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Progesterone Resistance and Endometriosis

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March 26, 2025

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Progesterone Resistance and Endometriosis

Objectives:

1. Define what is endometriosis and some theories or factors involved in the pathogenesis
2. Review the diagnostic criteria and common testing to help aid in diagnosis
3. Focus on a deeper understanding of progesterone resistance and its relation to endometriosis
4. Review DUTCH results of patients with diagnosed endometriosis and what markers may help with treatment/management
5. Review of the most common conventional hormonal treatments
6. Review research related to lifestyle and natural medicine management considerations for symptom control

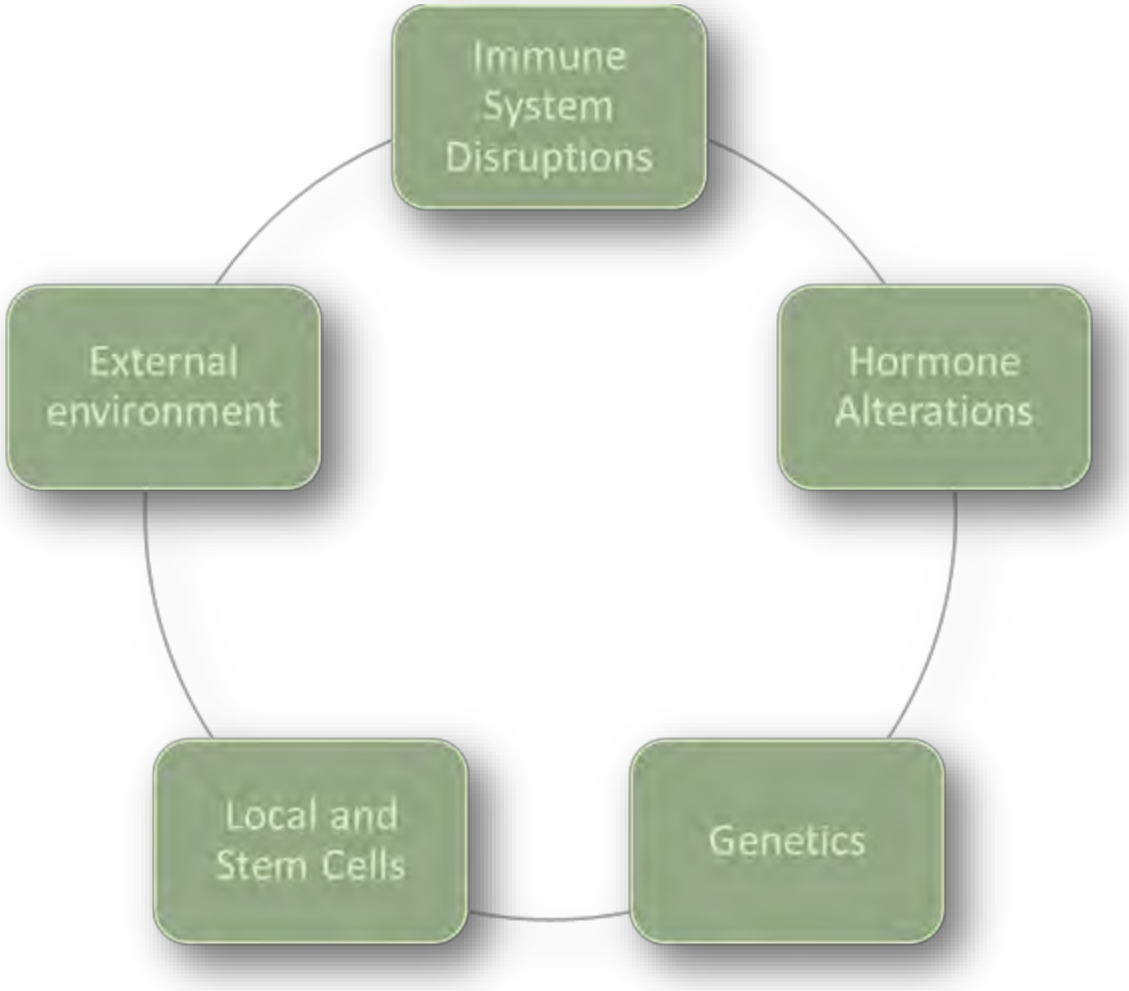
What is Endometriosis?

- Endometriosis (EM) is a chronic condition where endometrial-like tissue, attaches to areas outside the uterus, growing and shedding in response to estrogen and progesterone fluctuations
- This misplaced tissue can implant in various areas of the pelvic region, including the ovaries, fallopian tubes, bladder, and rectum
  - Rarely it is located outside of the pelvis
- The **cause of endometriosis is unknown**, though many contributing factors have been identified
- There is no specific way to prevent endometriosis
- It can develop at any age after the onset of menstruation; however, it is most commonly diagnosed in women between the ages of 25 and 40

What is Endometriosis?

- Endometriosis is a chronic inflammatory disorder that disrupts the coordinated progesterone and estrogen response throughout the reproductive tract
- Endometriosis was once thought of as primarily an estrogen-driven disease because estrogen promotes the growth of endometrial lesions
- However more research has identified there being a shift from E dominance alone to progesterone resistance in endometriotic tissues as another major contributing factor
- The endometrial lining of women with EM behaves differently from that of healthy controls
    - Both in the proliferative and secretory phases

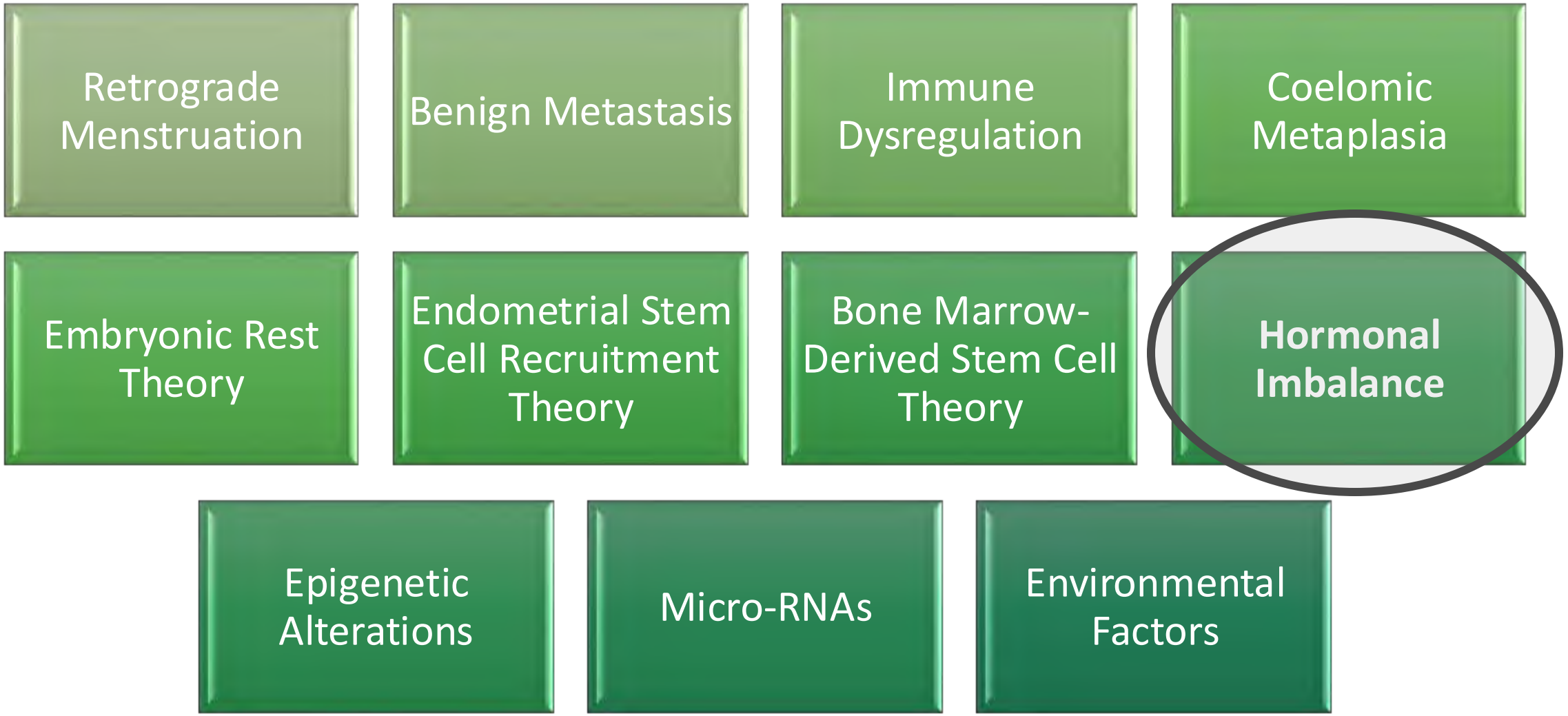
What is Endometriosis?



- EM research shows many factors other than just E dominance being the driver
- Many processes are occurring simultaneously and impact EM development and progression together

- Lamceva, J., Uljanovs, R., & Strumfa, I. (2023). The Main Theories on the Pathogenesis of Endometriosis. *International journal of molecular sciences*, *24*(5), 4254. https://doi.org/10.3390/ijms24054254

The Many Theories of the Pathogenesis of Endometriosis



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Symptoms

- Painful cycles
- Painful intercourse
- Bloody stools – less common
- Painful urination
- Non-cyclical pelvic pain
- Heavy bleeding
- Increased risk of anxiety and depression
- Higher rates of ectopic pregnancies
  - Need to check serial b-hCG early,
  - should double every 48hrs
  - Get TVUS once 1500IU/L to prove intrauterine
- Higher rates of Infertility


Picture from Google Images

Risk Factors

- Increasing age
- Alcohol use
- Early menarche
  - ≤ 11 years old
- Family history of endometriosis
- Low BMI
- Prolonged menstrual flow
  - greater than or equal to one week
- Short cycle interval
  - less than or equal to 27 days

- In very **small** studies they noted a link with increased endometriosis:
  - Red hair Color
  - Blue or green eyes, and freckles have been reported to increase the odds of diagnosis
  - Again, small studies but could there be some phenotypes that are more susceptible

How is Endometriosis Diagnosed?

- Symptom based
  - Go beyond just age of menarche, LMP, etc.
  - Get a thorough menstrual history
  - Check in with other systems – GI, pelvic floor, psych, immunology, etc.
- Physical exam
  - Bimanual pelvic exam may reveal tenderness, nodules, adnexal cyst, fixed uterus
- Bloodwork
  - Can help assess for potential hormone imbalances, inflammatory markers, etc.
  - FSH, LH, E2, Pg serum levels show no significant differences between endometriosis and healthy women
  - *Reminder – what is happening in the serum may not reflect what is happening at the local tissue level

How is Endometriosis Diagnosed?

- TVUS
  - Endometriomas
  - New techniques with saline infused TVUS may help identify superficial peritoneal lesions – more studies needed
  - Specialty trained clinicians can appropriately diagnose deep infiltrating endo
  - First-line for imaging

- MRI is unable to reliably diagnose minimal/mild endometriosis (Stage 1-2)
  - Expensive
  - Considered second-line for imaging
  - MRI was better at diagnosing lesions above the rectosigmoid, multifocal bowel lesions, and extra-pelvic lesions
  - May also consider in centers that lack expert TVUS technicians or symptoms highly suggest deep infiltrating and TVUS was negative

How is Endometriosis Diagnosed?

- Gold standard for many years was the requirement of laparoscopic surgery and proven visualization of lesions
  - 15-20 years ago, required a biopsy confirmation
  - A scoring system for people who had surgery – it is the only way to stage
    - Gives points based on the size, location, and severity of adhesions
    - Stage 1- 4
    - The severity of the disease does not always correlate with symptoms or ability to get pregnant
    - There is no international agreement on how to classify/stage EM
    - Most staging systems show no or very little correlation with patient outcomes

Surgical laparoscopic management of EM

- Controversy over cutting it all out - resection
  - May cause more scarring or tissue damage
  - Some lesions really need to be resected d/t location and restriction to other organs
- Different surgical techniques may have better outcomes
  - Ablation vs excision debate
- Laser Ablation may be better for deep endometriosis
  - Cons: may not get all endometriosis and could damage surrounding tissue
- Argon Beam Ablation
  - Less likely to damage normal surrounding tissue – more superficial
  - Cons: may not get all the EM

Laparoscopic Surgery and Impacts on Fertility

New data showing a decrease in AMH levels after surgical management of endometriomas

The AMH levels drop after surgery – indicating a decline in ovarian reserve

Igniting new discussions about the impact of resecting endometriomas in women with already low AMH

ELSEVIER

Fertility and Sterility

Volume 97, Issue 6, June 2012, Pages 1472-1478

Original article

Effect of laparoscopic excision of endometriomas on ovarian reserve: serial changes in the serum antimüllerian hormone levels

Hale Goksever Celik M.D. [a], Erbil Dogan M.D. [b], Emre Okyay M.D. [b], Cagnur Ulukus M.D. [c], Bahadir Saatli M.D. [b], Sezer Uysal M.D. [d], Meral Koyuncuoglu M.D. [c]

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https://doi.org/10.1016/j.fertnstert.2012.03.027

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Using DUTCH testing in your Endometriosis work-up

Every Sample Tells a Story

- How can a urine test help with management of endometriosis?
  - Urine is looking at how the body utilized and then metabolized those hormones out
  - We can often see patterns associated with inflammation, oxidative stress, poor estrogen detoxification, imbalances between parent hormones, and 5a metabolite preferences

Serum and Urine Hormones Are Complementary

Serum

- Hormones (**mostly non-bioavailable**) are in transit TO tissues
- Collection represents blood levels at that single point in time

  - Production

    ↓

    Blood Stream

Urine

- **Free & bioavailable hormones** that have been taken up by tissues *throughout the body* AND metabolized.
- Collection represents average levels over hours of time
- Blood stream

  ↓

  Tissue Uptake

  ↓

  Utilization
  Metabolism

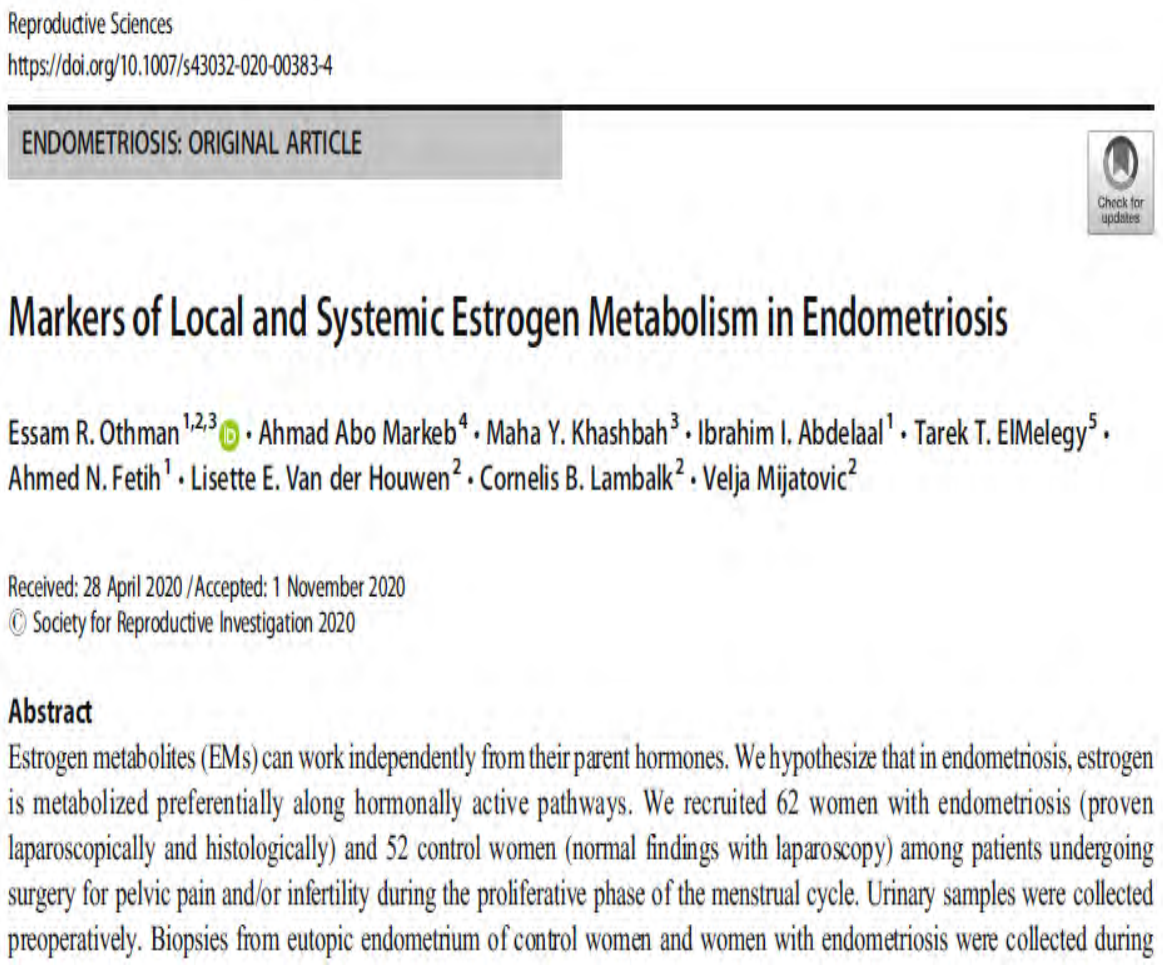
  ↓

  Blood stream → Kidneys →

Urine x4 Samples

Urinary Markers for Estrogen Metabolism in EM

- Women with EM metabolized estrogens differently
- Favoring 2OHE2, 4OHE1,4OHE2



Reproductive Sciences
https://doi.org/10.1007/s43032-020-00383-4

ENDOMETRIOSIS: ORIGINAL ARTICLE

Check for updates

Markers of Local and Systemic Estrogen Metabolism in Endometriosis

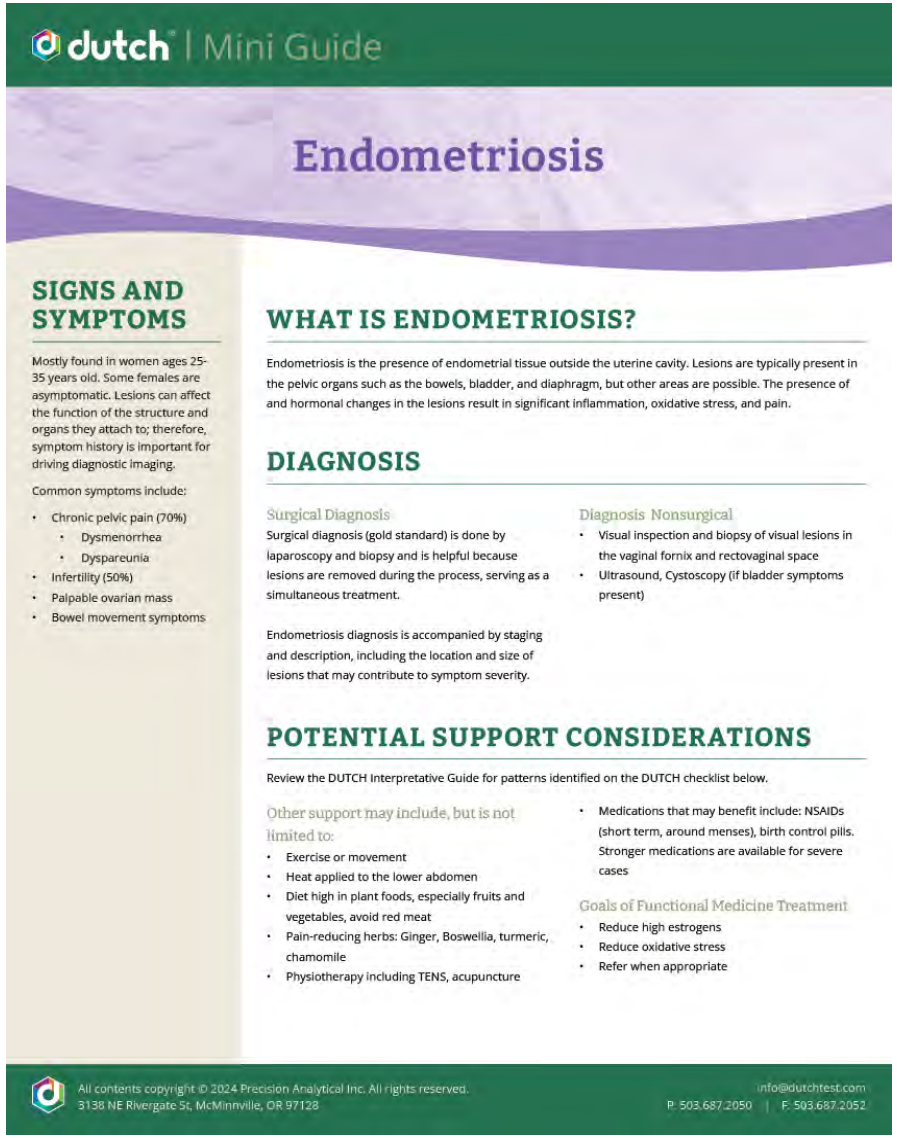
Essam R. Othman[1,2,3] · Ahmad Abo Markeb[4] · Maha Y. Khashbah[3] · Ibrahim I. Abdelaal[1] · Tarek T. ElMelegy[5] · Ahmed N. Fetih[1] · Lisette E. Van der Houwen[2] · Cornelis B. Lambalk[2] · Velja Mijatovic[2]

Received: 28 April 2020 / Accepted: 1 November 2020

Abstract

Estrogen metabolites (EMs) can work independently from their parent hormones. We hypothesize that in endometriosis, estrogen is metabolized preferentially along hormonally active pathways. We recruited 62 women with endometriosis (proven laparoscopically and histologically) and 52 control women (normal findings with laparoscopy) among patients undergoing surgery for pelvic pain and/or infertility during the proliferative phase of the menstrual cycle. Urinary samples were collected preoperatively. Biopsies from eutopic endometrium of control women and women with endometriosis were collected during

Endometriosis Mini Guide – DUTCH Checklist



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Endometriosis

SIGNS AND SYMPTOMS

Mostly found in women ages 25-35 years old. Some females are asymptomatic. Lesions can affect the function of the structure and organs they attach to; therefore, symptom history is important for driving diagnostic imaging.

Common symptoms include:

- Chronic pelvic pain (70%)
  - Dysmenorrhea
  - Dyspareunia
- Infertility (50%)
- Palpable ovarian mass
- Bowel movement symptoms

WHAT IS ENDOMETRIOSIS?

Endometriosis is the presence of endometrial tissue outside the uterine cavity. Lesions are typically present in the pelvic organs such as the bowels, bladder, and diaphragm, but other areas are possible. The presence of and hormonal changes in the lesions result in significant inflammation, oxidative stress, and pain.

DIAGNOSIS

Surgical Diagnosis

Surgical diagnosis (gold standard) is done by laparoscopy and biopsy and is helpful because lesions are removed during the process, serving as a simultaneous treatment.

Endometriosis diagnosis is accompanied by staging and description, including the location and size of lesions that may contribute to symptom severity.

Diagnosis Nonsurgical

- Visual inspection and biopsy of visual lesions in the vaginal fornix and rectovaginal space
- Ultrasound, Cystoscopy (if bladder symptoms present)

POTENTIAL SUPPORT CONSIDERATIONS

Review the DUTCH Interpretative Guide for patterns identified on the DUTCH checklist below.

Other support may include, but is not limited to:

- Exercise or movement
- Heat applied to the lower abdomen
- Diet high in plant foods, especially fruits and vegetables, avoid red meat
- Pain-reducing herbs: Ginger, Boswellia, turmeric, chamomile
- Physiotherapy including TENS, acupuncture
- Medications that may benefit include: NSAIDs (short term, around menses), birth control pills. Stronger medications are available for severe cases

Goals of Functional Medicine Treatment

- Reduce high estrogens
- Reduce oxidative stress
- Refer when appropriate

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DUTCH CHECKLIST

Test patterns and markers associated with endometriosis

- ☐ **Low progesterone:** Progesterone can limit endometrial lesion growth and low progesterone may be associated with worse symptoms
- ☐ **High estrogens, particularly high estradiol:** When present, they can contribute to more aggressive lesion growth and oxidative stress
- ☐ **Poor phase 1 estrogen detox:**
  - ☐ High 4-OH-E1 (dial) or high *relative* 4-OH-E1 (slider bar) may result in increased oxidative stress and inflammation
  - ☐ High 16-OH-E1 (dial) or high *relative* 16-OH-E1 (slider bar) may cause increased endometrial tissue growth, increased oxidative stress and inflammation
- ☐ **Low phase 2 estrogen methylation** (slider bar) may prevent oxidative phase 1 metabolites from being neutralized, contributing to oxidative stress and increased estrogen receptor activity
- ☐ **Any abnormal cortisol findings:** Cortisol helps with pain and inflammation and can contribute to worse endometriosis symptoms when high or low
- ☐ **High inflammation.** These patterns are associated with high inflammation on the DUTCH test. The more patterns the patient has the higher the likelihood of high inflammation contributing to the endometriosis:
  - ☐ High 5a reductase activity
  - ☐ Low DHEA-S relative to etiocholanolone and androsterone
  - ☐ Fast cortisol clearance rate (CCR)
  - ☐ High free cortisol (acute) or low free cortisol (chronic)
  - ☐ Cortisol metabolism favoring THF (acute) or THE (chronic)
  - ☐ High kynurenate
  - ☐ High pyroglutamate
  - ☐ High indican
  - ☐ High quinolinate
  - ☐ High 8-OHdG

DUTCH Resources on Endometriosis

- **Webinar:** "Endometriosis and the DUTCH Test" with Jaclyn Smeaton, ND, MPH
- **Case Study:** "Endometriosis and the Estrobolome" with Christina O'Brien, DC, RDN, LD, DACNB, IFMCP

Find more DUTCH Education at: https://dutchtest.com/education/

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Endometriosis Mini Guide – DUTCH Checklist

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DUTCH CHECKLIST

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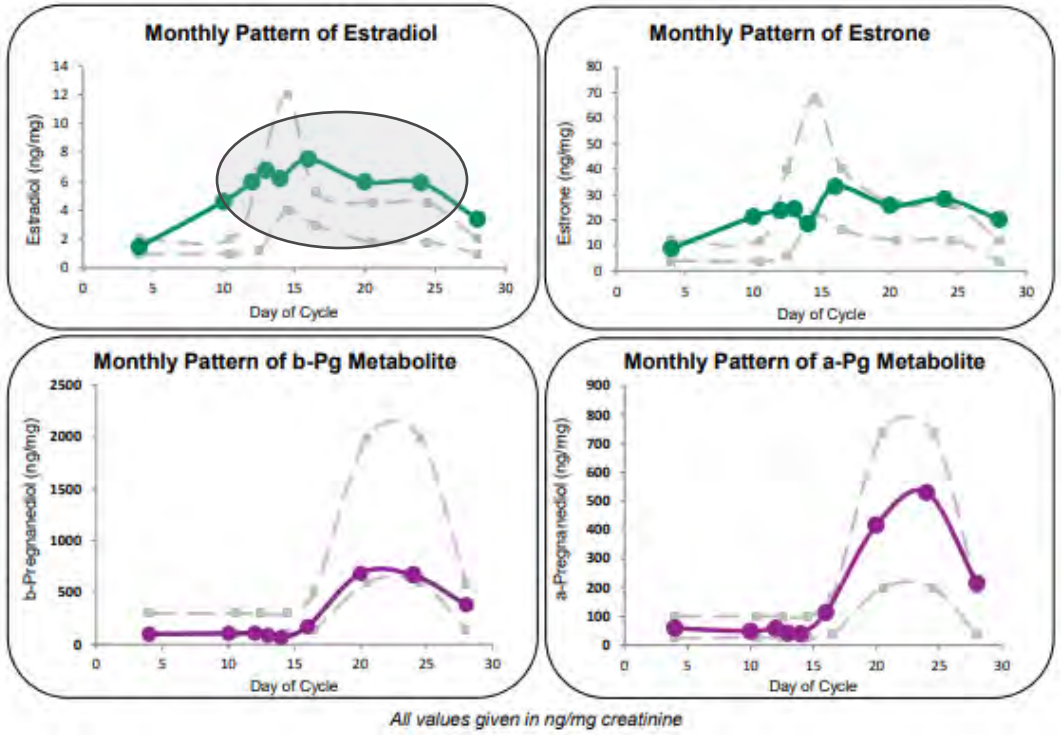
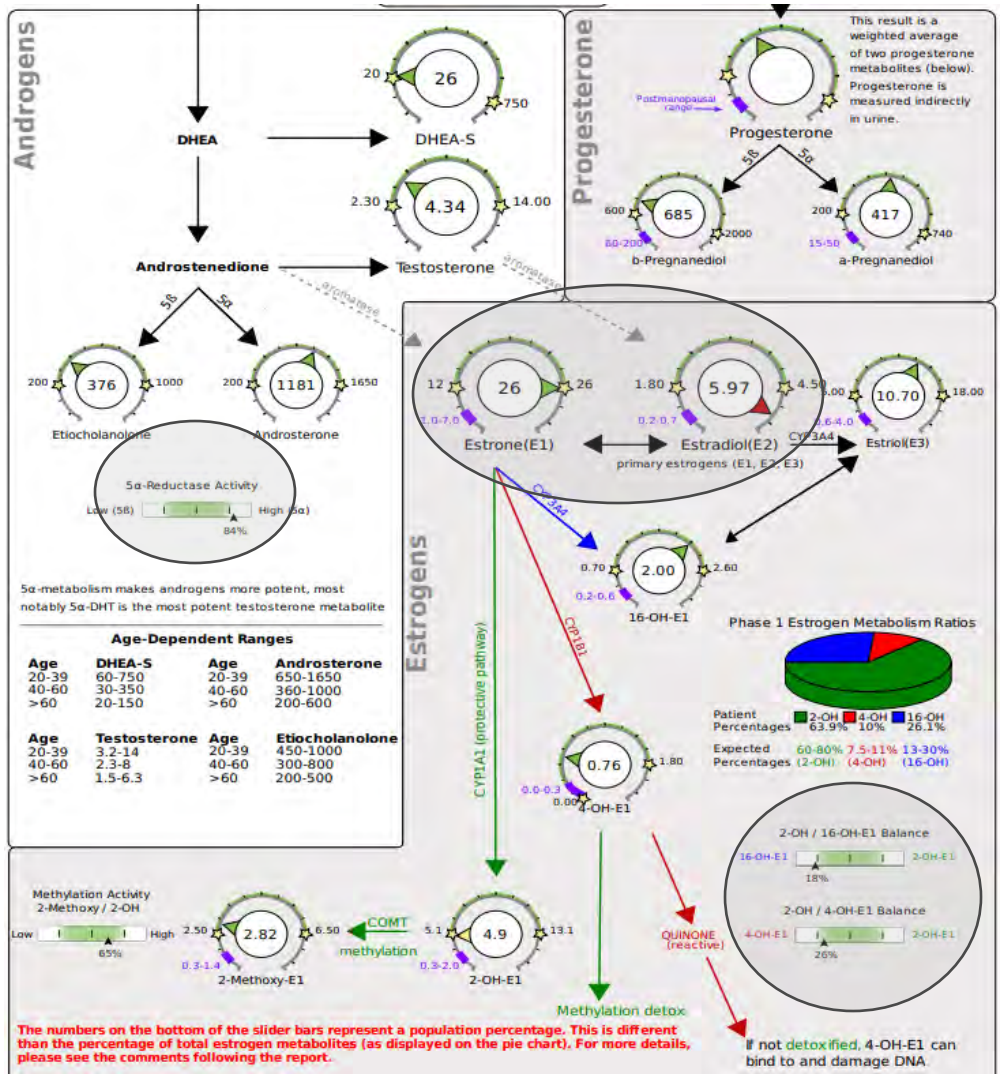
  - [x] High kynurenate
  - [x] High pyroglutamate
  - [ ] High indican
  - [ ] High quinolinate
  - [ ] High 8-OHdG

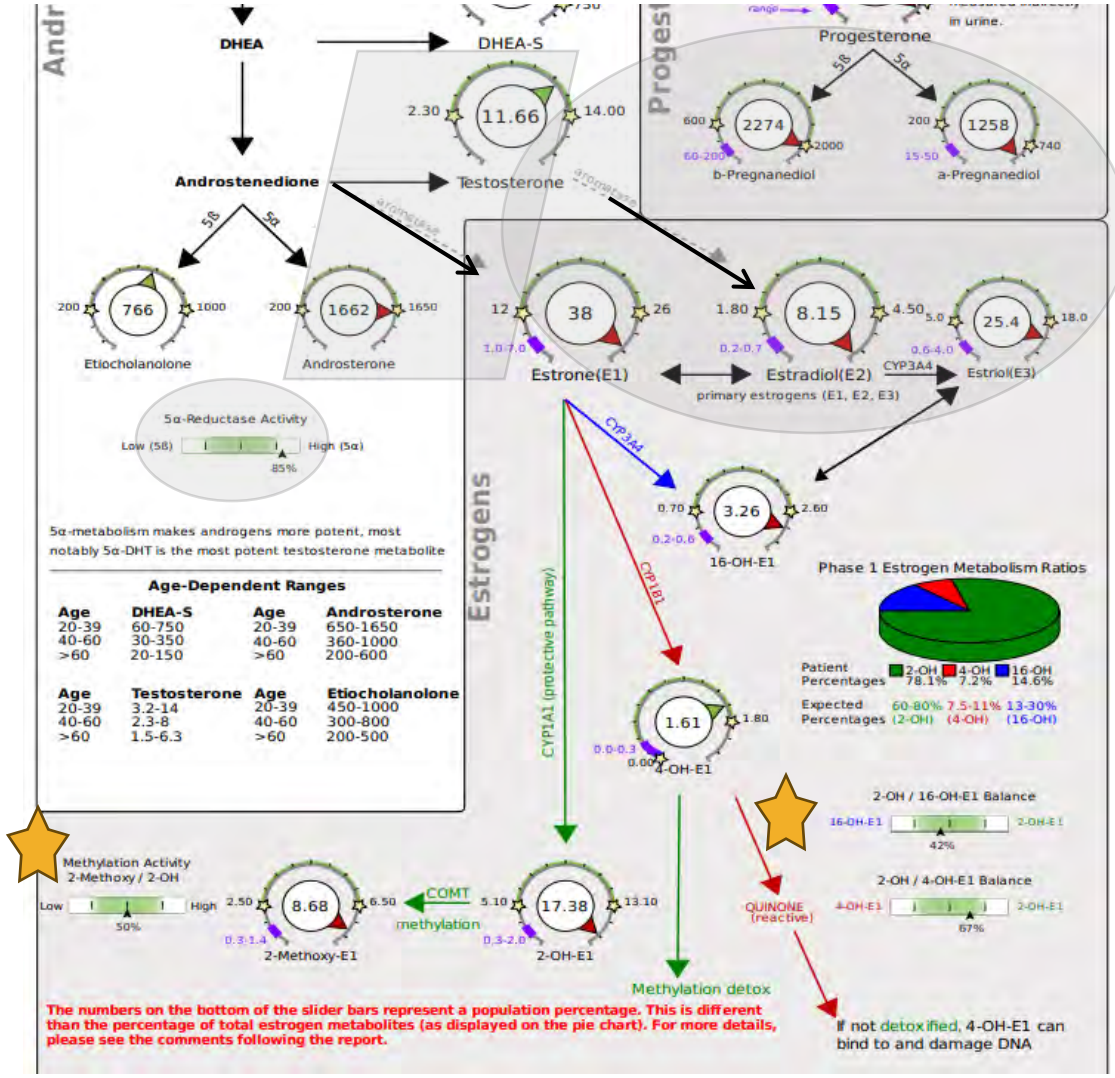
Endometriosis: A Classic Case



All values given in ng/mg creatinine

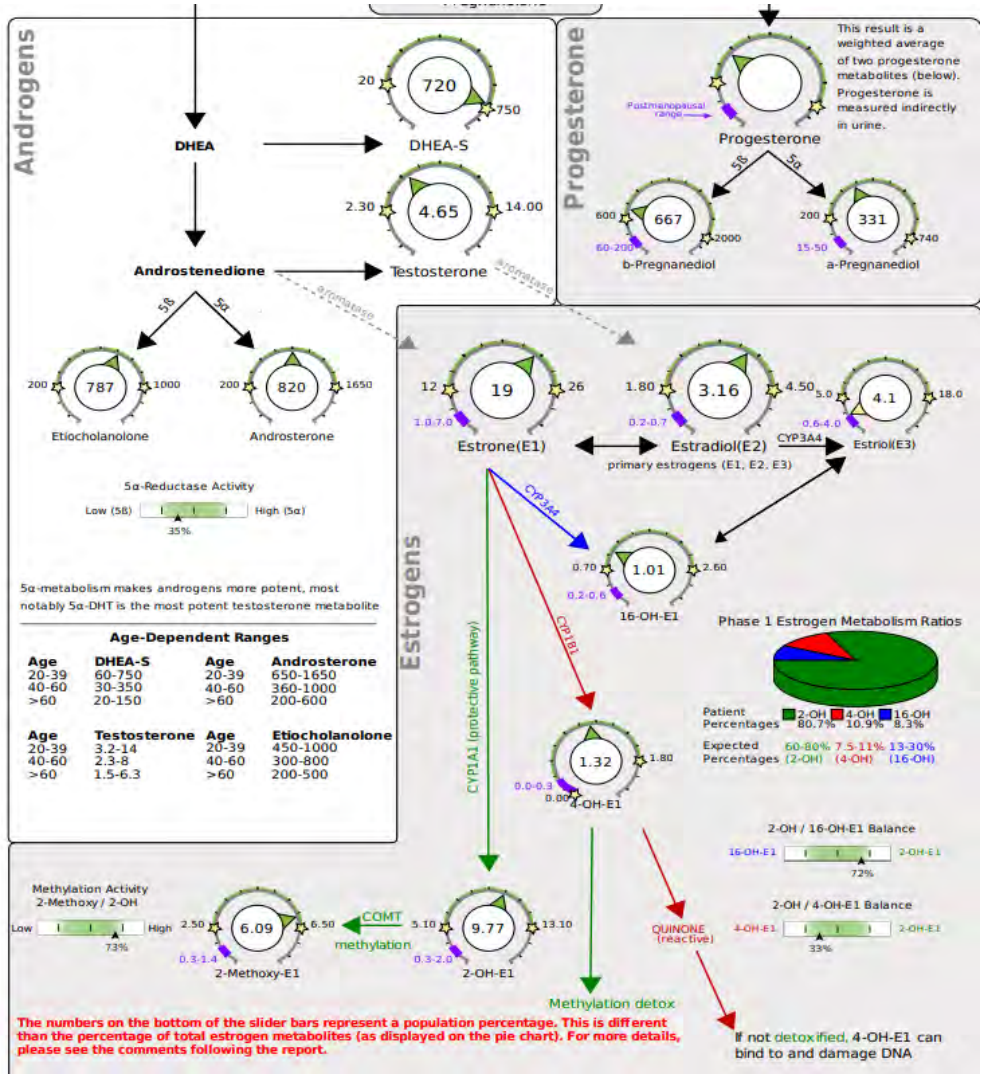


Here is an example of another classic case



- We see robust sex hormones all around
- Relatively speaking the estrogen is still higher than the progesterone
- Higher 5a preference
- Higher- end androgens
- E detox looks good

But what if the results look like a "cold" case?

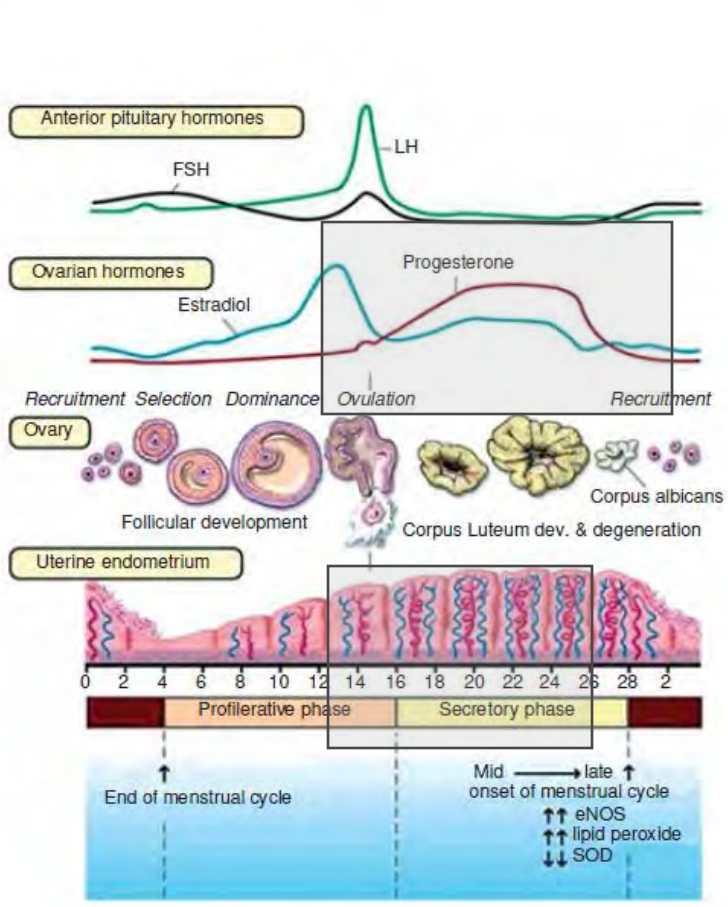


- Normal estrogen and progesterone
- No 5a preference
- Normal estrogen detox

- Now what?

Hormone imbalances: just one of many endometriosis factors

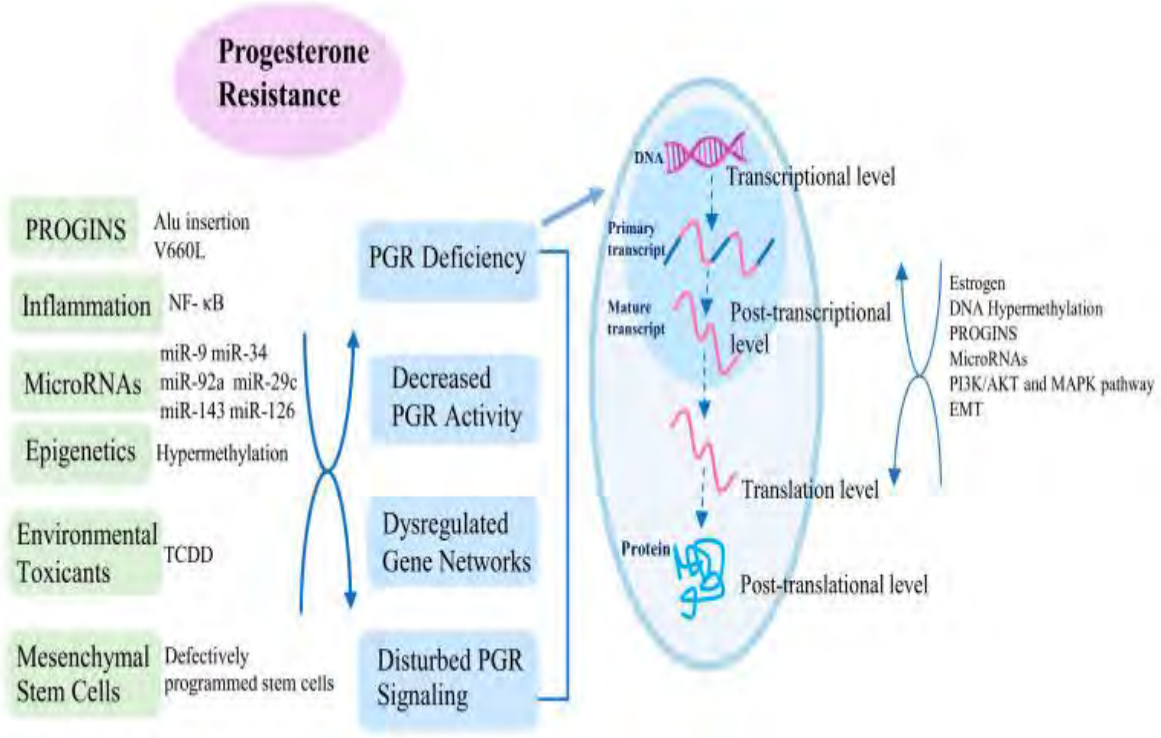
Progesterone and the Endometrium



- Progesterone (Pg) is produced in the ovaries, adrenal cortex, and placenta
- It is critical for embryo implantation, pregnancy maintenance, uterine growth, and mammary gland development
- Has anti-estrogenic effects that suppress endometrial proliferation
- It has decidualizing effects that drive the transition of the endometrium from proliferative to secretory phase
- Essentially it is switching the lining from a growing state to a receptive state

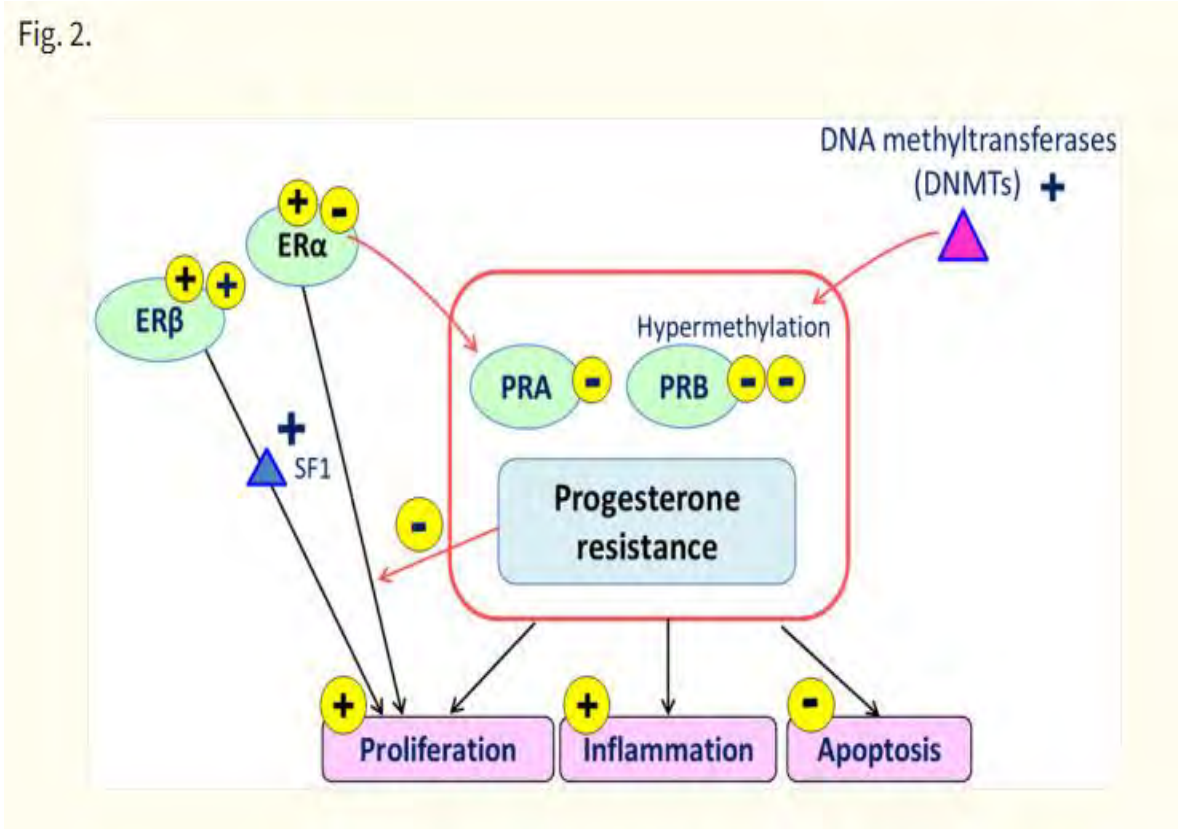
What is Progesterone Resistance?

- Defined as **endometrial** progesterone unresponsiveness with subsequent dysregulation of the progesterone signaling pathway and gene networks in the endometrium, which ultimately leads to attenuated progesterone actions (Zhang, 2023)
- Progesterone resistance has been found in both the endometriotic lesions and endometrial lining in women suffering with endometriosis



What is Progesterone Resistance?

- Pg resistance is the dysregulation of progesterone signaling combined with an endometrial tissue's inability to appropriately respond to progesterone exposure
  - Pg signaling is required to counteract E2-induced proliferation and to promote decidualization
  - In normal endometrium - Pg counteracts E2 action and exhibits anti-proliferative and anti-inflammatory roles
  - The loss of Pg responsiveness leads to both an increased growth of EM lesions and a non-receptive endometrium



Vannuccini, S., Clemenza, S., Rossi, M., & Petraglia, F. (2022). Hormonal treatments for endometriosis: The endocrine background. *Reviews in endocrine & metabolic disorders*, *23*(3), 333–355. https://doi.org/10.1007/s11154-021-09666-w

Progesterone Receptors (PGRs)

- Progesterone (Pg) binds to the PGRs inside the nucleus of the cell
- The effects of Pg are mediated through the PGRs and regulate gene expression
- Two major PGRs are progesterone receptor A (PR-A) and progesterone receptor B (PR-B)
  - Both bind to the same steroid hormones with similar binding activities BUT have different transcriptional activities
- Natural progesterone and synthetic progestin activity both are mediated by PGRs

Progesterone Receptors (PGRs)

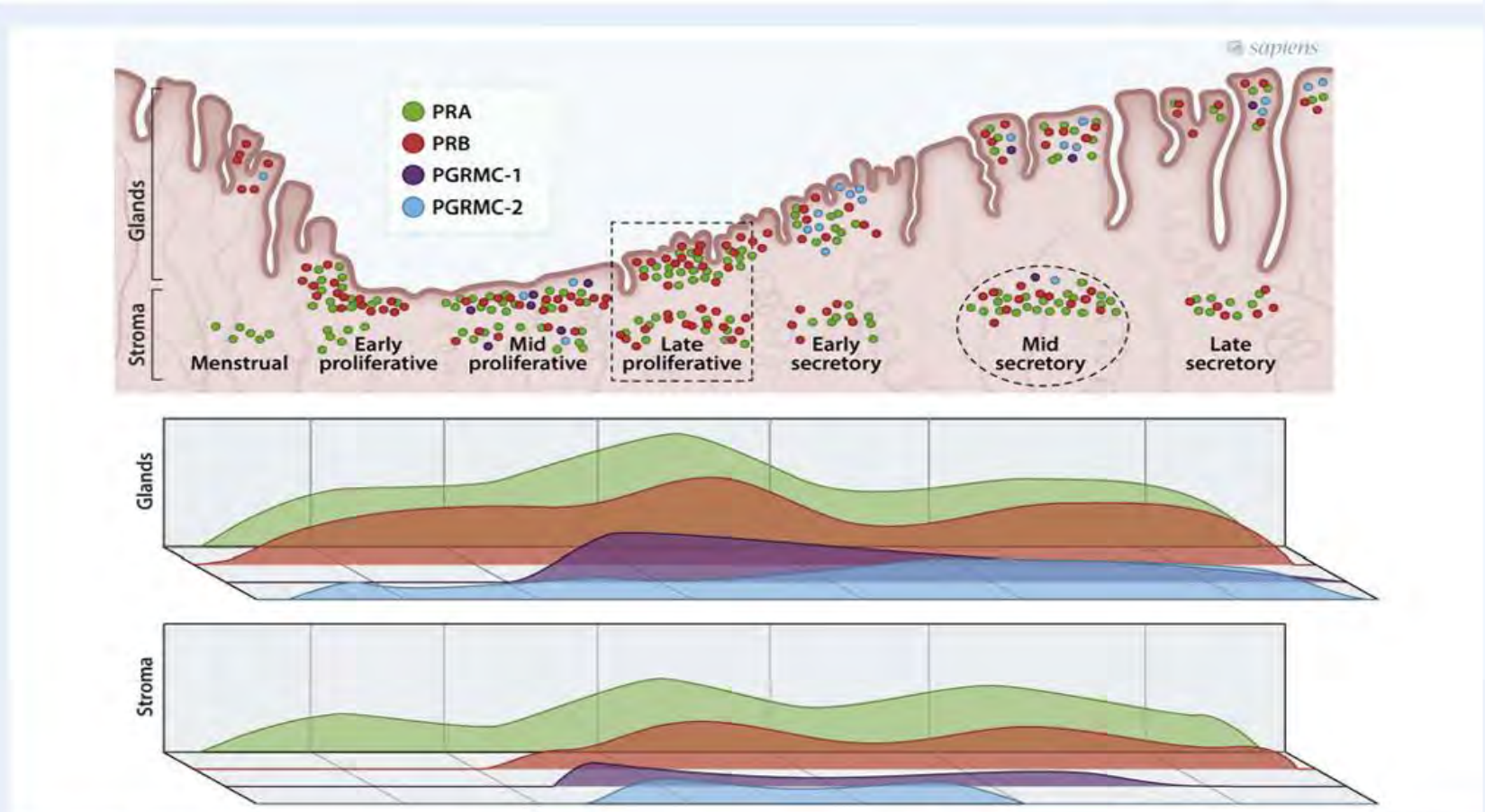


Figure 1 Schematic representation of nuclear progesterone receptors A (PRA) and B (PRB) and membrane receptors PGRMC-1 and PGRMC-2 during the menstrual cycle in human endometrium. The dot density indicates the abundance of the represented molecule at each cycle phase and tissue compartment (glands or stroma), according to immunolocalisation (Bedaiwy *et al.*, 2015; Keator *et al.*, 2012; Mote *et al.*, 1999), western blotting (Bedaiwy *et al.*, 2015), real-time PCR and *in situ* hybridisation (Keator *et al.*, 2012). Note, the maximal expression of PRA and PRB in the late proliferative phase (dotted rectangle) and the transient increase in stromal PRA expression at mid-secretory phase (dotted circle).

Figure from Fernando, et al, 2020

Hormonal alterations in the endometrium due to PR-A and PR-B disruptions

- **PR-A and PR-B are considered opposing systems for target cells to control progesterone responsiveness**

- PR-B has a strong activator transcriptional activity
  - PR-B dominant state promotes progesterone signaling
- PR-A has a weaker activity BUT suppresses the transcriptional activity of PR-B
  - PR-A dominant state decreases progesterone responsiveness

- The higher the PR-A/PR-B ratio = less progesterone responsiveness

Zhang, P., & Wang, G. (2023). Progesterone Resistance in Endometriosis: Current Evidence and Putative Mechanisms. *International journal of molecular sciences*, *24*(8), 6992. https://doi.org/10.3390/ijms24086992

PR-A/PR-B Ratio High in EM Lesions

- PR-B in EM lesions was undetectable
- PR-A was detected in all EM lesions
- PR-A/PR-B ratio high, impairing progesterone activity

JOURNAL ARTICLE

Progesterone Receptor Isoform A But Not B Is Expressed in Endometriosis

Get access

George R. Attia, Khaled Zeitoun, Dean Edwards, Alan Johns, Bruce R. Carr, Serdar E. Bulun

The Journal of Clinical Endocrinology & Metabolism, Volume 85, Issue 8, 1 August 2000, Pages 2897–2902, https://doi.org/10.1210/jcem.85.8.6739

Published: 01 August 2000 **Article history** ▾

PGR-B DNA Hypermethylation – Genetics/Epigenetics

- Increased methylation of the PGR-B gene promotor is related to reduced gene expression
- Increased methylation of PGR-B was only seen in ectopic endometrial cells but not in the eutopic endometrial cells

- Mechanism of action of why PGR-B is being hypermethylated is unknown
  - Speculation is it related to chronic inflammatory environment
  - Increased release of pro-inflammatory cytokines
  - Abnormal expression of micro-RNAs

A Brief Recap

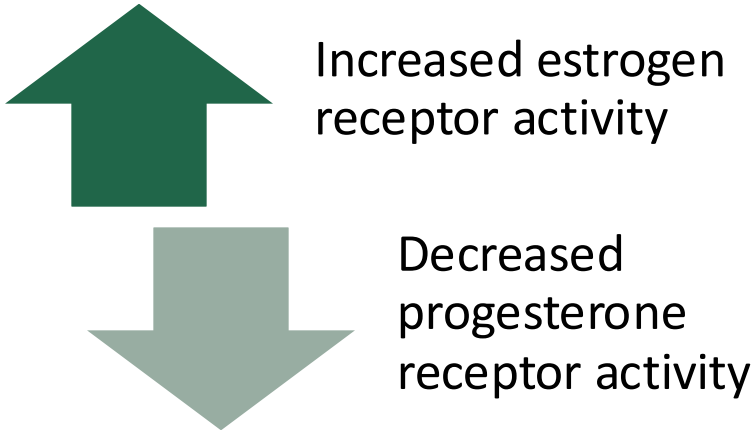
- A higher PR-A/PR-B ratio in EM tissues = a PR-A dominant state
- PR-A dominance = decreased progesterone responsiveness
- PR-B was undetectable in EM lesions = lack of progesterone signaling
- PR-B hypermethylation = decreased gene expression

I thought estrogen and progesterone were friends?

Hormone Imbalances – Estrogen Related Factors

- Serum levels of E2 are not significantly different in EM vs healthy subjects
- Estrogen dominance is caused by a **LOCAL** estrogen synthesis and an increased estrogen receptor (ER) activity in the endometriotic cells
  - An overproduction of E2 in local EM tissue drives ERβ signaling
  - An increased ERβ/ERα ratio has been observed in EM

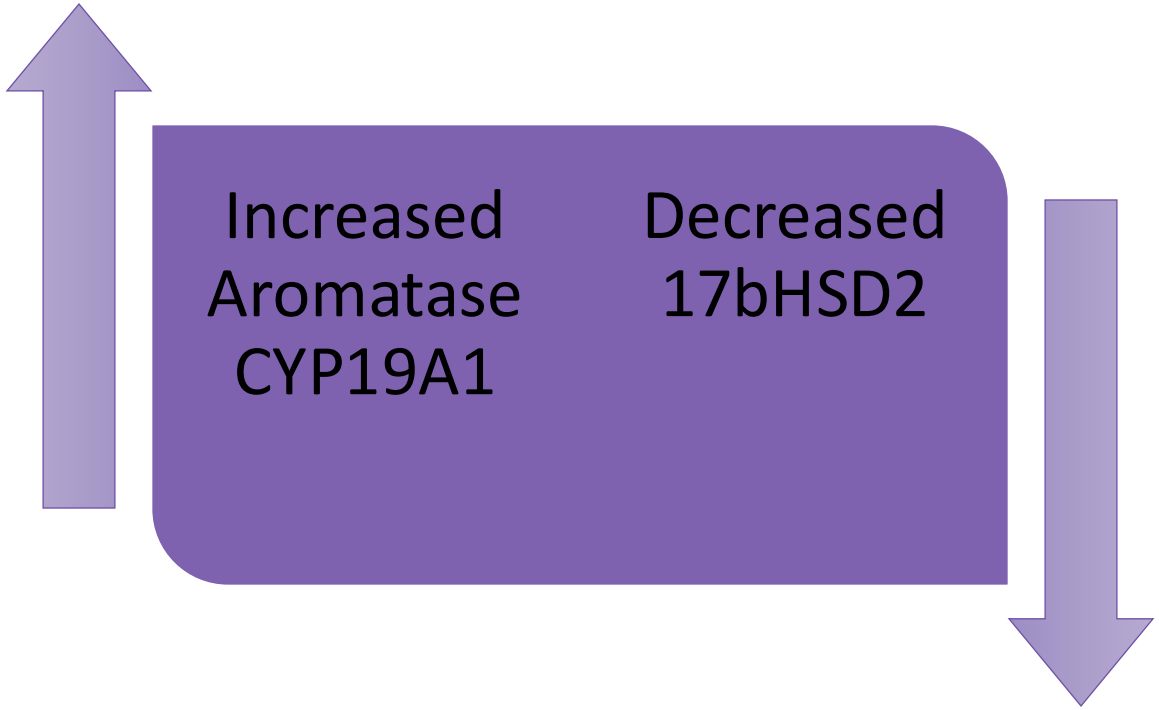
- ERβ triggers pathways that enhance lesion survival, remodel pelvic peritoneal tissue, produce inflammatory substances, stimulate nociceptors in pelvic tissues = **pain**



Hormone Imbalances – Estrogen Related Factors

Circulating hormone levels may be normal when the tissues are promoting local estrogen dominance

Hormone Imbalances – Estrogen Related Factors



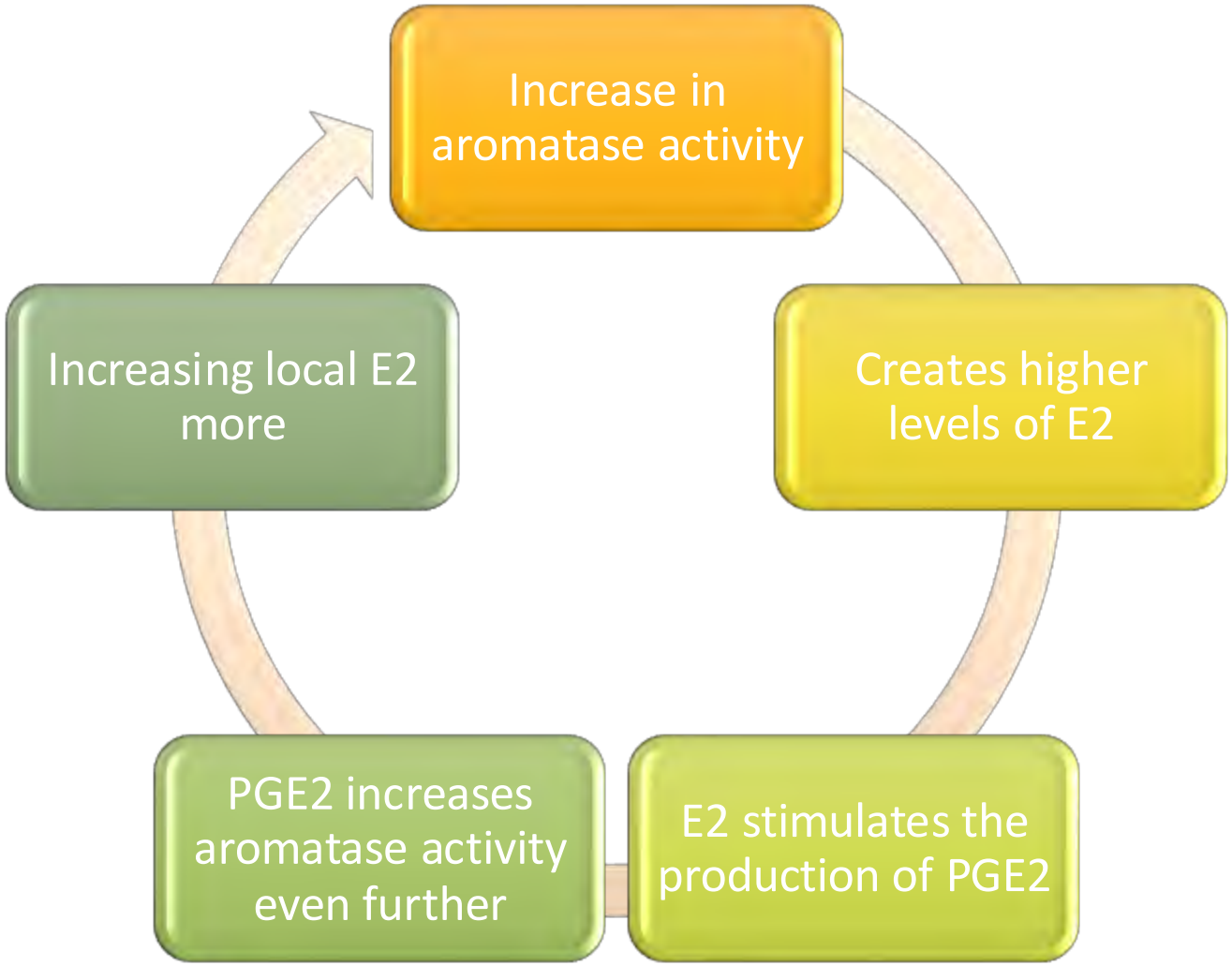
Local E2 levels are **increased in EM due to upregulation of aromatase gene CYP19A1** and **reduction of 17-hydroxysteroid dehydrogenase type 2 (17bHSD2)**

Vannuccini, S., Clemenza, S., Rossi, M., & Petraglia, F. (2022). Hormonal treatments for endometriosis: The endocrine background. *Reviews in endocrine & metabolic disorders*, *23*(3), 333–355. https://doi.org/10.1007/s11154-021-09666-w

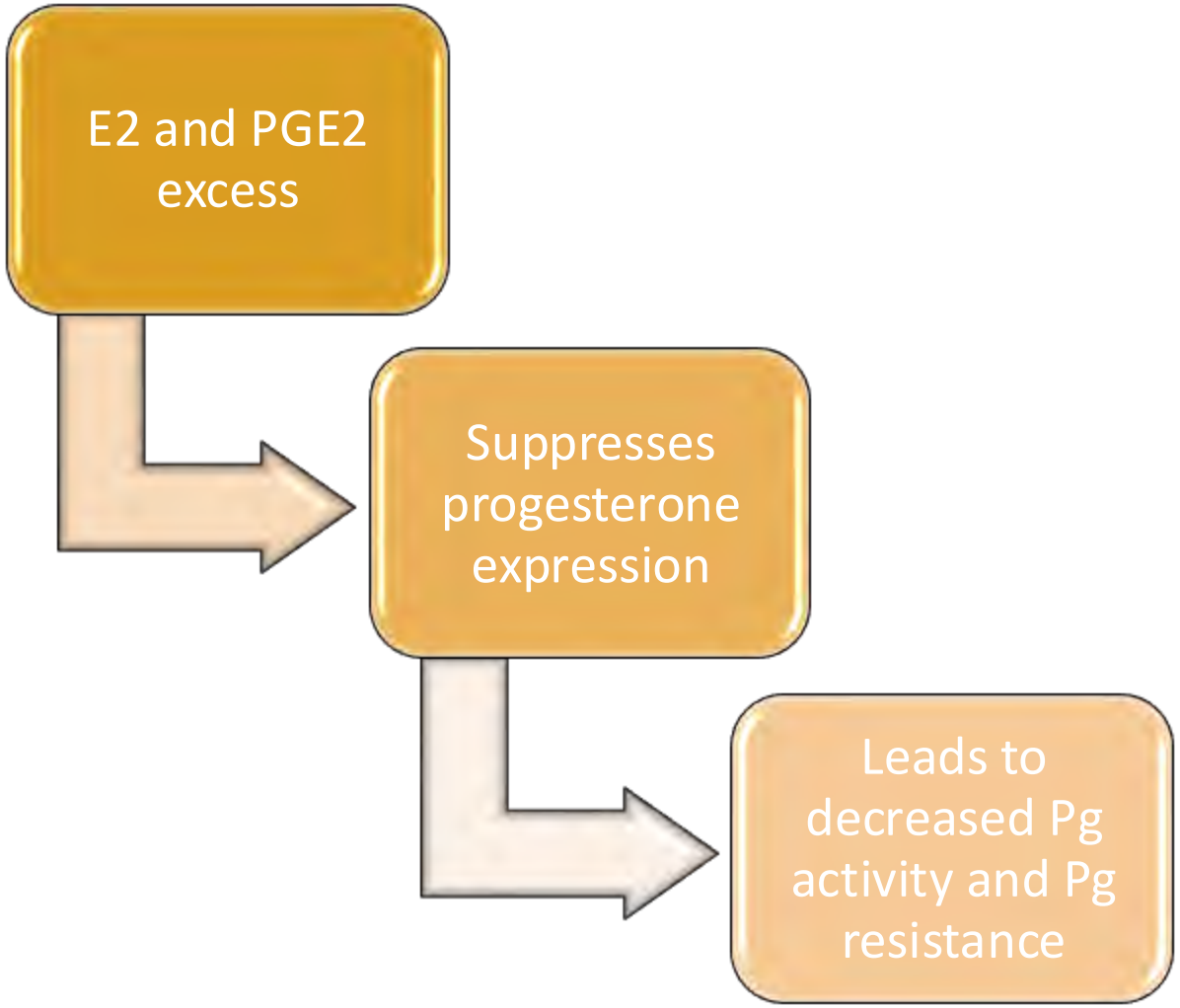
Hormonal Alterations in Endometriotic Tissues in EM

- Increased expression of the aromatase gene CYP19A1 in EM
  - Key enzyme in the conversion of:
    - testosterone → estradiol
    - androstenedione → estrone
- Estradiol stimulates production of prostaglandin E2 (PGE2) → which further stimulates aromatase activity
  - PGE2 plays an important role in survival and growth of EM lesions
  - PGE2 and E2 (ERa and ERb) appear to suppress PR expression leading to loss of Pg action and Pg resistance in endometrial lesions
- Allowing for higher amounts of local production of E2

Hormonal Alterations in Endometriotic Tissues



Hormonal Alterations in Endometriotic Tissues

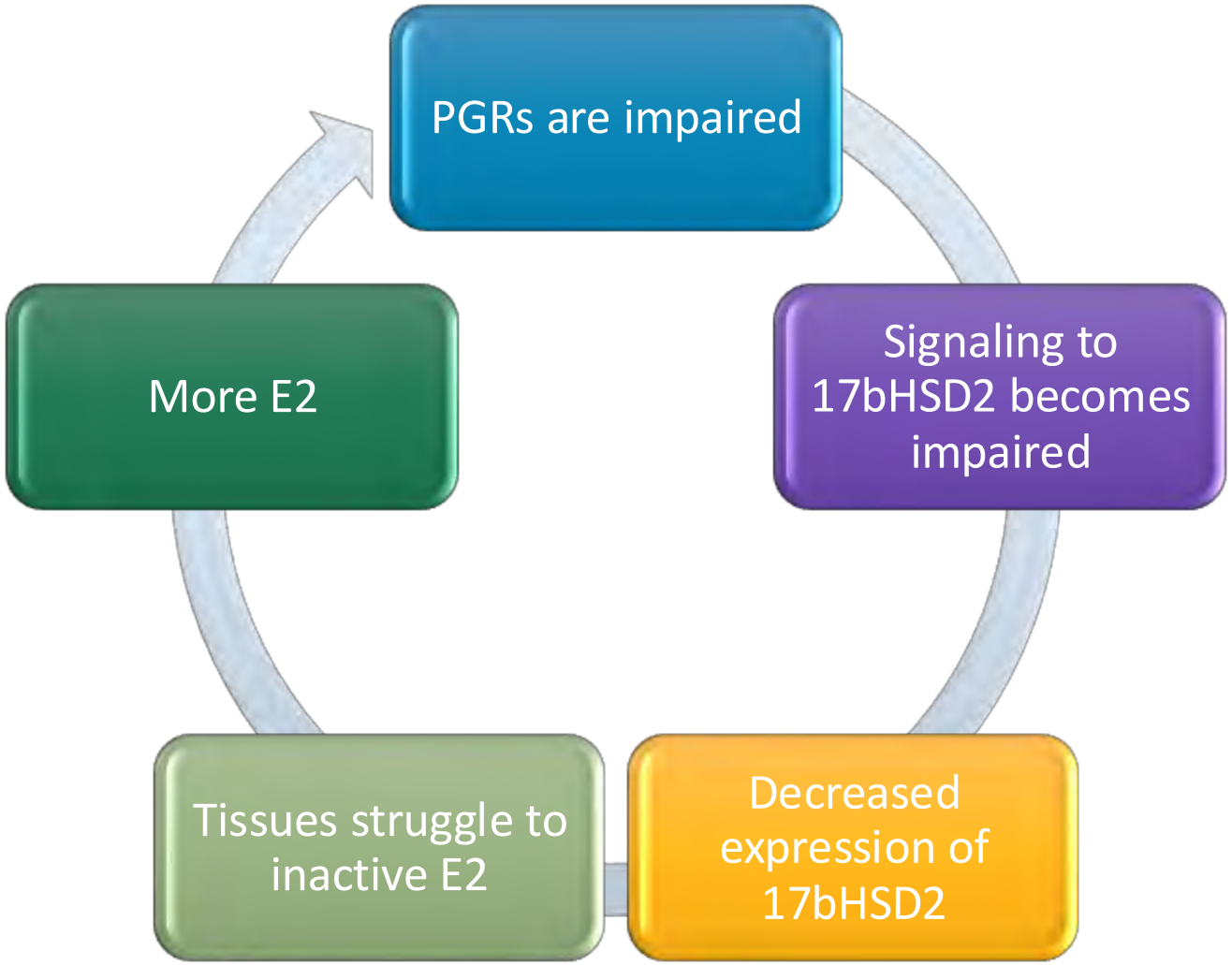


Hormonal Alterations in Endometriotic Tissues

- 17bHSD2 is induced by progesterone
  - Progesterone acts on progesterone receptors (PGRs) on stromal cells to induce a cascade of events that lead to the expression of the enzyme 17bHSD2
  - 17bHSD2 primary function is to convert E2 (potent) into E1(weak), reducing the **local** availability of E2
  - Particularly in the secretory phase of the menstrual cycle when progesterone levels are high

- In EM there is a **decreased expression of 17β-HSD2** → resulting in impaired inactivation of E2 → **More E2**

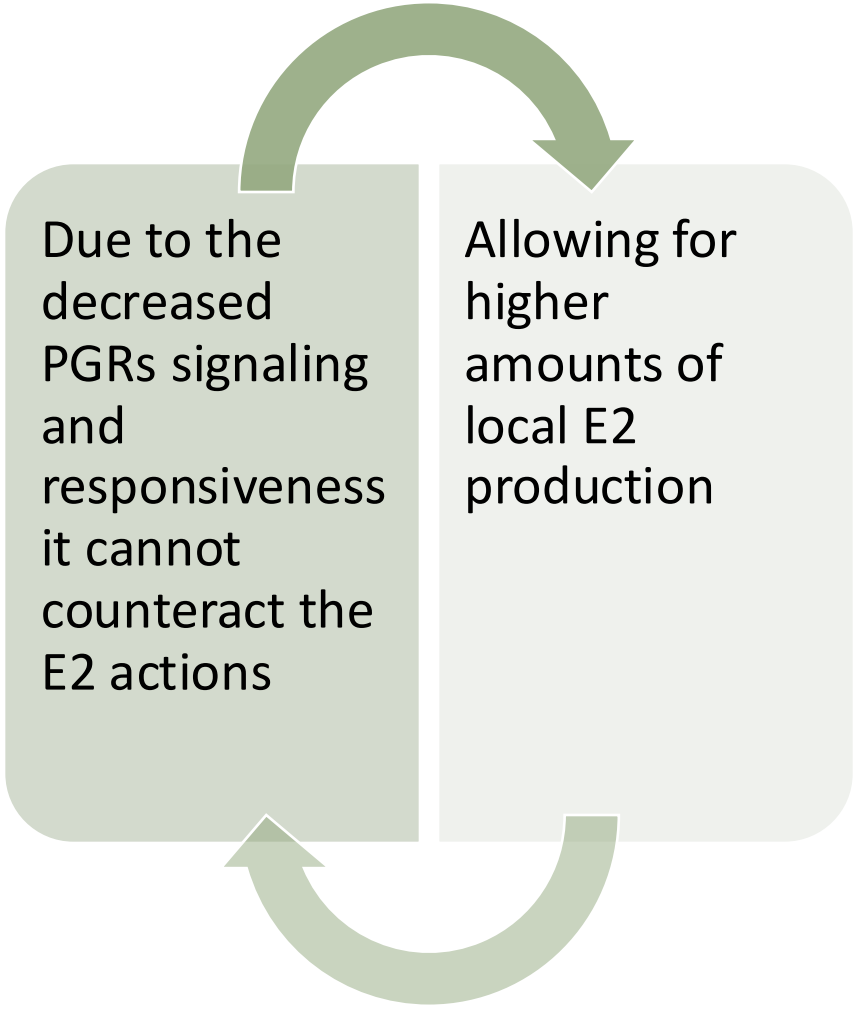
Hormonal Alterations in Endometriotic Tissues



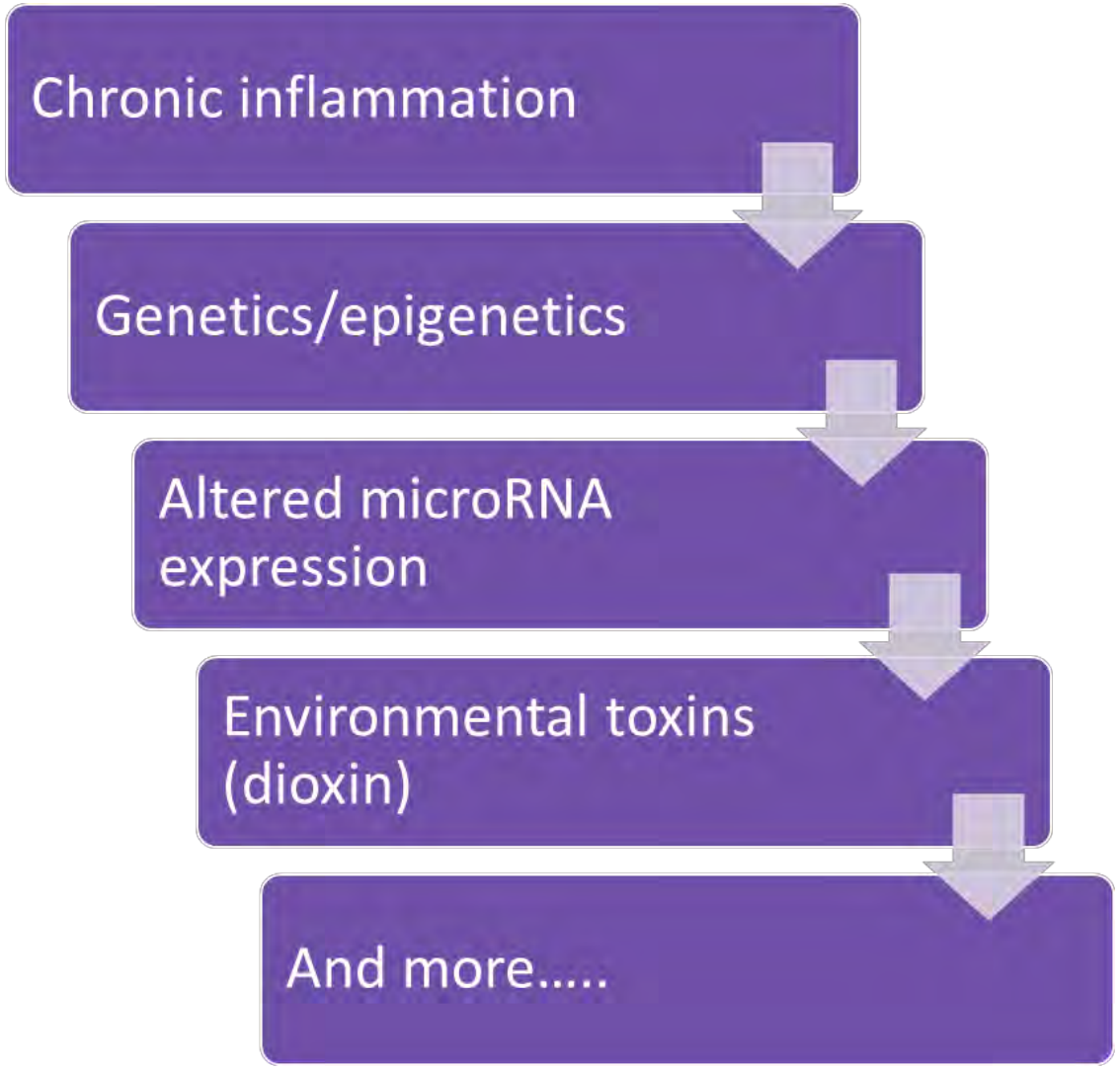
A Recap of Local Estrogen Production in EM

Promote EM Lesion growth	Mechanism
Aromatase (CYP19A1)	Converts androstenedione to E1 and testosterone to E2
Estradiol	E2 acts directly on EM lesions E2 stimulates the production of PGE2, which further stimulates aromatase E2 and PGE2 appear to suppress progesterone expression
Less 17βHSD2	Converts E2 to the less potent E1 Impaired or reduced 17βHSD2 fails to inactivate E2
PGE2	Stimulates aromatase PGE2 is made by E2 E2 and PGE2 appear to suppress progesterone expression
Impaired PGRs	Less progesterone activity leads to more unchecked E2 activity (Less 17BHSD2)
PR-A dominance	PR-A dominance leads to weak and ineffective progesterone activity

In Other Words



Other Factors Contributing to Progesterone Resistance



If progesterone resistance is a factor, then why are progestins the first-line treatment?

Progestins are NOT the Same as Progesterone

- Progestins are considered first-line treatment in EM
  - These are synthetic compounds that mimic the effects of progesterone by binding to its receptors
- Synthetic progestins have longer half-lives (several hours) compared to endogenous progesterone (5 to 7 mins)
- They have different impacts due to different chemical structures, metabolism, pharmacokinetics, binding affinities
  - Natural progesterone may not control symptoms to the degree progestins can

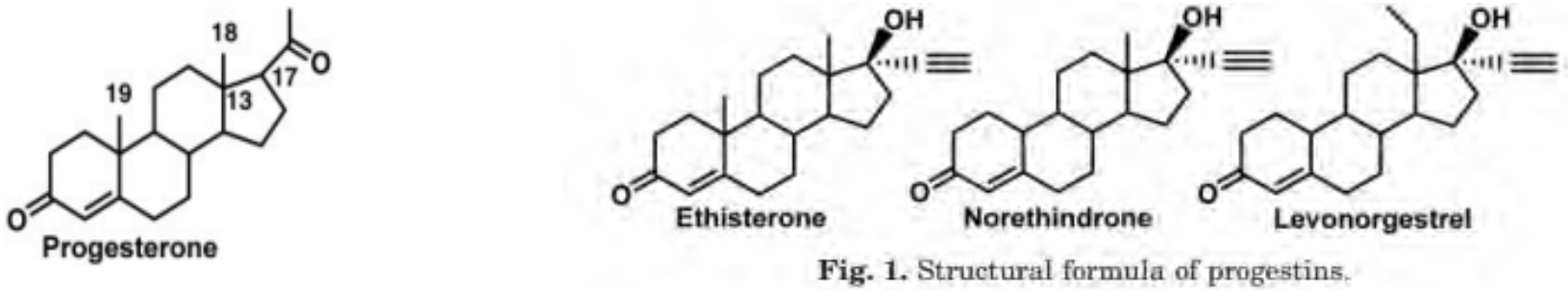


Fig. 1. Structural formula of progestins.

Image Citation: Petit-Topin, Isabelle & Turque, Nathalie & Fagart, Jérôme & Fay, Michel & Ulmann, André & Gainer, Erin & Rafestin-Oblin, Marie-Edith. (2009). Met909 Plays a Key Role in the Activation of the Progesterone Receptor and Also in the High Potency of 13-Ethyl Progestins. Molecular pharmacology. 75. 1317-24. 10.1124/mol.108.054312.

One third of women globally remain symptomatic with progestin use

PGRs lower in patients that did not respond to progestins

- Patients that did not respond to progestin-based therapies had significantly lower PGR levels than those who did respond
- Proposing the PGR status is strongly associated with response to progestin-based therapy

ENDOCRINE SOCIETY JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

J Clin Endocrinol Metab. 2018 Oct 23;103(12):4561–4568. doi: 10.1210/jc.2018-01227

Progesterone Receptor Status Predicts Response to Progestin Therapy in Endometriosis

Valerie A Flores [1,✉], Arne Vanhie [1], Tran Dang [1], Hugh S Taylor [1]

Author information · Article notes · Copyright and License information

PMCID: PMC6226602 PMID: 30357380

Abstract

Context

Progestin-based therapy is the first-line treatment for managing endometriosis-associated pain. However, response to progestins is currently variable and unpredictable. Predictive markers for response to progestin-based therapy would allow for a personalized approach to endometriosis treatment.

Types of Progestins

Pregnanes

- Medroxyprogesterone acetate, nomegestrol acetate

Estranes

- Norethindrone, norethindrone acetate (NETA), ethynodiol diacetate, norethynodrel
- More androgenic than gonanes

Gonanes

- Levonorgestrel, desogestrel, norgestimate, gestodene
- Commonly used in combination with estrogen – COC – for hyperandrogenism from PCOS or NCCAH

- Progestins can be categorized based on structural properties
- 3 major groups
  - Pregnanes
  - Estranes
  - Gonanes

Mechanisms of Hormonal Treatments

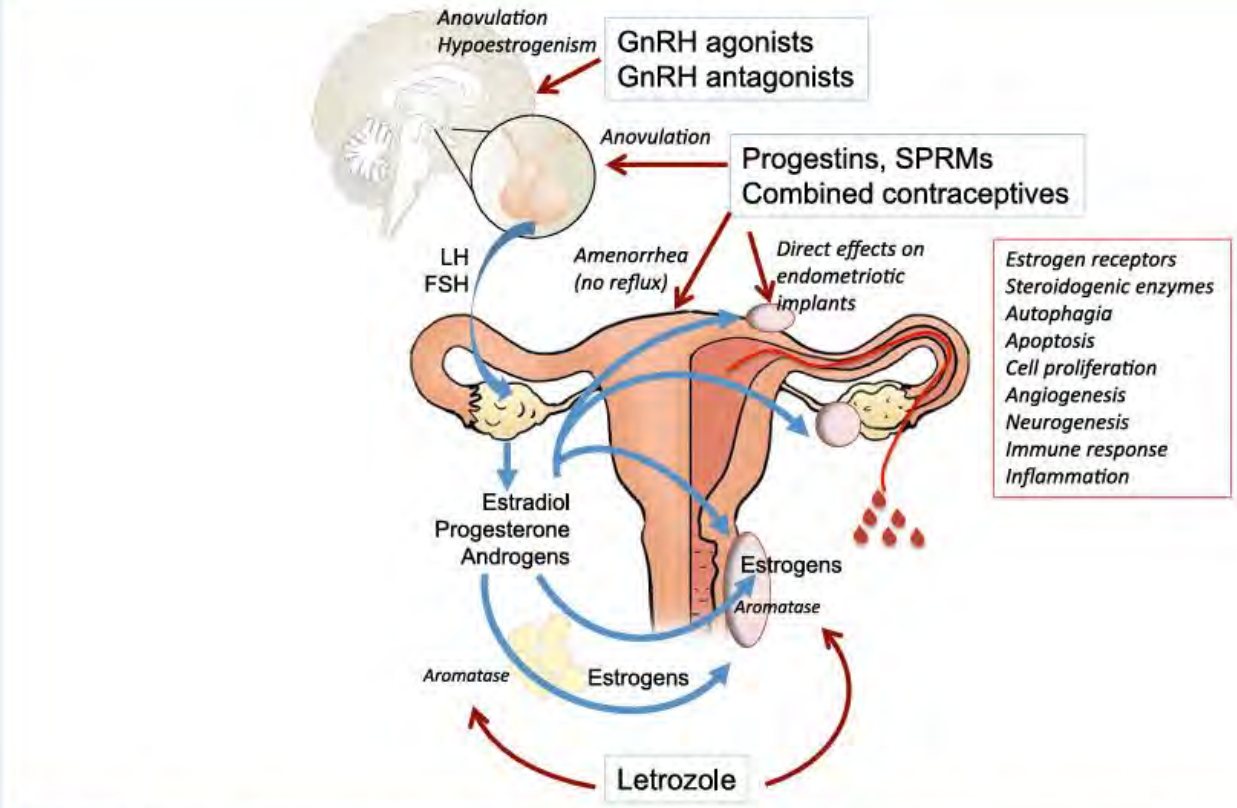


Figure 2 Therapeutic mechanisms of hormonal treatments for endometriosis. Progestins, selective progesterone receptor modulators (SPRMs) and combined contraceptives block ovulation through central inhibition of gonadotropin release, induce amenorrhea which prevents repeated menstrual reflux and have many direct effects on endometriotic implants. Gonadotropin-releasing hormone (GnRH) agonists and antagonists block ovulation and induce hypoestrogenism, while aromatase inhibitors such as letrozole reduce androgen aromatisation into estrogens, both in the adipose tissue and within endometriotic lesions.

Figure from Fernando, et al, 2020

Why not use natural or micronized progesterone instead of progestins?

Natural Progesterone or Micronized Progesterone

- There is not enough research supporting the use of micronized progesterone to control EM
- If used, simultaneous ovarian suppression may likely be necessary
- Cyclical use, for fertility benefits, has limited to no research supporting its ability to control EM
- Pharmacokinetics of oral, vaginal, or transdermal Pg are very different

Oral Micronized Progesterone

- Oral micronized progesterone (OMP):
  - OMP is not expected to provide stable progesterone levels throughout the day due to rapid pharmacokinetics.
  - Despite rapid pharmacokinetics, OMP provides the following benefits:
    - **Endometrial decidualization** (stabilizes endometrial growth, reduces heavy bleeding, hyperplasia, and the risk of endometrial cancer).
    - Reduces estrogen receptors and receptor functionality, **limiting the effects of high estrogens.**
    - Provides feedback to the hypothalamic-pituitary complex to **suppress FSH**, reducing the excess FSH seen with ovarian aging.
    - Promotes **diuresis**, reducing a feeling of "bloating" (a common complaint in perimenopause).
      - Bloating is also a common side effect of OMP use, unfortunately.
    - As part of first-pass metabolism, oral progesterone is metabolized via 5a-reductase and 5b-reductase. The 5a pathway makes alpha metabolites which act as GABA-A agonists in the brain, promoting calm mood and sleep. This is why OMP is taken at bedtime.

Memi E, et al. 2024;25(4):751-772.

Vaginal Micronized Progesterone

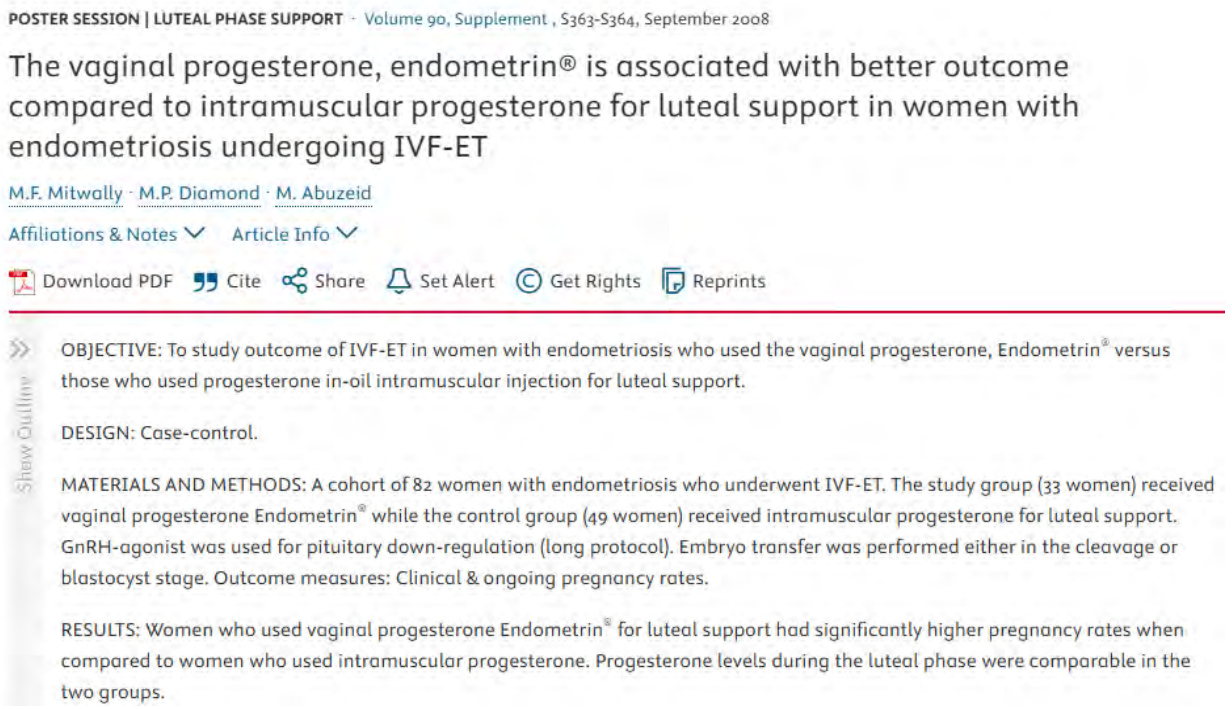
Considerations: Vaginal micronized progesterone (VMP)

- OMP is not tolerated by everyone.
  - Symptoms such as bloating, fatigue, and depression are not uncommon with oral progesterone.
- In these cases, off-label use of **vaginal** micronized progesterone (VMP) may be considered for increasing progesterone levels in the uterus and possibly surrounding tissues.
- **Note that VMP is intended to be inserted into the upper third portion of the vaginal vault to take advantage of the uterine first pass effect. Labial application of progesterone will not increase uterine concentrations to the same degree.**

- With this said, research on VMP for EM is limited and mostly related to fertility outcomes; More evidence is needed to establish the optimal dose and duration of VMP for EM.

Vaginal progesterone and positive IVF outcomes

- CONCLUSIONS: In women with endometriosis undergoing IVF-ET using a GnRH-agonist protocol, luteal support with vaginal progesterone Endometrin® was associated with significantly higher pregnancy rates when compared to those who used intramuscular progesterone luteal support
- This study does not address if vaginal progesterone helps control EM – but still worth noting routes of administration may have better outcomes
- Other studies show that vaginal progesterone may improve or normalize nCyclinE expression in the endometrium and that is why fertility improved



POSTER SESSION | LUTEAL PHASE SUPPORT · Volume 90, Supplement , S363-S364, September 2008

The vaginal progesterone, endometrin® is associated with better outcome compared to intramuscular progesterone for luteal support in women with endometriosis undergoing IVF-ET

M.F. Mitwally · M.P. Diamond · M. Abuzeid

Affiliations & Notes · Article Info

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Show Outline

OBJECTIVE: To study outcome of IVF-ET in women with endometriosis who used the vaginal progesterone, Endometrin® versus those who used progesterone in-oil intramuscular injection for luteal support.

DESIGN: Case-control.

MATERIALS AND METHODS: A cohort of 82 women with endometriosis who underwent IVF-ET. The study group (33 women) received vaginal progesterone Endometrin® while the control group (49 women) received intramuscular progesterone for luteal support. GnRH-agonist was used for pituitary down-regulation (long protocol). Embryo transfer was performed either in the cleavage or blastocyst stage. Outcome measures: Clinical & ongoing pregnancy rates.

RESULTS: Women who used vaginal progesterone Endometrin® for luteal support had significantly higher pregnancy rates when compared to women who used intramuscular progesterone. Progesterone levels during the luteal phase were comparable in the two groups.

Transdermal Progesterone

Transdermal (TD) Progesterone:

- There are no FDA-approved TD progesterone products.
- In Wren et al. 2000, it was found that TD progesterone **should not be used to protect the endometrium from hyperplasia.**
- In Leonetti et al. 2003, although some endometrial changes were noted with TD Pg the authors concluded that the study was too small and too short to make clinical conclusions.
- There have been **no long-term studies that support the use of TD progesterone for endometrial protection or endometriosis.**

Leonetti HB, et al. Obstet Gynecol. 1999;94(2):225-228.
Leonetti HB, et al. Fert Sterility. 2003;79(1):221-222.
Stute P, et al. Climacteric. 2016;19(4):316-328.
Vashisht A, et al. Gynecol Endocrinol. 2005;21(2):101-105.
Wren BG, et al. Cliimacteric. 2000;3(3):155-160.

Common Treatments

Medical Treatment Alternatives for EM-Associated Pain

Medical treatment	Indication	Priority	Adverse effects and complications	Comment
NSAID	Dysmenorrhea	First	Nausea, vomiting, GI irritation, vertigo, headache	
Combined oral contraceptives				
Cyclic	Dysmenorrhea	First	Nausea, weight gain, water retention, depression, intercyclic bleeding, breast tenderness, headache, decrease in menstrual bleeding	
Continuous	Dysmenorrhea Noncyclic chronic pelvic pain	Second	Nausea, weight gain, water retention, depression, intercyclic bleeding, breast tenderness, headache, amenorrhea	
Progestins				
MPA, NETA, CPA, DNG	Dysmenorrhea Noncyclic chronic pelvic pain	Second	Nausea, weight gain, water retention, depression, intercyclic bleeding, breast tenderness, headache, amenorrhea, delay in regulation of menstrual pattern	
LNG-IUS	Dysmenorrhea Dysparonia	Second or third	Bloating, weight gain, headache, breast tenderness	Effective in symptomatic rectovaginal endometriosis, Not approved for endometriosis by US FDA
GnRH agonists	Dysmenorrhea Dysparonia	Second or third	Hypoestrogenism (vasomotor symptoms, vaginal dryness, decrease in libido, irritability, decrease in bone mineral density)	Approved for endometriosis by FDA
Aromatase inhibitors	Dysmenorrhea Noncyclic chronic pelvic pain	Third	Hypoestrogenism ovulation induction	Should be combined with COC or GNRHa; Not approved for endometriosis by FDA
Danazol	Dysmenorrhea Noncyclic chronic pelvic pain	Second or third	Hyperandrogenism (acne, edema, decrease in breast size)	

Table from Gezer A, Oral E. Progestin Therapy in Endometriosis. *Women's Health*. 2015;11(5):643-652. doi:10.2217/whe.15.42

Medical Treatment Alternatives for EM-Associated Pain

Orilissa (Elagolix)

- Oral tablet, 150mg once a day or 200mg twice a day
- GnRH antagonist
- Approved for 6months at the higher dose
- Approved for 2 years at the lower dose
- Discontinue at recommended length of time due to BMD loss concerns
- Not a contraceptive

Newer Novel Treatment

Myfembree

- Combo of relugolix – a GnRH antagonist, estradiol, and norethindrone acetate
- Indicated for heavy bleeding and mod-to-severe pain with EM
- Tx limited to 24 months
- Newer, approved in 2022, limited long-term and safety data available
- Not a contraceptive

Okay but that progestin treatment did not work – what now?

- Change the type of progestin
- Switch from cyclic OCP to continuous
- Switch routes of administration
  - oral, IM, vaginal, IUD, etc.
- Switch regimen
  - POP, COC, IUD, GnRH agonist or antagonist, etc.
- Combine therapies
  - Ex: IUD with NETA add-back therapy

- **Important: Work on other factors that can improve immune, inflammation, oxidative stress, etc.**
  - Multi-systems approach – include GI, pain management, pelvic floor rehab, acupuncture, diet and lifestyle changes

What about other treatments to consider if 1/3 of women do not respond to progestins?

Investigational Non-steroidal Therapies

▸ Biomolecules. 2022 Nov 8;12(11):1654. doi: 10.3390/biom12111654

Emerging Drug Targets for Endometriosis

Marie-Madeleine Dolmans [1,2], Jacques Donnez [3,4,*]

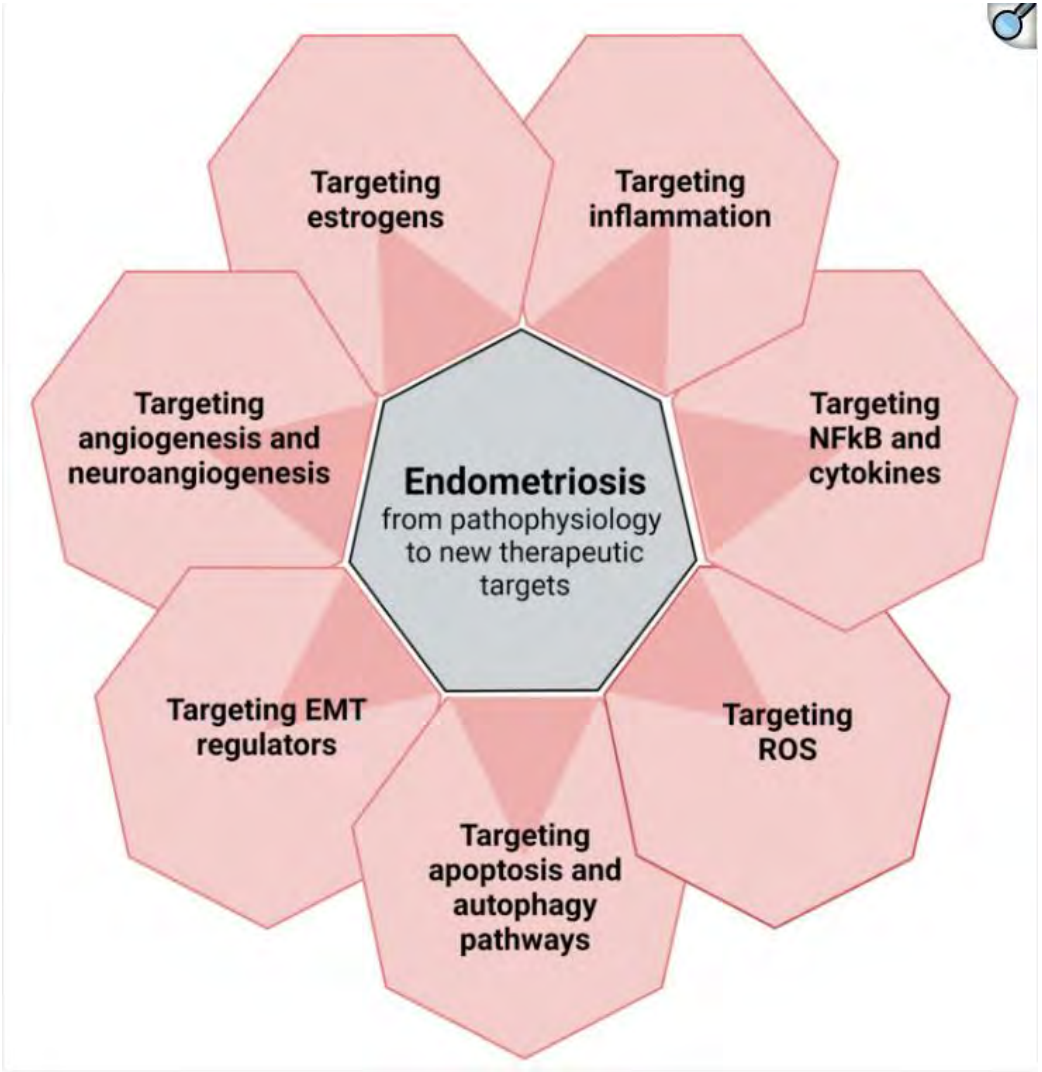
Editors: Jacqueline F Donoghue, Kazuhiro Tamura

▸ Author information ▸ Article notes ▸ Copyright and License information

PMCID: PMC9687824 PMID: 36359004

Abstract

Endometriosis is a chronic inflammatory disease causing distressing symptoms and requiring a life-long management strategy. The objective of this review is to evaluate endometriosis-related pathways and identify novel therapies to treat it. We focused on the crucial role of inflammation and inflammatory molecules in order to define new perspectives for non-hormonal treatment of the disease by targeting inflammation, nuclear factor kappa B and cytokines, or reactive oxygen species, apoptotic and autophagic pathways, regulators of epithelial-mesenchymal transition, and angiogenesis and neuroangiogenesis. Novel non-steroidal therapies targeting these pathways for endometriosis were explored, but multiple challenges remain. While numerous agents have been investigated in preclinical trials, few have reached the clinical testing stage because of use of inappropriate animal models, with no proper study design or reporting of preclinical strategies. Targeting estrogens is still the best way to control endometriosis progression and inflammation.



Investigational Therapies – Not FDA approved for EM

- **Aromatase Inhibitors**
  - Their action is based on the reduction of local estrogen and prostaglandins in endometriotic implants by inhibiting aromatase P450
  - Not FDA approved for EM
  - Some are considering use in combination with COC, progestins, or GnRH agonists for treatment-resistant rectovaginal EM (off-label)
  - High side effect profile
    - menopausal symptoms, hot flashes, decreased libido, joint pain, atrophy, significant reduction in BMD
  - Add-back therapy with Norethindrone acetate (NETA) may help alleviate some symptoms and preserve BMD.

Elbasueny, B., Geerts, M., Yang, E.C., Allaire, C., Yong, P.J., & Bedaiwy, M.A. (2023). Medical treatments of endometriosis: a review. Reproductive and developmental medicine, 7(3) 166-179.

Investigational Therapies – Not FDA Approved for EM

Metformin

- Inhibits PGE2 from inducing CYP19A1 → decreasing aromatase activity
- Decreasing secretion of inflammatory markers
- Inhibits angiogenesis (growth of new vessels)
- Associated with lower adhesions
- Positive effects on the gut microbiome
- Mainly rat studies
- Some studies using co-therapy with Letrozole

cancers MDPI

Cancers (Basel). 2022 Jan 24;14(3):577. doi: 10.3390/cancers14030577

Metformin as a Potential Treatment Option for Endometriosis

Żaneta Kimber-Trojnar [1], Dominik Franciszek Dłuski [1,*], Magdalena Wierzchowska-Opoka [1], Monika Ruszała [1], Bożena Leszczyńska-Gorzelak [1]

Editor: Takashi Kojima[1]

Author information · Article notes · Copyright and License information

PMCID: PMC8833654 PMID: 35158846

Abstract

Simple Summary

The aim of this article is to present current knowledge regarding the possibilities of using metformin in the pharmacological treatment of endometriosis. Metformin is an insulin

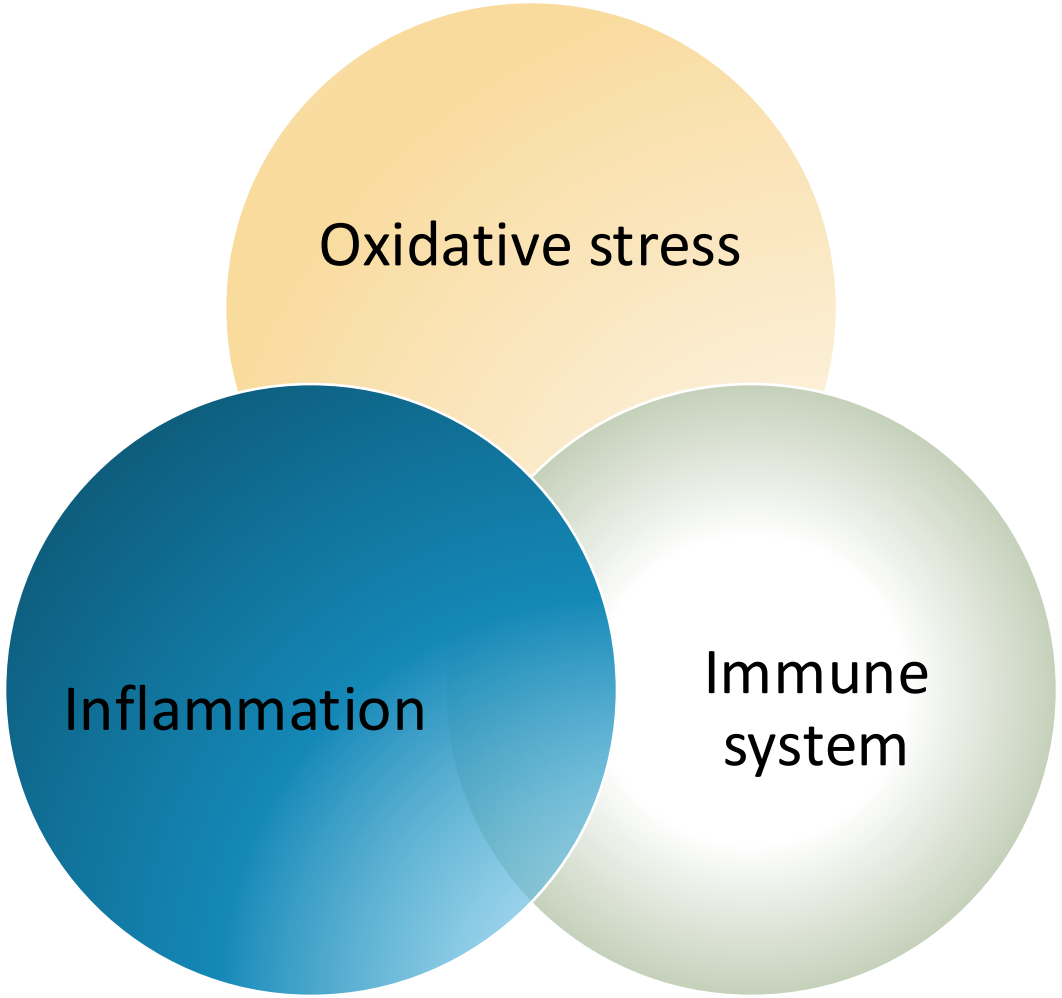
Investigational Therapies – Not FDA Approved for EM

Low-dose Naltrexone (LDN)

- Use in chronic pain and autoimmune diseases
- At low doses stimulates endorphin release
- Modulates immune cell function
- In PCOS studies, LDN was noted to decrease BMI, insulin, LH/FSH, and T levels, resulting in a 33% pregnancy rate.
- In pelvic pain syndrome, LDN therapy showed a reduction in symptoms without compromising fertility

Maksym, R. B., Hoffmann-Młodzianowska, M., Skibińska, M., Rabijewski, M., Mackiewicz, A., & Kieda, C. (2021). Immunology and Immunotherapy of Endometriosis. *Journal of clinical medicine*, *10*(24), 5879. https://doi.org/10.3390/jcm10245879

Find targeted therapies



Curcumin

- Vascular endothelial growth factor (VEGF) is a protein that stimulates the growth of blood vessels
- A decreased expression of VEGF was noted in patients that used Curcumin 50 µmol/l

Mol Med Rep. 2017 Oct;16(4):5611-5617. doi: 10.3892/mmr.2017.7250. Epub 2017 Aug 14.

Inhibitory effect of curcumin in human endometriosis endometrial cells via downregulation of vascular endothelial growth factor

Hong Cao [1], Yu-Xi Wei [1], Qi Zhou [2], Ying Zhang [2], Xiao-Peng Guo [3], Jun Zhang [1]

Affiliations + expand

PMID: 28849024 DOI: 10.3892/mmr.2017.7250

Abstract

Endometriosis, which affects up to 10% of women of reproductive age, is defined as endometrial-like gland and stroma tissue growths outside the uterine cavity. Despite increasing research efforts, there are no current effective treatment methods for this disease, therefore investigations for therapeutic strategies are of primary concern. In preliminary work, the authors demonstrated that curcumin inhibits endometriosis in vivo. The present in vitro study aimed to investigate the association between endometriotic stromal cells and curcumin and to clarify the underlying mechanism of action. A total of 14 patients with endometriosis were enrolled in the present study. The purity of endometrial stromal cell cultures was proven by standard immunofluorescent staining of vimentin. The cell proliferation and curcumin effects on endometrial stromal cells were assessed by the MTT assay and Hematoxylin and Eosin staining. For cell cycle analysis, phase distribution was detected by flow cytometry. Vascular endothelial growth factor (VEGF) protein expression was examined using immunohistochemistry staining. Apoptosis was assessed using Annexin V-fluorescein isothiocyanate staining. The results indicated that the treatment of curcumin decreased human ectopic and eutopic stromal cell growth. Following treatment with curcumin, human endometriotic stromal cells demonstrated an increased percentage of G1-phase cells and decreased percentages of S-phase cells, particularly in the group treated with 50 µmol/l curcumin. Treatment with curcumin additionally decreased expression of VEGF. The data provide evidence that curcumin reduces cell survival in human endometriotic stromal cells, and this may be mediated via downregulation of the VEGF signaling pathway.

NAC + ALA + Bromelain

- Combination of N-acetyl cysteine, Alpha-Lipoic Acid, and Bromelain
- Showed promising anti-inflammatory properties in EM in animal studies
- Need human studies

Mediators Inflamm. 2015 Apr 16;2015:918089. doi: 10.1155/2015/918089

The Combination of N-Acetyl Cysteine, Alpha-Lipoic Acid, and Bromelain Shows High Anti-Inflammatory Properties in Novel *In Vivo* and *In Vitro* Models of Endometriosis

C Agostinis [1], S Zorzet [2], R De Leo [1], G Zauli [1], F De Seta [1,3], R Bulla [2,*]

Author information · Article notes · Copyright and License information

PMCID: PMC4415658 PMID: 25960622

Abstract

To evaluate the efficacy of an association of N-acetyl cystein, alpha-lipoic acid, and bromelain (NAC/LA/Br) in the treatment of endometriosis we set up a new *in vivo* murine model. We explored the anti-inflammatory and proapoptotic effect of this combination on human endometriotic endothelial cells (EECs) and on endothelial cells isolated from normal uterus

NAC

- NAC 600mg, 3 tablets/day for 3 consecutive days for 3 months
- Significant improvements in dysmenorrhea, dyspareunia, and chronic pelvic pain
- Use of NSAIDs, size of endometriomas, and serum levels of CA125 all decreased
- 39/52 patients desiring pregnancy achieved pregnancy within 6months of therapy

Int J Environ Res Public Health. 2023 Mar 7;20(6):4686. doi: 10.3390/ijerph20064686

Efficacy of N-Acetylcysteine on Endometriosis-Related Pain, Size Reduction of Ovarian Endometriomas, and Fertility Outcomes

Emanuela Anastasi [1], Sara Scaramuzzino [2], Maria Federica Viscardi [2], Valentina Viggiani [3], Maria Grazia Piccioni [2], Laura Cacciamani [2], Lucia Merlino [2], Antonio Angeloni [1], Ludovico Muzii [2], Maria Grazia Porpora [2,*]

Editor: Paul B Tchounwou

Author information · Article notes · Copyright and License information

PMCID: PMC10048621 PMID: 36981595

Abstract

Background: Endometriosis is a chronic, estrogen-dependent, inflammatory disease, whose pivotal symptoms are dysmenorrhea, dyspareunia, and chronic pelvic pain (CPP). Besides the usual medical treatments, recent evidence suggests there are potential benefits of oral N-acetylcysteine (NAC) on endometriotic lesions and pain. The primary objective of this prospective single-cohort study was to confirm the effectiveness of NAC in reducing endometriosis-related pain and the size of ovarian endometriomas. The secondary objective was to assess if NAC may play a role in improving fertility and reducing the Ca125 serum levels. Methods: Patients aged between 18–45 years old with a clinical/histological diagnosis of endometriosis and no current hormonal treatment or pregnancy were included in the study. All patients received quarterly oral NAC 600 mg, 3 tablets/day for 3 consecutive days of the week for 3 months. At baseline and after 3 months, dysmenorrhea, dyspareunia and

Vitamin C and Vitamin E

- Vitamin C 500mg BID (1000mg/day) with Vitamin E 400 IU/day BID (800IU/day) for 8 weeks
- Significant improvements in severity of pelvic pain, dysmenorrhea, and dyspareunia

Pain Research and Management

Pain Res Manag. 2021 May 26;2021:5529741. doi: 10.1155/2021/5529741

The Effect of Combined Vitamin C and Vitamin E Supplementation on Oxidative Stress Markers in Women with Endometriosis: A Randomized, Triple-Blind Placebo-Controlled Clinical Trial

Leila Amini [1,2], Razieh Chekini [3,✉], Mohammad Reza Nateghi [4], Hamid Haghani [5], Tannaz Jamialahmadi [6,7], Thozhukat Sathyapalan [8], Amirhossein Sahebkar [9,10,11]

Author information · Article notes · Copyright and License information

PMCID: PMC8172324 PMID: 34122682

Abstract

Background

Endometriosis is a chronic and estrogen-dependent pelvic inflammatory disease, which may have various causes, such as oxidative stress. Dysmenorrhea, dyspareunia, and pelvic pain are well-known symptoms of endometriosis. The present clinical trial assessed the role of supplementation with antioxidant vitamins on the indices of oxidative stress as well as the severity of pain in women with endometriosis.

EGCG – Green Tea extract

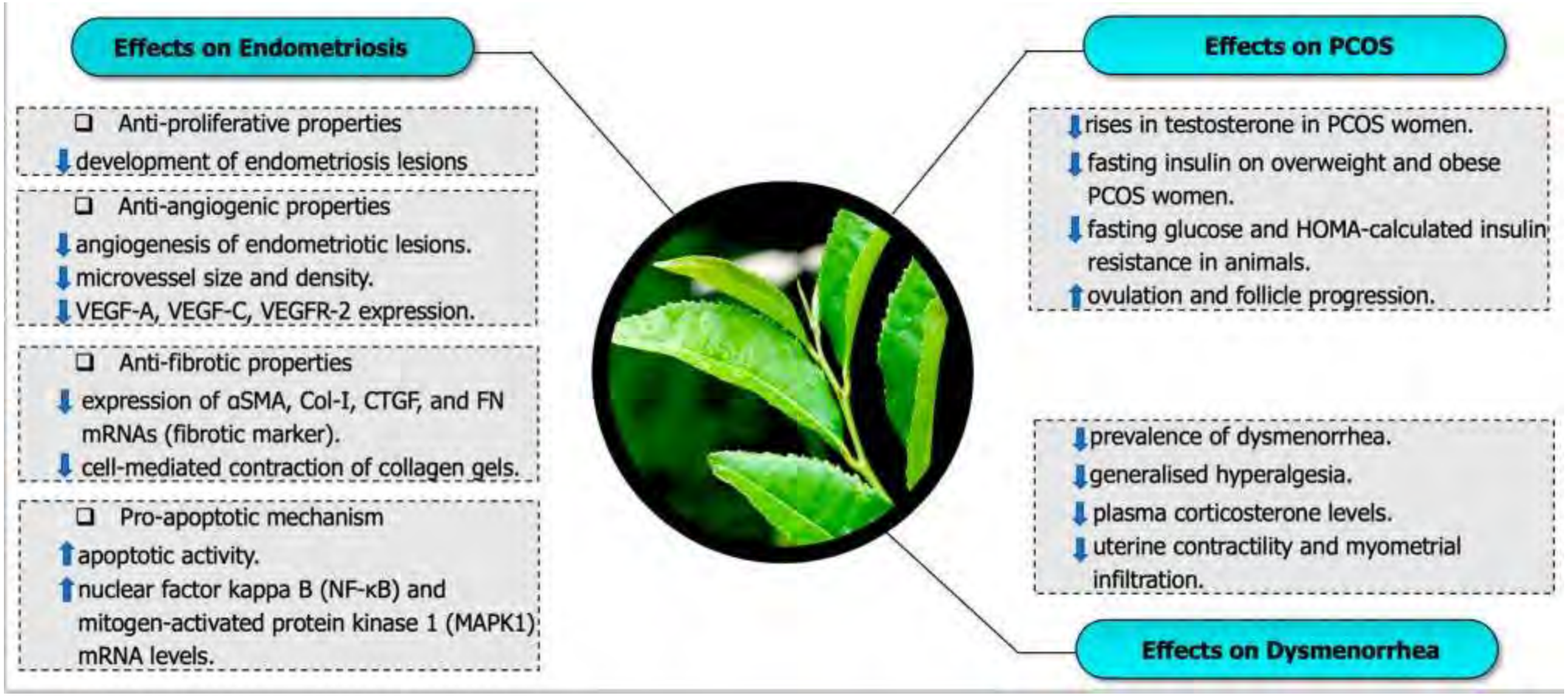


Figure from Kamal, et al, 2021

PEA + Transpolydatin

- One tablet, containing 400 mg of micronized N-palmitoylethanolamine (PEA) plus 40 mg transpolydatin, was administered twice daily on a full stomach for 90 days.
- Improved chronic pelvic pain and dysmenorrhea pain

› Eur J Obstet Gynecol Reprod Biol. 2013 Jun;168(2):209-13. doi: 10.1016/j.ejogrb.2013.01.009. Epub 2013 Feb 14.

The adjuvant use of N-palmitoylethanolamine and transpolydatin in the treatment of endometriotic pain

Emilio Giugliano [1], Elisa Cagnazzo, Ilaria Soave, Giuseppe Lo Monte, Jean Marie Wenger, Roberto Marci

Affiliations + expand

PMID: 23415738 DOI: 10.1016/j.ejogrb.2013.01.009

Abstract

Objective: To test the adjuvant use of the combination of N-palmitoylethanolamine and transpolydatin in the medical treatment of endometriotic pain.

Study design: We enrolled 47 patients admitted to the Outpatient Endometriosis Care Unit of Ferrara University from January 2011 to December 2011. They were divided into two groups according to the endometriosis site (group A: recto-vaginal septum; group B: ovary). One tablet, containing 400 mg of micronized N-palmitoylethanolamine plus 40 mg transpolydatin, was administered twice daily on a full stomach for 90 days. Each patient was requested to grade the severity of dysmenorrhea, chronic

Melatonin

Melatonin 10mg x 8 weeks

- treatment reduced daily pain scores by 39%
- dysmenorrhea by 38%
- improved sleep quality
- reduced the risk of using an analgesic by 80%
- Reduced brain-derived neurotropic factor (BNDF) levels independently of its effect on pain

Clinical Trial > Pain. 2013 Jun;154(6):874-81. doi: 10.1016/j.pain.2013.02.025. Epub 2013 Mar 5.

Efficacy of melatonin in the treatment of endometriosis: a phase II, randomized, double-blind, placebo-controlled trial

André Schwertner [1], Claudia C Conceição Dos Santos, Gislene Dalferth Costa, Alícia Deitos, Andressa de Souza, Izabel Cristina Custodio de Souza, Iraci L S Torres, João Sabino L da Cunha Filho, Wolnei Caumo

Affiliations + expand

PMID: 23602498 DOI: 10.1016/j.pain.2013.02.025

Abstract

Endometriosis-associated chronic pelvic pain (EACPP) presents with an intense inflammatory reaction. Melatonin has emerged as an important analgesic, antioxidant, and antiinflammatory agent. This trial investigates the effects of melatonin compared with a placebo on EACPP, brain-derived neurotrophic factor (BDNF) level, and sleep quality. Forty females, aged 18 to 45 years, were randomized into the placebo (n = 20) or melatonin (10 mg) (n = 20) treatment groups for a period of 8 weeks. There was a significant interaction (time vs group) regarding the main outcomes of the pain scores as indexed by

Ginger

- Ginger 500mg TID
- Ginger given 2 days prior to menses and continued through the first three days of the menstrual period had a significant reduction in pain
- Ginger vs NSAIDs were equally effective in reducing pain with no statistical difference

Cureus. 2021 Mar 6;13(3):e13743. doi: 10.7759/cureus.13743

Efficacy of Ginger in the Treatment of Primary Dysmenorrhea: A Systematic Review and Meta-analysis

Rizu Negi [1,✉], Suresh K Sharma [2], Rakhi Gaur [3], Anupama Bahadur [4], Prasuna Jelly [4]

Editors: Alexander Muacevic, John R Adler

Author information · Article notes · Copyright and License information

PMCID: PMC8021506 PMID: 33842121

Abstract

It has been evidenced that very few systematic reviews have examined the effectiveness of ginger for pain duration and its severity among women with primary dysmenorrhea. This meta-analysis was therefore performed to methodically incorporate and significantly evaluate randomized controlled ginger studies for the treatment of primary dysmenorrhea. The literature was searched using PubMed, Embase, Ovid, ClinicalKey, Medline, and electronic database. We have analyzed clinical trials by comparing ginger with placebo and non-steroidal anti-inflammatory drugs in women with primary dysmenorrhea. The primary outcomes assessed in our meta-analysis were pain severity and pain duration.

Acupuncture

- Reduction in dysmenorrhea
- Duration of pain was shortened
- Improvements in pelvic pain
- Improved well-being and quality of life scores
- Different techniques may have better efficacy results (auricular, warm needling, electroacupuncture, etc.)

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Acupuncture for clinical improvement of endometriosis-related pain: a systematic review and meta-analysis

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Abstract

Background

Endometriosis is a common chronic gynecological condition characterized by the presence of endometrial tissue outside the uterine cavity, leading to chronic inflammation, pelvic nodules

Pelvic Floor Therapies

- Pulsed high-intensity laser therapy
  - High-powered laser used to alleviate pain and promote healing
  - Stimulates tissue repair and reduces inflammation
- Transcutaneous Electrical Nerve Stimulation (TENS)
  - Sends mild electrical pulses to affected areas
  - Stimulates natural pain-relieving mechanisms
- Pulsed Electromagnetic Field Therapy (PEMF)
  - Non-invasion, exposes cells to pulsed magnetic fields
  - May aid in reducing pain and inflammation, promote tissue healing
- Manual physiotherapy
  - (visceral therapy, PT, hydrotherapy, therapeutic massage, etc.)

Gut Dysbiosis and Endometriosis – Repair the Microbiome

frontiers in Endocrinology

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Endometriosis and dysbiosis: State of art

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Abstract

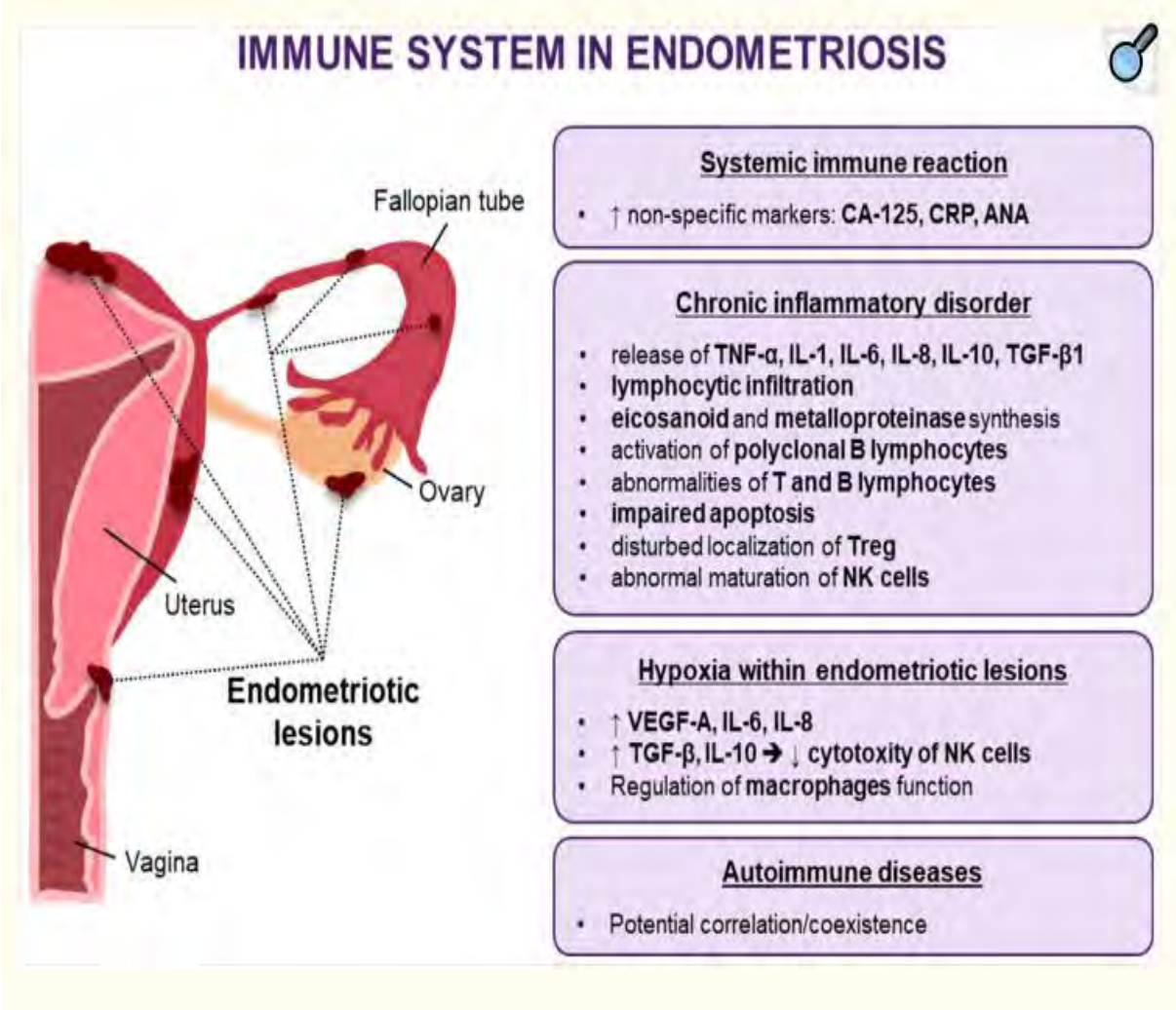
Endometriosis is a complex and heterogeneous disease affecting approximately 10% of reproductive age women. The hypothesis that alterations in the microbiota are involved in the pathogenesis of endometriosis has been postulated. Possible explanations for the implications of dysbiosis in endometriosis include the Bacterial Contamination hypothesis and immune activation, cytokine-impaired gut function, altered estrogen metabolism and signaling. Thus, dysbiosis, disrupt normal immune function, leading to the elevation of proinflammatory cytokines, compromised immunosurveillance and altered immune cell profiles, all of which may contribute to the pathogenesis of endometriosis. The aim of this review is to summarize the available literature data about the relationship between microbiota and endometriosis.

Immune System Dysregulation and EM

- Macrophages – change in number depending on the phase of the menstrual cycle –
  - Regulated by E and Pg –
  - Cyclic changes are noted in normal endometrium
  - During menses the number is significantly increased – clearing apoptotic cells and cell debris during endometrial shedding in normal endometrium
- Macrophages are **increased** in eutopic endometrium and peritoneal fluid in EM across all phases – no cyclical pattern
- The phagocytic action (the engulf and destroy) is **decreased** in EM tissue
  - Resulting in incomplete endometrial shedding and there is a survival of this sloughed off tissue in the peritoneal cavity
- Peritoneal macrophages release pro-inflammatory cytokines (TNFa, IL-6, IL-8, IL-1b) – which recruit neutrophils
- Macrophages produce VEGF – which promotes new blood vessels from existing ones (angiogenesis) in EM

Immune System Dysregulation and EM

- Peritoneal macrophages release pro-inflammatory cytokines (TNFa, IL-6, IL-8, IL-1b) – which recruit neutrophils
- Neutrophil counts in peritoneal fluid are **increased**
- Neutrophils express pro-inflammatory cytokines (VEGF, IL-8, CXCL10) – which cause progression of the disease



Maksym, R. B., Hoffmann-Młodzianowska, M., Skibińska, M., Rabijewski, M., Mackiewicz, A., & Kieda, C. (2021). Immunology and Immunotherapy of Endometriosis. *Journal of clinical medicine*, *10*(24), 5879. https://doi.org/10.3390/jcm10245879

Other DUTCH Endometriosis Resources

- Using the DUTCH test for Endometriosis Management by Dr. Kaitlin Tyre, ND
  - https://dutchtest.com/articles/supporting-endometriosis-dutch-test
- Endometriosis and the Estrobolome by Dr. Christina O'Brien, DC
  - https://dutchtest.com/case-studies/endometriosis-and-the-estrobolome
- Managing Endometriosis: Hormonal Insights and Nutritional Strategies by Cindy Dabrowska, RD
  - https://dutchtest.com/podcasts/managing-endometriosis-hormonal-insights-nutritional-strategies
- Reducing the Effects of Endometriosis: How Anti-Inflammatories, Including Melatonin, May Help by Dr. Alana Campbell, ND
  - https://dutchtest.com/articles/reducing-the-effects-of-endometriosis-how-anti-inflammatories-including-melatonin-may-help
- Endometriosis and the DUTCH test: The relationship between estrogen, progesterone, and cortisol dysregulation by Dr. Jaclyn Smeaton, ND
  - https://dutchtest.com/webinars/endometriosis-and-the-dutch-test-the-relationship-between-estrogen-progesterone-and-cortisol-dysregulation

In Summary

- Endometriosis is a multifactorial disease with involvement of genetics, immune, hormone, and environmental factors
- Endometriosis is both an estrogen dependent and a progesterone resistant process
- The endometrial tissues in women with EM behave very differently than women without EM
- Not all progestins work the same
- Natural progesterone may not work as well in EM due to progesterone unresponsiveness in the tissues
- Consider a multisystem approach for treatment plans
  - *This is important
- Keep studying the various theories involved for better management

Thank You!

Remember

1. The information in this presentation is provided for informational and educational purposes only and is not medical or treatment advice.

2. Any information and statements regarding dietary or herbal supplements have not been evaluated by the Food and Drug Administration and are not intended to diagnose, treat, cure, or prevent any disease.

3. The use of any information provided in this presentation is solely at your own risk.

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Thank You!

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Progesterone Resistance and Endometriosis

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