



**Dipartimento di Medicina Molecolare e dello Sviluppo
Ostetrica e Ginecologica**

Sanguinamenti uterini anomali: quale trattamento

Stefano Luisi



CIR^oNAR

CENTRO INTERUNIVERSITARIO PER LO STUDIO DELLE BASI
MOLECOLARI DELLE MALATTIE DELLA RIPRODUZIONE

Abnormal Uterine Bleeding

Childhood	Early puberty
	Hypo-pituitary-ovarian axis disorders
Adolescence	Ovulatory disorders
	Infections
	Unknown pregnancy
	Coagulopathy
Reproductive age (30-40 years)	Oral contraceptives
	Post pregnancy
	Disfunctional bleeding-anovulation
	Organic lesions
Perimenopause (50 years)	Disfunctional bleeding-anovulation
	Organic lesions
	Neoplasia
	Atrophy
Postmenopause (60 years)	Benign organic lesions
	HRT
	Neoplasia



Abnormal Uterine Bleeding



- ✓ In pubertà: 20%
- ✓ In età fertile: 30%
- ✓ In perimenopausa: 50%

- ✓ Impatto sulla qualità di vita della donna
 - ✓ Perdita di giorni lavorativi
 - ✓ Costi sanitari

Abnormal Uterine Bleeding: definition

Parameter	Normal	Abnormal	<input checked="" type="checkbox"/>
Frequency	Absent (no bleeding) = amenorrhea	<input type="checkbox"/>	
	Infrequent (>38 days)	<input type="checkbox"/>	
	Normal (≥ 24 to ≤ 38 days)	<input type="checkbox"/>	
	Frequent (<24 days)	<input type="checkbox"/>	
Duration	Normal (≤ 8 days)	<input type="checkbox"/>	
	Prolonged (>8 days)	<input type="checkbox"/>	
Regularity	Normal or "Regular" (shortest to longest cycle variation: $\leq 7\text{-}9$ days)*	<input type="checkbox"/>	
	Irregular (shortest to longest cycle variation: $\geq 8\text{-}10$ days)*	<input type="checkbox"/>	
Flow Volume (patient determined)	Light	<input type="checkbox"/>	
	Normal	<input type="checkbox"/>	
	Heavy	<input type="checkbox"/>	

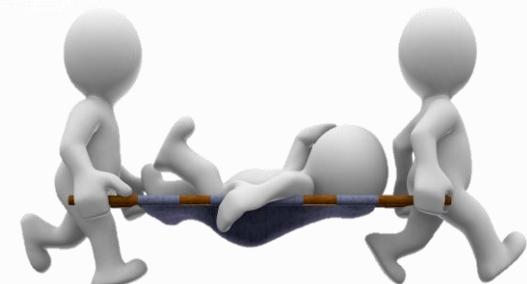
Intermenstrual Bleeding (IMB) Bleeding between cyclically regular onset of menses	None	<input type="checkbox"/>
	Random	<input type="checkbox"/>
	Cyclic (Predictable)	<input type="checkbox"/>
	Early Cycle	<input type="checkbox"/>

Unscheduled Bleeding on Progestin \pm Estrogen Gonadal Steroids (birth control pills, rings, patches or injections)	Not Applicable (not on gonadal steroid medication)	<input type="checkbox"/>
	None (on gonadal steroid medication)	<input type="checkbox"/>
	Present	<input type="checkbox"/>

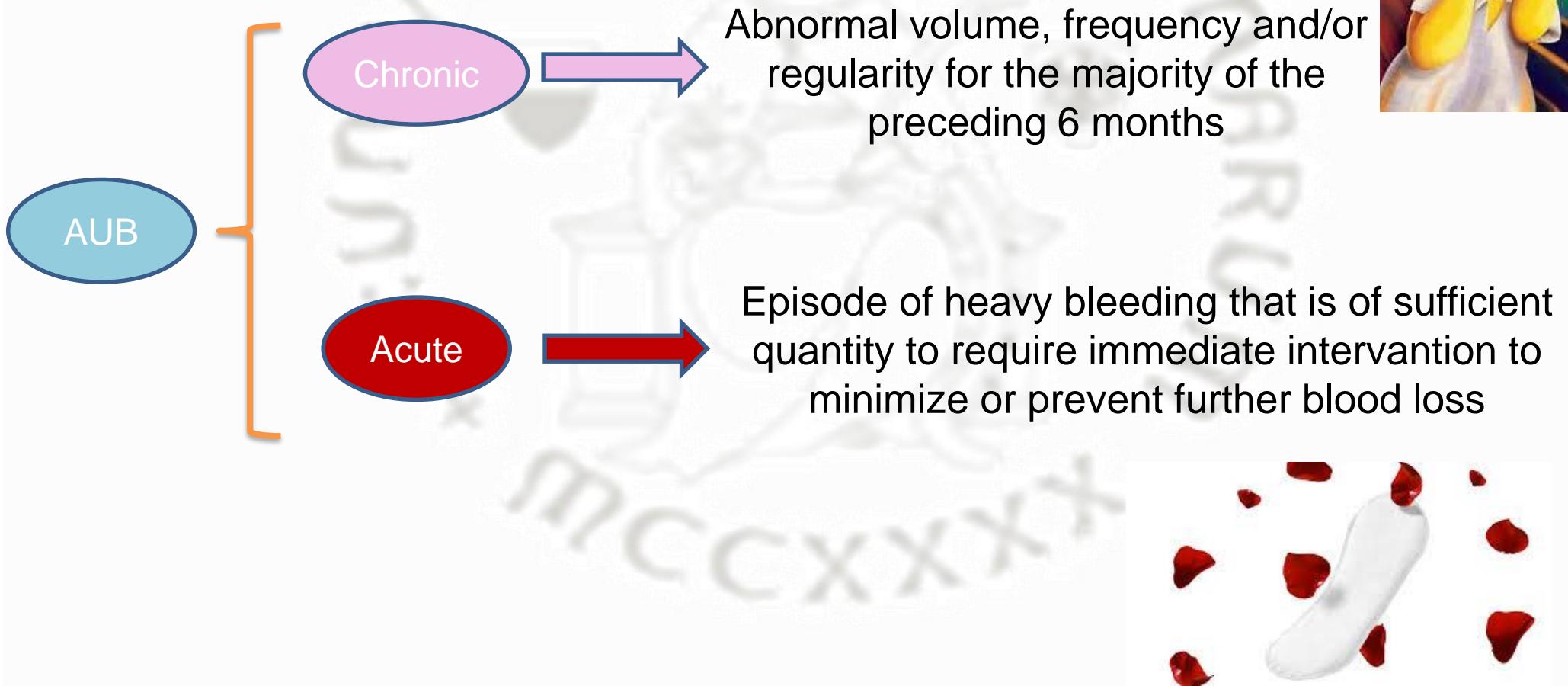
©Malcolm G. Munro MD

Heavy menstrual bleeding (HMB) is defined as excessive menstrual blood loss (> 80 ml) leading to interference with the physical, emotional, social and material quality of life of a woman.

This level of blood loss increases the risk of iron deficiency anaemia!



Abnormal Uterine Bleeding (AUB): classification

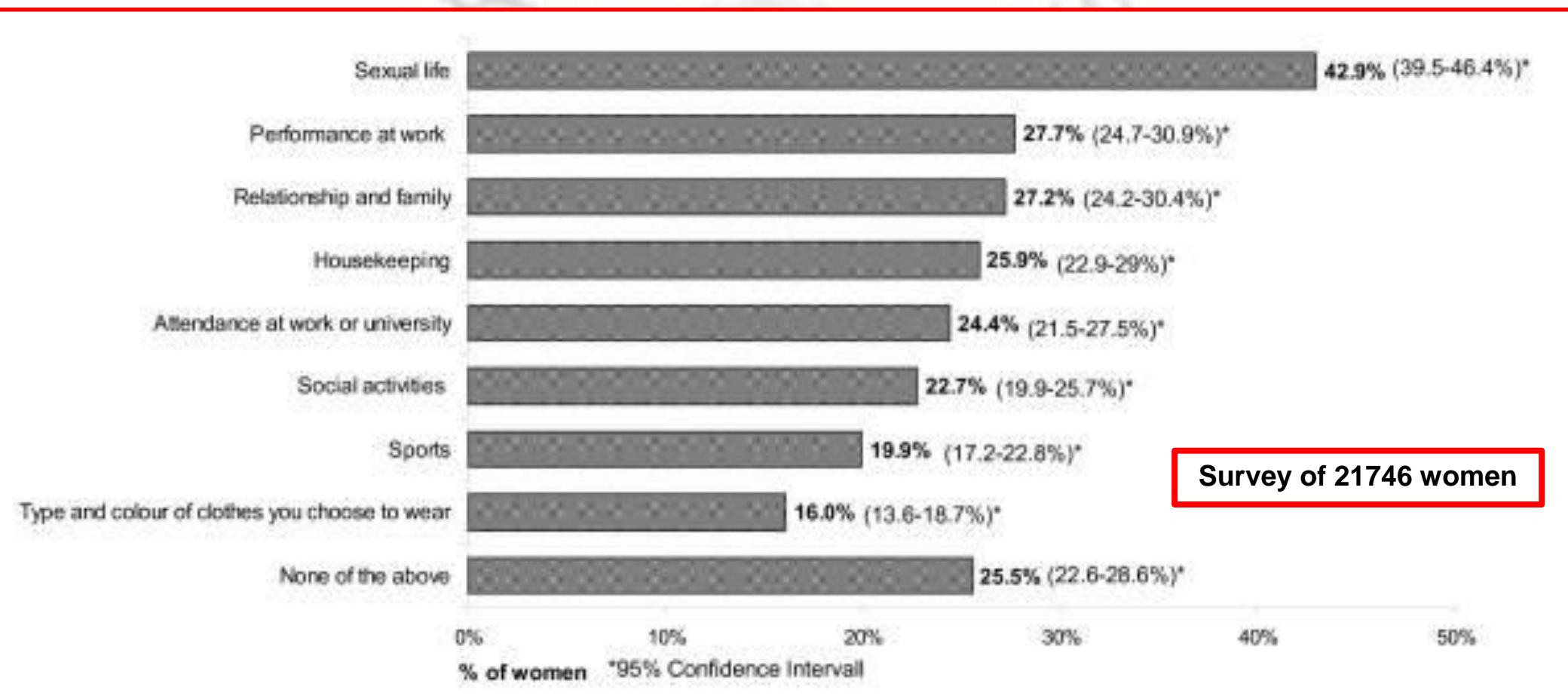


Pictorial blood loss assessment chart

Assorbenti	1	2	3	4	5	6	7	8	9	10	Fattore	Totale
							3	2			X 1	5
					3						X 5	30
	4	3	3								X 20	200
Coaguli		X	X								X 1	2
	X										X 5	5
Vestiti	X										X 1	1
											TOT. 243	

PBAC = 243

AUB and QoL: activities negatively affected by symptoms



Abnormal Uterine Bleeding: numbers

Gli AUB sono un grande problema di salute pubblica. Tra le donne di età compresa tra 30 e 49 aa, 1 su 20 donne ogni anno consulta il proprio medico di medicina generale per sanguinamento

20% delle donne è sottoposta ad isterectomia la cui causa principale è un flusso abbondante. Il 40% di queste ha un utero normale all'esame istologico

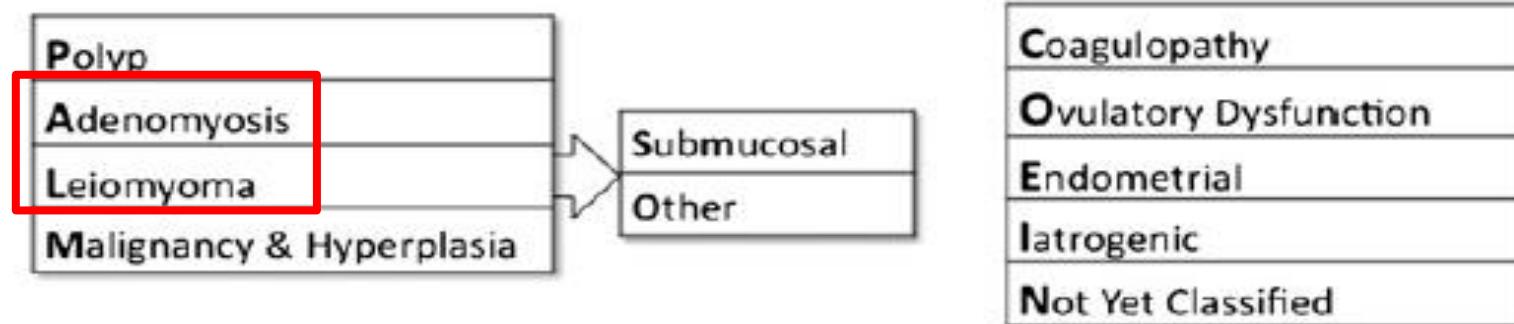
I disordini mestruali interferiscono significativamente con la qualità di vita di donne sane. Nel Regno Unito tali problemi sono associati alla perdita di 3.5 milioni di giornate lavorative all'anno e il costo associato al trattamento per sanguinamento eccessivo è di 65 milioni di pounds, raggiungendo l'alto costo dell'isterectomia

Nel 2002, nel Regno Unito sono state eseguite più di 13000 interventi chirurgici a causa di sanguinamenti mestruali abbondanti

PALM-COEIN Classification for Causes of Abnormal Bleeding

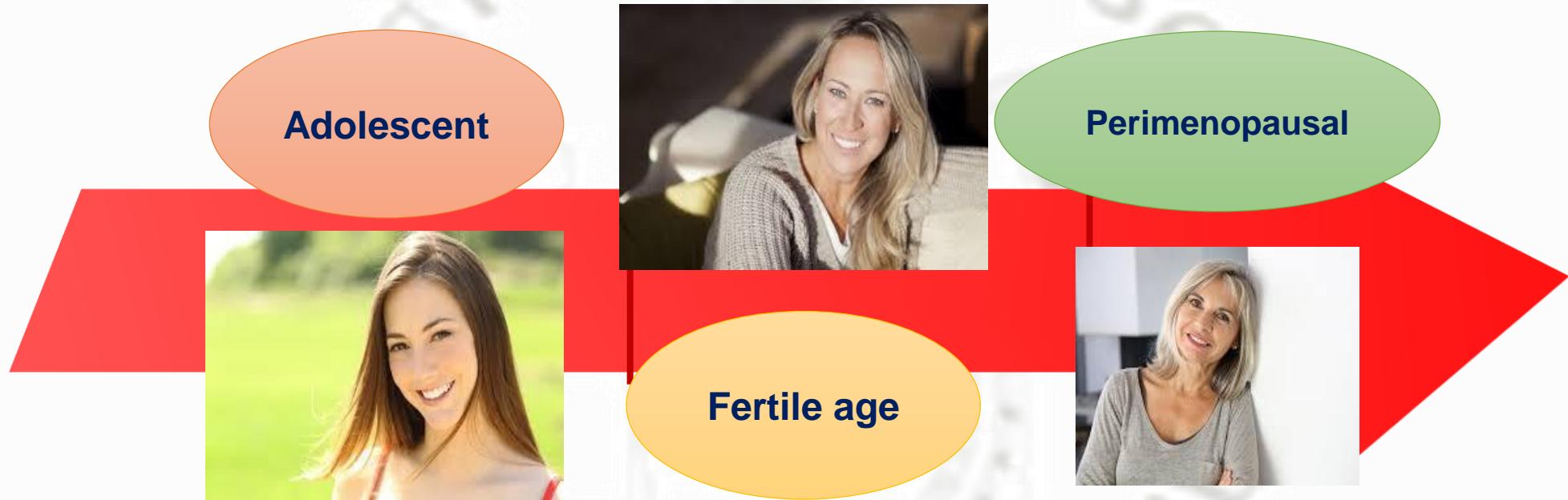
FIGO - Working group on menstrual disorders

The classification system is stratified into nine basic categories that are arranged according to the acronym PALM-COEIN



Abnormal Uterine Bleeding

The prevalence, causes and management of the AUB varies according to age



Come guidare il ragionamento di fronte ad una paziente con sanguinamenti uterini anomali: epidemiologia, classificazione, eziologia



AUB in adolescents

Non structural



Incidence: 12-37%

Coagulopathy

Ovulatory dysfunction

Iatrogenic

4%

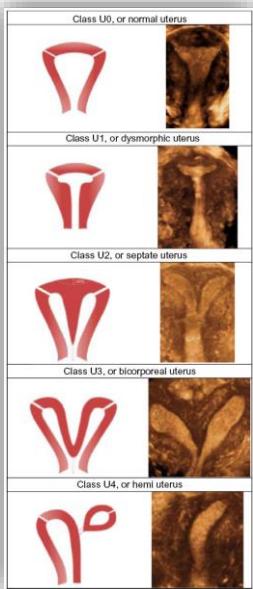
Breakthrough bleeding
Drugs

Von willebrand disease
Thrombocytopenia
Platelet dysfunction
Coagulation defects

1%

Anovulatory cycles
Polycystic ovary syndrome
Hyperprolactinemia
Hypothyroidism
Mental stress
Obesity or anorexia
Weight loss or extreme exercise

95%



Structural

- ✓ uterine malformations
- ✓ lacerations
- ✓ sexual abuse
- ✓ foreign body
- ✓ pregnancy

AUB in fertile age



- 50% non structural causes
- 30% uterine fibroids
- 20-25% adenomyosis
- 6-20% polyps
- 12% endometrial hyperplasia
- <5% endometrial cancer

Table 2.1 Medications that can be associated with abnormal uterine bleeding

Anticoagulants
Antidepressants (selective serotonin reuptake inhibitors and tricyclics)¹
Hormonal contraceptives
Tamoxifen
Antipsychotics (first generation and risperidone)^{2,3}
Corticosteroids
Herbs: ginseng,⁴ chasteberry,⁵ danshen⁶

Coagulopathy
Ovulatory dysfunction
Endometrial
Iatrogenic
Not yet classified

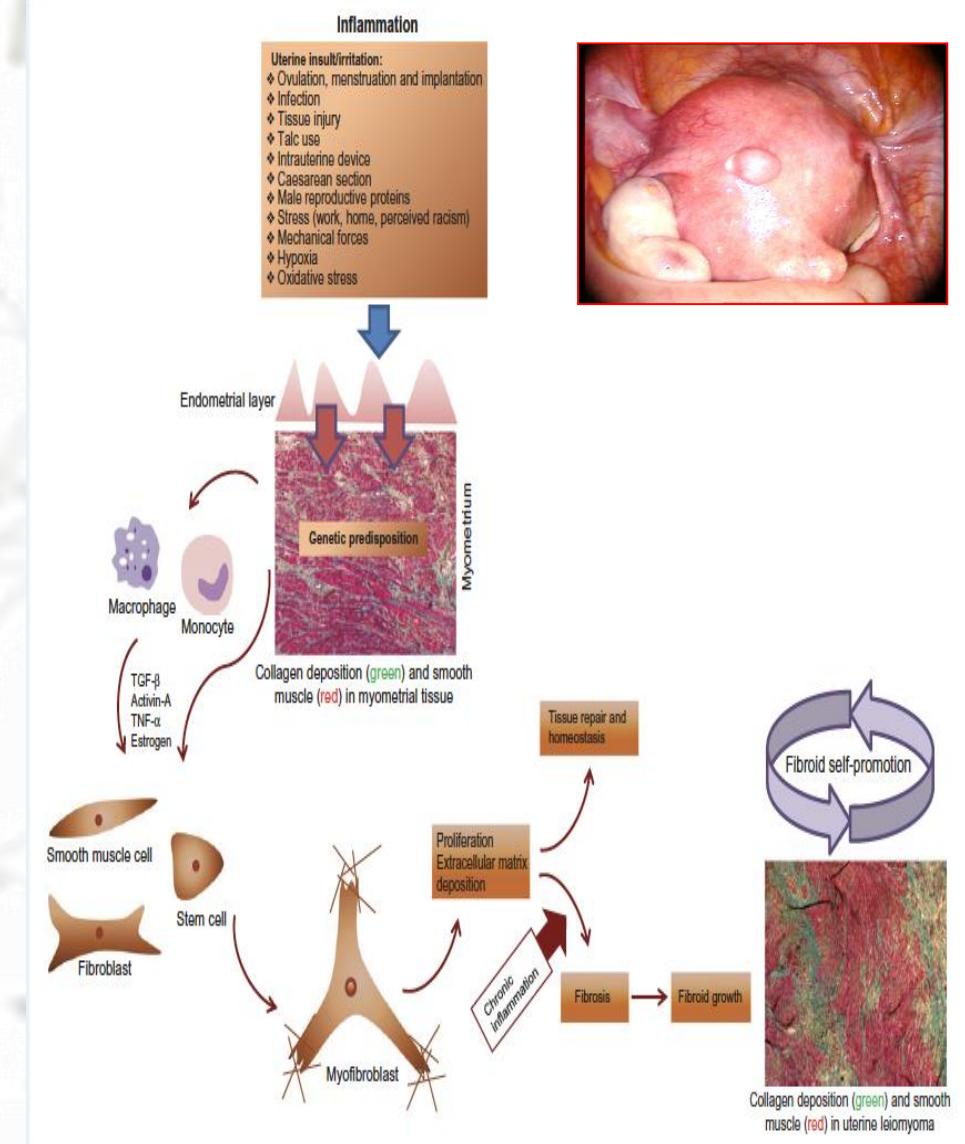


AUB in fertile age: uterine fibroids

❖ Uterine fibroids are benign lesions or neoplasms of the uterus that are composed of smooth muscle cells and fibroblasts and are rich in extracellular matrix

❖ Fibroids are common and occur in >70% of women

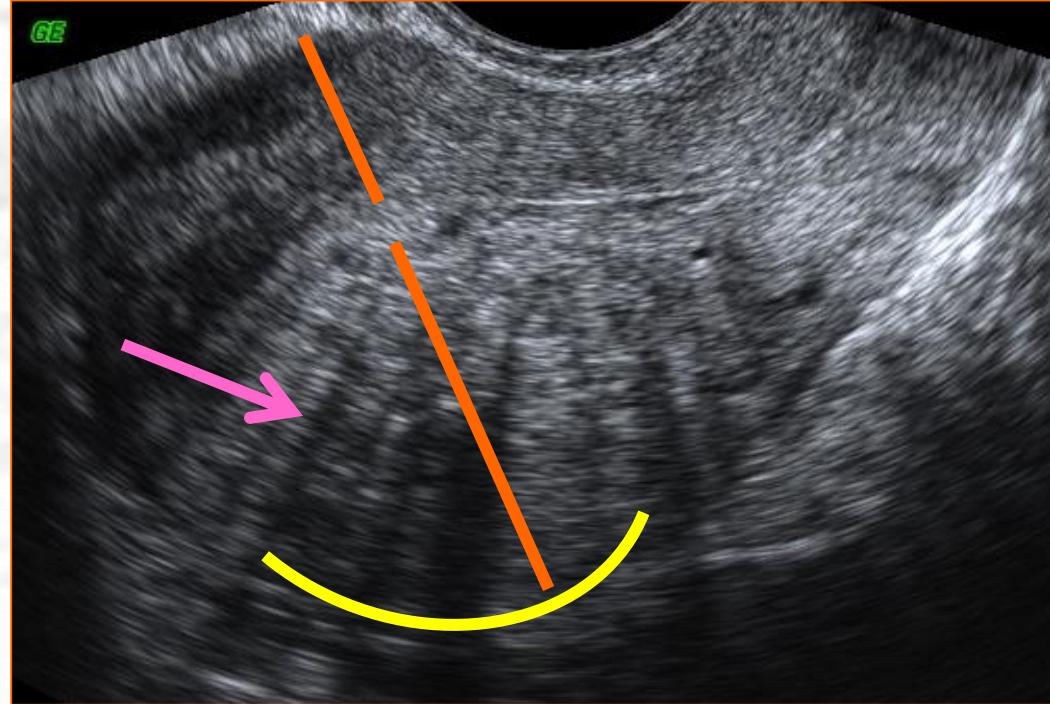
❖ Fibroids seem to develop and regulate gene expression in response to the menstrual cyclicity of gonadal steroids (mainly oestrogen and progesterone)



AUB in fertile age: adenomyosis

Presence of ectopic endometrial glands and stroma surrounded by hyperplastic smooth muscle within the myometrium

Despite the prevalence of the disease, its precise aetiology and physiopathology remain in part unknown



Some hypotheses have been developed

Invagination of the endometrium basalis into the myometrium through an altered or absent junctional zone

Tissue injury and repair (TIAR)

Stem cell theory

AUB in perimenopause

- 30% endometrial atrophy
- 30% HTR
- 10% polyps
- 10-15% endometrial cancer
- 5-10% endometrial hyperplasia
- 1% cervical cancer



Modifications of HPO:

- Reduction of FSH-sensitive follicles → increased FSH (shorter Follicular phase) → **REGULAR CYCLES, OVULATORS BUT SHORT**
- Slower growth of dominant follicle with possible anovulatory cycles ed inadequate luteal phase → stimulus estrogenic not balanced by progesterone



Normal cyclical menstrual alterations

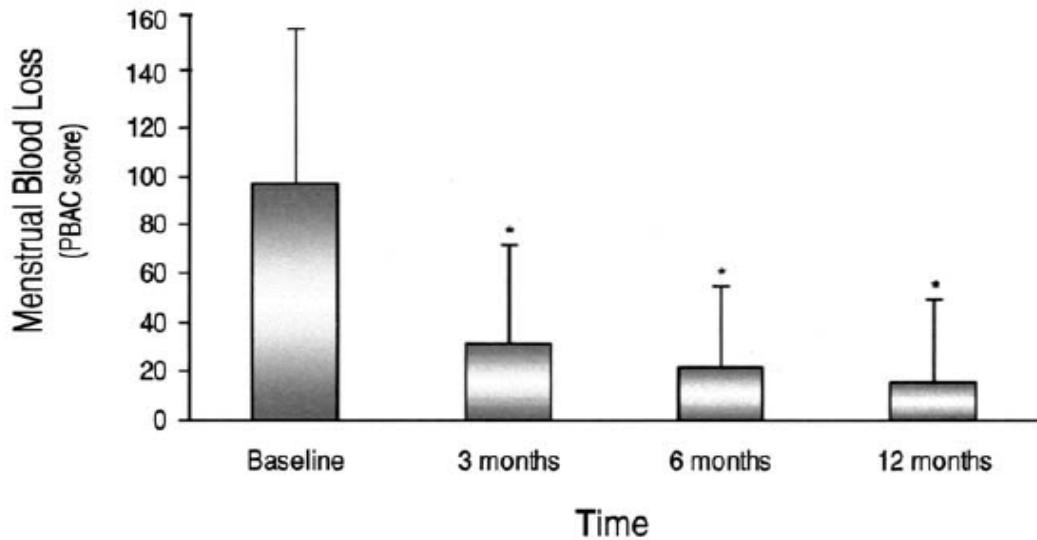
- ✓ Follicle number reduction
- ✓ Worst egg quality

		Ultima mestruazione					
-2	-1	0	+1	+2			
Transizione menopausale		Post-menopausa					
precoce	tardiva		precoce	tardiva			
Peri-menopausa							
Durata dello stadio	variabile	1 aa	4 aa	Fino alla morte			
Fase follicolare corta		Cicli di lunghezza variabile (>7gg diversi dalla norma)	>2 cicli saltati o intervallo di amenorrea >60gg	Assenza di cicli			
Fase del corpo luteo inadeguato							
Fase anovulatoria (50% ovulazioni rispetto a soggetti tra 20-30 anni)							
		↑ FSH ↓ E2 con ampie oscillazioni	Aumento FSH				

AUB: medical treatment

Insertion of an LNG IUS promptly benefited women with heavy menstrual bleeding

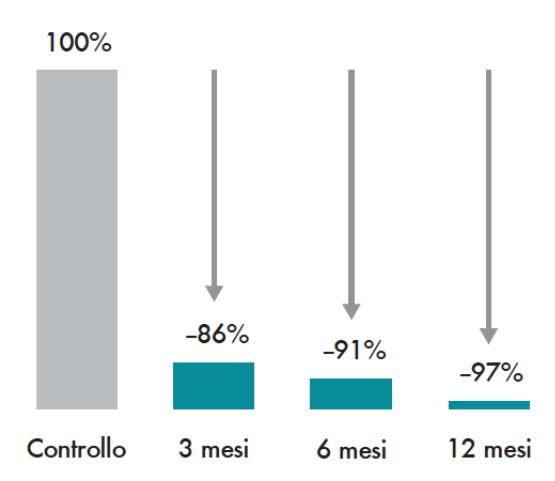
Estimated menstrual blood loss (mean \pm SD) before and after insertion of the levonorgestrel-releasing intrauterine system.
* $P<.001$ vs. baseline; PBAC = pictorial blood loss assessment chart.



- A profound reduction in menstrual blood loss occurred within 3 months after the IUS insertion
- 40% of participants had amenorrhea at the end of the study

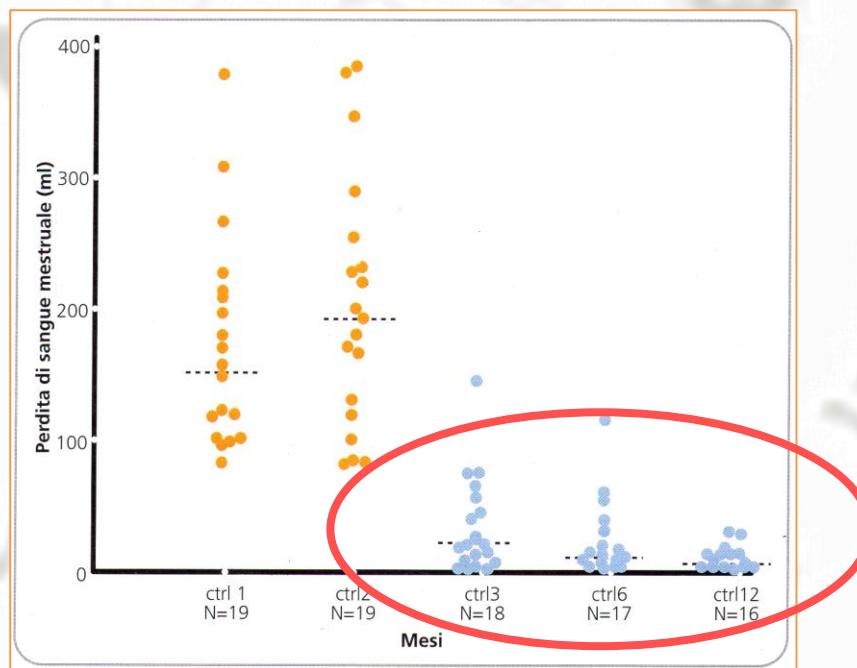
AUB: medical treatment

Figura 2. Riduzione della perdita ematica mestruale 3, 6 e 12 mesi dopo l'inserimento di MIRENA® in donne affette da menorrhagia.⁴



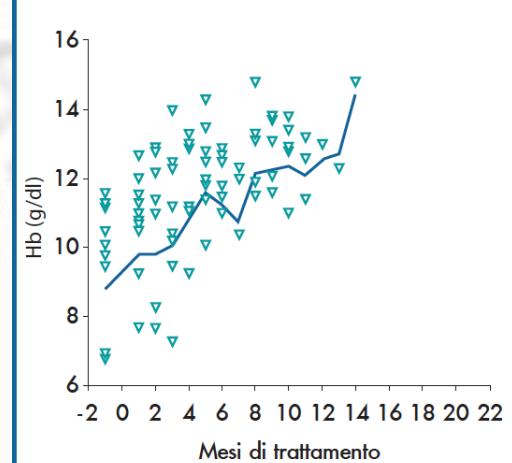
LNG-IUS is an effective therapeutic option conservative type also in selected cases of menometrorragie

Rosa e Silva JC et al. J Reprod Med 2005

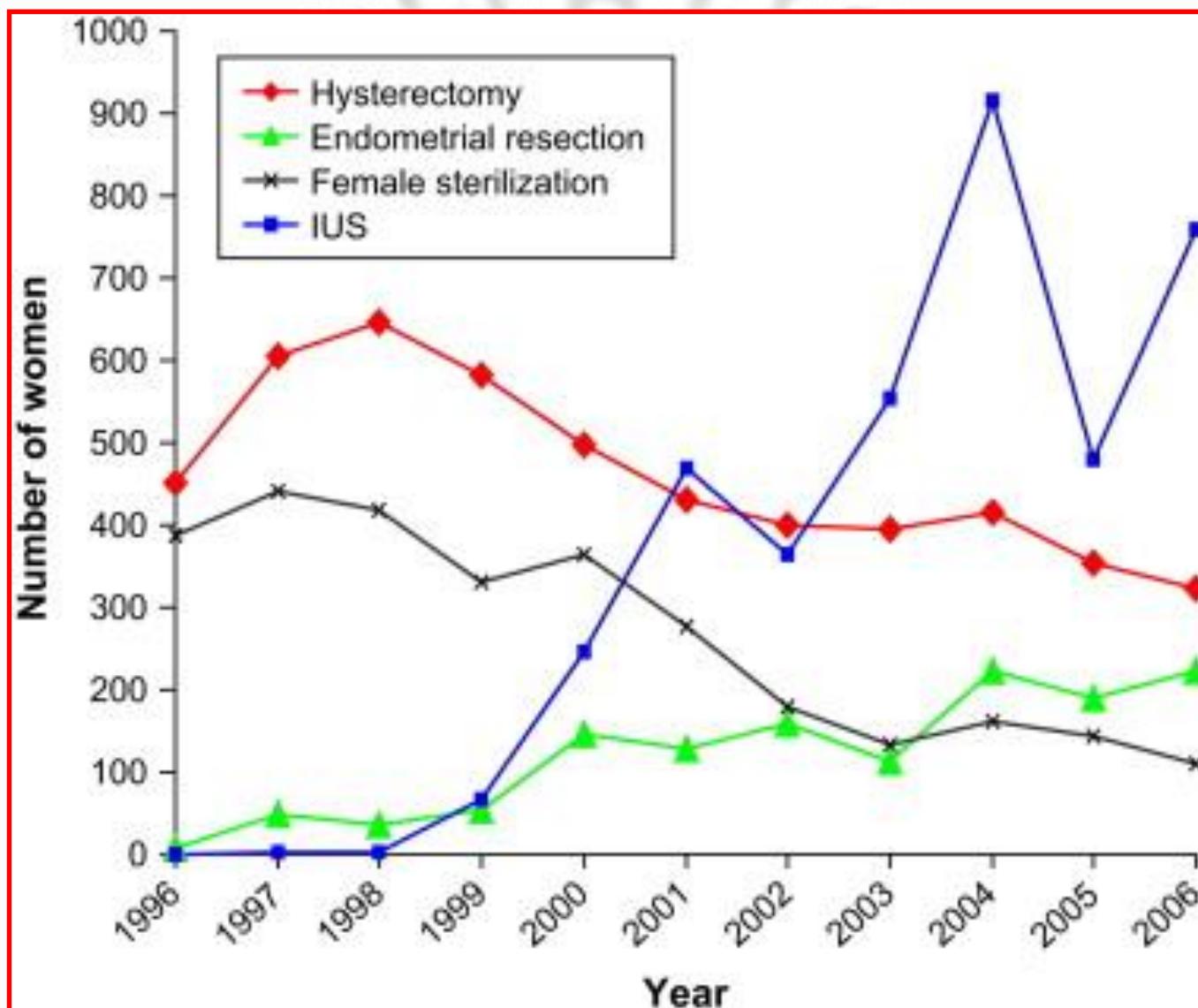


The average reduction of the flow is slightly less than 80% after one year and 2 in 3 women report amenorrhea and / or hypomenorrhea

Figura 1. Valori di emoglobina dopo l'inserimento di MIRENA®. La linea continua rappresenta i valori mediani.⁶

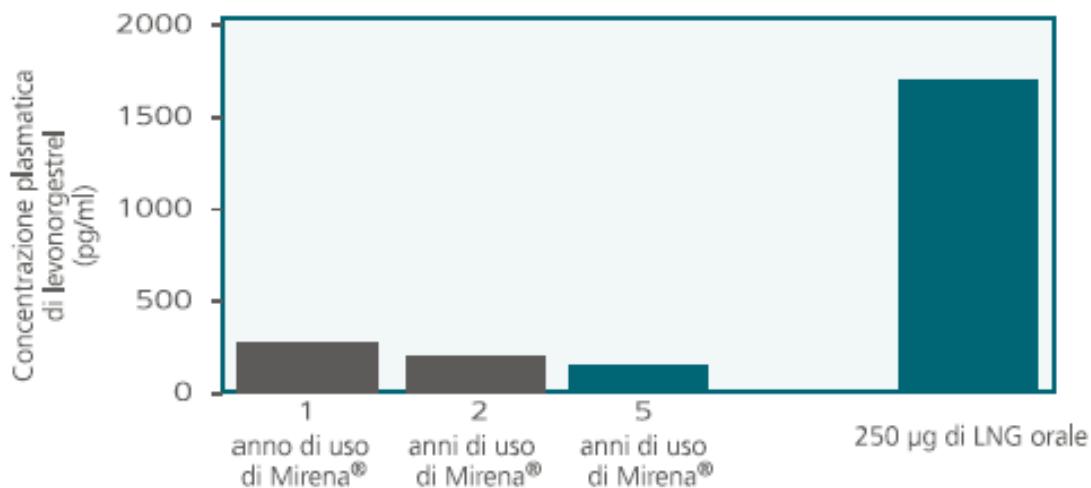


AUB: medical treatment



AUB: medical treatment

LNG-IUS: reduced systemic effects

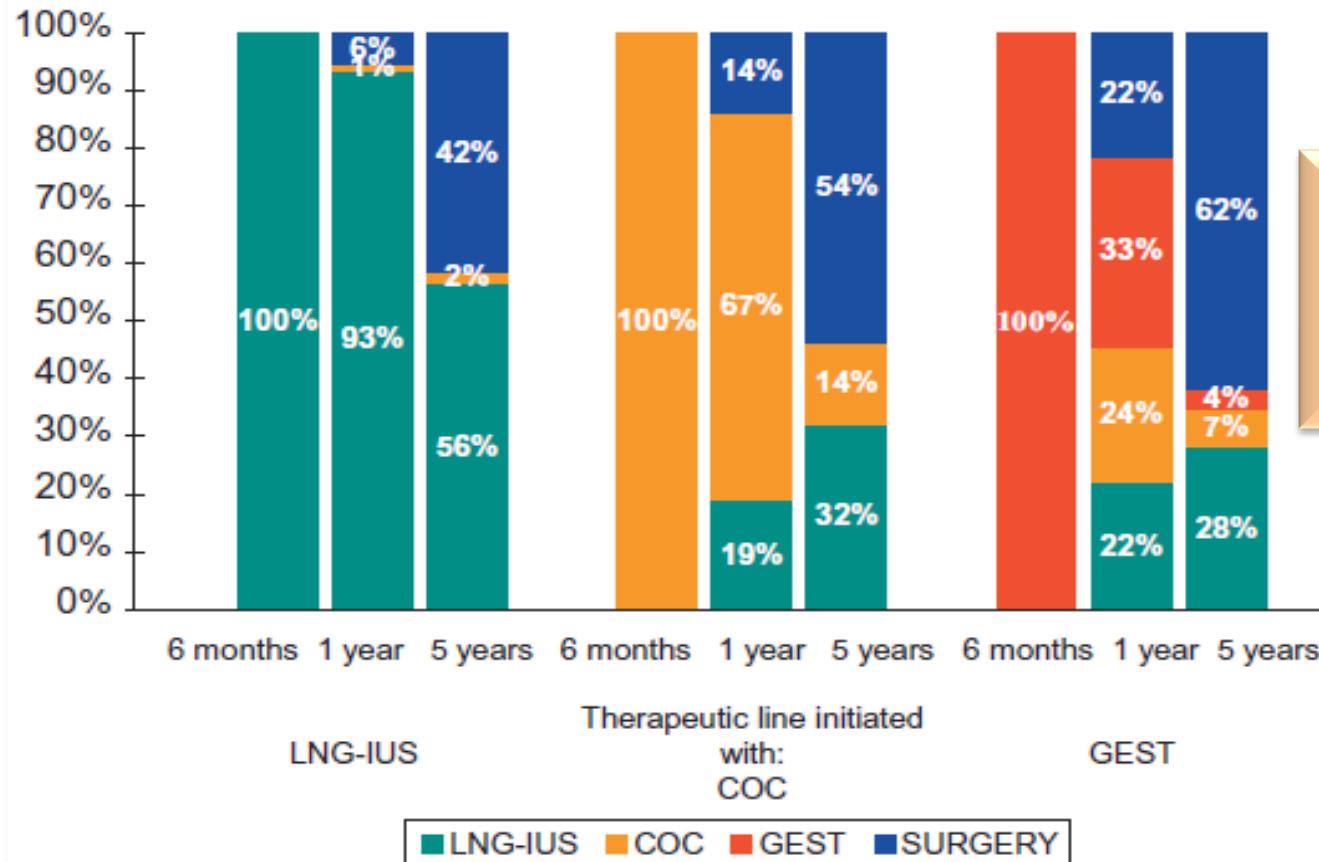


	LNG-IUS	LNG orale
Endometrio pg/ml	808±511	3,5
Serum ng/ml	0,1-0,2	1,7

The plasma concentration of Levonorgestrel remains stable and is significantly lower compared to oral therapy

AUB: medical treatment

Levonorgestrel IUS: European perspective



The lower effectiveness of treatment with COCs and progestogens leads to a rapid change of treatment

At the end of the first year LNG-IUS contributed 19% and 22% to therapeutic lines initiated with COC and progestogens respectively

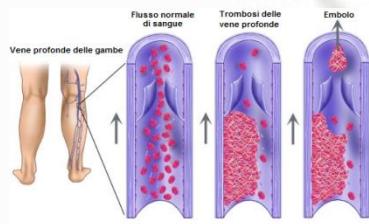
AUB: medical treatment

LNG-IUS: efficacy and safety

Trombosi Venosa Profonda

Familiarità: classe OMS 1

Pregressa: classe OMS 2

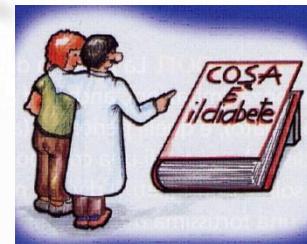


Obesità (BMI $\geq 30 \text{ kg/m}^2$) classe OMS 2



- **Classe OMS 1:** nessuna restrizione d'uso
- **Classe OMS 2:** i benefici superano i rischi
- **Classe OMS 3:** i rischi superano i benefici
- **Classe OMS 4:** rischio di salute inaccettabile

Diabete Mellito classe OMS 2 (se diabete gestazionale: classe OMS 1)



Fibromi uterini

Senza distorsione della cavità: classe OMS 1

Con distorsione della cavità: classe OMS 4



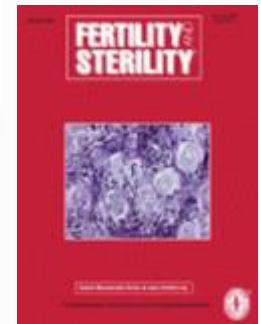
Fumo di sigaretta classe OMS 1



AUB: medical treatment

Adenomyosis: levonorgestrel IUS

Treatment of adenomyosis-associated menorrhagia with a levonorgestrel-releasing intrauterine device



Significant increase in hemoglobin, hematocrit
and serum ferritin

Lipid metabolism and clotting variables unchanged

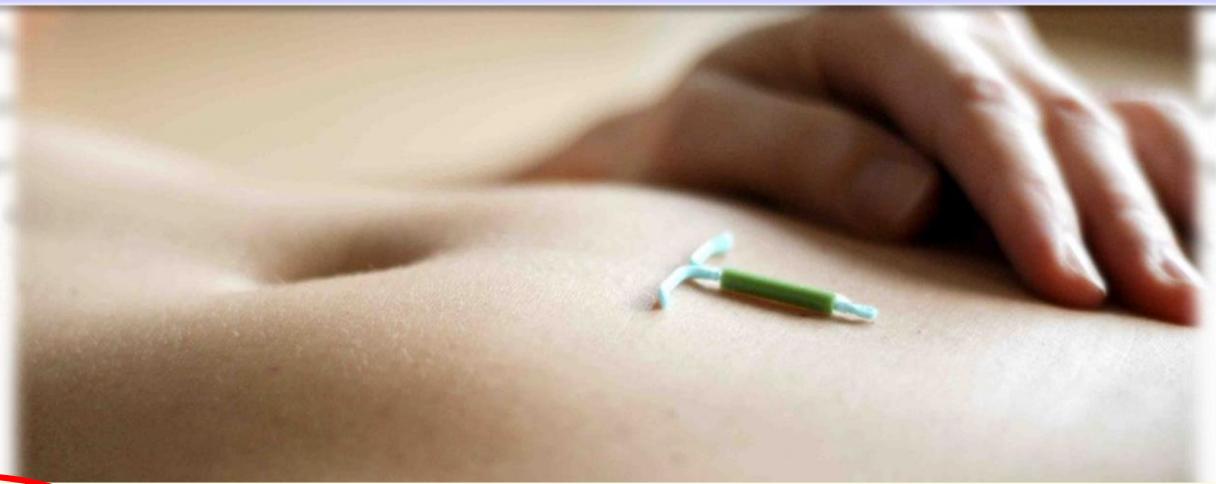
Significant and safe relief from adenomyosis-associated
menorrhagia can be obtained with the use of a levonorgestrel IUS

AUB: medical treatment

Adenomyosis: IUS and dysmenorrhea

LNG-IUS demonstrates significant and comparable improvements in health-related quality of life to hysterectomy, with superior effects on psychological and social life

Ozdegirmenci O. et al, Fertil Steril 2011



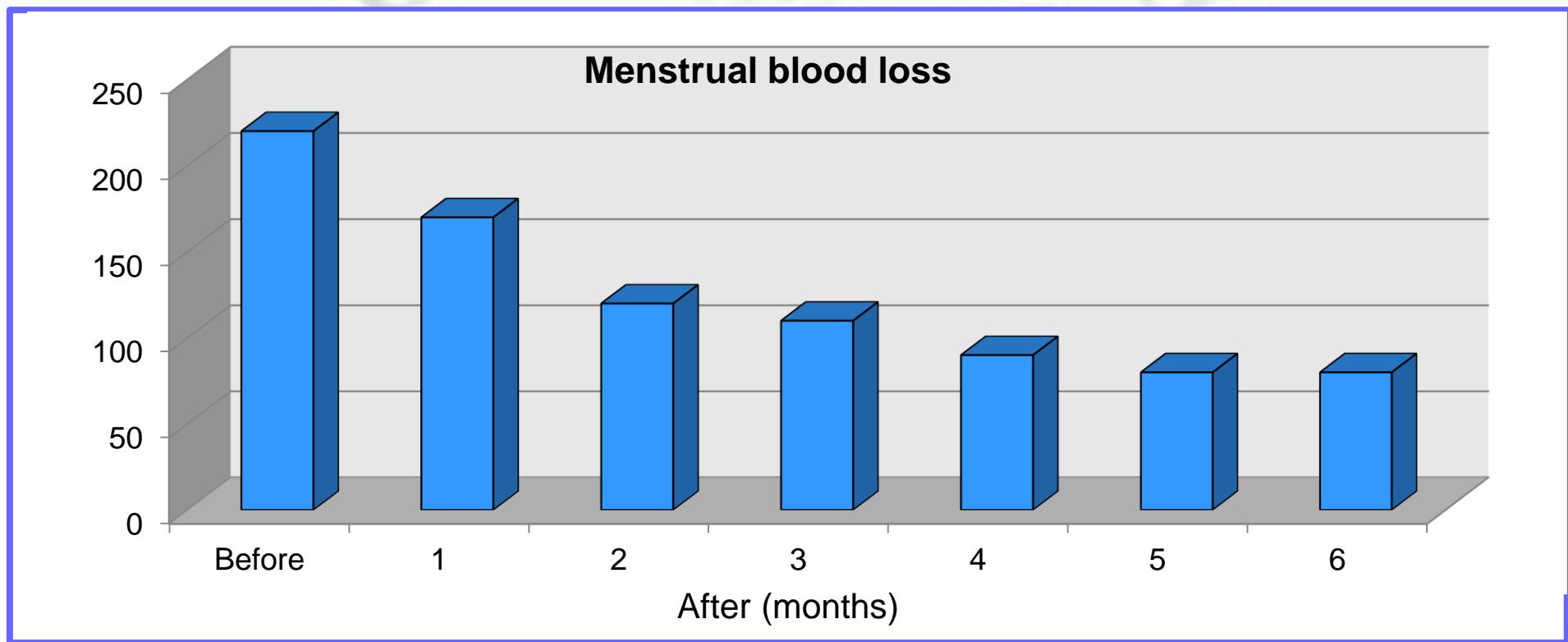
LNG-IUS appears to be an effective and long-term method in alleviating dysmenorrhea associated with adenomyosis during 3 years

Sheng J et al, Contraception 2009

AUB: medical treatment

Adenomyosis: vaginal treatment

Efficacy of vaginal danazol (200 mg) treatment in women with menorrhagia during fertile age



Daily vaginal administration of danazol tablet is efficacious and safe for reducing heavy menstrual bleeding in young women with menorrhagia

AUB: medical treatment

Adenomyosis: dienogest and pelvic pain

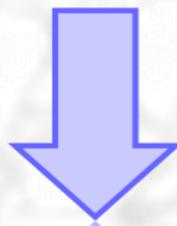
Efficacy and safety of dienogest in the treatment of symptomatic adenomyosis

70 patients with symptomatic adenomyosis were included in this study, of which 15 continued dienogest for up to 24 weeks

Dienogest significantly reduced adenomyosis-associated pelvic pain and is an effective and well-tolerated therapy

AUB and fibroids: medical treatment

The apparent importance of progesterone for the growth and development of uterine leiomyoma suggests that SPRMs may be a promising treatment for leiomyomas

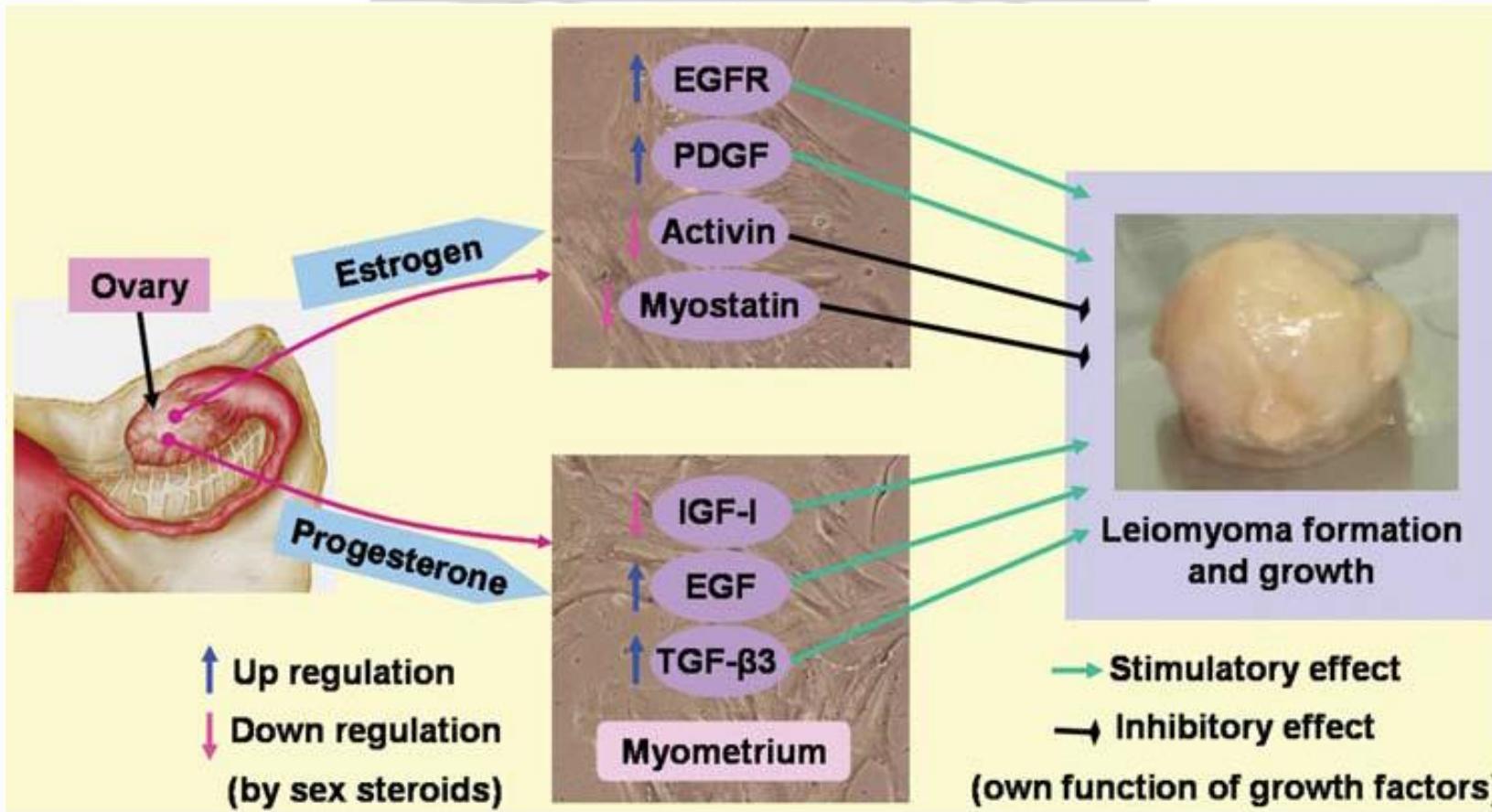


The greatest challenge is to identify a SPRMs compound with exquisite progesterone receptor selectivity to:

- act as a progestin in the endometrium
- act as an anti-progestin within the leiomyoma

AUB: medical treatment

Growth factor inhibitors

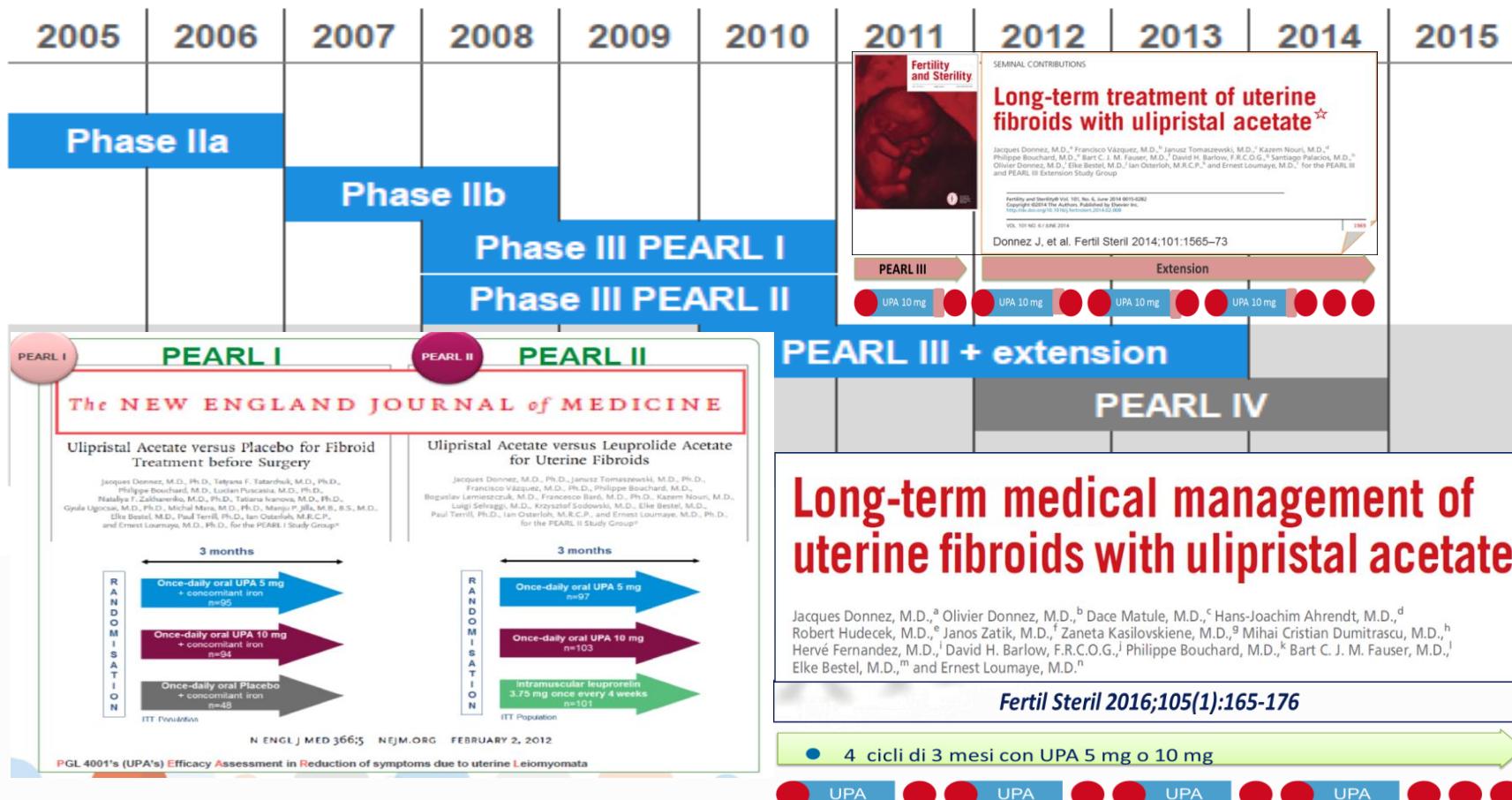


growth factor are considered the ultimate effectors of the steroid hormone actions because they have stimulatory or inhibitory effects on cell proliferation and leiomyoma formation

AUB: medical treatment

PEARL

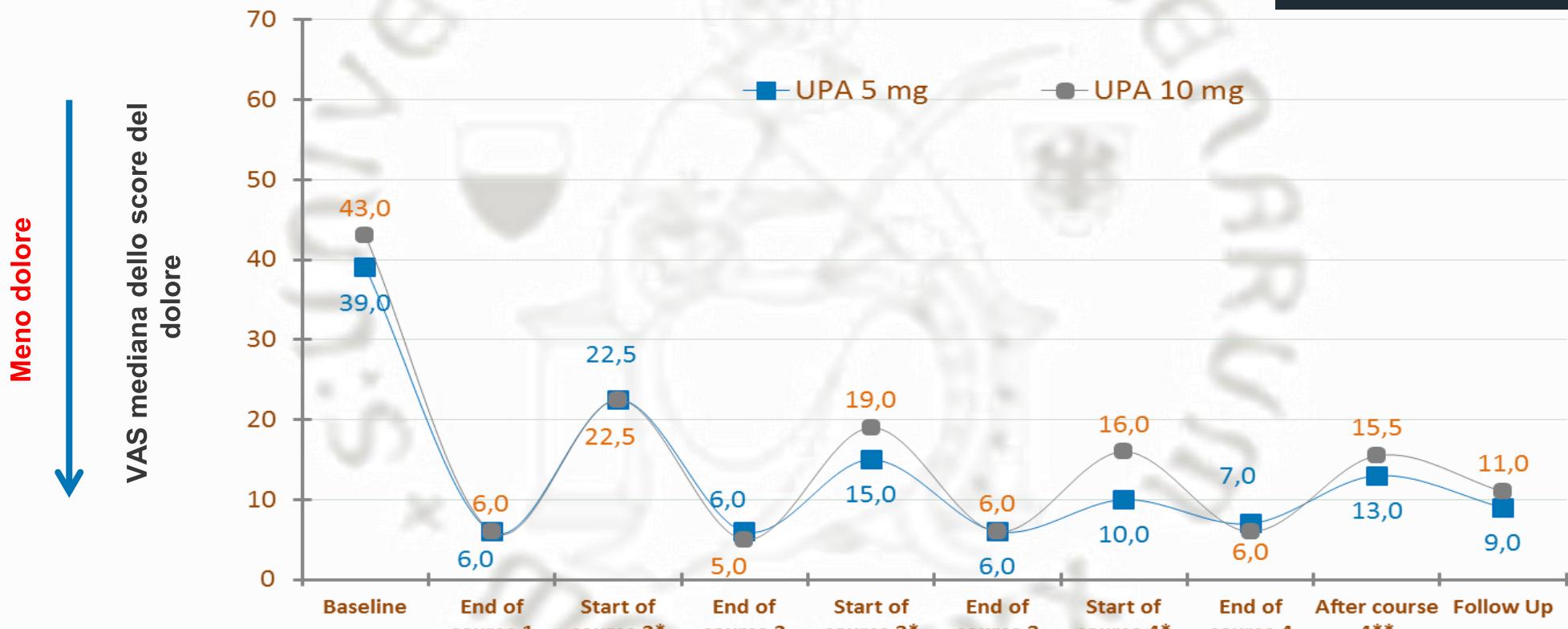
PGL4001's (UPA's) Efficacy Assessment in Reduction of symptoms to uterine Leiomyomata



AUB: medical treatment

Mediana dello score del dolore (VAS): tutte le pazienti

pain



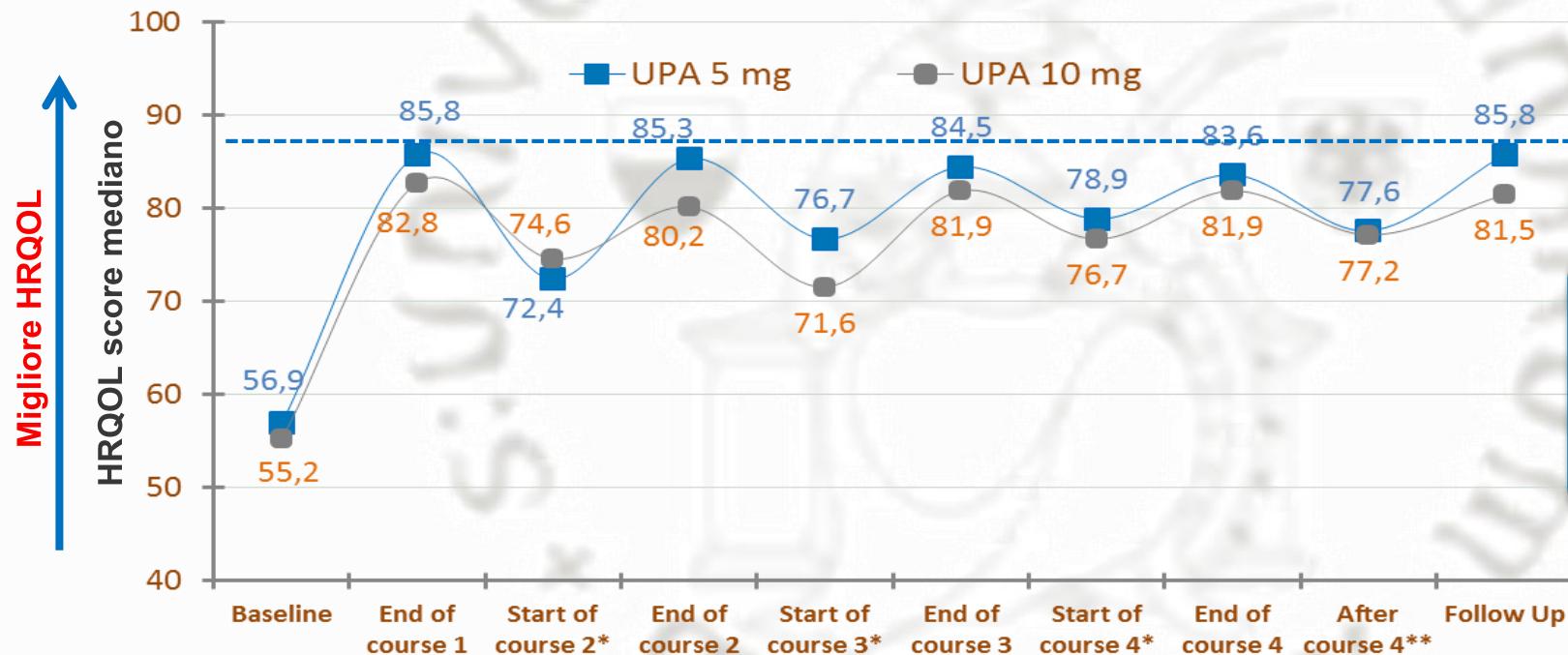
VAS: da 0, no dolore,
a 100, dolore peggiore possibile

* Durante mestruazioni

** all'inizio della II mestruazione dopo il IV ciclo

AUB: medical treatment

UFS-QoL: HRQoL score mediano totale (FAS1)



Livello riportato da soggetti sani

- HRQoL dominii valutati:
1. Ansia/timori
 2. Attività quotidiane
 3. Dinamismo/umore
 4. Autocontrollo
 5. Autocoscienza
 6. Attività sessuale

* Durante mestruazioni

** all'inizio della II mestruazione dopo il IV ciclo

AUB: medical treatment

8 CICLI RIPETUTI INTERMITTENTI ASPETTI ENDOMETRIALI



RESEARCH ARTICLE

Safety after extended repeated use of ulipristal acetate for uterine fibroids

Bart C. J. M. Fauser^{1*}, Jacques Donnez^{2†}, Philippe Bouchard^{3‡}, David H. Barlow^{4‡}, Francisco Vázquez^{5§}, Pablo Arriagada^{6¶}, Sven O. Skouby^{7||}, Santiago Palacios^{8**}, Janusz Tomaszewski^{9#}, Boguslaw Lemieszczuk¹⁰, Alastair R. W. William¹¹

¹ Department of Reproductive Medicine & Gynecology, University Medical Center Utrecht, Utrecht, The Netherlands, ² Société de Recherche pour l'Infertilité, Brussels, Belgium, ³ Endocrinology Unit, AP-HP Hopital Saint-Louis, Paris, France, ⁴ College of Medical Veterinary and Life Sciences, University of Glasgow, Glasgow, Scotland, UK and Hamad Medical Corporation, Doha, Qatar, ⁵ Centro de Estudios de Obstetricia y Ginecología Asociado, Lugo, Spain, ⁶ Gedeon Richter/Preglem S.A., Geneva, Switzerland, ⁷ Division of Reproductive Endocrinology, Dept OB/GYN, Herlev-Gentofte Hospital, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark, ⁸ Palacios Institute of women's Health, Madrid, Spain, ⁹ Prywatna Klinika Polozniczo-Ginekologiczna, Białystok, Poland, ¹⁰ Gabinet Lekarski Specjalistyczny Sonus, Warsaw, Poland, ¹¹ University of Edinburgh, Edinburgh, Department of Pathology Royal Infirmary of Edinburgh, Edinburgh, United Kingdom

Table 2. Summary of endometrium biopsy consensus and endometrium biopsy non-physiological descriptions (PAEC) (Full analysis set, N = 64).

	Screening	After course 4	After Course 8	3-month after course 8
Total Biopsies	52	61	48	24
Adequate Biopsies (^{1*})	50 (96.2%)	56 (91.8%)	43 (89.6%)	22 (91.7%)
Benign (^{2**})	50 (100%)	56 (100%)	43 (100%)	22 (100%)
Hyperplasia (^{2**})	0	0	0	0
Malignant neoplasm (^{2**})	0	0	0	0
Non-physiological changes observed by two or three pathologists**	9 (18.0%)	12 (21.4%)	7 (16.3%)	2 (9.1%)

The current study convincingly demonstrates that the extended intermittent administration of UPA 10 mg once daily for 3 months with drug-free intervals, bringing the total number treatment courses undertaken to 8, is well tolerated in women of reproductive age with symptomatic uterine myoma

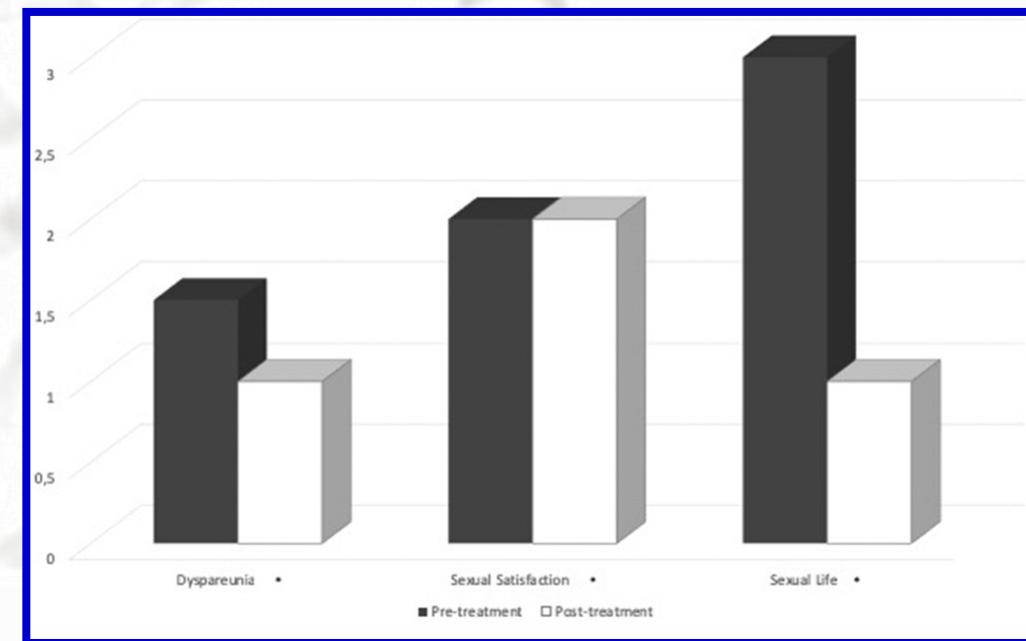
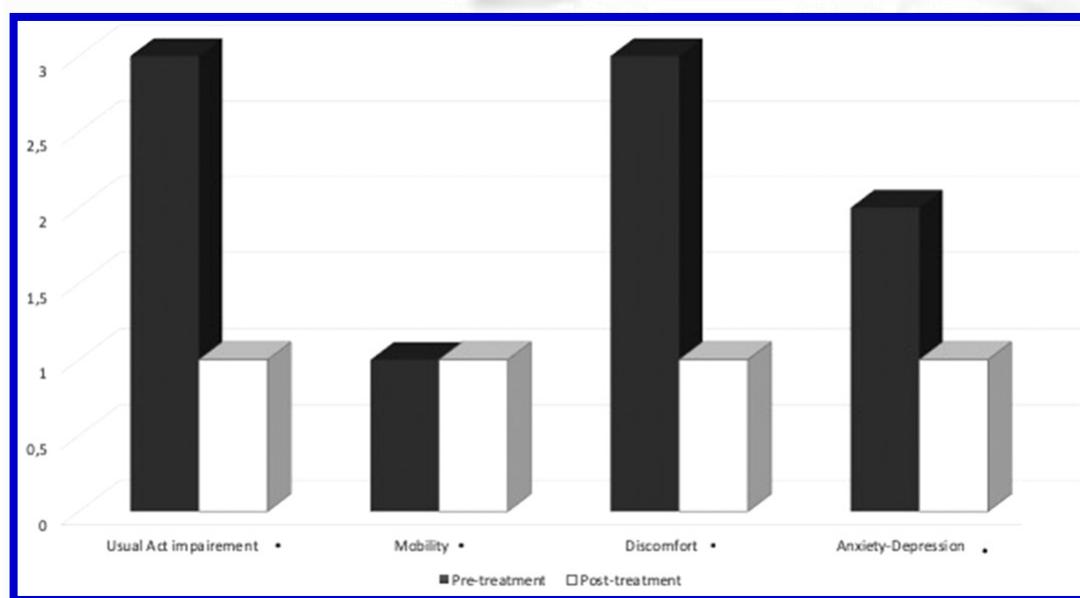
AUB: medical treatment

	DATA
1° TEST (prima dell'inizio del trattamento)	
Inizio del trattamento	
2° TEST (4 settimane dopo l'inizio del trattamento)	
3° TEST (8 settimane dopo l'inizio del trattamento)	
4° TEST (12 settimane dopo l'inizio del trattamento)	
5° TEST (2-4 settimane dopo l'interruzione del trattamento con Esmya)	



UPA on quality of life and sexual function of women with uterine fibromatosis

139 patients affected by uterine fibromatosis undergoing conservative UPA treatment were enrolled in this prospective observational cohort study. Women (average age 46.5 years) answered the questionnaires: QoL and sexuality were evaluated before and after ulipristal acetate treatment



This study provides a clear picture about QoL impact on women and confirms the effectiveness of the UPA in improving different aspects of daily and sexual life of patients undergoing medical treatment

Counseling.....



Medical treatment

Surgical treatment

Buonasera Professore,

Sono venuta da Lei in ospedale il 12/1 scorso. Mi e' stata proposta la terapia tramite ESMYA per un fibroma uterino che mi ha provocato dei cicli abbastanza abbondanti e con grumi.

Ho avuto modo di relazionarmi con il mio medico di base che mi ha convinto ad attendere il ciclo di fine gennaio e valutare la situazione in quanto contrario all'utilizzo di questi farmaci.

Sinceramente mi sono informata in modo più accurato su come si potesse basare la cura ed anche io ho avuto delle perplessità soprattutto per quello che concerne il fatto di dover interrompere il ciclo alla mia età aspettando la menopausa.

La ringrazio per la Sua cortesia nell'avermi ricevuto e nell' avermi spiegato la terapia, ma ora sono più tranquilla se aspetto qualche mese e valuto l'ingrossamento del fibroma e il suo eventuale sanguinamento, rimandando la decisione tra qualche tempo.

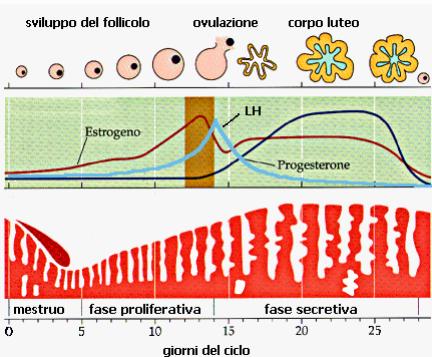
Cordialmente La saluto

Conclusions



Il sanguinamento uterino anomalo rappresenta un segnale di disfunzione di rilievo clinico di grande interesse pratico

Occorre affrontare l'argomento con un ampia visuale culturale, di tipo trasversale, tenendo presente gli aspetti endocrino-riproduttivi ma anche quelli oncologici



La conoscenza della fisiopatologia, la diagnostica differenziale e la successiva terapia costituiscono l'obiettivo da perseguire nella nostra pratica clinica, in maniera tale da individuare i segnali da valutare correttamente nella prevenzione di disturbi della funzione riproduttiva femminile

Department of Molecular and Developmental Medicine
University of Siena



Hospital “Santa Maria alle Scotte”

Menstrual disorders Center

