

**Dipartimento Materno-Infantile (DAIMI)
Ostetricia e Ginecologia, Azienda Ospedaliera Universitaria Careggi (AOUC)
Firenze**



A.G.E.O. E GLI ESPERTI

le nostre domande e le
loro risposte

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FIRENZE
25 - 26 OTTOBRE 2019

SESSIONE I
GINECOLOGIA E TERAPIA MEDICA

**Endometriosi: quale
gestione in ambulatorio**

Dr.ssa Silvia Vannuccini

L'endometriosi è una patologia endocrino-infiammatoria

Resistenza al
progesterone

↑
infiammazione

↑
Attività del
recettore
estrogenico e
produzione locale
degli estrogeni

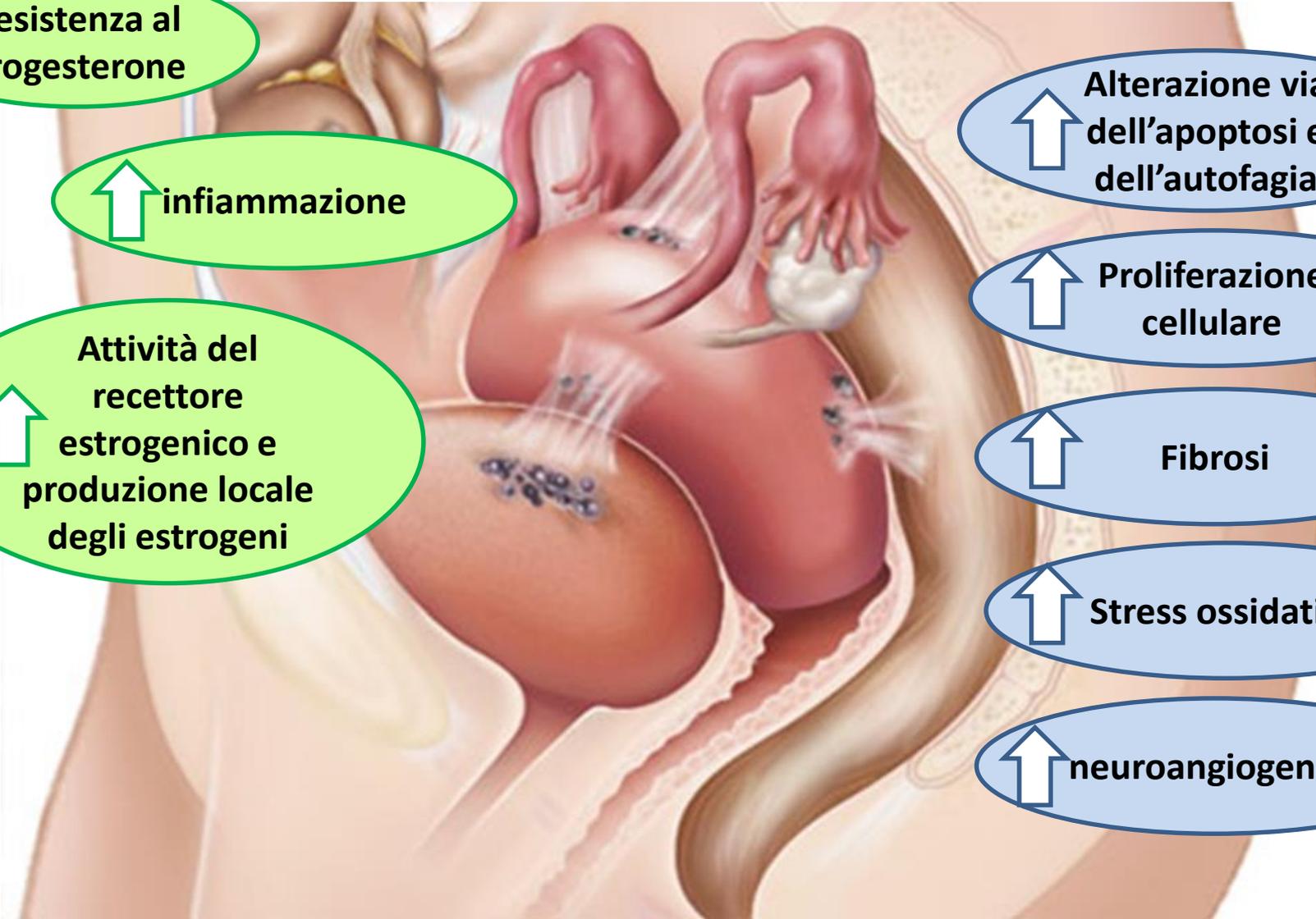
↑
Alterazione via
dell'apoptosi e
dell'autofagia

↑
Proliferazione
cellulare

↑
Fibrosi

↑
Stress ossidativo

↑
neuroangiogenesi



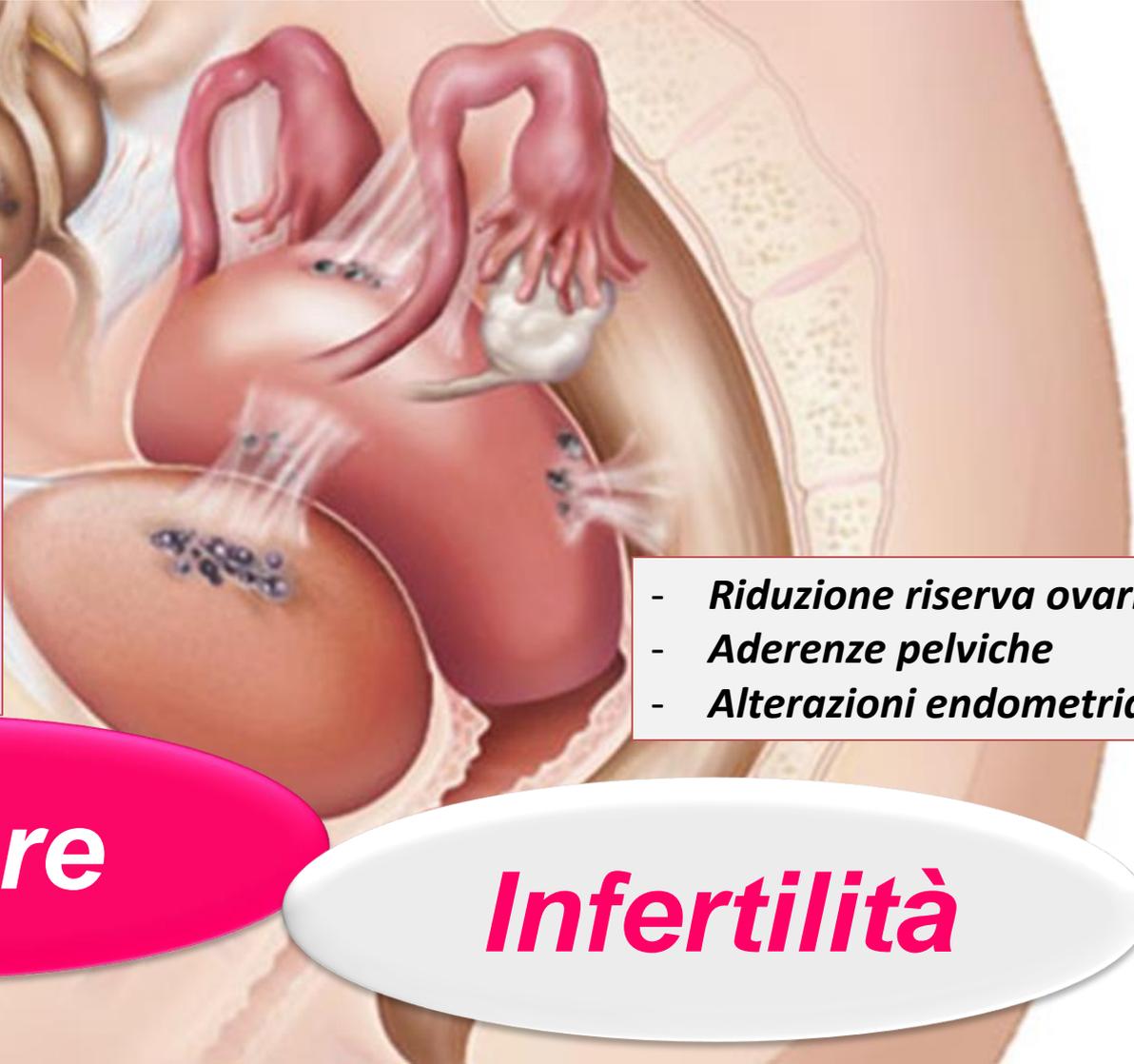
Endometriosi & sintomatologia

- *Dismenorrea*
- *Dispareunia*
- *Dolore pelvico non mestruale*
- *Disuria*
- *Dischezia*
- *Cefalea*
- *Dolore centrale*

- *Riduzione riserva ovarica*
- *Aderenze pelviche*
- *Alterazioni endometriali*

Dolore

Infertilità



Diagnosi di endometriosi: l'importanza dei sintomi

1 Evaluate presence of symptoms

- Persistent and/or worsening cyclic or constant pelvic pain
- Dysmenorrhea
- Deep dyspareunia
- Cyclic dyschezia
- Cyclic dysuria
- Cyclic catamenial symptoms located in other systems (eg, lung, skin)



L'endometriosi è sottodiagnosticata: 6 donne su 10 non sono identificate!

NOTA BENE!

2 Review patient history



Sintomi dolorosi legati al ciclo

3 Perform physical examination

4 Perform/order imaging



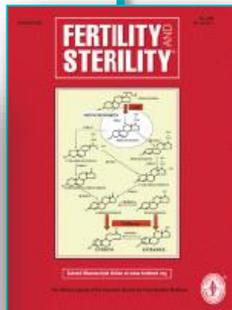
Dolore non responsivo ai FANS

Dismenorrea severa in adolescenza

Evoluzione della diagnosi di endometriosi

ASRM
Stadiazione
dell'endometriosi
I-II-III-IV stadio

**John
Albertson
Sampson**



**Linee guida di
società scientifiche
internazionali**

**Fenotipi di endometriosi:
OMA-SUP-DIE**

**Non è necessaria la
conferma istologica per fare
diagnosi di endometriosi**

1927

1985

2004

2017

2018

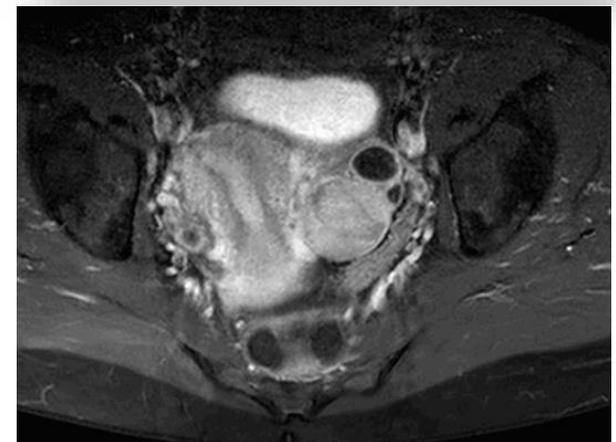
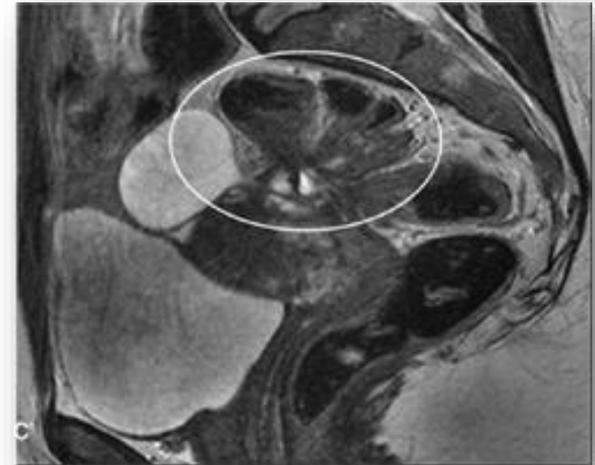
Diagnosi di endometriosi: imaging

Le tecniche di imaging (ecografia e risonanza magnetica) sono le metodiche più accurate per la diagnosi non invasiva di endometriosi

2D and 3D transvaginal ultrasound



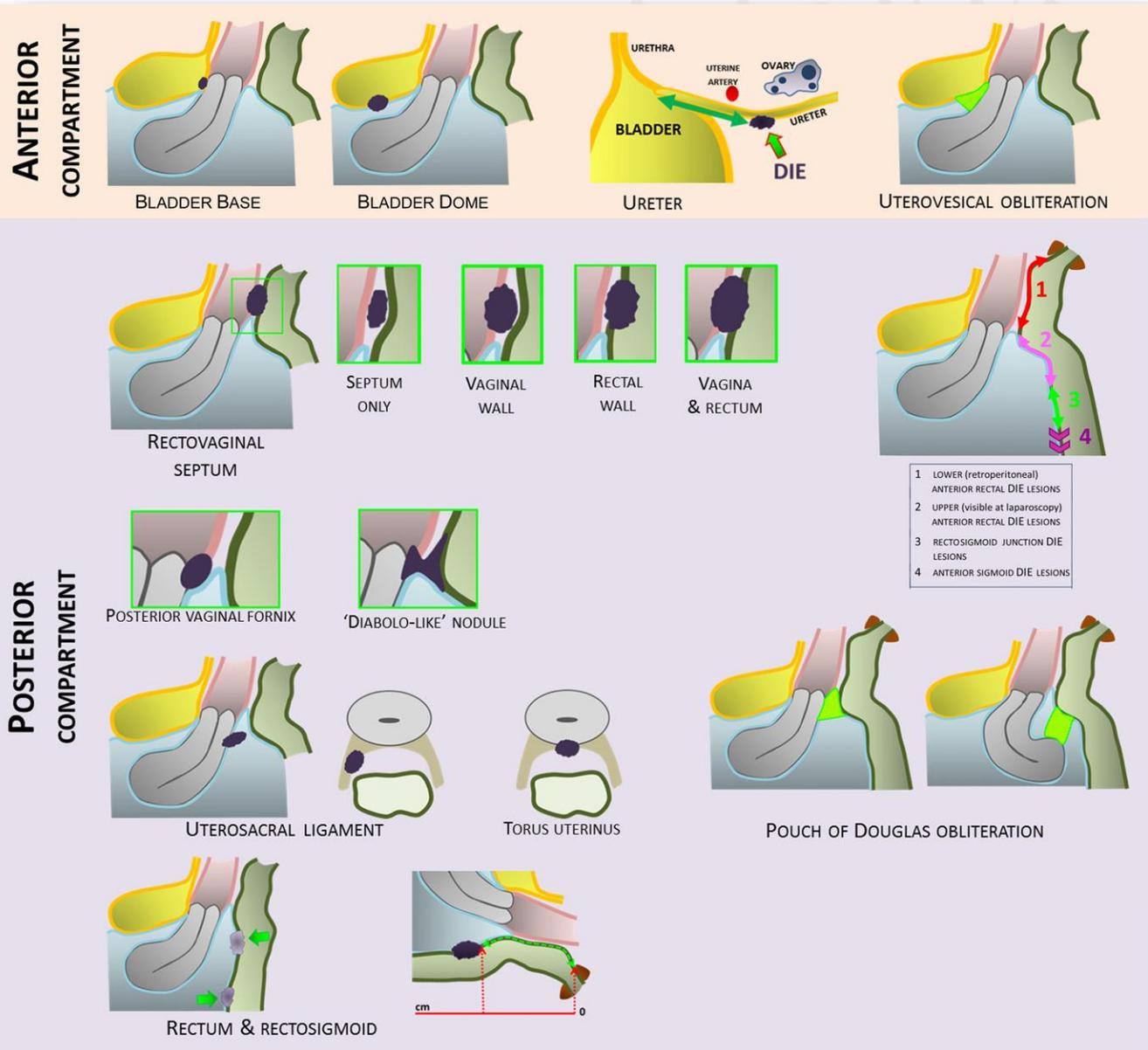
MRI



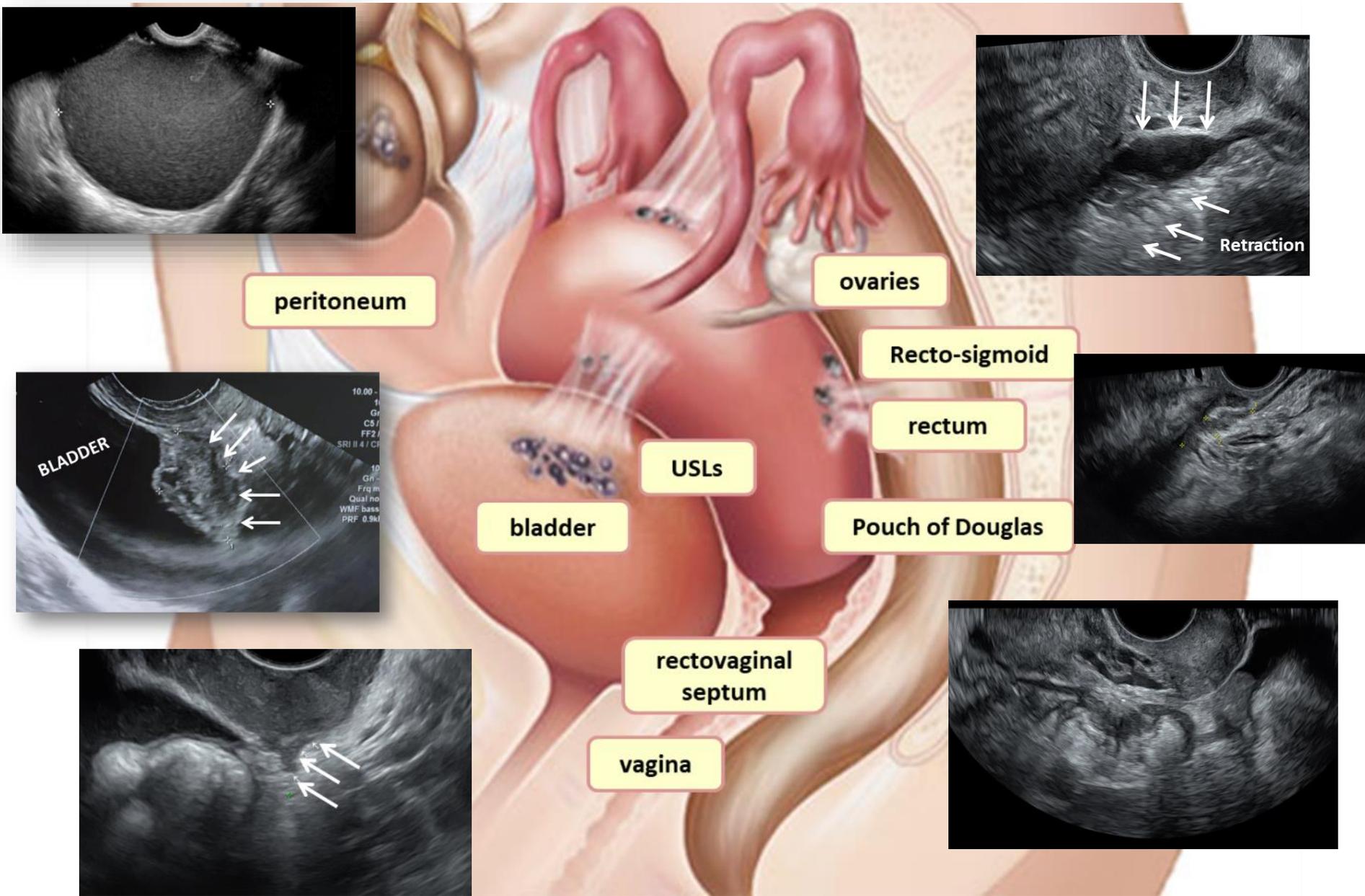
Diagnosis of endometriosis: transvaginal ultrasound

**IDEA
Consensus**

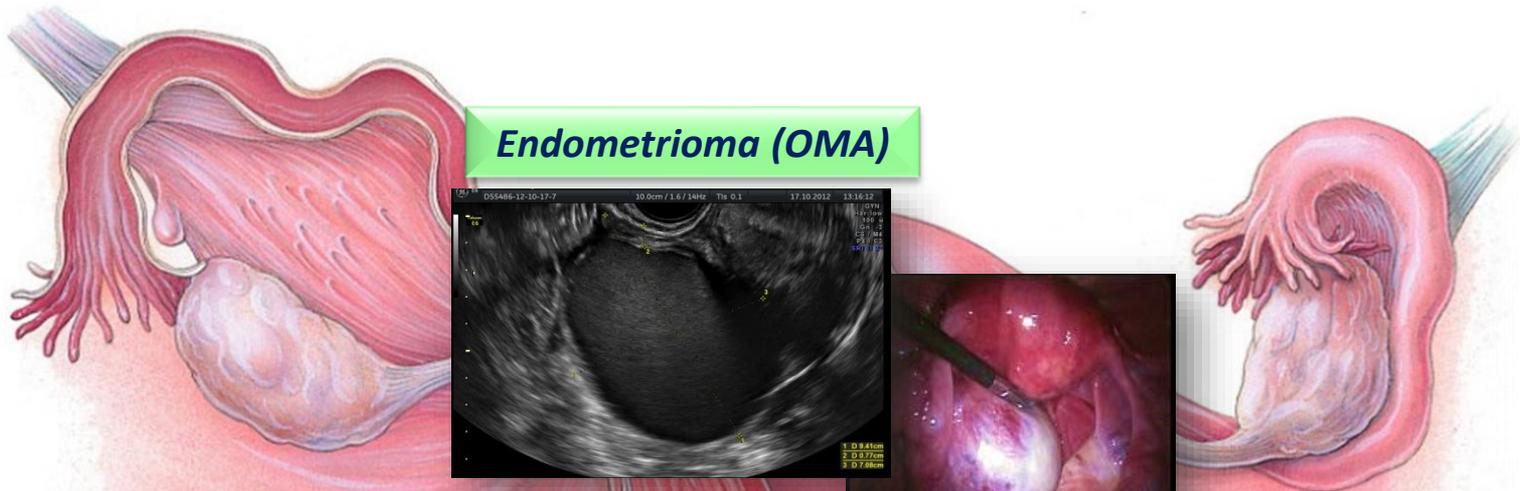
Valutazione sistematica della pelvi per l'identificazione di tutte le possibili localizzazioni endometriose mediante l'ecografia transvaginale



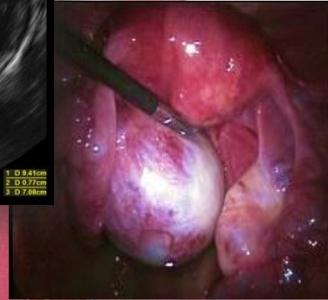
Correct site-specific diagnosis of endometriosis



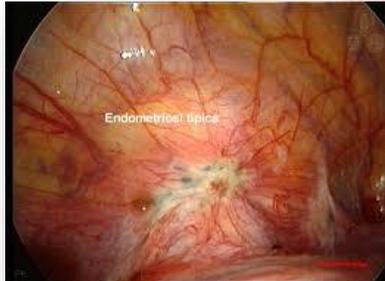
Endometriosis: pathogenetic mechanisms are similar in the different clinical forms



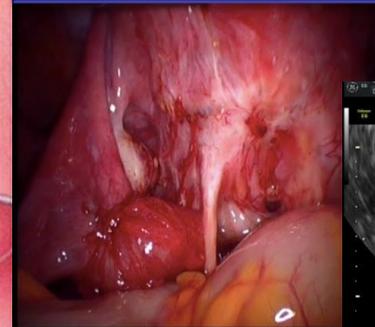
Endometrioma (OMA)



Superficial peritoneal endometriosis



Deep Infiltrating Endometriosis (DIE)



Coexistence of different forms of endometriosis and adenomyosis



endometrioma

DIE

Endometrioma and peritoneal lesions: 30%

Endometrioma and DIE: 40%

DIE and adenomyosis : 49%



superficial peritoneal endometriosis

adenomyosis

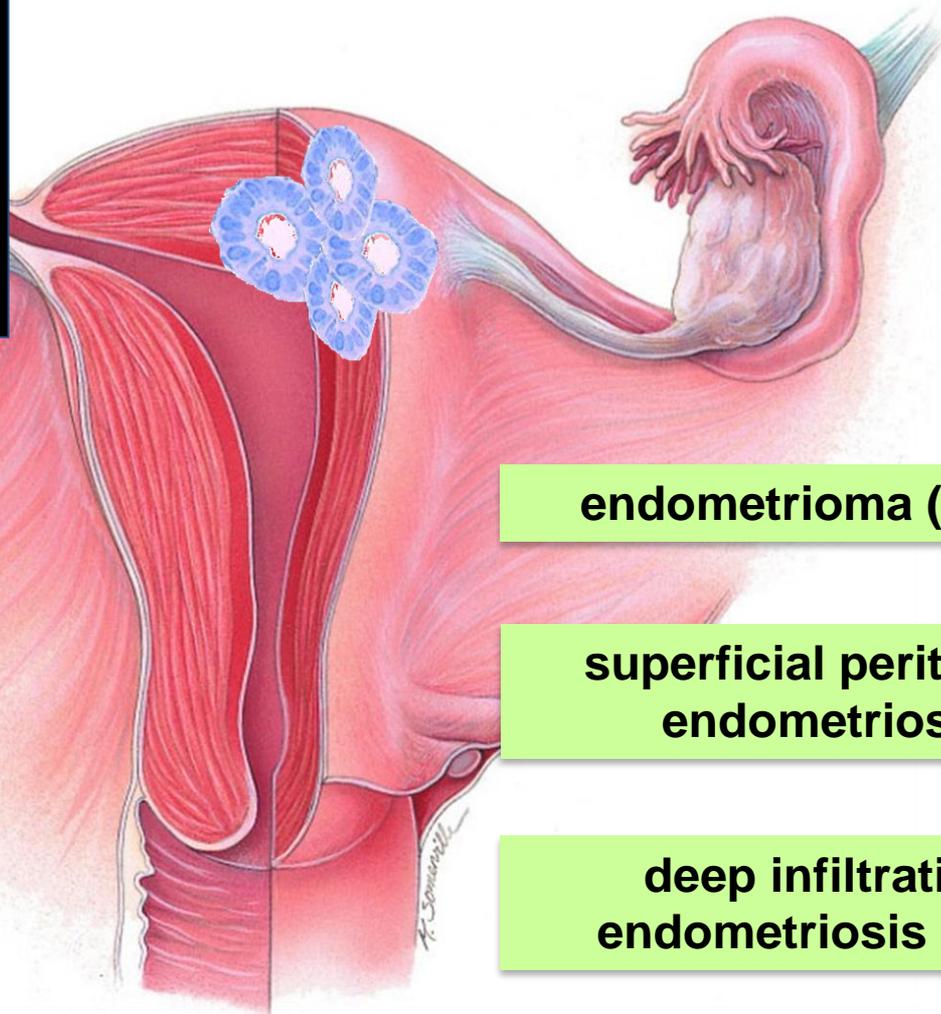
Endometriosis and the association with adenomyosis



Dysmenorrhea
Dyspareunia

Abnormal
uterine
bleeding

Infertility



endometrioma (OMA)

superficial peritoneal
endometriosis

deep infiltrating
endometriosis (DIE)

Management dell'endometriosi nel passato

Infertilità

Endometriosi

1

Chirurgia

2

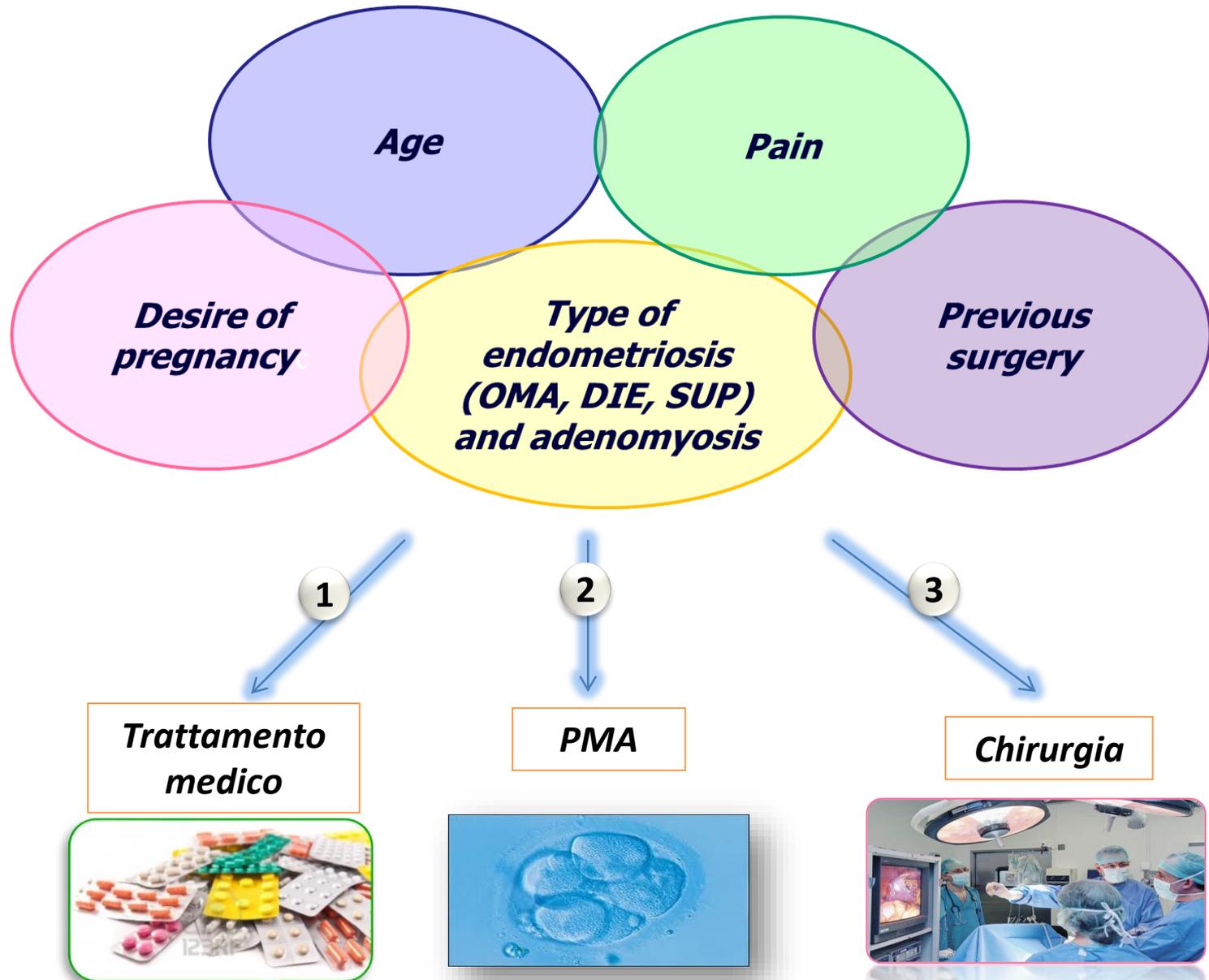
PMA

3

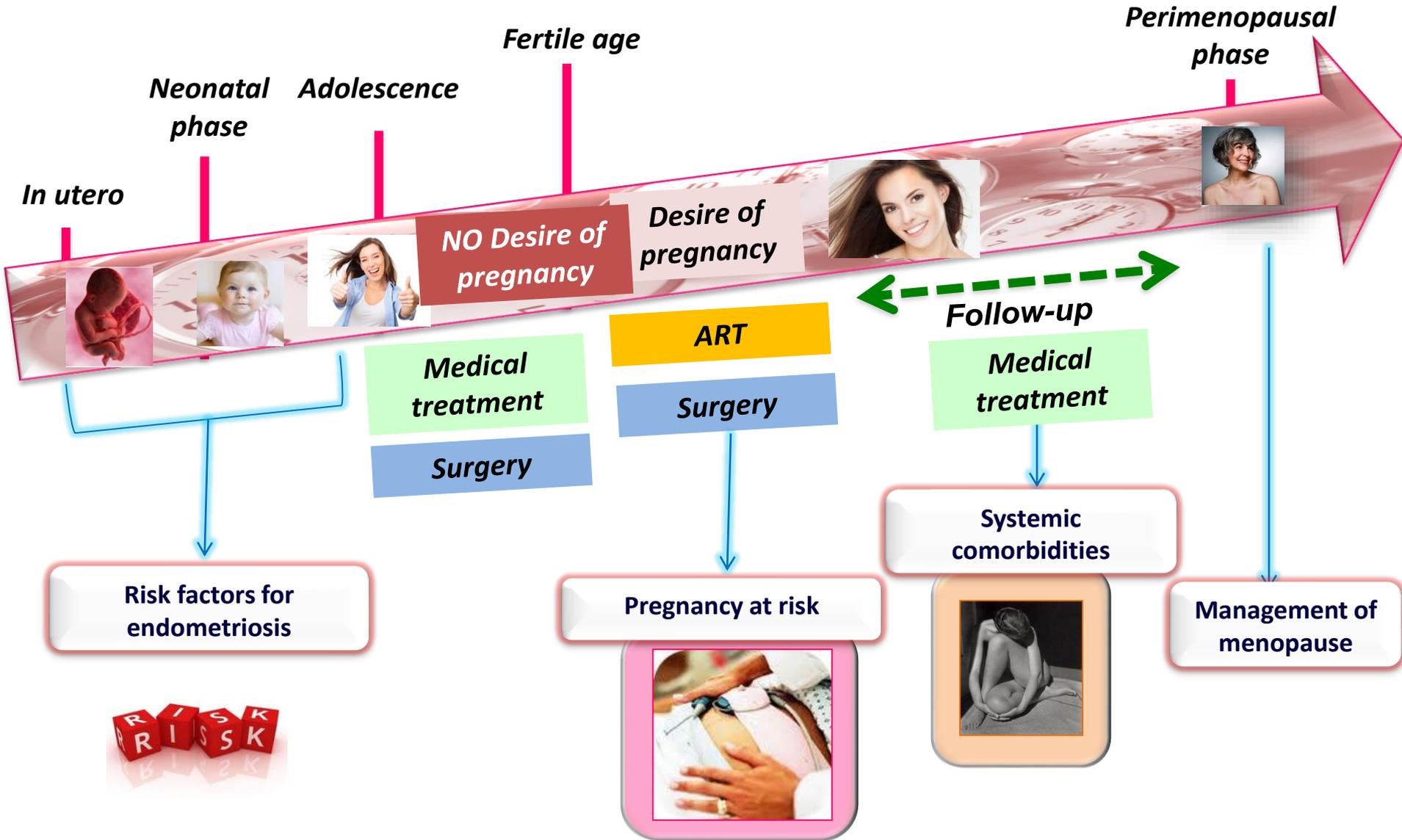
**Trattamento
medico**



Management of endometriosis: which factors to consider?



Endometriosis: natural history of a chronic disease



Criteria to consider for endometriosis treatment in young age

Pain



***Endometriosis phenotype
(OMA, SUP, DIE)***



Coexistence with adenomyosis



Medical treatment



Surgical treatment

Adolescent endometriosis: why to treat?

Alleviate symptoms

Improve quality of life

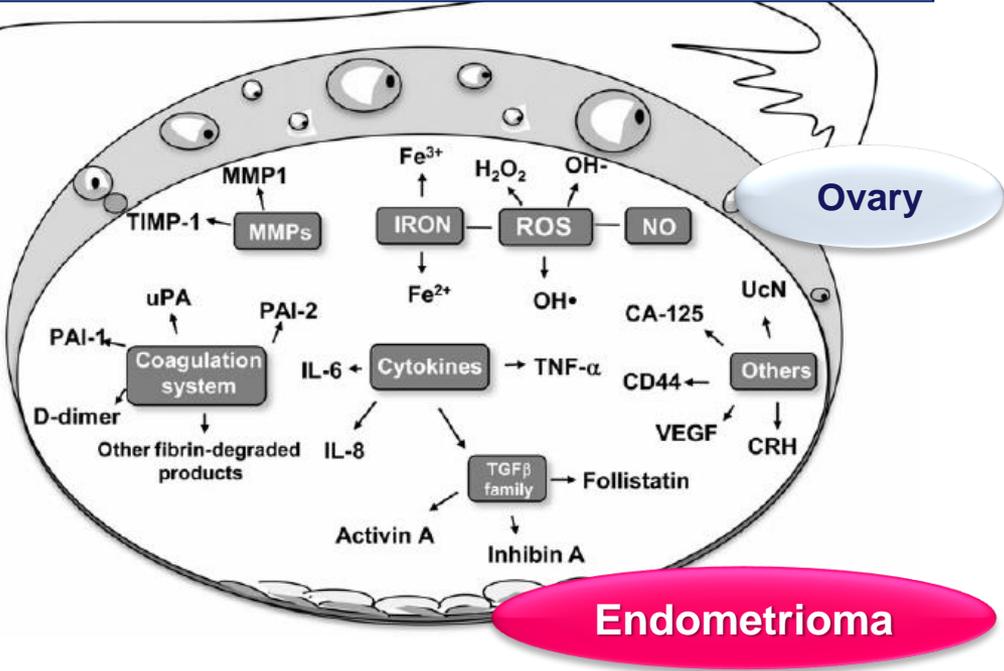
Minimize the impairment of future fertility



Endometriosis&infertility: ovarian reserve and OMA

Ovarian reserve reduction

The 'toxic' network of endometrioma fluid



An endometrioma may cause per se damage to the surrounding healthy ovarian tissue

Sanchez et al, Hum Reprod Update 2014
Muzii L, Hum Reprod, 2014

Fertility issues are a major concern in the long-term treatment strategy in women with endometriosis. Consider fertility preservation!

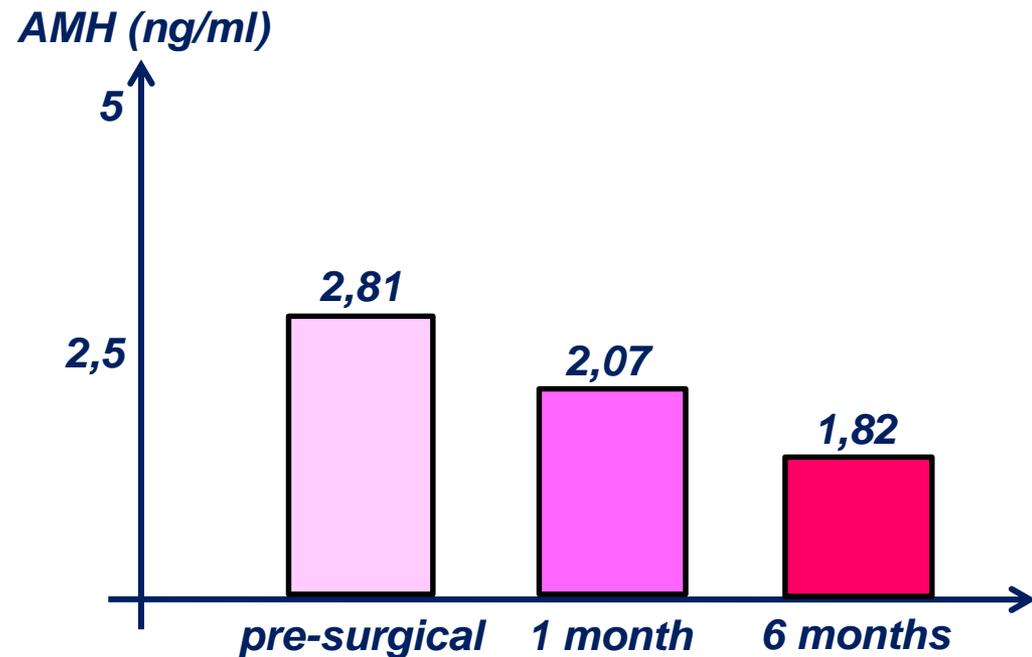
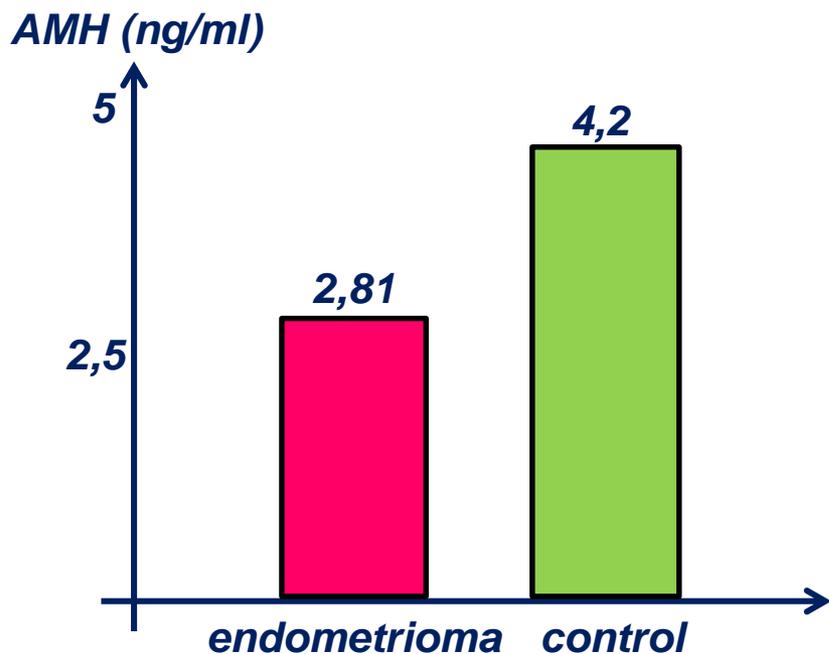
Streuli et al, EJOG, 2018

Endometriosis and ovarian reserve

Serum AMH is a markers of ovarian reserve

Effect of endometrioma

Effect of surgery on AMH



Endometriosis&infertility: ovarian reserve and surgery

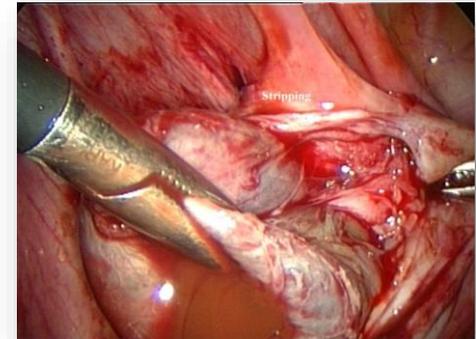
Previous surgery for endometrioma is a risk factor for infertility and poor ovarian response to hyperstimulation

Variable	OR (95% CI)	P
Age >32 years ^a	1.9 (1.4–2.5)	<0.001
Gravidity >0	0.7 (0.6–0.9)	<0.001
Peritoneal superficial endometriosis	3.1 (1.9–4.9)	<0.001
Previous history of surgery for endometriosis	1.9 (1.3–2.2)	<0.001

Santulli et al, Hum Reprod, 2016

variable	OR (95% CI)	p
Age > 35 y.o	1.7; 95% CI: 1.1–2.5	0.015
AMH level < 2 ng/ml	2.6; 95% CI: 1.7–4.0	< 0.001
AFC < 10	2.4; 95% CI:1.6–3.7	< 0.001
prior history of surgery for OMA	2.2, 95% CI: 1.1–4.2	0.019

Factors associated with presentation for infertility



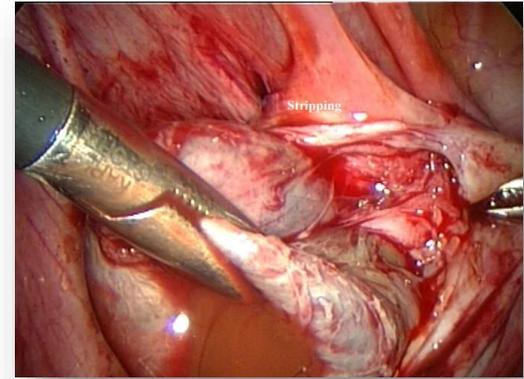
Factors associated with poor response to hyperstimulation

Endometriosis e chirurgia: recidiva

Il tasso di recidiva di endometriosi è alto:

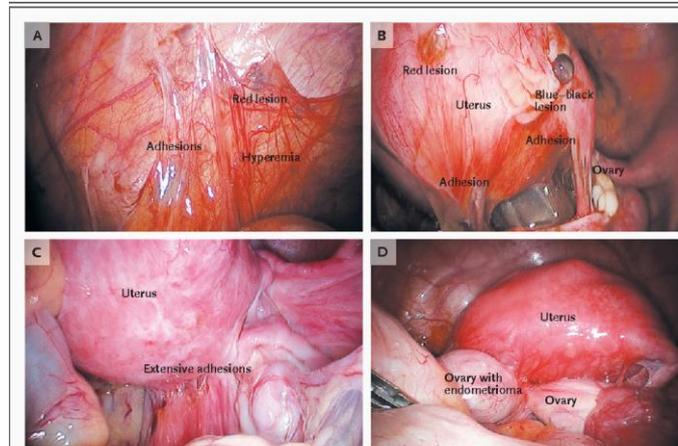
- 21.5% dopo 2 anni
- 40-50% dopo 5 anni

Guo, HRU, 2009



Le donne con storia di chirurgia per endometriosi hanno un aumentato rischio di chirurgia multipla

Hazard ratio (HR) 1.69 95% (CI 1.65–1.73)



Surgical treatment of endometriosis in young age



“Laparoscopy should be considered if adolescents with chronic pelvic pain who do not respond to medical treatment (NSAID and oral contraceptive pills) since endometriosis is very common under these circumstances”



Do not perform laparoscopy in adolescent women (<20 years) with moderate–severe dysmenorrhea and clinically suspected early endometriosis without prior attempting to relieve symptoms with estrogen–progestins or progestins

Endometriosis, surgery and quality of life

	Normal QoL(<i>n</i> = 42) 	Low QoL(<i>n</i> = 111) 	<i>p</i> -value
Age at first surgery	30.4 ± 5.5	26.5 ± 5.0	.000
Time since first surgery (months)	82 ± 51	115 ± 69	.003
Number of operation	1.6 ± 0.9	2.0 ± 1.2	.047
Multiple operations	15 (36%)	60 (54%)	.042

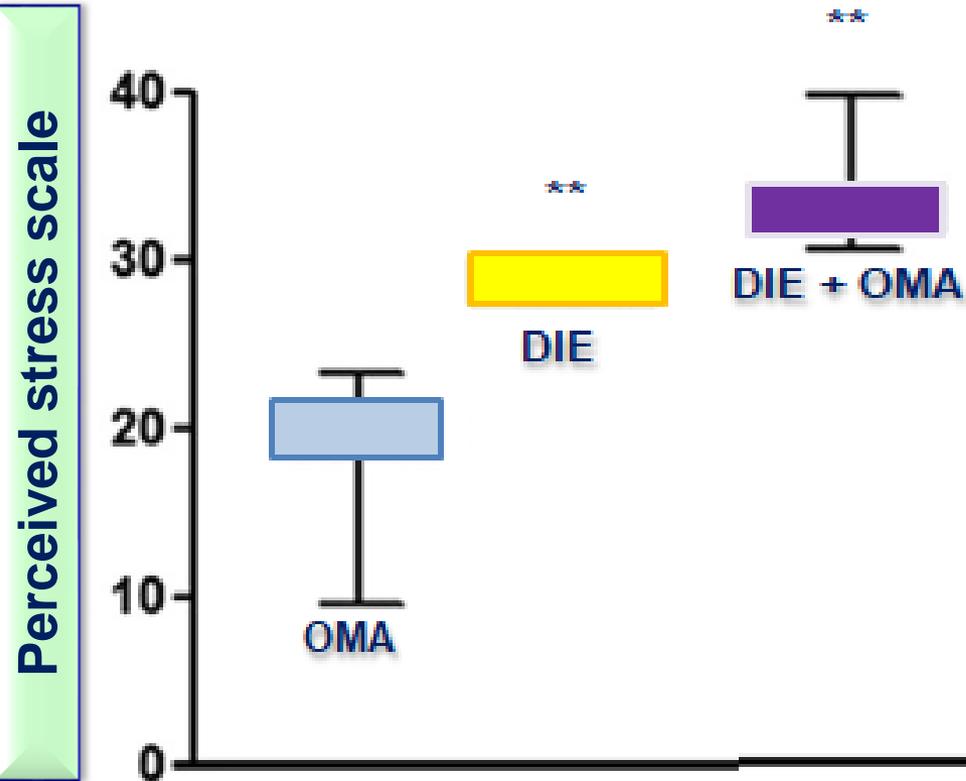
Prognostic factors for better QoL

first operation **at an older age**

a single surgical intervention

less symptom or lesion recurrence

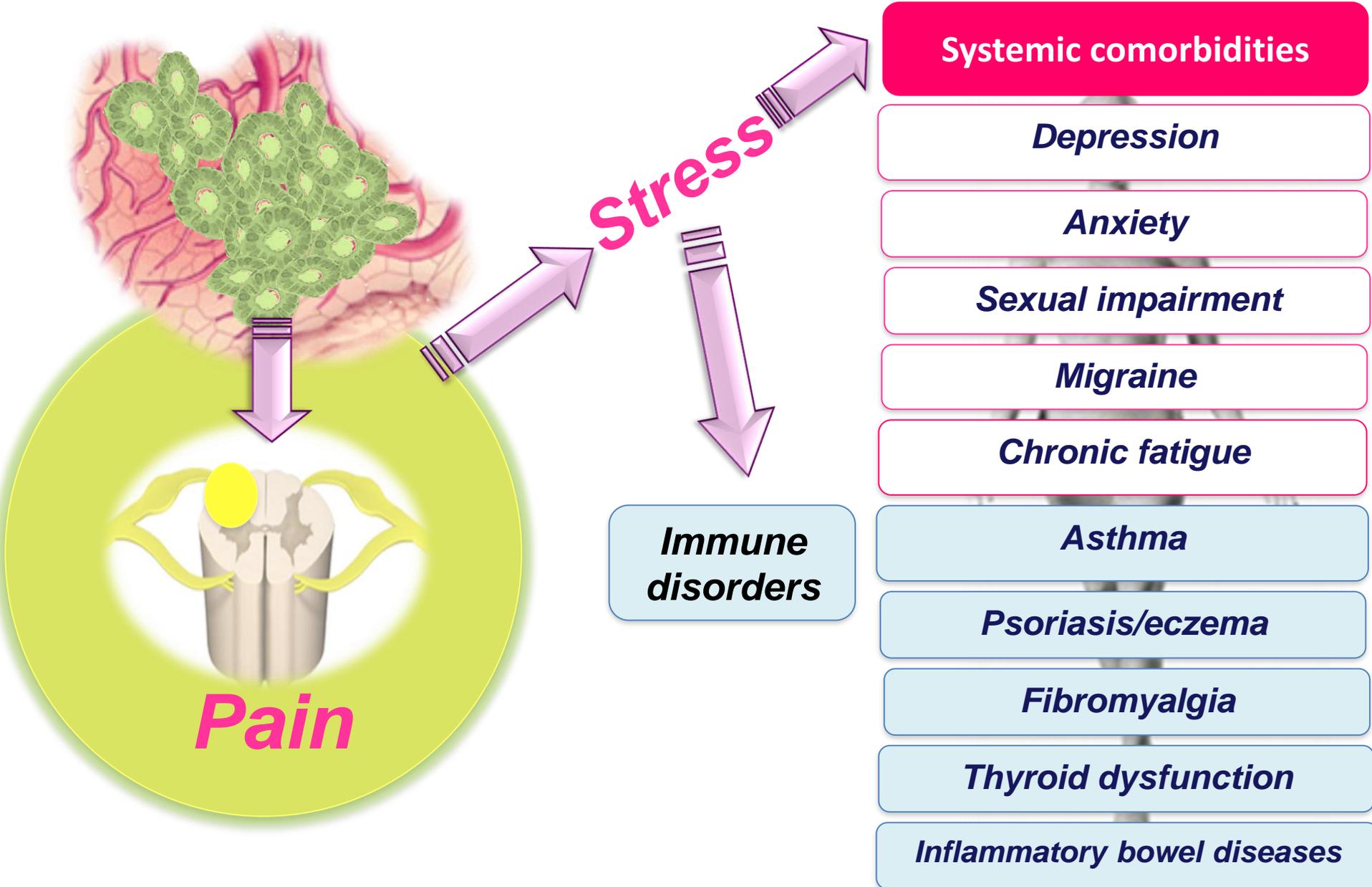
Endometriosis and stress



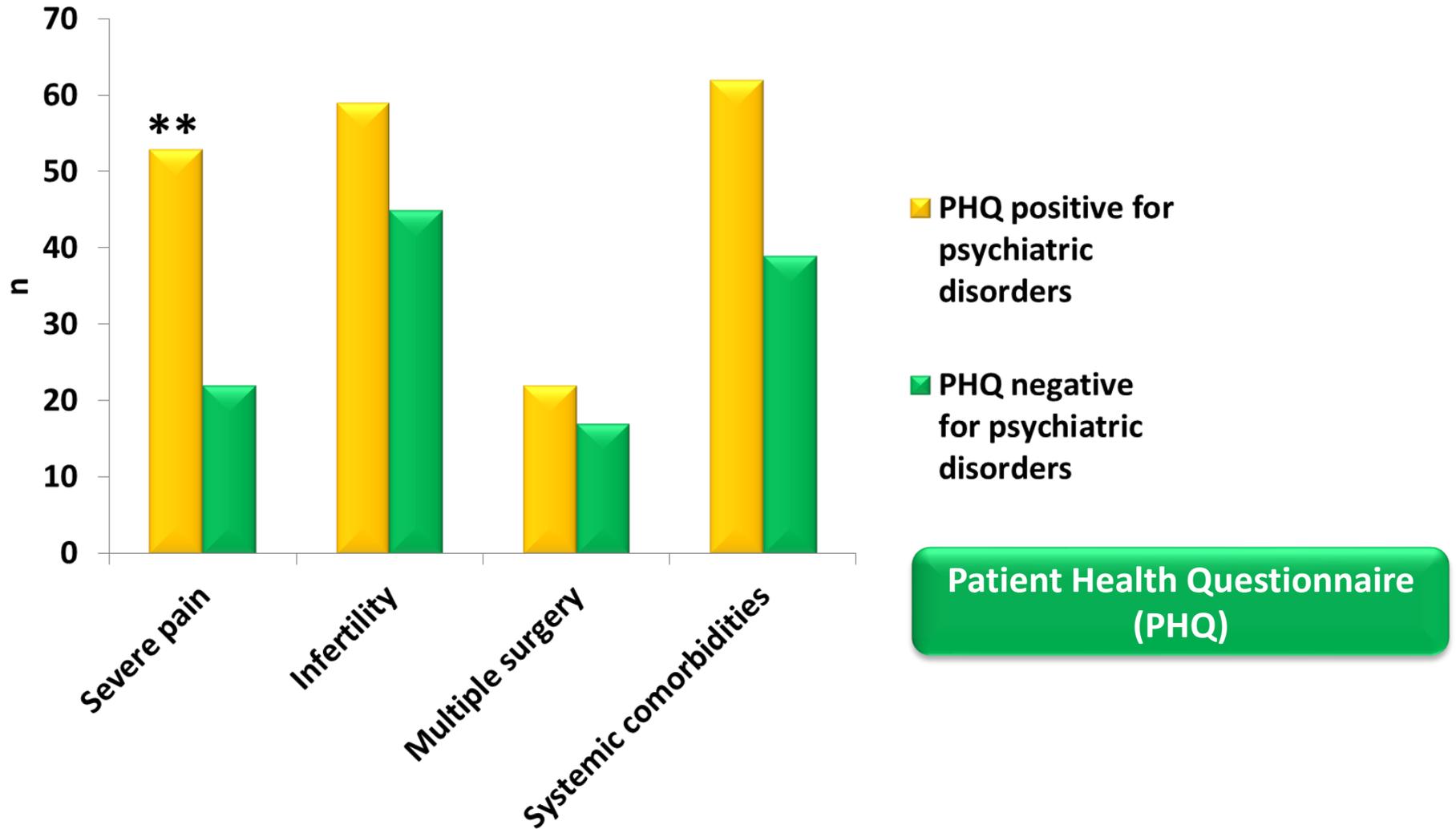
Women with endometriosis have high levels of perceived stress before surgery

Repetitive surgical procedures increased the perceived stress

Impact of pain and stress in endometriosis

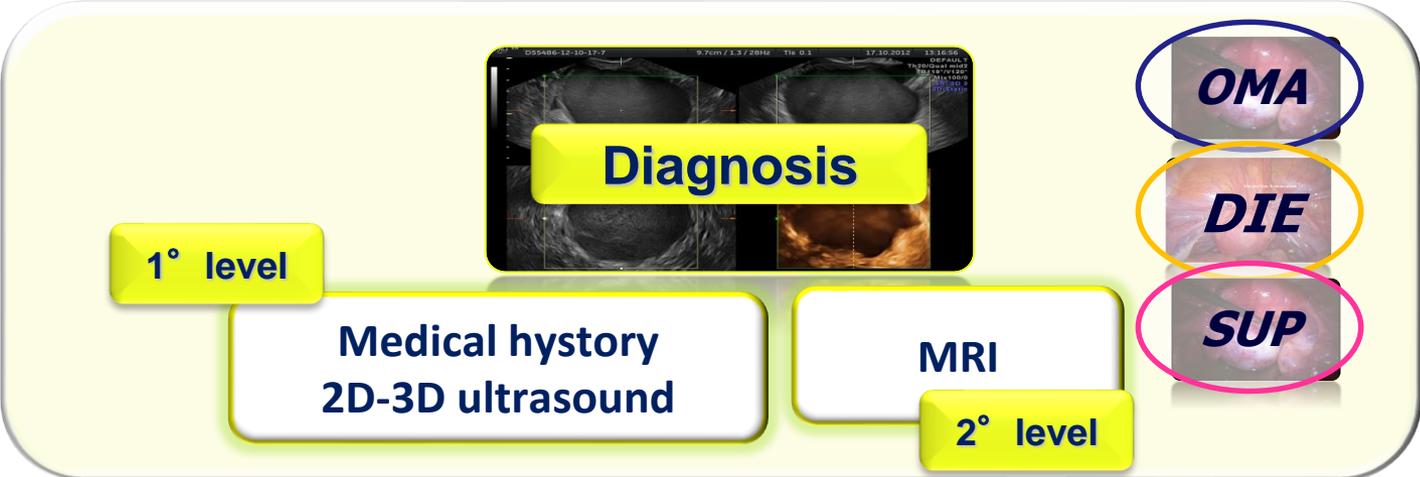


Endometriosis and psychiatric symptoms



Women with endometriosis showed a high frequency of psychiatric disorders, with a significant association with pain severity.

2019- Management of endometriosis in young women



Medical treatment

To reduce recurrence

- drug resistance
- symptoms

Surgical treatment

Fertility preservation

Management of endometriosis



2010



2013

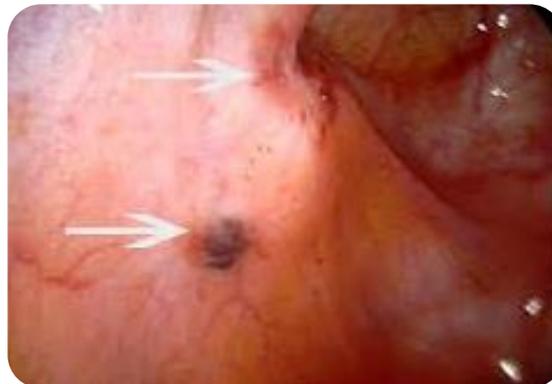


Empirical medical treatment for painful symptoms should be considered either prior to or without laparoscopic confirmation of endometriosis

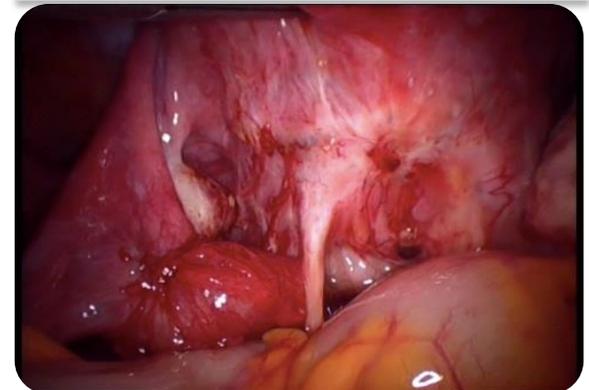
OMA



SUP



DIE



Medical treatment of endometriosis

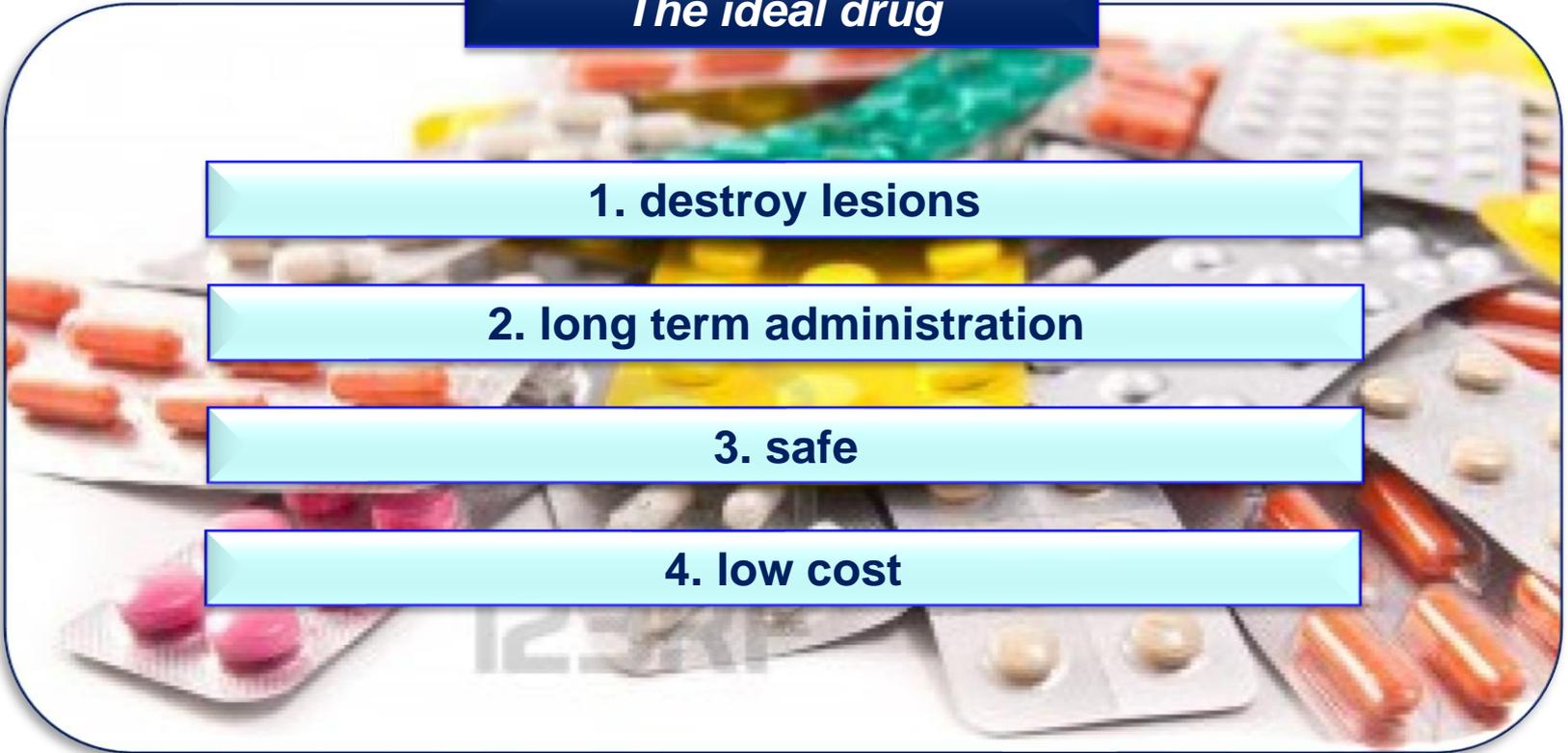
The ideal drug

1. destroy lesions

2. long term administration

3. safe

4. low cost



Indications for medical treatment

First line treatment

1. In women in reproductive age with pain and no desire of pregnancy: empirical treatment

2. When surgery is contraindicated or refused for previous surgical treatments

Second line treatment

3. To prevent or treat recurrence

Management of endometriosis

Medical treatment

Hormonal treatments

Progestins
(dienogest, NETA, MPA,
levonorgestrel, danazol)

**Oral
contraceptives**

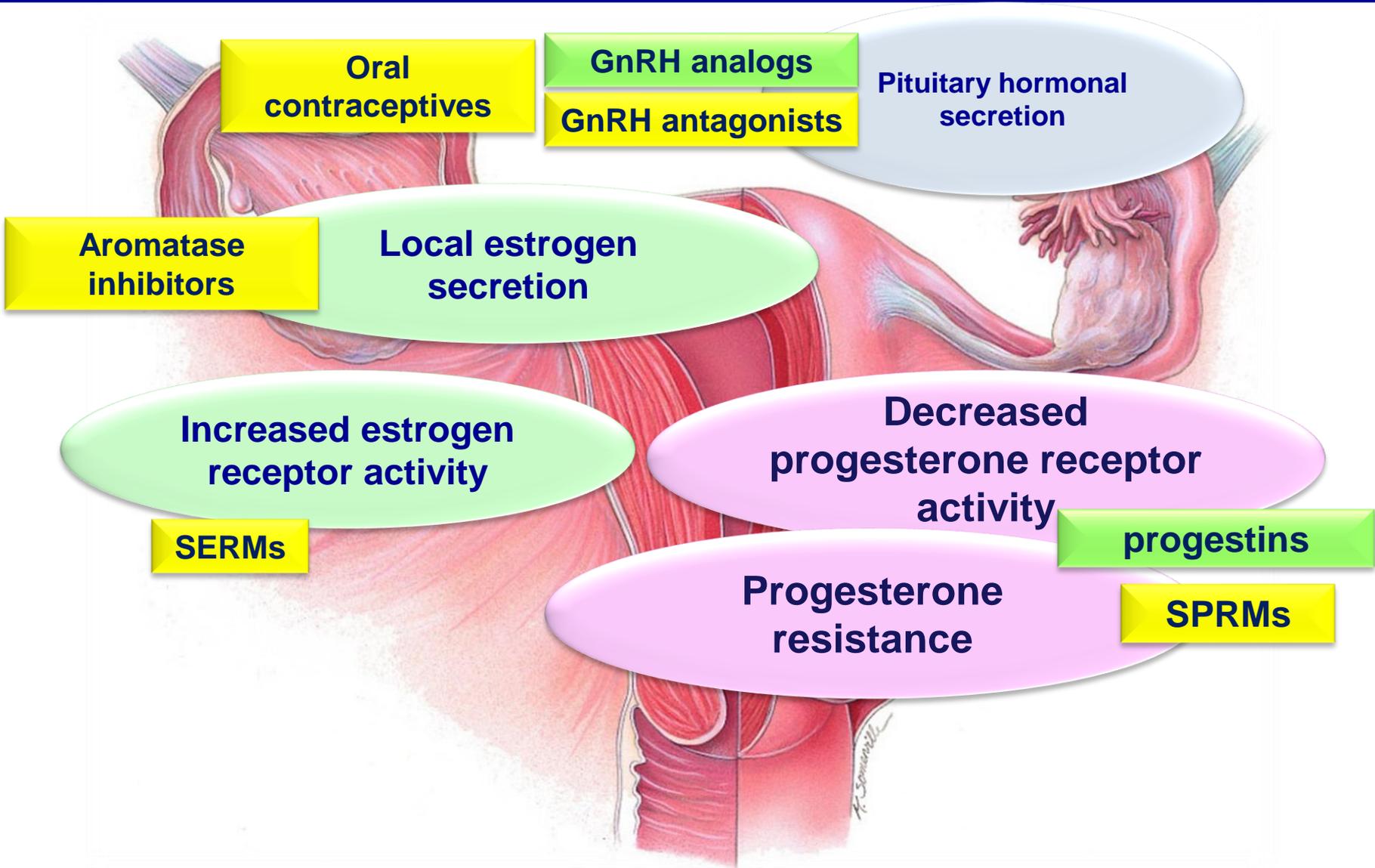
**GnRH analogs
GnRH antagonists**

+

Non-hormonal treatments:

- **Anti-inflammatory (NSAIDs, bromelin)**
 - **Anti-oxidants (omega-3)**
- **Immunomodulatory (lactoferrin)**

Endometriosis and hormonal treatment



Medical treatment of endometriosis in young age



it is reasonable to treat young girls with symptoms using the classical approach of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or estrogen/progestin oral contraceptives (OCs).

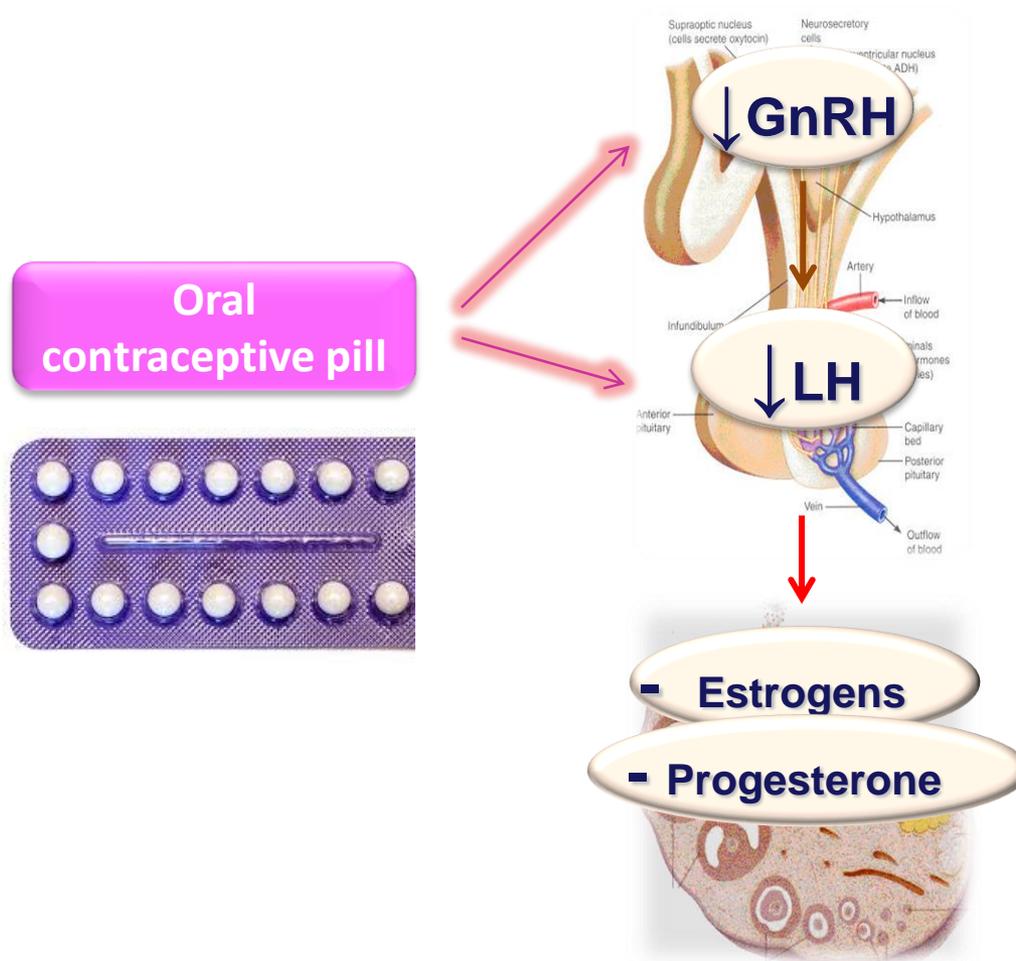
De Sanctis al, Best Pract Obstet Gynecol , 2018

Combinations with the lowest possible estrogen dose should be chosen, such as those with only 15–20 µg of EE or 1.5 mg of 17 β-estradiol (E2).

Vercellini et al, Fert Ster , 2018

Endometriosis and hormonal treatment

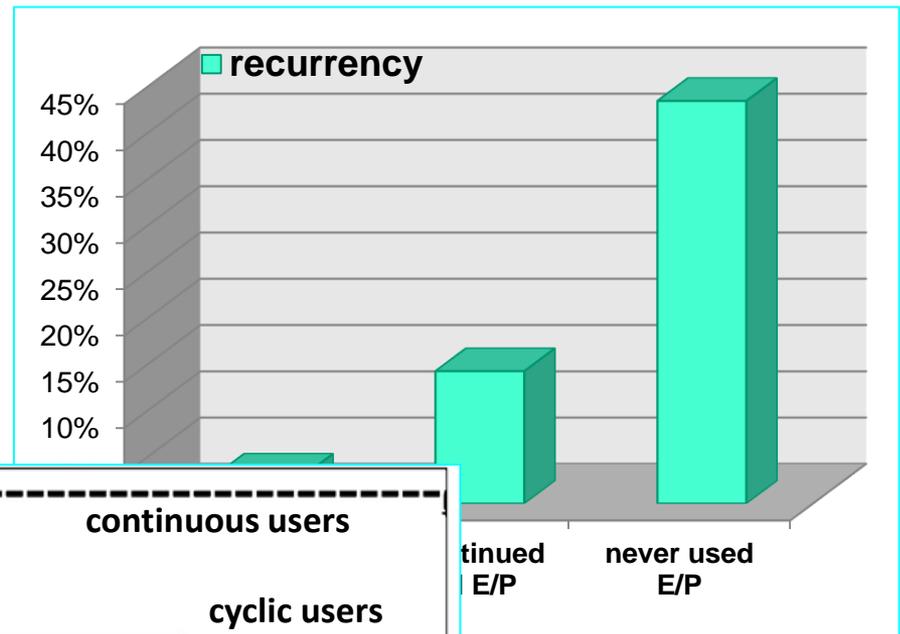
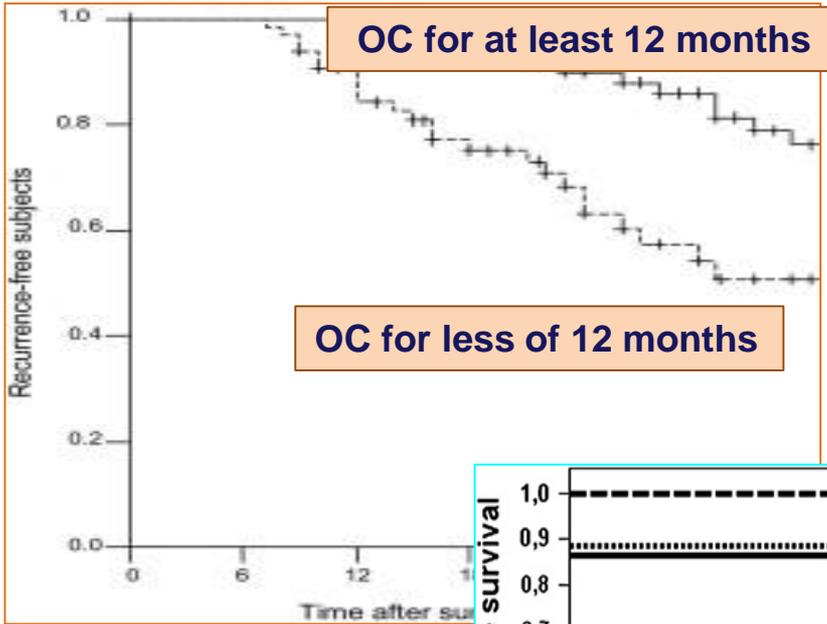
Blocking the ovarian function



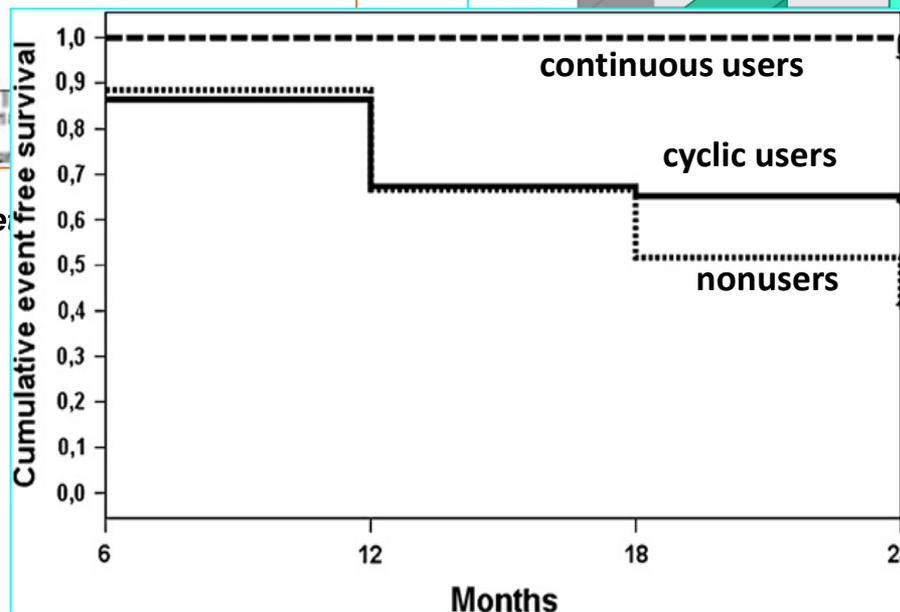
Medical treatment: estro-progestins

As first-line therapy

As post-operative therapy to prevent recurrence



Vercellini P et al.



al. Hum Reprod, 2009

Seracchioli R et al. Fertil Steril, 2010

2017

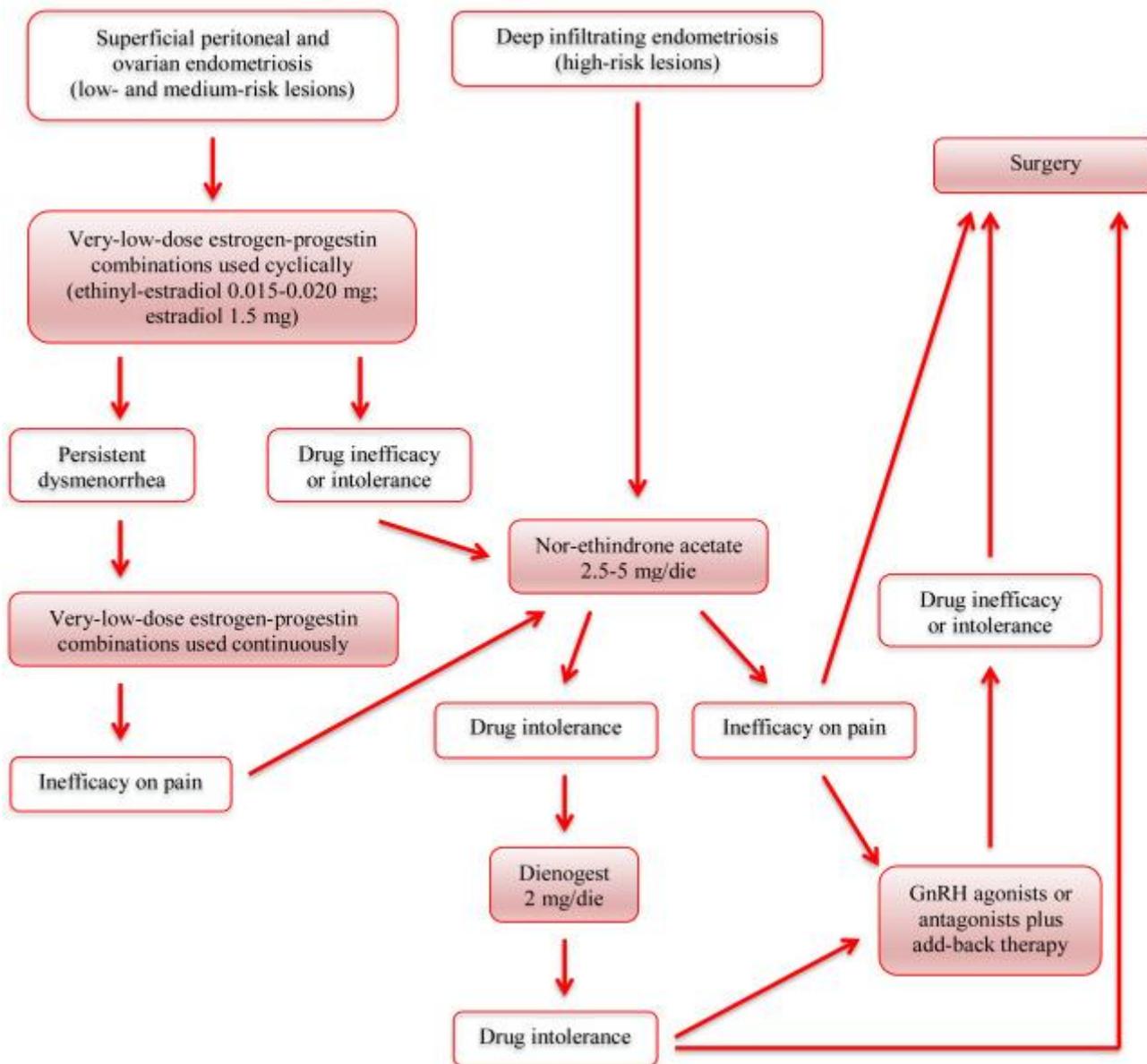


Progestin-only pills may be a better first-line treatment for endometriosis than combined estrogen-progestin contraceptive pills

Robert F. Casper, M.D.

Biologic data and limited clinical evidence support a potential adverse effect of long-term use of OCPs on the progression of endometriosis. In contrast, there is randomized, controlled trial data to support the use of oral progestin-only treatment for pelvic pain associated with endometriosis and for suppressing the anatomic extent of endometriotic lesions. Both norethindrone acetate and dienogest have regulatory approval for treating endometriosis and may be better than OCPs as a first-line therapy

Medical treatment of endometriosis: estro-progestins



limiting endometriotic implant metabolism

minimizing monthly withdrawal bleeding

continuous vs cyclic OC use

OCs are contraceptives by definition

Endometriosis and progestins: mechanisms of action

Increased estrogen sensitivity

Inhibition of HPO axis

progesterone resistance

Restore progesterone sensitivity

increased inflammation

Decreased PGs, COX-2, TNF α and ILs

1. Impaired apoptosis and autophagia

2. Increased oxidative stress

3. Increased cell proliferation/
Fibrosis

4. Increased acute inflammation

5. Invasion

6. Neuro-neoangiogenesis

Increased apoptosis

Reduce cell proliferation

Decreased VEGF and NGF

pain

infertility

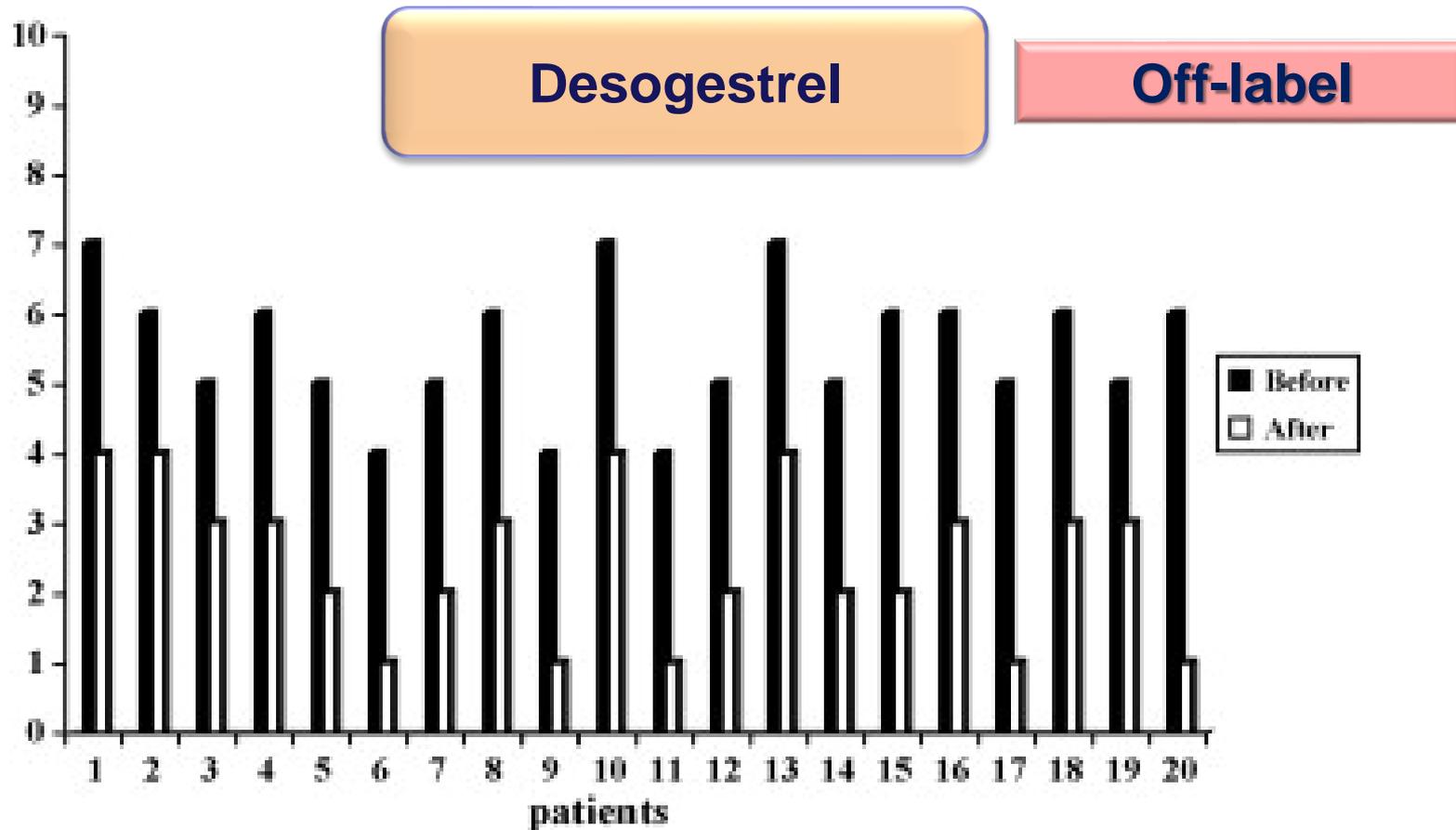
Endometriosis and progestins

Off-label	Medroxyprogesterone Acetate	Subcutaneous/intramuscular administration
	Desogestrel	Oral administration
	NETA	Oral administration
		Vaginal administration
	Levonorgestrel	Intrauterine administration
	Danazol	Vaginal administration

Label	Danazol	Oral administration
	Dienogest	Oral administration

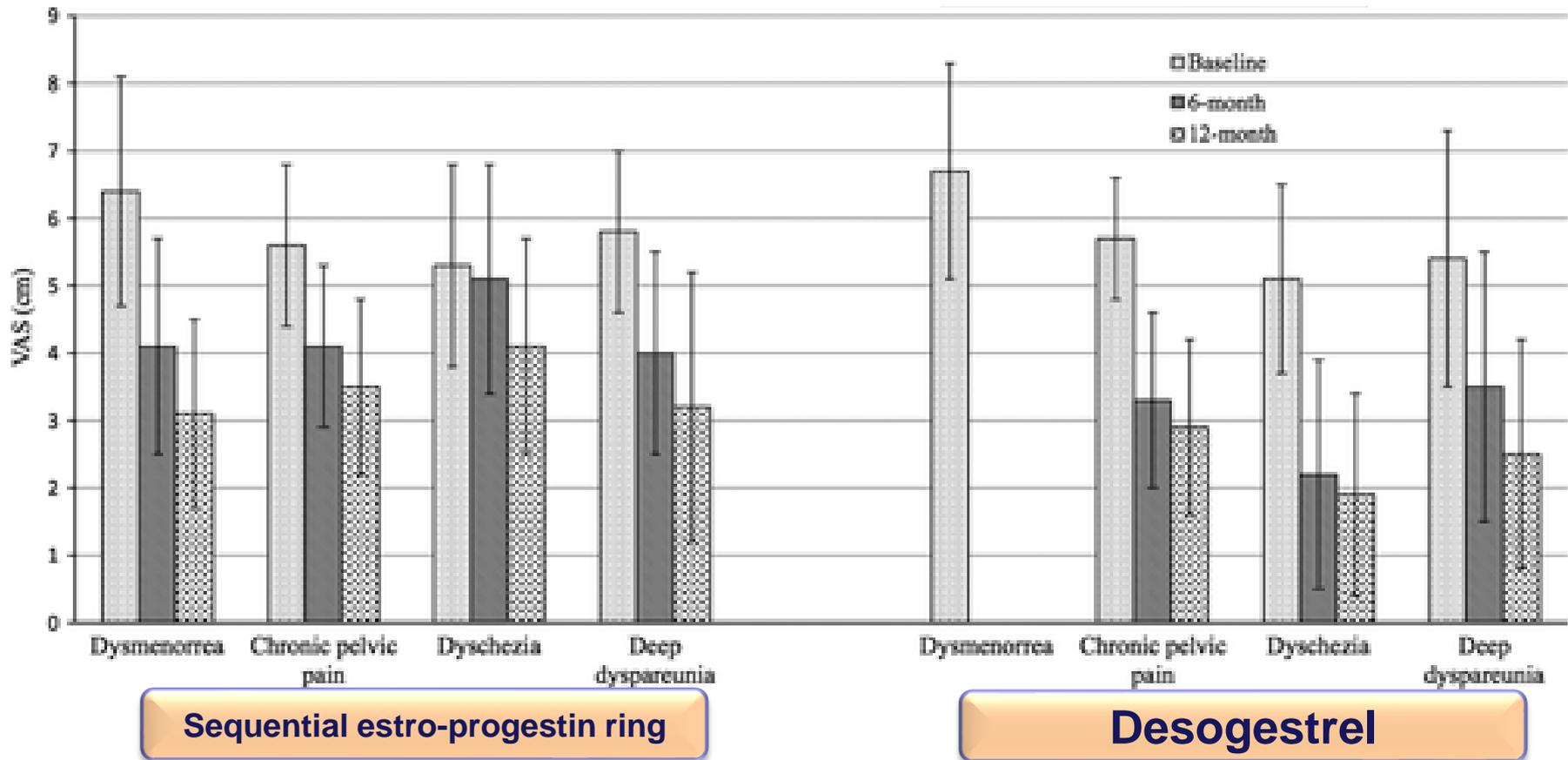
Desogestrel and endometriosis

A significant improvement of both pelvic pain and dysmenorrhea after 6-months treatment in endometriosis recurrence



Desogestrel and endometriosis

In rectovaginal endometriosis, at 12-month follow up, the rate of satisfied patients was higher in those treated with the desogestrel-only pill

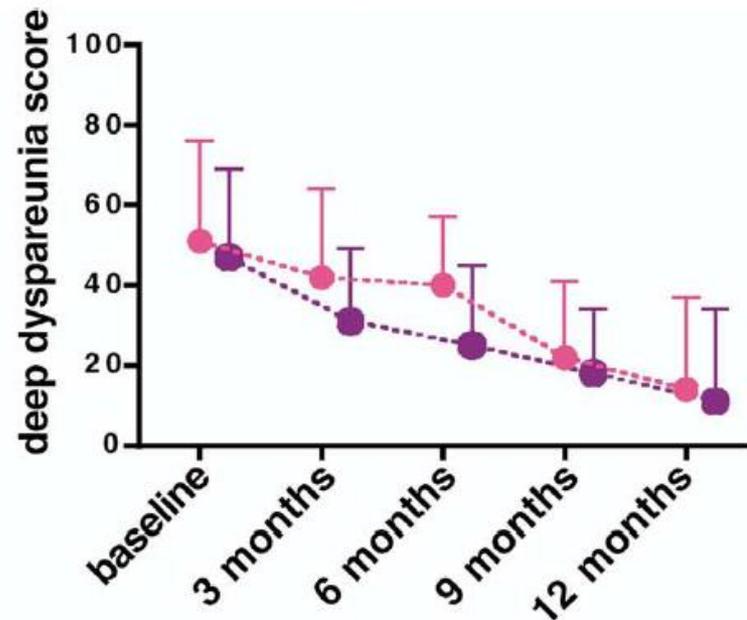
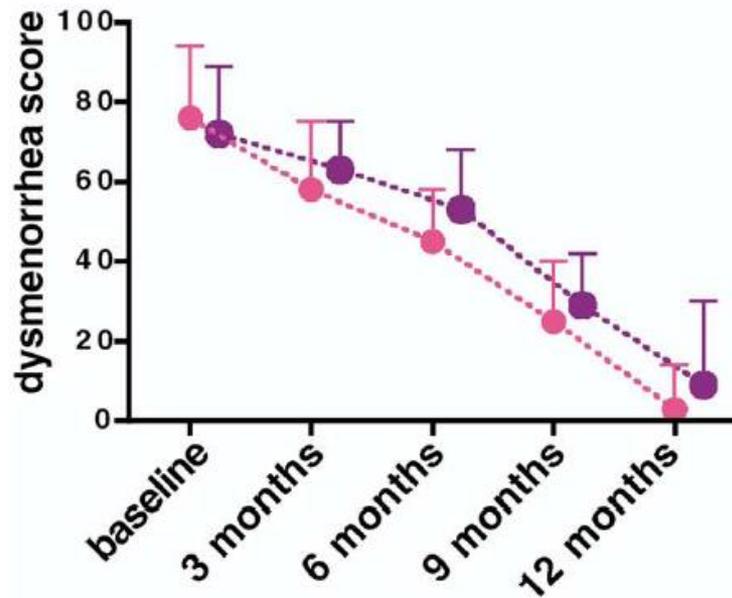


Norethindrone acetate and endometriosis

Low-dose norethindrone acetate (NETA) may be considered an effective, tolerable and inexpensive first choice for symptomatic rectovaginal endometriosis.

Off-label

**Approved by FDA US
5 mg/day continuously**



Continuous treatment with oral ethinyl E2 + cyproterone acetate (violet), or norethindrone acetate 2.5 mg/day (pink).

Norethindrone acetate and endometriosis

Continuous treatment with NETA provide improvement in gastrointestinal symptoms, chronic pelvic pain and deep dyspareunia in women with colorectal endometriosis

Ferrero et al. Hum Reprod, 2010

VAS	Baseline	6-months	12-months
Chronic pelvic pain	5.5 ± 1.3	4.1 ± 1.8	3.5 ± 1.6
Deep dyspareunia	5.7 ± 1.4	3.1 ± 1.1	2.8 ± 1.2
Dyschezia	5.1 ± 1.9	3.2 ± 1.2	2.5 ± 1.4
Diarrhoea	7.3 ± 0.6	2.7 ± 0.6	1.7 ± 0.6
Intestinal cramping	7.1 ± 1.8	4.0 ± 2.0	3.0 ± 1.5
Passage of mucus	4.3 ± 1.5	1.6 ± 0.8	1.0 ± 0.0



Endometriosis and Dienogest



Dienogest was approved for the treatment of endometriosis in Japan in 2007

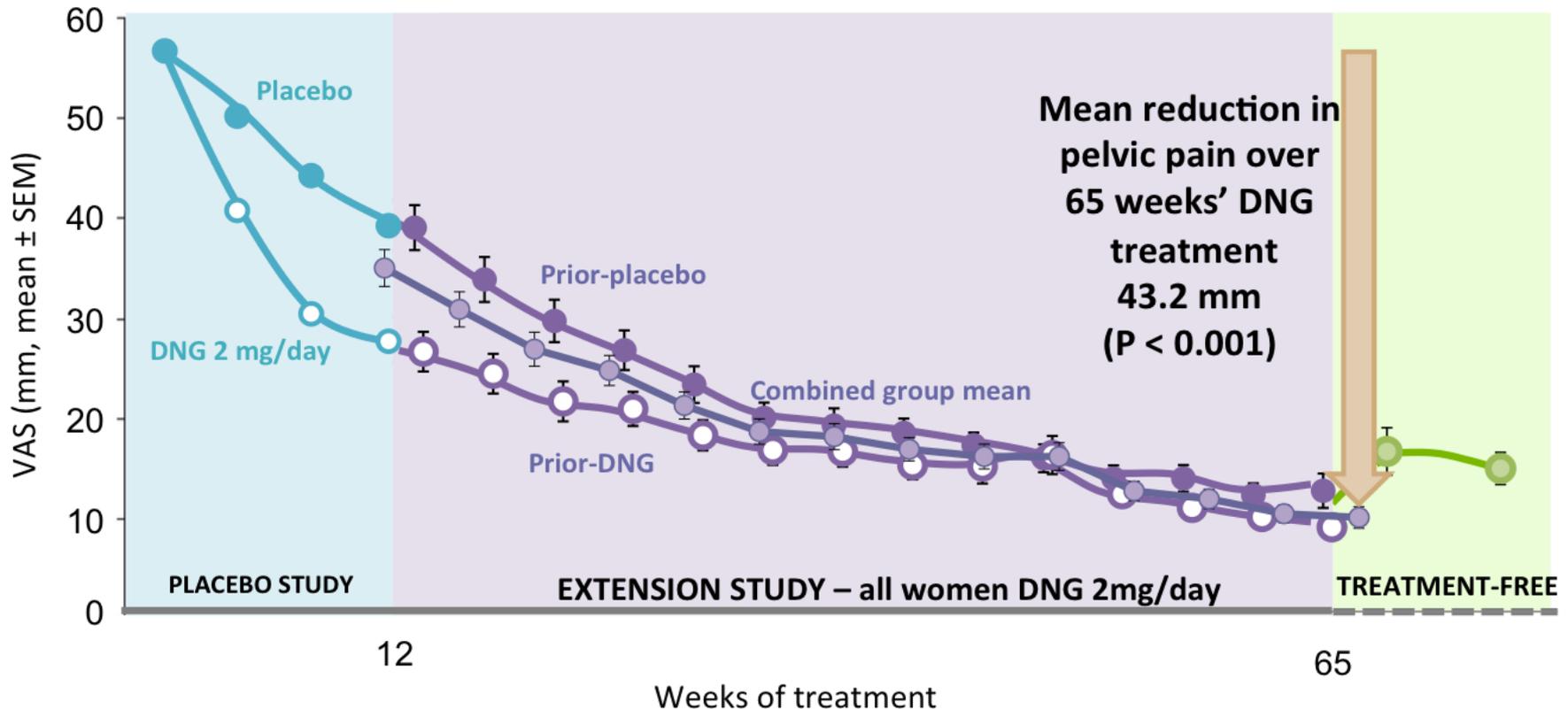
Approved in the EU in December 2009

The recommended dosage of oral dienogest is 2 mg once daily taken at the same time each day, with or without food

Treatment must be continuous without regard to vaginal bleeding. Non hormonal methods of contraception need to be used for the duration of dienogest therapy

Dienogest: long term studies

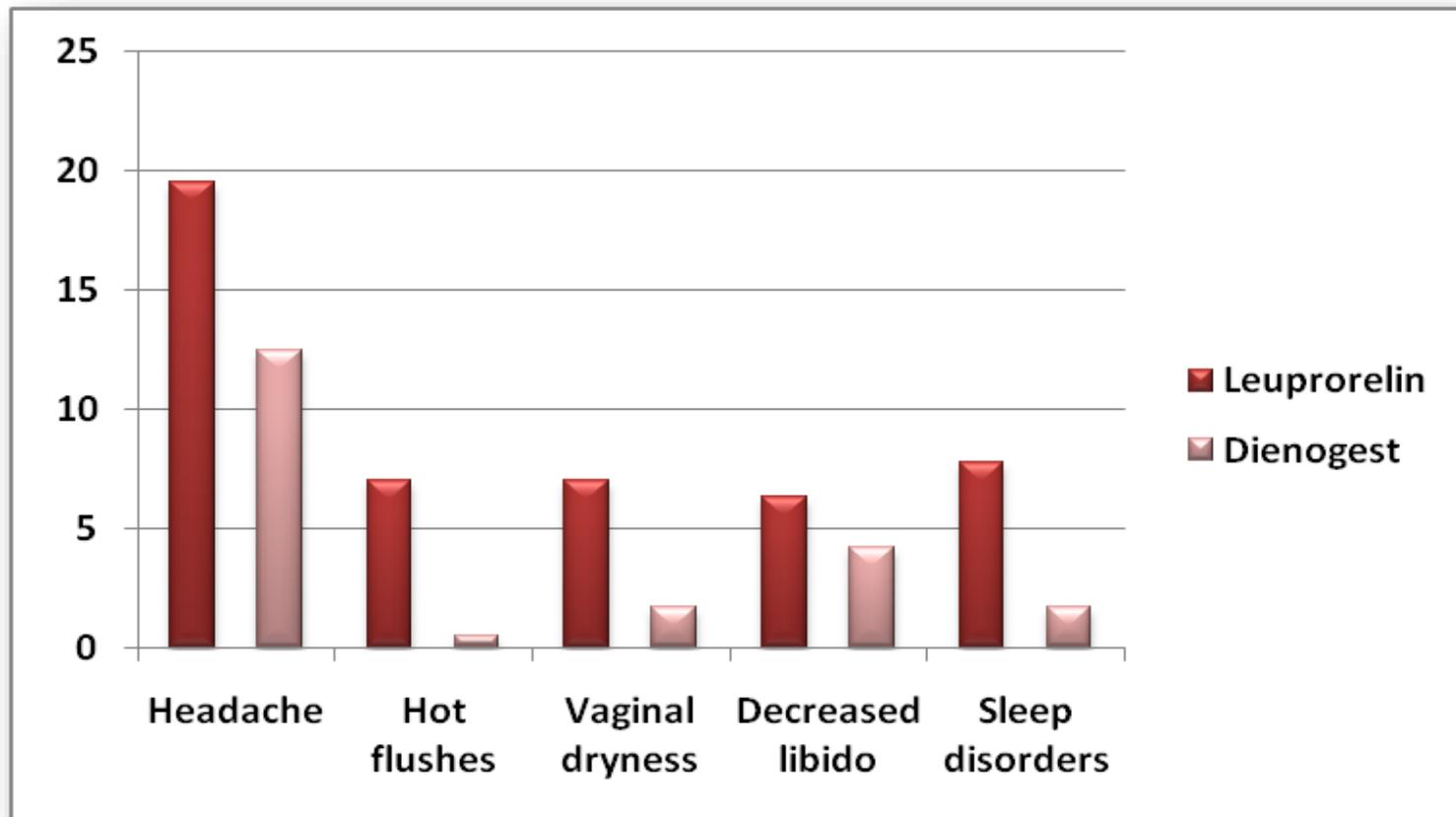
Long-term Extension Study Results: Visual Analogue Score for EAPP



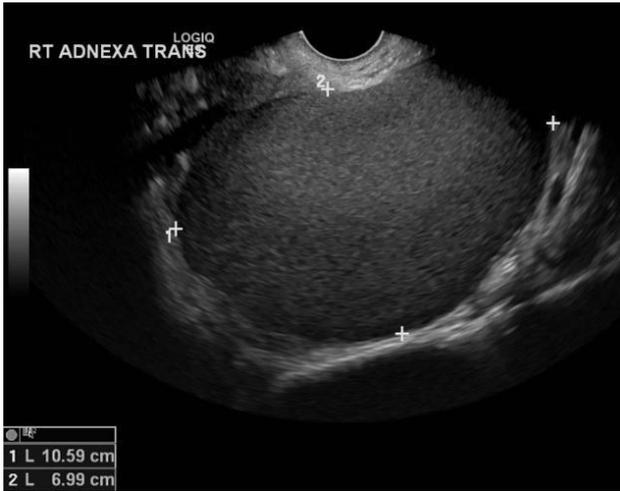
Dienogest 2 mg/day may represent a safe and effective long-term treatment option for women with endometriosis

Dienogest: tolerability

Compared with leuprorelin, dienogest was associated with less frequent hypoestrogenic symptoms

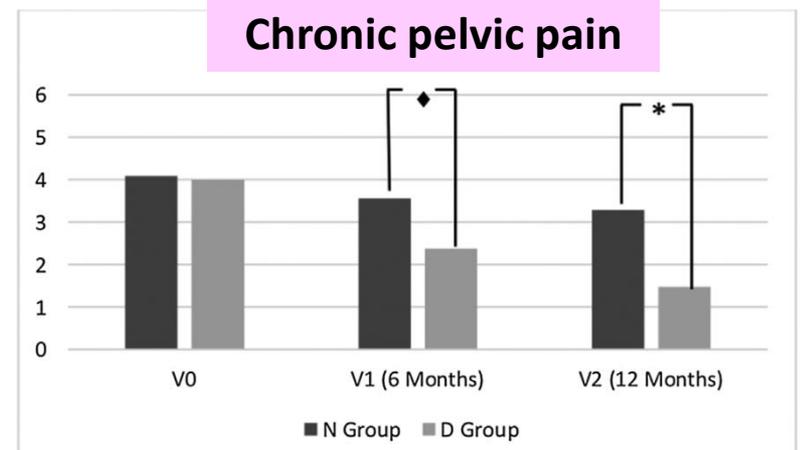
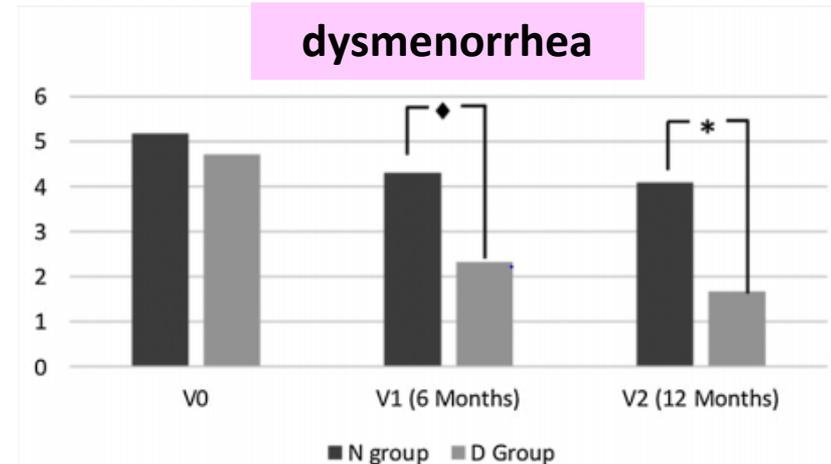


Dienogest and ovarian endometriosis



Both oral administration of dienogest (2mg/day) and NETA (2.5 mg/day) can reduce the size of ovarian endometriomas

Dienogest was more effective in reducing endometriosis related symptoms both after 6 and 12 months of treatment and was better tolerated



Dienogest for recurrence of ovarian endometrioma



Treatment with DNG immediately after the diagnosis of recurrent endometrioma



After 24 months of treatment with DNG, complete resolution of recurrent endometrioma was achieved in 57.1%

Koshiba et al, J Obstet Gynaecol Res. 2018



Mean size of recurrent endometriomas was 3.77 cm and decreased to 2.74 cm **after 24 weeks**



the mean VAS score was 5.03 at baseline and significantly decreased to 2.46 **after 24 weeks**

DNG therapy early after recurrence of postsurgical endometrioma appears to be viable for reducing the risk of repeated surgery.

Lee et al, Reprod Sci. 2018

Dienogest and deep endometriosis



Contents lists available at [ScienceDirect](#)

European Journal of Obstetrics & Gynecology and
Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Dienogest and deep infiltrating endometriosis: The remission of symptoms is not related to endometriosis nodule remission

A prospective cohort study including 30 women with a sonographic diagnosis of DIE (intestinal and posterior fornix) treated with dienogest 2 mg per day for 12 months.



Dyspareunia
Dysmenorrhea
pelvic pain
bowel pain

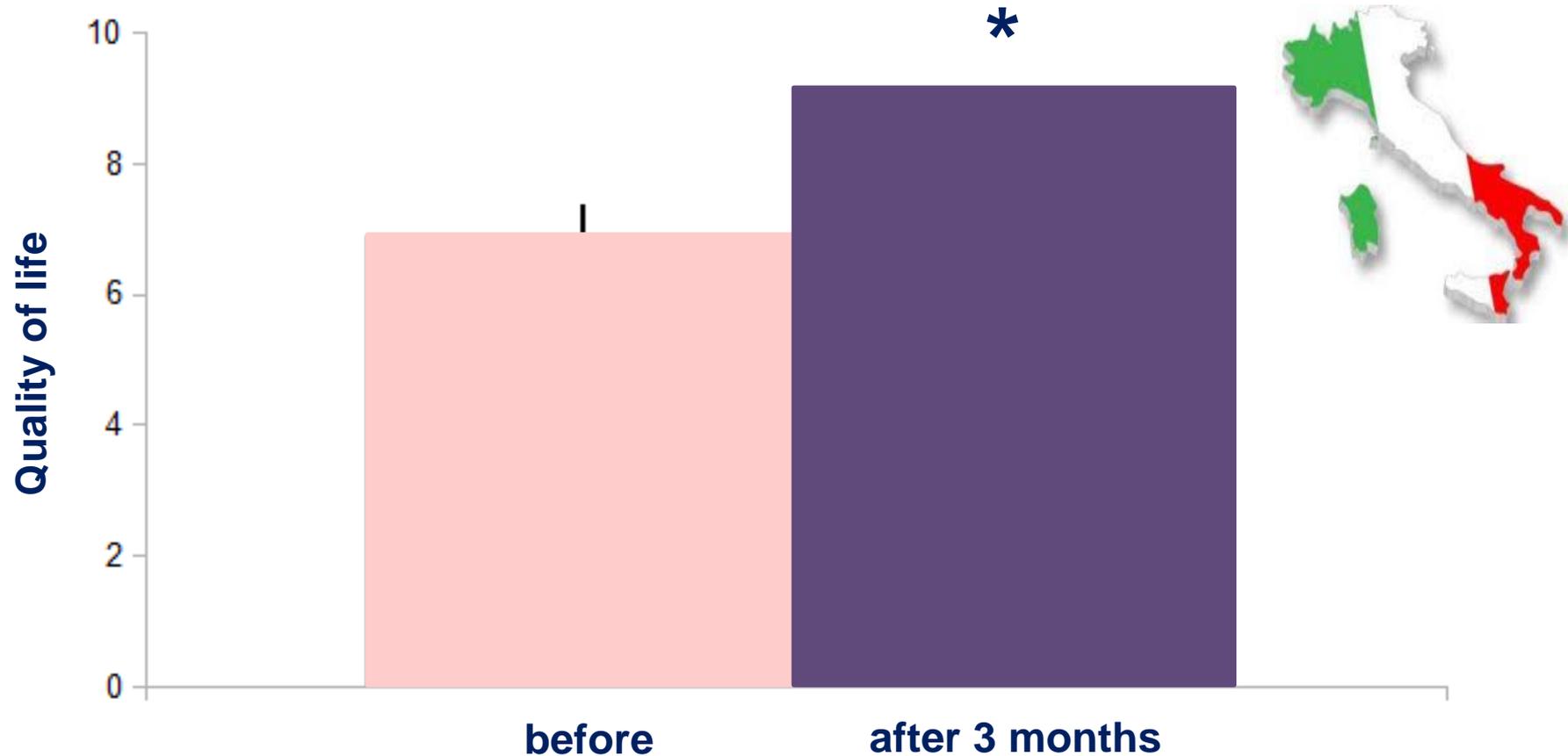


Quality of life

Dienogest is an effective medication to control symptoms of pain related to DIE, even without reducing the volume of DIE nodules.

Dienogest and endometriosis: quality of life

*Quality of life after dienogest treatment
Italian multicentric study*



Dienogest and endometriosis: quality of life

RESEARCH ARTICLE

Open Access



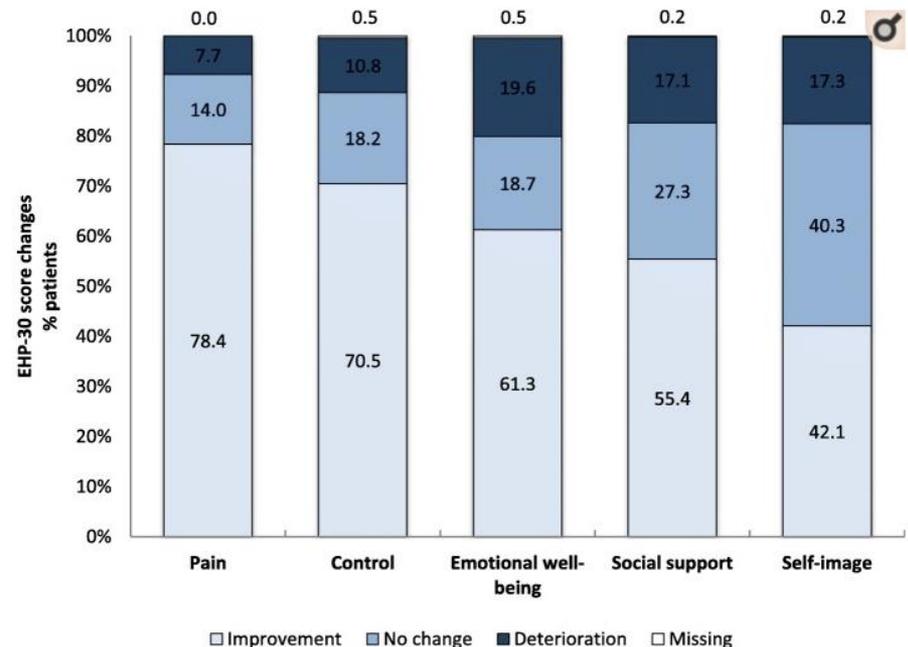
ASIA

Effectiveness of dienogest in improving quality of life in Asian women with endometriosis (ENVISIOeN): interim results from a prospective cohort study under real-life clinical practice

Dienogest therapy is effective in improving health-related quality of life (HRQoL) and endometriosis-associated pelvic pain (EAPP)

the “pain” domain was improved in 78.4% of patients

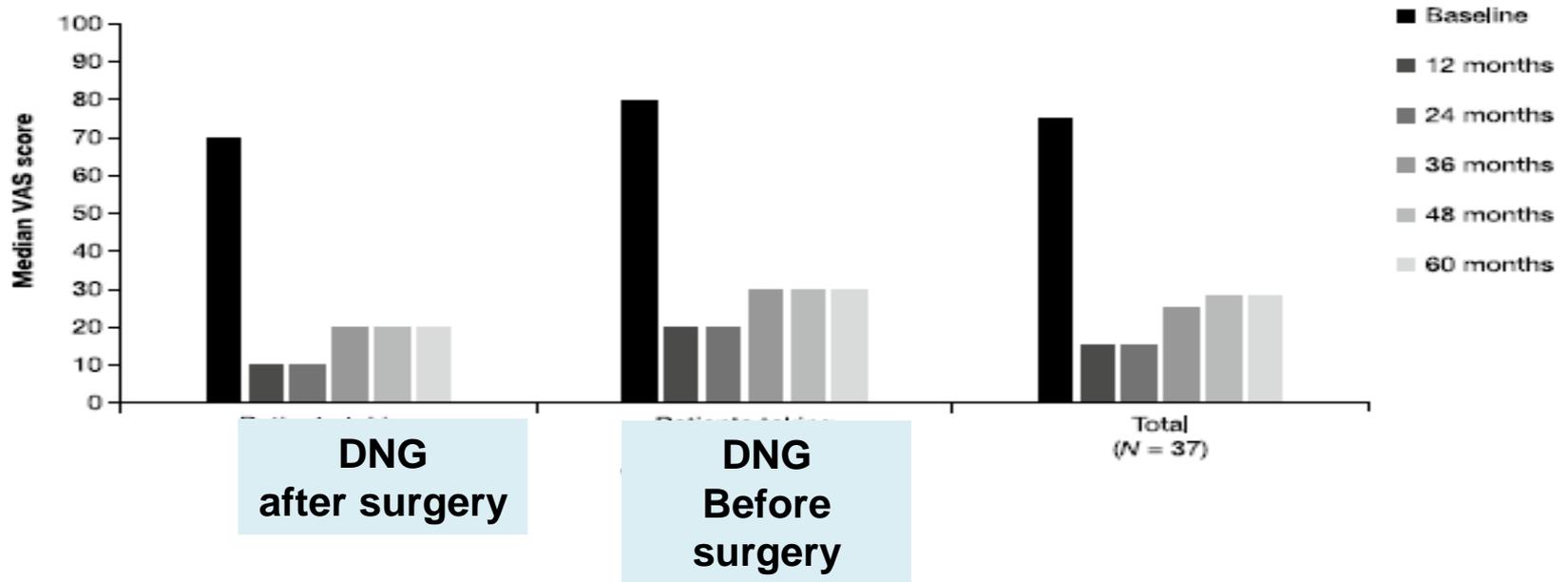
The use of dienogest as first-line therapy for long-term management of debilitating and chronic endometriosis-associated pain represents an interesting option



Dienogest: long term studies (3-5 ys)

Long-term (60-month) treatment with dienogest 2 mg once-daily in women with endometriosis effectively reduced pelvic pain and avoided pain recurrence post-surgery.

Up to 60 months



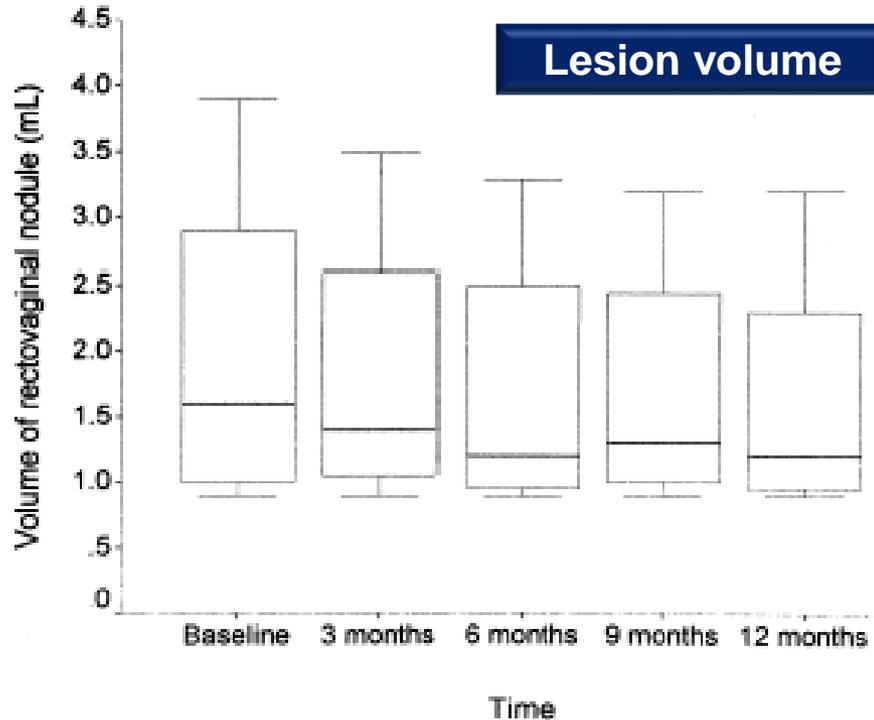
Levonorgestrel-IUS and endometriosis



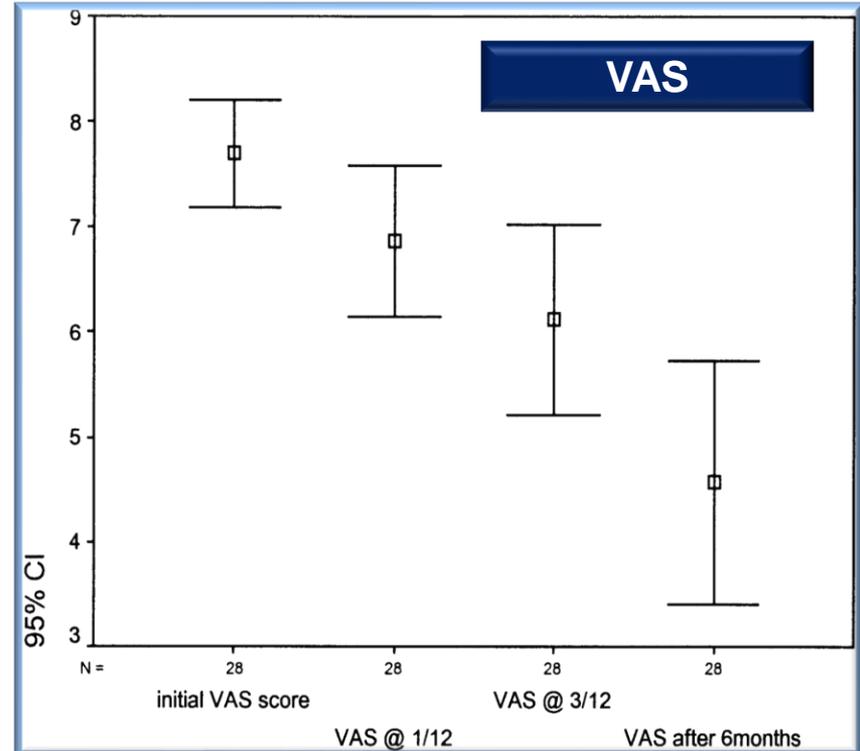
LNG-IUS reduces pelvic pain and lesions diameter in patients affected by DIE after 6-12 months therapy

Off-label

Lesion volume



VAS



Levonorgestrel-IUS and endometriosis

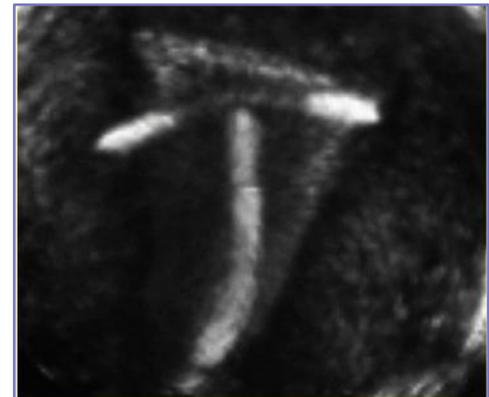


Royal College of Obstetricians and Gynaecologists
Setting standards to improve women's health

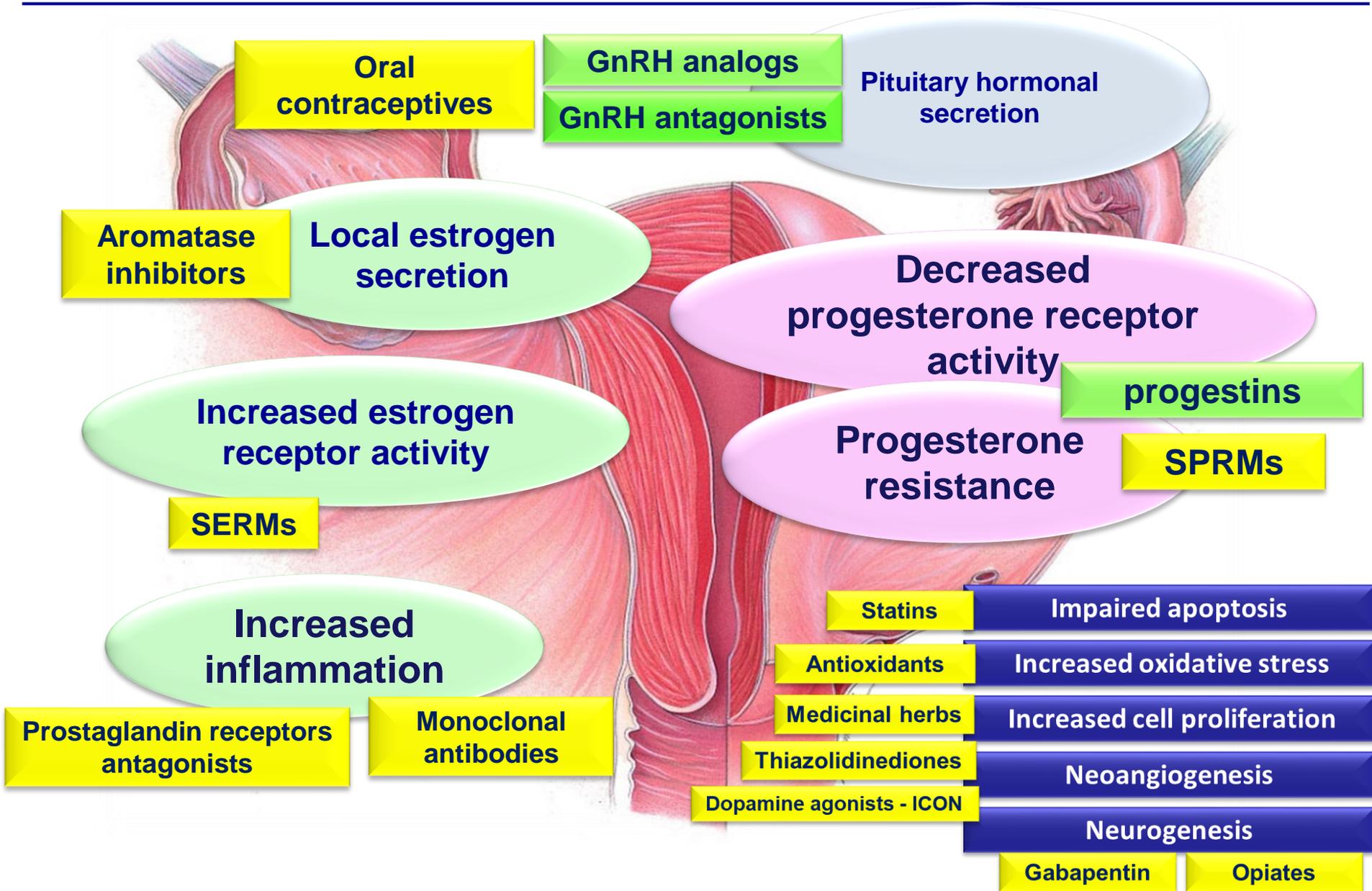
The levonorgestrel intrauterine system (LNG-IUS) is reported to **reduce endometriosis-associated pain with symptom control maintained over 3 years**

The best candidates:

- *No desire of pregnancy*
- *Dysmenorrhea*
- *40-50 ys*
- *Associated adenomyosis*
- *Intolerance to progestins used systemically*



Endometriosis: hormonal and non-hormonal treatment





6TH CONGRESS
OF THE SOCIETY OF ENDOMETRIOSIS
AND UTERINE DISORDERS
MAY, 28-30
Stockholm, Sweden



UPDATE ON ENDOMETRIOSIS AND UTERINE DISORDERS: DISPELLING MYTHS, REMOVING STIGMA



Society of Endometriosis and Uterine Disorders

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