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Pathophysiology and Pathogenesis of Endometriosis

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Introduction

- "Endometriosis is a chronic gynecological disorder defined by the presence of endometrial tissues outside the uterine cavity; these lesions encompass glands and stroma that respond to local, exogenous, and endogenous hormones" (Vitale et al., 2018). This is an excellent description of Endometriosis, a gynecological condition that presents in women of reproductive age. Affecting approximately 10-15% of this population (Vitale et al., 2018), the percentage jumps to 35-50% when discussing women of reproductive age with pelvic pain and infertility (Sourial, Tempest, & Hapangama, 2014).
- This topic of both personal and professional interest to me as it has affected numerous women in my orbit. Although I do have a personal investment in this condition, ultimately I chose to research endometriosis because of the nebulous nature of the disease.
- Although endometriosis is extensively researched, agreement among researchers and clinicians regarding a definitive pathophysiological process remains elusive. The goal of this poster is to explore the most prevalent theories of origin of endometriosis through the current literature surrounding them.

Signs & Symptoms

- Cyclic or non-cyclic chronic pelvic pain
- Dysmenorrhea
- Mittelschmerz
- Dyspareunia
- Irregular uterine bleeding
- Infertility

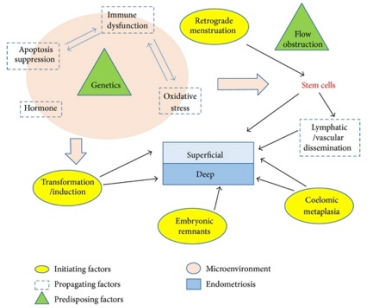

Figure 1. interaction between theorized factors at play in endometriosis pathogenesis (Sourial et al., 2014).

Presentation/ Diagnostics

- For some women, receiving a proper diagnosis of endometriosis can prove to be a long, frustrating, process. Burney and Giudice (2012) find that it takes approximately 6.7 years on average to receive a definitive diagnosis. Pain associated with endometriosis often, but not always, coincides with the timing of the menstrual cycle. The phrase "just period pain" is repeated often and is dismissive of very real concerns. That pain during the menstrual cycle is normal is a common misnomer.
- Further complicating the path to diagnosis is the fact that the severity of disease does not necessarily correlated with discomfort level. It very much depends on where in the body the disease is present. A woman can have advanced endometriosis and very little pain. Conversely, a mild case may cause an excruciating amount of pain.
- Currently there are no non-invasive biomarkers for diagnosis of endometriosis, and decisive diagnosis requires surgery, usually through laparoscopy (Sourial et al., 2014).
- A lack of noninvasive diagnostic tools greatly impairs the ability to follow a patient's progression and evaluate the effectiveness of surgical intervention. Adding to the confusion, there is currently no way to predict future disease progression once a surgical diagnosis has been made.

Theories of Pathophysiology

Retrograde Menstruation

Retrograde menstruation is the oldest and most widely accepted theory of origin of endometriosis. It was formulated in the 1920s and proposes that endometrial debris back flows through the fallopian tubes and into the pelvic cavity during menstruation (Sourial et al., 2014).

Although this is the longest-standing theory, it is controversial. It is estimated that up to 90% of healthy women experience retrograde menstruation (Burney & Giudice, 2012), however a small percentage of women develop endometriosis. This theory does not explain the presence of endometriosis in other, non-menstruating populations, such as pre-pubertal girls, newborns, and males (Sourial et al., 2014).

Coleomic Metaplasia

Coleomic metaplasia theory proposes that metaplasia causes epithelial tissue in the peritoneum to convert to endometrial tissue (Young, Brown, Saunders, & Horne, 2013). It is suspected that endocrine disrupting chemicals contribute to this transformation, but this is not well understood. Unlike other metaplastic diseases, endometriosis does not appear to worsen with age (Young et al., 2013). The occurrence of endometriosis primarily in the abdominal cavity also contradicts the nature of other metaplastic diseases.

Implantation theory is closely related to coleomic metaplasia, but goes a step further to propose that conversion to endometrial tissue is not enough to facilitate disease, but that cells must "Complete a process of adhesion, invasion, and proliferation" (Young et al., 2013, p. 559).

Apoptosis Suppression

A decrease in immune system scavengers in endometriosis naturally paves the way for a reduction in apoptosis. Sourial et al. (2014) observe, "The inhibition of the apoptosis of endometrial cells may also be mediated by the transcriptional activation of genes that normally promote inflammation, angiogenesis, and cell proliferation" (p. 4). In order to survive and proliferate, endometrial cells must be able to avoid destruction in an environment with such high cell turnover.

Hormones

Although there are many unknowns surrounding the etiology of endometriosis, its dependence on estrogen is widely supported. Estrogen facilitates the rapid turnover of the endometrium, and endometriotic lesions respond to and proliferate through increased amounts of estrogen. It is believed that endometriotic tissue has a decreased number of progesterone receptors (Burney & Giudice, 2012). According to Sourial et al. (2014), "Progesterone generally counteracts the proliferation promoting action of estrogen in the eutopic healthy endometrium" (p. 3). Endocrine disruptors in the environment have also been implicated in the facilitation of endometriosis. They act by mimicking estrogen in the body and can then move freely, binding with the body's estrogen receptors and increasing circulating levels (Sourial et al., 2014).

Oxidative Stress and Inflammation

Vitale et al. (2018) characterize oxidative stress as "An imbalance between reactive oxygen species (ROS) and antioxidants" (p.2). It has been observed that women with endometriosis have higher serum iron levels than those without. It is theorized that increased iron facilitates endometriosis by upending the balance between ROS and antioxidants and increasing the body's inflammatory response. The presence of macrophages contributes to this imbalance, as observed by Scutiero et al. Metabolism of iron by macrophages is increased in women with endometriosis (2017). Further, Scutiero et al. (2017) observe, "Peritoneal oxidative stress is currently thought to be a major constituent of the endometriosis-associated inflammation" (p.2). This cycle leads to prolonged inflammation and increased angiogenesis, fostering the proliferation of endometrial implants.

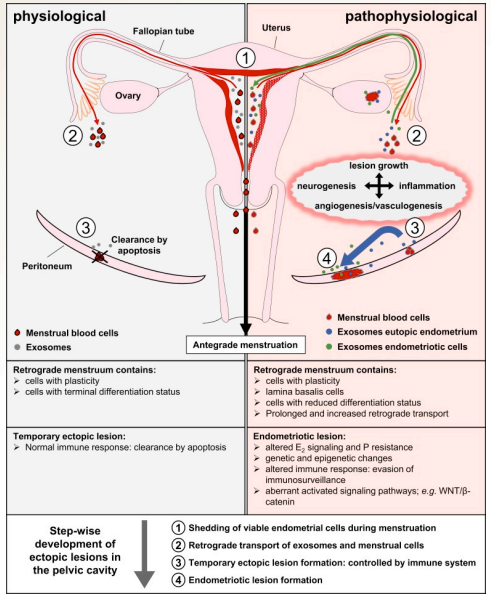

Figure 2. Overview of Multiple Theories of Endometriosis Development (Klemmt & Starzinski-Powitz, 2018)

Immune Dysfunction

Burney and Giudice (2012) observe strong support for the theory that women with endometriosis have a higher incidence of other autoimmune diseases, concluding that predisposition based on immune dysfunction is likely. The presence of endometriosis in individuals having undergone oophorectomy corroborates the theory of increased immune system involvement, specifically the innate immune system (Khan et al., 2018).

Endometriosis is an inflammatory condition, and women with the disease have "A higher concentration of activated macrophages, decreased cellular immunity, and a repressed natural killer (NK) cell function" (Sourial et al., 2014, p. 3). The accumulation of endometriotic lesions is advanced through angiogenesis due to increased vascular endothelial growth factors (Sourial et al., 2014).

Bacterial Contamination Hypothesis

The bacterial contamination hypothesis is relatively new, and proposes that the naturally bacteria-rich environment in the vagina inadvertently contributes to the facilitation of endometriosis, mainly through *Escherichia coli (E. coli)* contaminated retrograde menstruation and subsequent inflammation and immune response. Lipopolysaccharide (LPS) from *E. coli* and other gram-negative bacteria activate cells of the innate immune system. LPS then increases molecules like vascular endothelial cell growth factor (VEGF), which promote angiogenesis (Khan et al., 2017).

A parallel theory looks to the microbiome of the gut for an explanation of endometriosis development. The health of the gut is central to the cycling of estrogen, and disruptions in normal functioning can lead to increased levels of estrogen in the system (Laschke & Menger, 2016). Additionally, the level of macrophages in the peritoneum is believed to be increased by gut inflammation and permeability.

Mullerianosis

The theory of embryonic Mullerian rests, also known as mullerianosis theorizes that during fetal development mullerian tissue migrates into other areas of the body. This may serve as a precursor to development of endometriosis when puberty arises and reproductive hormones are activated (Burney & Giudice, 2012). This is similar to the metaplasia theory, and there is evidence of endometrial-like growths in the mullerian ducts of female fetuses (Klemmt & Starzinski-Powitz, 2018).

Significance of Pathophysiology/ Implications for Care

- Because there is no unifying theory on the pathophysiology of endometriosis, there is much room for interpretation of its significance. Although it is not a life-threatening condition, endometriosis can have deleterious effects on quality of life and the ability to conceive.
- Current management focuses on the reduction of inflammation and circulating estrogen, typically through birth control pills and ovarian cycle suppression (Sourial et al., 2014).
- Many women have multiple surgeries, some of which require serious procedures such as a bowel resection. Jacobson estimates that 75% of women who have had successful surgeries will have recurrent symptoms within two years (as cited in Young et al., 2013, p. 559).
- Although surgery is very common and does often provide relief, it is not without controversy. Some research argues that surgical intervention promotes disease recurrence (Sourial et al., 2014).
- Chronic pain and depression are not uncommon in this population.

Conclusion

Although there is an abundance of information available about endometriosis, there is little agreement among researchers in terms of conclusive theories of origin, and even less agreement regarding future progress. This is a condition that severely affects the quality of life of many women, and while the visibility of this condition has been increasing in recent years, there is much work to be done to eradicate it.

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