MEDICAL TREATMENT OF OF UTERINE FIBROID

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- ❖ PRESIDENT –Indian Association of Gynaecological Endoscopists (2020-21)
- ❖ SEC GENERAL ISAR (2018-20)

- ESHRE CERTIFIED REPRODUCTIVE ENDOSCOPIC SURGEON
- Centres recognised for ICOG fellowship – 6 months ART, Endoscopic surgery
- FOGSI recognised centres for Infertility and Endoscopic surgery training
- Special Interests : Infertility, Endoscopic surgery, Rec Pregnancy loss

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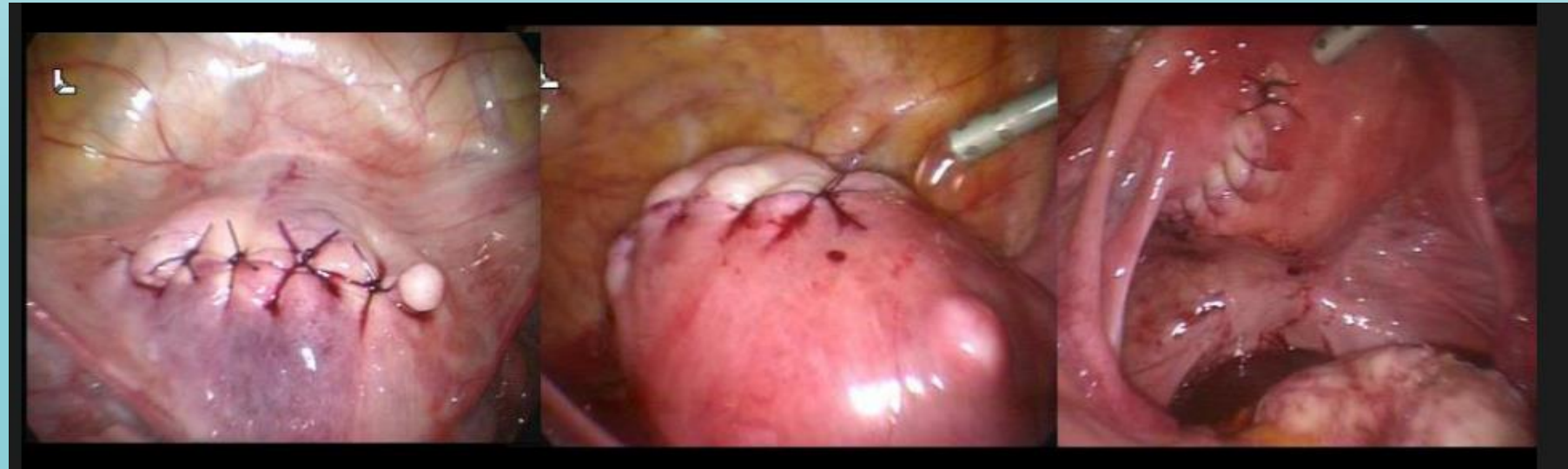
ENHANCING ENDOSCOPY SKILLS

LEARNING OBJECTIVES

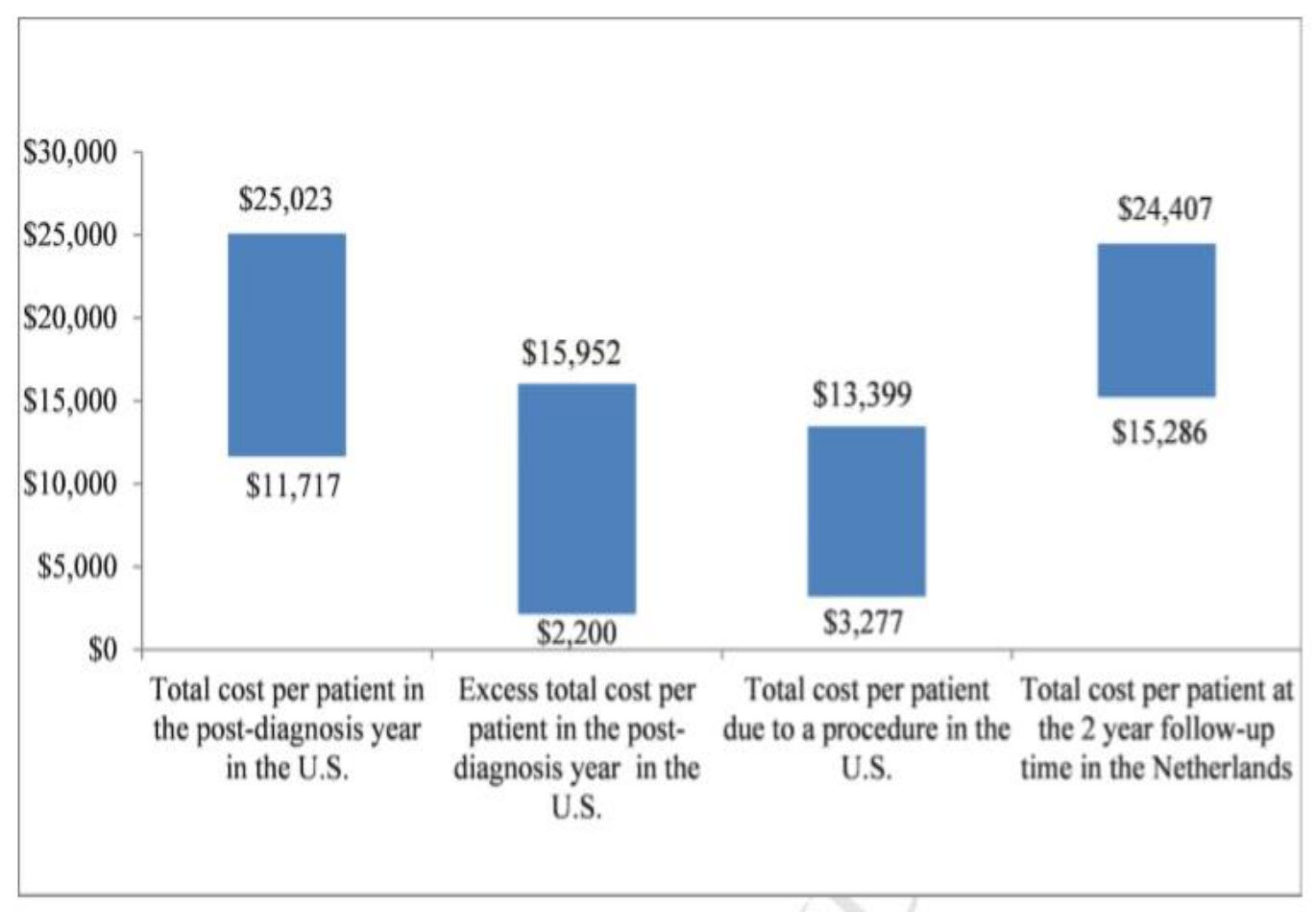
- Context - Burden of Myomas and Myomectomy
- Pathophysiology (with newer insights)
- Current options in the Management for Uterine Fibroids
- Summary

INTRODUCTION

- Most common tumor of the uterus - 20% of women in reproductive age group
- Leiomyomas-one-third of all hospital admissions to gynecology services and one of the commonest indications for hysterectomy
- Treatment of myomas - mainly surgical and expensive
- Out of 600,000 hysterectomies performed in the USA each year, around 200,000 are for fibroids
- Implications of surgical interventions and anesthesia
- Especially for patients wishing to preserve their fertility, include risk of bleeding during surgery, impact on uterine integrity (suture dehiscence, intrauterine adhesions in case of uterine cavity opening) and possible repercussions on future fertility (postoperative adhesions, need for cesarean section)



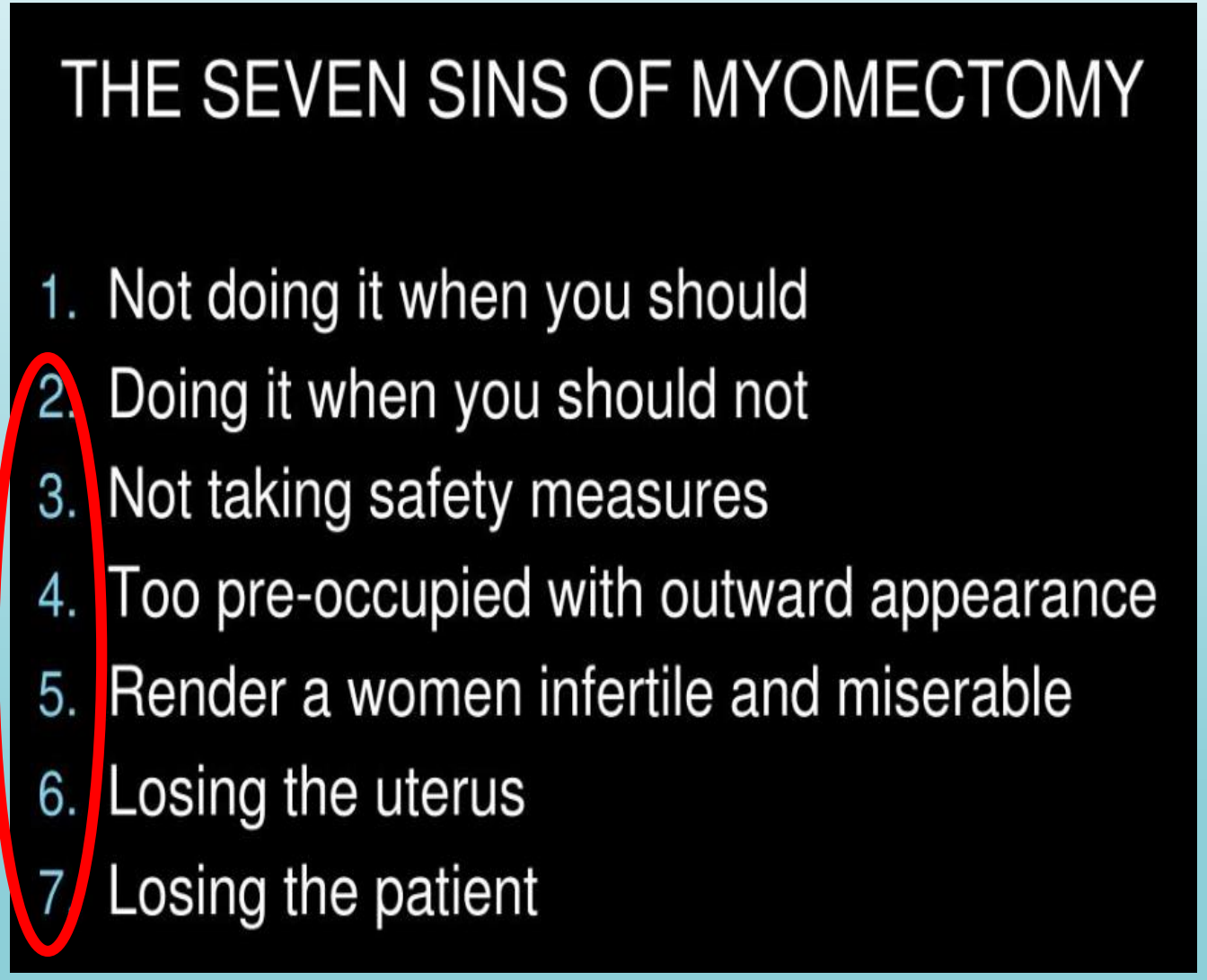
BURDEN OF MYOMECTOMY



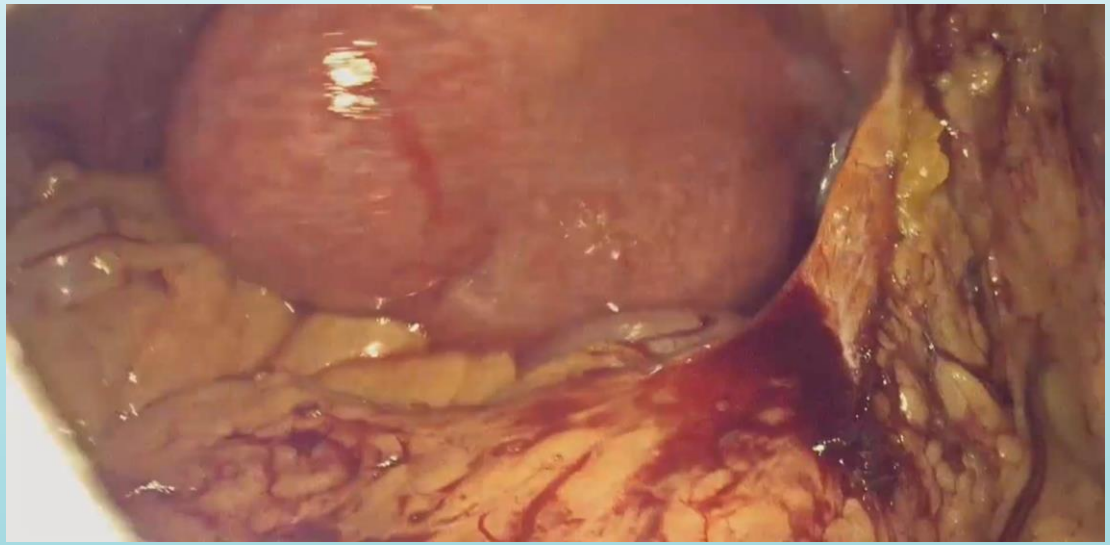
- The total annual direct cost of UF treatment was estimated at $3.5 billion to $10.3 billion in the U.S.A.
- The total annual costs for UF-related hospital admissions were $348 million in Germany, $120 million in France, and $86 million in England
- The total costs, sum of direct and indirect costs, ranged from $11,717 to $25,023 per patient per year
- MOHFW - nearly 20-25 million Indian women (2019) with myomas

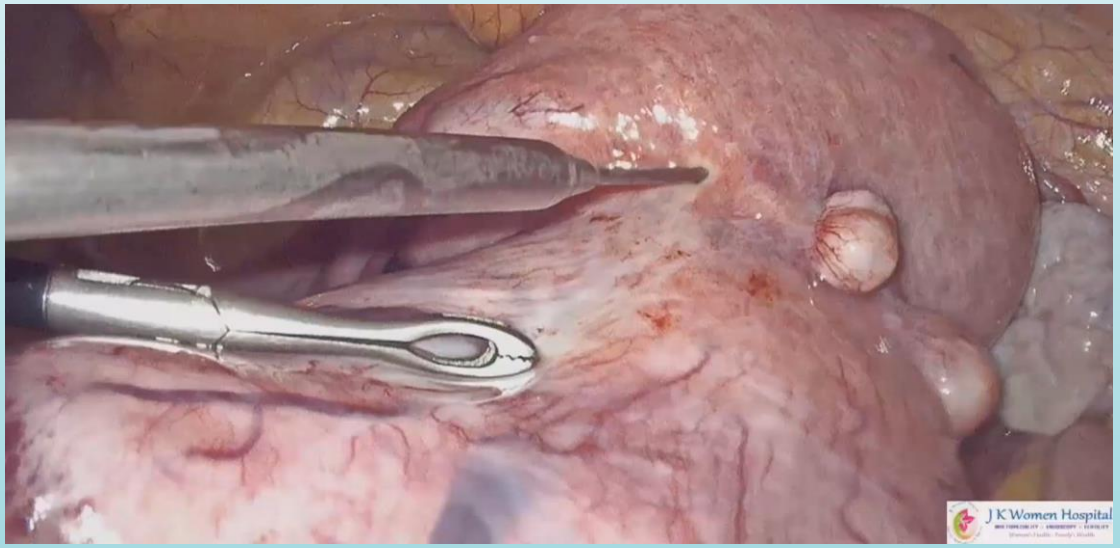
To Do or Not To Do..

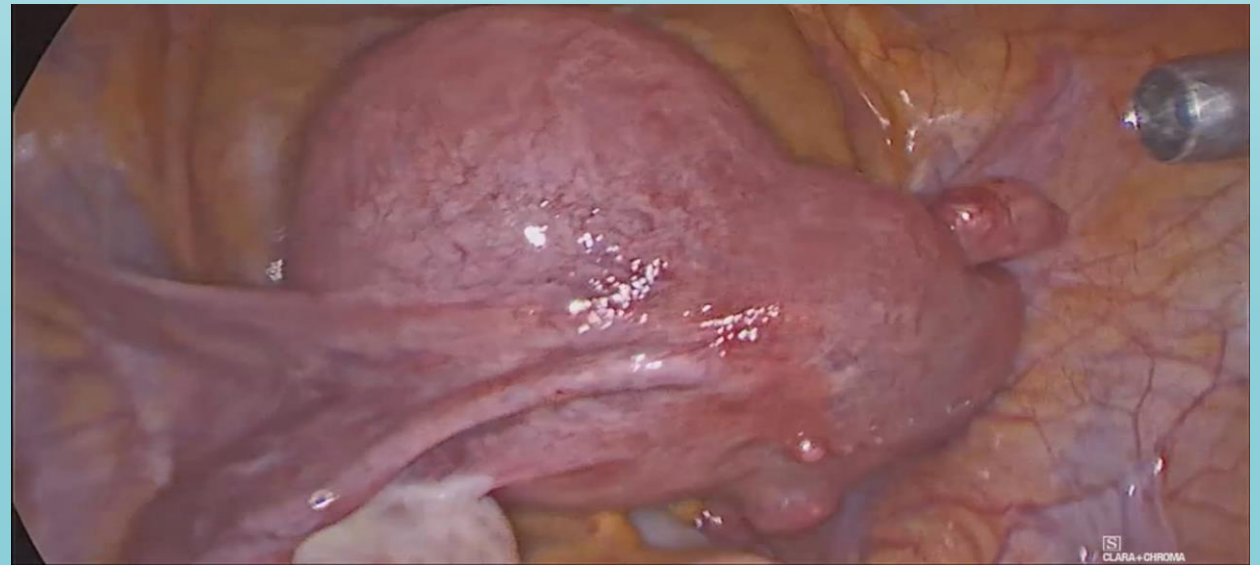
- Risk of Anesthesia, Medications (Vasopressin deaths)..
- Risk of Bleeding, Blood Transfusions, Improper closure..
- Risk of Hysterectomy (1-2%)..
- Risk of Adhesions (76%), Scar Integrity Concerns..



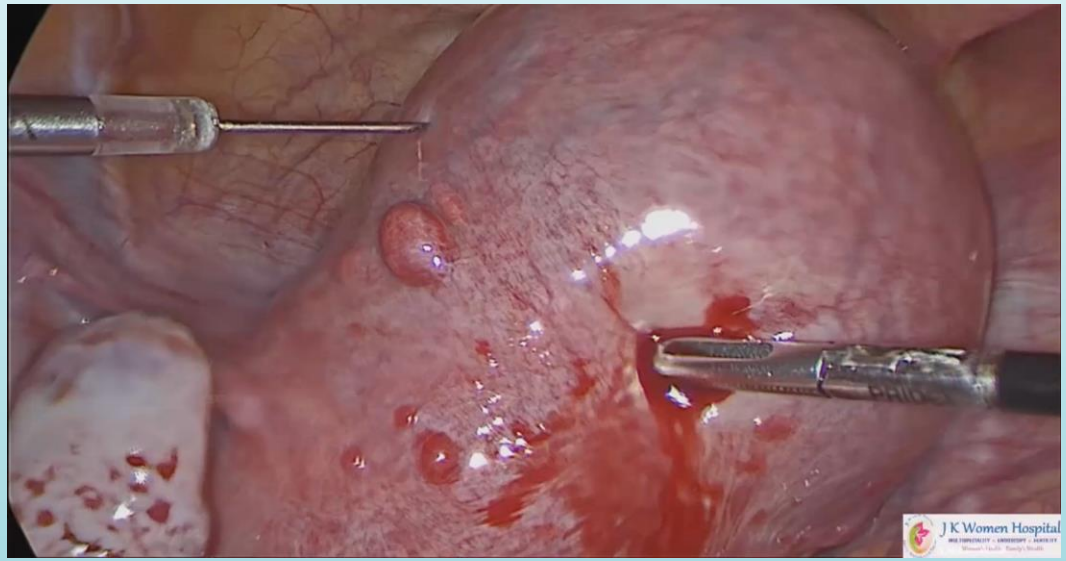
LAPAROSCOPIC MYOMECTOMY- CONTROVERSY CONTINUES

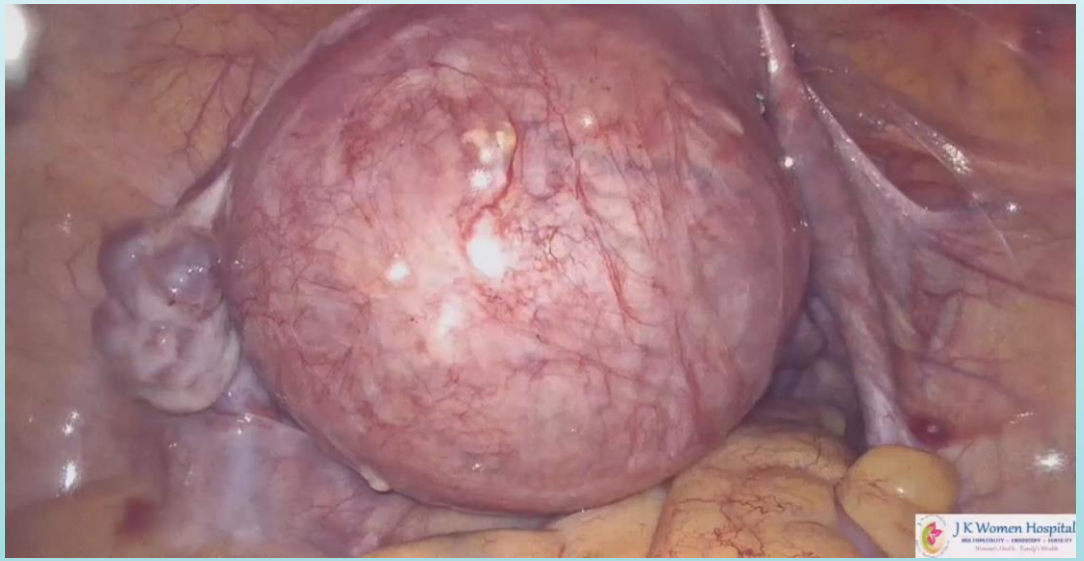


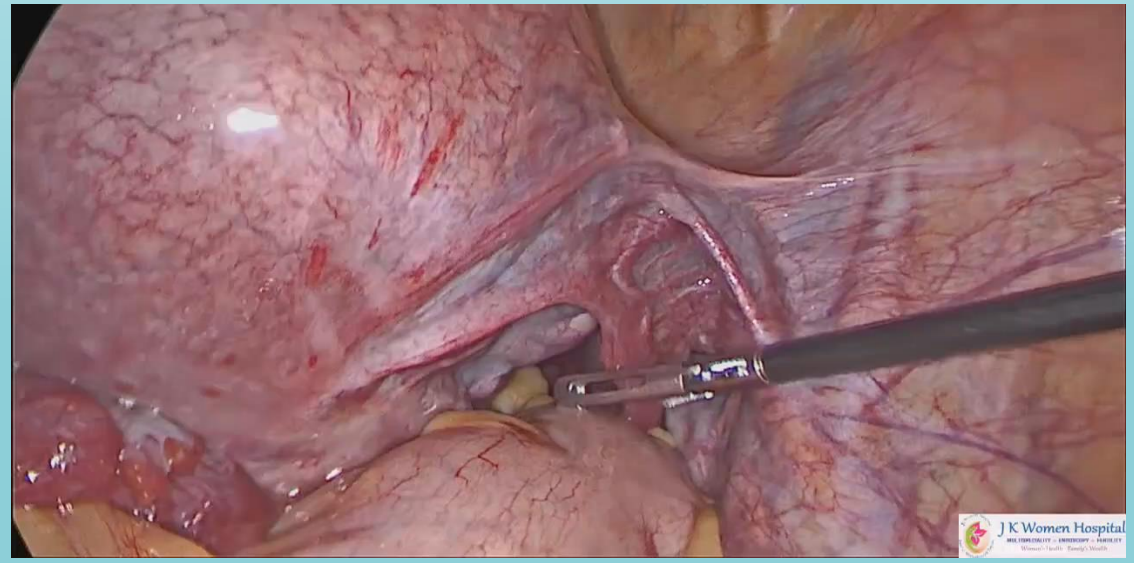


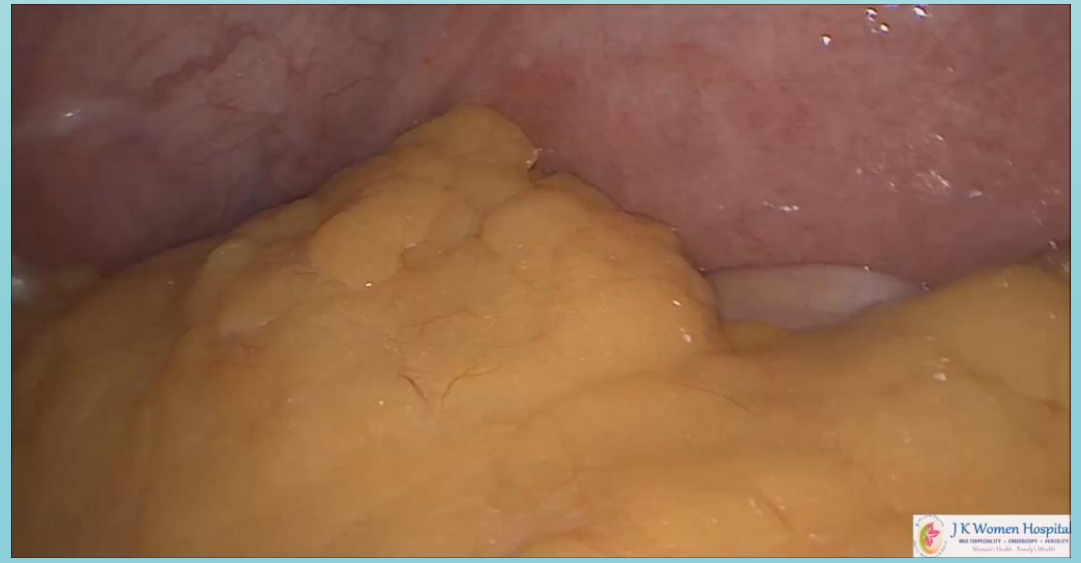


ACHIEVING HEMOSTATSIS

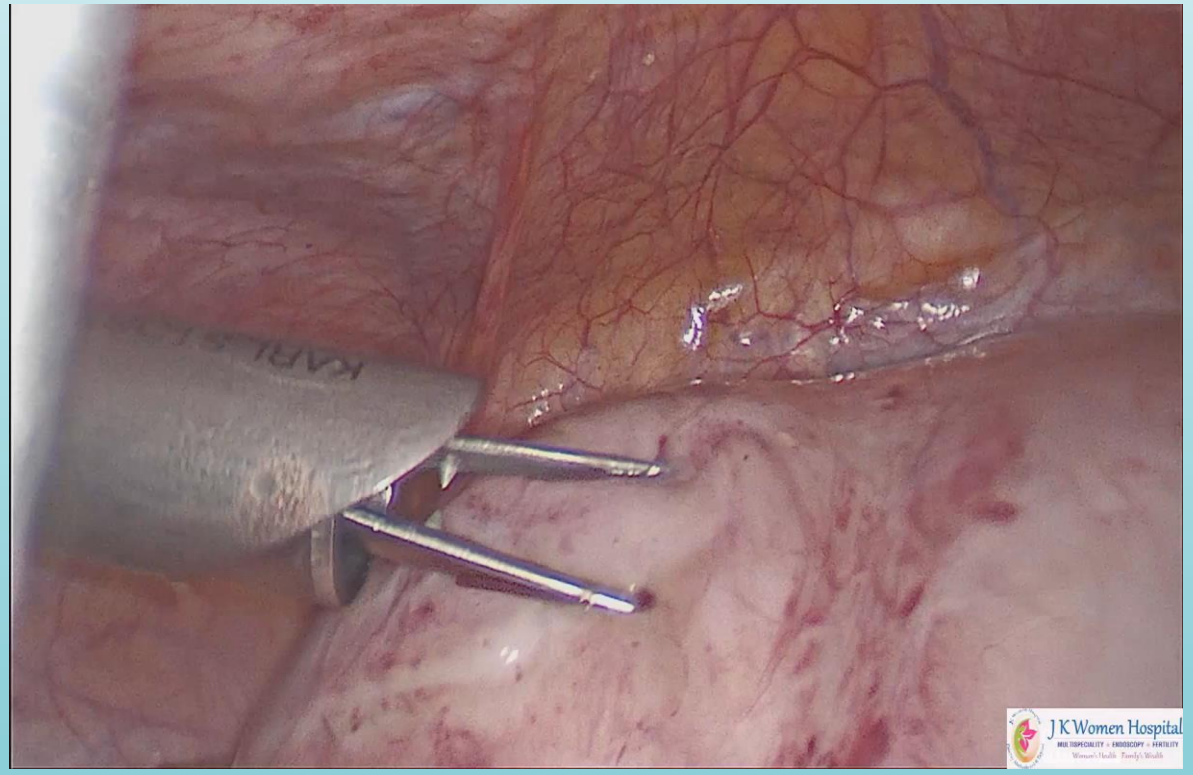


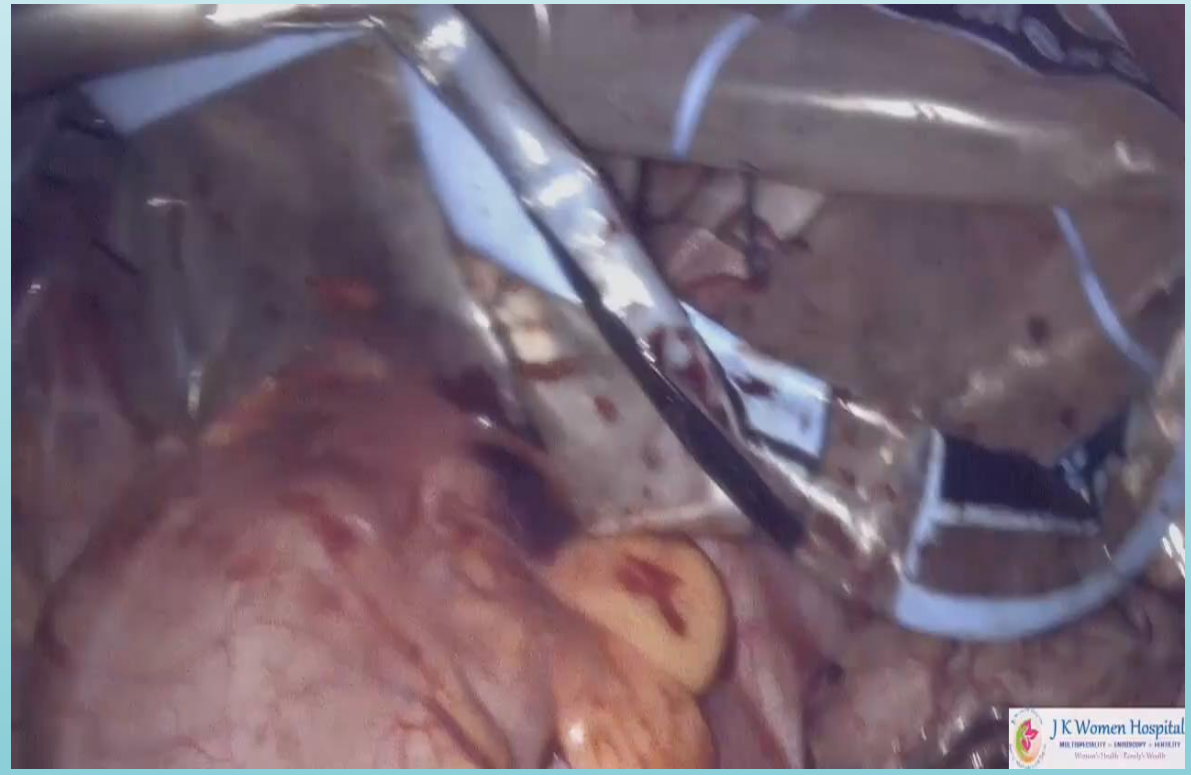






MORCELLATION & SARCOMA





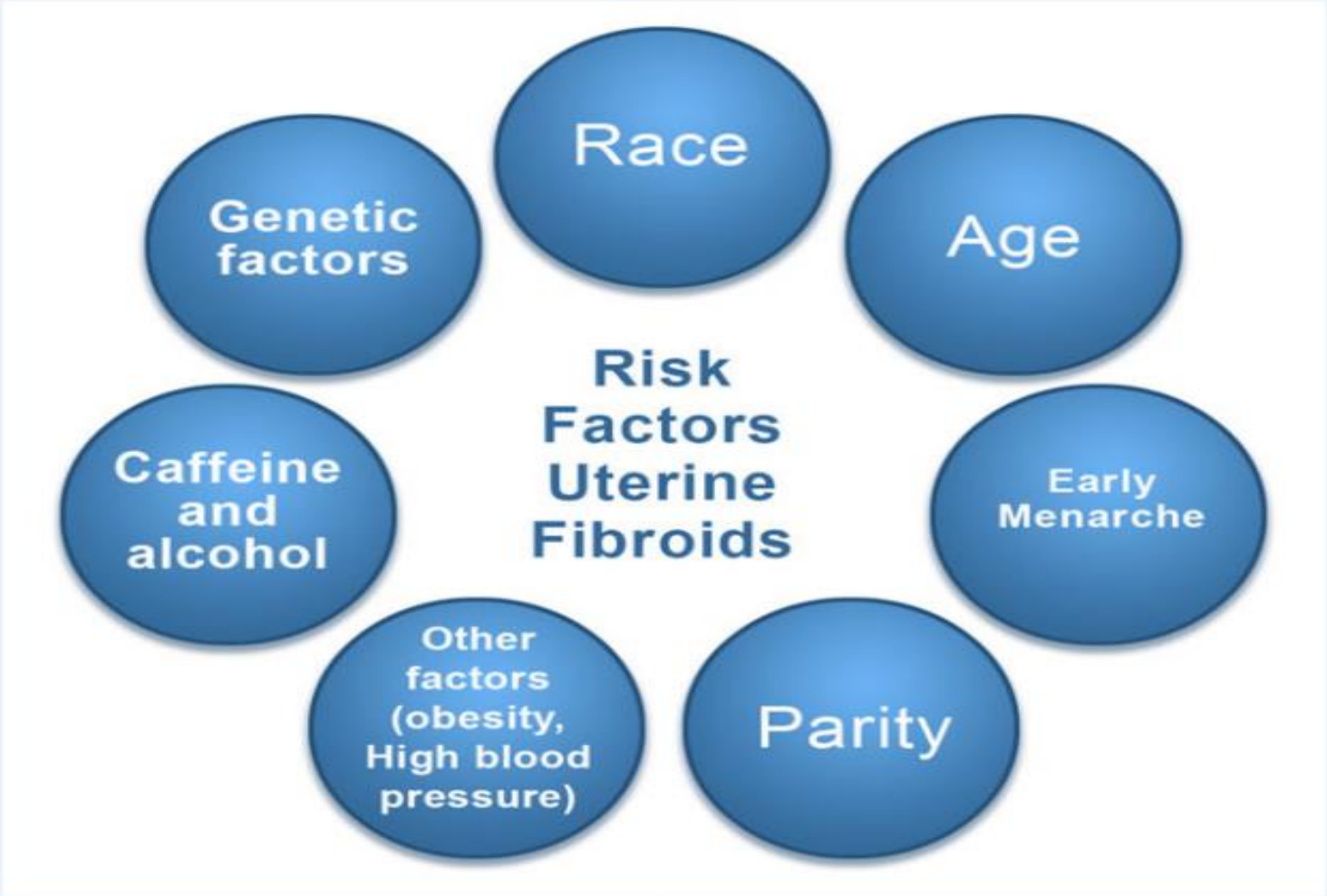


Figure 1 Risk factors for uterine fibroid. These include race, age, delayed pregnancy, early menarche, parity (protective effect), caffeine, genetic alterations, and others, such as obesity and a diet rich in red meat.

CURRENT OPTIONS

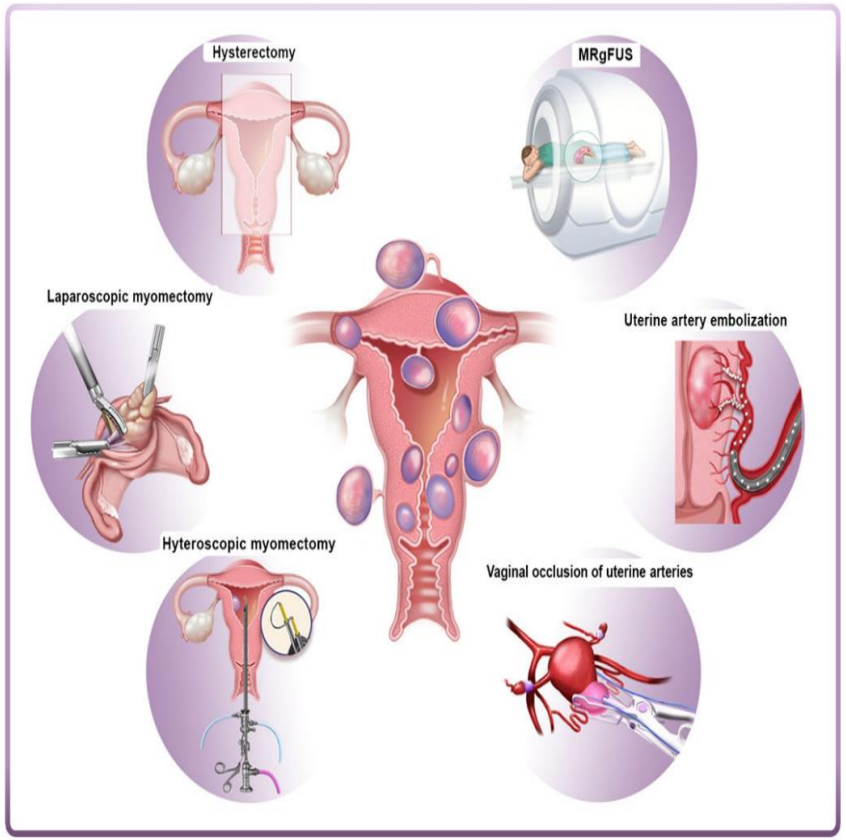


Figure 4 Current surgical and non-surgical management strategies of myomas. Left panel: hysterectomy, laparoscopic myomectomy and hysteroscopic myomectomy are the most widely used surgical interventions for myomas. Right panel: alternatives to surgical intervention include uterine artery embolization (UAE), high-frequency magnetic resonance-guided focused ultrasound surgery (MRgFUS) and vaginal occlusion of uterine arteries.

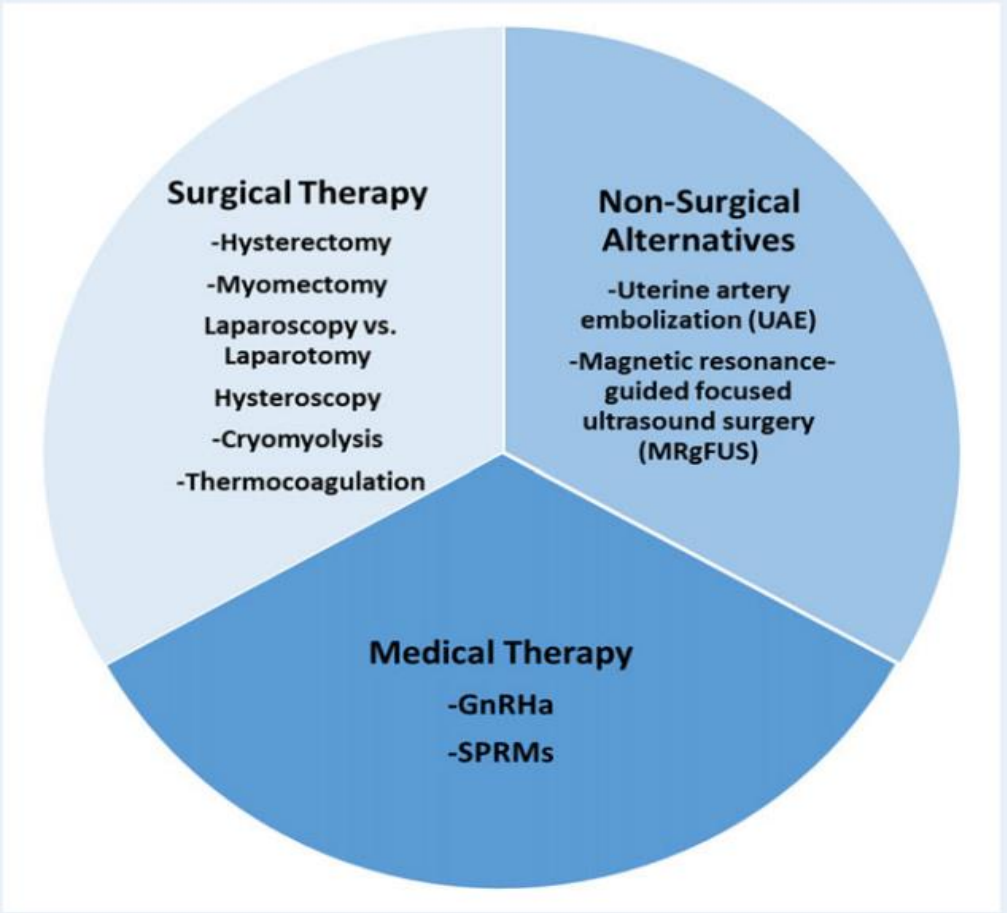


Figure 15 Surgical, non-surgical and medical therapy for the management of fibroids: the current armamentarium.

PATHOPHYSIOLOGY

- Exact etiology not known
- Monoclonal origin (arising from single cell)
- Genetic basis definite
- Various growth factors like TGFβ, EGF, IGF-1, IGF- 2, BFGFa

Epidemiological risk factors:

- Increased risk age 35 to 45 years , nulliparous or low parity , Black women, strong family history, obesity, early Menarche, Diabetes, hypertension.
- Decreased risk ↑↑ parity, exercise, ↑↑intake of green vegetables, Prog.only contraceptives, cigarette smoking

Genetic basis: Responsible for 40% cases of fibroids

- Translocation between Chromo. 12 & 14,
- Trisomy 12
- Rearrangement of short arm of Chromo 6
- Rearrangement of long arm of Ch. 10,
- Deletion of Ch.3 or Ch.7

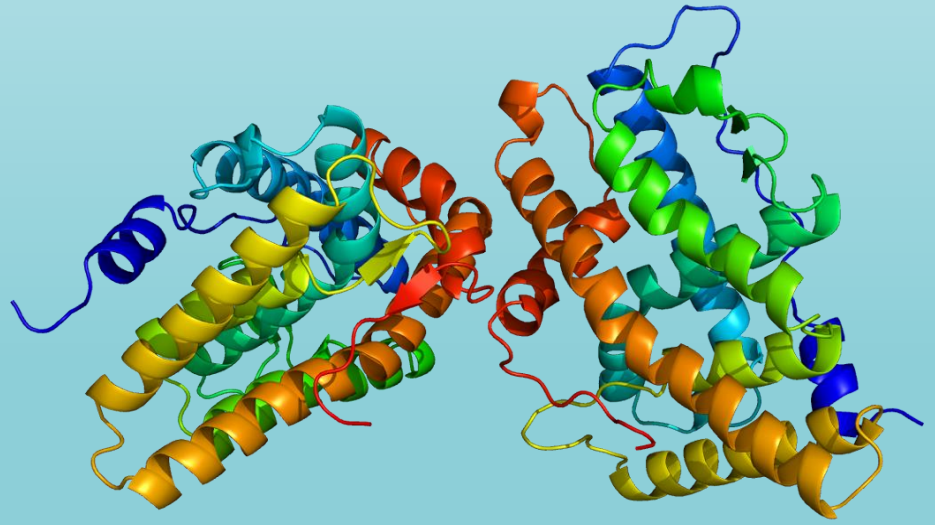
Estrogen, although not proven for causing myoma, definitely implicated in its growth.

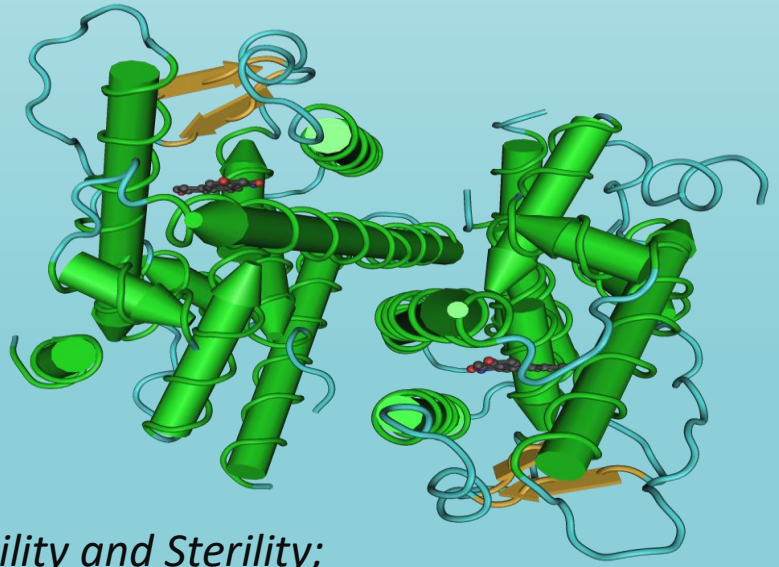
- Not detected before puberty & regresses after menopause.
- May increase during pregnancy
- Estrogen receptors are in higher concentrations
- Common in fifth decade due to anovulatory cycles with high or unopposed estrogen.

PROGESTERONE & ESTROGEN RECEPTORS [ER & PR]

- Progesterone and Estrogen are key growth factors
- Myoma cells express functional progesterone and estrogen receptors
- ER binding was 2X and PR binding was 3X higher in myomas compared to that of the normal myometrium

PR





ER

Fernimdez-Montoli et al. *GnRH-a and fibroid steroid receptors - Fertility and Sterility;*

PROGESTERONE PLAYS A VITAL ROLE IN PROMOTING UTERINE MYOMA GROWTH.

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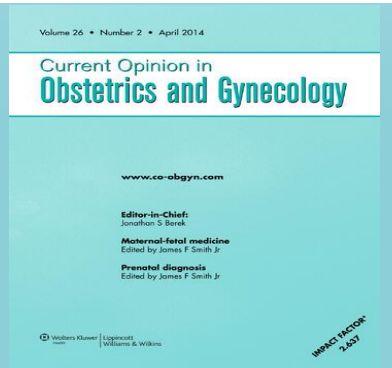
Volume 21, Issue 9
Sep 2006

Article Contents

Progesterone receptor modulator CDB-2914 down-regulates vascular endothelial growth factor, adrenomedullin and their receptors and modulates progesterone receptor content in cultured human uterine leiomyoma cells FREE

Qin Xu, Noriyuki Ohara, Wei Chen, Jin Liu, Hiroko Sasaki, Akira Morikawa, Regine Sitruk-Ware, Elof D.B. Johansson, Takeshi Maruo

Human Reproduction, Volume 21, Issue 9, 1 September 2006, Pages 2408–2416,



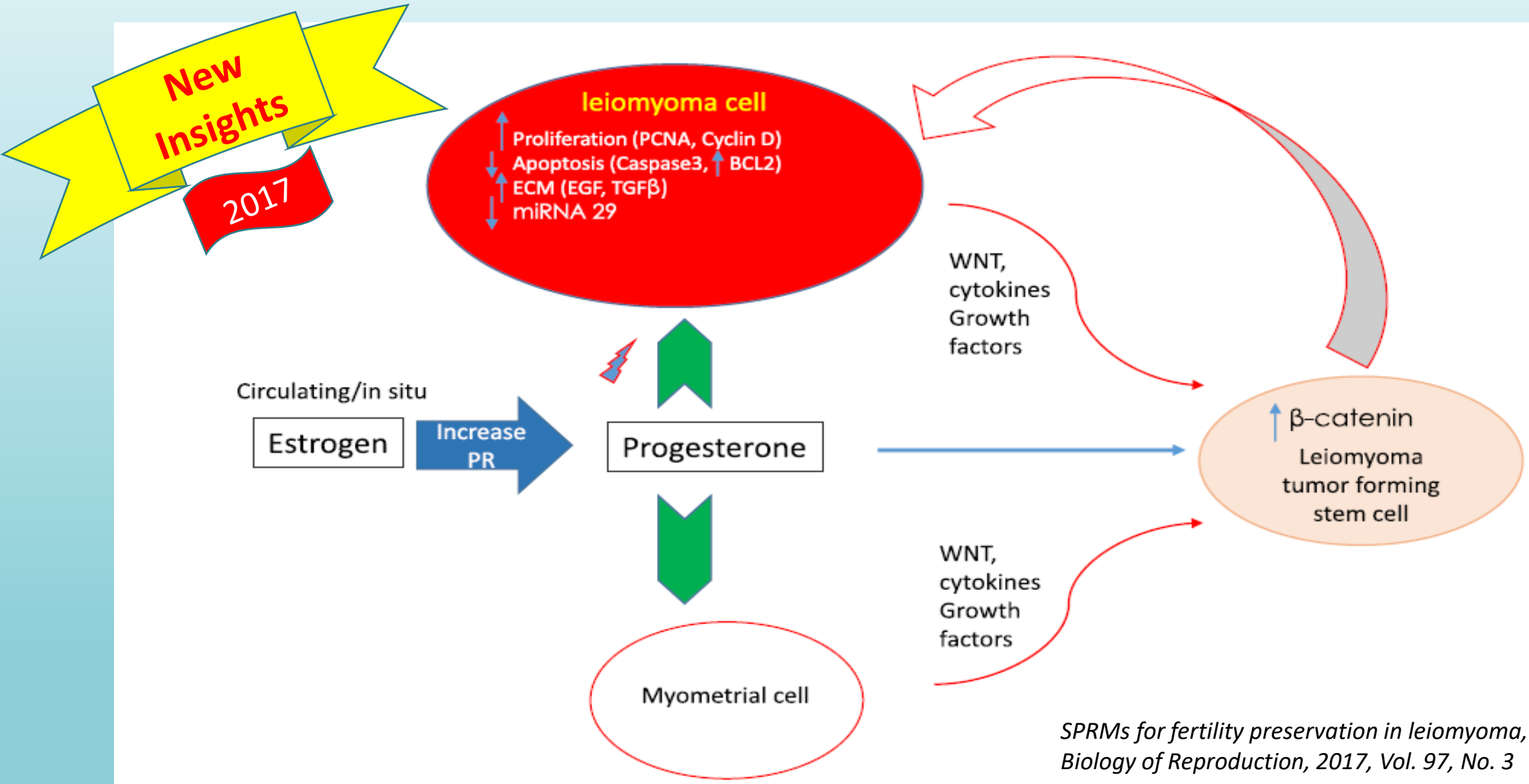
PROGESTERONE LINK WITH MYOMA GROWTH

Progesterone has *dual action on myoma growth*

1. Stimulates growth by up-regulation of Epidermal Growth Factor (EGF) & B-cell Lymphoma 2, a key protein in the inhibition of apoptosis

2. Down regulates tumour necrosis factor- alpha (TNF) expression

PROGESTERONE AND UTERINE MYOMAS



SPRMs for fertility preservation in leiomyoma, Biology of Reproduction, 2017, Vol. 97, No. 3

New Insights 2018

EXTRACELLULAR MATRIX IN UTERINE LEIOMYOMA PATHOGENESIS

Hum Reprod Update. 2018 Jan 1;24(1):59-85. doi: 10.1093/humupd/dmx032.

Extracellular matrix in uterine leiomyoma pathogenesis: target for future therapeutics.

Islam MS[1,2], Ciavattini A[3], Petraglia F[4], Castellucci M[1], Ciarmela P[1,5].

Extracellular matrix (ECM) accumulation and remodeling are thought to be crucial for fibrotic diseases such as uterine leiomyoma

ECM accumulation is affected by growth factors (TGF-β, activin-A and PDGF, cytokines (TNF-α), steroid hormones (estrogen and progesterone) and microRNAs (miR-29 family, miR-200c and miR-93/106b)

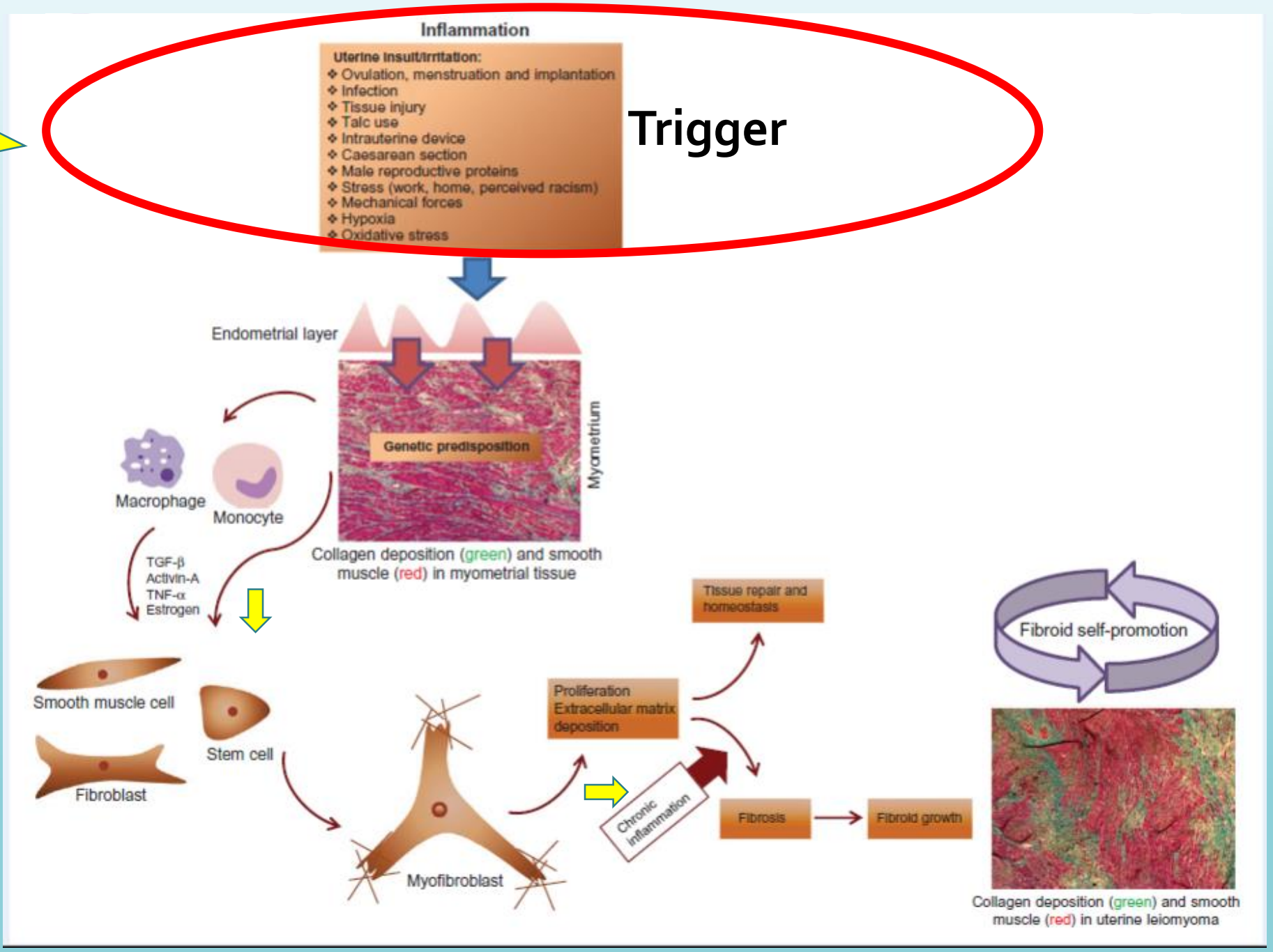
Among these, TGF-βs (1 and 3) and activin-A have been suggested as key players in the accumulation of excessive ECM (fibrosis) in leiomyoma.

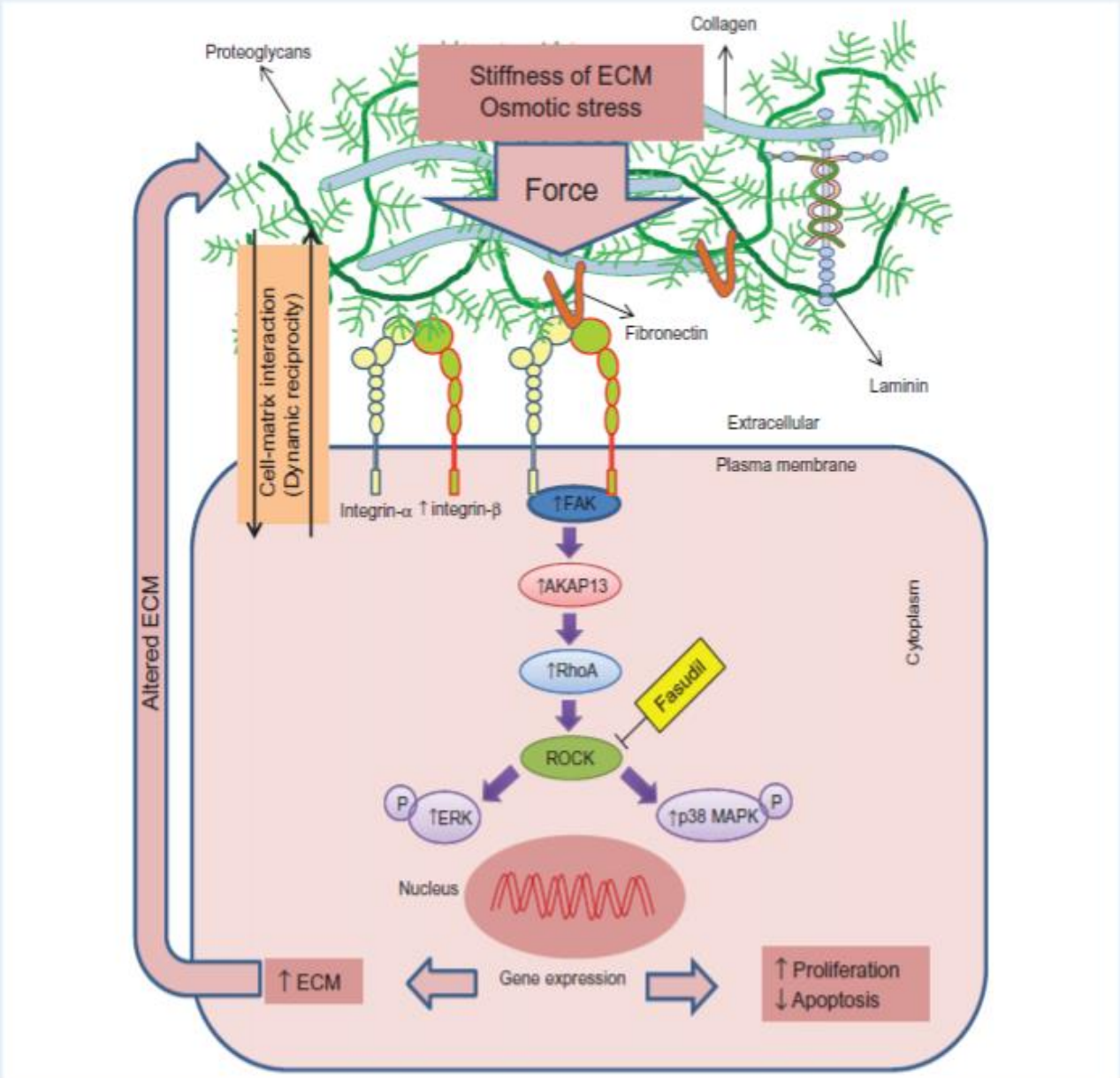
New Insights

2018

Fibroblast activation and differentiation into myofibroblasts.
Myofibroblasts produce ECM components to restore homeostasis and then should be eliminated by apoptosis.

Myofibroblasts become resistant to elimination by apoptosis and produce excessive amounts of ECM components, leading to fibrotic transformation. Once established, fibroids can promote their own growth.





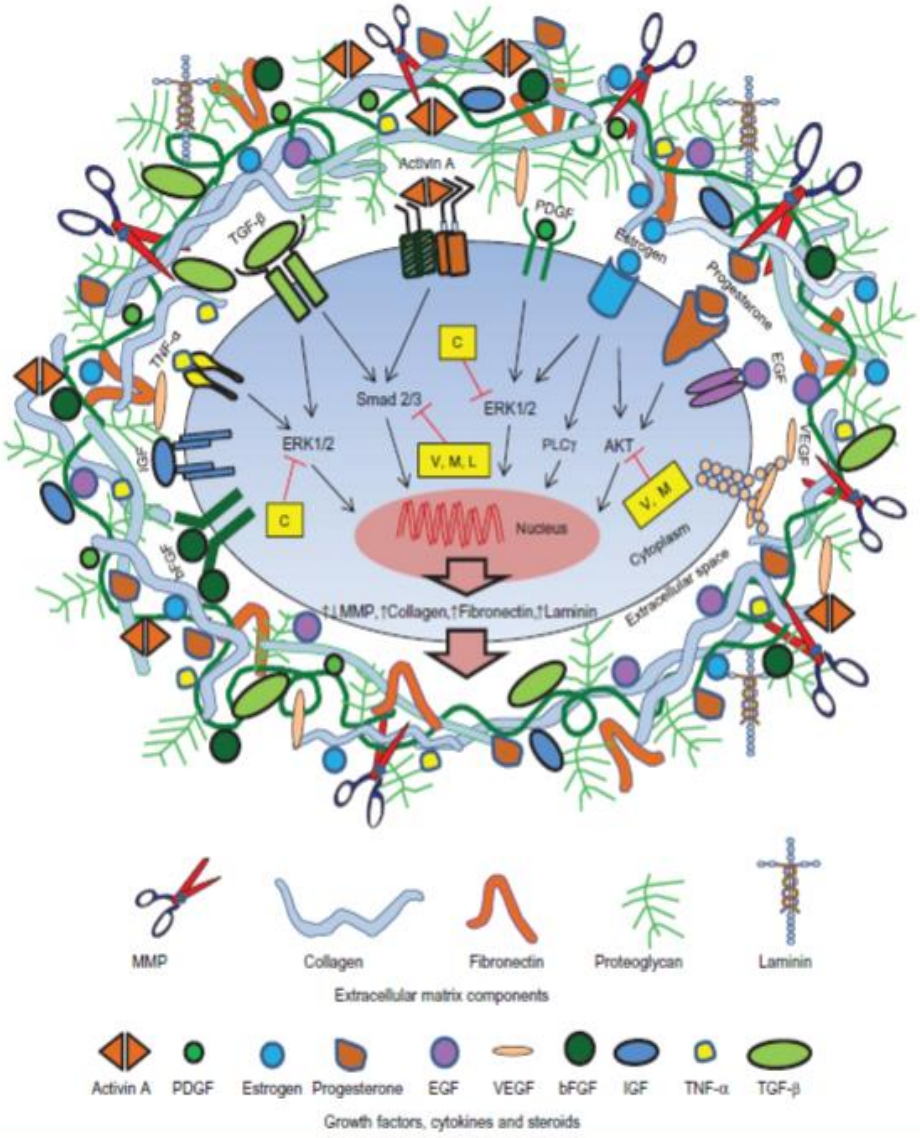


Figure 3 Regulation of extracellular matrix by growth factors, cytokines and steroid hormones in uterine leiomyoma. Extracellular matrix may act as both a reservoir of growth factors and a modulator of their actions. Compounds that can interrupt the signaling pathways are also listed (yellow squares). C, Curcumin; V, Vitamin D3; M, 2-Methoxyestradiol; L, Leuprolide acetate.

CLINICAL PRESENTATION OF UTERINE LEIOMYOMAS

i. Asymptomatic

ii. Abnormal uterine bleeding
- a. Menorrhagia
- b. Anemia

iii. Pelvic pressure
- a. Urinary frequency
- b. Urinary incontinence
- c. Difficulty with urination
- d. Hydronephrosis
- e. Constipation
- f. Tenesmus

iv. Pelvic mass

v. Pelvic pain

vi. Infertility*

vii. Obstetric complications

viii. Pregnancy related
- a. Myoma growth
- b. Red degeneration and pain
- c. Spontaneous miscarriage

Xi. Malignancy

x. Rare associations
- a. Ascites
- b. Polycythemia
- c. Familial syndromes, renal cell carcinoma

xi. Benign metastasizing

Adapted from Sabry and Al-Hendy. Innovative oral treatments of uterine leiomyoma. Obstet Gynecol Int. 2012;2012:943635.27

MYOMAS AND INFERTILITY

1. Displacement of the cervix that may reduce exposure to sperm
2. Enlargement or deformity of the uterine cavity that may interfere with sperm migration and transport
3. Obstruction of the proximal fallopian tubes
4. Altered tubo-ovarian anatomy, interfering with ovum capture
5. Increased or disordered uterine contractility that may hinder sperm or embryo transport or nidation
6. Distortion or disruption of the endometrium and implantation due to atrophy or venous ectasia over or opposite a submucous myoma
7. Impaired endometrial blood flow
8. Endometrial inflammation or secretion of vasoactive substances

MYOMAS AND IMPACT ON REPRODUCTION

Table 5: Summary of the main detrimental effects of myomas and myomectomy

Myomas	Myomectomy
Infertility	Surgical complications
Importance of location, dimension and number	Adhesion formation
Pregnancy complications	Uterine rupture during labour or pregnancy
Miscarriage	
Pelvic pain	
Placental abruption	
Placenta previa	
IUGR	
Malpresentation	

IUGR, intra-uterine growth restriction.

OUTCOME OF MYOMECTOMY

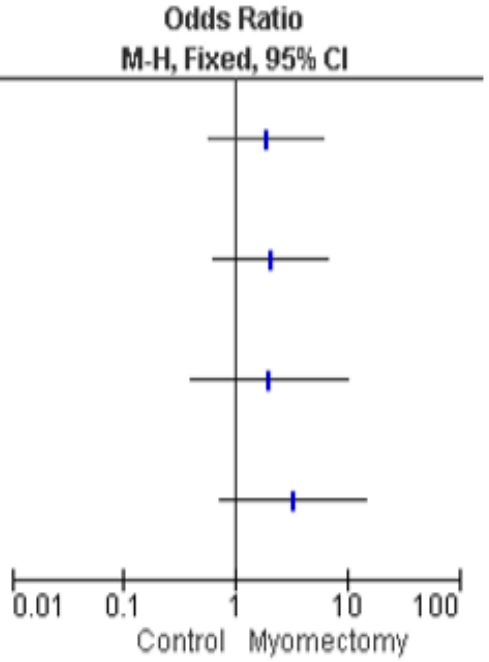
Surgical treatment of fibroids for subfertility (Review)

Metwally M, Cheong YC, Horne AW

THE COCHRANE COLLABORATION®

Figure 3. Forest plot of comparison: 1 Myomectomy versus control, outcome: 1.2 Clinical pregnancy rate.

Study or Subgroup	Myomectomy Events	Myomectomy Total	Control Events	Control Total	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Intramural					
Casini 2006	13	23	9	22	1.88 [0.57, 6.14]
1.2.2 Submucous					
Casini 2006	13	30	6	22	2.04 [0.62, 6.66]
1.2.3 Intramural/Subserous					
Casini 2006	6	17	3	14	2.00 [0.40, 10.09]
1.2.4 Intramural/Submucous					
Casini 2006	8	22	3	20	3.24 [0.72, 14.57]



OUTCOME OF MYOMECTOMY

Cochrane

Trusted evidence.
Informed decisions.
Better health.

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Surgical removal of fibroids does not improve fertility outcomes

Published:
14 November 2012

Authors:
Metwally M, Cheong YC, Horne AW

Primary Review Group:
Gynaecology and Fertility Group

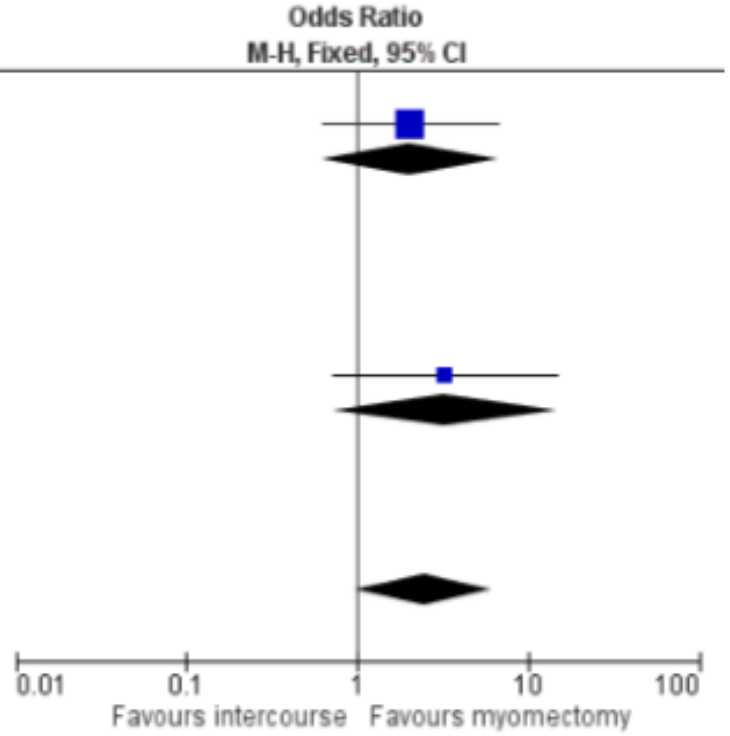
See the full Review on **the Cochrane Library**

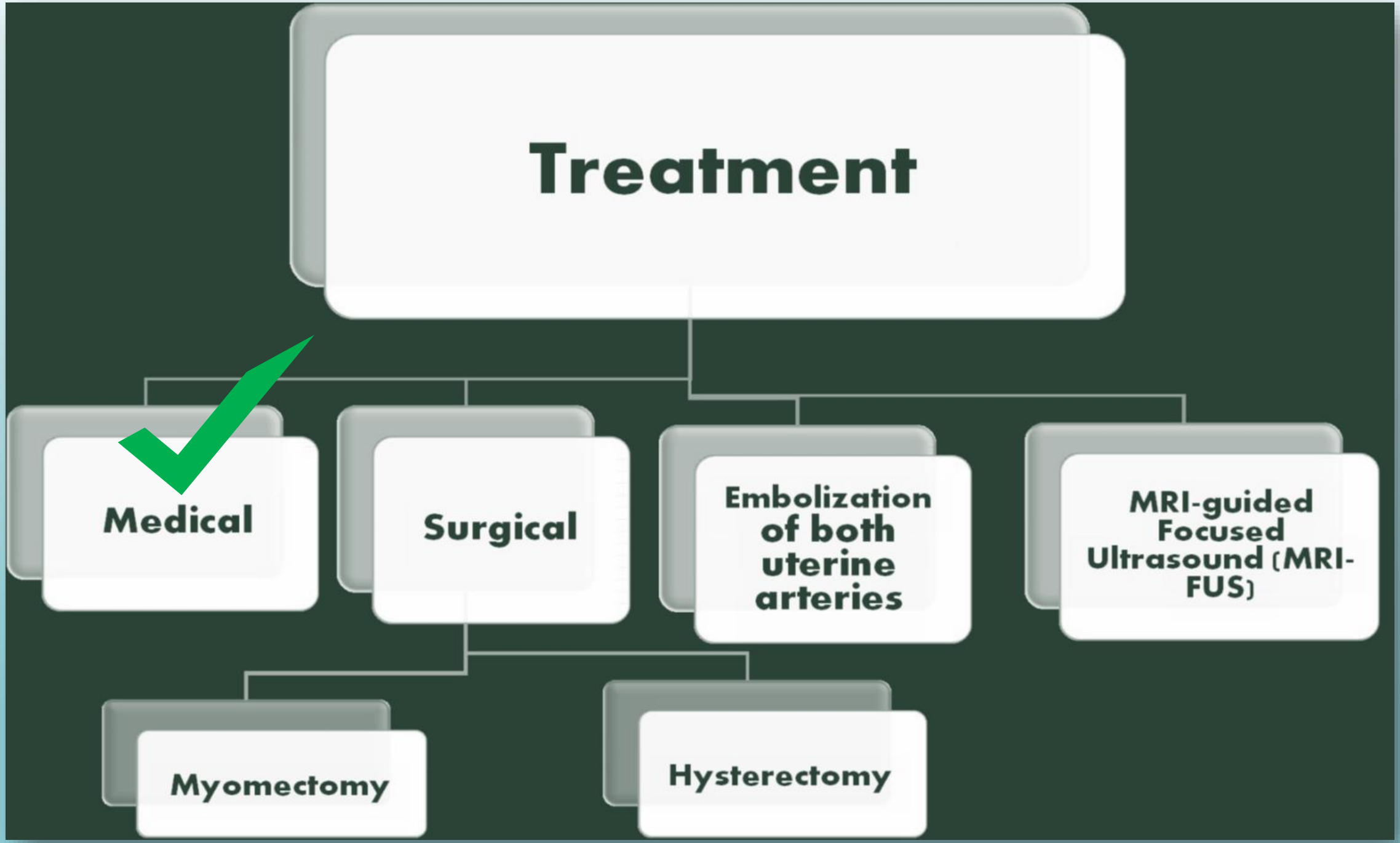
Fibroids are the most common benign tumours of the female genital tract and commonly affect women of reproductive age. Fibroids occur in different parts of the womb and can vary in size and shape. Fibroids can lead to a variety of symptoms including heavy periods, pain, difficulty to conceive, or problems with pregnancy such as miscarriage and premature labour. In women wishing to preserve their fertility, it is possible to remove the fibroid while preserving the womb, an operation known as myomectomy. This procedure can be performed by open surgery, laparoscopic surgery (a key-hole through the abdomen) or hysteroscopic surgery (a key-hole through the neck of the womb) depending on the site and size of the fibroid. This review included three studies with 474 participants and aimed to answer two questions. Firstly, whether myomectomy led to an improvement in fertility; and secondly, if the procedure is beneficial, what is the ideal surgical approach. Only one study was found that examined the effect of myomectomy on fertility and it found no significant benefit. However, there are some concerns regarding how the data were analysed and therefore

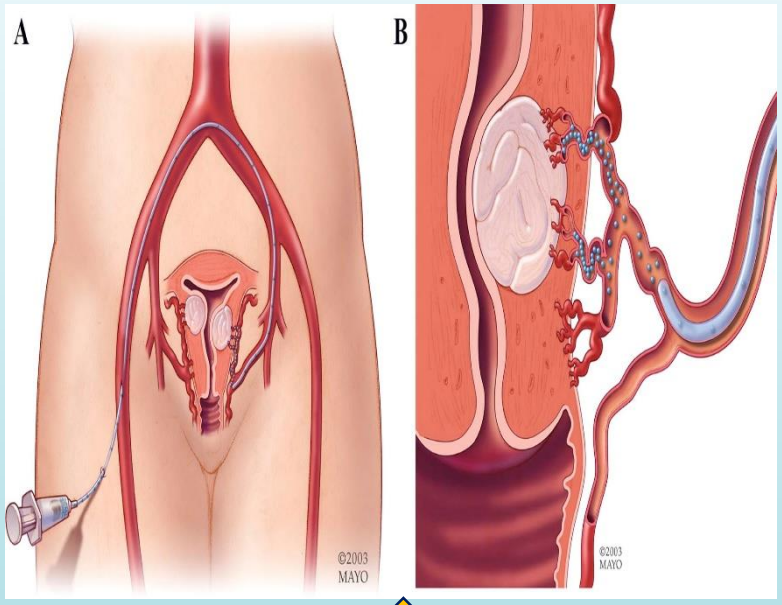
OUTCOME OF MYOMECTOMY

Figure 4. Forest plot of comparison: 1 Hysteroscopic myomectomy vs regular fertility-oriented intercourse in women with unexplained subfertility and submucous fibroids.Outcome: 1.1 Clinical pregnancy per woman randomised.

Study or Subgroup	Operative hysteroscopy Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Removal of submucous fibroids only vs regular fertility-oriented intercourse						
Casini 2006	13	30	6	22	66.2%	2.04 [0.62, 6.66]
Subtotal (95% CI)		**30**		**22**	**66.2%**	**2.04 [0.62, 6.66]**
Total events	13		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.18 (P = 0.24)						
1.1.2 Removal of mixed submucous-intramural fibroids vs regular fertility-oriented intercourse						
Casini 2006	8	22	3	20	33.8%	3.24 [0.72, 14.57]
Subtotal (95% CI)		**22**		**20**	**33.8%**	**3.24 [0.72, 14.57]**
Total events	8		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.53 (P = 0.13)						
Total (95% CI)		**52**		**42**	**100.0%**	**2.44 [0.97, 6.17]**
Total events	21		9			
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 1.89 (P = 0.06)						
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%						

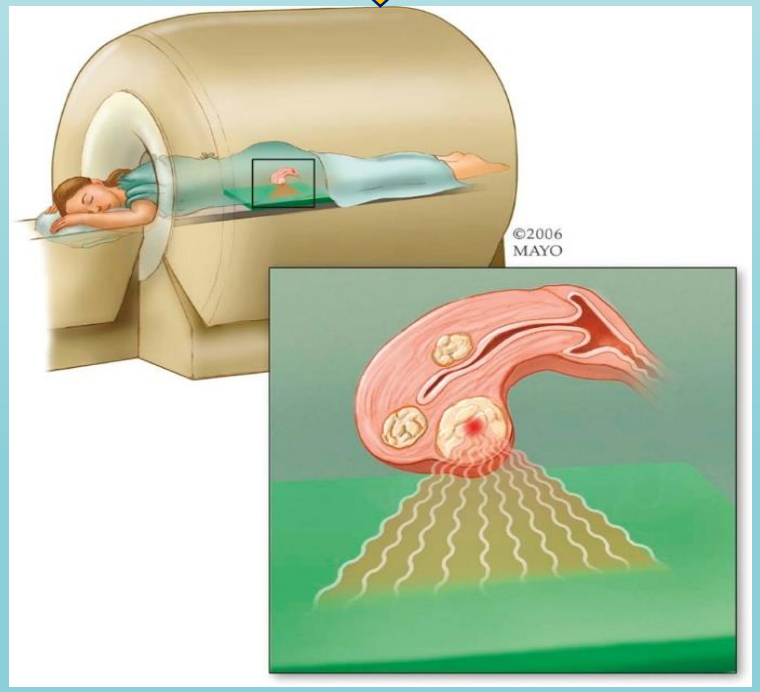


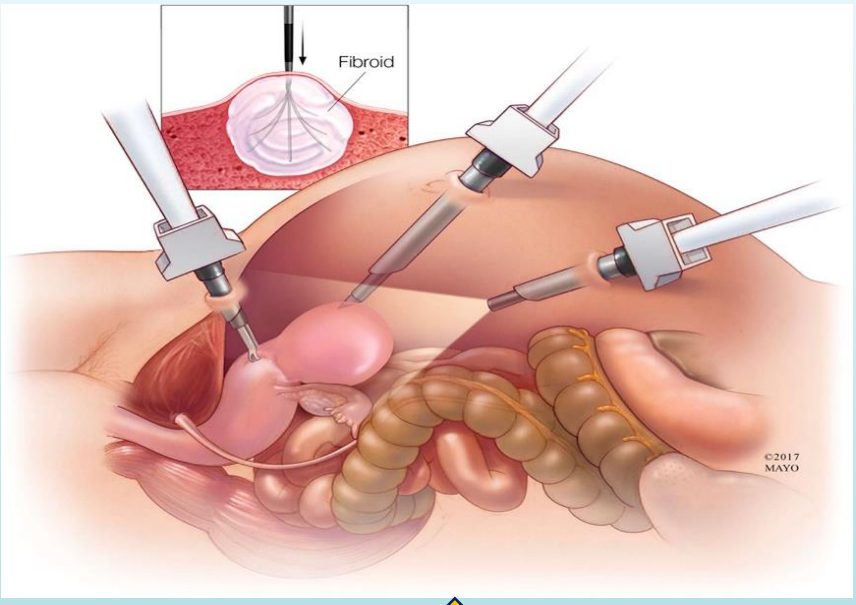

Treatment
Medical
Surgical
Embolization of both uterine arteries
MRI-guided Focused Ultrasound (MRI-FUS)
Myomectomy
Hysterectomy



- Comparable with hysterectomy in quality of life improvement
- Reduced Ovarian function, Re intervention rates , pregnancy rates -14-69%

MRgFUS- Symptomatic improvement-80%,
Re intervention 23%- 4yrs





RFVTA- 96% improvement, 11%-
Re intervention-3 years

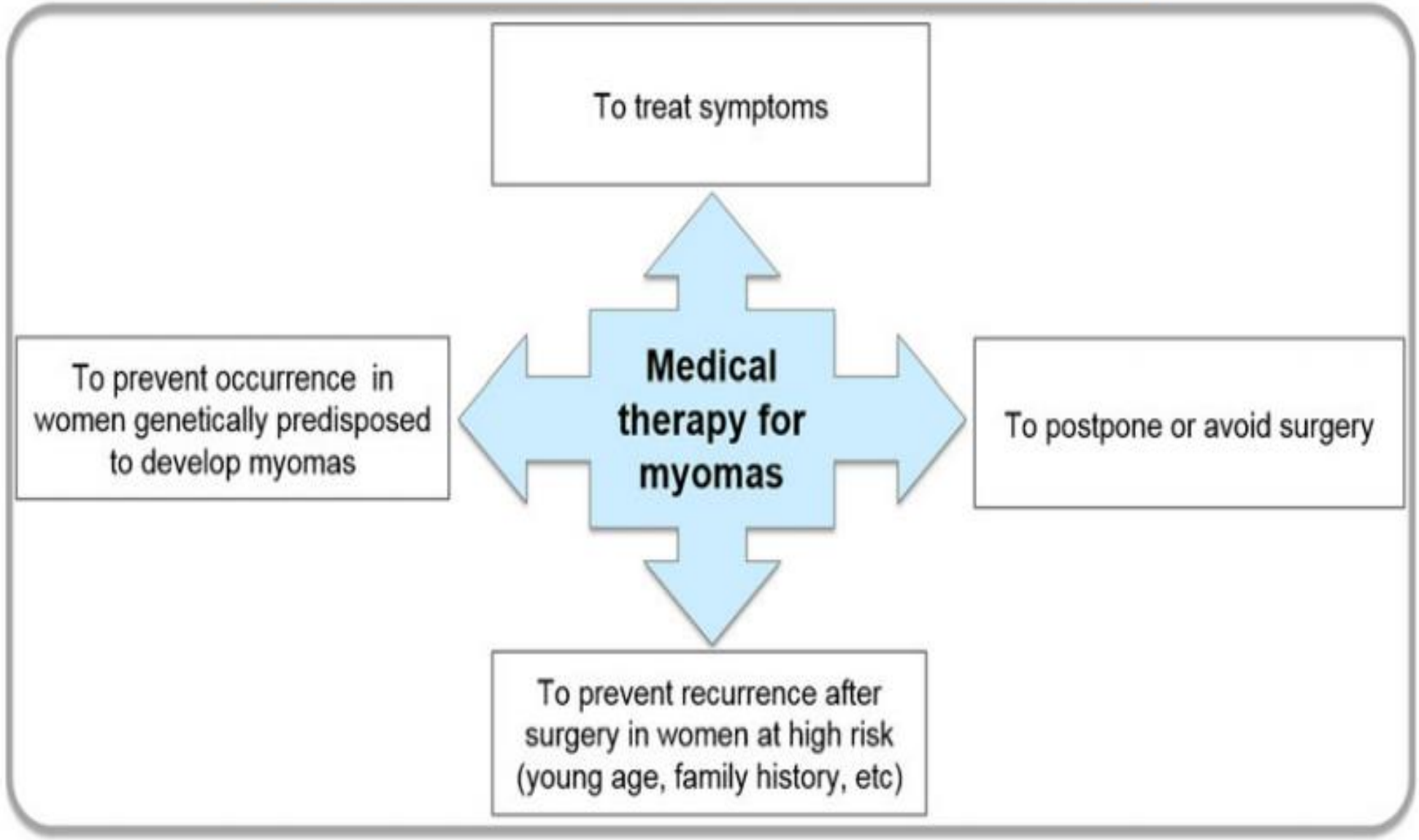
CASE FOR MEDICAL TREATMENT

- Choice of medicines
- Symptomatic control while minimizing risks and complications

Therapeutic drugs may offer alternative options for many UF patients:

- young UF patients who want to preserve their fertility
- perimenopausal age group
- who desire more conservative management approach
- who want to avoid repeat surgeries
- who are unfit for surgery

New perspectives: medical therapy for myomas



PHARMACOLOGICAL TREATMENT

I. **Gonadotropin-releasing hormone (GnRH) agonists** - bridging or presurgical treatment; creates artificial menopausal state, resulting in reversible reduction of uterine and fibroid volume and aiding in the correction of anemia.

However, GnRH agonists frequently cause side effects, and the use of these drugs is approved only for short-term therapy because of safety concerns

II. **Progestins** are often associated with breakthrough bleeding that limit their use and they may promote proliferation of fibroids.

III. **Levonorgestrel-releasing intrauterine system (LNG-IUS)** - patients who do not have large uteri distorted by myomas - irregular bleeding is frequent, expulsion of the device is more common than in women without fibroids, and the effect on fibroid volume is variable.

PHARMACOLOGICAL TREATMENT

IV. **Combined oral contraceptive Pills (COCs)** have limited efficacy as well as lack of ability to reduce tumor size.

V. **GnRH antagonists** as cetrorelix and ganirelix have been used, not proven efficacy. High cost, requirement of daily administration, and lack of clinical trial-based evidence of their superiority over the agonist

VI. **Selective estrogen receptor modulators (SERM)**: Only preclinical data appeared to be promising (tamoxifen or raloxifene) - clinical trial results were unsatisfactory

VII. **Selective Progesterone receptor modulators (SPRM):**

COMBINED ORAL CONTRACEPTIVE PILLS (COCS)

- As uterine fibroid growth is stimulated by both estrogens and progestins, COCs were considered as a risk factor for fibroid growth in the past
- However, a recent meta-analysis suggests that uterine fibroids should not be considered a contraindication for COC use
- In the short-term, COCs can be used to improve heavy menstrual bleeding associated with fibroids
- Primary action through their suppressive effects on endometrial proliferation
- No effect on decreasing uterine fibroid volume or uterine size
- Close monitoring of uterine myoma and uterine size is recommended
- Trials with COCs may still be effective in some women with uterine fibroids due to their advantages of easy accessibility, oral administration, and low cost although no proven efficacy

Current medical treatment of uterine fibroids, Obstet Gynecol Sci. 2018 Mar; 61(2): 192–201.

PROGESTINS

- Same as COCS – concerns of increase in size of myoma/uterus as well as lack of proven efficacy – but short term use has shown benefits.
- Depot medroxyprogesterone acetate (DMPA) with 6 months use in myoma induced menorrhagia showed:
  - 30% patients were amenorrheic, 70% had an improved bleeding pattern, and 15% had an increase in hematocrit
  - Uterine and fibroid volumes were decreased by 48% and 33%, respectively
- Oral progestogens:
  - Lynestrenol, an oral progestogen, compared with leuprolide, a GnRH agonist, and demonstrated no significant difference between the treatments in improving pelvic pain and uterine bleeding
  - Dienogest, an oral progestogen, compared with leuprolide, showed significant decrease in tumor volume with both treatments (50% and 60%, respectively)
- Although progestogens may be effective in some cases, we should be cautious of associated histopathological changes that mimick leiomyosarcoma or smooth-muscle tumors of unknown malignant potential, such as an increase in cellularity and mitotic activity

Current medical treatment of uterine fibroids, Obstet Gynecol Sci. 2018 Mar; 61(2): 192–201.

LNG-IUS

- Significant decrease in menstrual blood loss and uterine volume, while hematocrit increased.
- No change in fibroid volume, as measured by MRI
- LNG-IUS is effective for up to 5 years, thus potentially long-term treatment option and no additional patient's compliance needed
- Risk of expulsion in cases of endometrial distortion or very large uteri

Current medical treatment of uterine fibroids, Obstet Gynecol Sci. 2018 Mar; 61(2): 192–201.

GnRH AGONISTS

- GnRH agonists (synthetic peptides) are more potent and have a longer half-life than native GnRH
- When administered, they increase follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion initially, known as the flare effect, followed by receptor down-regulation and 1–3 weeks later by a hypogonadotropic hypogonadal state - “pseudomenopause”
- This hypoestrogenic state contributes to the pharmacologic efficacy of GnRH agonists, as leiomyoma growth is stimulated by estrogen. Several studies have shown that tumor shrinkage is proportional to the number of estrogen receptor (ER)-positive cells
- Cochrane Systematic Review, a systematic review of 26 randomized controlled trials to determine the efficacy of GnRH agonists prior to hysterectomy or myomectomy:
  - Improvement in both pre- and postoperative hemoglobin levels
  - Significant reductions in uterine volume, fibroid volume, and duration of hospital stay were noted.
  - Blood loss and rate of vertical incisions were also reduced for both myomectomy and hysterectomy
  - Laparoscopic Myomectomy - reduces operative time, intraoperative bleeding, and the risk of blood transfusion
  - Hysteroscopic resection of submucosal myomas - decreased operative times, fluid absorption, and the difficulty of the hysteroscopic procedure.

Current medical treatment of uterine fibroids, Obstet Gynecol Sci. 2018 Mar; 61(2): 192–201.

GnRH AGONISTS

- Menopausal symptoms, such as hot flashes and atrophic vaginitis, and a decrease in bone mineral density (BMD) after long-term use – so only short-term adjuvant therapy in most patients
- Long-term GnRH agonist therapy necessitates the use of hormonal add-back therapy to offset some of the hypoestrogenic symptoms and preserve BMD
- GnRH agonists induce histological changes that complicate surgical intervention - Leuprolide acetate preoperatively results in myoma degeneration and obliteration of the interface between the myoma and myometrium – difficult enucleation

Current medical treatment of uterine fibroids, Obstet Gynecol Sci. 2018 Mar; 61(2): 192–201.

GnRH ANTAGONISTS

- GnRH antagonists act immediately to suppress the secretion of FSH and LH by blocking pituitary GnRH receptors – leads to reduction in estradiol levels and improvement in bleeding patterns and reduction in uterine fibroid size
- Effect as early as 3 weeks after initiation of treatment and patients experience faster symptom relief
- Cetrorelix acetate, a GnRH antagonist, for 4 weeks prior to surgical treatment resulted in a significant reduction in tumor volume and uterine volume compared
- Ganirelix, another GnRH antagonist, decreased tumor and uterine volume within 19 days
- Further research into dosing and adverse effects is needed.

Current medical treatment of uterine fibroids, Obstet Gynecol Sci. 2018 Mar; 61(2): 192–201.

GnRH ANTAGONISTS

- **Elagolix (NBI-56,418), a short acting second-generation non-peptide GnRH antagonist, advantage of an oral dosing**
  - **Primarily researched in endometriosis as opposed to uterine leiomyomas**
  - **Elagolix has shown promise as it successfully suppresses LH and FSH in a dose-dependent manner with a better side-effect profile than the other agents in this category**
  - **Proof-of-concept study was conducted in 2017:**
    - **Efficacy of Elagolix for UFs and heavy menstrual bleeding**
    - **Oral 300 mg BID regimen of Elagolix showed a 36% mean reduction in leiomyoma and uterine volume when compared to a placebo that had a 7% mean increase**
- **Relugolix (TAK-385) is a highly selective orally active GnRH antagonist.**
  - **Investigational drug that completed a small phase III trial for the treatment of pain symptoms associated with Ufs**
- **OBE2109, another oral agent, is currently undergoing clinical trials for heavy menstrual bleeding associated with UFs.**

Donnez et al; Emerging treatment options for uterine fibroids. Expert Opinion on Emerging Drugs; 2018
Ali et al; Successes and failures of uterine leiomyoma drug discovery. Expert Opinion on Drug Discovery; 2018

Current medical treatment of uterine fibroids, Obstet Gynecol Sci. 2018 Mar; 61(2): 192–201.

AROMATASE INHIBITORS

- Mechanism is not completely understood – clinically relevant local aromatase activity in uterine fibroid
- AIs block the extragonadal conversion of androgens into estrogens - standard adjuvant therapy for postmenopausal women with ER-positive breast cancer as they cause in situ estrogen inhibition. These properties useful for the medical treatment of uterine fibroids
- AIs are as effective as GnRH analogues in shrinking fibroid volume, despite stable levels of circulating estrogen. These observations suggest that the inhibition of aromatase in fibroid tissue is a key mechanism in hormone-dependent fibroid growth
- Letrozole (2.5 mg daily) and Anastrozole (1 mg daily) studied for the treatment of symptomatic uterine fibroids
  - Observational studies have shown a reduction in fibroid size and improvement of symptoms
  - One randomized trial has compared letrozole and the GnRH agonist triptorelin for 12 weeks of treatment in premenopausal women with symptomatic uterine fibroids
  - Cochrane review of one eligible study concluded that the evidence was still insufficient

SPRMs for fertility preservation in leiomyoma, Biol of Reprod. 2017, Vol. 97, No. 3
Current medical treatment of uterine fibroids, Obstet Gynecol Sci. 2018 Mar; 61(2)

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS)

- Estrogen stimulates the growth of uterine fibroids through ER-α. The primary roles of estrogen and ER-α in myoma growth are permissive, in that they enable tissue to respond to progesterone by inducing the expression of PR
- Selective estrogen receptor modulators (SERMs) (nonsteroidal ER ligands) have tissue-specific ER agonist and/or antagonist estrogenic actions via tissue-specific alterations in gene expression. These medications were originally used for the treatment of ER-positive breast cancer. Two of the most commonly studied SERMs in the treatment of uterine fibroids include tamoxifen and raloxifen
- Tamoxifen has an agonist action on endometrial ERs and carries the risk of leading to endometrial pathology.
  - RCT - tamoxifen 20 mg daily vs. placebo in women with symptomatic uterine fibroids treated for a 6-month duration showed a significant improvement in menstrual blood loss but no improvement in fibroid size or uterine volume
  - Many side effects, including hot flush, dizziness, and benign endometrial thickening reported
  - Negative side effects outweigh the marginal benefits and it is not recommended for the treatment of symptomatic uterine fibroids
- Raloxifene has no agonist effect on the endometrium and only subtle antiestrogenic effects on mammary tissue.
  - A Cochrane review that on the use of raloxifene in the treatment of symptomatic uterine fibroids.- effect of raloxifene on fibroid size and bleeding patterns is unclear; thus, larger controlled trials are needed before this agent can be recommended

SPRMs for fertility preservation in leiomyoma, Biol of Reprod. 2017, Vol. 97, No. 3
Current medical treatment of uterine fibroids, Obstet Gynecol Sci. 2018 Mar; 61(2)

SELECTIVE PROGESTERONE RECEPTOR MODULATORS (SPRM)

- Progesterone stimulates proliferative activity in uterine fibroid cells, but not in normal myometrial cells
- Compared with the normal female myometrium, uterine fibroids overexpress ERs and progesterone receptors (PRs), and there is complex cross-talk between the ER and PR signaling pathways
- It has been shown that uterine fibroids grow primarily during the secretory phase of the menstrual cycle
- Progesterone increases mitotic activity and cellularity resulting in stimulation of cell proliferation, the accumulation of extracellular matrix, and cellular hypertrophy
- Progesterone is therefore essential for fibroid growth, and these observations have stimulated research for the development of progesterone antagonist and/or SPRM drugs

SPRMs for fertility preservation in leiomyoma, Biol of Reprod. 2017, Vol. 97, No. 3
Current medical treatment of uterine fibroids, Obstet Gynecol Sci. 2018 Mar; 61(2)

SELECTIVE PROGESTERONE RECEPTOR MODULATORS (SPRM)

- Mifepristone - a synthetic 19-norsteroid SPRM with primarily PR antagonist activity
- Patients treated with mifepristone compared with placebo showed significant reduction in uterine size, resolution of anemia, and improvement in symptoms of menorrhagia
- Cochrane review of 3 randomized controlled trials evaluating mifepristone for the treatment of symptomatic fibroids demonstrated significantly reduced bleeding and improved quality of life in users of mifepristone, but no significant reduction in fibroid volume
- Mifepristone is not recommended on the basis of this systematic review until better-powered randomized controlled trials are conducted

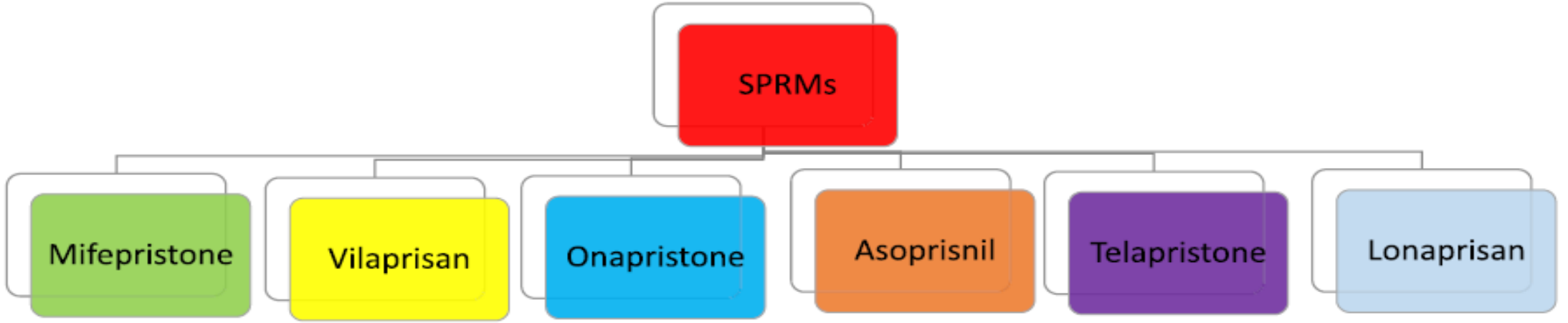
SPRMs for fertility preservation in leiomyoma, Biol of Reprod. 2017, Vol. 97, No. 3
Current medical treatment of uterine fibroids, Obstet Gynecol Sci. 2018 Mar; 61(2)

SELECTIVE PROGESTERONE RECEPTOR MODULATORS (SPRM)

- Selective progesterone receptor modulators (SPRMs) are new class of synthetic steroid ligands with a PR-target and tissue selective effects of mixed agonist and antagonist activities
- SPRMs have tissue-specific effects at PRs, and they can have either a complete PR agonist or antagonist profile or a mixed agonist/antagonist profile, depending on site
- SPRMs are poised to provide additional options in the management of myomas and may provide a viable alternative to surgery in women seeking fertility preservation **(medical myomectomy)**

SPRMs for fertility preservation in leiomyoma, 2017, Vol. 97, No. 3

COMPARISON OF SPRM



- First SPRM with antagonistic effect
- Current use: pregnancy termination
- Safety concerns & having no effect on UF size limit its use in UF

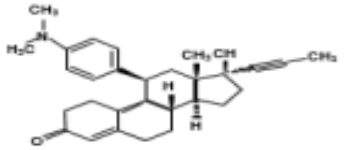
- Novel SPRM
- passed 12 week phase I study of 1 and 5 mg to stop menstrual bleeding
- Further evaluation in UF is currently conducted

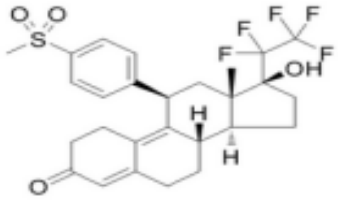
- Has Antagonistic activity
- Investigated for Breast cancer and Endometriosis

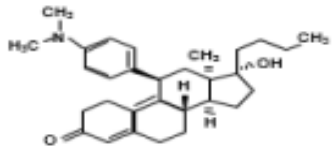
- Investigated for Endometriosis and UF.
- Failed phase 3 clinical trial in 2008 due to changes in the endometrial lining of the uterus

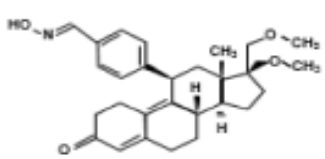
- Known as Proellex
- Investigated for Endometriosis and UF
- Phase III studies suspended due to significant increases in liver enzymes
- Now phase II study for the safety/efficacy of 2,6 mg delivered vaginally for 2,18 weeks.

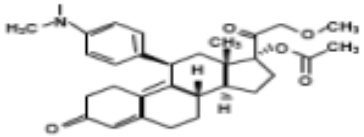
- Investigated for Breast cancer

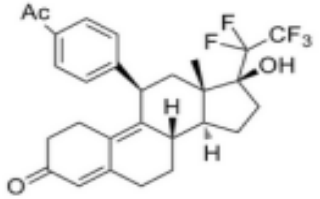

Mifepristone (RU-486)



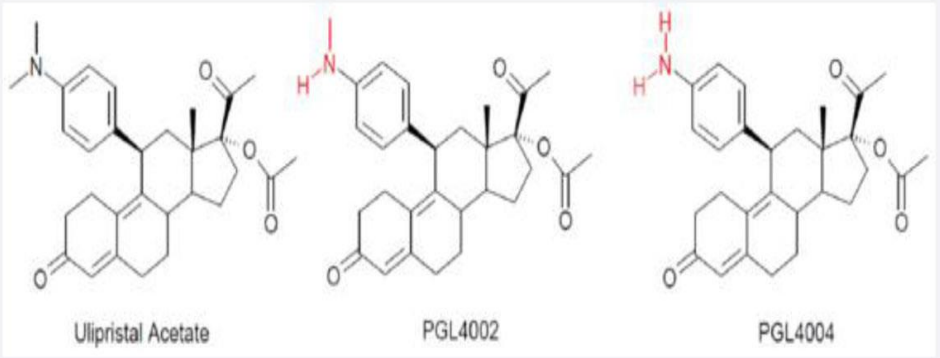

Onapristone (ZK98299)


Asoprisnil (J-867)


Telapriston acetate (CDB-4124)



ULIPRISTAL ACETATE (UPA)

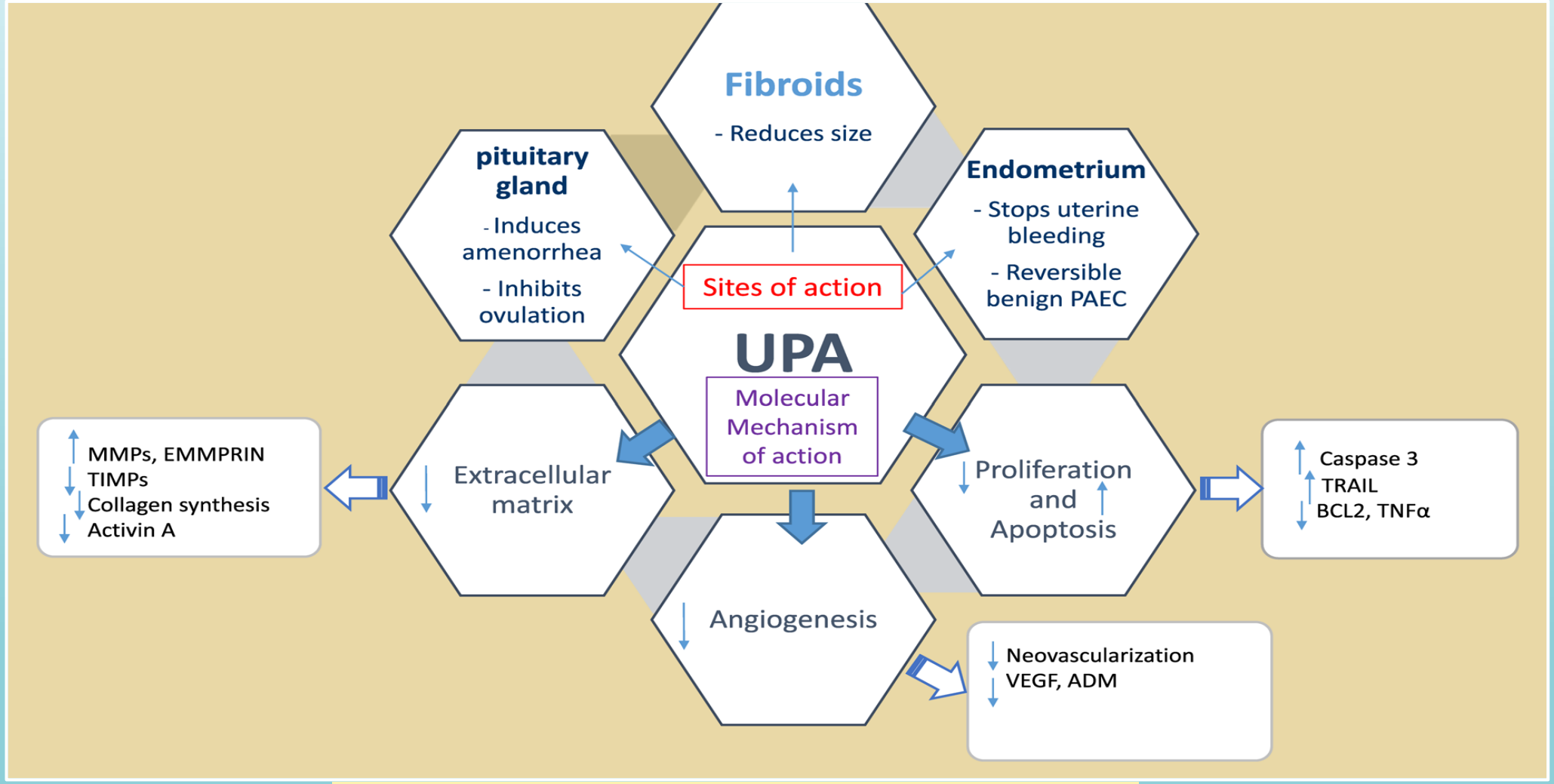


Synthetic steroid derived from 19-norprogesterone, which is a selective PR modulator that binds to PR-A and PR-B with high affinity. UPA is tissue selective, and has tissue-specific mixed agonist/ antagonist effects with preferential binding noted in the uterus, cervix, ovaries, and hypothalamus

UPA is characterized by its superior selectivity for PRs, even higher than P4 itself

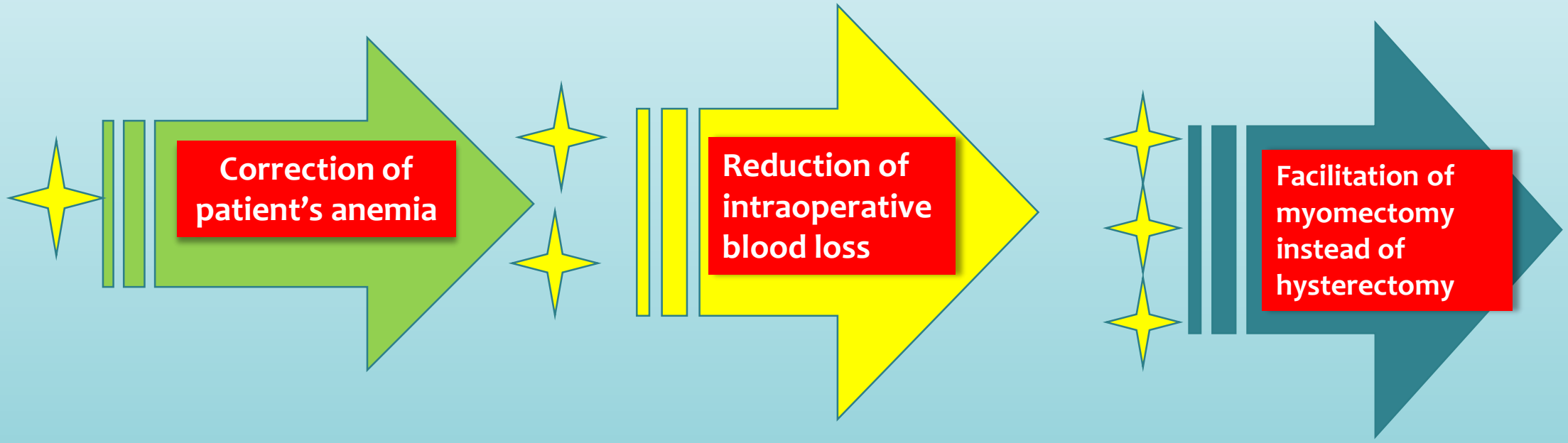
- **it increases apoptosis and decreases proliferation via numerous mechanisms**
- **increase in alkaline phosphatase activity**
- **upregulation of cleaved caspase-3**
- **downregulation of both TNF-α and Bcl-2 expression**

MECHANISM OF ACTION OF ULIPRISTAL ACETATE (UPA)



SPRMs for fertility preservation in leiomyoma, 2017, Vol. 97, No. 3

CLINICAL BENEFITS OF ULIPRISTAL



SPRMs for fertility preservation in leiomyoma, 2017, Vol. 97, No. 3

ULIPRISTAL CLINICAL STUDIES

PEARL I

PEARL II

PEARL III

PEARL IV

PGL4001 (Ulipristal acetate) Efficacy Assessment in Reduction of symptoms due to uterine Leiomyomata

PHASE 3 CLINICAL TRIAL IN EUROPE

	PEARL I	PEARL II	PEARL III	PEARL IV
Study **Phase 3** Clinical Trial	Ulipristal Acetate (UPA) vs Placebo for Fibroid treatment before surgery	UPA vs Leuprolide Acetate for Uterine Fibroids	Long term treatment of uterine fibroids with UPA	Efficacy and safety of repeated use of UPA in uterine fibroids
Conclusion	Treatment with UPA for 13 weeks effectively controlled excessive bleeding due to uterine fibroids and reduced the size of the fibroids	Both the 5-mg and 10-mg daily doses of ulipristal acetate were non inferior to once monthly leuprolide acetate in controlling uterine bleeding and were significantly less likely to cause hot flashes.	Repeated 3-month courses of oral UPA 10 mg once daily effectively control bleeding and pain, reduce fibroid volume, and restore QoL over the long term in many women with symptomatic fibroids, providing an effective and well-tolerated long-term medical treatment for fibroids	Repeated 12-week courses of oral ulipristal acetate (5 and 10 mg/d) effectively and safely control bleeding and pain, reduce fibroid volume, and restore quality of life in patients with symptomatic fibroids

VENUS I TRIAL- FIRST PHASE 3 TRIAL IN US POPULATION

2016

- OBJECTIVE: To assess the efficacy and safety of UPA vs placebo in achieving amenorrhea and improving activity score
    - In this US-based study, UPA was superior to placebo in rate of and time to amenorrhea.
    - UPA also significantly improved patients' activity scores and was well tolerated.

J. Simon et al, FERTILITY & STERILITY, 106 (3) , 2016, e376

2nd PHASE 3 Trial in US

VENUS II Trial

2017

- **OBJECTIVE:** Determine efficacy and safety of UPA vs placebo (PBO) for treatment of symptomatic UF.

- Consistent with VENUS I and the European studies (PEARL studies), both doses of UPA were superior to placebo in the proportion of women achieving amenorrhea and time to amenorrhea

- Both UPA 10 mg and 5 mg were generally well tolerated

- Numerically greater responses in efficacy were observed with UPA 10 mg vs 5 mg, though the safety profiles were similar

J. Liu et al, FERTILITY & STERILITY, 108, 2017, o-65

A decrease of uterine fibroid & normal morphology of the endometrial cavity was noted.

- **Three months after a daily dose of 5mg UPA, the patient had a clinical pregnancy which was confirmed with transvaginal ultrasound**

- **Spontaneous pregnancy after UPA to reduce fibroid size may support the potential clinical utility of this selective progesterone receptor modulator in the management of women with pregnancy desire and uterine fibroids,**

SPRM's & LIVER INJURY

- Following reports of rare serious liver injury, including liver failure, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) carried out a full evaluation and concluded that UPA may have contributed to the development of some of the reported cases. The PRAC, therefore, recommended measures to minimize liver injury, including contraindication when liver problems are known and liver tests before, during, and after stopping treatment.

EMA's safety committee (PRAC) has recommended women to stop taking 5-mg ulipristal acetate for uterine fibroids while a safety review is ongoing. No new patients should start treatment with the medicines, which will be temporarily suspended throughout the EU during the review

13/03/20

OTHER SPRMS- TRIAL

- Vilaprisan is an investigational selective progesterone receptor modulator(SPRM) and emerging medical treatment
- Study data indicates that treatment with vilaprisan can achieve higher efficacy at a lower dose than ulipristal acetate, perhaps due to optimization of the molecular structure of vilaprisan, which was developed to maximize specificity for the progesterone receptor, while eliminating structural elements that could induce undesirable liver effects.
- Unlike other compounds containing structural motifs known to impact liver function, vilaprisan has a metabolic elimination pathway involving CYP3A, which should result in a favorable hepatic safety profile.

European Journal of Obstetrics & Gynecology and Reproductive Biology

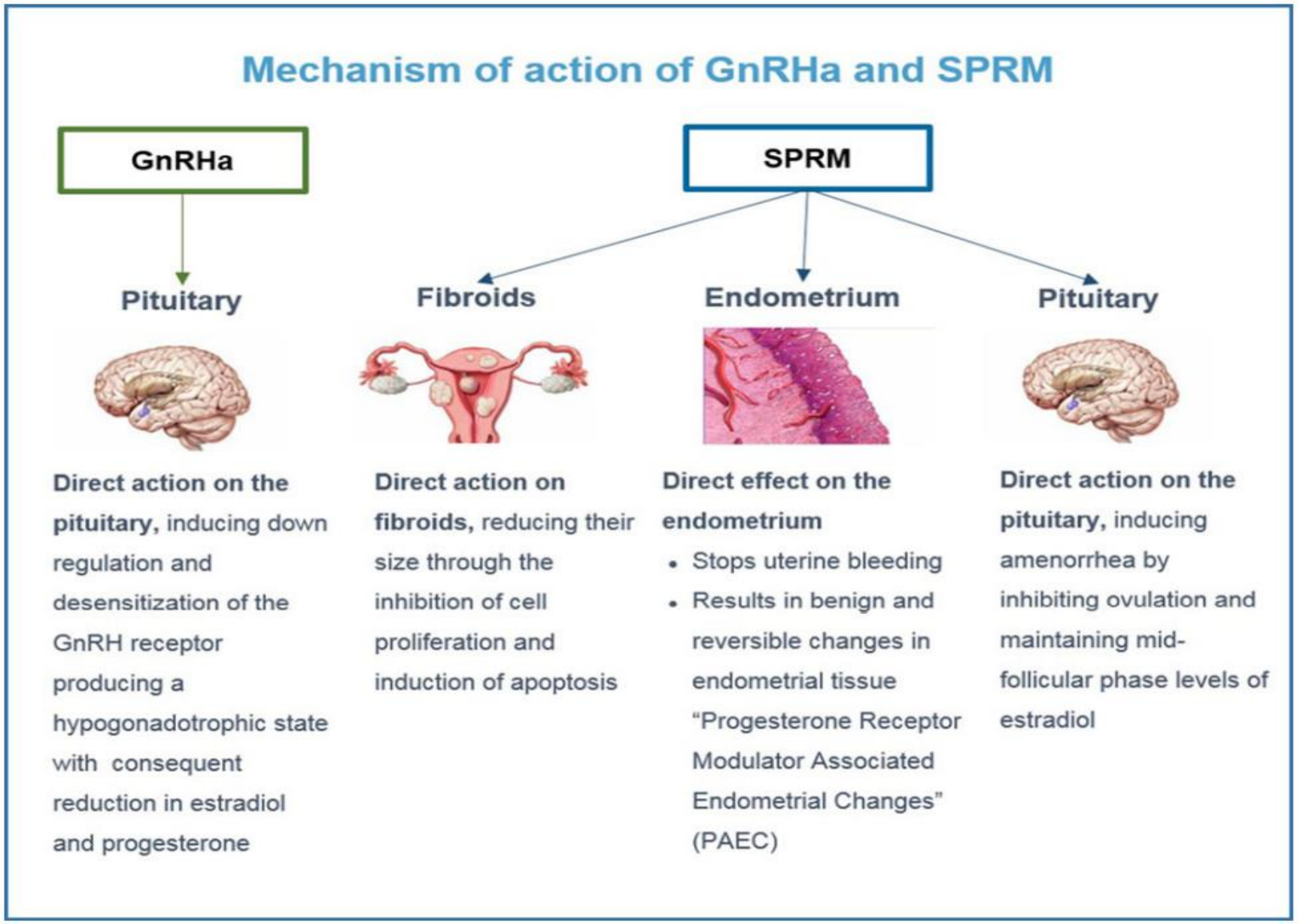


Figure 5 Mode of action of GnRH agonists and SPRMs (Selective Progesterone Receptor Modulators). GnRH agonists have a direct impact on the pituitary. SPRMs have a direct impact on fibroids, endometrium and the pituitary.

SUMMARY OF MEDICAL TREATMENTS USED IN CLINICAL PRACTICE FOR MANAGEMENT OF UTERINE LEIOMYOMAS

Drug class	Action	Benefits	Risks	Side-effects (%)	Authors
COC	Inhibits ovulation; inhibits sex steroid secretion	17% decrease in the risk of leiomyoma growth; decreases bleeding and increases hematocrit	Thromboembolic events; hepatocellular adenoma (rare)	Spotting; mastalgia; headache; gastrointestinal upset	Qin *et al.*; Orsini *et al.*
Progestogens	May inhibit ovulation and sex steroid synthesis; decidualizes endometrium, inducing a "pseudopregnancy" state	Improves bleeding in up to 70%; amenorrhea in up to 30%; may decrease uterine volume in up to 50%	Loss of bone mass (prolonged use of depot MPA)	Irregular bleeding/spotting; ovarian follicular cysts	Venkatachalam *et al.*; Ichigo *et al.*
LNG-IUS	Endometrial atrophy	Reduces bleeding intensity in up to 99%; decreases uterine volume in about 40%	Device expulsion	Ovarian cysts; acne	Kriplani *et al.*; Sayed *et al.*
GnRH-a	Hypoestrogenism due to gonadotrophin secretion inhibition	Uterine volume decrease in up to 50%; high rates of amenorrhea	Loss of bone mass with prolonged use	Hot flashes (>90%); vaginal atrophy; headache; mood disorders	Friedman *et al.*; Tummon *et al.*; Dawood *et al.*
SPRM	Inhibits ovulation; inhibits progesterone action on fibroid tissue	Improves bleeding in up to 98% of patients; decreases fibroid volume in up to 53%	Long term endometrial safety is unknown	Benign endometrial changes after short term use	Donnez *et al.*; Williams *et al.*

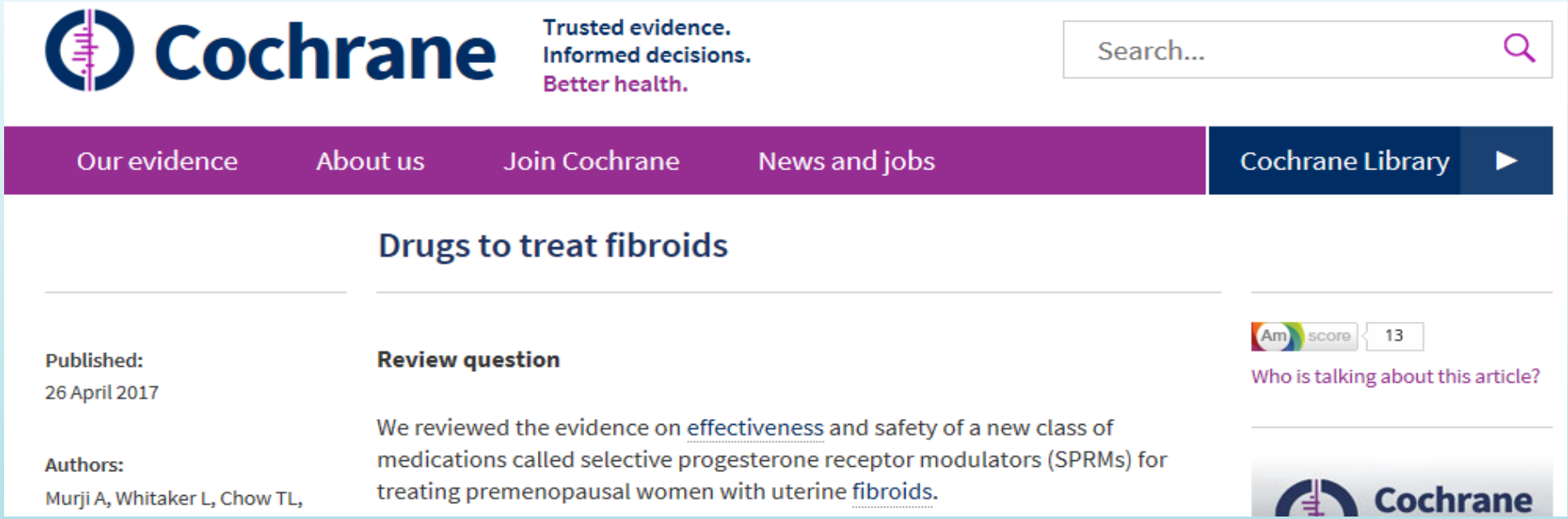
NSAID: Non-steroid anti-inflammatory drugs, LNG-IUS: Levonorgestrel releasing intrauterine system, COC: Combined oral contraceptive, GnRH-a: Gonadotropin-releasing hormone analog, SPRM: Selective progesterone receptor modulators, MPA: Medroxyprogesterone acetate

LOW QUALITY EVIDENCE

- GnRHa increased hemoglobin levels before surgery and decreased uterine and fibroid size, compared with no treatment or placebo
- Blood loss, need for blood transfusion, operation time during hysterectomy and postoperative complications were reduced
- An SPRM drug (ulipristal acetate) had similar benefits, particularly reduced bleeding

MODERATE QUALITY EVIDENCE

- The main outcome measures were changes in symptoms (fibroid-related symptom severity, quality of life, menstrual bleeding, pelvic pain)
- When compared with placebo , SPRMs improved fibroid-related symptoms (by an average effect of 20 points on a 100-point scale), improved women's quality of life (by an average effect of 22 points on a 100-point scale) and resulted in a small decrease in menstrual bleeding
- Between 24% and 96% of women treated with SPRMs had no period at all (compared with 3% taking placebo)
- Review authors could draw no conclusions about changes in pelvic pain, as this was not consistently evaluated



MODERATE QUALITY EVIDENCE

- Two studies compared SPRMs versus a GnRH agonist (leuprolide) and found that both drugs (SPRMs and leuprolide) were effective in improving symptoms related to fibroids (improving quality of life, reducing menstrual bleeding, causing cessation of periods, decreasing pelvic pain)
- Women treated with SPRMs were more likely to develop changes to the endometrium than women treated with placebo or leuprolide. These changes are benign and reversible once SPRMs are discontinued.
- In summary, SPRMs improve fibroid-related symptoms, quality of life and menstrual bleeding.

LOW TO MODERATE QUALITY EVIDENCE

- **Quality of life - Tibolone may have a very small to large benefit on QoL, compared to GnRH analogues alone. No benefit of Raloxifene**
- **Bone mass - Raloxifene may have a moderate to large benefit for preserving bone mass when used for up to 6 months, while Tibolone may have a small to moderate bone mass-preserving effect. Estriol and Ipriflavone may have had a large effect in decreasing the loss of bone mass associated with the use of GnRH analogues. The effect of Medroxyprogesterone (MPA) on bone mass was uncertain.**

LOW TO MODERATE QUALITY EVIDENCE

- **Vasomotor symptoms - Tibolone may have a large effect in decreasing vasomotor symptoms compared to use of GnRH analogues without add-back therapy. MPA may also have decreased vasomotor symptoms**
- **Adverse effects - Tibolone could lead to a greater uterine size (increased by 8-39 cm3) and increased bleeding. MPA may also have resulted in a increased uterine size (by 77 cm3 to 606 cm3). Conjugated estrogens could also result in greater uterine size.**

NEW DRUG DISCOVERY ATTEMPTS

- Targeted Gene Therapy
- Local Injection of Collagenase extract from Clostridium
- Vitamin D antagonists
- Danazol
- Cabergoline
- Green tea extracts
- Somatostatin analogs such as lanreotide

Donnez et al; Emerging treatment options for uterine fibroids. Expert Opinion on Emerging Drugs; 2018
Ali et al; Successes and failures of uterine leiomyoma drug discovery. Expert Opinion on Drug Discovery; 2018

2018 RESEARCH FINDINGS

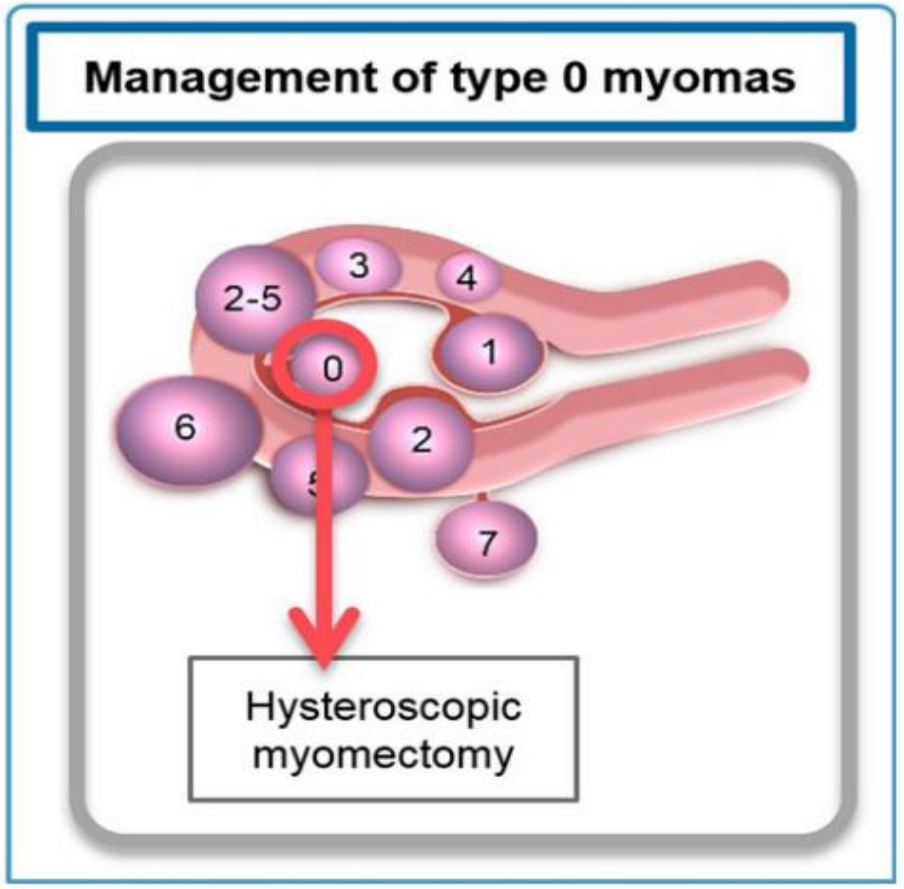
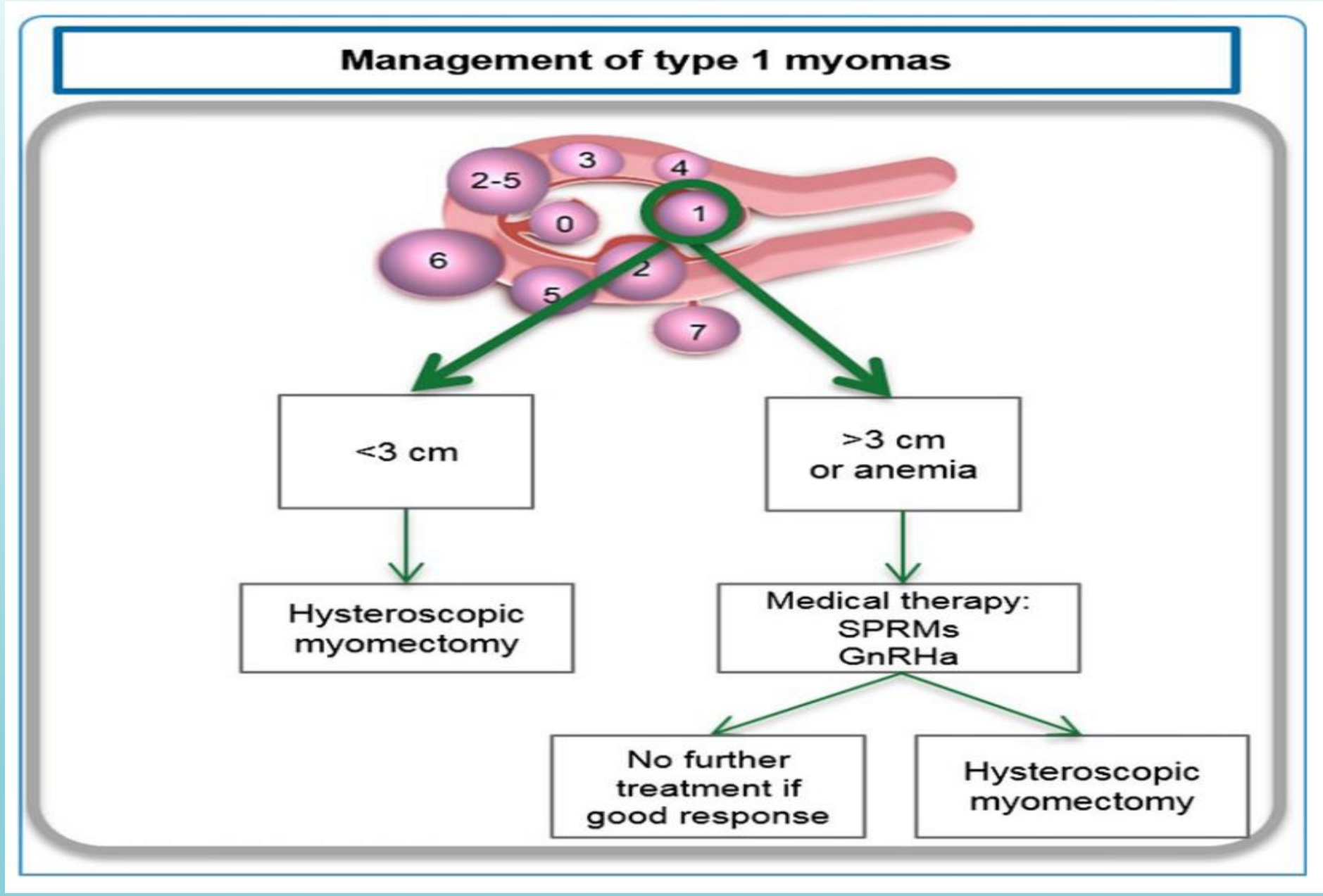
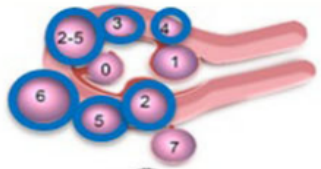


Figure 7 Management of type 0 myomas. Hysteroscopic myomectomy is the most appropriate approach. Fibroid classification cartoon republished with permission from Munro *et al.* (2011).


Management of type 1 myomas
2-5
3
4
0
1
6
2
5
7
<3 cm
>3 cm
or anemia
Hysteroscopic
myomectomy
Medical therapy:
SPRMs
GnRHa
No further
treatment if
good response
Hysteroscopic
myomectomy

Women of reproductive age with type 2 myomas or multiple myomas type 2 to 5 or myomas type 2-5 according to desire for pregnancy



Desire for pregnancy

Long-term intermittent SPRM therapy
(2 courses of 3 months)

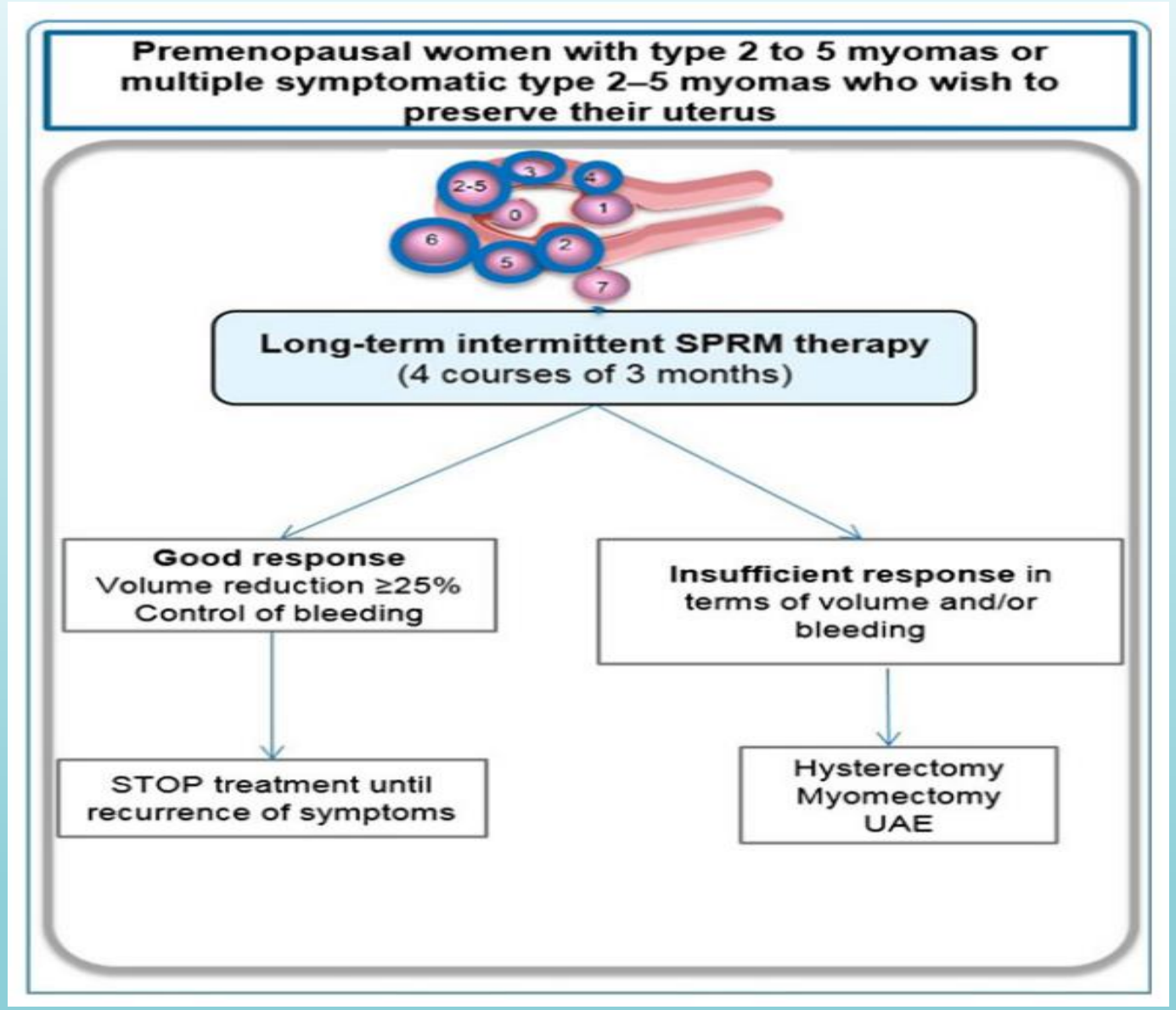
- **Very good response**
  Volume reduction >50%
  and restoration of the uterine cavity
  - Try natural conception+
- **Good response**
  Volume reduction ≥25-50%
  Control of bleeding
  - Try natural conception+ (if the uterine cavity is restored)
  - If the cavity remains distorted or if the myoma remains large due to great volume at baseline → Myomectomy
- **Insufficient response**
  in terms of volume and/or bleeding
  - Myomectomy

+ or IVF if this is indicated

No desire for pregnancy

Long-term intermittent SPRM therapy
(4 courses of 3 months)

- **Good response**
  Volume reduction ≥25%
  Control of bleeding
  - STOP treatment until recurrence of symptoms
- **Insufficient response**
  in terms of volume and/or bleeding
  - Myomectomy


Premenopausal women with type 2 to 5 myomas or multiple symptomatic type 2–5 myomas who wish to preserve their uterus
2-5
3
4
1
0
6
2
5
7
Long-term intermittent SPRM therapy
(4 courses of 3 months)
Good response
Volume reduction ≥25%
Control of bleeding
Insufficient response in terms of volume and/or bleeding
STOP treatment until recurrence of symptoms
Hysterectomy
Myomectomy
UAE

KEY FINDINGS

1) As an adjunct to surgery, SPRMs, by inducing bleeding control and fibroids volume reduction, restore hemoglobin levels and facilitate surgery if surgery remains mandatory after medical therapy.
2) More than one course of SPRM can maximize its potential benefits.
3) Thanks to the sustained effect (up to 6months), additional intermittent 12weeks courses of SPRM may be proposed for long term medical management of fibroids.
4) More than 90% of patients have their bleeding controlled.
5) Seventy-five-80% experience signify cant reduction in fibroid volume of >25%.

Donnez et al; Emerging treatment options for uterine fibroids. Expert Opinion on Emerging Drugs; 2018

SUMMARY

- Surgical management is still the mainstay, but results are inconsistent
- Medical management may offer symptom relief and volume reduction, but infertility outcome benefit is unproven
- Role of SPRM significant
- Newer modalities are still in experimental phase

FUTURE RESEARCH

- Future clinical trials should focus on prevention strategies, such as preventing occurrence in women genetically predisposed to this condition, and avoiding recurrence after surgery in women at high risk (namely young women or those with a family history).