Medical Management of Symptomatic Endometriosis:

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Definition:

Endometriosis is defined as the presence of endometrial tissue out side the uterus, which induces a chronic inflammatory reaction.

Some woman experience painful symptoms and /or infertility ,other have no symptoms at all.

Exact prevalence of endometriosis is unknown but estimates range from 2-10% in general population but up to 50% in infertile woman.

_Adolescent with genital tract anomaly 40%

_Women and adolescent with pelvic pain 70%

1 in 10 women have endometriosis during their reproductive years

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

INTRODUCTION

According to the Practice Committee of the American Society for Reproductive Medicine, "endometriosis should be viewed as a chronic disease that requires a life-long management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures

Learning Objectives

- Describe various pathophysiologic bases of medical therapy in the management of symptomatic pelvic endometriosis
- Cite the randomized control trials that have compared different medical therapies for pain control
- Apply the knowledge derived from basic science data and clinical trials to treatment paradigms for endometriosis

Pathophysiologic Bases of Treatment

- Retrograde menstruation/transplantation
  - Peritoneal angiogenesis, proliferation, invasion, inflammation, innervation
- Coelomic metaplasia
- Genetic predisposition
  - Multifactorial/Polygenic trait
- Immunomodulation
- Environmental triggers
  - PCBs, TCDD, Cadmium
- Congenital anomalies
  - Obstructive

Therapeutic Basis of Treatment
Related to Pathogenesis

Retrograde transplantation

STOP SEEDING OF
MENSTRUAL DEBRIS

COCs, Progestins, LNG-IUD, GnRH-a, Androgens, Aromatase Inhibitors, Anti-estrogens

Therapeutic Basis of Treatment
Related to Pathophysiology

Endometriosis is:

Estrogen Dependent
Progesterone
Resistant
Angiogenic
Inflammatory

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Evidence That Endometriosis is Estrogen Dependent

- Unusual before menarche (has been reported in thelarche)
- Prolongd E2 exposure
  - early menarche
  - nulliparity (more menses)
  - xenoestrogen exposure (Messmer, 2004)
- Animal models
  - trophic effects of E2 in mice implants (Osteen, 2007)

Endometriosis and Progesterone

- Lesions are P4 resistant
- Progestins are commonly used (counter-intuitive)
- Because they
  - have anti-angiogenic effects
  - are immunomodulatory
  - are anti-inflammatory
  - oppose E2 action

Evidence of Inflammation

- Observe high levels of inflammatory cytokines (IL-8, IL-1, TNF-α) in peritoneal fluid (PF) in women with 'osis
- PF activated macrophages secrete inflammatory cytokines
- PF activated macrophages cannot phagocytose endometrial cells
- Levels of ENDO I (haptoglobin) increased
- In systemic circulation, higher levels of TNF-α and IL-8

Endometriotic Lesions / PF

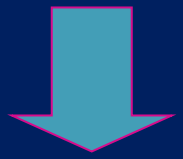
- Lesions are invasive
  - Matrix metalloproteinase -1, 2, 3, 7, 11
  - Plasminogen activator
  - Cathepsin D
- Lesions are angiogenic
  - VEGF (most studied)

Local E2 Production in Endometriosis

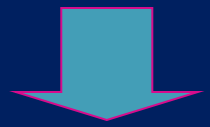
Aromatase
androstenedione

E1

E2



growth factors, PGFE2, PGF2a



adhesions, angiogenesis, proliferation
(so endogenous lesions locally produce E2)

Treatment of Endometriosis

- Surgical
- Medical (first-line)
- Surgical followed by post-op medical

Currently Available Medical Options for Endometriosis

- GOAL: minimize proliferation/reduce pain
- Inhibit inflammation (NSAIDs)
- Minimize menstrual volume/frequency (OCPs, progestogens/ L-IUS, anti-progestogens - RU486, gestrinone)
- Oppose E2 action (OCPs, progestogens/L-IUS, anti-progestogens)

Current Available Medical Options

- Create a hyperandrogenic state (equivalent to progestins action on the endometrium and inhibition of gonadotropin secretion: Danazol)
- Aromatase inhibitors (inhibits E2 synthesis)

Pelvic Pain Results With Cyclic OCPs

Citation	Tx	Relief (%)	Sample
Kistner, 1956	Enovid	79	110
Riva, 1961	Enovid	90	83
Riva, 1962	Enovid	69	132
Kourides, 1969	EE/Norgestrel	84	19
Vercellini, 1993	EE/Desogstrl	88	24
Harada, 2008	EE/NET	$P<.0001$	51

Continuous OCPs

- N = 50 monitored prospectively
- No control
- Rx: EE 0.02mg / Desogestrel 0.15mg
- Mode: continuously for 2 years
- Conclusion: Pain relief in 96%

- *Vercellini, Fertil Steril, 2003; 80(3), 560-563*

Oral Progestin Tx

Author	Rx, mg	N	Time (mo)	Relief (%)
Luciano, 1988	MPA, 50	21	4	88
Schlaff,1990	Mgstrl, 40	9	4	86
Vercellini, 2002	CyprAc, 2.5	45	12	33
Delale	NET Ac, 5-70	52	> 6	94
Vercellini, 2009	NET Ac, 2.5	45	12	80
Herada, 2009	Dienogest 2	128	6	$P<.05$

Depot MPA v GnRHa

- Prospective, double blind, multi-center
- N=136 (depot MPA 104mg)
- N=138 (depot GnRHa 11.25mg, q 3 mo x 2 with 12 mo follow-up)
- Drop-outs (%): MPA, 35 ; GnRHa, 26

– Schlaff, *Fertil Steril* 2006, 85;314-325

Depot MPA v GnRHa: Results

- Pain, dysmenorrhea, dyspareunia: equal improvement
- Greater improvement in duration: agonist
- MPA: less vasomotor instability, more BTB
- Bone density loss:
  - Spine : MPA (1.1%) , GnRHa (3.95%)
  - Hip : MPA (0.3%) , GnRHa (1.65%)

Schlaff, 2006

Levonorgestrol IUS

- Prospective, randomized trial (N = 82)
- N = 39 (LNG-IUS)
- N = 43 (GnRHa)
- Results
  - Equivalent pain reduction both groups
  - No differences in QOL improvement between groups
  - More bleeding events in IUS group

Petta, *Hum Reprod* 2005, 20; 1993-1998

Danazol Therapy

Author	N	Time (mo)	Dose (mg)	↓AFS Score%	↓Pain (%)
Dmowski	10	6	800	65	88
Shaw	103	6	600	52	68
Kennedy	24	6	600	20	87
Rock	107	6	400-800	33	75
Henzl	80	6	800	43	78

GnRH Agonist Therapy

Author	Agonist	N	Duration	↓ Score	↓ Pain
Diugi	LeuAc	52	6	-	89
Surrey	LeuAc	10	6	55	72
Henzl	Naf	77	6	43	73
Steingld	Histrln	16	6	78	63
Rock	Gosrln	208	6	56	75
Shaw	Gosrln	204	6	60	74
Dmwski	Busrln	22	6	67	69
Wright	LeuAc	9	3	20	

Medical Therapies Under Investigation

- Oral GnRH antagonists
- Aromatase Inhibitors
- P_4 receptor modulators
- TNF-α blockers
- Angiogenesis inhibitors
- Metalloproteinase inhibition
- Estrogen receptor inhibition
- PPAR-γ agonists
- Chinese herbs (nociceptor neurons)
- Nutrition: omega-3, green tea

Letrozole + Norethisterone Acetate

- Study design: open-label, nonrandomized 6 month trial
- N = 82
- N = 41, Letrazole 2.5mg/NETAc 2.5mg/Calcium/Vit D, 1000mg/800IU daily
- N = 41, NETAc 2.5mg daily

- *Ferrero, Hum Reprod 2009, 24; 3022-3041*

Letrazole + NETAc: Results

- Significant decrease in pain by 3 months in both groups (*P*<.001)
- At 3 and 6 months, pain (*P*<.001) and dyspareunia (*P*=.002) less in letrazole group
- Adverse events more frequent with letrazole (P=.02): vasomotor sx, mood, myalgias, BTB

Ferrero *Hum Reprod* 2009

Investigated Add-Back

Therapy	6 months	12 months
Progestin alone		
MPA	X	
NETAc	X	X
E + P	X	X
P + Bisphos	X	X
PTH	X	

Management of Endometriosis

- Surgical
- Medical
- Post-op Medical

OCPs To Prevent Endometrioma Recurrence

- N = 239 / age 20 to 40 / nulliparous / prospective RCT
- Endometrioma (s) pre-op ± 4cm
- All underwent L-scope for excision/cystectomy
- Groups
  - A; Nonusers (n = 79)
  - B: Cyclic users (n = 81) : EE (20)/Gestodone (0.075)
  - C: Continuous (n = 79)
- Follow-up sono q6 mo for 24 mo
- Recurrence defined as 'oma ± 1.5cm

Seracchioli R, et al Fertil Steril 2010;93:52-56

OCPs To Prevent Endometrioma Recurrence: Results

- Study completion: n = 217 of 239 starting
- By group completed: A(n=69), B(n=75), C(n=73)
- Total of 37 recurrences: A(20), B(11), C(6)
- *P significant between users and non users*
- *P not significant between cyclic and continuous*

- Seracchioli, et al. *Fertil Steril* 2010;93:52-56

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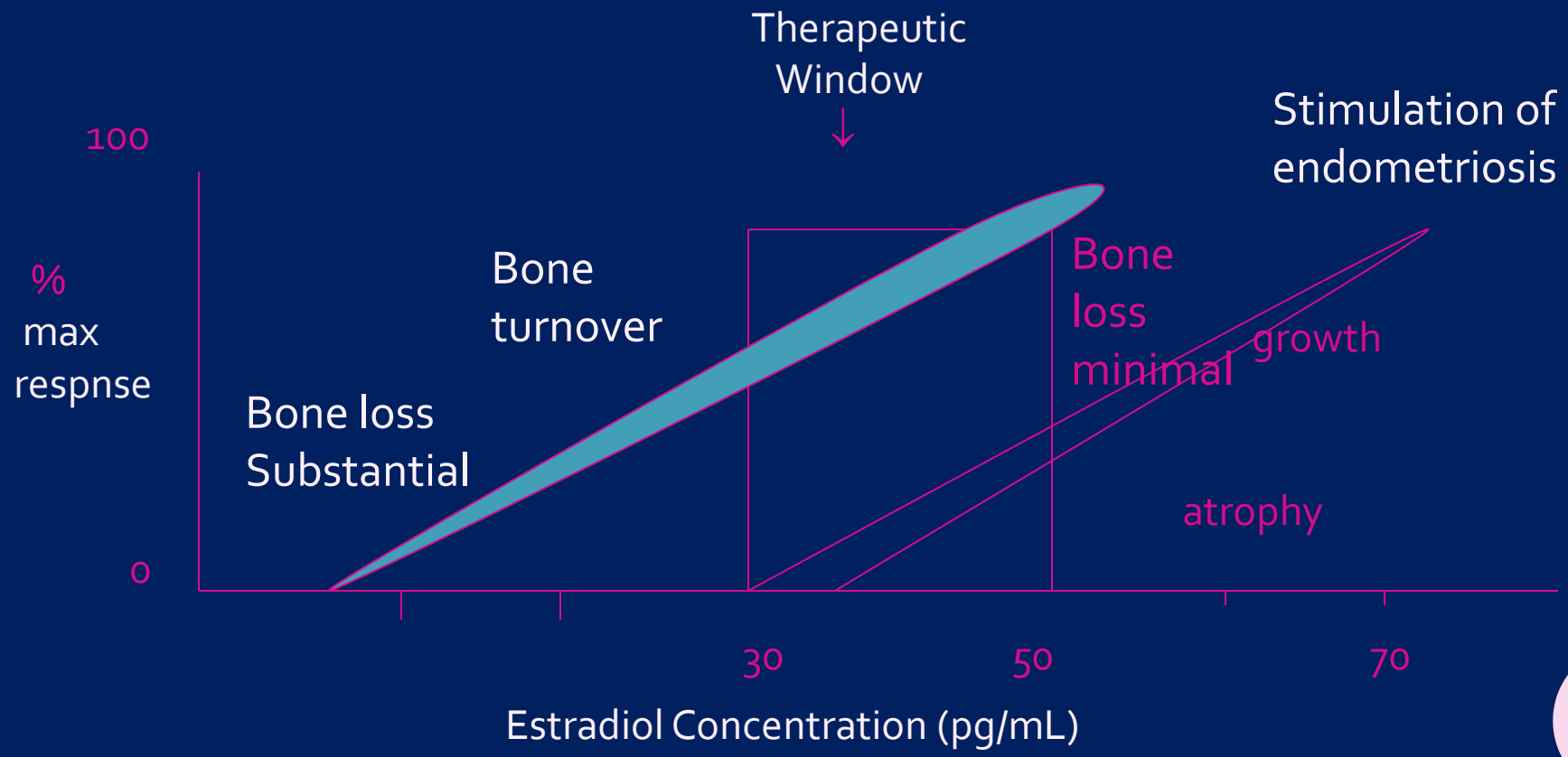
Estrogen Threshold Hypothesis

- Can we get the E2 level at a minimum to treat disease and minimize side effects?
- E2 effects on different tissue are dose-related
- Assumption: all women have the same threshold
  - Barbieri, *Am J Obstet Gynecol* 1992;166, 740-745

Estrogen Threshold Response



Barbieri, *Am J Obstet Gynecol* 1992

Long Term GnRHa: Results

- Pelvic Pain: Improved in all groups (with higher estrogen doses, less pain improvement and more dropout)
- Vasomotor: virtually eliminated in all 3 add-back groups
- BMD: no significant bone loss in all 3 add-back groups

GnRHa and OCPs as Add-Back

- Prospective, randomized 6 month trial
- GnRHa ± OCP (EE 30/desogestrol 0.15)
- N = 27 (14 controls, 13 add-back)
- ↓ dysmenorrhea, ↓ pain
- Δ AFS score ↓ in add-back group (*P* = 0.02)
- ↓ dyspareunia: control > OCP add-back
- ↓ vasomotor instability: OCP > control

Freundl, *Gynecol Obstet Invest* 1998, 45 (Suppl 1), 22

Long-Term GnRHa and Progestin Add-Back for Endometriosis: One Year Clinical Trial

- RCT, prospective, double-blind, n = 201
- FOUR treatment groups:
  - GnRHa + daily placebo tabs
  - GnRHa + daily NetAc (5mg)
  - GnRHa + daily NetAc (5mg) + CEE (0.625mg)
  - GnRHa + daily NetAc (5mg) + CEE (1.25mg)

- Horstein, Surrey, Weisberg, Casino *Obstet Gynecol* 1998,91:16-24

Norethindrone Acetate as Add-Back: Mechanisms of Action

- NetAc undergoes hepatic metabolism to EE
- 2-pronged effect:
  - EE provides bone effect and reduces vasomotor instability
  - Net has direct effect on endometrium
- Result: Synergy with GnRHa

Progestins as Add-Back

- MPA: reduces vasomotor instability, not effective at suppressing disease or symptoms (20 - 30mg/d x 6 mo)[1]
- MPA: effective at 100mg[2]
- Net: effective at up to 2.4mg/d x 6 mo, but ↓BMD[3]
- NetAc: effective at 5mg/d x 12 months[4]

1. Cedars *Obstet Gynecol* 1990, 75; 641-645
2. Surrey *Fertil Steril* 1990, 53; 620-626
3. Bergovist *Gynecol Endocrinol* 1997, 11;187-194
4. Hornstein *Obstet Gynecol* 1998, 91;15-24

E/P Add-Back vs GnRHa Alone: Randomized Trials

Kilhoma, 1995, n=88	Goserelin	TDE/MPA	6 months
Gregoriou, 1997, n=40	Leuprolide	E2/NETA	6 months
Moghissi, 1998 n=345	Goserelin	CEE/MPA	6 months
Franke, 2000 n=41	Goserelin	EE/NETA	6 months
Irahara, 2001 n=21	Leoprolide	CEE/MPA	6 months

E/P Add-Back vs GnRHa Alone

Kilhoma	Sx ↓ both groups	↓ vasomotor with add-back	BMD: Not evaluated
Gregoriou	Sx ↓ both groups	↓ vasomotor with add-back	BMD: -4% vs -0.9%
Moghissi	Sx ↓ both groups	↓vasomotor with add-back	BMD: -4% vs -1.9%
Franke	Not evaluated	↓ Kupperman index w/ adbk	-5% vs -0.2%
Irahara	Not evaluated	↓Kupperman index w/ adbk	-6.3% vs -0.8%

Estrogen Threshold Hypothesis: Is There an E2 level "just right"

- Low enough to prevent disease stimulation
- High enough to inhibit hot flashes
- High enough to inhibit bone loss
- Why not just use progestin alone as add-back?

Long-Term Follow-up For Prolonged GnRH

- Endpoints: Patients in the 1-year study were followed for 12 months after completion for symptom recurrence and return to normal BMD
- Pain: suppressed pain up to 12 months post-therapy
- GnRHa alone: needs 18 months for BMD to return to normal
    - *Surrey Obstet Gynecol 2002, 99;709-719*

Can You Defer Add-Back?

- Randomized 6 month trial
- Group A: GnRHa + (medrogestone 10mg) x 6 mo
- Group B: GnRHa alone, then add-back mo 4 - 6
- Group C: GnRHa alone x 6 months
- Equal disease improvement in all groups
- Lowest BMD loss and vasomotor sx with immediate add-back
- Greatest rate of bone loss: during first 3 months
    - *Kessel Br J Obstet Gynecol 1996, 103;15-17*

Add-Back Dosing and GnRHa Compliance

- Industry-based study
- Retrospective analysis of > 1200 patients starting GnRHa for 'osis ± add-back
- 32% used add-back (most common was Net)
- Compliance higher with add-back (5.8 ± 3 mo vs 4.3 ± 2.6 mo, *P*<.01)

- Fuldeore *Curr Med Res Opin* 2010, 26(3),729-736

Down-Regulation for Endometriosis: Extended or Retreatment

- Norethindrone acetate daily 5mg
- Add Estradiol if vasomotor instability persists

How to reduce concerns of estrogen in add-back formulation

Just use a progestin

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The ideal medical treatment

- Reduce pain
- Block the growth
- Prevent the recurrences
- For long-term use
- Low cost

- Few side effects
- Does not affect fertility

Dienogest:

Qualitative and quantitative composition

Each tablet contains 2 mg dienogest.

Excipient: each tablet contains 62.8 mg lactose monohydrate.

Therapeutic indications

Treatment of endometriosis.

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Posology

The dosage of Dienogest is one tablet daily without any break, taken preferably at the same time each day with some liquid as needed. The tablet can be taken with or without food.
Tablets must be taken continuously without regard to vaginal bleeding. When a pack is finished the next one should be started without interruption.
Treatment can be started on any day of the menstrual cycle.

Any hormonal contraception needs to be stopped prior to initiation of Dienogest. If contraception is required, nonhormonal methods of contraception should be used (e.g. barrier method).

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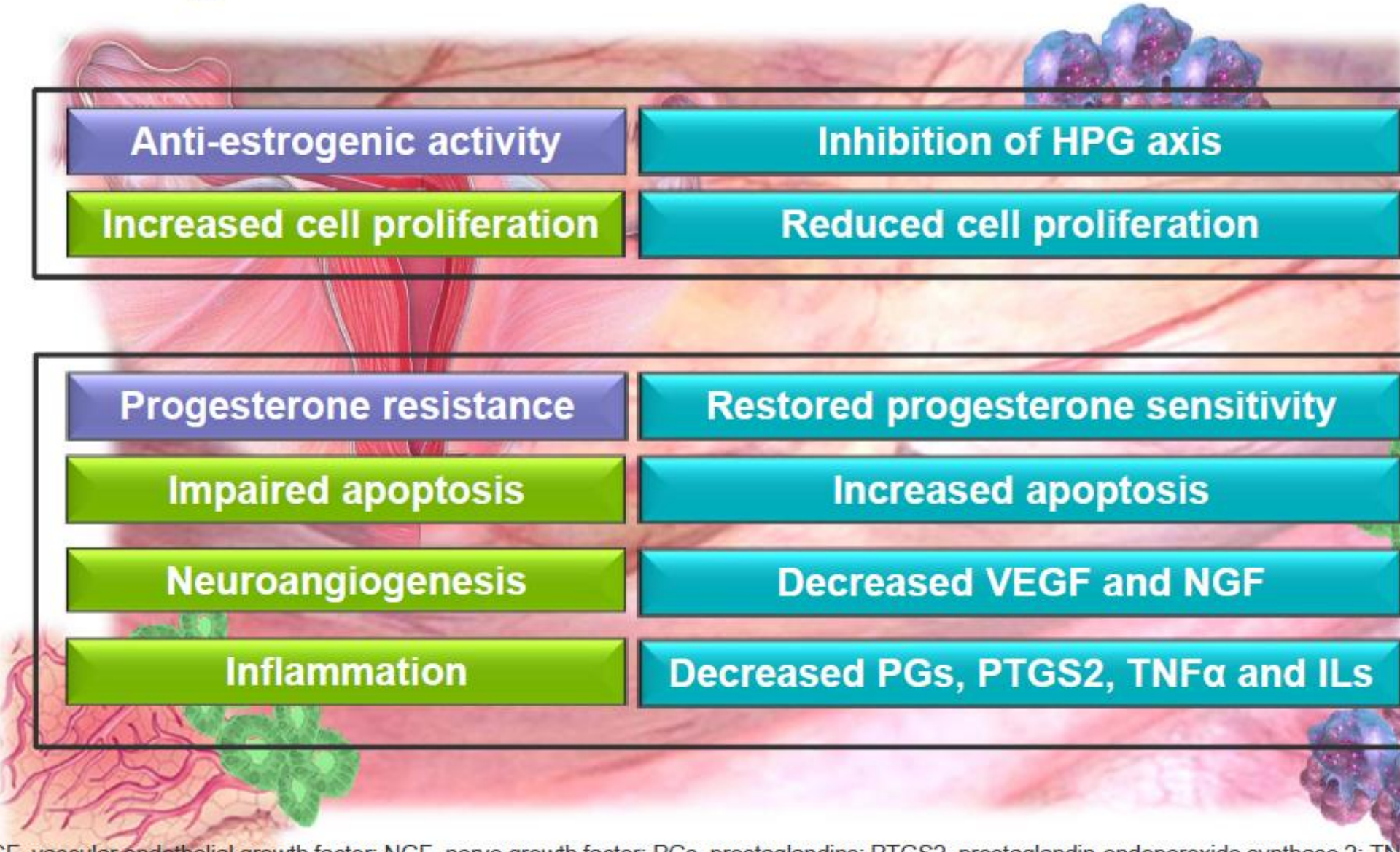
Dienogest mechanism of action[1–3]

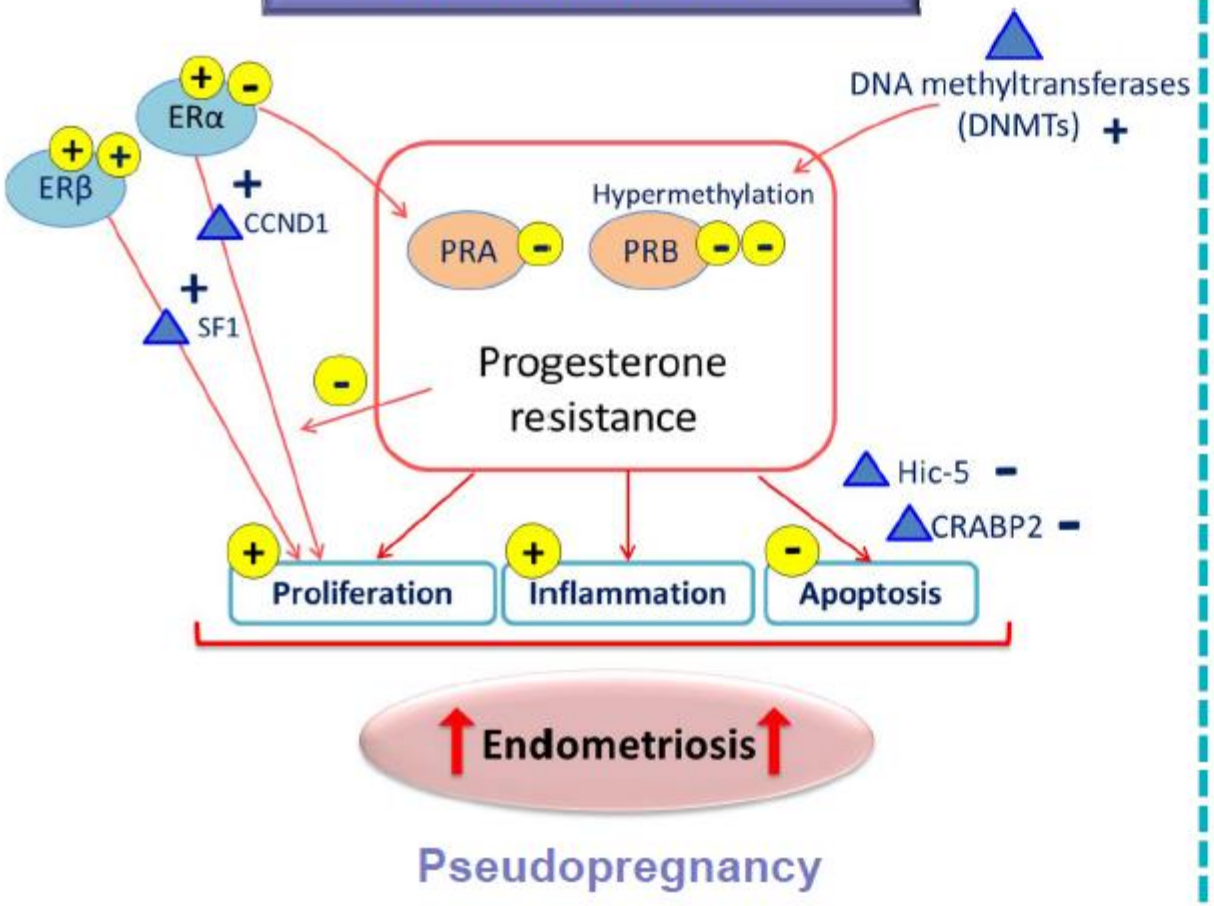


GF, vascular endothelial growth factor; NGF, nerve growth factor; PGs, prostaglandins; PTGS2, prostaglandin-endoperoxide synthase 2; TN
rosis factor; IL, interleukin; HPG, hypothalamic-pituitary-gonadal.

azzeri L *et al*. J Endometriosis 2010; 2(4): 169–181. 2. Shimizu Y *et al*. Steroids 2011; 76(1–2): 60–67. 3. Mita S *et al*. Fertil Steril 2014; 101

The rationale for progestins

Mechanism of action[1–2]



Pseudopregnancy

Pros[2]

Long-term efficacy

Cons[2]

Breakthrough bleedi

Headache

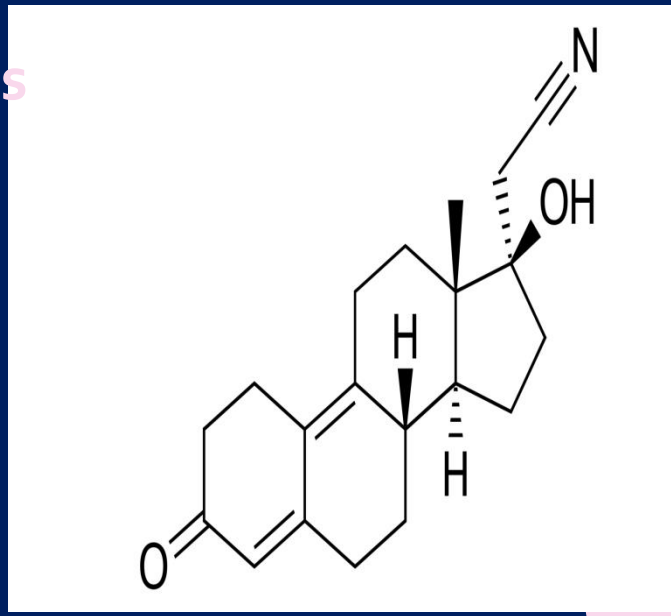
Bloating

1. Bulun SE. N Engl J Med 2009; 360(3): 268–279. 2. Lazzeri L *et al.* J Endometriosis 2010; 2(4): 169–181.

Dienogest is a progestin, or a synthetic progestogen, of the 19-nortestosterone group

It is available in combination with estradiol valerate (as Natazia, Qlaira) or ethinylestradiol (as Valette) for use as an oral contraceptive, and by itself as Visanne, Dinagest) for the treatment of endometriosis in Europe, Australia, and Japan

Although available in combination with estrogen as a contraceptive in the United States, dienogest is not available in this country by itself. In addition to its progestogenic effects, dienogest has antiandrogenic activity, and as a result can improve androgenic symptoms such as acne.



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Treatment can be started on any day of the menstrual cycle.

Any hormonal contraception needs to be stopped prior to initiation of Dienogest. If contraception is required, nonhormonal methods of contraception should be used (e.g. barrier method).

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Management of missed tablets:

The efficacy of Dienogest may be reduced in the event of missed tablets, vomiting and/or diarrhea (if occurring within 3–4 hours after tablet taking). In the event of one or more missed tablets, the woman should take one tablet only, as soon as she remembers, and should then continue the next day at her usual time.

A tablet notabsorbed due to vomiting

Pharmacokinetic properties

Absorption

Orally administered dienogest is rapidly and almost completely absorbed. Peak serum concentrations of 47 ng/mL are reached at about 1.5 hours after single ingestion. Bioavailability is about 91%. The pharmacokinetics
of dienogest are dose-proportional within the dose range of 1–8 mg.

Distribution

Dienogest is bound to serum albumin and does not bind to SHBG or corticoid binding globulin. 10% of the total serum drug concentration is present as free steroid, 90% is non-specifically bound to albumin.

The apparent volume of distribution of dienogest is 40 L.

Metabolism

Dienogest is completely metabolized by the known pathways of steroid metabolism, *CYP3A4 is the major* enzyme involved in the metabolism of dienogest.
The metabolites are excreted very quickly so that, in plasma, unchanged dienogest is the dominating fraction.
The metabolic clearance rate from serum (Cl/F) is 64 mL/min .

Elimination. Dienogest is excreted in the form of metabolites which are excreted at a urinary to fecal ratio of about 3:1 after oral administration of 0.1 mg/kg. The half-life of urinary metabolite excretion is 14hours. Following oral administration approximately 86% of the dose administered is eliminated within 6 days, the bulk of this amount excreted within the first 24 hours, mostly with the urine.

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Additional information on special populations

Pediatric population

Dienogest is not indicated in children prior to menarche. The safety and efficacy of Dienogest in adolescents (menarche to 18 years) has not yet been established.

Geriatric population

There is no relevant indication for use of Dienogest in the geriatric population.

Patients with hepatic impairment

Dienogest is contraindicated in patients with present or past severe hepatic disease (see Section 4.3 within this chapter).

Patients with renal impairment

There are no data suggesting the need for a dosage adjustment in patients with renal impairment

Tumors

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (relative risk = 1.24) of having breast cancer diagnosed in women who are currently using oral contraceptives, mainly using estrogen-progestogen preparations. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. The risk of having breast cancer diagnosed in users of progestogen-only preparations is possibly of similar magnitude to that associated with COC. However, for progestogen-only preparations, the evidence is based on much smaller populations of users and so is less conclusive than that for COCs

Osteoporoseis

In patients who are at an increased risk of osteoporosis a careful risk-benefit assessment should be performed

before starting Dienogest because endogenous

estrogen levels are moderately decreased during treatment with
Dienogest

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Interaction with other medicinal products and other forms of interaction

Effects of other medication on Dienogest

Individual enzyme-inducers or inhibitors (CYP3A4)

Progestogens including dienogest are metabolized mainly by the CYP3A4 system located both in the intestinal mucosa and in the liver. Therefore, inducers or inhibitors of CYP3A4 may affect the progestogen drug metabolism.

An increased clearance of sex hormones due to enzyme induction may reduce the therapeutic effect of Dienogest and may result in undesirable effects (e.g. changes in the uterine bleeding profile).

A reduced clearance of sex hormones due to enzyme inhibition may increase the exposure to dienogest and may result in undesirable effects

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Take Home Points

- As long as the patient has endogenous 17β-estradiol production, surgery is not curative, only cytoreductive
- Medical therapy, either primary or post-op, is adjunctive and effective in outcome improvement for ANY disease stage
- Always consider add-back when GnRHa is used
- Treatment of the Adolescent

RCT, Double-Blind, Placebo-Controlled

Author, Yr	Procedure	Follow-up	% improved
Sutton 1994 N=32	Ablation/ LUNA	6 mo	63%
N=31	Diagnostic	6 mo	22%
Abbot,2004 N=20	Excision	6 mo	80%
N=19	Diagnostic	6 mo	32%

Endometriomas

- Cochrane data review
- 2 randomized trials comparing excision v. drainage/ablation by L-scope
- Excision:
  - Lower recurrence rate
  - Less pain, less repeat surgery
  - Higher spontaneous pregnancy rates

Endometrioma Resection and Ovarian Reserve

- 93 patients with resection of 'oma followed by an IVF cycle
- No follicular growth in 12 ovaries operated
- Frequency of severe ovarian damage: 13% had no follicles at time of hCG trigger
- BE CONSERVATIVE AND PRESERVE OVARIAN BLOOD FLOW

Thank you for your attention

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