

Symposium
Symposium

Medical Treatment in endometriosis

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**1 in 10 women have endometriosis
during their reproductive years**



Symptoms

Typical

- Dysmenorrhea
- Dyspareunia
- Diffuse / chronic pelvic pain

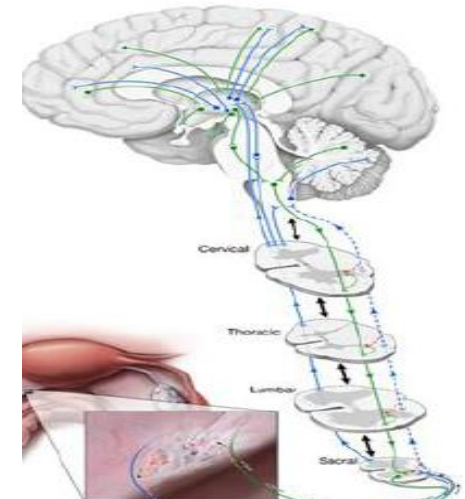
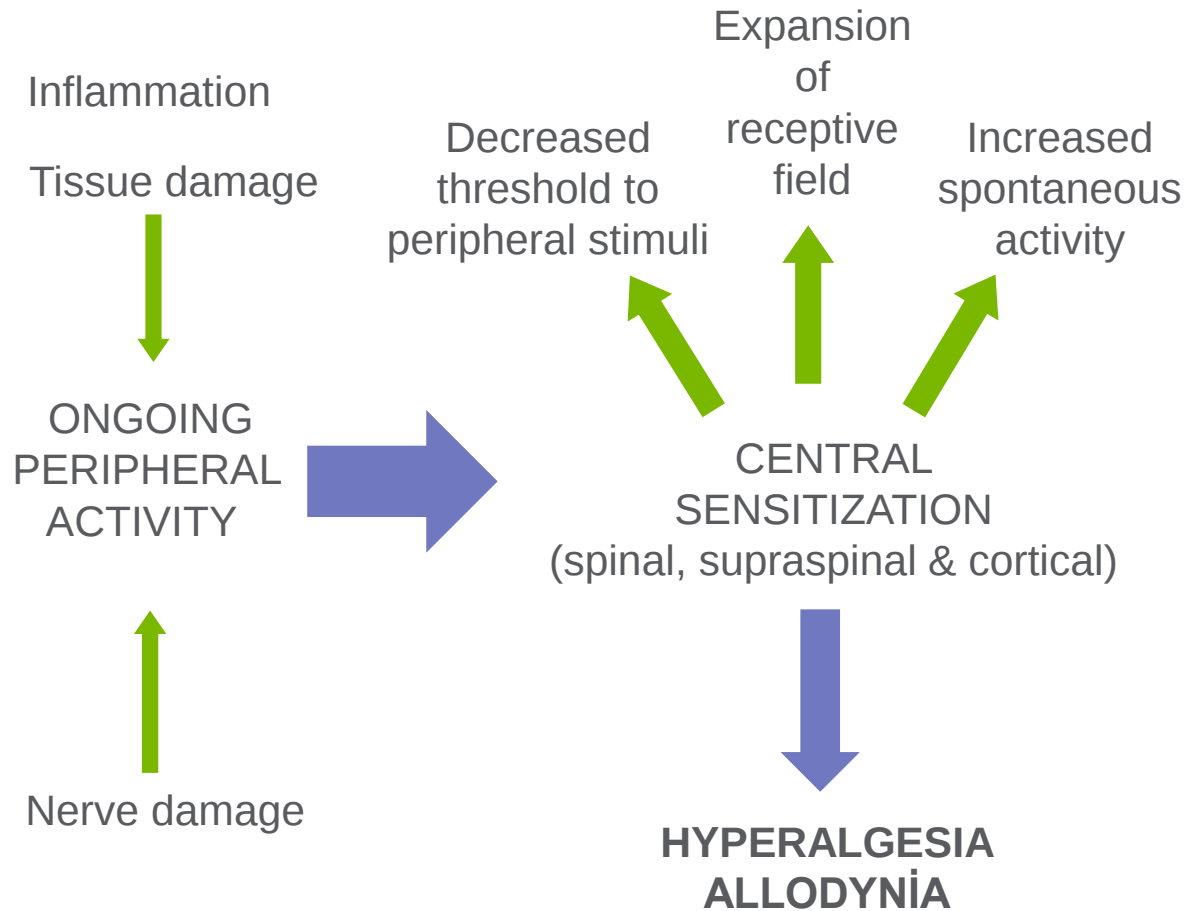
Other

- Perimenstrual symptoms (dyschezia, dysuria, haematuria , rectal bleeding)
- Back / shoulder pain
- Chronic fatigue
- May be asymptomatic

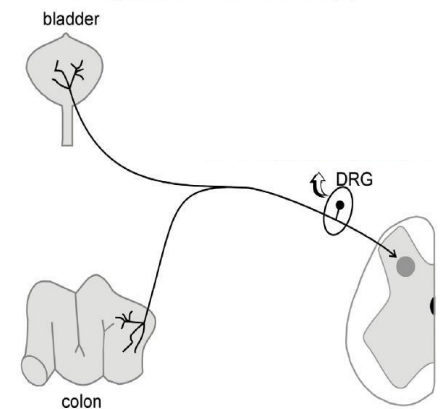
- Etiology is unknown in more than half of the cases
- Presentation similar to other conditions
 - ✓ Irritable bowel syndrome
 - ✓ Painful bladder syndrome
 - ✓ Pelvic inflammatory disease
 - ✓ Post-surgical adhesions
 - ✓ Pelvic congestion syndrome
 - ✓ Urolithiasis
 - ✓ Musculoskeletal, neurological and psychological problems



Mechanisms of Pain in Endometriosis



P.R. Brumovsky, C.F. Gebhart / *Autonomic Neuroscience: Basic and Clinical* 153 (2010) 106–115



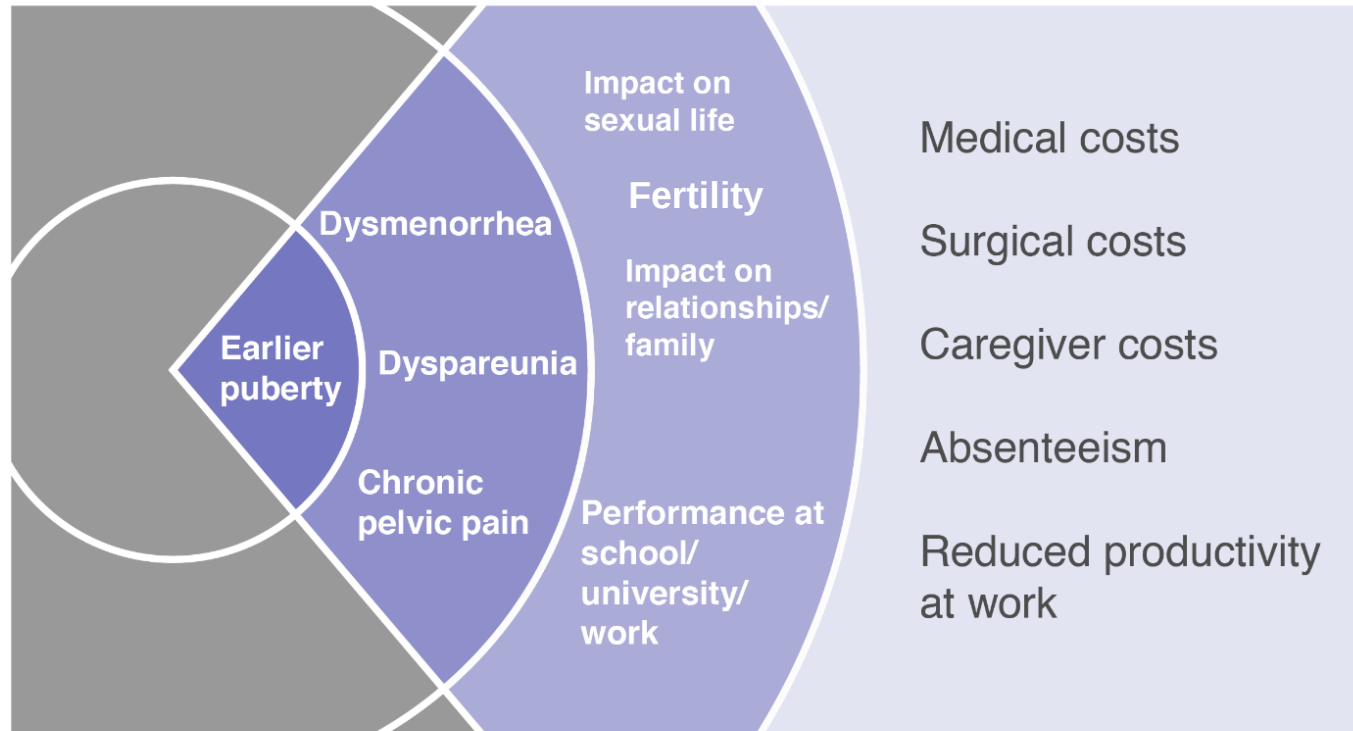
The Widening Impact of Endometriosis

Nnoaham KE et al. Fertility and Sterility 2011. 96(2) 366–383.

Individual impact



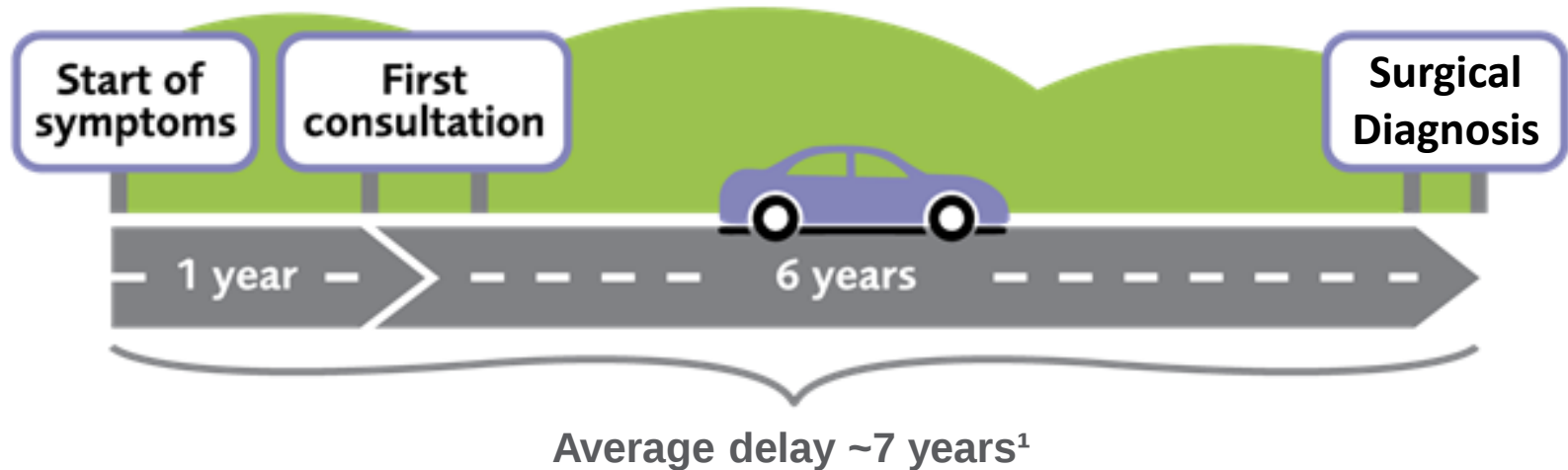
Societal impact



Delay in diagnosis

What's Behind the Long Diagnostic Delay?

1. Nnoaham KE et al. Fert Steril 2011; 96(2): 366–383;



- A lack of awareness and trivialization of symptoms may occur in primary care
- Variable presentation and non-specific nature of symptoms
- Symptom overlap with other conditions – irritable bowel syndrome, pelvic inflammatory disease etc.
- No single, agreed upon, simple diagnostic tool

Why Diagnose Early? Can Earlier Diagnosis Impact the Outcome?

We do know:

- Persistent pain becomes chronic

We don't know:

- Who will develop progressive disease
- Who will regress
- Who will stay stable
- Decrease in
 - Chronic pain risk?
 - Infertility risk?

*Confirmed diagnosis is associated with an increase in QoL compared with patients with suspected endometriosis**

* Bernuit D et al. J Endometriosis 2011;3(2):73-85



Which Diagnostic Options Should We Consider?

In the vast majority of cases, history and pelvic exam alone

- Allows for presumptive diagnosis
- Sufficient to start first-line treatment (and improve QoL)

However, imaging is useful

- Diagnosis of ovarian endometrioma
- Deep endometriosis – bowel/bladder

Laparoscopy should be diagnostic & therapeutic

- Provides definitive diagnosis
- Assists pain

QoL, quality of life

SOGC Clinical Practice Guideline. Endometriosis: Diagnosis and management. *J Obstet Gynecol Can* 2010



Laparoscopy: Advantages and Disadvantages

Advantages	Disadvantages ²⁻³
• Gold standard investigation technique¹	• Facilities/surgical expertise not universally available
• Possibility to diagnose and treat during one procedure	• Not all patients are suitable for invasive techniques
	• False-positive and false-negative findings
	• Risk of complications

1. Kennedy S, Bergqvist A, Chapron C et al. Hum Reprod 2005;20:2698-2704

2. Brosens IA, Brosens JJ. Eur J Obstet Gynecol Reprod Biol 2000;88:117-119

3. Al-Jefout M, Dezarnaulds G, Cooper M et al. Hum Reprod 2009;24:2972-2973

Is Surgical Diagnosis Always Necessary?

- The common belief that a preliminary laparoscopy must always be performed, should be challenged¹
- The success depends on the skill of the surgeon; complete removal of all lesions is not feasible
- 20–40% of women shows no improvement after surgery²
- Recurrence rate following surgery is 40–50% in 5 years, which then necessitates further surgery³

1. Vercellini P et al., Best Pract Res Clin Obstet Gynaecol 2008;22(2):275–306

2. Leyland N et al. J Obstet Gynaecol Can 2010; 32(7 Suppl 2): S1–S32.

3. Guo SW. Hum Reprod Update 2009; 15: 441–461.



The False Dichotomy

“Endometriosis is best viewed primarily as a medical disease with surgical back-up. Individuals with chronic superficial or presumed disease should be treated medically, reserving surgery for those having large endometriomas or palpable disease that fails to respond to treatment”

– ASRM 2014



& / or



The Goals of Endometriosis Management



Treat the symptoms

- If the symptom is pain, alleviate the pain
- If the symptom is infertility, assist fertility



Preserve fertility



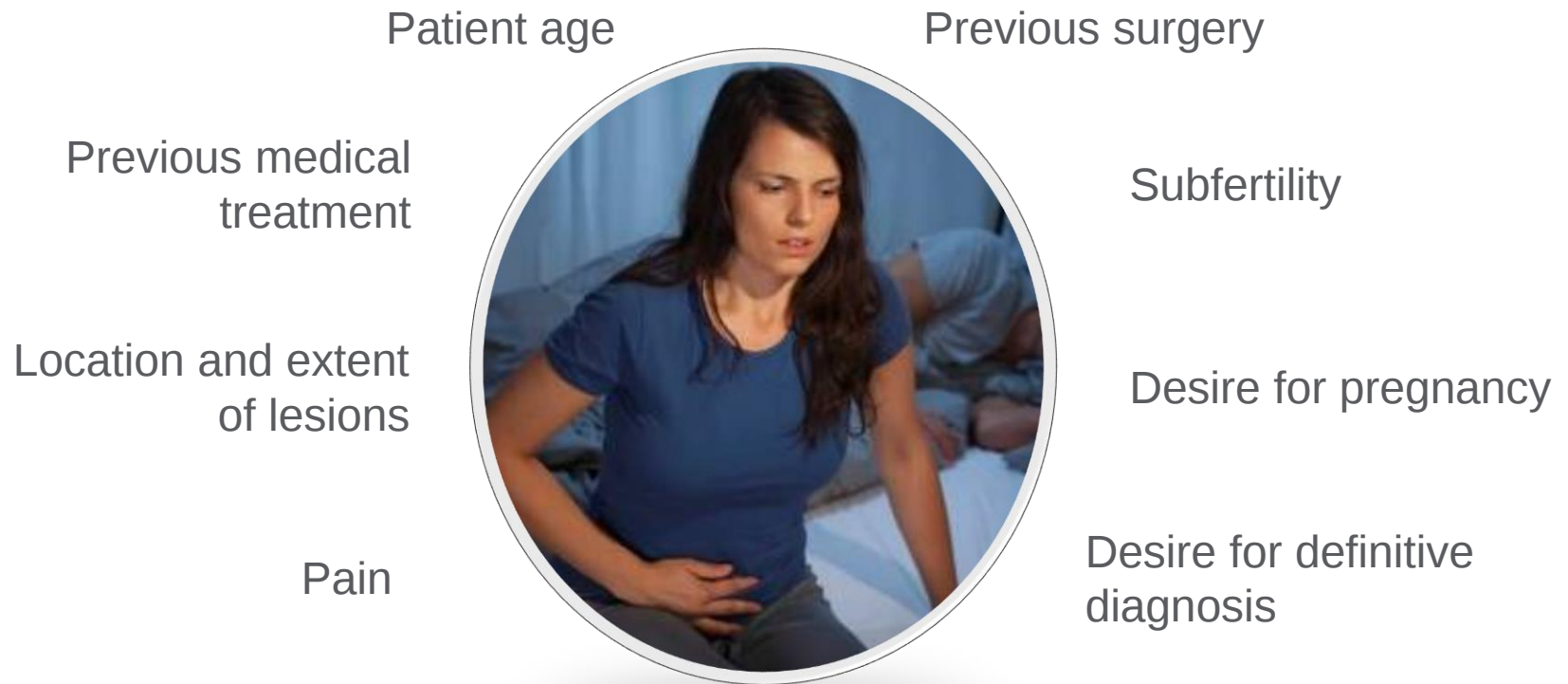
Prevent the progression to chronic pain



Keep surgeries to a minimum

- Identify patients who will really benefit, and find the best time for surgery
- Importance of post-surgical maintenance

Our Patients are All Different



Individualization of Treatment

“Women with endometriosis often require individualized care over a long-term period, where priorities may change depending upon the type and severity of symptoms, impact of these symptoms, current or future fertility goals and lifestyle factors.”

– World Endometriosis Society Consensus 2013

Objectives

- Establish the rationale for early, evidence-based treatment of pelvic pain associated with endometriosis
- Provide a stepwise approach to managing pelvic pain associated with endometriosis with a view to life long management
- A view on treatment scenarios with DIENOGEST®



Endometriosis

Significance of disease depends on the clinical presentation (pain and/or infertility)

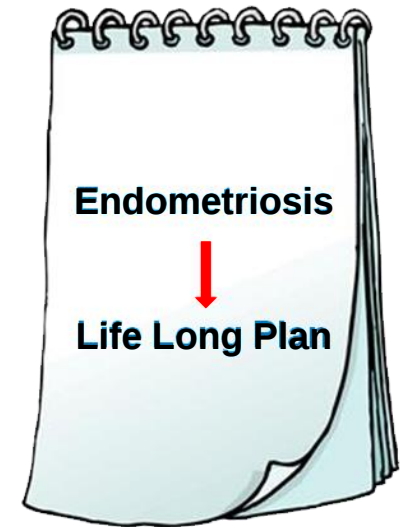
- Typical pain symptoms:
 - Dysmenorrhea
 - Dyspareunia
 - Diffuse chronic pelvic pain

Affects 10% of reproductive age women

Chronic, relapsing disorder

Individual variation

Requires long-term plan for management



Fraser IS. J Hum Reprod Sci 2008

Mahutte NG, Kayisli U, Arici A. Endometriosis in Clinical Practice.2005

SOGC Clinical Practice Guideline. Endometriosis: Diagnosis and management. J Obstet Gynecol Can 2010

The Patient Experience Matters

***The “Pragmatic Approach” to
treatment of endometriosis***

Treat the Patient

NOT THE LESIONS

Why Medical Therapy

- Is the cornerstone of treatment of endometriosis
 - Suppression of typical pain symptoms is part of the lifelong treatment plan
- Easy to administer
- Avoid surgical risk and complications
- More options than ever before – able to individualize therapy



Treatment Options

* Not approved for the treatment of endometriosis/symptoms of endometriosis

COCs, combined oral contraceptive; GnRH, gonadotropin releasing hormone; IM, intramuscular; LNG-IUS, levonorgestrel-releasing intrauterine system; NSAIDs, nonsteroidal anti-inflammatory drugs; SC, subcutaneous



Medical management

- COCs*
- Progestin only (oral, IM, SC)
- GnRH agonist + addback
- LNG-IUS*
- Danazol
- Aromatase inhibitors*
- NSAIDs, other analgesics

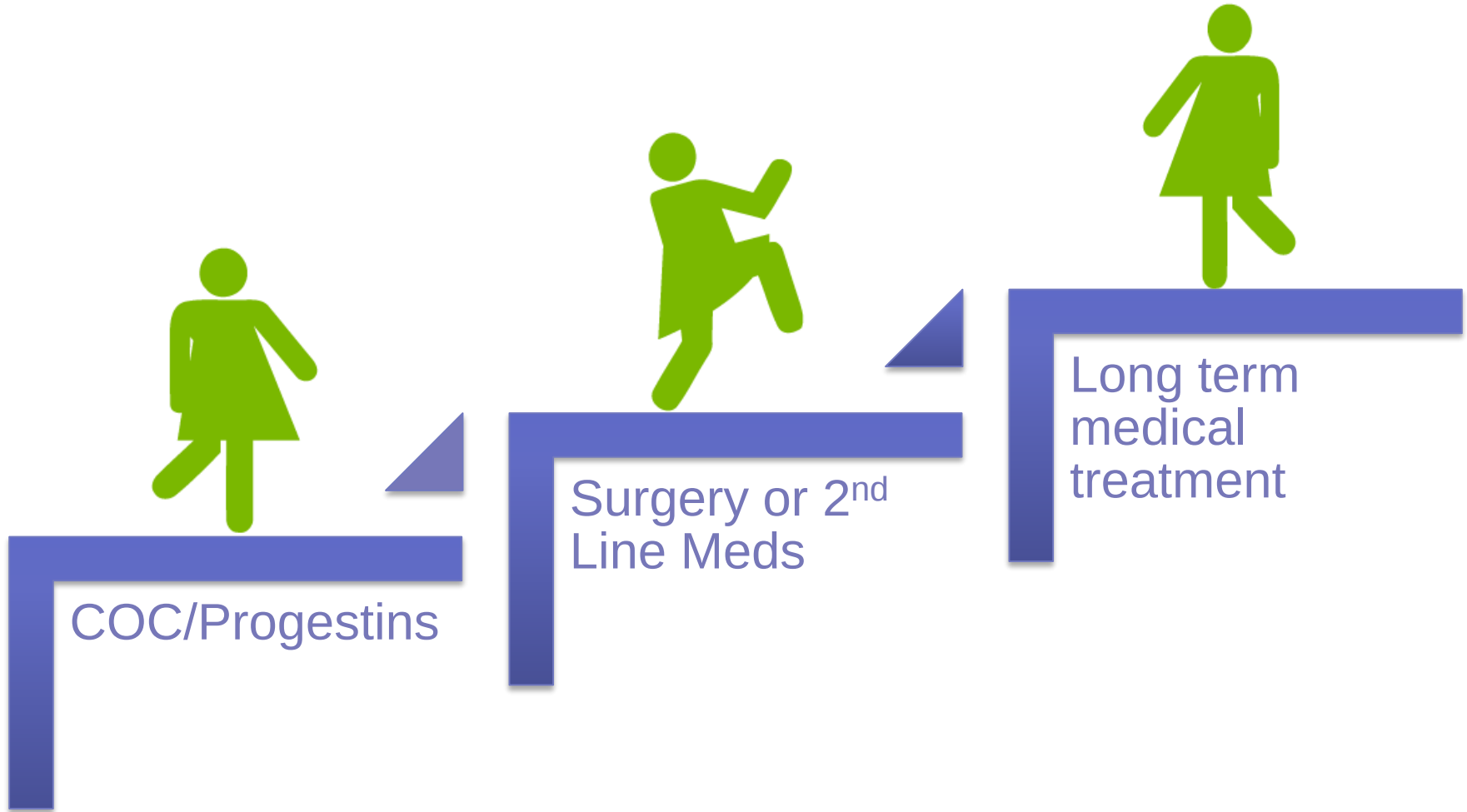


Surgical management

- Excision vs ablation
- Conservative vs Definitive

But – expertise & resources are not
always available & recurrence is
common

Stepwise Approach to Endometriosis Management



COC, combined oral contraceptive

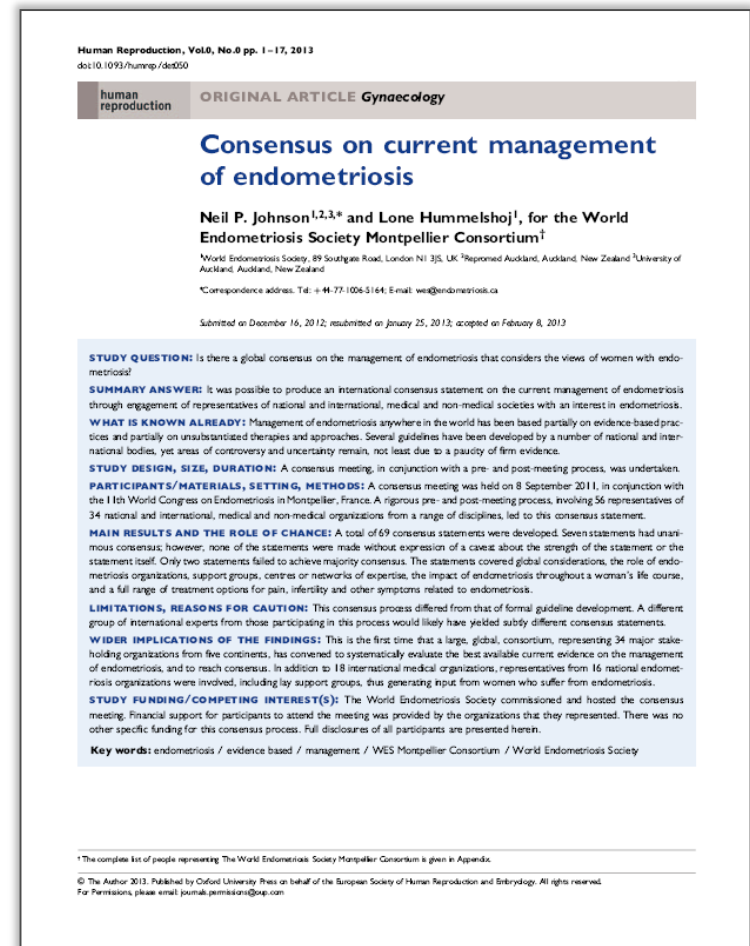
World Endometriosis Society: International Consensus on Endometriosis

- Advocates early, proactive management of pelvic pain

“Management of pelvic pain should not be delayed in order to obtain surgical confirmation of endometriosis”

- Strongly supported by an extensive, international experienced and well-respected group of key opinion leaders, representatives of medical societies and patient groups

Johnson NP and Hummelsoj L. Hum Reprod 2013; 28(6): 1552–1568.

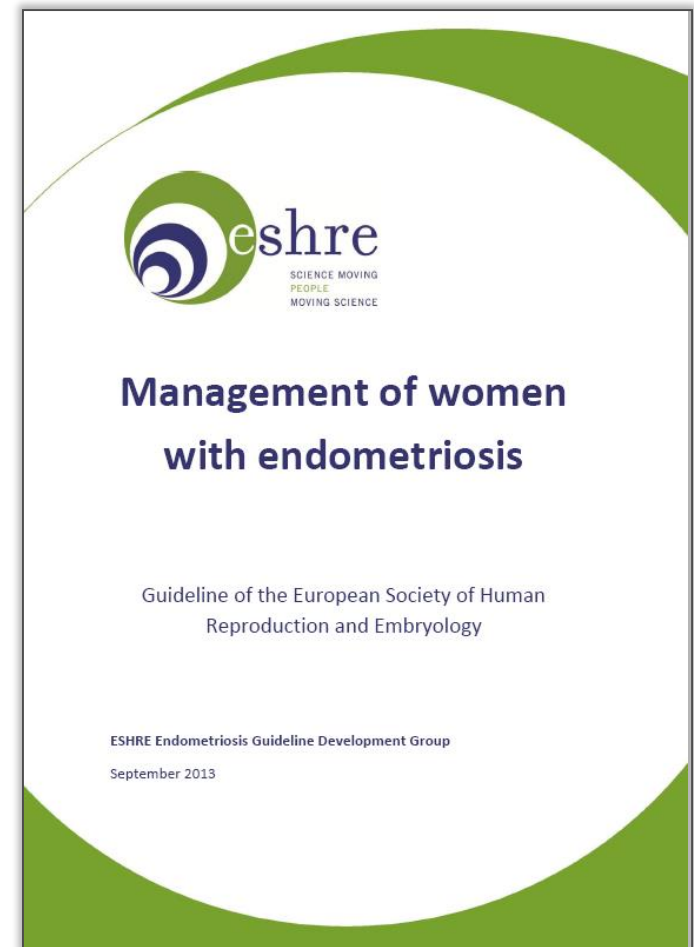


ESHRE Guidelines Update 2013

- Supports argument for the pragmatic approach:
 - “If medical pain treatment relieves pain, many women will not be interested whether or not their pain symptoms were due to peritoneal endometriosis”
- Recommendations:

“Counsel women with symptoms presumed to be due to endometriosis thoroughly, and empirically treat them with adequate analgesia, combined hormonal contraceptives or progestogens.”

ESHRE Guideline 2013.



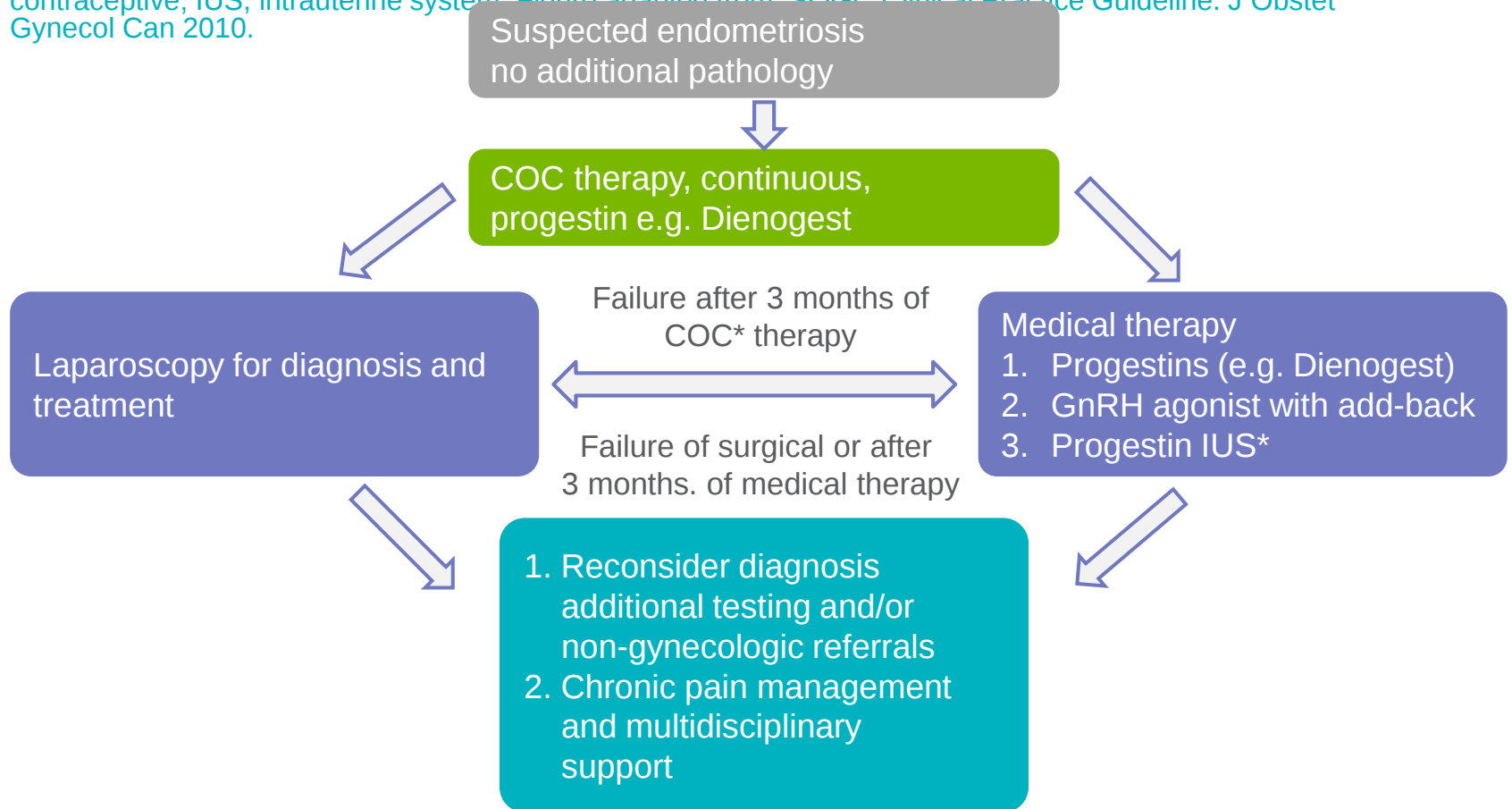
We Need to Plan

- Need to consider the short and long-term needs of patients
 - Symptom & pain control
 - Prevent chronic pain
 - Fertility needs
 - Optimum time for surgery
- Surgery can be timed using medical and diagnostic tools to minimize the need for repeat procedures



Suggested Stepwise Approach

* Not approved for the treatment of endometriosis/symptoms of endometriosis; COC, combined oral contraceptive; IUS, intrauterine system. Figure adapted from: SOGC Clinical Practice Guideline. J Obstet Gynecol Can 2010.



When is Surgery Indicated?

- **Laparoscopy should ideally be diagnostic & therapeutic¹**
- **Patients with pelvic pain**
 - No response/contraindications to medical therapy
 - Acute adnexal event (torsion, rupture)
 - Deep disease involving bowel, bladder, ureters or pelvic nerves (after failed medical management)
- **Patients with known or suspected ovarian endometrioma**
 - Uncertainty of diagnosis affects management (as with chronic pelvic pain)
 - Infertility and associated factors (e.g., pain, pelvic mass)



▶ At the right time for the patient

Choosing when to Operate is Key

- ~1 in 4 women ► additional surgical treatment within 4 years of initial surgery¹
- Initial surgery in younger women ► risk of reoperation increased^{2,3}
- First operation ► usually better response than subsequent procedures⁴
- Should avoid excessive repeat laparoscopic procedures⁵



1. Weir E et al. J Minim Invasive Gynecol 2005; 12: 486–93;
2. Cheong Y et al. J Obstet Gynaecol 2008; 28: 82–85;
3. Shakiba K et al. Obstet Gynecol 2008; 111: 1285–1292;
4. Abbott et al. Fertil Steril 2004; 82: 878–884;
5. WES Consensus statement 2013.

Typical Treatment Scenarios with Dinogest® in Canada

1. Empirical Therapy:

Women with or without the diagnosis of endometriosis and pelvic pain

2. First line/second line after COCs

3. Postoperative therapy-suppression of recurrent ovarian disease/pain

4. Treatment of disease of the ovaries or deeply infiltrative endometriosis



Summary

- We need to identify, diagnose & start appropriate treatment earlier
 - There is increasing support globally for empirical treatment of endometriosis
- Endometriosis requires lifelong management and timing of surgeries may be critical for women's later quality of life
- Canadian guidelines have pioneered a stepwise approach to treatment



Presentation Objective

- Review the Mode of action and clinical evidence of Visanne® therapy in the management of pelvic pain associated with endometriosis

What do we Want from Endometriosis Treatment?

- Alleviate the different types of pain symptoms
- Improve quality of life
- Reduce lesions
- Acceptable side effect profile, suitable for long-term use
- Maintain/improve fertility (or even allow conception)
- Prevent disease recurrence

“The ideal treatment should relieve pain, induce regression of endometriotic lesions, even in the severe forms, and allow conception”

– Soares SR, et al. *Fertil Steril* 2012

Vercellini P, et al. *Best Pract Res Clin Obstet Gynaecol* 2008.
Streuli I et al. *Expert Opin Pharmacother* 2013. 14(3):291-305.
Soares SR, et al. *Fertil Steril* 2012; 98(3): 529-55.

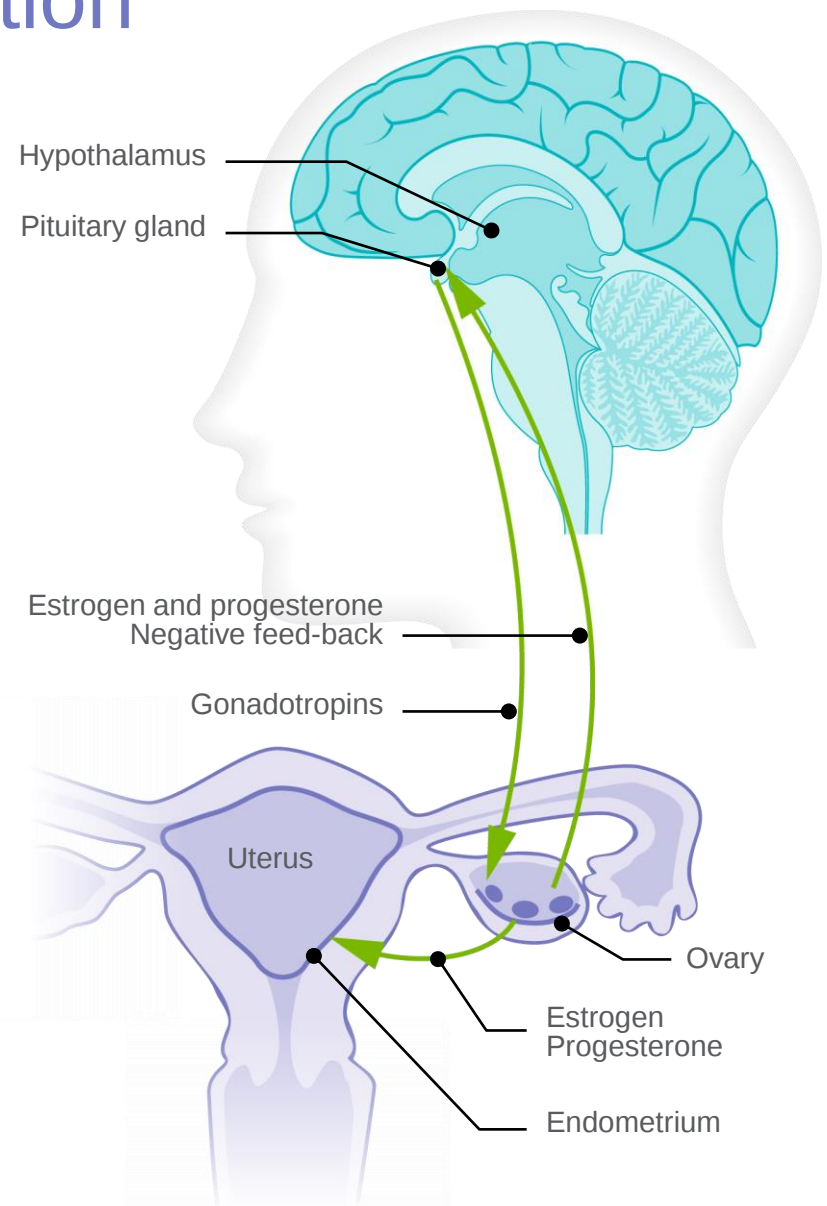
Dienogest: Mode of Action

- **Central effects**

- **Inhibition of gonadotropin secretion:** moderate suppression of circulating estradiol
- **Ovarian function:** anovulation (2mg dose)

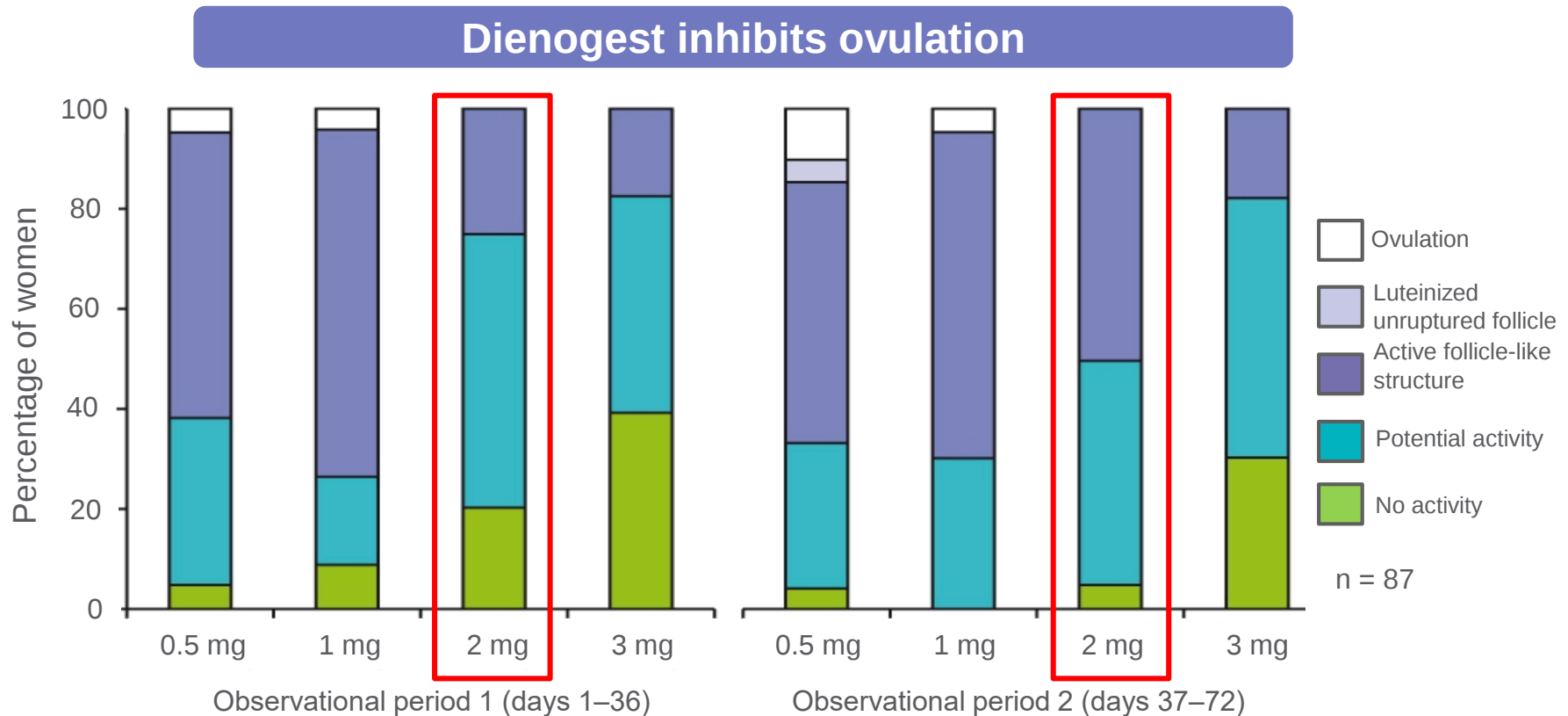
- **Local effects**

- Anti-proliferative
- Anti-inflammatory
- Anti-angiogenic



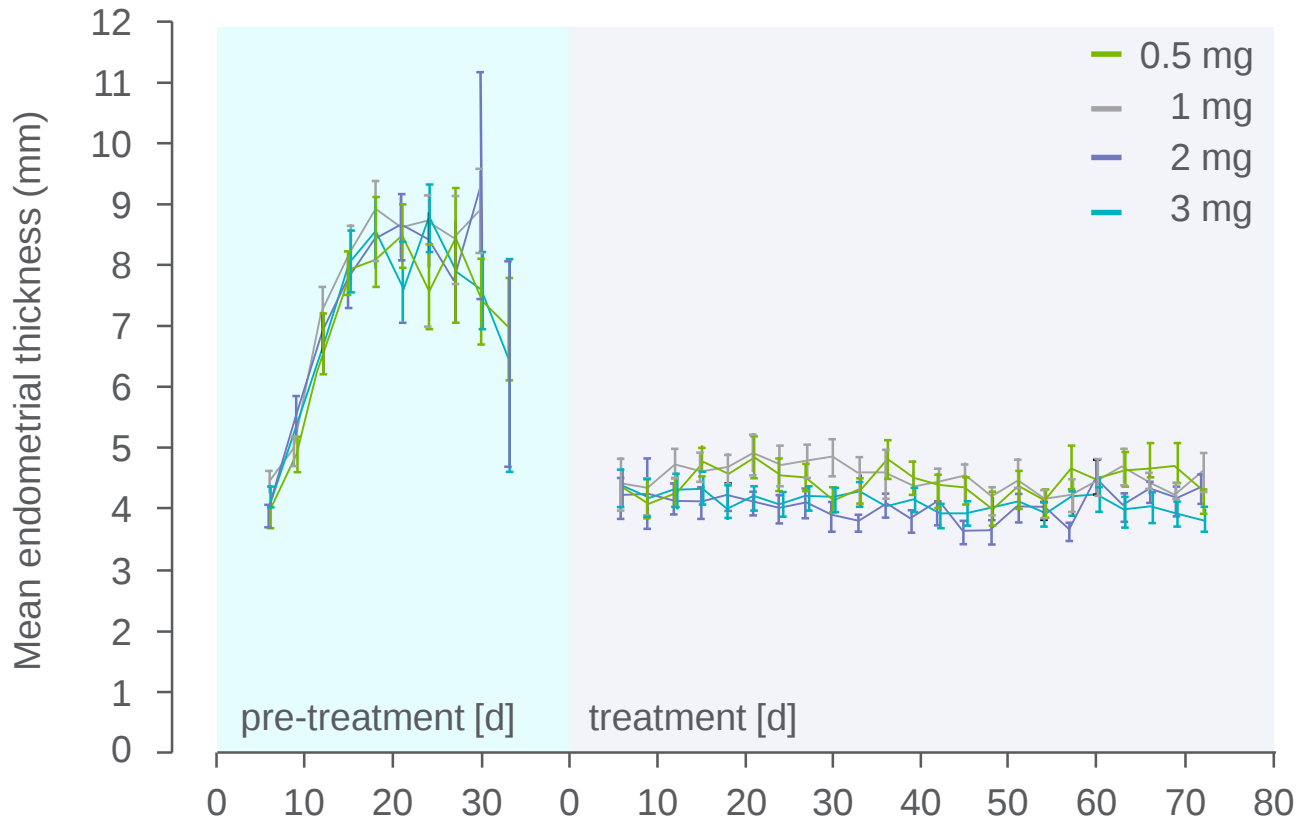
Klippling C et al. J Clin Pharmacol 2012; 52: 1704–1713.
McCormack PL. Drugs 2010; 70: 2073–2088. Sasagawa S et al.
Steroids 2008; 73: 222–231. Shimizu Y et al. Steroids 2011; 76:
60–67. Katayama H et al. Hum Reprod 2010; 25: 2851–2858.

Ovarian Activity During Dienogest Treatment



Dienogest Strongly Suppresses Endometrial Growth

Klipping C, et al. J Clin Pharmacol 2012; 52: 1704–1713



- Results indicate a strong endometrial effect with dienogest
- Substantial suppression of endometrial growth even with the lowest dose

Comprehensive Clinical Development Program for Dienogest 2mg

Study type	Study duration	Sample size (n)	Main efficacy end-points	Publication
Open-label dose-range finding	24-week	64	<u>Lesion reduction</u> rAFS score with 2 nd look laparoscopy	Köhler <i>et al.</i> (2010)
Placebo-controlled double-blind	12-week	198	<u>Pain relief</u> : VAS	Strowitzki <i>et al.</i> (2010)
Open-label extension of placebo-controlled study	53-week	168		Petraglia <i>et al.</i> (2012)
Open-label leuprolide acetate-controlled	24-week	186		Strowitzki <i>et al.</i> (2010) Strowitzki <i>et al.</i> (2012)

rAFS=revised American Fertility Society; VAS=visual analog scale.

Köhler G *et al.* Int J Gynaecol Obstet 2010; 108: 21–25. Strowitzki T *et al.* Eur J Obstet Gynecol Reprod Biol 2010; 151: 193–198. Petraglia F *et al.* Arch Gynecol Obstet 2012; 285(1):167–173. Strowitzki T *et al.* Hum Reprod 2010; 25: 633–641. Strowitzki T *et al.* Int J Gynecol Obstet 2012; 117: 228–233.

Dienogest 2mg Significantly Reduces Endometriotic Lesions

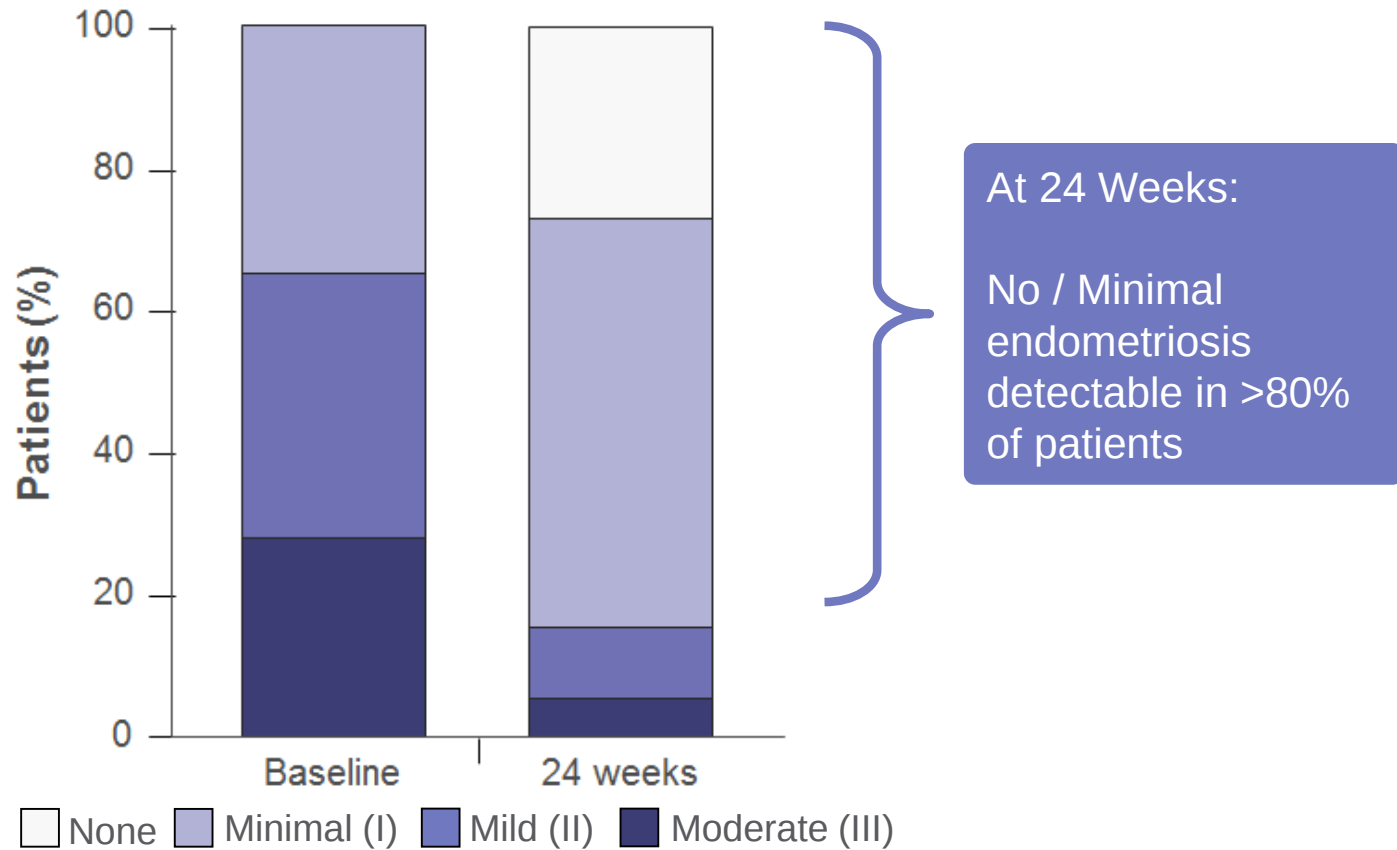
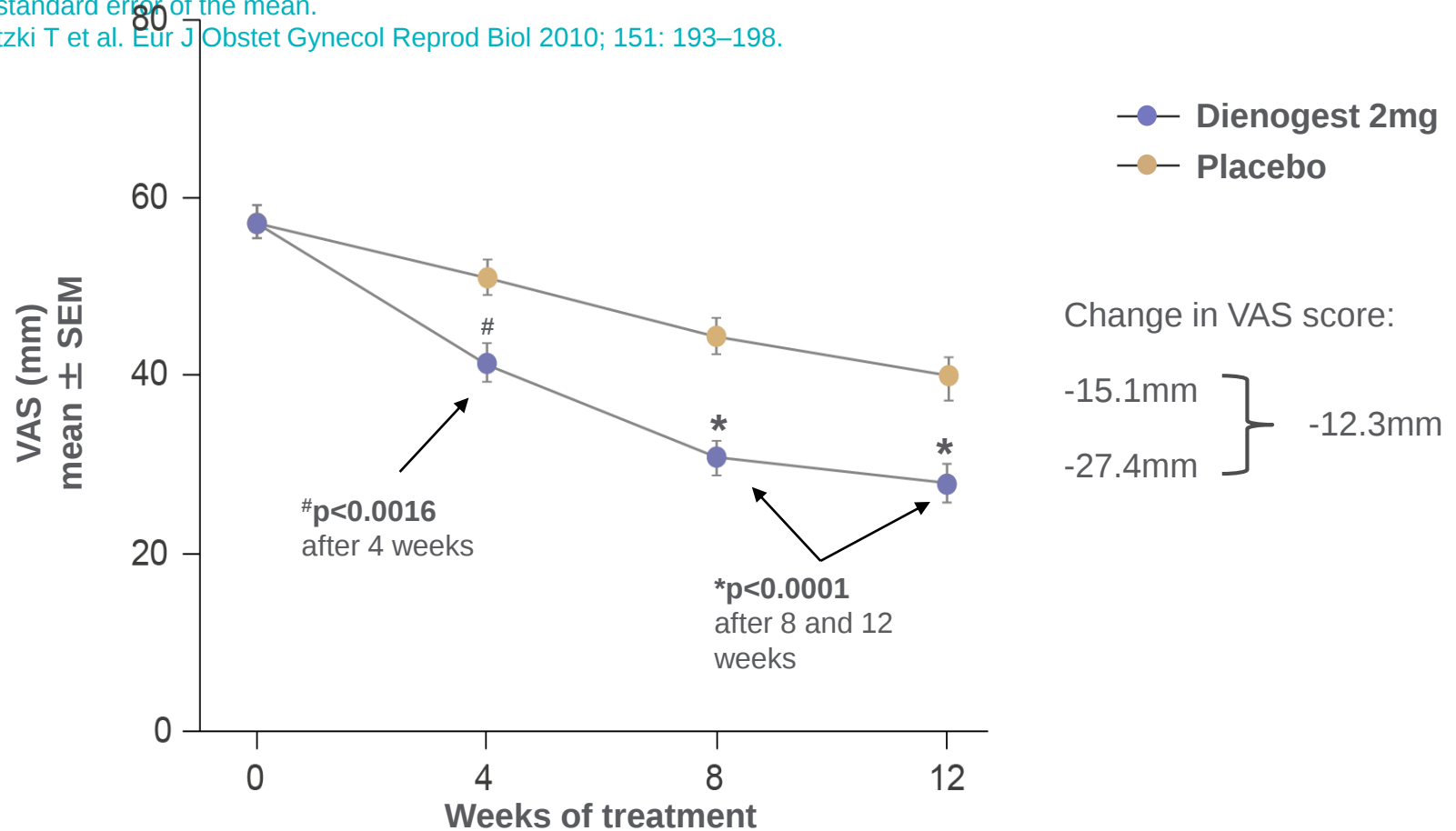


Figure adapted from Köhler G et al. Int J Gynaecol Obstet 2010; 108: 21–25.

Dienogest 2mg Demonstrated a Significant Reduction in Pain vs Placebo

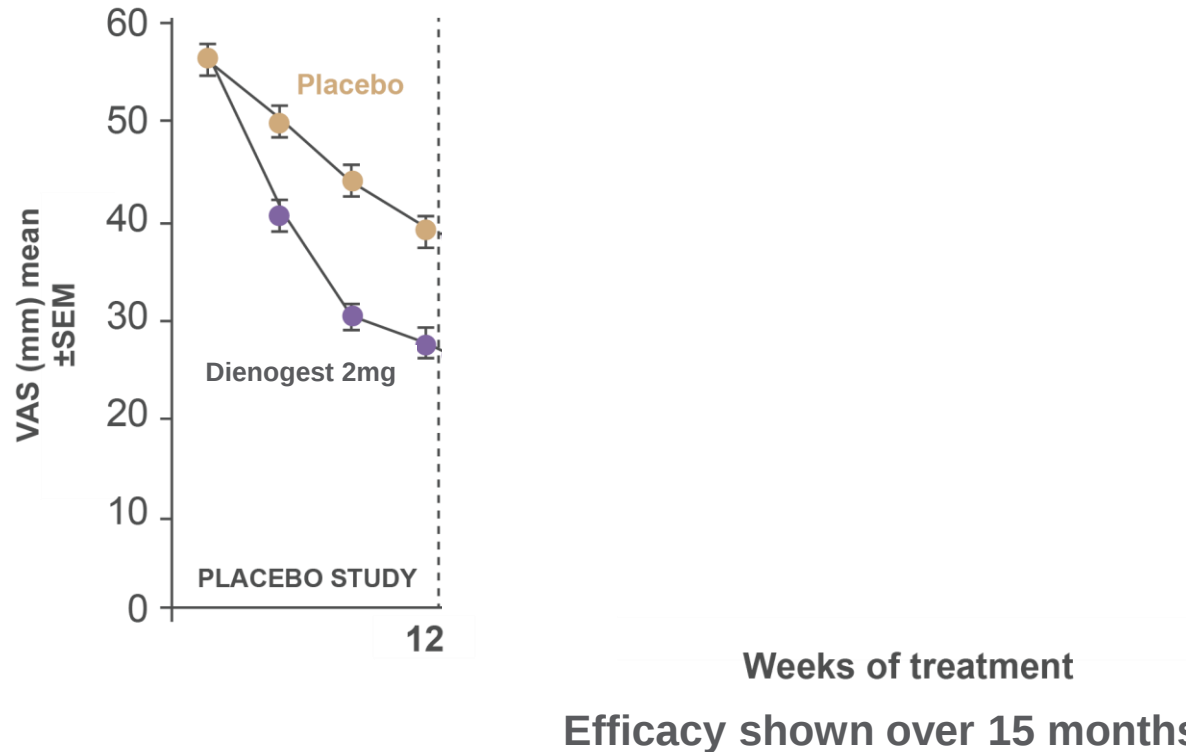
dienogest n=102; placebo n=96,
SEM=standard error of the mean.

Strowitzki T et al. Eur J Obstet Gynecol Reprod Biol 2010; 151: 193–198.



Significant Reduction in Pain

Sustained over a Long-term Extension Period



n=168 (extension study, all dienogest); * follow-up: patient subgroup n = 34

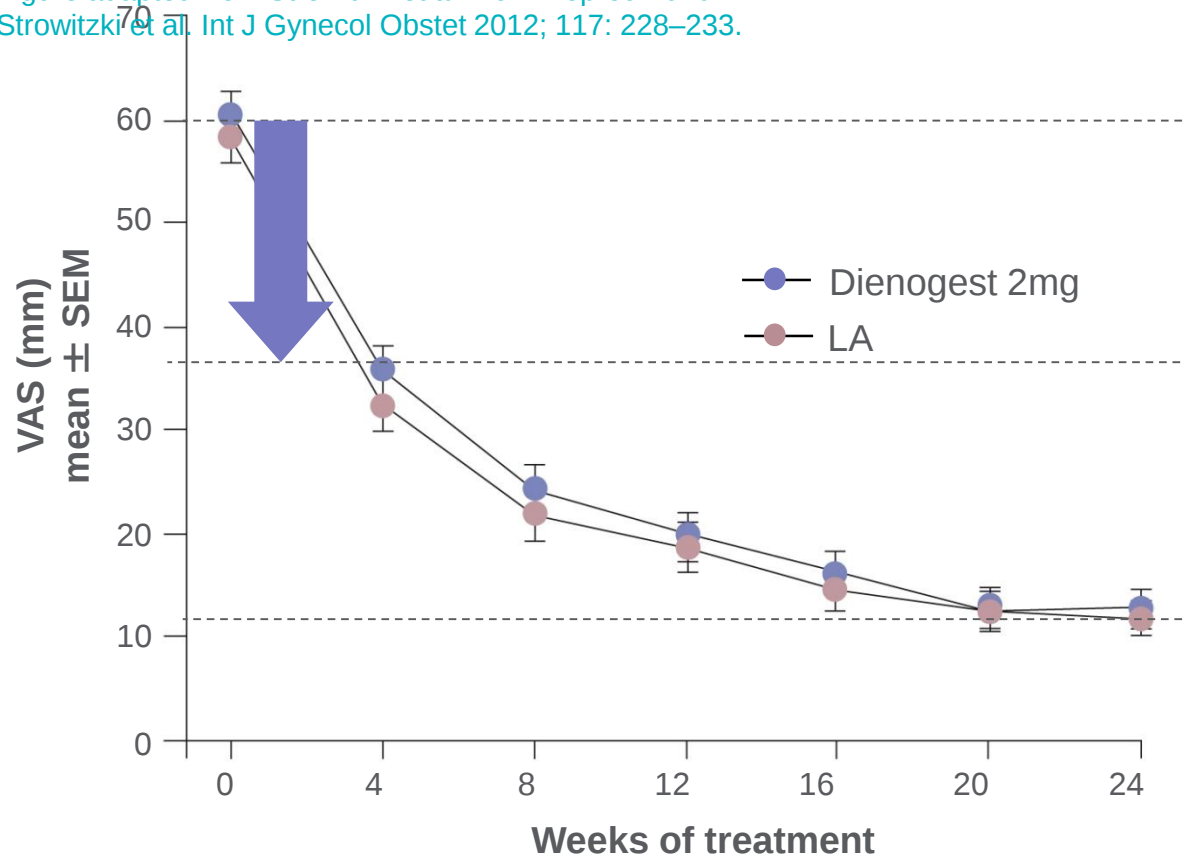
Figure adapted from Strowitzki T et al. Eur J Obstet Gynecol Reprod Biol 2010; 151: 193–198 and Petraglia F et al. Arch Gynecol Obstet 2012; 285(1): 167–173.

Dienogest 2mg was Equivalent in Efficacy to Leuprolide Acetate (LA) for Reducing Pain

dienogest n = 124; LA n = 128

Figure adapted from Strowitzki et al. Hum Reprod 2010.

Strowitzki et al. Int J Gynecol Obstet 2012; 117: 228–233.



- Non-inferiority of dienogest 2mg relative to LA was demonstrated ($p < 0.0001$)

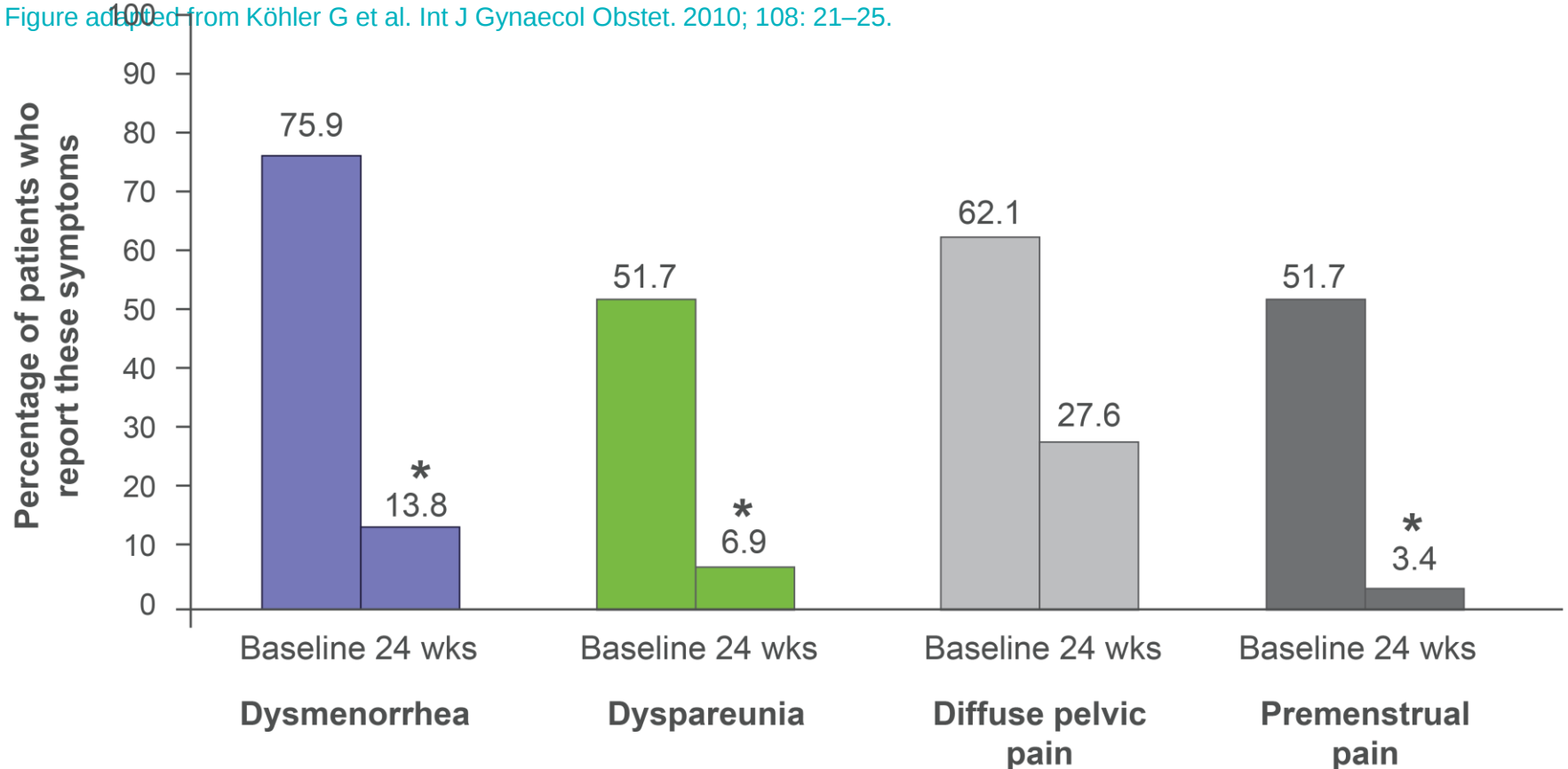
- 40% of the total pain reduction was in the first 4 weeks of treatment

Dienogest 2mg was Associated with Symptom Improvements in Substantial Proportions of Women

* Statistically significant changes

Data based on the full analysis set, excluding patients for whom data were unavailable.

Figure adapted from Köhler G et al. Int J Gynaecol Obstet. 2010; 108: 21–25.



Symposium
Symposium

Safety and Tolerability Aspects



Frequency of Adverse Drug Reactions (ADRs) During Treatment with Dienogest 2mg (Pooled Analysis)

Reported ADRs over up to 15 months of dienogest 2mg treatment:

Most frequently reported ADRs	% of Patients
Headache	9.0
Breast discomfort	5.4
Depressed mood	5.1
Acne	5.1

- ✓ **Low in frequency**
- ✓ **Generally mild to moderate in intensity**
- ✓ **Usually subsided within the first 3 months**

Köhler G et al. Int J Gynaecol Obstet 2010; 108: 21–25. Strowitzki T et al. Eur J Obstet Gynecol Reprod Biol 2010;151: 193–198. Strowitzki T et al. Hum Reprod 2010; 25: 633–641. Petraglia F et al. Arch Gynecol Obstet 2012; 285(1): 167–173.

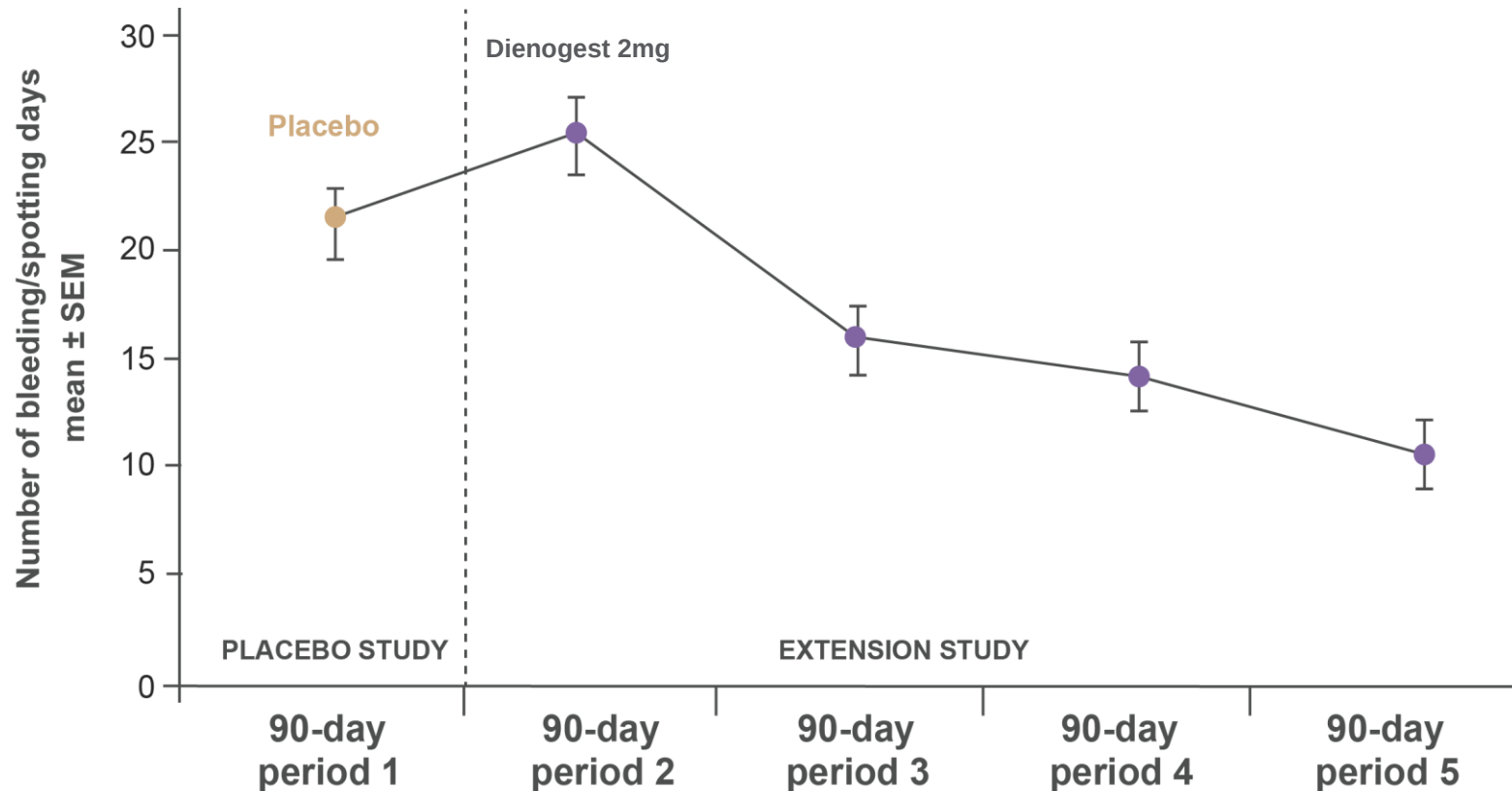
Bleeding Patterns with Dienogest 2mg: Key to Acceptance is Appropriate Counseling

Petraglia F et al. Arch Gynecol Obstet 2012; 285(1): 167–173. Strowitzki T et al. Eur J Obstet Gynecol Reprod Biol 2010; 151: 193–198. Strowitzki T et al. Hum Reprod 2010; 25: 633–641

- **Bleeding irregularities**
 - Greater in first 3 months, but decreases with continued use
- **Amenorrhea**
 - By 6 months: ~30% amenorrhea
- **In trials, less than 1% discontinuation due to irregular bleeding**
 - No effect on patient acceptance or compliance
- Counseling regarding expectations of bleeding, with acceptance that the problem diminishes over time



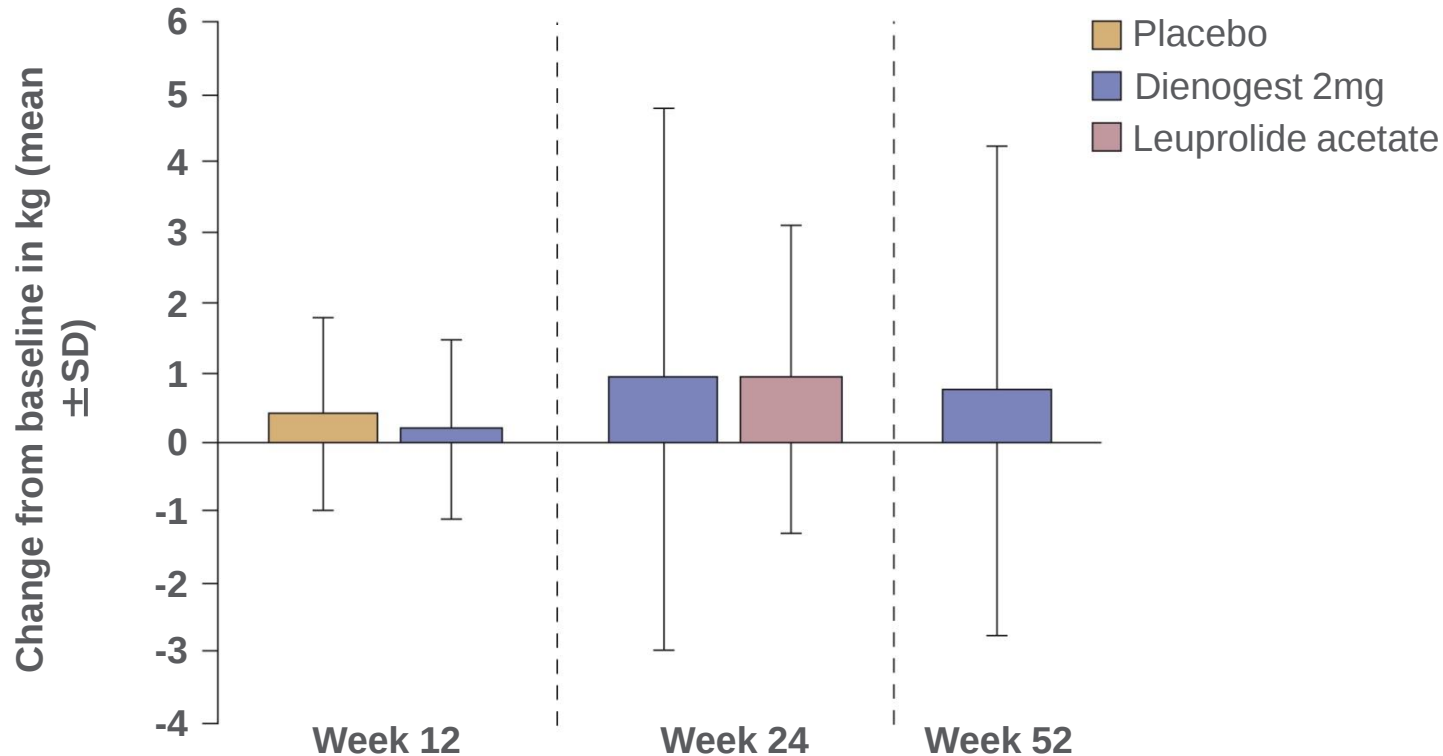
Number of Bleeding/Spotting Days Decreased with Continued Dienogest 2mg Treatment



Seitz C et al. Poster presented ASRM 65th Annual Meeting . Georgia USA . October 17-21 2009. Publication: Fertil Steril 2009; 92:S107 (Abstract).

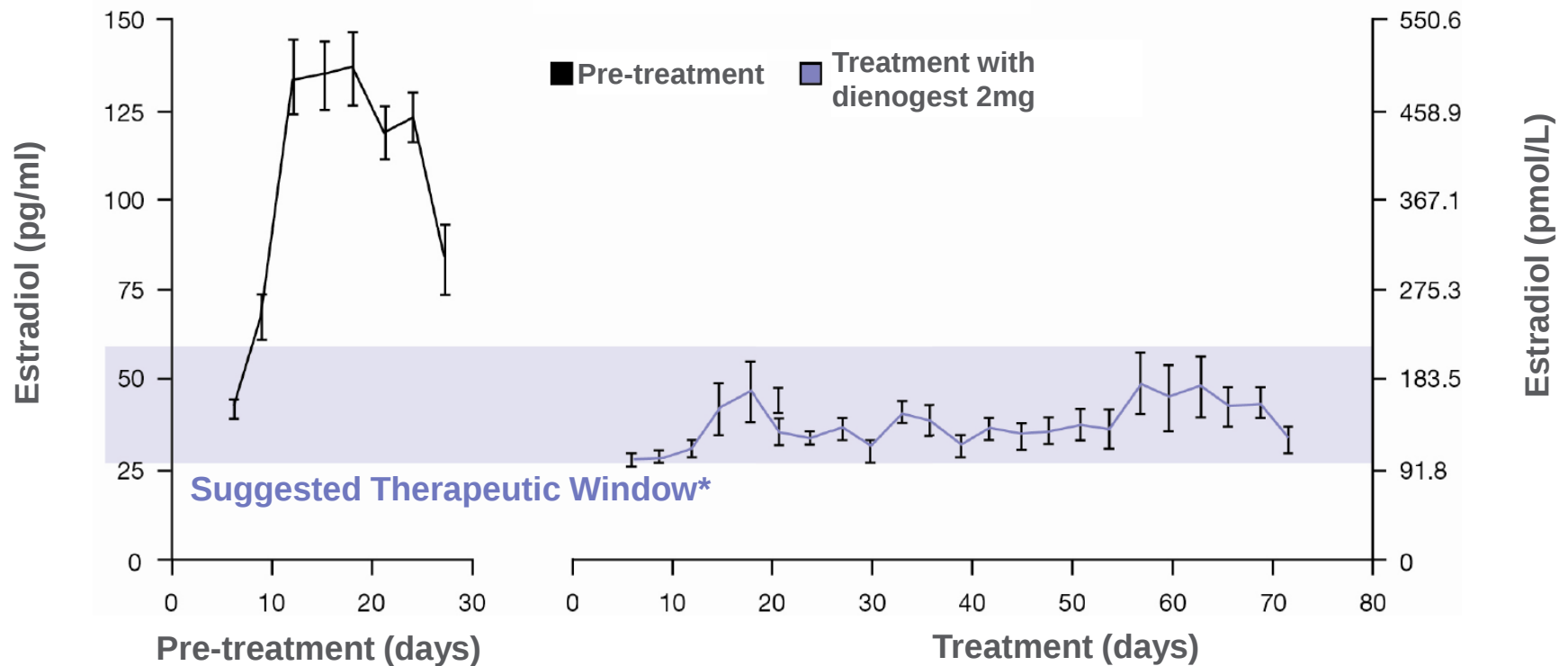
No Relevant Body Weight Changes with Dienogest 2mg Treatment

Pooled data analysis from clinical trials



Strowitzki T et al. Eur J Obstet Gynecol Reprod Biol 2010; 151: 193–198. Strowitzki T et al. Hum Reprod 2010; 25: 633–641.
Petraglia F et al. Arch Gynecol Obstet 2012; 285(1): 167–173.

Estradiol (E2) Levels During Dienogest 2mg Treatment Remain within Suggested Therapeutic Window



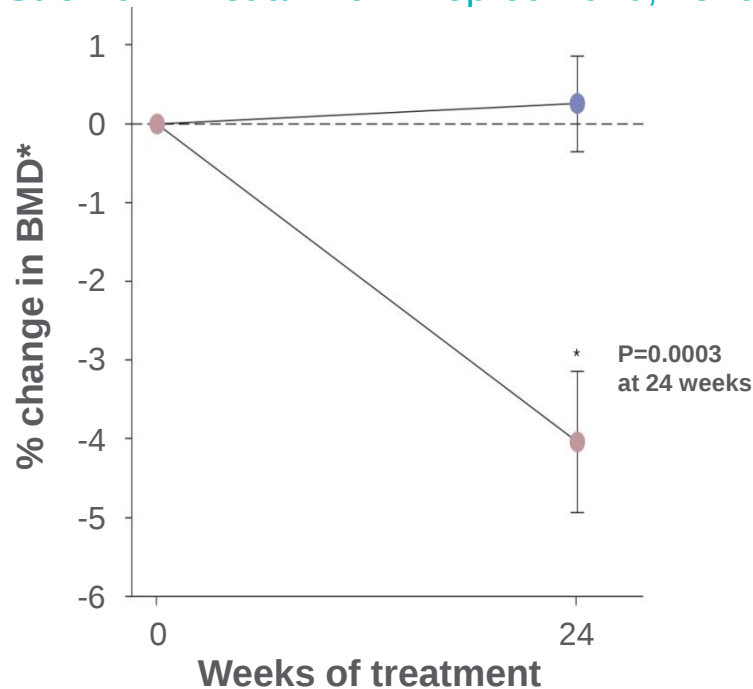
Klipping C et al. J Clin Pharmacol 2012; 52: 1704–1713.

* Barbieri RL. J Reprod Med 1998; 43: 287–292.

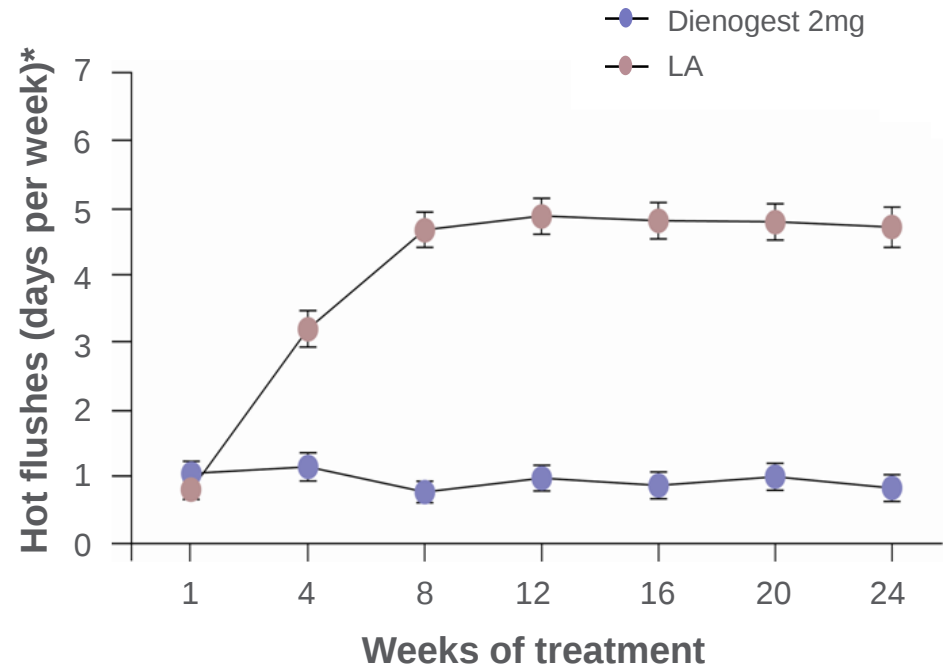
Minimal Change in Bone Mineral Density and no Increase in Hot Flushes

*mean $\pm$ SEM

Strowitzki T et al. Hum Reprod 2010; 25: 633–641.



Bone mineral density did not decrease during 24 weeks of treatment with dienogest 2mg



No increase in frequency of hot flushes during dienogest 2mg treatment

Clinical Experience with dienogest[®]

- Most patients present with chronic disease and a long history of different medications
- But: No “typical” dienogest[®] patient in terms of symptom severity, stage of the disease or age
- We have patients taking Visanne[®] for years since the launch of dienogest in Germany. Basically it's a long-term treatment.
- Some of our patients have experience with Visanne[®] for more than 3 years.
- Accumulating evidence in extra-genital endometriosis (e.g.: chest and bladder endometriosis)



Clinical Experience with dienogest®

- The majority of patients report pain relief within the first cycle.
- Common side effects are bleeding irregularities.
- If irregular bleeding occurs we encourage patients to continue dienogest®, since bleeding days will become rare with time.



Summary

What do we want from endometriosis treatment?

- Alleviate the different types of pain symptoms
- Improve quality of life
- Reduce lesions
- Show acceptable side effect profile, suitable for long-term use
- Prevent disease recurrence
- Maintain/improve fertility

Advantages and disadvantages of hormonal treatment of endometriosis

Symposium

Medication characteristic	Dienogest®	GnRH-analogs	Combined oral contraceptives
Efficacy demonstrated in clinical trials	Very good	Very good	Limited data
Change in bleeding patterns	Higher rate of irregular bleeding initially	Higher rate of amenorrhoe	Good cycle control
Long-term use	Yes	Limited (6 months)	Yes
Costs	Moderate	High	Low
Hypoestrogenic side effects	No	High	No
Application	Oral	Injection	Oral
Approved for endometriosis	Yes	Yes	No

Summary

In randomized controlled trials dienogest® has proven to:

- ✓ Alleviate the different types of pain symptoms
 - ✓ Improve quality of life
 - ✓ Reduce lesions
 - ✓ Show acceptable side effect profile, suitable for long-term use
 - Prevent disease recurrence
 - Maintain/improve fertility
- 

Thank you

