Symposium

Medical Treatment in endometriosis

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Gynecologist

Infertility & Laparoscopy Fellowship

1 in 10 women have endometriosis during their reproductive years

Crosignani, P, Olive D et al. Hum Reprod Update 2006;12(2): 179–189.

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

Sinaii N, Plumb K, Cotton L et al. Fertil Steril 2008.

Mechanisms of Pain in Endometriosis

Inflammation

Tissue damage

ONGOING PERIPHERAL ACTIVITY

Nerve damage

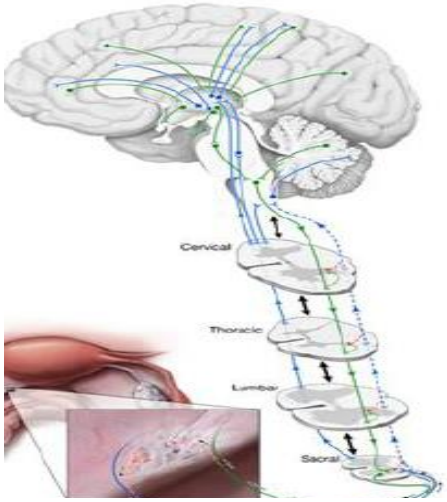
Decreased threshold to peripheral stimuli

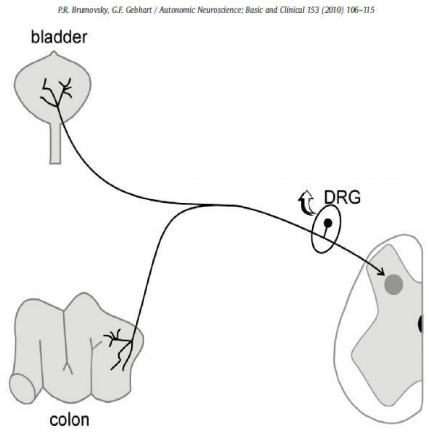
Expansion of receptive field

Increased spontaneous activity

CENTRAL SENSITIZATION (spinal, supraspinal & cortical)

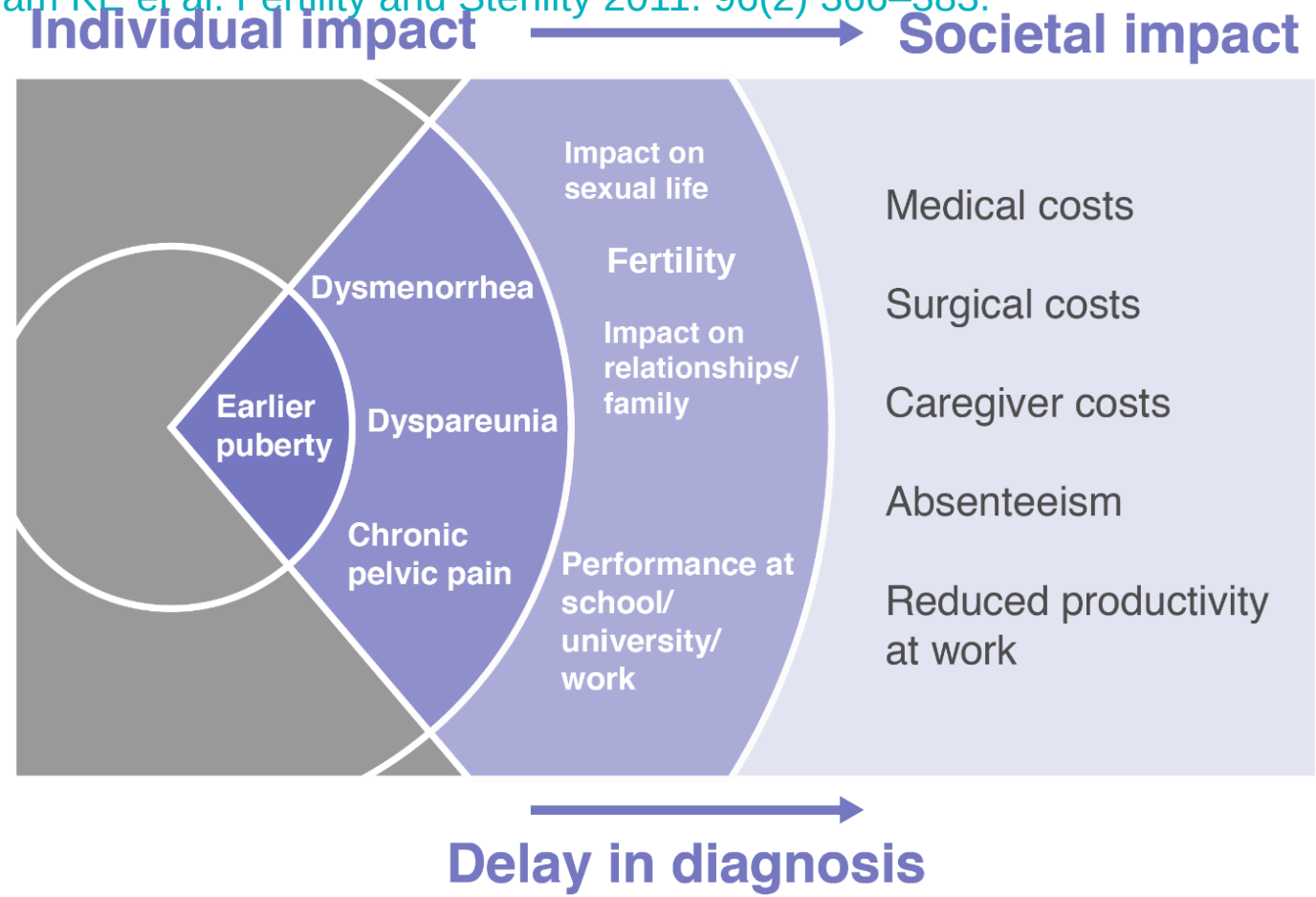
HYPERALGESIA ALLODYNİA





The Widening Impact of Endometriosis

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



What's Behind the Long Diagnostic Delay?

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

Average delay ~7 years[1]

- 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 technique[1]	• 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 challenged[1]
- 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 surgery[2]
- Recurrence rate following surgery is 40–50% in 5 years, which then necessitates further surgery[3]

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

ASRM. Fertil Steril 2014; 101(4); 927–935.

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

Leyland N et al. J Obstet Gynaecol Can 2010; 32(7 suppl 2): s1–s32.

Our Patients are All Different

Patient age

Previous surgery

Previous medical treatment

Subfertility

Location and extent of lesions

Desire for pregnancy

Pain

Desire for definitive diagnosis

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

Johnson and Hummelshoj *et al.* Consensus on current management of endometriosis 2013 Hum Reprod

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)

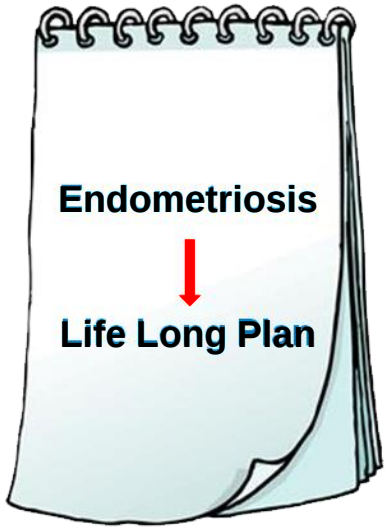
- Typical pain symptoms:
  - Dysmenorrhea
  - Dyspareunia
  - Diffuse chronic pelvic pain

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

Vercellini P. et al. Endometriosis: current and future medical therapies. Best Pract Res Clin Obstet Gynaecol 2008

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

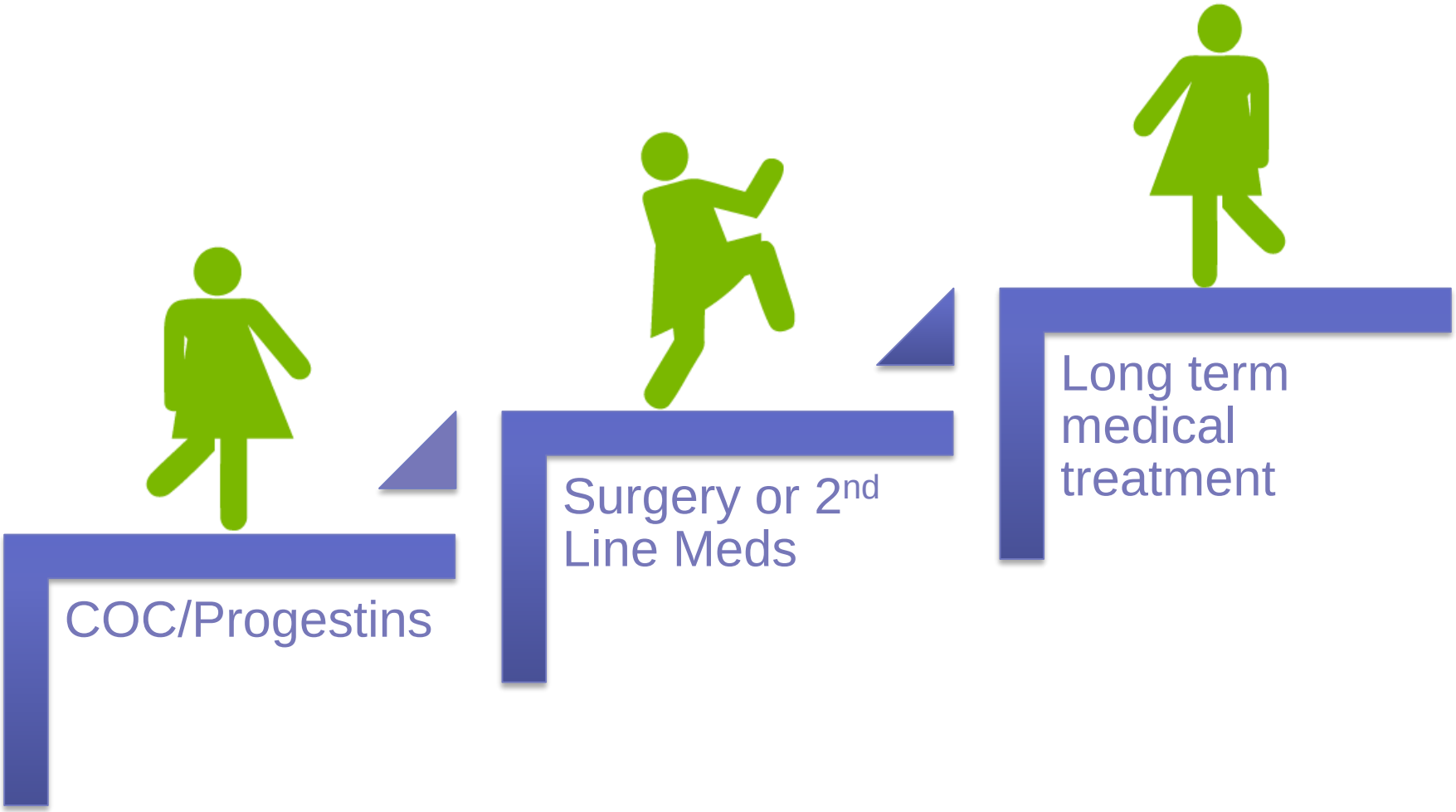
- COCs*
- Progestin only (oral, IM, SC)
- GnRH agonist + addback
- LNG-IUS*
- Danazol
- Aromatase inhibitors*
- NSAIDs, other analgesics

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

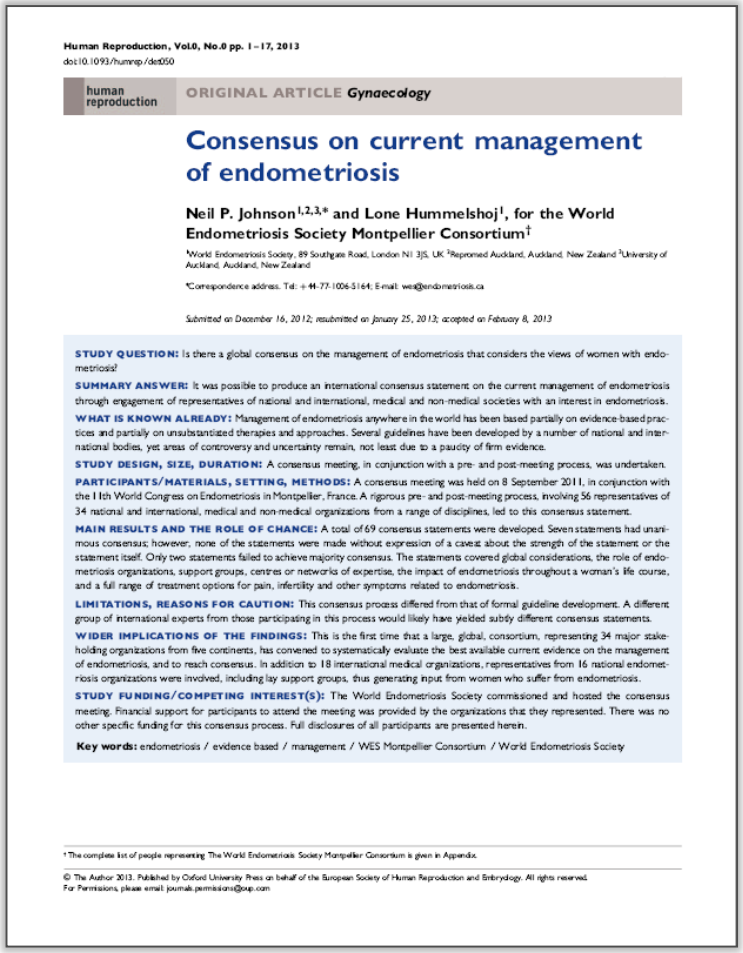
World Endometriosis Society: International Consensus on Endometriosis

- 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.



Human Reproduction, Vol.0, No.0 pp. 1–17, 2013
doi:10.1093/humrep/det050

human reproduction ORIGINAL ARTICLE *Gynaecology*

Consensus on current management of endometriosis

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Submitted on December 16, 2012; resubmitted on January 25, 2013; accepted on February 8, 2013

STUDY QUESTION: Is there a global consensus on the management of endometriosis that considers the views of women with endometriosis?

SUMMARY ANSWER: It was possible to produce an international consensus statement on the current management of endometriosis through engagement of representatives of national and international, medical and non-medical societies with an interest in endometriosis.

WHAT IS KNOWN ALREADY: Management of endometriosis anywhere in the world has been based partially on evidence-based practices and partially on unsubstantiated therapies and approaches. Several guidelines have been developed by a number of national and international bodies, yet areas of controversy and uncertainty remain, not least due to a paucity of firm evidence.

STUDY DESIGN, SIZE, DURATION: A consensus meeting, in conjunction with a pre- and post-meeting process, was undertaken.

PARTICIPANTS/MATERIALS, SETTING, METHODS: A consensus meeting was held on 8 September 2011, in conjunction with the 11th World Congress on Endometriosis in Montpellier, France. A rigorous pre- and post-meeting process, involving 56 representatives of 34 national and international, medical and non-medical organizations from a range of disciplines, led to this consensus statement.

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 69 consensus statements were developed. Seven statements had unanimous consensus; however, none of the statements were made without expression of a caveat about the strength of the statement or the statement itself. Only two statements failed to achieve majority consensus. The statements covered global considerations, the role of endometriosis organizations, support groups, centres or networks of expertise, the impact of endometriosis throughout a woman's life course, and a full range of treatment options for pain, infertility and other symptoms related to endometriosis.

LIMITATIONS, REASONS FOR CAUTION: This consensus process differed from that of formal guideline development. A different group of international experts from those participating in this process would likely have yielded subtly different consensus statements.

WIDER IMPLICATIONS OF THE FINDINGS: This is the first time that a large, global, consortium, representing 34 major stakeholding organizations from five continents, has convened to systematically evaluate the best available current evidence on the management of endometriosis, and to reach consensus. In addition to 18 international medical organizations, representatives from 16 national endometriosis organizations were involved, including lay support groups, thus generating input from women who suffer from endometriosis.

STUDY FUNDING/COMPETING INTEREST(S): The World Endometriosis Society commissioned and hosted the consensus meeting. Financial support for participants to attend the meeting was provided by the organizations that they represented. There was no other specific funding for this consensus process. Full disclosures of all participants are presented herein.

Key words: endometriosis / evidence based / management / WES Montpellier Consortium / World Endometriosis Society

[‡]The complete list of people representing The World Endometriosis Society Montpellier Consortium is given in Appendix.

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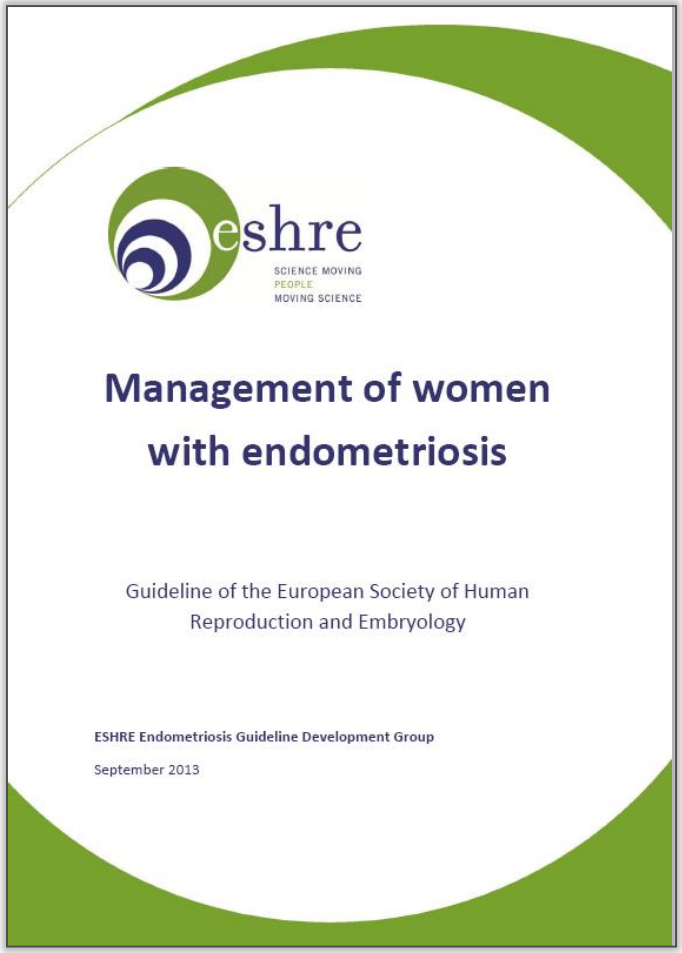
ESHRE Guidelines Update 2013

- 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.

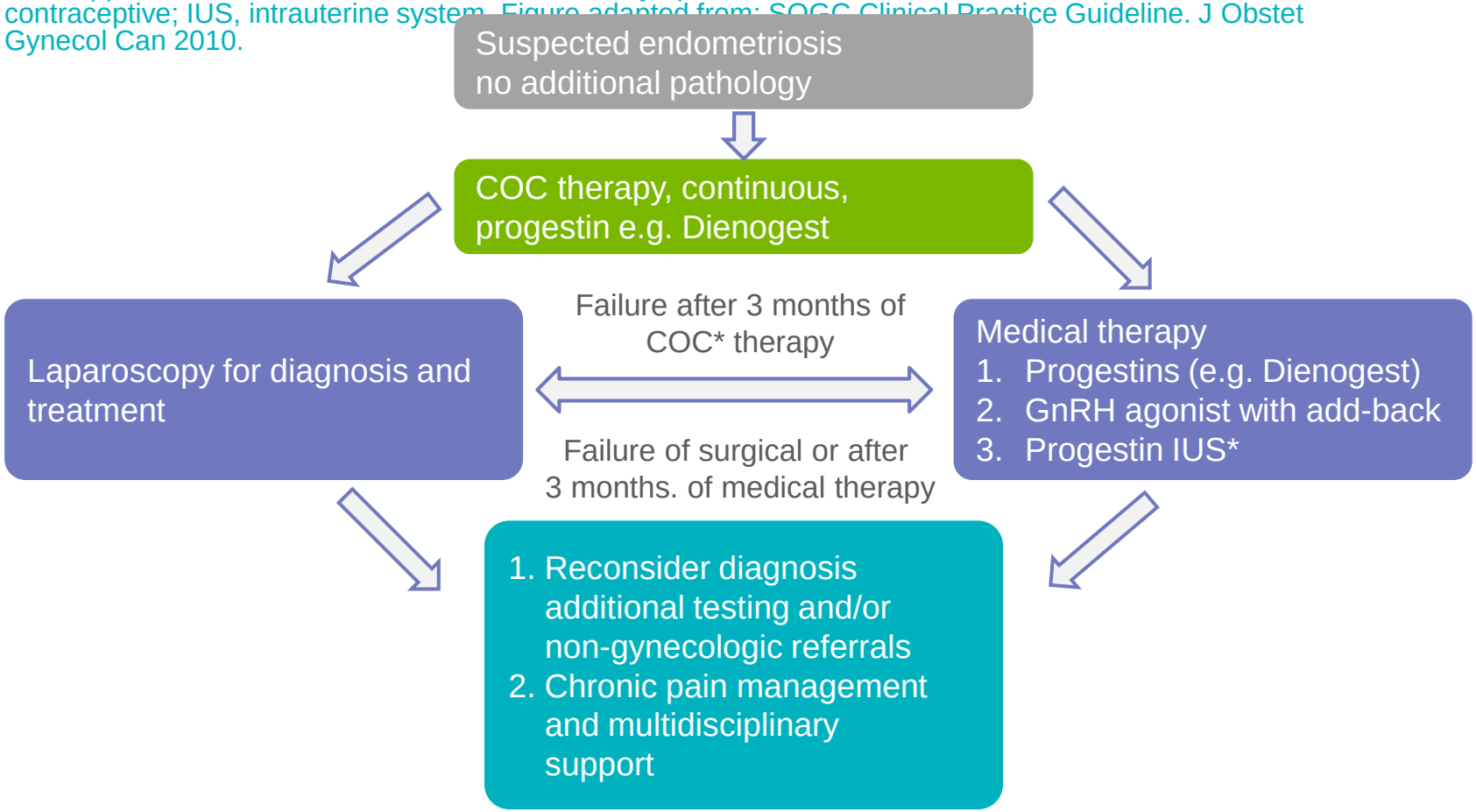


We Need to Plan

- 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 & therapeutic[1]**
- **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

SOGC Endometriosis Clinical Practice Guidelines 2010.

Choosing when to Operate is Key

- ~1 in 4 women ► additional surgical treatment within 4 years of initial surgery[1]
- Initial surgery in younger women ► risk of reoperation increased[2,3]
- First operation ► usually better response than subsequent procedures[4]
- Should avoid excessive repeat laparoscopic procedures[5]

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

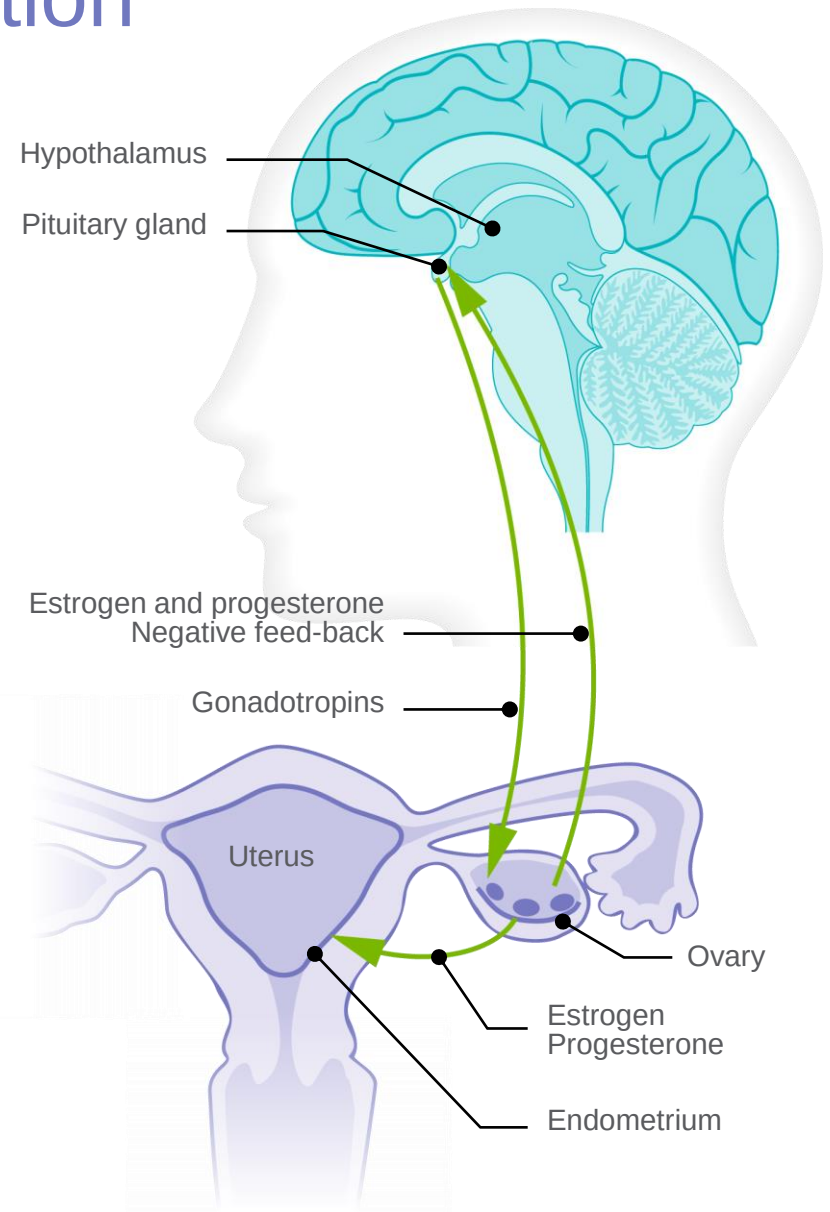
"The ideal treatment should relieve pain, induce regression of endometriotic lesions, even in the severe forms, and allow conception"

– 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.

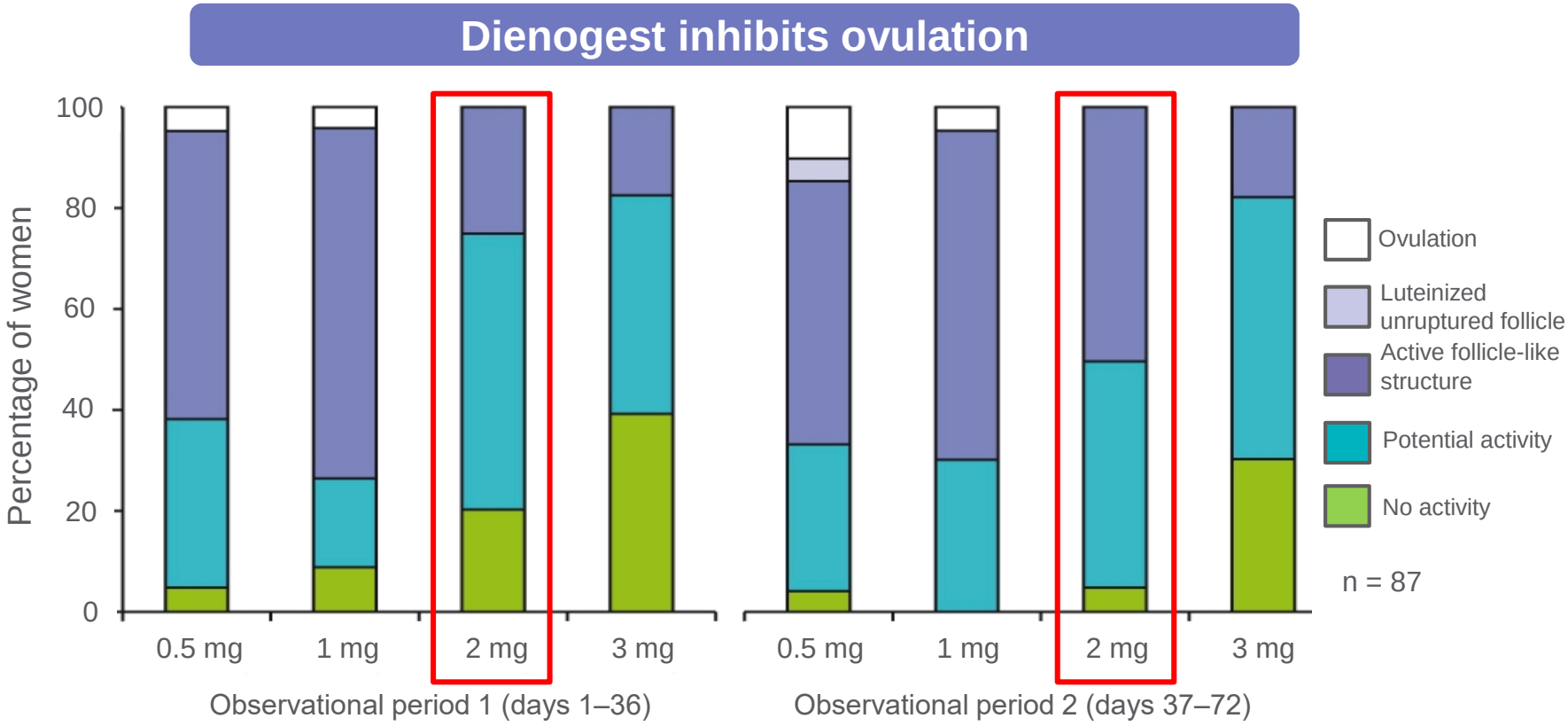
Dienogest: Mode of Action

- **Central effects**
  - **Inhibition of gonadotropin secretion**: moderate suppression of circulating estradiol
  - **Ovarian function**: anovulation (2mg dose)
- **Local effects**
  - Anti-proliferative
  - Anti-inflammatory
  - Anti-angiogenic



Klipping 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.

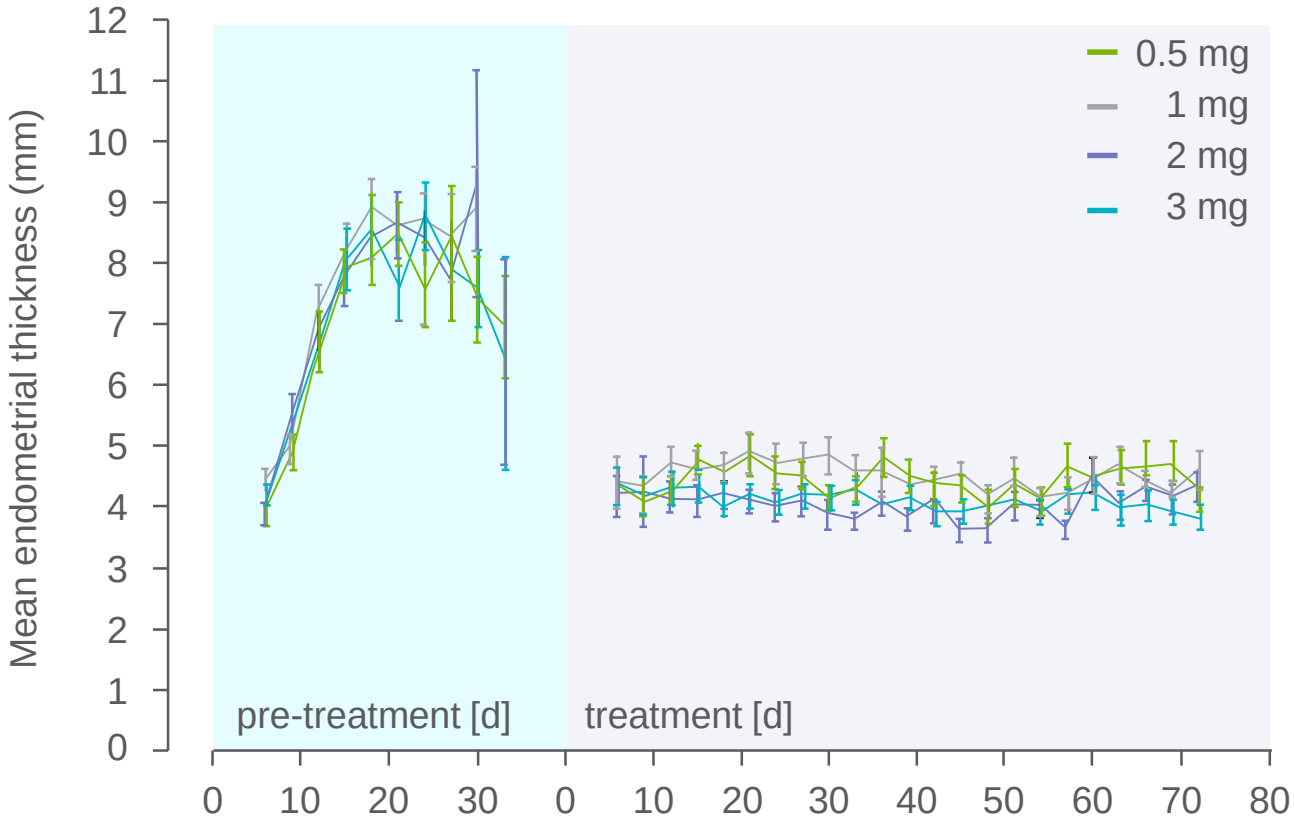
Ovarian Activity During Dienogest Treatment



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

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

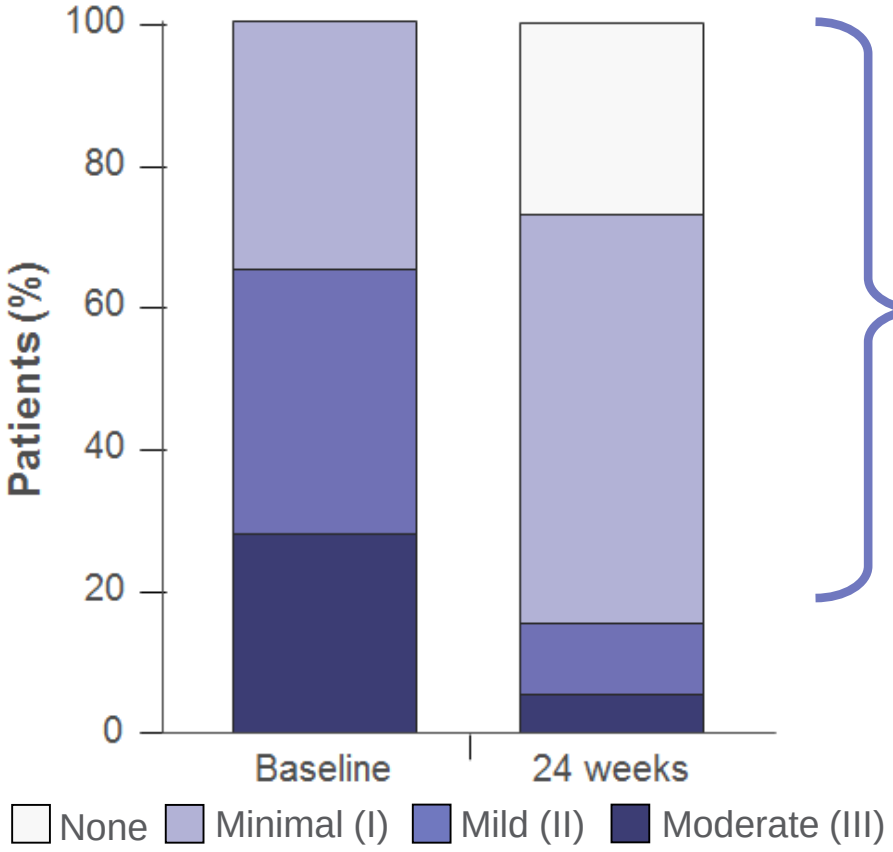
Comprehensive Clinical Development Program for Dienogest 2mg

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



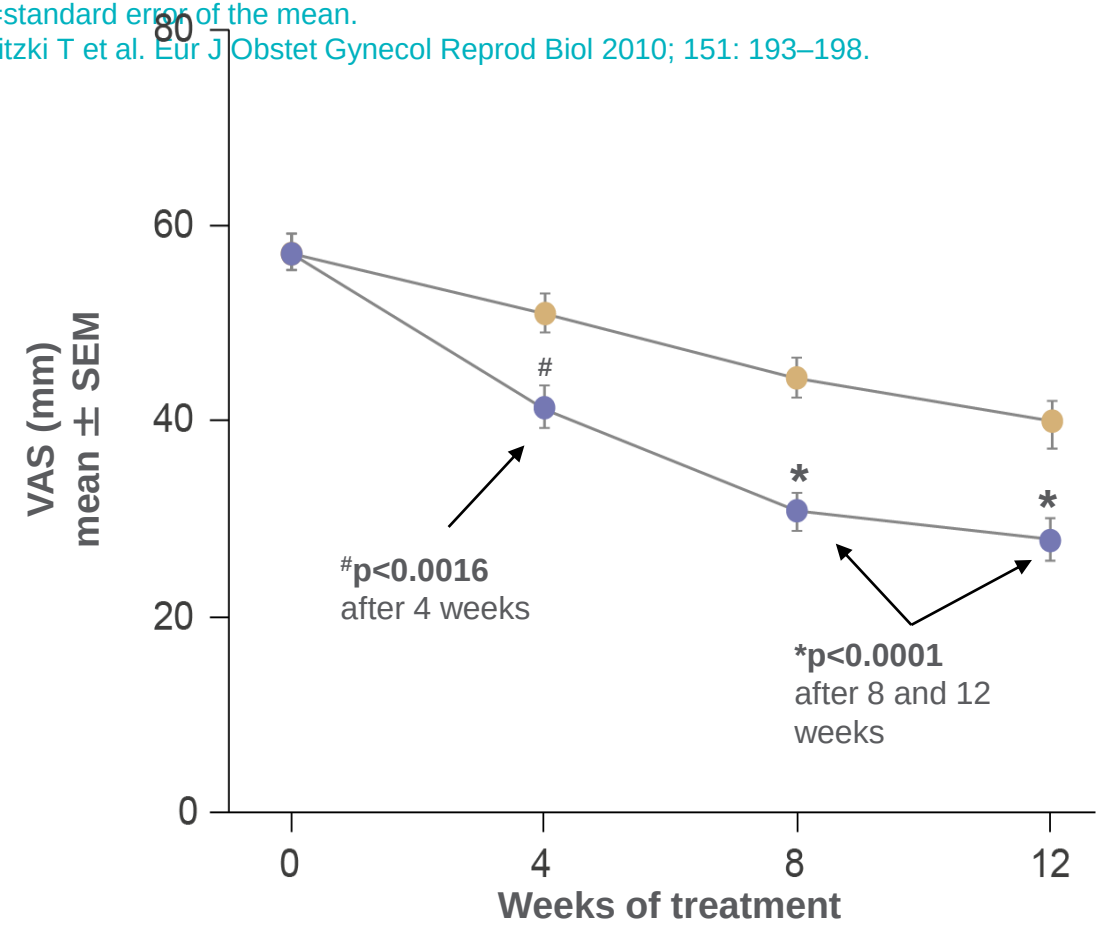
At 24 Weeks:

No / Minimal endometriosis detectable in >80% of patients

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.



Change in VAS score:

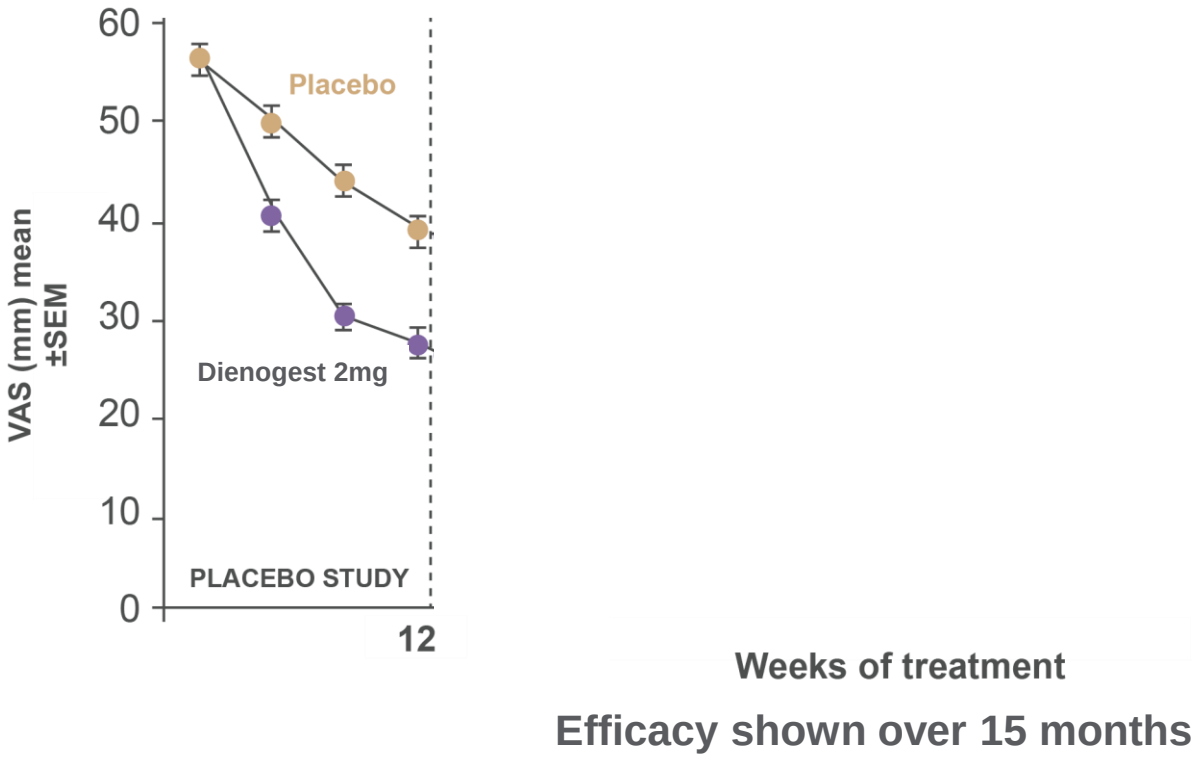
-15.1mm

-27.4mm

-12.3mm

Significant Reduction in Pain

Sustained over a Long-term Extension Period



Efficacy shown over 15 months

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

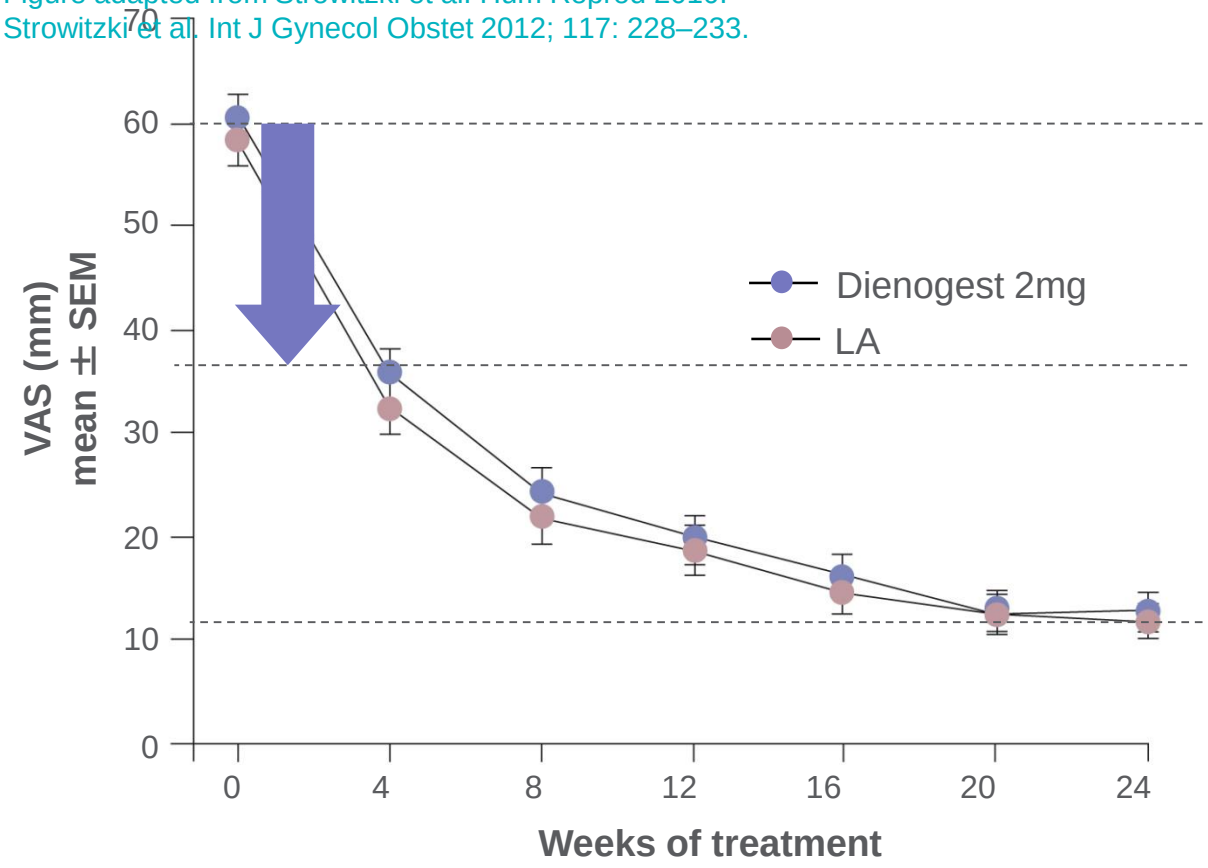
Figure adapted from Strowitzki T et al. Eur J Obstet Gynecol Reprod Biol 2010; 151: 193–198 and Petraglia F et al. Arch Gynecol Obstet 2012; 285(1): 167–173.

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.



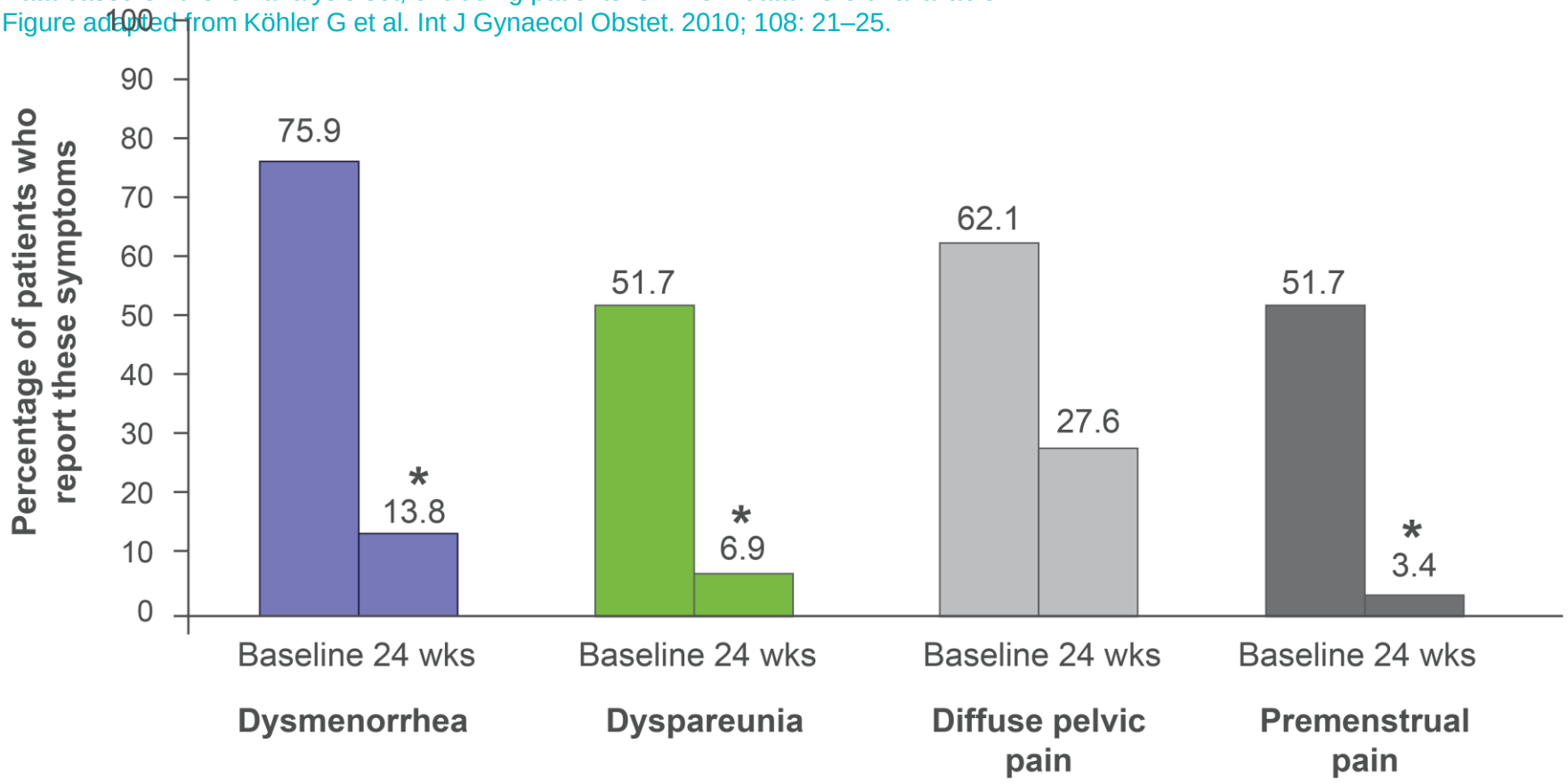
- Non-inferiority of dienogest 2mg relative to LA was demonstrated ($p<0.0001$)
- 40% of the total pain reduction was in the first 4 weeks of treatment

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

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**

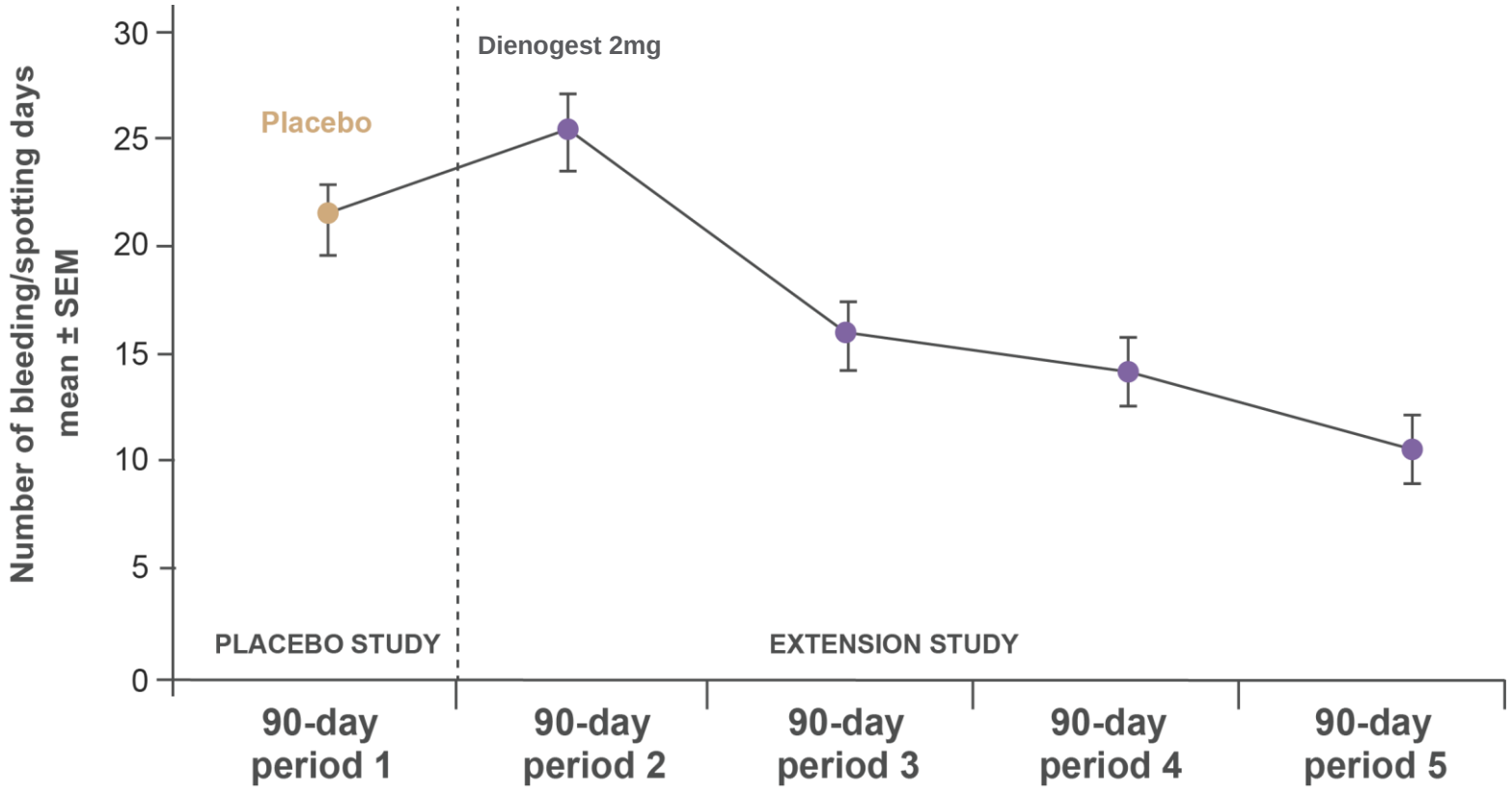
Köhler G et al. Int J Gynaecol Obstet 2010; 108: 21–25. Strowitzki T et al. Eur J Obstet Gynecol Reprod Biol 2010;151: 193–198. Strowitzki T et al. Hum Reprod 2010; 25: 633–641. Petraglia F et al. Arch Gynecol Obstet 2012; 285(1): 167–173.

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

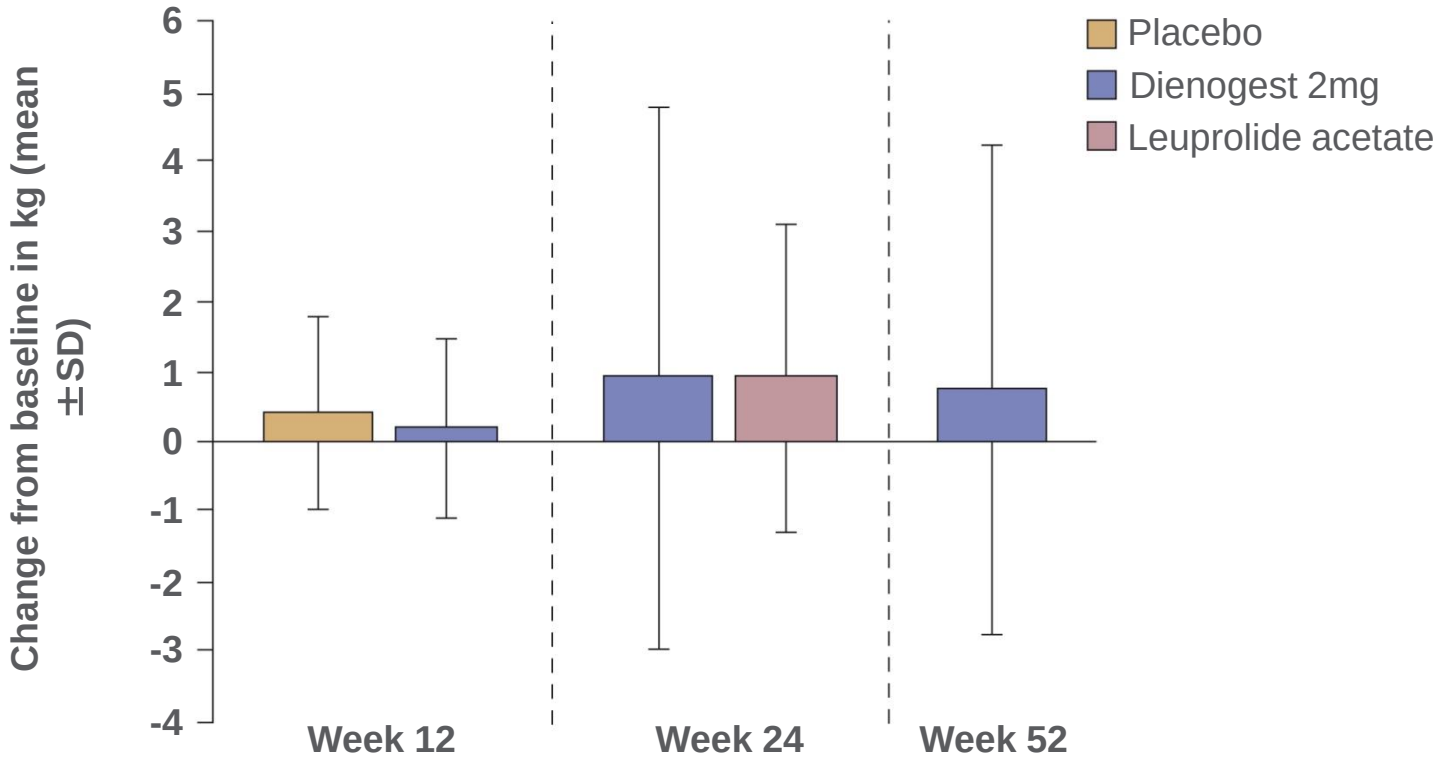
Number of Bleeding/Spotting Days Decreased with Continued Dienogest 2mg Treatment



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

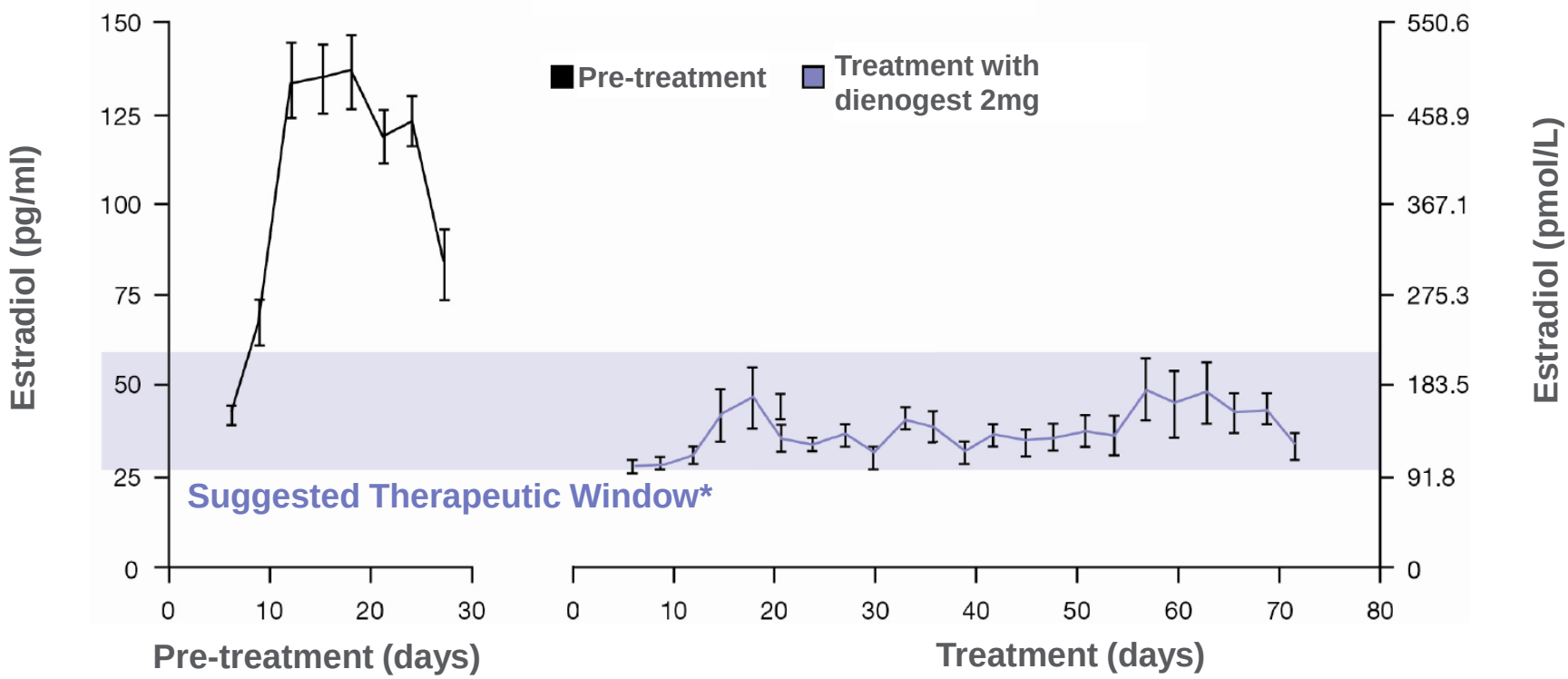
No Relevant Body Weight Changes with Dienogest 2mg Treatment

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

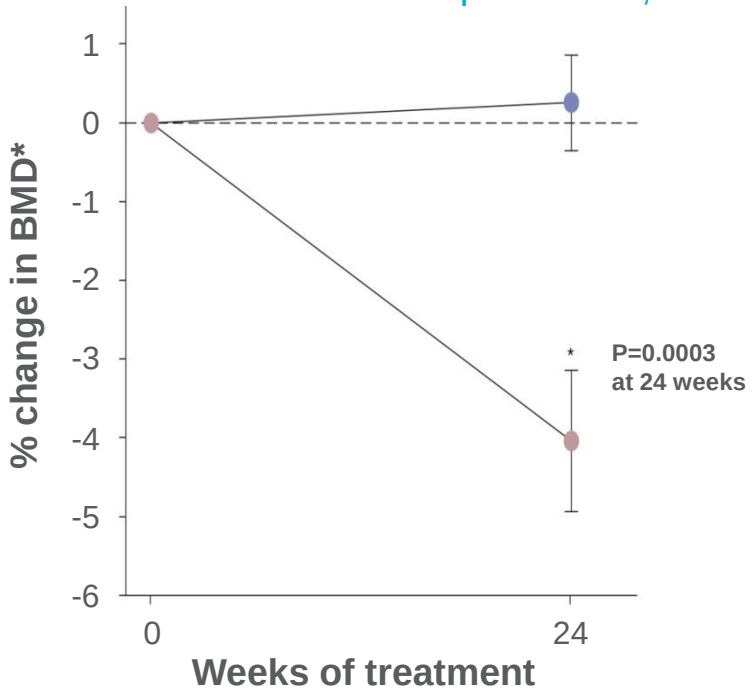


Klipping C et al. J Clin Pharmacol 2012; 52: 1704–1713.
* Barbieri RL. J Reprod Med 1998; 43: 287–292.

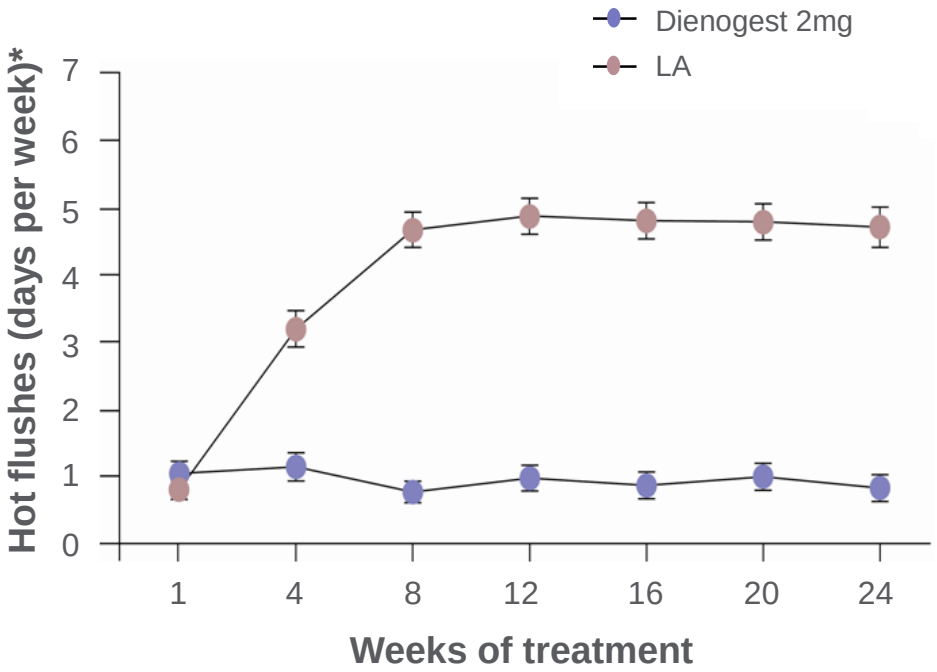
Minimal Change in Bone Mineral Density and no Increase in Hot Flushes

*mean ± 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 dienogst®, 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

Soares SR et al. Fertil Steril 2012; 98(3): 529–555.

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