Lara Briden, ND

Endometriosis and the microbiome – harnessing the power of anti-inflammatory and immune-modulating treatments

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1. Endometriosis is an inflammatory disease
2. Endometriosis is dependent on estrogen
Immune profile of endometriosis

- Impaired innate immunity and natural killer (NK) cell activity
- Increased pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α
- Presence of auto-antibodies including phospholipid antibodies, lupus anticoagulant, and anti-endometrial antibodies
- Deficiency of T-regulator (Treg) lymphocytes
Treg deficiency and angiogenesis

- Women with endometriosis have fewer Treg cells in the peritoneal fluid
- Treg deficiency in mice promotes the growth of endometriosis lesions and angiogenesis [PMID: 28575420]
A novel concept of 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
Possible role of bacteria

- Women with a history of a gynecological *infection* are twice as likely to develop endometriosis [PMID: 26962775]
- **Antibiotics** can relieve the symptoms of endometriosis [PMID: 28624114]
Lipopolysaccharide (LPS)

Monocytes & Macrophages

Endotoxin (LPS)

Gram Negative Bacteria

Inflammatory Mediators Release

Inflammation
LPS may be involved in the etiology of endometriosis

- Women with endometriosis have more gram-negative bacteria and LPS in their menstrual and peritoneal fluid. [PMID: 20627244]
- Together with estradiol, LPS may play a role in the etiology of endometriosis [PMID: 25355803]
Perfect storm for inflammation

- Estradiol
- Immune genotype and dysfunction
- Endometrial deposits
- LPS toxin
- Progesterone resistance
- Endometriosis
Perfect storm for inflammation

- Immune genotype and dysfunction
- LPS toxin
- Estradiol

- Endometriosis
- Progesterone resistance
- Endometrial deposits
..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?
Endometriosis in patients with irritable bowel syndrome: Specific symptomatic and demographic profile, and response to the low FODMAP diet

Judith S. Moore¹,², Peter R. Gibson¹, Richard E. Perry² and Rebecca E. Burgell¹

¹Department of Gastroenterology, Central Clinical School, Monash University and Alfred Hospital, Melbourne, Victoria, Australia
²Intus, Digestive and Colorectal Care, Christchurch, New Zealand

Correspondence: Mrs Judith S. Moore, Faculty of Medicine, Nursing and Health Sciences Block B, level 6, The Alfred Centre, 99 Commercial Road, Melbourne, Vic. 3181, Australia.
Email: Judith.moore@monash.edu

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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.
Gluten and A1 Casein

- Gluten-free diet improves symptoms in 75% of endometriosis sufferers [PMID: 23334113]
- A1 casein induces inflammatory response in the gut as compared to A2 casein [PMID: 24986816]
Other immune-disruptors

- Eggs and other food sensitivities
- High histamine foods
- Environmental toxins
- Mold toxins
Dioxin exposure in the womb

- *In utero* dioxin exposure causes **progesterone resistance** and a *transgenerational* risk of **endometriosis** [PMID: 27423904]
Berberine-containing herbs

- Neutralize the bacterial toxin LPS [PMID: 24602493]
- Inhibit the release of inflammatory cytokines [PMID: 27294302]
- Treat SIBO [PMID 24891990]
- Repair intestinal permeability [PMID: 21592990]
Prospect of an effective probiotic

- Double-blind, placebo-controlled clinical trial of probiotic *Lactobacillus gasseri OLL2809* for endometriosis.
- Pain was significantly reduced in the treatment group after 12 weeks [PMID: 21153437]
Selenium

- Lower tissue levels in women with endometriosis [PMID: 16634350]
- Anti-inflammatory and immune-modulating
- Upregulates Treg cells [PMID: 20453397]
- Support the corpus luteum and progesterone [PMID: 25362850]
- Depleted by SIBO
The possible role of zinc in the etiopathogenesis of endometriosis.
..curcumin regresses endometriosis by drastic elevation of mitochondria-mediated apoptotic pathway suggesting therapeutic potential of curcumin as an anti-endometriotic drug.
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]
Front-line prescription

- casein-free
- gluten-free diet
- zinc 30 mg
- selenium 150 mcg
- turmeric
Of the 47 women in the NAC treatment group, 24 canceled their laparoscopy due to a disappearance of cysts, reduction of pain, or pregnancy. [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]
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.

Summary

- The possible role of LPS bacterial endotoxin
- Berberine
- Gluten-free, dairy-free diet
- Low-FODMAP diet (New Zealand study)
- Probiotic
- Zinc and selenium
- Turmeric
- N-acetylcysteine
- Resveratrol
THANKS

Questions?

www.larabriden.com

@larabriden

lara@larabriden
ATMS
Australian Traditional-Medicine Society
PO Box 1027 Meadowbank NSW 2114