



UNIVERSITÀ
DEGLI STUDI
FIRENZE



Azienda
Ospedaliero
Universitaria
Careggi



Recent Developments in
The Transmission of Human Life

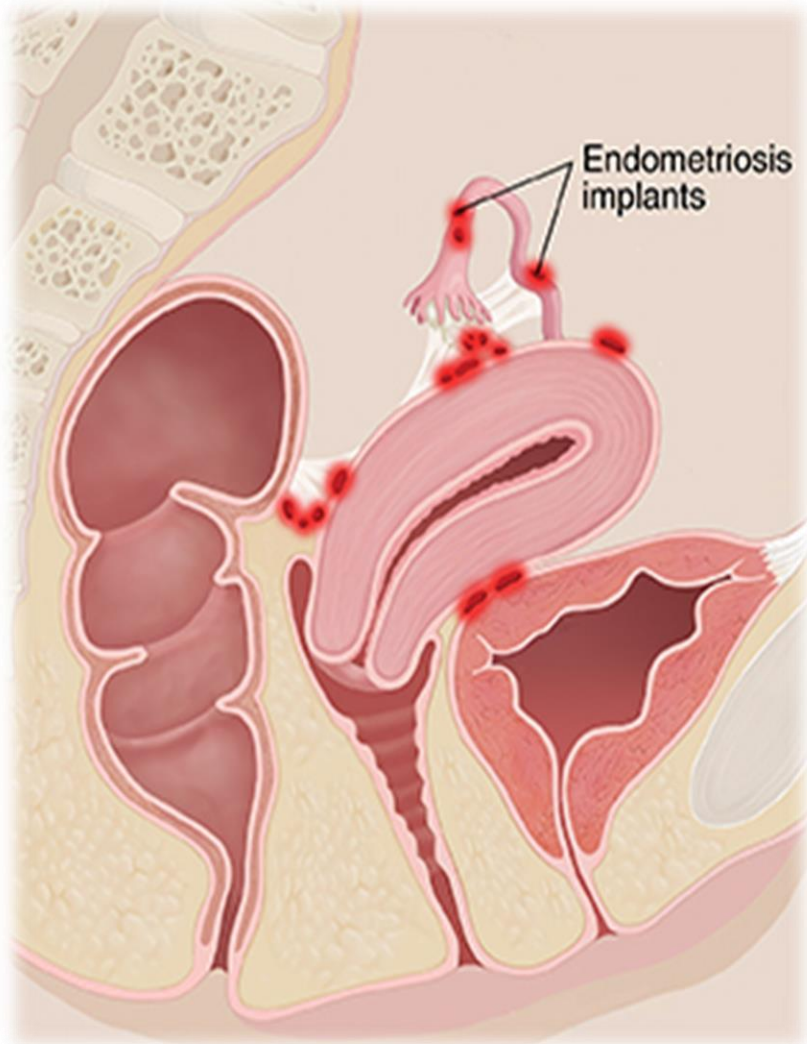
19-21 January 2023
Berlin, Germany



Have we a validated pathogenesis after
almost 100 years from the Samson's
Theory?

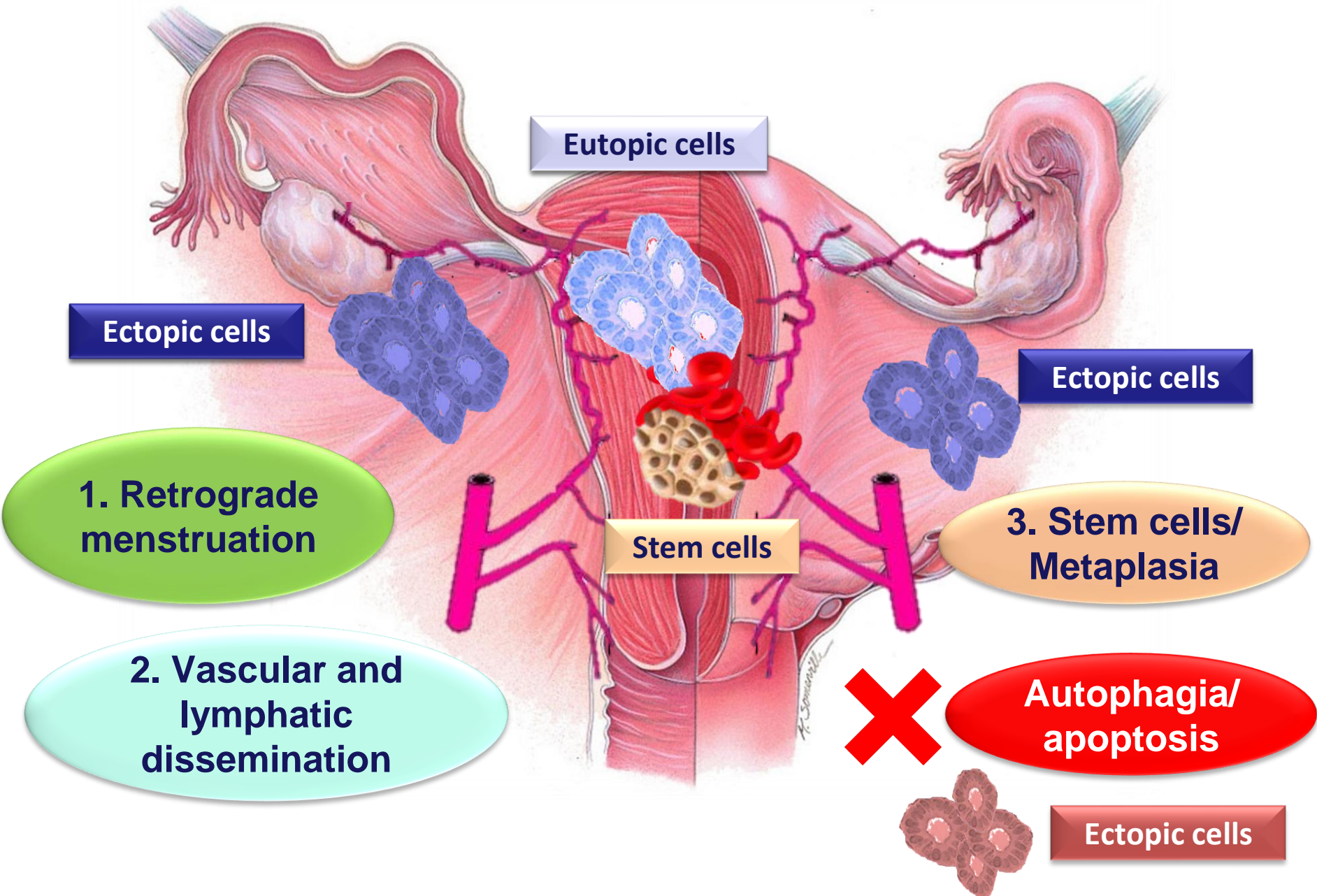
Prof. Felice Petraglia

Endometriosis

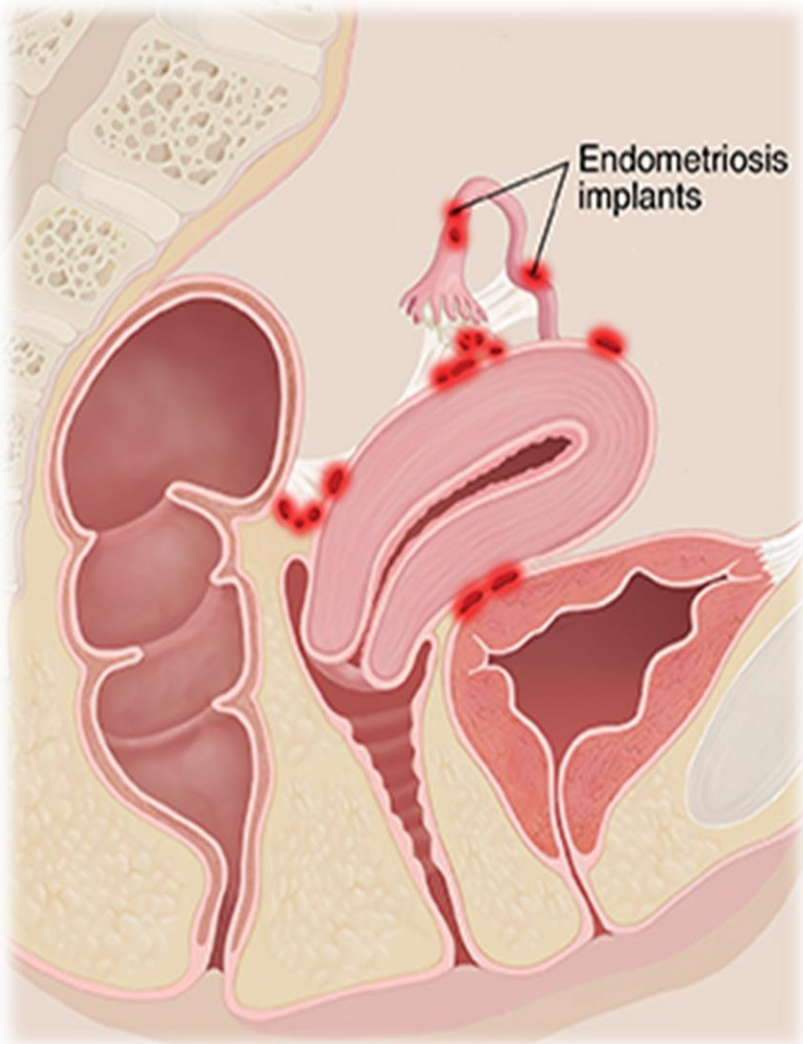


**How do eutopic
endometrial cells
become ectopic?**

Endometriosis: the mechanisms



Endometriosis



**What is the most
recognized
pathogenesis on
2023?**

Pathogenesis of endometriosis on 2023

Increased estrogen sensitivity

progesterone resistance

increased inflammation

1. Impaired apoptosis and autophagia

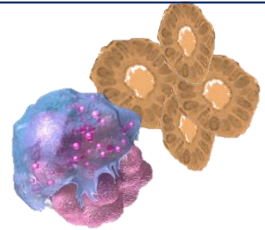
2. Increased oxidative stress

3. Increased cell proliferation

4. Acute inflammation

5. Invasion

6. Chronic inflammation, fibrosis
Neuro-neoangiogenesis



ROS

TGF- β

cytokines

CRH

Ucn

VEGF

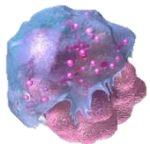
NGF

TGFb

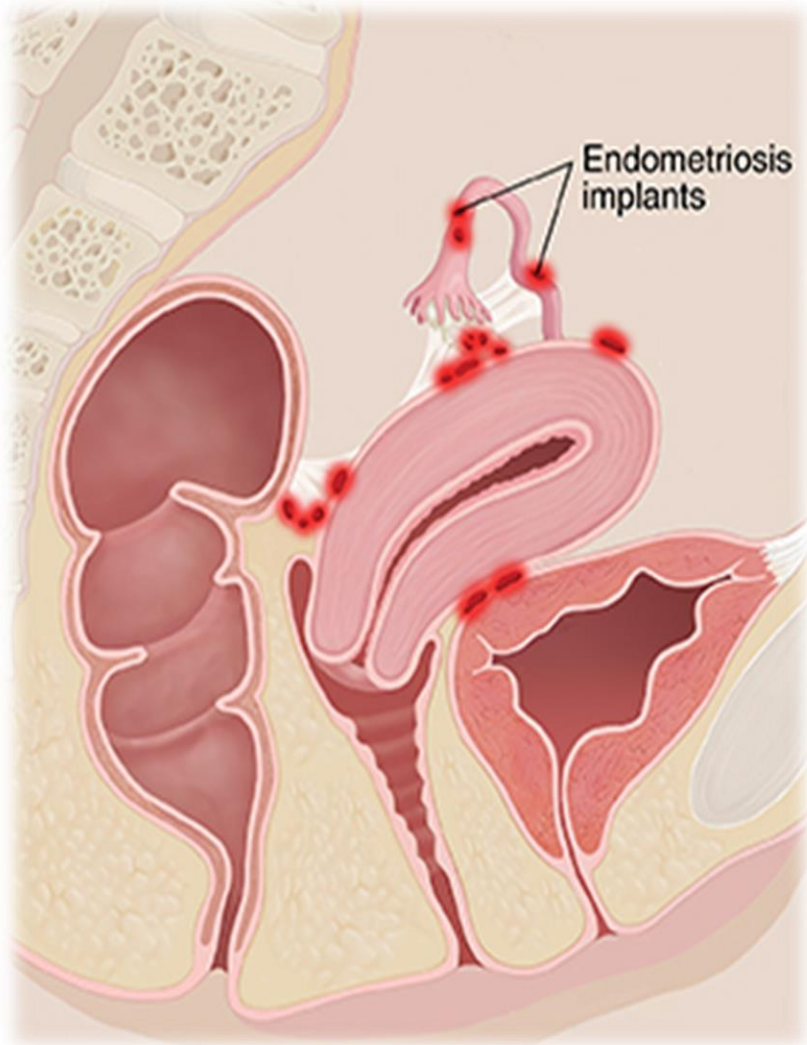
synaptophysin

pain

infertility

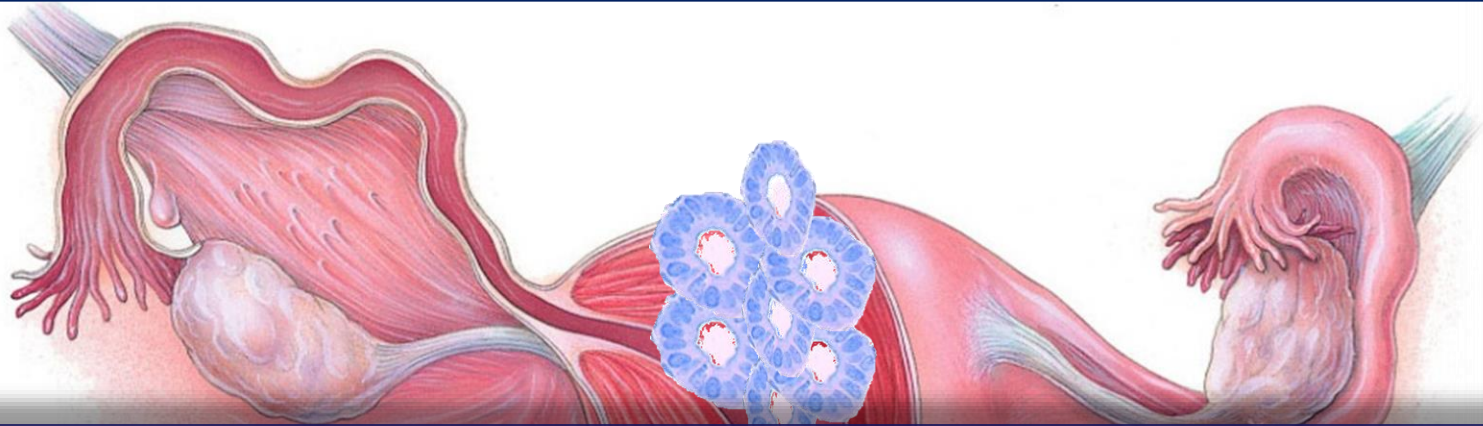


Endometriosis



Why is clinically relevant to understand the pathogenesis?

Pathogenesis of endometriosis



Genetic and epigenetic factors

*DNA mutation
polymorphism*

*DNA metabolism
miRNAs*

*Sex steroid hormones
Inflammation*

Non-invasive diagnosis of endometriosis: miRNAs

Original Research

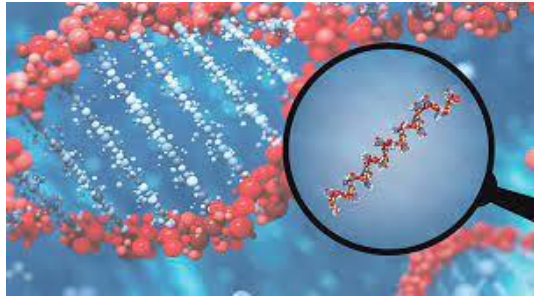
ajog.org

GYNECOLOGY

Accurate diagnosis of endometriosis using serum microRNAs

2020

Sarah Moustafa, MD; Martina Burn, MD¹; Ramanaiah Mamillapalli, PhD¹; Sepide Nematian, MD; Valerie Flores, MD; Hugh S. Taylor, MD



- miR-125b-5p
- miR-150-5p
- miR-342-3p
- miR-451a
- miR-3613-5p
- let-7b

Circulating microRNA biomarkers can reliably differentiate between endometriosis and other gynecological pathologies



Journal of
Clinical Medicine

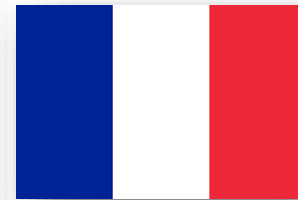
2022

MDPI

Article

Salivary MicroRNA Signature for Diagnosis of Endometriosis

Sofiane Bendifallah^{1,2,*}, Stéphane Suisse³, Anne Puchar^{1,2}, Léa Delbos^{4,5}, Mathieu Poilblanc^{6,7}, Philippe Descamps^{4,5}, Francois Golfier^{6,7}, Ludmila Jornea⁸, Delphine Bouteiller⁹, Cyril Touboul^{1,2}, Yohann Dabi^{1,2} and Emile Darai^{1,2}



Saliva-based diagnostic miRNA signature for endometriosis

Pathogenesis of endometriosis on 2023

Increased estrogen sensitivity

progesterone resistance

increased inflammation

1. Impaired apoptosis and autophagia

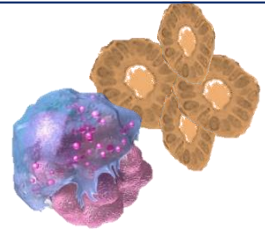
2. Increased oxidative stress

3. Increased cell proliferation

4. Acute inflammation

5. Invasion

6. Chronic inflammation, fibrosis
Neuro-neoangiogenesis



ROS

TGF- β

cytokines

CRH

Ucn

VEGF

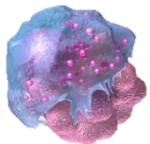
NGF

TGFb

synaptophysin

pain

infertility



Pathogenesis of endometriosis: Increased estrogen receptors activity

Genetic/Epigenetic variations

Han and O'Malley HRU 2014

Rahmioglu et al HRU 2014

↑ DNA methyltransferase

Steroidogenic factor 1

Hypermethylation

aromatase

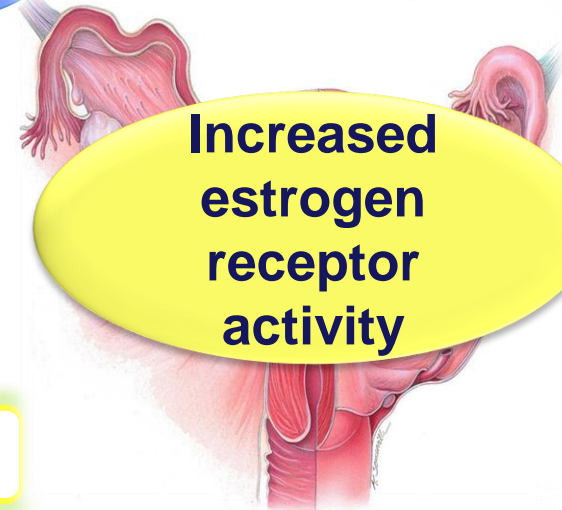
Estradiol

Hypomethylation

Cell proliferation

Inflammation

**Increased
estrogen
receptor
activity**



Drugs decreasing ovarian estrogen secretion

GnRH analogs

- Goserelin
- Leuprolide
- Nafarelin
- Buserelin
- Triptorelin

[Cochrane Database of Systematic Reviews](#) | [Review - Intervention](#)

Gonadotrophin-releasing hormone analogues for pain associated with endometriosis

✉ [Julie Brown, Alice Pan, Roger J Hart](#) Authors' declarations of interest

Version published: 08 December 2010 [Version history](#)

OK

Randomised controlled trials showed that treatment for 3 months with a GnRH agonist may be as effective as 6 months in terms of pain relief

NO!

The endometriotic lesions returned to the original volume within **6 months of follow-up** after cessation of treatment and pain comes back

OK

The administration of GnRH-a for a period of 3 to 6 months prior to ART may increase the odds of clinical pregnancy by 4-fold



Endometriosis and oral GnRH antagonists: Elagolix

The NEW ENGLAND JOURNAL of MEDICINE

2017

ORIGINAL ARTICLE

Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist

H.S. Taylor, L.C. Giudice, B.A. Lessey, M.S. Abrao, J. Kotarski, D.F. Archer, M.P. Diamond, E. Surrey, N.P. Johnson, N.B. Watts, J.C. Gallagher, J.A. Simon, B.R. Carr, W.P. Dmowski, N. Leyland, J.P. Rowan, W.R. Duan, J. Ng, B. Schwefel, J.W. Thomas, R.I. Jain, and K. Chwalisz

ELAGOLIX: a new oral, nonpeptide GnRH antagonist

150 mg once/day

200 mg twice/day

6-month phase 3 trials

Elaris Endometriosis I and II [EM-I and EM-II])

Women with surgically diagnosed endometriosis and moderate or severe endometriosis-associated pain.



August 2018

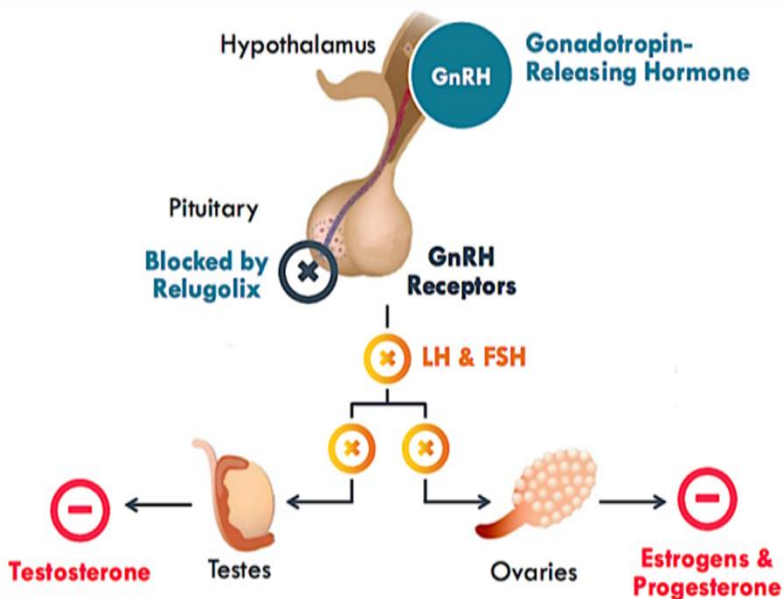
Endometriosis and oral GnRH antagonists: Relugolix

ORIGINAL ARTICLE: ENDOMETRIOSIS

Relugolix, an oral gonadotropin-releasing hormone receptor antagonist, reduces endometriosis-associated pain in a dose-response manner: a randomized, double-blind, placebo-controlled study

Yutaka Osuga, M.D., Ph.D.,^a Yoshifumi Seki, M.Sc.,^b Masataka Tanimoto, B.Pharm.,^b Takeru Kusumoto, M.Sc.,^b Kentarou Kudou, M.Sc.,^b and Naoki Terakawa, M.D., Ph.D.^c

Fert Ster, 2020



Phase 2, multicenter, randomized, double-blind, placebo-controlled study

EDELWEISS
study

ORIGINAL ARTICLE: ENDOMETRIOSIS

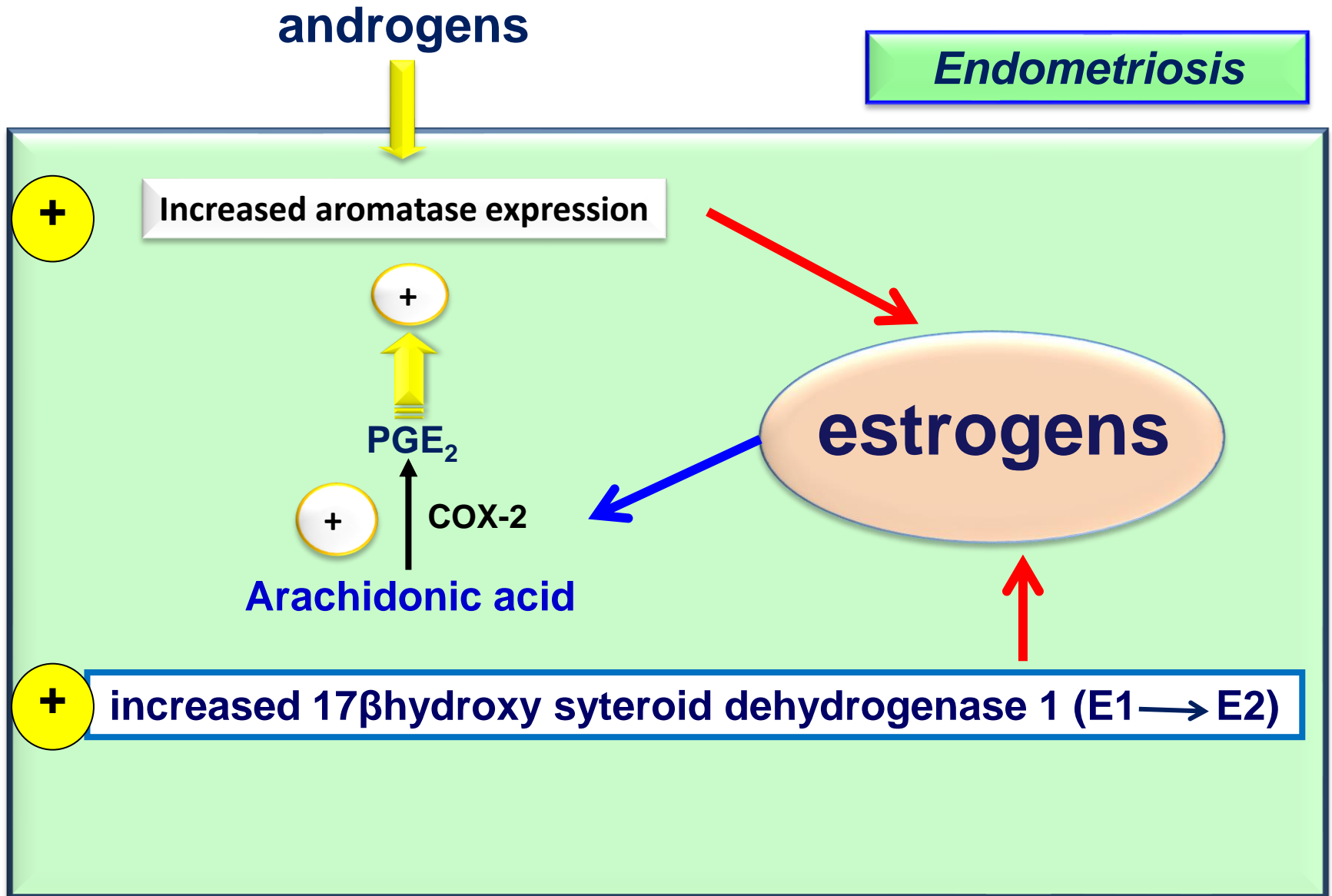
Treatment of endometriosis-associated pain with linzagolix, an oral gonadotropin-releasing hormone–antagonist: a randomized clinical trial

Fert Ster, 2020

Jacques Donnez, M.D., Ph.D.,^a Hugh S. Taylor, M.D., Ph.D.,^b Robert N. Taylor, M.D., Ph.D.,^c Mark D. Akin, M.D.,^d Tatyana F. Tatarchuk, M.D., Dr. Sc.,^e Krzysztof Wilk, M.D.,^f Jean-Pierre Gotteland, Ph.D.,^g Veronique Lecomte, Pharm.D.,^g and Elke Bestel, M.D.^g

Phase 2b, double-blind, placebo-controlled, dose-ranging study

Pathogenesis of endometriosis: increased local estrogen production



Drugs decreasing peripheral estrogen secretion

Aromatase inhibitors

A Randomized, Double-blind, Double-dummy, Parallel- Group, Multi-center Phase IIb Study

to Assess the Efficacy and Safety of Different Dose Combinations of an Aromatase Inhibitor and levonorgestrel in an Intravaginal Ring Versus Placebo and Leuprorelin / Leuprolide Acetate in Women With Symptomatic Endometriosis.

phase IIb study

Intravaginal ring for 12 weeks

placebo

**Leuprolide acetate
(subcutaneous depot)**

Anastrozole
300-600-1050 µg/d

levonorgestrel

272 participants

Pathogenesis of endometriosis on 2023

Increased estrogen sensitivity

progesterone resistance

increased inflammation

1. Impaired apoptosis and autophagia

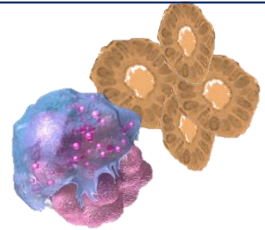
2. Increased oxidative stress

3. Increased cell proliferation

4. Acute inflammation

5. Invasion

6. Chronic inflammation, fibrosis
Neuro-neoangiogenesis



ROS

TGF- β

cytokines

CRH

Ucn

VEGF

NGF

TGFb

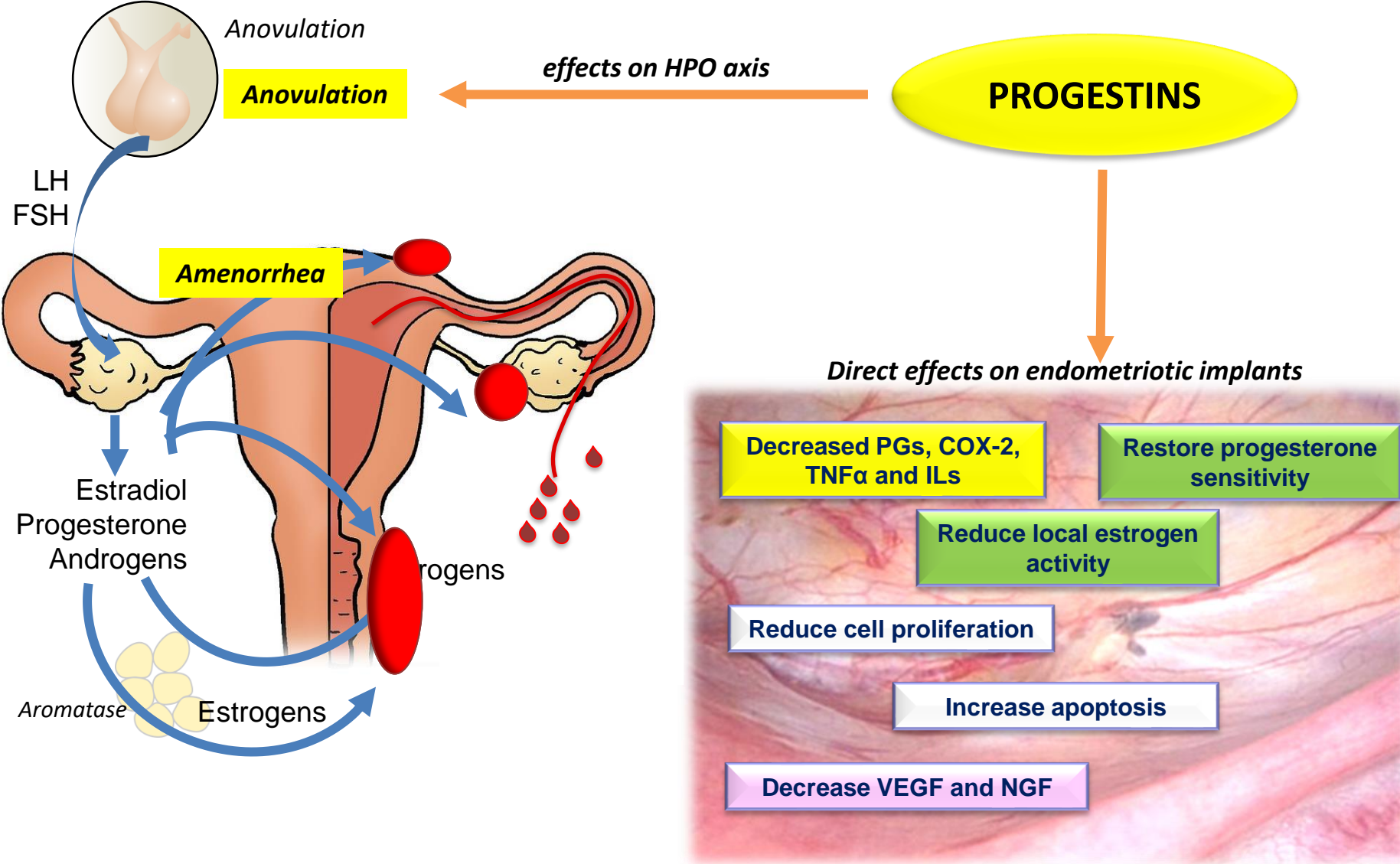
synaptophysin

pain

infertility



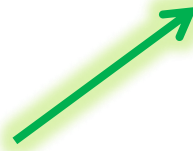
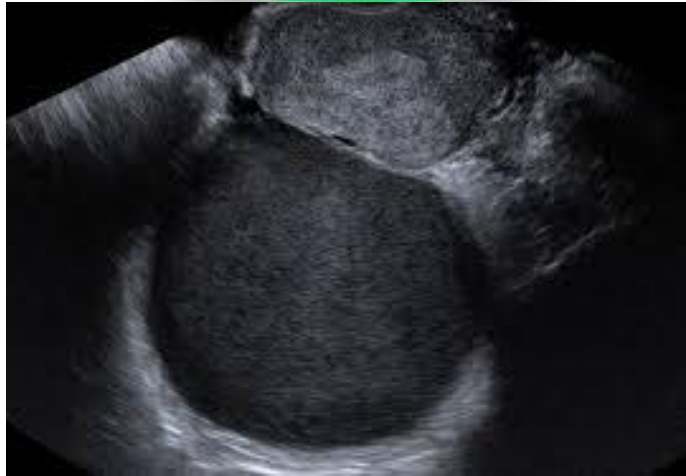
Endometriosis and progestins: mechanisms of action



Reis, Petraglia, HRU 2020;
Vannuccini, Petraglia. Review EndoMetabDisor 2021

Dienogest and ovarian endometriosis

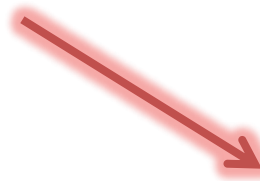
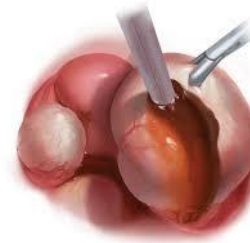
DNG 2 mg/day orally



Reduction of OMA volume up to 76%

Effective in reduction of pain symptoms
(dysmenorrhea and pelvic pain)

Del Forno et al, EJOG, 2019
Vignali et al, Gynecol Endocrinol, 2020
Angioni et al, Gynecol Endocrinol, 2020



AFTER SURGERY FOR OMA

Endometrioma recurrence after 5 ys follow up:
Placebo 69%
Dienogest for 60 months: 4%

Ota et al, JEPPD, 2015

After 24 months of treatment with DNG, complete resolution of recurrent OMA in **57.1%**

Koshiba et al, J Obstet Gynaecol Res. 2018

DNG EARLY after recurrence of postsurgical OMA reduces the risk of repeated surgery.

Lee et al, Reprod Sci. 2018

No recurrence after 24 months of DNG, with better compliance than GnRH agonists + COC

Seo et al, EJOG, 2019

Dienogest for DIE: long term treatment



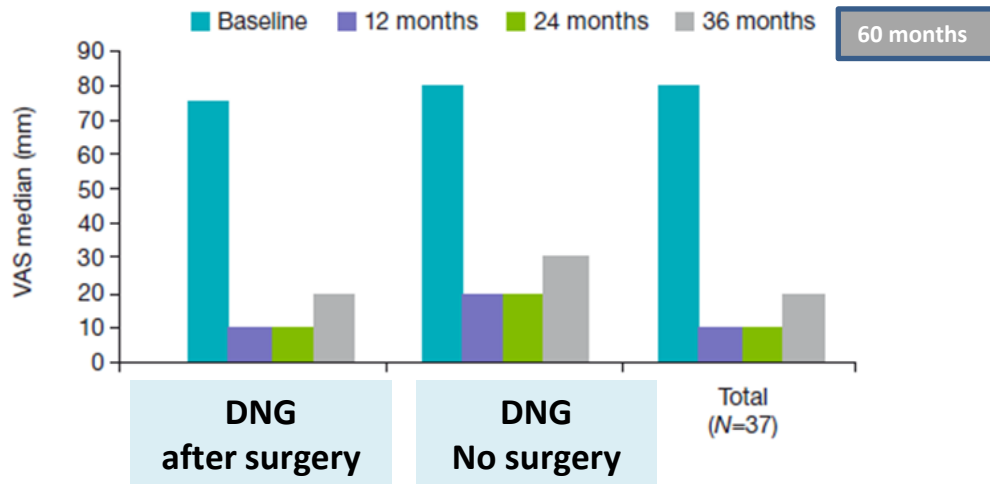
Dyspareunia
Dysmenorrhea
pelvic pain
bowel pain



Quality of life

Dienogest is an effective medication to control symptoms of pain related to DIE, even without reducing the volume of DIE nodules.

Leonardo-Pinto et al, EJOG, 2017



Up to 60 months

Long-term (60-month) treatment with DNG in women with endometriosis effectively reduced pelvic pain and avoided pain recurrence post-surgery.

Romer, Arch Gynecol Obstet. 2018

Dienogest for recurrence of endometriosis

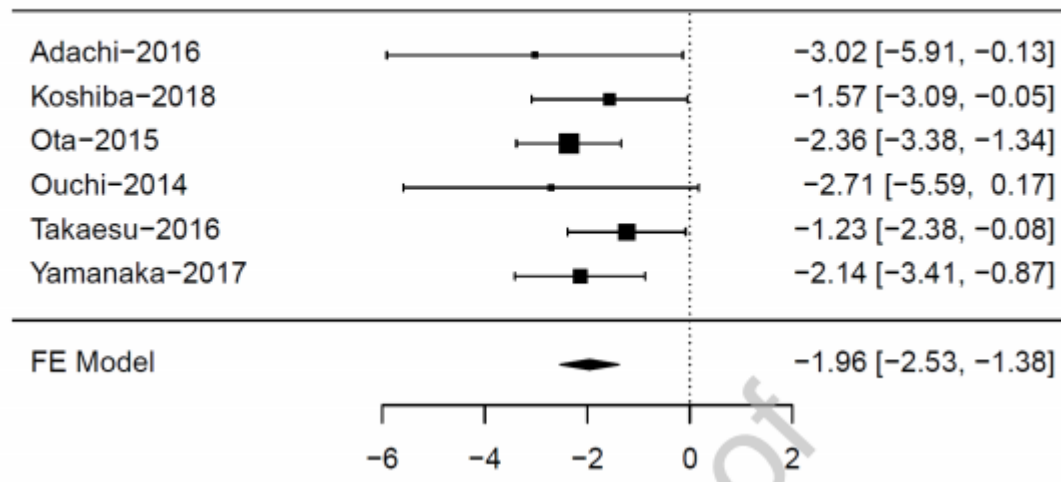
Meta-Analysis > J Minim Invasive Gynecol. Nov-Dec 2020;27(7):1503-1510.

doi: 10.1016/j.jmig.2020.05.007. Epub 2020 May 16.

Dienogest and the Risk of Endometriosis Recurrence Following Surgery: A Systematic Review and Meta-analysis

Andrew Zakhari¹, Darl Edwards¹, Michelle Ryu², John J Matelski³, Olga Bougie⁴, Ally Murji⁵

Figure 4. Log Odds of Endometriosis Recurrence for Dienogest Compared to Controls



Patients receiving dienogest after conservative surgery for endometriosis had significantly lower risk of postoperative disease recurrence than those who were expectantly managed.

Pathogenesis of endometriosis on 2023

Increased estrogen sensitivity

progesterone resistance

increased inflammation

1. Impaired apoptosis and autophagia

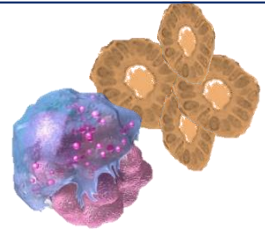
2. Increased oxidative stress

3. Increased cell proliferation

4. Acute inflammation

5. Invasion

6. Chronic inflammation, fibrosis
Neuro-neoangiogenesis



ROS

TGF- β

cytokines

CRH

Ucn

VEGF

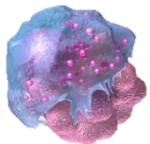
NGF

TGF β

synaptophysin

pain

infertility



Endometriosis: drugs inhibiting autophagy

Original Article

The inhibition of reactive oxygen species (ROS) by antioxidants inhibits the release of an autophagy marker in ectopic endometrial cells

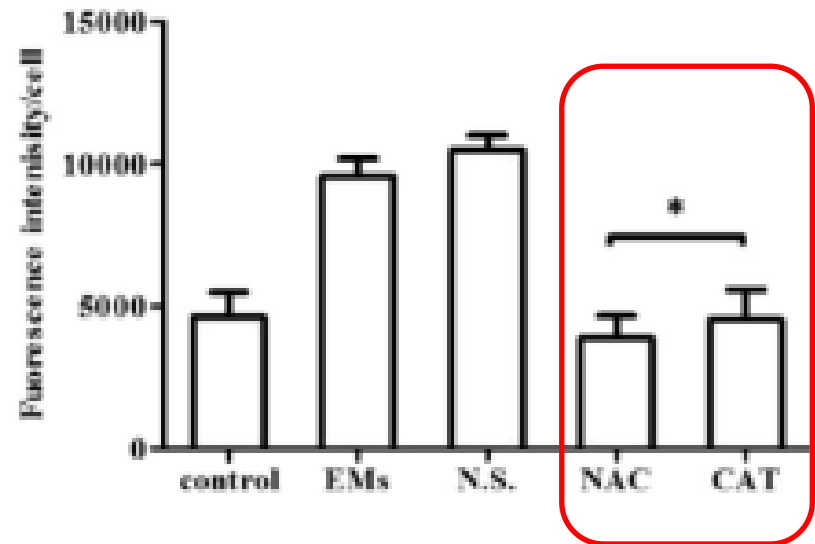
Huixia Lu ^a, Hong Hu ^a, Yi Yang ^b, Shaobo Li ^{c,*}

Taiwan J Obstet Gynecol, 2020



The antioxidants N-acetyl-L-cysteine or catalase significantly reduced levels of the autophagy marker LC3 and caused levels of Beclin-1 to significantly decrease.

Antioxidant therapy shows potential to treat endometriosis by acting on autophagy



Endometriosis: drugs increasing apoptosis



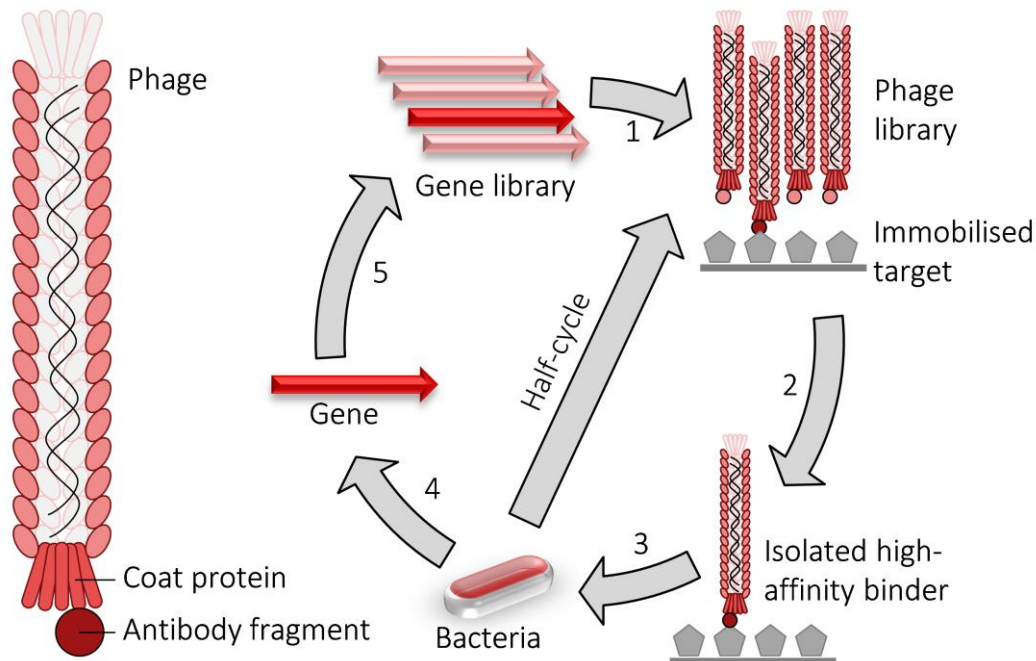
Received 21 Nov 2013 | Accepted 22 Jun 2014 | Published 22 Jul 2014

DOI: 10.1038/ncomms5478

OPEN

Development of pro-apoptotic peptides as potential therapy for peritoneal endometriosis

K. Sugihara¹, Y. Kobayashi², A. Suzuki³, N. Tamura², K. Motamedchaboki², C.-T. Huang², T.O. Akama², J. Pecotte⁴, P. Frost⁴, C. Bauer⁴, J.B. Jimenez Jr.⁴, J. Nakayama⁵, D. Aoki³ & M.N. Fukuda²



an endometriosis-targeting peptide that is internalized by cells (z13), using phage display, linked with an apoptosis-inducing peptide

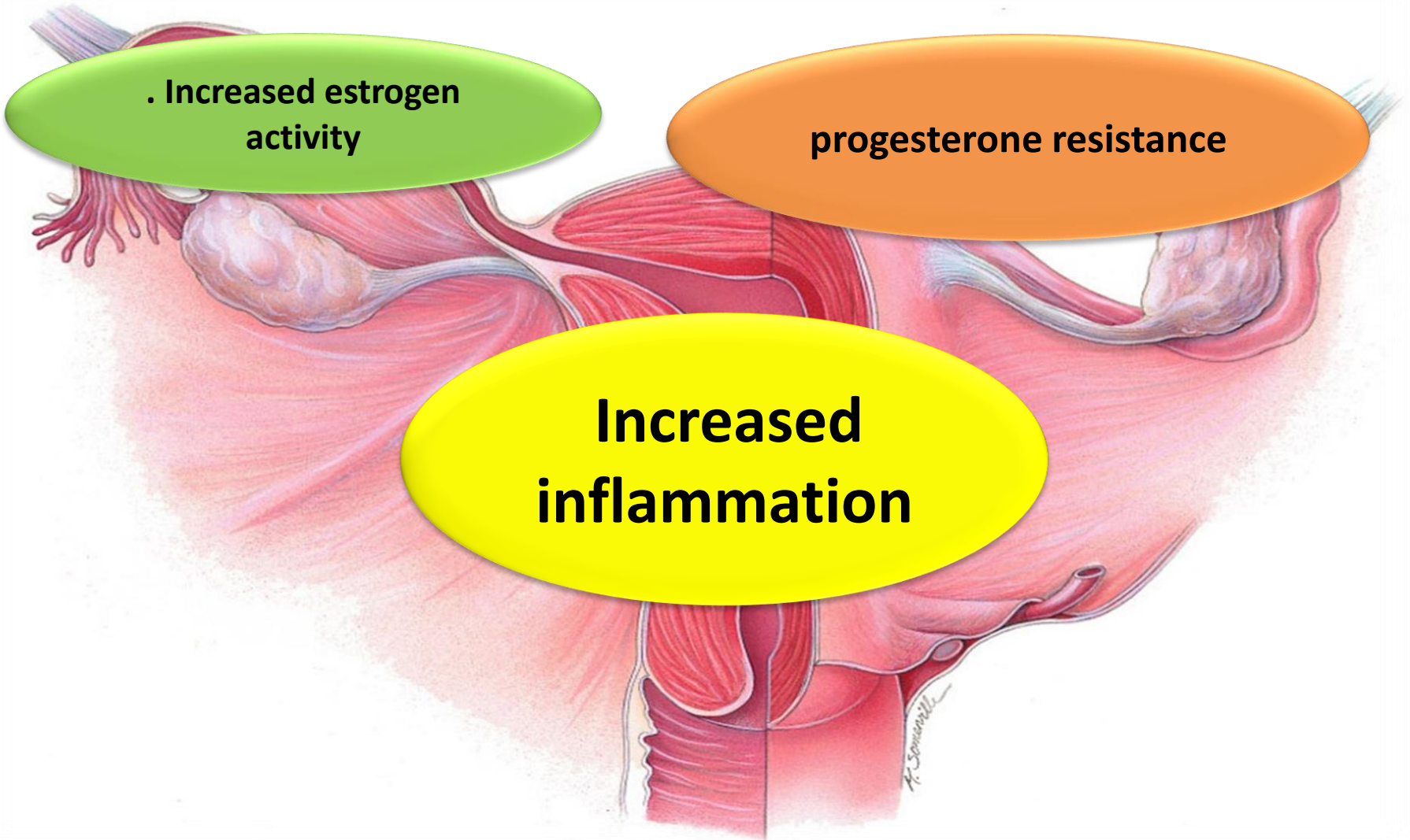
Endometrial cells in endometriosis lesions selectively underwent apoptosis with no effect on neighbouring organs

Endometriosis: pathogenesis on 2023

. Increased estrogen activity

progesterone resistance

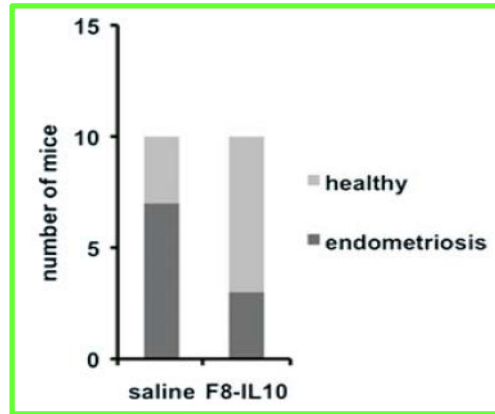
Increased inflammation



Endometriosis: inflammation and monoclonal antibodies



Anti-IL-10



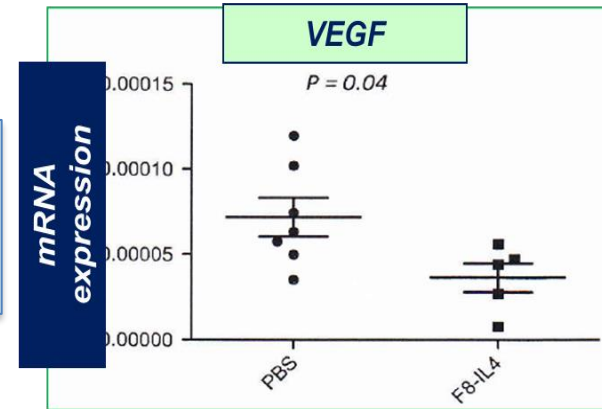
Antibody carriers for pharmacodelivery of anti-inflammatory IL10 in endometriotic lesions

Neri D et al, Hum Reprod 2011

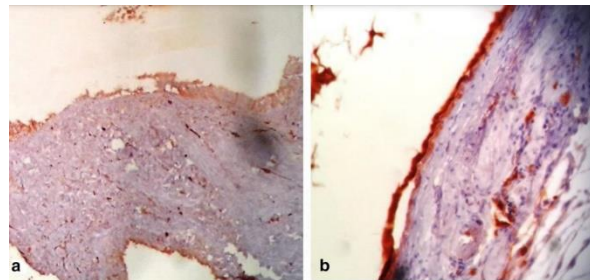
Anti-IL-4

Antibody anti-IL-4 induces an impairment in adhesion, invasion, and vascularization of endometriotic lesions

Quattrone F. et al, Repro Sci 2015



Anti-IL-6



Treated

Non treated

Tocilizumab significantly suppressed the volume of endometriotic lesions

EI-Zayadi et al, Immunologic Research, 2020



Endometriosis: pain and cannabinoids

Improvement of pain from gynecologic conditions

National guidelines cannot recommend cannabis-based products because the lack of evidences

Randomized clinical trials on the use of cannabinoids for the treatment of endometriosis are currently ongoing.

> [Obstet Gynecol.](#) 2022 Feb 1;139(2):287-296. doi: 10.1097/AOG.0000000000004656.

Medical Cannabis for Gynecologic Pain Conditions: A Systematic Review

[Angela L Liang](#)¹, [Erin L Gingher](#), [Jenell S Coleman](#)

Affiliations + expand

PMID: 35104069 DOI: [10.1097/AOG.0000000000004656](#)

Association of endocannabinoids with pain in endometriosis

[Thomas Andrieu](#)¹, [Andrea Chicca](#)², [Daniele Pellegata](#)², [Nick A Bersinger](#)¹, [Sara Imboden](#)^{1, 3}, [Konstantinos Nirgianakis](#)^{1, 3}, [Juerg Gertsch](#)², [Michael D Mueller](#)^{1, 3}

Affiliations + expand

[Review](#) > [J Minim Invasive Gynecol.](#) 2022 Feb;29(2):169-176. doi: 10.1016/j.jmig.2021.11.017. Epub 2021 Nov 25.

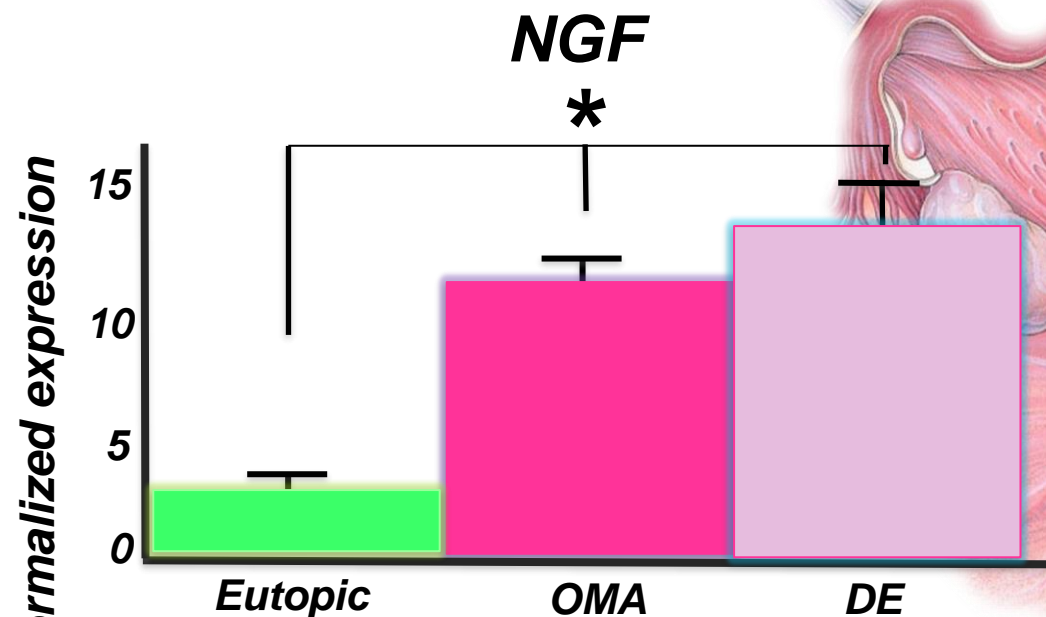
Cannabidiol for the Management of Endometriosis and Chronic Pelvic Pain

[Megha Mistry](#)¹, [Paul Simpson](#)², [Edward Morris](#)¹, [Ann-Katrin Fritz](#)³, [Babu Karavadra](#)¹, [Carole Lennox](#)⁴, [Ed Prosser-Snelling](#)¹

Affiliations + expand

PMID: 34839061 DOI: [10.1016/j.jmig.2021.11.017](#)

Endometriosis: pathogenesis on 2023

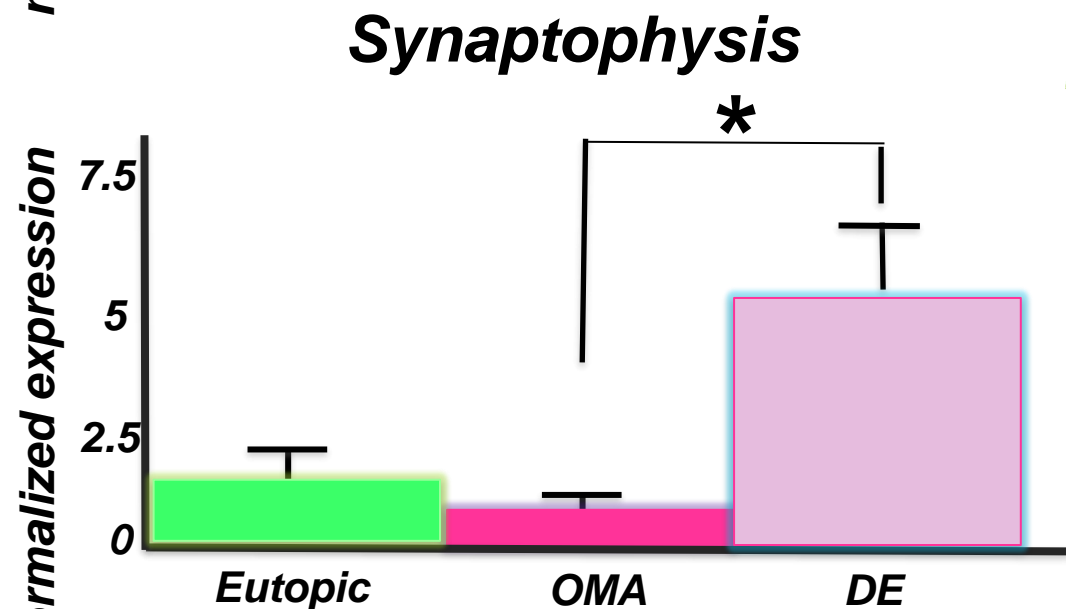


1. Impaired apoptosis/autophagy

2. Increased cell proliferation

3. Increased acute inflammation

5. Neuroangiogenesis



VEGF

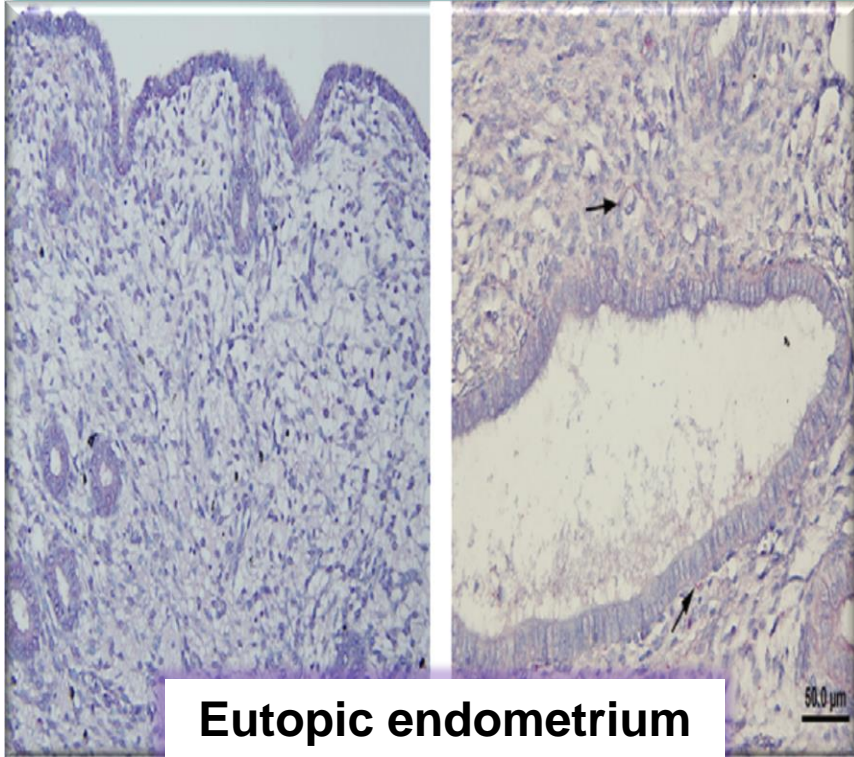
Tissue factor

NGF

Synaptophysin

Endometriosis: pathogenesis and diagnosis

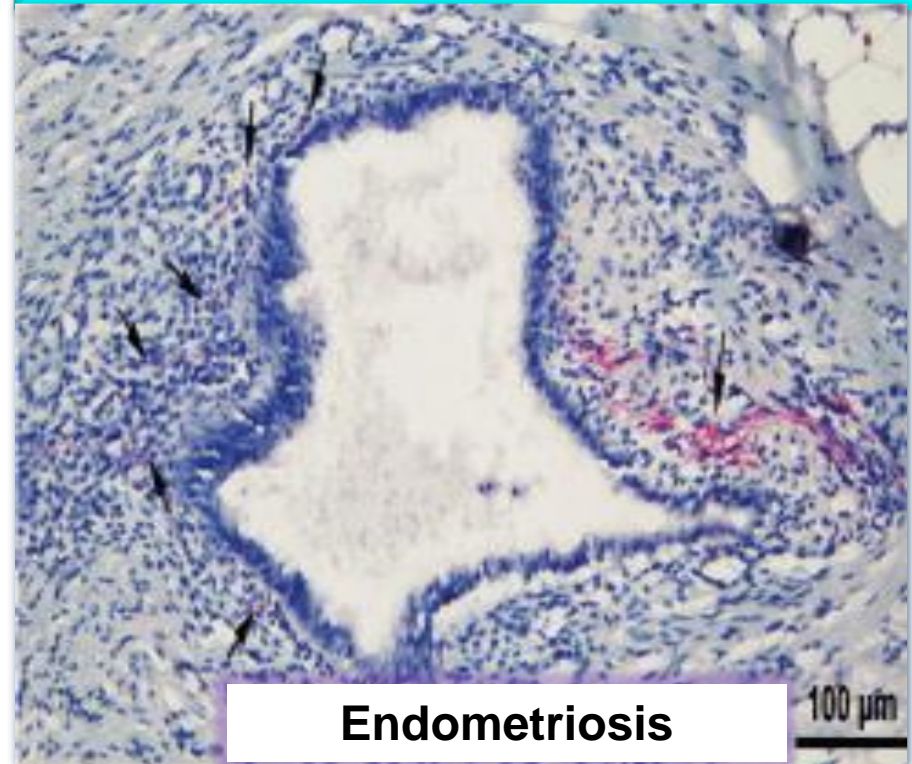
Neurogenesis in eutopic endometrium



Eutopic endometrium

Increased nerve fiber density, sensory C fibers and adrenergic nerve fibers in the endometrium

Neurogenesis in ectopic endometriosis



Endometriosis

Increased nerve fibres stained with PGP9.5 in the peritoneal endometriotic lesions

Endometriosis: neuroangiogenesis and future drugs

Phase 2

Quinagolide is a selective D2 receptor agonist

It antagonizes VEGF receptor-2 reducing neoangiogenesis (in vitro)

Randomised, double-blind, placebo-controlled, proof-of-mechanism phase 2 trial investigating the effect of quinagolide extended-release **vaginal ring** on reduction of lesions assessed by high-resolution magnetic resonance imaging in women with **endometrioma, deep infiltrating endometriosis, and/or adenomyosis.**



The LANN Technique to Reduce Postoperative Functional Morbidity in Laparoscopic Radical Pelvic Surgery

Marc Possover, PhD, Jens Quakernack, MD, Vito Chiantera, MD

Nerve sparing surgery

Review > *Semin Reprod Med.* 2017 Jan;35(1):72-80. doi: 10.1055/s-0036-1597305.

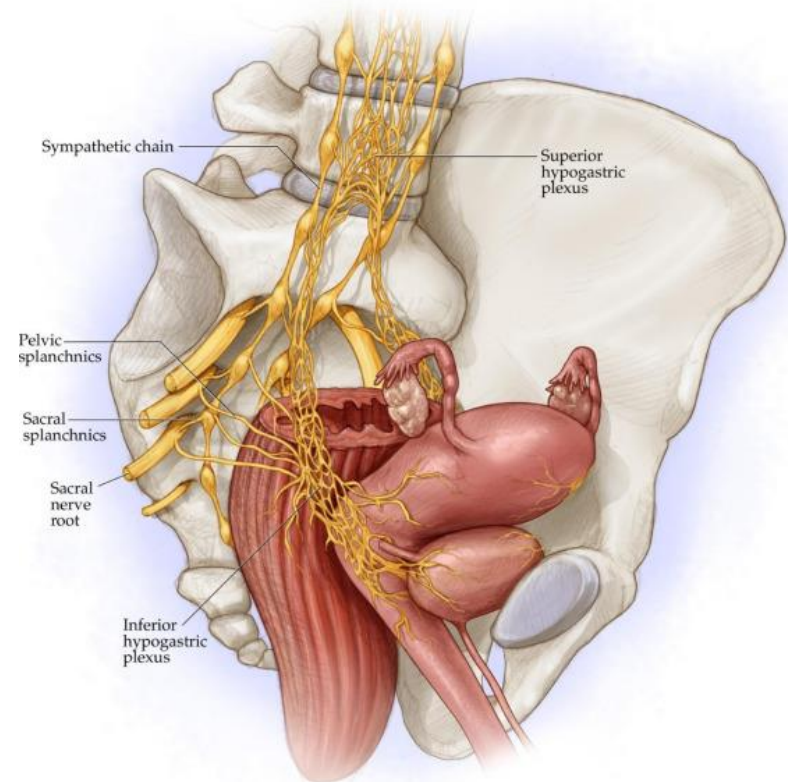
Epub 2016 Dec 12.

Nerve Sparing and Surgery for Deep Infiltrating Endometriosis: Pessimism of the Intellect or Optimism of the Will

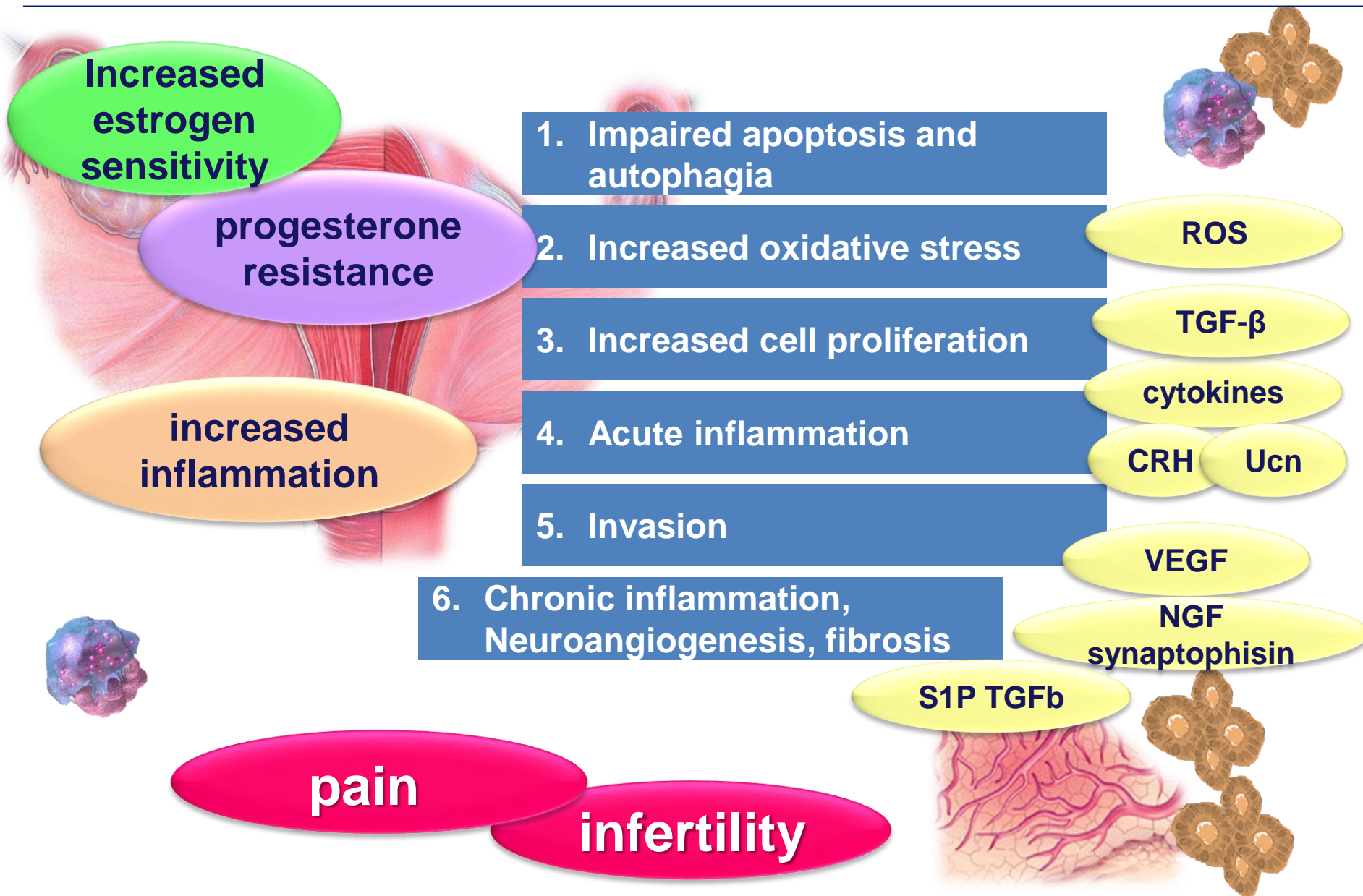
Basma Darwish ¹, Horace Roman ¹

surgical treatment of deep infiltrating endometriosis with the aim to prevent urinary, rectal, and sexual dysfunction

good outcomes in terms of bladder morbidity; digestive and sexual functions more complex to restore

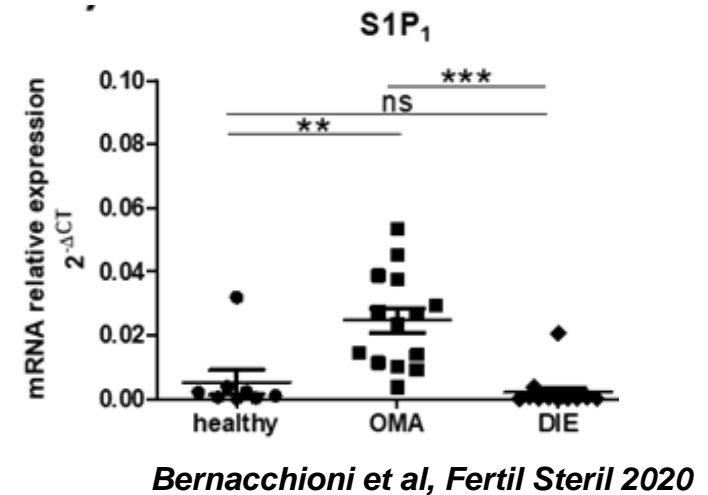
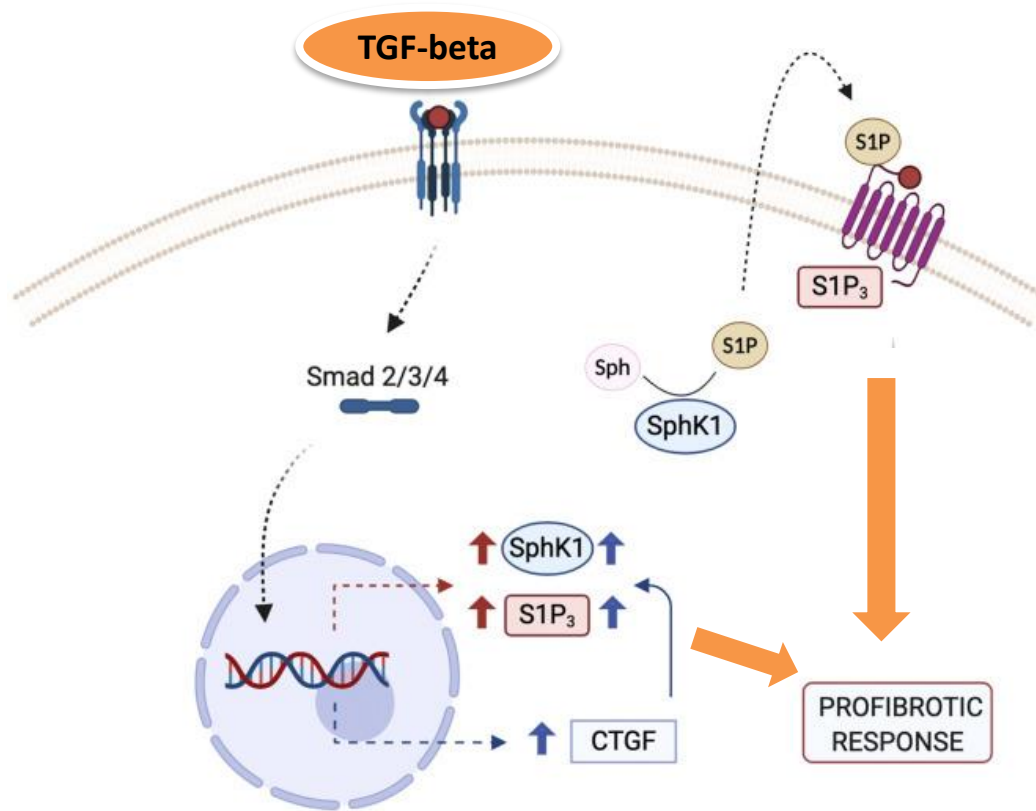


Pathogenesis of endometriosis on 2023



Endometriosis: pathogenesis and fibrosis

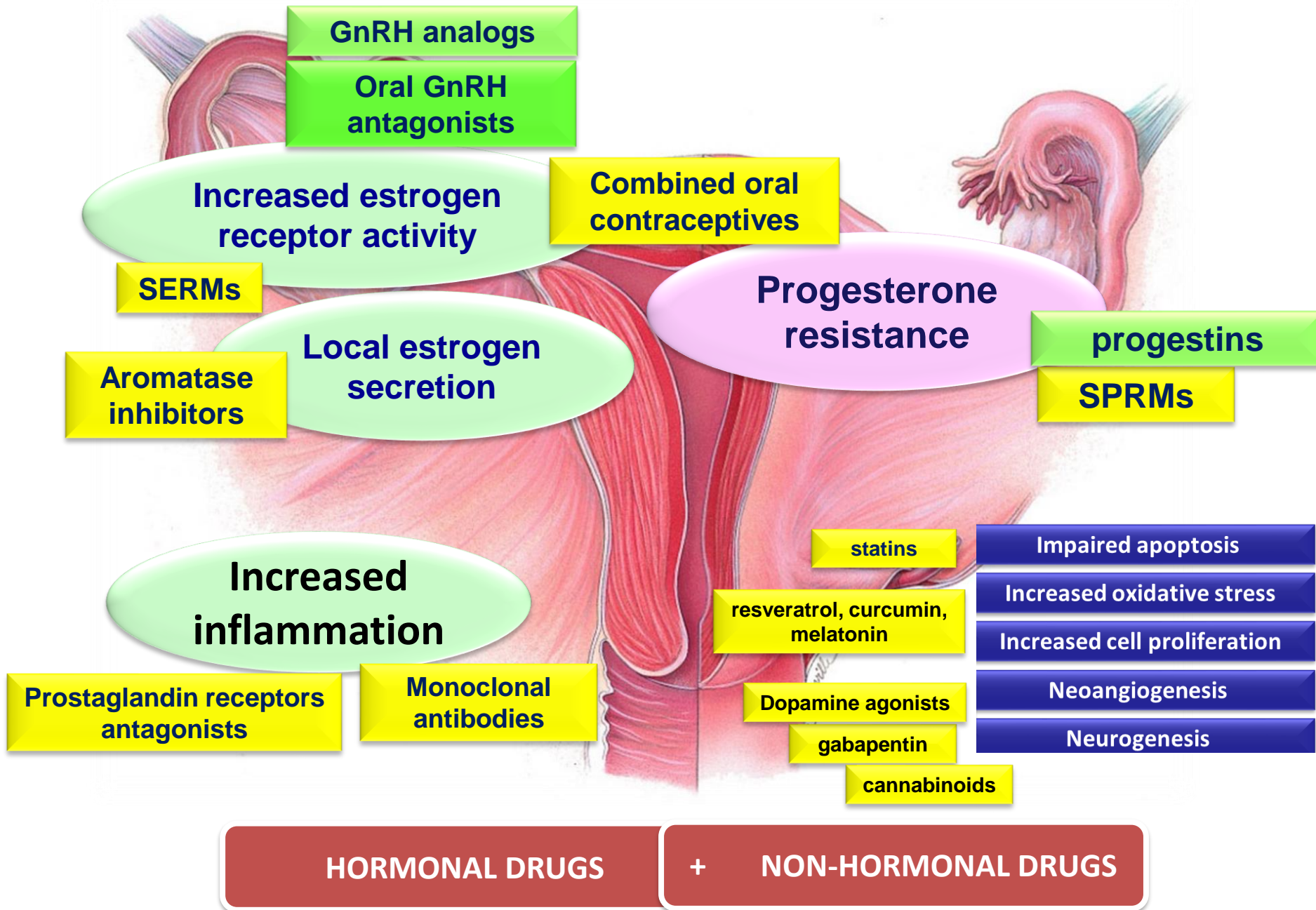
Spingosine-1-phosphate is dysregulated in endometriosis



S1P signaling is implicated in TGFβ1-induced fibrosis

Fingolimod is an oral treatment of multiple sclerosis, modulating S1P .

Endometriosis: pathogenesis and medical treatments



Endometriosis: clinical implications of pathogenesis

Increased estrogen sensitivity

progesterone resistance

increased inflammation

Impaired apoptosis and autophagia

Increased oxidative stress

Increased cell proliferation

Neuro-neoangiogenesis

Fibrosis

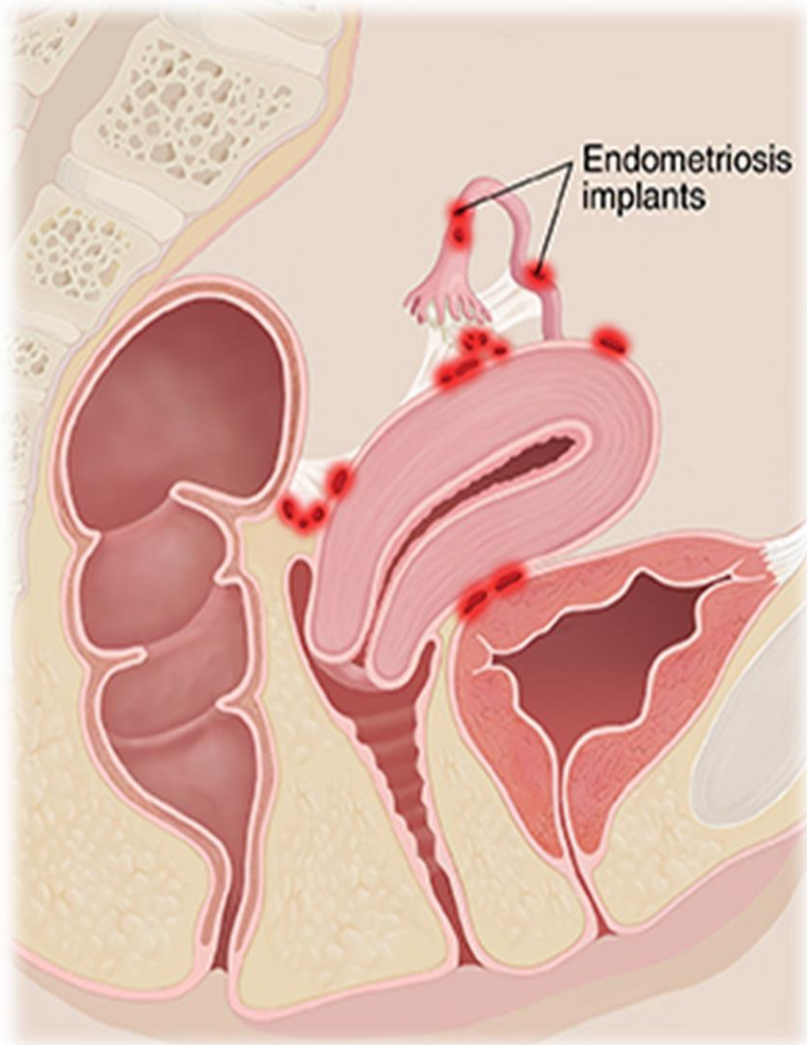
Pathogenetic mechanisms

New diagnostic markers

New drugs

Personalized treatment

Endometriosis 2023



It is clinically relevant to understand the pathogenesis for the diagnostic and therapeutic implications!!




9TH CONGRESS
OF THE SOCIETY OF ENDOMETRIOSIS
AND UTERINE DISORDERS

SEUD
CONGRESS
2023

ENDOMETRIOSIS AND UTERINE DISORDERS:
**STRATEGIC MANAGEMENT AND CHALLENGES
IN THE NEW MILLENNIUM**

MARCH 15-18
ABU DHABI, UAE

 Society of Endometriosis
and Uterine Disorders

Congress President:
Pr. Ghassan Lotfi, UAE

SEUD President:
Dr Francisco Carmona, Spain

Location:
Abu Dhabi

WWW.CONGRESS.SEUD.ORG
FOLLOW US  @Official_SEUD