

ENDOMETRIOSI NUOVE FRONTIERE NEL TRATTAMENTO MEDICO

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ENDOMETRIOSIS: RELATED HEALTH PROBLEMS

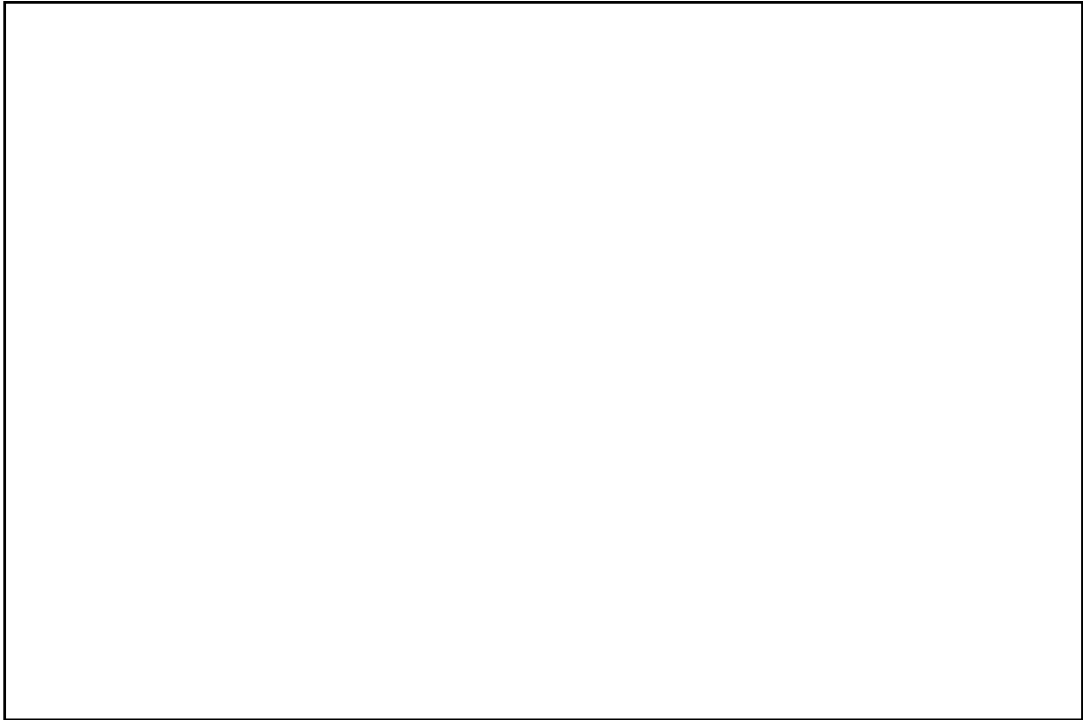
PAIN SYMPTOMS

- **Dysmenorrhoea**
- **Dyspareunia**
- **Pelvic pain**
- **Lower abdominal pain**
- **Back pain**
- **Dyschezia**
- **Loin pain**
- **Pain on micturition**
- **Pain on exercise**

ADNEXAL MASSES

INFERTILITY

**“Endometriosis: regular review”
Prentice A, BMJ 2001**



ENDOMETRIOSI: TRATTAMENTO IDEALE

ERADICAZIONE MALATTIA



**ripristino anatomia e funzionalità
sfera genitale interna**

TERAPIA SINTOMATICA

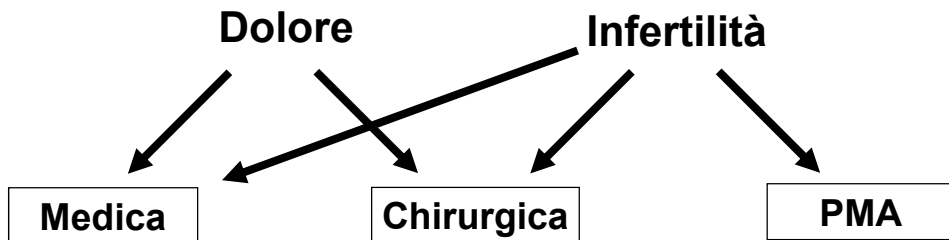
Dolore

Infertilità

Medica

Chirurgica

PMA



ENDOMETRIOSI

Efficacia della terapia

Variabili di valutazione

INFERTILITÀ

Pregnany Rate

- Concause di sterilità
- Età e anni di sterilità
- Tasso grav. spont.

DOLORE

- Validata scala dolore
- Valutazione tempo-dipend.
- Effetto placebo
- Soglia del dolore individuale

TERAPIA MEDICA E STERILITA'

Schemi proposti

- Prechirurgico
- Postchirurgico
- Terapia unica

ATTUALMENTE LE TERAPIE MEDICHE A DISPOSIZIONE NON HANNO UN RUOLO NEL TRATTAMENTO DELLA STERILITÀ ENDOMETRIOSI-ASSOCIATA (LIVELLO DI EVIDENZA IA)

The American College of Obstetricians and Gynecologists
Int J Gynaecol Obstet 2000

Royal College of Obstetricians and Gynaecologists
Guideline No. 24, 2000

ESHRE
Guideline Development Group. Hum Reprod 2005

American Society for Reproductive Medicine
Fertil Steril 2006

Cochrane Database Syst Rev
2007

**LONG-TERM PITUITARY DOWN-REGULATION BEFORE IN VITRO FERTILIZATION (IVF) FOR WOMEN WITH ENDOMETRIOSIS
Sallam HN t al - Cochrane Database Syst Rev 2006**

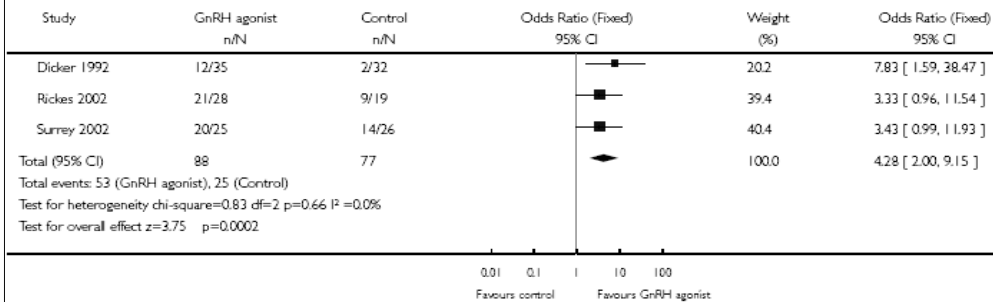
The administration of GnRH agonists for a period of three to six months prior to IVF or ICSI in women with endometriosis increases the odds of clinical pregnancy by fourfold.

Analysis 01.02. Comparison 01 GnRH agonist versus no agonist before IVF or ICSI, Outcome 02 Clinical pregnancy rate per woman

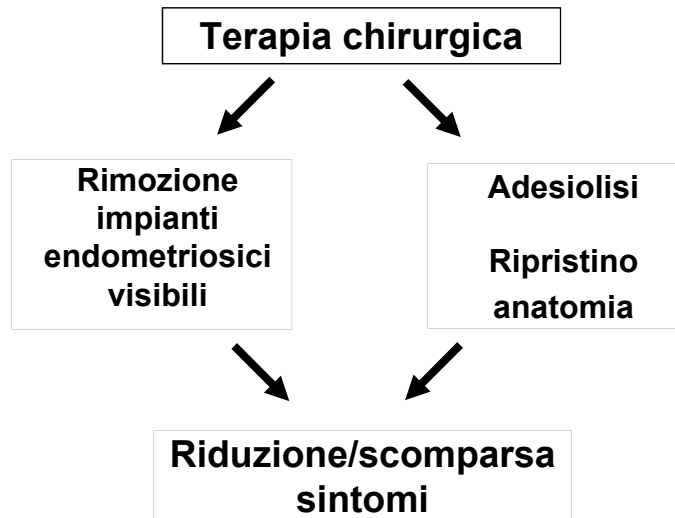
Review: Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis

Comparison: 01 GnRH agonist versus no agonist before IVF or ICSI

Outcome: 02 Clinical pregnancy rate per woman



ENDOMETRIOSI e DOLORE PELVICO



LIMITI DELLA CHIRURGIA

- **Limitato valore clinico-predittivo della stadiazione**
- **Rischio di recidive**
- **Rischio di reintervento**
- **Rischio di complicanze**
 - **endometriosisi profonda**
 - **endometriosisi del setto retto-vaginale**
- **↓ qualità di vita post-chirurgica**
- **Centri di riferimento**

Table 3 Proportion of women initially hospitalized for minor or intermediate surgery for endometriosis in 1996–1997 or 1997–1998 who were readmitted to the hospital over the subsequent 4 years and the number of readmissions

No. of readmissions	No. of patients	%	Cumulative %
0	5670	70.9	70.9
1	1786	22.3	93.2
2	398	5.1	98.3
3+	139	1.7	100.0
Total	7993	100.0	100.0

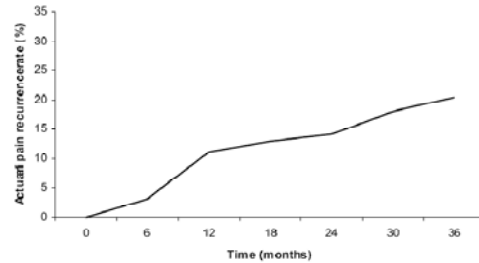
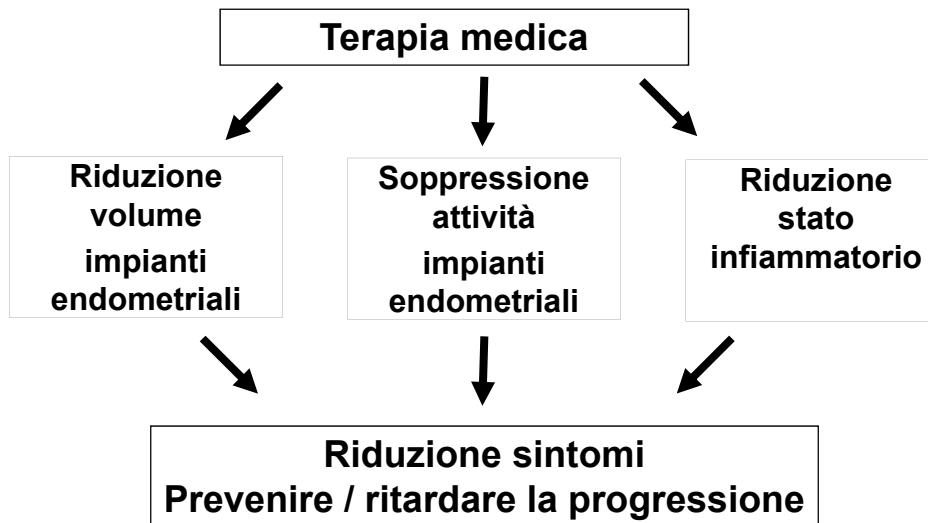


Figure 1 The graph shows the actuarial rate of pain recurrence over 36 months.

Endometriosis: What is the risk of hospital admission, readmission, and major surgical intervention?
Weir E et al – J Min Inv Gyn 2005

Surgical treatment of deep endometriosis and risk of recurrence
Vignali M et al – J Min Inv Gyn 2005

ENDOMETRIOSI e DOLORE PELVICO



TERAPIA MEDICA

PROGRAMMA TERAPEUTICO DI LUNGA DURATA



INVESTIGATIONAL ENDOMETRIOSIS

TRADITIONAL DRUGS

- GnRH-agonist / antagonist
- OC
- Progestogens
- danazol
- NSAI

CURRENT INVESTIGATIONS FUTURE PERSPECTIVES

- Aromatase inhibitors
- Immunomodulators agents
- Angiogenesis inhibitors
- SPRM (Selective Progesterone Receptor Modulator)
- Antioxidative substances
- Gene therapy

Chlouber RO et al
Exp Opin Invest Drugs 2006

GNRH AGONIST: CLINICAL APPLICATIONS

In the 1990s, GnRH-a were considered to be the therapeutic standard reference for medical treatment of endometriosis

GnRH agonists	Present clinical applications
Leuprorelin (leuprolide acetate)	Prostate cancer, breast cancer, <u>endometriosis</u> , uterine fibroids, CPP, <i>in vitro</i> fertilization
Goserelin	Prostate cancer, breast cancer, <u>endometriosis</u> , uterine fibroids, assisted reproduction, endometrial thinning, CPP
Buserelin	Prostate cancer, <u>endometriosis</u> , uterine fibroids, assisted reproduction
Histerelin	Prostate cancer, uterine fibroids, CPP
Nafarelin	<u>Endometriosis</u> , uterine fibroids, CPP, <i>in vitro</i> fertilization
Triptorelin	Prostate cancer, breast cancer, <u>endometriosis</u> , uterine fibroids, assisted reproduction, endometrial thinning, CPP

CPP: Central precocious puberty; GnRH: Gonadotropin-releasing hormone.

Wilson, Exp Opin Inv Drugs 2007

Author/s	n	Comparison	Dose	Duration	Outcome	Notes
Henzl et al (1988) ⁸	213 (70/73/70)	Nafarelin (nasal) vs. danazol (PO)	400 or 800 µg/d 800 µg/d 800 mg/d	6 months	Significant decrease in pain scores	Endometriosis diagnosed by laparoscopy, 2nd-look laparoscopy. All treatment groups showed improvement
Fedele et al (1989) ¹⁸	62 (30/32)	Buserelin (nasal) vs. danazol	1200 µg/d 600 µg/d	6 months	Marked pain improvement with therapy in both groups	Endometriosis diagnosed by laparoscopy. Pregnancy outcome similar
Kennedy et al (1990) ¹⁷	82 (55/27)	Nafarelin (nasal) vs. danazol, (PO)	400 µg/d 600 mg/d	6 months	Combined pain scores: improved in both groups	Significant improvement in total AFS and active disease scores
Shaw (1990) ³⁹	73 (50/23)	Nafarelin (nasal) vs. danazol (PO)	400 µg/d 600 mg/d	6 months	Combined pain scores: improved in both groups	2nd-look laparoscopy
Rolland and van der Heijden (1990) ²⁶	170 (107/63)	Nafarelin (nasal) vs danazol (PO)	400 µg/d 400 mg/d	6 months	Pain scores: no difference between groups	Highly significant decrease in mean AFS scores with no difference between groups
Diugi et al (1990) ²⁵	63 (32/31)	Leuprolide depot vs placebo	3.75 mg/ placebo	6 months	Symptomatic improvement in active treatment group	Endometriosis diagnosed by laparoscopy: phase III trial
Nafarelin European Endometriosis Trial Group (1992) ⁴⁰	263 (171/92)	Nafarelin (nasal) vs. danazol (PO)	400 µg/day 600 mg/day	6 months	Combined pain score decreased; no significant group difference	Significant improvement within both groups
Wheeler et al (1992) ¹¹	253 (128/125)	Leuprolide depot vs danazol (PO)	3.75 mg	Monthly/ 24 weeks	No between-group difference, improvement in both	Total AFS scores: significant decrease with no difference between groups
Fedele et al (1993) ²⁴	35 (19/16)	Buserelin (inhalant) vs. expectant management	1200 mg/ mo	24 weeks	Similar efficacy	2nd-look laparoscopy: both groups improved
Rock et al (1993) ¹²	315 (208/107)	Zoladex (goserelin/subcutaneous vs danazol (PO)	3.6 mg/mo 800 mg/d	24 weeks	Similar efficacy	Endometriosis diagnosed by laparoscopy
Bergquist (1998) ⁴¹	49 (24/25)	Triptorelin (IM)/placebo	3.75 mg/mo	6 months	Agonist very effective by 2-3 months of treatment	Endometriosis diagnosed by laparoscopy

GNRH-a INCIDENZA DI EFFETTI COLLATERALI

Journal of Minimally Invasive Gynecology (2006) 13, 539–545

GnRH analogs: Options for endometriosis-associated pain treatment

THE JOURNAL OF
MINIMALLY INVASIVE
GYNECOLOGY

Frances R. Batzer, MD, MBE

Table 1 Side effects of GnRH agonists

Hot flashes (80%–90%)
Sleep disturbances (60%–90%)
Vaginal dryness (30%)
Joint pain (30%)
Breakthrough bleeding (20%–30%)
Headaches (20%–30%)
Mood change (10%)
Bone loss (decrease bone density 5%–6%)
Adverse lipid changes (increase LDL, decrease HDL)

GnRH-a: add-back therapy prospective controlled studies							
Author	n	Study Design	Leuprolide (IM) + norethindrone	3.75 mg/mo	Norethindrone 5 mg/10 mg	24 Weeks	Outcomes
Surrey & Judd (1992) ⁵⁶	20 (10/10)	Prospective, randomized, masked trial	Leuprolide (IM) + norethindrone	3.75 mg/mo	Norethindrone 5 mg/10 mg	24 Weeks	Pain efficacy similar, amelioration of menopausal symptoms with norethindrone
Surrey et al (1995) ⁵⁷	37 (10/9/18)	Prospective, randomized, open-label	Leuprolide + norethindrone + etidronate / control untreated	3.75 mg/mo	Norethindrone 2.5 or 10 mg Etidronate 400 mg/14 d/mo	48 weeks	Pain efficacy similar
Mukherjee et al (1990) ⁵⁸	26 (11/15)	Prospective, randomized, blinded	Leuprolide + etidronate	3.75 mg/mo	Etidronate 400 mg/14 days every other month	6 months	—
Moghissi et al (1998) ⁴⁴	306 (109/99/98)	Prospective, placebo-controlled, open-label, for goserelin, double-blinded for HRT, multicenter	Goserelin IM - conjugated E2/MPA or placebo	3.6 mg/mo	CEE 0.3 mg or 0.625 mg MPA 5mg	24 Weeks	Similar pain efficacy
Hornstein et al (1998) ⁴⁵	201 (51/55/47/48)	Prospective, randomized, double-blind, multicenter	Leuprolide (IM)	3.75 mg/mo	Norethindrone 5 mg/+ placebo or CEE 0.625 mg or 1.25 mg	1 year	Similar efficacy at 8 months; recurrence of pain in CEE 1.25 mg
Frankie et al (2000) ⁴⁶	41 (23/18)	Prospective, randomized, placebo-controlled, double blind	Goserelin (IM)	3.6 mg/mo	Placebo or estradiol 2 mg / norethisterone acetate 1 mg	24 weeks	Similar efficacy
Pierce et al (2000) ⁵¹	45 (31/14)	Prospective, randomized, long-term, follow-up	Goserelin (IM)	3.6 mg/mo	Placebo or estradiol 2 mg norethisterone acetate 1mg	2 yr active treatment/6 year follow-up	Similar efficacy
Surrey and Hornstein (2002) ⁵⁹	123/1 year follow-up 60/2 years follow-up	Prospective, randomized, double-blind, placebo-controlled, multicenter [population for '98 study]	Leuprolide acetate	3.75 mg/mo	Placebo or Norethindrone 5 mg + CEE 0.625 mg or 1.25 mg	12 months of therapy 2 years follow-up	Similar efficacy
Fernandez et al (2004) ⁵⁴	78 (39/39)	Randomized, double-blind, placebo-controlled	Leuprolide	3.75 mg/mo	Prormegestone + placebo/or estradiol 2 mg + prormegestone 0.5 mg	1 year	Similar efficacy

COSTI

Principio	Commerciale	Somministratz.	Costo
EP		x 6 mesi	10 € x 6
Noretis. ac. 10 mg	Primolut-nor	Die x 6 mesi	6 € x 6
MAP iniett. 150mg	Depo-provera	Ogni 3 mesi x 2	5 € x 3
IUD-Ing	Mirena	Una	184 €
Danazolo 20 mg	Danatrol	400 mg/die x 6	50 € x 6
Leuprorelina 3.75	Enantone	Ogni mese x 6	197 € x 6
Triptorelina 3.75	Decapeptyl	Ogni mese x 6	190 € x 6
Goserelin 3.6	Zoladex	Ogni mese x 6	205 € x 6

All the agents are formally indicated by the Italian Ministry of Health for the treatment of endometriosis except COCs

GnRH ANTAGONIST

- Competitive blocking of pituitary GnRH receptors
- Action onset is immediate, time related and reversible

• Absence of flare-up phase	→ initial worsening of symptoms? → dose-free intervals can be interspersed without risk of exacerbation if retreatment is postponed until symptoms recur
• Administration at last once a week (3 mg)	→ drop out ?
• More expensive	→ long term adherence to therapy ?
• Two small series support its effectiveness but no randomized study has been published to date	
• Development of GnRH antagonist with long-term action	

Batzer FR – J Min Inv Gyn 2006

1. Because of the severity of side effects with GnRH agonists GnRH agonist or antagonist treatment is usually not considered a first line option for treatment of endometriosis pain.
2. At present, long-term use of GnRH agonists with add-back therapy may be considered in women who are refractory to OC or progestins.

ACOG Committee Opinion No. 310. Obstet Gynecol 2005

ORAL CONTRACEPTIVES AND ENDOMETRIOSIS

Source, year	Schedule	Pain relief <i>n</i> (%)
Vercellini <i>et al.</i> , 1993	Desogestrel 0.15mg + ethinylestradiol 0.02mg cyclically for 6 mo.	17/23 (74)
Vercellini <i>et al.</i> , 1996	Desogestrel 0.15mg + ethinylestradiol 0.02mg cyclically for 12 mo.	23/40 (57)
Parazzini <i>et al.</i> , 2000	Gestodene 0.75mg + ethinylestradiol 0.03mg cyclically for 12 mo.	32/46 (70)
Vercellini <i>et al.</i> , 2003	Desogestrel 0.15mg + ethinylestradiol 0.02mg continuously for 24 mo.	48/50 (96)

CONTRACCETTIVI ORALI E ENDOMETRIOSI

Uso off-label



Efficacia nel dolore associato a endometriosi

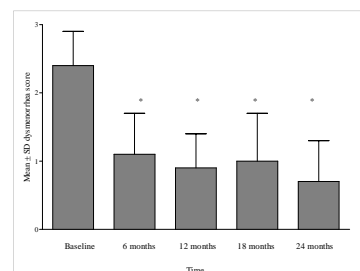
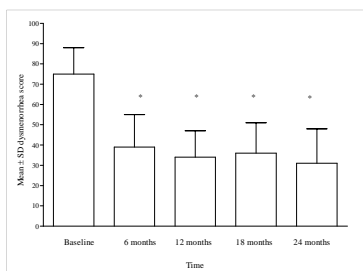


Scarsi studi di confronto con altri farmaci

- Schema di somministrazione
- Tipo di progestinico

CONTINUOUS USE OF AN ORAL CONTRACEPTIVE FOR ENDOMETRIOSIS-ASSOCIATED RECURRENT DYSMENORRHEA THAT DOES NOT RESPOND TO A CYCLIC PILL REGIMEN

Variations of intensity of dysmenorrhea after switch from cyclic to continuous oral contraceptive use



(A) Visual Analog Scale score

(B) Verbal Rating Scale score.

* $p < .001$ compared with corresponding baseline value

Vercellini P et al - Fertil Steril 2003

MODERN COMBINED ORAL CONTRACEPTIVES FOR PAIN ASSOCIATED WITH ENDOMETRIOSIS.

Davis L et al - Cochrane Database Syst Rev 2007

AUTHORS' CONCLUSIONS

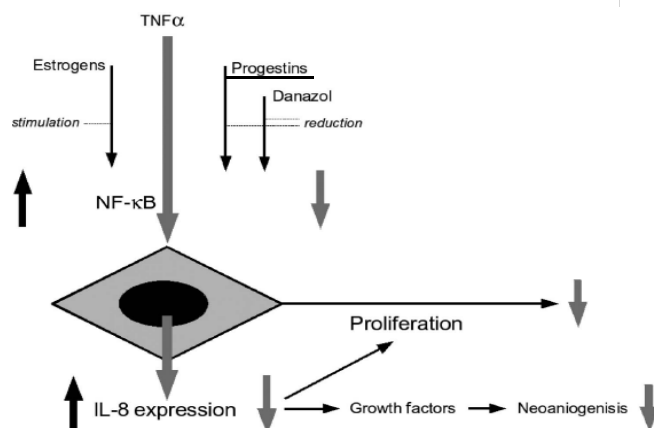
- Limited data
- No difference in outcomes between OCs and GnRH-a

- **UsO OFF-LABEL**
- Possibile impiego di prima linea in donne senza desiderio riproduttivo
- Possibili trattamenti a lungo termine
- Efficacia dei bassi dosaggi
- Carezza di dati sul tipo di progestinico
- Preferibile la somministrazione continua
- Alta incidenza di recidive alla sospensione

PROGESTINICI e ENDOMETRIOSI

- Inibizione della secrezione ipofisaria di LH e FSH e degli ormoni ovarici
- Induzione di uno stato anovulatorio ipoestrogenico
- Inibizione dell'impianto e crescita attraverso l'inibizione delle metalloproteinasi
- Proprieta' anti-angiogeniche

- **ORALE**
- **I.M. / S.C.**
- **VAGINALE**



ACTIVITIES OF VARIOUS PROGESTOGENS

	Progesterogenic activity	Glucocorticoid activity	Androgenic activity	Anti-androgenic activity	Anti-mineralocorticoid activity
Progesterone	+	-	-	+	+
Levonorgestrel	+	-	+	-	-
Desogestrel	+	-	+	-	-
Gestodene	+	-	+	-	(+)*
Norgestimate	+	-	+	-	-
Cyproterone acetate	+	+	-	+	-
Dienogest	+	-	-	+	-
Drospirenone	+	-	-	+	+

* negligible activity at therapeutic doses

Schindler A - Maturitas 2003

PROGESTINS: TRIALS INDICATING EFFICACY OF ORAL FORMULATIONS

Table 3 Oral progestins in the management of endometriosis: Outcomes of clinical trials

Study	Progestin	Design	Dose (mg)	Duration (mos)	No. of patients	Control	Overall satisfaction/symptom relief (% of patients)
Moghissi and Boyce ¹²	MPA	Retrospective	30	3	35	None	100
Roland et al ¹⁴	MPA	Retrospective	10	3	24	None	100
Luciano et al ¹⁵	MPA	Retrospective	50	6	21	None	88
Telimaa et al ¹⁶	MPA	Randomized	100	6	17	Danazol 600 mg and placebo	NS vs danazol p <.01 vs placebo 86
Schlaff et al ¹⁸	Megestrol acetate	Retrospective	40	2	29	None	86
Overton et al ¹⁹	Dydrogesterone	Randomized	40 vs. 60 (luteal phase)	6	32	Placebo	60 mg: 70 40 mg: 36.5*
Vercellini et al ²⁰	Cyproterone acetate	Randomized	12.5	6	45	Ethinyl E ₂ 0.02 mg + desogestrel 0.15 mg	33*
Muneyvirici-Delale and Karacan ²¹	NET Ac	Retrospective	5-70	≥6	52	None	94.2
Snaith ²²	NET Ac	Retrospective	600-4800 (cumulative)	1.8-7	28	None	79
Vercellini et al ²³	NEL Ac	Randomized	2.5	12	45	Ethinyl E ₂ 0.01 mg + cyproterone 3 mg	80*
Cosson et al ²⁴	Dienogest	Randomized	2	16	13	Triptorelin	85*
Timonen and Johansson ²⁵	Lynestrenol	Retrospective	5-7.5	1.5-7	20	None	90

MPA = medroxyprogesterone acetate; NET Ac = norethindrone/norethisterone acetate; NS = nonsignificant.
*Nonsignificant vs. control.

Surrey E - J Min Inv Gynecol 2006

PROGESTINS AND ENDOMETRIOSIS

- Little research has been conducted into the effectiveness of the progestins for the treatment of endometriosis
- Due to the lack of large-scale, appropriately controlled, randomized trials, or dose-ranging studies, no single agent can be demonstrated to be truly efficacious.
- Results suggest that the different progestins are equally effective
- When taken continuously, progestins relieve endometriosis-associated pain as effectively as the other hormonal drugs
- The progestins control pain symptoms in approximately 75%
- Symptoms often recur following treatment

Kennedy S - Human Reprod 2005
Prentice A - Cochrane Database of Systematic Reviews 2000
Vercellini P - Hum Reprod Update 2003

DIENOGEST

CLINICAL STUDY PHASE III

A multicenter, open one-arm study to investigate the safety and efficacy of daily oral administration of 2 mg Dienogest tablets (Endometrion / SH T00660AA) for the treatment of endometriosis over 52 weeks

SAFETY VARIABLES

- Bleeding pattern
- Adverse events
- Standard safety laboratory
- Gynecological safety

EFFICACY VARIABLES

Visual analog scale for pelvic pain

DIENOGEST IS AS EFFECTIVE AS TRIPTORELIN IN THE TREATMENT OF ENDOMETRIOSIS AFTER LAPAROSCOPIC SURGERY: RESULTS OF A PROSPECTIVE, MULTICENTER, RANDOMIZED STUDY

Cosson M et al – Fertil Steril 2002

PROGESTINICI INIETTABILI MAP FORMULAZIONE DEPOT (DMPA)

- **Ampiamente utilizzati a scopo contraccettivo da oltre 12 milioni di donne nel mondo.**
- **Somministrazione di 150 mg i.m. ogni 3 mesi.**
- **Uso clinico per endometriosi off-label**
 - Primi risultati nel 1996
 - Nuove formulazioni 104 mg (DMPA-SC 104):
primo nuovo trattamento approvato negli ultimi 15 anni dall'US
FDA per uso clinico nel dolore associato ad endometriosi

PROGESTINICI INIETTABILI

- **Depot MPA seems to be an effective, safe, and low-cost treatment for pelvic pain associated with endometriosis**
- **Women should be carefully counselled**
 - prolonged delay in resumption of ovulation is a contra-indication to the use of DMPA in women wanting children in the near future
 - Additionally, uterine breakthrough bleeding may be prolonged, repeated and troublesome to correct
 - treatment cannot be interrupted in the event of side effects, rendering clinical management complicated when these are severe or scarcely tolerable
- **Its indication of choice is residual symptomatic endometriosis following definitive surgery**

Vercellini P et al - Best Pract Res Clin Obstet Gynaecol 2008



Available online at www.sciencedirect.com



European Journal of Obstetrics & Gynecology and
Reproductive Biology 125 (2006) 9–28



European Journal of
Obstetrics & Gynecology
and Reproductive Biology

www.elsevier.com/locate/ejogrb

Review

Non-contraceptive uses of levonorgestrel-releasing hormone system (LNG-IUS)—A systematic enquiry and overview

Rajesh Varma^{*}, Deepali Sinha, Janesh K. Gupta

OFF-LABEL USE

LNG-IUS studies assessing therapeutic effect in women with endometriosis					
Author	Year of publication	Study type	Sample size	Comparison	Outcomes (within 1-year follow up unless stated otherwise)
Petta et al. [56]	2005	RCT	82 With endometriosis, dysmenorrhoea and chronic pelvic pain	39 LNG-IUS vs. 43 GnRH analogue	6 Months follow up: Comparable reductions in pelvic pain and improved quality of life measures Greater amenorrhoea with GnRH than LNG-IUS (98% vs. 70%)
Vercellini et al. [57]	2003	RCT	40 Parous women, not desiring fertility, with endometriosis associated dysmenorrhoea and receiving conservative surgical treatment of endometriosis	20 Post-operative LNG-IUS and endometriotic surgery vs. 20 endometriotic surgery alone 10% Drop out from LNG-IUS group	Decreased recurrence of dysmenorrhoea in LNG-IUS vs. surgery alone group (10% vs. 45%, $p = 0.03$) 28% or 50% LNG-IUS users had amenorrhoea or oligoamenorrhoea Comparable levels of patient satisfaction (75% and 50%)
Lockhat et al. [58,59]	2004, 2005	Prospective	34 With symptomatic mild-moderate endometriosis	No comparison (1-year and 3-year follow up)	Decreased dysmenorrhoea and/or non-cyclical pelvic pain and AFS staging of endometriosis 68% Continuation rate at 1 year 56% Continuation rate at 3 years
Vercellini et al. [60]	1999	Prospective	18 Parous women who had history of previous endometriotic surgery and had recurrent dysmenorrhoea	No comparison	Amenorrhoea in 24% Oligoamenorrhoea in 47% Decreased dysmenorrhoea by 45% Decreased menstrual blood loss by 76% 75% Satisfaction rates
Fedele et al. [61]	2001	Prospective	11 Symptomatic women with rectovaginal endometriosis	No comparison	Decreased pelvic pain, dyspareunia, dysmenorrhoea related to endometriosis Decreased size of endometriosis lesions (ultrasound)

LEVONORGESTREL-RELEASING INTRAUTERINE DEVICE (LNG-IUD) FOR SYMPTOMATIC ENDOMETRIOSIS FOLLOWING SURGERY.

Abou-Setta AM et al - Cochrane Database Syst Rev. 2006

Authors' conclusions:

- Only one small RCT has shown that postoperative use of the LNG-IUS reduces the recurrence of painful periods in women who have had surgery for endometriosis.
- There is a need for further well-designed RCTs of this approach.

Study	LNG-IUS n/N	No LNG-IUS n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 Painful periods Vercellini 2002	2/20	9/20		100.0	0.14 [0.02, 0.75]
Subtotal (95% CI)	20	20		100.0	0.14 [0.02, 0.75]

Total events: 2 (LNG-IUS), 9 (No LNG-IUS)
Test for heterogeneity: not applicable
Test for overall effect: z=2.29 p=0.02



DANAZOLO



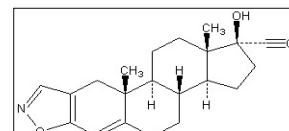
DANAZOL FOR PELVIC PAIN ASSOCIATED WITH ENDOMETRIOSIS.

Selak V et al - Cochrane Database Syst Rev 2007

5 RCT

Authors' conclusions:

- Danazol is effective in treating the symptoms and signs of endometriosis (evidence level Ib).
- However, its use is limited by the occurrence of androgenic side effects.



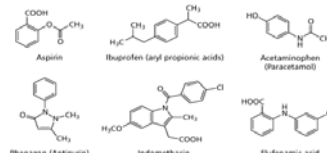
FANS



NON-STEROIDAL ANTI-INFLAMMATORY DRUGS FOR PAIN IN WOMEN WITH ENDOMETRIOSIS

Allen C et al - Cochrane Database Syst Rev 2005

Authors' conclusions: There is inconclusive evidence to show whether NSAIDs (naproxen) are effective in managing pain caused by endometriosis. There is no evidence to show whether any individual NSAID is more effective than another. As shown in other Cochrane reviews, women using NSAIDs need to be aware of the possibility that these drugs may cause unintended effects.



PRE AND POST OPERATIVE MEDICAL THERAPY FOR ENDOMETRIOSIS SURGERY

C Yap et al - Cochrane Database of Systematic Reviews 2004

11 RCT

There is insufficient evidence from the studies identified to conclude that hormonal suppression in association with surgery for endometriosis is associated with a significant benefit with regard to any of the outcomes identified. There may be a benefit of improvement in AFS scores with the pre-surgical use of medical therapy.



PRE-OPERATIVE TREATMENT

Although hormonal therapy prior to surgery improves rAFS scores, there is insufficient evidence of any effect on outcome measures such as pain relief.

Evidence Level 1a - ESHRE Guidelines 2008

POST-OPERATIVE TREATMENT

Compared to surgery alone or surgery plus placebo, postoperative hormonal treatment does not produce a significant reduction in pain recurrence at 12 or 24 months, and has no effect on disease recurrence.

Evidence Level 1a – ESHRE 2008 Guidelines



TERAPIA MEDICA: INDICAZIONI ATTUALI

DONNE SENZA ATTUALE DESIDERIO DI GRAVIDANZA

Terapia di prima linea

- **in assenza di masse endopelviche**
- **in caso di rischio di t. chirurgica invalidante**

- **Terapia adiuvante post-operatoria**

- **Recidiva sintomatologica dopo pregressa chirurgia**

INVESTIGATIONAL ENDOMETRIOSIS
Chlouber RO et al – Exp Opin Invest Drugs 2006

**CURRENT
INVESTIGATIONS** —
**FUTURE
PERSPECTIVES**

- Aromatase inhibitors
- Immunomodulators agents
- Angiogenesis inhibitors
- SPRM (Selective Progesterone Receptor Modulator)
- Antioxidative substances
- Gene therapy

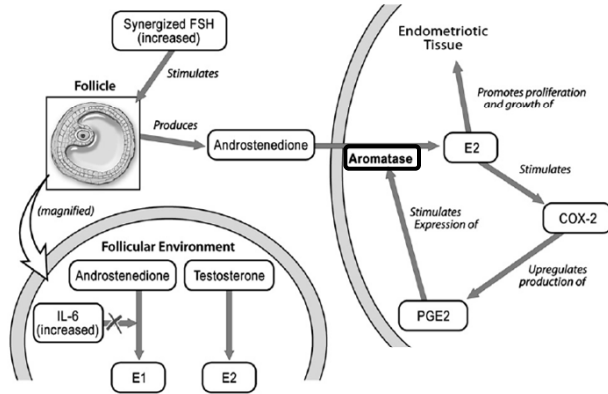
**MOLECULAR BASIS FOR TREATING ENDOMETRIOSIS WITH AROMATASE
INHIBITORS**

Bulun SE et al - Hum Reprod Update 2000

AROMATASI

- enzima del citocromo P450 che catalizza la conversione degli androgeni in estrogeni
- espresso nelle cellule della granulosa, sinciziotrofoblasto placentare, tessuto adiposo, fibroblasti cutanei e cerebrali.
- livelli alti in impianti endometriosisici ovarici ed extraovarici

ROLE OF AROMATASE IN PERSISTENT ENDOMETRIOTIC STATE

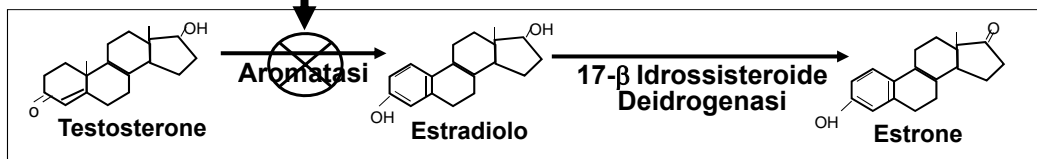


Gupta S et al - Fertil Steril 2008

AROMATASI

- aumentata conversione di androgeni in E2 in impianti endometriosisi
- escrezione di E2 dal tessuto endometriosiso fattore importante nella formazione, sopravvivenza e crescita di focolai endometriosisi, con meccanismi di tipo paracrino

INIBITORI DELL'AROMATASI



**Inibitori steroidei
irreversibili**
- exemestano
- formestano

**Inibitori non-steroidi
reversibili**
- Anastrozolo
- letrozolo

INIBITORI DELL'AROMATASI

- **Both classes of inhibitor reduce circulating oestrogen to 1-10% of pre-treatment levels in postmenopausal subjects or in premenopausal women whose ovaries have been rendered non-functional by other treatments.**
- **No clinical studies have demonstrated complete ovarian blockade with aromatase inhibitors**
- **as a potential therapy for endometriosis, these compounds should only be given to postmenopausal women to block oestrogen formation in the skin and adipose tissue as well as in endometriotic tissue or combined with other treatments.**

Vignali M et al - Fertil Steril 2002

INIBITORI DELL'AROMATASI

TREATMENT OF ENDOMETRIOSIS AND CHRONIC PELVIC PAIN WITH LETROZOLE AND NORETHINDRONE ACETATE: A PILOT STUDY

Ailawadi RK et al - Fertil Steril 2004

THE EFFECTS OF POST-SURGICAL ADMINISTRATION OF GOSERELIN PLUS ANASTROZOLE COMPARED TO GOSERELIN ALONE IN PATIENTS WITH SEVERE ENDOMETRIOSIS: A PROSPECTIVE RANDOMIZED TRIAL

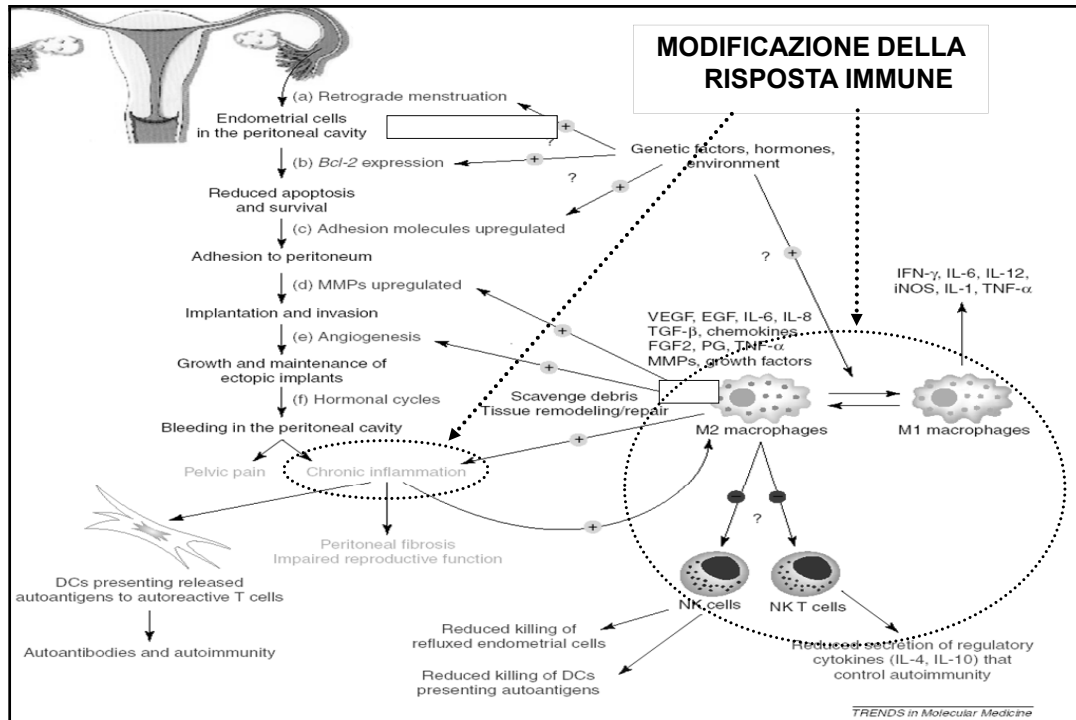
Soysal S et al - Hum Reprod 2004

SUCCESSFUL TREATMENT OF REFRACTORY ENDOMETRIOSIS-RELATED CHRONIC PELVIC PAIN WITH AROMATASE INHIBITORS IN PREMENOPAUSAL PATIENTS

Verma A et al - Eur J Obstet Gynecol Reprod Biol 2009

LETROZOLE AND DESOGESTREL-ONLY CONTRACEPTIVE PILL FOR THE TREATMENT OF STAGE IV ENDOMETRIOSIS

Remorgida V et al - Aust N Z J Obstet Gynaecol 2007



Role of altered immunologic factors in endometriosis-associated infertility.			
Affected immunologic factors	Levels of the immunologic factor in women with endometriosis	Mechanistic actions of affected immune factors	Effect of altered immune factor levels on fertility
Follicular fluid studies			
VEGF	Decreased	Decreases follicle health and vascularisation	Decreased embryo quality and implantation rates
IL-6	Increased	Decreases aromatase activity within follicles	Decreased intrafollicular E ₂ levels, leading to decreased fertility and fertilizing capacity
Peritoneal fluid studies			
RANTES	Increased	Attracts monocytes and memory T-cells to inflamed areas	Increased inflammation, cytotoxic effects on healthy cells, and OS produced, leading to decreased fertility
IL-10	Increased	Prevents p27 down regulation in developing granulosa cells	G ₀ arrest of granulosa cell cycle, resulting in low-quality oocytes
VEGF	Increased	Induces the formation of angiogenesis promoting fibrin matrix in the peritoneal cavity	Increased adhesion of free endometrial tissue within the peritoneal cavity
TNF-α	Increased	Causes increased prostaglandin production by endometrial epithelial cells	Increased adhesion of free endometrial tissue within the peritoneal cavity, and increased inflammation, leading to subfertility
TNF-α	Increased	Decreases the effect of TIMP	Increase effects of MMP, leading to increased endometriotic tissue invasiveness
PAPP-A	Increased	Increases follicular androstenedione syntheses	Increased conversion of androstenedione to E ₂ by endometriotic tissue, leading to increased tissue proliferation
Cathepsin D	Increased	Initiates harmful proteolytic events	Degradation of basement membrane and extracellular matrix components
Altered immune factors in peritoneal fluid and their adverse effects on spermatozoa			
IL-6	Increased	Induces the release of gp130 by sperm	Decreased sperm motility
TNF-α	Increased	Initiates a Caspase cascade	Sperm apoptosis and a/ oligospermia
TNF-α	Increased	Induces ROS production from spermatozoa	Sperm plasma membrane lipid peroxidation and abnormal sperm function

ENDOMETRIOSI e TERAPIA IMMUNOMODULANTE

IMMUNE SYSTEM AND ENDOMETRIOSIS

Colacurci N. et al - Acta Eur Fertil 1991

TREATING ENDOMETRIOSIS AS AN AUTOIMMUNE DISEASE

Nothnick WB - Fertil Steril 2001

**Agenti in grado di
stimolare l'immunità
cellulo-mediata**

**Agenti in grado di
ridurre la risposta
infiammatoria**

AGENTI IN GRADO DI STIMOLARE L'IMMUNITÀ CELLULO-MEDIATA

- **Citochine interleuchine (IL-1 e 2)**
- **Interferone (IFN- α -2b)**
- **Immunomodulatori sintetici**
 - **analogo della guanosina loxoribina**
 - **agonista del recettore nicotinico colinergico levamisolo**

LAPAROSCOPIC INTRAPERITONEAL INJECTION OF HUMAN INTERFERON-A-2B IN THE TREATMENT OF PELVIC ENDOMETRIOSIS: A NEW MODALITY.

Ali AFM et al – Obstet Gynecol 2000

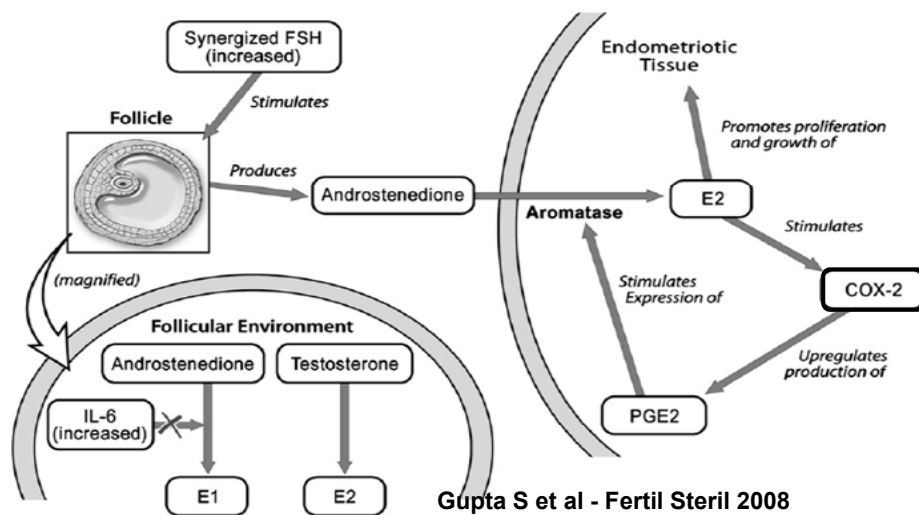
**Iniezione laparoscopica intraperitoneale di IFN- α -2b in 25 donne
affette da endometriosi pelvica allo stadio II-III.**

**Al second look a 3 mesi è stata rilevata una riduzione
significativa della stadiazione con 4 casi di guarigione completa**

AGENTI IN GRADO DI RIDURRE LA RISPOSTA INFIAMMATORIA

- Inibitori della ciclo-ossigenasi (COX-2)
- Pentossifillina
- Antagonisti del TNF- α
- Antagonisti della leptina

ROLE OF COX-2 IN PERSISTENT ENDOMETRIOTIC STATE

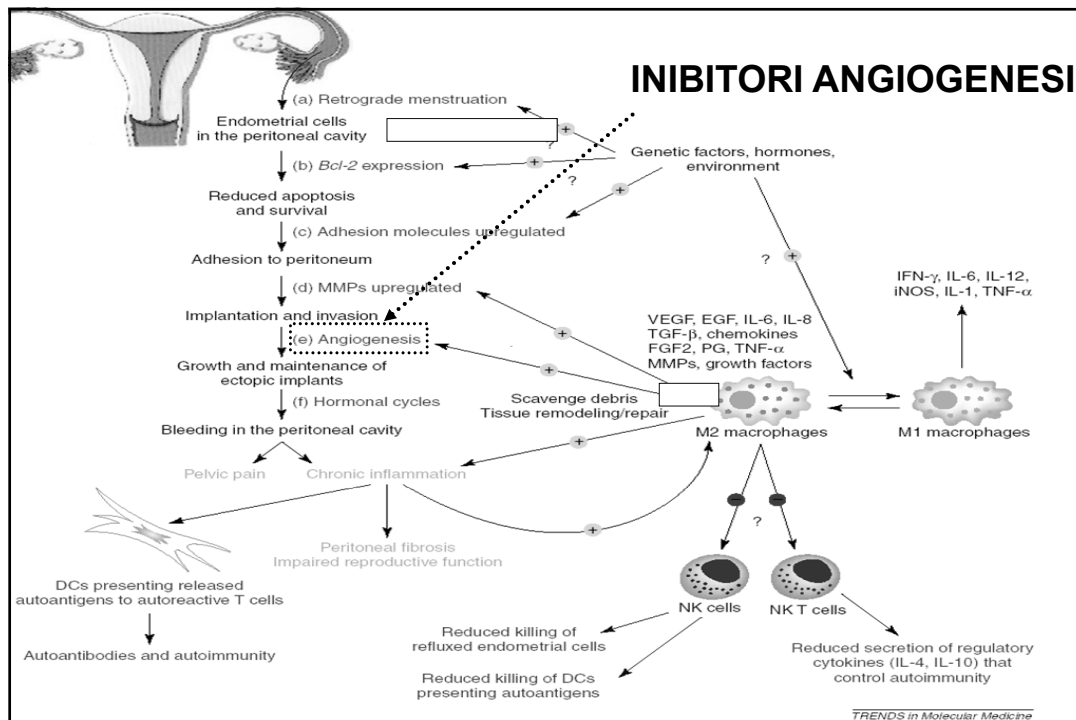


PGE(2) production in endometriosis is up-regulated by increased levels of the enzyme cyclo-oxygenase-2 (COX-2) in this tissue. COX-2 is stimulated by E2, IL-1 β and PGE(2) itself in endometriotic cells. Thus, there is a positive feedback loop that favours continuous formation of E(2) and PGE(2) in endometriosis

INIBITORI DELLA COX-2

Indometacina, ibuprofene, nimesulide,
celecoxib, rofecoxib

The treatment with a COX-2 specific inhibitor is effective in
the management of pain related to endometriosis
Cobellis L et al - Eur J Obstet Gynecol Reprod Biol 2004



VEGF E ANGIOGENESI ENDOMETRIOSICA

- **Angiogenesis is under the control of inducers, including fibroblast growth factor, hepatocyte growth factor, TGF- and - , and vascular endothelial growth factor (VEGF)**
- **The expression of VEGF by endometriotic implants provides a mechanism for the neovascularization that is commonly observed around these lesions, particularly in haemorrhagic red implants.**
- **Elevated concentrations of VEGF have also been identified in peritoneal fluid of women with endometriosis. A positive correlation exists between the severity of endometriosis and the concentration of VEGF in peritoneal fluid.**

McLaren J et al - Hum Reprod Update 2000
Donnez J et al - Hum Reprod 1998

INIBITORI DELL'ANGIOGENESI

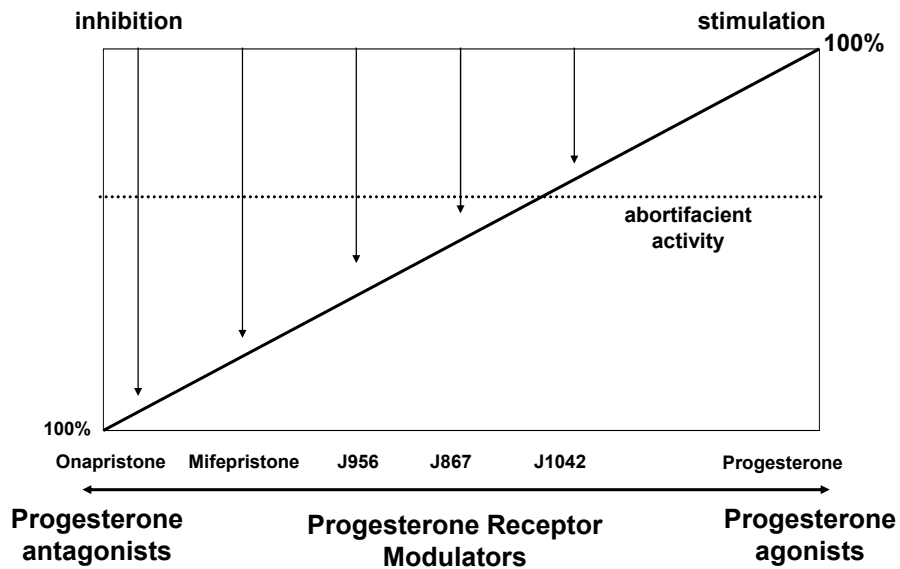
- **Inibitori del VEGF**
- **Agenti angiostatici (TNP470, endostatina, rapamicina)**

• **Studi in laboratorio e su modelli animali**

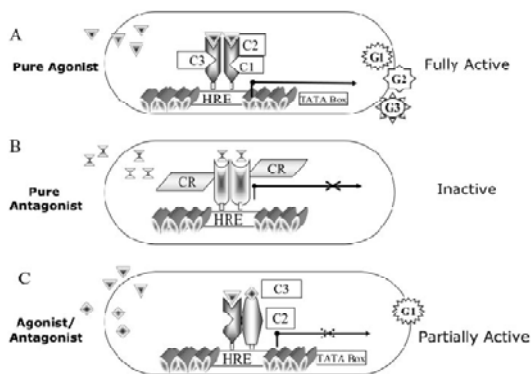
• **Un solo studio sull'uomo**

Chishima F et al - Am J Reprod Immunol 2002

SELECTIVE PROGESTERONE RECEPTOR MODULATOR



SPRM and ENDOMETRIOSIS



- inhibition of the estrogen receptor gene transcription by the PRA isoform
- atrophy of spiral arteries
- blockade of progesterone-dependent growth factors
- inhibition of angiogenesis
- cell cycle blockade
- apoptosis modulation
- suppress endometrial prostaglandin production

↓
selectively suppression of E2-dependent endometrial growth

↓
induction of reversible amenorrhoea without systemic effects of estrogen deprivation

Chwalisz K t al
Endocr Rev 2005

PROGESTERONE ANTAGONISTS AND ENDOMETRIOSIS

Mifepristone (RU 486) in three different dosage

5 mg/daily x 6 m	50 mg/daily x 6 m	100 mg/daily x 6 m
Pelvic pain reduction Uterine cramping absence	Pelvic pain reduction Uterine cramping absence	Pelvic pain reduction Uterine cramping absence
Uterine bleeding	Recommended dose	Side effects (antiglucocorticoid effects)
Kettel et al, Am J Obstet Gynecol 1998		

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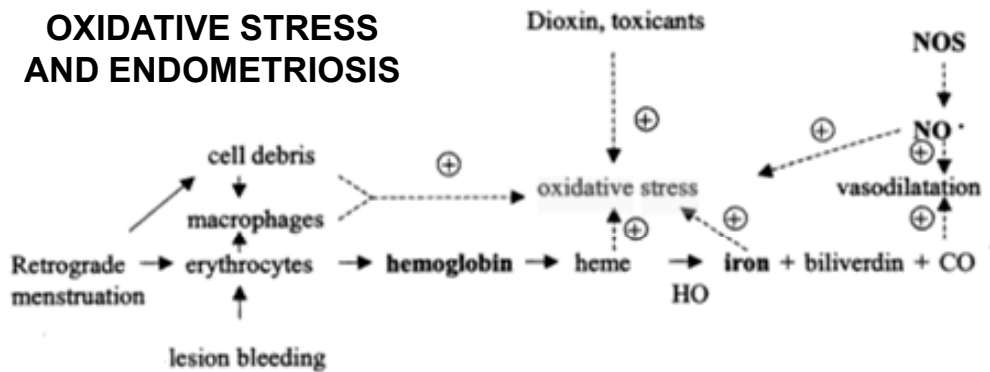


clinical studies ongoing

optimal preliminary results

Chwalisz K and Spitz I - 2002

OXIDATIVE STRESS AND ENDOMETRIOSIS



The development of OS in the local peritoneal environment may be one of the links in the chain of events leading to endometriosis.

The presence of elevated concentrations of free radicals and lowered antioxidant potential leads to OS. with increase of the growth and adhesion of endometrial cells in the peritoneal cavity

Gupta S – Reprod biomed Online 2006
Van Langendonck A et al - Fertil Steril 2002

OXIDATIVE STRESS AND ENDOMETRIOSIS

**Agents with antioxidant activity are able to improve
endometriosis-related symptoms**

Harel Z et al – Am J Obstet Gynecol 1996

**Effect of vitamins C and E supplementation on peripheral
oxidative stress markers and pregnancy rate in women with
endometriosis**

Mier-Cabrera J - Int J Gynaecol Obstet. 2008

HERBAL AND DIETARY THERAPIES FOR PRIMARY AND SECONDARY DYSMENORRHOEA

Proctor ML et al - Cochrane Database Syst Rev 2001

**It has been proposed that omega-3 and omega-6 fatty acids
may improve endometriosis-related symptoms, selectively
modulating biosynthesis and biochemistry activity of specific
prostaglandins involved in pelvic pain.**

**Dietary supplementation with vitamin B6, vitamin B1, vitamin
E, Mg, and omega-3 fatty acids (fish oil) involves analgesic and
anti-inflammatory properties in women with endometriotic
lesions**

**Overall there is insufficient evidence to recommend the use of
any of the other herbal and dietary therapies considered in this
review for the treatment of primary or secondary
dysmenorrhoea**

SELECTED FOOD INTAKE AND RISK OF ENDOMETRIOSIS

Parazzini F. et al - Hum Reprod 2004

Data from two case-control studies conducted in Northern Italy 1984-1999

- Cases: 504 women <65 years with a laparoscopically diagnosis of endometriosis
- Controls: 504 women (median age 34 years, range 20-61) admitted for acute non-gynaecological, non-hormonal, non-neoplastic conditions.

Table II. Risk of endometriosis and intake of selected foods

Food item	Frequency of consumption (no. of cases/ no. of controls) ^a			Odds ratio estimates ^b (95% CI)			χ^2 (trend)
	1 (low)	2 (intermediate)	3 (high)	1 ^b	2	3	
Milk	80/103	186/174	236/227	1+	1.3 (0.9-2.0)	1.4 (0.9-2.0)	NS
Beef and other red meat	158/202	139/173	206/129	1+	0.9 (0.6-1.3)	2.0 (1.4-2.8)	12.7 (<i>P</i> = 0.0004)
Liver	192/242	301/260	-	1+	1.1 (0.8-1.5)	-	-
Carrots	228/192	99/133	172/179	1+	0.7 (0.5-1.1)	0.7 (0.5-1.0)	NS
Green vegetables (all types)	185/121	220/215	99/168	1+	0.6 (0.4-0.8)	0.3 (0.2-0.5)	28.5 (<i>P</i> = 0.0001)
Fresh fruit (all types)	116/99	169/139	218/266	1+	0.8 (0.6-1.2)	0.6 (0.4-0.8)	10.0 (<i>P</i> = 0.002)
Eggs	110/140	145/111	248/251	1+	1.8 (1.2-2.8)	1.4 (1.0-2.0)	NS
Ham	150/192	109/136	244/176	1+	1.3 (0.9-1.9)	1.8 (1.3-2.5)	11.1 (<i>P</i> = 0.001)
Fish	207/167	183/211	112/126	1+	0.7 (0.5-1.0)	0.7 (0.5-1.1)	NS
Cheese	138/133	160/209	206/162	1+	0.6 (0.5-1.0)	0.8 (0.6-1.2)	NS
Whole-grain foods	355/351	82/80	67/73	1+	1.0 (0.7-1.4)	0.8 (0.6-1.3)	NS
Batter	283/332	221/172 ^c	-	1+	1.5 (1.0-2.0)	-	-
Margarine	454/453	50/50 ^c	-	1+	1.2 (0.7-1.9)	-	-
Oil	97/71	335/372	72/61	1+	0.6 (0.4-0.9)	0.7 (0.4-1.3)	NS
Coffee	204/185	123/119	177/200	1+	0.9 (0.6-1.3)	0.8 (0.5-1.1)	NS
Total alcohol intake	246/247	129/129	129/128	1+	1.0 (0.7-1.4)	0.9 (0.6-1.3)	NS

A significant reduction in risk emerged for higher intake of green vegetables and fresh fruit (OR=0.6), whereas an increase in risk was associated with high intake of beef and other red meat (OR=2.0)

HORMONAL SUPPRESSION TREATMENT OR DIETARY THERAPY VERSUS PLACEBO IN THE CONTROL OF PAINFUL SYMPTOMS AFTER CONSERVATIVE SURGERY FOR ENDOMETRIOSIS STAGE III-IV.

Sesti F et al - Fertil Steril 2007

Dietary therapy was a protocol consisting of nutritional intake in addition to vitamins (B6, A, C, E), minerals salts (Ca, Mg, Se, Zn, Fe), VSL3 lactic ferments

Pain symptom scores in study subjects before conservative pelvic surgery for severe endometriosis and at 12 months' follow-up, according to treatment allocation.

Symptom	Placebo (n = 110)	GnRH-a (n = 39)	Estroprogestin (n = 38)	Dietary therapy (n = 35)	<i>P</i> values between groups
Dysmenorrhoea					
Baseline value	7.9 ± 1.2	7.7 ± 1.0	8.2 ± 1.1	8.1 ± 1.1	NS
12-month value	6.4 ± 1.3	5.9 ± 0.9	5.5 ± 1.2	6.4 ± 1.0	<.001
Nonmenstrual pelvic pain					
Baseline value	8.0 ± 1.4	8.4 ± 0.9	8.5 ± 0.8	8.5 ± 0.8	NS
12-month value	6.2 ± 0.9	5.0 ± 1.1	5.0 ± 0.8	4.7 ± 1.1	<.001
Deep dyspareunia					
Baseline value	6.8 ± 1.2	6.9 ± 1.0	6.8 ± 1.2	7.2 ± 1.2	NS
12-month value	4.8 ± 1.2	4.3 ± 1.2	4.5 ± 1.3	5.0 ± 1.1	<.001

Postoperative hormonal suppression treatment or dietary therapy are more effective than surgery plus placebo to obtain relief of pain associated with endometriosis stage III-IV and improvement of quality of life.

GENOMIC APPROACHES FOR TREATMENT OF ENDOMETRIOSIS

**Estrogen/ Progesterone
receptor polymorphism**

immune function

- patient at risk
- prognosis (recurrence)
- hormonal treatment option

GENETICS AND ENDOMETRIOSIS

**CYP17 AND CYP19 GENE POLYMORPHISMS IN WOMEN
AFFECTED WITH ENDOMETRIOSIS**

Vietri MT et al - Fertil Steril 2008

**ARG72PRO P53 POLYMORPHISM IN ITALIAN WOMEN: NO
ASSOCIATION WITH ENDOMETRIOSIS.**

Vietri MT et al - Fertil Steril

GENERAL GYNECOLOGY

**Toward gene therapy of endometriosis:
transductional and transcriptional targeting
of adenoviral vectors to endometriosis cells**

Essam-Eldin R. Othman, MD; Zeng B. Zhu, MD; David T. Curiel, MD, PhD; Nilufar Khatoun, MSc;
Hosam T. Salem, MD, PhD; Essam Al-Din M. Khalifa, MD; Ayman Al-Hendy, MD, PhD

**Toward gene therapy of endometriosis:
adenovirus-mediated delivery of dominant negative
estrogen receptor genes inhibits cell proliferation,
reduces cytokine production, and induces
apoptosis of endometriotic cells**

Fertility and Sterility® Vol. 88, No. 2, August 2007

Essam-Eldin R. Othman, M.D.,^{a,b} Salama Salama, Ph.D.,^b Nahed Ismail, Ph.D., M.D.,^c
and Ayman Al-Hendy, Ph.D., M.D.^b

THERAPEUTIC MANAGEMENT OF ENDOMETRIOSIS**Evidence based
medicine**

- Patients' oriented
- Woman's need
- Resolution of complaints

**Clinical
practice**

- Lesions oriented
- Surgeon's need
- Eradication of implants