TERAPIA DELL'ENDOMETRIOSI: TRATTAMENTO MEDICO

F. Barbieri

VI Corso di aggiornamento su diagnosi e terapia della sterilità di coppia
Dalla diagnosi alla prevenzione, un approccio sempre più multidisciplinare
Sabato 1 aprile 2017 Centro congressi Hotel NH Mantegna Padova

- Endometriosis, defined as the presence of ***endometrial-like*** tissue outside the uterus, is associated with a ***chronic inflammatory reaction***. ***Cellular proliferation, invasion, and neoangiogenesis*** are key to the establishment, progression, and recurrence of the disease.

- In addition, sloughing of the ***estrogendependent*** ectopic endometrial tissue leads to a chronic inflammatory process mediated by the ***overproduction of inflammatory mediators*** such as ***cytokines and prostaglandins***.

- That inflammation, with its resultant ***adhesions and scarring***, mediates the patient's symptoms of ***pain*** and other morbidities such as ***infertility***

KENNEDY S, BERGQVIST A, CHAPRON C, D'HOOGHE T, DUNSELMAN G, GREB R, ET AL. ESHRE GUIDELINE FOR THE DIAGNOSIS AND TREATMENT OF ENDOMETRIOSIS. HUM REPROD 2005;20:2698–704.

ENDOMETRIOSIS, A ***CHRONIC*** AND ***RECURRENT DISEASE***, REPRESENTS A CHALLENGE TO HEALTH-CARE PROVIDERS AND A BURDEN ON THE HEALTH CARE SYSTEM.

THE REPORTED PREVALENCE OF ENDOMETRIOSIS IS BETWEEN **2% AND 10% IN THE GENERAL POPULATION**, **50% IN THE *INFERTILE* POPULATION**

MORE THAN **60% IN PATIENTS WITH *CHRONIC PELVIC PAIN (CPP)***

GIUDICE LC, KAO L. ENDOMETRIOSIS. LANCET 2004;364:1789–99.

ILANGAVAN K, KALU E. HIGH PREVALENCE OF ENDOMETRIOSIS IN INFERTILE WOMEN WITH NORMAL OVULATION AND NORMOSPERMIC PARTNERS [LETTER]. FERTIL STERIL 2010;93:E10.

BARBIERI RL. HORMONE TREATMENT OF ENDOMETRIOSIS: THE ESTROGEN THRESHOLD HYPOTHESIS. AM J OBSTET GYNECOL 1992;166:740–5.

Treatment

- Recogniz
  - Pain
  - Prese y
- Counseli
  - Disea able
  - Optir nexistent

«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»
Practice Committee of the ASRM, 2014

CRITERIA FOR THE IDEAL MEDICATION FOR ENDOMETRIOSIS

CURATIVE *RATHER THAN SUPPRESSIVE*

TREATS PAIN AND FERTILITY AT THE SAME TIME

ACCEPTABLE ***SIDE EFFECT PROFILE***

LONG-TERM USE SHOULD BE **SAFE** AND **AFFORDABLE**

NON-CONTRACEPTIVE *NATURE*

NO INTERFERENCE WITH SPONTANEOUS OVULATIONS AND NORMAL IMPLANTATION

BEDAIWY. FUTURE OF ENDOMETRIOSIS MEDICAL THERAPY. FERTIL STERIL 2017.

CRITERIA FOR THE IDEAL MEDICATION FOR ENDOMETRIOSIS.

ENHANCES *SPONTANEOUS* ***CONCEPTION***

NO TERATOGENIC POTENTIAL AND SAFE TO USE PERICONCEPTIONALLY

INHIBITS THE GROWTH OF ALREADY EXISTING LESIONS

ABORTS THE DEVELOPMENT OF NEW LESIONS

EFFICACIOUS FOR ALL ***ENDOMETRIOSIS PHENOTYPES*** *INCLUDING* ***SUPERFICIAL DISEASE***, ***ENDOMETRIOMAS***, ***DEEP INFILTRATING ENDOMETRIOSIS***, *AND* ***EXTRAPELVIC ENDOMETRIOSIS*** *AND* ***ADENOMYOSIS***

BEDAIWY. FUTURE OF ENDOMETRIOSIS MEDICAL THERAPY. FERTIL STERIL 2017.

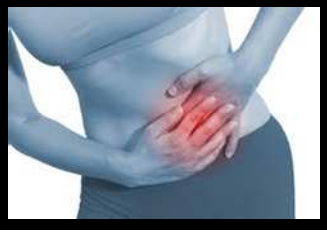
- Understanding the pathogenesis and the endocrinology of endometriosis allows for the improvement of the currently existing treatment options and the introduction of new treatments.

- **Currently**, **successful treatment of endometriosis-associated pain is based on *suppressing estrogen production*** and inducing amenorrhea. This creates a relatively hypoestrogenic environment that inhibits ectopic endometrial growth and prevents disease progression

- This treatment strategy, however, several limitations.

Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. Am J Obstet Gynecol 1992;166:740–5.

- Almost ***all currently available treatments of endometriosis*** are ***suppressive, not curative*.**
- They are associated with the **temporary relief of symptoms** during treatment.
- On treatment discontinuation, ***recurrence*** of the symptoms is the rule.
- For instance, endometriosis associated pain can continue after medical treatment or conservative surgery.



- After medical treatment or surgical treatment, the **recurrence of endometriosis** was estimated to be

  - **21.5%at 2 years**

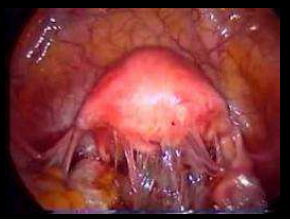
  - **40% to 50%at 5 years**

- After surgical treatment, the ***recurrence*** rate of clinically detectable endometriosis tends to be ***higher in older women with advanced stages of the disease*** and ***lower in women with infertility***

Parazzini F, Bertulessi C, Pasini A, Rosati M, Di Stefano F, Shonauer S, et al Determinants of short term recurrence rate of endometriosis. Eur J Obstet Gynecol Reprod Biol 2005;121:216–9.

- In a 7-year follow-up study, the reoperation rate increased with increasing time since the initial surgery

Shakiba K, Bena JF, McGill KM, Minger J, Falcone T. Surgical treatment of endometriosis: a 7-year follow-up on the requirement for further surgery. Obstet Gynecol 2008;111:1285–92.



- **The current treatment options for endometriosis-associated pain are contraceptive in nature**.

- This is, in part, mediated by blocking the hypothalamopituitary-ovarian axis and inducing a suppression of ovulatory function.

- In addition, the associated endometrial atrophy with hormone therapy (HT) hinders embryo implantation. This represents a challenge for endometriosis patients with painful symptoms who wish to become pregnant.

- Consequently,

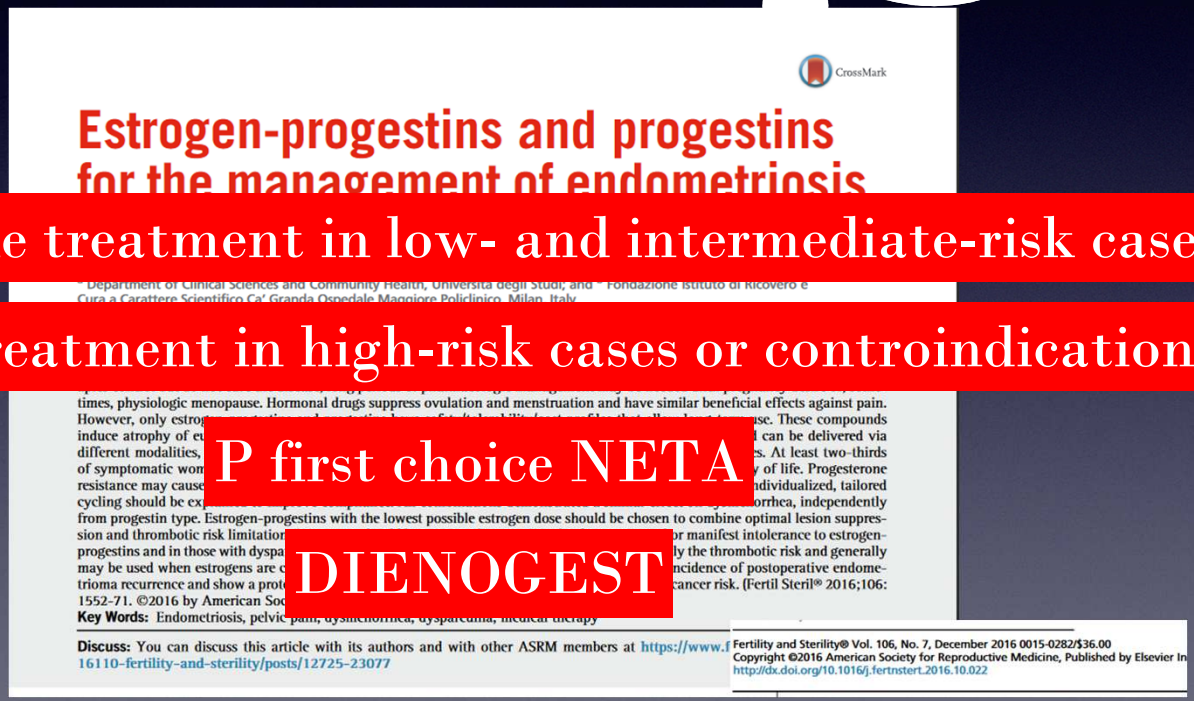
in women desirous of pregnancy who have painful endometriosis

nonsteroidal anti-inflammatory drugs (NSAIDs)

appear to be the only medical option consistent with the maintenance of fertility.

Hormonal treatment: THE PRESENT

BENEFITS
HARM
COSTS


CrossMark

Estrogen-progestins and progestins for the management of endometriosis

times, physiologic menopause. Hormonal drugs suppress ovulation and menstruation and have similar beneficial effects against pain. However, only estrog... induce atrophy of e... different modalities, ... of symptomatic wom... resistance may cause ... cycling should be ex... from progestin type. Estrogen-progestins with the lowest possible estrogen dose should be chosen to combine optimal lesion suppression and thrombotic risk limitation ... progestins and in those with dyspa... may be used when estrogens are c... trioma recurrence and show a prot... 1552-71. ©2016 by American Soc...

Key Words: Endometriosis, pelvic pain, dysmenorrhea, dyspareunia, medical therapy

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.f... 16110-fertility-and-sterility/posts/12725-23077

Fertility and Sterility® Vol. 106, No. 7, December 2016 0015-0282/$36.00
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http://dx.doi.org/10.1016/j.fertnstert.2016.10.022

EP first line treatment in low- and intermediate-risk cases

P first line treatment in high-risk cases or controindication EP

P first choice NETA

DIENOGEST

Fertil Steril, Dec 2016

Hormonal treatment: THE PRESENT

CrossMark

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

Robert F. Casper, M.D.

Division of Reproductive Sciences, University of Toronto, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, and TRIO Fertility

P first line treatment

For decades, combined estrogen-progestin oral contraceptive pills (OCPs) have been the first-line treatment for menstrual and pelvic pain associated with endometriosis without any clinical evidence of efficacy. Initial relief provided by OCPs is likely a result of improve-

EP increase risk of endometrial cells attachement

Key Words: Dienogest, endometriosis, norethindrone acetate, oral contraceptives, progestins

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/14320-23361

Fertil Steril, 2017

Estrogen-progestins and progestins

- Endometriosis-associated chronic pelvic inflammation result in lesion progression, adhesion formation, tissue fibrosis, neurotropism, pain symptom development, and infertility
- Estradiol has proinflammatory and antiapoptotic effects on endometrial cells, especially when ectopically located.
- Conversely, **progestins** inhibit inflammatory pathways and responses, and induce apoptosis in endometriotic cells

Vercellini P, Vigano P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol 2014;10:261–75.

Reis FM, Petraglia F, Taylor RN. Endometriosis: hormone regulation and clinical consequences of chemotaxis and apoptosis. Hum Reprod Update2013;19:406–18.

Estrogen-progestins and progestins

- Current monophasic estrogen-progestins used for contraceptivepurposes generally contain limited amounts of ethinyl-estradiol, compared with those used in the past, and have a prevalent progestin effect.

- Moreover, ***both estrogen-progestins and progestins reduce the amount of uterine bleeding or abolish it***, thus potentially greatly limiting the number of erythrocytes regurgitated in the pelvis.

Donnez J, Binda MM, Donnez O, Dolmans MM. Oxidative stress in the pelvic cavity and its role in the pathogenesis of endometriosis. Fertil Steril 2016;106:1011–7.

Vercellini P, Crosignani P, Somigliana E, Vigano P, Buggio L, Bolis G, et al. The ''incessant menstruation'' hypothesis: a mechanistic ovarian cancer model with implications for prevention. Hum Reprod 2011;26:2262–73.

Estrogen-progestins and progestins

- This should result in a ***reduction of the pelvic oxidative stress burden*** derived by an excess of free peritoneal iron and heme secondary to erythrophagocytosis and lysis by pelvic macrophages .

- In fact, a vast amount of data points to excessive oxidative stress originating from retrograde menstruation as the ***source of inflammation*** that triggers ***macrophage activation***, with associated ***antiapoptotic and neurotropic effects***

Donnez J, Binda MM, Donnez O, Dolmans MM. Oxidative stress in the pelvic cavity and its role in the pathogenesis of endometriosis. Fertil Steril 2016;106:1011–7.

Vercellini P, Crosignani P, Somigliana E, Vigano P, Buggio L, Bolis G, et al. The ''incessant menstruation'' hypothesis: a mechanistic ovarian cancer model with implications for prevention. Hum Reprod 2011;26:2262–73.

Notwithstanding the strong rationale supporting the use of estrogen-progestins and progestins in the management of symptomatic endometriosis,

between one-fourth and one-third of patients treated with these compounds do not respond to therapy

Vercellini P, Cortesi I, Crosignani PG. Progestins for symptomatic endometriosis: a critical analysis of the evidence. Fertil Steril 1997;68:393–401.

Vercellini P, Fedele L, Pietropaolo G, Frontino G, Somigliana E,Crosignani PG. Progestogens for endometriosis: forward to the past. Hum Reprod 2003;9:387–96.

Vercellini P, Crosignani P, Somigliana E, Vigano P, Frattaruolo MP, Fedele L.''Waiting for Godot'': a commonsense approach to the medical treatment of endometriosis. Hum Reprod 2011;26:3–13.

Vercellini P, Giudice LC, Evers JL, Abrao MS. Reducing low-value care in endometriosis between limited evidence and unresolved issues: a proposal. Hum Reprod 2015;30:1996–2004.

Ferrero S, Alessandri F, Racca A. Leone Roberti Maggiore U. Treatment of pain associated with deep endometriosis: alternatives and evidence. Fertil Steril 2015;104:771–92.

- Progesterone resistance has been adduced to explain this unexpected outcome

- ***In endometriosis, local estrogens are overproduced***, and the ***expression of progesterone receptors may be altered*** or their ***activity diminished***. This can result in attenuated or dysregulated progesterone response and secondary silencing of progesterone-responsive genes

Cakmak H, Taylor HS. Molecular mechanisms of treatment resistance in endometriosis: the role of progesterone-HOX gene interactions. Semin Reprod Med 2010;28:69–74.

Bulun SE, Monsivais D, Kakinuma T, Furukawa Y, Bernardi L, Pavone ME, et al. Molecular biology of endometriosis: from aromatase to genomic abnormalities. Semin Reprod Biomed 2015;33:220–4.

"Despite the above epigenetic mechanism that mediates progesterone resistance, ***at least two-thirds of women with symptomatic endometriosis* still respond to estrogen-progestin and progestin therapy.**"

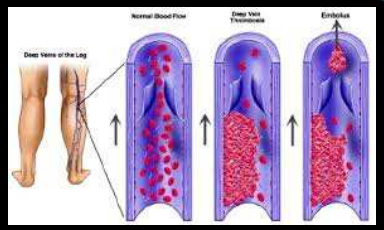
The availability of such a safe, well tolerated, and relatively inexpensive therapeutic modality enabling long-term disease control would be considered a substantial success for any other human chronic inflammatory disorder.

"

However, safety is particularly important here because ***patients may need long periods of treatments*** even during advanced reproductive years.

"

The main issue is the ***risk of venous and arterial thrombosis associated with estrogen-progestin*** ***and progestin use,*** because several population-based and case-control studies demonstrated an increased risk of both complications.



risk of venous and arterial thrombosis associated with estrogen-progestin

THE NUMBER OF
VENOUS THROMBOTIC EVENTS IN ***NONUSERS OF ESTROGEN-PROGESTINS*** IS
4–5 PER 10,000 WOMAN-YEARS.

THE RELATIVE RISK (RR) INCREASES IN RELATION TO THE TYPE OF PROGESTIN USED AND THE ESTROGEN DOSE

LIDEGAARD Ø, NIELSEN LH, SKOVLUND CW, SKJELDESTAD FE, LØKKEGAARD E. RISK OF VENOUS THROMBOEMBOLISM FROM USE OF ORAL CONTRACEPTIVES CONTAINING DIFFERENT PROGESTOGENS AND OESTROGEN DOSES: DANISH COHORT STUDY, 2001–9. BMJ 2011;343:D6423.

MANZOLI L, DE VITO C, MARZUILLO C, BOCCIA A, VILLARI P. ORAL CONTRACEPTIVES AND VENOUS THROMBOEMBOLISM: A SYSTEMATIC REVIEW AND META-ANALYSIS. DRUG SAF 2012;35:191–205.

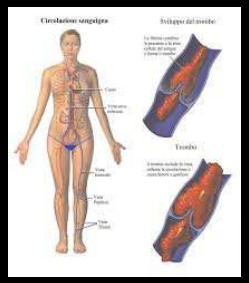
VINOGRADOVA Y, COUPLAND C, HIPPISLEY-COX J. USE OF COMBINED ORAL CONTRACEPTIVES AND RISK OF VENOUS THROMBOEMBOLISM: NESTED CASE-CONTROL STUDIES USING THE QRESEARCH AND CPRD DATABASES. BMJ 2015;350:H2135.

risk of venous and arterial thrombosis associated with estrogen-progestin

RR INCREASE
FOR ESTROGEN-***PROGESTIN COMBINATIONS***

2–3
CONTAINING LEVONORGESTREL, NORETHISTERONE, AND NORGESTIMATE

4–6 FOR
THOSE CONTAINING DESOGESTREL, GESTODENE, CYPROTERONE ACETATE, AND DROSPIRENONE



risk of venous and arterial thrombosis associated with estrogen-progestin

TO THE SCANT AVAILABLE INFORMATION, THE THROMBOTIC RISK ASSOCIATED WITH ESTROGEN-PROGESTIN COMBINATIONS CONTAINING ***DIENOGEST*** IS SIMILAR TO THAT OBSERVED WITH PREPARATIONS CONTAINING THE CURRENTLY AVAILABLE THIRD- AND FOURTH-GENERATION PROGESTINS

ZILLER M, ZILLER V, HAAS G, REX J, KOSTEV K. RISK OF VENOUS THROMBOSIS IN USERS OF HORMONAL CONTRACEPTIVES IN GERMAN GYNECOLOGICAL PRACTICES: A PATIENT DATABASE ANALYSIS. ARCH GYNECOL OBSTET 2014;289:413–9.

risk of venous and arterial thrombosis associated with estrogen-progestin

ESTROGEN DOSE

A ***20%–25% REDUCTION IN RISK*** WAS OBSERVED ***IN USERS OF ORAL CONTRACEPTIVES (OCS) CONTAINING 0,02 MG ETHINYL-ESTRADIOL (EE)*** COMPARED WITH THOSE USING AN OC CONTAINING 0,03–0,04 MG EE

LIDEGAARD Ø, NIELSEN LH, SKOVLUND CW, SKJELDESTAD FE, LØKKEGAARD E. RISK OF VENOUS THROMBOEMBOLISM FROM USE OF ORAL CONTRACEPTIVES CONTAINING DIFFERENT PROGESTOGENS AND OESTROGEN DOSES: DANISH COHORT STUDY, 2001–9. BMJ 2011;343:D6423.

risk of venous and arterial thrombosis associated with estrogen-progestin

PROGESTIN-ONLY PREPARATIONS (NORETHISTERONE AND DESOGESTREL PILLS) CONFER NO INCREASED RISK OF VENOUS THROMBOEMBOLISM.

RRS FOR VENOUS THROMBOTIC EVENTS OF 7.9 (95% CI 3.5–17.7) AND 6.5 (4.7–8.9) WERE OBSERVED IN TRANSDERMAL PATCH AND VAGINAL RING USERS, RESPECTIVELY

risk of venous and arterial thrombosis associated with estrogen-progestin

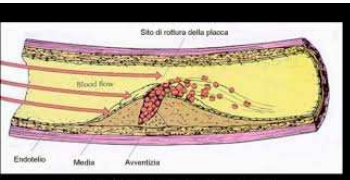
WHEREAS THE ***RR*** WAS ***NOT SIGNIFICANTLY INCREASED*** IN USERS OF

PROGESTIN-ONLY SUBCUTANEOUS IMPLANTS

AND

LEVONORGESTREL-RELEASING INTRAUTERINE DEVICE (LNG-IUD)

LIDEGAARD Ø, NIELSEN LH, SKOVLUND CW, LØKKEGAARD E. VENOUS THROMBOSIS IN USERS OF NONORAL HORMONAL CONTRACEPTION: FOLLOW-UP STUDY, DENMARK 2001–10. BMJ 2012;344:E2990.



Formazione del trombo su placca lesionata

risk of venous and arterial thrombosis associated with estrogen-progestin

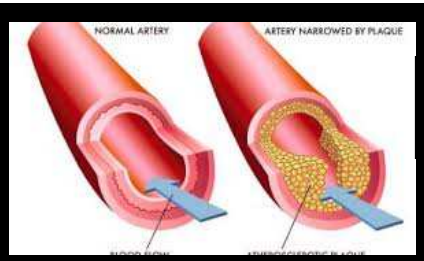
ARTERIAL THROMBOSIS

THE **BASELINE RISK IN**
NONUSERS OF HORMONAL CONTRACEPTION
WAS
2.1 PER 10,000WOMAN-YEARS FOR **THROMBOTIC STROKE**

1.0 PER 10,000 WOMAN-YEARS FOR MYOCARDIAL INFARCTION

IN A DANISH HISTORICAL COHORT STUDY

THE RISK OF ARTERIAL THROMBOSIS WAS **ASSOCIATED**
MORE WITH EE DOSE THAN WITH THE PROGESTIN TYPE CONTAINED



risk of venous and arterial thrombosis associated with estrogen-progestin

ARTERIAL THROMBOSIS

IN USERS OF OCS CONTAINING 0,03–0,04 MG EE, RR WAS ABOUT DOUBLED

WHEREAS

THE RR INCREASE WAS 20%–50% IN USERS OF OCS CONTAINING 0,02 MG EE.

A SLIGHTLY HIGHER RR WAS OBSERVED **WITH THE USE OF THE TRANSDERMAL PATCH AND THE VAGINAL RING**

THE USE OF PROGESTIN-ONLY SYSTEMS, INCLUDING THE LNG-IUD, DID NOT SIGNIFICANTLY INCREASE THE RISK

LIDEGAARD Ø, LØKKEGAARD E, JENSEN A, SKOVLUND CW, KEIDING N. THROMBOTIC STROKE AND MYOCARDIAL INFARCTION WITH HORMONAL CONTRACEPTION. N ENGL J MED 2012;366:2257–66.

risk of venous and arterial thrombosis associated with estrogen-progestin

ARTERIAL THROMBOSIS

VENOUS THROMBOTIC EVENTS ARE THREE TO FOUR TIMES MORE FREQUENT THAN ARTERIAL THROMBOTIC EVENTS, BUT GENERALLY MUCH LESS SEVERE.

THE USE OF OCS IN 1,000 WOMEN CAUSE ONE ADDITIONAL VENOUS THROMBOTIC EVENT EACH YEAR.
CONSIDERING THAT MORTALITY FROM VENOUS THROMBOEMBOLISM IN 20–44-YEAR-OLD WOMEN IS 1%, OC USE WOULD CAUSE ONE ADDITIONAL DEATH EACH YEAR EVERY 100,000 USERS.

risk of venous and arterial thrombosis associated with estrogen-progestin

ARTERIAL THROMBOSIS

BASED ON THE ABOVE DATA, ESTROGEN-PROGESTIN COMBINATIONS CONTAINING ***SECOND-GENERATION PROGESTINS*** SHOULD BE GENERALLY ***PREFERRED*** COMPARED WITH THOSE CONTAINING THIRD AND FOURTH-GENERATION PROGESTINS

PREPARATIONS WITH **THE LOWEST POSSIBLE EE DOSE** SHOULD CONSTITUTE THE FIRSTLINE CHOICE, CONSIDERING THAT THE ESTROGEN CONTENT AFFECTS THE RISK OF BOTH VENOUS AND ARTERIAL THROMBOSIS.


Cochrane Library
Cochrane Database of Systematic Reviews

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

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

NonHormone treatment: THE PRESENT

FANS

- No evidence on the use of FANS for endometriosis, **only one study published in 1985 (naproxen)**
- recent study discussed the COX-2 inhibitor ROFECOXIB, withdrawn from the market in some European countries due to severe side effects
- side effects associated with frequent use of NSAIDs, including inhibition of ovulation, risk of gastric ulceration and cardiovascular disease

2017

Hormonal treatment: THE PRESENT

GnRH AGONISTS

Buserelin, Goserelin, Leuprolide, Nafarelin, Triptorelina, Leuprorelina

- Down-regulation of the pituitary-ovarian axis and hypoestrogenism
- available as a depot which can be administered every 1-3 months intramuscularly
- Effective in relieving painful symptoms (similar to danazol and LNG-IUS)
- Common hypoestrogenic side effects: hot flushes, sleep disturbances, vaginal dryness, decreased libido, mood swings, headache, bone mineral depletion
- NOT more than 6 month as a single treatment ("add-back" therapy)

M.A. Bedaiwy, Fertility and Sterility, 2017

Hormonal treatment:
THE PRESENT

LNG-IUS

- 20 μg/daily over a 5-years period.
- Fewer adverse effects than systemic progestins
- It may be not protective in preventing the onset of ovarian endometriomas associated with ovulation
- Limited data on the effectiveness of the LNG-IUS on dyspareunia and dyschezia, confirm that benefits on pelvic pain are maintained during the entire 5-years period.

Hormonal treatment:
THE PRESENT

Tricyclics and antiepileptics

Imipramin, amitriptilin, GABA ergics

Central sensitization is being increasingly recognized as a key factor in the pathogenesis of endometriosis-associated pain in addition to the peripheral nociceptive effect of endometriotic lesions

Central sensitization amplifies pain signaling from the periphery

It is associated with myofascial trigger points and psychological comorbidities

Therefore, treatments to reduce central sensitization are required in some patients, although there is little research in this area for women with endometriosis.

Hoffman D. Central and peripheral pain generators in women with chronic pelvic pain: patient centered assessment and treatment. Curr Rheumatol Rev 2015;11:146–66.
Brawn J, MorottiM, Zondervan KT, Becker CM, Vincent K. Central changes associated with chronic pelvic pain and endometriosis. Hum Reprod Update 2014;20:737–47.
Stratton P, Khachikyan I, Sinaii N, Ortiz R, Shah J. Association of chronic pelvic pain and endometriosis with signs of sensitization and myofascial pain. Obstet Gynecol 2015;125:719–28.
Yosef A, Allaire C, Williams C, Ahmed AG, Al-Hussaini T, Abdellah MS, et al. Multifactorial contributors to the severity of chronic pelvic pain in women. Am J Obstet Gynecol 2016;215:760.e1–14.
Peters A, Van Dorst E, Jellis B, Van Zuuren E, Hermans J, Trimbos J. A randomized clinical trial to compare two different approaches in women with chronic pelvic pain. Obstet Gynecol 1991;77:740–4.

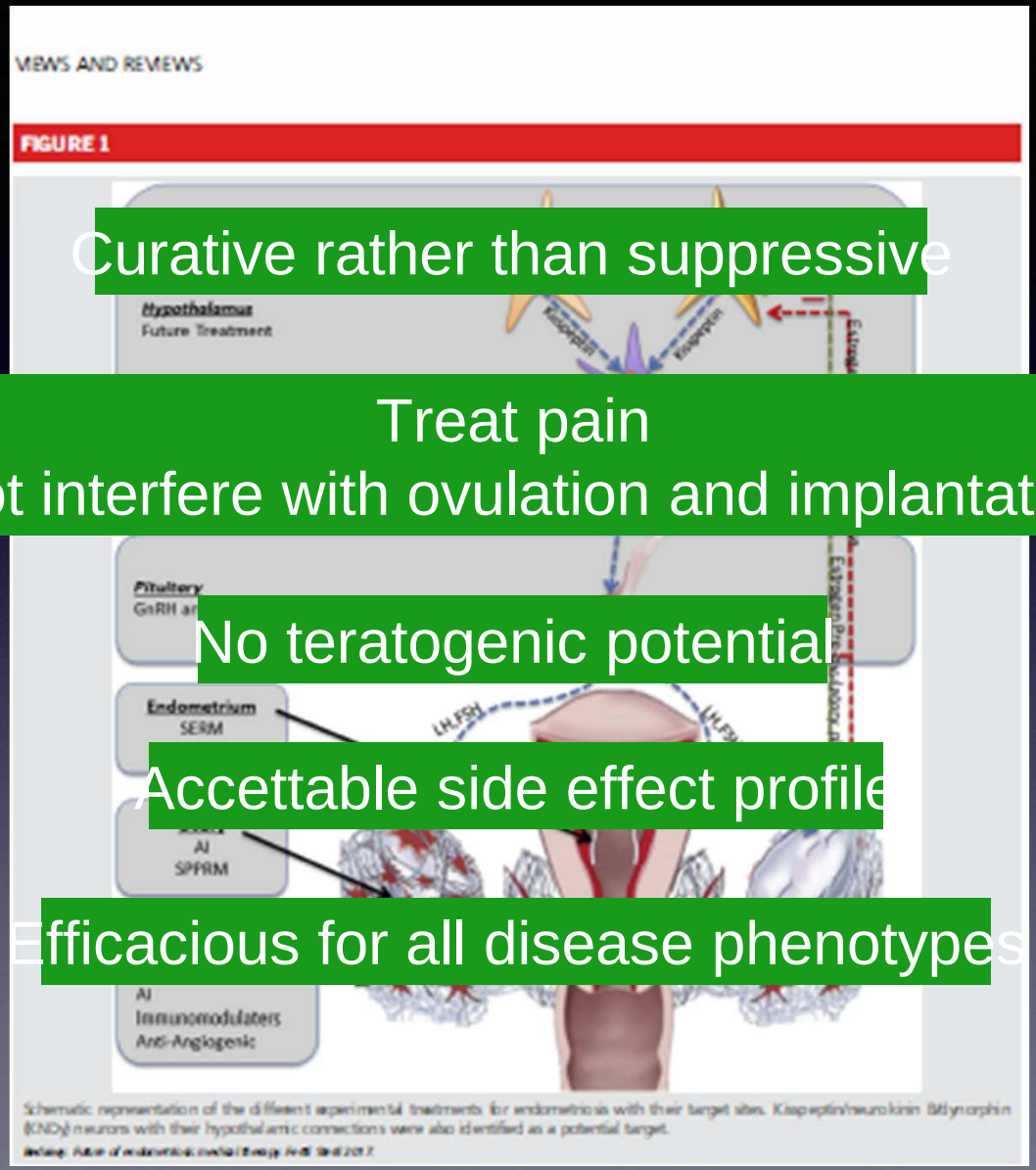
Hormonal treatment:
THE PRESENT

To date there is no optimal medical treatment for endometriosis and its associated symptoms. This is, in part, due to lack of understanding of the pathogenesis and natural history of the disease.

Consequently, the search continues for a medical treatment based on a more accurate understanding of the different disease mechanisms that is efficacious in treating endometriosis-associated comorbidities.

The limitations of the currently available options pose a challenge and present an opportunity to seek novel therapies for endometriosis.

Ideally, medications for endometriosis



Schematic representation of the different experimental treatments for endometriosis with their target sites. Kisspeptin/neurokinin B/dynorphin (KND) neurons with their hypothalamic connections were also identified as a potential target.

Curative rather than suppressive

Treat pain
Not interfere with ovulation and implantation

No teratogenic potential

Accettable side effect profile

Efficacious for all disease phenotypes

Hormonal treatment: THE FUTURE

GnRH Antagonists

Partial suppression of estradiol: a new strategy in endometriosis management?

CrossMark

Donnez J, Fertil Steril 2017

A NEW WAY OF ACHIEVING PARTIAL ESTRADIOL SUPPRESSION

A new class of drug particularly capable of partial estradiol suppression is orally active GnRH antagonist, which includes Elagolix (AbbVie), OBE2109 (ObsEva SA), Relugolix (Myovant), and ASP1707 (Astellas), all currently in phase 2 or 3 of clinical development in the United States and/or

VOL. 107 NO. 3 / MARCH 2017

Fertility and Sterility®

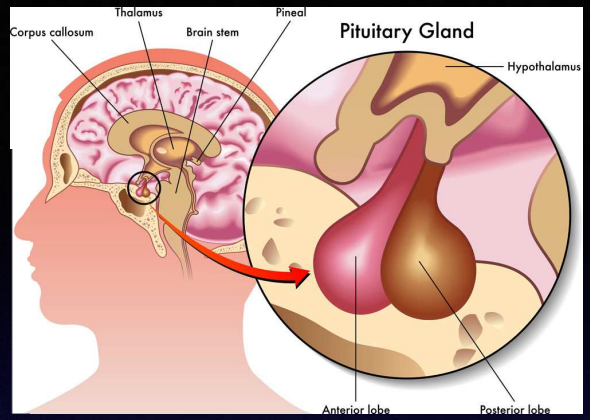
GnRHant

Cetrorelix(3 mg/8w)
Elagolix(150mg/d)
OBE2109 (50-100 mg)
Relugolix
ASP1707

Efficacy, safety, tolerability, rapid reversibility

Hormonal treatment: THE FUTURE

GnRH Antagonists



Direct pituitary gonadotropin suppression

Competitive occupancy and inactivation GnRHr

Dose-dependent hypoestrogenic environment (serum E2 <50 pg/ml)

No or few hypoestrogenism related symptoms

modulators, and antiangiogenic agents. Further research is needed into central sensitization, local neurogenesis, and the genetics of endometriosis to identify additional treatment targets. A wider range of medical options allows for the possibility of precision health and a more personalized treatment approach for women with endometriosis. (Fertil Steril® 2017;107:555–65. ©2017 by American Society for Reproductive Medicine.)

Key Words: Antiangiogenic agents, endometriosis, fut … omodulators

Discuss: You can discuss this article with its authors … nbers at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/14208-23388

↓ Pain

↓endometriotic cells proliferation (TNFα)

Hormonal treatment: THE FUTURE

AROMATASE INHIBITORS

Letrozole (2.5 mg)
Anastrozole (1mg)
3rd generation

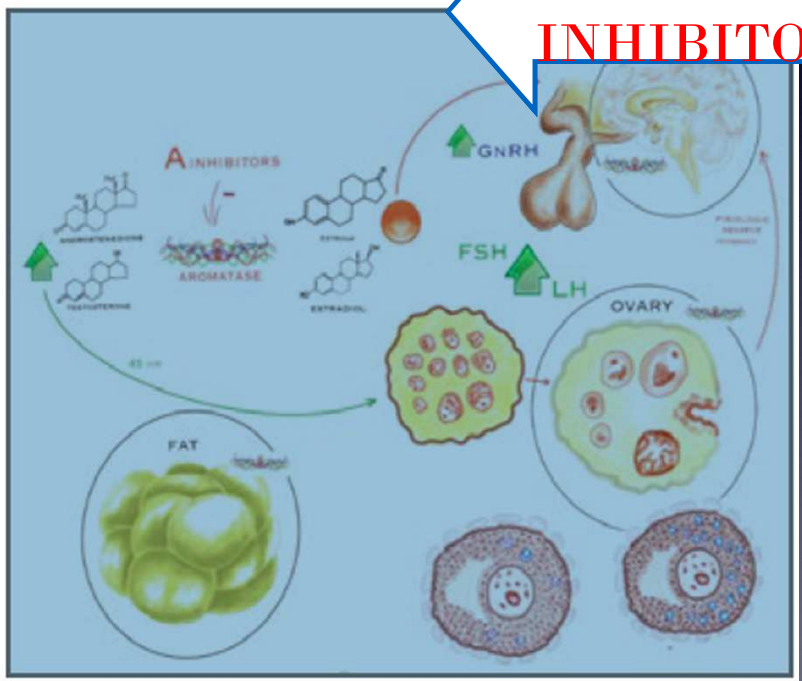


Figura 2 Meccanismo d'azione degli Inibitori delle Aromatasi

Endometrial and endometriotic tissue present high levels of Aromatase activity (generate E)

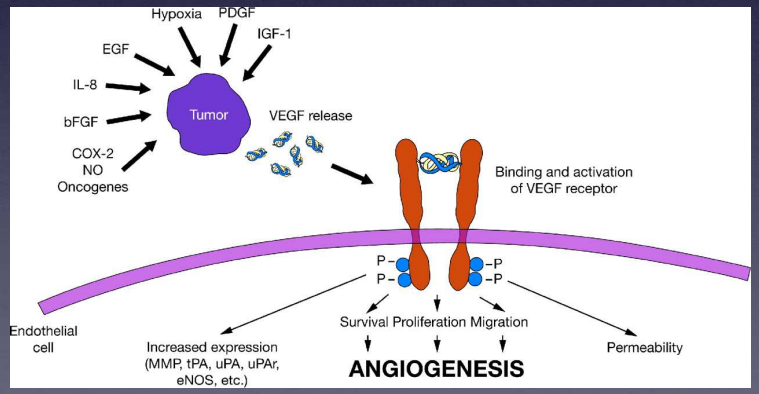
Enzyme activity permanently blocked

Hormonal treatment:
THE FUTURE

1-Inhibit local estrogen production

AROMATASE INHIBITORS

2-↓ VEGF secretion in peritoneal fluid (animal)

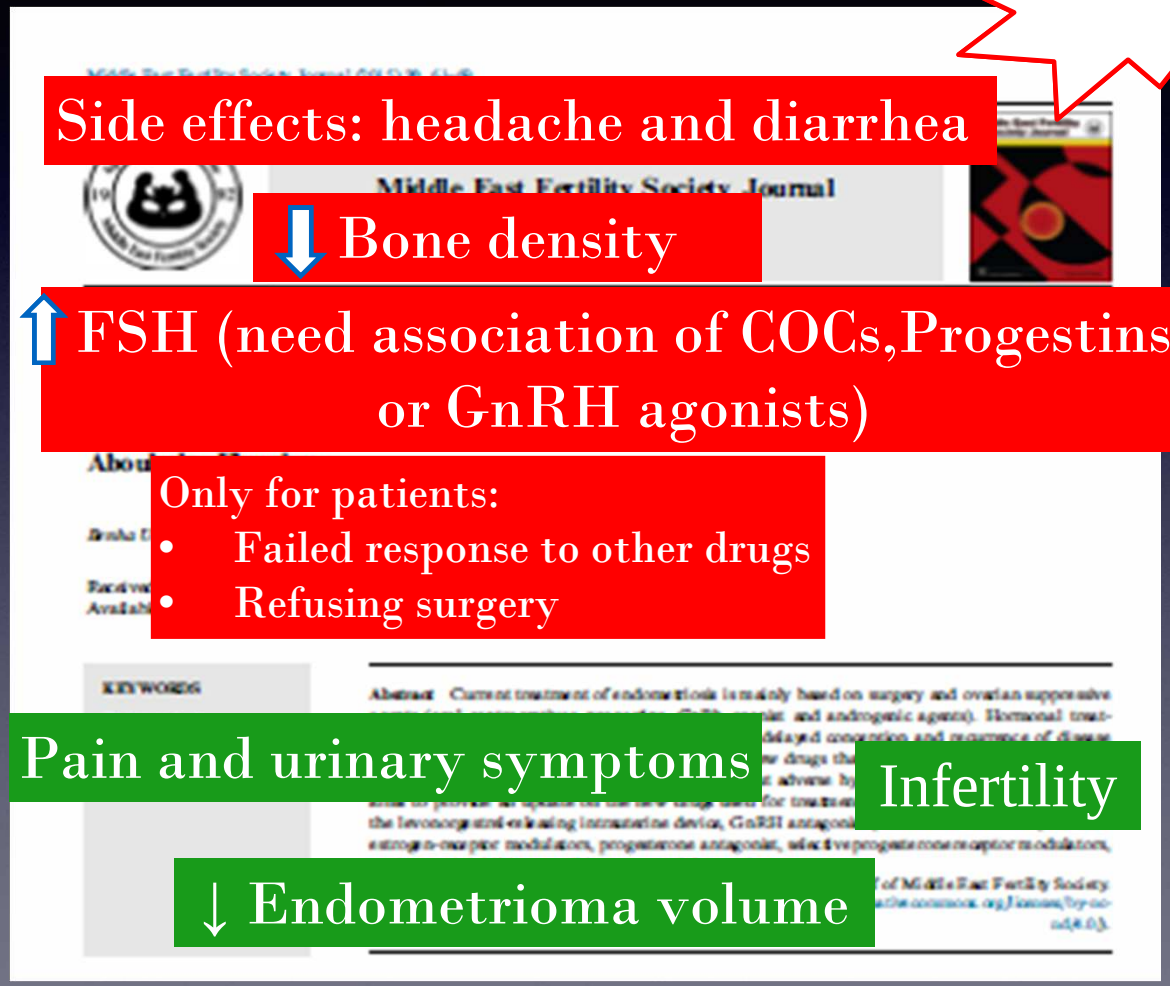


Reproductive-age women: need an FSH suppressing agent

Hormonal treatment:
THE FUTURE

AROMATASE INHIBITORS

OFF-LABEL



Side effects: headache and diarrhea

⇩ Bone density

⇧ FSH (need association of COCs,Progestins or GnRH agonists)

Only for patients:
- Failed response to other drugs
- Refusing surgery

Pain and urinary symptoms

Infertility

↓ Endometrioma volume

Hormonal treatment: THE FUTURE

Raloxifene
Bazedoxifene
2nd and 3rd generation
TSEC
(Tissue-Selective Estrogen Complex)

SERMs

Act as either agonists or antagonists of ER

- ER β subunit Agonists
  - → Bone-prevent osteoporosis
  - → Mammary- prevent breast cancer
  - → ENDOMETRIUM-ANTI-E EFFECT

↓Estrogen-mediated cell proliferation
Implant regression

Hormonal treatment: THE FUTURE

SPRMs

Mifepristone (dose dep)
UPA (UliPristal Acetato)
Asoprisnil
Tanaproget

AMENORRHEA WITHOUT HYPOESTROGENISM (W)

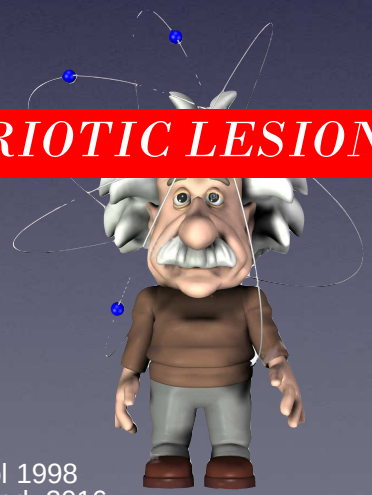
- *Pure agonist to mixed agonist/ antagonist of pure antagonist*

PAIN

- *Inhibition of cellular proliferation (RU486, UPA)*

REGRESSION AND ATROPHY OF ENDOMETRIOTIC LESIONS

- *Proapoptotic effect (UPA, Asoprisnil)*
- *Anti-inflammatory effect (UPA) (↓COX2 expression)*
- *↓ endometrial matrix Metalloproteinase expression (T R)*



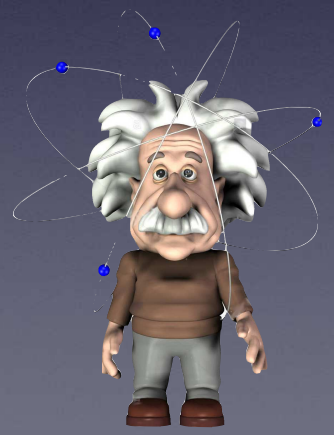
Kettel LM, Am J Obstet Gynecol 1998
M.A. Bedaiwy Semin Reprod Med, 2016

Nonhormone treatments: THE FUTURE

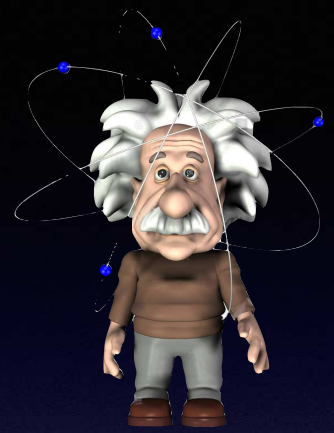
IMMUNOMODULATORS

Altered immune function
↓
Endometriosis

Decrease inflammatory response



Nonhormone treatment:
THE FUTURE



IMMUNOMODULATORS

Tumor Necrosis Factor (TNF)-α Inhibitors

- *TNF-α is a proinflammatory cytokine able to initiate inflammatory cascades, and is increased in the peritoneal fluid and serum of women with endometriosis.*
- *DECREASE PRODUCTION OR RELEASE OF TNF-A FROM MACROPHAGES*
- *Inhibit endometriosis development and adhesions in rats*
- *No improvement in humans pain (relief 30% as placebo) or endometriotic lesions*
- *ETANERCEPT, IFLIXIMAB (monoclonal anti TNF-α antibody)*

Lu, Cochrane Syst Rev, 2013

Nonhormone treatment:
THE FUTURE

IMMUNOMODULATORS

LOXORIBINE
LIPOXINE

NK

REDUCTION NK AND ATROPHY OF ENDOMETRIOTIC LESIONS ®

IFN-α 2β intraperitoneal

PENTOXYFILLINE

Cochrane Database of Systematic Reviews

Pentoxifylline for endometriosis

New search | Review | Intervention

DongHao Lu, Huan Song, Yalun Li, Jane Clarke, Gang Shi

First published: 18 January 2012

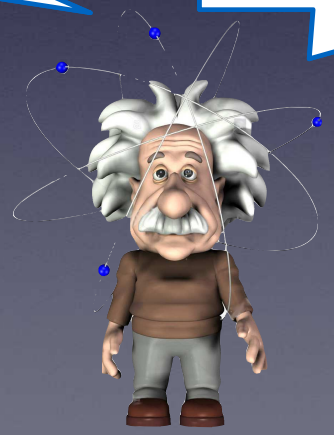
*There is **still not enough evidence** to support the use of pentoxifylline in the management of premenopausal women with endometriosis in terms of subfertility and relief of pain outcomes" (334 PT)*

Nonhormone treatment:
THE FUTURE

ANTIANGIOGENIC AGENTS

NEOANGIOGENESIS
↓
Endometriosis

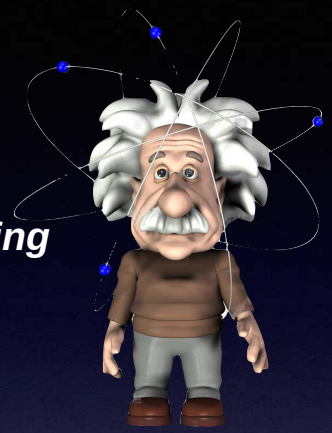
↓
Initiation
Growth
Recurrence



VEGF and VEGFR

Laschke MW, Hum Reprod Update 2012; 18(6):682–702
M.A. Bedaiwy Semin Reprod Med, 2016

Nonhormone treatment: THE FUTURE



ANTIANGIOGENIC AGENTS

Clinical evidence for efficacy and safety of most of them is still lacking

STATIN

- INHIBIT Human endometrial growth cells (RW)
- REDUCE angiogenesis®

ROMIDEPSIN (histone deacetylase inhibitor)

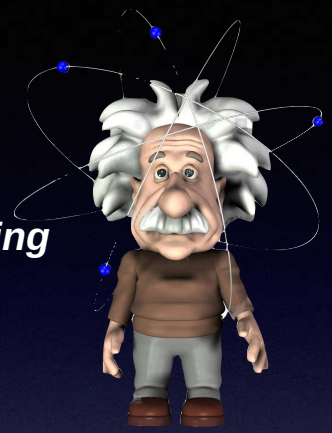
- REDUCE VEGF active secretion (target at trascriptional level)
- HIGH AFFINITY and SPECIFICITY aberrant endometrial tissue
- NO toxicity, infertility, teratogenic effect
- ELIMINATE PREEXISTING PATHOLOGIC VESSELS DESTROY E IMPLANTS

DOPAMINERGIC AGONIST (Cabergoline, Quinagolide)

- REDUCE VEGF and VEGFR2 expression
- HIGH AFFINITY endometrial tissue
- Anti-inflammatory effect
- ANTIANGIOGENIC ACTIVITY

Laschke MW, Hum Reprod Update 2012; 18(6):682–702
M.A. Bedaiwy Semin Reprod Med, 2016

Nonhormone treatment: THE FUTURE



ANTIANGIOGENIC AGENTS

Clinical evidence for efficacy and safety of most of them is still lacking

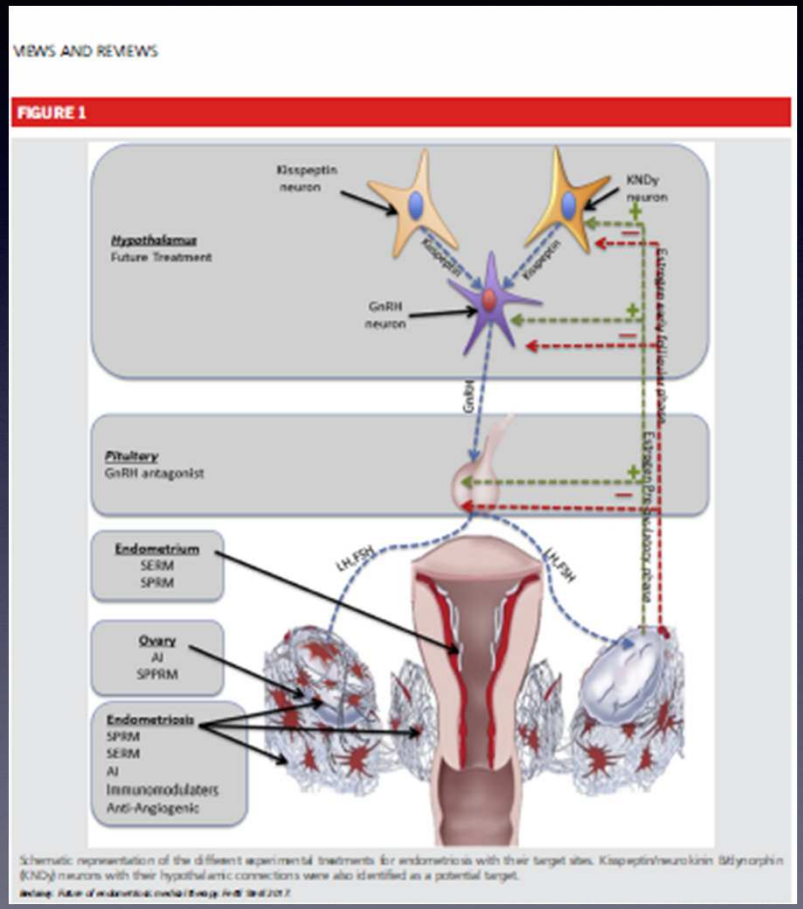
DOPAMINERGIC AGONIST (Cabergoline, Quinagolide)

- REDUCE VEGF and VEGFR2 expression
- HIGH AFFINITY endometrial tissue
- Anti-inflammatory effect
- ANTIANGIOGENIC ACTIVITY
- ↓ENDOMETRIOMA SIZE
- ↓ENDOMETRIOTIC LESION SIZE (gnrha w)

PPAR peroxisome proliferator receptor gamma

- REDUCE VEGF and VEGFR2 expression
- Endometriotic lesion size
- Rosiglitazone e pioglitazone in r (r cv)

FUTURE DIRECTIONS



Schematic representation of the different experimental treatments for endometriosis with their target sites. Kisspeptin/neurokinin B/dynorphin (KNDy) neurons with their hypothalamic connections were also identified as a potential target.

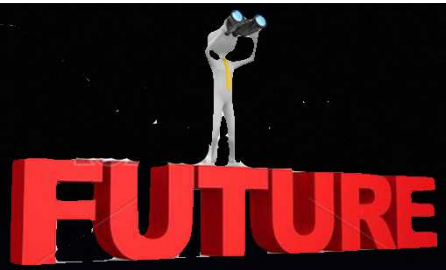
SNC EVALUATION

- KNDy neurons in arcuate nucleus (involving 3 neuropeptides- Kisspeptin, Neurokinin B and Dynorphin) affect and may control pulsatile GnRH release
- ↓ gray matter volume in brain regions involved in pain perception
- LOCAL Neurogenesis

- Fisioterapia
- Terapie cognitive
- Neuromodulatori
- Iniezioni su trigger point

GENIC THERAPY

Experimental endometriosis model



Everolimus, mTOR (mammalian target of rapamycin) inhibitor

- Recent evidence point the ***impairments of angiogenesis and apoptosis processes*** in endometriosis development
- **Mammalian target of rapamycin** (mTOR) pathway regulates the function of many proteins involved in proliferation and **apoptosis** via the mTOR/AKT pathway
- mTOR inhibition in endometriosis foci could improve **apoptosis** process and be effective in the treatment of endometriosis.

  Everolimus is a rapamycin analogue that selectively inhibits mTOR"

Through its apoptosis-promoting effect, everolimus suppressed endometriotic foci without negatively affecting ovarian reserve. These findings support the hypothesis that everolimus merits further study on the way to developing a new endometriosis drug

T. Kacan, Geburtshilfe Frauenheilkd, 2017

grazie

Repeated failure or controindications of medical treatment

Endometrioma > 3-4 cm

Enhancing or Restoring fertility

Pain has an element of blank;

It cannot recollect

When it began, or if there were

A day when it was not.

It has no future but itself,

Its infinite realms contain

Its past, enlightened to perceive

New periods of pain.

Emily Dickinson