# SPM Emerging Area

## Inflammation resolution and endometriosis

### Research Highlights

- Endometriosis (EMS; Figure 1) is a painful chronic inflammatory disorder impacting women of reproductive age that can lead to infertility.[1,2]
- Specialized pro-resolving mediators (SPMs) such as lipoxins (LXs), resolvins (Rvs), protectins (PDs), and maresins (MaRs) are lipid mediators derived from polyunsaturated fatty acids that actively coordinate the resolution of inflammation.[3,4]
- Patients with EMS have been shown to have reduced levels of SPMs (specifically LXA4) in their endometrial tissues (Figure 2).[5,6]
- Emerging preclinical research using rodent models and cell studies has demonstrated that specific SPMs may (Table 1):[6-12]
  - o Reduce the development and growth of endometrial lesions
  - o Attenuate levels of multiple proinflammatory and angiogenic factors in endometrial lesions or peritoneal fluid cells
  - o Inhibit COX-2 expression in endometrial lesion leading to reduced peritoneal fluid PGE2 levels
  - o Downregulate aromatase expression and estrogen signaling

### Introduction

Endometriosis (EMS) is an estrogen-dependent inflammatory disorder characterized by the presence of endometrium (the tissue lining the inner cavity of the uterus) outside the uterine cavity such as the fallopian tubes, ovaries, and pelvic peritoneum.[1] On rarer occasions the ectopic endometrial tissue can spread beyond pelvic organs. EMS affects up to 10-15% of all women of reproductive age.[2] Common symptoms of EMS include pain associated with periods (dysmenorrhea), intercourse (dyspareunia), defecation (dyschezia) and urination (dysuria); chronic lower back and pelvic pain; and heavy menstrual bleeding. However, 20-25% of patients may be asymptomatic.[2] A major complication of EMS is infertility, which affects up to 30-50% of women with EMS.[13]

### Rationale for inflammation management in EMS

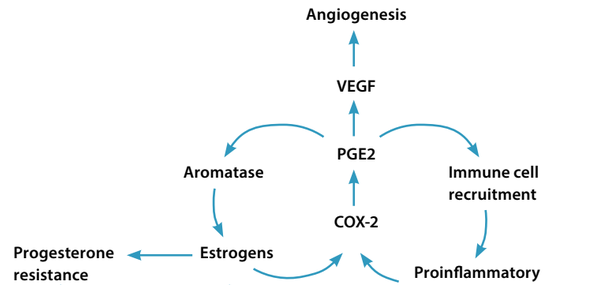
#### Endometrial lesions are major drivers of inflammation (Figure 1)

- Ectopic tissue that forms in EMS secretes proinflammatory cytokines (e.g., IL-1, IL-6, IL-8, and TNF-α), transforming growth factor (TGF)-β, vascular endothelial growth factor (VEGF), and chemokines (e.g., MCP-1), which promote a proliferative and angiogenic environment that enhances development and progression of EMS.[14]
- These proinflammatory mediators also increase cyclooxygenase-2 (COX-2) expression, which produces prostaglandin E2 (PGE2) that in turn induces aromatase (CYP19A1) production, leading to the biosynthesis of estrogens.[15]
- Excessive productions of both estrogen and PGE2 can further induce COX-2 expression, forming a positive feedback loop between inflammation and estrogen production in EMS.[16]

#### Proinflammatory state disrupts hormone regulation and immune function (Figure 1)

- Proinflammatory mediators in EMS lead to progesterone resistance via decreasing levels of progesterone receptor isoforms and disrupting receptor functions.[17]
- These inflammation-driven changes in progesterone signaling facilitate estrogen dominance and the establishment and maintenance of ectopic implants.[17]
- The proinflammatory state seen in EMS has been shown to suppress macrophage-mediated phagocytosis and clearance of the ectopic cells and endometrial fragments in the peritoneal cavity, which contribute to the survival of EMS lesions.[18] A more proinflammatory immune cell environment has also been described in EMS.[19]

**Figure 1. Brief summary of chronic inflammatory state, hormone dysregulation, and immune dysfunction in EMS.[14-19]**




#### Current pharmacological options are not optimal

- Oral contraceptives are an important treatment option for EMS-associated pain, as the pill helps prevent ovulation, decrease retrograde menstruation process, and inhibit proliferation of endometrial lesions.[20] However, it is not an option for women who want to become pregnant. Also, lesions and symptoms often return once treatment stops.
- An oral gonadotropin-releasing hormone (GnRH) antagonist has been approved by the FDA for the management of moderate to severe pain associated with EMS.[21] The higher dose regimen can be recommended for up to 6 months. However, a known adverse effect of the GnRH antagonist is a marked decrease in bone mineral density in the femoral neck, hip, and particularly lumbar spine,[21] for which add-back hormone therapy and regular bone density monitoring are necessary to minimize the negative impact.
- Pain medication such as the nonsteroidal anti-inflammatory drugs (NSAIDs) is another common treatment choice for EMS-associated pain, but clinical evidence of its effectiveness is very limited.[22] Further, NSAIDs are considered "resolution-toxic" via disrupting the productions of pro-resolving mediators and impairing inflammation resolution and tissue recovery.[23]

## References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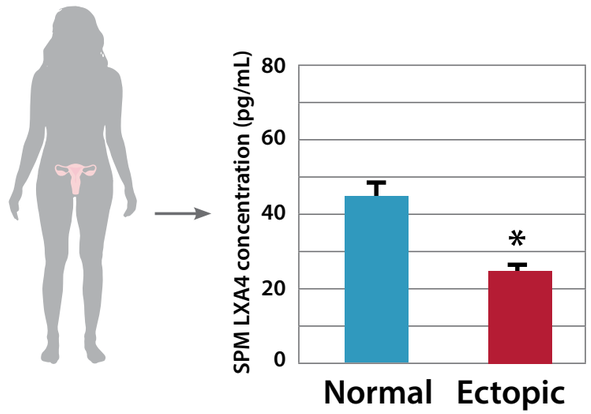
### Surgical options are associated with high risks and complications

- Surgical treatments such as laparoscopy are the primary treatment for patients with EMS and infertility and for patients who are not responding to other therapies. However, a recent study showed that although removing endometrial lesions resulted in a short-term reduction in inflammation, levels of proinflammatory cytokines returned to presurgery levels after 3 months, indicating that surgery was unable to remove all traces of the endometrial lesions or other disease-promoting factors.[24]
- The EMS recurrence rate after surgery was estimated to be 21.5% at 2 years and 40-50% at 5 years.[25] Also, surgery itself is an inflammatory event[26] and is associated with postoperative formation of adhesions.[19]

### SPMs and inflammation resolution

- Specialized pro-resolving mediators (SPMs) are lipid mediators derived from polyunsaturated fatty acids.[3] Several groups of SPMs have been identified such as lipoxins (LXs), resolvins (Rvs), maresins (MaRs), and protectins (PDs), which work together as "resolution agonists," actively coordinating the resolution of inflammation to bring about the resolution of the inflammatory cascade and return the tissue to homeostasis.[3]
- Mechanistic studies have demonstrated that SPMs decrease proinflammatory mediator production, limit neutrophil infiltration, and stimulate macrophage clearance of apoptotic neutrophils and cellular debris.[4]
- Given the link between EMS and inflammation, assessing the impact of SPMs and pro-resolving therapies is a promising area of research.

**Figure 2. Concentrations of SPM LXA4 in ectopic and normal endometrial tissue obtained from human patients.**




*p<0.001. Adapted from: Chen S et al. 2014.[5]

### In patients with EMS, SPM levels are reduced

- One study examined the endometrial biopsies from 30 women with confirmed EMS and 19 women without EMS. The concentration of SPM LXA4 (the only SPM measured in this study) was significantly decreased in ectopic endometrial tissue by nearly twofold compared with normal endometrial tissue (Figure 2).[5]
- A second study compared endometrial biopsies from 27 women with EMS and 20 control participants and also reported decreased LXA4 levels in ectopic tissue compared with normal tissue, confirming findings of the first study.[6] LXA4 was the only SPM measured in this study.

### Emerging preclinical data of SPMs involving animal and cell models of EMS

Preclinical research on the impact of SPMs in various *in vivo* and *in vitro* models is growing rapidly. Table 1 summarizes the data on SPMs in models of EMS.

**Table 1. Summary of SPM impact in preclinical animal and cell models of EMS**

| ***In vivo* models of *de novo* EMS or established EMS** | |
|---|---|
| **Summary** | **Key findings** |
| **Reduced endometrial lesion mass** | • **SPM LXA4 administration (i.p. injection) significantly inhibited the size, weight, or development of *de novo* endometrial lesions compared with control.[6,8-11]**<br>• **SPM LXA4 administration (i.p. injection) significantly reduced the progression of established endometrial lesions.[11]**<br>• **Mice with ability to biosynthesize SPM RvE3 from EPA had fewer endometrial lesions compared with mice with defective ability to biosynthesize RvE3, suggesting a protective role of RvE3.[7]** |
| **Reduced proinflammatory milieu** | **Treatment with the SPM LXA4:**<br>• **Decreased the mRNA expression and concentration of IL-1β, IL-6, TNFα, MCP-1, and VEGE in peritoneal fluid cells.[6,9]**<br>• **Significantly downregulated mRNA expression and concentration of multiple proinflammatory and angiogenic factors (e.g., IL-1β, IL-6, IL-10, MCP-1, TGF-β, and VEGE) in endometrial lesion.[10,11]**<br>• **Significantly inhibited COX-2 expression in endometrial lesion and peritoneal fluid cells, leading to reduced peritoneal fluid PGE2 levels.[11]**<br>• **Significantly alleviated inflammatory signs as indicated by decreased permeability of blood vessels in endometrial cysts.[12]** |
| **Modulated estrogen metabolism and signaling** | **Treatment with the SPM LXA4:**<br>• **Significantly downregulated aromatase mRNA expression, estrogen signaling, and estrogen-regulated genes involved in cell proliferation.[11]**<br>• **Had no effect on ovarian function.[8,10]** |
| ***In vitro* model using human endometrial stromal cells from women with EMS** | |
| **Summary** | **Key findings** |
| **Reduced proinflammatory milieu** | **Treatment of human endometrial stromal cells with the SPM LXA4 inhibited levels of IL-1β-induced inflammatory factors including IL-6, IL-8, MCP-1, TNF-α, and VEGF.[6]** |
| **Reduced cell proliferation and invasiveness** | **Treatment of human endometrial stromal cells with the SPM LXA4 suppressed cell proliferation and attenuated cell invasive activity.[6]** |

### Conclusions

The development of EMS is characterized by altered estrogen metabolism and signaling that is closely linked to a chronic proinflammatory state. Clinical evidence has demonstrated that levels of specific SPMs are reduced in the endometrial tissue of women with EMS. Although the impact of enhancing inflammation resolution via improvement of SPM status has not yet been tested in human clinical studies, emerging data in preclinical models suggest that administering specific SPMs may have the potential to attenuate multiple factors attributable to the development of EMS.