

**Convegno Nazionale  
Fertilità di Coppia:  
“Ri”Parliamone**



**Comacchio (FE)  
18 ottobre 2019  
Palazzo Bellini**

# Terapia medica dei fibromi in donne con desiderio di prole

Prof. Giuseppe Morgante

Clinica Ostetrica e Ginecologica  
Dipartimento di Medicina  
Molecolare e dello Sviluppo

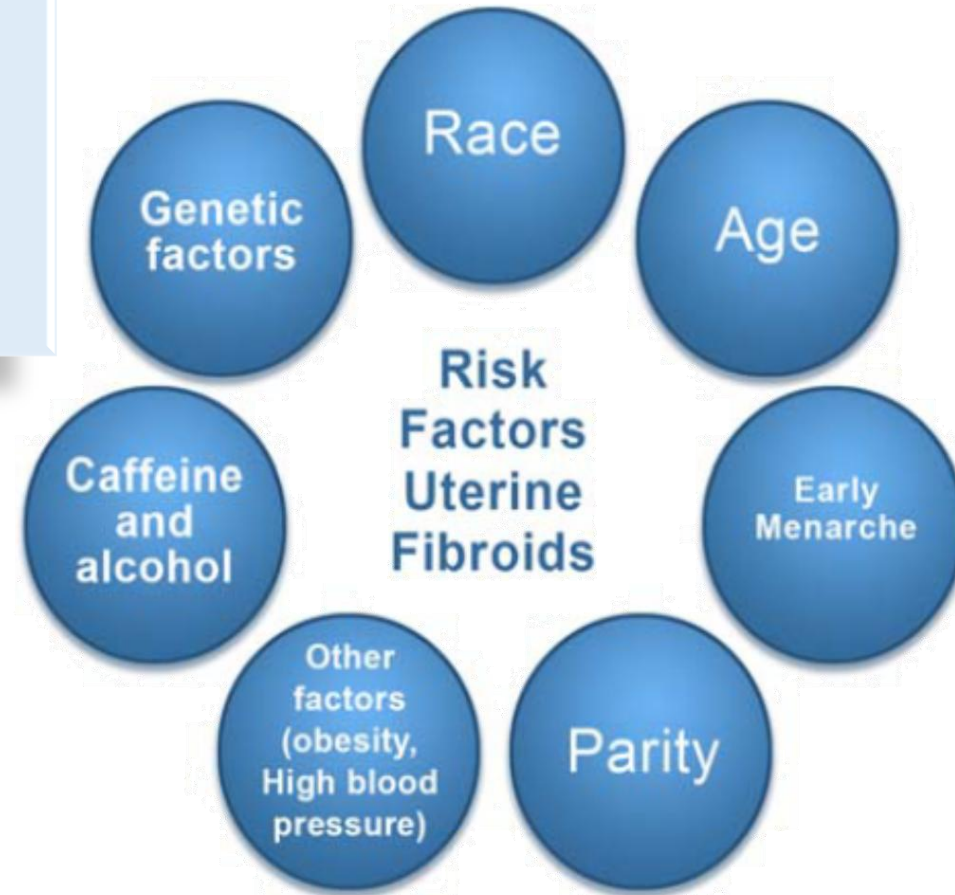
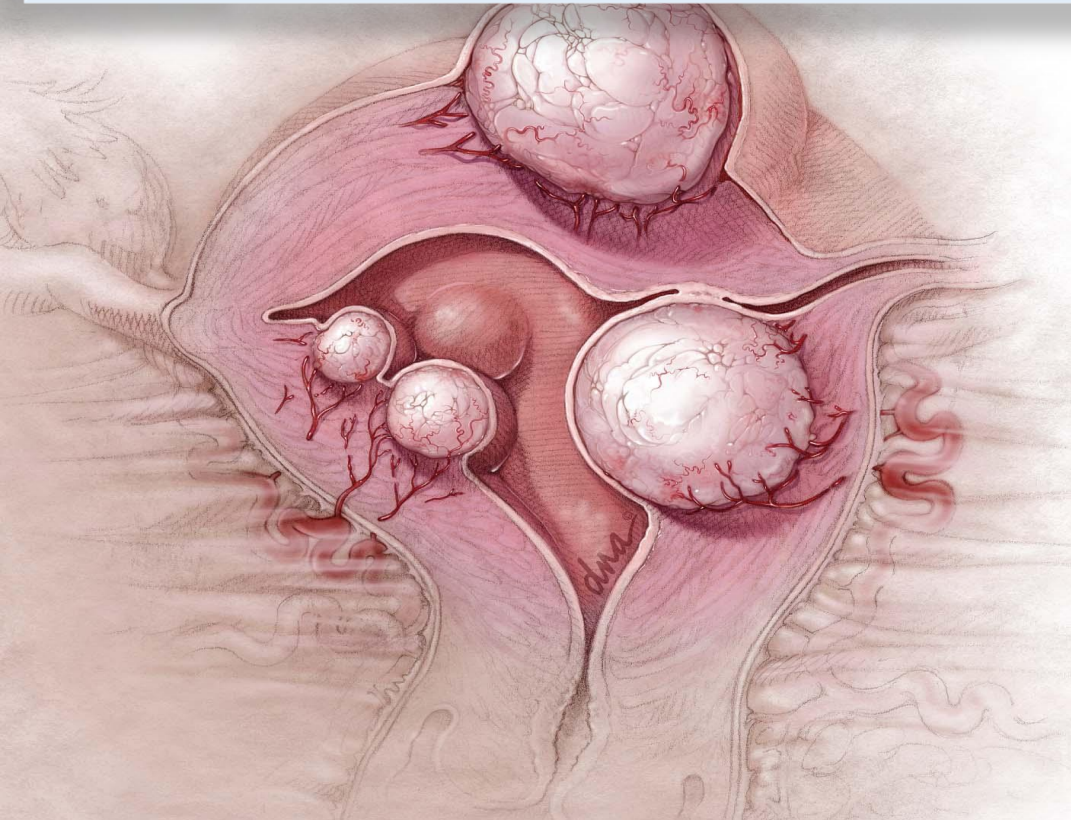


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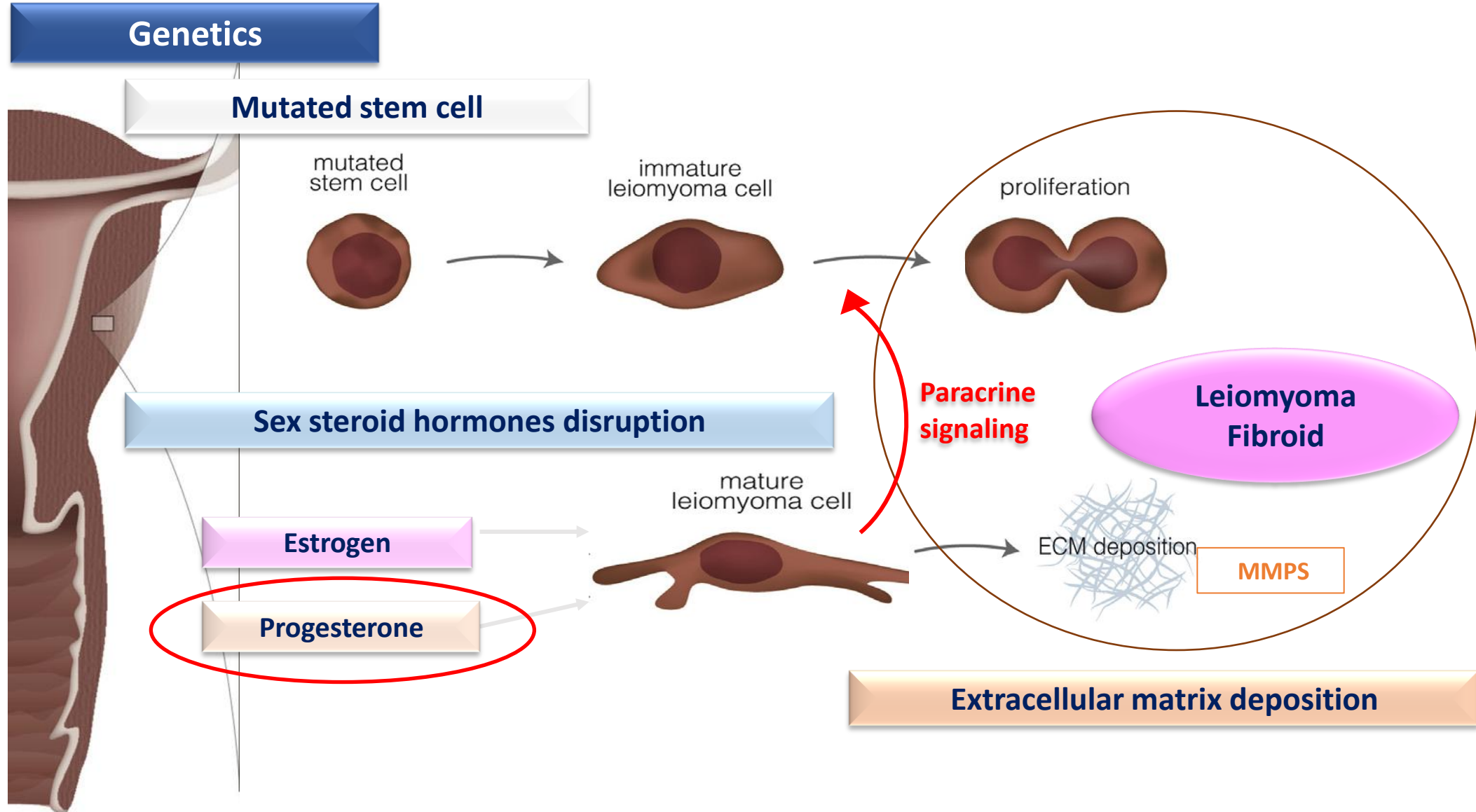
# Uterine fibroids

Fibroids are benign tumors that originate from the uterine smooth muscle tissue (myometrium) whose growth is dependent on estrogen and progesterone.

Fibroids are rare before puberty, increase in prevalence during the reproductive years, and decrease in size after menopause

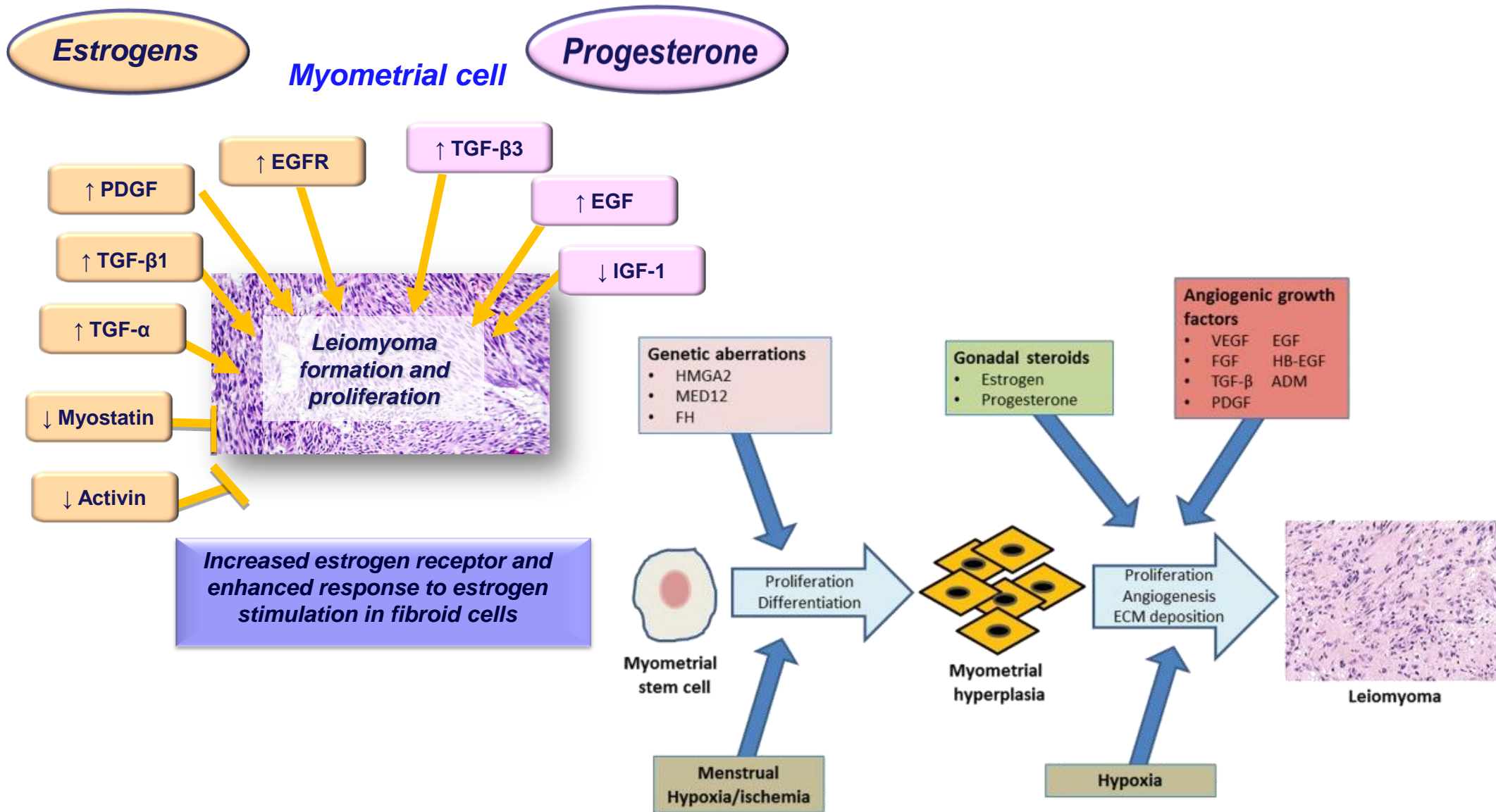


# Pathogenesis of uterine fibroids





# Effects of hormones on myometrial cells



FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age

Malcolm G. Munro<sup>a,b,\*</sup>, Hilary O.D. Critchley<sup>c</sup>, Michael S. Broder<sup>d</sup>, Ian S. Fraser<sup>e</sup>; for the FIGO Working Group on Menstrual Disorders



# FIGO classification PALM-COEIN 2011

Polyp
Adenomyosis
<b>Leiomyoma</b>
Malignancy & Hyperplasia

Submucosal

Other

Coagulopathy
Ovulatory Dysfunction
Endometrial
Iatrogenic
Not Yet Classified



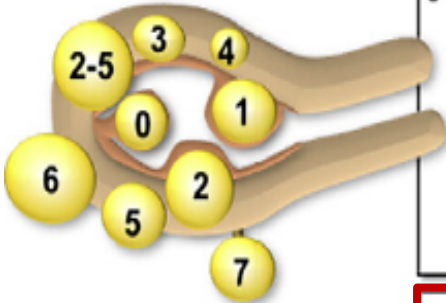
Polyp
Adenomyosis
Leiomyoma
Malignancy & hyperplasia

Submucosal

Other

Coagulopathy
Ovulatory dysfunction
Endometrial
Iatrogenic
Not yet classified

### Leiomyoma subclassification system



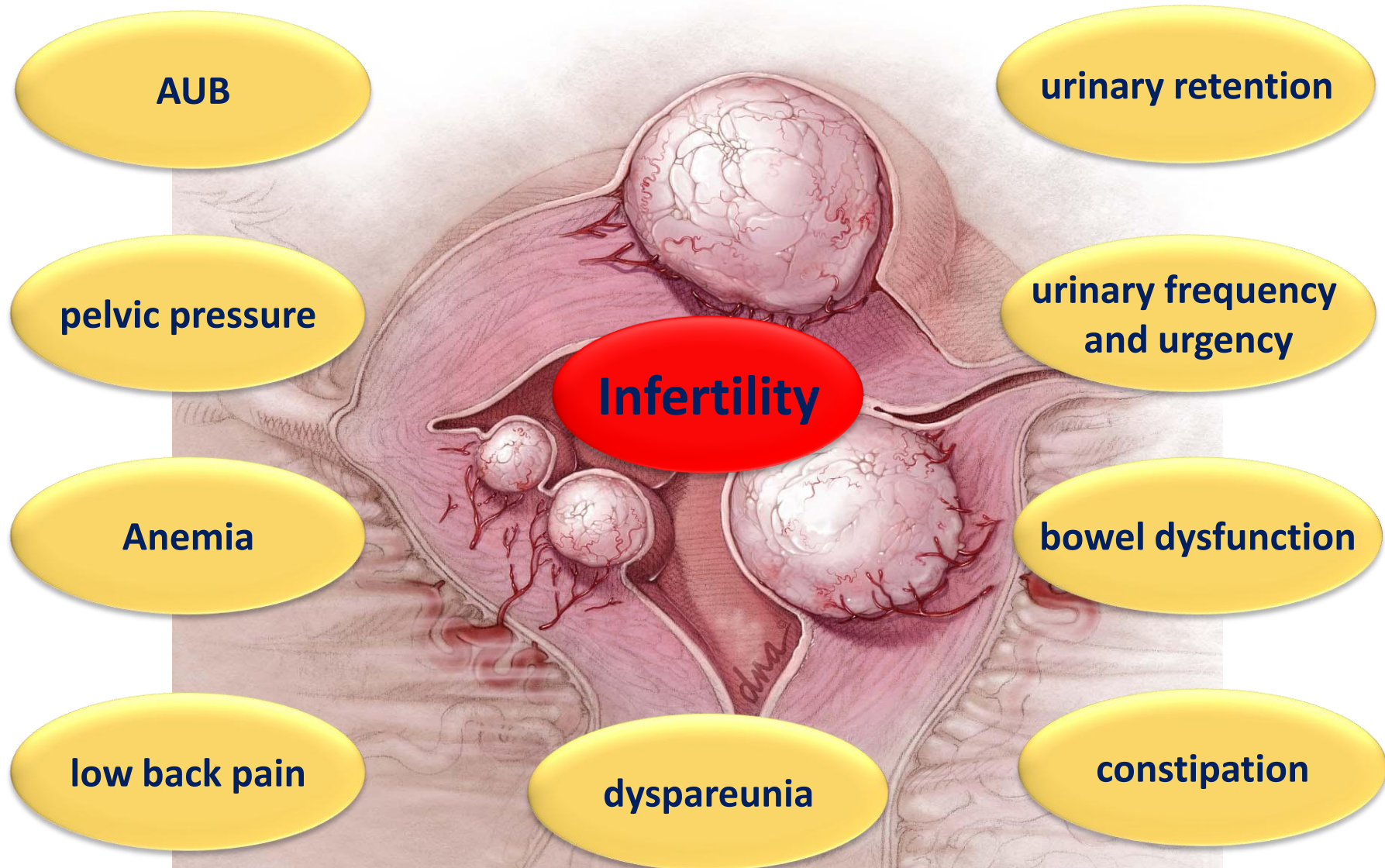
SM - Submucosal	0	Pedunculated intracavitary
	1	<50% intramural
	2	≥50% intramural
O - Other	3	Contacts endometrium; 100% intramural
	4	Intramural
	5	Subserosal ≥50% intramural
	6	Subserosal <50% intramural
	7	Subserosal pedunculated
	8	Other (specify e.g. cervical, parasitic)

**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	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.
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# Uterine fibroids: symptoms and signs





## Fibroids and infertility: an updated systematic review of the evidence

Elizabeth A. Pritts, M.D.,<sup>a</sup> William H. Parker, M.D.,<sup>b</sup> and David L. Olive, M.D.<sup>a</sup>

<sup>a</sup> Wisconsin Fertility Institute, Middleton, Wisconsin; and <sup>b</sup> Department of Obstetrics and Gynecology, University of California, Los Angeles, California

Objective 1 → To investigate the effect of fibroids on fertility

**TABLE 2**

Effect of fibroids on fertility: all locations.

Outcome	Number of studies/substudies	Relative risk	95% confidence interval	Significance
---------	------------------------------	---------------	-------------------------	--------------

Clinical pregnancy rate  
Implantation rate  
Ongoing pregnancy rate  
Spontaneous abortion rate  
Preterm delivery rate

Pritts. *Fibroids and infertility*

**TABLE 3**

Effect of fibroids on fertility: submucous fibroids.

Outcome	Number of studies/substudies	Relative risk	95% confidence interval	Significance
---------	------------------------------	---------------	-------------------------	--------------

Clinical pregnancy rate	4	0.363	0.179–0.737	$P = .005$
Implantation rate	2	0.283	0.123–0.649	$P = .003$

Ongoing pregnancy rate  
Spontaneous abortion rate  
Preterm delivery rate

Pritts. *Fibroids and infertility*

**TABLE 4**

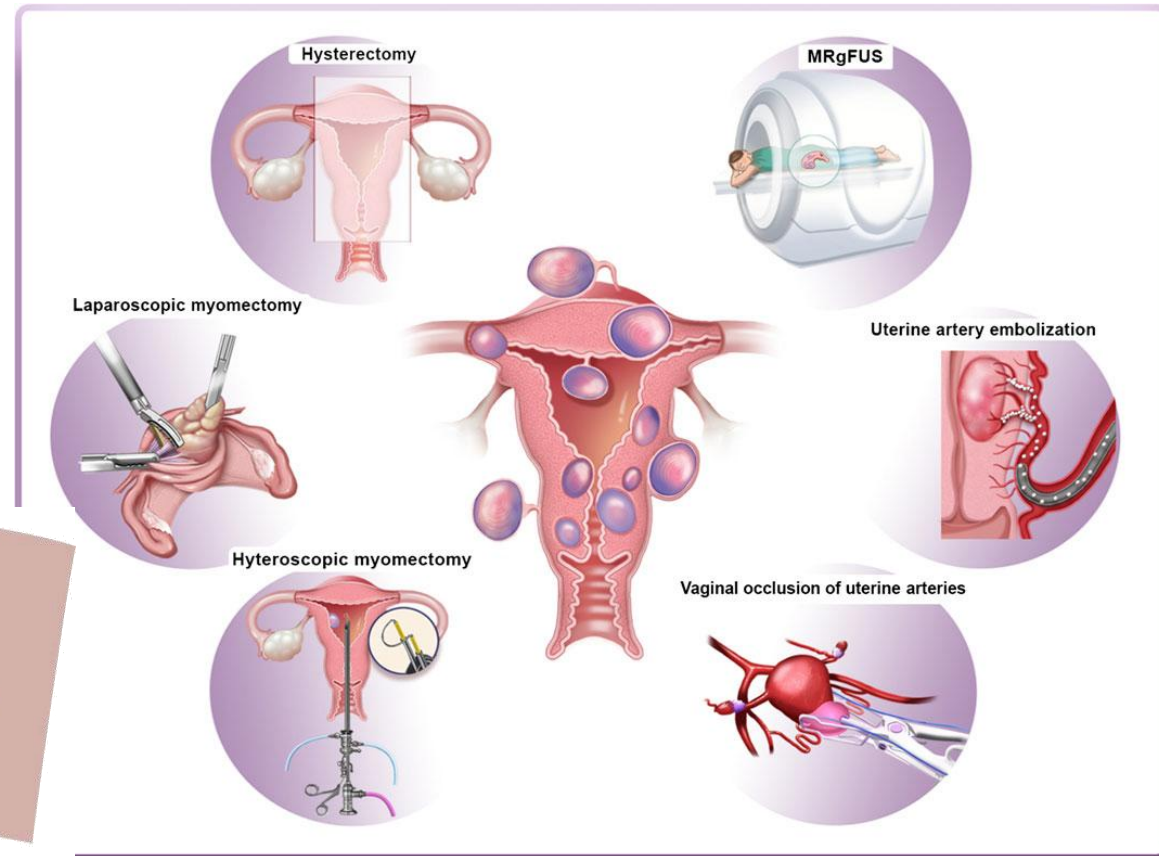
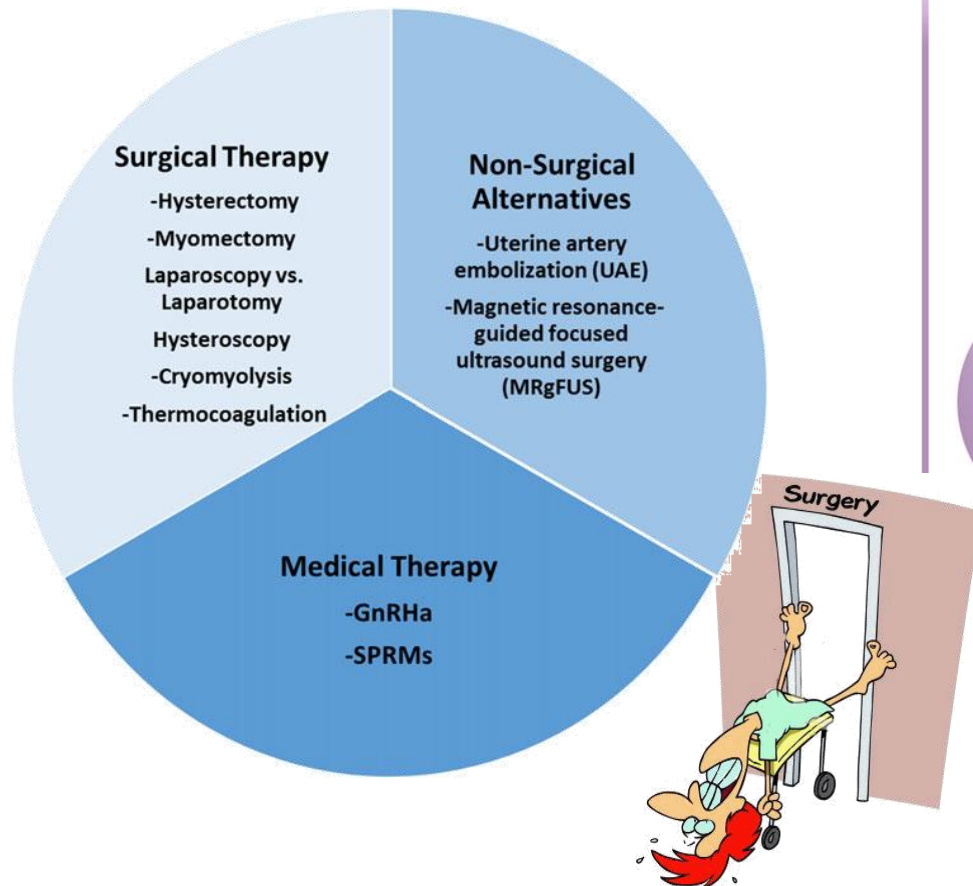
Effect of fibroids on fertility: no intracavitary involvement.

Outcome	Number of studies/substudies	Relative risk	95% confidence interval	Significance
Clinical pregnancy rate	24	0.897	0.800–1.004	Not significant
Implantation rate	14	0.792	0.696–0.901	$P < .001$
Ongoing pregnancy/live birth rate	16	0.780	0.690–0.883	$P < .001$
Spontaneous abortion rate	16	1.891	1.473–2.428	$P < .001$
Preterm delivery rate	2	2.767	0.797–9.608	Not significant

Pritts. *Fibroids and infertility*. *Fertil Steril* 2009.

# Therapy for the management of fibroids: the current armamentarium

Hysterectomy, laparoscopic myomectomy and hysteroscopic myomectomy are the most widely used surgical interventions for myomas

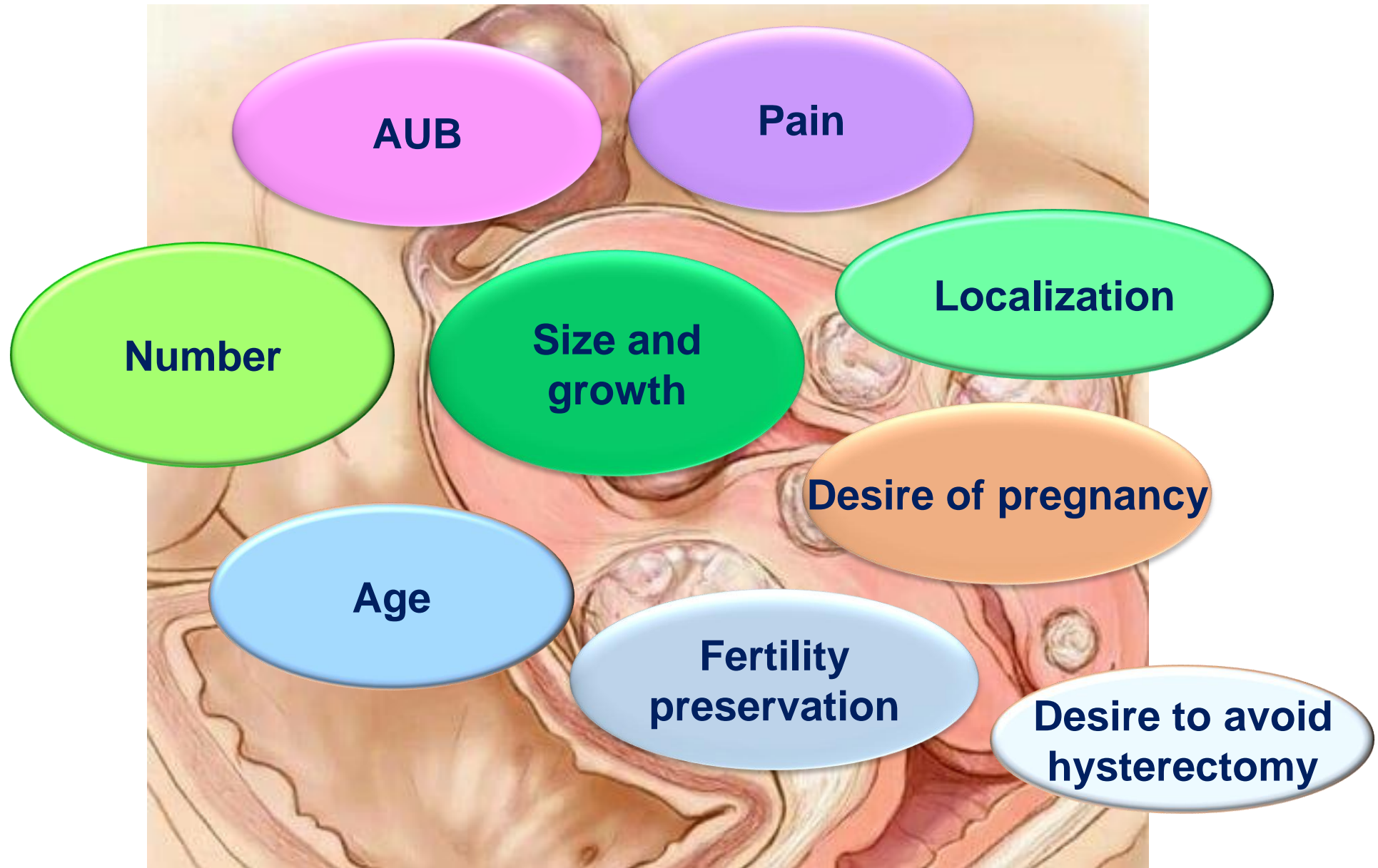


Alternatives to surgical intervention include uterine artery embolization (UAE), high-frequency magnetic resonance-guided focused ultrasound surgery (MRgFUS) and vaginal occlusion of uterine arteries



# Factors influencing the management of uterine fibroids

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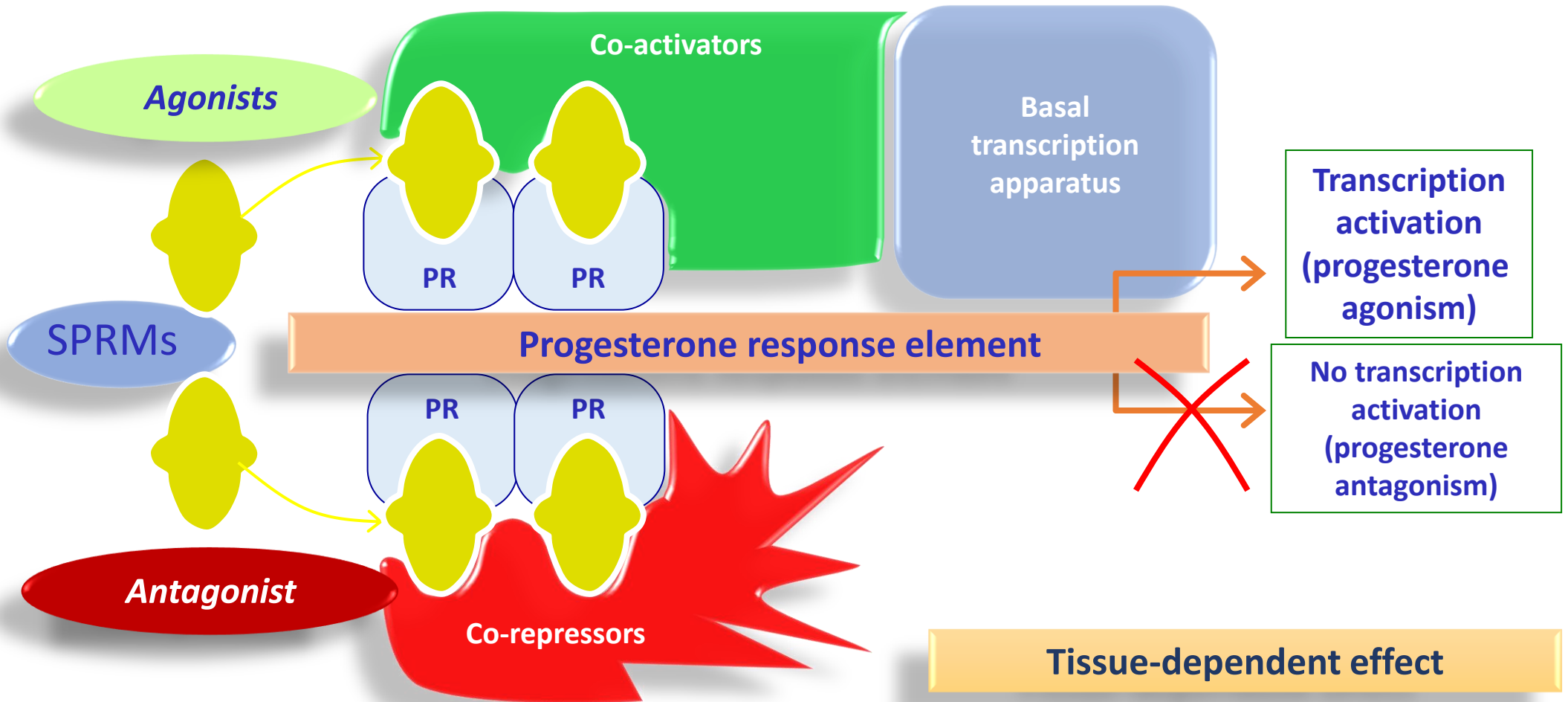


# Medical therapies for the management of fibroids

<i>Therapy</i>	<i>Advantages</i>	<i>Disadvantages</i>
Oral contraceptives	Oral administration	No reduction in fibroid size Inconsistent bleeding
Progestin	Oral administration	No reduction in fibroid size Inconsistent bleeding
LNG-IUS	Prolonged effect Concomitant contraception	No reduction in fibroid size Spontaneous expulsion of the device Contraindicated in the presence of submu- cous fibroids
GnRHa	Sustained release (1 month) Fibroid volume reduction Indicated for fibroids	Injectable therapy Fibroid regrowth upon treatment cessation Temporary treatment (maximum 6 months) due to adverse events (menopausal symptoms, bone mineral density loss)
UPA	Oral administration Fast bleeding control Sustained fibroid volume reduction Indicated for fibroids	Progesterone receptor modulator-associated endo- metrial changes



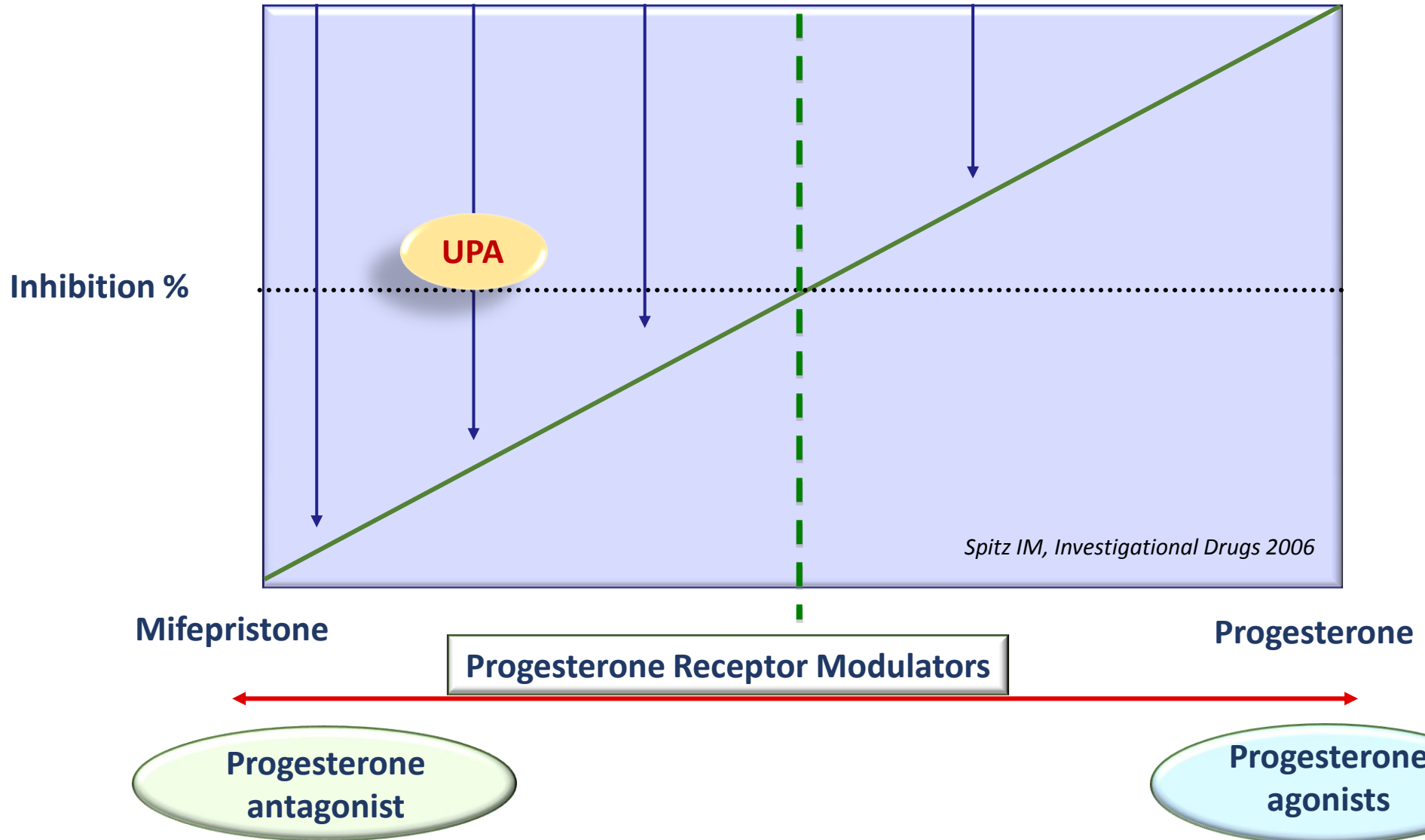
# SPRMs act as both progesterone agonists and progesterone antagonists



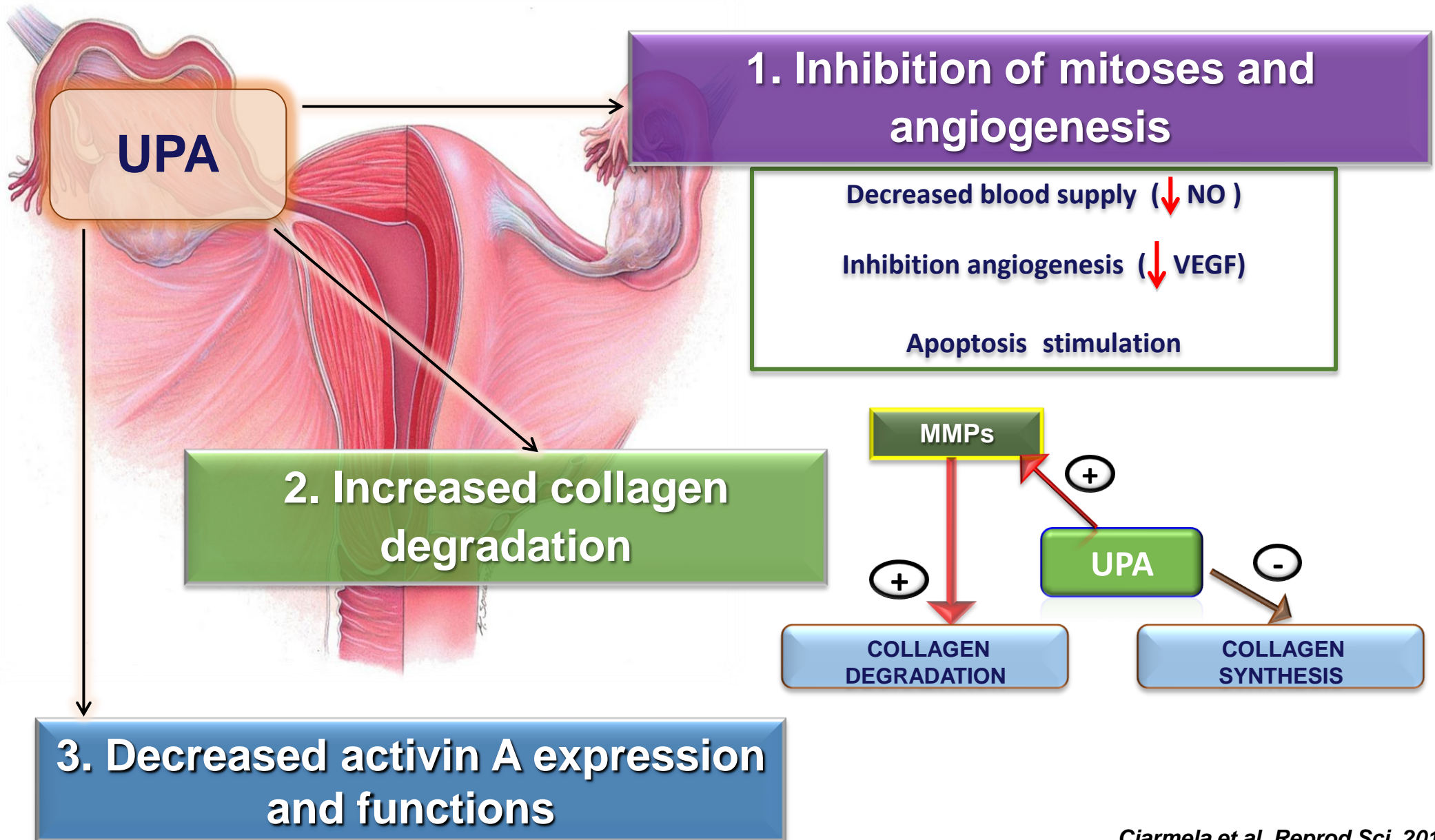


# Selective Progesterone Receptor Modulators (SPRMs)

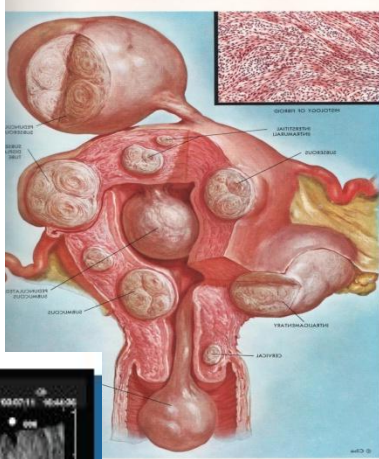
Pure antagonists  
(maximum inhibition)



# SPRMs: mechanisms of action on uterine fibroids



# SPRMs (UPA): mechanisms of action on uterine fibroids



## AZIONE DIRETTA SUL FIBROMA

- Riduzione del volume del fibroma
- Inibizione della proliferazione cellulare, induzione dell'apoptosi, azione antifibrotica

## AZIONE DIRETTA SULL'ENDOMETRIO

- Riduzione rapida del bleeding
- cambiamenti benigni e reversibili del tessuto endometriale (PAEC)

## AZIONE SULL'ASSE IPOTALAMO-IPOFISI

- Inibizione del picco di LH
- I livelli di estradiolo sono mantenuti come in fase medio follicolare



# Uterine fibroid management: from the present to the future

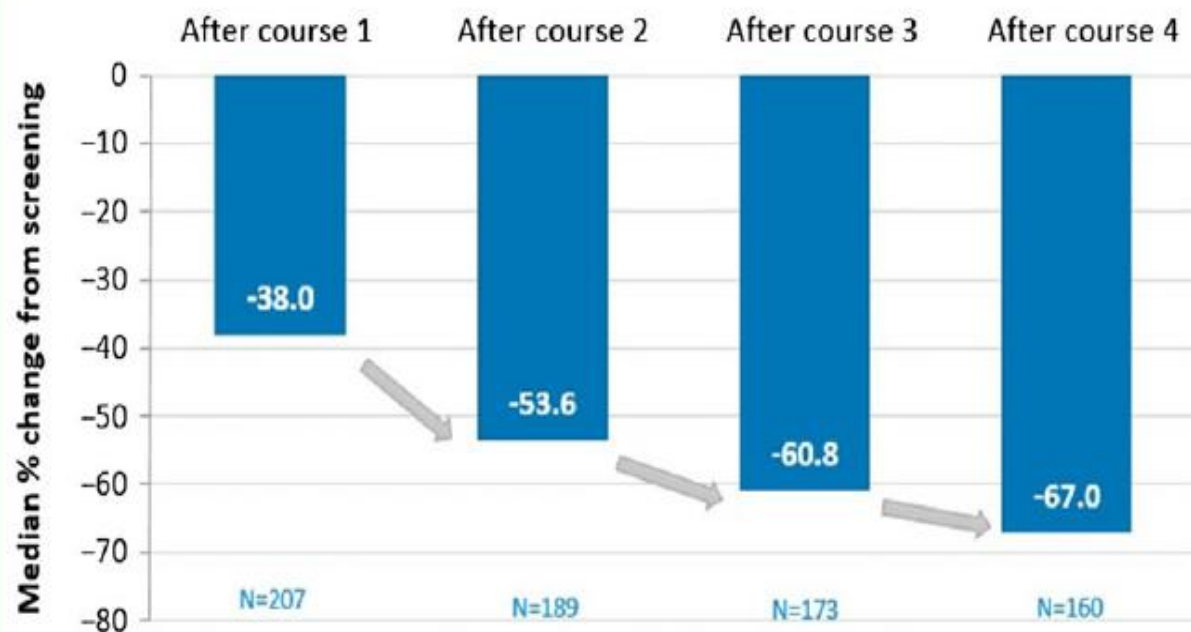
Jacques Donnez<sup>1,\*</sup> and Marie-Madeleine Dolmans<sup>2</sup>

2016

Riduzione del volume  
dei fibromi

## Long-term intermittent therapy with SPRMs

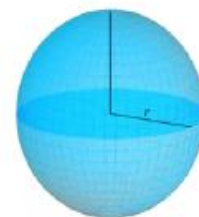
Fibroid volume reduction\* after treatment courses 1,2,3 and 4 (UPA 5 mg)



\* Volume of 3 largest fibroids combined

ULIPRISTAL  
ACETATO

$$\text{Volume} = \frac{4}{3} \pi r^3$$



# SPRMs: side-effects

**Breast tenderness (4%)**

**Feeling dizzy (2%)**

**Headaches (7%)**

**Mood changes (4%)**

**Nausea (6,5%)**

**Pelvic pain (8,5%)**

**Tiredness (5,5%)**

**Insomnia (2%)**

**Hot flush (12%)**

**Ovarian cyst (1,5%)**

**Endometrial thickening >16mm (10-15%)**

**Nonphysiological endometrial changes (PAEC) (12%)**

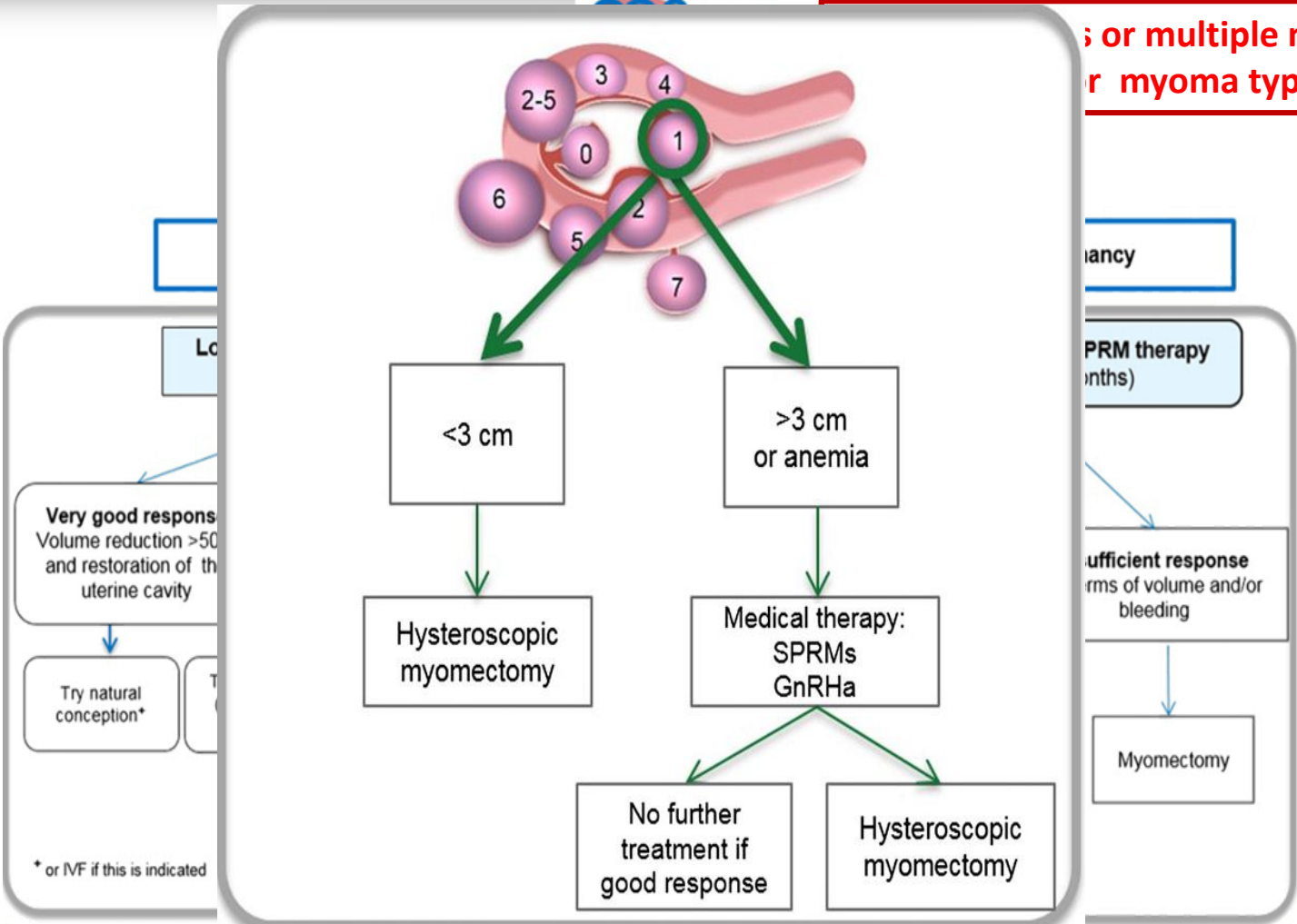


# Uterine fibroid management: from the present to the future

Jacques Donnez<sup>1,\*</sup> and Marie-Madeleine Dolmans<sup>2</sup>

# ULIPRISTAL ACETATO E FERTILITÀ

or multiple myomas type  
or myoma type 2-5





# SPRMs: Ulipristal acetate (UPA)

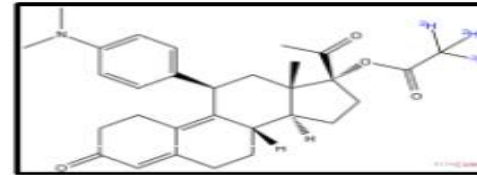


AGENZIA ITALIANA DEL FARMACO

DETERMINA 31 luglio 2014

Riclassificazione del medicinale per uso umano «Esmya» (ulipristal acetato), ai sensi dell'articolo 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. 805/2014). (14A06424) (GU Serie Generale n. 186 del 14-8-2014)

Articoli	Classificazione ai fini della rimborsabilità
1	Il medicinale ESMYA (ulipristal acetato) nelle confezioni sotto indicate è classificato come segue:
2	Confezione:
3	«5 mg - compressa - uso orale - blister (ALU/PVC/PE/PVDC)» 28
4	compressa:
	A.I.C. n. 042227013/E (in base 10) 188P25 (in base 32)
	<u>Classe di rimborsabilità: A Nota 51</u>
	Prezzo ex factory (IVA esclusa): € 149,10
	Prezzo al pubblico (IVA inclusa): € 246,08
	Validità del contratto: 24 mesi
	Sconto obbligatorio alle strutture pubbliche sul prezzo Ex Factory come da condizioni negoziali.



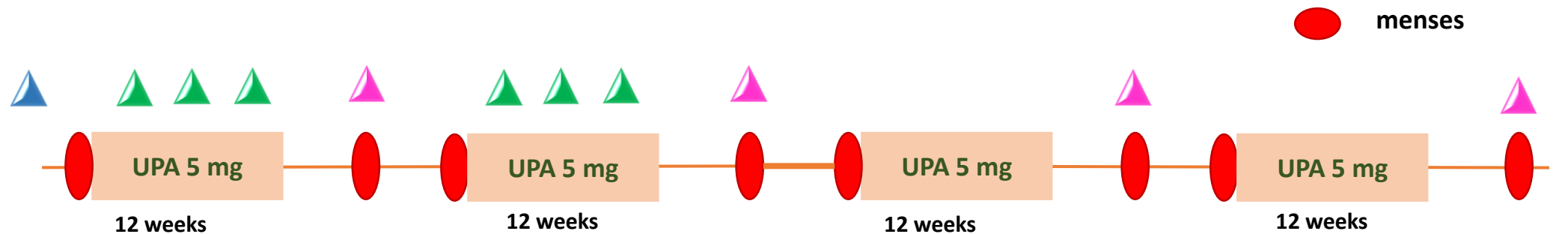
efficacy is reduced in patients with a distorted uterus (8). Since February 2012, ulipristal acetate (UPA) is also approved in Europe for preoperative fibroid treatment (9). For the many

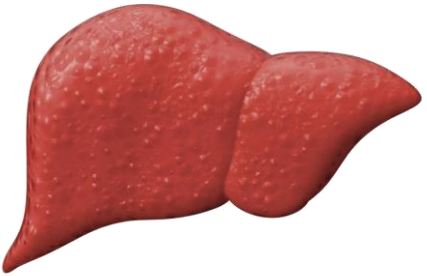
Melis GB, Piras B, Marotto MF, Orrù MM, Maricosu G, Piloni M, et al. Pharmacokinetic evaluation of ulipristal acetate for uterine leiomyoma treatment. Expert Opin Drug Metab Toxicol. 2012;8:901-8.

- ImMESSo in commercio in Italia a fine 2014 con indicazione nel trattamento intermittente (fino a 4 cicli) dei sintomi da moderati a gravi di fibromi uterini in donne adulte in età riproduttiva.
- Nota 51

- Se non sono rilevati problemi al fegato, è possibile utilizzare un singolo ciclo di Esmya in donne che stanno per sottoporsi a un intervento chirurgico per i loro fibromi; Esmya può essere utilizzato per più di un ciclo solo in donne che non possono sottoporsi a un intervento chirurgico.

# Safety of repeated use of ulipristal acetate in uterine fibroids: liver tests and monitoring



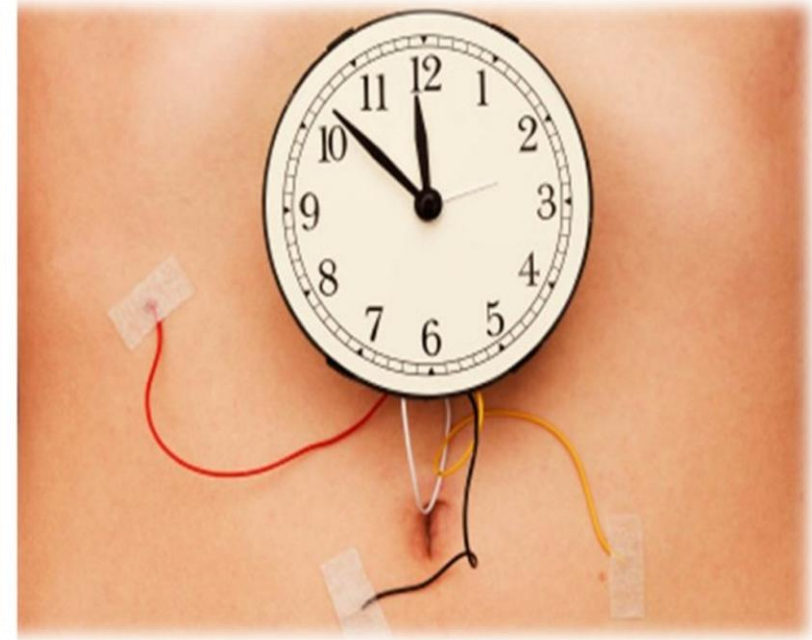
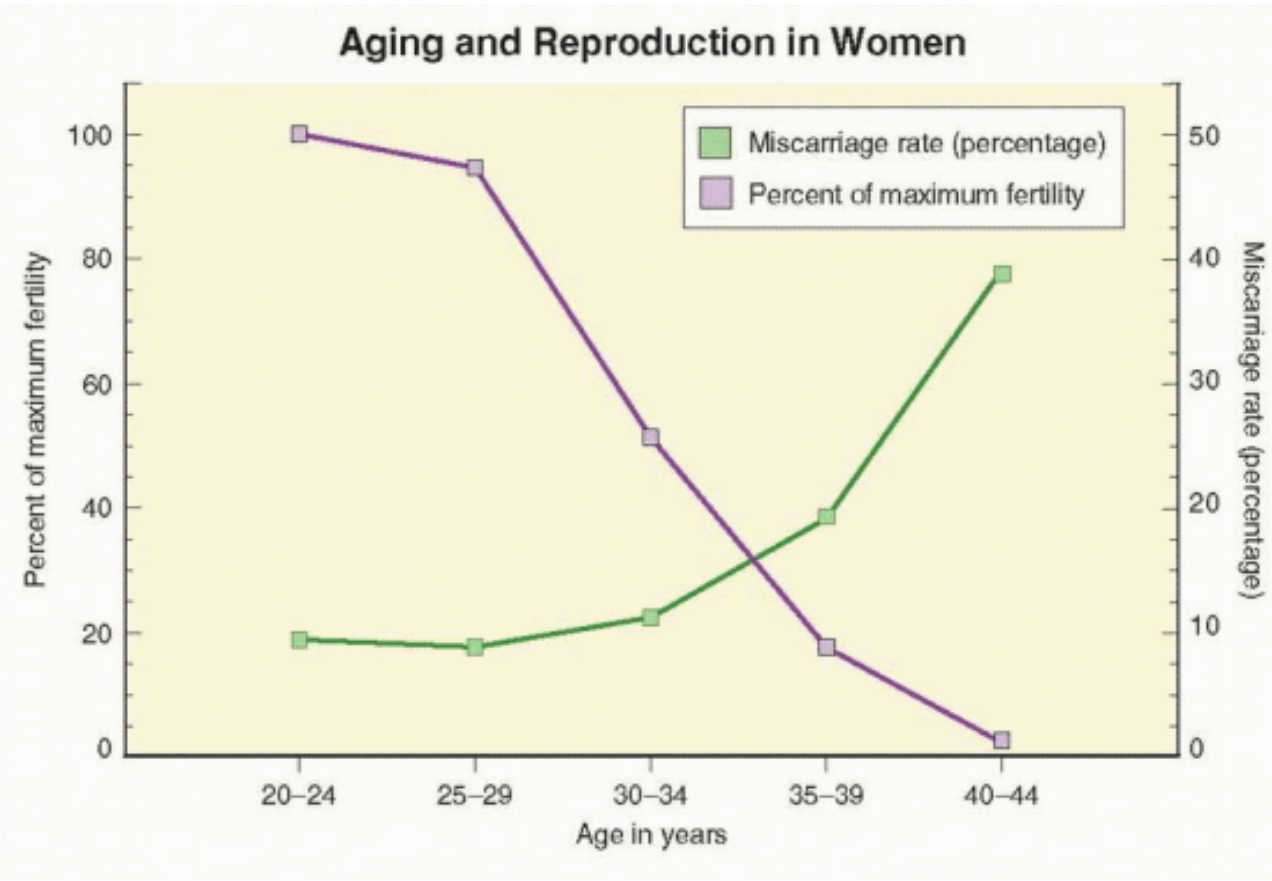
- ▲ Monitoraggio delle funzionalità epatiche prima dell'inizio del trattamento
  - ▲ Monitoraggio mensile delle funzionalità epatiche (nei primi due cicli)
  - ▲ Monitoraggio delle funzionalità epatiche 2-4 settimane dopo l'interruzione del trattamento
- 

- ✓ Il trattamento **non deve essere iniziato** se i livelli degli enzimi epatici sono **più di 2 volte il limite superiore** di normalità (ALT o AST >2 il range di riferimento, isolati o in combinazione con bilirubina > 2 x il limite superiore).
- ✓ Durante il trattamento se il test è anormale (**livelli di enzimi epatici (ALT/AST) superiori a 3 volte il limite superiore** di normalità), il medico deve **interrompere il trattamento** e monitorare attentamente la paziente.
- ✓ Una scheda paziente sarà inclusa nella confezione del medicinale per informare le pazienti sulla necessità di monitoraggio del fegato e per contattare il proprio medico nel caso in cui sviluppino sintomi di danno epatico (come stanchezza, ingiallimento della pelle, urine scure, nausea e vomito)



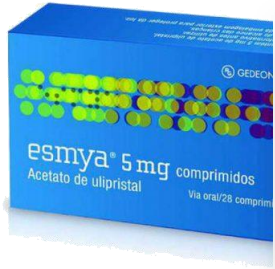


# Riserva ovarica



# UPA in donne che devono essere sottoposte a IVF: quale ruolo?

## “Pre-treatment with ulipristal acetate before ICSI procedure: a case report”



- ✓ 35-year-old nulliparous
- ✓ Before ICSI procedure → 3-month treatment with Esmya 5 mg for 84 days
- ✓ Myomas size was reduced



- ✓ Pregnancy obtained
- ✓ No fibroid growth was observed through the pregnancy
- ✓ 38th week: PROM and vaginal delivery. No PPH. No neonatal complication
- ✓ Post-partum visit: normal size of the uterus. No myomas regrowth. No maternal anemia

• Esmya treatment does not have any adverse effect on the quality of embryos in the morphological assessment during the ICSI procedure.

• Pregnancy does not induce changes in fibroid size following earlier treatment with ulipristal acetate.

• Treatment of uterine fibroids is recommended before planned pregnancy to minimize the risk of obstetric complications.

# UPA in donne che devono essere sottoposte a IVF: quale ruolo?



- ✓ 42-year-old nulliparous
- ✓ 46mm intramural fibroid distorting the uterine cavity contour and a 21mm isthmic fibroid.
- ✓ 3 AID → 3 COH+AID → 2 IVF-ET → 3 FET (Failed!!)
- ✓ The patient underwent two fresh fertility preserving IVF cycles, with cryopreservation of 9 day-3 embryos, followed by a 12 weeks course of Ulipristal (5 mg per day)

Cycle#	COH protocol	# of oocytes Retrieved	# of 2PN	# of ET	Cryo/thawed	Pregnancy
1	GnRH-antagonist	8	8	2	6	No
2	FET			2	2	No
<i>Normal diagnostic hysteroscopy</i>						
3	FET			2	2	No
4	FET			2	2	No
5	GnRH-antagonist	5	4	2	0	No
6	GnRH-antagonist	5	4	0	4	No
7	GnRH-antagonist	11	5	0	5	No
<i>Ulipristal 5mg/day for 12 weeks</i>						
8	FET			2	2	No
9	FET			3	3	Yes

- ✓ Seven days after completion of UPA course, TVS revealed shrinkage of her intramural and isthmic fibroids to 27 and 13 mm, respectively
- ✓ Forty-five days after completion of UPA treatment the patient underwent her first unsuccessful FET with her own previously cryopreserved embryos. Her 2nd FET cycle, started 76 days following UPA led to conception

# UPA in donne che devono essere sottoposte a IVF: quale ruolo?

Pochi dati sono presenti in letteratura sulla fertilità o sul tasso di gravidanze in seguito a cicli di UPA



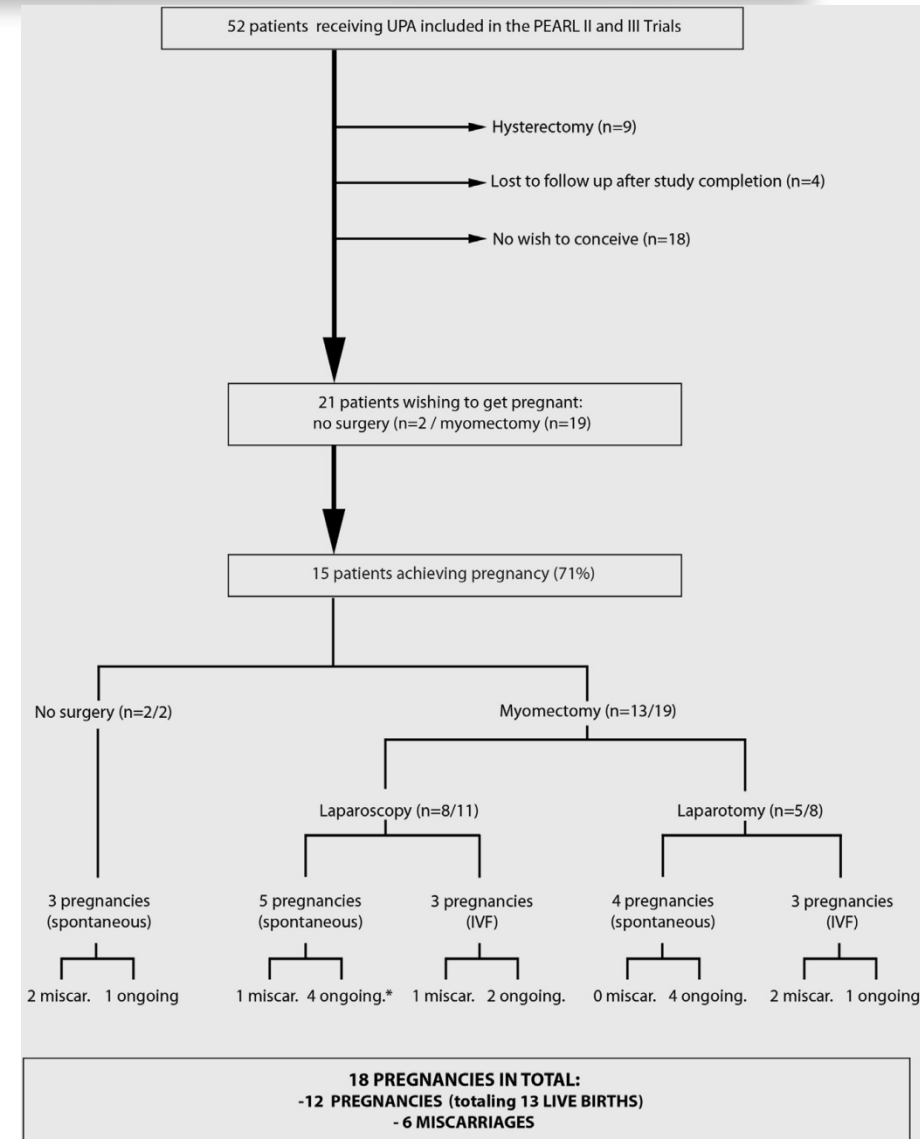
**Fertility  
and Sterility®**

2014

## First series of 18 pregnancies after ulipristal acetate treatment for uterine fibroids

Mathieu Luyckx, M.D.,<sup>a</sup> Jean-Luc Squifflet, M.D., Ph.D.,<sup>a</sup> Pascale Jadoul, M.D.,<sup>a</sup> Rafaella Votino, M.D.,<sup>a</sup> Marie-Madeleine Dolmans, M.D., Ph.D.,<sup>a,b</sup> and Jacques Donnez, M.D., Ph.D.<sup>c</sup>

- Pregnancy rate of 71% in the group of patients wishing to conceive
- Pregnancies were obtained after UPA treatment in 15 women also who did not undergo surgery (2)
- No neonatal complications
- No patients experienced problems related to their fibroids during pregnancy or after delivery
- Long-term follow-up has shown no significant regrowth of symptomatic fibroids in a large majority of women



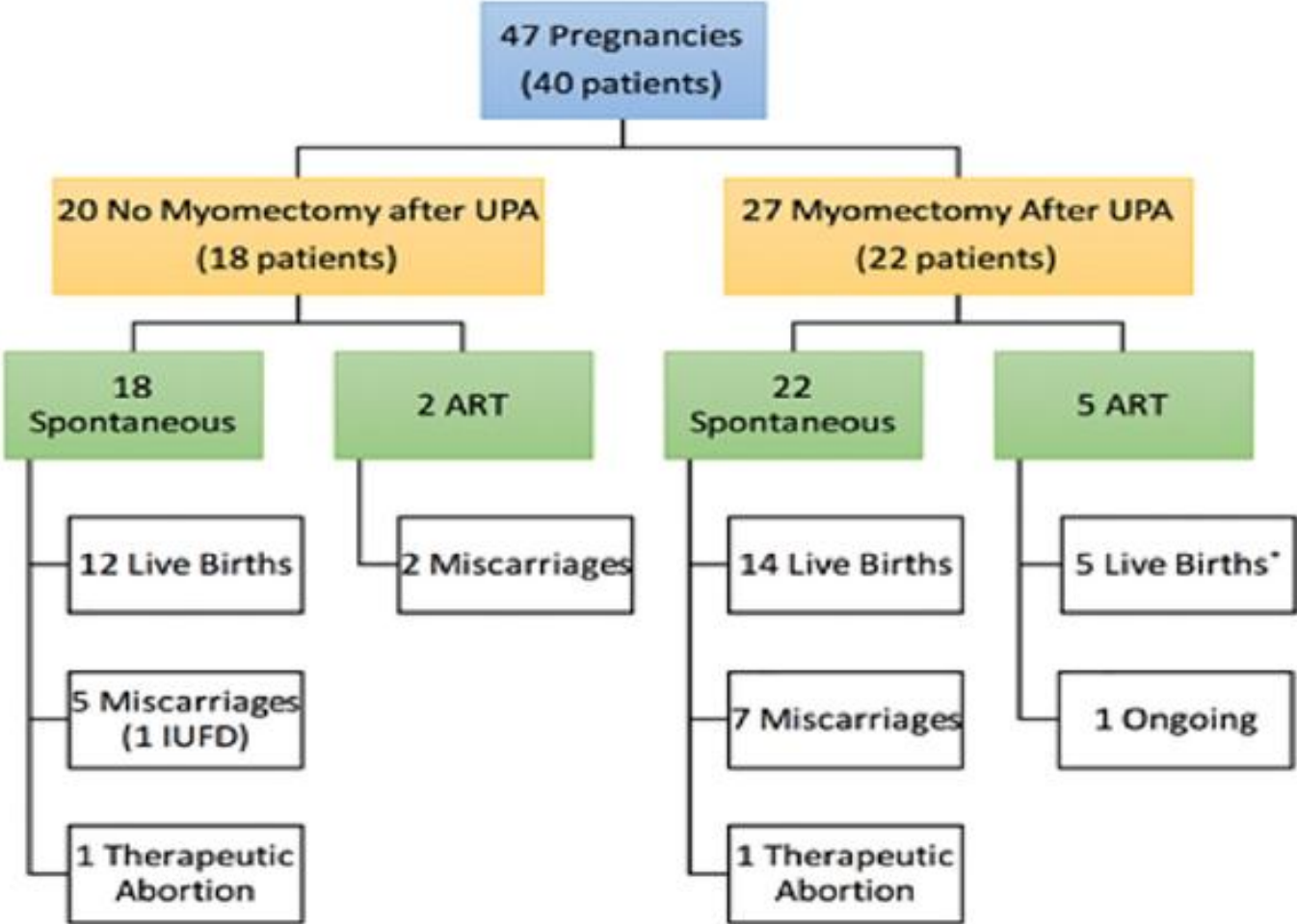


# Pregnancy Outcomes Following Ulipristal Acetate for Uterine Fibroids: A Systematic Review

C De Gasperis-Brigante BSc, S S.Singh MD, G Vilos MD, S Kives MD, A Murji MD

8/2018

Case series of two Canadian tertiary referral centres



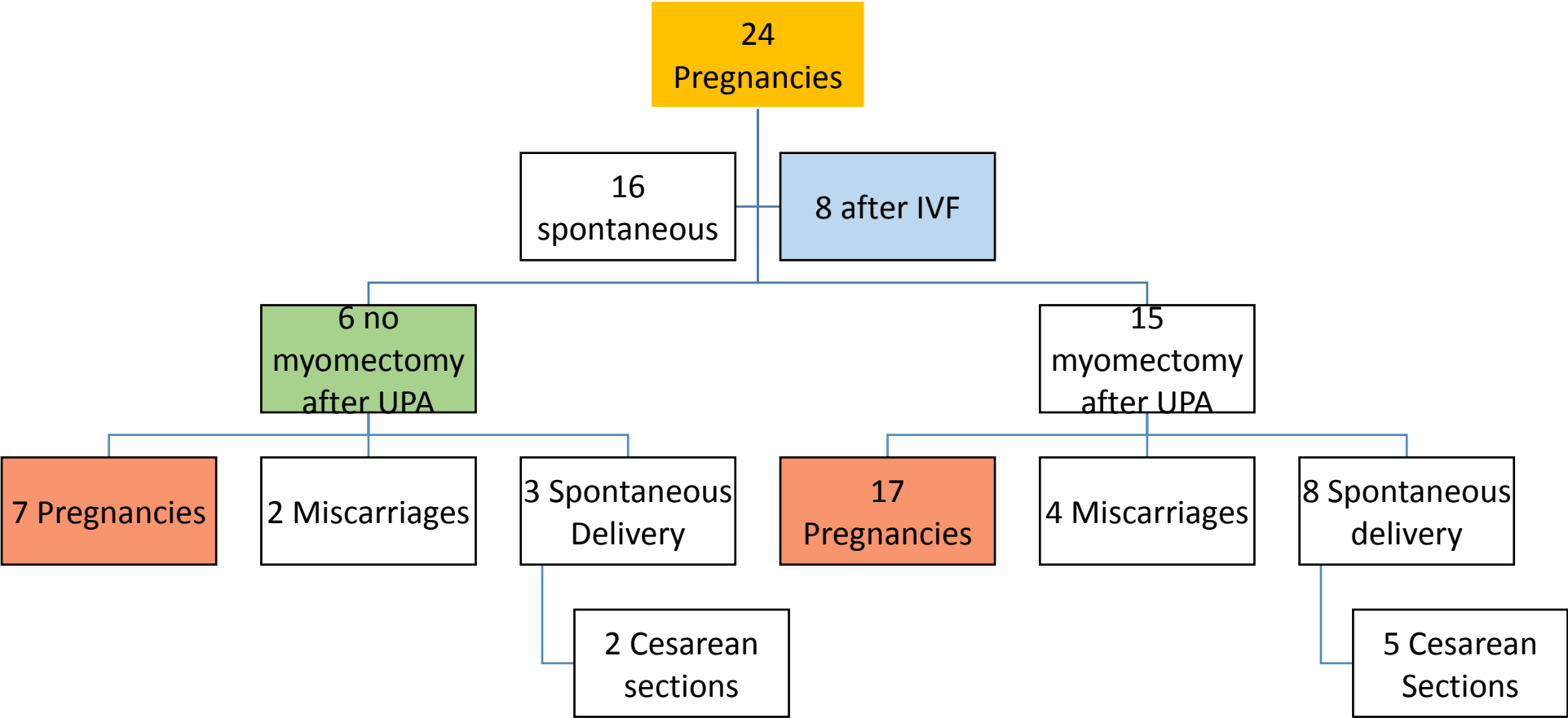
# Pregnancy Outcomes Following Ulipristal Acetate for Uterine Fibroids: A Systematic Review

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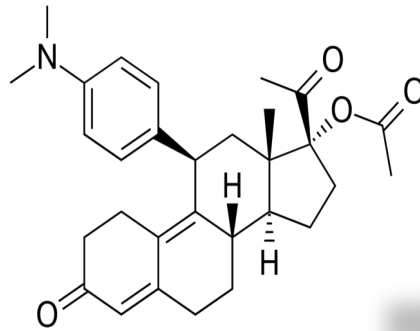
8/2018



## Case series of sistematic review



# PRESS



**A normal uterine cavity at sonohysterography was considered the condition to proceed to ART**

# The role of Ulipristal Acetate in infertile women with submucosus fibroids: our results

40 patients with infertility and submucosal myoma (Type 1 and Type 2) were referred to our fertility clinic



27 were enrolled in the study and received 1 to 3 cycle of UPA treatment



Patients' Characteristics	
Age	33.72 ± 1.77
BMI	23.44 ± 1.86
Nulliparous	20 (74)*
Primiparous	7 (26)*
Previous miscarriage	14 (52)*
Number UPA cycle	1.8±0.58
Patients with one fibroid	15 (55)*
Patients with two fibroids	12 (45)*

Patients' biochemical parameters	Before UPA	Before IVF	P value
FSH	9.83 ±1.14	10.04±1.26	0.0034
AMH	1.15 ± 0.26	1.11±0.23	0.095
Hb	11.06 ± 0.66	11.51±0.50	0.0001
Hct	36.58 ± 1.47	37.11±1.19	0.0027

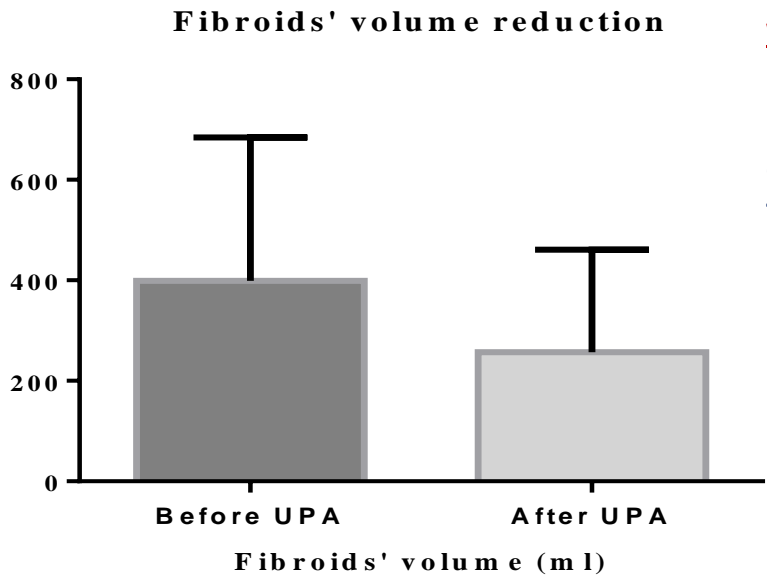


Data are expressed as median ± Standard Deviation  
\*Data are expressed as absolute number (percentage)



# The role of Ulipristal Acetate in infertile women with submucosus fibroids: our results

✓The mean diameter of the fibroids distorting the cavity was 5.5 (raging from 3.7 to 6.3 cm), while the mean volume was 65.4 ml (ranging from 48 to 107 ml)



✓The patients received a mean of 1.8 cycle leading to a mean reduction in the volume of the myoma of 41% (range 16 to 76)

✓Only one patient did not respond to UPA treatment and showed a volume augmentation of 9.2% and was therefore excluded from the study and referred to surgery after the first 3-month cycle.

IVF outcomes	
Oocyte retrieval	4.44±1.29
Number Embryos obtained	3.44±1.20
Biochemical pregnancy	15 (57.6)*
Ongoing pregnancy	13 (50)*
Healthy babies delivered	9 (34.6)*



Data are expressed as median ± Standard Deviation  
 \*Data are expressed as absolute number (percentage)

# The role of Ulipristal Acetate in infertile women with submucosus fibroids: our results

- ✓ First series, where UPA has been used in patient with fibroids distorting the uterine cavity prior to IVF treatment, demonstrating an **ongoing pregnancy rate of 50%**
- ✓ **Mean volume reduction of 41%** and only one patient was referred to surgery because no fibroid size reduction was detected
- ✓ We didn't observe **any complication during pregnancy**, related to excessive growth of the myomas.
- ✓ Pre ART UPA treatment does not impairs embryos quality or foetal morphology and the subsequent pregnancy did not affect fibroid size



**Restoration of normal uterine cavity by UPA treatment, improves pregnancy rate and may avoid surgery**