Modern Management of Uterine Fibroids and Endometriosis: New Medical and Surgical Options

MCGILL ANNUAL UPDATE FOR FAMILY PHYSICIANS

DECEMBER 2, 2020

CLEVE ZIEGLER, M.D. FRCS

Disclosures

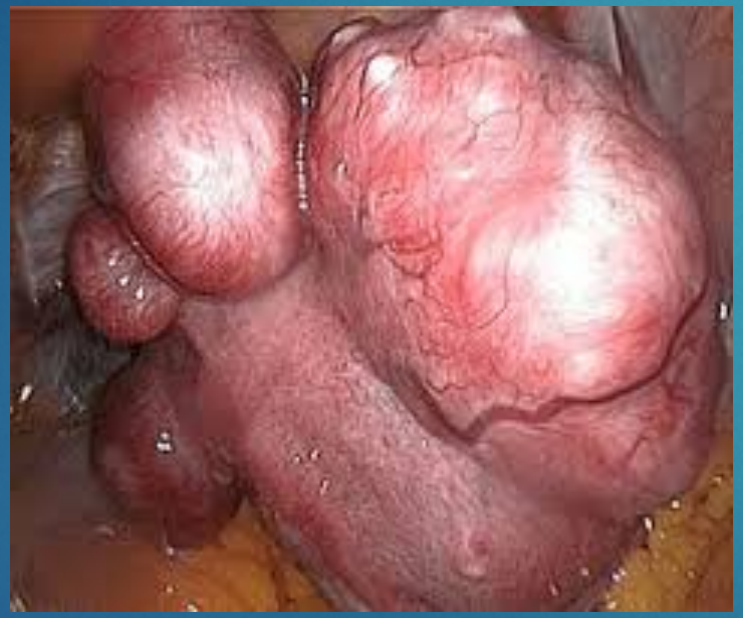
- Advisory Board Member: Abbvie, Allergan, Bayer, Biosyent, Merck, Pfizer
- Speaker: Abbvie, Bayer, Biosyent, Merck, Pfizer

Leaning Objectives:

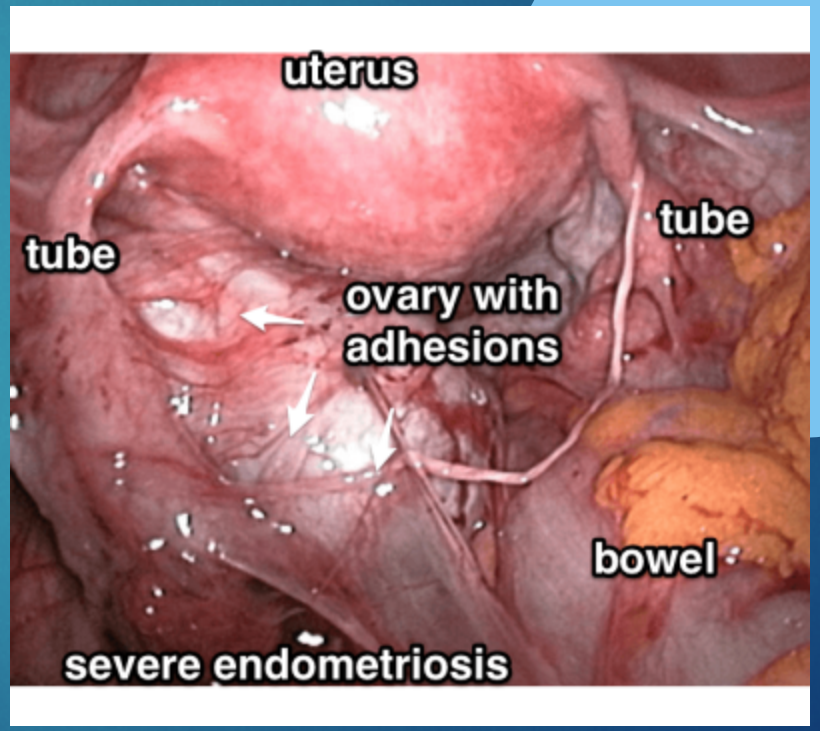
- As a result of attending this session, participants will be able to:
- 1. Understand the range of medical and surgical options available to treat uterine fibroids
- 2. Develop an approach to the investigation and medical management to suspected endometriosis
- 3. Understand the mechanism of action, indication and side effect profile of GnRH antagonists

Uterine Fibroids and Endometriosis

Fibroids



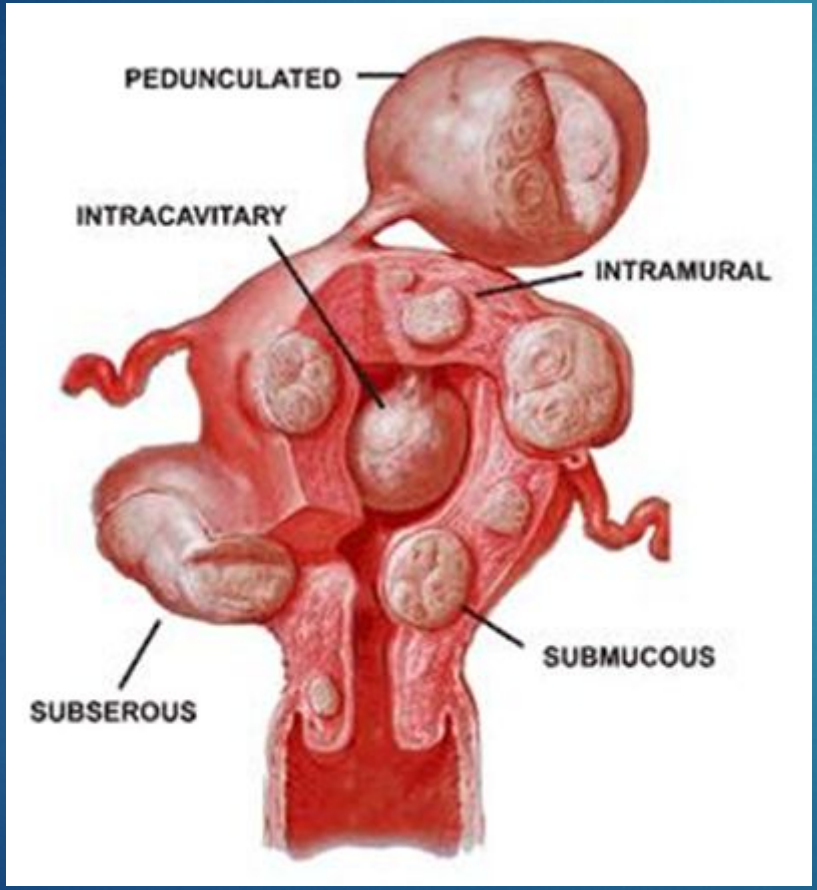
Endometriosis

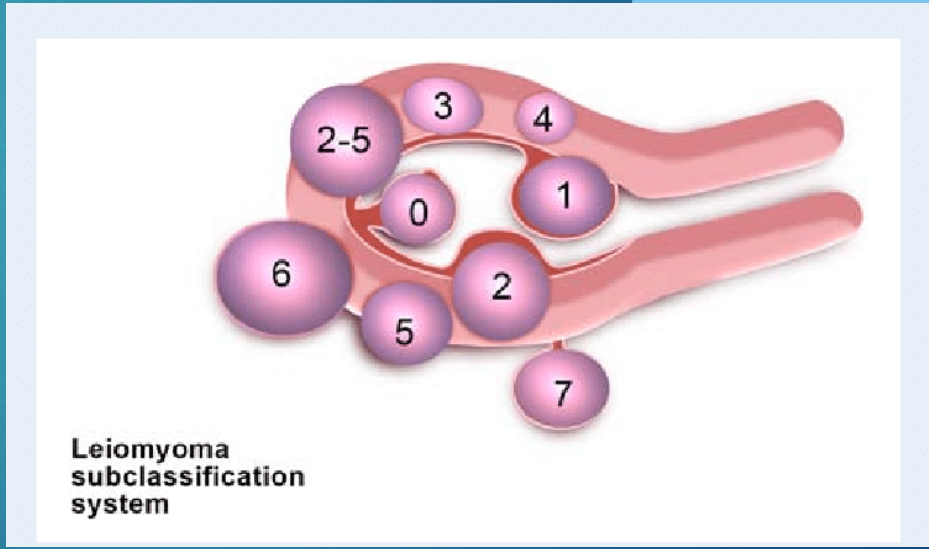


Menstrual Disorders: Cost

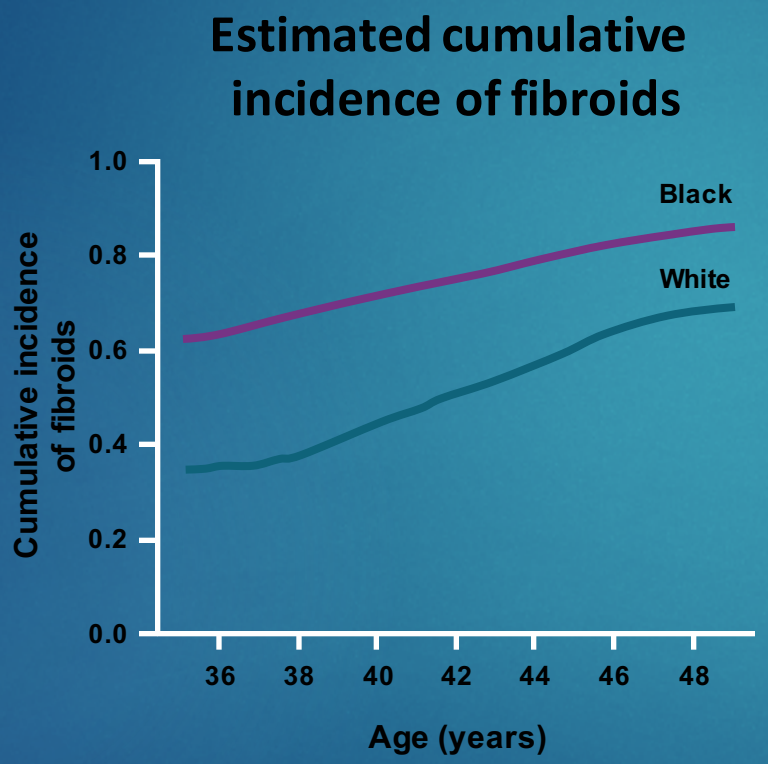
- Affects 250,000 Canadian women /year
- 10-15% of ER visits in women 15-44
- 40% require regular analgesics
- 25% reduction in productivity during menses
- Economic cost 8-10% of total wages
- 20% of women with abnormal bleeding undergo hysterectomy

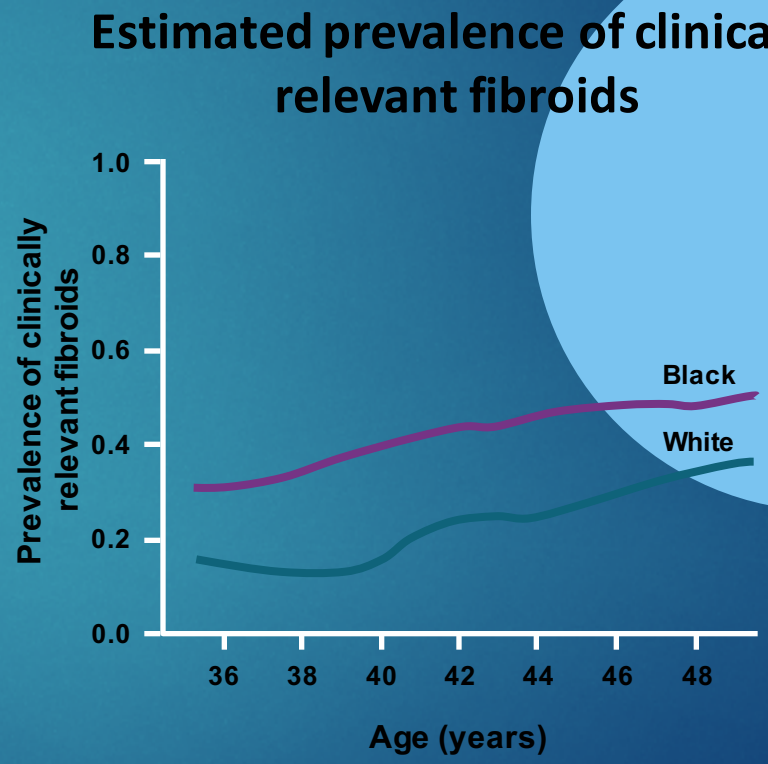
Uterine Fibroids



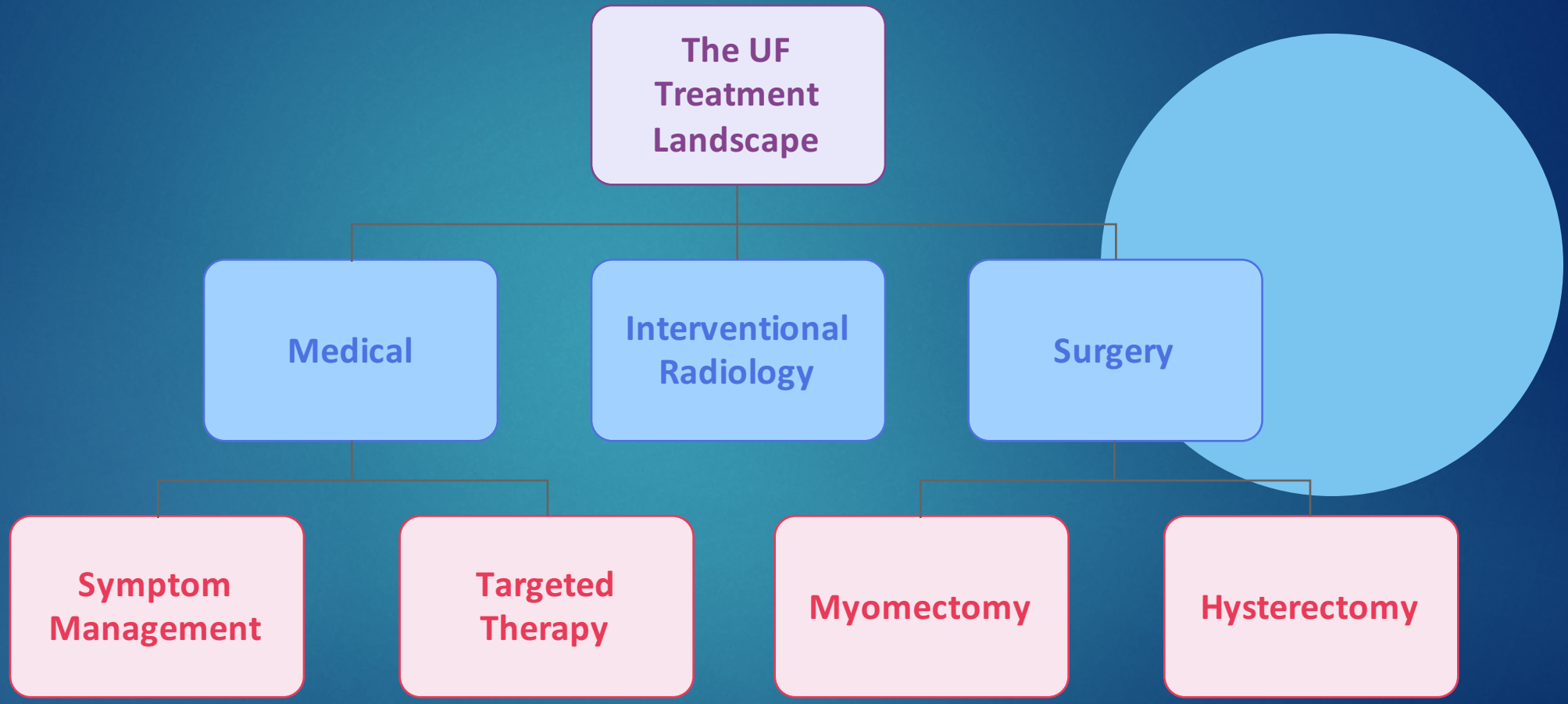


Uterine Fibroids Are Common





Baird DD, et al. *Am J Obstet Gynecol* 2003;188:100-7


The UF Treatment Landscape
Medical
Interventional Radiology
Surgery
Symptom Management
Targeted Therapy
Myomectomy
Hysterectomy

Uterine Fibroids

- Medical Management:

- Tranexamic Acid
- Hormonal Contraceptives
- LNG IUS
- Ulipristal Acetate
- GnRH Agonists
- **GnRH Antagonists**

- Surgical Management:

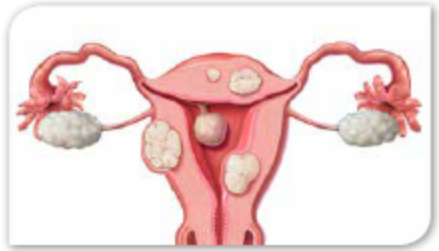
- Uterine Preserving (Myomectomy)
- Hysteroscopic
- Laparoscopic
- Open
- Uterine Artery Embolization
- **New Options**

- Hysterectomy

SPRMs Modulate Progesterone Effect Primarily by Targeting Fibroids, Endometrium and the Pituitary

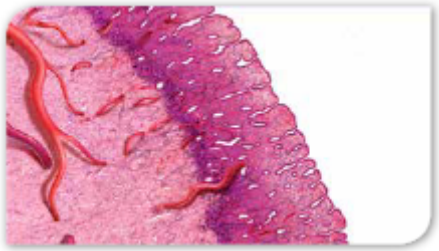
SPRM

Fibroids



Direct action on **fibroids**, reducing their size through the inhibition of cell proliferation and induction of apoptosis

Endometrium

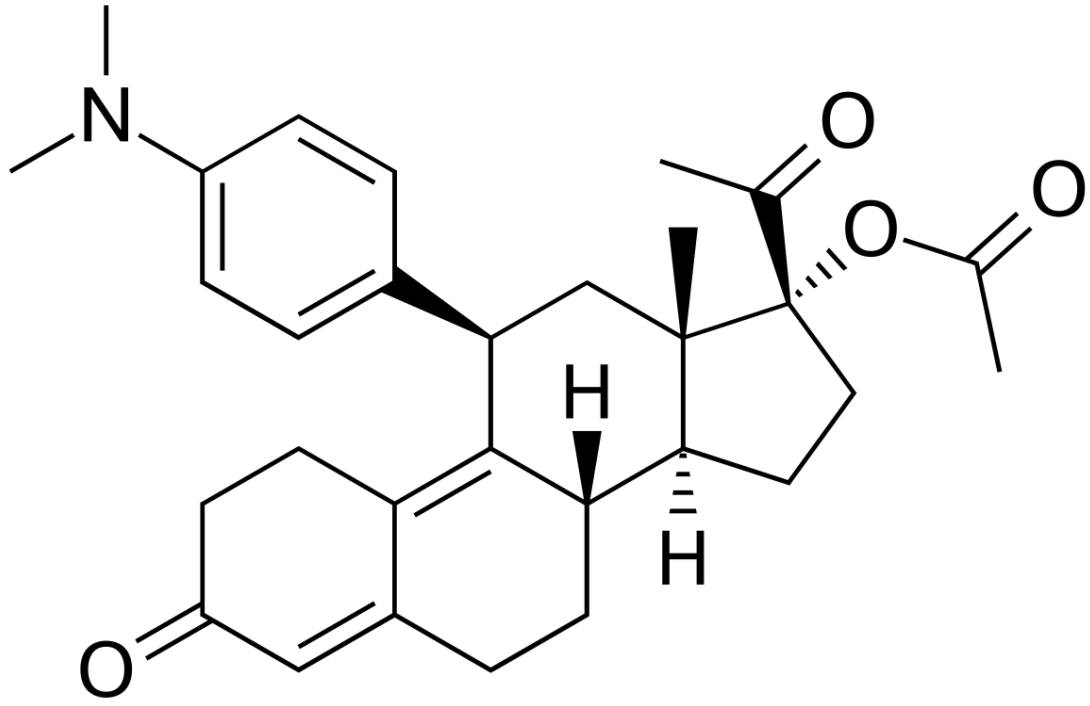


Direct effect on the **endometrium** and stops uterine bleeding. Benign and reversible changes in the endometrial tissue termed “Progesterone Receptor Modulator Associated Endometrial Changes” (PAEC)

Pituitary

Direct action on the **pituitary**, inducing amenorrhea by inhibiting ovulation and maintaining mid-follicular phase levels of estradiol

Fibristal

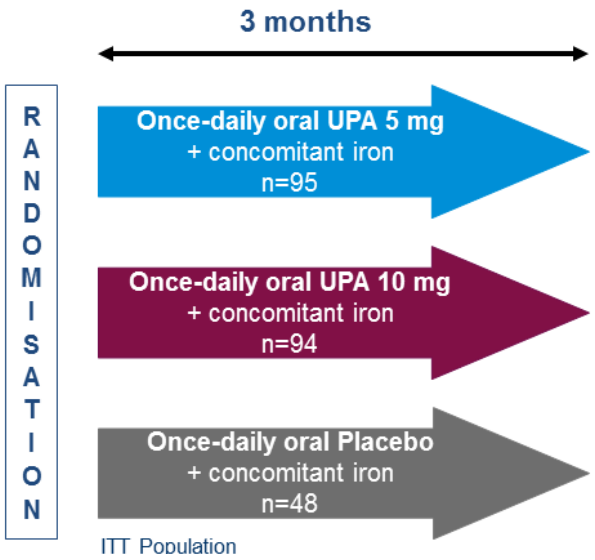


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ulipristal Acetate versus Placebo for Fibroid Treatment before Surgery

Jacques Donnez, M.D., Ph.D., Tetyana F. Tatarchuk, M.D., Ph.D., Philippe Bouchard, M.D., Lucian Puscasiu, M.D., Ph.D., Nataliya F. Zakharenko, M.D., Ph.D., Tatiana Ivanova, M.D., Ph.D., Gyula Ugocsai, M.D., Ph.D., Michal Mara, M.D., Ph.D., Manju P. Jilla, M.B., B.S., M.D., Elke Bestel, M.D., Paul Terrill, Ph.D., Ian Osterloh, M.R.C.P., and Ernest Loumaye, M.D., Ph.D., for the PEARL I Study Group*

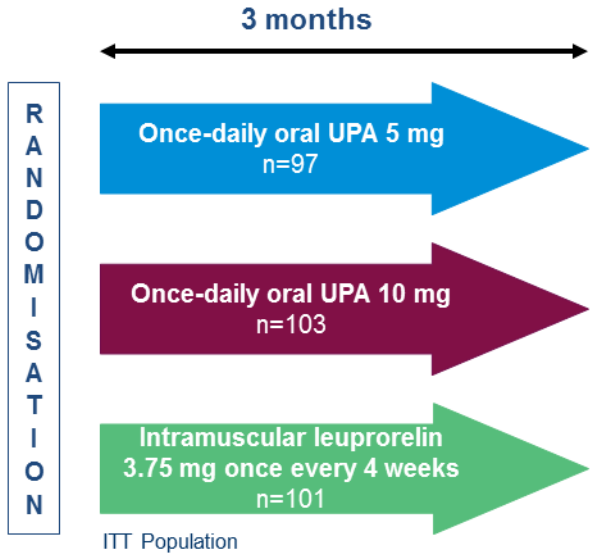


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

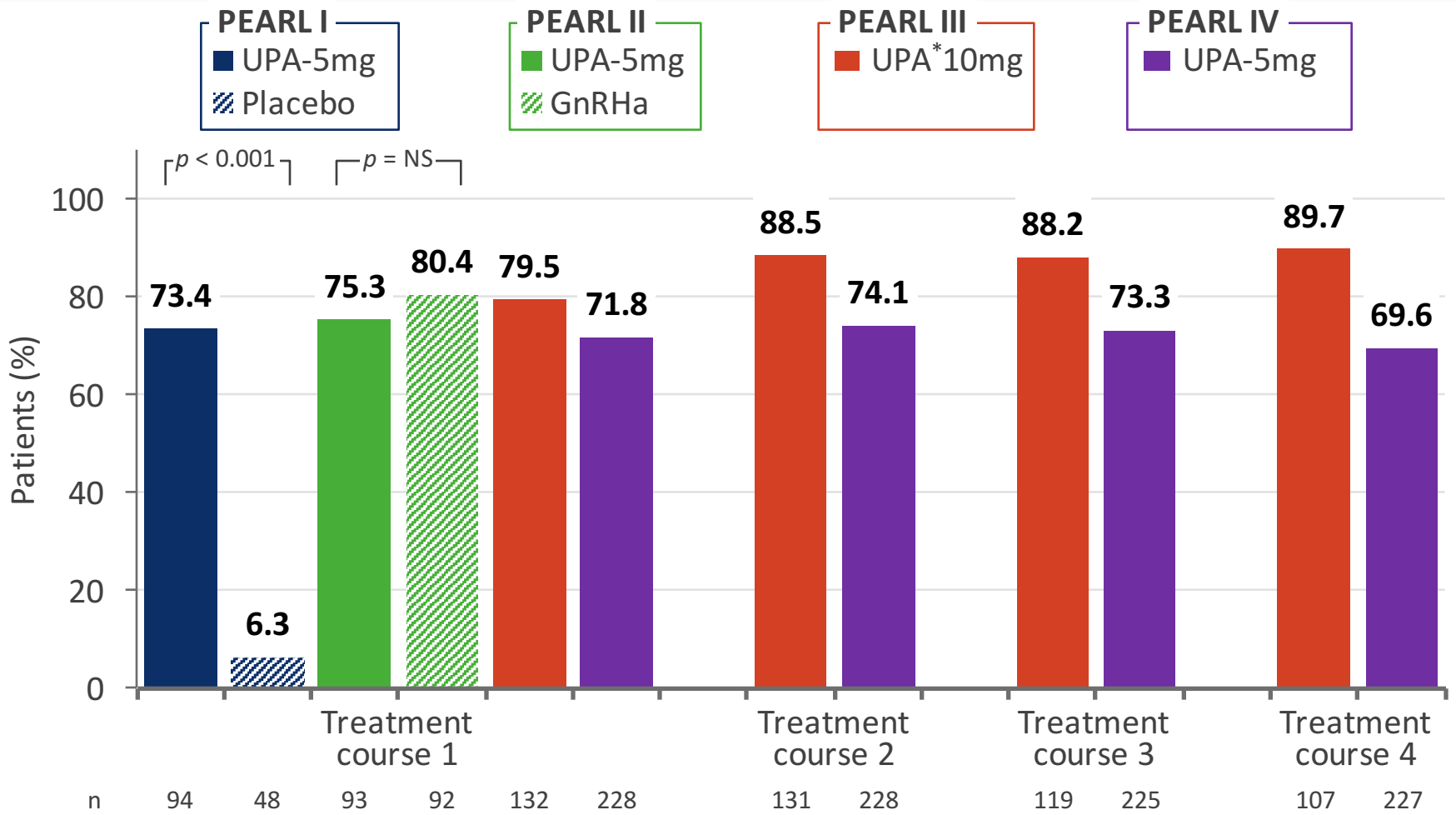
Ulipristal Acetate versus Leuprolide Acetate for Uterine Fibroids

Jacques Donnez, M.D., Ph.D., Janusz Tomaszewski, M.D., Ph.D., Francisco Vázquez, M.D., Ph.D., Philippe Bouchard, M.D., Boguslav Lemieszczuk, M.D., Francesco Baró, M.D., Ph.D., Kazem Nouri, M.D., Luigi Selvaggi, M.D., Krzysztof Sodowski, M.D., Elke Bestel, M.D., Paul Terrill, Ph.D., Ian Osterloh, M.R.C.P., and Ernest Loumaye, M.D., Ph.D., for the PEARL II Study Group*



Efficacy: Amenorrhea

Proportion of patients in amenorrhea at the end of each treatment course



1. Donnez et al. *N Engl J Med*. 2012;366:409–20; 2. Donnez et al. *N Engl J Med*. 2012;366:421–32;
3. Donnez et al. *Fertil Steril*. 2014;101:1565–73.e1-18; 4. Donnez et al. *Fertil Steril*. 2016;105:165–73.e4

NS, non-significant;
*10-mg UPA dose not licensed

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4 September 2020
EMA/455818/2020

PRAC recommends revoking marketing authorisation of ulipristal acetate for uterine fibroids

A review by EMA's safety committee (PRAC) has confirmed that 5-mg ulipristal acetate (Esmya and generic medicines) used for the treatment of symptoms of uterine fibroids can cause liver injury, including the need for liver transplantation. The PRAC has therefore recommended the revocation of the marketing authorisations of these medicines.

The PRAC considered all the available evidence in its review, including reported cases of serious liver injury. Patient and healthcare professional representatives, including experts in gynaecology, were also consulted. Since it was not possible to identify which patients were most at risk or measures that could reduce the risk, the PRAC concluded that the risks of these medicines outweighed their benefits and that they should not be marketed in the EU.

The use of 5-mg ulipristal acetate medicines for uterine fibroids had already been suspended as a precautionary measure while awaiting the outcome of this review.

Ulipristal acetate is also authorised as a single-dose medicine for emergency contraception. This recommendation does not affect the single-dose ulipristal acetate emergency contraceptive (ellaOne and other trade names) and there is no concern about liver injury with these medicines.

The PRAC recommendation will now be forwarded to EMA's human medicines committee (CHMP), which will adopt the Agency's opinion.

Important Safety Information
FIBRISTAL (ulipristal acetate tablets, 5 mg)
Voluntary Withdrawal in Canada due to Risk of Drug-Induced Liver Injury

Allergan

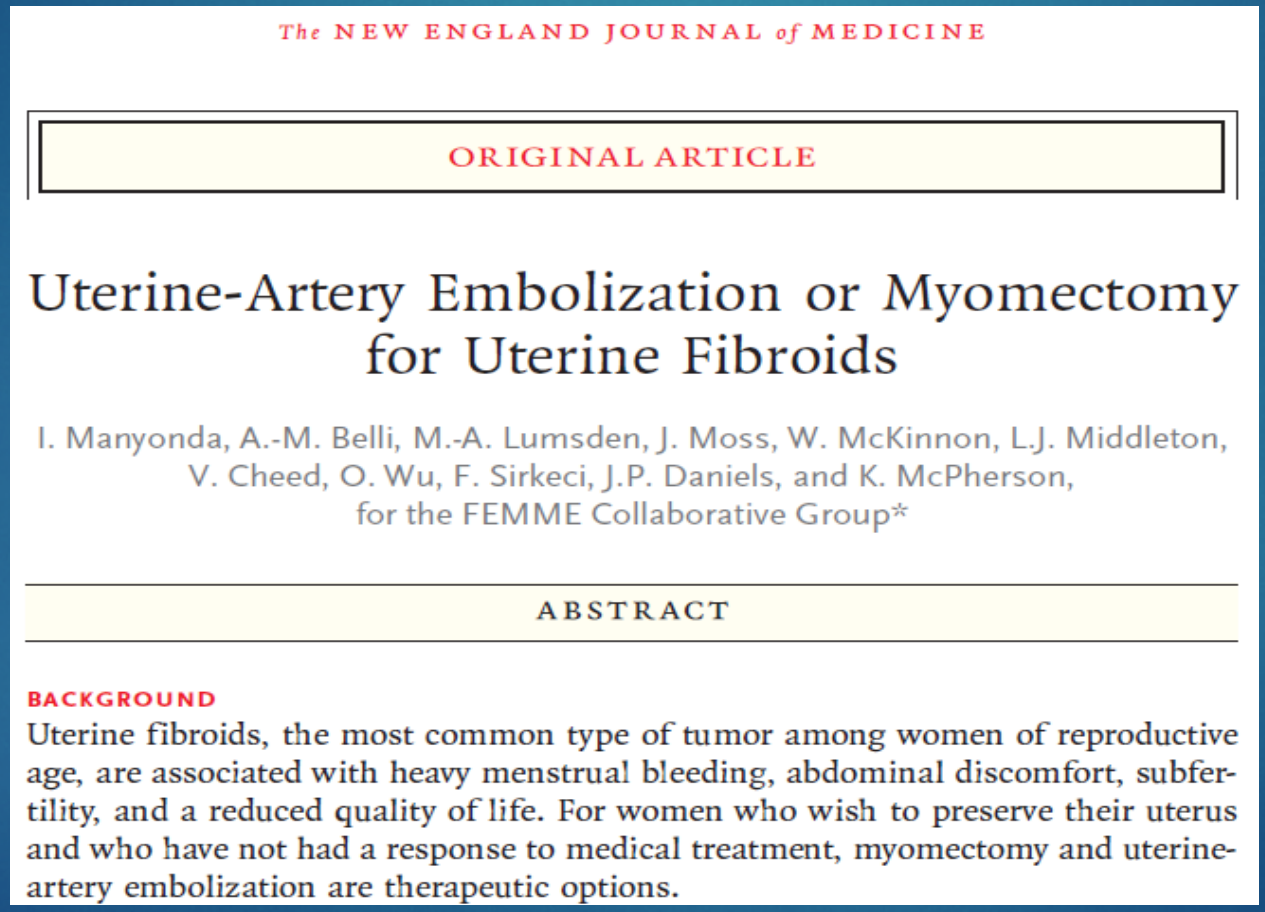
2020/09/30

Audience
Healthcare professionals including obstetricians, gynecologists, primary care physicians with interest in women's health, hepatologists, emergency room physicians, and pharmacists.

Key messages

- **Following rare international cases of severe liver injury requiring liver transplantation, the manufacturer of FIBRISTAL, Allergan Inc., is voluntarily withdrawing the product from the Canadian market. FIBRISTAL was approved in Canada to treat signs and symptoms of uterine fibroids in women of reproductive age.**
- **On September 24, 2020, Allergan Inc. initiated the recall of FIBRISTAL from the Canadian market to the retail pharmacy level.**
- **Healthcare professionals are advised to:**
  - **not prescribe or dispense FIBRISTAL**
  - **contact patients under their care who are currently being treated with FIBRISTAL to stop treatment, and review alternative treatment options**
  - **advise patients who have been taking FIBRISTAL to immediately contact a healthcare professional if they experience signs and symptoms of liver injury such as nausea, vomiting, stomach ache, severe tiredness, yellowing of the eyes or skin, or dark urine, which could occur after stopping treatment**
  - **perform liver function monitoring within 2-4 weeks after treatment with FIBRISTAL has stopped and investigate further if liver function is abnormal**

Uterus Conserving Options



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Uterine-Artery Embolization or Myomectomy for Uterine Fibroids

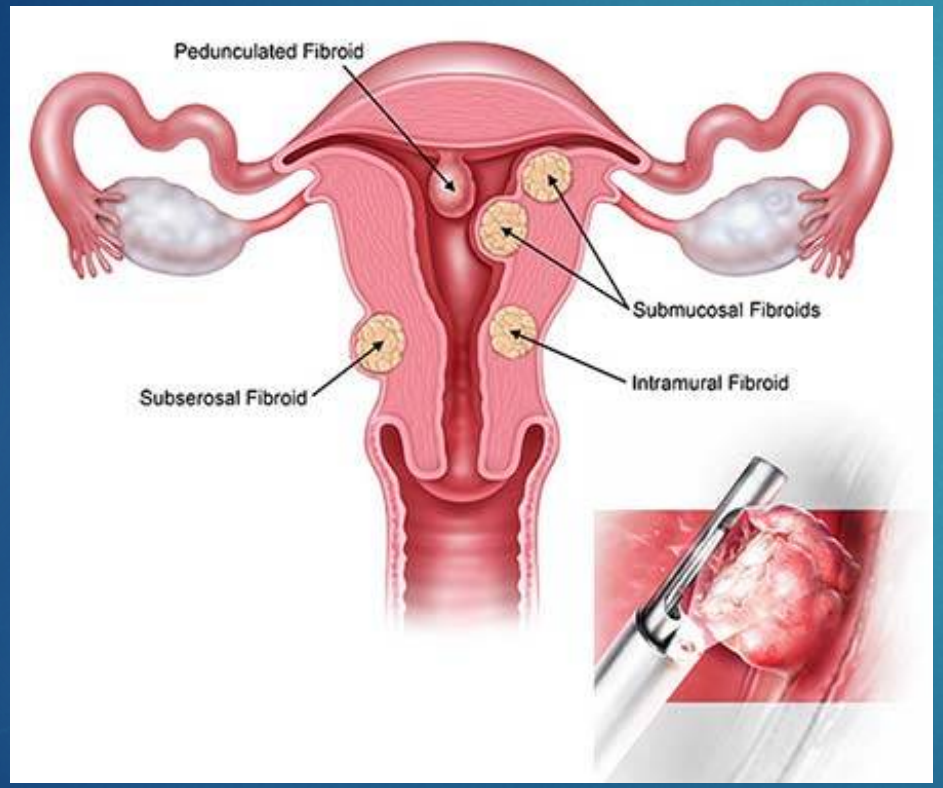
I. Manyonda, A.-M. Belli, M.-A. Lumsden, J. Moss, W. McKinnon, L.J. Middleton, V. Cheed, O. Wu, F. Sirkeci, J.P. Daniels, and K. McPherson, for the FEMME Collaborative Group*

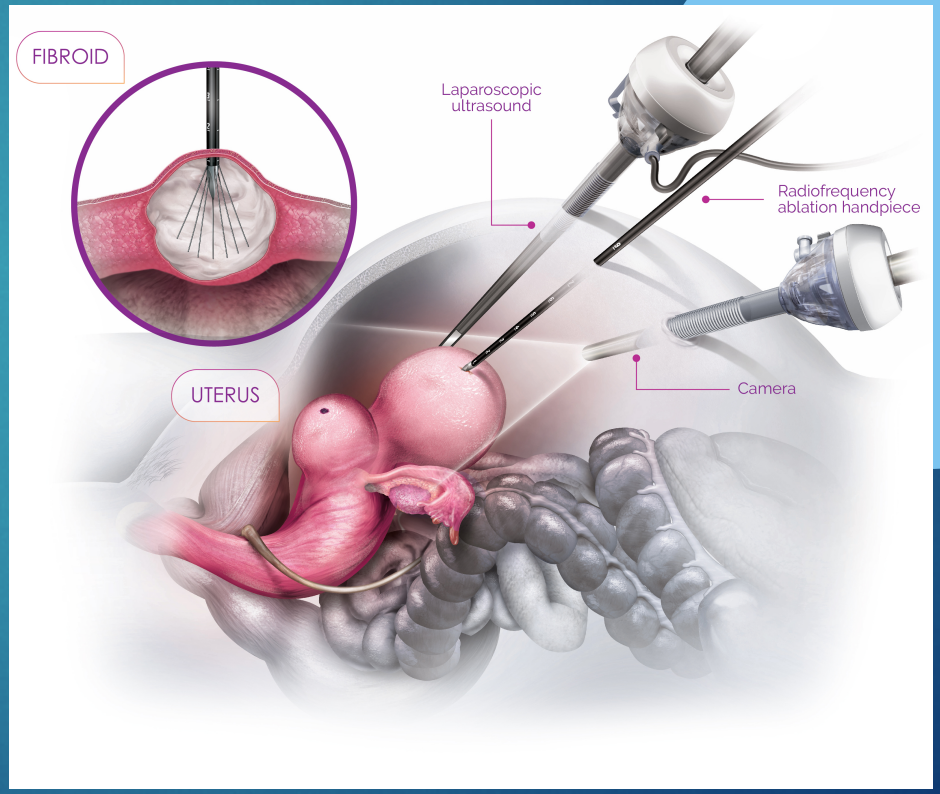
ABSTRACT

BACKGROUND

Uterine fibroids, the most common type of tumor among women of reproductive age, are associated with heavy menstrual bleeding, abdominal discomfort, subfertility, and a reduced quality of life. For women who wish to preserve their uterus and who have not had a response to medical treatment, myomectomy and uterine-artery embolization are therapeutic options.

Minimally Invasive Surgery





Making Hysterectomy Safer

Received: 1 November 2018 | Revised: 27 April 2019 | Accepted: 13 May 2019

DOI: 10.1111/aogs.13670

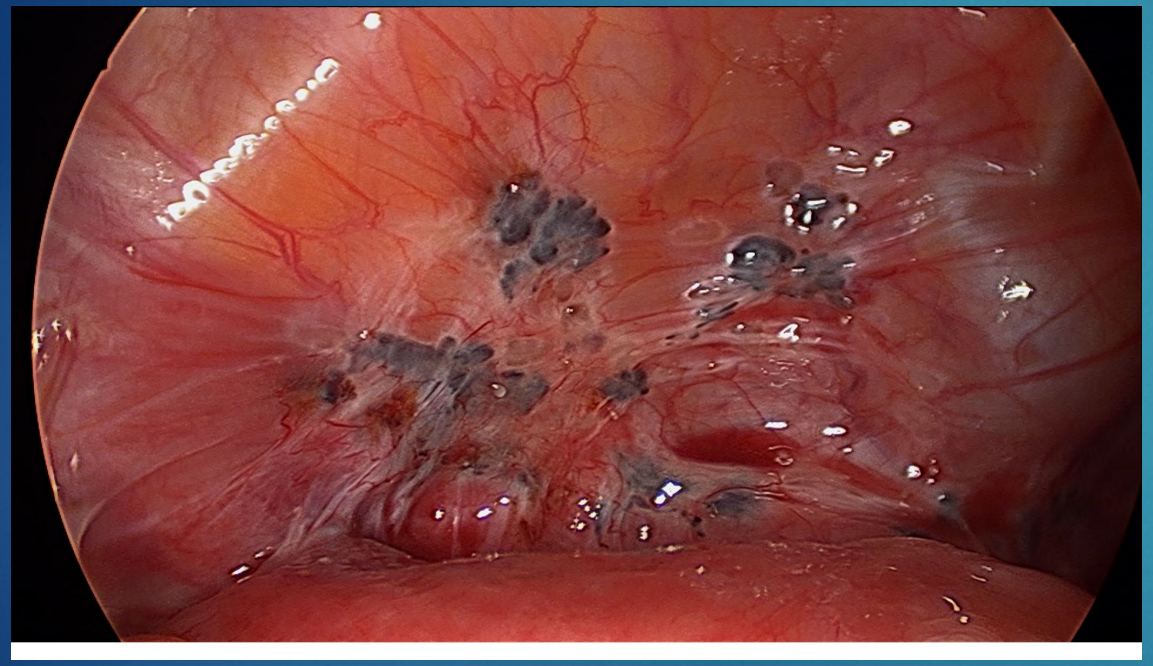
ORIGINAL RESEARCH ARTICLE

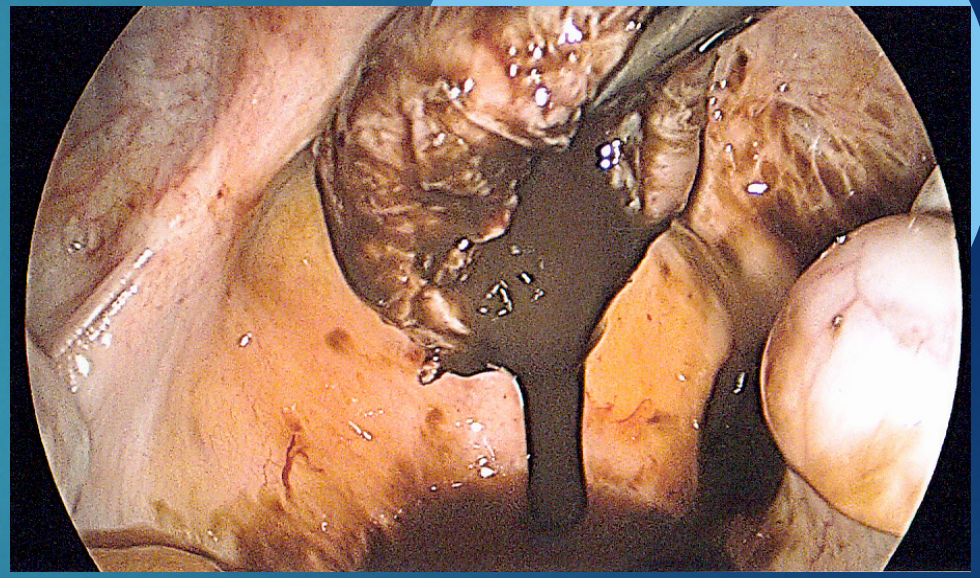
AOGS
Acta Obstetricia et Gynecologica Scandinavica

Outpatient vs inpatient total laparoscopic hysterectomy: A randomized controlled trial

Ulla J. Christiansen[1] | Anne R. Kruse[1] | Peter G. Olesen[1] | Finn F. Lauszus[1] | Ulrik S. Kesmodel[2] | Axel Forman[3]

Endometriosis





Diagnostic Challenges

Pain is the main symptom of endometriosis[1]

Most women diagnosed with endometriosis experience:[2]

- Dysmenorrhea
- Non-menstrual pelvic pain
- Dyspareunia

Pain and other clinical features are shared with a range of diseases leading to delays in diagnosis[1]

1. Barbieri R. OBCM 2017; 29(3)
2. De Graaff AA, et al. Hum Reprod. 2013;28(10):2677-2685.

Endometriosis-associated Pelvic Pain: Contemporary Approach

It is possible to initiate medical management based on **patient history, pelvic exam and imaging**[1]

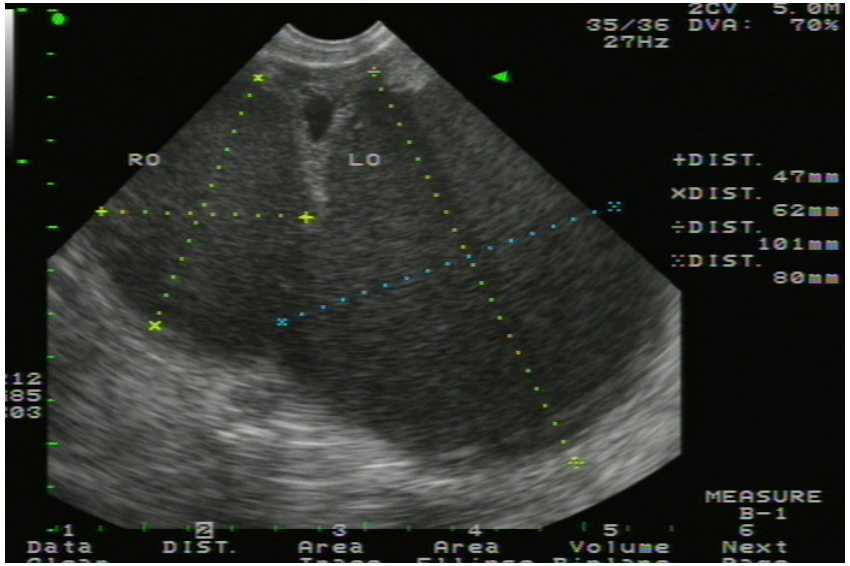
Diagnostic laparoscopy is not required before treatment in all patients presenting with pelvic pain (SOGC)[1]

"A non-surgical diagnosis of endometriotic disease is feasible"[2]

MRI: magnetic resonance imaging

1. SOGC Guidelines. Endometriosis: Diagnosis and Management. JOGC 2010; 32(7 Suppl 2):S1-32.
2. Vercellini P et al. JOGC 2018; 40:726–749.

Imaging and Tests for Endometriosis



Ultrasonography is the first-line investigational tool for suspected endometriosis

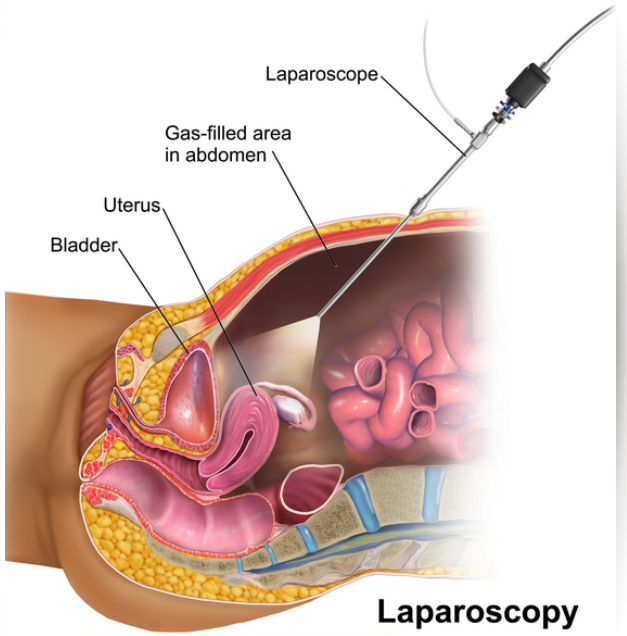
However, diagnosis of endometriosis is limited to ovarian endometrioma in most settings

No reliable serum markers for diagnosing endometriosis

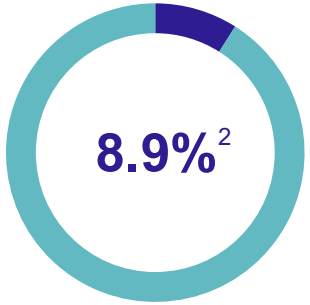
Image courtesy of Dr. S. Singh.

SOGC Guidelines. Endometriosis: Diagnosis and Management. JOGC 2010; 32(7 Suppl 2):S1-32.

Laparoscopy and Histology



Laparoscopy and histology are the traditional gold standard for diagnosis[1]



Overall risk of any complication

However, it is not required prior to starting treatment

In the ideal situation, laparascopy should be reserved for diagnosis and concomitant treatment

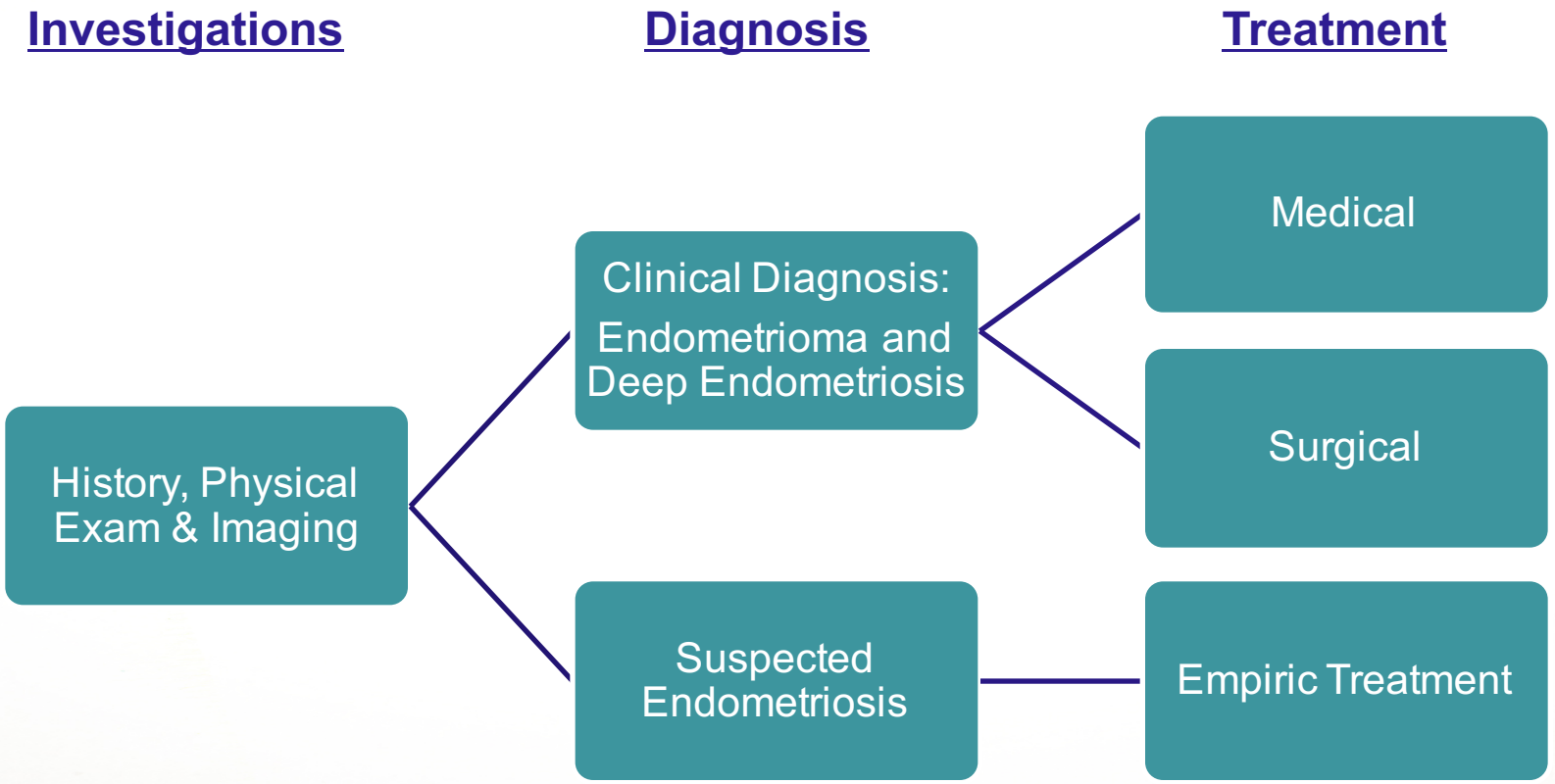
Pre-operative planning and appropriate skill sets are crucial

ASRM: American Society of Reproductive Medicine

1. SOGC Guidelines. Endometriosis: Diagnosis and Management. JOGC 2010; 32(7 Suppl 2):S1-32.
2. Chapron C et al. Hum Reprod 2002;17:1334–42.

Non-surgical Diagnosis of "Endometriotic Disease" Is Possible

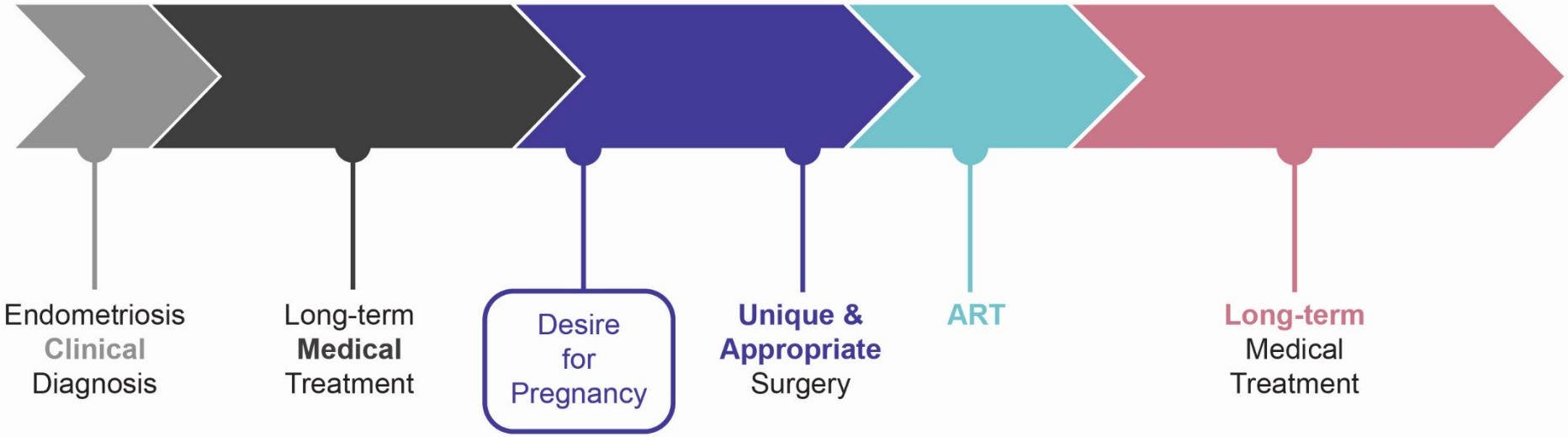
Clinical vs. Suspected Diagnosis of Endometriosis



Bazot M & Darai E. Fertil Steril 2017; 108(6): 886-894. Vercellini P et al. J Obstet Gynaecol Can. 2018; 40(6):726-49

A Proposed Treatment Paradigm

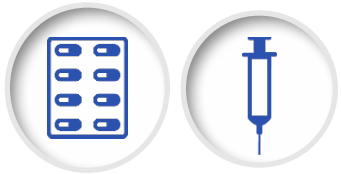
‘’Endometriosis Life”



ART, assisted reproductive technology.
Chapron, (2018)

Treatment Options

Combined Hormonal Contraceptives (CHC)



Progestins

Androgen therapy

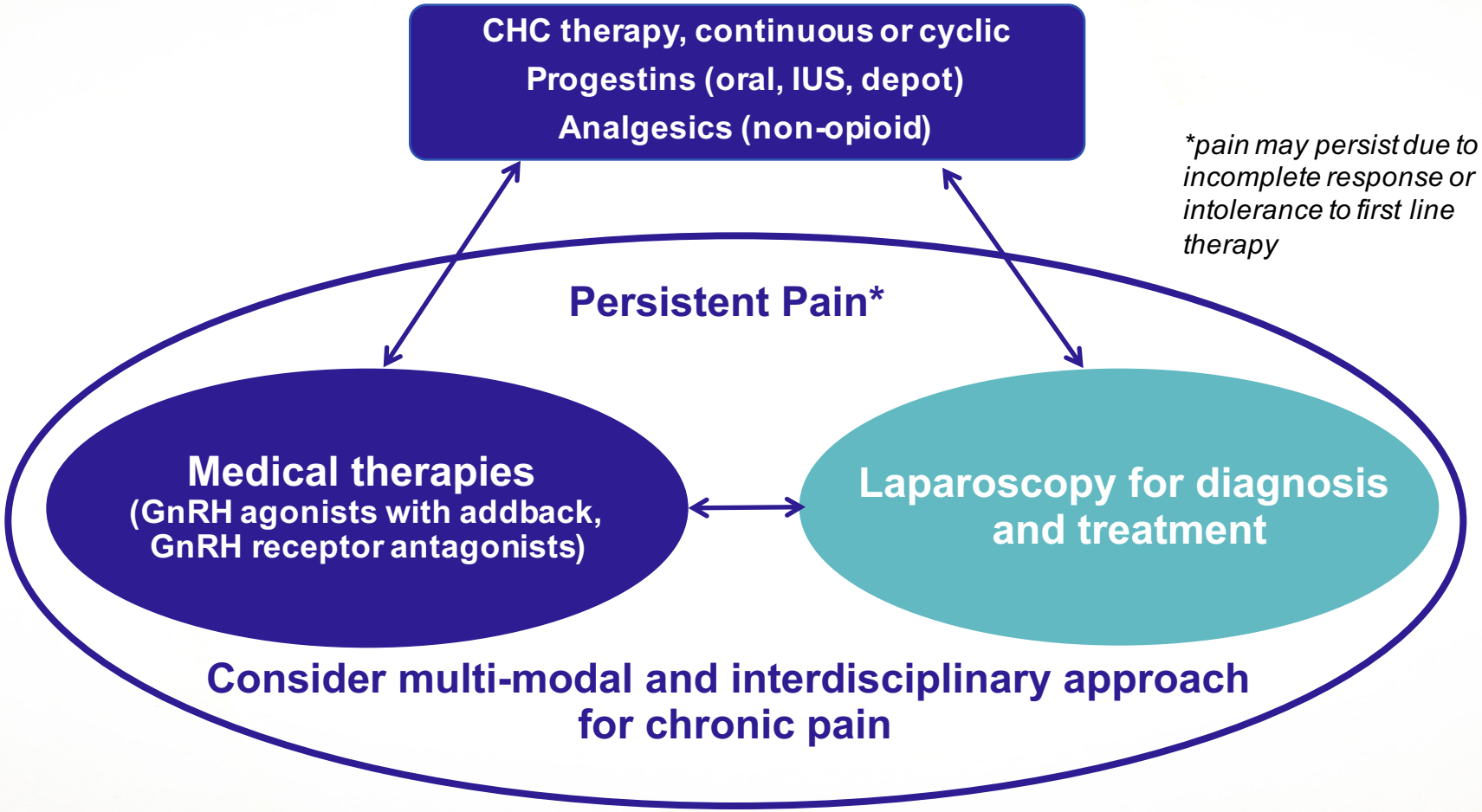
GnRH agonists

GnRH receptor antagonists

Surgery

GnRH: gonadotrophin releasing hormone

Treatment Algorithm for Endometriosis-Associated Pain



Consider additional imaging, consultation and evaluation for comorbid conditions

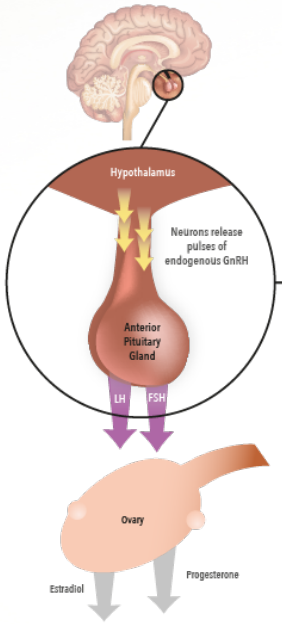
CHC: combined hormonal contraceptive; GnRH: gonadotrophin releasing hormone;
IUS: intrauterine system; Adapted from ESHRE, UK NICE guidelines for endometriosis, WES Consensus, SOGC

GnRH ***Anta***gonists

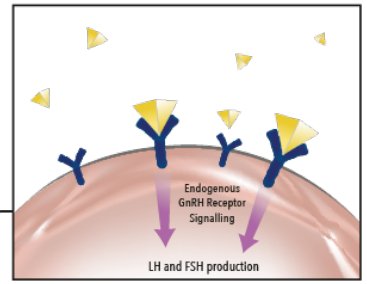
- Elagolix
- Relugolix
- Linzagolix

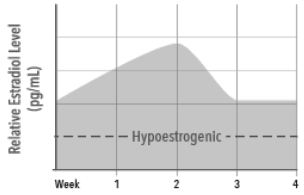
- Small molecules
- Oral
- Dose dependant hypoestrogenism

GnRH Agonists vs. Oral GnRH Receptor Antagonists: Mechanisms of Action



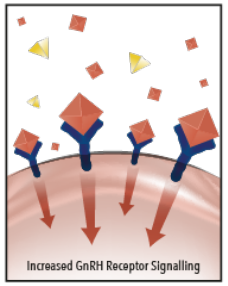
Pulsatile GnRH release

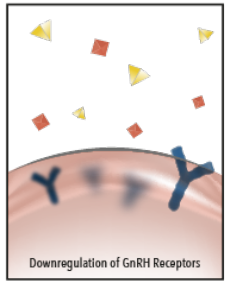


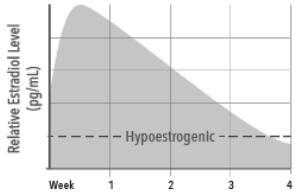


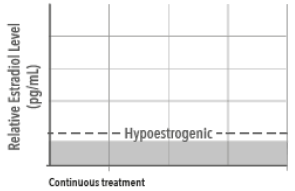
Physiological changes in estradiol

Depot GnRH agonists



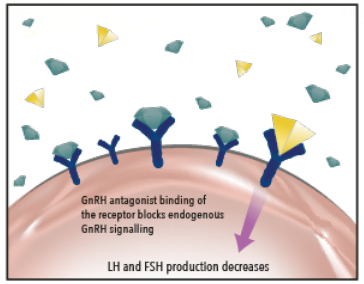


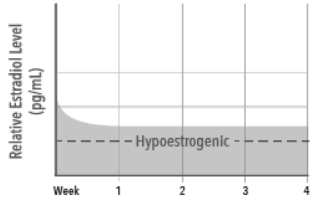




- Sustained stimulation causes initial flare
- Continuous exposure leads to desensitization of GnRH receptors and profound inhibition of the HPO axis

Oral GnRH receptor antagonists





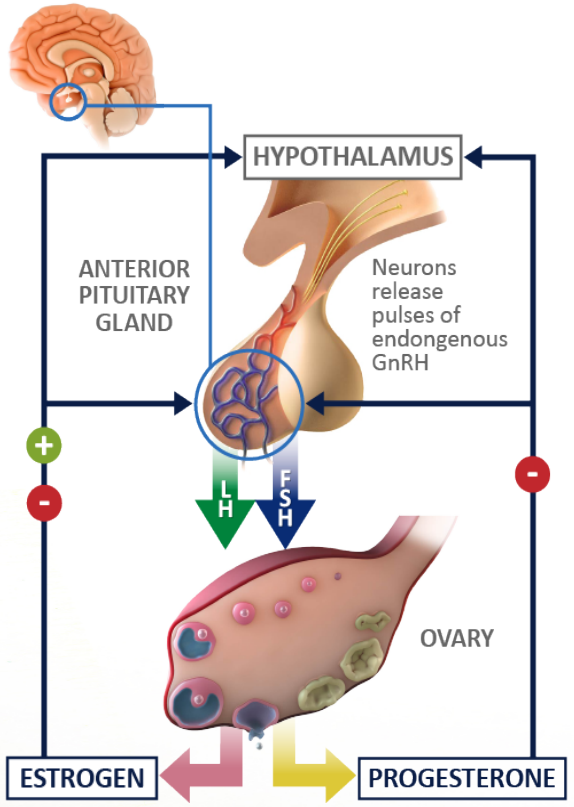
Competitive GnRH receptor antagonists allow dose-dependent suppression of HPO axis

GnRH: gonadotropin-releasing hormone; HPO: hypothalamic-pituitary- ovarian.

1. Nussey S, Whitehead S. Endocrinology: An Integrated Approach. Oxford: BIOS Scientific Publishers. London, UK; 2001. https://www.ncbi.nlm.nih.gov/books/NBK29/?report=printable. Accessed October 9, 2017. 2. Knobil E. Endocrinology 1992; 131:1005-1006. 3. Reed BG, Carr BR. In: De Groot LJ et al, eds. NCBI Bookshelf. Endotext. South Dartmouth, MA; updated May 2015. Accessed November 2, 2017. 4. Zito G et al. Biomed Res Int 2014; 2014:191967. 5. Gordon K et al. J Clin Endocrinol Metab 1991; 73:1262-1268.

Elagolix Is a GnRH Receptor Antagonist

Female Hypothalamic-Pituitary-Gonadal Axis



Elagolix

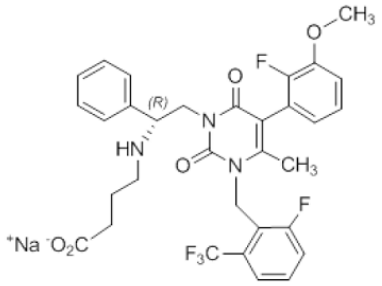
- Oral, non-peptide, highly potent, GnRH receptor antagonist
- Results in dose-dependent suppression of gonadotropins and ovarian sex steroids
  - Hormone suppression is rapid, reversible, and dose-dependent
  - Partial estradiol suppression at 150 mg QD
  - Nearly full estradiol suppression at 200 mg BID

BID: *bis in die;* GnRH: gonadotropin-releasing hormone; QD: *quaque die*.

1. Diamond MP et al. Reprod Sci 2014; 21:363-371; 2. Ng J et al. J Clin Endocrinol Metab.2017; 102:1683-1691.

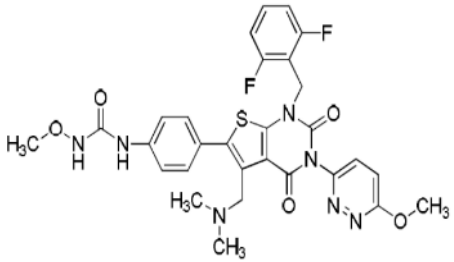
GnRH Receptor Antagonists in Development

ELAGOLIX[1]



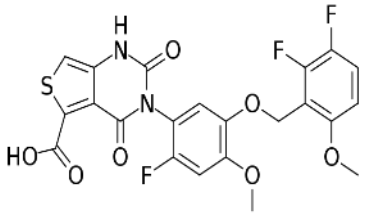
- The only drug approved in the US as Oriahnn for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women
- Phase 3 development in uterine fibroids
  - **300 mg BID with or without E_2/NETA***

RELUGOLIX[2]



- Approved as Relumina (Japan) for the management of symptomatic uterine fibroids as monotherapy
- Phase 3 development in uterine fibroids and endometriosis
  - 40 mg relugolix once daily with E2/NETA*

LINZAGOLIX[3]

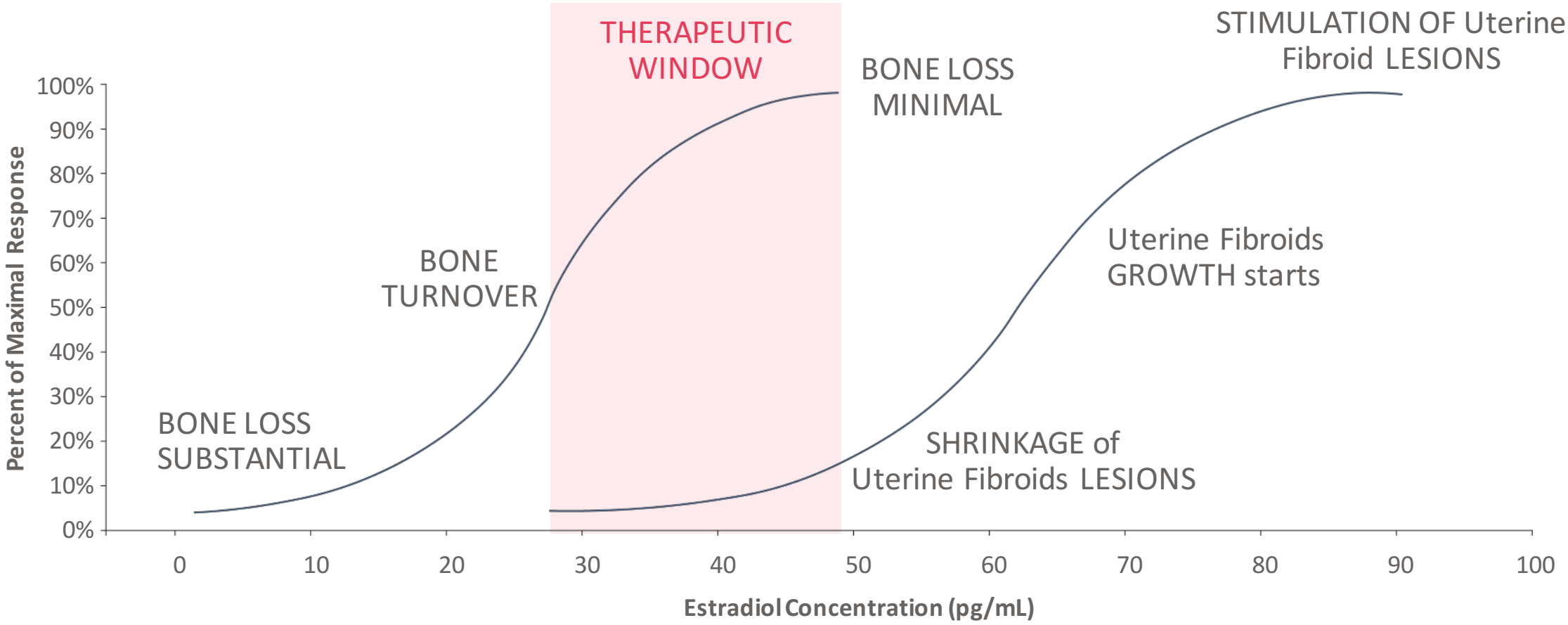


- Phase 3 development in uterine fibroids
  - 100 mg once-daily monotherapy
  - 200 mg once daily with E2/NETA*

*estradiol 1 mg / norethindrone acetate 0.5 mg

1. Farris M et al. Therapeutics and Clinical Risk Management 2019:15:157-178
2. Elsharoud A et al. Drugs of the Future 2019, 44(2):131-143
3. http://www.jefferies.com/CMSFiles/Jefferies.com/files/ObsEva.pdf

Estradiol Levels Within the Therapeutic Window May Improve Symptoms and Maintain Bone Health



Adapted from Barbieri RL et al.[1]

1. Barbieri RL. Am J Obstet Gynecol1992; 166(2): 740-745.

Effect on Ovulation and Estradiol

Ovulation Rate

- During the course of a 3-menstrual cycle study in healthy women:

Healthy Women	Elagolix 150 mg QD	Elagolix 200 mg BID
Approximate rates over 3-menstrual cycle	50%	32%

Estradiol levels

- In phase 3 studies, in women with endometriosis

Women with Endometriosis	Elagolix 150 mg QD	Elagolix 200 mg BID
Approximate estradiol level	50 pg/mL (183.55 pmol/L) [partial suppression]	12 pg/mL (44.05 pmol/L) [nearly full suppression]

BID: *bis in die;* QD: quaque die.

1. ORILISSA (elagolix) Product Monograph. AbbVie Corporation October 2018.

GnRH Antagonists: Endometriosis

GnRH Antagonists for Endometriosis: Recent Studies

No direct head-to-head data available – caution advised when comparing clinical studies with different assessment measures

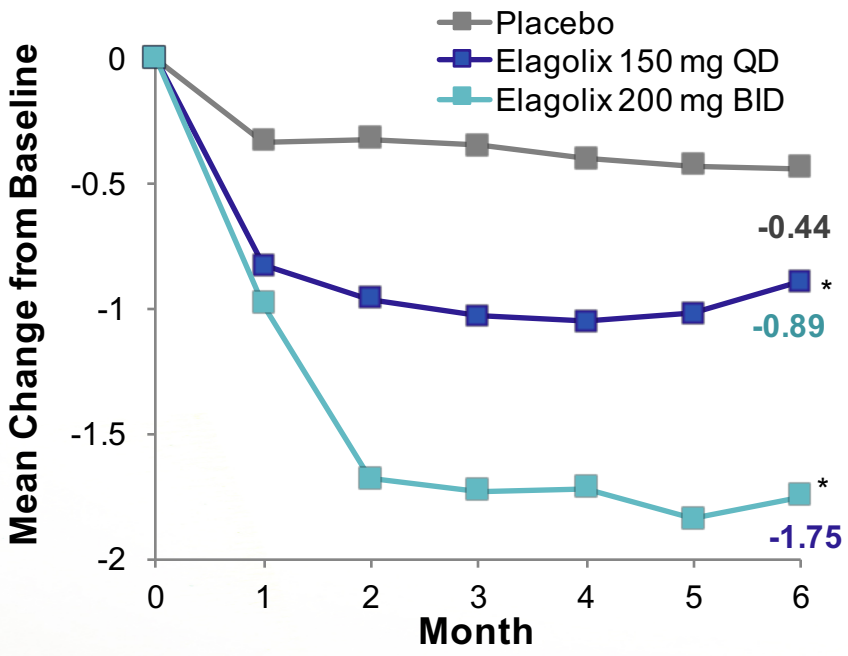
	Relugolix Combination Therapy		Elagolix Monotherapy Week 24*			
Dose	**40 mg QD**		**150 mg QD**		**200 mg BID**	
Responder Rate *(placebo)*	SPIRIT 1	SPIRIT 2	Elaris EM-1	Elaris EM-2	Elaris EM-1	Elaris EM-2
Dysmenorrhea	**74.5%** (26.9%)	**75.2%** (30.4%)	**42.1%** (23.1%)	**46.2%** (25.4%)	**75.3%** (23.1%)	**76.9%** (25.4%)
Non-Menstrual Pelvic Pain	**58.5%** (39.6%)	**66.0%** (42.6%)	**45.7%** (34.9%)	**51.6%** (40.6%)	**62.1%** (34.9%)	**62.2%** (40.6%)
Bone Mineral Density Loss, Lumbar Spine *(placebo)*	**-0.70%** (0.21%)	**-0.78%** (0.02%)	**-0.32%** (0.47%)	**-0.72%** (0.56%)	**-2.61%** (0.47%)	**-2.49%** (0.56%)

*Co-primary endpoints in ELARIS EM-1 and EM-2 tested at Week 12

Effect of Elagolix on Dysmenorrhea Over Time

Change in Dysmenorrhea Score at Month 6

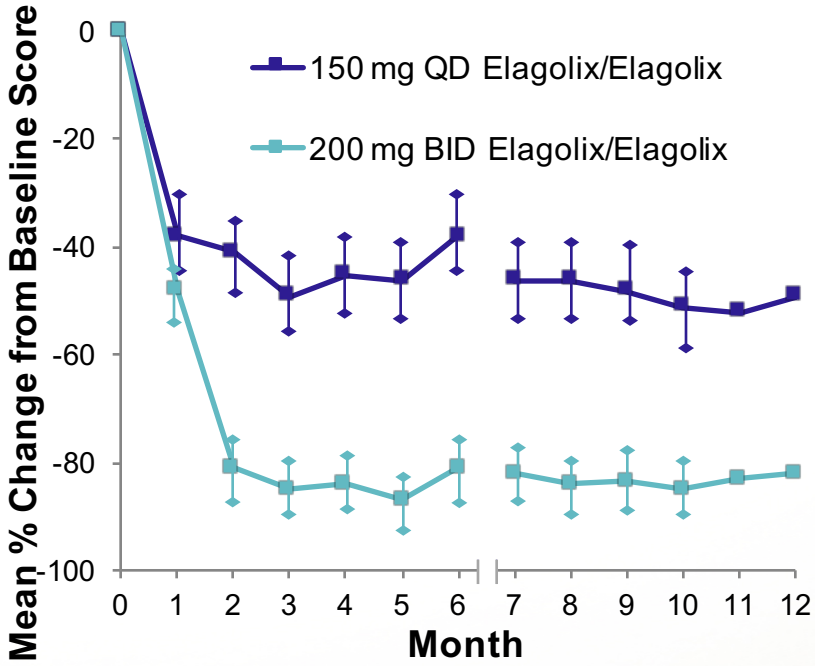
Baseline score approx. 2.1



Elaris EM-I

Effect of Elagolix on Dysmenorrhea Over 12 Months of Continuous Treatment

Baseline score approx. 2.1



Elaris EM-I | Elaris EM-III

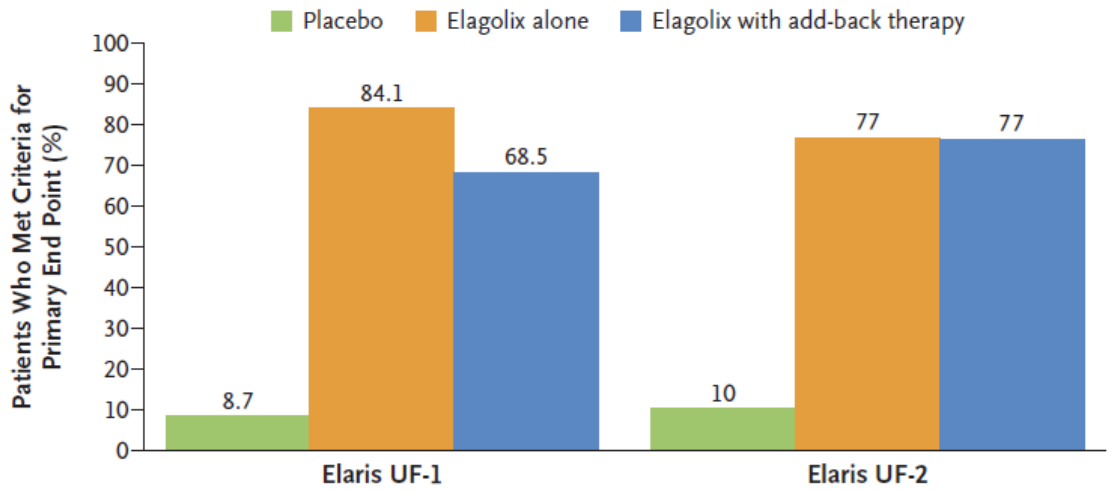
*P<0.001; Bars represent 95% CI; N range across studies/doses: Baseline=138-149; Extension Month 1=136-148; Extension Month 6=110-122.
BID: *bis in die;* QD: *quaque die*.

1. Taylor H et al. N Engl J Med 2017; 377:28-40; 2. Surrey E et al. Obstet Gynecol 2018; 132:147-160.
3. ORILISSA (elagolix) Product Monograph. AbbVie Corporation October 2018.

The NEW ENGLAND JOURNAL of MEDICINE

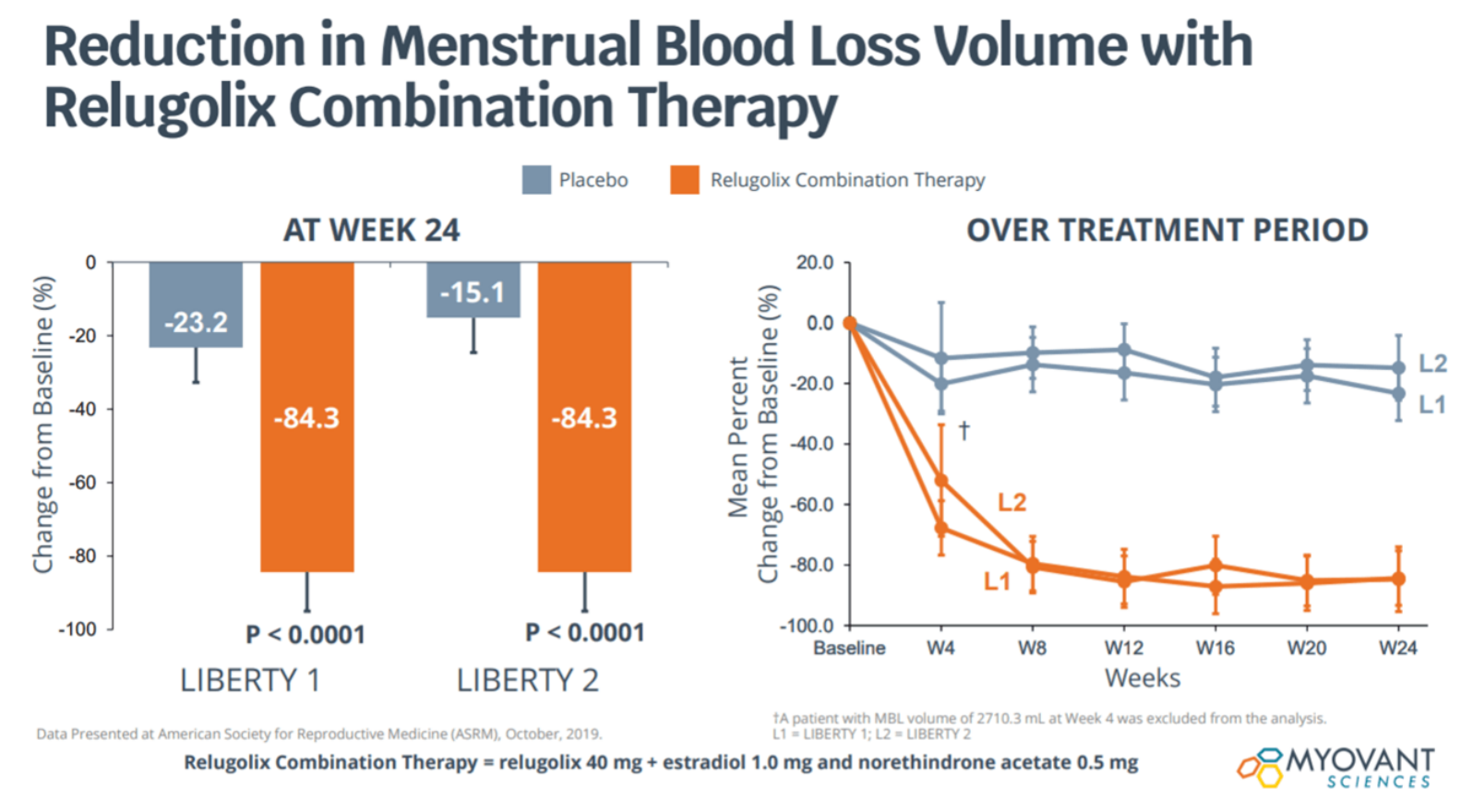
ORIGINAL ARTICLE

Elagolix for Heavy Menstrual Bleeding in Women with Uterine Fibroids



Difference from placebo — % (95% CI)		75.4 (66.2–84.6)	59.8 (51.1–68.5)		66.4 (55.5–77.3)	66.0 (57.1–75.0)
Risk ratio (95% CI)		9.7 (5.0–18.9)	7.9 (4.1–15.5)		7.1 (3.8–13.4)	7.2 (3.9–13.5)
Two-sided P value			<0.001			<0.001
No. of women	102	104	206	94	95	189
No. imputed by multiple imputation	8	3	16	6	11	12

Relugolix


Reduction in Menstrual Blood Loss Volume with Relugolix Combination Therapy
Placebo
Relugolix Combination Therapy
AT WEEK 24
Change from Baseline (%)
0
-20
-40
-60
-80
-100
-23.2
-84.3
-15.1
-84.3
P < 0.0001
P < 0.0001
LIBERTY 1
LIBERTY 2
OVER TREATMENT PERIOD
Mean Percent Change from Baseline (%)
20.0
0.0
-20.0
-40.0
-60.0
-80.0
-100.0
†
L2
L1
L2
L1
Baseline
W4
W8
W12
W16
W20
W24
Weeks
Data Presented at American Society for Reproductive Medicine (ASRM), October, 2019.
†A patient with MBL volume of 2710.3 mL at Week 4 was excluded from the analysis.
L1 = LIBERTY 1; L2 = LIBERTY 2
Relugolix Combination Therapy = relugolix 40 mg + estradiol 1.0 mg and norethindrone acetate 0.5 mg
MYOVANT SCIENCES

Goal of Management !