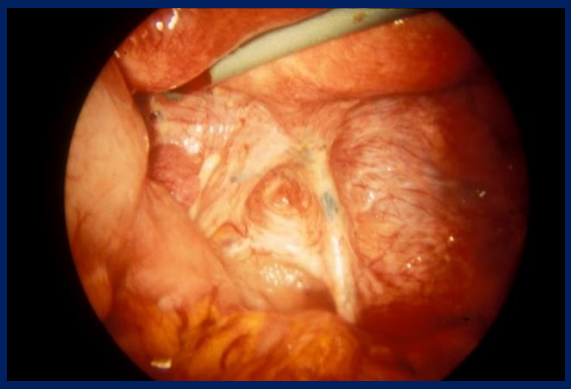
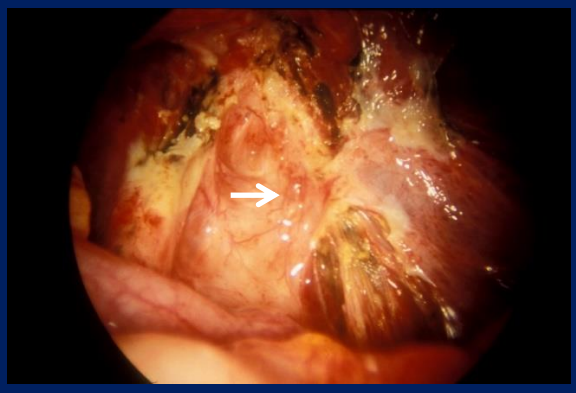
# Endometriosis Concepts and Theories





**Dan C. Martin**

***Foreword by John A Rock***

# Endometriosis
# Concepts and Theories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The main file for the next edition is periodically updated at www.danmartinmd.com/files/endotheory.pdf



Additional Resource:

Endometriosis Concepts: http://www.endometriosisconcepts.com/


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# Introduction

"*Please don't refer to endometriosis, adenomyosis, or fibroids as "benign disease" – nope, not benign, they are "common and morbid."*""

Linda G Griffith, Ph.D., 2020

*"Studying endometriosis is like nailing Jell-O to a tree."*

Donna Vogel, MD, Ph.D., 2000

Symptoms suggesting endometriosis were reported as early as 1855 BC (Kahun Medical Papyrus, Egyptian). (Redwine 2012, Nezhat 2012) The first description of endometriotic nodules may be Hippocrates (400 BC) noting that "part of the vagina hardens." (Whiteley 2003) Intraabdominal lesions with history compatible with endometriosis were noted in 1690 (Shroen). The histology of endometriosis and adenomyosis was described in 1860 (Rokitansky) and difficulty in recognition was documented in 1899 (Russell).

Sampson's publications beginning in 1918 expanded the study of endometriosis. Sampson (1925a) proposed the term "endometriosis" to replace the earlier "adenomyoma," "adenomas of the endometrial type," and other terms.

The articles summarized in this review are only a small part of what is published. A PubMed search for endometriosis 2/17/2023 listed 32,794 articles with 1,912 articles (5.3 daily) in the past year compared with 3.5 and 2.8 daily in the previous four years and nine years.

# Overview

- Endometriosis is heterogenous with more than 65 overlapping, visual and anatomic phenotypes published in 16 papers from 1921 to 2014. And there are many microscopic, biochemical, histochemical, immunological, genetic, and epigenetic phenotypes. It presents with heterogenous signs, symptoms, and behaviors and has a non-uniform response to hormonal, surgical, and anti-inflammatory therapy. The prevalence varies from 0.9% to 22% overall, 2.1% to 77.1% in infertile women, and

1.4% to 50.0% in fertile women (Simpson 1980, Guo 2006). It can regress, progress, or remain stable. There is debate about diagnostic criteria. Possible components of the criteria include endometriotic (endometrial-like) glands and stroma, evidence of bleeding, transition from a cell of origin to an endometriotic cell, vascularization, fibrosis, and the presence of CD10, IFITM1, BER-Ep4, Calretinin, CD34, antiendometrial antibodies or other characteristics.

- There are age-dependent, diagnosis, symptom, sign, and

imaging differences in appearances, depth of infiltration, and volume of lesions.

- The diffuse locations of endometriosis may be explained by retrograde menstruation, peritoneal dispersion, attachment, infiltration, and growth; peritoneal or pleural metaplasia; and hematogenous or lymphatic dissemination of Müllerian or non-Müllerian stem cells.
- Nodular rectovaginal lesions of 4 cm can be asymptomatic while 0.08 mm lesions have been associated with pain. Tenderness

can be found 27 mm from a visible lesion.

- Endometriosis can be hidden deep or behind adhesions; it can be missed in plain sight. Clinically unrecognized endometriosis was described as early as 1899 and nodules as large as 5 cm have been discovered beneath adhesions or scar and in ovaries, the retroperitoneum, tubes, lymphatics including nodes, open pockets, cryptic pockets, large and small bowel, appendices, epiploic fat, mesentery, and omentum. Surface endometriosis may not be visualized on the peritoneum when

it is microscopic, including stem cells.

- Coelomic metaplasia, immune overload, immune dysfunction, immune dysregulation, escape from immune surveillance, immune maturation, neuroimmune maturation, inflammatory induction, stem cells, epigenetic, and genetic changes may play a role in both women and men.
- Pulmonary, pleural, and mediastinal endometriosis may be a) retrograde menstruation with dissemination through diaphragmatic fenestrations or infiltration through the diaphragm,

b) hematogenous dissemination, c) diaphragmatic lymphatic dissemination, or d) coelomic metaplasia of the pleura.

- Retroperitoneal, retrocervical, and cul-de-sac endometriosis may be a) Müllerian remnants, b) pelvic lymphatics, c) retrograde with retraction, or d) hematogenous.
- Hematogenous sites may include pulmonary, spinal, dermal, and other distal sites.
- Early endometriosis may start with normal Müllerian (endometrium, endosalpinx or remnants) cells or non-Müllerian (peritoneal) stem cells. These undergoes reactive,

biochemical, hormonal, immunologic, epigenetic, and genetic changes in developing later and more severe forms of endometriosis. Bone marrow stem cells may engraft previous foci of endometriosis. Peritoneal metaplasia may be recruitment into preexistent endometriosis.

- Bone marrow–derived stem cells may engraft and “differentiate into multiple cell types including endothelial, muscle, stromal, and epithelial cells.” (Mamillapalli 2021) They are not specific for endometriosis.

- Sites of surgical transplantation include C-section scar, surgical excision scar including laparoscopy incisions, drain sites, episiotomies, and vaginal tears.
- *Inflammatory* stimuli can include estrogens, menstrual debris, surgical trauma, and infection.
- Fibrotic collagen reaction (fibrogenesis) with muscular metaplasia starts as part of a local inflammatory reaction with prolonged exposure to activated platelets or immune cells leading to increased expression of α-smooth muscle actin as part a pathologic process that Guo

(2018) characterizes as wounds undergoing repeated tissue injury and repair (ReTIAR).

- Neuroimmunologic maturation, decreased immunologic load, control by the hypothalamic-pituitary-adrenal axis, homeostasis of the sympathetic nervous system, immunocompetence, apoptosis, autolysis, and autophagy can limit infiltrative or expansive growth.
- Genetics, epigenetics, clonality, repeated tissue injury and repair (ReTIAR), peritoneal metaplasia as recruitment into preexistent endometriosis, engrafting of bone-

marrow stem cells into endometrium or endometriosis, neuroimmunologic maturation, neuroendocrine axis interaction, and homeostasis of the sympathetic nervous system also appear important.

## Resources

Laparoscopic Appearance of Endometriosis
1988 Images: https://www.danmartinmd.com/files/lae1988.pdf

Laparoscopic Appearance of Endometriosis, Second Edition
URL for updates: https://www.danmartinmd.com/files/coloratlas1990.pdf

Endometriosis Concepts
http://www.endometriosisconcepts.com

Endometriosis Concepts and Theories (PDF)
https://danmartinmd.com/files/endotheory.pdf

DanMartinMD.com links
https://danmartinmd.com/links.html

Dan Martin, MD at Google Scholar
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Endometriosis Foundation of America
https://www.endofound.org/

Endometriosis.org
http://endometriosis.org/

Endometriosis Association
https://endometriosisassn.org/

GynSurgery.com
https://www.gynsurgery.org/