Recent Developments in the Transmission of Human Life

19-21 January 2023

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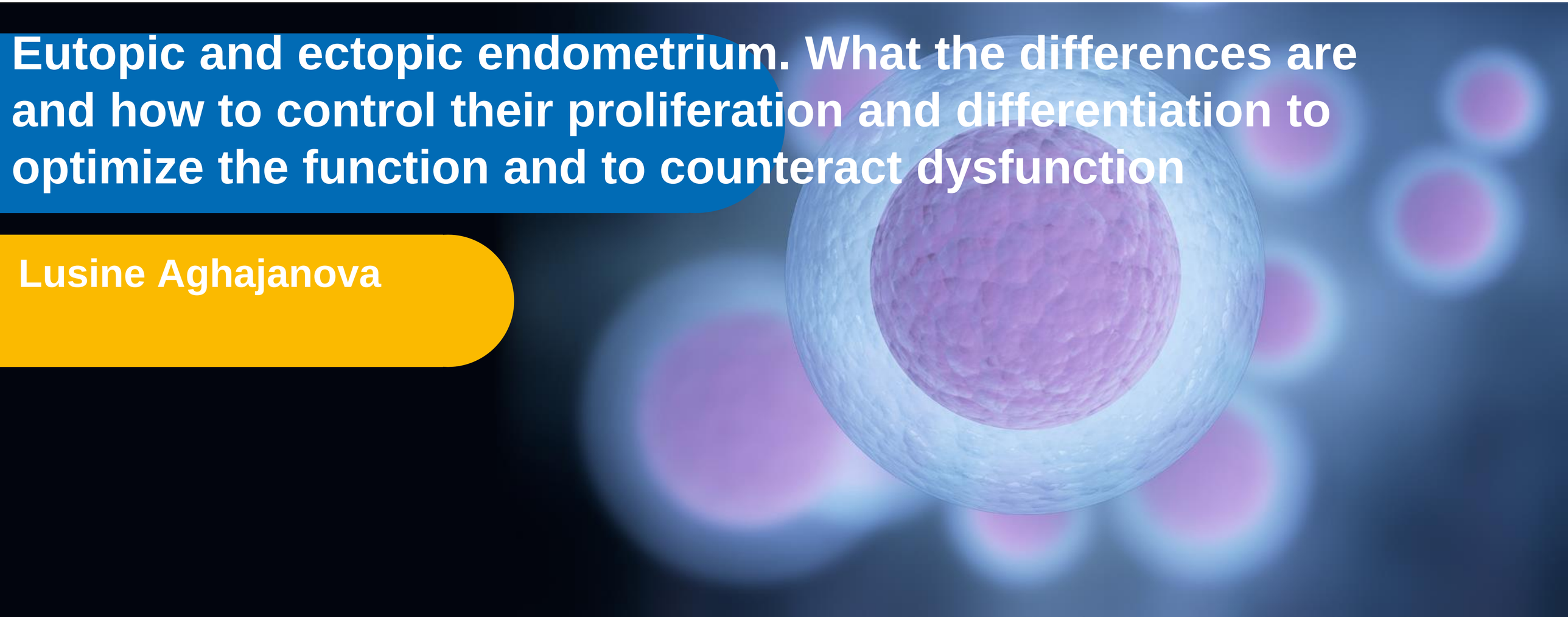
Recent Developments in the Transmission of Human Life

Eutopic and ectopic endometrium. What the differences are and how to control their proliferation and differentiation to optimize the function and to counteract dysfunction

Lusine Aghajanova



Eutopic and ectopic endometrium. What the differences are and how to control their proliferation and differentiation to optimize the function and to counteract dysfunction

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Faculty Disclosure

I have no potential conflict of interest to declare

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Objectives

- To review concepts of endometriosis, eutopic and ectopic endometrium
- To review function of both types of the endometrium
- Endometrial stem cells in endometriosis and non-endometriosis patients
- Review epigenetic abnormalities in endometriotic cells
- Understand concept and cause of progesterone resistance
- Understand pathogenesis of infertility in endometriosis
- Describe various treatment options in the management of endometriosis related pain and infertility with endometrial dysfunction

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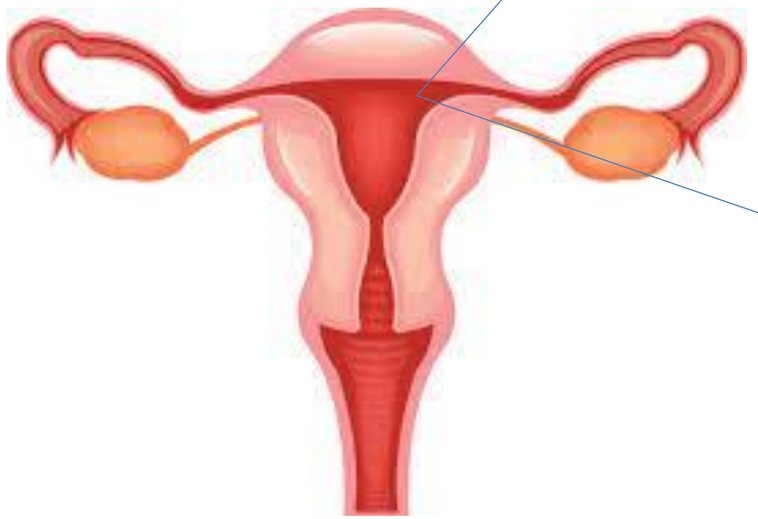
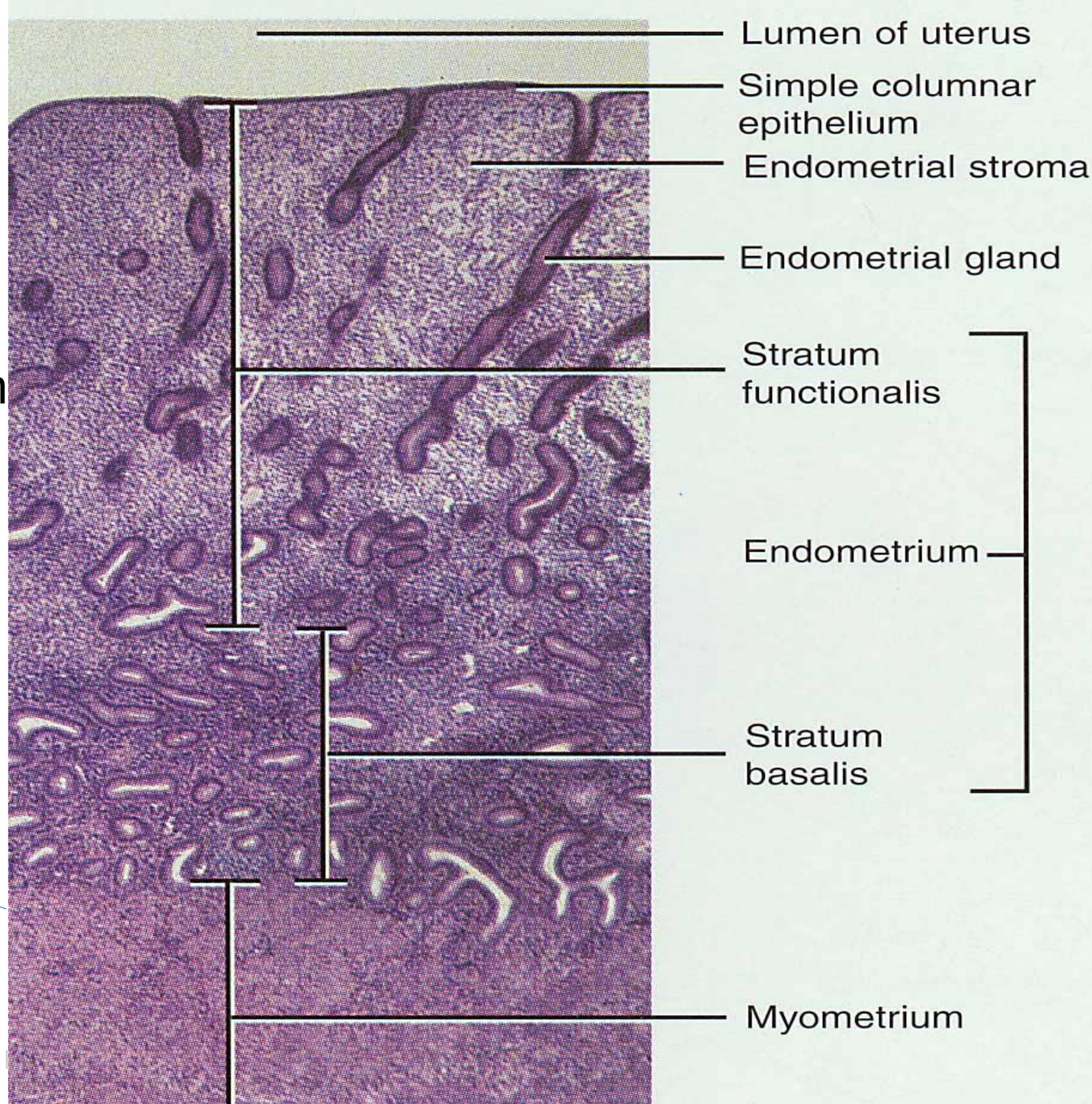
Endometrial histology

3-13 mm

1 mm





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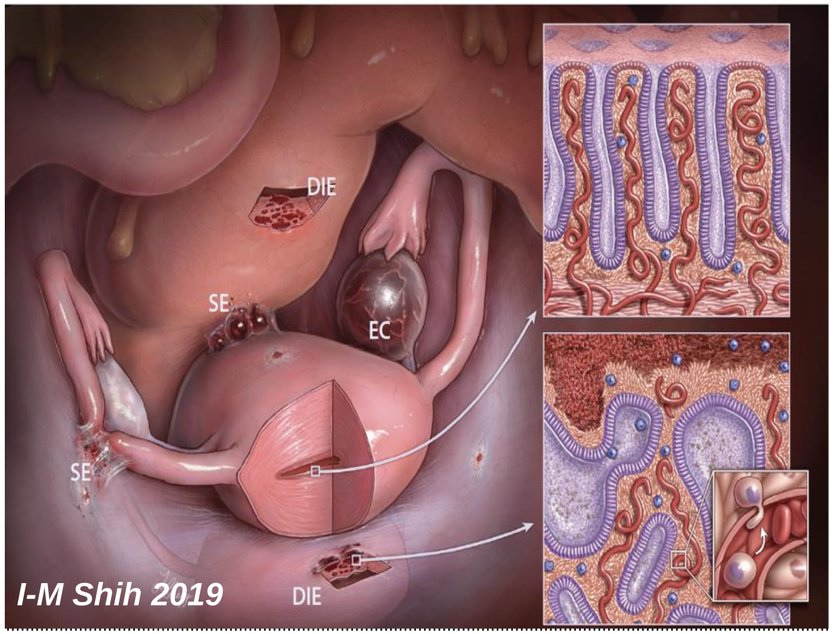
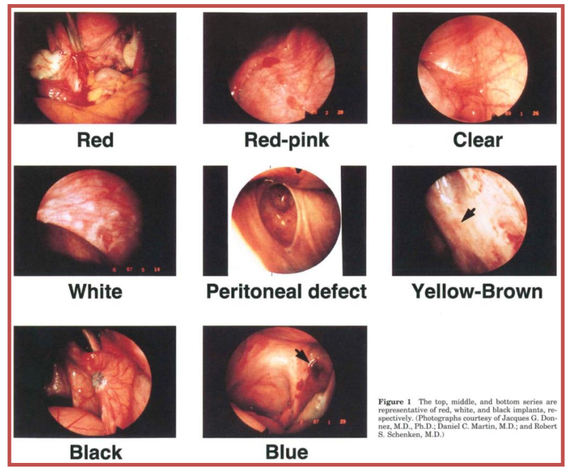
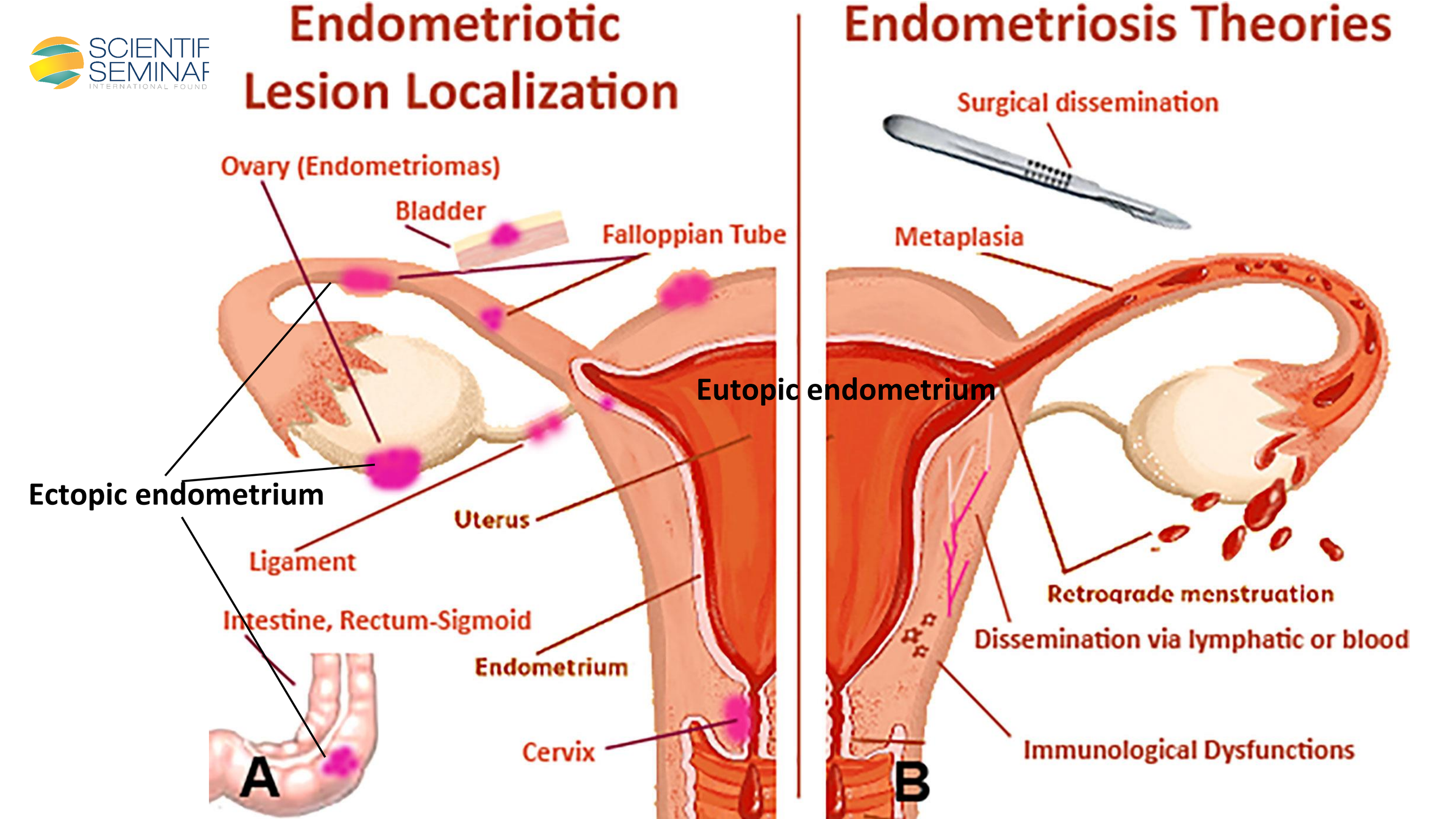
Lets talk about Endometriosis

- Chronic, E2-dependent, inflammatory disease of endometrial-like tissue invading extra-uterine structures → inflammation, fibrosis, pelvic pain, infertility.
- Affects
  - 6-10% ~200M women, teens
  - 35-50% women with pelvic pain and infertility
- Severely impacts QoL and is associated with poor pregnancy outcomes and other chronic disorders
- Diagnosis: surgery, imaging and symptoms
- Disease lesions, presenting Sx highly variable, not always correlating with extent of disease. Multiple subtypes
- Unpredictable responses to Rx's (lowering E_2/surgical)
- No cure





Eskanazi 1997, Missmer 2004, Nnoaham 2011, Simoens 2012, Kvaskoff 2015, Cochrane Rev 2016, Santulli 2016, Saraswat 2016, Soliman 2016, Glavind 2017, Kohl 2017, Zullo 2017, Evans 2017, Shafrir 2018, Agarwal 2019, Farland 2019 , Breintoft 2021, ESHRE guidelines 2022

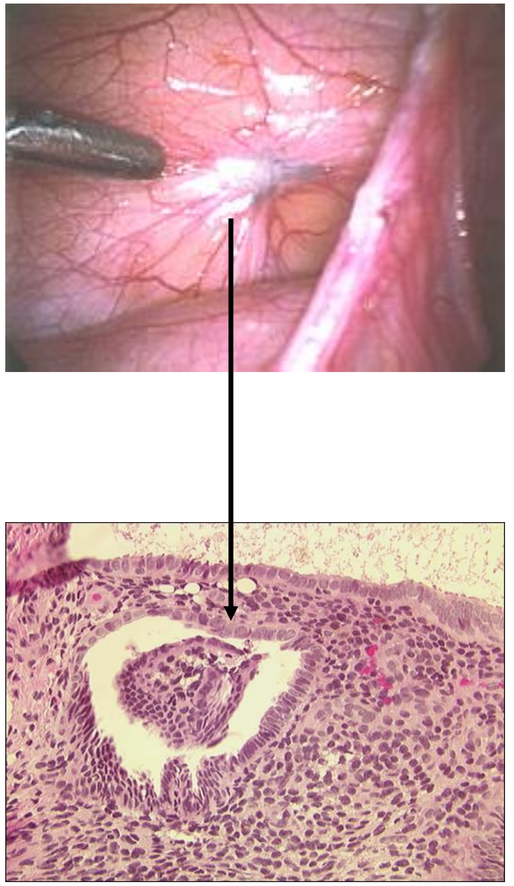

Endometriotic Lesion Localization
Ovary (Endometriomas)
Bladder
Falloppian Tube
Ectopic endometrium
Uterus
Ligament
Intestine, Rectum-Sigmoid
Endometrium
Cervix
A
Endometriosis Theories
Surgical dissemination
Metaplasia
Eutopic endometrium
Retrograde menstruation
Dissemination via lymphatic or blood
Immunological Dysfunctions
B

Endometriosis epidemiology

- **Risks**
  - **increased:**
    - menarche < 10 yo, low birth wt (<5.5 lb), BMI >25, nullparity, in utero DES exposure, + FHx, EtOH>100g/day (E_2)
    - Caucasian, Asian > African American, Hispanic
    - Mullerian anomalies, reproductive tract obstruction
    - Environmental triggers - in utero, postnatal, adult
      - PCBs (polychlorinated biphenyl), TCDD (dioxin), cadmium etc
  - **decreased:**
    - smoking, lactation > 23 mos, parity > 3 children (E2)
  - **no association:**
    - height, waist/hip ratio, caffeine, hair color

- **Health Care Costs:**

– total costs estimated in US $72 B in U.S. 2009, 2016



National Center for Health Statistics. 1987.
• Giudice LC, Kao LC, 2004.
• Messmer et al: Am J Epi 2004; Fertil Steril 2004
• Burney R, Giudice LC, 2008.

Pathogenesis of Endometriosis
Theories

Sampson's theory: Retrograde menses and peritoneal implantation

Fragments attach to the peritoneum, establish a blood supply, survive, proliferate, invade

But, all women have retrograde menstruation, but not all women have endometriosis.

Halban's theory: Hematogenous or lymphatic spread to distant tissues

Does not explain gravity dependent disease sites

Meyer's theory: Coelomic metaplasia

Low incidence of pleural disease

Immunogenic defect

Profound inflammatory response

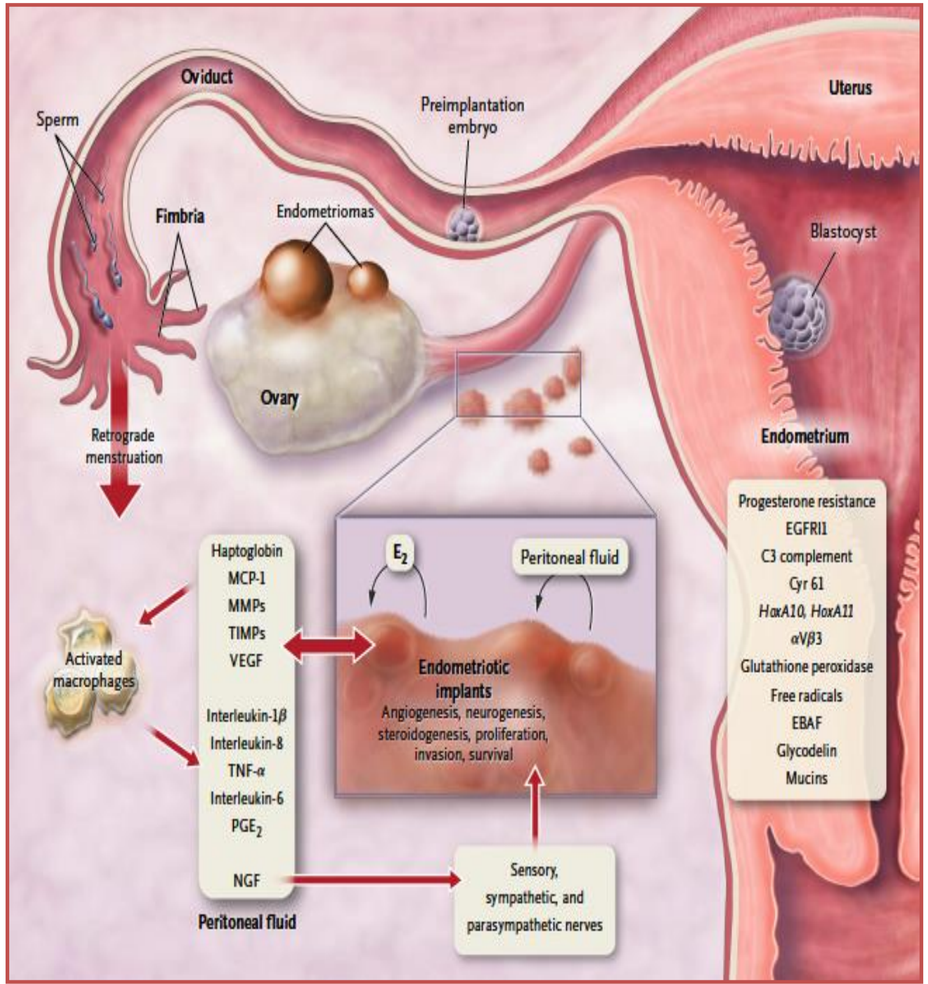
But suboptimal immune response

implants not adequately cleared

Increased survival and growth of implants (decreased apoptosis)

Iatrogenic dissemination

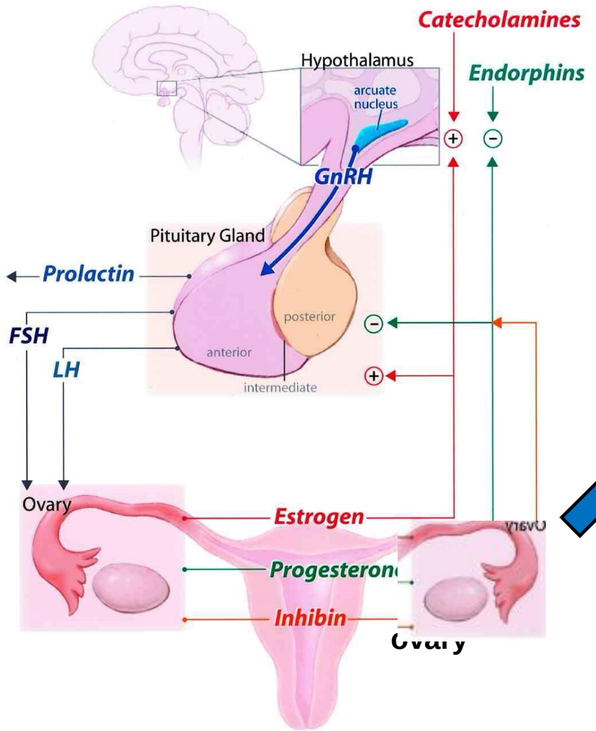
- C/S scar endometriosis etc



Burney R, Giudice LC. Pathogenesis of Endometriosis. Fertil Steril 2012; Brosens Placenta 2013; Vercellini et al. Nat Rev Endocrinol 2014; Zondervan Nat Med 2018; NEJM 2020.

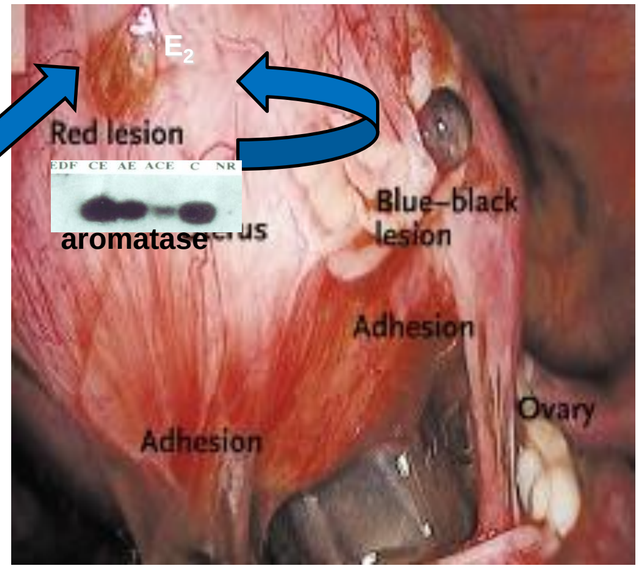
E_2 Sources that Stimulate Disease and Inflammation

HPO axis



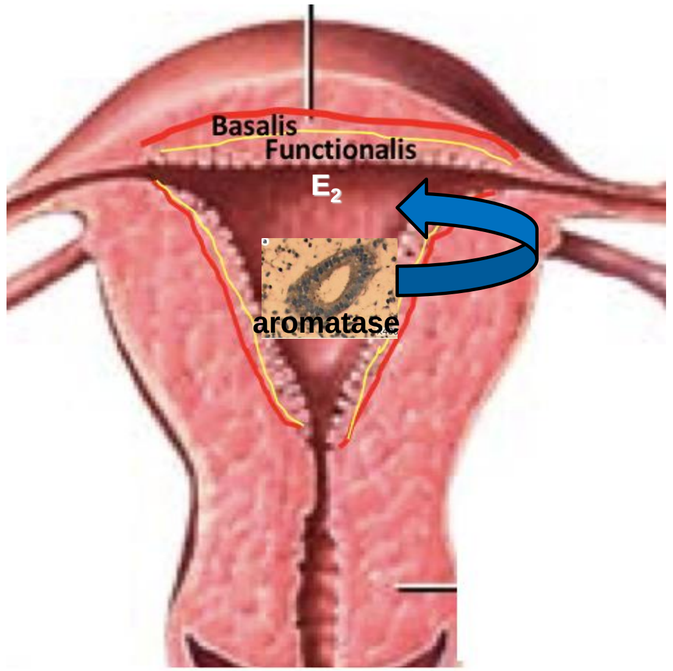
E_2

Lesions



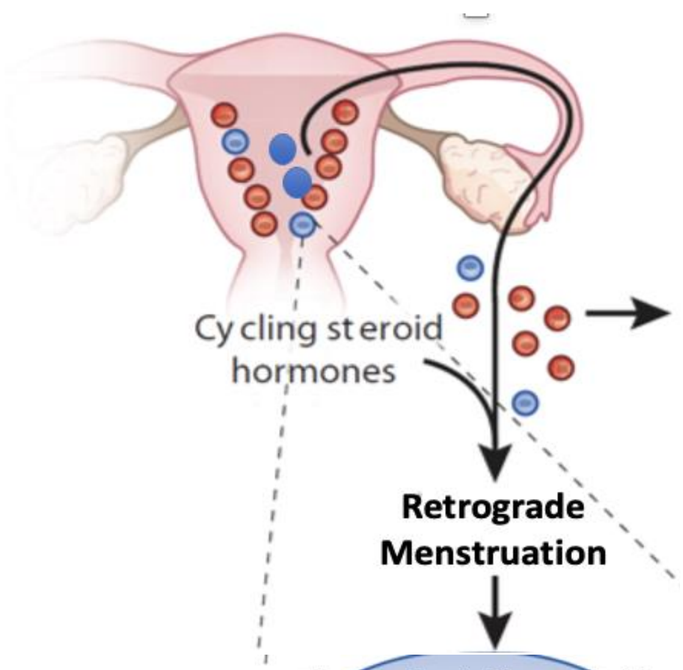
Endometrium

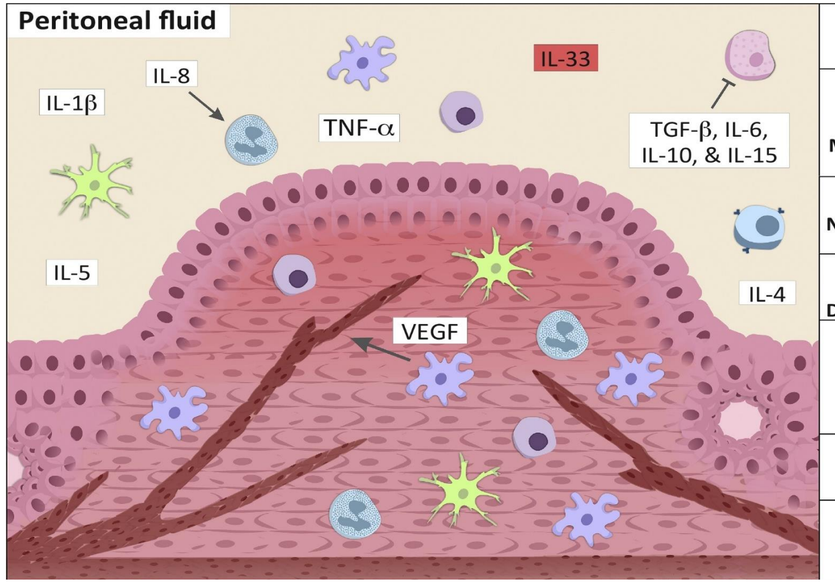
express **aromatase** and synthesize own E_2



Courtesy of L Giudice

Molecular Aberrations in Endometriosis





Neutrophil	·Recruited early in lesion formation ·Promote angiogenesis ·Reduced apoptosis
Macrophage	·Reduced phagocytic capacity ·Promote angiogenesis ·Enhance ESC proliferation and invasiveness ·Increased inflammatory cytokine expression ·Co-localize with nerve fibres
Natural killer cell	·Reduced cytotoxic capacity mediated by macrophage-ESC interaction, IL-6, TGF-β, IL-10, and IL-15
Dendritic cell	·Implications in angiogenesis and lesion development
T cell	·T_H2 cytokine profile ·Increased T_H17 cells; IL-17 promotes inflammation and angiogenesis ·Increased peritoneal T_{REGs} ·T_{REGs} enhance ESC proliferation and invasion
B cell	·Anti-endometrial antibodies
Epithelial cell / Stromal cell / Endothelial cell	

Lesions contain multiple cell types and establish a complex and dynamic peritoneal environment of inflammatory, angiogenic and endocrine signals

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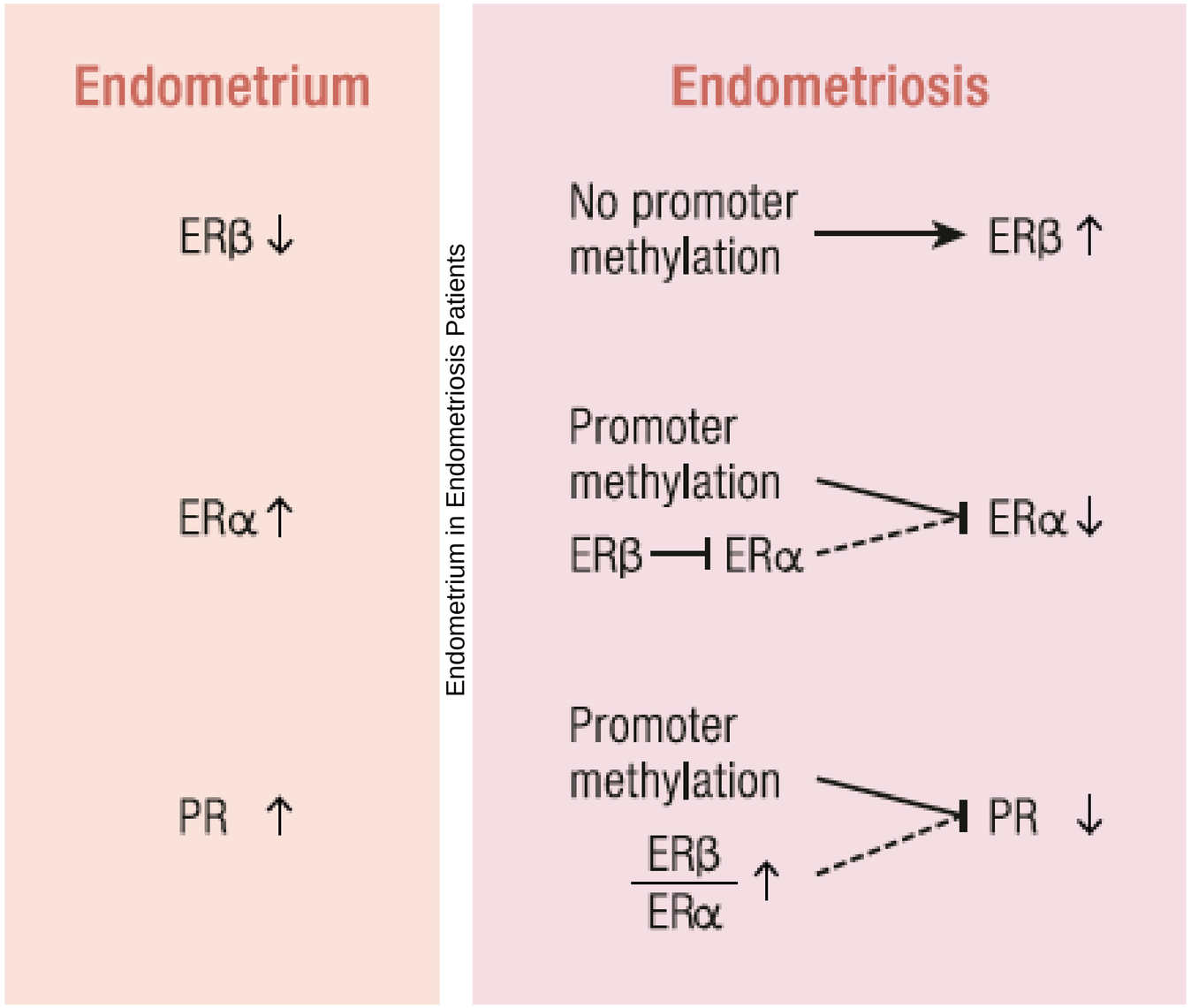
Endometriosis pathophysiology

- Enhanced E_2 signaling
- Disrupted P_4 signaling
- Inflammation
- Pain
- Infertility

Bulun Endocr Rev 2019

Courtesy of L Giudice

Progesterone Resistance in Lesions



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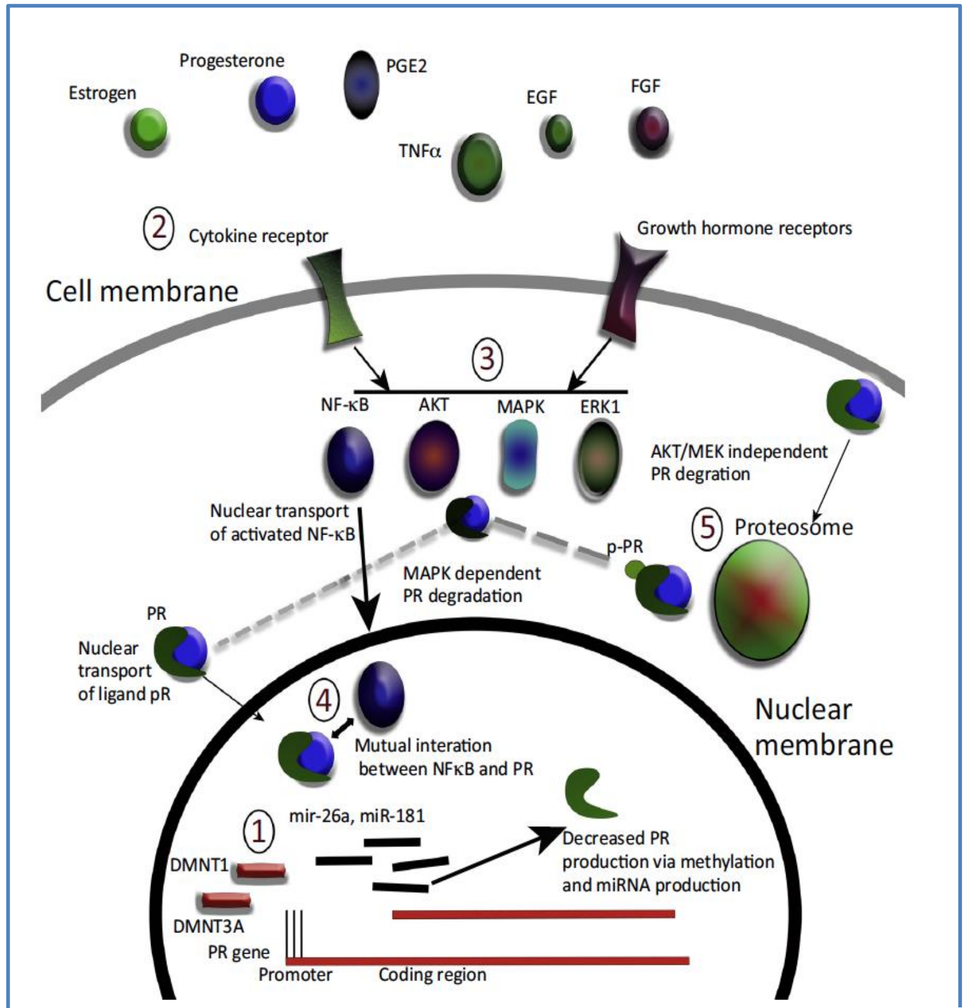


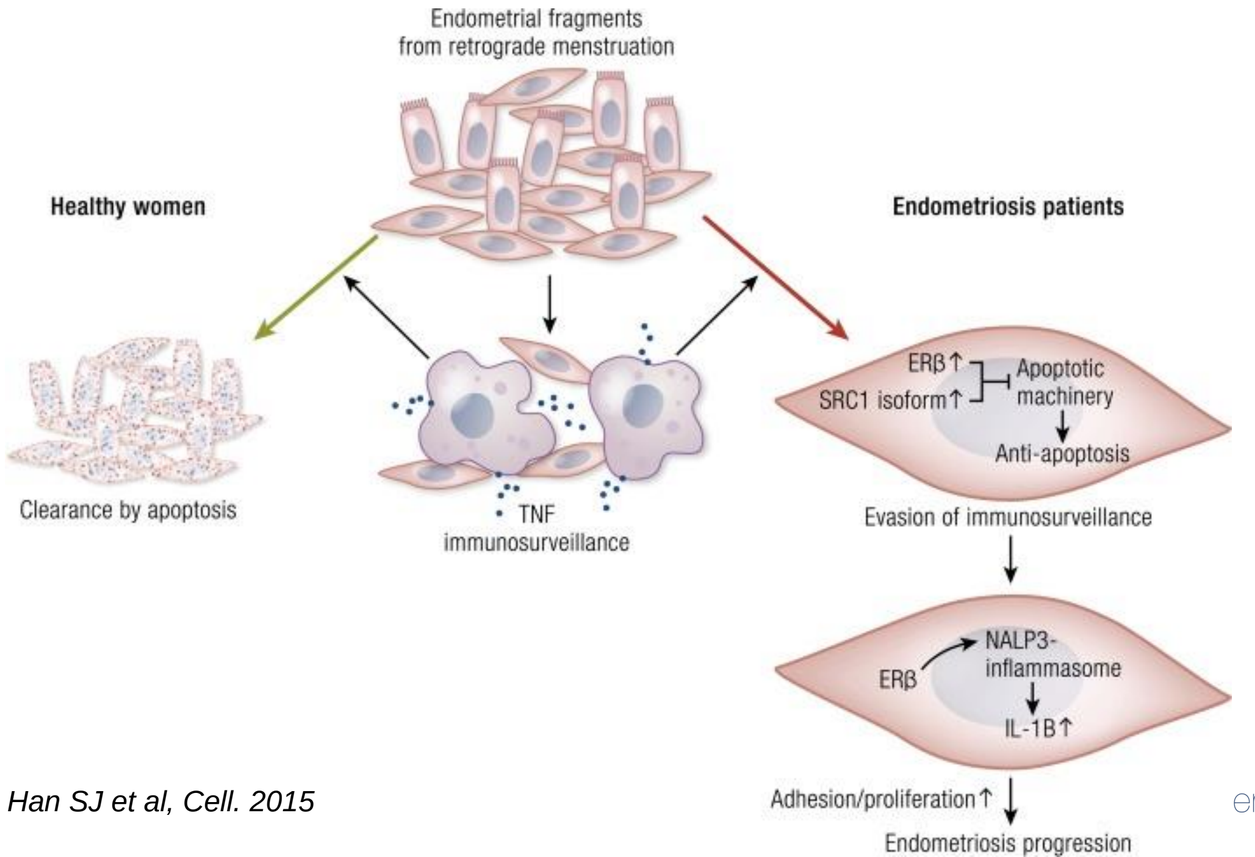
McKinnon, Mueller, Montgomery, Trends Endocrinol Metab 2018;29(8):535

- Transcriptional regulation PR
- Post-transcriptional over-expression miR-26a and miR-181
- Cytokines, hormones, growth factors stimulate receptors, activate AKT, ERK1, MAPK pathways that suppress PR activity
- Inflammation (TNFα, EGF, FGF) stimulates NFκB activation that has mutual interaction with PR leading to reduced PR expression

Increased cell death, enhanced proliferation and progesterone resistance

Nongenomic action of ERβ promote endometriosis progression

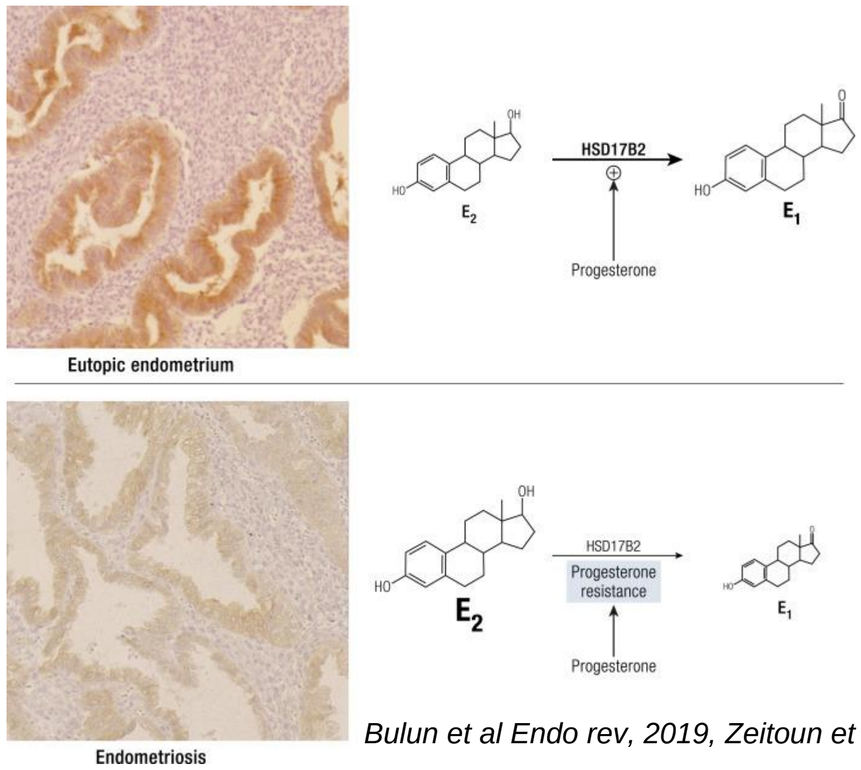
- ERβ in endometriotic tissue affects apoptosis by preventing TNF-induced cell death
- It enhances adhesion and proliferative activities of endometriotic tissues via SRC1 and IL-1β



Han SJ et al, Cell. 2015

Progesterone resistance due to HSD17B2 deficiency in endometriotic epithelium.

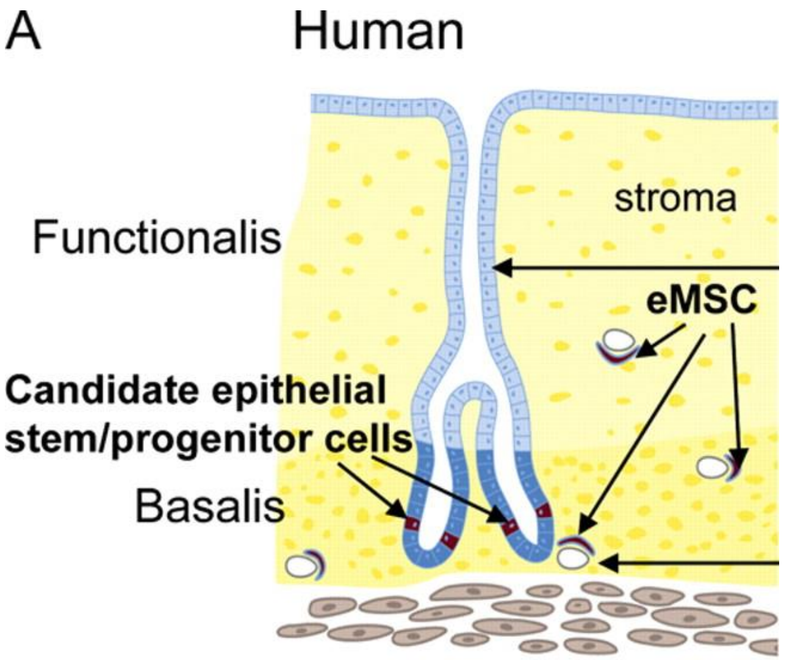
- HSD17B2 is expressed in eutopic endometrial epithelial cells in secretory phase (high P4), converts potent E2 to weak E1.
- In endometriosis HSD17B2 is severely deficient => E2 excess.
- Hence, in endometriotic endometrium progesterone action is decreased due to high E2 and deficiency of HSD17B2, but its deficiency in endometriosis is a consequence of progesterone resistance (vicious cycle)



Bulun et al Endo rev, 2019, Zeitoun et al, JCEM 1998

Endometrial stem cells

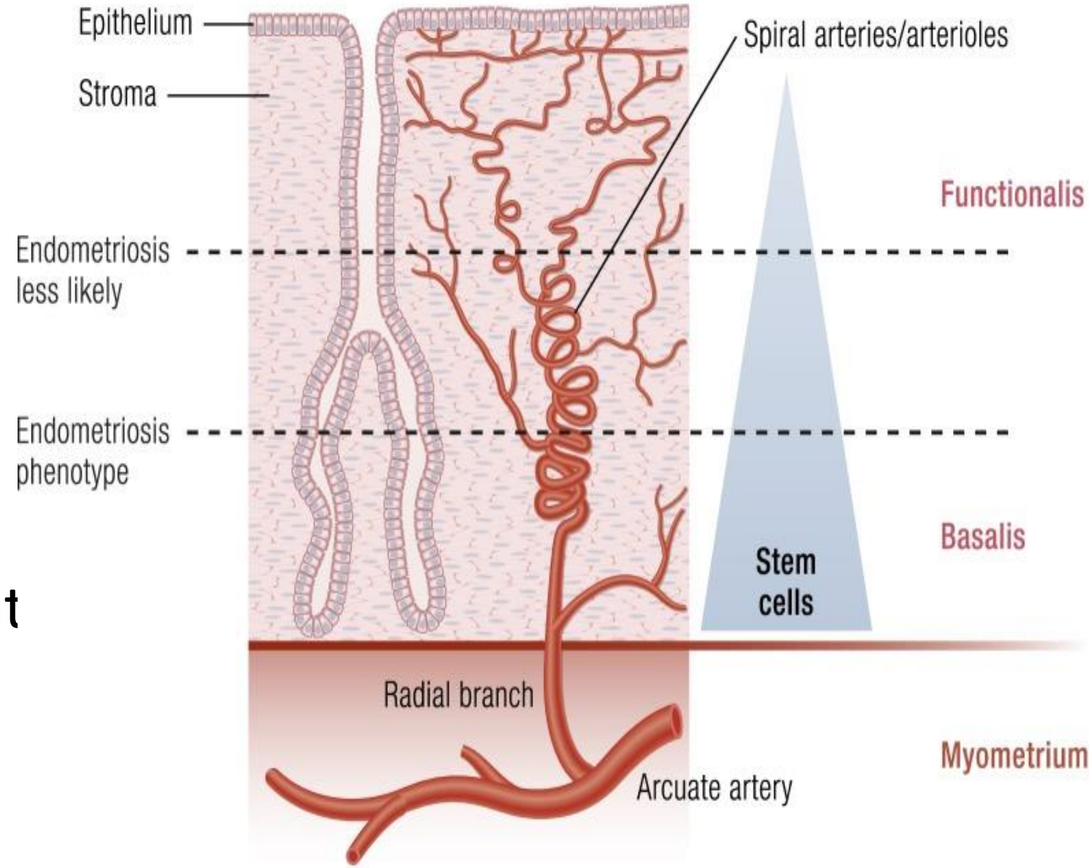
- Endometrium contains epithelial, mesenchymal, endothelial stem/progenitor cells *(Gargett, Masuda 2010; Alcaraz et al., 2009)*.
- Located perivascularly in basalis and functionalis, and co-express CD146 and PDGF-Rβ, also SUSD2 identified as a single marker *(Schwab, Gargett 2007; Masuda et al., 2012).*
- Strong similarities between transcriptomes of $CD146^{+}$/ $PDGF\text{-}R\beta^{+}$ eMSC with fibroblasts *(Spitzer et al., 2012)*.



Gargett & Masuda. Mol Hum Reprod 2010;16:818-834

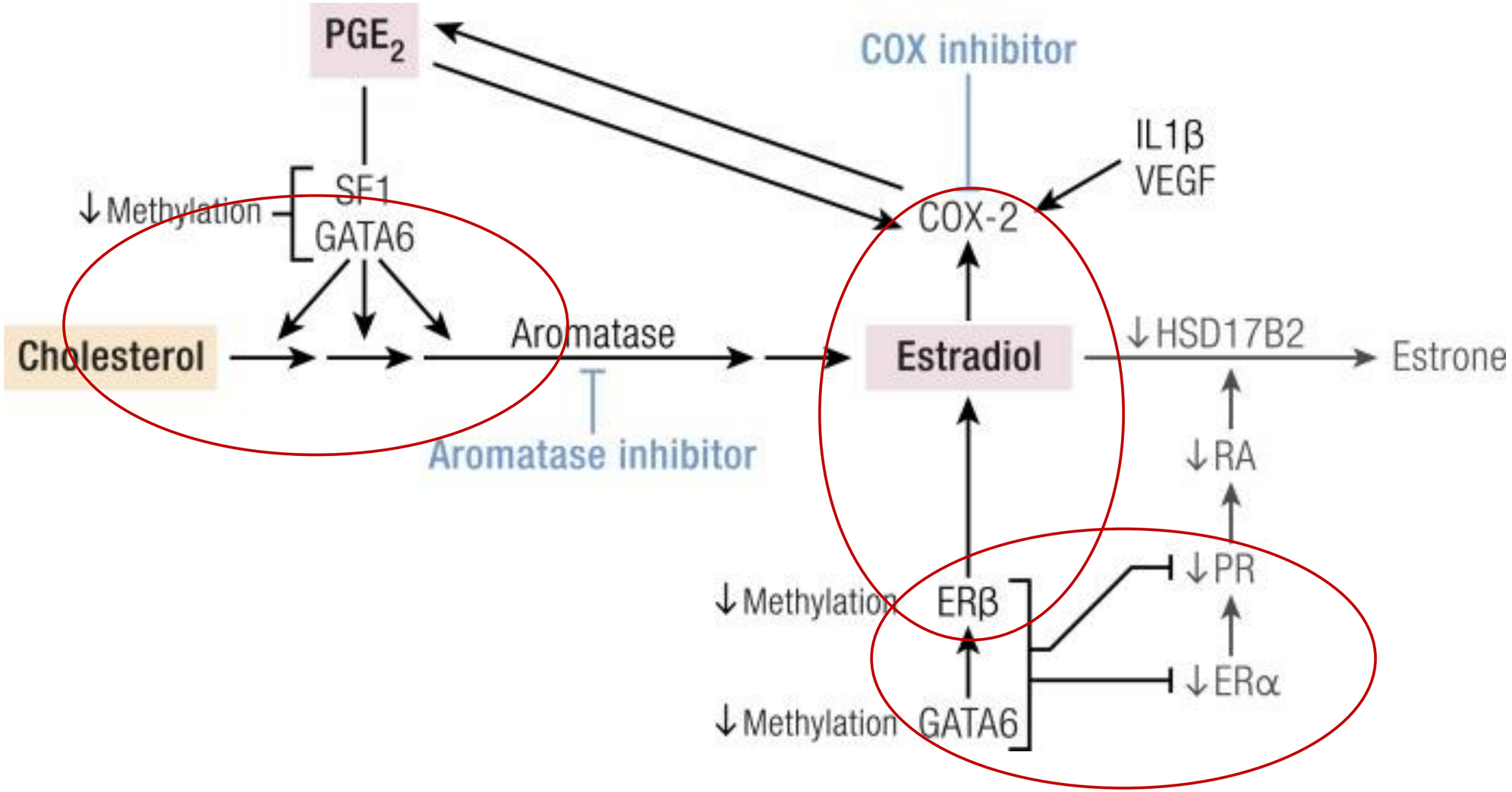
Stem cells in endometriosis

- During menstruation, women with endometriosis shed more basalis cells, including progenitor cells, than healthy individuals
- Progenitor cells can more easily generate endometrium in ectopic locations than differentiated cells and further expand on Sampson's theory of retrograde menstruation
- BM-MSC may differentiate into endometrial cells at other sites, without first being localized in endometrium, contributing to endometriotic lesions.
- eMSC from endometriosis pts did not decidualize properly after differentiation to stromal cells, demonstrating P4-resistance



Bulun et al Endo rev, 2019,
Leyendecker et al Hum Reprod 2002
Barragan etc al, BoR, 2016
Bonavina, Taylor, Front Endocrinol, 2022

Key estrogen-dependent mechanisms in endometriosis: summary



Bulun et al Endo rev, 2019,

Medical Management of Endometriosis-Associated Pelvic Pain

Decrease E2 levels
Reduce menstrual flow
Reduce inflammation

NSAID and OCP
- —Suppress prostaglandin levels
- — Suppress estrogen stimulation and menstrual flow
- —Can use OCP, vaginal ring, patches, cyclic or continuous
- —Failure rate = 20-25%

Danazol- type of androgen (FDA approved)
- Causes anovulation by attenuating the midcycle surge of LH
- Side effects: androgenic symptoms in 80% of patients
- Efficacy: danazol group - 60%; placebo group - 18%

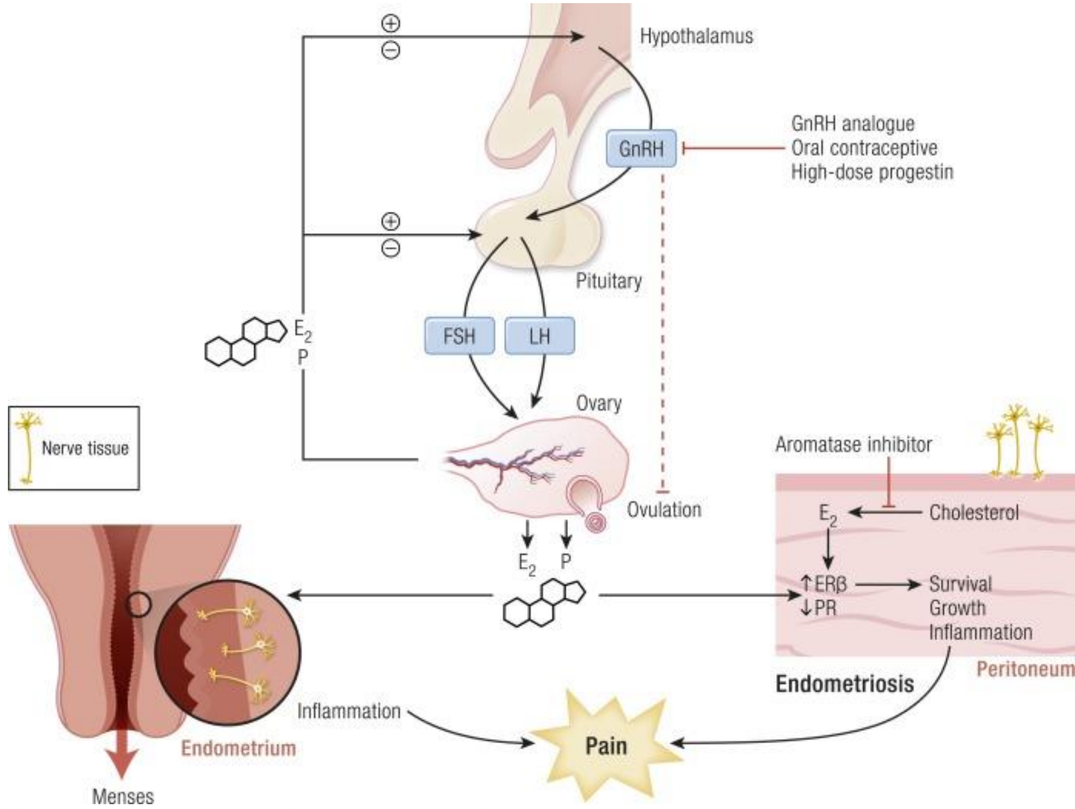
Progestins
- Theoretically cause decidualization and atrophy of implants
- Side effects: AUB, N/V, bloating, breast tenderness, depression
- Relative progesterone resistance of endometriotic implants renders progestins variably effective

Aromatase inhibitor (e.g., letrazole)
- Add back norethindrone acetate QD

GnRH analogues (FDA approved), expensive
- Leuprolide acetate (Lupron) 20% after 6 mos; 50% after 1 yr.
- Side effects: vasomotor symptoms, vaginal dryness, decreased libido, irritability and bone mineral density loss
- With add back therapy (norethindrone + Premarin)

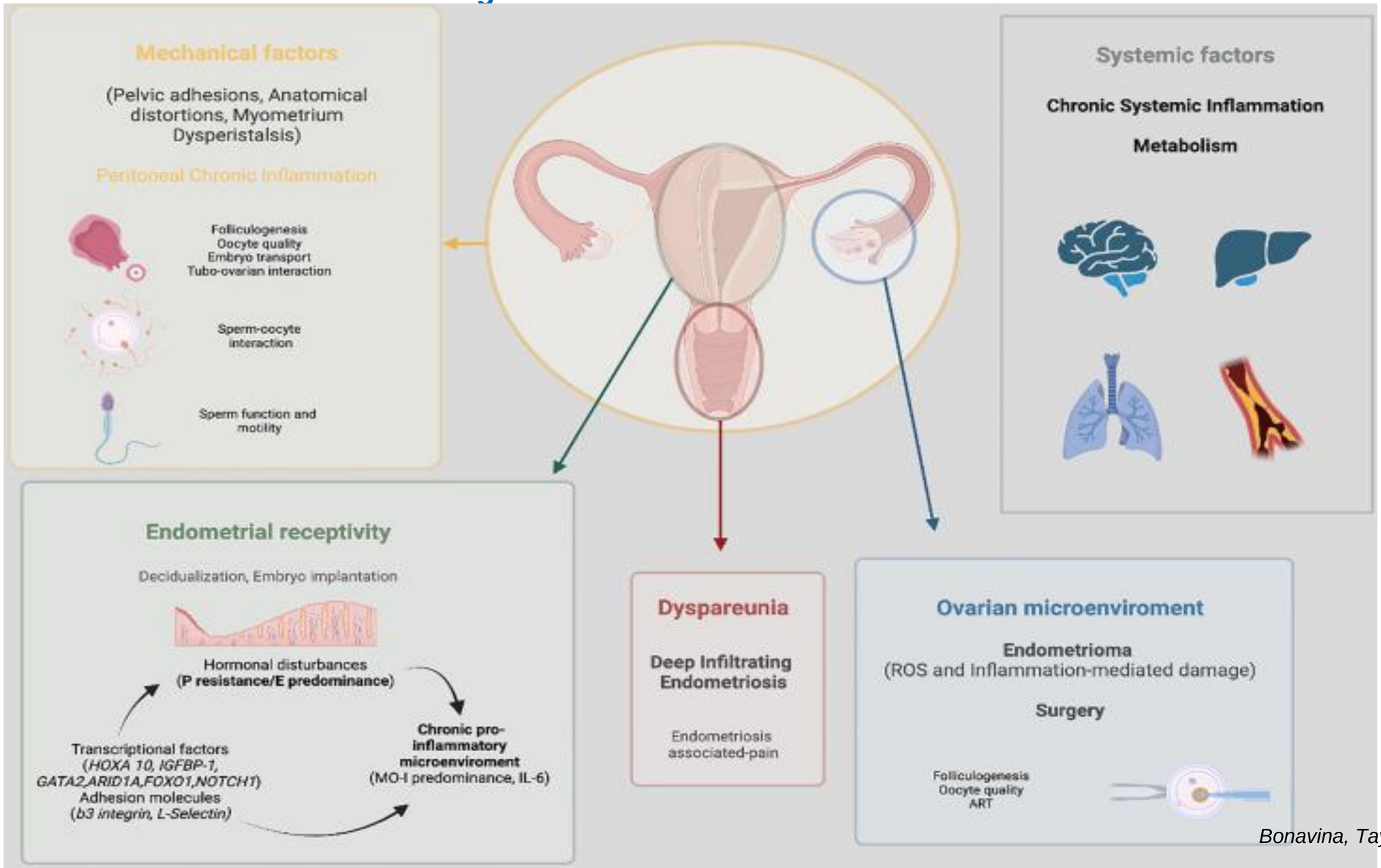
GnRH antagonist (FDA approved), oral
- for management of moderate to severe pain associated with endometriosis

Levonorgestrel-releasing-IUD (Mirena)
- Effective in reducing endometriosis-associated pelvic pain



Endometriosis & Infertility

Putative Etiologies



Bonavina, Taylor, Front Endocrinol, 2022

Treatment of Infertility

Removal of disease

-In stage I/II endometriosis, the benefit of laparoscopic treatment is insufficient to recommend laparoscopy to increase the likelihood of pregnancy, but ok to do for pain

-In severe endometriosis (stage III/IV), surgery improves success rates

Ovulation induction

-First line therapy on <35yo with Stage I/II

-Can be initial therapy for women >35yo

-Insemination with either clomiphene, letrozole or FSH

Assisted reproductive technology (IVF)

- For women with stage III/IV endometriosis who fail to conceive after surgery or also have advanced reproductive age, IVF-ET is an effective alternative (ASRM)

- IVF preferred to another surgery

<u>Medical suppression of ovarian function</u>

- GnRH agonist or antagonist, OCP, or aromatase inhibitor, or combination.
- Can consider after failed infertility treatment/failed transfer, to bridge to next steps

Future treatment strategies

- miRNAs, Prostaglandin receptor inhibitors (EP2/PP4)

- Stem cells

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Eutopic and ectopic endometrium: function, dysfunction and management

Take-home messages

✓Endometriosis is characterized by an **estrogen**-dependent chronic inflammatory process that affects primarily pelvic tissues

✓The underlying pathologic mechanisms in the eutopic and ectopic endometrium involve defectively programmed endometrial mesenchymal progenitor/stem cells

✓Endometriotic stromal cells display specific epigenetic abnormalities that alter expression of key transcription factors such as excessive production of GABA-6, SF-1, and ER-*β*, which collectively cause estrogen-dependent inflammation, and deficient expression of PR, which causes progesterone resistance

✓Decreased apoptosis and enhanced proliferation of endometriotic cells promote implant survival

✓Endometriosis and endometriosis-related pain currently managed by ovulation suppression, E2-production suppression and anti-inflammatory meds, and surgical removal of pelvic lesions

✓ Infertility is usually managed by fertility treatment including IVF, protocols utilize GnRH-agonists and aromatase inhibitors

THANK YOU

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