Dipartimento di Medicina Molecolare e dello Sviluppo
Ostetrica e Ginecologica

Endometriosi e fibromatosi uterina: la terapia medica, indicazioni e strategie

Stefano Luisi

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

Endometriosis: definition

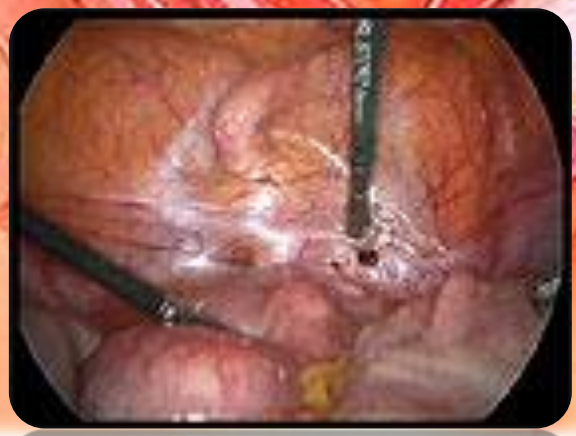
Endometriosis is a common, benign, estrogen-dependent, chronic gynaecological disorder characterized by the presence of uterine endometrial tissue outside of the normal location

Peritoneum

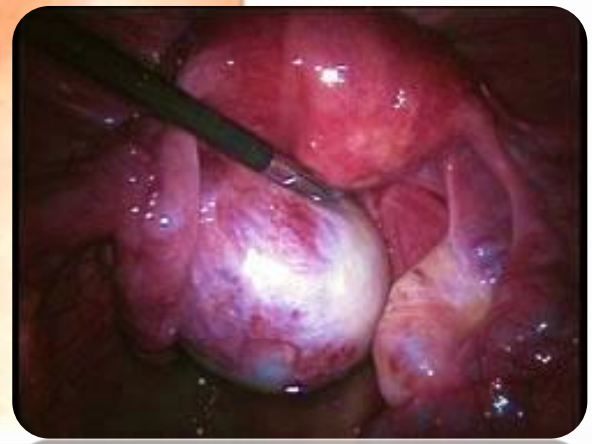
Ovary

Deep endometriosis

- ✓ Rectovaginal pouch
- ✓ Uterosacral ligaments
- ✓ Bowel
- ✓ Bladder
- ✓ Ureter

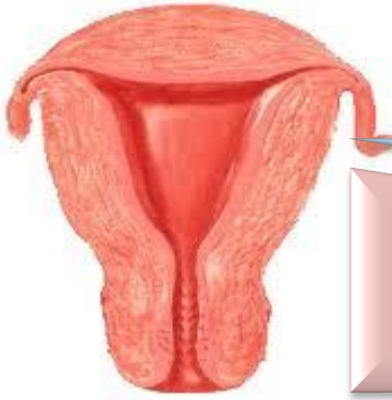


Superficial peritoneal endometriosis



Endometrioma

Endometriosis and pain



Chronic pain

Mestruation-related pain

- *Dysmenorrhea*
- *Dyspareunia*
- *Dysuria*
- *Dyschezia*

- *Chronic pelvic pain*
- *Headache*

HPA axis activity

Central sensitisation

Psycological state

Autonomic nervous system

Brawn et al, Hum Reprod Update 2014

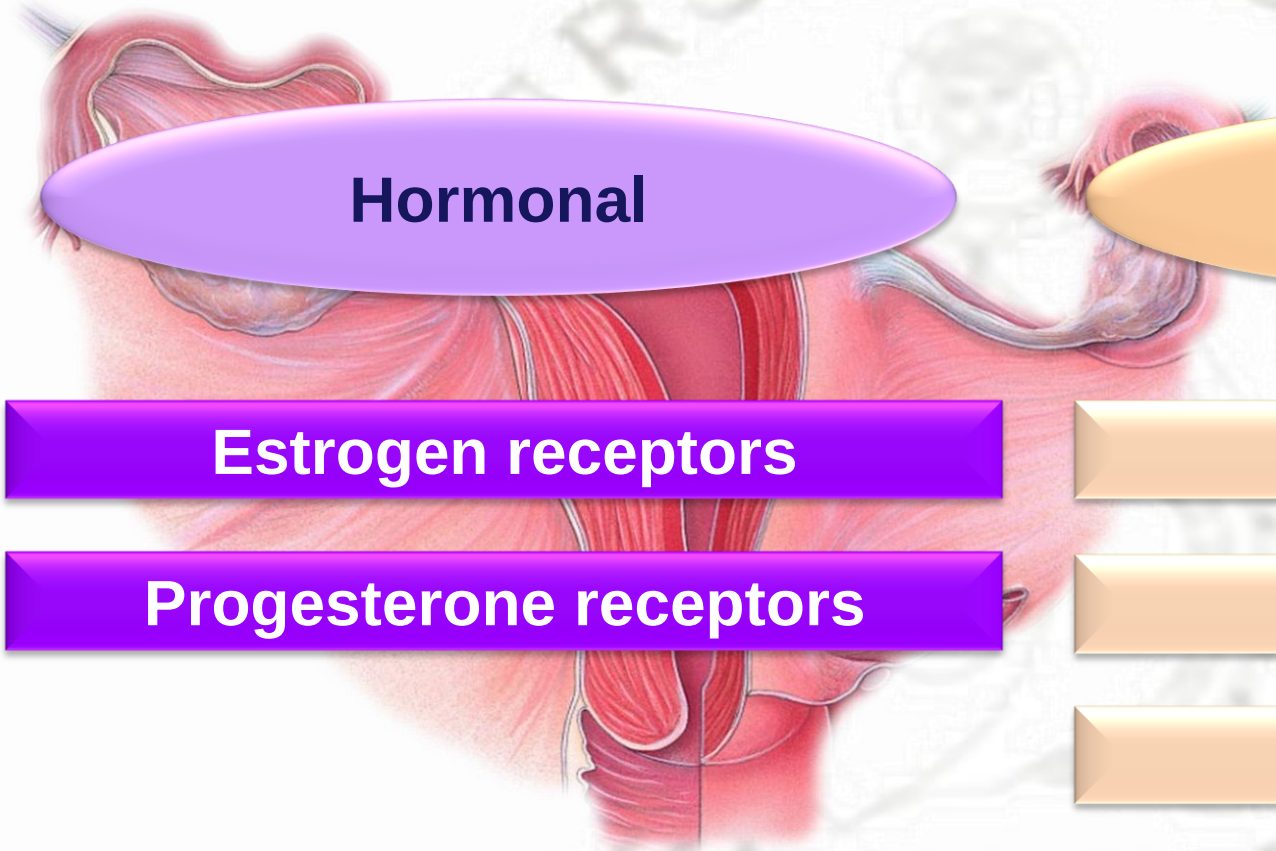
Endometriosis is a disease with high impact on women's health

For many women, endometriosis has a negative impact on the ability to work, on family relationships and self-esteem

"Endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures"

Huntington and Gilmour, Pain, 2005

Medical treatment for endometriosis: targets



Hormonal

- Estrogen receptors
- Progesterone receptors

Non - hormonal

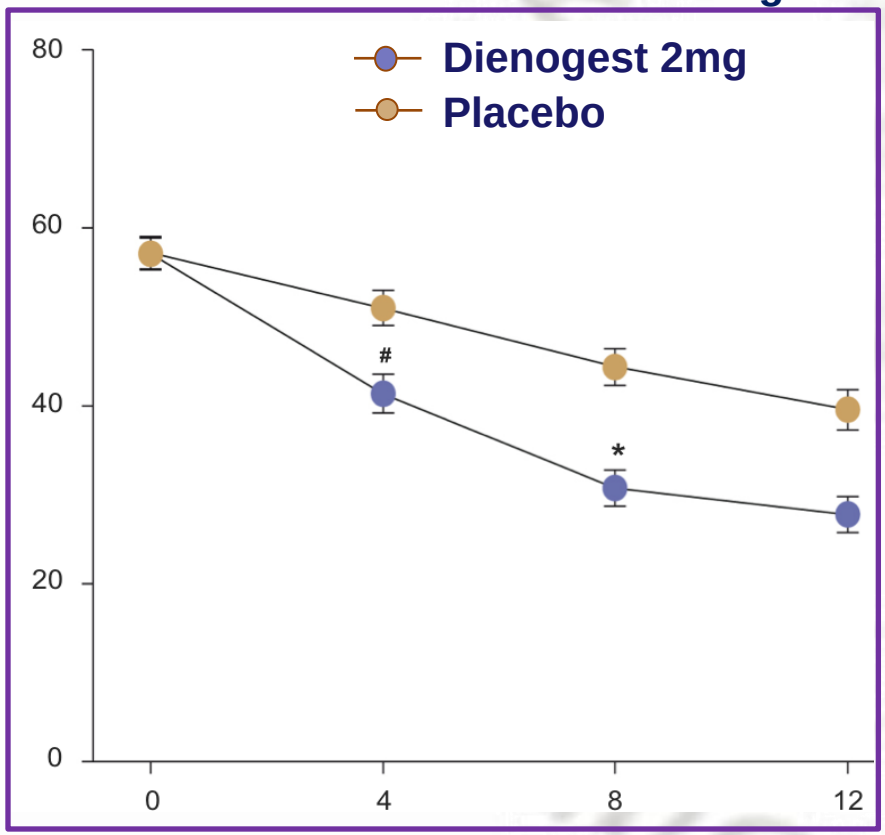
- Apoptosis
- Inflammation
- Oxidative stress
- Neoangiogenesis

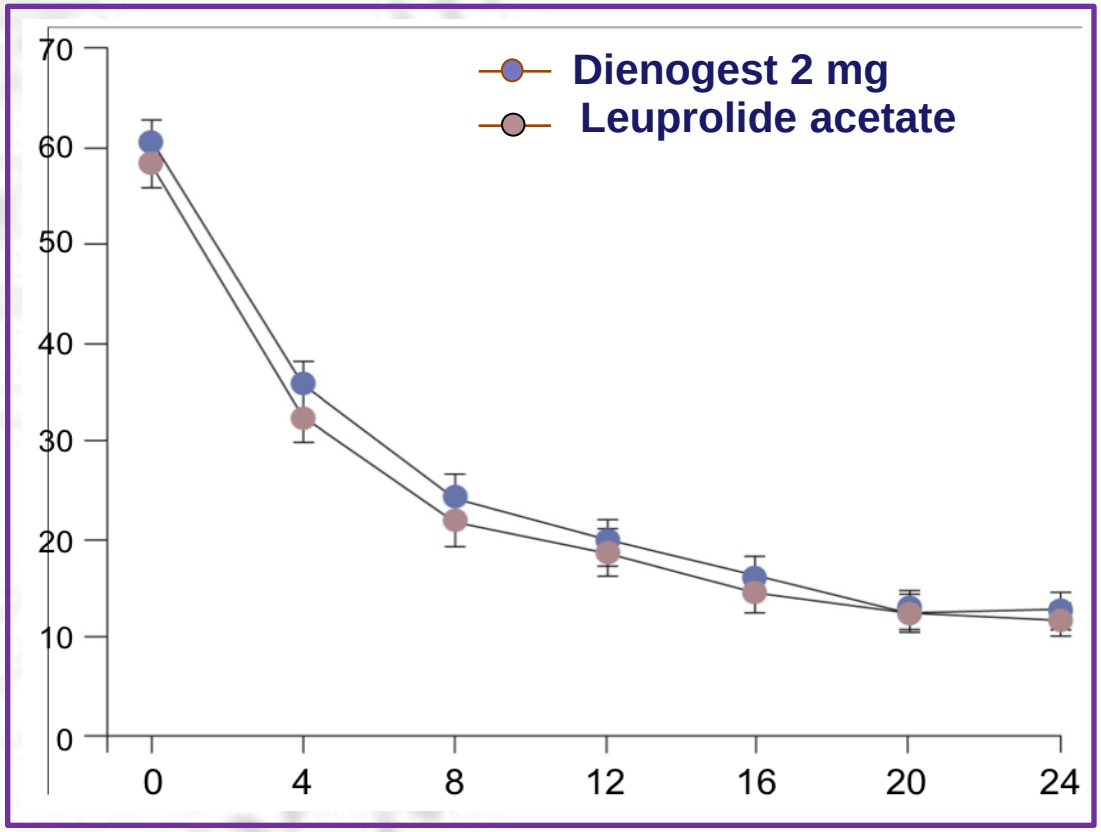
Dienogest and endometriosis

Dienogest vs Placebo

Dienogest vs Leuprolide Acetate

Visual Analogue Score of Pain Reduction





Weeks of treatment

# *P*<0.0016 after 4 weeks
* *P*<0.0001 after 8 and 12 weeks

Non-inferior versus
leuprolide acetate (*P*<0.0001)

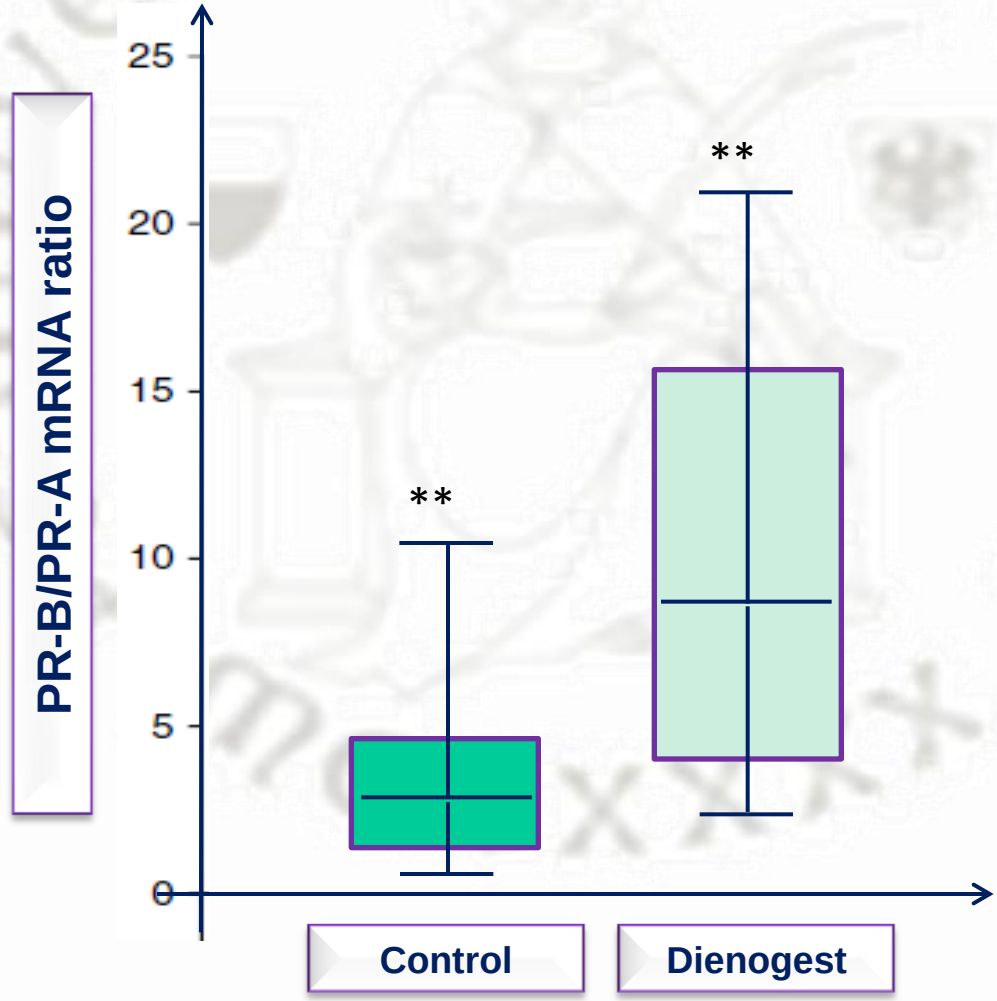
Strowitzki T et al. Eur J Obstet Gynecol Reprod Biol, 2010

Strowitzki T et al. Hum Reprod, 2010

Dienogest: mechanism of action

1. Progesterone resistance

Dienogest improves progesterone resistance

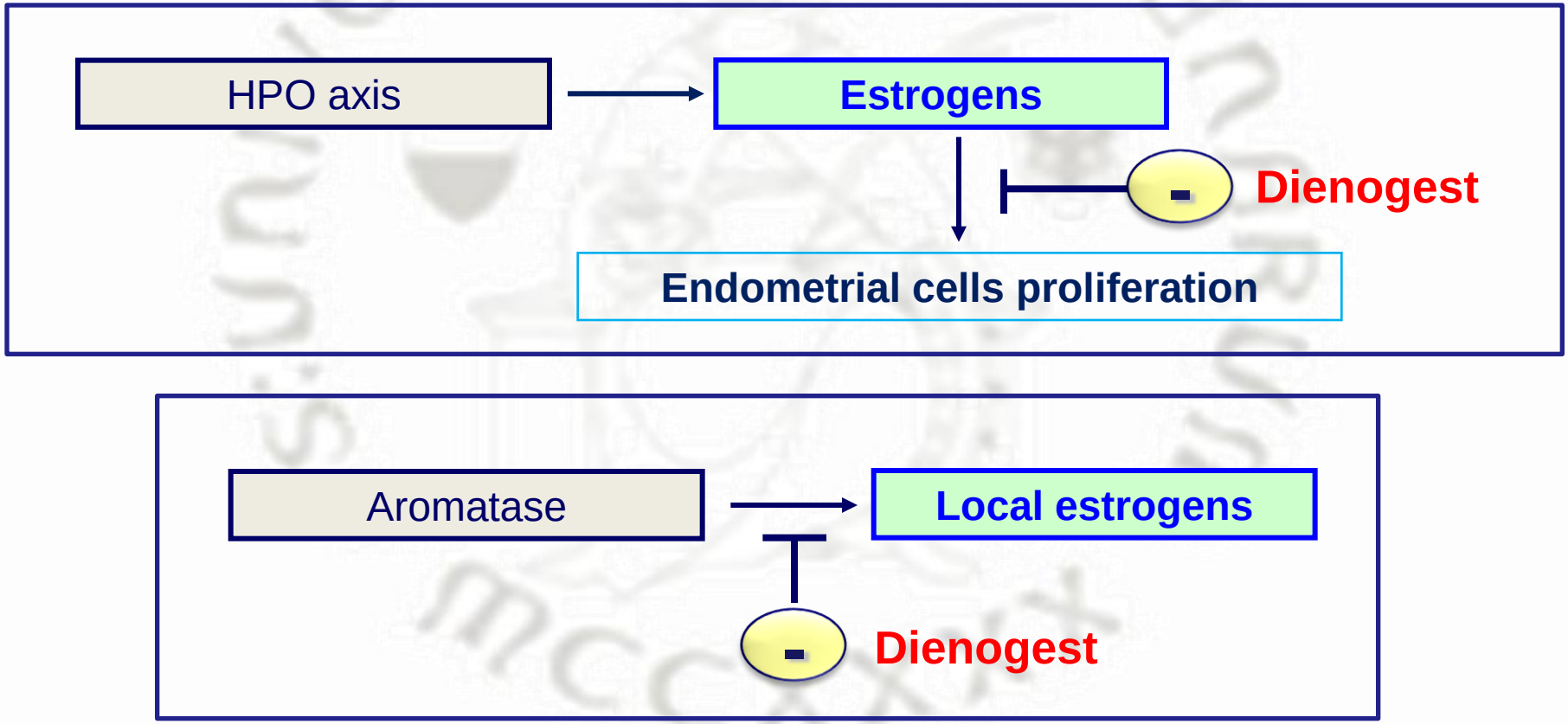


Hayashi A et al. J of Ovar Res, 2012

Dienogest: mechanism of action

2. Anti-estrogenic effect

Reduction of cell proliferation
Inibition of local aromatase



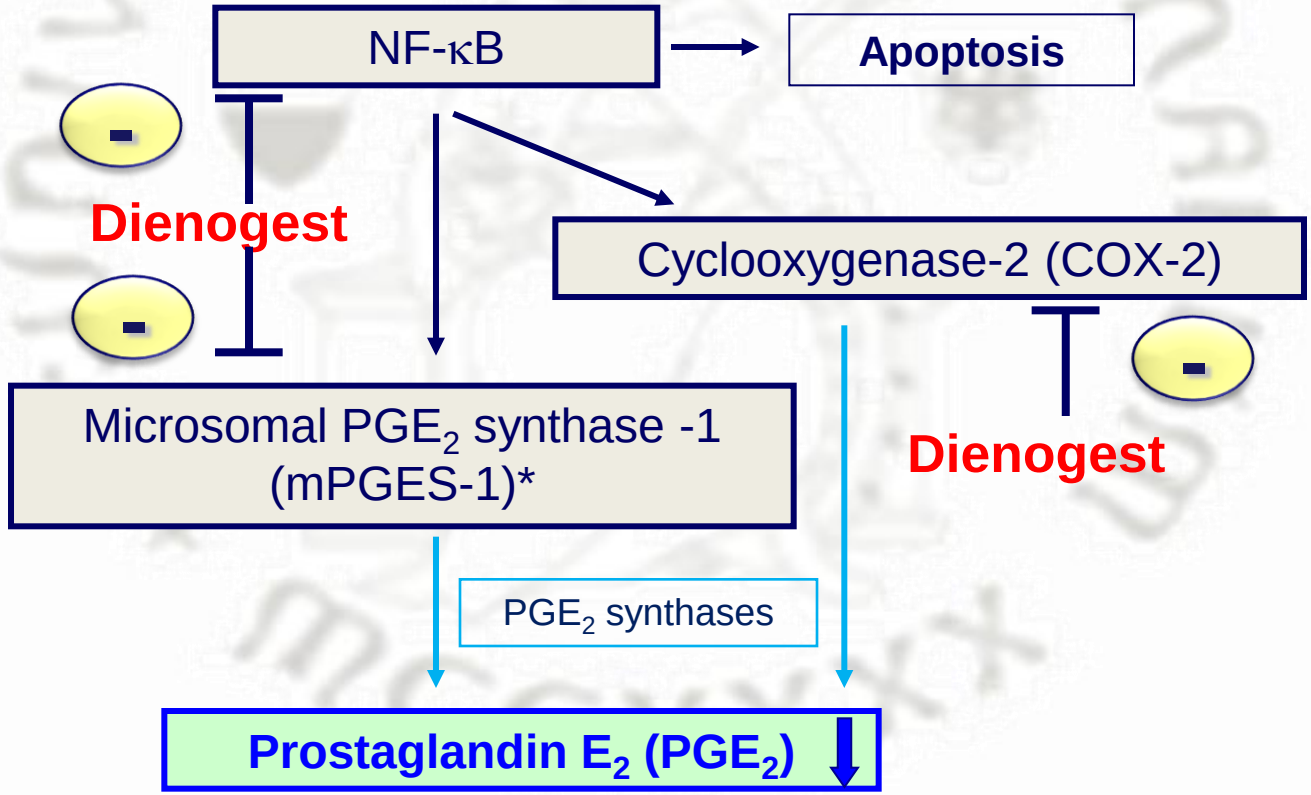
Lazzeri L et al. Journal of Endometriosis, 2010
Shimizu Y et al. Steroids 2011
Mita S et al, Fertil Steril 2014

Dienogest: mechanism of action

3. Pro-apoptotic effect

4. Anti-inflammatory effect

Inhibition of COX-2 and PGE-2 synthases



Lazzeri L et al. Journal of Endometriosis, 2010

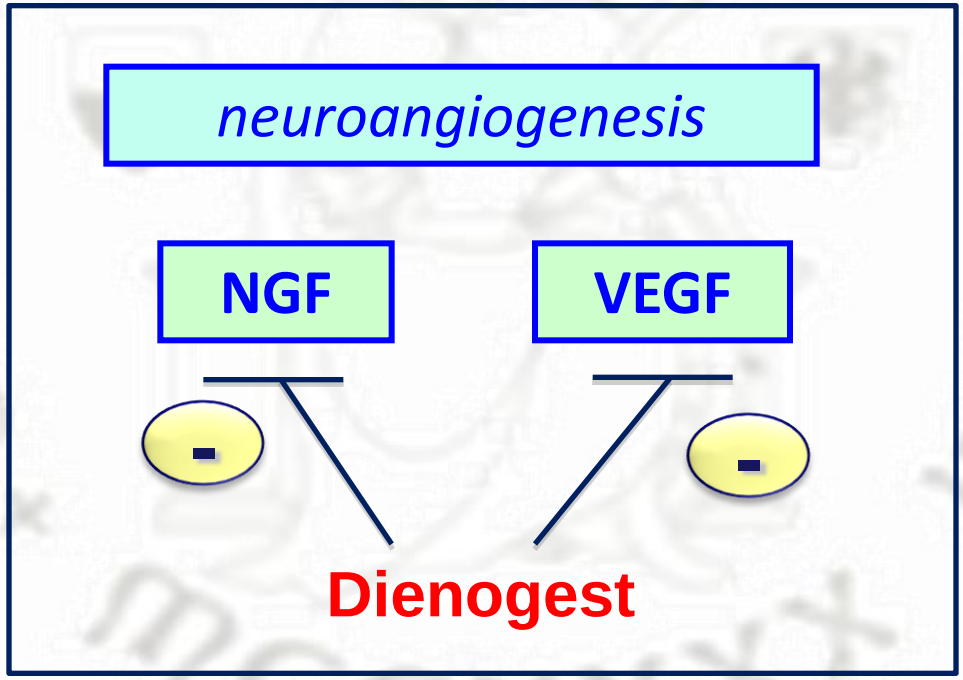
Shimizu Y et al. Steroids 2011

Mita S et al, Fertil Steril 2014

Dienogest: mechanism of action

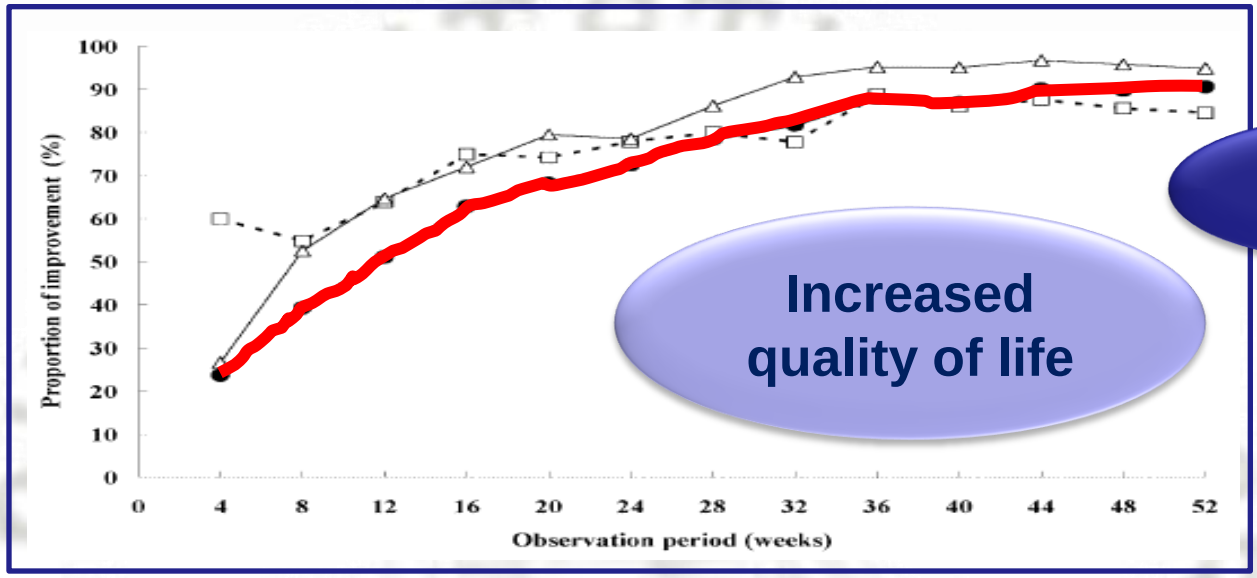
5. Anti-neuroangiogenic effect

Inhibition of growth factors



Lazzeri L et al. Journal of Endometriosis, 2010
Shimizu Y et al. Steroids 2011
Mita S et al, Fertil Steril 2014

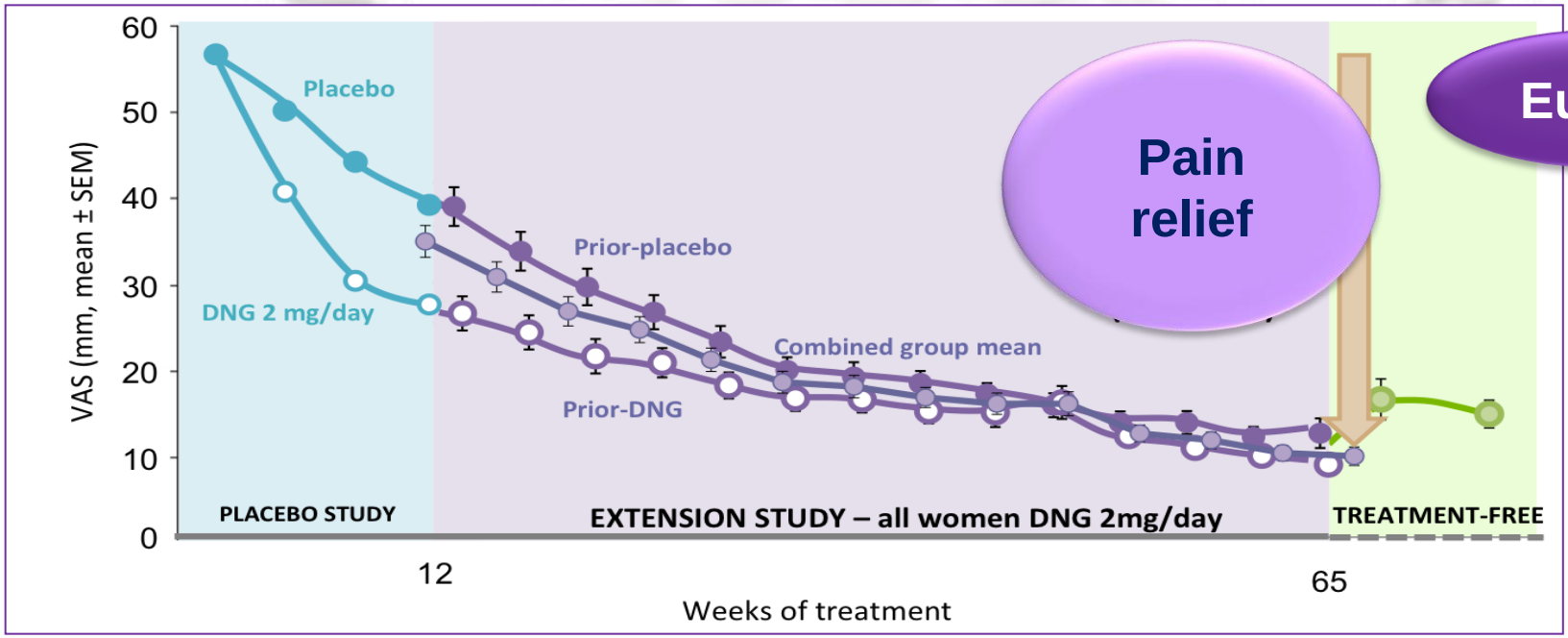
Endometriosis and progestins: dienogest



Increased quality of life

Japan

Harada M et al. 2011



Pain relief

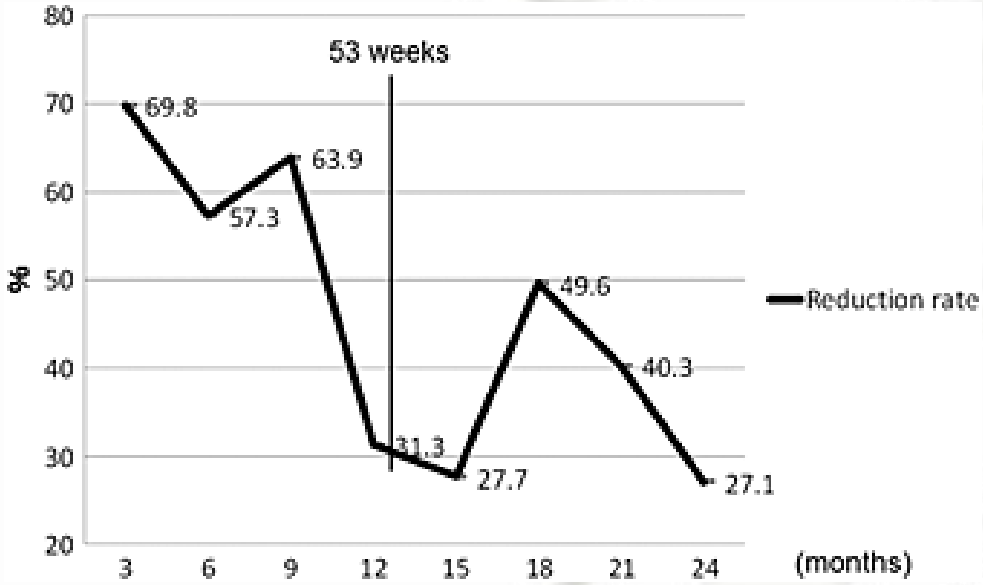
Europe

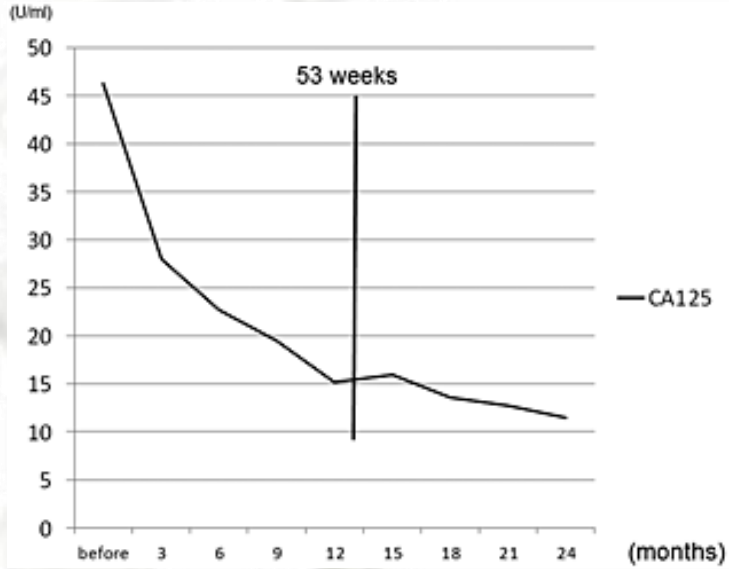
Petraglia F et al. 2012

Endometriosis and progestins: dienogest

Ovarian chocolate cysts size

Japan





Long term DNG treatment beyond one year for endometriosis proved to be effective and safe. Ovarian chocolate cysts were markedly reduced by short-term use of DNG

Sugimoto K et al. 2015

Endometriosis and progestins: dienogest

JEPPD
ISSN 2035-9969
Journal of Endometriosis and Pelvic Pain Disorders 2015; 7(2): 63-67
DOI: 10.5301/je.5000219
ORIGINAL ARTICLE

Long-term administration of dienogest reduces recurrence after excision of endometrioma

Yoshiaki Ota[1], Masaaki Andou[1], Shiori Yanai[1], Saori Nakajima[1], Mika Fukuda[1], Mizuki Takano[1], Shozo Kurotsuchi[1], Keiko Ebisawa[1], Tomonori Hada[1], Ikuko Ota[2]

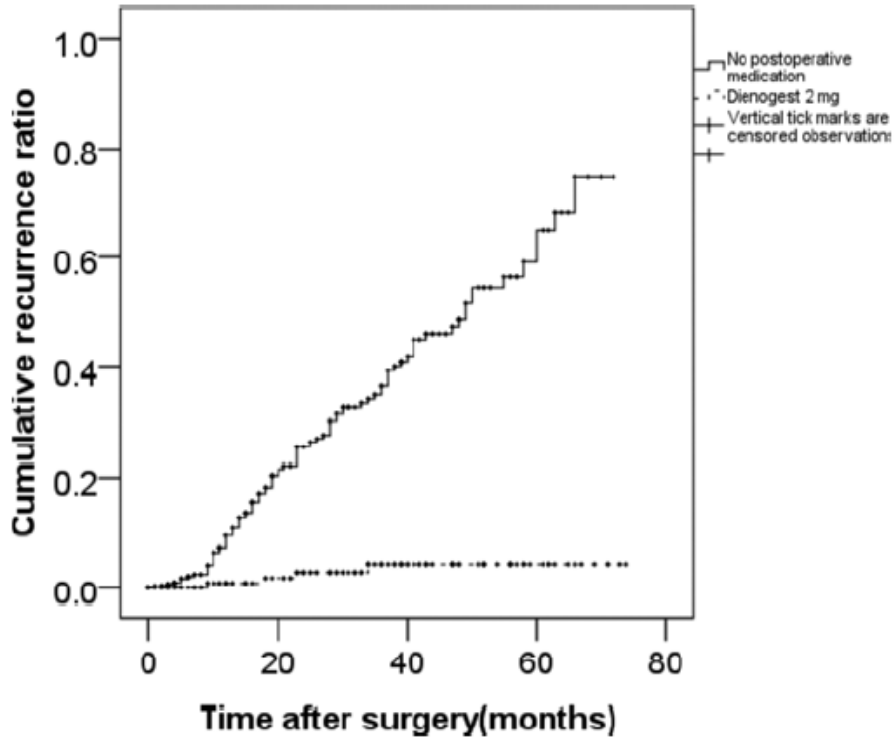
Japan

568 women (32.8±5.7 years):

- **151 dienogest**
- **417 placebo**

5 year duration of observation

60 months dienogest usage

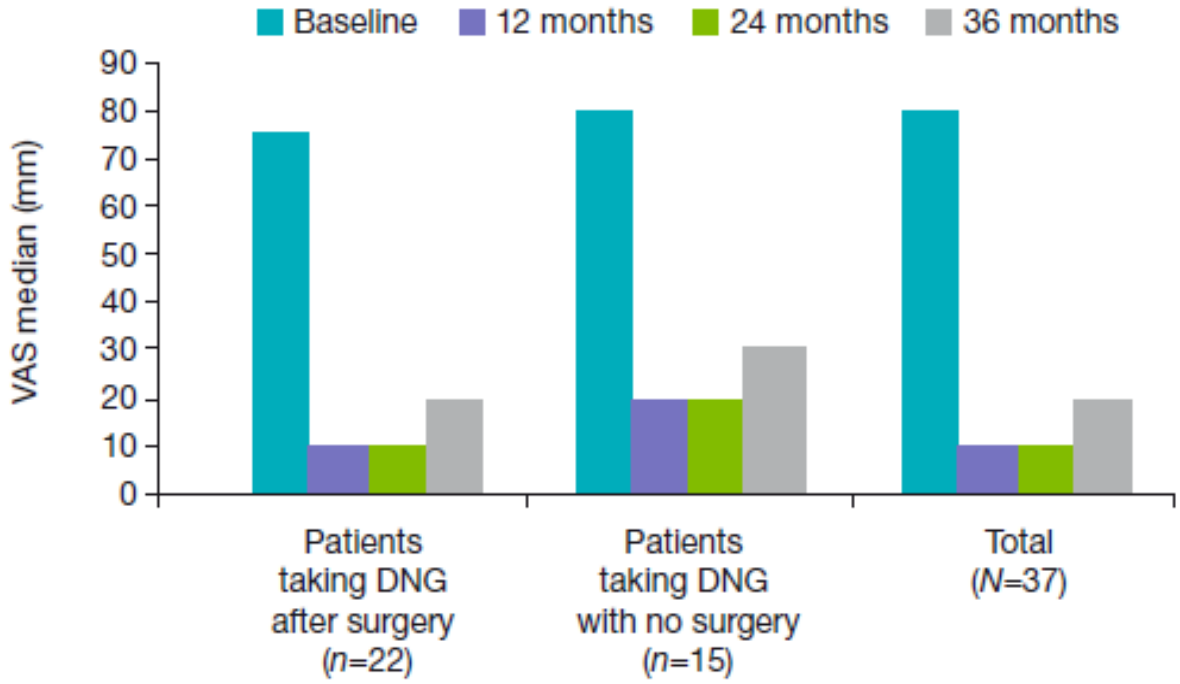


Endometrioma frequency recurrence: Placebo 69%, Dienogest 4%

Ota Y et al. JEPPD 2015

Endometriosis and progestins: dienogest

Germany

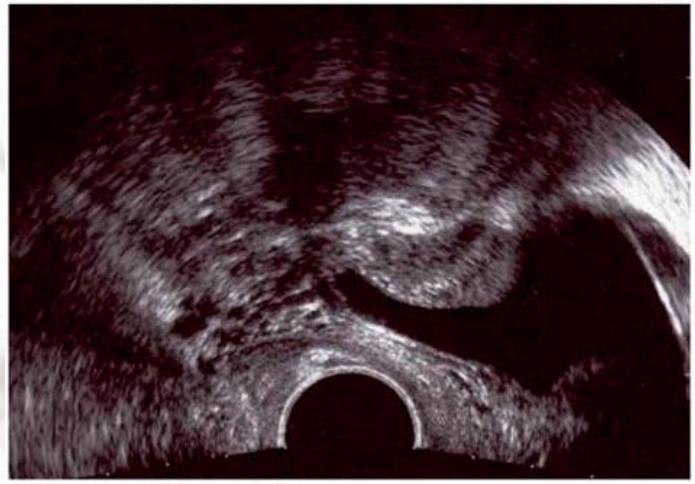


Real-life data on 37 patients with endometriosis showed that dienogest 2mg once daily effectively reduced EAPP in patients with endometriosis or avoided pain recurrence after surgery for at least 3 years

Romer T. Presented at the 2nd Congress of the SEUD, 12-14th May 2016, Barcelona

Bladder endometriosis and dienogest

We performed a pilot study on the effect of a new progestin dienogest on bladder endometriosis



Six patients were treated for 12 months with dienogest 2 mg/daily

Pain, urinary symptoms, quality of life, nodule volume and side effects were recorded

During treatment, symptoms improved very quickly and the nodules exhibit a remarkable reduction in size

Decrease of nodule size, the improvement of symptoms, quality of life scores and the lack of significant side effects suggesting that dienogest could be the first line medical treatment in such patients

Angioni S. et al. Gynecol Endocrinol 2015

Dienogest and endometriosis

Dienogest treatment improves quality of life in women with endometriosis

Stefano Luisi[1], Fabio Parazzini[2], Stefano Angioni[3], Saverio Arena[4], Paolo Berretta[5], Massimo Candiani[6], Vito Cela[7], Luigi Fedele[2], Pietro Litta[8], Antonio Maiorana[9], Luigi Nappi[10], Maria Grazia Porpora[11], Maurizio Rosati[12], Fulvio Zullo[13], Claudia Tosti[1], Felice Petraglia[1]

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ABSTRACT

Background: The aim of this study was to assess the efficacy of dienogest treatment in improving quality of life in women with endometriosis.

Methods: This was a prospective observational multicenter study at the universities of Siena, Milano, Cagliari, Perugia, Busto Arstizio, Pisa, Padova, Palermo, Foggia, Roma, Pescara and Catanzaro, including 142 patients with a diagnosis of endometriosis who received dienogest 2 mg once daily, for up to 90 days. Each patient underwent an evaluation of pelvic pain measured by visual analogue scale (VAS) from 0 to 10 points, and of quality of life measured by a mental and physical index before and after treatment.

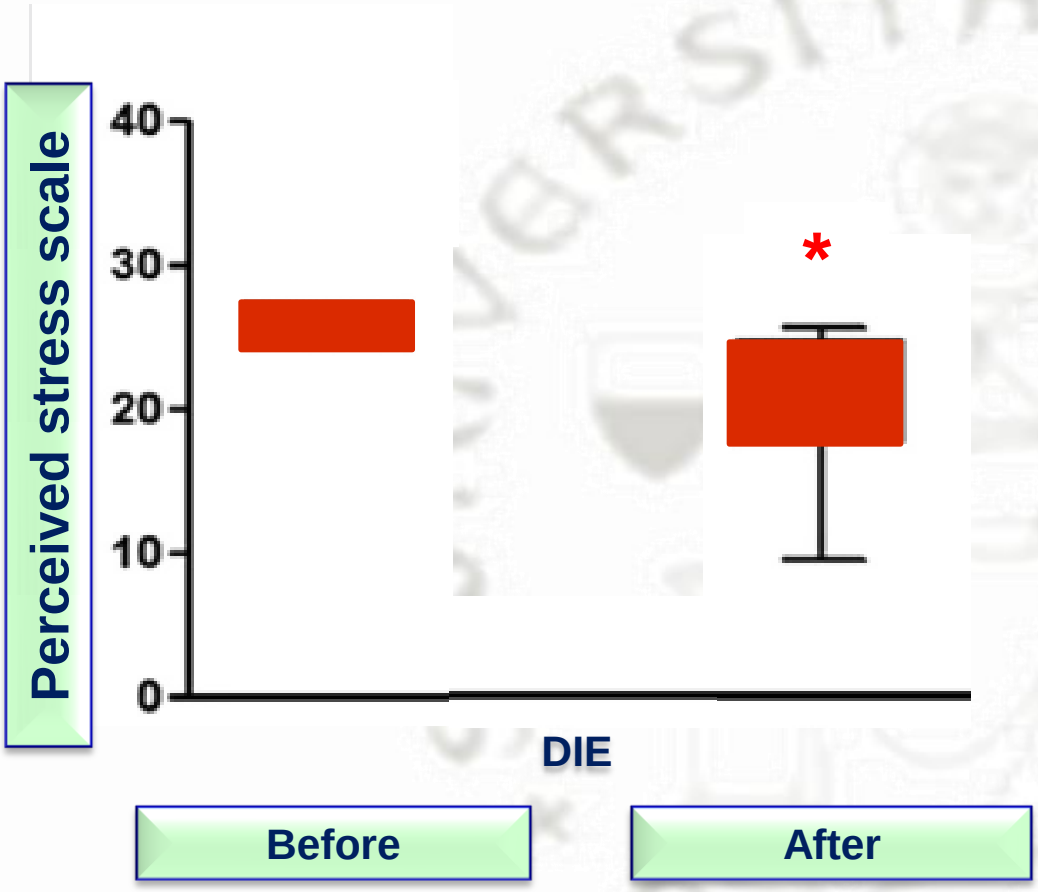
Results: The mean ± SD of VAS was 8.2 ± 1.6 in women with endometriosis, and this progressively and significantly decreased to 5.9 ± 2.6 at the end of the study. Mental index score values increased from 39.0 ± 9.8 to 46.0 ± 9.1 ($p<0.001$); likewise, the physical index increased from 39.6 ± 9.6 to 47.7 ± 8.5 ($p<0.001$). During the treatment period, the most frequent adverse events (AEs) were headache (30.8%), followed by bleeding (29.4%), depression (26.6%), breast tenderness (23.8%) and acne (2.0%), but these were transitory, and none led to withdrawal from the study.

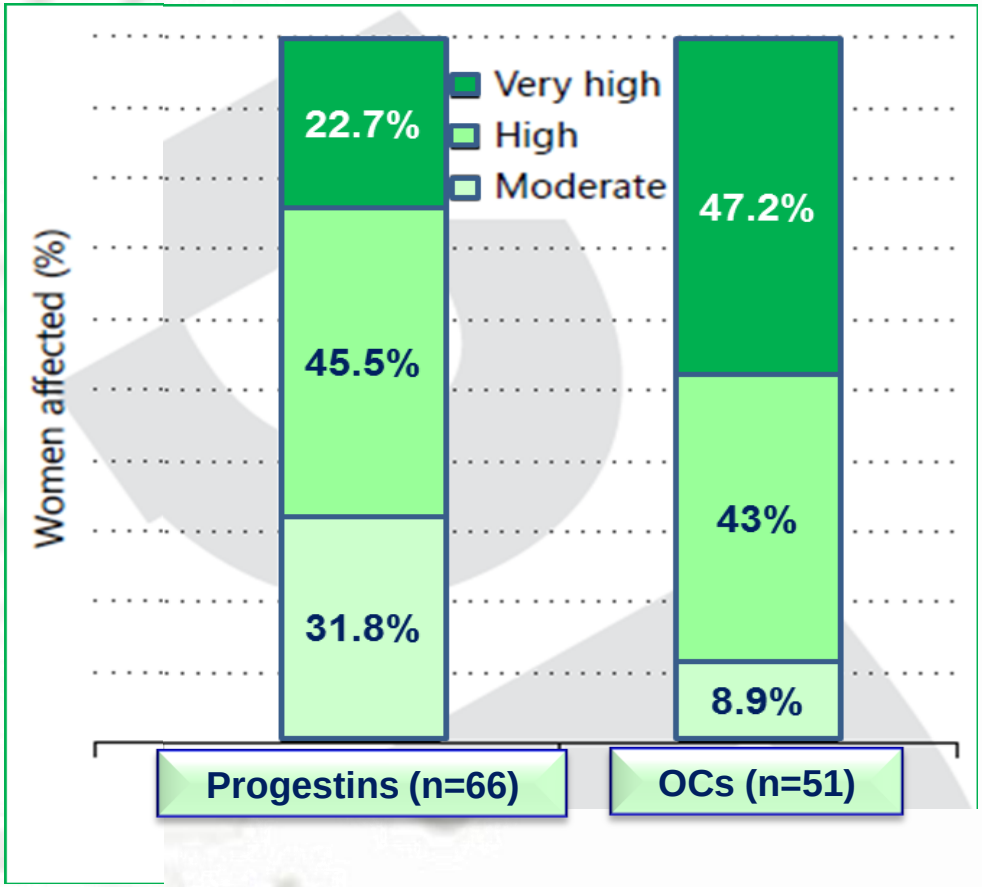
Conclusions: The present prospective study showed that dienogest is an effective and well-tolerated treatment improving the quality of life in endometriotic women.

Keywords: Dienogest, Endometriosis, Pelvic pain, Quality of life, Stress

Luisi S. et al. JEPPD, 2016

Pain in endometriosis





Surgical treatment improves the levels of perceived stress in women with DIE

Progestins treatment is associated with a large percentage of patients with a moderate perceived stress

Lazzeri et al, Fertil Steril 2014

Lazzeri et al, Gynecol Obstet Invest 2014

Endometriosis: role of hormonal contraception and progestins

Progestin-only pills may be a better first-line treatment for endometriosis than combined estrogen-progestin contraceptive pills

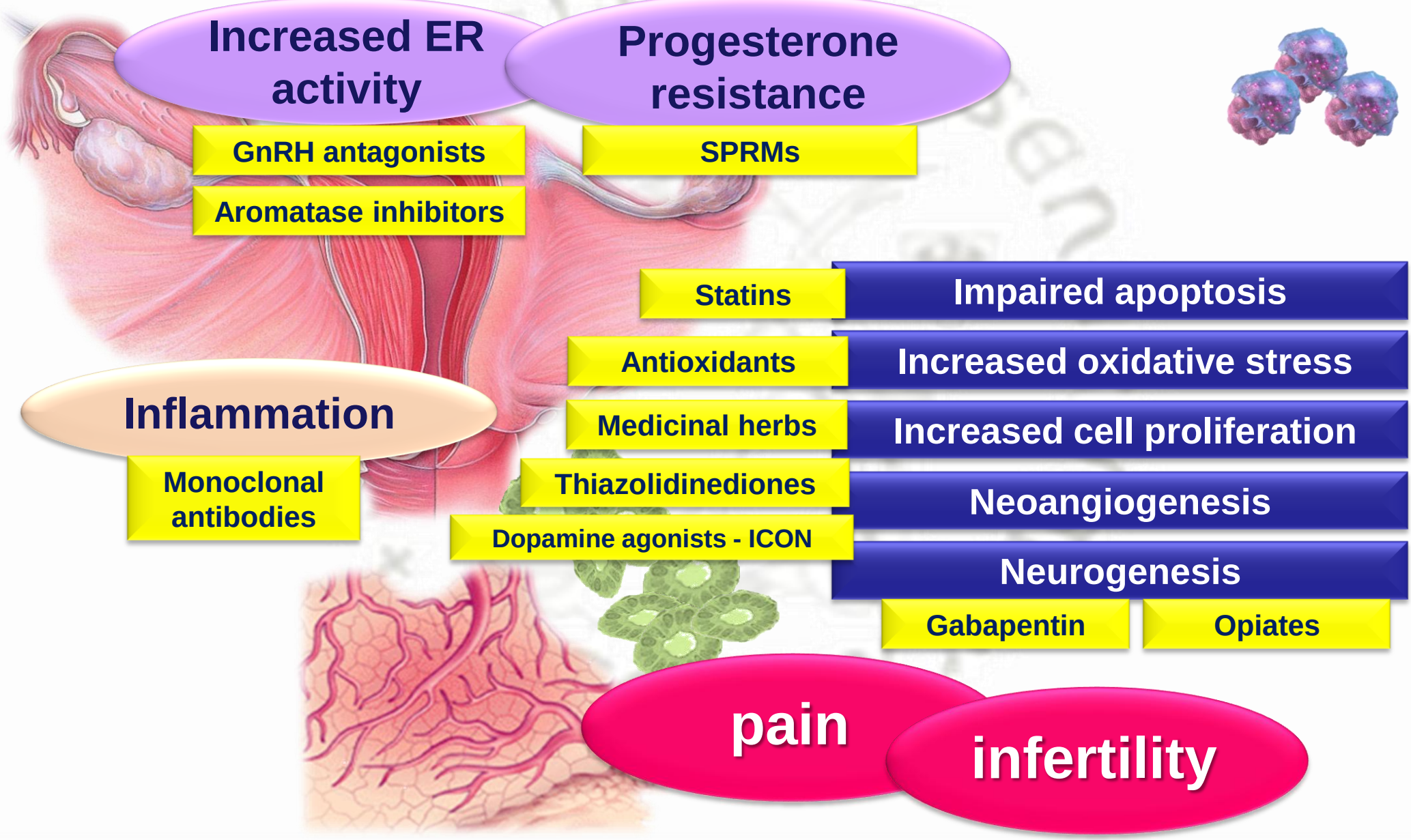
Based on controlled trial data, it appears that women with suspected or confirmed endometriosis as MAY DO BETTER with oral progestin-only treatment the first-line therapy because progestins have demonstrated benefits in reducing pain and suppressing the anatomic extent of endometriotic lesions

Oral progestins alone

- can be used at any age
- do not increase the risk of thrombosis
- inhibit ovulation
- induce amenorrhea with very few side effects

Casper RF et al. Fertil and Steril, 2017

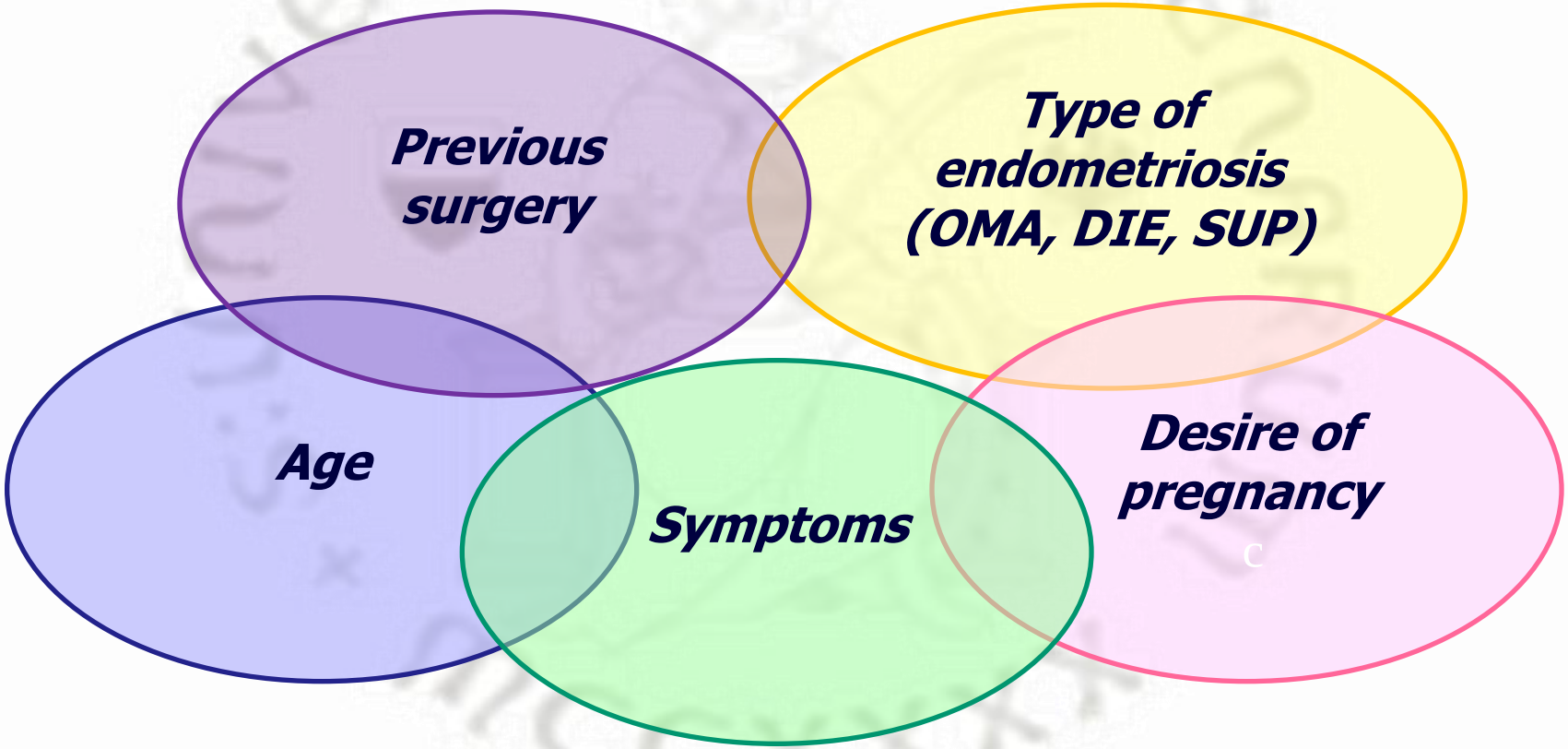
The strategy for selecting the new drugs for endometriosis



Management of endometriosis

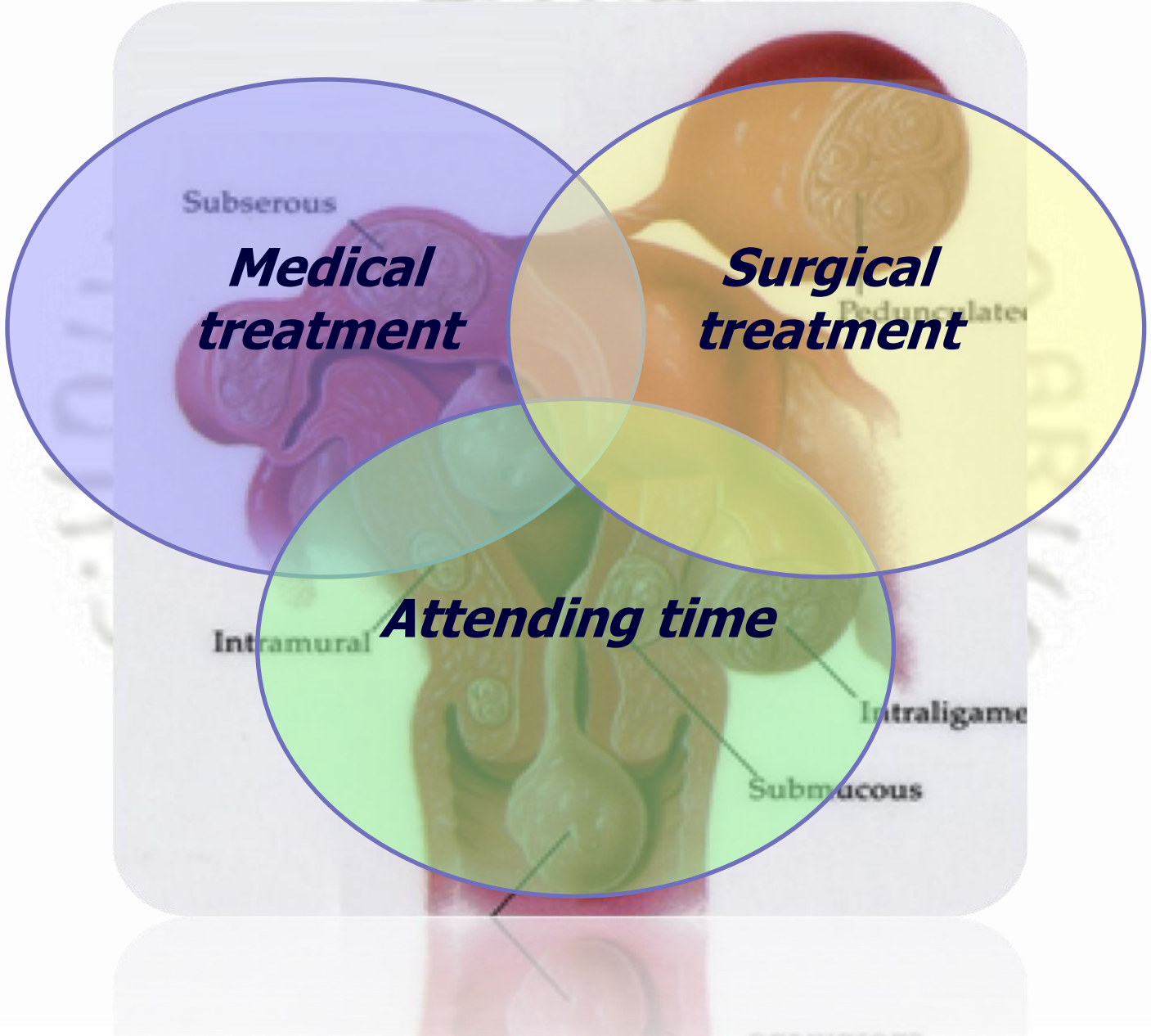
Diagnosis

What to consider between diagnosis and treatment?



Infertility clinic	Surgical treatment	Medical treatment

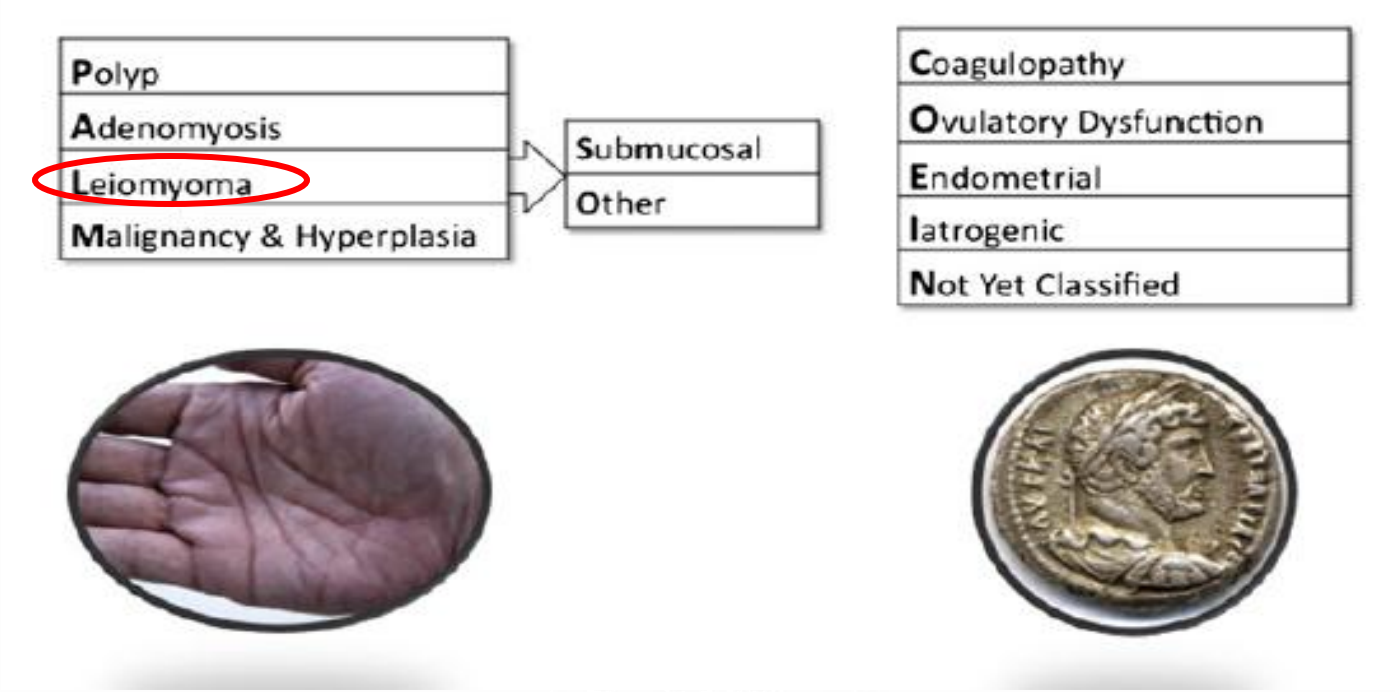
Uterine fibroids



PALM-COEIN Classification for Causes of Abnormal Bleeding

FIGO - Working group on menstrual disorders
Chair Ian Fraser

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



Fraser I et al, Fertil Steril 2011

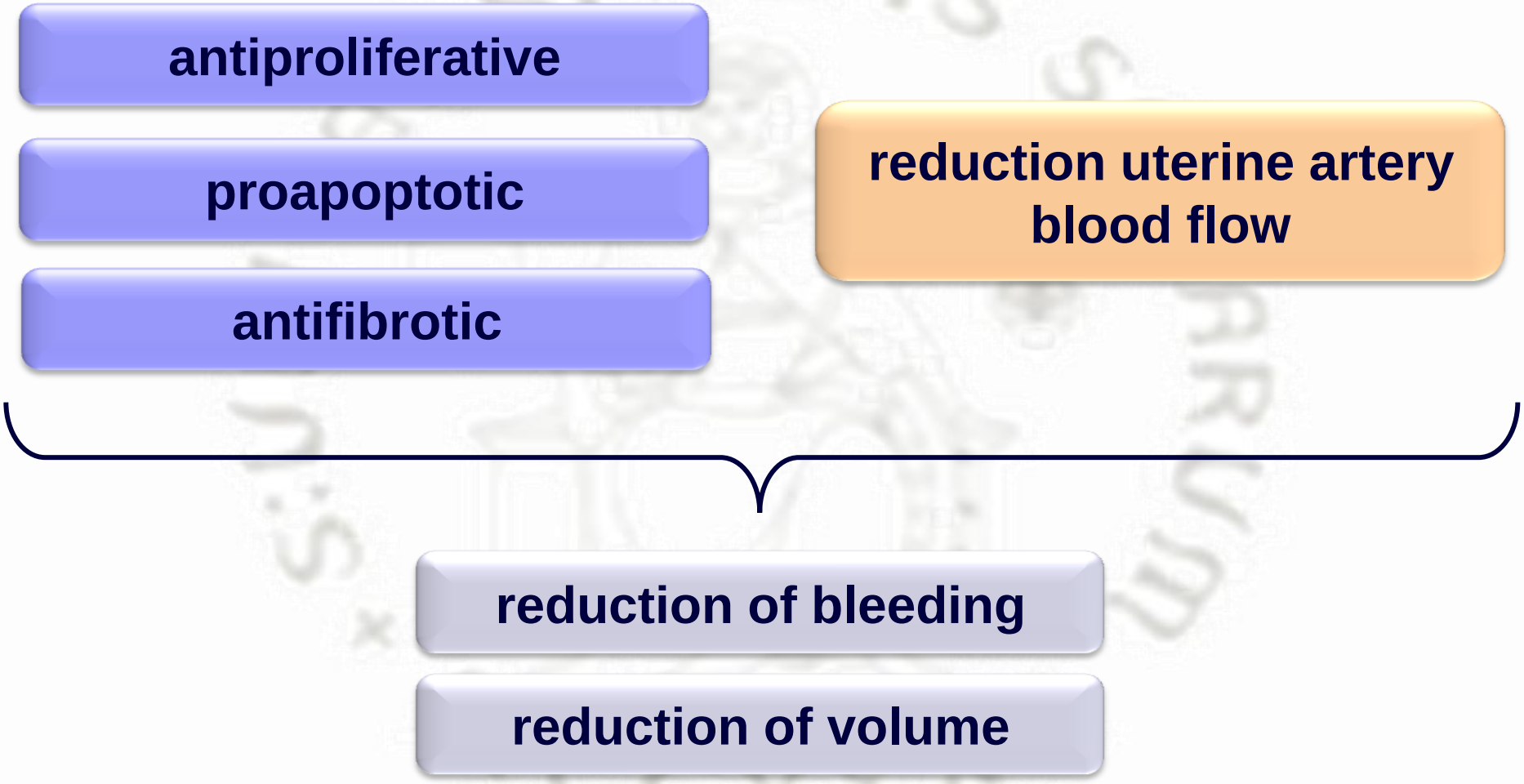
Aims of medical treatment

Although fibroids can be asymptomatic, approximately 20–40% are symptomatic, leading patients to seek therapy

- ✓ **Reduce bleeding**
- ✓ **Improve quality of life**
- ✓ **Preoperative measure to control myoma size, bleeding**

Most current medical therapies target myomas by manipulating their hormonal environment

Mechanisms of action SPRMs on HMB



SPRMs actions

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:

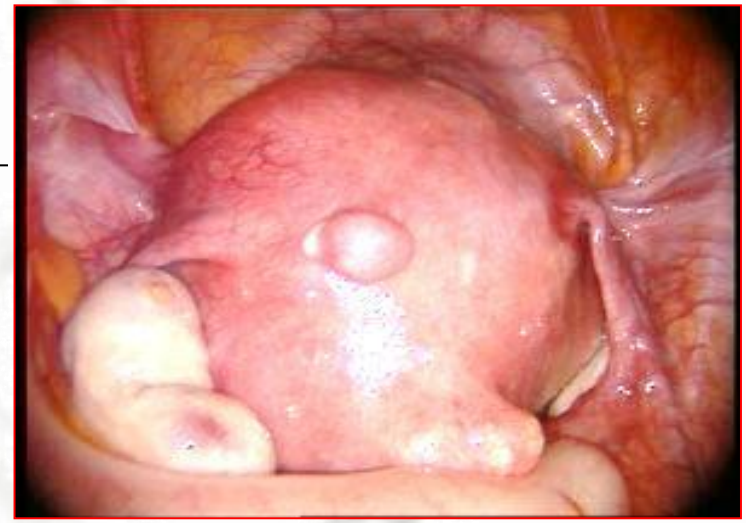
- act as a progestin in the endometrium
- act as an anti-progestin within the leiomyoma

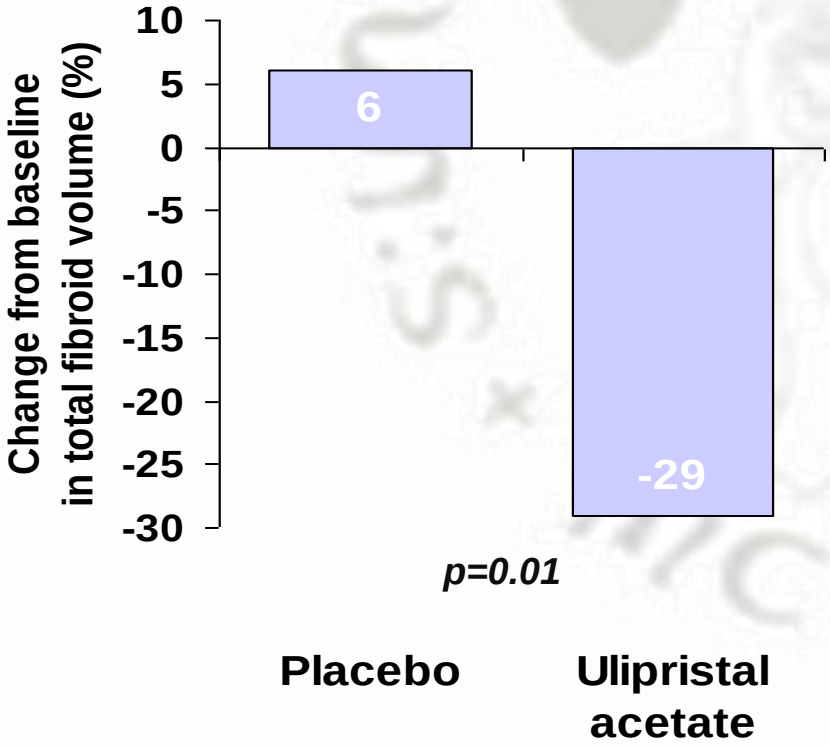
Ohara N. et al, Clin Exp Obstet Gynecol 2005
Spitz IM, Curr Opin Obstet Gynecol. 2009

Ulipristal acetate trials: 10 mg

Ulipristal acetate 10 mg

3-month administration





- *Reduces leiomyoma volume*
- *Improves leiomyoma-specific QoL*
- *No significant adverse events*

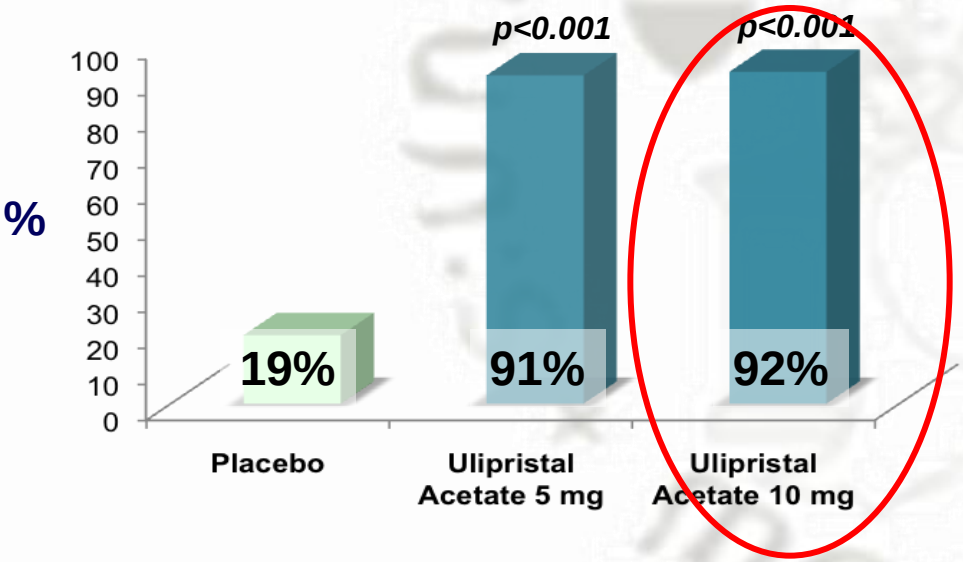
Levens ED et al, Obstet Gynecol. 2008

Ulipristal acetate trials: 5 vs 10 mg

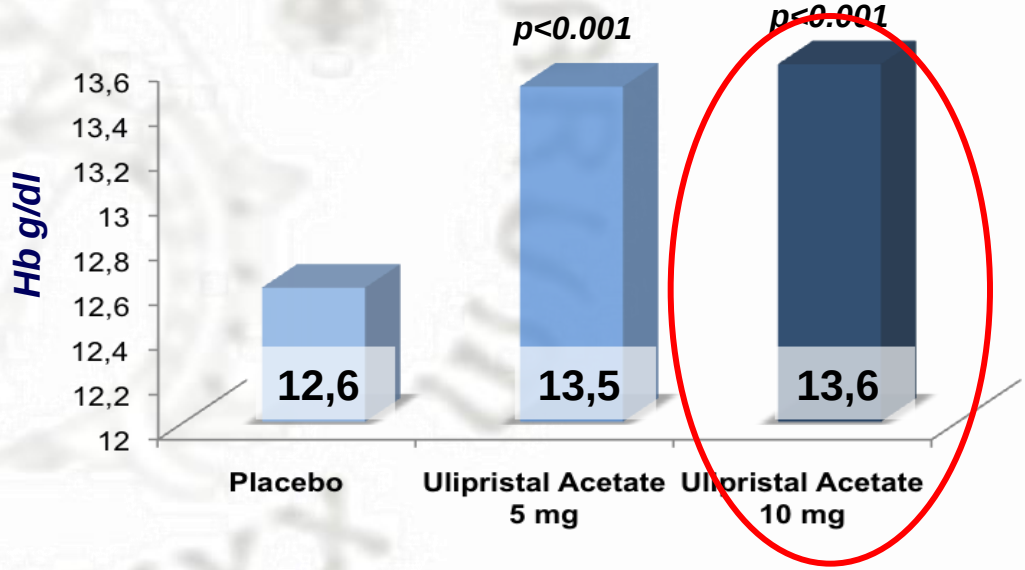
PEARL I

Ulipristal Acetate versus Placebo for Fibroid Treatment before Surgery

Reductions in bleeding (13 weeks)



Haemoglobin g/dl (13 weeks)



Normalizzazione del sanguinamento In oltre il 90% delle pazienti nei bracci di trattamento con UPA

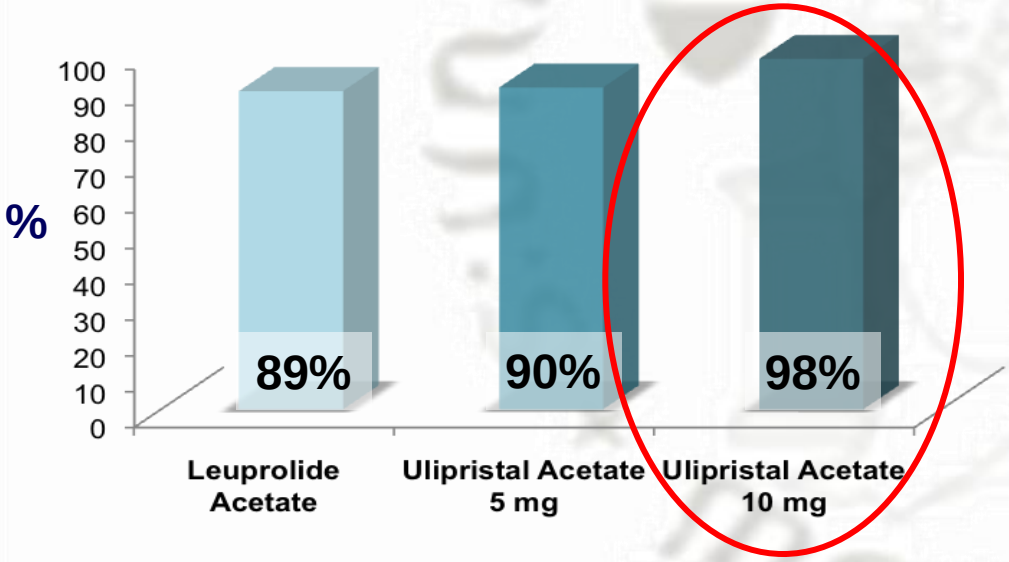
Donnez J. et al, NEJM 2012

Ulipristal acetate (5 vs 10 mg) vs leuprolide acetate

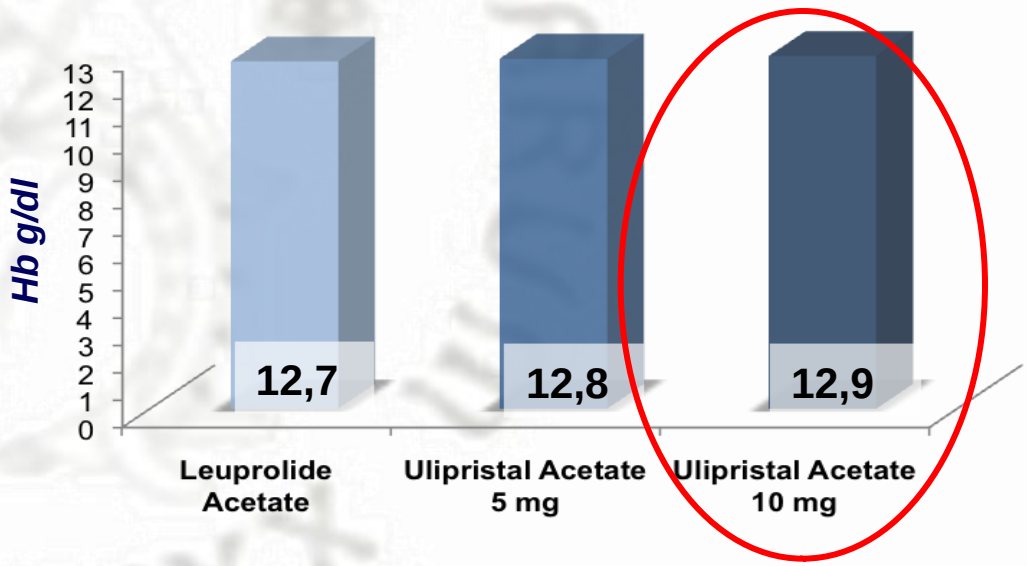
PEARL II

Ulipristal Acetate versus Leuprolide Acetate for Uterine Fibroids

Reductions in bleeding (13 weeks)



Haemoglobin g/dl (13 weeks)

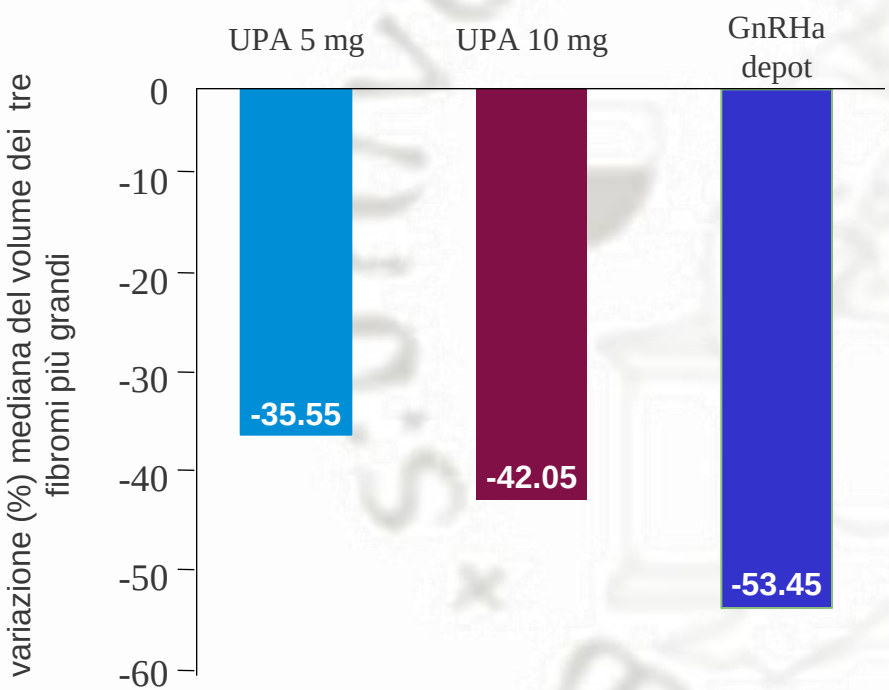


Donnez J. et al. NEJM 2012

Effetto sulla riduzione del volume dei fibromi

PAZIENTI NON ANDATE IN CHIRURGIA

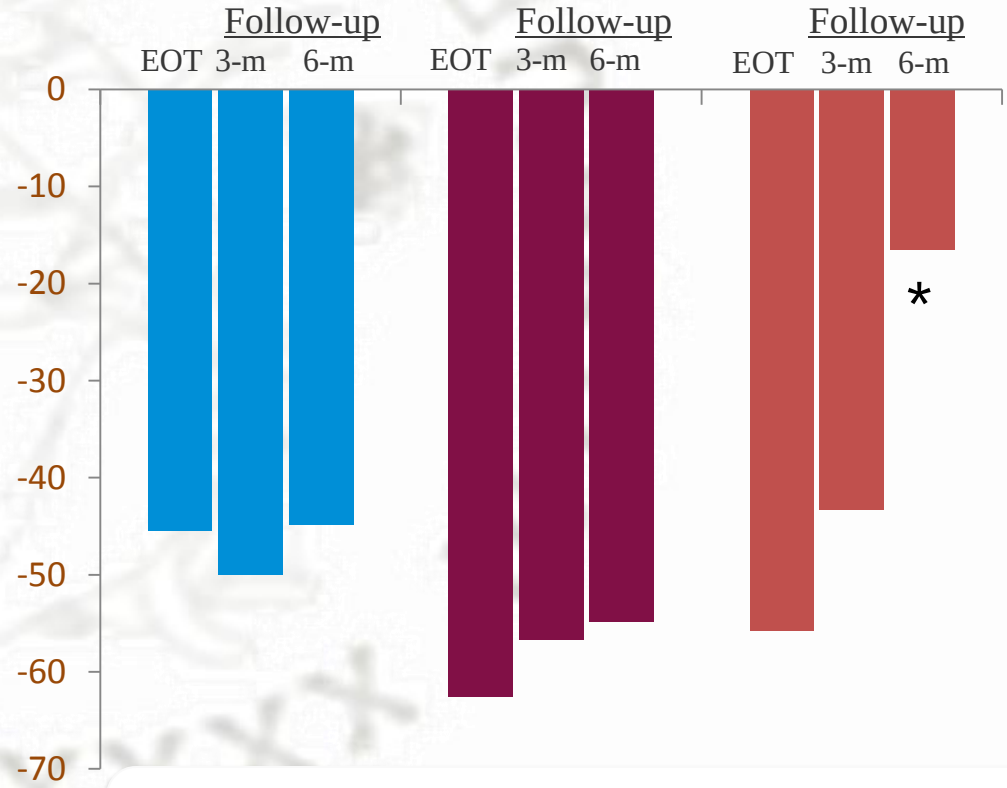
Riduzione percentuale dal basale alla settimana 13 (PP population)



Nessuna differenza significativa tra GnRHa ed UPA

*P<0.05

Riduzione % mediana del volume dei tre fibromi più grandi dopo la fine del trattamento

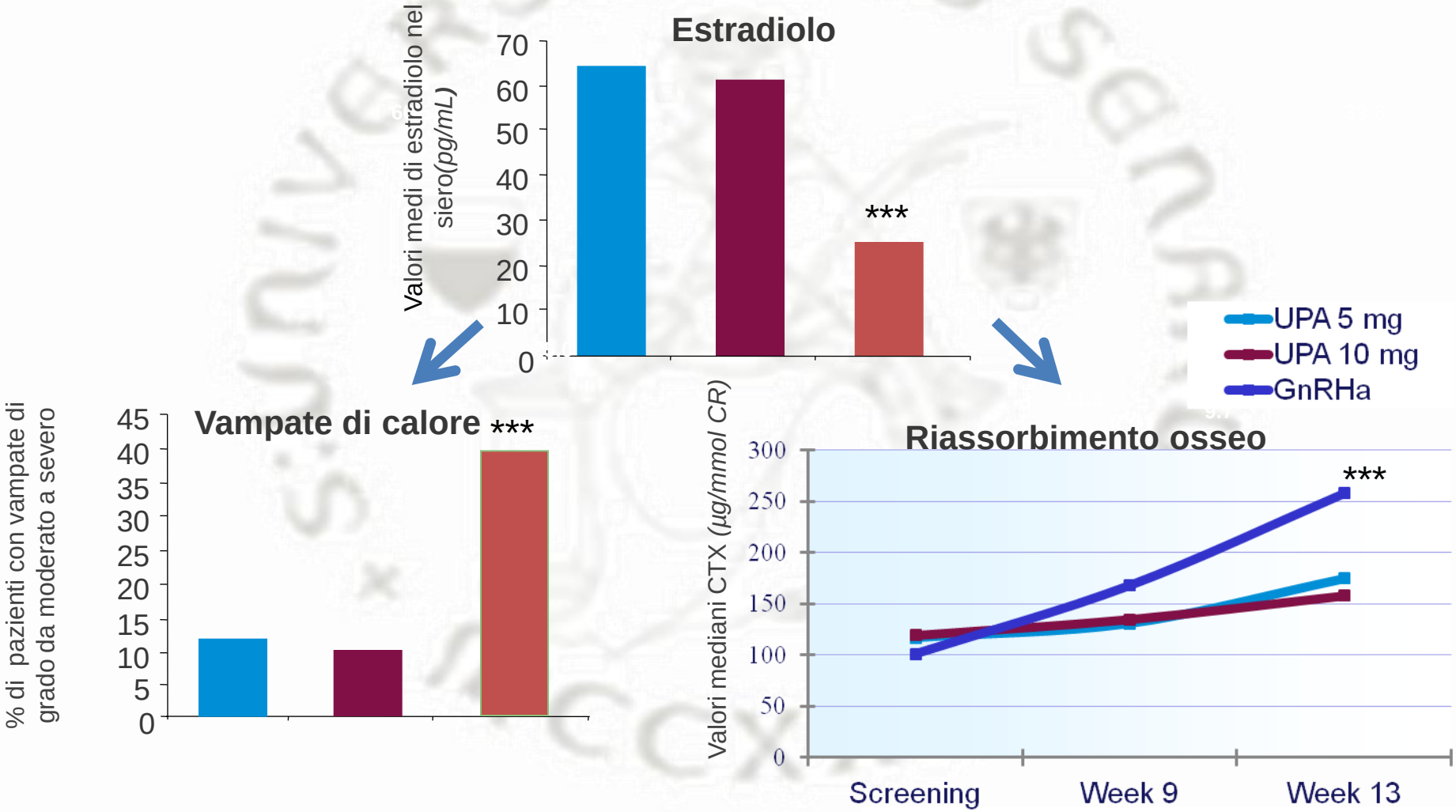


La riduzione da EOT (sett 13) a 6 mesi di follow-up per UPA 5 mg e UPA 10 mg tende a mantenersi a differenza del braccio GnRHagonista

Donnez J, et al. N Engl J Med 2012;366:421−32

Profilo di sicurezza e tollerabilita’

UPA ha un profilo di sicurezza superiore al GnRH



Donnez J, et al. N Engl J Med 2012;366:421−32

***P<0.001

PEARL I PEARL II

PEARL I E PEARL II: conclusioni

Ulipristal acetato si è dimostrato:

- Efficace nella riduzione del **sanguinament**o mestruale abbondante in oltre il **90%** dei soggetti.

- Efficace nel controllo del sanguinamento e più **rapido** rispetto all' agonista del GnRH.
  Il controllo avviene in media entro 5-7 giorni dalla prima somministrazione rispetto ai 30 giorni dell' agonista del GnRH.

- Efficace nella riduzione del **volume del fibroma**: parità di efficacia rispetto all'agonista del GnRH, ma questa riduzione è **mantenut**a più a lungo nel tempo.
  La riduzione si è mantenuta per tutti **i 6 mesi** del periodo di follow-up.

- Superiore nel profilo **di tollerabilità e sicurezza** rispetto all'analogo del GnRH, grazie al mantenimento di normali livelli estrogenici endogeni; ciò evita la comparsa dei tipici **sintomi post-menopausali.**

PEARL III: estensione

PEARL III & ESTENSIONE

SEMINAL CONTRIBUTIONS

Long-term treatment of uterine fibroids with ulipristal acetate ☆

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Donnez J, et al. Fertil Steril 2014;101:1565–73

PEARL III: conclusioni

PEARL III & ESTENSIONE

Controllo del sanguinamento
La maggior parte delle pazienti **(circa 80%)** è entrata in **amenorrea** con effetto ottenuto già nel primo ciclo di trattamento e incrementato nei cicli successivi (circa 90%)
Il **controllo del sanguinamento** è ottenuto dopo una mediana di **2,0 giorni** dall'inizio del secondo ciclo di trattamento con UPA

Riduzione del volume dei fibromi
Dopo il 2° ciclo di UPA **l'80%** delle pazienti ha avuto una **riduzione** clinicamente significativa del **volume dei fibromi** (**63%).**
Dopo 4 cicli di UPA il volume dei 3 fibromi più grandi si è ridotto del **72%**

Tollerabilità e Sicurezza
La ripetizione dei cicli non aumenta l'incidenza dei PAECs, che sono reversibili entro 3 mesi dalla fine del trattamento

I risultati di questo studio indicano che l'uso di più di un ciclo di UPA massimizza i benefici del trattamento, tuttavia:
Ciò deve essere confermato da altri studi controllati con cicli ripetuti di trattamento (PEARL IV). La durata del trattamento attualmente approvata è al massimo di **2 cicli** di 3 mesi di trattamento ciascuno

PEARL IV: conclusioni

PEARL IV parte1

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Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids

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Lo studio PEARL IV ha confermato **l'efficacia** del trattamento ripetuto di cicli di 3 mesi ciascuno di **UPA 5 mg** sul controllo del sanguinamento, la riduzione del volume dei fibromi e della severità dei sintomi in pazienti con fibromi uterini sintomatici

Questi risultati sono in linea con quelli ottenuti nei precedenti studi PEARL

L'uso **di più di un ciclo di UPA massimizza i benefici** del trattamento

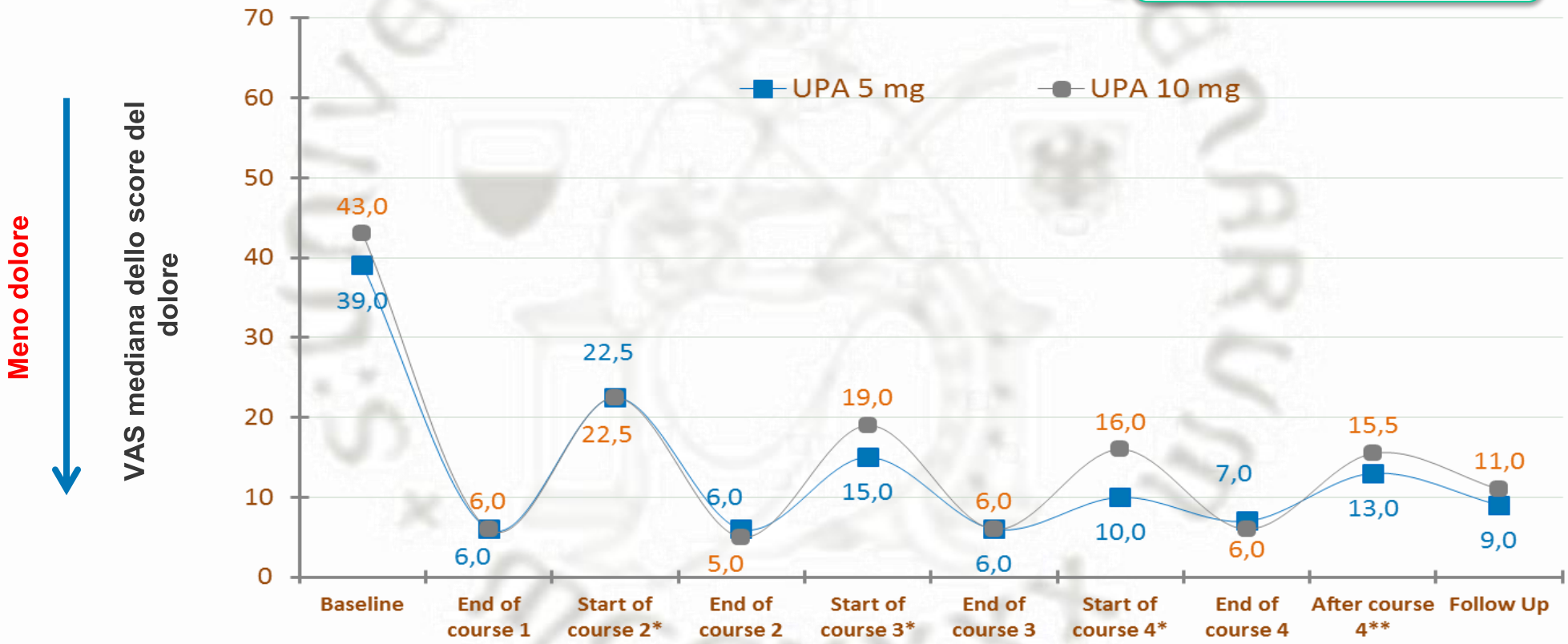
Il profilo di **sicurezza** di UPA è stato confermato **nel tempo**

UPA 5 mg è una dose sicura ed efficace

UPA: effetto sul dolore

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

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

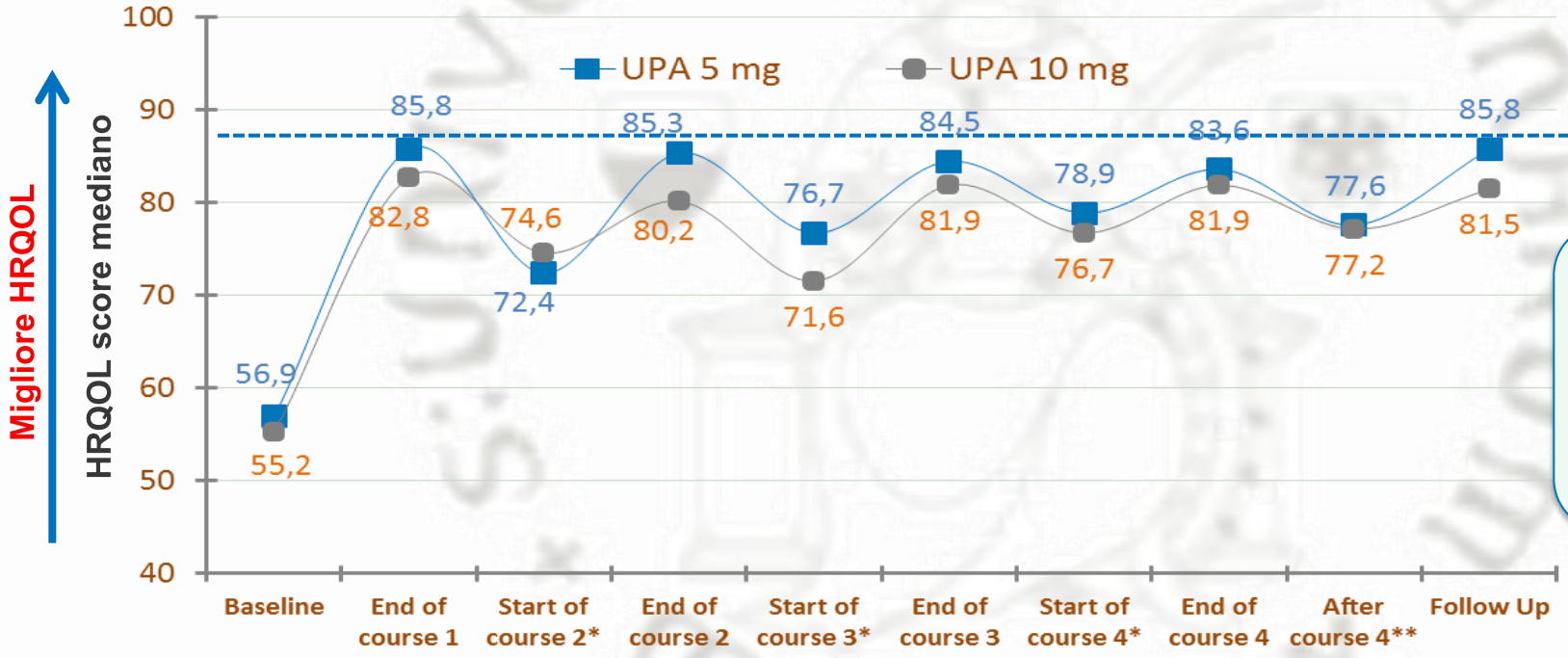


* Durante mestruazioni
** all'inizio della II mestruazione dopo il IV ciclo

Donnez J, et al. Fertil Steril 2016

UPA: effetto sulla qualità della vita

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

Donnez J, et al. Fertil Steril 2016

PEARL I a IV: conclusioni

Negli studi clinici fino ad oggi UPA ha dimostrato:

- Efficacia nella riduzione del sanguinamento mestruale abbondante in oltre il 90% delle pazienti
- Maggior rapidità rispetto al GnRH-agonista: il controllo del sanguinamento si raggiunge in media entro 5-7 giorni dalla prima somministrazione, rispetto ai 30 giorni dell'analogo
- Efficacia nella riduzione del volume dei fibromi:
  - parità di efficacia rispetto al GnRH agonista nella riduzione del volume
  - la riduzione ottenuta si mantiene nel tempo (follow up – 6 mesi)
- Cicli ripetuti intermittenti di UPA massimizzano i benefici del trattamento in termini di efficacia
- Profilo di sicurezza e tollerabilità confermati con la ripetizione dei cicli di terapia

PEARL IV: estensione

8 CICLI RIPETUTI INTERMITTENTI
PARAMETRI DI LABORATORIO
Emoglobina, Enzimi Epatici, ColesteroloTotale, HDL, LDL & Trigliceridi

PLOS ONE

RESEARCH ARTICLE

Safety after extended repeated use of ulipristal acetate for uterine fibroids

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Table 3. Summary of laboratory parameters (Full analysis set, N = 64).

	Screening		After course 4		3 months post treatment course 4		After course 8	
Parameter (unit), normal range	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Hemoglobin (g/dL), 11.5–15.5	63	12.8 ± 1.57	64	13.0 ± 1.36	63	12.8 ± 1.34	48	13.3 ± 0.95
Creatinine (umol/L), 45–84	63	61.4 ± 8.5	64	60.8 ± 8.6	63	63.0 ± 10.0	48	64.3 ± 9.8
Total bilirubin (umol/L), 0–19	63	6.5 ± 3.3	64	7.0 ± 3.6	63	7.1 ± 3.9	47	7.3 ± 3.0
AST (U/L), 0–37	63	21.3 ± 5.0	64	20.5 ± 4.5	63	21.1 ± 6.6	48	19.5 ± 4.8
ALT (U/L), 0–47	63	18.6 ± 6.7	64	16.0 ± 6.1	63	17.2 ± 10.6	48	16.8 ± 6.6
Total Cholesterol (mmol/L), 0–5.17	63	5.3 ± 0.79	60*	5.5 ± 0.82*	63	5.3 ± 0.72	49	5.3 ± 0.94
HDL (mmol/L), 1.04–25.88	63	1.7 ± 0.36	60*	1.7 ± 0.41*	63	1.7 ± 0.38	49	1.7 ± 0.35
LDL (mmol/L), 0–2.58	62	3.1 ± 0.73	60*	3.3 ± 0.79*	63	3.1 ± 0.70	49	3.1 ± 0.84
Triglycerides (mmol/L), 0–1.69	63	1.3 ± 0.88	60*	1.2 ± 0.73*	63	1.1 ± 0.70	49	1.3 ±0.82

Safety assessments including vital sign measurements, laboratory investigations, demonstrated that the extended repeated administration schedule, with a drug-free interval, was well tolerated

PLOS ONE, 2017

PEARL IV: estensione

8 CICLI RIPETUTI INTERMITTENTI ASPETTI ENDOMETRIALI

PLOS ONE

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 Lemieszczuk[10‡], Alistair R. W. William[11‡]

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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

PLOS ONE, 2017

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