ENDOMETRIOSIS CONCEPTS AND THEORIES

theory081617 - revised 6/16/18

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INTRODUCTION

This document focuses on concepts and theories that can offer students and patients an overview of what is happening and may also be reasonable in guiding research direction. However, therapy should be based on data and not on theory. A discussion of the Tomato Effect regarding problems of basing therapy on theory rather data is in this file.

It generally takes 5 theories to explain what I have seen and 10 or more to explain all I have read. This does not include Batt's 8 types and Laganà's unified theory as they include multiple theories. Since theories are only theories and since they have a habit of changing, you may also do well to follow changes in research that includes stem cell, inflammation and infectious diseases. Note that this document is updated periodically, but remains at the same URL: http://www.danmartinmd.com/files/theory081617.pdf

- The 5 needed to explain what I have seen:
  - Retrograde menstruation with peritoneal dispersion, attachment and infiltration
  - Replacement of endometrial cells by endometriotic cells or differentiation of stem cells into endometriotic cells
  - Immunologic maturation and competence
  - Surgical scar or traumatic vaginal tear implantation
  - Inflammatory induction
- 5 or more of the following are needed to explain what I have read:
  - Müllerianosis as Müllerian tissue in the normal embryologic Müllerian area
  - Müllerianosis as Müllerian tissue in non-Müllerian areas (choristoma)
  - Genetic predisposition
  - Genetic abnormalities
  - Epigenetic changes
  - Lymphatic dissemination
  - Hematogenous dissemination

TOMATO EFFECT

The tomato effect in medicine occurs when an effective treatment for a certain disease is ignored or rejected because it does not make sense in the light of accepted theories of disease mechanisms and treatment of these diseases. The tomato effect interferes with the acceptance and use of useful remedies. (Goodwin & Goodwin, JAMA, 1984;251: 2387-2390) Treatment decisions should be based on results. The results do not have to fit a theory.

According to Goodwin & Goodwin (1984), the only three issues that matter in picking a therapy:

- Does it help?
- How toxic is it?
- How much does it cost?

Goodwin & Goodwin's 3 issues can be expanded to risks, benefits, costs, acceptability, availability, insurance coverage and other associated concerns of using a therapy.

We do not have to understand how a therapy works for it to work. The results of surgical or medical therapy stand on their therapeutic outcomes, not on an opinion or a theory.

Discussions of theory are not discussions about the effectiveness of treatment. Excision, coagulation, vaporization or other forms of ablation do not depend on theory. Coagulation for superficial endometriosis was successful for many of my patients. Excision was good for many of the patients with deep endometriosis in my practice (DCM), just as they were in Dr. David Redwine's. His reoperation rate of 55%, with only 19% having histologic endometriosis, was like mine in the 1980s. (Redwine DB. Fertil Steril, 1991;56, 628-634)

In the later years of my practice, although the persistent pain rate remained relatively constant, I stopped doing as many repeat laparoscopies. Repeat laparoscopy after excision did not frequently succeed when success for a patient was defined as pain relief lasting more than six months. Note that less than 3 months relief is non-specific and may be a placebo response. I focused more on talking with them about their questions and concerns, helping them with realistic expectations, considering hormonal suppression, encouraging physical therapy, considering stress therapy, deciding about judicious use of narcotics, and more.

THEORIES AND CONCEPTS

1. Simpson 1980 - Genetic predisposition is generally seen as an observation, not a theory.
2. Russell 1899, Redwine 1988 - Müllerianosis (Mülleriosis) as a remnant or fragment of Müllerian tissue in or near the normal area of embryologic Müllerian development. See Nerune 2016 & Rei 2018 for male persistent Müllerian duct.
3. Iwanoff 1898, Sampson 1921 - Coelomic metaplasia of ovarian serosa
4. Meyer 1923, Gruenwald 1942 - Coelomic metaplasia of peritoneum
5. Halban 1925, Jerman, 2015 - Lymphatic spread (metastasis)
6. Halban 1925 - Hematogenous vascular spread (metastasis)
7. Batt 2013, Laganà 2017 - Müllerianosis as organoid remnant of Müllerian tissue in the normal area of embryologic Müllerian development.
8. Sampson 1921 - Peritoneal implantation from internally menstruating ovaries.

9. Sampson 1927 - Retrograde menstruation theory includes:
    - Retrograde menstruation of tissue fragments
    - Peritoneal dispersion
    - Attachment
    - Inflammation
    - Infiltration
    - Growth
10. Revisions of both Sampson and Müllerian theories include:
    - Metaplastic replacement of endometrial cells by endometriotic cells.
    - Gaetje 1997 - Invasion based on E-cad- epithelial cells
    - Starzinski-Powitz 2001, 2003 - Differentiation of stem cells into endometriotic cells
    - Klemmt 2017 - Other stem cell concerns include stem cell signaling, stem cell migration, immunogenicity, peritoneal cavity homeostasis, dysregulation of Wnt and/or Hox genes, phenotype and microRNA analysis.
11. Direct Implantation - Surgical scars or traumatic vaginal tears
12. Hamartoma - neoplastic Müllerian growth in the normal Müllerian area.
13. Choristoma - neoplastic Müllerian tissue in non-Müllerian areas
14. Halme 1988, Hill 1992, Northick 2016 - Lack of immunologic competence results in an inadequate response of the peritoneal defense system to the normal retrograde flow that is present in most women. Results in evasion of apoptosis of endometrial cells
15. Koninckx 1991 updated in Gordts 2017 - Deep endometriosis is endometriotic diseases. Superficial endometriosis either converts into endometriotic disease or is stopped by the immune system.
16. Koninckx 1992 - Deep endometriosis has 3 phenotypes
17. Evers 1994, Koninckx 1994 - Mild endometriosis is transient.
18. Fernandez 1995 - Bone marrow-derived cells in endometriosis
19. Nisolle 1997 - Peritoneal, ovarian, and rectovaginal nodules are three different entities
20. Leyendecker 1998 - Intrauterine tissue injury and repair at endometrial-muscularis interface (TIAR) due to intrauterine trauma.
21. Gazvani 2002 - Peritoneal environment associated with development
22. Bulun 2004 - Inflammatory reaction exponentially increases local aromatase activity
23. Chan 2004 - Endometriosis is clonal
24. Marsh & Laufer 2005 and Cabana et al. 2010 - Inflammatory induction
25. Ohlsson Teague 2009 - MicroRNA-regulated pathways associated with endometriosis
26. Brosens 2013 - Progressive disease
27. Raposo 2013 - Extracellular vesicles involved in intercellular communication (signaling)
28. Kobayashi 2014 - Infectious precursors or induction
29. Gargett et al. 2014, Brosens 2015 - Perinatal retrograde dissemination is like Sampson but suggests an earlier occurrence shortly after birth.
30. Forte 2014 - Chromosomal anomalies and instability can alter gene expression

31. Guo 2015 - Repeated tissue injury and repair (ReTIAR) due to cyclic bleeding in endometriosis.
32. Laux-Biehlmann 2015 - Pain due to activation of peripheral nerve endings in response to retrograde and extra-uterine menstruation
33. Nerune 2016 - Persistent Müllerian Duct Syndrome (PMDS) in men.
34. Laganà 2017 - "Unus pro omnibus, omnes pro uno" is a combination of many of the other theories
35. Vigano 2017 - Fibrotic condition with endometrial stroma and epithelium.
36. Liu 2017 - Epithelial-mesenchymal transition, fibroblast-to-myofibroblast transdifferentiation, smooth muscle metaplasia, fibrosis, vascularity, hormonal receptors, and proteins involved in epigenetic modifications. Differences may result from the different lesional microenvironments.
37. Makiyan 2017 - Congenital primordial germ cells remnants
38. Anglesio 2017 - Cancer-associated driver mutations
39. Klemmt 2017 - Lack of apoptosis, evasion of immunosurveillance, angiogenesis, neurogenesis, exosomes, plasticity, aberrant activated signaling pathways.
40. Brosens 2018 - Requires active neo-angiogenesis.
41. Panir 2018 - Non-coding RNA associated with endometriosis
42. Other concerns include peripheral mononuclear cells recruitment, inflammatory cytokines, angiogenic cytokines, fibrogenic cytokines, and more.

INFECTION

Marsh and Laufer and Cabana et al. did not exclude infection as the source of the inflammation in their publications. See "Subtle Inflammatory Lesions" below.

Gazvani et al. (J Endometriosis Pelvic Pain Disorders, 2013;5:2-9) suggested that C. albicans may contribute to the pathogenesis of endometriosis by modulating cytokine production.

Kobayashi et al. (Mol Med Rep, 2014; 9, 9-15. doi:10.3892/mmr.2013.1755) concluded that infection and/or sterile inflammation are involved in endometriosis development.

Khan et al. (J Endometriosis Pelvic Pain Disorders 2016;8:2-7) found higher intrauterine microbial colonization with endometriosis.

Cicinelli et al. (Fertil Steril 2017; DOI 10.1016/j.fertnstert.2017.05.016) concluded that chronic endometritis may represent a facilitating factor for the development of endometriosis.

Canis et al. (J Gynecol Obstet Hum Reprod. 2017 Mar;46(3):219-227) considered "occult pelvic inflammatory disease" as a potential initiating events for endometriosis."

But, none of these of clarified why infection did not result in overt pelvic inflammatory disease.

SUBTLE INFLAMMATORY LESIONS

An additional concern is raised by inflammatory lesions suggestive of endometriosis in adolescents and children. (Marsh and Laufer 2005, Cabana et al. 2010) If these are infectious, then antibiotics can treat active infection and potentially decrease long-term morbidity.

1. If endometriosis is related to infection, then antibiotics may decrease the morbidity of endometriosis
2. If an infection is only coincidental, antibiotics with may:
   - Treat infection
   - Decrease chronic pelvic pain
   - Decrease pelvic inflammatory disease

Marsh EE, Laufer MR. Endometriosis in premenarcheal girls who do not have an associated obstructive anomaly. Fertil Steril 83 (3):758-760, 2005

Cabana MD, Foster-Barber AE, Hong T, Martin DC, Shenkin B. Teen troubled by a trembling leg. Contemporary Pediatrics. 27(6):22-27, 2010

MÜLLERIOSIS, MÜLLERIANOSIS & UNUS PRO OMNIBUS, OMNES PRO UNO.

Retrograde reflux, Müllerianosis, and Mülleriosis theory are incomplete. Although it is easy to see and understand retrograde menstruation, dispersion and initial attachment, the intricate interactions that control or fail to control persistence, infiltration, and growth, in addition to the histologic, biochemical, and immunologic differences between endometrial and endometriotic lesions, are still matters of research. In contrast, congenital, non-midline, Müllerian remnants such as accessory and cavitated uterine masses (Acien et al. Hum Reprod, 2012; 27, 683-694) are non-inflammatory, organoid examples of another variation on Müllerian concerns.

Ron Batt has eight forms of Müllerian abnormalities. Four of those are congenital and four are acquired. (Batt & Yeh, Reprod Sci, 2013;20, 1030-1037) His presentation of this at the Endometriosis Foundation of America is at
https://player.vimeo.com/video/125963026

Antonio Lagana's Unus pro omnibus, omnes pro uno includes multiple theories and is an excellent summary. (Med Hypotheses, 2017; 103:10-20)

A 2017 review of the molecular and cellular pathogenesis of endometriosis is:
Klemmt P, Starzinski-Powitz A. Molecular and cellular pathogenesis of endometriosis. Current Women s Health Reviews, 2017, 13(999):1-11. DOI: 10.2174/1573404813666170306163448
https://www.researchgate.net/publication/316840373_Molecular_and_Cellular_Pathogenesis_of_Endometriosis

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https://www.researchgate.net/publication/316840373_Molecular_and_Cellular_Pathogenesis_of_Endometriosis

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