annually, and this major surgery is associated with morbidity and mortality.

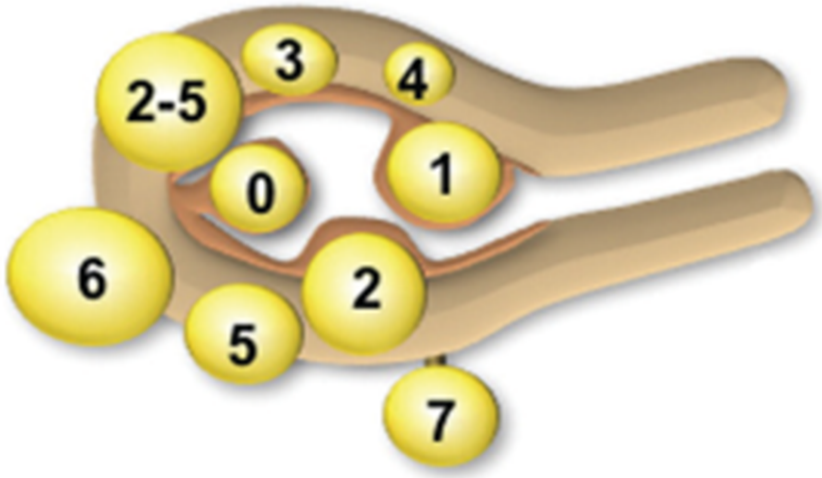
The Clinical Presentation of Uterine Leiomyomas

- Asymptomatic
- Abnormal uterine bleeding
  - Menorrhagia
  - Anemia
- Pelvic pressure
  - Urinary frequency
  - Urinary incontinence
  - Difficulty with urination
  - Hydronephrosis
  - Constipation
  - Tenesmus
- Pelvic mass
- Pelvic pain
- Infertility
- Obstetric complications
- Pregnancy related
  - Myoma growth
  - Red degeneration & pain
  - Spontaneous miscarriage
- Malignancy
- Rare associations
  - Ascites
  - Polycythemia
  - Familial syndromes, renal cell carcinoma
- Benign metastasizing

Diagnosis of Uterine Leiomyoma

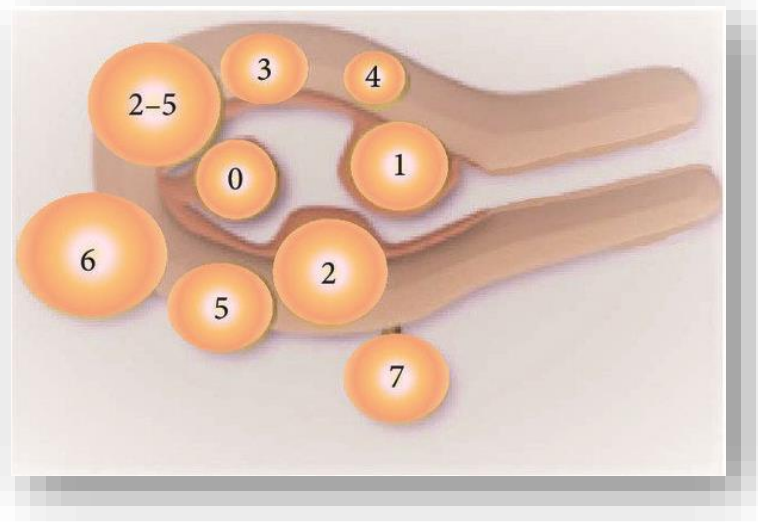
- Pelvic examination: Enlarged, irregular, firm, non-tender ut.
- Ultrasound: Trans-vaginal ultrasound, if uterus <375 ml volume, <4 myomas in number well-defined, hypoechoic
- Saline sonohysterography: For submucous fibroids or polypi
- MRI: Best method for exact mapping, numbering of fibroids
- Hysteroscopy: Diagnosis of submucous fibroids

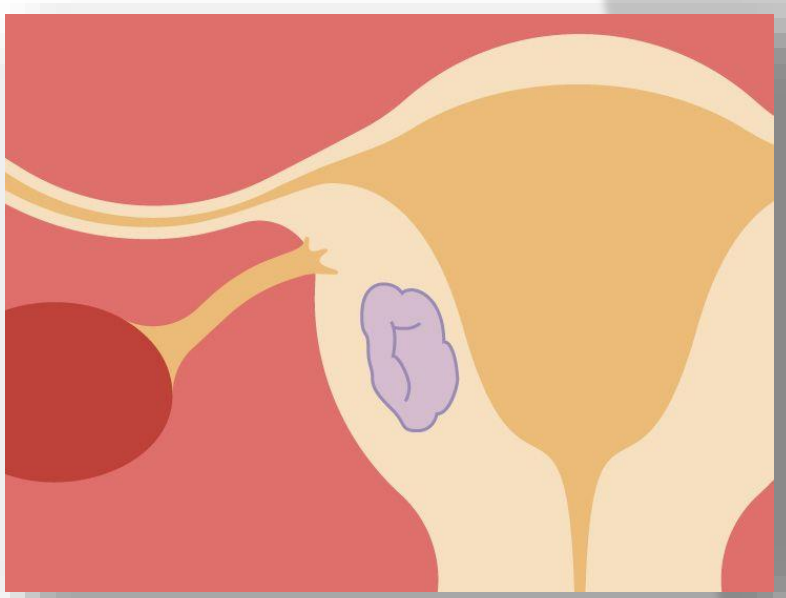
Leiomyoma Subclassification System



S – Submusosal	0	Pedunculated intracavitary
	1	< 50% intramural
	2	≥ 50% intramural
O – Other	3	Contacts endometrium; 100% intramural
	4	Intramural
	5	Subserosal ≥ 50% intramural
	6	Subserosal < 50% intramural
	7	Subserosal pedunculated
	8	Other (specify e.g. cervical, parasitic)

Hybrid leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below	
	2-5	Submusocal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.



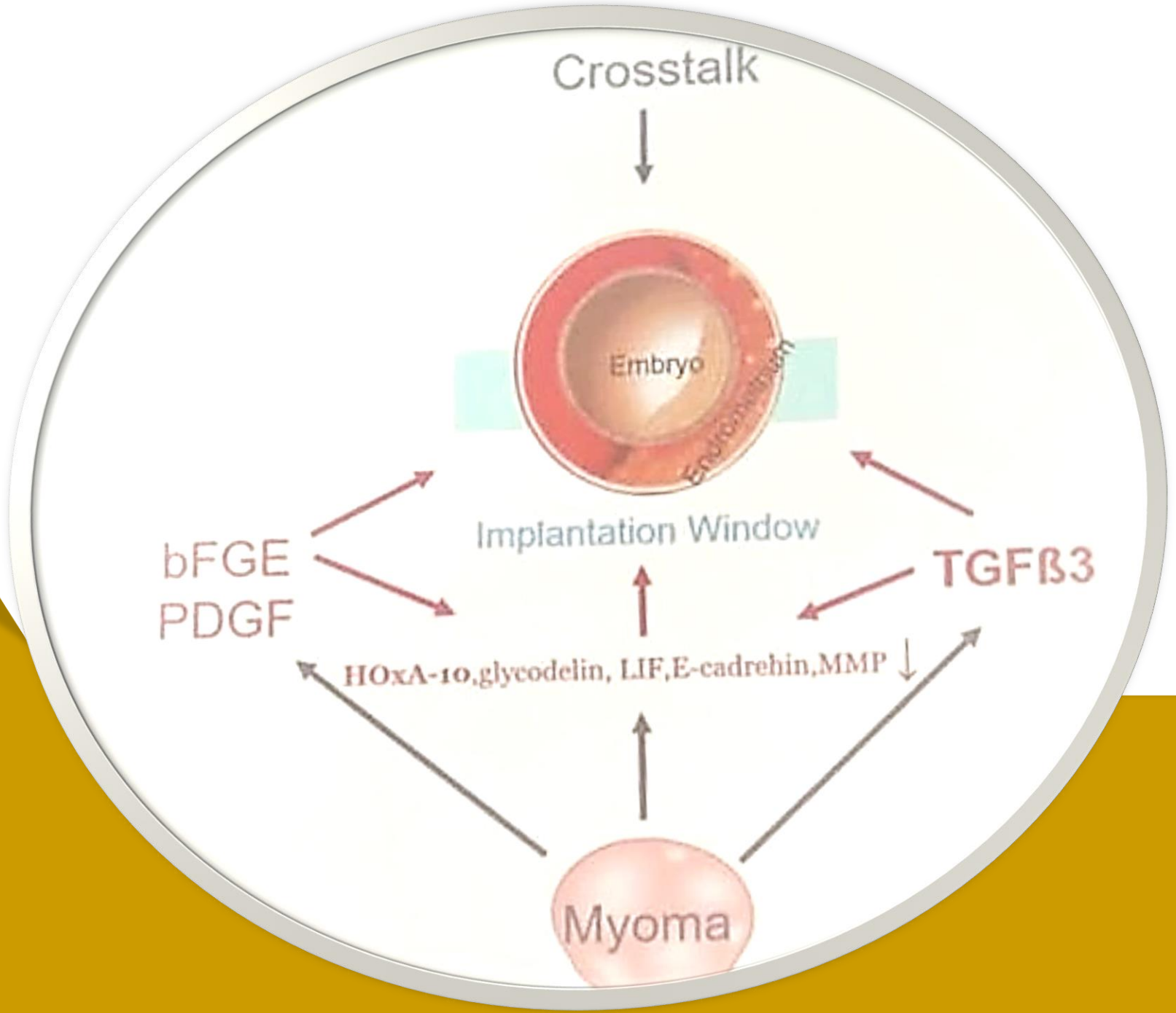


- **It may hypothesized that the closer fibroids are to the endometrial lining, the worse reproductive outcome are to be expected, hence FIGO type 3 fibroids may be expected to have a more deleterious impact on embryo implantation than type 4-5 fibroids.**

Type 3 and >2 cm
Worst prognosis

- **The main current therapeutic option for uterine myomas is surgery, which includes hysterectomy and myomectomy .**

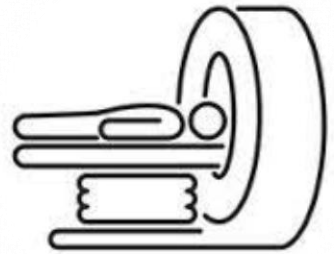
- **Apart from procedure-associated morbidity, the surgical approach may affect future patients' fertility by damaging the uterine integrity .**

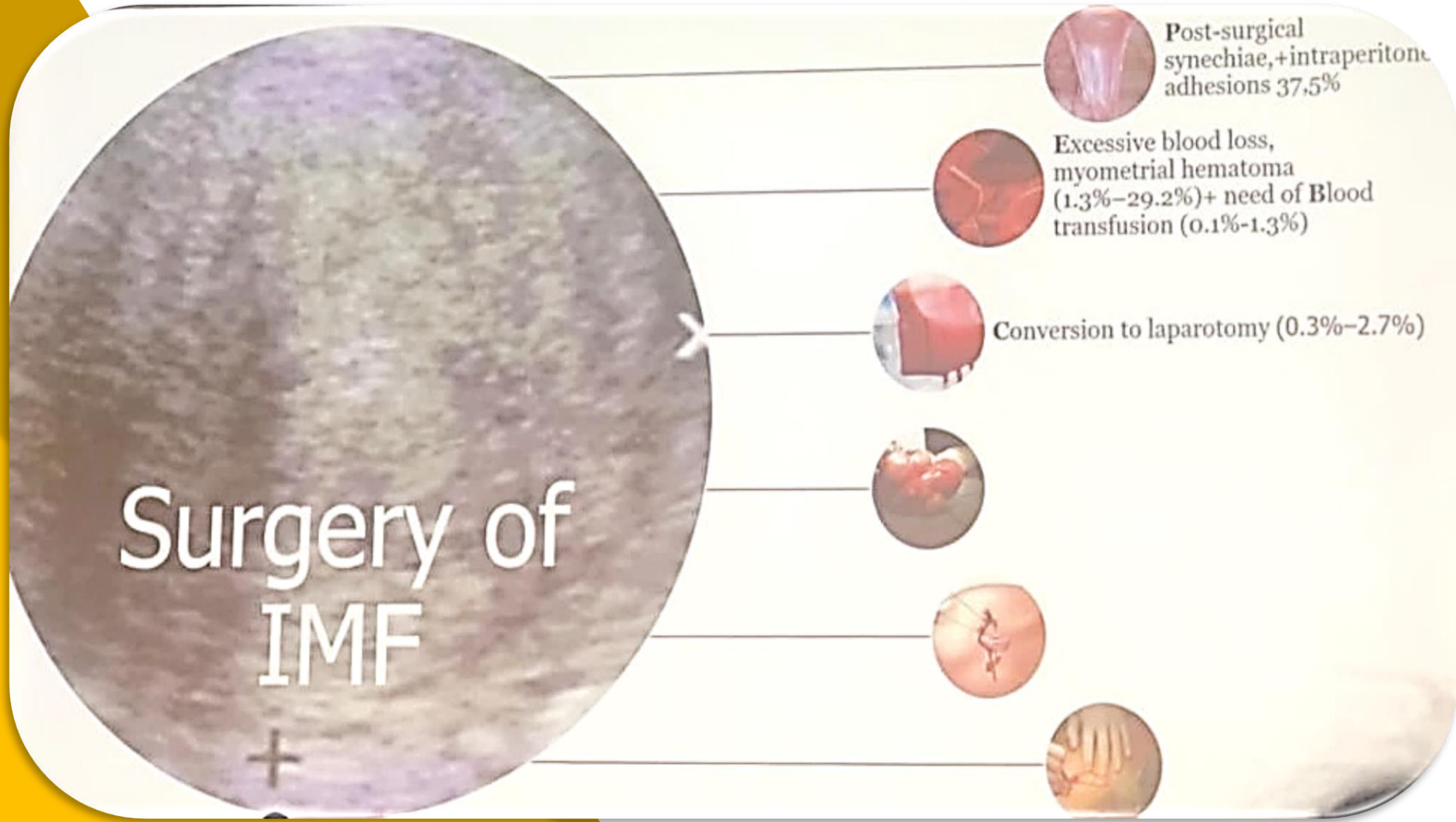

Crosstalk
Embryo
Endometrium
Implantation Window
bFGE
PDGF
TGFß3
HOxA-10,glycodelin, LIF,E-cadrehin,MMP ↓
Myoma

❖ Surgical Therapy:
Hysterectomy
Myomectomy
Laparoscopy vs. laparotomy
Hysteroscopy
Cryomyolysis
Thermocoagulation

❖ **Medical treatment: Are there new alternatives?**

❖ Nom-surgical Alternatives:
UAE
Magnetic resonance-guided
Focused surgery




Surgery of IMF
+
Post-surgical synechiae,+intraperitone adhesions 37.5%
Excessive blood loss, myometrial hematoma (1.3%–29.2%)+ need of Blood transfusion (0.1%-1.3%)
Conversion to laparotomy (0.3%–2.7%)

How to avoid recurrence after myomectomy?

- The rate of recurrence
- The evaluation after risk
- How to avoid after recurrence?

Risk factors of recurrence

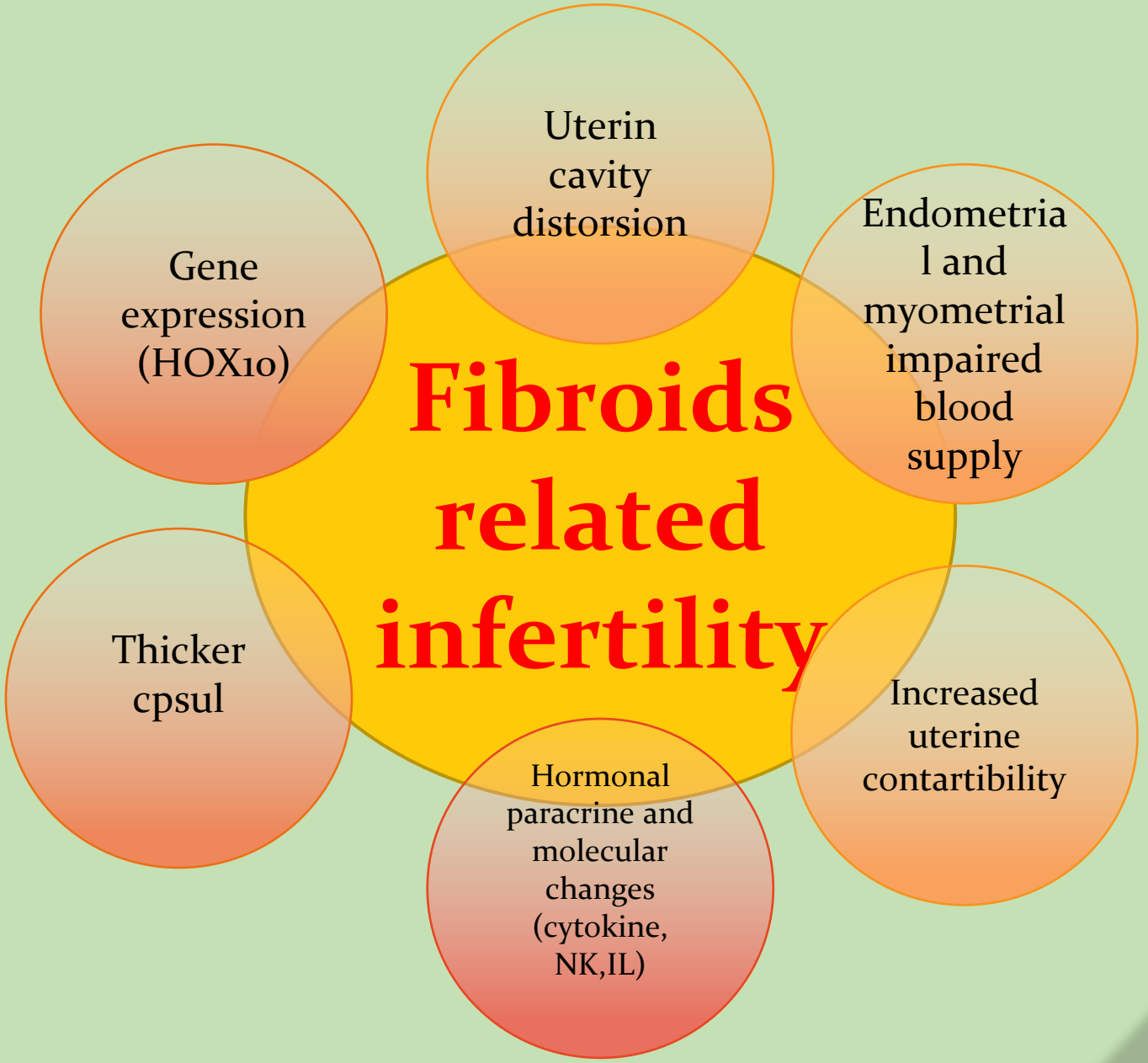
- Age >40
- Menarche <13
- Fibroid >5
- Number of UFs>4
- High long no-coding RNA-19 level
- Low TET1 level

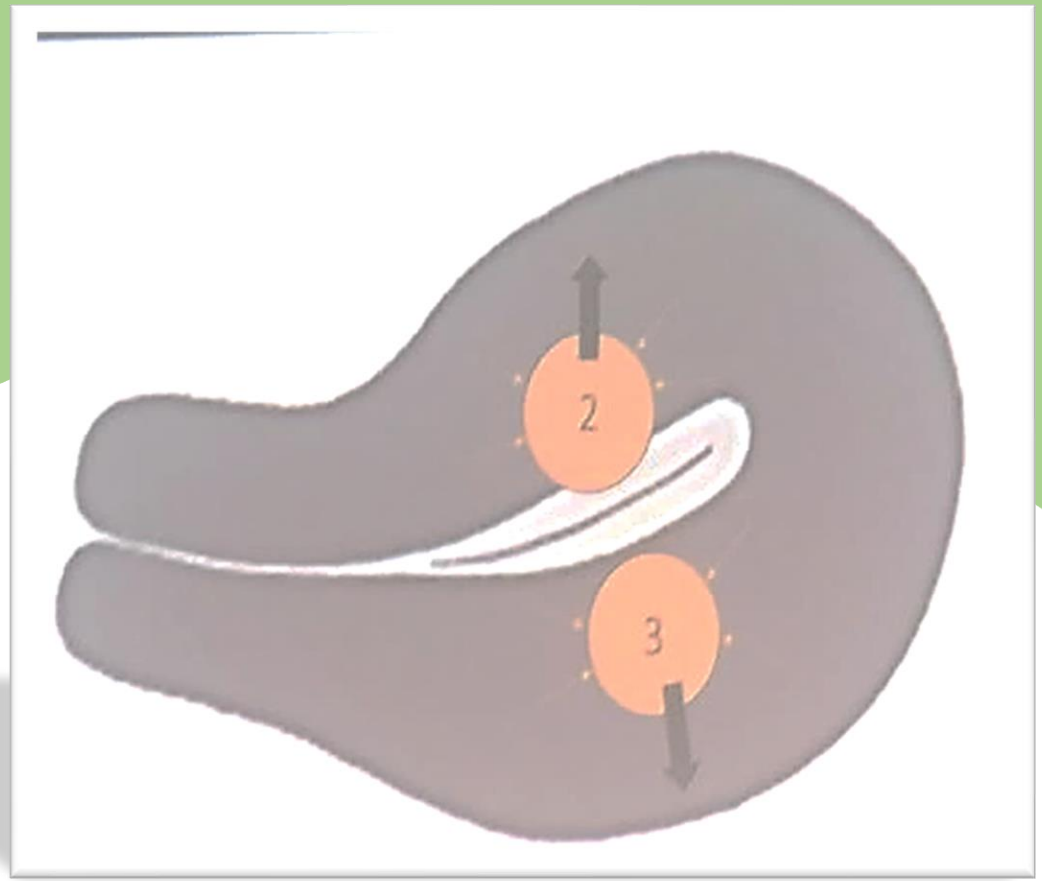
(Ten Eleven Translocation enzyme)

Time of recurrence

- At 1 year : 5-10%
- At 2 Years : 35-40%
- At 3 years : +/- 50%
- At 4 years : +/- 70%

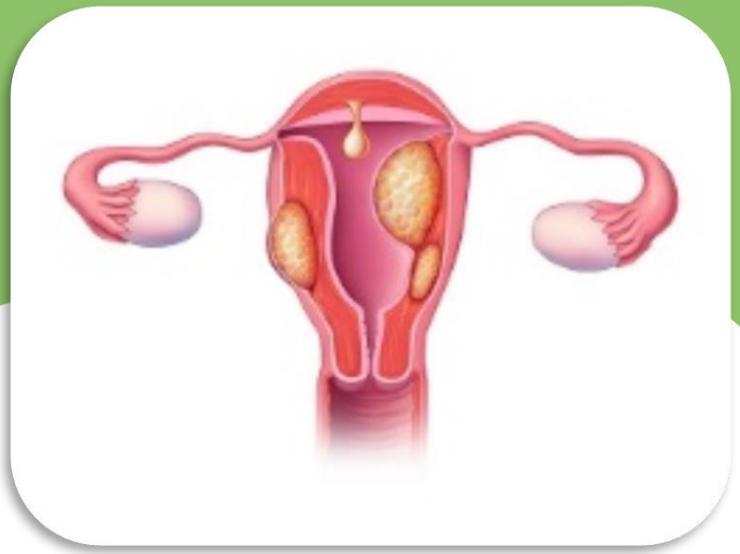
- Vitamin 1000 IU/d one year
- Recurrence rate of Ufs is reduced by 50% but P=0.17

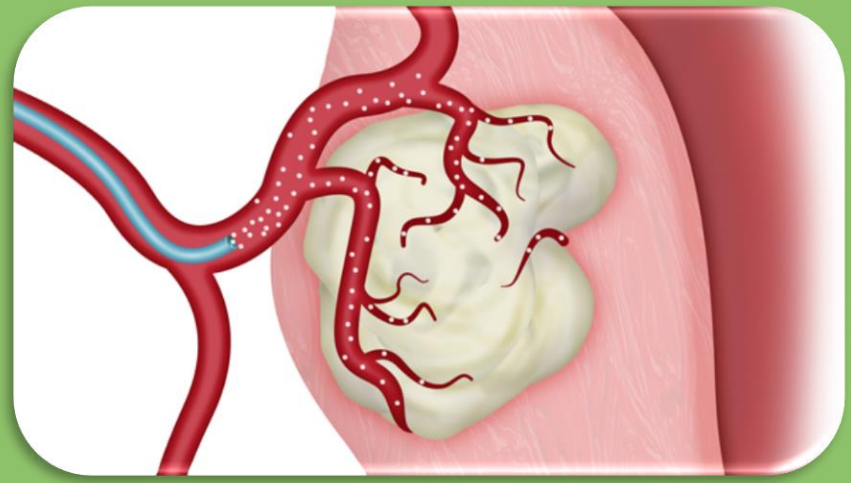

Uterin cavity distorsion
Endometrial and myometrial impaired blood supply
Gene expression (HOX10)
Fibroids related infertility
Thicker cpsul
Increased uterine contartibility
Hormonal paracrine and molecular changes (cytokine, NK,IL)

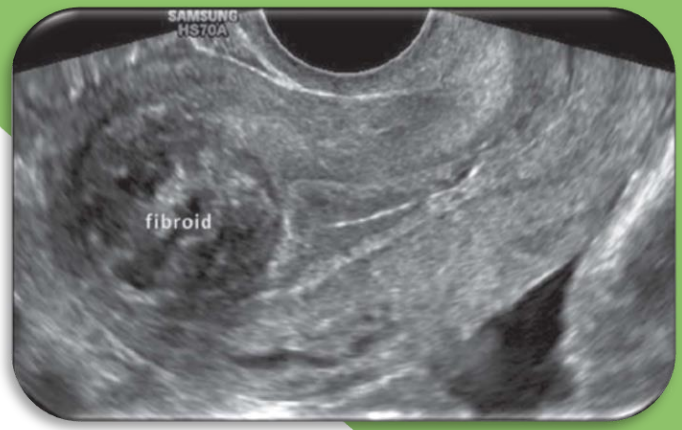


Associated with a reduction in size may favor blastocyst implantation =goal of medical treatment

Medical Agent for the Treatment of Uterine Leiomyomas







- Mechanical influences
- Influences on peristaltic
- Influences on junctional zone
- Influences on blood flow
- Influences on endometrial reciptivity

Gonadotropin-Releasing Hormone Analogues

- Gonadotropin-releasing hormone analogues can effectively **reduce uterine leiomyoma volume**, **reduce heavy menstrual bleeding**, and **restore hemoglobin levels** by inducing an iatrogenic reversible menopause.

- GnRHa **increases apoptosis and decreases angiogenesis** and the inflammatory reactions in leiomyoma lesions.

- possible mechanism : **inhibition of the growth** of human uterine leiomyoma could be its **direct effect** on the GnRH receptors.

- FDA-approved →**Lupron Depot (3.75 mg/month)** which is administered concomitantly with iron therapy →**hematologic improvement** of patients with anemia →should not be used for more than 3 months .

- The effects are **temporary**, and re-growth of the leiomyomas to their pretreatment sizes within a few months after the cessation .

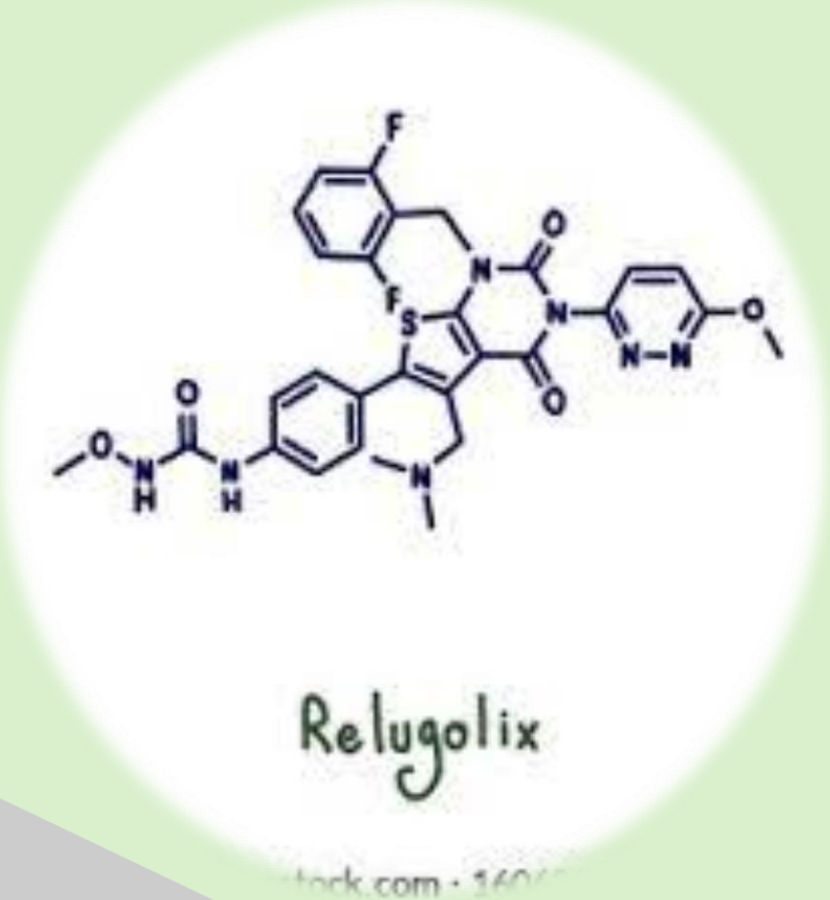
- The symptoms of **pseudomenopause** and the adverse impact on **bone density** limit the long-term use of GnRHa.

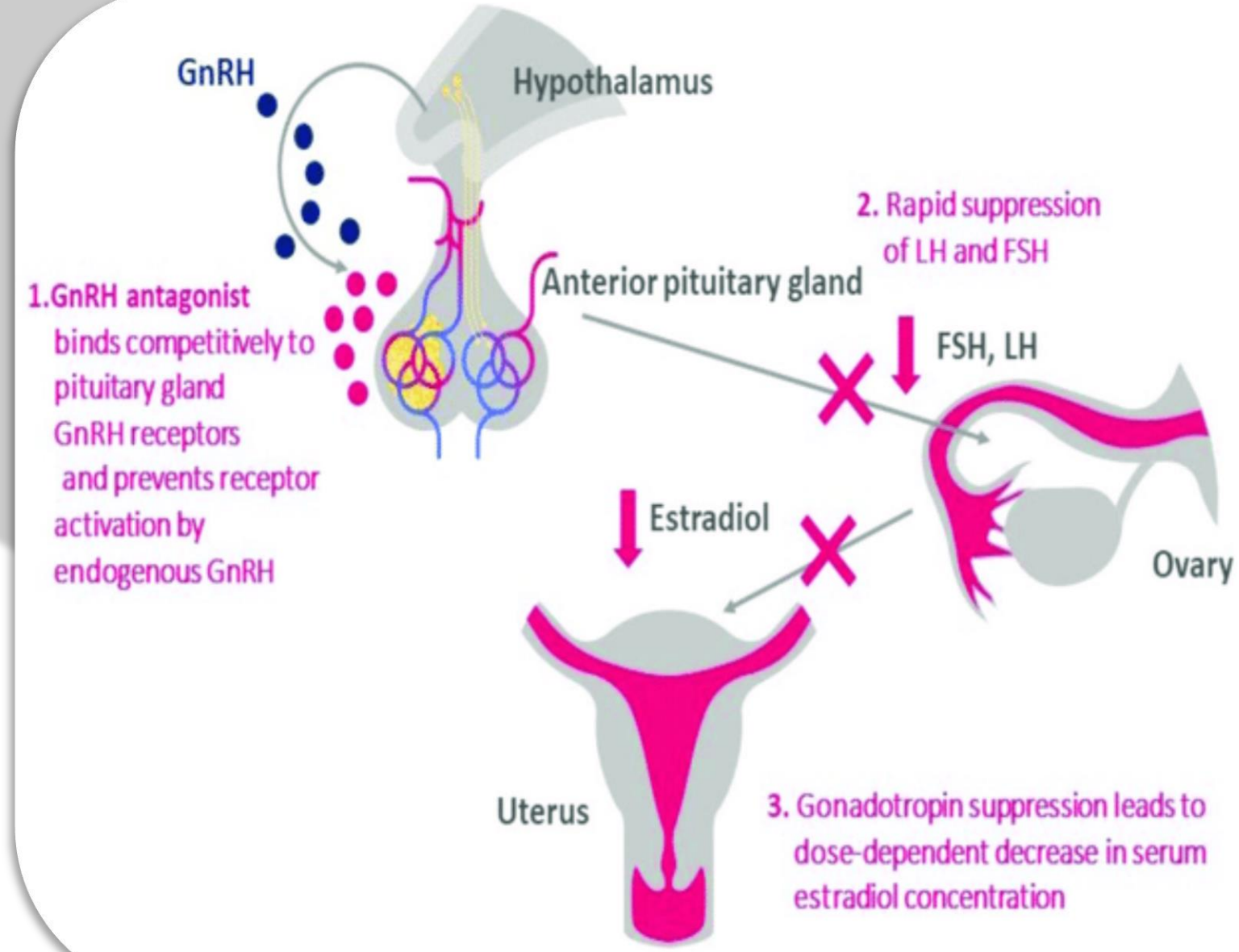
- The long-term (more than 6 months with add-back therapy)→ to minimize the continued bone loss and the menopausal symptoms.

Examples of Add-Back Regimens

- ✓ Progesterone
- ✓ Estrogens
- ✓ Combined Estrogen and Progestagen
- ✓ Tibolone
- ✓ Raloxifene

Gonadotropin-Releasing Hormone Antagonists



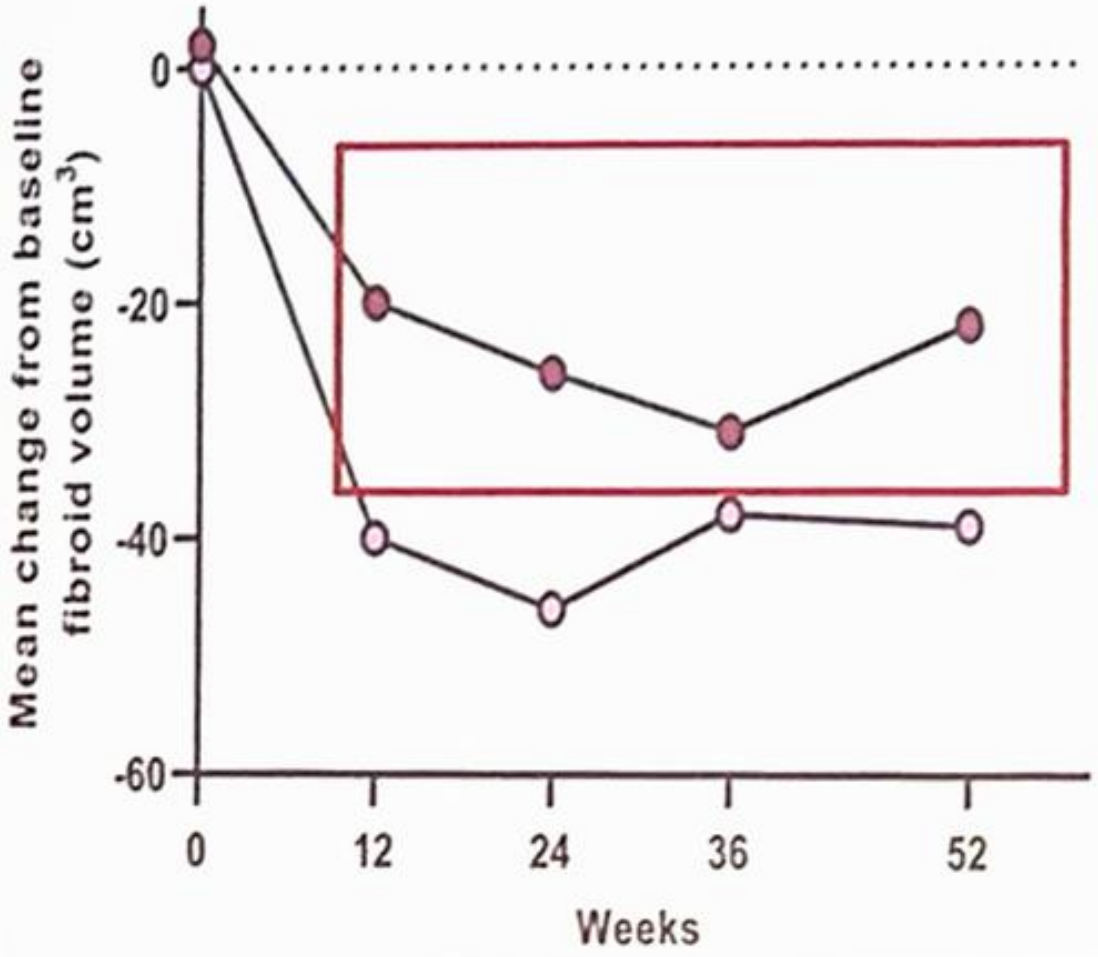


Clinical Benefits of GnRH Antagonists

1. Oral delivery
2. Rapid reversibility
3. Immediate gonadotropin suppression – no flare effect
4. Dose-dependent partial or full estrogen suppression

Donnez J, Fertil Steril. 2020; 114(1): 44-55

Reductions in volume of fibroids after 52 weeks



Linzagolix 200 +ABT*

Linzagolix 200 mg and Linzagolix 200 mg + ABT*

ABT*: estradiol 1 mg and norethindrome acetate 0

- They are characterized by the **absence of the flare effect** and cause a **rapid, sustained, and dose-dependent drop of serum estrogen**, permitting to avoid hormonal add-back therapy.

- In fact, according to the '**E2 threshold hypothesis**', partial suppression of E2 (serum levels between 20 and 50 pg/mL) may be sufficient to both control symptoms of the estrogen-dependent disease and to prevent hypoestrogenic detrimental effects .

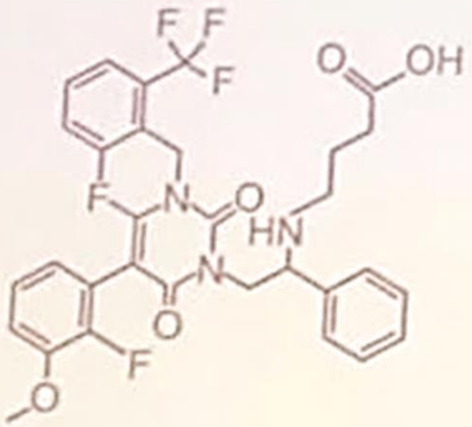
- **Selective GNRH receptor antagonist**
- **Dose-dependent suppression of serum estradiol**
- **Oral available:**
- >80% oral bioavailability
- No food effect
- **Half-life of about 14 to 15 h**
- **Administered ance a day**
- **Only GNRH antagonist being developed with two dose options and :**
- **Spproved in EU and UK for treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age**
- **In development for endometriosis associated pain(EAP)**

- **Elagolix, relugolix, and linzagolix are new-generation .**

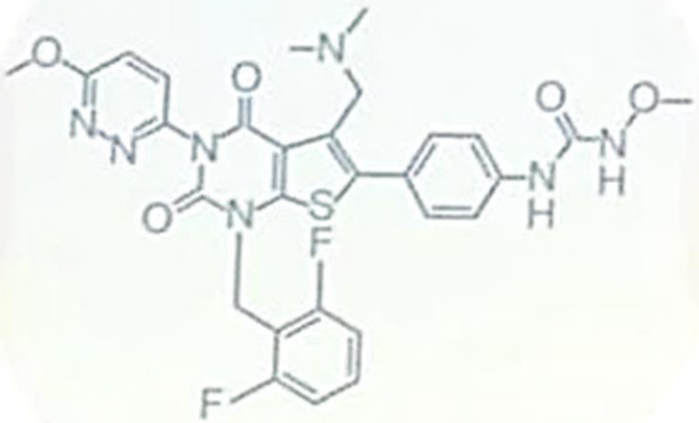
- Whereas elagolix and relugolix have been approved in some countries for treating endometriosis and uterine myomas ,respectively, linzagolix is currently in late experimental clinical status .

Oral GnRH antagonists

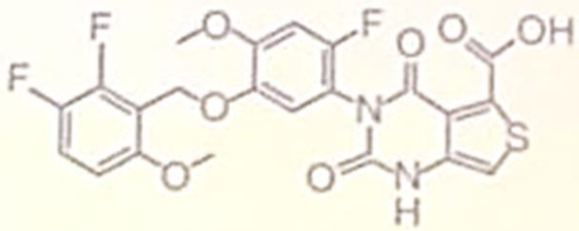
Elagolix



Relugolix



Linzagolix



Promising GnRH Antagonist (ELAGOLIX)

- A new well-tolerated nonpeptide which is **used orally** and **rapidly rendered bioavailable** after administration .
- The effect of the compound is **rapidly reversed after discontinuation**.
- Elagolix may enable **dose-related pituitary and gonadal suppression** in premenopausal women as part of treatment strategies for reproductive hormone-dependent disease states.

- **Linzagolix** is a new oral GnRH antagonist with a promising pharmacokinetic profile for a **single daily administration**. This drug modulates the suppression of serum E2, alone or with add-back therapy, in a dose-dependent manner .

- **linzagolix** seems to promptly and significantly improve symptoms (HMB and pain) associated with both gynecological diseases with good tolerability.

- This drug may show the potential to be a stand-alone treatment option in women with contraindication to other hormonal therapies or who simply refuse them.

Linzagolix

- ***Introduction to the compound***
  is an oral non-peptide GnRH antagonist. Chemically it is a 3-{5-[(2,3-difluoro-6-methoxyphenyl) methoxy]-2-fluoro-4-methoxyphenyl}-2,4-dioxo-1,2,3,4-tetrahydrothieno[3,4-d] pyrimidine-5-carboxylic acid

- ***Therapeutic target and mechanism of action***
  immediate and persistent chemical bond with the GnRH receptor on the pituitary cells. linzagolix has a **dose-dependent mechanism** of action. The levels of the **gonadotropins and then of the ovarian sex hormones drop**, impacting the pathogenetic of sex-hormone-dependent diseases .

Linzagolix

C. Pharmacodynamics

- Highly potent and selective antagonist of the GnRH receptor .
- Prompt dose-dependent suppression of E2 is achieved with an immediate positive impact on HMB and pelvic pain.
- It has the advantage of having low pharmacodynamic variability with minimal intraday fluctuation of E2 .

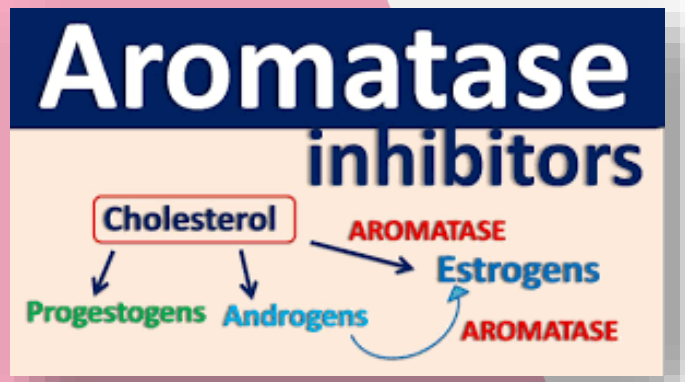
D. Pharmacokinetics and metabolism

- **half-life → 15–18 hours, a high oral bioavailability, a low volume of distribution, with no accumulation in the fatty tissue.**
- **The lack of food effect, or interaction with CYP3A4 enzymes and transporters' inhibitors, ensure a low risk of drug-todrug interaction in case of add-back therapy .**

Selective Estrogen Receptor Modulators

- **Tamoxifen** is one of the oldest known SERMs, → may cause endometrial carcinoma due to its partial agonistic effect on the endometrium.
- **Raloxifene** (theoretically) → only slightly affected collagen biosynthesis in control myometrium cells. (inhibited collagen biosynthesis in leiomyoma cells)
- **"Lasofoxifene"** → awaiting FDA approval. However!! the results of early trials suggest that there were no significant benefits compared to raloxifene for the skeleton, breast, heart, or reproductive tract.

Aromatase Inhibitors



- Block both **ovarian and peripheral** estrogen production within 1 day of treatment .
- **Letrozole** suppressed the production of estrogens, particularly
estrone and estradiol(76% to 79%).
- Aromatase inhibitors have been shown to be effective against leiomyomas with dosing regimens that included **2.5 mg/d of letrozole and 1 mg/d of anastrozole.**
- AIs should be considered in women with leiomyomas on a **short-term basis** or in women who want to **avoid surgical intervention to preserve their potential fertility.**

Antiprogesterones

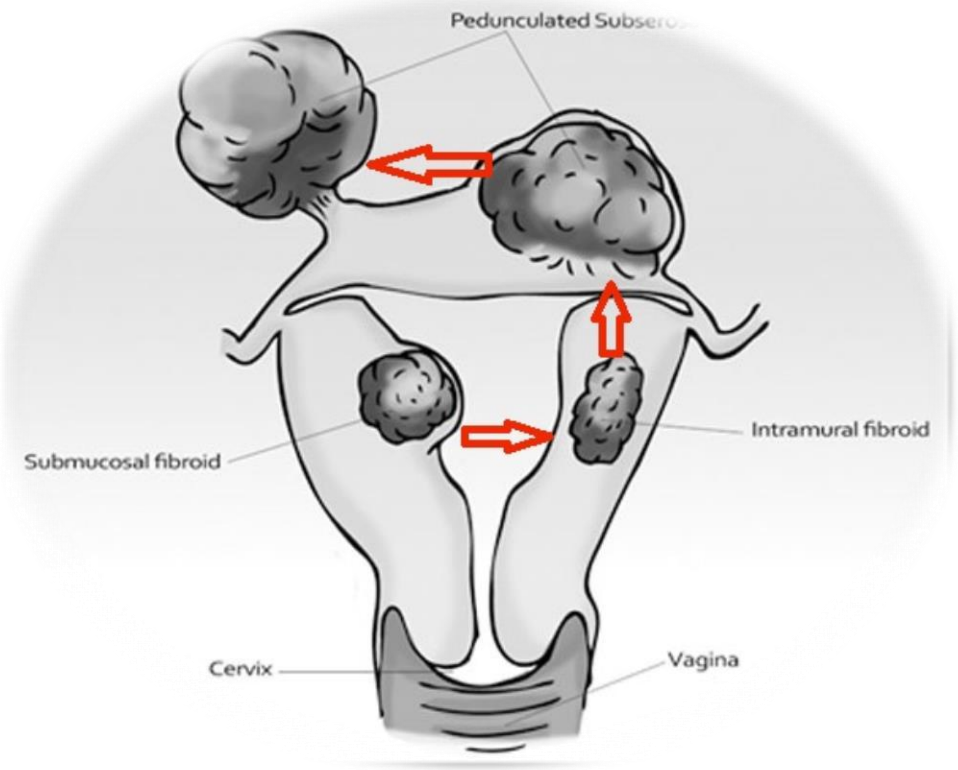
- Recent findings suggest that **volume maintenance and growth** of human uterine leiomyomas are also heavily **progesterone dependent**, and hence antiprogesterone could reverse leiomyoma growth effects.

Mifepristone

- Mifepristone (RU486), a well-known **oral antiprogesterone compound.**
- It is potential therapeutic agent for uterine leiomyomas with a dose that ranges from 5 mg to 50 mg over a 3-month period.
- **↓leiomyoma size** (26%- 74%) and **improved leiomyoma-related symptoms** (63%- 100% ↓amenorrhea).
- **Side Effects** :transient ↑transaminases, endometrial.

Ulipristal/CDB-2914 (VA 2914, ellaOne, ella)

- Ulipristal is an FDA-approved SPRM that is indicated for
  emergency contraception .
- It is structurally similar to mifepristone and seems to be effective in the treatment of uterine leiomyomas .
- ↓pain, ↓bleeding, ↓ leiomyoma size between 17% and 24%, improvement in quality of life.
- Similar to other SPRMs, ulipristal may be associated with endometrial thickening and endometrial hyperplasia.



Cabergoline

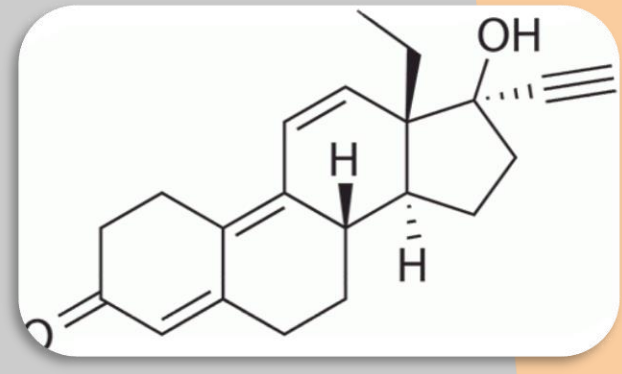
- Carbergoline is a well-known **dopamine agonist** → therapeutic option for uterine leiomyomas.
- It is a well-known dopamine agonist that is effectively used in the treatment of prolactinoma and for the inhibition of lactation.
- They reported comparative results in terms of the **shrinkage of the leiomyomas** and **the improvement in the sonographic, clinical, and intraoperative outcomes.**

Danazol

- Danazol is a synthetic steroid that inhibits steroidogenesis through multienzymatic actions, in addition to its suppressor effect on sex hormone binding globulin.

- It reportedly induced a significant 24% volume reduction.

Gestrinone

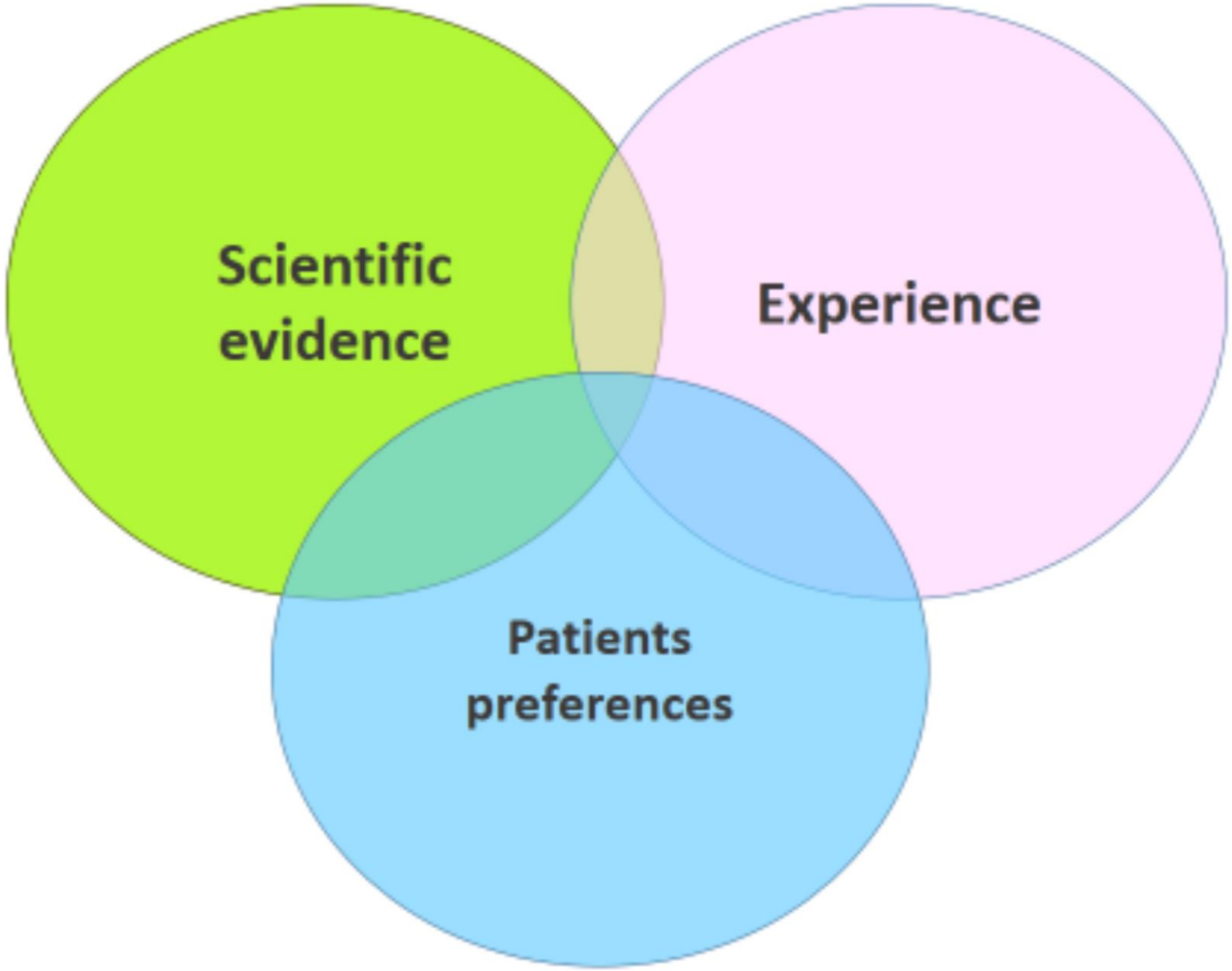


- Gestrinone is a steroid that possesses antiestrogen receptor and antiprogesterone receptor properties in various tissues including the endometrium.

- It is a contraceptive agent and also exhibits several unfavorable side effects, such as mild androgenicity, weight gain, seborrhea, acne, hirsutism, and occasional hoarseness.

The Levo-Norgestrel Intrauterine Contraceptive Device

- The device continually delivers 20 mcg LNG per day to the inner wall of the uterus for at least 7 years → strong suppression of the uterine endometrium.
- In women with uterine leiomyoma-associated menorrhagia →significant reductions in menorrhagia **without reductions in the myoma or uterine size.**
- LNG-IUS is contraindicated with congenital or acquired uterine anomaly including fibroids if they distort the uterine cavity .


Scientific evidence
Experience
Patients preferences

CONCLUSION

- Effective medical treatments for women with **abnormal uterine bleeding** associated with **uterine fibroids** include the levonorgestrel intrauterine system, gonadotropin-releasing hormone analogues,selective progesterone receptor modulators, oral contraceptives, progestins,and danazol.

- Effective medical treatments for women **with <u>bulk symptoms associated</u>** with fibroids include selective progesterone receptor modulators and gonadotropin-releasing hormone analogues.

Treatment of women with uterine leiomyomas must be individualized based on **symptomatology,size and location of fibroids,age,need and desire of the patient to preserve fertility or the uterus**,the availability of therapy, and the experience of the therapist.

- Oral gonadotrophin-releasing hormone antagonists are effective in treating myoma-associated symptoms and improving quality of life, whereas addition of add-back therapy reduces side effects.

شرکت MERCK شما را دعوت می کند:

Post ASRM

برای کسانی که
تلاش می کنند
هیچ چیزی غیرممکن نیست ...

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زمان برنامه: 7-5
مکان: هتل پارسیان آزادی، سالن الماس

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برای پیوستن به برنامه اینجا را کلیک کنید

MERCK

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THANK YOU
AND HAVE A NICE DAY