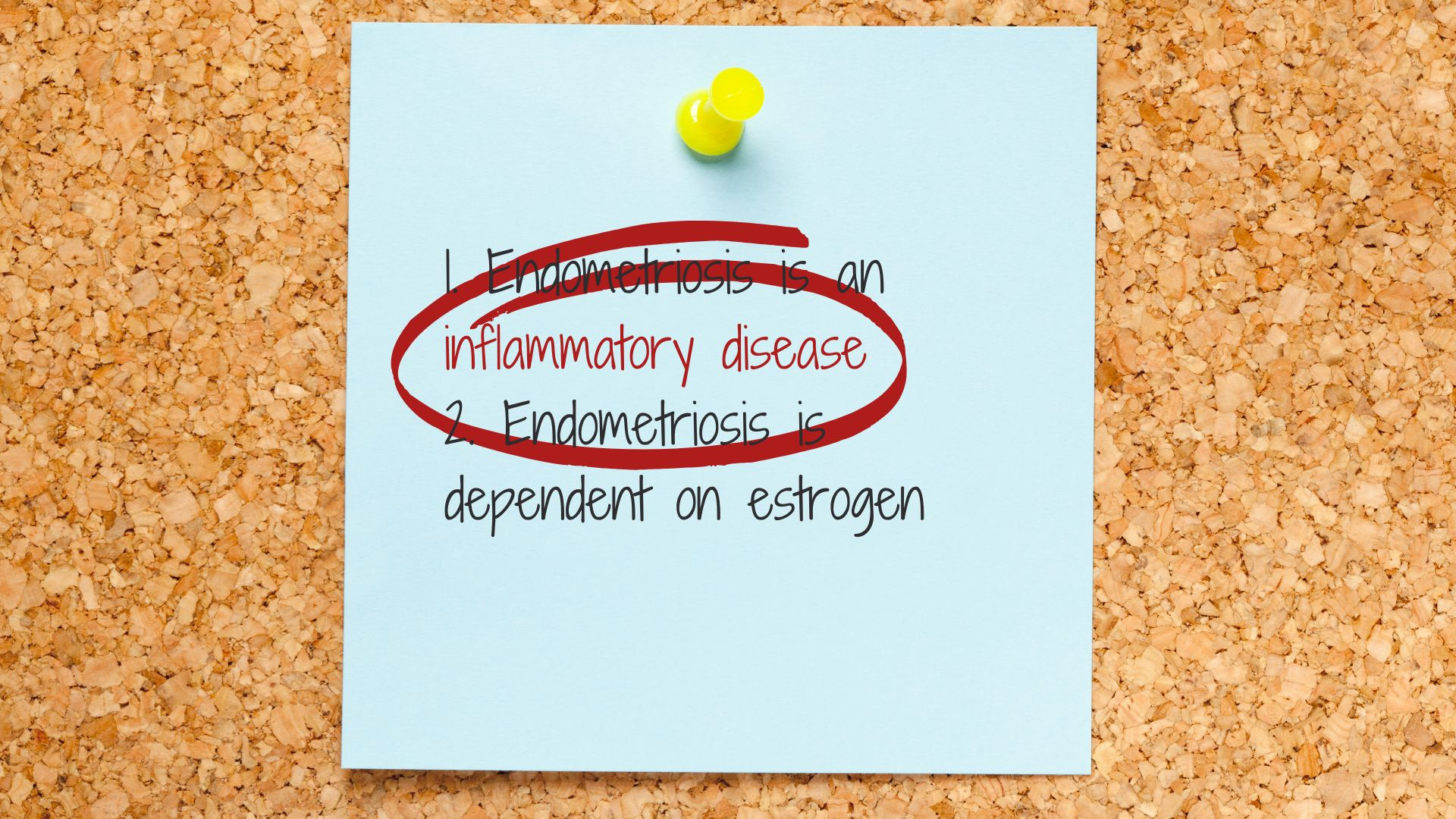
Endometriosis, immune dysfunction, and the microbiome

Lara Briden BSc, ND

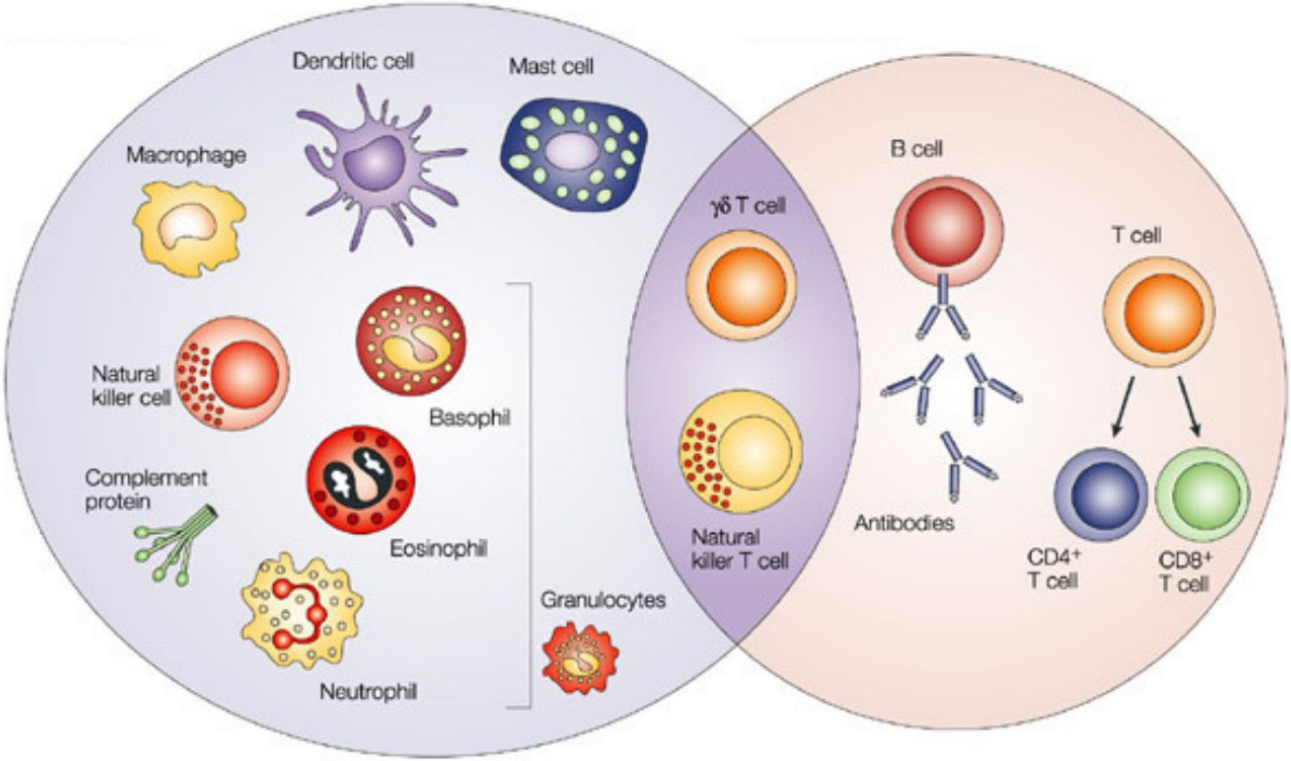
AIMA NZ Conference 2019

1. Endometriosis is an inflammatory disease
2. Endometriosis is dependent on estrogen


1. Endometriosis is an
inflammatory disease
2. Endometriosis is
dependent on estrogen

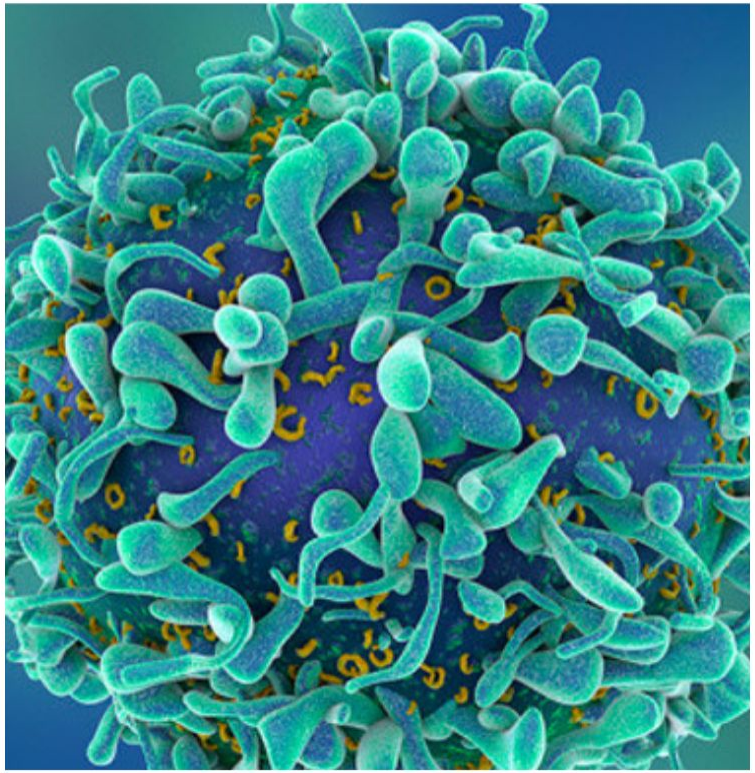
Innate immunity

Adaptive immunity



Involvement of immune cells in the pathogenesis of endometriosis. PMID: 29316073

Treg lymphocyte dysfunction



With endometriosis, there are increased numbers of Treg cells in the pelvis but reduced activity and function.

“

...a dysregulated immune response wherein the decrease in activated Treg cells exaggerates local inflammation and angiogenesis, and thus facilitates endometriosis progression.

Exacerbation of endometriosis due to regulatory T cell dysfunction.
J Clin Endocrinol Metab. 2017 May 26. PMID 28575420

Review studies

- Immunological aspects of endometriosis: a review. Ann Transl Med. 2015. PMID: 26244140
- What do we know about regulatory T cells and endometriosis? A systematic review. J Reprod Immunol. 2017. PMID: 28463710
- Involvement of immune cells in the pathogenesis of endometriosis. J Obstet Gynaecol Res. 2018. PMID: 29316073
- Altered Immunity in Endometriosis: What Came First? Immunol Invest. 2018. PMID: 29873595

REVIEW ARTICLE

WILEY Reproductive Medicine and Biology

Bacterial contamination hypothesis: a new concept in endometriosis

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Abstract

Background: Endometriosis is a multifactorial disease that mainly affects women of reproductive age. The exact pathogenesis of this disease is still debatable. The role of bacterial endotoxin (lipopolysaccharide, LPS) and Toll-like receptor 4 (TLR4) in endometriosis were investigated and the possible source of endotoxin in the pelvic environment was examined.

Methods: The limulus amoebocyte lysate test was used to measure the endotoxin levels in the menstrual fluid and peritoneal fluid and their potential role in the growth of endometriosis was investigated. Menstrual blood and endometrial samples were cultured for the presence of microbes. The effect of gonadotrophin-releasing hormone agonist (GnRHa) treatment on intrauterine microbial colonization (IUMC) and the occurrence of endometritis was investigated.

Main findings (Results): Lipopolysaccharide regulates the pro-inflammatory response in the pelvis and growth of endometriosis via the LPS/TLR4 cascade. The menstrual blood was highly contaminated with *Escherichea coli* and the endometrial samples were colonized with other microbes. A cross-talk between inflammation and ovarian steroids or the stress reaction also was observed in the pelvis. Treatment with GnRHa further worsens intrauterine microbial colonization, with the consequent occurrence of endometritis in women with endometriosis.

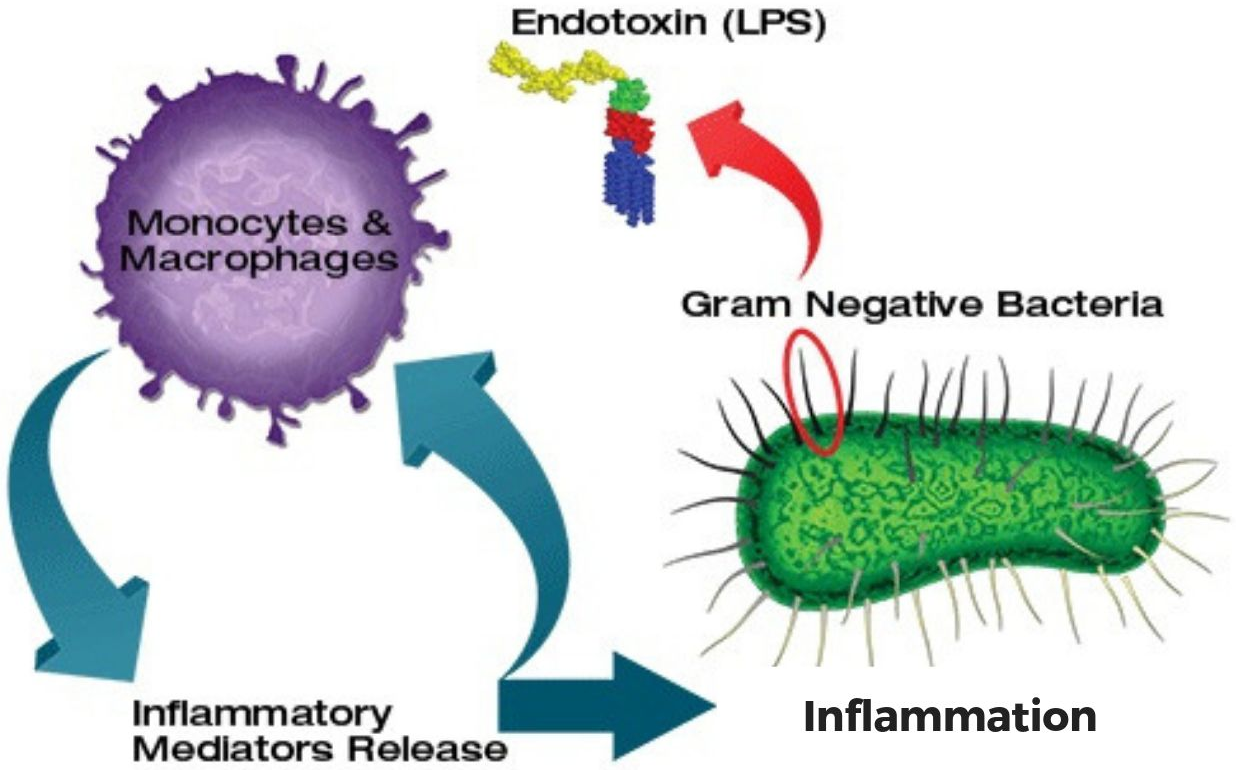
Conclusion: For the first time, a new concept called the "bacterial contamination hypothesis" is proposed in endometriosis. This study's findings of IUMC in women with endometriosis could hold new therapeutic potential in addition to the conventional estrogen-suppressing agent.

KEYWORDS
bacterial endotoxin, endometriosis, gonadotrophin-releasing hormone agonist, menstrual blood,

..the inflammatory mediator LPS derived from bacterial contamination could be the primary cause in the growth regulation of endometriosis, either alone or in combination with ovarian steroids."

Khan et al. Reprod Med Biol. 2018
PMID: 29692669

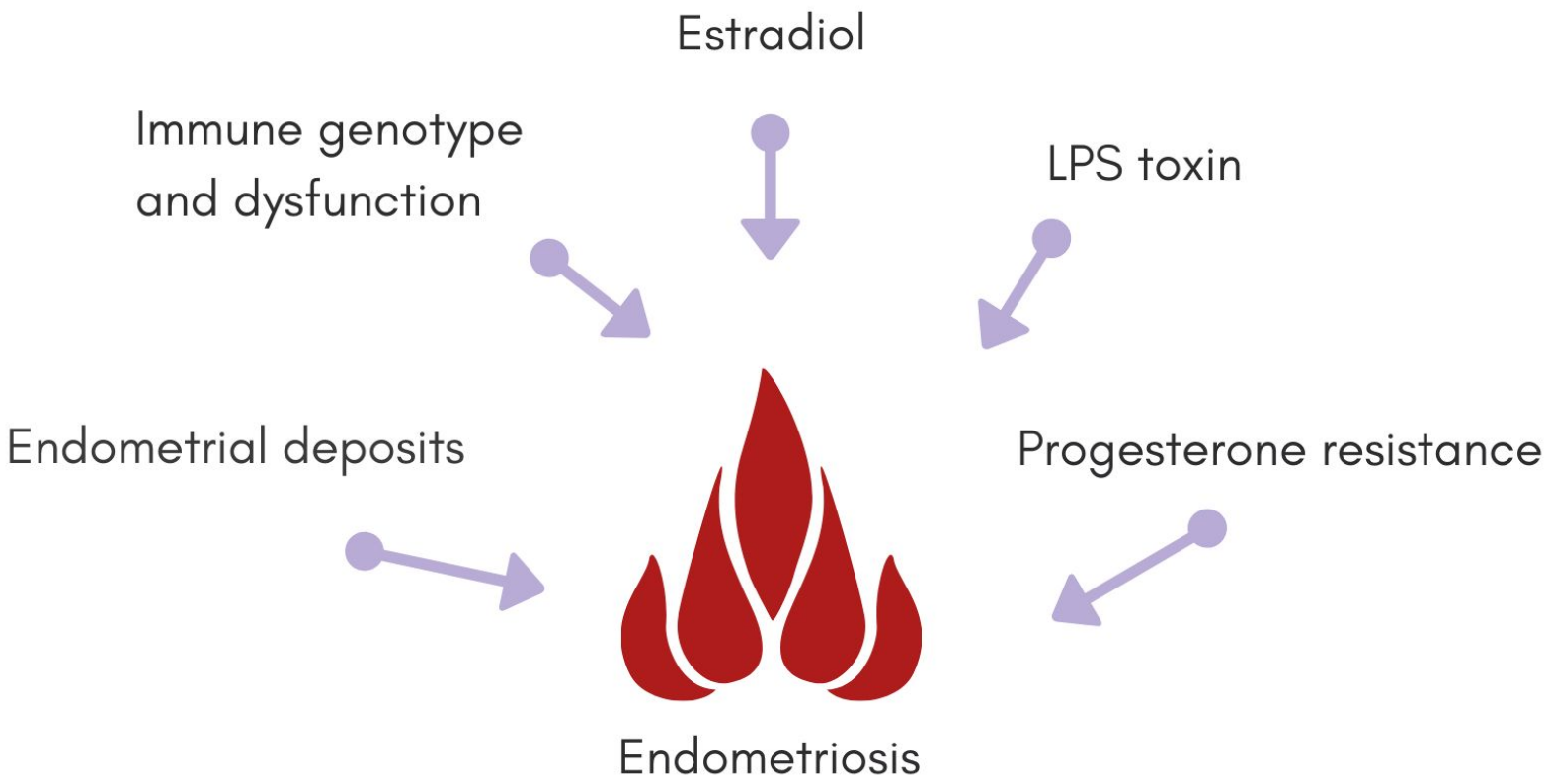
Lipopolysaccharide (LPS)



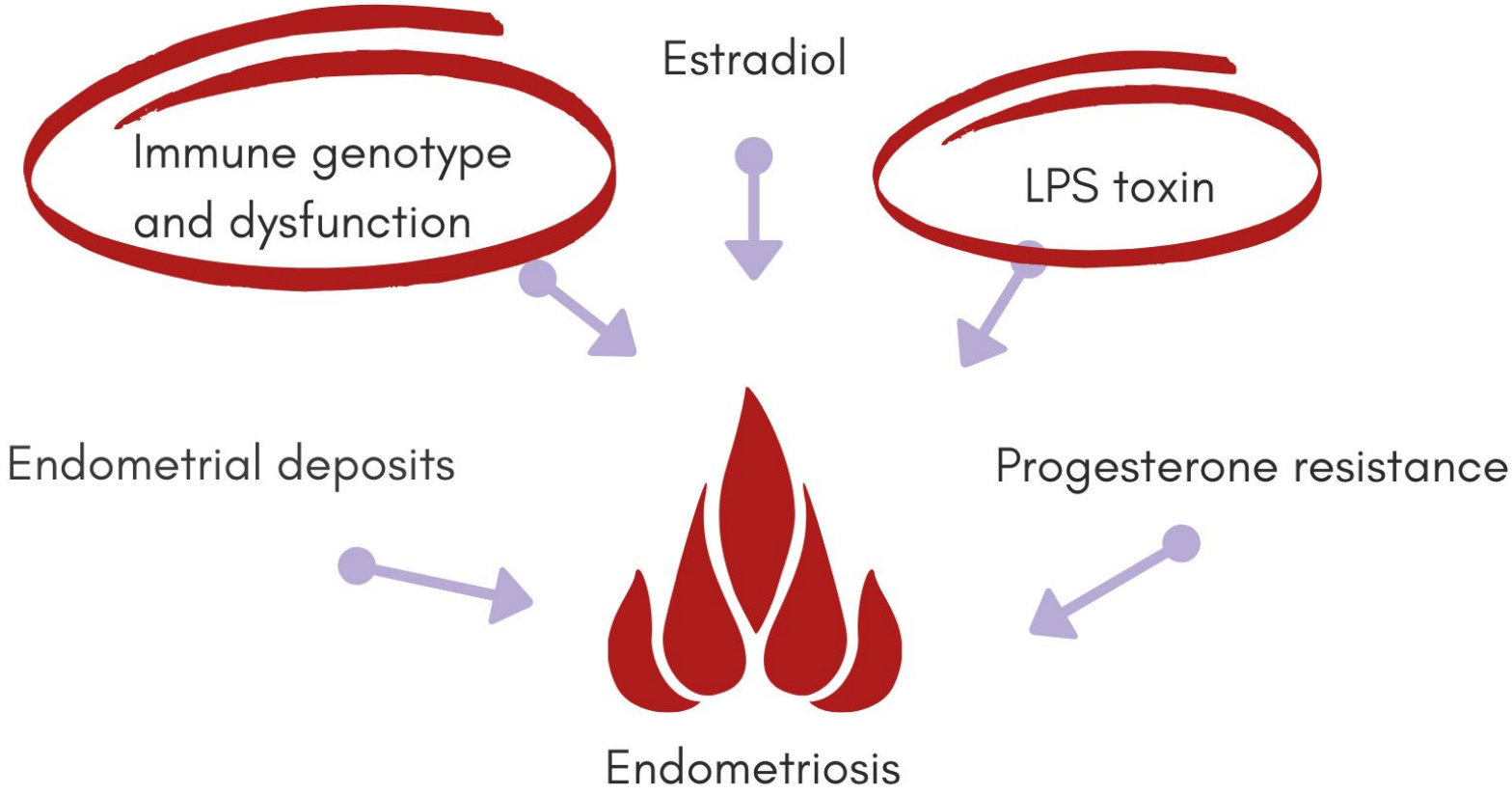
Together with estradiol,
LPS may play a role in the etiology of endometriosis.

17β-estradiol and lipopolysaccharide additively promote pelvic inflammation and growth of endometriosis.
Reprod Sci. 2015 May;22(5):585-94 PMID: 25355803

Perfect storm for inflammation



Perfect storm for inflammation



Berberine-containing herbs

- Neutralise the bacterial toxin LPS [PMID: 24602493]
- Inhibit the release of inflammatory cytokines [PMID: 27294302]
- Improve adenomyosis [PMID: 29285168]
- Repair intestinal permeability [PMID: 21592990]
- Treat SIBO [PMID 24891990]

Aust N Z J Obstet Gynaecol 2017; 1–5

ANZJOG

DOI: 10.1111/ajo.12594

ORIGINAL ARTICLE

Endometriosis in patients with irritable bowel syndrome: Specific symptomatic and demographic profile, and response to the low FODMAP diet

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Accepted: 11 December 2016

Background: Women with endometriosis are frequently misdiagnosed with irritable bowel syndrome (IBS) for some time before a correct diagnosis is made. Visceral hypersensitivity is a key feature in both conditions.

Aims: To determine if there are distinct symptom patterns in women with IBS and endometriosis, and to determine the response of these women to a low FODMAP diet in comparison to those with IBS alone.

Materials and methods: A retrospective analysis of prospectively collected data from women attending a specialist IBS service in Christchurch New Zealand. Data from those who met Rome III criteria for IBS were sorted into two groups: concurrent endometriosis and those with IBS alone. Demographics and symptom patterns were identified from a prospective questionnaire. A low FODMAP (fermentable oligosaccharides disaccharides, monosaccharides and polyols) diet was taught to all women as the primary therapeutic intervention. Responses to the diet were noted against their ultimate disposition.

Results: Of the 160 women who met Rome III criteria for IBS, 36% had concurrent endometriosis. The presence of dyspareunia ($P > 0.0001$), referred pain ($P = 0.005$), bowel symptoms exacerbated by menstruation ($P = 0.0004$) and a family history of endometriosis ($P = 0.0003$) were associated with concurrent endometriosis. Seventy two percent of these women reported a >50% improvement in bowel symptoms after four weeks of a low FODMAP diet compared with 49% in those with no known endometriosis ($P = 0.001$, odds ratio 3.11, 95% CI, 1.5–6.2).

"*This is the first study to show a therapeutic benefit of a low FODMAP diet in patients with endometriosis.*"

Moore et al. Aust N Z J Obstet Gynaecol. 2017. PMID: 28303579

...there may be a direct link between pathological changes of the gut microbiota and the onset and progression of endometriosis.

The gut microbiota: a puppet master in the pathogenesis of endometriosis?
Am J Obstet Gynecol. 2016 Jul;215(1). PMID: 26901277

Gluten and A1 Casein

- Gluten-free diet improved symptoms in 75% of endometriosis sufferers. [PMID: 23334113]
- A1 casein induces an inflammatory response in the gut. [PMID: 24986816]

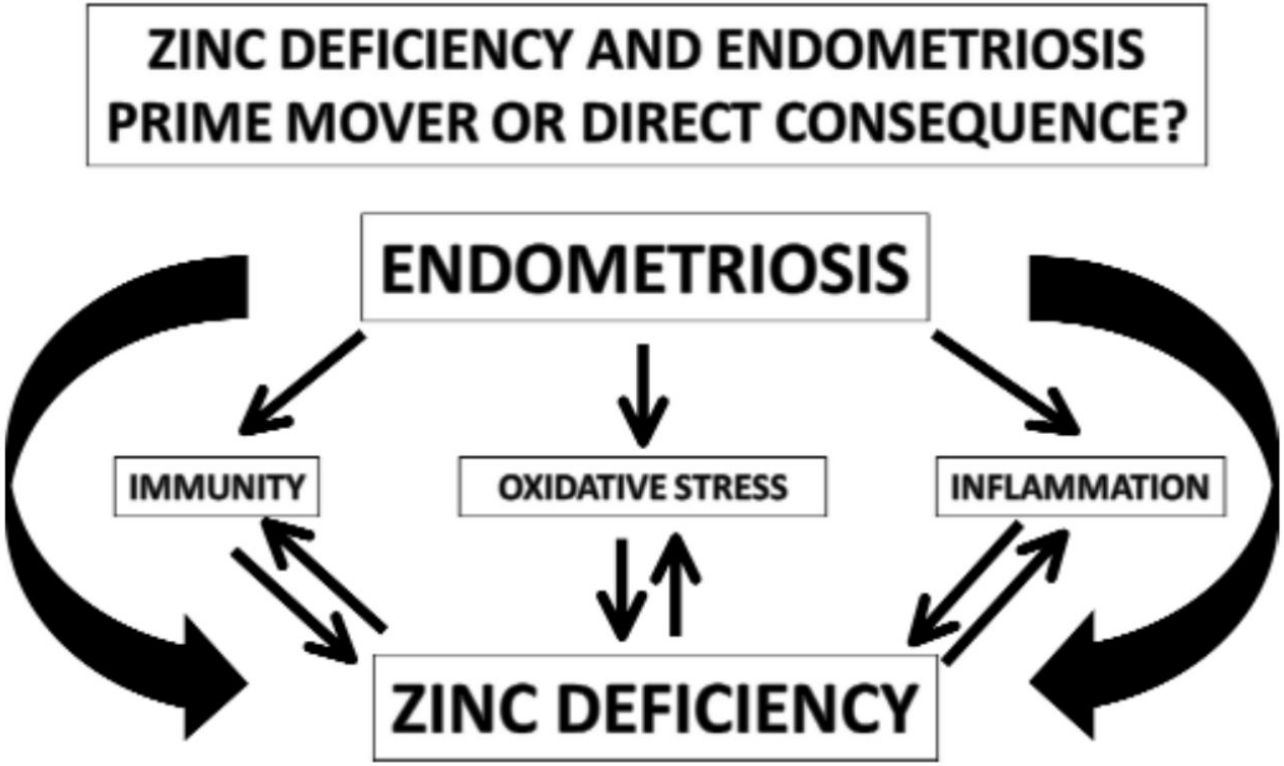
Other immune-disruptors

- Eggs and other food sensitivities
- Mast cell activation and histamine
- Environmental toxins
- Mold toxins

Dioxin exposure in the womb

In utero dioxin exposure causes inheritable progesterone resistance and *a transgenerational* risk of endometriosis.

Bruner-Tran et al. Reprod Toxicol. 2017. PMID: 27423904



The possible role of zinc in the etiopathogenesis of endometriosis.
Clin Exp Obstet Gynecol. 2014;41(5):541-6. PMID 25864256

Research Article

A Promise in the Treatment of Endometriosis: An Observational Cohort Study on Ovarian Endometrioma Reduction by N-Acetylcysteine

Maria Grazia Porpora,[1] Roberto Brunelli,[1] Graziella Costa,[2] Ludovica Imperiale,[1] Ewa K. Krasnowska,[2] Thomas Lundeberg,[3] Italo Nofroni,[4] Maria Grazia Piccioni,[1] Eugenia Pittaluga,[2] Adele Ticino,[1] and Tiziana Parasassi[2]

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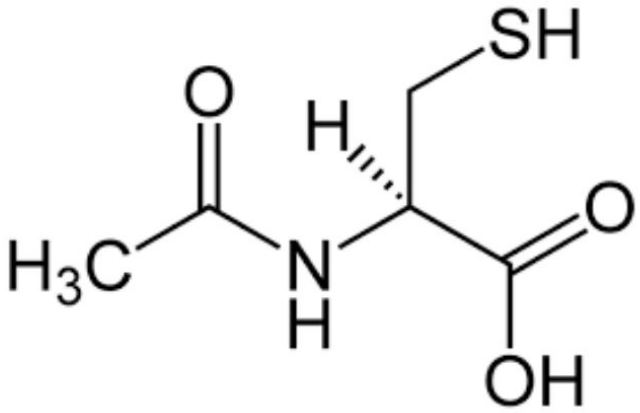
Academic Editor: Martin Kohlmeier

Urged by the unmet medical needs in endometriosis treatment, often with undesirable side effects, and encouraged by N-acetylcysteine (NAC) efficacy in an animal model of endometriosis and by the virtual absence of toxicity of this natural compound, we performed an observational cohort study on ovarian endometriosis. NAC treatment or no treatment was offered to 92 consecutive Italian women referred to our university hospital with ultrasound confirmed diagnosis of ovarian endometriosis and scheduled to undergo laparoscopy 3 months later. According to patients acceptance or refusal, NAC-treated and untreated groups finally comprised 73 and 72 endometriomas, respectively. After 3 months, within NAC-treated patients cyst mean diameter was slightly reduced (−1.5 mm) versus a significant increase (+6.6 mm) in untreated patients ($P = 0.001$). Particularly, during NAC treatment, more cysts reduced and fewer cysts increased their size. Our results are better than those reported after hormonal treatments. Twenty-four NAC-treated patients—versus 1 within controls—cancelled scheduled laparoscopy due to cysts decrease/disappearance and/or relevant pain reduction (21 cases) or pregnancy (1 case). Eight pregnancies occurred in NAC-treated patients and 6 in untreated patients. We can conclude that NAC actually represents a simple effective treatment for endometriosis, without side effects, and a suitable approach for women desiring a pregnancy.

Of the 47 women in the NAC treatment group, 24 canceled their laparoscopy due to a disappearance of cysts, reduction of pain, or pregnancy.

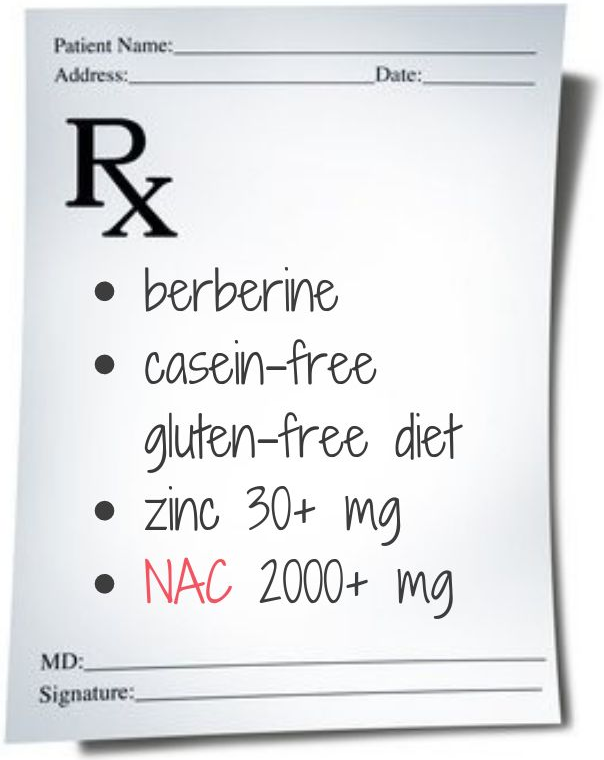
Porpora et al. Evid Based Complement Alternat Med. 2013. PMID: 23737821

N-acetyl cysteine



- Downregulates NF-κB and reduces inflammatory cytokines.
- Precursor to glutathione which upregulates activity of NK cells and Treg cells.
- Reduces oxidative stress.
- May influence apoptosis and angiogenesis. [PMID: 28367412]

Front-line prescription



...curcumin regresses endometriosis by drastic elevation of mitochondria-mediated apoptotic pathway suggesting therapeutic potential of curcumin as an anti-endometriotic drug.

Curcumin as anti-endometriotic agent.
Biochem Pharmacol. 2012 Mar 15;83(6):797-804. PMID 22227273

Curcumin

- Downregulates NF-κB and promotes apoptosis [PMID 22227273]
- Suppresses local production of estrogen [PMID: 24639774]
- Inhibits angiogenesis [PMID: 17569210]
- Supports glutathione [PMID: 16433888] and Treg cells [PMID: 19839007]

Arch Gynecol Obstet
DOI 10.1007/s00404-017-4549-8

MATERNAL-FETAL MEDICINE

Retinoic acid regulates endometriotic stromal cell growth through upregulation of Beclin1

Huixia Lu[1] · Shaobo Li[1] · Qi Wu[1,2]

Received: 4 May 2017 / Accepted: 20 September 2017

Abstract

Purpose To elucidate the role of retinoic acid (RA) in autophagy-mediated endometriosis.

Methods The mRNA and protein expressions of autophagy markers were examined in Ishikawa cells and endometriotic stromal cells (ESCs) after RA treatment. Beclin1 expression was specifically analyzed in clinical samples of endometriosis. The effect of Beclin1 knockdown on ESC growth was assessed, and the effect of autophagy inhibition on the sensitivity of endometriotic cells to RA was analyzed.

Results RA treatment enhanced the autophagy in ESCs, and Beclin1 expression showed a negative correlation with the clinical stage of endometriosis. Beclin1 knockdown enhanced ESC growth, whereas RA treatment reversed this effect. Furthermore, inhibition of autophagy by chloroquine (CQ) and Beclin1 knockdown did not show any positive effect on the sensitivity of endometriotic cells to RA.

Conclusions RA treatment induces autophagy and Beclin1 may play an important role in endometriosis progression.

Keywords Retinoic acid · Autophagy · Endometriosis · Beclin1

Introduction

Endometriosis refers to the condition that endometrial tissues (glands and stroma) grow outside of uterine cavity. It is a common disease typically associated with chronic pain. Clinical features include irregular menstruation [1] and infertility, as high as 40% of infertility rate [2]. Its exact pathogenesis remains unclear, and so far, the most accepted hypothesis about endometrial implantation supports Sampson's hypothesis [3] that the exfoliated endometrial tissue from uterus is shed through the fallopian tubes and reaches the peritoneal cavity during menstruation [4–6]. The shed endometrial cells can survive, implant, grow and invade at ectopic locations and eventually develop into endometriotic lesions [5]. In addition, the ectopic endometrial cells display a high invasive capability.

Autophagy is a process by which the cytoplasmic components of the cell are degraded and recycled for energy generation. It is also described as self-eating and is an important process in the development of multiple diseases. To date, approximately 30 yeast genes and 16 human genes have been identified as autophagy-related genes (ATGs). Among these, Beclin1, a mammal homologous gene of yeast autophagy-related genes Atg6/Vps30, has been shown to play a key role

Retinoic acid treatment induces autophagy in endometriosis tissue.

Lu et al. Arch Gynecol Obstet. 2018.
PMID: 29063947

Protective effects of resveratrol against endometriosis are mediated through a network of several cell signaling pathways which, in turn, cause suppression of proliferation in endometriotic lesions, induction of apoptosis, reduction of inflammation, angiogenesis and oxidative stress, and inhibition of adhesion and invasion.

Resveratrol and endometriosis: In vitro and animal studies and underlying mechanisms . Biomed Pharmacother. 2017 Jul;91:220-228. PMID 28458160

Summary

- Consider the possible role of bacterial endotoxin (LPS)
- Berberine
- Low-FODMAP diet
- Gluten-free, dairy-free diet
- Zinc
- N-acetylcysteine
- Turmeric
- Vitamin A
- Resveratrol

Questions?

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