

OSPEDALE
EVANGELICO



VILLA
BETANIA

FONDAZIONE EVANGELICA BETANIA

**Endometriosi: terapia farmacologica e
medicina alternativa.**
Giuseppe De Francesco

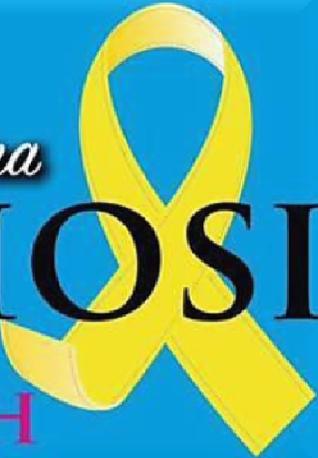


19 marzo 2016
Roma

ENDOMETRIOSI

Team Italy

WORLDWIDEMARCH



Written declaration on endometriosis



European Parliament

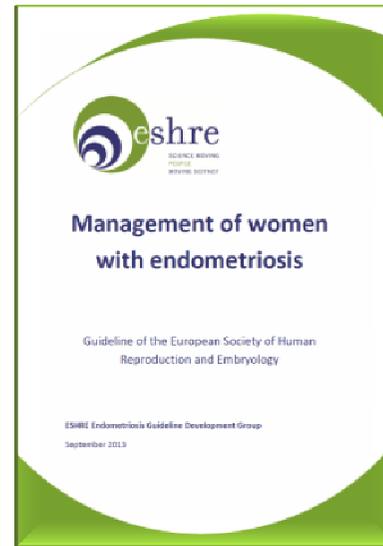
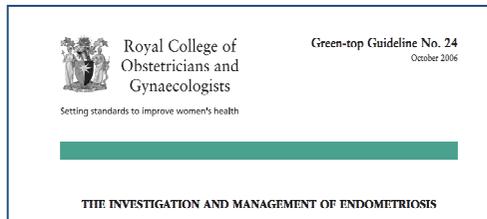
A. acknowledging that endometriosis is a debilitating disease affecting an estimated **- 14 million women -** and girls in the European Union, with significant costs for the individual and state,

B. noting that sick leave alone due to endometriosis costs an estimated **- €30 billion -** in the EU annually,

C. concerned about recent international data indicating a diagnostic delay of over **- 9 years -** as well as frequent misdiagnosis due to lack of awareness and understanding of symptoms,

2005

GUIDELINES



Treatment of pelvic pain associated with endometriosis

The Practice Committee of the American Society for Reproductive Medicine
Birmingham, Alabama

GUIDELINES



COLLÈGE NATIONAL
DES GYNÉCOLOGUES
ET OBSTÉTRICIENS FRANÇAIS

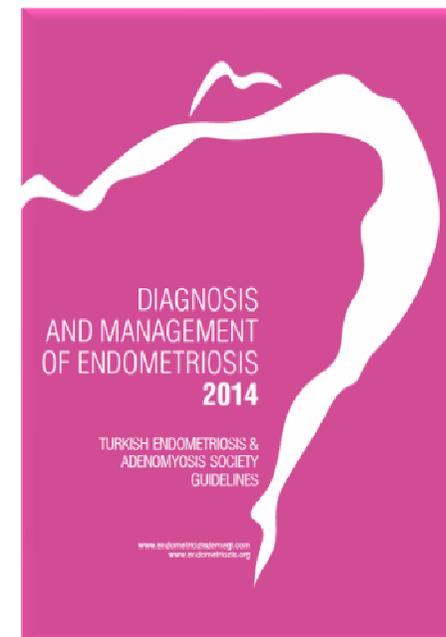
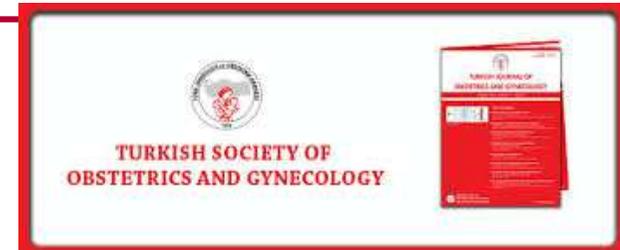
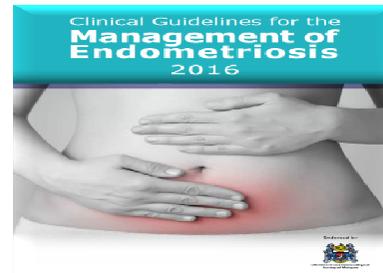


GUIDELINES

Endorsed by



Obstetrical and Gynaecological
Society of Malaysia



GYNECOLOGY

Variation in outcome reporting in endometriosis trials: a systematic review



Martin Hirsch, BM; James M. N. Duffy, MBChB; Jennie O. Kuznir, BMedSci;
Colin J. Davis, FRCOG; Maria N. Plana, MD; Khalid S. Khan, MRCOG; on behalf of the
International Collaboration to Harmonize Outcomes and Measures for Endometriosis

Variation in outcome reporting within published endometriosis trials prohibits **comparison**, **combination**, and **synthesis** of data.

This limits the usefulness of research to inform clinical practice, enhance patient care, and improve patient outcomes.



American Journal of Obstetrics & Gynecology APRIL 2016

April,
2016

GYNECOLOGY

Variation in outcome reporting in endometriosis trials: a systematic review



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International Collaboration to Harmonize Outcomes and Measures for Endometriosis

In the absence of a core outcome set for endometriosis we recommend the use of the 3 most common pain (dysmenorrhea, dyspareunia, and pelvic pain) and subfertility (pregnancy, miscarriage, and live birth outcomes).



American Journal of Obstetrics & Gynecology APRIL 2016

April,
2016

GYNECOLOGY

Variation in outcome reporting in endometriosis trials: a systematic review

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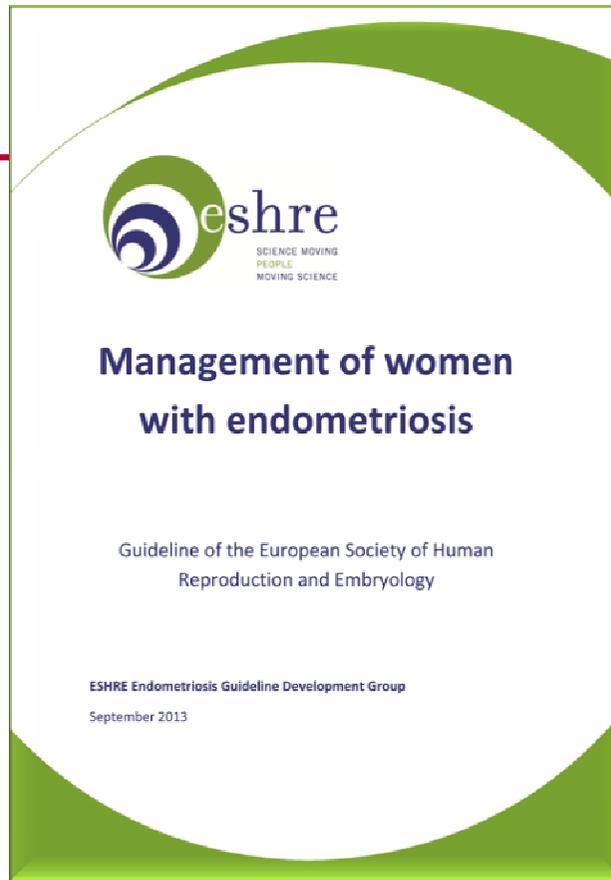


International consensus among stakeholders is needed to establish a core outcome set for endometriosis trials.



American Journal of Obstetrics & Gynecology APRIL 2016

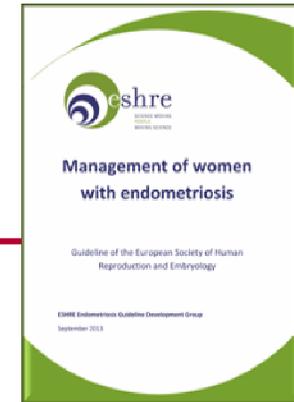
April,
2016



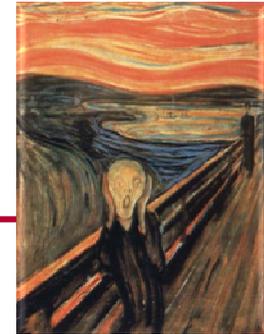
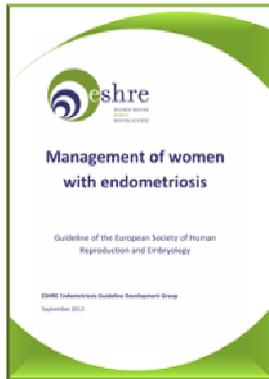
Human Reproduction, Vol.29, No.3 pp. 400–412, 2014

➤ **European Society of Human Reproduction and Embryology:**

- **American Society of Reproductive Medicine**
- **Royal College of Obstetricians and Gynaecologists**
- **Society of Obstetrics and Gynecology of Canada**
- **Collège National des Gynécologues et Obstétriciens Français**
- **Deutsche Gesellschaft für Gynäkologie und Geburtshilfe**



Human Reproduction, Vol.29, No.3 pp. 400–412, 2014

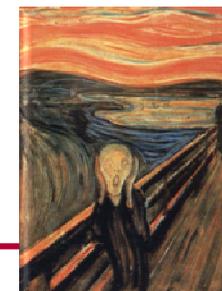
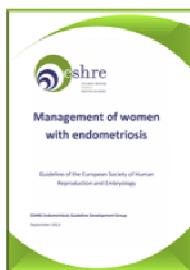


Recommendation

The GDG recommends clinicians to counsel women with symptoms presumed to be due to endometriosis thoroughly, and to empirically treat them with adequate analgesia, combined hormonal contraceptives or progestagens.

GPP

**Human Reproduction, Vol.29, No.3 pp. 400–412,
2014**



Recommendations

Clinicians are recommended to prescribe hormonal treatment [hormonal contraceptives (level B), progestagens (level A), anti-progestagens (level A), or GnRH agonists (level A)] as one of the options, as it reduces endometriosis-associated pain (Vercellini, et al., 1993, Brown, et al., 2012, Brown, et al., 2010).

A-B

The GDG recommends that clinicians take patient preferences, side effects, efficacy, costs and availability into consideration when choosing hormonal treatment for endometriosis-associated pain.

GPP

quotidiano**sanità**.it

Il Quotidiano della Sanità italiana

28 FEBBRAIO 2017



Il ‘ddl Gelli’ è legge.

“Disposizioni in materia di sicurezza delle cure e della persona assistita, nonché in materia di responsabilità professionale degli esercenti le professioni sanitarie”



N. 259-262-1312-1324-1581-1769-1902-2155-B

CAMERA DEI DEPUTATI

PROPOSTA DI LEGGE

APPROVATA, IN UN TESTO UNIFICATO,
DALLA CAMERA DEI DEPUTATI

il 28 gennaio 2016 (v. stampato Senato n. 2224)

MODIFICATA DAL SENATO DELLA REPUBBLICA

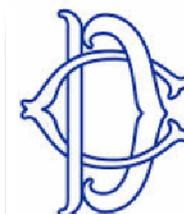
l'11 gennaio 2017

D'INIZIATIVA DEI DEPUTATI

**FUCCI; FUCCI; GRILLO, CECCONI, DALL'OSSO, DI VITA, LO-
REFICE, MANTERO, BARONI, SILVIA GIORDANO; CALABRÒ,
FUCCI, ELVIRA SAVINO; VARGIU, BINETTI, GIGLI, MON-
CHIERO; MIOTTO, LENZI, AMATO, BELLANOVA, BENI, PAOLA
BRAGANTINI, BURTONE, CAPONE, CARNEVALI, CASATI, D'IN-
CECCO, FOSSATI, GELLI, IORI, MURER, PATRIARCA, PIC-
CIONE, SBROLLINI; MONCHIERO, RABINO, OLIARO, BINETTI,
MATARRESE, GIGLI; FORMISANO**

Disposizioni in materia di sicurezza delle cure e della
persona assistita, nonché in materia di responsabilità
professionale degli esercenti le professioni sanitarie

*Trasmessa dal Presidente del Senato della Repubblica
il 12 gennaio 2017*



Camera
dei
Deputati

2017

ART 6 . Qualora l'evento si sia verificato a causa di

«IMPERIZIA»

la punibilità è esclusa quando sono rispettate :

1) «Raccomandazioni previste dalle linee guida»

ovvero in mancanza di queste :

2) «Buone pratiche clinico-assistenziali»

sempre che le raccomandazioni previste dalle predette linee guida risultino :

3) «Adeguate alle specificità del caso concreto».



ART 6

«Buone pratiche clinico-assistenziali»

- *Chi definisce «Le buone pratiche clinico-assistenziali»?*
- *Sono sempre basate sul parere degli esperti :
I Consulenti Tecnici ?(CTU? CTP?)*
- *La Norma lascia margini eccessivi alla discrezionalità di
Consulenti Tecnici (CTU-CTP) ?*



ART 6



~~«...Sempre che le raccomandazioni previste dalle predette linee guida risultino adeguate alle specificità del caso concreto».~~

Ogni paziente rappresenta un « Caso concreto ».

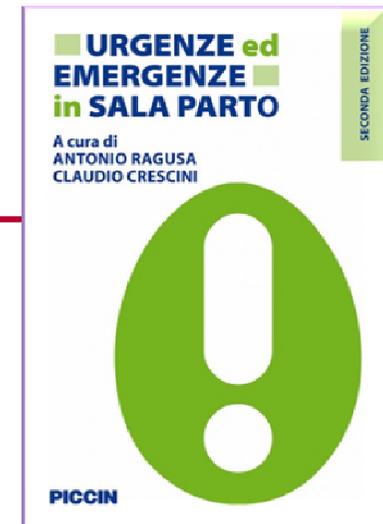
- La Norma lascia margini eccessivi alla discrezionalità dei Giudici?

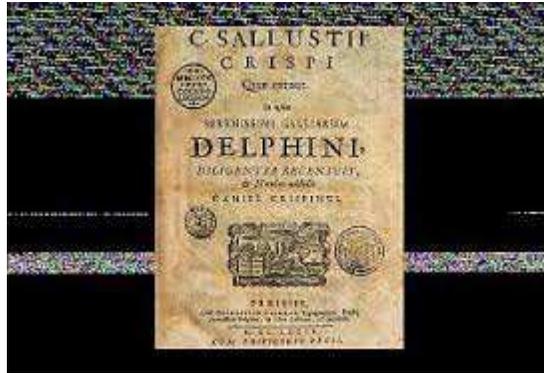
PROTOCOLLI e LINEE GUIDA

«... Protocolli - Linee Guida - Regole - sono importanti, essenziali, addirittura indispensabili per assistere la persona, ma essi non sono il punto di arrivo dell'assistenza, bensì il suo punto di partenza.

Partenza senza la quale non è possibile concepire di assistere la persona nella sua interezza.

I protocolli devono dissolversi nel gesto clinico reale, vero, che se vuole essere terapeutico, deve essere **individualizzato**, entrare pericolosamente nell'alterità dell'altro, per farne proprie le sofferenze ed il patire»





Linee guida

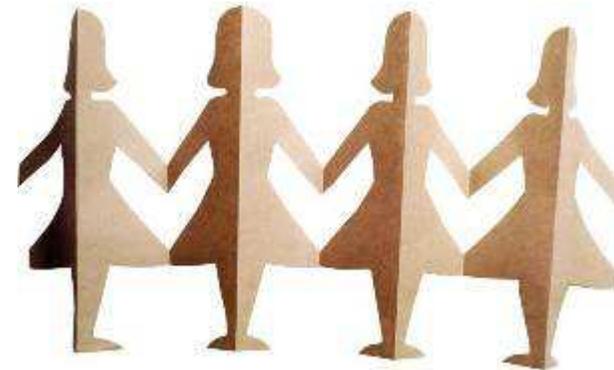
« ...Ad usum delphini...? »

L'endometriosi è una patologia che ha un grande impatto sulla salute delle donne

- E' la piu' frequente patologia proliferativa benigna che colpisce le donne in eta' fertile
- I dati epidemiologici dimostrano un'incidenza pari a 0,25 nuovi casi donna per 1000 donne-anno
- 175 milioni di donne worldwide tra i 15 e i 45 anni
- La prevalenza nella popolazione femminile è del 7,5%
(10-15% delle donne tra i 15 e i 50 è affetto da endometriosi)

1- dolore pelvico

2- infertilita' femminile



Nell' endometriosi il punto chiave è capire la patogenesi per poter stabilire le opzioni terapeutiche

Treatment Overview

- **EXPECTANT MANAGEMENT**

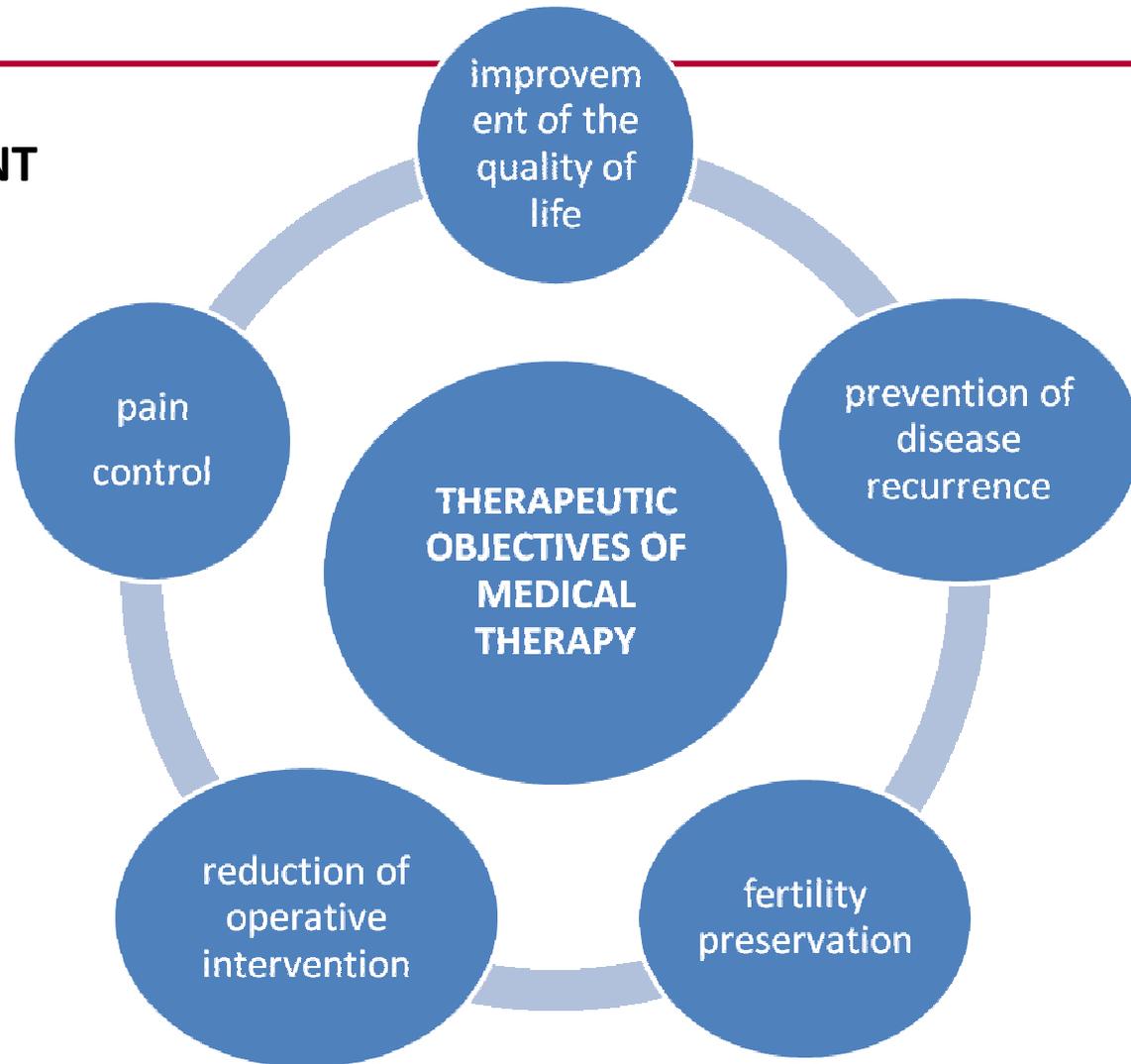
- **ANALGESIA**

- **HORMONAL THERAPY**

- OCP's cyclic or continuous,
- Progestins
- GnRH agonists

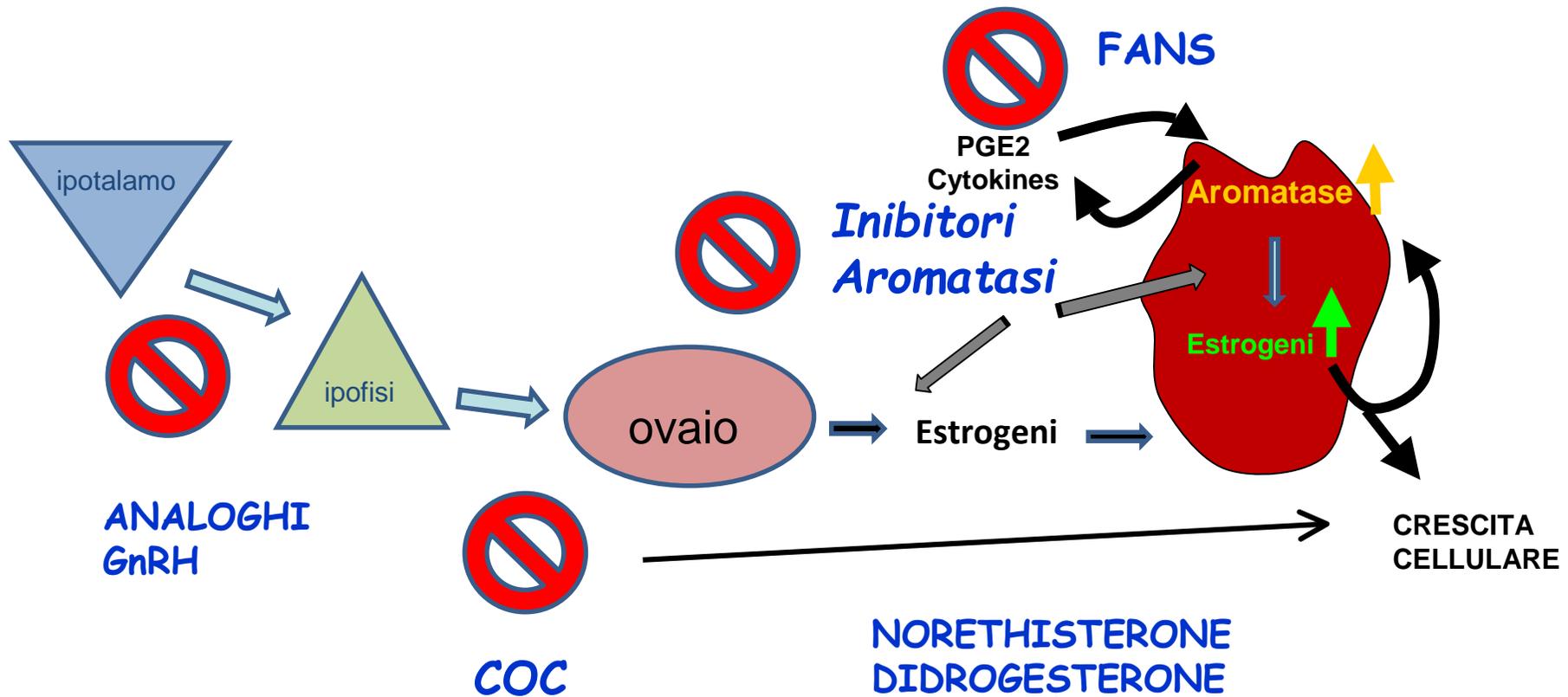
- **SURGICAL THERAPY**

- Conservative (keep ovaries and uterus)
- Definitive (Hyst, BSO)



Mohamed A. Bedaiwy et al, Fertil Steril, 2017

Siti di azione farmaci



Ricavato: da Giudici NEJM 2010, Budinetz 2010 minerva gin. Vercellini P, Somigliana E, Viganò P, et al. Endometriosis: current therapies and new pharmacological developments. Drugs 2009, RCP

Trattamenti medici per l'endometriosi

Meopausa iatrogena

- GnRH Analoghi
- Inibitori dell'aromatasi

Sintomatica

Farmaci anti infiammatori non
steroidi

Pseudo Gravidanza

- Estro-progestinici
- Progestinici
- Danazolo
- Gestrinone
- Modulatori selettivi del R per gli estrogeni (SERMs) (Tamoxifene, Raloxifene)
- Modulatori selettivi per il Recettore del Progesterone (SPRMs) (Ulipristal acetato)

Condotta di Attesa

- Pazienti asintomatiche
- Pazienti infertili con endometriosi minima o lieve

TERAPIA MEDICA:

- Analgesici, FANS (Diclofenac, Ibuprofene, Naprossene sodico).
Il piu' usato è il Naprossene sodico per la sua lunga durata d'azione (550 mg per os/12 ore)
- Utilizzati per il trattamento della dismenorrea e riducono il dolore nel 72% dei casi)
- Non hanno impatto sull'evoluzione della malattia

Nonsteroidal Anti-inflammatory Agents

Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis (Review)

Brown J, Crawford TJ, Allen C, Hopewell S, Prentice A

Comparison of NSAIDs (naproxen) versus placebo

No evidence of a positive effect on pain relief (OR) 3.27, 95% (CI) 0.61 to 17.69;).

Additional analgesia (OR 0.12, 95% CI 0.01 to 1.29;)

Experience side effects (OR 0.46, 95% CI 0.09 to 2.47;)

ALL INCONCLUSIVE

Brown J, Cochrane Rev, 2017

Ormonal Treatment

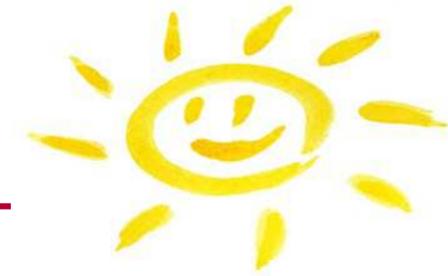
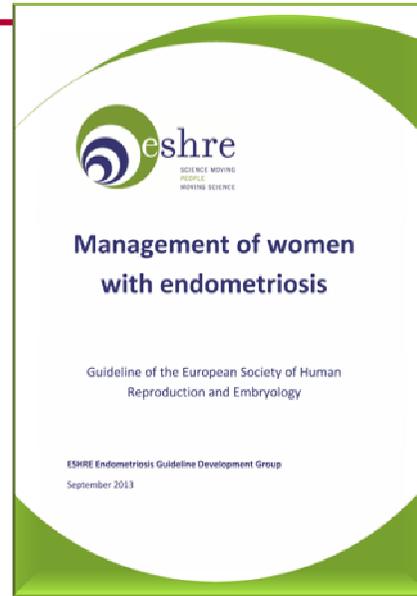
Table 1 Mechanisms of medical treatment options for endometriosis-associated pain

Medications	Mechanism
Combined hormonal contraceptives	Inhibition of ovulation
Progestins	Decidualization and atrophy of implants Suppression of matrix metalloproteinases ²⁰ Inhibition of angiogenesis ²¹
Cyproterone acetate	Antiandrogenic effect mediated by a competitive inhibition on the cytoplasmic testosterone receptor and a negative feedback effect on the hypothalamo-pituitary-ovarian axis
GnRH agonists	Suppression of gonadotropin secretion and secondary suppression of ovarian steroidogenesis
Aromatase inhibitors	Inhibition of the aromatase enzyme with inhibition of the conversion of testosterone and androstenedione to estradiol and estrone, respectively
Danazol	Central inhibition of pituitary gonadotropin secretion, direct inhibition of endometriotic implant growth, and direct inhibition of ovarian enzymes responsible for estrogen production

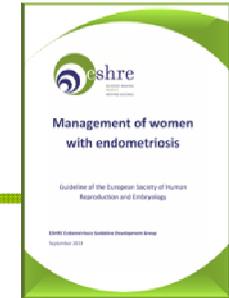
Mohamed A. Bedaiwy et al, Semin Reprod Med, 2016

Combination Hormonal Contraceptive





Human Reproduction, Vol.29, No.3 pp. 400–412, 2014



Recommendations

Clinicians can consider prescribing a combined hormonal contraceptive, as it reduces endometriosis-associated dyspareunia, dysmenorrhea and non-menstrual pain (Vercellini, et al., 1993).

B

Clinicians may consider the continuous use of a combined oral contraceptive pill in women suffering from endometriosis-associated dysmenorrhea (Vercellini, et al., 2003).

C

Clinicians may consider the use of a vaginal contraceptive ring or a transdermal (estrogen/progestin) patch to reduce endometriosis-associated dysmenorrhea, dyspareunia and chronic pelvic pain (Vercellini, et al., 2010).

C



Combination Hormonal Contraceptive

Nonrandomized cohort study with follow-up of more than 17,000 women for up to 23 years

Interval since last use (months)	No of cases	Rate per 1000 woman years	Relative risk (95% confidence interval)*
Never†	106	0.56	1.0
0-12‡	10	0.22	0.4 (0.2 to 0.7)
13-24	3	0.77	1.4 (0.3 to 4.0)
25-48	2	0.27	0.5 (0.1 to 1.8)
49-72	5	0.77	1.4 (0.4 to 3.2)
73-96	4	0.69	1.2 (0.3 to 3.2)
≥ 97	8	0.66	1.2 (0.5 to 2.3)

Current users and recent users had a lower rate of endometriosis than non-users

Vessey MP et al., BMJ, 1993;



Combination Hormonal Contraceptive

FIGURE 1

A flow-chart of participants through the trial. OCP: oral contraceptive pill.

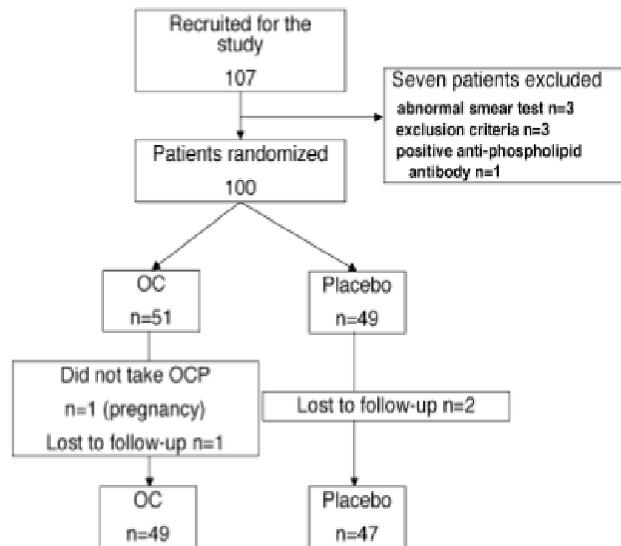
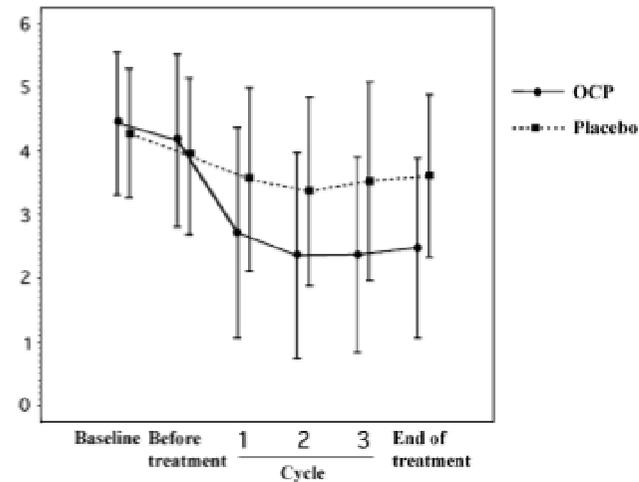


FIGURE 2

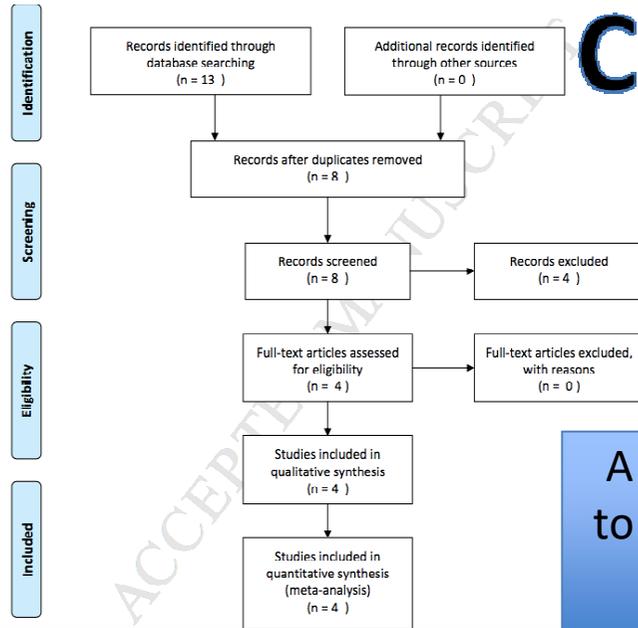
Changes in mean dysmenorrhea score during the trial. OCP: oral contraceptive pill.

Total dysmenorrhea score (m + SD)



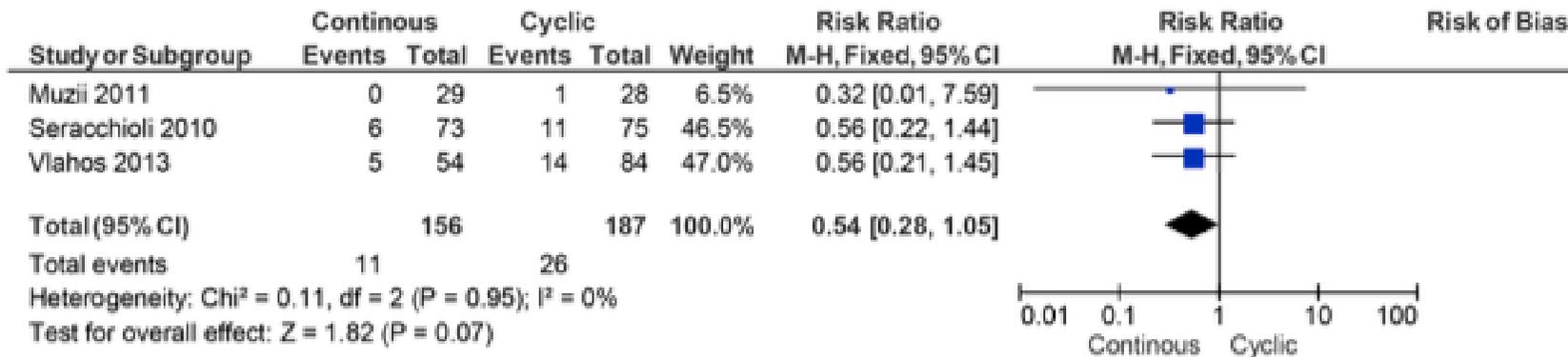
Low- dose OCPs are an effective treatment with few adverse effects for dysmenorrhea associated with endometriosis

Combination Hormonal Contraceptive



Continuous versus Cyclic Oral Contraceptives after Laparoscopic Excision of Ovarian Endometriomas

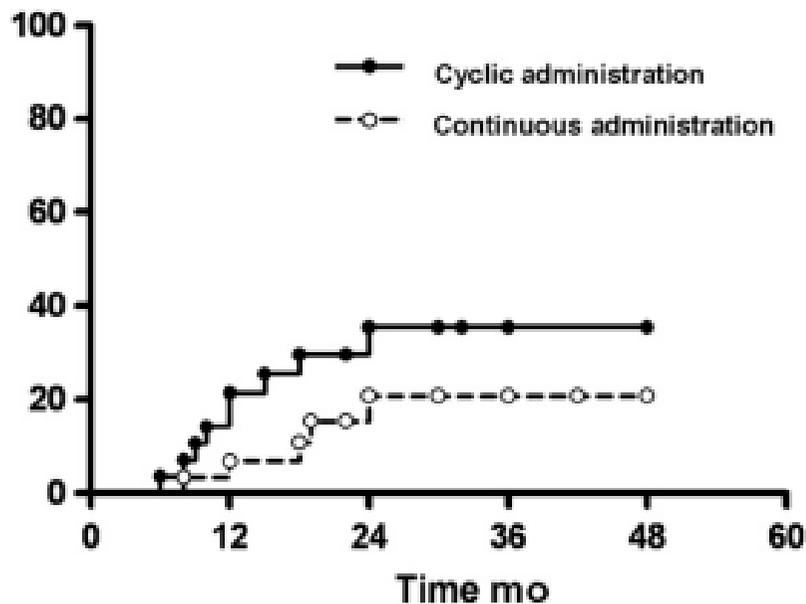
A continuous oral contraceptive regimen, as opposed to a cyclic regimen, may be suggested after surgery for endometriomas because of lower dysmenorrhea recurrence rates.



Muzii L et al., Am J Obstet Gynecol, 2016

Oral Estroprogestins after Laparoscopic Surgery to Excise Endometriomas: Continuous or Cyclic Administration?

Multicenter randomized 57 patients



Results of a Multicenter Randomized Study

Although both regimens were equally effective insofar as postoperative pain and recurrence of endometrioma, when compared with the CYC regimen, the CON regimen seems to be associated with significantly more adverse effects and discontinuation rates

Trattamento medico dell'endometriosi: uso dei progestinici ed estroprogestinici

Desogestrel

Etonogestrel

Etonogestrel + EE

Dienogest

Perché la via vaginale?

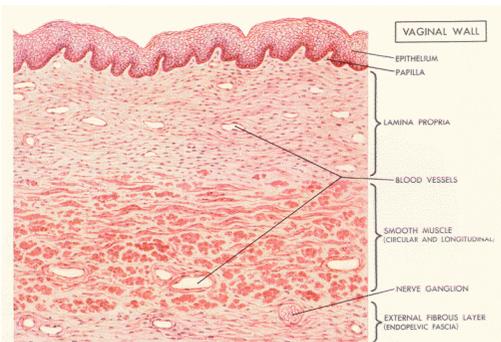
VANTAGGI

Gli ormoni vengono assorbiti rapidamente

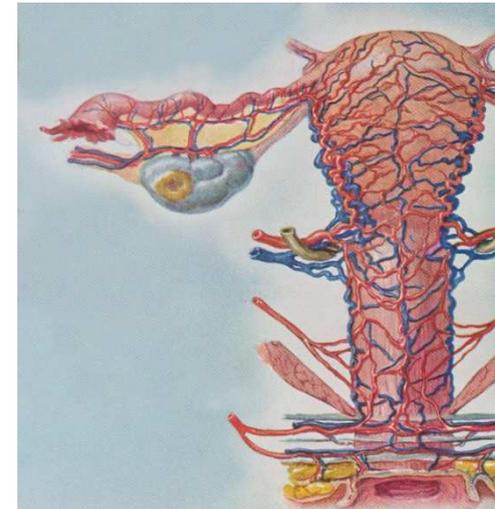
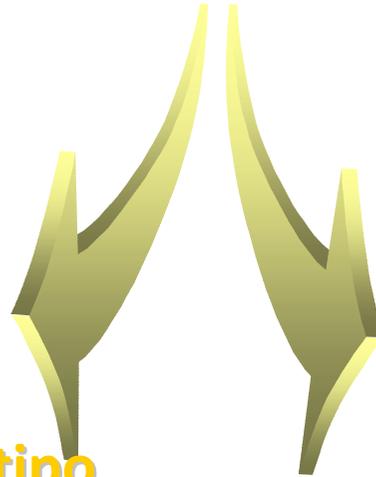
Grazie alle

CARATTERISTICHE ANATOMO-FISIOLOGICHE DELLA VAGINA

Organo facilmente distensibile



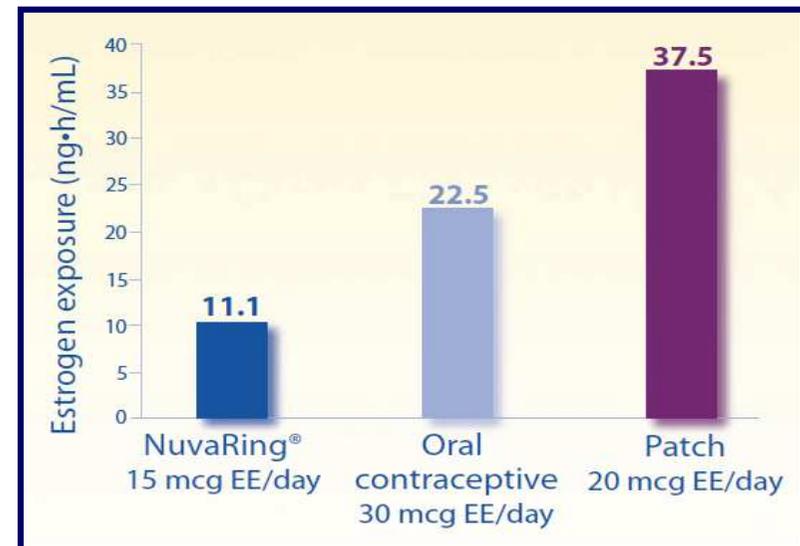
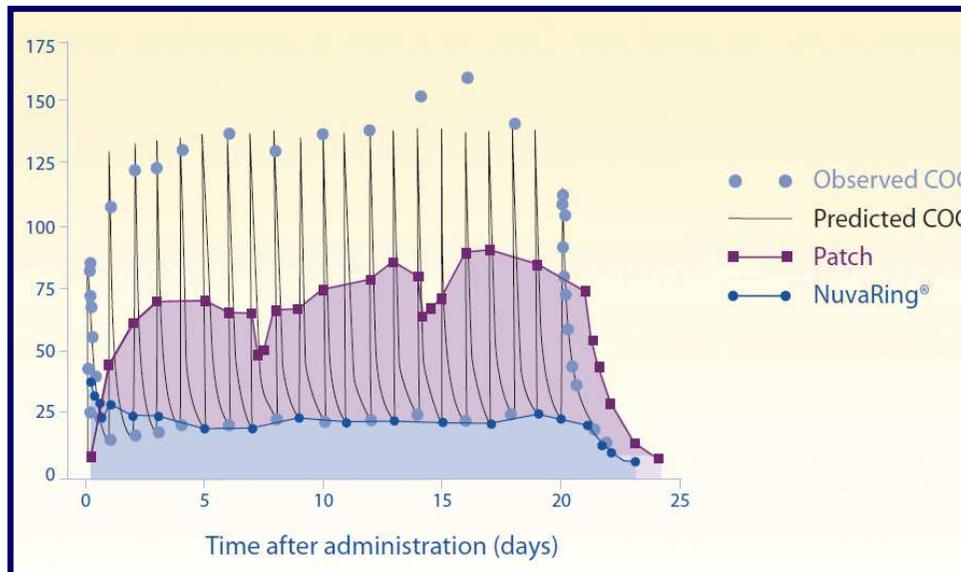
Epitelio di rivestimento di tipo mucoso facilmente permeabile



Ricca vascolarizzazione

La somministrazione vaginale e il costante rilascio ormonale evita le fluttuazioni associate con la somministrazione giornaliera

NuvaRing rilascia quantità minori e meno variabili di EE rispetto alla pillola e il cerotto



l'esposizione sistemica di EE per il Nuvaring era **3.4 volte minore** rispetto al gruppo cerotto ($P < 0.05$) e **2.1 volte minore** rispetto al gruppo pillola ($P < 0.05$)

- **Migliore controllo del ciclo** (Milsom et al., 2006)
- **Meno effetti collaterali estrogeno-dipendenti** (Lopez 2010; Cochrane)

Vaginal Hormonal Ring vs Transdermal Contraceptive Patch

- Come con tutti i farmaci, l'adesione al regime previsto è essenziale per il successo del trattamento per endometriosi sintomatica.
- Nonostante l'efficacia potenzialmente elevata dei COC, l'efficacia in uso tipico è bassa → assunzione quotidiana della pillola

Comparison of contraceptive ring and patch for the treatment of symptomatic endometriosis

*Paolo Vercellini, M.D.,^a Giussy Barbara, M.D.,^a Edgardo Somigliana, M.D., Ph.D.,^b
Stefano Bianchi, M.D.,^c Annalisa Abbiati, M.D.,^a and Luigi Fedele, M.D.^a*

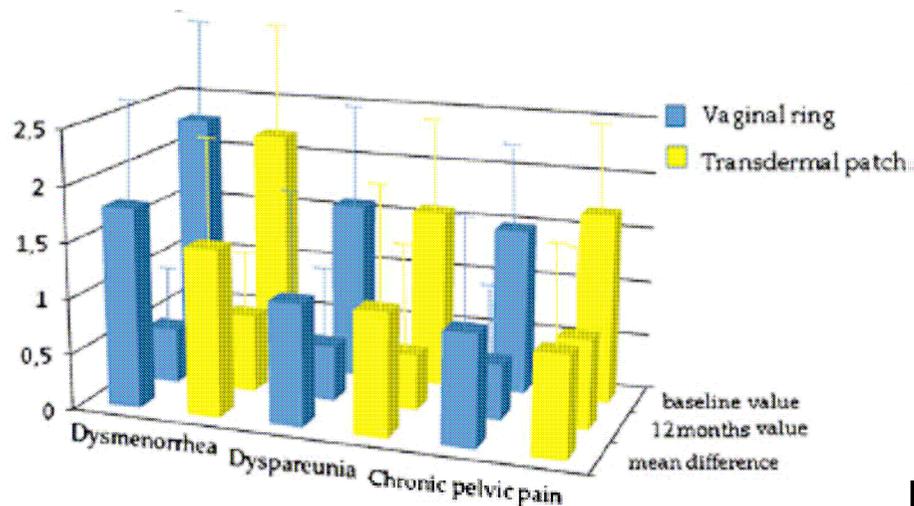
Studio di coorte. Comparare l'efficacia e la tollerabilità dell'anello vaginale vs il cerotto transdermico nella gestione del dolore pelvico ricorrente dopo chirurgia conservativa per endometriosi

207 donne con ricorrente, moderato o grave dolore pelvico dopo chirurgia conservativa per endometriosi.

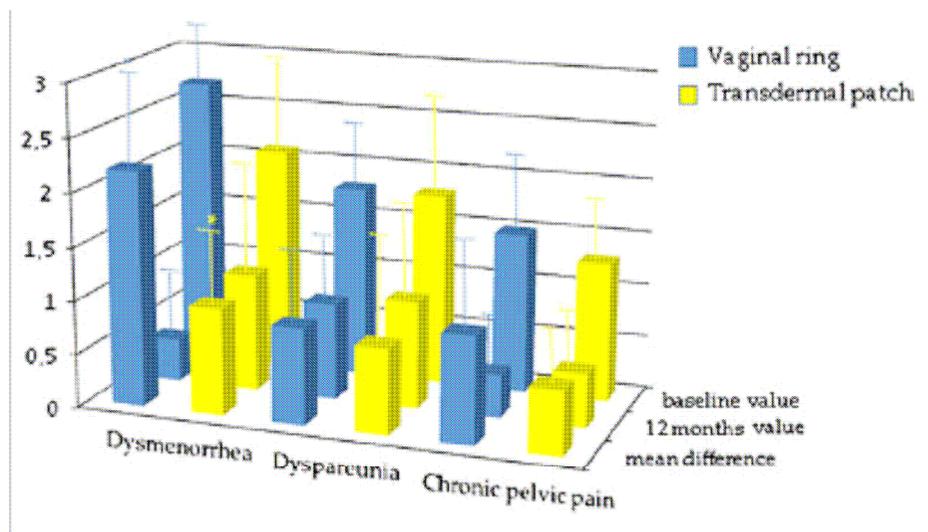
Trattamento continuo - 12 mesi - con anello vaginale o cerotto transdermico

Vaginal Hormonal Ring

senza endometriosi rettovaginale



con endometriosi rettovaginale



I sintomi dolorosi sono stati ridotti da entrambi i trattamenti, l'anello è più efficace rispetto al cerotto in pazienti con lesioni retto-vaginali.

Il 72% delle utilizzatrici dell'anello vaginale e il 48% delle utilizzatrici del cerotto erano soddisfatte del trattamento ricevuto.

Vaginal Hormonal Ring - Continuous Hormonal Treatment

- 4 gruppi, 1 anno di follow-up
 - A : 1 anello per 3 settimane + 1 settimana d'intervallo (N = 108)
 - B : 2 anelli consecutivi per 6 settimane + intervallo (N = 107)
 - C : 4 anelli consecutivi per 12 settimane + intervallo (N = 105)
 - D : 17 anelli consecutivi per 51 settimane + intervallo (N = 109)
- **Giorni totali di sanguinamento minori col regime continuativo**
- **Giorni totali di bleeding e spotting simili in tutti i regimi**
- **Sanguinamento irregolare migliore rispetto all'uso continuativo dei COC**
- **Efficacia nel range atteso**

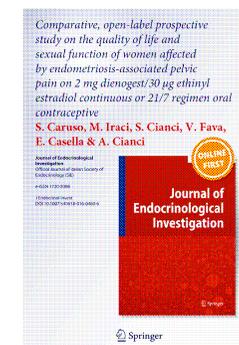
Miller et al., 2005



ORIGINAL ARTICLE

Comparative, open-label prospective study on the quality of life and sexual function of women affected by endometriosis-associated pelvic pain on 2 mg dienogest/30 µg ethinyl estradiol continuous or 21/7 regimen oral contraceptive

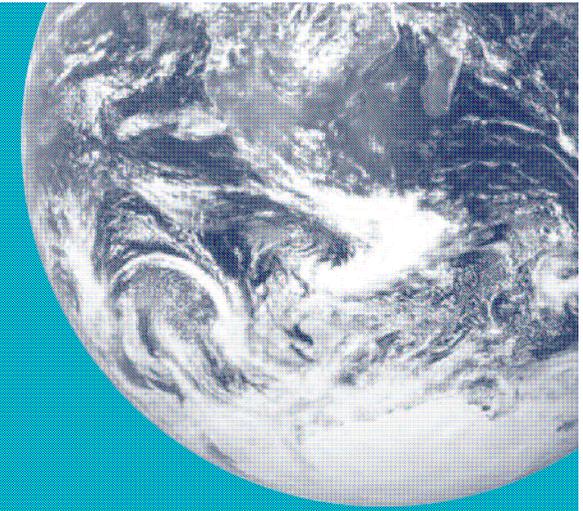
S. Caruso^{1,2} · M. Iraci¹ · S. Cianci¹ · V. Fava^{1,2} · E. Casella¹ · A. Cianci^{1,2}



Conclusions

Women on DNG/EE COC continuous regimen reported a reduction of endometriosis-associated pelvic pain and there was an improvement of their sexual activity and their QoL that was better than the DNG/EE 21/7 conventional regimen.

2016



IF THE AIM IS OVARIAN
CANCER PREVENTION
AND ESTROGEN MEDIATED
BENEFITS, NOT ONLY ENDOMETRIOSIS
SUPPRESSION, ARE CONTRACEPTIVES
WITH ETHINILESTRADIOL BETTER
THAN PROGESTOGENS ALONE?

L. DEL PUP

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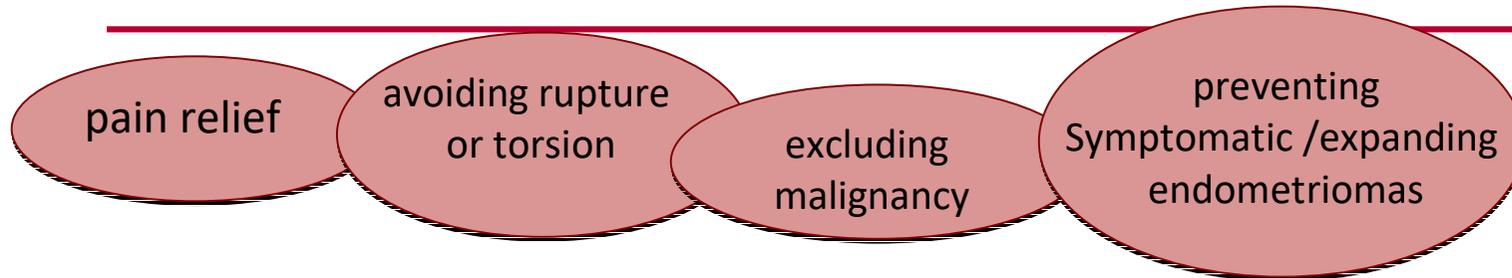
Gynecological Oncology, National Cancer Institute, Aviano (PN), Italy

Conclusions :

When the aim of the treatment is ovarian cancer prevention and estrogen mediated benefits, like contraception and non contraceptive OCs benefits, the EE plus DNG pill seems better than DNG alone or at least not contraindicated in endometriosis patients.

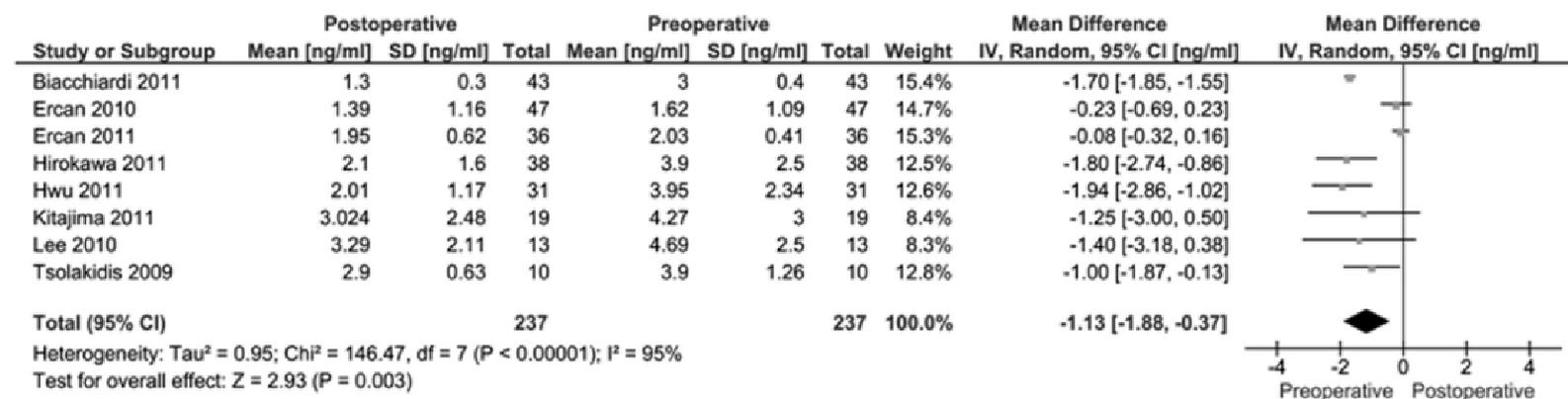
2014

Treatment Goals for Endometriomas



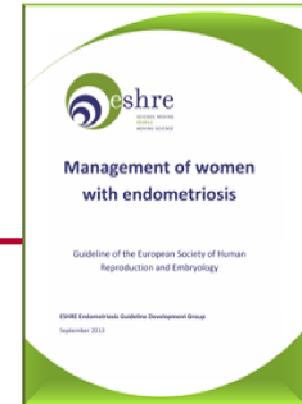
IMPACT ON OVARIAN RESERVE

serum anti-Mullerian hormone (AMH)



The results of this study suggest a negative impact of excision of endometriomas on ovarian reserve as evidenced by a significant postoperative fall in circulating AMH.

IS THERE A ROLE FOR SECONDARY PREVENTION OF DISEASE AND PAINFUL SYMPTOMS IN WOMEN TREATED FOR ENDOMETRIOSIS?



After cystectomy for ovarian endometrioma in women not immediately seeking conception, clinicians are recommended to prescribe hormonal contraceptives for the secondary prevention of endometrioma (Vercellini, et al., 2010).

A

Human Reproduction, Vol.29, No.3 pp. 400–412, 2014

COC nelle pazienti con Endometriosi

- I COC sono ampiamente usati in maniera off label per ridurre il dolore associato ad endometriosi
- Ci sono 3 problemi circa il loro uso :
 - La componente estrogenica dei COC può stimolare progressione della patologia
 - Assenza di robuste evidenze a supporto del uso di COC nell' endometriosi
 - Nessun consenso sui benefici dei COC per l'endometriosi

Assenza di robuste evidenze a supporto del uso di COC nell' endometriosi

- Limitati dati sull' efficacia e la sicurezza a lungo termine
- Solo uno studio, placebo controllato, sull' utilizzo dei COC per il dolore in pazienti con endometriosi ¹
 - 100 donne randomizzate con una bassa dose di COC o placebo per 4 cicli
 - Significativo sollievo dalla dismenorrea con COC rispetto al placebo
 - Nessuna differenza nel dolore pelvico non mestruale

1. Harada T et al, Fertil Steril, 2008;90(5):1583-8;.

Assenza di robuste evidenze a supporto del uso di COC nell' endometriosi

- Nessun consenso riguardo a protective role of COCs against the development of endometriosis:
 - A retrospective non-controlled trial¹
 - 70 women with confirmed endometriosis and chronic pelvic pain
 - 22 patients treated with COCs had some or complete improvement in pain after 3 months
 - 36 had no improvement with COCs after 3 months

75 % of COC users with histologically confirmed endometriosis at laparoscopy did not respond to hormonal therapy within 3 months prior to laparoscopy

¹ Jenkins TR et al, J Minim Invasive Gynecol, 2008

Nessun consenso sui benefici dei COC per l'endometriosi

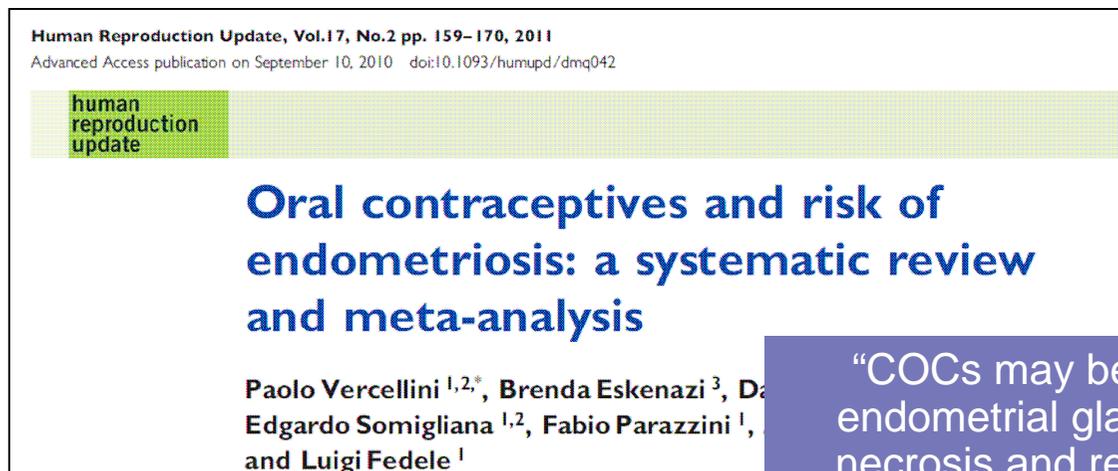
- I potenziali benefici dei COC per il dolore pelvico cronico dopo chirurgia conservativa non sono chiari ¹
 - Non tutti i tipi di dolore rispondono ugualmente ai COC
 - Nessun effetto sulla dispareunia
 - Non vi è accordo sugli effetti post operativi dei COC sul dolore pelvico cronico

● I potenziali vantaggi dei COC somministrati in maniera ciclica o continua è ancora dibattuta ^{2,3}

1. Seracchioli R, Mabrouk M, Manuzzi L et al. *Hum Reprod* 2009.
2. Ferrero S, et al. *Expert Opin Pharmacother* 2010;
3. Kappou D, et al. *Minerva Ginecol* 2010

Gli Estrogeni dei COCs possono stimolare la progressione della malattia

- ~~Endometriosi è una - patologia estrogeno-dipendente -~~
- COC riducono la - **componente estrogenica endogena** - ma si sa poco sull' impatto della - **componente estrogenica esogena** - somministrata sulla malattia.
- Ciò può portare a stimolare la malattia o mascherare lo sviluppo ²



“COCs may be a ‘rescue factor’ for regurgitated endometrial glands that would otherwise undergo necrosis and resorption during the physiologically hypoestrogenic menstrual milieu”

Vercellini P, et al. Hum Reprod Update 2011

1. Kappou D, Matalliotakis M, Matalliotakis I. *Minerva Ginecol* 2010.
2. Crosignani P, Olive D, Bergqvist A et al. *Hum Reprod Update* 2006

Gli estrogeni potrebbero aumentare il rischio di endometriosi infiltrante profonda



Human Reproduction, Vol.26, No.8 pp. 2028–2035, 2011

Advanced Access publication on June 4, 2011 doi:10.1093/humrep/der156

human
reproduction

ORIGINAL ARTICLE *Gynaecology*

Oral contraceptives and endometriosis: the past use of oral contraceptives for treating severe primary dysmenorrhea is associated with endometriosis, especially deep infiltrating endometriosis

Charles Chapron^{1,2,3,*}, Carlos Souza^{1,4}, Bruno Borghese^{1,2,3}, Marie-Christine Lafay-Pillet¹, Pietro Santulli^{1,2,3,5}, Gérard Bijaoui¹, François Goffinet⁶, and Dominique de Ziegler¹

Chapron C *et al*, *Hum Reprod*, 2011.

Cochrane Review: "OCs for pain associated with endometriosis"

Modern combined oral contraceptives for pain associated with endometriosis (Review)

Davis L, Kennedy SS, Moore J, Prentice A



THE COCHRANE
COLLABORATION®

- Solo **uno studio** incontra i criteri di inclusione, in quanto sono state incluse 57 **donne**

References to studies included in this review

Vercellini 1993 *[published data only]*

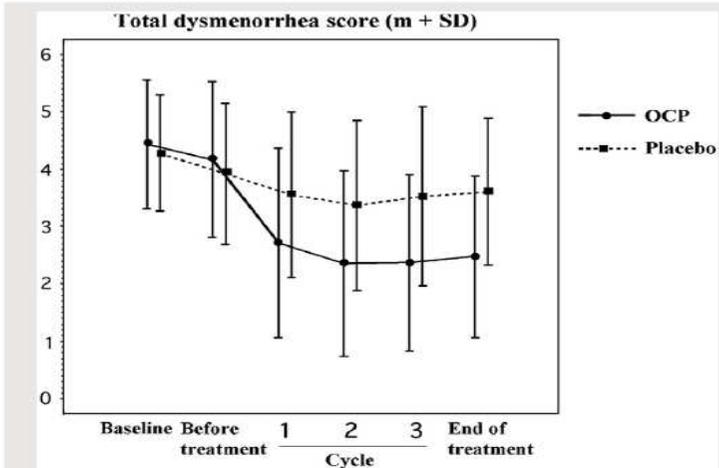
Vercellini P, Trespidi L, Colombo A, Vendola N, Marchini M, Crosignani PG. A gonadotrophin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. *Fertility and Sterility* 1993;**60**(1):75-9.

- **campione**, **0** senza il confronto diretto contro un farmaco già attivo
- **onde**
- Ulteriori analisi sono necessarie per valutare completamente il ruolo degli OC nel trattamento dei sintomi dell' endometriosi

Davis LJ, Kennedy SS, Moore J, Prentice A. Oral contraceptives for pain associated with endometriosis. *Cochrane Database of Systematic Reviews* 2007, Issue 3.

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

FIGURE 1



Changes in mean dysmenorrhea score determined by linear analogue scale comparing an oral contraceptive pill (OCP) with placebo. Source: Harada et al. 2008 (8). Copyright Elsevier, and the American Society for Reproductive Medicine.

Casper. Progestin-only pills for endometriosis. *Fertil Steril* 2017.

TABLE 1

Number of different oral contraceptive pills (OCPs) used for relief of symptoms in 441 women with diagnosed endometriosis globally and broken down by country.

No. of OCPs tried	Global (n = 441)	United States (n = 110)	Canada (n = 53)	Italy (n = 60)	France (n = 25)	Germany (n = 32)	United Kingdom (n = 48)	Brazil (n = 76)	South Korea (n = 7)
1	28	28	34	40	52	32	25	20	46
2	28	23	22	35	36	15	36	33	29
3-5	28	29	28	16	8	41	31	27	24
6-10	15	15	16	8	4	13	6	20	0
>10	2	3	0	0	0	0	2	0	0

Note: Values are percentages unless otherwise indicated.
Source: Bemuit et al. 2011 (10). With permission from Bayer Global; data on file.

Casper. Progestin-only pills for endometriosis. *Fertil Steril* 2017.

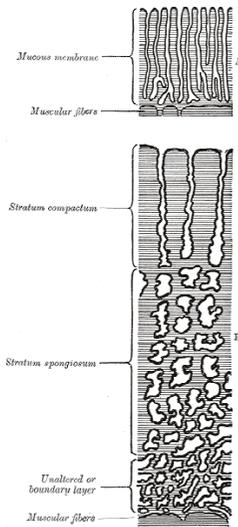
COC nei pazienti con endometriosi

- Conclusioni

- La componente estrogenica dei COCs può essere controproducente in una patologia estrogeno dipendente come l' endometriosi
- Mancanza di una robusta evidenza sull' utilizzo dei COC nell' endometriosi
- Nessun beneficio da parte dei COCs per il dolore non mestruale associato ad endometriosi
- Se l' endometriosi è sospettata, COC potrebbero non essere il trattamento migliore
- Vi sono altri trattamenti medici con maggiori evidenze

Progestins

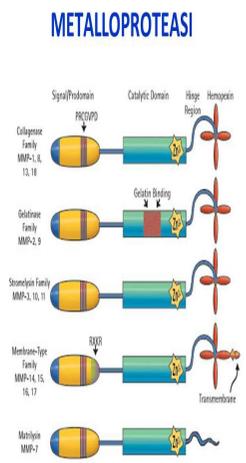
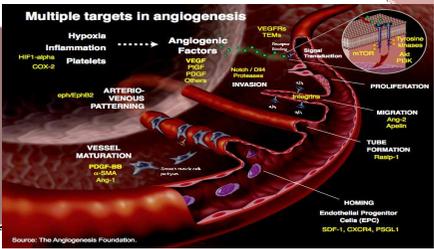
next line of treatment for patients with endometriosis-associated pain who cannot take (due to contraindications or side effects) or fail combined hormonal contraceptives.

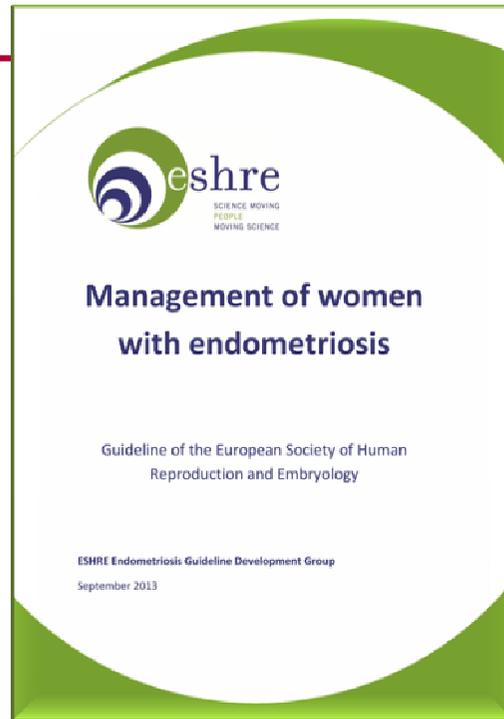


inhibit the growth of endometriotic tissue by inducing **decidualization** followed by **atrophy** of the endometriotic implants.

suppression of **matrix metallo proteinases-mediated growth** and implantation of ectopic endometrium

inhibition of **angiogenesis**





Human Reproduction, Vol.29, No.3 pp. 400–412, 2014

Recommendations



Clinicians are recommended to use progestagens [medroxyprogesterone acetate (oral or depot), dienogest, cyproterone acetate, norethisterone acetate or danazol] or anti-progestagens (gestrinone) as one of the options, to reduce endometriosis-associated pain (Brown, et al., 2012).

A

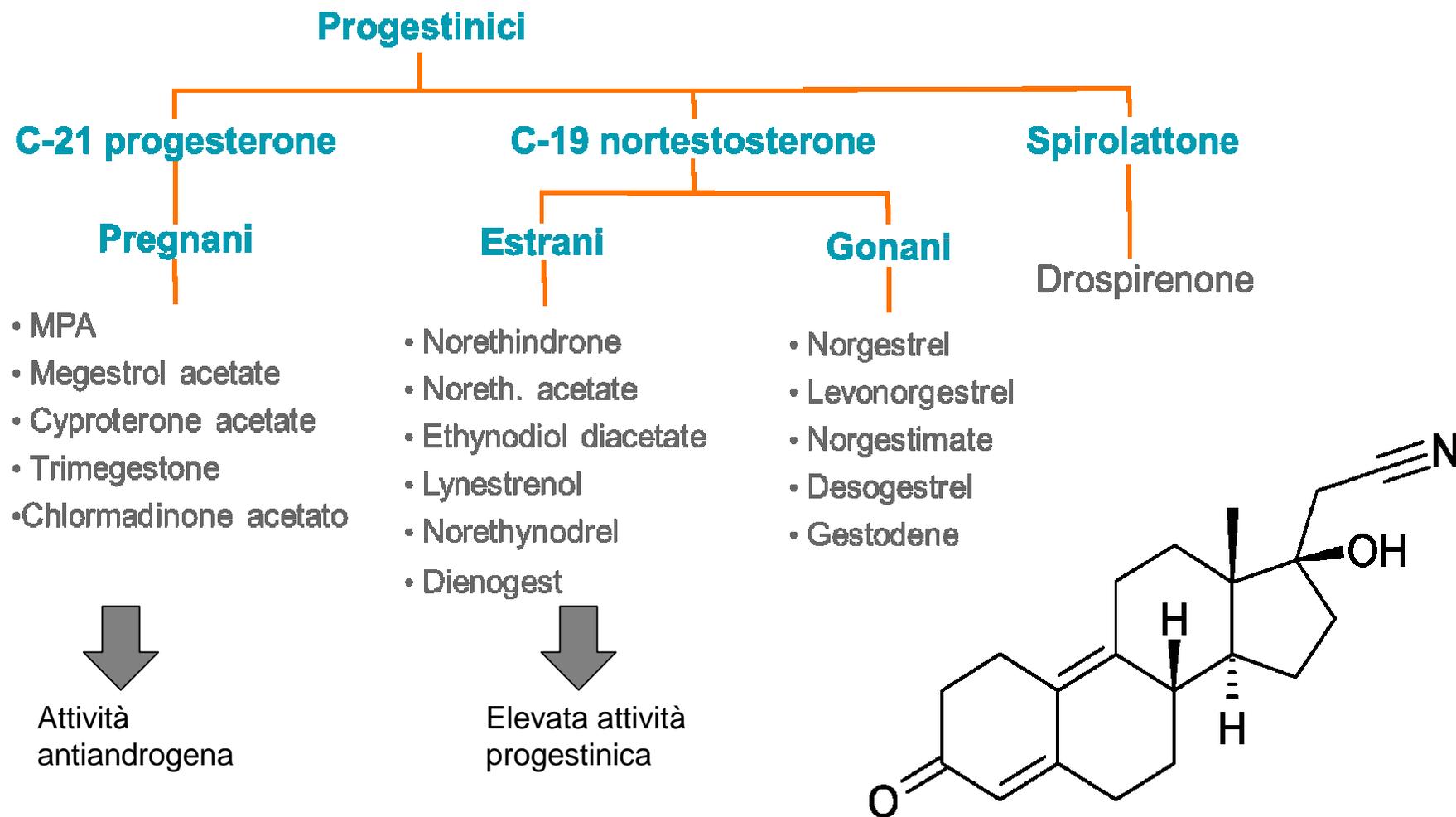
The GDG recommends that clinicians take the different side-effect profiles of progestagens and anti-progestagens into account when prescribing these drugs, especially irreversible side effects (e.g. thrombosis, androgenic side effects).

GPP

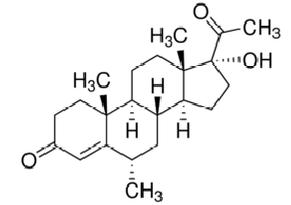
Clinicians can consider prescribing a levonorgestrel-releasing intrauterine system as one of the options to reduce endometriosis-associated pain (Ferreira, et al., 2010, Gomes, et al., 2007, Petta, et al., 2005).

B

Classificazione progestinici

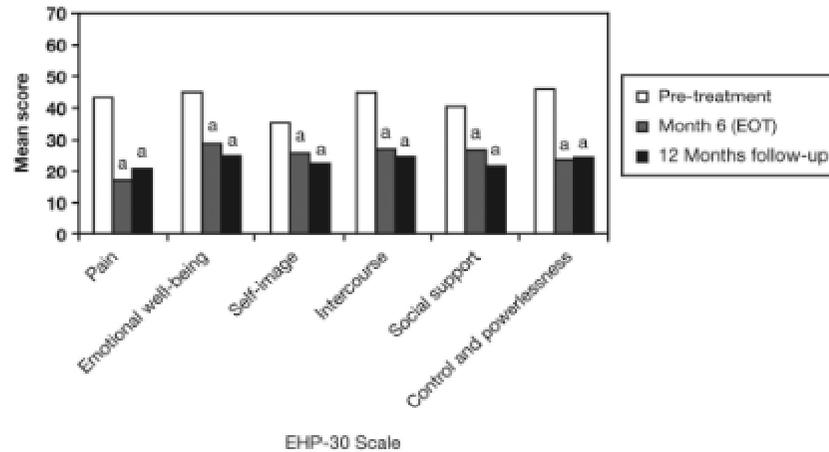


Medroxyprogesterone and Depot MPA

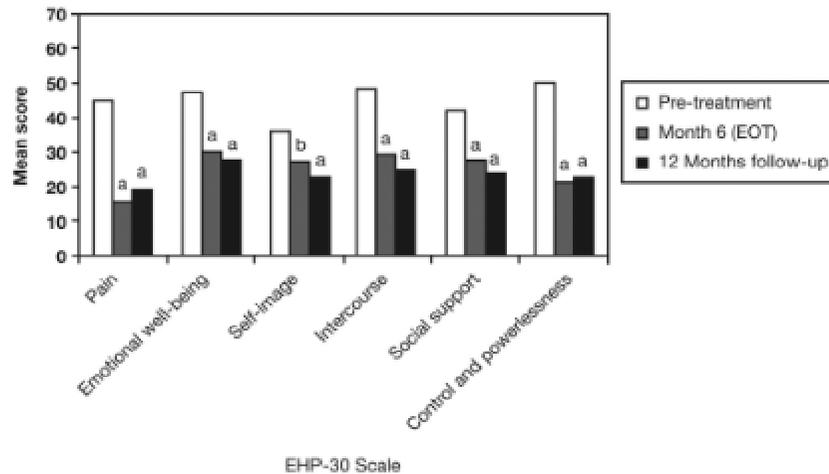


Crosignani PG et al., Hum Reprod 2006;

(A) DMPA-SC 104 group



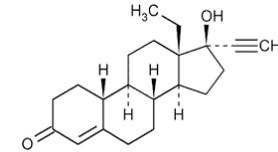
(B) Leuprolide group



MPA up to 100 mg orally per day, or depot MPA 150 mg IM every 3 months, can induce amenorrhea.

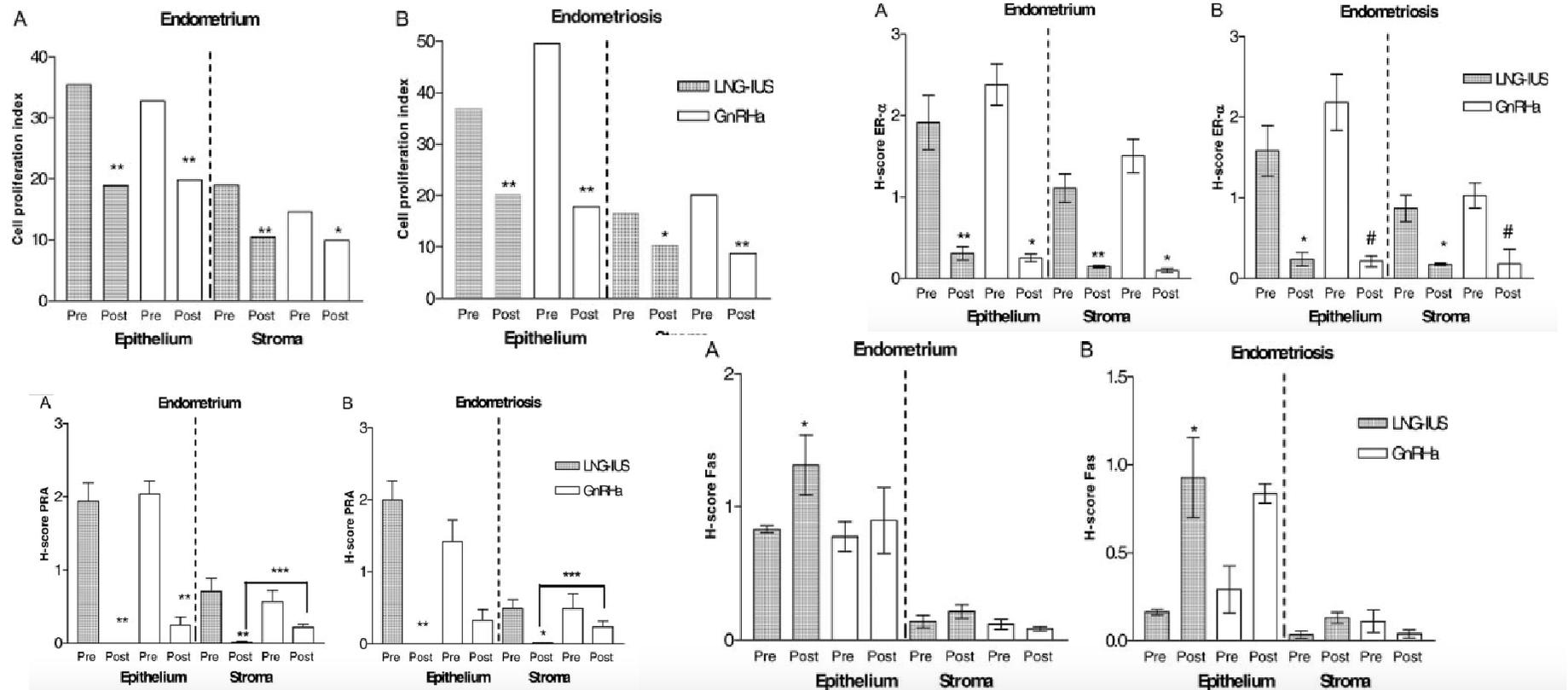
Statistically equivalent to GnRHa ($P < 0.02$) reductions of all five signs and symptoms of endometriosis (dysmenorrhoea, dyspareunia, pelvic pain, pelvic tenderness and induration) compared with leuprolide treatment

Levonorgestrel-Releasing Intrauterine System

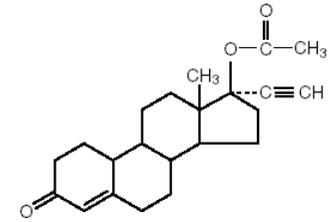


Gomes MK et al., Hum Reprod 2009

LNG-IUS **reduced** both cell proliferation and the expression of PRA and ER- α and increased **Fas expression in the eutopic and ectopic endometrium** of patients with endometriosis. Some of these actions were not observed with GnRHa.



netisterone Acetato



90 consecutive endometriosis patients

Vercellini et al. Fertil Steril 2016

Satisfied plus very satisfied women after 6 months of treatment was 71%
(Dienogest 72%)

Tolerated in 58% of patients
(Dienogest 80%)

The starting dose is 2,5 mg and could be increased to 15 mg

NETA effective as dienogest (DNG) for pain relief, psychological status, sexual functioning, and health-related quality of life, although less expensive

DANAZOLO (17 α -etinil testosterone)

Conosciuto fin dal 1970 per le proprietà androgeniche e soppressive la funzione ovarica in virtù delle quali trovò un primo utilizzo nella terapia dell'endometriosi.

Per molto tempo il danazolo è stato usato per il trattamento della endometriosi; attualmente eventualmente, si preferisce ricorrere ai farmaci agonisti del GnRH per i minori effetti collaterali. Il danazolo trova impiego nel trattamento della mastopatia fibrocistica, nella menorragia,[†] nella mastodinia associata al ciclo mestruale, nella porpora idiopatica trombocitopenica,

200-600 mg/die

MECCANISMO D'AZIONE: inibisce il picco di LH di meta' ciclo

induce anovulazione cronica

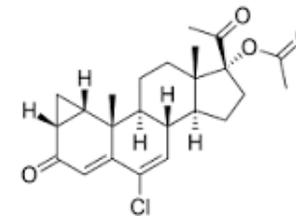
Aumenta testosterone libero in circolo

EFFETTI SECONDARI: Aumento di peso

Ritenzione idrica, acne, irsutismo, aumento COL Totale e LDL, aumento di adenomi epatici e carcinoma ovarico

Cyproterone Acetate

Vercellini P et al., Fertil Steril 2002

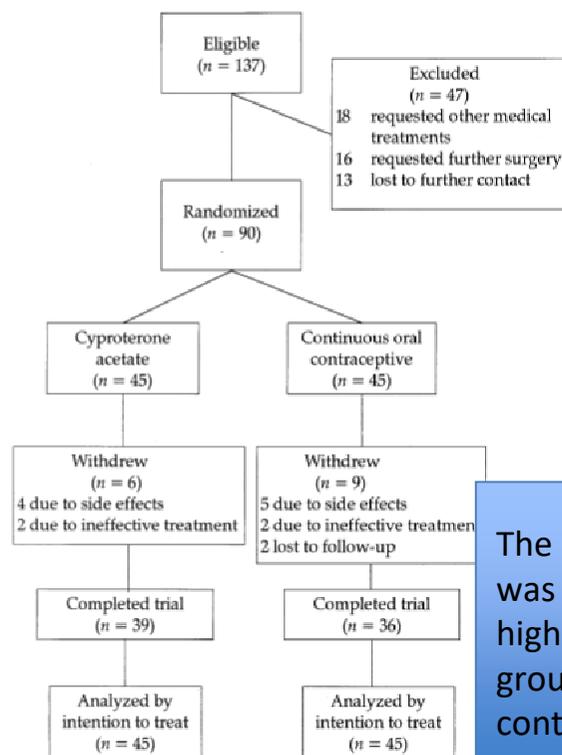


synthetic oral progestin with anti-androgenic activity mediated by a competitive inhibition on the androgen receptor.

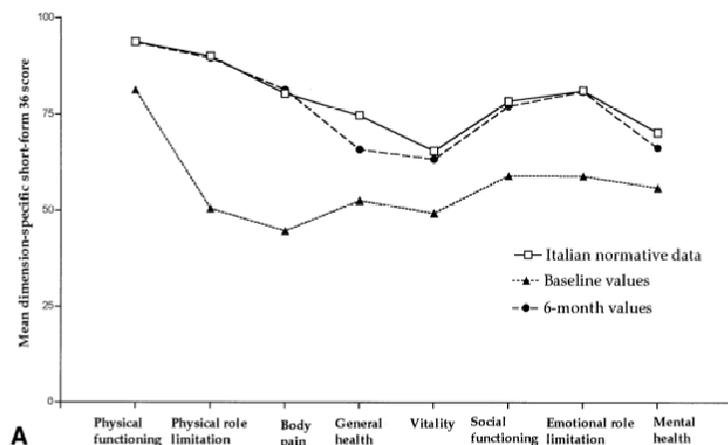
combined with ethiny-loestradiol

FIGURE 1

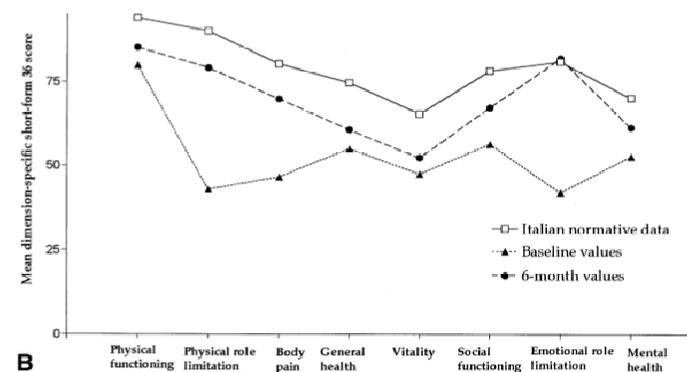
Trial profile.



Short Form-36 general health survey profile of dimension-specific scores in patients with endometriosis-associated pain before and at 6-month treatment, compared with 1032 healthy Italian women 25 to 34 years of age. (A), Cyproterone acetate group (n = 39). (B), Oral contraceptive group (n = 36).

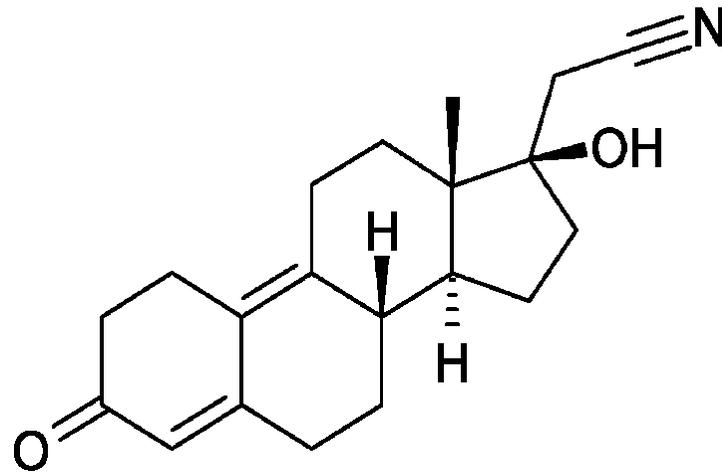


The proportion of satisfied women was slightly and non-significantly higher in the cyproterone acetate group than in the oral contraceptive group.

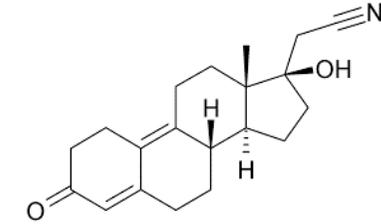


Dienogest

- Progestinico approvato di recente (2013) per il trattamento dell'endometriosi: Dienogest 2mg, 1 compressa al giorno x 28 giorni in continuo (senza pause)



Dienogest



Vercellini et al. Fertil Steril 2016

compared with prior use of NETA 2.5 mg, DNG 2 mg produced comparable ameliorations in overall pain relief, psychological status, sexual functioning, or health-related quality of life.

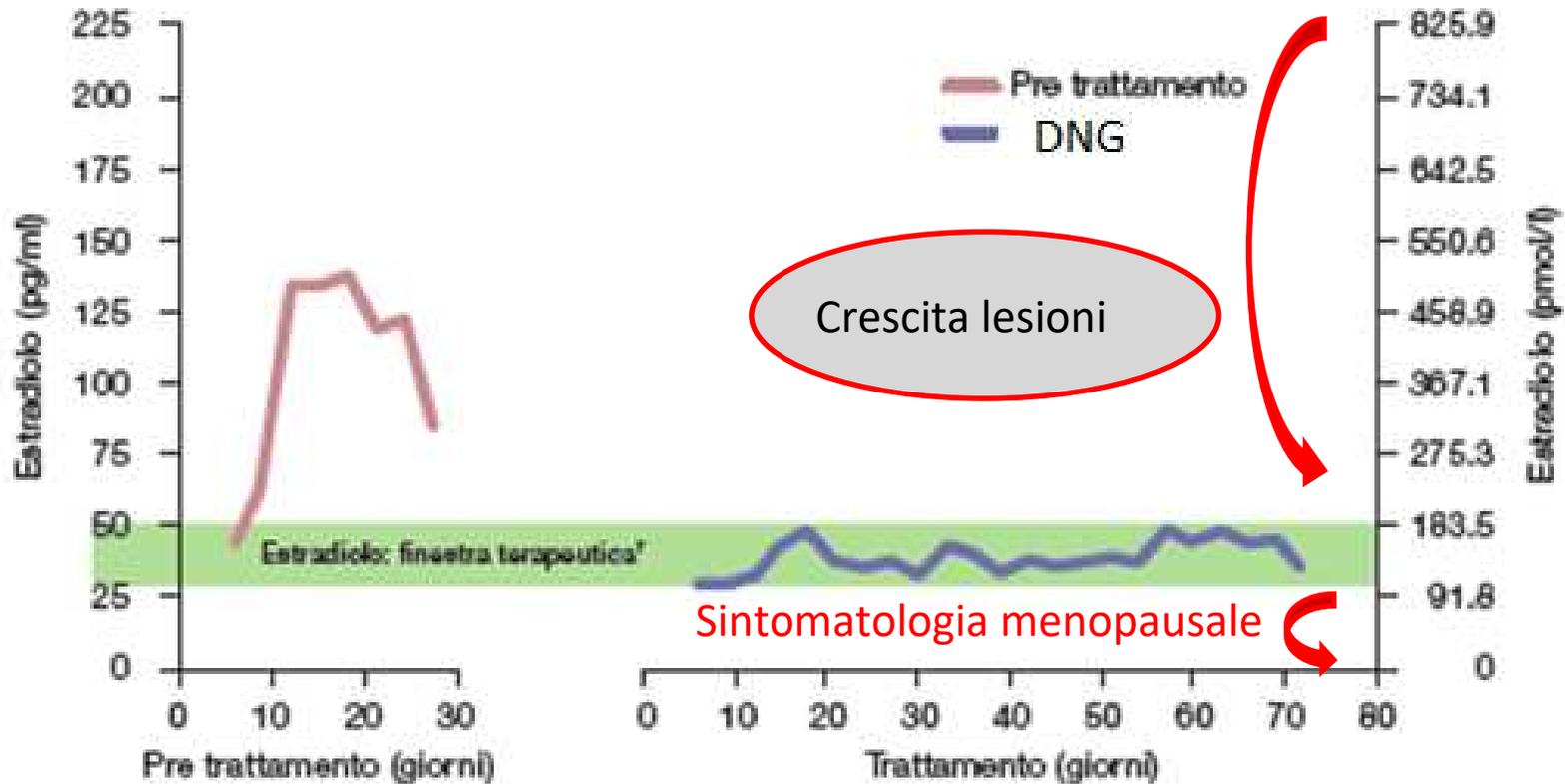
2-mg oral pill taken daily

References	Patients	Intervention	Length of treatment (weeks)	Primary outcome
Cosson [20]	120	DNG 2 mg/day after surgical laparoscopy Triptorelin 3.75 mg intramuscular every 28 days	16	rASRM
Harada [13]	262	DNG 2 mg/day Intranasal buserelin acetate 900 µg/day	24	VAS
Strowitzki [21, 22]	229	DNG 2 mg/day Leuprolide acetate 3.75 mg/month	24	VAS
Momoeda [19]	187	DNG 1, 2 e 4 mg/day	24	VAS
Köhler [12]	68	DNG 1, 2 e 4 mg/day	24	rASRM
Strowitzki [18]	144	DNG 2 mg/day Placebo	12	VAS
Momoeda [24]	114	DNG 2 mg/day	52	VAS
Petraglia [23]	152	DNG 2 mg/day	36–52	VAS

DNG was better tolerated. Higher cost compared with NETA, the authors proposed that DNG should be used in women who do not tolerate NETA.

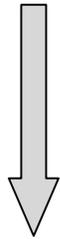
CON IL DIENOGEST 2mg die, I LIVELLI DI ESTRADIOLO RIMANGONO ENTRO LA FINESTRA TERAPEUTICA PER RIDURRE I SINTOMI DELL' ENDOMETRIOSI

Finestra terapeutica ideale



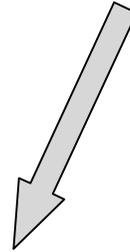
Dienogest: Diversi meccanismi d'azione

**EFFETTO
CENTRALE**



**Inibizione della
secrezione di
gonadotropine**

**EFFETTI
LOCALI**

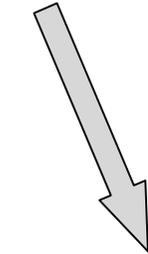


Antiproliferativo

**EFFETTO INIBITORIO DIRETTO DEL
TESSUTO ENDOMETRIALE,
INDIPENDENTE DALL' EFFETTO
CENTRALE SUL RECETTORE
PROGESTINICO**



Antinfiammatorio



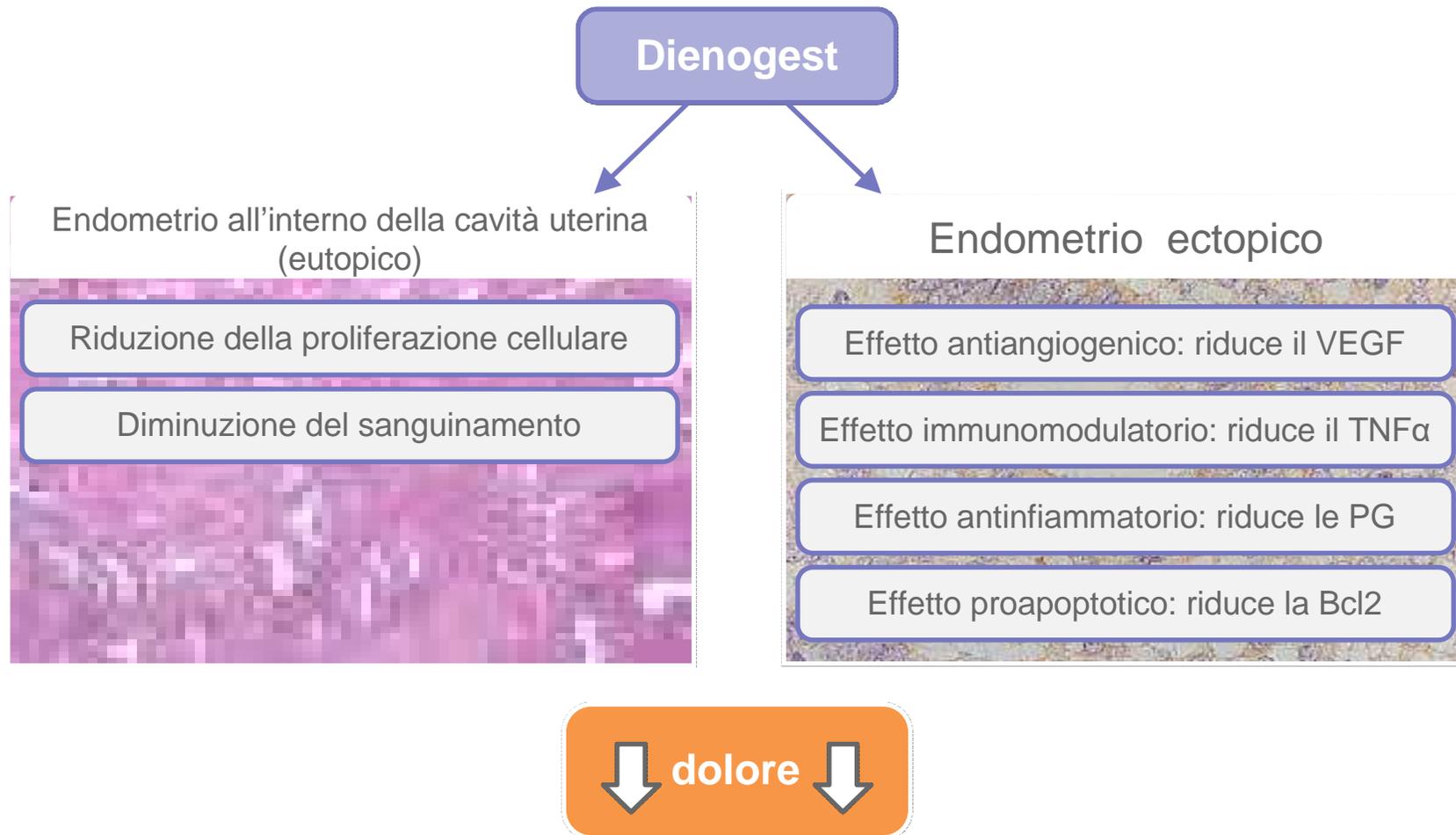
Antiangiogenico

**MODULAZIONE DELLE
METALLOPROTEINASI CHE
REGOLANO LA RISPOSTA
DEL TESSUTO
ENDOMETRIALE AGLI
ESTROGENI A UN LIVELLO
PARACRINO**

1. McCormack PL. *Drugs* 2010
2. Sasagawa S *et al.* *Steroids* 2008
3. Kippling C *et al.* *J Clin Pharmacol* 2011
4. Katsuki Y *et al.* *Eur J Endocrinol* 1998
5. Fischer OM *et al.* *Gynecol Obstet Invest* 2011
6. Shimizu Y *et al.* *Steroids* 2011
7. Horie S *et al.* *Fertil Steril* 2005

8. Mita S *et al.* *Fertil Steril* 2011
9. May K *et al.* *Minerva Ginecol* 2008
10. Katayama H *et al.* *Hum Reprod* 2010
11. Nakamura M *et al.* *Eur J Pharmacol* 1999
12. Sacco K *et al.* *Gynecol Endocrinol* 2012
13. Becker CM *et al.* *Microvasc Res* 2007

Meccanismo d'azione

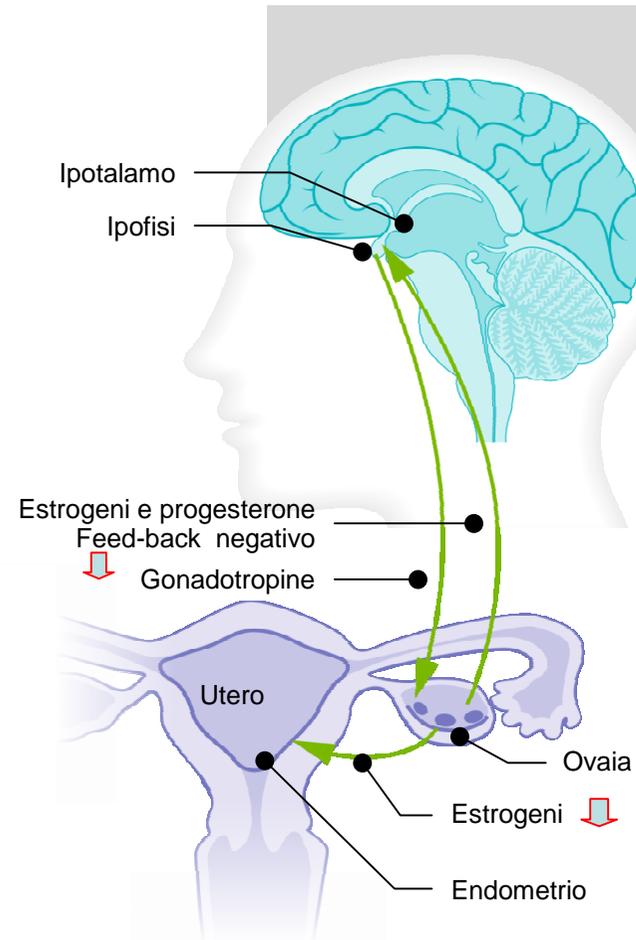


PGs=prostaglandine; TNF=fattore di necrosi tumorale
VEGF=fattore di crescita dell'endotelio vascolare.

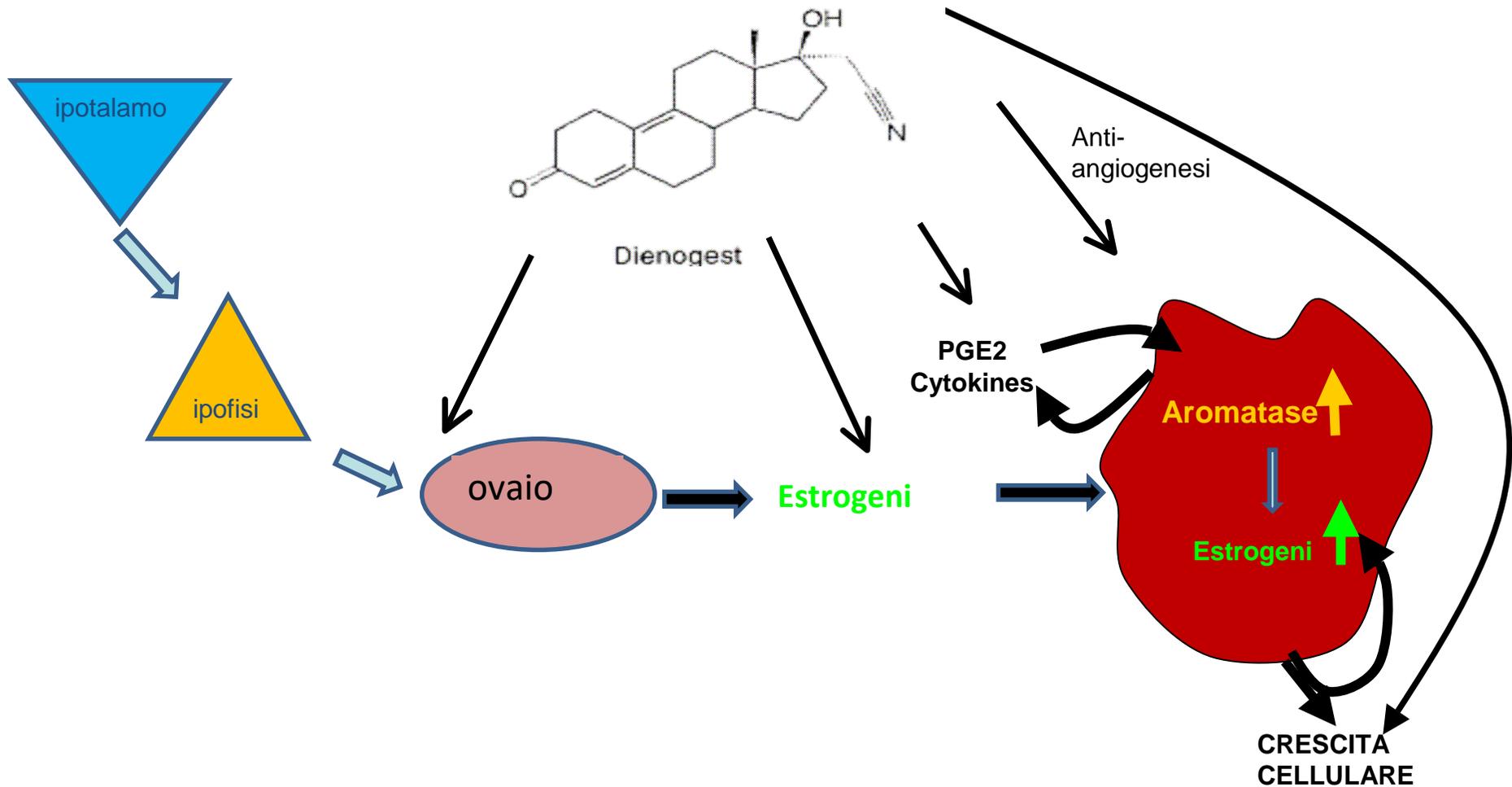
Azione centrale del Dienogest nell' endometriosi

- L' inibizione della secrezione di gonadotropine causa un ambiente iperprogestinico e ipoestrogenico che porta ad una decidualizzazione del tessuto endometriale^{1,2}

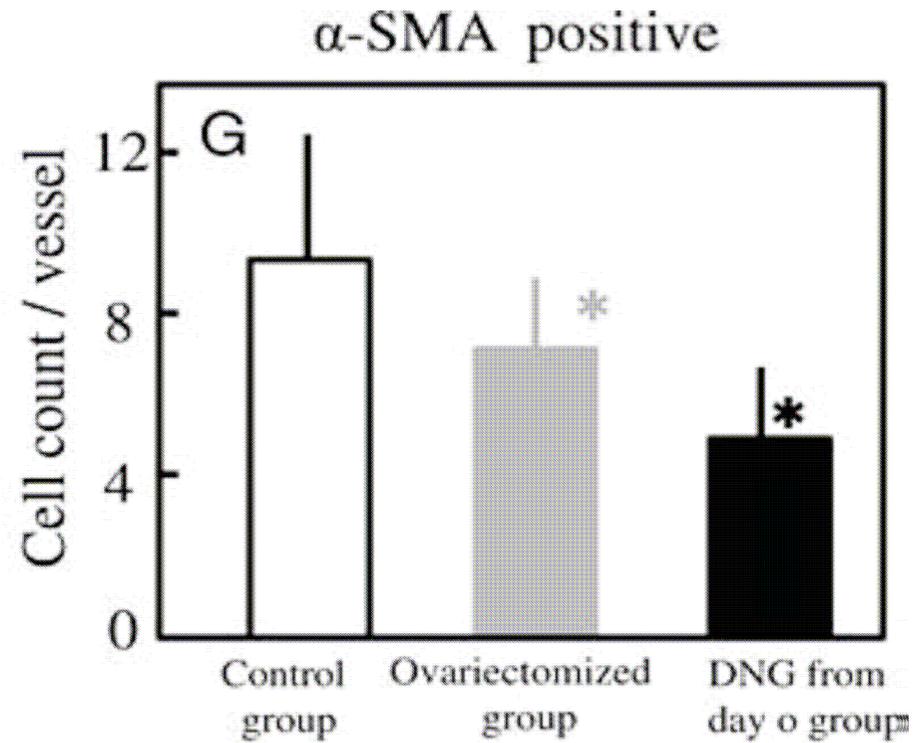
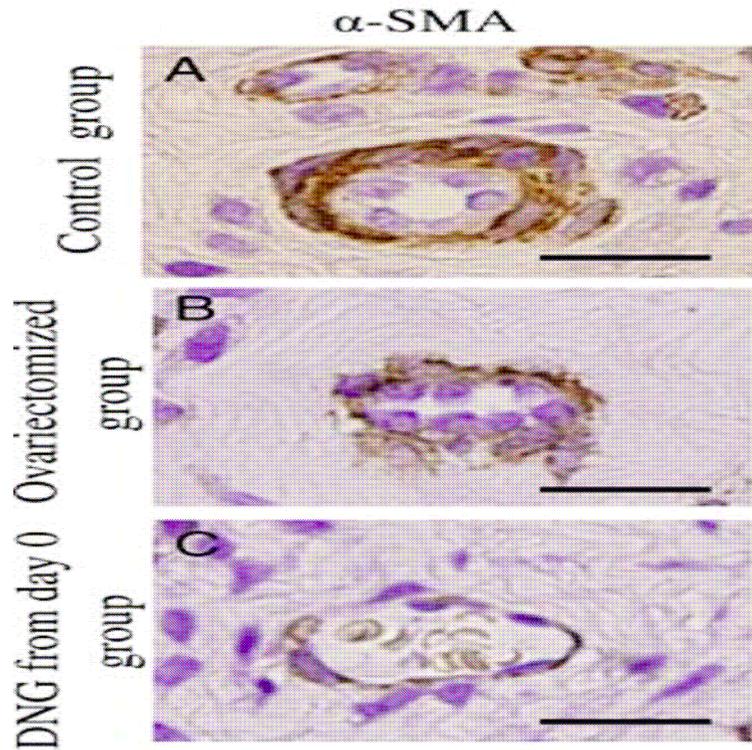
Il Dienogest riduce moderatamente la produzione endogena di E2, sopprimendo gli effetti trofici su endometrio e lesioni endometriose



SITI AZIONE DIENOGEST



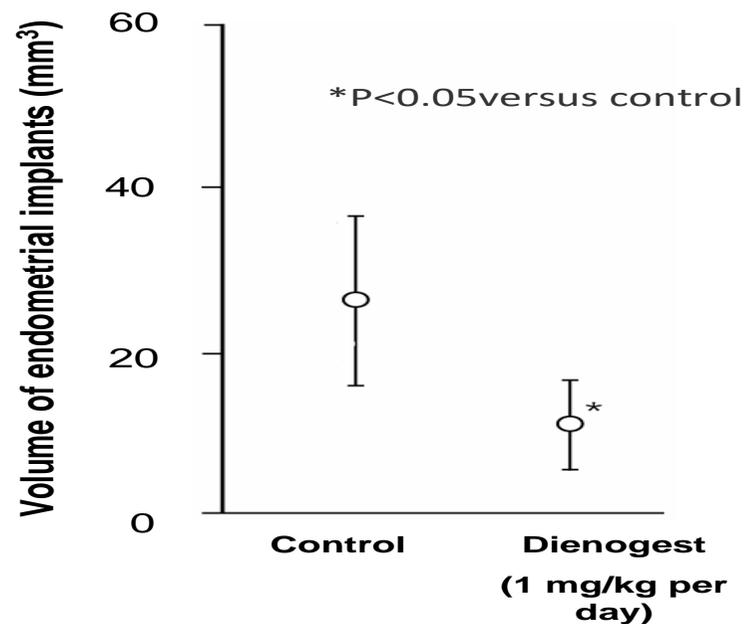
Effetto antiangiogenico



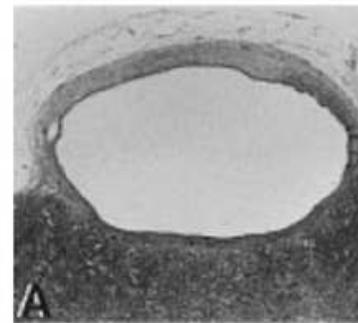
RESULTS: The DNG-administered group showed significant suppression of angiogenesis of endometrial autografts, as indicated by the reduced size of the microvascular network and decreased microvessel density compared with those of control animals

Effetto Anti-proliferativo

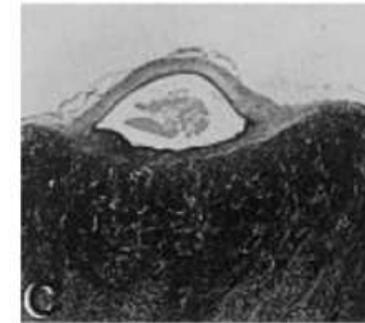
- Endometriosi sperimentalmente ridotta mediante autotrapianto nei ratti
- Seguito da trattamento con dienogest



Riduzione degli impianti (cisti murali) in:



Ratto controllo nella fase di proestro



Ratto a cui si somministra dienogest

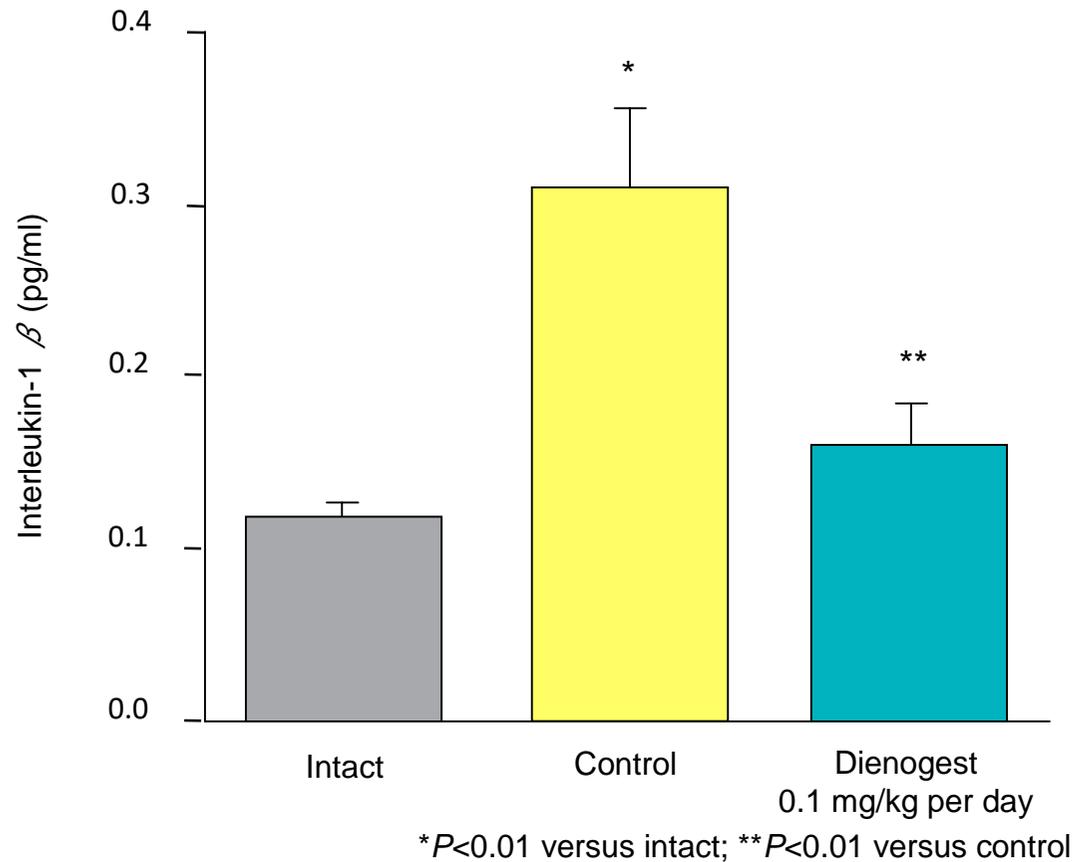
Dienogest riduce il volume degli impianti endometriali ^{1,2}

1. Katsuki Y, et al. *Eur J Endocrinol* 1998;**138**:216–226;

2. Fischer OM, et al. *Gynecol Obstet Invest* 2011;**72**:145–151

Effetto antinfiammatorio

- Endometriosi sperimentale indotta in topi mediante trapianto
- Effetto non presente con buserelina e danazolo



Dienogest in the treatment of endometriosis-associated pelvic pain:
a 12-weeks, randomized, double-blind, placebo-controlled study

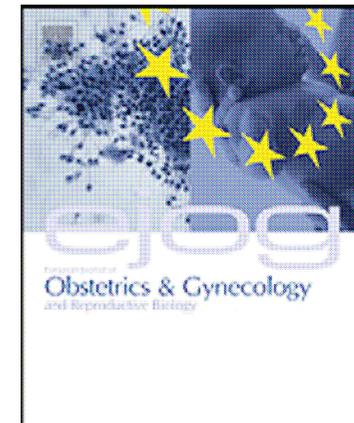
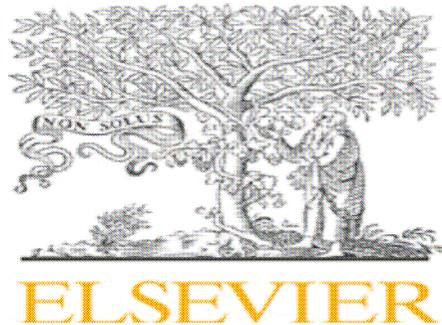
Thomas Strowitzki **a,***, Thomas Faustmann **b**, Christoph Gerlinger **c**, Christian Seitz **d**

a Department of Gynecological Endocrinology and Reproductive Medicine, University of Heidelberg, Vossstrasse 9, 69115 Heidelberg, Germany

b Bayer Schering Pharma AG, Global Medical Affairs Women's Healthcare, Berlin, Germany

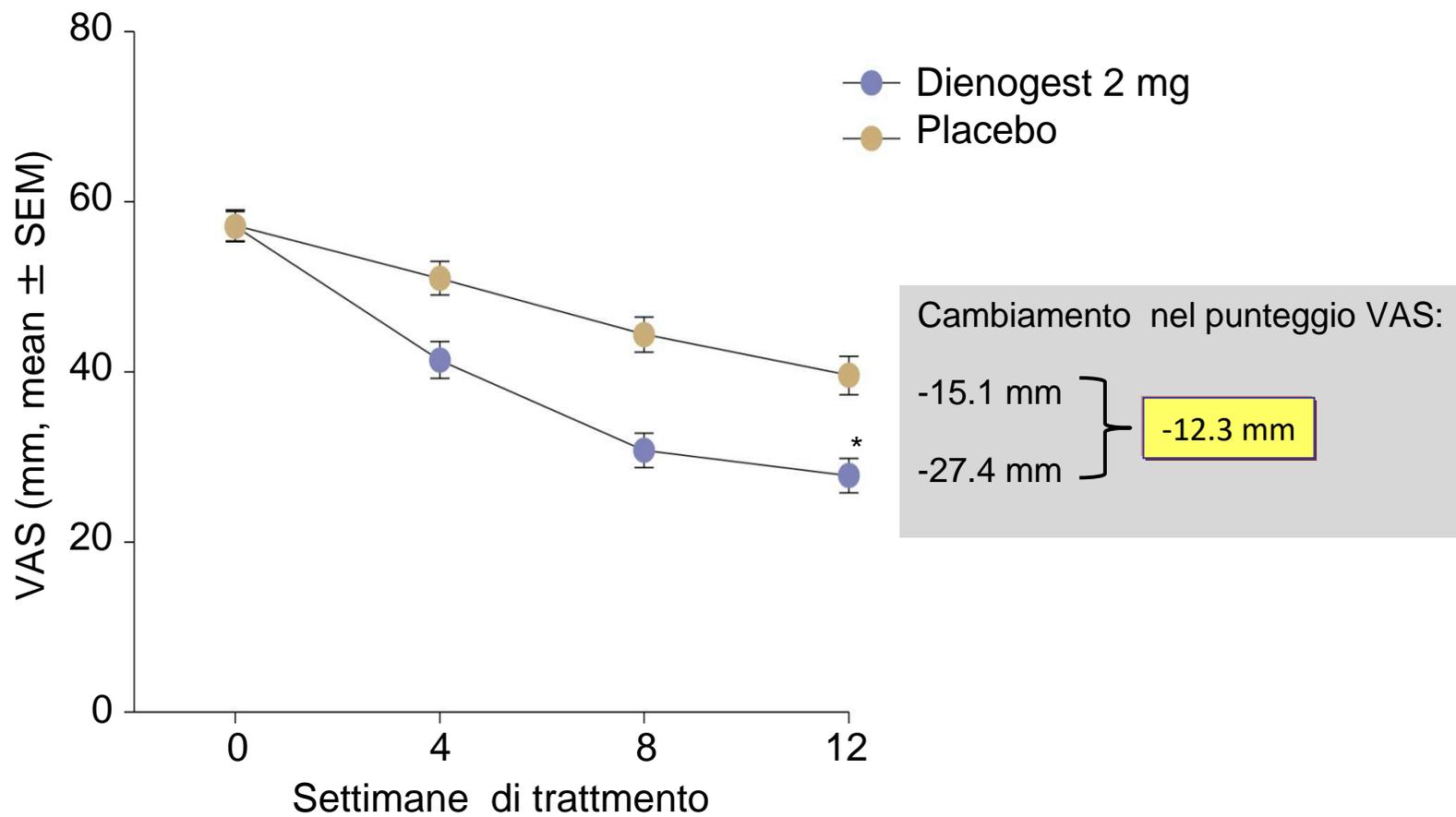
c Bayer Schering Pharma AG, Global Biostatistics, Berlin, Germany

d Bayer Schering Pharma AG, Global Clinical Development Women's Healthcare, Berlin, Germany



Riduzione del dolore pelvico

Dienogest 2 mg versus Placebo



Superiorità versus placebo ($P < 0.0001$)

STUDIO DI DOSE-RANGING

A dose-ranging study to determine the efficacy and safety of 1, 2, and 4 mg of dienogest daily for endometriosis

Günter Köhler ^a, Thomas A. Faustmann ^b, Christoph Gerlinger ^c, Christian Seitz ^d, Alfred O. Mueck ^e

^a Department of Gynecology and Obstetrics, University of Greifswald, Greifswald, Germany

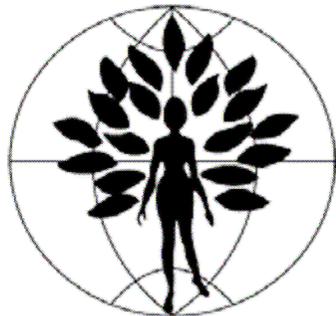
^b Bayer Schering Pharma AG, Global Medical Affairs Women's Healthcare, Berlin, Germany

^c Bayer Schering Pharma AG, Global Biostatistics, Berlin, Germany

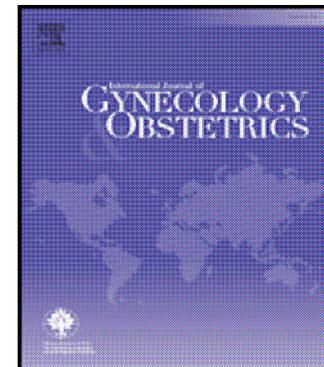
^d Bayer Schering Pharma AG, Global Clinical Development Women's Healthcare, Berlin, Germany

^e Center of Endocrinology and Menopause, University Women's Hospital of Tübingen, Tübingen, Germany

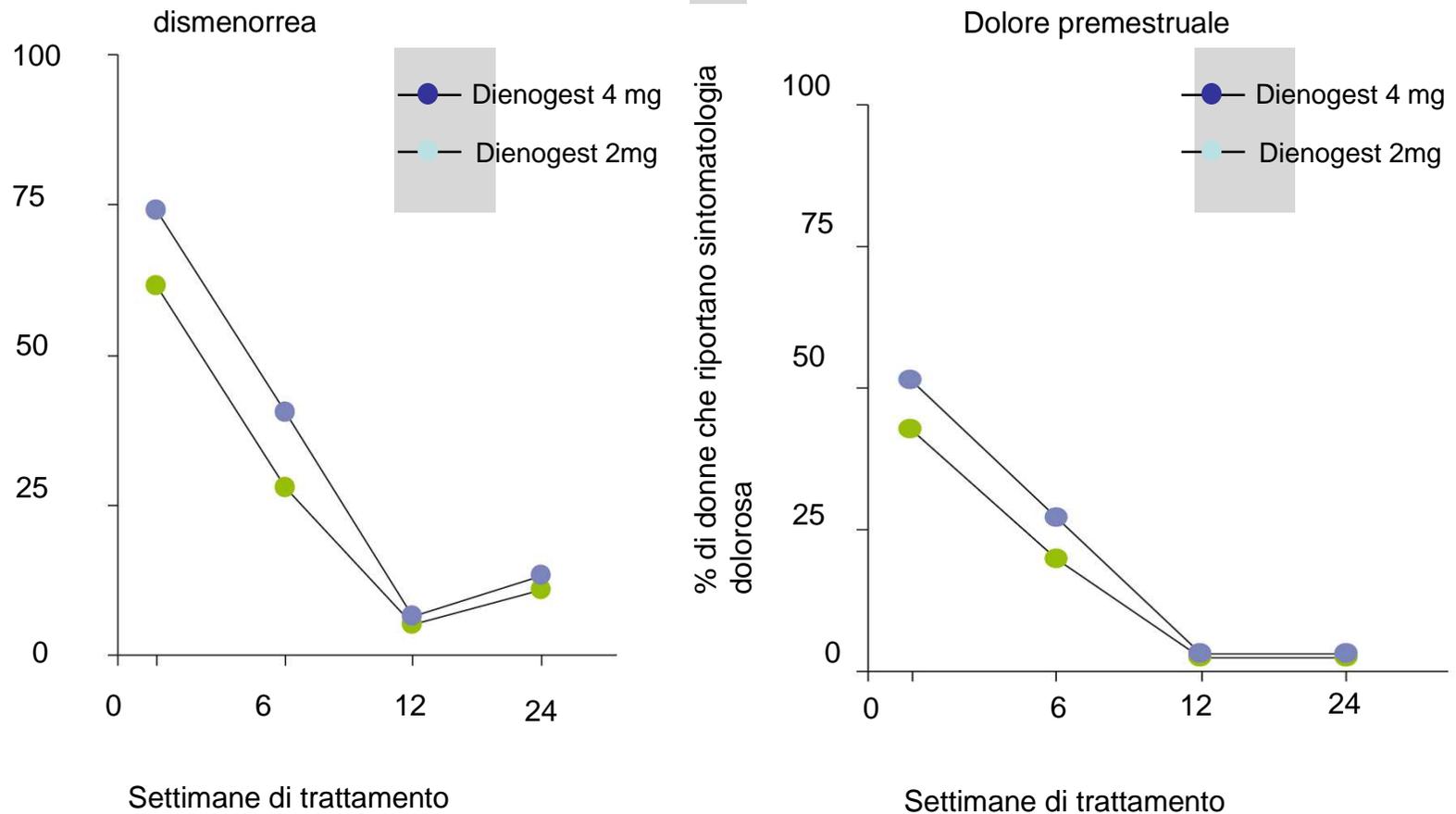
2010



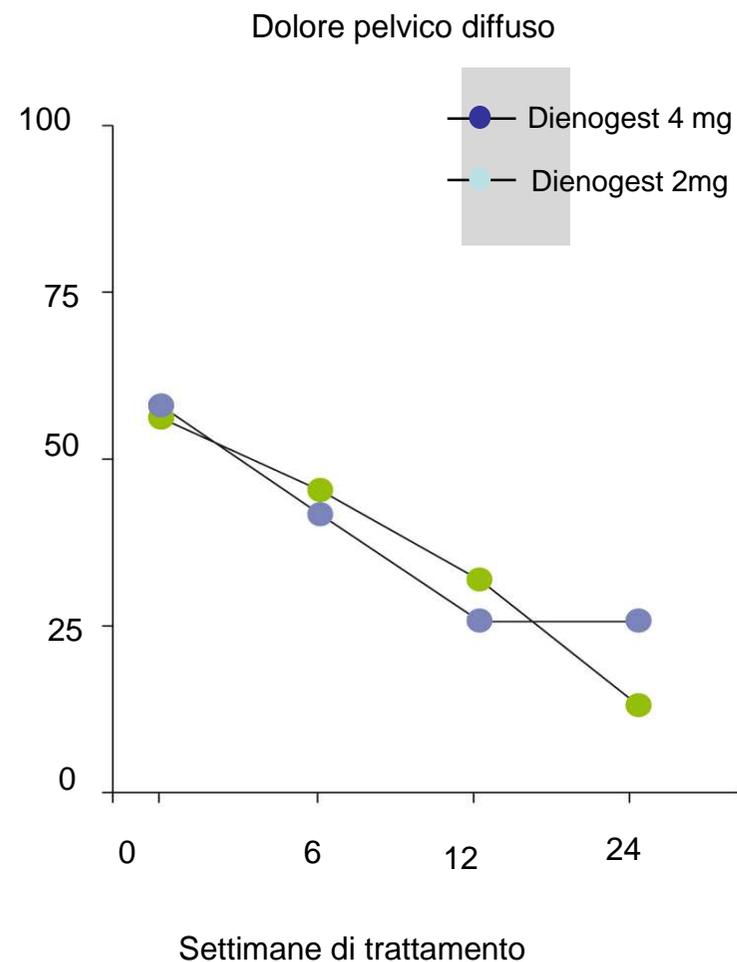
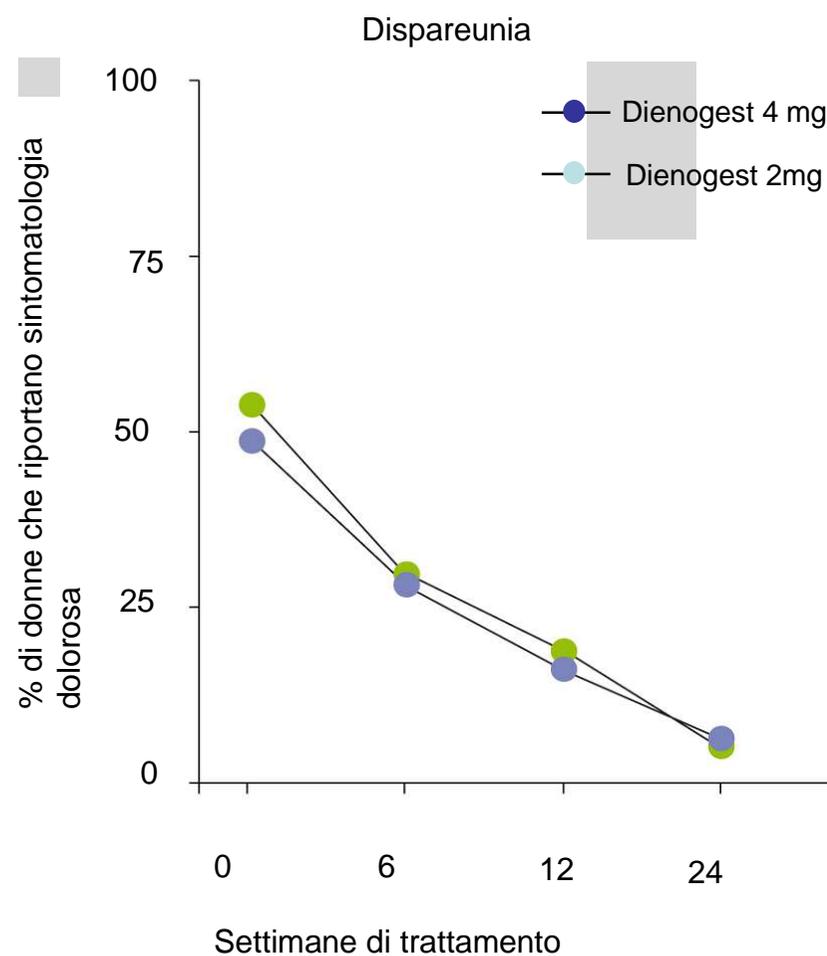
www.figo.org



Effetto sulla sintomatologia dolorosa



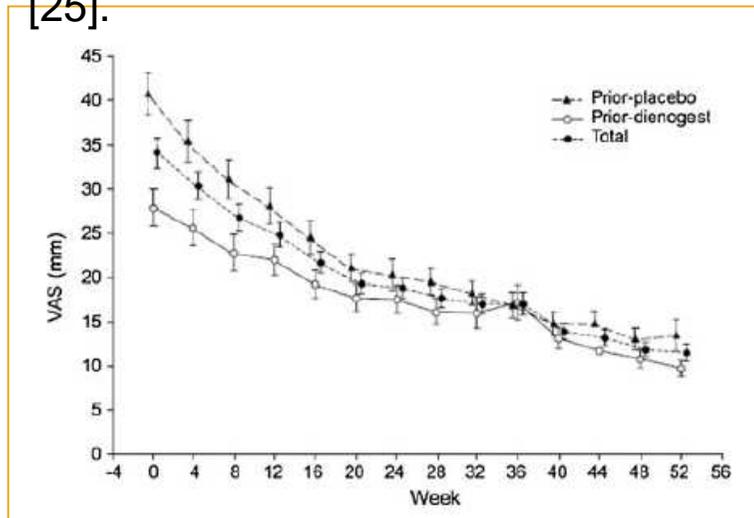
Effetto sulla sintomatologia dolorosa



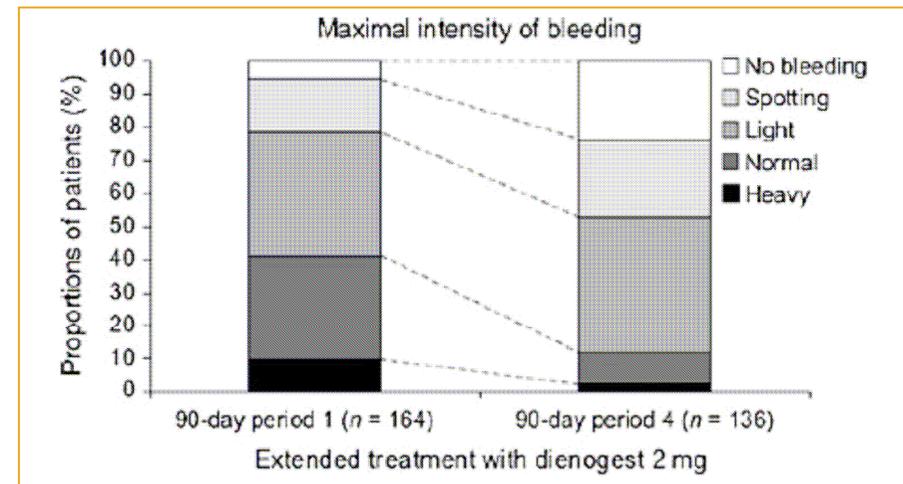
Dienogest: efficacia a lungo termine

Scopo: valutare l'efficacia e la sicurezza del dienogest come un trattamento a lungo termine per l'endometriosi, con follow-up dopo la sospensione del trattamento.

Studio multicentrico (Italia, Germania, Ukraina) 90 settimane durata complessiva dello studio [25].



Significativa diminuzione del dolore pelvico ($p < 0.0001$)



Progressiva riduzione dei giorni di bleeding/spotting

Il trattamento con Dienogest a lungo termine ha mostrato efficacia e profilo di sicurezza favorevoli, con diminuzione progressiva del dolore e delle irregolarità mestruali durante la prosecuzione del trattamento; la diminuzione del dolore pelvico persisteva per almeno 24 settimane dopo la sospensione del trattamento.



www.igo.org

Contents lists available at [SciVerse ScienceDirect](#)

International Journal of Gynecology and Obstetrics

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



Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis: a 24-weeks, randomized, multicentre, open-label trial

T. Strowitzki J. Marr, C. Gerlinger, T. Faustmann, and C. Seitz

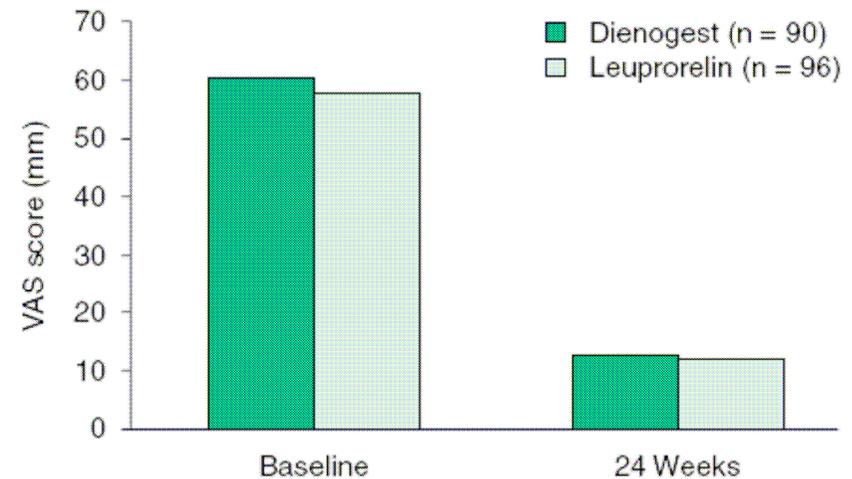
¹Department of Gynecological Endocrinology and Reproductive Medicine, University of Heidelberg, Vossstrasse 9, 69115 Heidelberg, Germany ²Bayer Schering Pharma AG, Global Clinical Development Women's Healthcare, 13353 Berlin, Germany ³Bayer Schering Pharma AG, Global Biostatistics, 13353 Berlin, Germany Bayer Schering Pharma AG, Global Medical Affairs Women's Healthcare, 13353 Berlin, Germany

2010

Dienogest: efficacia comparabile ai GnRH Agonisti- Leuprorelin

Efficacia del dienogest rispetto a leuprorelin nel trattamento dell'endometriosi, associato dolore pelvico

I risultati di uno studio randomizzato, in aperto, in cui le pazienti con endometriosi confermata laparoscopicamente hanno ricevuto dienogest orale 2 mg una volta al giorno o leuprorelina 3.75mg per via intramuscolare ogni 4 settimane per 24 settimane. L' endpoint primario di efficacia era la riduzione dal basale a 24 settimane del dolore pelvico valutata con una scala analogica visiva (VAS)



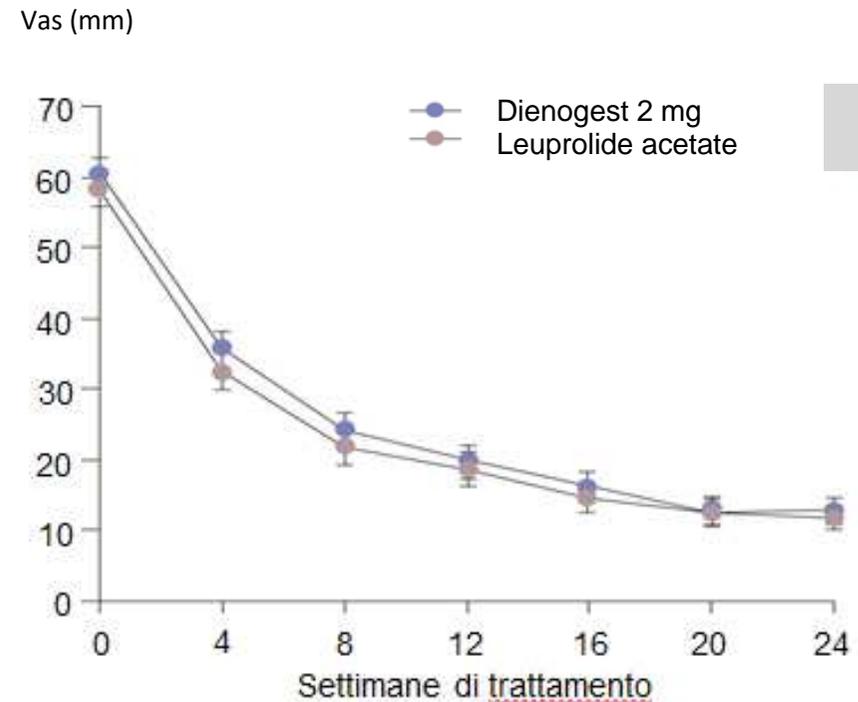
Efficacia comparabile, ma vantaggi in termini di sicurezza e tollerabilità

Infatti gli agonisti del GnRH, anche se accettati come terapia altamente efficace, sono associati a sintomi di deprivazione estrogenica (comprese le vampate di calore, secchezza vaginale, mal di testa e una diminuzione libido) e demineralizzazione ossea che limita il trattamento a 6 mesi

Dienogest (n=120) and Leuprolide acetate (n=128)

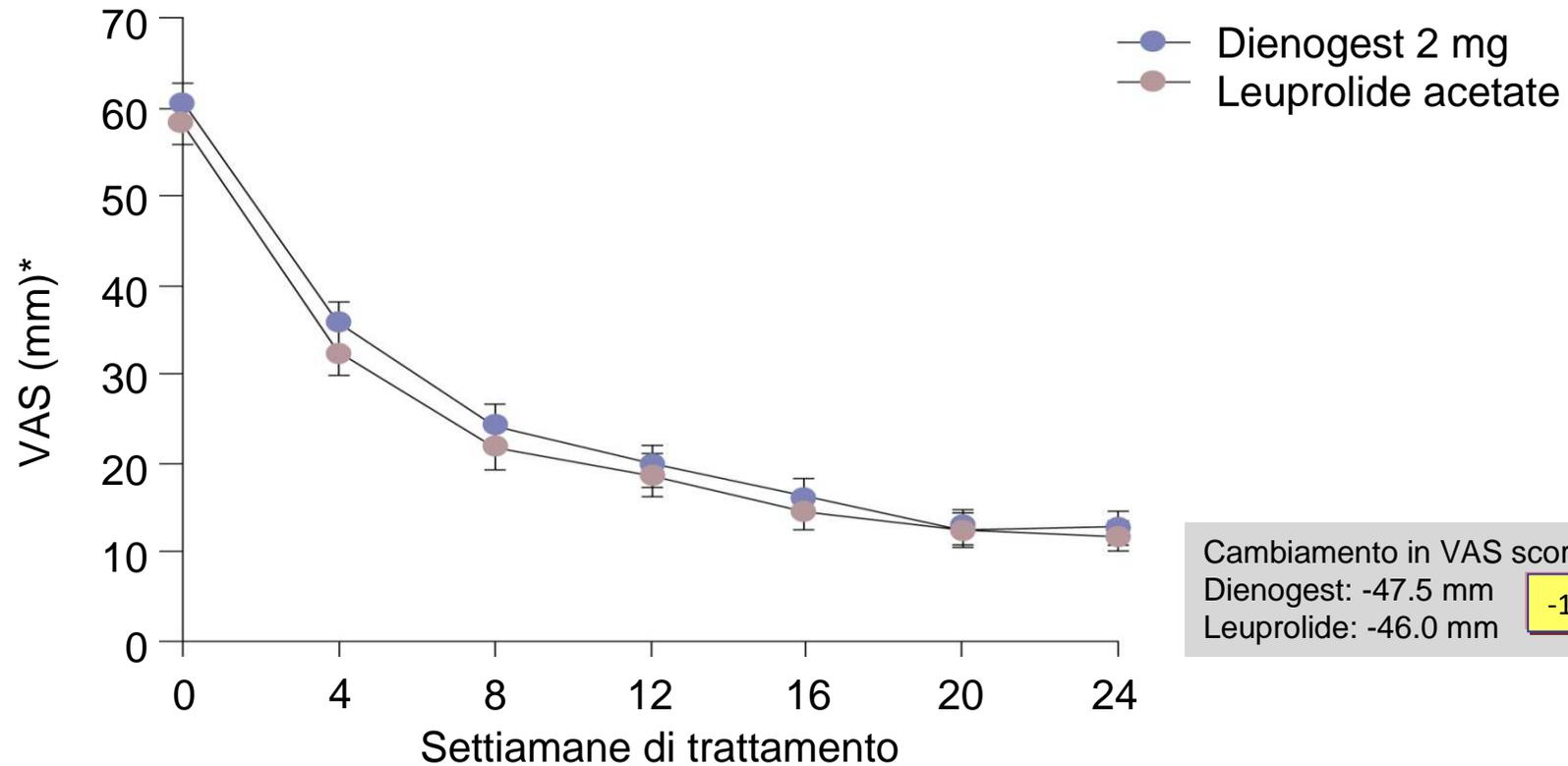
Efficacia:

- Riduce efficacemente e velocemente il dolore (già dopo 4 we di utilizzo)
- Studi clinici hanno dimostrato che ha un'efficacia simile agli analoghi



Efficacia: riduzione del dolore

Dienogest 2 mg versus Leuprolide Acetate



Cambiamento in VAS score:
Dienogest: -47.5 mm
Leuprolide: -46.0 mm

-1.5 mm

Non-inferiore al leuprolide acetate

($P < 0.0001$)

* mean \pm SEM

VAS, visual analogue scale.

Strowitzki T et al. Hum Reprod 2010

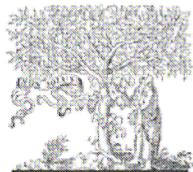
Long-term use of dienogest for the treatment of endometriosis

Mikio Momoeda¹, Tasuku Harada², Naoki Terakawa², Takeshi Aso³, Masao Fukunaga⁴, Hiroshi Hagino⁵ and Yuji Taketani¹

Aim: To investigate the safety and efficacy of 52 weeks of dienogest treatment in patients with endometriosis.

Methods: One hundred and thirty-five patients with endometriosis received 2 mg of dienogest orally each day

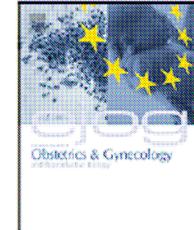
Conclusion: The long-term effect of dienogest on bone mineral density was slight, whereas the efficacy increased cumulatively.



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European Journal of Obstetrics & Gynecology and Reproductive Biology

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

Maintenance therapy with dienogest following gonadotropin-releasing hormone agonist treatment for endometriosis-associated pelvic pain

Jo Kitawaki*, Izumi Kusuki, Kaoruko Yamanaka, Izumi Suganuma

Department of Obstetrics and Gynecology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, 465 Kajii-cho, Kamigyo-ku, Kyoto 602-8566, Japan

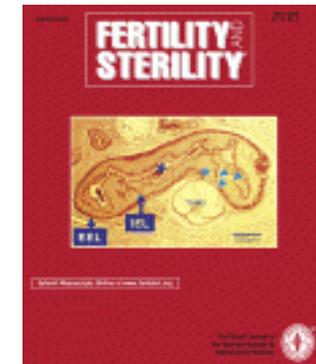
Conclusioni degli autori: Il Dienogest mantiene l'effetto dei GnRH agonisti (somministrati per 4-6 mesi) sul dolore pelvico associato ad endometriosi per 12 mesi

Obiettivo: Esaminare il dienogest a lungo termine dopo una terapia con analoghi nel GnRH, valutando l'effetto sul dolore pelvico e le modifiche al profilo di sanguinamento

2009

Dienogest is as effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis—a randomized, double-blind, multicenter, controlled trial

*Tasuku Harada, M.D.,^a Mikio Momoeda, M.D.,^b Yuji Taketani, M.D.,^b Takeshi Aso, M.D.,^c
Masao Fukunaga, M.D.,^d Hiroshi Hagino, M.D.,^e and Naoki Terakawa, M.D.^a*



Objective: To compare the efficacy and safety of dienogest (DNG) with intranasal buserelin acetate (BA) in patients with endometriosis.

Design: Phase III, randomized, double-blind, multicenter, controlled trial.

Setting: Twenty-four study centers in Japan.

Patient(s): Two hundred seventy-one patients with endometriosis.

Conclusion(s): DNG is as effective as intranasal BA in alleviating endometriosis, and causes less BMD loss.

2002

Dienogest is as effective as triptorelin in the treatment of endometriosis after laparoscopic surgery: results of a prospective, multicenter, randomized study

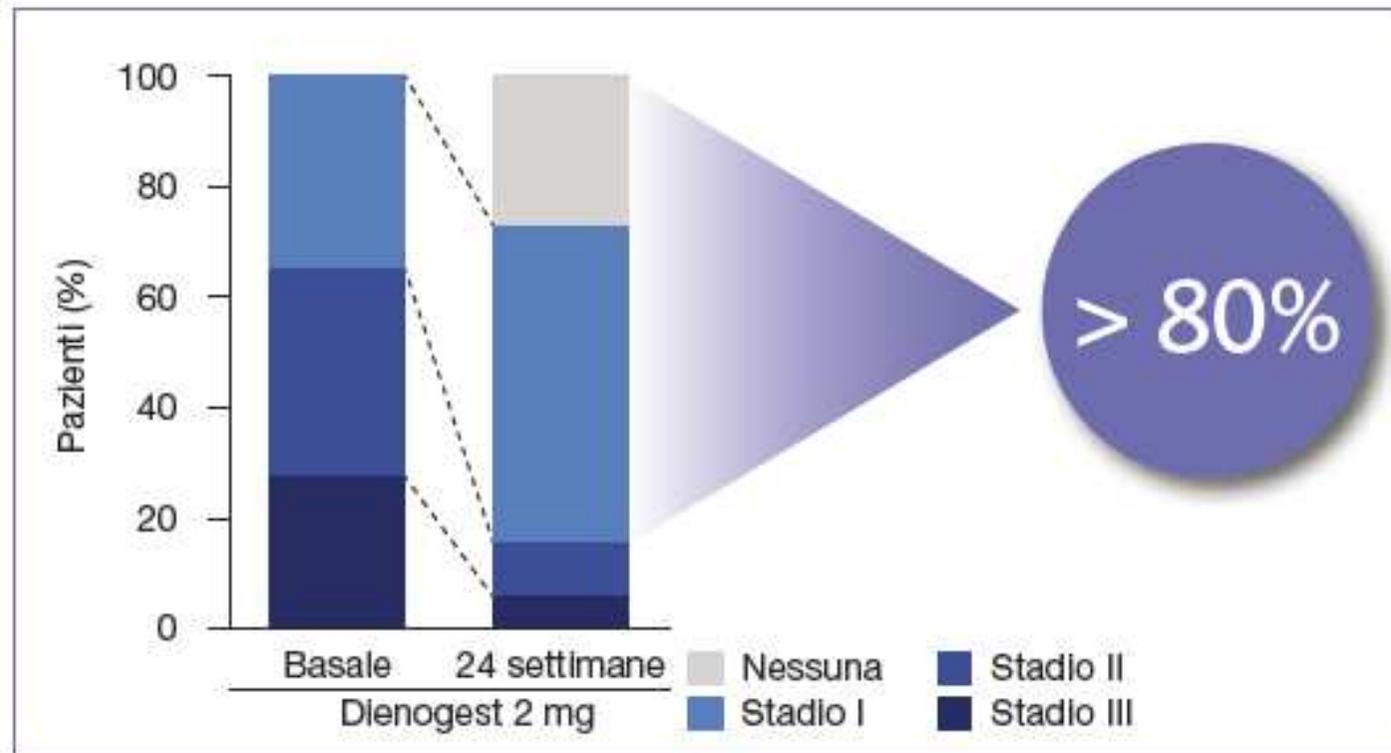
*Michel Cosson, M.D.,^a Denis Querleu, M.D.,^a Jacques Donnez, M.D.,^b
Patrick Madelenat, M.D.,^c Philippe Koninckx, M.D.,^d Alain Audebert, M.D.,^e and
Hubert Manhes, M.D.^f*

Objective: To compare the efficacy of Dienogest versus Decapeptyl® at 3.75 mg as consolidation therapy for surgery in the treatment of endometriosis.

Conclusione: Dienogest è efficace nella terapia di mantenimento dopo chirurgia dell'endometriosi come la triptorelina



Efficacia: riduzione delle lesioni

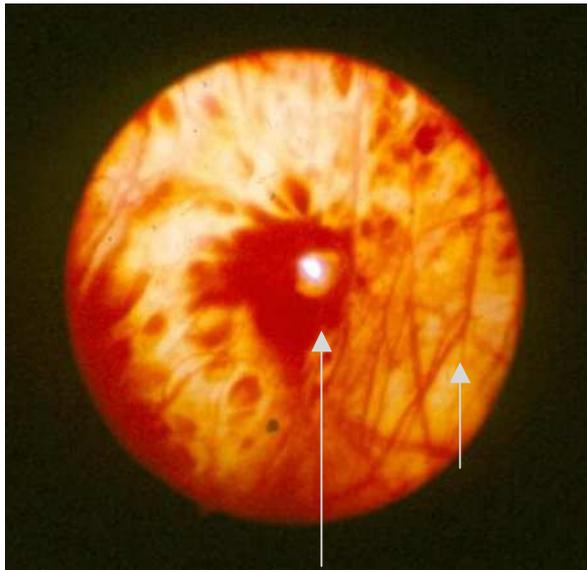


laparoscopia pre e post trattamento

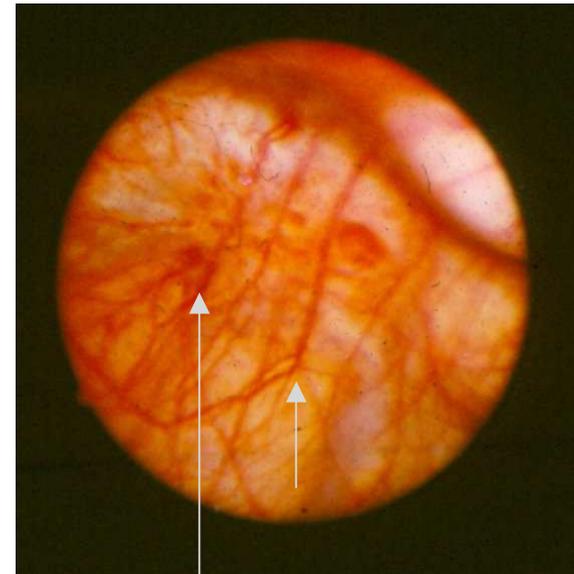
Dopo 24 settimane di trattamento più dell'80% delle pazienti aveva un'endometriosi minima o non evidenza di patologia.

Effetto sulle lesioni:

- Effetto del Dienogest sulla lesione endometriotica nel cavo del douglas in una paziente trattata con dienogest 2mg per 24 settimane

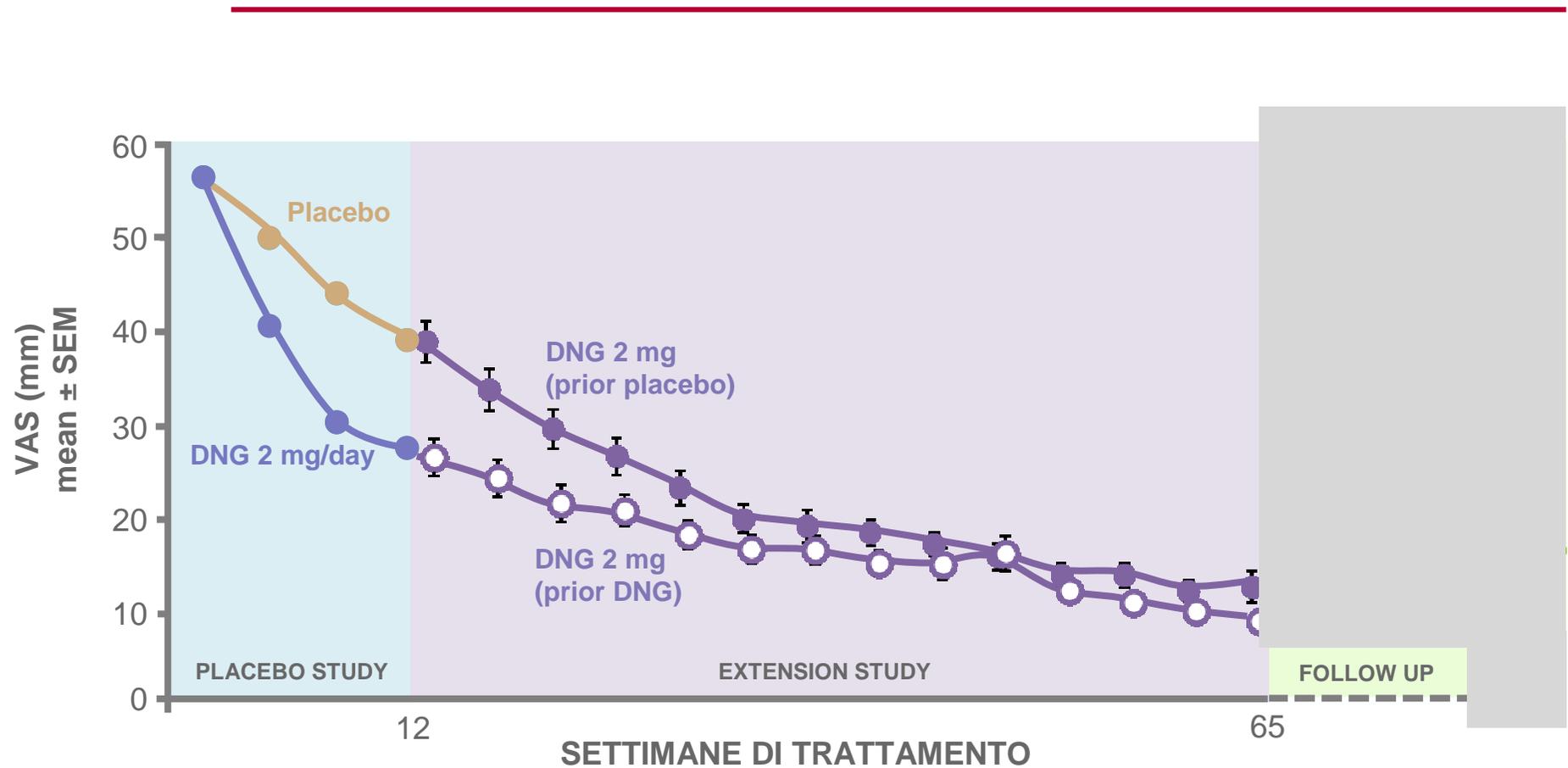


Prima della terapia con DNG



Dopo 24 settimane di
terapia con DNG

Riduzione dolore pelvico studio a lungo termine



Efficacia mantenuta

Effect and safety of high-dose dienogest (20 mg/day) in the treatment of women with endometriosis

Adolf E. Schindler · Alexandra Henkel ·
Claudia Moore · Michael Oettel

21 donne sono state reclutate per questo studio di 24 settimane

La dose utilizzata di 20 mg è 10 volte la dose approvata in molti paesi europei ed asiatici

Nessun mutamento clinicamente significativo a carico dell' emostasi della funzione tiroidea e adrenergica, dell' metabolismo di lipidi e carboidrati, della funzione epatica , sul bilancio elettrolitico e sui principali parametri ematologici

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

Yoshiaki Ota¹, Masaaki Andou¹, Shiori Yanai¹, Saori Nakajima¹, Mika Fukuda¹, Mizuki Takano¹, Shozo Kurotsuchi¹, Keiko Ebisawa¹, Tomonori Hada¹, Ikuko Ota²

- ❖ Studio di coorte, retrospettivo
- ❖ Obiettivo: valutare se la somministrazione nel lungo termine del DNG dopo escissione dell'endometrioma riduce le recidive (a 5 anni)
- ❖ 568 donne che tra il 2008 e il 2013 hanno subito un intervento di rimozione dell'endometrioma:

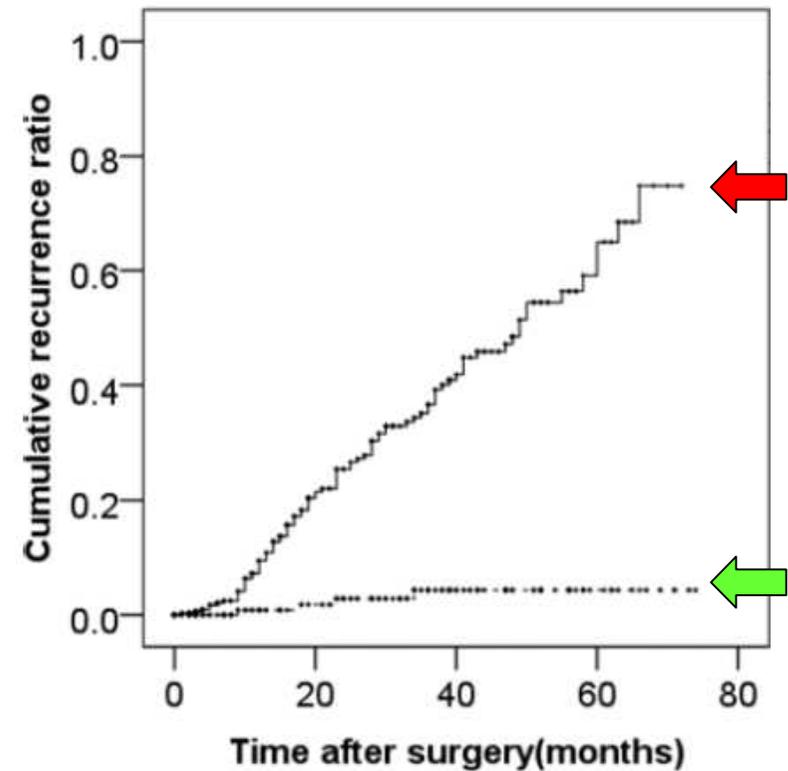
417 non hanno seguito alcuna terapia

151 hanno assunto DNG 2 mg/die

Risultati

- A 5 anni dall'intervento la recidiva dell'endometrioma è stata del
 - ❖ **22,4%** (93/416) nel gruppo senza terapia
 - ❖ **2,6%** (4/151) nel gruppo DNG

Tassi di recidiva cumulativi



Risultati

- ❖ Il 3,6% (15/417) delle pazienti nel gruppo senza terapia ha subito un nuovo intervento
- ❖ **Nessuna paziente nel gruppo DNG ha subito ulteriori interventi**

- ❖ Nel gruppo DNG non è stata osservata alcuna modificazione dei livelli sierici dei lipidi e degli enzimi epatici
- ❖ L'effetto avverso più riferito è stata la metrorragia, non è stato rilevato nessun caso di anemia
- ❖ È stato osservato un decremento della densità minerale ossea nel 4,6% delle pazienti (7/151)

Conclusioni

- DNG 2 mg/die si è dimostrato efficace nel ridurre sia le recidive postoperatorie dell'endometrioma che la necessità di un nuovo intervento chirurgico.

Trattamento medico dell'endometriosi: uso di progestinici ed estroprogestinici

Desogestrel

Etonogestrel

Etonogestrel + EE

Dienogest

Desogestrel-only contraceptive pill versus sequential contraceptive vaginal ring in the treatment of rectovaginal endometriosis infiltrating the rectum: a prospective open-label comparative study

UMBERTO LEONE ROBERTI MAGGIORE, VALENTINO REMORGIDA, CAROLINA SCALA, EMANUELA TAFI, PIER L. VENTURINI & SIMONE FERRERO

Department of Obstetrics and Gynecology, San Martino Hospital and National Institute for Cancer Research, University of Genoa, Genoa, Italy

143 pazienti con endometriosi del setto retto vaginale.

Confronto di efficacia tra Cerazette e Nuvaring

End point primario: tasso di gradimento delle pazienti

End point secondari: efficacia sulla sintomatologia e sul volume
dei noduli

Risultati: Entrambi i trattamenti si sono rivelati efficaci ma le pazienti hanno mostrato un piu' elevato tasso di gradimento verso Cerazette (($p = 0.004$).)

Key Message

Both a desogestrel-only contraceptive pill and a sequential combined contraceptive vaginal ring are effective for the management of bowel endometriosis-related symptoms. The decrease in the volume of the nodules, the adherence to therapy and the rate of patients requiring surgery were similar between the two study groups. More women treated with a desogestrel-only contraceptive pill are satisfied with their treatment compared with those using a sequential combined contraceptive vaginal ring.

Desogestrel ed endometriosi



Available online at www.sciencedirect.com



European Journal of Obstetrics & Gynecology and
Reproductive Biology 135 (2007) 188–190



European Journal of
Obstetrics & Gynecology
and Reproductive Biology

www.elsevier.com/locate/ejogrb

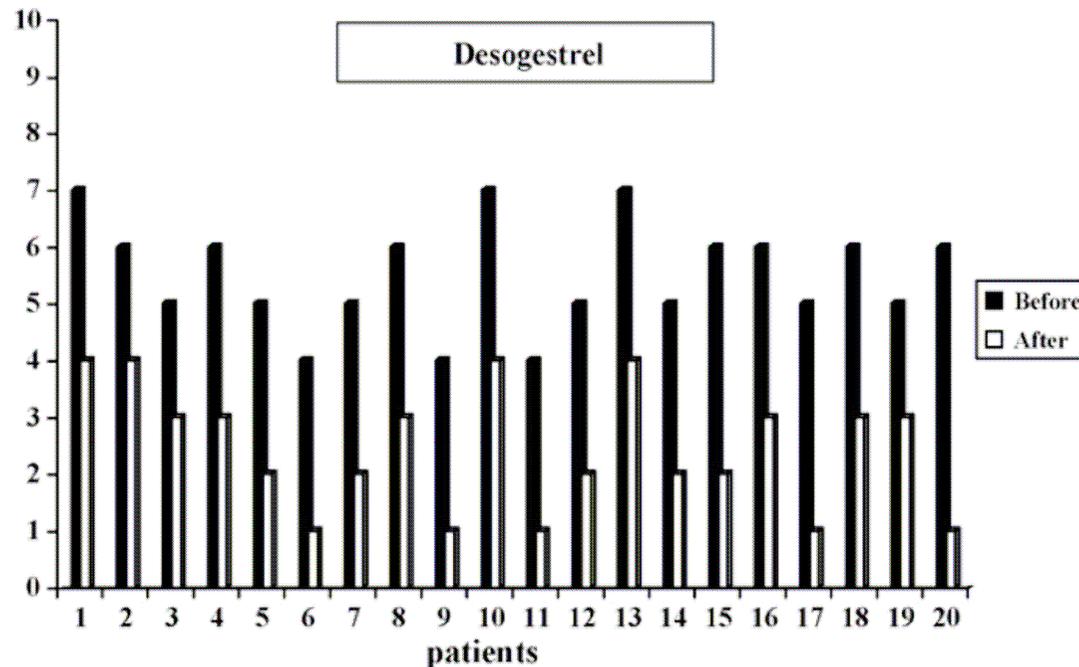
Use of a progestogen only preparation containing desogestrel
in the treatment of recurrent pelvic pain after conservative
surgery for endometriosis

Sandro Razzi, Stefano Luisi, Caterina Ferretti, Francesco Calonaci,
Massimo Gabbanini, Massimo Mazzini, Felice Petraglia*

Desogestrel é un progestinico derivato da 19 nortestosterone con una minima affinità per i recettori androgenici ed altamente selettivo per i recettori del progesterone

Disegno: Studio prospettico randomizzato per valutare gli effetti del desogestrel nel trattamento della dismenorrea e/o dolore pelvico dopo chirurgia conservativa vs 20 mg EE + 150 mg di desogestrel
Campione: n= 40 donne tra i 23 e i 35 aa con endometriosi I-II
Durata dello studio: 6 mesi

Desogestrel ed endometriosi



CONCLUSIONI:
Il Desogestrel é efficace per il controllo del dolore pelvico ricorrente post terapia chirurgica in pazienti con una lieve-moderata endometriosi

RISULTATI:
miglioramento significativo ($p < 0.001$) del VAS pain score (Visula Analogue Scale) dopo 6 mesi di trattamento rispetto al basale

Migliore performance del solo progestinico anche dal punto di vista metabolico e come effetto sul peso corporeo

Letrozole and desogestrel-only contraceptive pill for the treatment of stage IV endometriosis

Valentino REMORGIDA,¹ Luiza Helena ABBAMONTE,¹ Nicola RAGNI,¹
Ezio FULCHERI² and Simone FERRERO¹

¹Department of Obstetrics and Gynaecology, and ²Unit of Anatomy and Histopathology, Di.C.M.I., San Martino Hospital and University of Genoa, Genoa, Italy

Results:

None of the women included in the study completed the six-month treatment because all patients developed ovarian cysts; the median length of treatment was 84 days (range, 56–112). At interruption of treatment, all women reported significant improvements in dysmenorrhoea and dyspareunia. Pain symptoms quickly recurred at three-month follow up. There were no severe adverse effects of treatment; no significant change in the mineral bone density was observed during treatment.

Conclusions:

The combination of letrozole and desogestrel induces a relief of pain symptoms in women with endometriosis but it causes the development of ovarian cysts. Pain symptoms quickly recur after the completion of treatment.

**LETROZOLO E IL CONTRACCETTIVO A BESE DI SOLO PROGESTINICO
DESOGESTREL NEL TRATTAMENTO DELL'ENDOMETRIOSI ALLO STADIO IV.
Remorgida et al., Australian and New Zealand Journal of Obstetrics and
Gynaecology 2007**



letrozole 2.5 mg
(Femara®), vs Cerazette

Presenza dei sintomi

	<u>Baseline (n)</u>	<u>Interruzione del trattamento (n)</u>	<u>P-value</u>
Dismenorrea	12/12 (100%)	0/12 (0.0%)‡	< 0.001
Dispareunia profonda	6/9 (66.7%)	0/9 (0.0%)	0.005
Dolopre pelvico cronico	7/12 (58.3%)	4/12 (33.3%)	0.207

Intensità dei sintomi §

Dismenorrea	8.7 ± 1.9	0.8 ± 0.7‡	P = 0.028
Dispareunia profonda	6.5 ± 2.7	0.6 ± 0.5	P = 0.002
Dolopre pelvico cronico	6.0 ± 1.9	3.2 ± 2.6	P = 0.097

Sintomi dolorosi valutati al momento dell'interruzione del trattamento

La combinazione del Letrozolo e del desogestrel induce un miglioramento dei sintomi dolorosi in donne con endometriosi

Sintomi del dolore a 3 e 6 mesi di follow-up

	<u>Baseline (n)</u>	<u>3 mesi</u>	<u>6 mesi</u>
Presenza dei sintomi			
Dismenorrea	12/12 (100%)	11/12 (91.7%)	12/12 (100.0%)
Dispareunia profonda	6/9 (66.7%)	6/9 (66.7%)	6/9 (66.7%)
Dolore pelvico cronico	7/12 (58.3%)	7/12 (58.3%)	7/12 (58.3%)
Intensità dei sintomi §			
Dismenorrea	8.7 ± 1.9	6.8 ± 1.7§	8.8 ± 1.4
Dispareunia profonda	6.5 ± 2.7	5.6 ± 2.2	6.4 ± 1.9
Dolore pelvico cronico	6.0 ± 1.9	5.9 ± 2.0	6.0 ± 1.5

I sintomi del dolore ritornano rapidamente dopo la fine del trattamento.

Trattamento medico dell'endometriosi: uso dei progestinici ed estroprogestinici

Desogestrel

Etonogestrel

Etonogestrel + EE

Dienogest

TRATTAMENTO DELL'ENDOMETRIOSI PELVICA CON L'IMPIANTO SOTTOCUTANEO ALL'ETONOGESTREL

Yisa, et al J Fam Plann Reprod Health Care 2005

Sono state trattate cinque donne con forte endometriosi pelvica

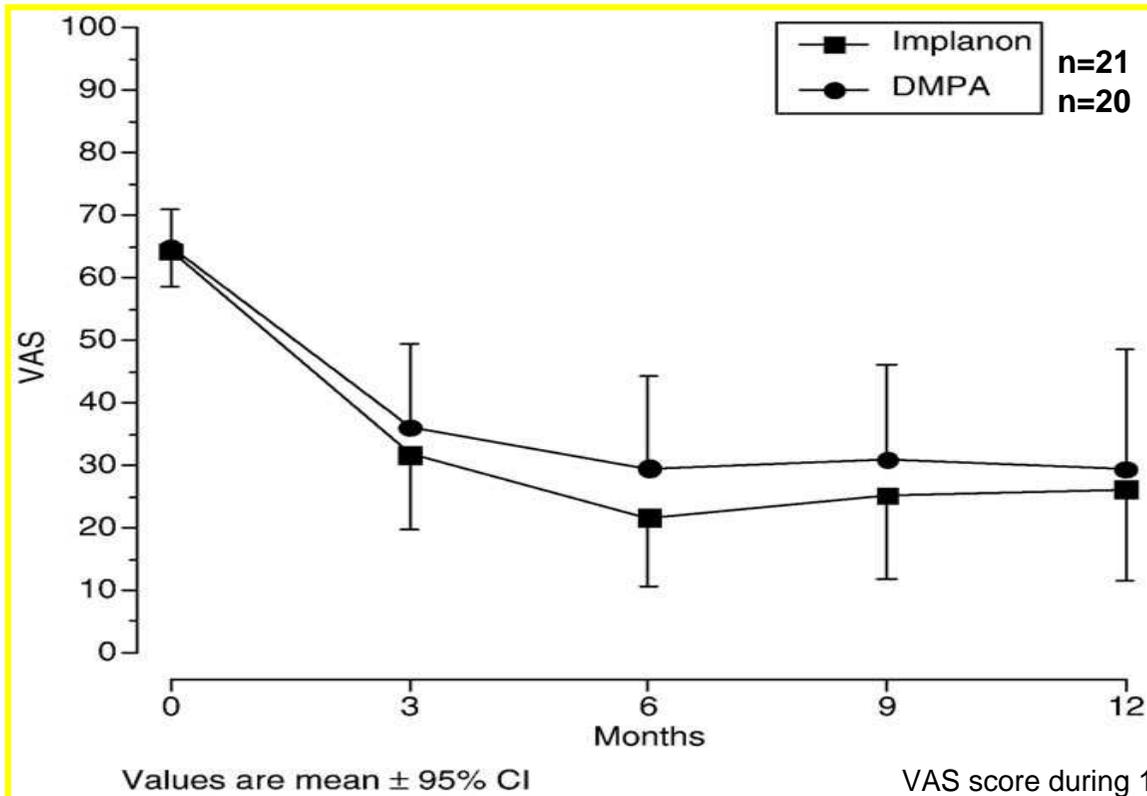


L'impianto sottocutaneo all'Etonogestrel rappresenta un'opzione di trattamento terapeutico per le donne con sintomi di endometriosi pelvica severa

NEXPLANON® VERSUS MEDROXYPROGESTERONE ACETATE: EFFETTI SUGLI INDICATORI DEL DOLORE IN PAZIENTI CON ENDOMETRIOSI SINTOMATICA: STUDIO PILOT

Katharina Walch, Gertrud Unfried, Johannes Huber, Christine Kurz, Michael van Trotsenburg, Elisabeth Pernicka, René Wenzl Contraception. 2009

Quarantuno pazienti con forte dismenorrea, dolore pelvico non mestruale e dipareunia associati ad endometriosi sono state randomizzate a ricevere o Nexplanon o DMPA per 1 anno (eta' 22-44 anni)



Con riferimento all'alleviamento del dolore, l'efficacia terapeutica in presenza di endometriosi sintomatica dell'impianto era risultata nel 68% di riduzione della sintomatologia. Per il DMPA la riduzione è stata del 53%

The Effects of Implanon in the Symptomatic Treatment of Endometriosis

Jirawat Ponpuckdee MD*,
Surasak Taneepanichskul MD*

Studio in aperto senza gruppo controllo. Valutazione dell'efficacia dell'impianto sottocutaneo nel trattamento dell'endometriosi sintomatica in 50 donne. L'intensità del dolore è stata determinata tramite la Visual Analogue Scale, prima dell'inserimento e a 4 e 12 settimane dopo l'inserimento. Valutazione della soddisfazione vs il trattamento

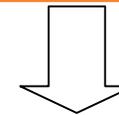
Table 3. Pain symptom score (VAS) in patients with endometriosis before and during therapy

Baseline	Month 1	Month 3
7.08 (5.2-10)	3.72 (0-8.2)	0.84 (0-5.4)*

* P < 0.05

Valutazione soddisfazione:

- molto soddisfatte 12%
- soddisfatte 68%
- incerte 20%



80% delle donne erano soddisfatte o molto soddisfatte

GESTRINONE

2,5 mg 2-3 volte a settimana

Derivato del 19- Nortestosterone

Effetto androgenico

Effetto antiprogesterinico

Effetto antiestrogenico

Stessi effetti collaterali del danazolo ma meno pronunciati

Per gli effetti anabolizzanti, il suo impiego nelle manifestazioni sportive è stato vietato dal CIO (Comitato Olimpico Internazionale)

2 capsule alla settimana equivalenti (5 mg), la prima viene somministrata il 1° giorno del ciclo mestruale, durata trattamento 6 mesi.

Gestrinone è stato approvato per l'uso in diversi paesi, ma non negli Stati Uniti; in Italia, pur essendo stato approvato, per problemi di sito produttivo vi sono difficoltà di reperimento.

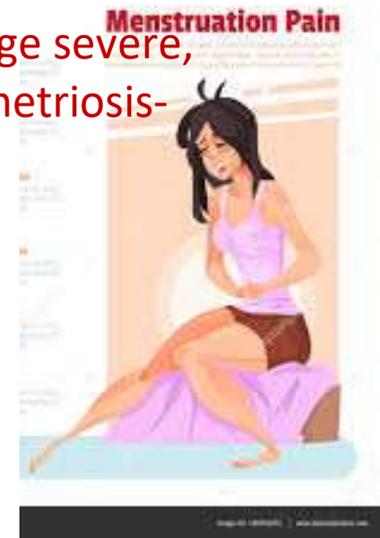
Aromatase Inhibitors

Aromatase inhibitors (AIs) inhibit local estrogen production in endometriotic implants, in the ovary, brain, and adipose tissue.

Table 1. Summary of study characteristics and interventions for endometriosis from individual studies included in systematic review of aromatase inhibitors

Study (year)	Study type	Menopausal status	Number of women	Mean age	Interventions	Treatment in months
Ailawadi et al. ¹⁹ (2004)	Nonrandomised	Premenopausal	10	29.9	2.5 mg letrozole + 2.5 mg norethindrone acetate + calcium and vitamin D supplement	6
Hefler et al. ²⁰ (2005)	Nonrandomised	Premenopausal	10	31.2	0.25 mg anastrozole PV + calcium and vitamin D supplement	6
Razzi and Fava ¹⁹ (2004)	Case report	Premenopausal	1	20	2.5 mg letrozole + calcium and vitamin D supplement	3
Takayama et al. ¹⁶ (1998)	Case report	Postmenopausal	1	57	1 mg anastrozole + calcium supplement + 10 mg alendronate	9
Shippen and West ¹⁷ (2004)	Case report	Premenopausal	2	25	1 mg anastrozole + 200 mg prometrium + 12.5–30 mg rofecoxib + vitamin D supplement	6
Fatemi et al. ¹⁸ (2005)	Case Report	Postmenopausal	1	57	Letrozole	18
Amsterdam et al. ²² (2005)	Prospective nonrandomised	Premenopausal	15	23–46	1 mg anastrozole + 0.2 micrograms ethinyl E ₂ + 0.1 mg levonorgestrel	6
Soysal et al. ²¹ (2004)	RCT	Premenopausal	97	31.3/32.4	3.6 mg goserelin ± 1 mg anastrozole vs 3.6 mg goserelin	6

reserved to manage severe, intractable endometriosis-associated pain



aromatase inhibitors in combination with GnRH analogues significantly improved pain ($P \ll 0.0001$) compared with GnRH analogues alone

INIBITORI DELLA AROMATASI

inibiscono o inattivano l'enzima aromatasi

INIBITORI DI TIPO 1 IRREVERSIBILI

inattivatori enzimatici steroidei analoghi dell'androstenedione si legano irreversibilmente al medesimo sito della molecola dell'aromatasi

INIBITORI DI TIPO 2 REVERSIBILI

inibitori enzimatici non steroidei si legano reversibilmente al gruppo eme dell'enzima aromatasi

Formestane (II gen, i.m., Lentaron)

Exemestane (III gen, os,)

Anastrozolo (III gen, os, arimidex)

Letrozolo (III gen, os, femara)

Soppressione sintesi di estrogeni

Soppressione dolore

INIBITORI AROMATASI ED ENDOMETRIOSI PROFONDA

Letrozole and norethisterone acetate in colorectal endometriosis
Ferrero S et al, Eur J Obstet Gynecol Reprod Biol 2010

Aromatase inhibitors in recurrent ovarian endometriomas: report of
five cases with literature review.
Seal S et al, Fertil Steril 2011

Aromatase inhibitors in the treatment of bladder endometriosis.
Ferrero S, et al, Gynecol Endocrinol 2011

INIBITORI AROMATASI IN ASSOCIAZIONE A PROGESTINICI O GnRH

Letrozole and norethisterone acetate versus letrozole and triptorelin in the treatment of endometriosis related pain symptoms: a randomized controlled trial

Table 1 Intensity of pain symptoms at baseline and during treatment

	VAS scale			Multidimensional categorical rating scale		
	group T (n = 18)	group N (n = 17)	p	group T (n = 18)	group N (n = 17)	p
Dysmenorrhea						
- baseline	8.7 ± 1.1 (n = 18)	8.6 ± 1.3 (n = 16)	0.881	3 (2-3) (n = 18)	3 (0-3) (n = 17)	0.890
Nonmenstrual pelvic pain						
- baseline	6.1 ± 1.4 (n = 16)	6.0 ± 1.4 (n = 14)	0.783	2 (0-3) (n = 18)	2 (0-3) (n = 17)	0.957
- 3 months of treatment	3.2 ± 1.3 (n = 15)	3.3 ± 1.5 (n = 14)	0.782	1 (0-2) (n = 17)	1 (0-2) (n = 17)	0.818
- 6 months of treatment	1.2 ± 1.3 (n = 9)	2.0 ± 1.8 (n = 14)	0.286	0 (0-2) (n = 10)	1 (0-2) (n = 16)	0.171
p value: 3 month of treatment vs baseline	< 0.001	< 0.001		< 0.001	< 0.001	
p value: 6 month of treatment vs baseline	< 0.001	< 0.001		0.004	< 0.001	
p value: 6 month of treatment vs 3 month	0.001	< 0.001		0.063	0.156	
Deep dyspareunia^a						
- baseline	6.4 ± 1.9 (n = 12)	6.6 ± 2.1 (n = 14)	0.801	2 (0-3) (n = 14)	2 (0-3) (n = 15)	0.501
- 3 months of treatment	3.4 ± 1.2 (n = 11)	3.6 ± 1.5 (n = 14)	0.635	1 (0-2) (n = 13)	1 (0-2) (n = 15)	0.853
- 6 months of treatment	2.0 ± 0.9 (n = 4)	2.2 ± 1.4 (n = 13)	0.727	1 (0-1) (n = 6)	1 (0-2) (n = 14)	0.406
p value: 3 month of treatment vs baseline	< 0.001	< 0.001		0.031	< 0.001	
p value: 6 month of treatment vs baseline	0.022	< 0.001		0.042	< 0.001	
p value: 6 month of treatment vs 3 month of treatment	0.088	< 0.001		0.076	0.125	

Combining letrozole with oral norethisterone acetate was associated with a lower incidence of adverse effects and a lower discontinuation rate than combining letrozole with triptorelin

Ferrero S et al, Reprod Biol Endocrinol 2011

Systematic review of the effects of aromatase inhibitors on pain associated with endometriosis

S Patwardhan, A Nawathe, D Yates, GR Harrison, KS Khan

Letrozolo (Femara)

Anastrozolo (arimidex)

Conclusion

Aromatase inhibitors appear to have a promising effect on pain associated with endometriosis, but the strength of this inference is limited due to a dearth of the evidence available.

Outcome study (year)	n	Interventions	Follow up (months)	Mean (SD)		P values
				Pre-treat	Post-treat	
Pelvic pain*						
Soysal <i>et al.</i> ²¹ (2004)	97	Goserelin + anastrozole (treatment group) Goserelin (control group)	24		1.8 (1.0)	<0.001
Ailawadi <i>et al.</i> ¹⁹ (2004)	10	Norethindrone + letrozole	6	6.22 (2.07)	2.52 (2.09)	<0.005
Hefler <i>et al.</i> ²⁰ (2005)	10	Vaginal anastrozole	6	1.9 (1.4)	2.0 (1.4)	0.9
Amsterdam <i>et al.</i> ²² (2005)	15	Anastrozole + Alesse (OCP)	6	8.24 (1.76)	4.24 (2.7)	0.00005
Razzi and Fava ¹⁵ (2004)	1	Letrozole	7	9	1	<0.01
Lesion size**						
Ailawadi <i>et al.</i> ¹⁹ (2004), ASRM score	10	Norethindrone + letrozole	6	44.1 (29.7)	5.4 (5.64)	0.0013
Hefler <i>et al.</i> ²⁰ (2005)	10	Vaginal anastrozole	6	4.2	4.2	NS
Takayama <i>et al.</i> ¹⁶ (1998)	1	Anastrozole	9	900 mm ²	9 mm ²	Significant
Quality of life***						
Hefler <i>et al.</i> ²⁰ (2005)	10	Vaginal anastrozole	6	84.4 (16.3)	88.3 (14.4)	0.03 (physical functioning)
		Vaginal Anastrozole	6	63.9 (35.6)	74.7 (20.0)	0.01 (social functioning)
Bone density****						
Soysal <i>et al.</i> ²¹ (2004)	97	Goserelin + anastrozole (treatment group) Goserelin (control group)	24		27.1 (46.3)	0.46 (spine)
					25.2 (28.9)	
Ailawadi <i>et al.</i> ¹⁹ (2004)	10	Norethindrone + letrozole	6	No summary results tabulated		0.04 (hip), NS (spine)
Amsterdam <i>et al.</i> ²² (2005)	15	Anastrozole + Alesse (OCP)	6	No summary results tabulated		0.2 (hip), 0.5 (spine)
Takayama <i>et al.</i> ¹⁶ (1998)	1	Anastrozole	9		6.2% reduction in spine	Not provided

Current Endometriosis Treatment: LIMITATIONS

Suppressive Rather than Curative Therapy

After medical treatment or surgical treatment, the recurrence of endometriosis was estimated to be 21.5% at 2 years and 40% to 50% at 5 years

Table 1 Risk factors for recurrence of endometriosis as reported by various published studies

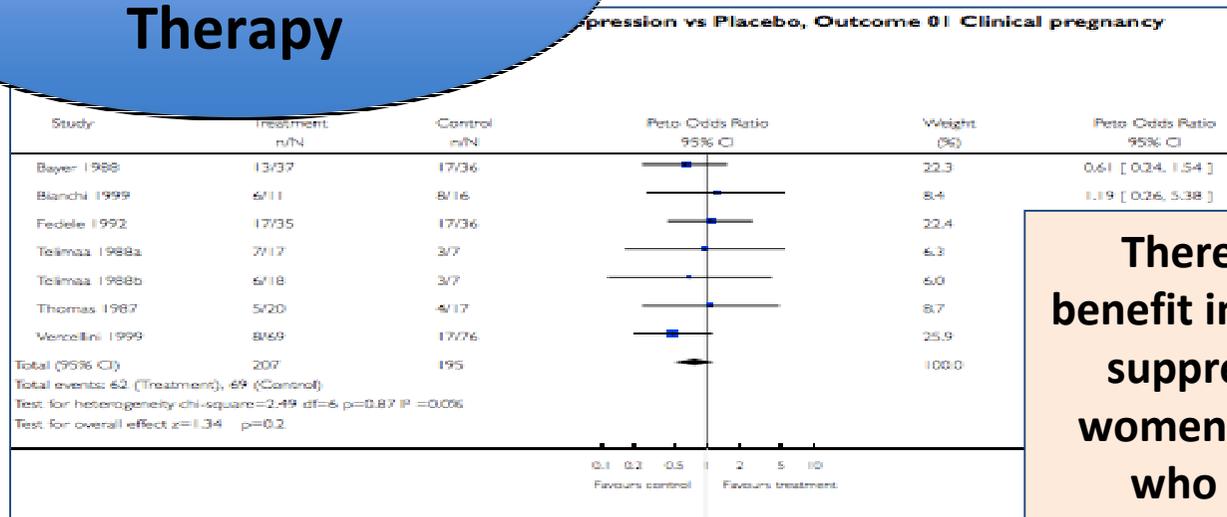
Author and year of publication	Risk factors
Abbott et al. (2003)	rAFS > 70
Bullelli et al. (2001)	EA can be protective
Busacca et al. (1999a)	rAFS stage, previous surgery
Fedele et al. (2004)	Younger age Pregnancy is protective
Fedele et al. (2005)	Extent of surgical excision
Ghezzi et al. (2001)	Laterality of lesions
Jones and Sutton (2002)	Bilateral cysts
Kikuchi et al. (2006)	rAFS score, older age
Koga et al. (2006)	Previous medical treatment, size
Li et al. (2005)	Previous surgical history, bilateral pelvic involvement, involvement of left-side pelvic, high post-operation rAFS score, younger age, painful nodule in the Douglas pouch, use of clomifene Protective factors: number of pregnancies and post-operative progestin treatment
Liu et al. (2007)	For recurrence of disease: rAFS score, younger age, previous use of medication For dysmenorrhea: rAFS score
Namnoum et al. (1995)	Ovarian preservation
Parazzini et al. (2005)	rAFS stage, older age
Saleh and Tulandi (1999)	Size of the cyst
Vercellini et al. (2006)	Younger age at surgery (for dysmenorrhea) Post-operative medical treatment (for disease recurrence)
Vercellini et al. (2008)	OC use is a protective factor
Vignali et al. (2005)	Younger age (for pain) Obliteration of the Douglas pouch (for clinical signs) Completeness of the first surgery (for reoperation)
Waller and Shaw (1993)	rAFS stage

Current Endometriosis Treatment:

LIMITATIONS

Contraceptive Rather than Fertility-Promoting Therapy

systematic review of 25 trials



There is no evidence of benefit in the use of ovulation suppression in subfertile women with endometriosis who wish to conceive.



Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis (Review)

Sallam HN, Garcia-Velasco JA, Dias S, Arici A, Abou-Setta AM

The administration of GnRH agonists for a period of three to six months prior to IVF or ICSI in women with endometriosis increases the odds of clinical pregnancy by fourfold. Data regarding adverse effects of this therapy on the mother or fetus are not available at present.

Current Endometriosis Treatment: LIMITATIONS

Deep Infiltrating Endometriosis and Extrapelvic Disease

General Thoracic Surgery



Catamenial pneumothorax revisited: Clinical approach and systematic review of the literature

IMAGES IN REPRODUCTIVE MEDICINE

A gonadotropin-releasing hormone agonist versus a continuous oral contraceptive pill in the treatment of bladder endometriosis

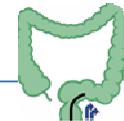


*Luigi Fedele, M.D.,^a Stefano Bianchi, M.D.,^a Sa...
and Luca Carmignani, M.D.^b*



Deep endometriosis infiltrating the recto-sigmoid: critical factors to consider before management FREE

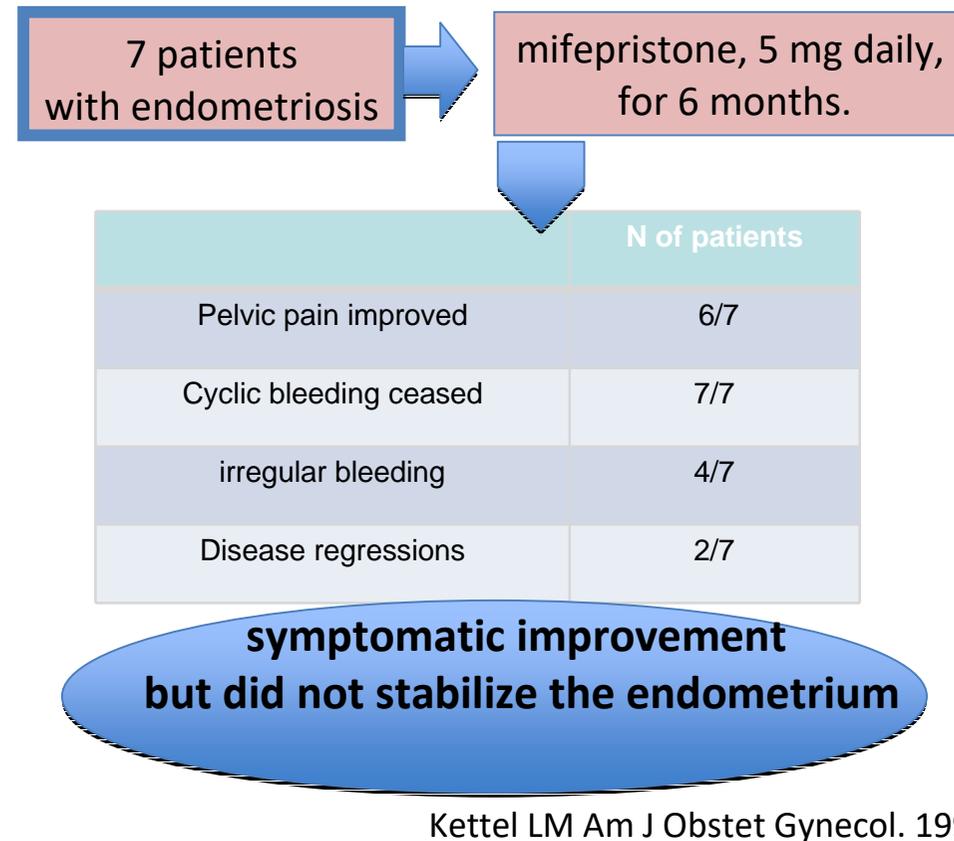
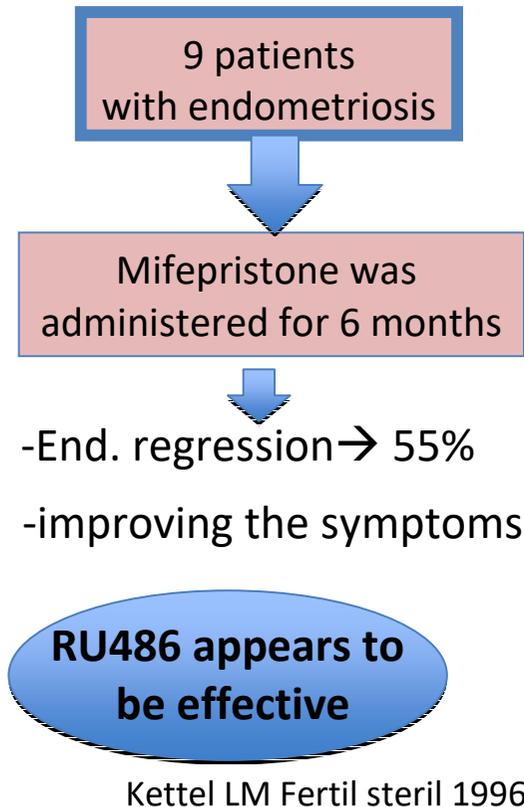
Mauricio Simões Abrão ✉, Felice Petraglia, Tommaso Falcone, Joerg Keckstein, Yutaka Osuga, Charles Chapron



Failure of medical treatment is frequently encountered with these aggressive disease phenotypes. Consequently, a large proportion of these patients will require extensive multidisciplinary surgeries.

Investigational Treatments

Selective Progesterone Receptor Modulators



Since then, these findings were never substantiated in RCT compared with placebo or other hormonal alternatives

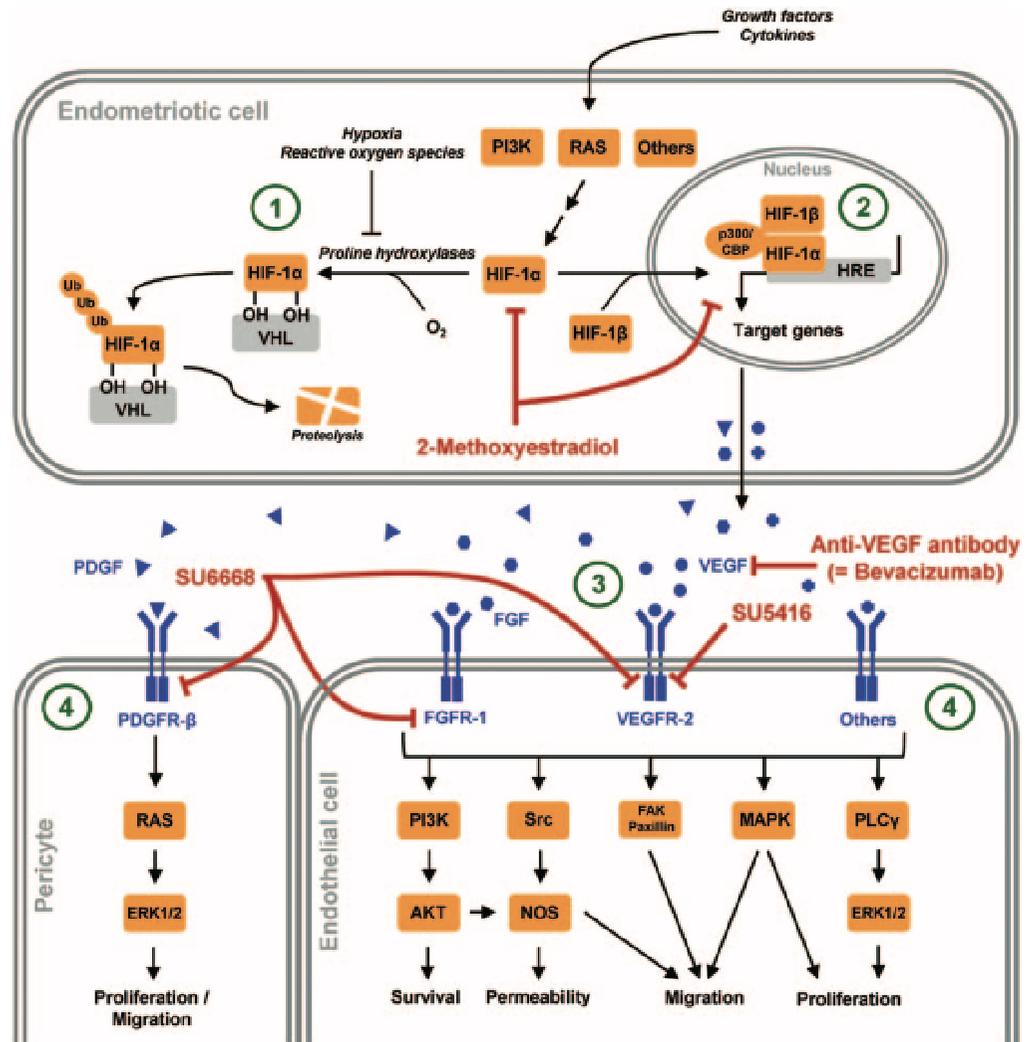
Non Hormonal Treatments

- Antiangiogenic Agents
- Tumor Necrosis Factor- α Blockers
- Pentoxifylline
- Peroxisome Proliferator Receptor Gamma Ligands

Antiangiogenic Agents

Anti-angiogenic compounds may inhibit the establishment of new endometriotic lesions in early stages of the disease or after surgical treatment.

growth factor inhibitors, endogenous angiogenesis inhibitors, fumagillin analogues, statins, cyclo-oxygenase-2 inhibitors, phytochemical compounds, immunomodulators, dopamine agonists, peroxisome proliferator-activated receptor agonists, progestins, danazol and gonadotropin-releasing hormone (GnRH) agonists



Tumor Necrosis Factor- α Blockers

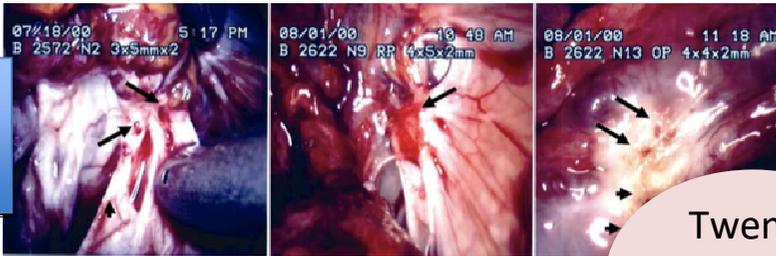
a proinflammatory cytokine able to initiate inflammatory cascades.
it is increased in the peritoneal fluid and serum of women with endometriosis.



THE COCHRANE
COLLABORATION®

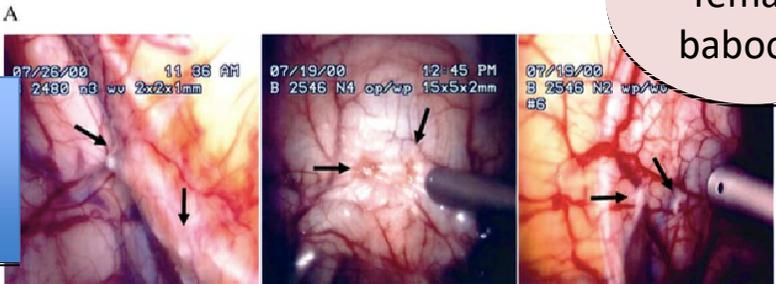
The results of review showed no evidence of an effect of infliximab, one of the known anti-TNF- α drugs, on pelvic pain reduction

Laparoscopic aspects of endo- metriosis in 25 days after PBS as placebo

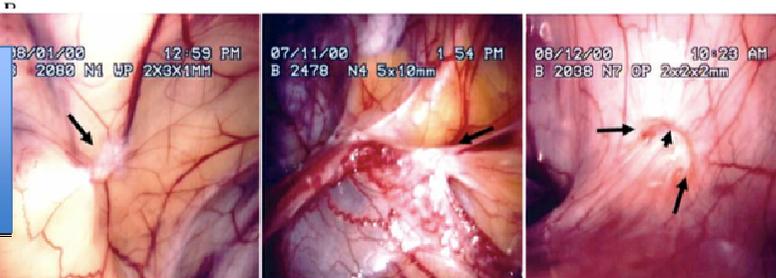


Twenty female baboons

Laparoscopic aspects of endometriosis 25 days after the start of injections with r-hTBP1



Laparoscopic aspects of endometriosis 25 days after the start of injections with Antide GnRH



Pentoxifylline

nonselective phosphodiesterase inhibitor that is known to have immunomodulatory properties that could be used for endometriosis-associated pain.



lack of evidence to recommend pentoxifylline for pain relief not to improve the chances of spontaneous pregnancies.

Figure 3. Forest plot of comparison: 2 Secondary outcomes, outcome: 2.1 Clinical pregnancy per woman randomised.

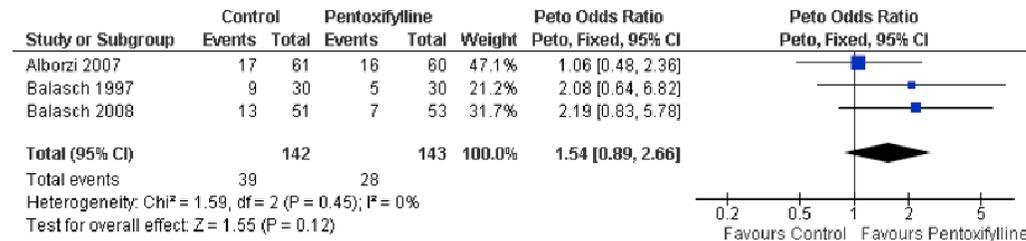


Figure 4. Forest plot of comparison: 1 Primary outcomes, outcome: 1.3 Reduction in pain - three month

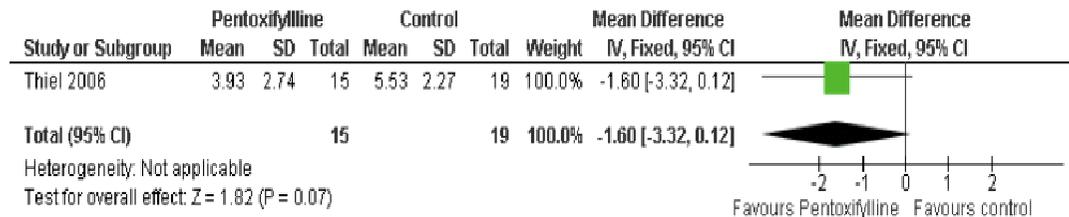
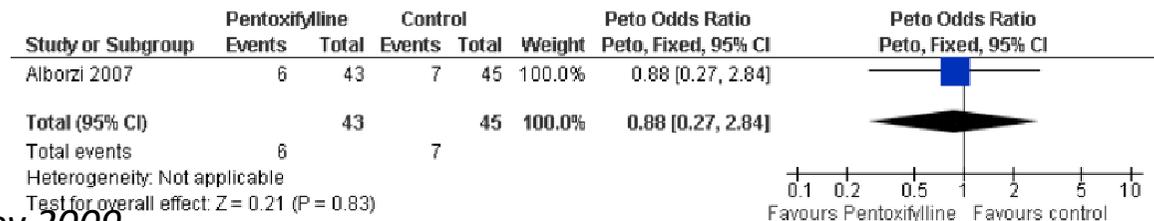


Figure 5. Forest plot of comparison: 2 Secondary outcomes, outcome: 2.3 Rates of recurrence.



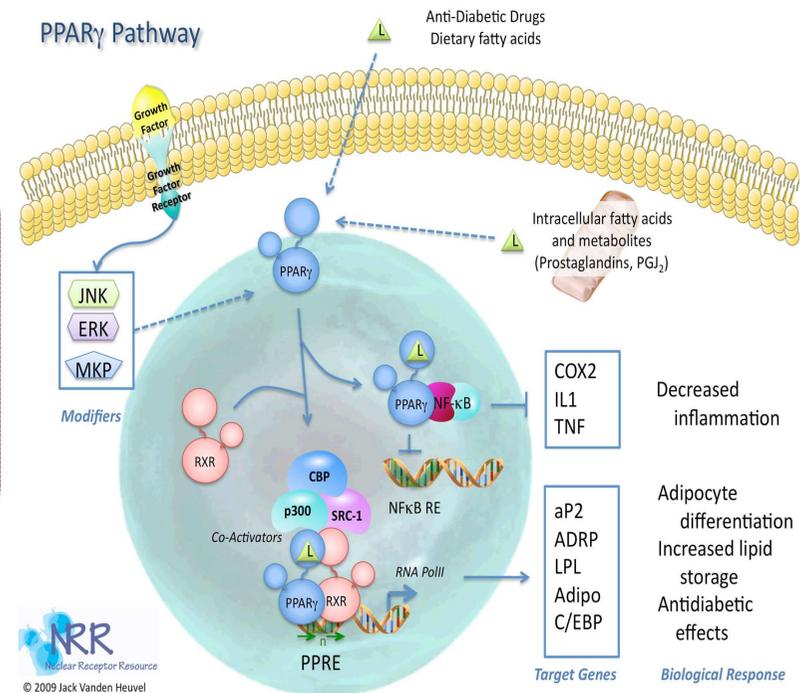
Peroxisome Proliferator Receptor Gamma Ligands



Rosiglitazone and pioglitazone are members of this family.



Rosiglitazone is associated with increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes



Androgens

- Danazol has multiple levels of action
- central inhibition of pituitary gonadotropin secretion
 - direct inhibition of endometriotic implant growth
 - direct inhibition of ovarian enzymes responsible for estrogen production.

Side effects reported in available studies

Study	Indication	Treatment	N	Side effects
Mais et al. ¹⁸	Abnormal uterine bleeding	200 mg vaginal danazol daily	20	Vaginal dryness (n = 1) Weight gain (n = 3) Spotting (n = 2) Bloating (n = 1)
Luisi et al. ¹⁹	Menorrhagia	200 mg vaginal danazol daily for 6 months	55	Vaginal irritation (n = 2)
Bhattacharya et al. ²⁰	Endometriosis	200 mg vaginal danazol daily for 6 months	19	none
Ferrero et al. ¹⁴	Endometriosis	100 mg vaginal danazol daily for 6 months	15	Seborrhea, oily skin, acne (n = 4) Headache (n = 3) Weight gain (n = 2) Vaginal irritation (n = 2)
Razzi et al. ²¹	Endometriosis	200 mg vaginal danazol daily for 12 months	21	Vaginal irritation (n = 4)
Igarashi et al. ¹³	Endometriosis	1500 mg vaginal danazol ring monthly	56	Colpitis (n = ?)
Igarashi et al. ²²	Adenomyosis	400 mg danazol IUD	14	Spotting (n = ?) IUD expulsion (n = 1)
Mizutani et al. ²³	Pre-hysterectomy	100 mg vaginal danazol daily for 2 to 6 months	8	Acne (n = 1)
Takeda and Adachi ²⁴	Endometriosis	Endometrioma cyst puncture with 50 mg danazol solution injection	17	None
Igarashi ¹⁷	Endometriosis/adenomyosis	2 to 3.5 g danazol vaginal ring releasing 95 mg per day or 175 mg danazol IUD for 4 months	39	Weight gain (n = 1)
Okamura et al. ²⁵	Endometriosis	Danazol suppository, 3 months to 1+ year, dose N/A	52	None
Cobellis et al. ²⁵	Endometriosis	300 mg to 400 mg danazol IUD for 6 months	18	Spotting (n = 2) IUD expulsion (n = 1)

review of 334 in 12 reported studies showed that vaginally administered danazol is effective and well tolerated in the treatment of rectovaginal endometriosis.

Gn-RH Antagonists

15 pt

Use of GnRH antagonists in the treatment of endometriosis

GnRH antagonist cetrorelix (Cetrotide) 3 mg once weekly over 8 weeks



	N of patients
symptom-free period	15/15; 100%
Regression disease	9/15; 60%

Küpker W et al reprod biomed 2002

Elagolix for the Treatment of Endometriosis: Effects on Bone Mineral Density

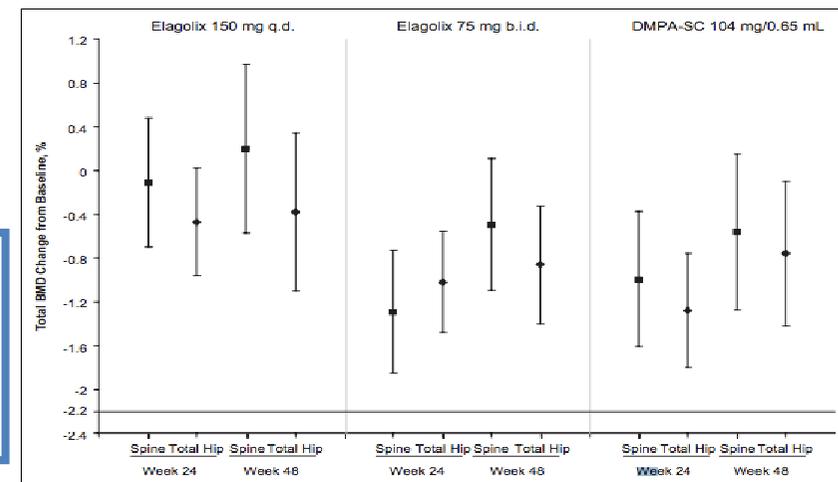
252 endometriosis-associated pain

Elagolix

VS

Medroxyprogesterone Acetate

This study showed that similar to DMPA-SC, elagolix treatment had minimal impact on BMD over a 24-week period and demonstrated similar efficacy on endometriosis-associated pain.



Bruce C et al reprod scienc 2014



**OSPEDALE
EVANGELICO**  **VILLA
BETANIA**

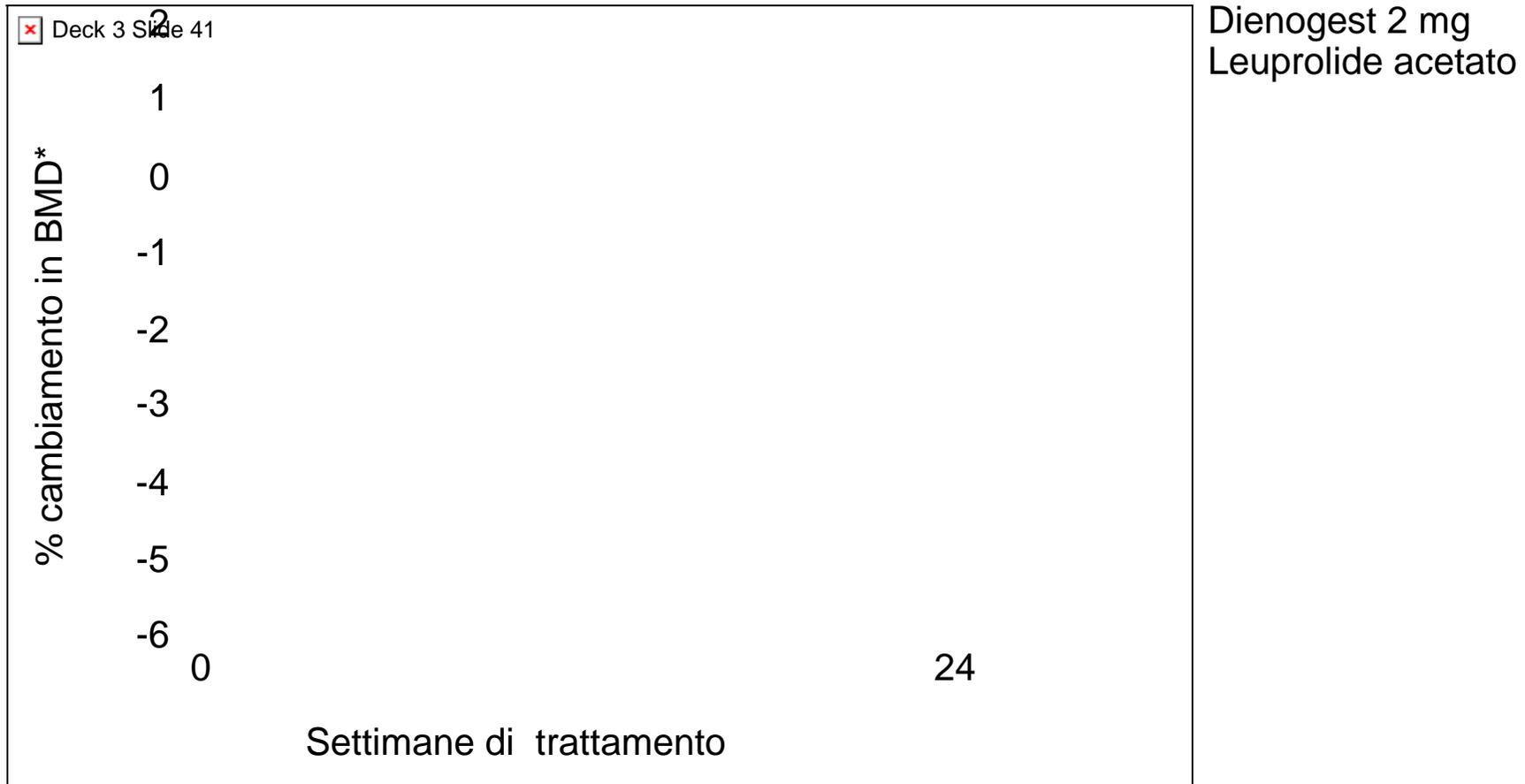
FONDAZIONE EVANGELICA BETANIA

www.villabetania.org/ginecologia



Cambiamento di minerale ossea (BMD)

Dienogest (n=120) and Leuprolide acetate (n=128)



*mean \pm SEM

SEM, standard error of the mean

Strowitzki T *et al. Hum Reprod* 2010

Significativa differenza in favore del dienogest versus leuprolide acetato ($P=0.0003$)

Confronto con i farmaci di riferimento

Analoghi del GnRH

- Elevata e rapida efficacia nella riduzione del dolore
- Utilizzo limitato a 6 mesi x gli effetti collaterali
- Effetti collaterali simil menopausa (vampate, secchezza vaginale..)
- Importante riduzione della densità minerale ossea

Dienogest

- Analoga efficacia e rapidità
- Nessuna limitazione temporale (studi ad 1 anno e oltre)
- Effetti collaterali (cefalea, nausea e spotting) comuni soprattutto nei primi mesi di assunzione.
- Nessun effetto o minimo rilevato

Dienogest reduces HSD17 β 1 expression and activity in endometriosis

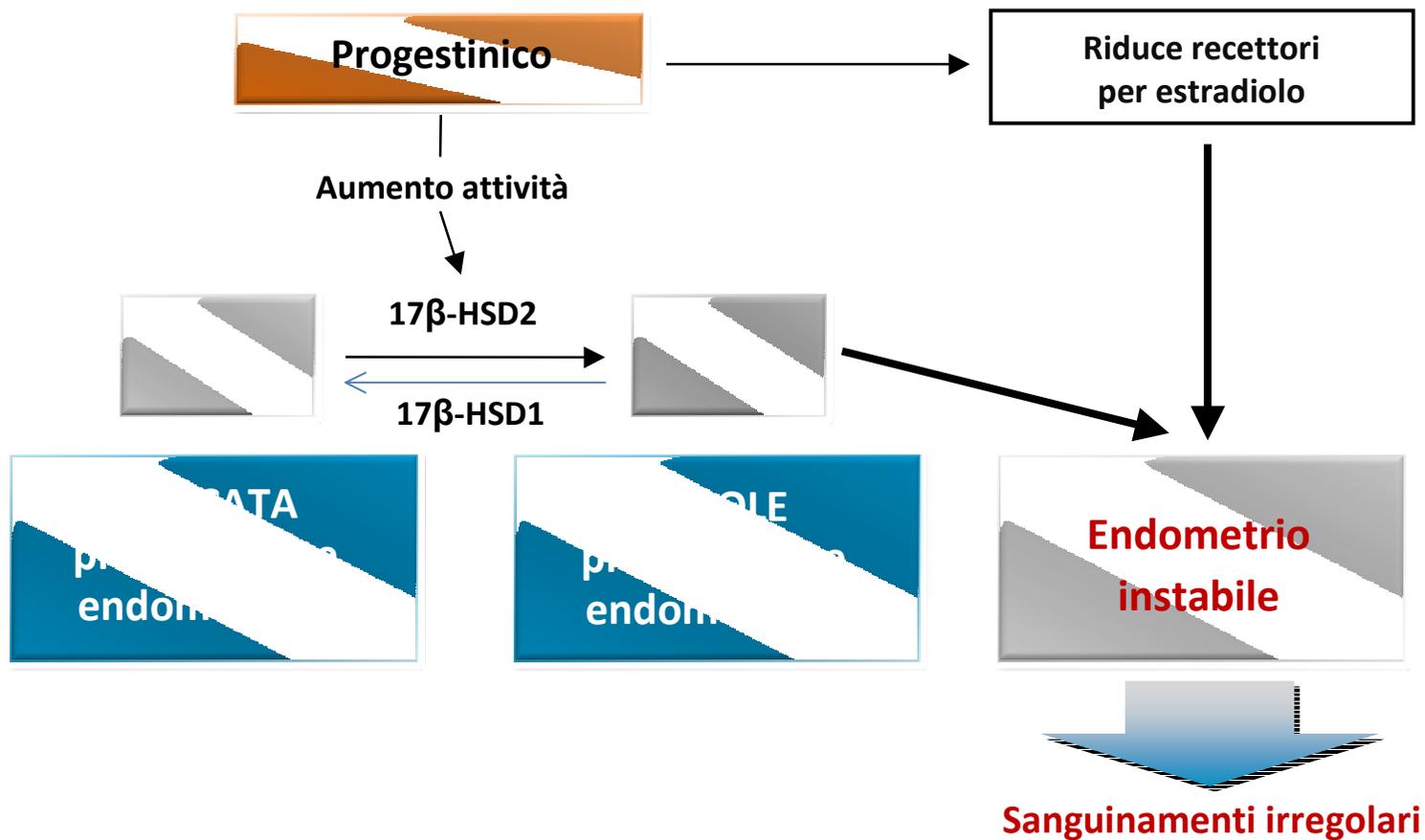
Taisuke Mori, Fumitake Ito, Hiroshi Matsushima, Osamu Takaoka, Akemi Koshiba, Yukiko Tanaka, Izumi Kusuki and Jo Kitawaki

Department of Obstetrics and Gynecology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kamigyo-ku, Kyoto 602-8566, Japan

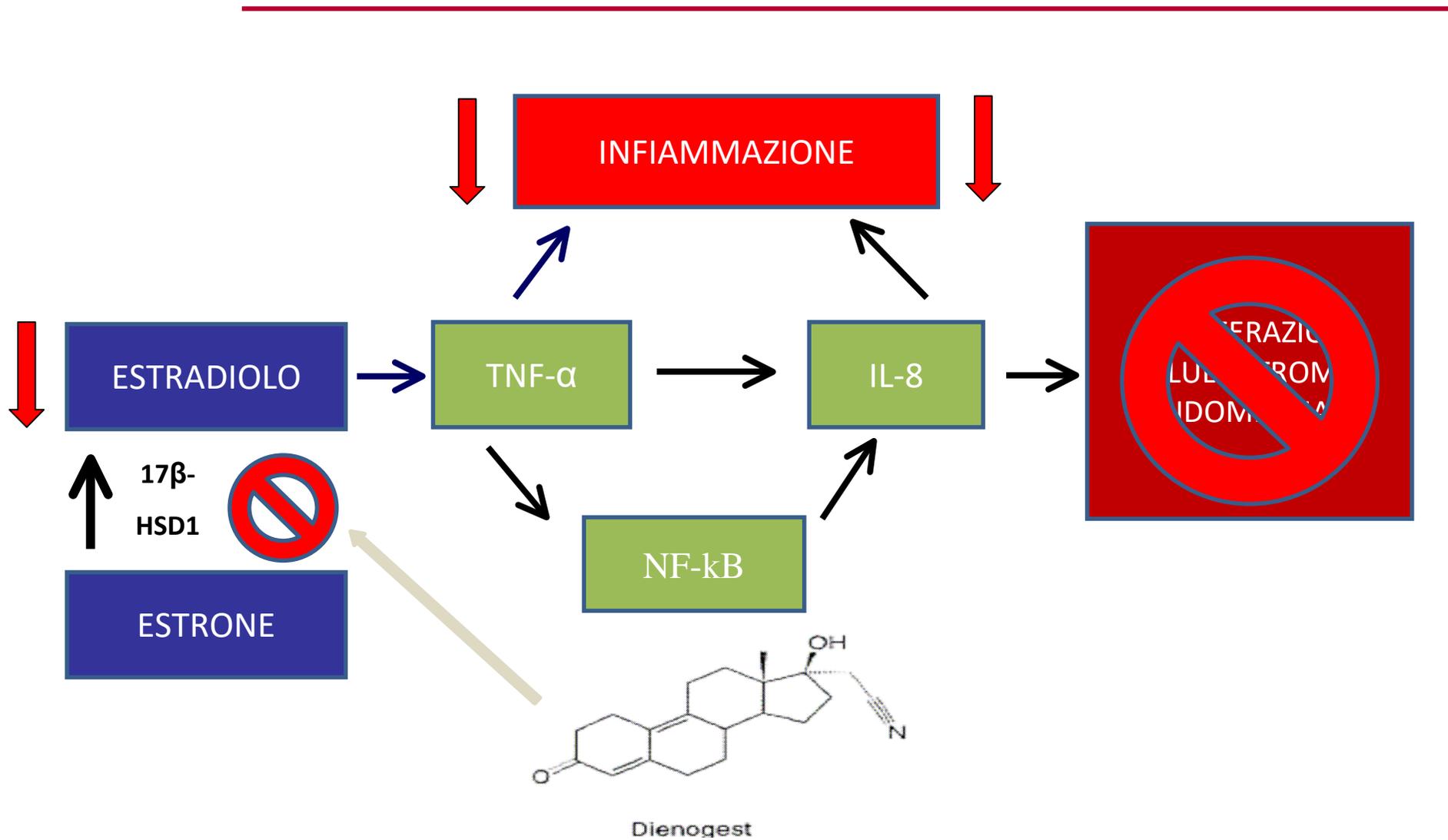
Correspondence
should be addressed
to T Mori
Email
moriman@koto.kpu-m.ac.jp

In this study, we demonstrated DNG-mediated inhibition of mRNA expression, catalytic activity, and protein expression of HSD17 β 1 in endometriosis. Taken together with the previous findings that DNG inhibits aromatase in endometriosis (Shimizu *et al.* 2011, Yamanaka *et al.* 2012), DNG exerts comprehensive inhibition of abnormal estrogen production by the inhibition of two key enzymes that regulate estradiol production (Fig. 3). These actions of DNG contribute, in part, to its therapeutic effect on endometriosis.

Effetto progestinici sull'endometrio



MECCANISMO D' AZIONE PROPOSTO

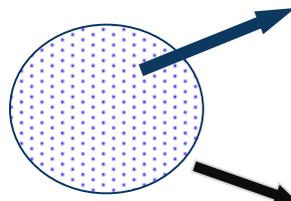


NEXPLANON



Contraccettivo ormonale, a lunga durata d'azione, **efficace per 3 anni**
Impianto sottocutaneo radio-opaco, biocompatibile, contenente **68 mg di etonogestrel, metabolita attivo del desogestrel** precaricato in un applicatore monouso

- Elevata efficacia contraccettiva (99.95%)
- Alto tasso di prosecuzione
- Rilascio costante e continuo del progestinico
- rapido ritorno alla fertilità

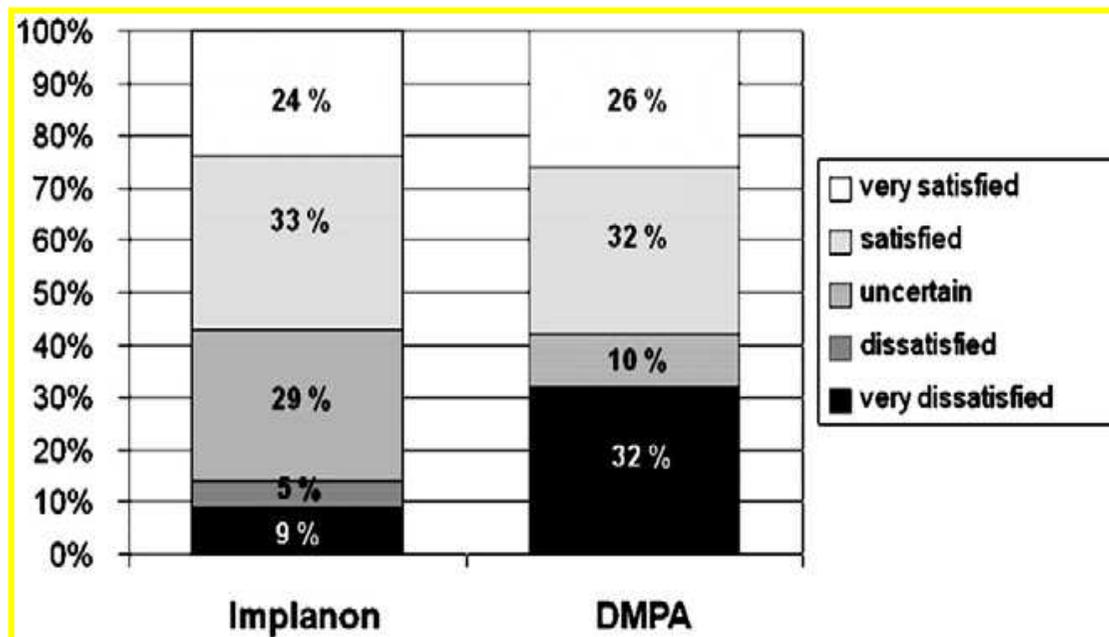


- Core:
- 37% ethylene vinyl acetate (EVA) copolymer
 - 60% etonogestrel (68 mg)
 - 3% barium sulfate (15 mg)

Rate-controlling membrane: (0.06 mm)
100% EVA



Un'alta percentuale di donne sono risultate soddisfatte o veamente soddisfatte dall'utilizzo del Nexplanon®



L'impianto sottocutaneo all'Etonogestrel Nexplanon® potrebbe essere un'opzione efficace, sicura, ben tollerata e comoda nel trattamento di donne con endometriosi sintomatica che hanno bisogno anche di contraccezione.

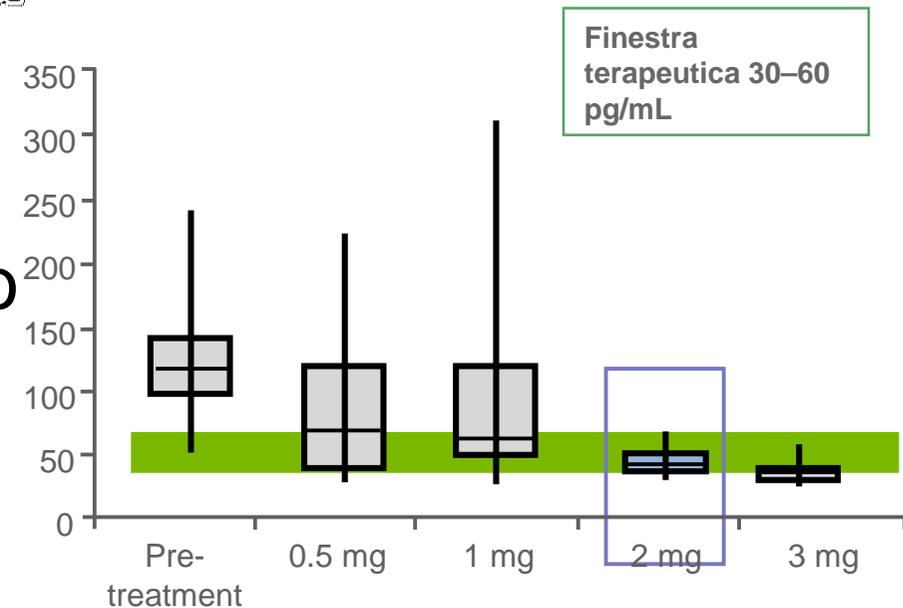


Perche' 2mg

2mg e 4mg hanno una efficacia sulla sintomatologia e sulla riduzione delle lesioni simile...

Ma

Il 4 mg abbassa l'estradiolo circolante sotto la finestra terapeutica aumentando i possibili effetti ipoestrogenici



Terapia a più di 18 mesi

Obiettivo dello studio

Esperienza a lungo termine con dienogest in pazienti con endometriosi fino a **30 mesi**

N=10

	RISPOSTA TERAPEUTICA
RIDUZIONE DEL DOLORE	10/10
ADENOMIOSI	2/5
CISTI OVARICHE CIOCCOLATO	2/2

Takagi H, et al. 2011 (Abstract).

Adverse Drug Reactions With Frequency \geq 1% in Pivotal Clinical Trials With Visanne® (N=303)

MedDRA System Organ Class	MedDRA Term	n	%
Disordini del metabolismo e della nutrizione	Aumento di peso	11	3.6
Alterazioni psichiatriche	Depressed mood	9	3.0
	Alterazioni del sonno	7	2.3
	Nervosismo	4	1.3
	Diminuzione della libido	5	1.7
Disordini del sistema nervoso	Mal di testa	20	6.6
	Emicrania	4	1.3
Disordini Gastrointestinali	Nausea	11	3.6
	Dolore Addominale	5	1.7
Disordini della pelle e del tessuto sottocutaneo	Acne	6	2.0
	Alopecia	4	1.3
Disordini del sistema riproduttivo e della mammella	Mastodinia	16	5.3
	Cisti Ovariche	8	2.6
	Sanguinamenti uterini/vaginali anche con spotting	4	1.3
Disordini di tipo generale	Condizioni di astenia	7	2.3
	Irritabilità	4	1.3

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, N = total number, n = number of subjects

Note: The most appropriate MedDRA term (version 11.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

Use of dienogest over 53 weeks for the treatment of endometriosis

Kouhei Sugimoto¹, Chie Nagata², Hiroshi Hayashi¹, Satoshi Yanagida¹ and Aikou Okamoto¹

- ❖ Obiettivo: valutare l'efficacia e la sicurezza del DNG in terapia superiori alle 53 settimane
- ❖ Popolazione: 75 pazienti (età media 39,4 anni) sono state trattate con DNG 2 mg per un periodo medio di 87 settimane (range 53-120 settimane)

37 pazienti con adenomiosi
26 pazienti con cisti endometrioidiche
12 pazienti in fase post chir.

1 anno
9 mesi

1 anno
6 mesi

} Fase III o IV

Risultati: diametro delle cisti

- ❖ Dopo 15 mesi di terapia con DNG 2 mg/die il diametro delle cisti cioccolato si è ridotto del 69,8%
- ❖ A 18 mesi, in seguito all'interruzione della terapia le dimensioni delle cisti tendono ad aumentare.
- ❖ La ripresa della terapia porta nuovamente ad una riduzione del 27,1% in 24 mesi

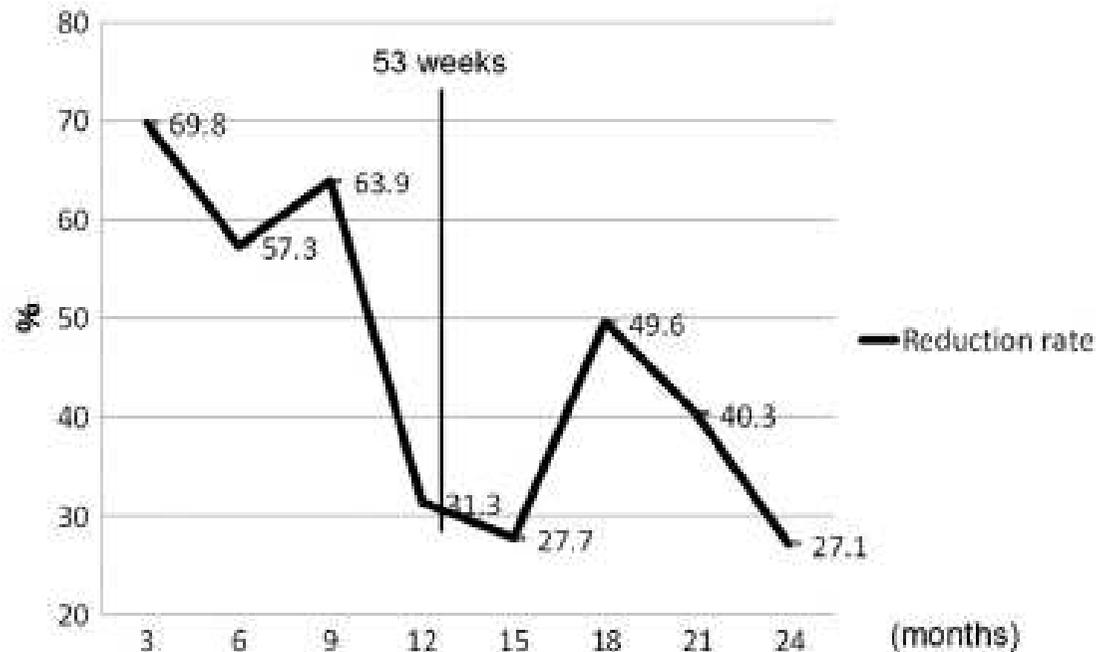


Figure 1 Average reduction rate of endometriotic cyst. Ovarian endometriotic cysts were reduced satisfactorily until 15 months. At 18 months, ovarian endometriotic cysts increased slightly, because of a short cessation of dienogest in some cases.

Risultati: spessore del miometrio

- ❖ Nelle pazienti con adenomiosi lo spessore del miometrio mostra una graduale riduzione dalle 53esima settimana al 21esimo mese

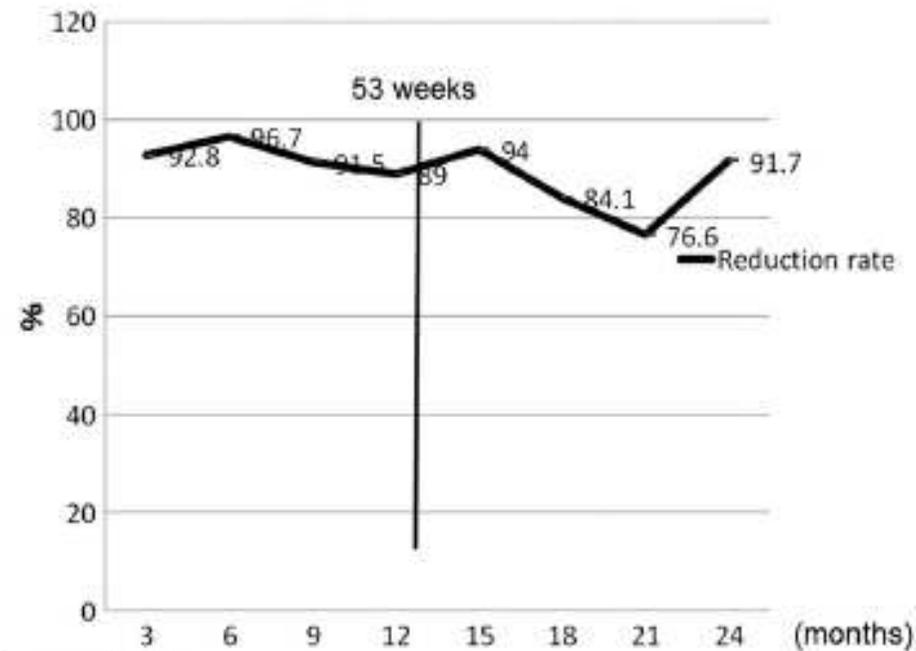
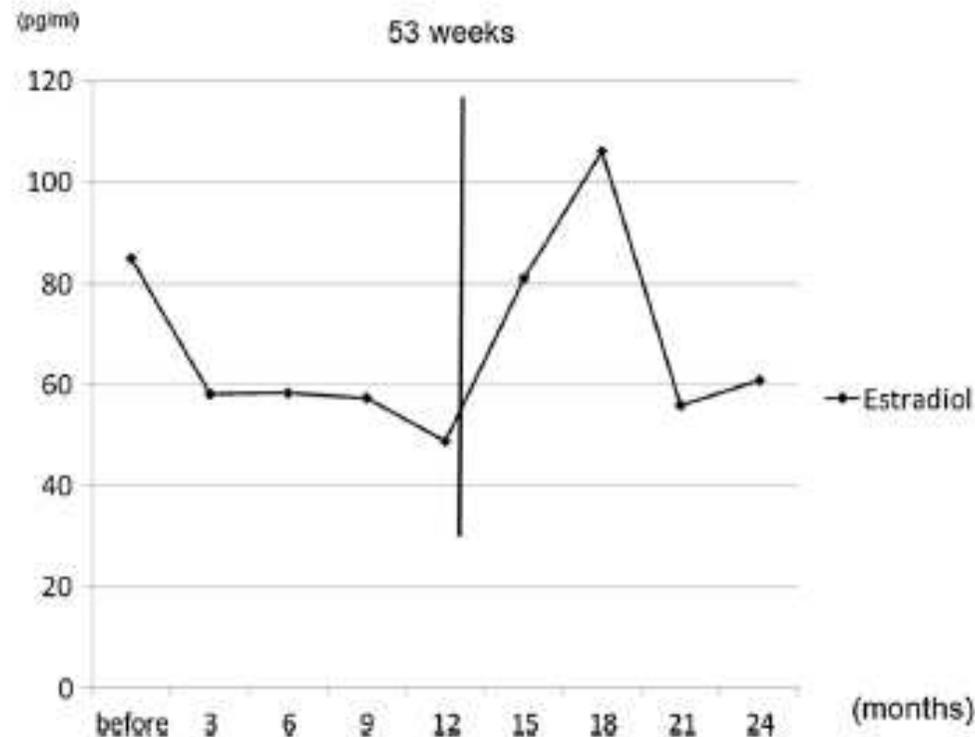


Figure 2 Average reduction rate of adenomyosis. The myometrium thickness of adenomyosis barely reduced from 53-120 weeks.

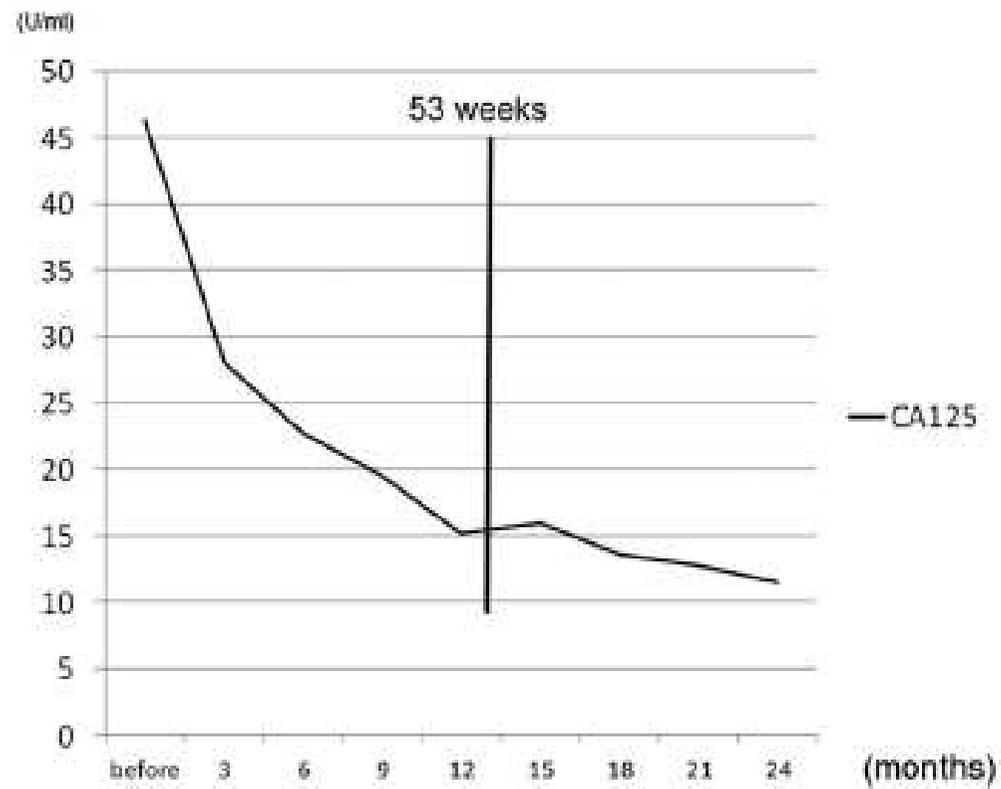
Risultati: livelli di estradiolo

- ❖ I livelli di estradiolo sierico diminuiscono rapidamente entro i primi 3 mesi di terapia, fino a raggiungere un plateau di 60 pg/ml. L'incremento tra il 15esimo e il 18esimo mese è in linea con la sospensione precoce del trattamento



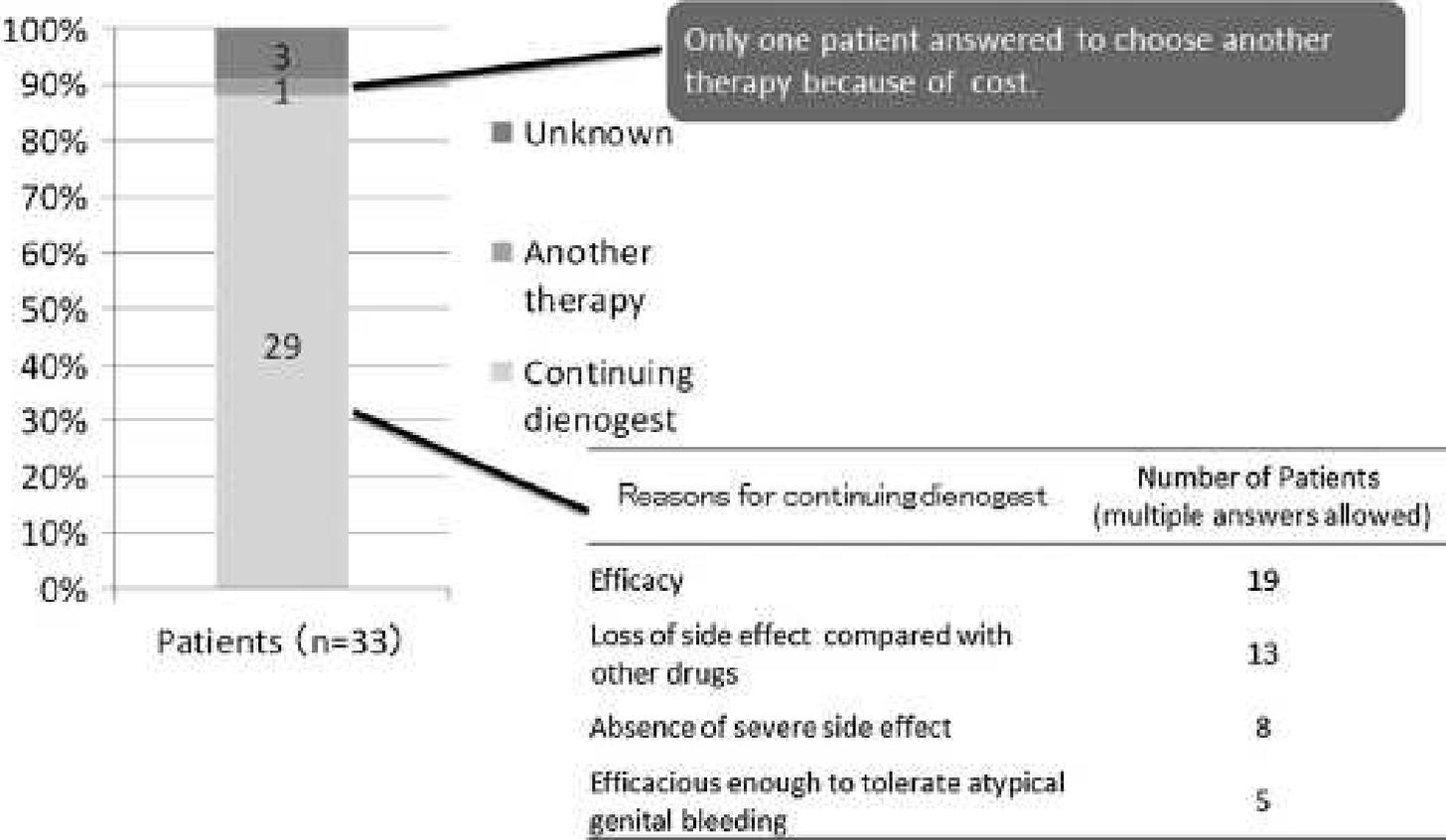
Risultati: Ca125

- ❖ I livelli di Ca125 si riducono di circa il 50% dopo 6 mesi



Risultati: soddisfazione delle pazienti

❖ Continueresti la terapia col Dienogest?

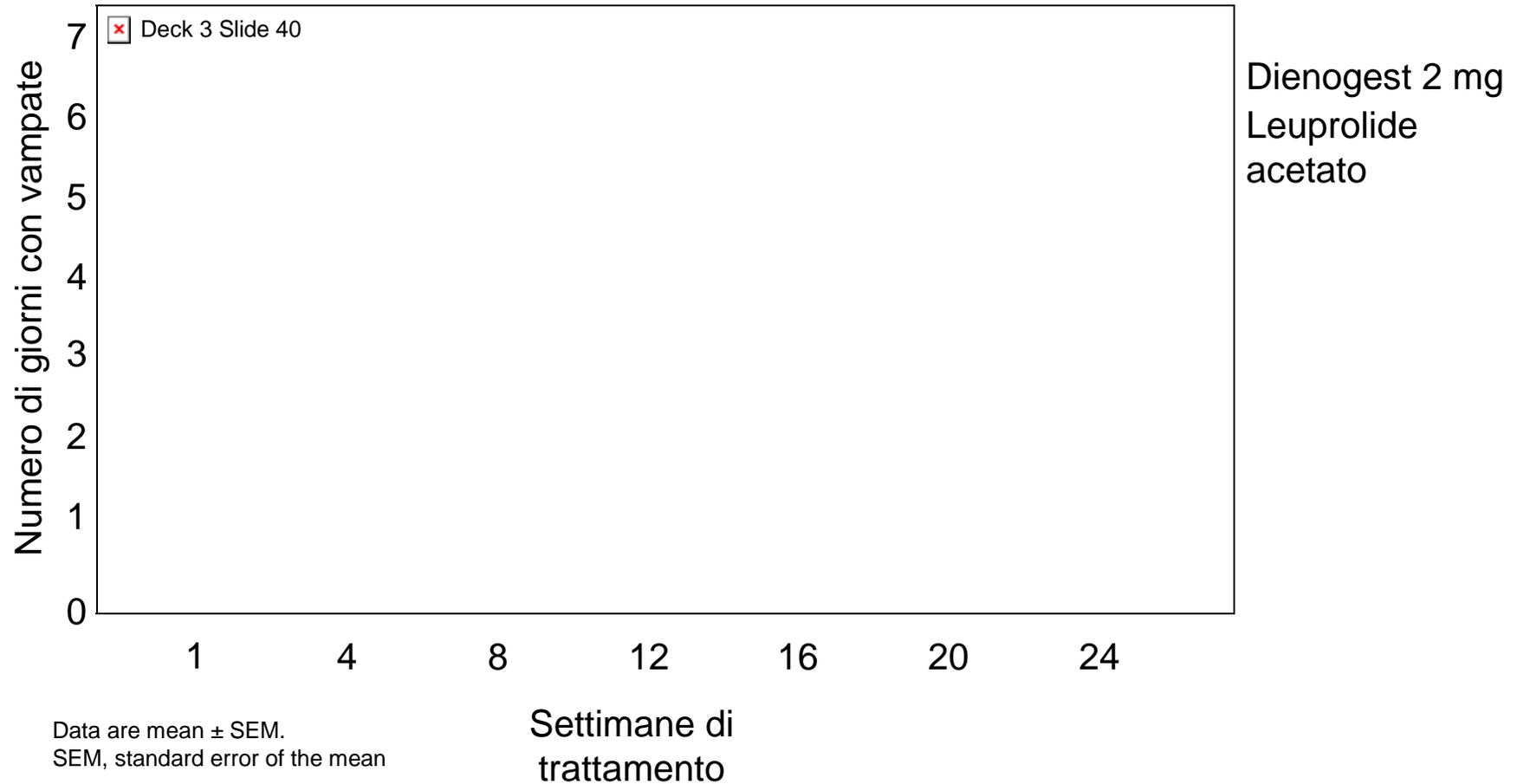


Conclusioni

- ❖ Il trattamento con Dienogest per periodi superiori alle 52 settimane si è dimostrato efficace e sicuro.
- ❖ La riduzione delle cisti cioccolato avviene in maniera importante (-30%) già dopo 3 mesi di trattamento.
- ❖ La regressione dell'adenomiosi richiede periodi di trattamento più lunghi.
- ❖ Il questionario somministrato alle pazienti ha evidenziato un elevato grado di soddisfazione.

Numero di vampate

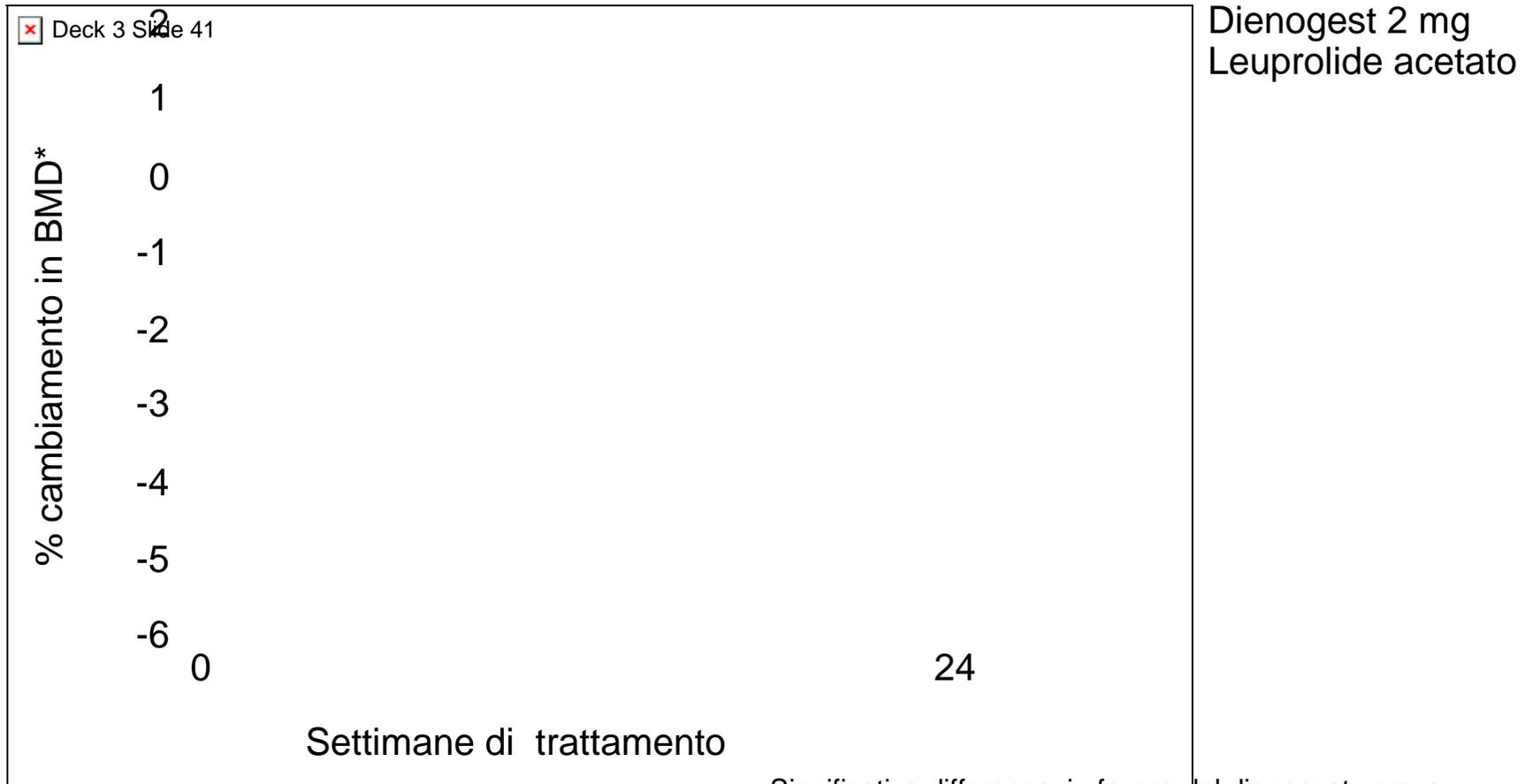
Dienogest 2 mg versus Leuprolide Acetato



Data are mean \pm SEM.
SEM, standard error of the mean

Cambiamento di minerale ossea (BMD)

Dienogest 2 mg versus Leuprolide Acetato



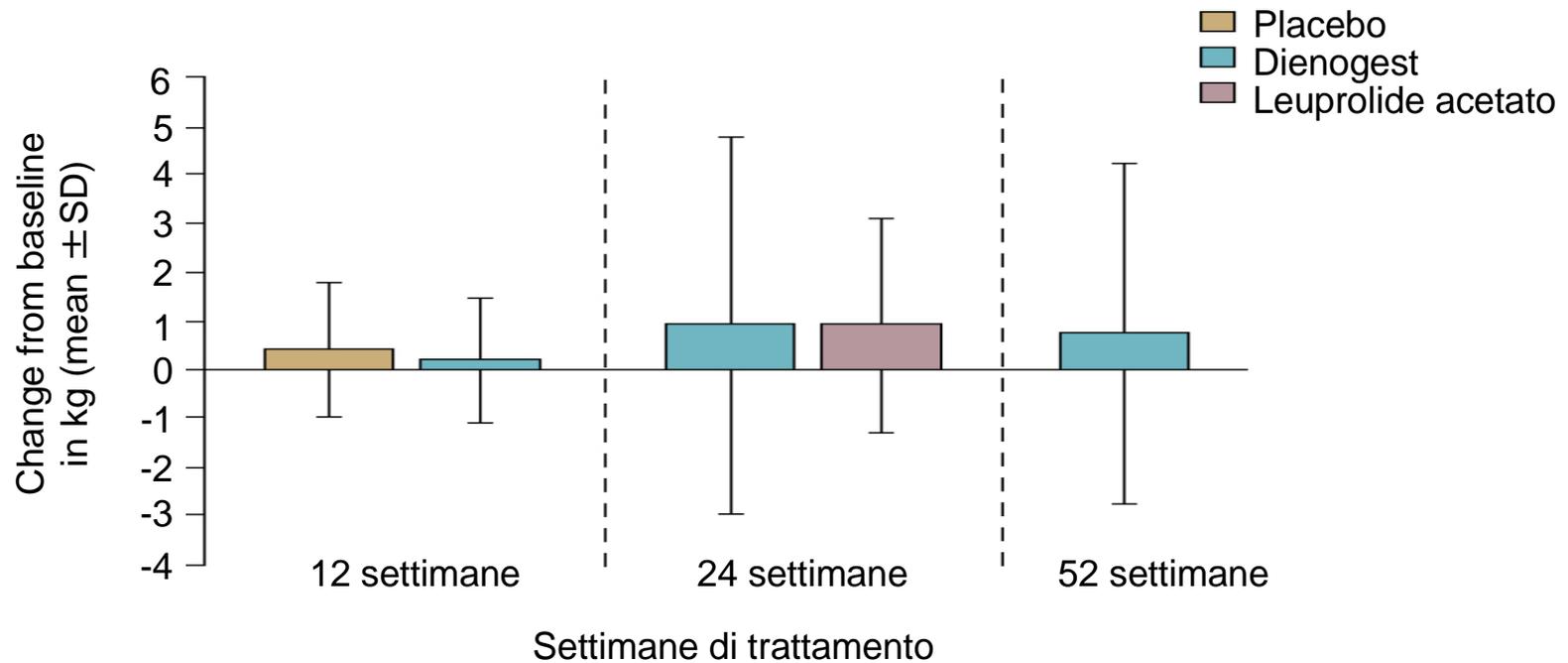
*mean \pm SEM

SEM, standard error of the mean

Strowitzki T *et al. Hum Reprod* 2010

Dienogest 2 mg e massa corporea

- Dienogest non è associato a un rilevante aumento di peso



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

Strowitzki T et al. *Hum Reprod* 2010

Petraglia et al. *Arch Gynecol Obstet* 2012

Livelli di lipidi nel plasma Dienogest 2 mg versus Placebo

Parameter (normal reference range)	Dienogest 2 mg		Placebo	
	Basale	Fine studio	Basale	Fine studio
Trigliceridi; mmol/L (0.8–1.94)	0.96 ± 0.51	1.11 ± 0.68	0.99 ± 0.73	1.08 ± 0.86
Total colesterolo; mmol/L (4.14–6.73)	4.79 ± 0.95	4.87 ± 1.03	4.94 ± 1.12	4.95 ± 1.11
HDL-C; mmol/L (1.09–2.28)	1.48 ± 0.31	1.48 ± 0.34	1.55 ± 0.38	1.55 ± 0.33
LDL-C; mmol/L (1.97–5.65)	2.89 ± 0.73	2.93 ± 0.77	2.95 ± 0.75	2.95 ± 0.76

Mean (± SD) lipid concentrations at baseline and after 12 settimane di dienogest o placebo treatment.
SD, standard deviation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

DIENOGEST 2 mg

Effetto su libido e trofismo vaginale

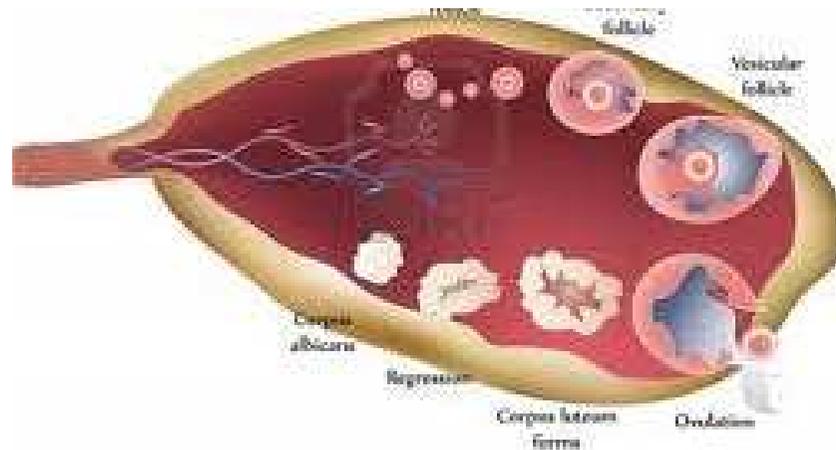
Donne con endometriosi confermata e trattata con dienogest (2 mg orale al giorno, n=120) versus leuprolide acetato (3.75 mg IM ogni 4 settimane, n=128) per 6 mesi.

	Dienogest	Leuprolide acetato
Diminuzione della libido	4.2%	6.3%
Secchezza vaginale	1.7%	7.0%

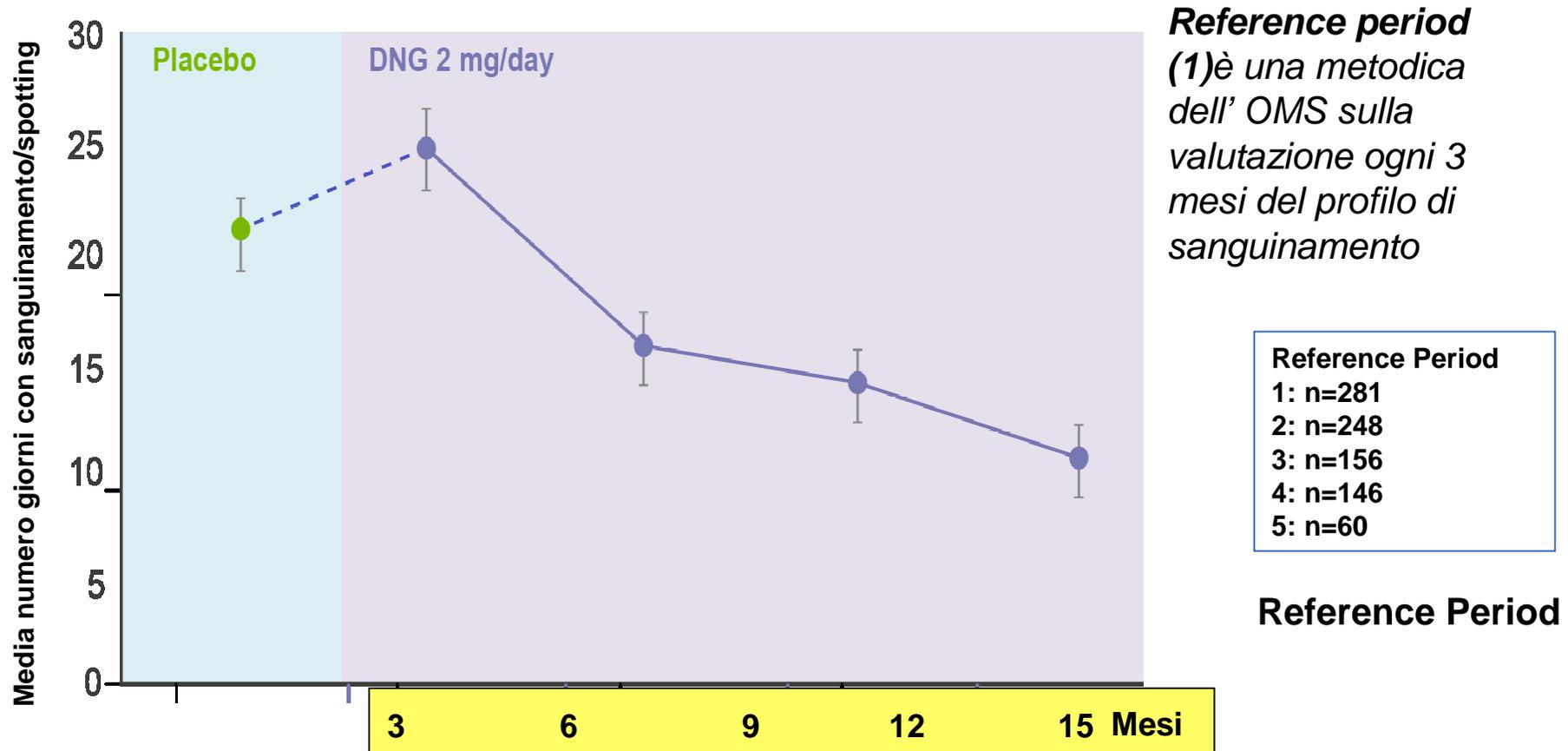
IM, intramuscular

RITORNO DELL' OVULAZIONE

- In uno studio su 87 donne che assumevano vari dosaggi di Dienogest il 69% di queste aveva un picco di LH entro 43 giorni, dal termine della terapia
- Se si considera il valore ematico di progesterone superiore a 1,6 ng/ml come indicativo di una ovulazione, solo 2 donne su 87 hanno non hanno raggiunto tale valore al termine del follow-up



Numero di giorni con spotting/sanguinamenti con Dienogest 2 mg



Strowitzki T et al. *Eur J Obstet Gynecol Reprod Biol* 2010
Strowitzki T et al. *Hum Reprod* 2010
Petraglia F et al. *Arch Gynecol Obstet* 2011
Visanne® Product Monograph, October 12, 2011

(1)Rodriguez G, Faundes-Latham A, Atkinson LE. An approach to the analysis of menstrual patterns in the critical evaluation of contraceptives. *Stud Fam Plann* 1976;7:42-51.

Profilo di sanguinamento

Tipo di sanguinamento	Primo periodo di 90 giorni (n=290)	Quarto periodo di 90-giorni di trattamento (n=149)
Amenorrea	1.7%	28.2%
Sanguinamento infrequente	27.2%	24.2%
Sanguinamento frequente	13.4%	2.7%
Sanguinamento irregolare	35.2%	21.5%
Sanguinamento prolungato	38.3%	4.0%
Sanguinamento normale	19.7%	22.8%

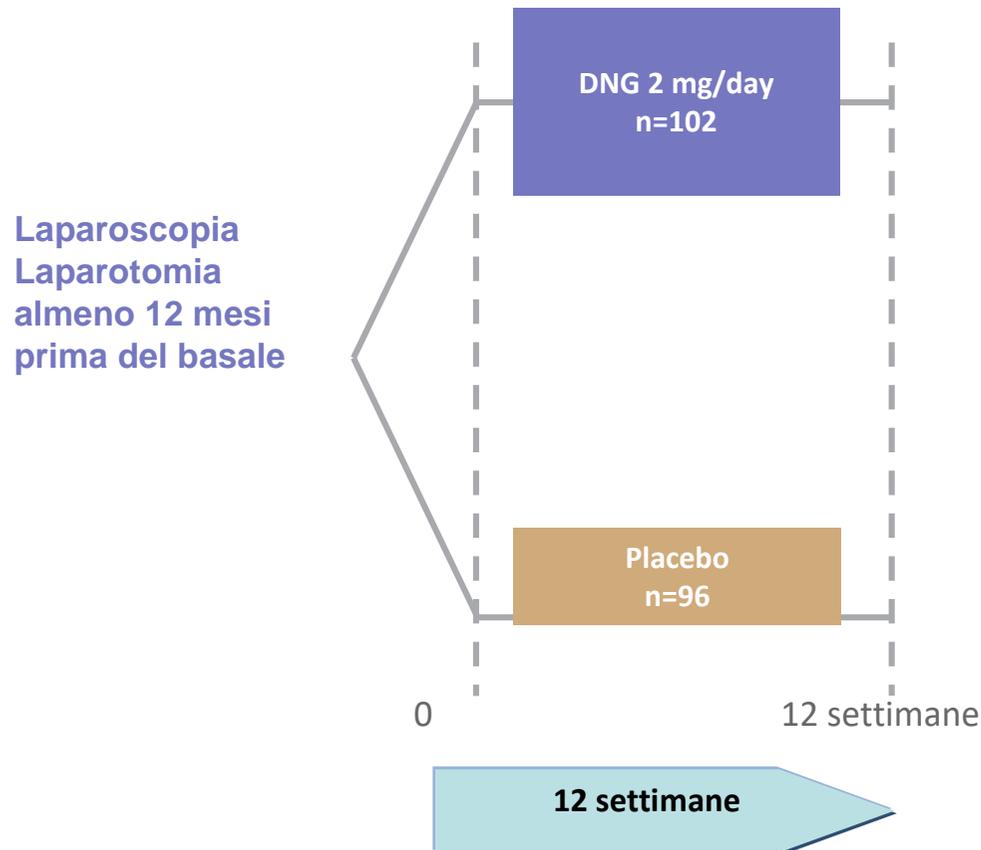
Il profilo di sanguinamento diviene meno regolare dopo l'inizio del trattamento con dienogest 2 mg. Frequenza ed intensità dei sanguinamenti diminuiscono con il proseguimento della terapia.

La variazione nello schema di sanguinamento solo occasionalmente è stata riportata come evento avverso ed era inoltre associata ad un basso tasso di abbandono, a dimostrare un elevato livello di accettabilità. Nello studio a lungo termine, solo due donne su 168 hanno sospeso il trattamento a causa del profilo di sanguinamento.

Trattamento con endometriosi a più di 18 mesi

- Donne trattate da 18 a 30 mesi
- N=10
- Il principale effetto collaterale è il sanguinamento irregolare (diminuito o sparito nel tempo)
- Nessuna anomalia ematochimica o fattore della coagulazione.
- Estradiolo è rimasto nel range 34.0–68.9 pg/mL
- Nessun decremento della densità ossea

OBIETTIVO E DIAGRAMMA DI FLUSSO DELLO STUDIO



Obiettivo: Studiare l'efficacia e la sicurezza del Dienogest 2 mg comparato al placebo nel trattamento del dolore pelvico associato ad endometriosi (EAPP).

Endometriosi laparoscopicamente confermata stadi dal 1 al 4 del r-ASRM. Gli stadi più rappresentati erano il 3 e 4

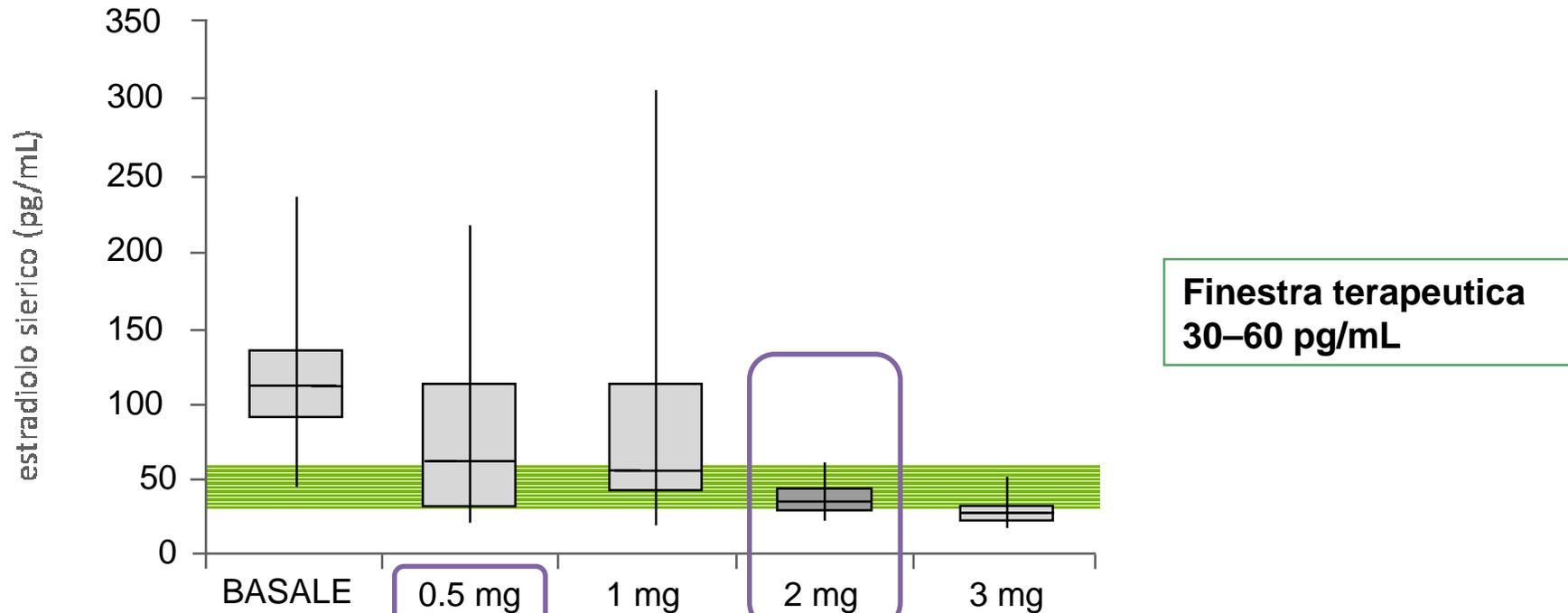
Criteri di valutazione: VAS ogni 4 settimane

Analisi di laboratorio e diario giornaliero delle pazienti per scrivere eventi avversi e sanguinamenti per i dati sulla sicurezza.

Finestra terapeutica

- La finestra terapeutica o «*estrogen threshold hypothesis*» ipotizza una interrotta crescita delle lesioni endometriose sotto i 50pg/ml di concentrazione di estradiolo

Livelli di estradiolo

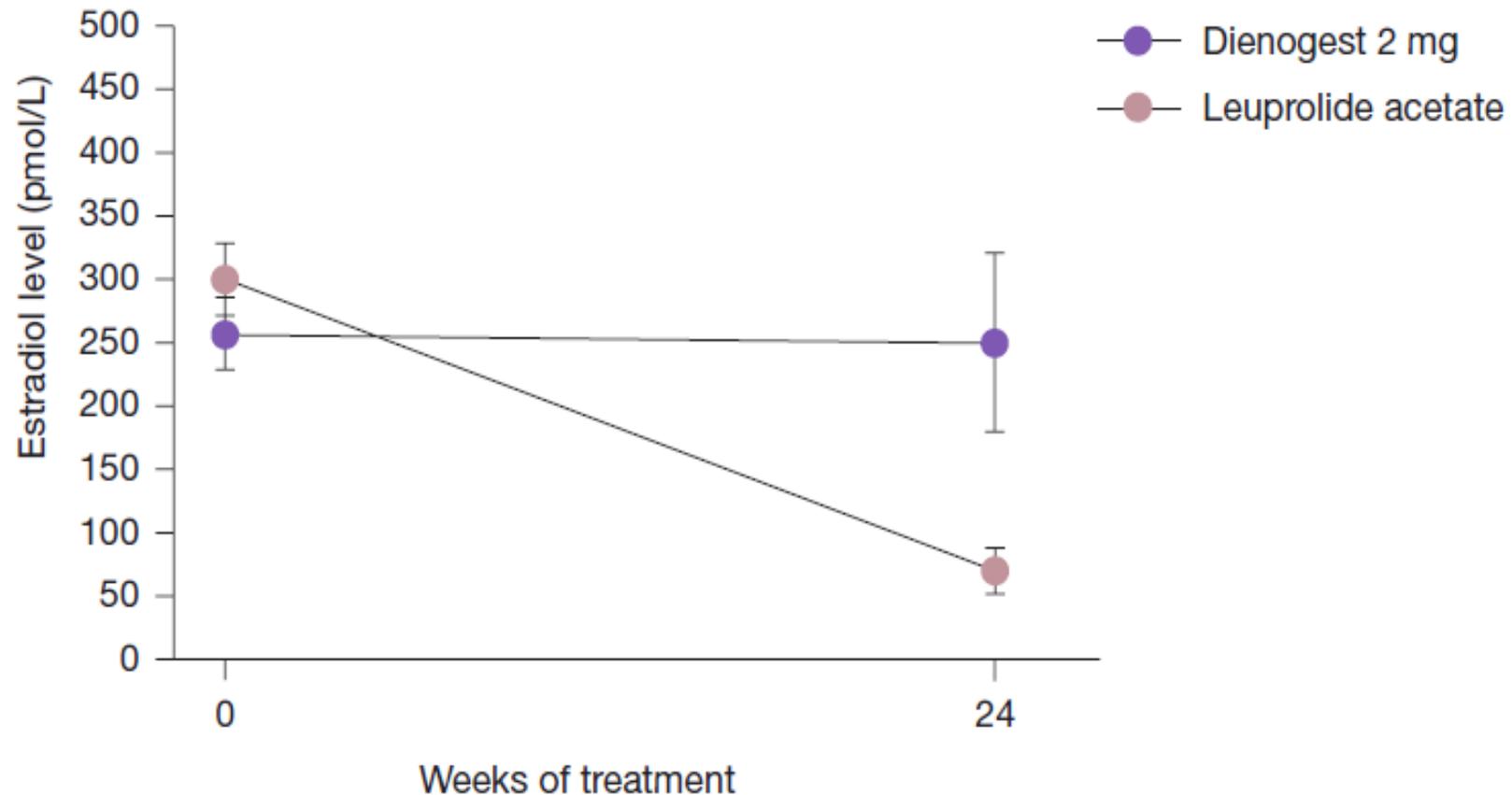


CON IL DIENOGEST ALLA DOSE DI 2mg AL GIORNO, I LIVELLI DI ESTRADIOLO RIMANGONO ENTRO LA FINESTRA TERAPEUTICA PER RIDURRE I SINTOMI DELL' ENDOMETRIOSI

Klippping C, et al. *J Clin Pharmacol* 2011

Barbieri R, *J Repro Med* 1998

Livelli di estradiolo nel tempo



Strowitzki T, Marr J, Gerlinger C, Faustmann T, Seitz C. Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis: a 24-week, randomized, multicentre, open-label trial. *Hum Reprod* 2010; 25(3): 633–641.

Current Endometriosis Treatment:

Endometrioma: Lack of

Effective Medical Treatment

treatment goals for endometriomas

pain relief

avoiding rupture or torsion

excluding malignancy

preventing Symptomatic /expanding endometriomas



After cystectomy for ovarian endometrioma in women not immediately seeking conception, clinicians are recommended to prescribe hormonal contraceptives for the secondary prevention of endometrioma (Vercellini, et al., 2010).

A

The results of this study suggest a negative impact of excision of endometriomas on ovarian reserve as evidenced by a significant postoperative fall in circulating AMH.

Current Endometriosis Treatment:

Endometrioma: Lack of Effective Medical Treatment

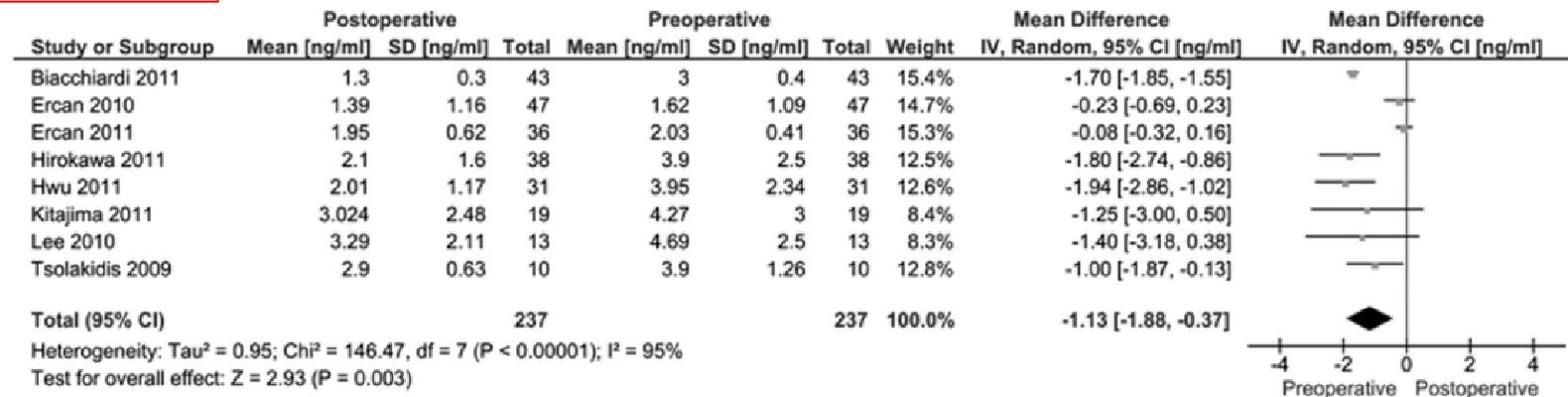


After cystectomy for ovarian endometrioma in women not immediately seeking conception, clinicians are recommended to prescribe hormonal contraceptives for the secondary prevention of endometrioma (Vercellini, et al., 2010).



serum anti-Mullerian hormone (AMH)

IMPACT ON OVARIAN RESERVE



The results of this study suggest a negative impact of excision of endometriomas on ovarian reserve as evidenced by a significant postoperative fall in circulating AMH.

ART. – 5 - (Buone pratiche clinico assistenziali e raccomandazioni previste dalle linee guida)

Gli esercenti le professioni sanitarie, nell'esecuzione delle prestazioni sanitarie con finalità preventive - diagnostiche - terapeutiche - palliative - riabilitative - si attengono –

- salve le specificità del caso concreto,
- alle raccomandazioni previste dalle linee guida



ART. – 5 - (Buone pratiche clinico assistenziali e raccomandazioni previste dalle linee guida)



In mancanza delle suddette raccomandazioni, gli esercenti le professioni sanitarie si attengono alle

➤ **buone pratiche clinico-assistenziali**



Art.5_(commento) Il Termine : - **“si attengono”** -

~~risulta eccessivamente vincolante e rischia di limitare l'autonomia~~
decisionale dei professionisti sanitari. Considerato che le linee guida, di fatto, forniscono raccomandazioni cliniche e norme di buona pratica per informare la pratica professionale, ma decisioni e azioni professionali devono sempre essere guidate dalle caratteristiche cliniche del paziente individuale, oltre che dalle sue preferenze e aspettative.

UPDATE DELLA
LETTERATURA

