Endometriosis Concepts and Theories

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This document is updated periodically. An update may be available at

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“Studying endometriosis is like nailing Jell-O to a tree.”

Donna Vogel, MD, PhD, NIH Endometriosis 2000

Introduction

This document covers symptoms since 1855 BC (Egyptian Papyrus), histology of ovarian endometriosis or endometrioid cancer in 1860 (Rokitansky), theory since 1870 (Waldeyer), difficulty in recognition since 1899 (Russell), and other concerns and theories. A theory may be useful at several levels including guiding research, acting as a framework for education, understanding possibilities in endometriosis, explaining why changes occur in endometriosis, and explaining why treatment might work. In contrast, the Tomato Effect discusses how theory has interfered with treatment. Medical Reversal is a parallel concern that can interfere.

No concept or theory is entirely adequate. It takes eighteen to introduce what I have seen or published and many more to discuss what I have read. This is a work in progress and will be periodically updated and posted at the addresses above.

- Endometriosis is heterogenous with more than 65 published, overlapping, visual and anatomic phenotypes and many biochemical, histochemical, immunological, and genetic phenotypes. It presents with heterogenous signs and symptoms and has a non-uniform response to hormonal, surgical, and anti-inflammatory therapy.
- There are age-dependent changes in appearances and depth of infiltration.
- Retrograde menstruation, peritoneal dispersion, attachment, infiltration, and growth; peritoneal metaplasia; and hematogenous or lymphatic dissemination of Müllerian or non-Müllerian stem cells can explain the diffuse locations of endometriosis.
- Coelomic metaplasia, inflammatory induction, and stem cells 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.
- 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 starts with normal Müllerian (endometrium or remnants) or non-Müllerian cells (bone marrow stem cells). These undergoes reactive, biochemical, hormonal, immunologic, and genetic changes in developing later forms of endometriosis.
- Sites of surgical transplantation include C-section scar, surgical excision scar including peritoneal excision sites, drain sites, episiotomies, and vaginal tears.
- Inflammatory stimuli can include menstrual debris, surgical trauma, and infection.
- Fibrotic collagen reaction with muscular metaplasia starts as part of a local reaction.
- Immunologic maturation, immunocompetence, apoptosis, and autophagy limit growth.
Retropertitoneal, rectovaginal, and retrocervical endometriosis may be Müllerian remnants (Koninckx 1992, Donnez 2001, Signorile 2009, 2010 & 2012), lymphatic metastasis, the result of retrograde with retraction, or hematogenous metastasis. However, hidden, retroperitoneal endometriosis in women and any endometriosis in men are rare. Rei (2018) found only 17 cases in men in the world literature from 1971 to 2018. The 17 male cases and retroperitoneal cases in women are limited to the genital and lower abdomen areas and are therefore not a model for the diffuse locations of female endometriosis. Also, if organoid, a Müllerian remnant could be expected to look like an accessory and cavitated uterine mass (Acién 2012). In contrast, the location of most female cases of endometriosis, including retroperitoneal, can also be explained with retrograde, hematogenous, lymphatic, or extensional dissemination.

Furthermore, various forms of trauma such as delivery, uterine curettage, intraabdominal surgery, retroperitoneal menstruation, intraperitoneal hemorrhage, or occult pelvic inflammatory diseases may mitigate the ongoing course and chance of recurrence. That might even include intraabdominal surgery as an inflammatory or fertile site for peritoneal implantation.

This review covers the source of the cell of origin, methods of dissemination (metastasis), and why, how, and when the cell of origin (early endometriosis) transitions to late endometriosis. Some theories include cell of origin, dissemination and metastasis as one concept. This discussion considers those to be, at least partially, independent.

- **Cell of Origin**
  - Müllerian, Endometrium
    - Whole Tissue Endometrial Fragments
    - Precursors in normal whole tissue endometrial fragments
    - Precursors in traumatized endometrium
    - Mesenchymal Cells
    - Stromal Stem Cells
    - Epithelial Stem Cells
    - Intrauterine Changes
  - Müllerian, Embryonic Remnants
    - Organized Fragments
    - Stem Cells
    - Müllerian Remnants (any congenital)
    - Müllerianosis (organoid and non-organoid)
    - Müllerosis (non-organoid and projected to include dissemination and transition)
  - Non-Müllerian Metaplastic (Differentiation) Theories
    - Peritoneal or Pleural Mesothelial Coelomic Metaplasia
    - Mesenchymal Stem Cells
    - Bone Marrow Stem Cells

- **Dissemination (Metastasis)**
  - Retrograde Menstruation, Implantation and Infiltration
  - Hematogenous Dissemination
  - Lymphatic Dissemination
  - Uterocervical Extension
  - Traumatic / Surgical transplantation
  - Growth (expansion or infiltration)
  - Embryonic Dissemination
    - The usual Müllerian area is the upper vagina, the uterus, and the tubes.
    - Dissemination of embryonic rests to non-Müllerian areas.
      - Pelvic peritoneal area, ovaries
      - Other body areas (bowel, diaphragm, lungs, eyes, and others)
• Transition

The transition from normal Müllerian or non-Müllerian stem cells to later forms of endometriosis such as infiltrating or endometrioma appears to hold the most potential for future research and therapeutic options. Transition involves the cellular, histological, biochemical, reactive, immunological, genetically driven, genetic, gene regulatory (non-hereditary epigenetic), hormonal, and other changes that distinguish late endometriosis from endometrium, Müllerian remnants, or non-Müllerian stem cells. Those changes involve the local environment, implantation, growth, exposure to endocrine-disrupting chemicals, inflammation, environmental gene regulation, immune system maturation, immune system competence, endotoxins, progenitor cell differentiation, proliferation, biochemical changes immunologic changes, apoptosis, anti-apoptosis, autophagy, reactive oxygen species, fibrosis, muscular metaplasia, macrophage migration inhibitory factor, clonality, microRNA, signaling, nerve activation, cancer-associated driver mutations, fibroblast to myofibroblast transdifferentiation, neurogenesis, angiogenesis, genetic dysregulation and more that are covered in this document.

The articles listed in this review are only a small part of what is published. A PubMed search for endometriosis 3/31/20 listed 27,717 articles that include many parts of the endometriosis story. That included 1,381 in 2019 (3.7 articles daily) and 439 in 2020 (4.9 articles daily). In addition, scholar.google.com lists 388,000 articles (increase of 23,000 since 4/13/19) and the NIH GEO database has more than 291,000 array- and sequence-based data.

Concerns include theories, heterogeneity of endometriosis, non-standardized approaches, results of treatment, biochemical testing, immunologic testing, stromal markers, epithelial markers, inflammatory reaction, fibrosis, muscular metaplasia, histology, histochemistry, spontaneous resolution of endometriosis, stages, phenotypes, aromatase production, hormonal levels, miRNA, embryology, neonatal development, genetics, environmental gene regulation (non-hereditary epigenetics), organoid development, stromal type endometriosis, endometriosis in men, bone marrow stem cells in endometriosis, differentiated stem cells, primordial germ cells, programmed death (apoptosis), oxidative stress, angiogenesis, neuroangiogenesis, and transitions into mesenchymal cells.

Concepts and Theories

1. Kahun Medical Papyrus 1825 BC vs. 1855 BC – Discussed in Redwine 2012 and Nezhat 2012 as the oldest known medical text. This hieroglyphic text discusses symptomatology such as pelvic pain but is not sufficiently specific to determine if the pelvic symptoms were those of endometriosis. Additional historical findings from Redwine (2012) and Nezhat (2012) include Hippocrates’ (400 BC) notation that “a part of the vagina hardens” may be the first description endometriotic nodules. Johnstone’s (1777) described an isolated rectal stricture, Rutter (1808) added the scirrhoue characteristic, and Seymour (1830) noted a rectovaginal location. Chocolate cysts with iron noted on chemical analysis and probable endometriomas or hemorrhagic corpus lutea (see Martin 1990) were reported by Lobstein (1820). Also, see Hippocrates (466 – 377 BC), Müller 1830, and Knapp 1999.

Redwine DB. Googling Endometriosis - The Lost Centuries. https://drive.google.com/file/d/1UlBmdgddjD5eO-1TxW0mpky_vT97f2U2/view?usp=sharing

2. Hippocrates’s (466 – 377 BC) – From Whiteley 2003 and quoted in Redwine 2012 - Hippocrates’s theories were based purely on observation and experience. His observation “… when, in a woman who has not given birth, the menses stay away or are not able to find a way out, disease occurs, and this happens—either the mouth of the womb closes, or it doubles back upon itself, or a part of the vagina hardens” may be the first description of nodules. Kathleen Whiteley PhD thesis (2003) http://uir.unisa.ac.za/handle/10500/1620
3. Shroen 1690 – Shroen is referenced in Knapp 1999 as describing “ulcers” that Knapp concluded were endometriosis. The symptoms Shroen described were more of pain than fever and are compatible with endometriosis. Histologic description was in its infancy in the 17th century and is not in the paper. If the term “ulcers” in the seventeenth century can mean the same as the current concept of “lesions,” then this may have been endometriosis. See Knapp 1999 for Shroen and five 18th century reference.
5. Rokitansky1860 – Rokitansky published a description of the histology of “ein ovarial-cystosarcom” as what we now call either an ovarian endometrioma or endometrioid cancer. His description of the findings in a 68-year old can be interpreted as either cancer or endometriosis. He also discussed adenomyosis and endometrial polyps. From Batt R. Intellectual Development of Carl Von Rokitansky. Batt 2011b
6. Waldeyer 1870 – Waldeyer concluded that epithelial ovarian cysts were from metaplasia (metamorphosis) developing in nests of cells in the germinal epithelium of an ovary. This might be the first recognition of a progenitor cell for epithelial cells. The germinal epithelium of an ovary had also been considered as the precursor to eggs. See Iwanoff 1898 for coelomic metaplasia and Lauchlan 1972 for metaplasia from a secondary Müllerian system. See Zamecnik 2013 for case report of metaplasia in men.
10. Von Recklinghausen 1896 (quoted in Casler 1919) – The Wolffian theory proposes that adenoma (later called endometriosis) result from intermingling when the Wolffian and Müllerian ducts cross in fetal development. Also used as one possibility of uterine adenomyosis by Cullen in 1897.
11. Russell 1899 – Clinically unrecognized, intraovarian endometriosis was discovered in an ovary with adhesions. Discusses theories including remnants of the germinal epithelium, extension of tubal epithelium, a Wolffian body, and a Müller’s Duct remnant. See Waldeyer 1870 for germinal epithelium, Marchand 1879 for extension of tubal epithelium and Sampson 1921 and 1927a for endometriosis within adhesions.
12. Füth 1903 – Illustration of recto-corporeal endometriosis labeled as being in the recto-vaginal septum reported in Lockyer 1918.
13. Clark 1908 (quoted in Kelly 1931) – Clark developed useful electrosurgery.
14. Stevens 1910 – Isolated small vaginal wall nodules with characters of diffuse adenomyoma of the uterus. Stevens contended that a Wolffian origin was more than likely for the small adenomyoma than Müllerian origin.
15. Lockyer 1913, Cullen 1914, Stevens 1916 – Rectovaginal lesion with fibrous and muscular components like adenomyoma that are compatible with what would later be called rectovaginal endometriosis. They concluded these were in the rectouterine (Lockyer) and rectovaginal (Lockyer, Cullen, Stevens) septum. But, see Martin 2001 and Batt 2014 for normal location of the rectovaginal pouch and rectovaginal septum. Lockyer, Cullen, and Stevens’ findings were in the normal area of the rectovaginal pouch, not the normal area of the septum. Lockyer supported Wolffian remnants theory.
16. Stevens 1916 – Adenomyomatous growths arise in the uterus and invading the rectum, sigmoid, and other parts. These may have an endometrial, Müllerian duct, Wolffian remnants or peritoneal endothelium origin.
17. Hueter 1918, Meyer 1919, Meyer 1924, Alifano 2006 – Inflammatory coelomic metaplasia of mesoderm may include both peritoneum and pleura.
19. Lockyer 1918 – This first classification was of the anatomic location of adenomyomas that were later called endometriosis.
20. Casler 1919 – Report of cyclic bleeding from ovarian adenoma (later called endometriosis) through a vaginal fistula after hysterectomy. Also discusses Von Recklinghausen’s Wolffian theory of intermingling when the Wolffian and Müllerian systems cross in fetal development.
21. Sampson 1921 – Discusses peritoneal implantation from internally menstruating ovaries, differences between native endometrium and “adenomas of endometrial type” both “in structure and function,” and adenomyosis as different than adenomyoma. “Adenomas of endometrial type” preceded his use of the term endometriosis. Adhesions between the rectum and uterus had adenoma of the endometrial type in 72% of cases.
22. Sampson 1922, Halban 1924, Jerman 2015, Jerman 2020 – Lymphatic spread (metastasis) of the endometrium
24. Sampson 1924 – There are multiple appearances including red raspberries, purple raspberries, blueberries raspberries, hemorrhagic blebs, and clear blebs. Invading lesions are older than superficial lesions. See age related changes in Karnaky 1969, Redwine 1987, Davis 1988, Koninckx 1991
25. Sampson 1925 – Discusses endometriosis phenotypes, true endometrial (Müllerian) tissue derived from the uterine or tubal mucosa, pseudo-endometrial tissue which arises from remnants of the Wolffian body, metaplasia of the peritoneal serosa, transplantation, and distant metastasis. He concludes that endometriosis is a Müllerian derivative. This may be the first mention of “endometriosis.”
27. Sampson 1927a, Nap 2004a, Nap 2004b, Nap 2012 – Sampson suggested retrograde menstrual as “a,” not “the,” source of endometriosis. He suggested additional theories, such as coelomic metaplasia and venous dissemination might cause some lesions. He added the transition from endometrium to endometriosis to his 1921 observation that endometriosis was different in “both in structure and in function”.
Retrograde menstruation theory includes:
- Endometriosis differs from endometrium in structure and function. Histologically normal endometrium and endometriosis can coexist, and a transition can be seen. See Karnaky 1969 regarding animal research and Koninckx 2018 for the transition from endometrium to endometriosis. Also see Evers 1994, Koninckx 1994, Koninckx 1999, Harrison 2000, and Nap 2004a.
- The cell of origin - Endometriolar fragments or cells
- Dissemination - Retrograde menstruation of tissue fragments or cells
- Peritoneal dispersion
- Attachment
- Inflammation
- Infiltration
- Growth
  o Fibrosis
  o Entrapment
  o Muscular metaplasia
His 1927a article also discussed endometriosis within the adhesions of hemorrhagic cysts.
Revisions of dispersion (retrograde menstruation, lymphatic, hematogenous, traumatic, surgical), congenital (Müllerianosis (organoid), Mülleriosis (non-organoid), secondary Müllerian system) and metaplasia theories have been expanded to include the role of stem cells, replacement of endometrial cells by late endometriotic cells, differentiation of stem cells into endometriotic cells, and other concerns reviewed in the references that follow.
28. Sampson 1927b – Discusses use of extirpated uterine specimens to develop the data for his 1918 article and how that expanded into this study demonstrating the vascular dissemination of endometrial tissue. See Yovich 2020 for review with Sampson’s 1927b illustrations. See Vallvé-Juanico 2019 for circulating stromal cells.
29. Hunter 1927 – Early research on grafting of endometrial fragments.
31. Ferguson 1929, Nora 1956, Steck 1965, Kaunotz 1979, Rock 1981, Donnez 1984 – Direct implantation of endometrium or endometriosis in surgical scars, drain sites, amniocentesis needle tract or traumatic vaginal tears may be from denuded surface, trauma, or inflammation.
32. Novak 1931 – Metaplasia due to hormonal stimulation
34. Sampson 1940 – Discusses the detail needed for research including attention paid to small implants, sketches, section of sections to be submitted, supervision of technicians, and giving cutting instructions. Noted that endometriosis can remain small and superficial. See Goldstein 1980 on close-up view, Redwine 1988a on near-contact laparoscopy, and Martin 2006 on STARD.
35. Geist 1941 (reviewed in Brosens 2011) – Geist advocated the use of androgens in gynecological disorders. Brosens (2011) is a free download at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3135985/

36. Karnaky 1948, Karnaky 1969 – Karnaky proposed the use of the synthetic estrogen diethylstilbestrol (DES) to produce amenorrhea and suppress endometriosis.

37. Fallon 1946 – 13 to 19-year-old with endometriosis

38. Clark 1948 – 11-year-old with endometriosis.


40. Scott & TeLinde 1950 – Early discussion of excision and fulguration (ablation)

41. Meigs 1953 – Meigs recommended early and frequent childbearing as prophylaxis.


43. Fallas 1956 – Cervical and upper vaginal agenesis associated with retrograde menstruation and severe endometriosis.

44. Kistner 1958 – Kistner proposed a state of “pseudopregnancy” to reproduce the improvement noted in endometriosis during and after pregnancy. He postulated that decidualization that results in necrosis and elimination of superficial endometriotic implants. Also, see Klemmt 2006 & Aoyagi 2017.

45. Freidman 1959 – Müllerian epithelium was noted in an exophytic bladder in a male. This AFIP slide was reported in Oliker 1971.

46. Kantor 1963 – Endometriosis due to retrograde menstruation may be a different disease than endometriosis due to embryonal rests. Two phenotypic disease theory.

47. Merrill 1966 – “Merrill factor” (quoted in Suginami 1991) is a metaplasia-inducing substance such as estrogen and a factor liberated from degenerating menstrual endometrium. Also, see Thomas 1996.


49. Karnaky 1969, Redwine 1987, Davis 1988, Koninckx 1991 – There is a 4 to 20-year progression from an initial water blister lesion (clear papule) to red to hemorrhage to scar to scar with blue dome cysts (black only appearance) to deep infiltrating endometriosis. Diagnosed endometriosis in the absence of hemosiderin. See Sampson 1924.

50. Karnaky 1969 – Endometrium and endometriosis respond differently to antiestrogen therapy. He further notes that the differences in humans were not seen in monkeys and questions if monkey research might be on transplanted, native endometrium and not endometriosis. He felt this supported the theory of coelomic metaplasia.

51. Oliker 1971 – This is the first report of endometriosis in a 46 XY male. See Friedman 1959 for Müllerian epithelium, Melicow 1967 for prostatic endometrial cancer, and Nerune 2016 for male pseudohermaphroditism. Seventeen reports of endometriosis or endometrial cancer were summarized in Rei 2018. Most were older and on estrogen therapy.

52. Lauchlan 1972 – Differentiation of precursor tissue in a secondary Müllerian system may be responsible for endometriosis outside the normal Müllerian developmental area. He felt that pelvic endometriosis was most compatible with retrograde while distal, non-abdominal sites might be hematogenous dissemination or metaplasia. He also noted that endometriosis is histologically different from endometrium with a mixture of cell types. See Cullen 1914 for fibrous and muscular components. (Author’s Note: Many peritoneal endometriotic lesions
are outside the normal Müllerian area including ileum, appendix, cecum, lateral gutters, and diaphragm.)


54. Kistner 1975 – Surgery improves pregnancy rates. “Early implantations on the surface of the “peritoneum should be excised. Electrocoagulation is not recommended because of the possibility of subsequent adhesions to the small intestine or the adnexal structures.”


57. Malinak 1979 – Nodules and large implants require excision. Small lesions with no nodules or infiltration can be fulgurated (coagulated). Recurrence rates were 12% to 40%.

58. Mettler 1979 – Reported on ovarian cyst resection but concluded that more than “coagulation of endometriotic foci cannot be performed via the laparoscope.” See Semm 1980. Note: Mettler and Semm were co-workers at the University of Kiel.

59. Goldstein 1980 – Endometriosis in adolescents as young as 10.5 years old with petechial lesions. Karnaky 1969 discussed young girls. Also, see Schifrin 1973

60. Goldstein 1980, Redwine 1988a – A “close-up” or “near-contact” view is better for recognizing subtle, atypical, consisting of petechial-like areas, appearances of endometriosis. Redwine’s (1988a) “near-contact” is more descriptive of the technique.

61. Simpson 1980 – Genetic predisposition is generally seen as an observation, not a theory.

62. Semm 1980 – The depth of coagulation is not adequate for large nodules, and laparoscopic partial excision needs to precede coagulation for those.

63. Koninckx 1980 – After ovulation, peritoneal fluid contains concentrations of progesterone and of 17 β-estradiol that are 5 to 20 times higher than plasma concentrations in women with ovulatory cycles but not in women with unruptured luteinized follicles. Since viable endometrial cells were found in the peritoneal fluid of over 50% of women, both with and without endometriosis, pelvic endometriosis could be the consequence of infertility caused by an unruptured luteinized follicle. Cells were likely from retrograde menstruation as they occurred with and without endometriosis. See Dmowski 1981, Halme 1983 & Halme 1984 for hormonal or immunologic factors and Dorien 2017 for update.


66. Blumenkrantz 1981 – Blood in the peritoneal dialysis catheter just before menstruation was regularly observed in 9 of 11 premenopausal women maintained on peritoneal dialysis for end-stage renal failure. Peritoneal bleeding at other times during the menstrual cycle was not seen in any of these patients. Likewise, peritoneal bleeding in men or nonmenstruating women on chronic peritoneal dialysis was exceedingly rare, was not periodic, and usually was due to recognizable causes. These observations suggest that retrograde menstrual bleeding into the peritoneal cavity is the rule rather than the exception in women on peritoneal dialysis and possibly in all menstruating women. See Watkins 1937, Watkins 1938, Koninckx 1980, Dmowski 1981, Halme 1984, Halme 1988, and Dorien 2017.


70. Badawy 1983 – Macrophages and lymphocytes were the dominant cells in peritoneal fluid of women. These cells were significantly increased in endometriosis patients, as compared with control subjects. In addition, peritoneal fluid acid phosphatase, PGF2 alpha and PGE2, and complement components C3c and C4 were significantly increased in patients with endometriosis. These cellular changes and their activation in peritoneal fluid may explain infertility associated with endometriosis.

71. Halme 1984, Halme 1988 – Halme noted that retrograde menstruation was more common than endometriosis. Therefore, other factors, either hormonal or immunologic, influence the development of endometriosis. See Koninctx 1980 for peritoneal fluid endometrial cells, Dmowski 1981 for the role of the immune system, and Dorien 2017 for discussion of the possibilities of involvement of endometrial epithelial/stromal cells, involvement of bone marrow stem cells, induction by other substances in menstrual fluid, and the findings being the consequence rather than the cause of endometriosis.

72. Semm 1984 (German), Semm 1987 (English) – “The surgical excision of endometriosis implants is still considered the optimal treatment of pelvic endometriosis.”

73. Malinak 1984 – Recurrence rates are likely higher than published due to asymptomatic recurrence.


75. Vernon 1986 – There are differences in prostaglandin production in the four (4) surface phenotypes examined. “Petechial implants may be more pathologically influential than older implants.” “A patient who presents with severe, progressive dysmenorrhea but is shown at laparoscopy to have minimal disease may have exaggerated pain symptoms as a result of the presence of the more biochemically active, petechial implants, whereas a patient with extensive disease may have minimal pain symptoms due to the presence of primarily inactive, powder-burn implants.” See Davis 1993

76. Taylor 1986 – Clarifies that CO2 laser thermal burn (cautery) is more significant than penetration at low power densities with thermal coagulation of 2.7 mm at 30 watts/cm2. Also, see Luciano 1987.

77. Thomas 1987 – Hormonal suppression with gestrinone after laparoscopy decreases the risk of progression compared with no suppression. Spontaneous regression occurred in both groups. See Dmowski 1975.

78. Luciano 1987 – The thermal effect of CO2 laser and electrosurgery are similar at high power density. Depths of coagulation less than 0.2 mm at > 58,000 watts/cm². See Taylor 1986.

80. Martin 1988a, Angioni 2006 – Deep excision to the vagina with laparoscopic colpotomy. Drs. Richard “Pete” Hollis, Harry Reich and Gordon Davis were instrumental in the development of these deep excisional techniques.

81. Halme 1988, Hill 1992, Giudice 2004, Northick 2016, Pavone 2016, Koninckx 2018 – 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. The inadequate immunologic response results in evasion of apoptosis allowing endometriosis cells to continue to live. According to the peritoneal immune surveillance hypothesis, only women with a local and/or systemic immune defect develop late endometriosis. In Koninckx 2018 called late endometriosis “endometriotic disease.”

82. Redwine 1988a – Redwine’s “near-contact” is a more descriptive term than Goldstein’s 1980 “close-up” view needed for recognizing subtle, atypical, and petechial-like appearances of endometriosis.


84. Batt 1989 – Medial ureteral position due to an attenuated uterosacral ligament or as the medial border of a large fossa associated with endometriosis is congenital.

85. Martin 1989 – The diagnosis of endometriosis at laparoscopy increased from 42% in 1982 to 72% in 1988. The greatest change was in “subtle” lesions, which increased from 15% in 1986 to 65% in 1988. Thirteen of the 20 laparoscopic surface appearances of endometriosis were phenotypic. In 2018, we do not know if only some or all these have similar or contrasting characteristics. Vernon (1986) used four other descriptive superficial phenotypes.

86. Martin 1989, Davis 1993 – The type of procedure should consider the depth of infiltration. The definition of deep decreased from 5 mm in 1989 to less than 3 mm in 1993. Clinically, this definition was not overly useful as it could only be determined after the lesions were excised. The concept then changed over several years to peritoneal and infiltrating lesions. Infiltration and pain were generally associated with fibrosis and depth. (Ripps 1991, Ripps 1992, Khare 1996, Vigano 2017, and Liu 2017). Furthermore, even superficial appearance could be associated with infiltration to 4 mm. (Koninckx 1991)

87. Cornillie 1990 – In-phase cyclic changes are different in deep (≥5 mm), intermediate (2 to 4 mm), and superficial (<1 mm) endometriosis

88. Martin 1990 – The gross characteristics of a chocolate cyst are not always predictive of the histology. 25 (61%) of 41 chocolate cysts were histologically confirmed to be endometriosis, 5 cysts (12%) were nondiagnostic, whereas 11 (27%) were corpus luteum or albicans. Those with a flattened appearance and red or red and brown mottled ridges were usually endometriosis, while those with a dark uniform base, an intracavitary clot, or a yellowish rim generally were corpus lutea or albicans. See Lobstein (1820) in Redwine 2012.

89. Cornillie 1991 – Endometriat protein PP14 positivity varies in deep (≥5 mm), intermediate (2 to 4 mm), and superficial (<1 mm) endometriosis.

91. Koninckx 1991 – Infiltration found in 4% of superficial appearing vesicles at 5-6 mm and 3% of polyploid lesions at 3-4 mm. The data is in table 3.

92. Portz 1991, Vitale 2018 – Reactive oxygen species (ROS) or free radicals may increase the growth and adhesion of endometrial cells in the peritoneal cavity, promoting endometriosis and infertility.

93. Ripps 1991 – Pain and tenderness are associated with fibrosis (scarring) of implants.

94. Suginami 1991 – Suginami concluded that the multiple sites or endometriosis were most compatible with coelomic metaplasia. Pulmonary implants may be from dissemination through fenestrations (called perforations in Maniglio 2018).

95. Oosterlynck 1991 – Natural killer (NK) activity and the cytotoxicity against autologous endometrial cells were similarly decreased in women with endometriosis and correlated with the severity of the disease. The decreased cytotoxicity to endometrial cells in women with endometriosis is mainly because of a defect in NK activity but is also partially because of a resistance of the endometrium to NK cytotoxicity. Oosterlynck 1994 and Gazvani 2002.

96. Ripps 1992 – Persistent focal tenderness is associated with implants having a mean depth of 5.3 mm and volume of 1.2 cm³.

97. Koninckx 1992 – Deep endometriosis in the area of the rectovaginal pouch has three phenotypes. Types I and II can present as superficial (<3 cm), intermediate 3 to 5 cm) and deep (0.5 cm or deeper) lesions. Type III a form of adenomyosis externa with most of the volume hidden in a retroperitoneal location and is generally deeper than 1.0 cm. Type III is compatible with a Müllner rest origin. Also see Donnez 1997 and Nisolle 1997.

98. Thomas 1993 – The only clear recommendation for treatment is in symptomatic patients. The short-term effects of medication and surgery may be placebo. But, see Thomas 1996.


100. Hoshiai 1993 – Serial laparoscopies in symptomatic patients confirm that the development of endometriosis is non-linear, even when symptomatic. They have examples of progression, regression, and regression followed by progression. It is possible, if not likely, that asymptomatic patients could add progression followed by regression. See Evers 1994, Martin 1999, and the “Pimple Model” (Martin 2005).


102. Davis 1993, Vercellini 1991 – Adolescents with functional pain, cyclic pain, abdominal pain, nausea, constipation, and diarrhea during menses have the greatest proportion of red lesions. See Vernon 1986.

103. Adamyan 1993, Martin 2001, Batt 2014 – Rectovaginal endometriosis is retrocervical. Some retrocervical endometriosis is not rectovaginal. The normal area of the rectovaginal septum is distal to the distal margin of most, if not all, lesions.
105. Adamson 1994. – Surgery or no treatment is better than medical therapy for fertility.
106. Oosterlynck 1994 – CA-125 levels, but not natural killer (NK)-mediated cytotoxicity, decrease after excision. These data suggest that natural killer activity is a primary deficiency in women with endometriosis and the elevated CA-125 is a consequence of endometriosis. See Oosterlynck 1991, Margatho 2018 for response to etonogestrel (ENG) implant and levonorgestrel-releasing intrauterine system (LNG-IUS), and review in Gazvani 2002.
107. Evers 1994, Koninckx 1994, Koninckx 1999, Harrison 2000, Nap 2004a, Koninckx 2018 – Endometriosis in its superficial form is generally transient, self-limiting, and cause little or no long-term damage. This has been called the “Pimple Model” (Martin 2005) as almost everyone has pimples, most are mild and resolve spontaneously, some get worse, and some come and go. (Hoshiai 1993 and Martin 1999) Some are inflammatory, can get better on medication (estrogenic BCPs, Accutane, antibiotics), can cause scarring, and are treated with surgery (dermabrasion). Koninckx endometriotic disease theory (1994, 1999) of the transition of some early, transient, subtle endometriosis to late, deep infiltrating and ovarian endometriomas evolved into the genetic/epigenetic theory (2018). See Halme 1988 and others for immune competence models that explain why transient is not the common pathway. See Sampson 1921 and 1927a for transition from endometrium to endometriosis. See Giudice 2004 for intrauterine precursors. See Deans 2015 for clarification of definitions of “epigenetics.”
108. Wild 1994, Nisolle 2000, Witz 2002 – Endometrial stromal cells and epithelial cells can attach to the peritoneum within one hour, and the mesothelium can be replaced by 24 hours. These observations were in research animals. Research as this level in humans will likely continue to be unethical without a significant paradigm shift in technology.
109. Sutton 1994 – Pain relief at three months is not significantly different between a patient who had endometriosis removed and those who had a diagnostic laparoscopy only. At six months the placebo response had resolved, and pain recurred in the diagnostic only group.
110. Shapiro 1994, Landin-Romero 2018 – Eye desensitization and reprocessing that was initially used for trauma and substance abuse has since been exported to areas including pain management.
111. Tran 1994, 2012 – Inflammatory appearance added to staging. Also see review in Bouquet de Joliniere 2019.
113. Perper 1995 – Menstrual cramps (dysmenorrhea) are related to the number of implants.
114. Fernandez 1995 – Bone marrow-derived cells are found in endometriosis. See Miyazaki 2018 for pluripotent stem cells.
115. Abu-Hijleh 1995 – Diaphragmatic lymphatics drain into retrosternal (parasternal) lymphatic trunks that carry lymph to the great veins after it filters through mediastinal lymph nodes may be the source of mediastinal cases such as Yasukawa 2018.
116. Khare 1996 – Differences in collagen types suggest that ovarian endometriosis may be metastatic while pelvic wall-infiltrating endometriosis is metaplastic.
117. Thomas 1996 – There is evidence of some improvement of endometriosis spontaneously, it was more marked with gestrinone therapy. The striking finding was that there is a tendency for endometriosis to worsen over time if untreated, but this does not occur in women on gestrinone therapy.


121. Gaetje 1997 – Invasion based on E-cad- epithelial cells

122. Regidor 1997 – The expression of gap junction connexins (Cx) in the human endometrium is highly regulated by steroid hormones. Aberrant expression of Cx43 was found in the epithelium of nearly all endometriotic glands whereas Cx26, typical for human uterine epithelium cells, was only detected in 18 cases; in 17 it was co-expressed with Cx43. The stromal compartment of the tissues did not express any connexins investigated. Staining for Cx32 was absent in all endometriotic tissues. The patterns described demonstrate an aberrant connexin expression and a different hormonal regulation pattern in endometriotic tissues compared to the normal cyclic uterine endometrium, thus indicating a high dedifferentiation from the normal situation. Although the connexin expression in the endometriotic implants was aberrant, this work suggests that it is still under hormonal control. Patients treated with GnRH agonists showed a complete down-regulation of the connexins studied and showed a significant improvement in their pain symptomatology. See Grund 2018 for cell-cell interactions.

123. Leyendecker 1998 – Intruterine tissue injury and repair at the endometrial-muscularis interface (TIAR) due to intruterine trauma.

124. Vandivier 1998 – Vandivier quoted Dr. Frank Ling as discussing that ‘When in doubt, cut it out’ does not make sense when many patients are no better after surgery than before surgery. A team approach to pain management employing not just gynecologists, but also psychologists, nutritionists, and physical therapists is needed.

125. Balas 1998, Balas 2000, Brownson 2006, Green 2009 – The slow adoption of new research findings is related to several factors including time delays that include the times from research to submission, acceptance, location, acquisition by bibliographic databases, incorporation into reviews and textbooks, and implementation. The last two have total delays of 15.3 to 22.3 years. Nobody wants inappropriate care, but there is not much evidence that insisting on appropriateness, which is the vaguely defined consensus of experts, can lead to better patient care. A major problem with appropriateness is that it based on consensus of experts—the lowest level of evidence-based medicine.

126. Risch 1998, Cottreau 2003, Olsen 2008 – Risch’s 1998 hypothesis that androgens can stimulate ovarian epithelial cell proliferation and cancer was expanded to include danazol therapy for endometriosis by Cottreau (2003). But the androgen hypothesis and danazol conclusions were rejected by Olsen (2008).

127. Ling 1999, Jenkins 2008, and Momoeda 2014 – The decreased pain on hormonal suppression with estrogen/progestin or GnRHα (agonists or antagonists) is more common with endometriosis but also occurs with other estrogen sensitive condition such as adenomyosis and myomata. Dr Ling’s data is:

- 82% (27 of 33) of women with endometriosis had pain relief on leuprolide
• 73% (8 of 11) of women with no endometriosis had pain relief on leuprolide
• Fisher exact test 0.67. The result is not significant at p < .05.

128. Knapp 1999 – Knapp concluded that 17th and 18th century reports of ulcerated, inflammatory lesions were compatible with endometriosis despite characteristics compatible with current descriptions. Histology was in its infancy and not discussed. His descriptions of the symptomatology are consistent with endometriosis. If the term “ulcer” in the 17th century can also mean any lesion, then the description may be accurate. Includes Shroen 1690 and five 18th century references. Also see Redwine 2012 & Nezhat 2012 for symptomatology in 1855 BC vs. 1825 BC

129. Martin 1999 – Discusses retroperitoneal endometriosis in a Rhesus monkey that converted to surface endometriosis when she bled and opened the cystic lesion, a rectovaginal nodule was not seen at laparoscopy or laparotomy, a 14-year old who progressed from a flat peritoneal stromal endometriosis to pockets with polypoid endometriosis at age 15, the patient with the two perirectal pockets with only one having an entrance, and deep endometriosis that failed to respond to coagulation. Of note, the 14/15-year old had 3 laparoscopies between ages 14 and 18, suppression for several years, and three children. She was doing well at age 35.

130. Bulun 1999 – The enzyme, aromatase, is aberrantly expressed in endometriotic stromal cells and catalyzes the conversion of C19 steroids to estrogens, which then stimulate cyclooxygenase-2 to increase the levels of PGE2. PGE2, in turn, is a potent inducer of aromatase activity in endometriotic stromal cells. The clinical relevance of local aromatase expression in endometriosis was exemplified by the successful treatment of an unusually aggressive form of recurrent endometriosis in a postmenopausal woman using an aromatase inhibitor. See Noble 1996 & 1997 1997, Attar 2006, Maia 2008, Northnick 2016, Mori 2019


132. Martin 2001 – The retrovaginal (RV) length distal to a recovaginal nodule is increased due to contraction of the RV pouch and may be lengthened RV septum. See Takeuchi 2005 for a conclusion that the septum fractured rather than lengthening. See Adamyan 1993 for retrocevical endometriosis and Batt 2014 for retrocervical septum.


134. Rier 2001 – TCDD-exposed rhesus monkeys with endometriosis exhibit long-term alterations in systemic immunity associated with elevated serum levels of specific PHAH congeners. Exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) correlated with increased peripheral blood mononuclear cells (PBMC) tumor necrosis factor-alpha (TNF-alpha) secretion in response to stimulation by T-cell mitogen and decreased cytolytic activity against NK-sensitive target cells.


136. Gazvani 2002 – The peritoneal environment can influence the development of endometriosis. In women with endometriosis, there appears to be an alteration in the function of peritoneal macrophages, natural killer cells and lymphocytes. Furthermore, growth factors and inflammatory mediators in the peritoneal fluid, produced mainly by peritoneal macrophages, are altered in endometriosis, indicating a role for these immune cells and mediators in the pathogenesis of this disease.

137. Kats 2002 – Macrophage migration inhibitory factor is higher in early (subtle red) than in late (blue, black, or white) lesion appearances. See Hogg 2020 review.
138. Batt 2003 – Congenital anomalies associated with possible Müllerian defects or rests include peritoneal pockets. These findings suggest Müllerian anomaly as the source for these focal lesions. See Martin 1988b, pages 5&6, for acquired pockets.

139. Giudice 2004 – A growing body of evidence indicates that a combination of genetic, hormonal, environmental, and immunologic factors plays a role in the pathogenesis of this disorder. A lack of adequate immune surveillance in the peritoneum is thought to be a cause of the disorder. According to this hypothesis, only women with a local and/or systemic immune defect develop endometriosis. The endometrium of women with endometriosis is believed to be abnormal and predisposes to successful establishment of ectopic disease. This view is compelling, especially since most women have some degree retrograde menstruation but only 6 to 10% of endometriosis. Conditions that might predispose to establishment include genetics, environmental factors, and immune surveillance (activation of peritoneal macrophages with increased cytokine production).


141. Petta 2005 – Levonorgestrel-releasing intrauterine system is useful for the treatment of pain

142. Takeuchi 2005 – Takeuchi saw no continuity between the rectovaginal septum and the lesion. Endometriosis in the contracting rectovaginal pouch may tear away from the septum, and the tissue behind the upper vagina may be loose connective tissue or scar rather than elongated septum.

143. Martin 2005 – The “pimple model” was presented as part of “Clinical and Research Aspects of Endometriosis” at the University of Tennessee Health Sciences Center, Department of Obstetrics and Gynecology rounds November 15, 2005. Almost everyone has pimples, most are mild and resolve spontaneously, some get worse, and some come and go. (Hoshiai 1993, Martin 1999) Some are inflammatory, can get better on medication (estrogenic BCPs, Accutane, antibiotics), can cause scarring, and are treated with surgery (dermabrasion).

144. Chan 2004 – Endometriosis is clonal

145. Marsh & Laufer 2005 and Cabana et al. 2010 – Inflammation may be a precursor, facilitator, or early presentation. Inflammatory induction of coelomic metaplasia or of a damaged peritoneum as a fertile ground for implantation may precede endometriosis. Endometrial or endometrioid stroma can be challenging to recognize in inflammation (Clement 2007), and the conclusions that inflammatory and reactive lesions are endometriosis is reasonable. However, neither Marsh and Laufer (2005) nor Cabana et al. (2010) used stromal markers such as CD10. Nor did they exclude infection, endotoxins, or other causes of inflammation (Khan 2014, Khan 2016, Canis 2017) as the source of the inflammation.

146. Agrawal 2005 – Before clinicians recommend antioxidants, randomized controlled trials with sufficient power are necessary to prove the efficacy of antioxidant supplementation in disorders of female reproduction.


148. Martin 2006 – Discusses the use of standards for reporting of diagnostic accuracy (STARD) criteria such as specific and recorded features for a normal or abnormal laparoscopy,
histologic criteria, distance of observation, clinical palpation, exam under anesthesia, intraoperative palpation, and palpation with instrumentation.

149. Attar 2006 – Steroidogenic acute regulatory protein (StAR) and aromatase are essential for E(2) production and are expressed in endometriosis. There is a positive feedback loop that favors continuous formation of E2 and PGE2 in endometriosis. Also, the eutopic endometrium of patients with endometriosis is capable of aberrantly expressing the enzyme aromatase. See Noble 1996 & 1997, Bulun 1999, Maia 2008, Northnick 2016, Mori 2019.

150. Batt 2007 – There was “no evidence of pelvic endometriosis found at the time of a bilateral oophorectomy” and therefore, Agrawal’s (2006) case of intramedullary endometriosis of the conus medullaris argues 1) for Müllerianosis and against a pelvic source for hematogenous or lymphatic dissemination or 2) for undiagnosed pelvis endometriosis as a source of venous or lymphatic dissemination.

151. Muzii 2007 – Endometriotic tissue covered the inner cyst wall for a surface that varies between 10% and 98% of the entire wall (median value 60%). The mean cyst wall thickness was 1.4 mm. The mean value of maximal depth of endometriosis penetration in the endometrioma wall was 0.6 mm. In 99% of the cases the maximal penetration of the endometriotic tissue was ≤1.5 mm. The maximum penetration was 2 mm. See Martin 1990, Martin 1991, and Muzii 2013.

152. Meng 2007 – Menstrual blood-derived stem cells (MenSCs) may contribute to endometriosis. See Chen 2019 for discussion of their use as an alternative source for research and application in regenerative medicine.

153. Kodati 2008 – Theory that menstrual, endometrial cells can adhere to peritoneum traumatized by Shigella or Shigella-like microorganisms.


155. Olsen 2008 – Olsen found no evidence that PCOS, acne, hirsutism or danazol use was associated with ovarian cancer except for serous borderline tumors that were positively associated with a history of PCOS. The results do not support the hypothesis that androgen-related disorders increase the risk of ovarian cancer. See Risch 1998 and Cottreau 2003.

156. Guo 2009 – There is a need for identification of prognostic biomarkers for recurrence.

157. Mier-Cabrera 2009 – A high antioxidant diet at 150% of the suggested daily intake of vitamin A (1050 microg retinol equivalents), 660% of the recommended daily intake (RDI) of vitamin C (500 mg) and 133% of the RDI of vitamin E (20 mg) was associated with diminished peripheral oxidative stress markers and enhanced antioxidant markers in women with endometriosis. See Mier-Cabrera 2009 Nishihara 2018 & Samimi 2019

158. Burney 2009 – MicroRNAs (miRNAs) have significant regulatory influence on the expression of target genes involved in both physiologic and pathologic conditions. There is incomplete transitioning from proliferative to secretory phase endometrium in women with endometriosis. Early secretory endometrium (ESE) from women with endometriosis is characterized by a miRNA expression profile that differs from that of healthy ESE. Among the miRNAs underexpressed in ESE in the setting of endometriosis are members of the miR-9 and miR-34 families. See Ohlsson Teague 2009, Saare 2017, Agrawal 2018, Hu 2019

159. Ohlsson Teague 2009 – MicroRNAs (miRNAs) and their cognate mRNA target sequences appear to constitute pathways that promote endometriosis. Functional analysis suggested that the 673 miRNA targets constitute molecular pathways previously associated with
endometriosis, including c-Jun, CREB-binding protein, protein kinase B (Akt), and cyclin D1 (CCND1) signaling. These pathways appeared to be regulated both transcriptionally as well as by miRNAs at posttranscriptional level. See Burney 2009, Agrawal 2018, Hu 2019


161. Khan 2010 – Bacterial endotoxins such as lipopolysaccharide in the pelvis across the phases of the menstrual cycle. This lipopolysaccharide derived from higher colony formation of Escherichia coli in menstrual blood may promote the growth of endometriosis after its binding with toll-like receptor 4 (TLR4). Also see Khan 2016 for bacterial contamination hypothesis.

162. Chapron 2010 – Among 15 patients with non-operated associated asymptomatic posterior DIE lesions, a second surgical procedure indicated for pain symptoms was necessary for only one patient (6.7%).

163. Signorile 2010 & 2012 – Fetal tissue compatible with endometriosis on H&E, H&VG and immunohistochemistry stains (CD10, Era, CA125, cytokeratin 7, vimentin, and desmin) was found in the rectovaginal septum, proximity of the Douglas pouch, and the mesenchymal tissue close to the posterior wall of the uterus. This is the same anatomic area studied by Konincx (1992) with Type III being the most suggestive of a congenital rest and Donnez (2001) on metaplasia from Müllerian remnants.

164. Adamson 2010 – The Endometriosis Fertility Index is the only validated tool to determine fertility after surgery. Fertility rates after endometriosis surgery are based 50% of the surgical findings and 50% on history. https://www.fertstert.org/article/S0015-0282(09)03714-5/fulltext

165. Surrey 2010 – Add back therapy adds to patient acceptance & safety of GnRH therapy.

166. Ferrero 2010 – The symptoms of endometriosis can be subtle with only 38% suspected on unfocused histories. Ferrero reported that 62% were suspected on focused history.

167. Batt 2011a – Dr. Batt’s book “A History of Endometriosis” presents the great leap forward that occurred from 1860 to 1946 from a statistical grouping of signs and symptoms through treating symptoms to treating diseases. The pathophysiology of endometriosis was initially defined in an era when surgery was the only treatment. https://www.springer.com/us/book/9780857295842

168. Umezawa 2010 – Prenatal and postnatal diesel exhaust exposure is toxic and enhances the activation of mast cells and prolongs the persistence of collagen fibers in the induced rat model of endometriosis.

169. Acién 2012 – Accessory and cavitated uterine masses (ACUM) are non-inflammatory, organoid examples of how Müllerian remnants can appear. These are also known as juvenile cystic adenomas (JCA) and may rarely have accessory tubes resulting in pregnancy. (Alkhateeb 2005, Branquinho 2012, Dadhwal 2017)

170. Redwine 2012, Nezhat 2012 – Clinical descriptions suggesting the presence of endometriosis were found in the oldest known medical text the Medical Papyrus (1825 BC) or Egyptian concepts (1855 BC). These are introduced in Redwine 2012 and Nezhat 2012.

171. Batt 2013, Laganà 2017 – Müllerianosis as an organoid remnant of Müllerian tissue in the native area of embryologic Müllerian development. Organoid remnants are not what is more commonly called endometriosis.

172. Batt 2013 – Hamartoma is a neoplastic Müllerian growth in the native Müllerian area.
173. Brosens 2013 – Endometriosis is a progressive disease. A delay of several years before diagnosis is associated with advanced endometriosis in adolescents. Brosens suggests early ultrasound and endoscopy for diagnosis and therapy. This tertiary care study of patients seen after years of delay for pelvic pain and pelvic masses can be contrasted with Knox 2019 that followed adolescents with dysmenorrhea for an average of 10.2 years during which time 18.6% were diagnosed with endometriosis. All of Knox’s cases of endometriosis were mild. See Knox 2019.

174. Raposo 2013 – Extracellular vesicles involved in intercellular communication (signaling)

175. Zamecnik 2013 – Endometriosis occurring in paratesticular mesothelial cyst in a man had endometrioid epithelial cells expressing a mesothelial type that favored metaplastic pathogenesis of the lesion. Reviewed in Rei 2018.

176. Muzii 2013 – Ovarian damage can be due to both endometriosis and surgery.

177. Batt 2014 – Concluded that the retrocervical location of rectovaginal endometriosis implied that this is the retrocervical septum. See Adamyann 1993 and Martin 2001 for retrocevical position.

178. Becker 2014 – Harmonization to six surgical phenotypes (clear, red, white, blue/black, brown, and vascular) are discussed. Becker is an open access at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4230690/


181. Forte 2014 – Chromosomal anomalies and instability can alter gene expression

182. Khan 2014 – Occult non-recognized endometriosis found in 15.2% of women with visible endometriosis (15.2%) and 6.4% of controls (6.4%). There are three patterns of occult microscopic endometriosis based on patterns of Ber-EP4 (epithelial cell marker), CD10 (stromal cell marker), Calretinin (mesothelial cell marker), estrogen/progesterone receptors (ER/PR) and Ki-67 (cell proliferation marker). Also see Martin 1989 for increase with awareness of subtle appearances, Khan 2010 for endotoxins, Hopton 2014 for “near-contact” laparoscopy, and Khan 2016 for cross-talk between inflammation and ovarian steroids or the stress reaction.

183. Hopton & Redwine 2014 – Khan (2014) confirms that most (84.8%) women with endometriosis do not have occult endometriosis.


185. Parra-Herran 2014 – There is a high sensitivity and specificity of interferon-inducible transmembrane protein 1 (IFITM1) comparing normal and sarcomatous endometrial samples with leiomyoma, usual type, and cellular leiomyoma. See Sun 2019. CD10 expression is not specific to endometrial stromal cells and is found in other cells such as vascular endothelial cells, uterine fibroids, leiomyosarcoma. hematopoietic, renal tubular and smooth muscle cells. IFITM1 is more specific for endometrial stromal cells than CD10.

186. Bobek 2014 – The occurrence of circulating endometrial cells (CECs) in peripheral blood (PB) in evidence of an active endometrial disease and may be useful as a marker for endometriosis. See Pospisilova 2019 for increased sensitivity of tests for CECs. Also see Sampson 1927b, Vallvé-Juanico 2019, and Kiss 2020.

188. Sugamata 2015 – Leukotriene receptor antagonist (LTR-A), an anti-allergic drug, is associated with apoptotic fibroblasts and degeneration of collagen fibers and may this decrease the transition to deep infiltrating endometriotic disease. http://dx.doi.org/10.4236/ojog.2015.56045

189. Abrão 2015 – In women with deep endometriosis, surgery is the therapy of choice for symptomatic patients when deep lesions do not improve with medical treatment.

190. Guo 2015 – Repeated tissue injury and repair (ReTIAR) due to cyclic bleeding in endometriosis.

191. Laux-Biehlmann 2015 – Pain due to activation of peripheral nerve endings in response to retrograde and extra-uterine menstruation

192. Deans 2015 – Deans and Maggert discuss epigenetics definitions that require heritability as contrasted those definitions that are more concerned with environmentally mediated phenotypes and plasticity. They concluded that the latter definition is of gene regulation rather than epigenetics and note that definition is more commonly used in such fields as ecology, physiology, and psychology. Those in the field of genetics are more commonly concerned about inter-generational heritability. Understanding the differences between the definitions is important in interpreting the mechanisms. Most studies of endometriosis fit the gene regulation definition rather than a heritable definition.

193. Liang 2016, 2018, 2019 – Estrogen plays a role in maintaining balance of nerve interaction and can also be part of dysfunction of nerve interaction and the pro-endometriotic niche in endometriosis. Blocking the molecular components derived from the endometriotic lesion, suppressing the recruitment and activity of immunosuppressive cells, inhibiting the mobilization of BMSC and constricting the angiogenesis process may represent potential approaches to preventing the progression of endometriosis

194. Huang 2016 – Dioxin-like CB126, but not non-dioxin-like CB153, significantly enhanced 17β-estradiol (E2) biosynthesis in a dose-dependent manner. CB126 triggered the inflammatory response by directly stimulating the secretion of inflammatory factors and indirectly reducing the level of lipoxin. A PCB-treated endometriosis mouse model confirmed that CB126 rather than CB153 increased the levels of both E2 and inflammatory factors in peritoneal fluid and promoted the development of endometriotic lesions. These effects were mediated by the AhR receptor

195. Canis 2016, Canis 2017 – The extent or the surgical phenotype of the disease may be related to the initial anatomic localization, type, and severity of the trauma. The local natural history of endometriotic lesions may depend on the tissue on which they have developed. If the trauma is stopped and the injured tissue is repaired, the severity will not increase significantly. True recurrences of the disease may be rare unless a new trauma induces further endometriotic lesions.

196. Koninckx 2016 – There are four phenotypic types of endometriosis: subtle, typical, cystic ovarian, and deep infiltrating.

197. Nerune 2016 – Persistent Müllerian Duct Syndrome (PMDS), a rare form of internal male pseudohermaphroditism in men. This includes references from 2009. Also, see Melicow 1967 and Oliker 1971 for 46 XY males.

198. Khan 2016 – The bacterial contamination hypothesis reviews the lipopolysaccharide regulation of the pro-inflammatory response in the pelvis and growth of endometriosis via
the LPS/TLR4 cascade. Menstrual blood was highly contaminated with Escherichia coli and the endometrial samples were colonized with other microbes. Cross-talk between inflammation and ovarian steroids or the stress reaction was also observed in the pelvis. GnRHa treatment may worsen intrauterine microbial colonization, with the consequent occurrence of endometritis in women with endometriosis.


200. Tiboni 2016 – Animal defects on therapeutic or lower levels doses of aromatase inhibitors include skeletal anomalies, abnormal head morphology, increased anogenital distance in female fetuses, urinary tract system anomalies, and placental enlargement.

201. Bruner-Tran 2016 – Bruner-Tran, et al., investigated heritable, germline, epigenetic changes such as reduced progesterone sensitivity, in mice after exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and demonstrated a transgenerational occurrence. They could not determine if those changes lead to the development of endometriosis or were a consequence of the inflammatory nature of the disease. See Deans 2015 for clarification of definitions of “epigenetics.”

202. Smarr 2016 – Endocrine disrupting chemicals (EDCs), such as 2,3,7,8-tetrachlorodibenzop-dioxin (TCDD), dioxin-like polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), polybrominated diphenyl ethers (PBDEs), perfluoroalkyl and polyfluoroalkyl substances (PFAAs), and select metals may be involved in the development and severity of endometriosis. See Rier 1993, 1995 & 2001 on TCDD and Peinado 2020 on bisphenols.

203. Laganà 2017 – “Unus pro omnibus, omnes pro uno” is a combination of many concepts into a process that begins during embryogenesis. Components include Hox (homeobox) genes, Wnt (wingless) genes, Müllerian derivatives and remnants, genital ridge leakage during organogenesis, human embryonic stem cells (hEmSC), endometrial stem progenitor cells (hESP), stem/progenitor cells residing in adult uterus, mesenchymal stem cells from bone marrow, and embryonic ectopic implantation. Updated at Laganà 2018

204. Gordin 2017 – Whether the original cell comes from the endometrium, endometrial pale cells, other stem cells, bone marrow cells, embryonic cells, neonatal cells, adult cells or another source of endometrial or potentially endometriotic cells is not as important as the genetic and epigenetic changes that are associated with the specific phenotypes of endometriosis. See Deans 2015 for clarification of definitions of “epigenetics.”

205. Dorien 2017 – Dorien et al. confirms the previous literature on the presence of endometrial cells in the peritoneal fluid of most women using with primary antibodies against epithelial cell adhesion molecule (Ep-CAM; endometrial epithelial cells), CD10 (endometrial stromal cells), prekeratin (epithelial/mesothelial cells), vimentin (endometrial/mesothelial/immune cells), calretinin (mesothelial cells), and CD68 (macrophages). They also reviews the literature on the possibilities of involvement of endometrial stem cells rather than endometrial epithelial/stromal cells, involvement of bone marrow stem cells, induction by other substances in menstrual fluid, and the finding being the consequence rather than the cause of endometriosis. See Koninckx 1980 for unruptured luteinized follicle and Halme 1983 &1984 for hormonal or immunologic factors.

206. 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.

207. Makiyan 2017 – Congenital primordial germ cells remnants can be the source.
208. Anglesio 2017 – Cancer-associated driver mutations can be present in deep infiltrating endometriosis. See Guo 2018, Lac 2019, Guo 2020

209. Aoyagi 2017 – Kistner proposed a state of “pseudopregnancy” to reproduce the improvement noted in endometriosis during and after pregnancy. He postulated that decidualization that results in necrosis and elimination of early, superficial endometriotic implants. Also, see Kistner 1958 & Klemmt 2006

210. Kohl Schwartz 2017 – Mild endometriosis, as in superficial lesions, is related to a great extent to an inflammatory disorder, possibly leading to defective folliculogenesis, fertilization, or implantation, presenting an increased risk of miscarriage.

211. Parasar 2017 – Mouse embryonic stem cells (mESCs) express both glandular (CD9) and stromal (CD13) markers of human endometrium, suggestive of a novel endometrial precursor cell population. This model represents a potential key step in elucidating the mechanisms of ectopic endometrial tissue growth.

212. Gruber-Dujardin 2017 – Immunohistochemical coexpression of epithelial and mesenchymal markers (CK, vimentin, sometimes together with SMA and desmin), most obvious in poorly differentiated endometriosis and resembling distinct mesothelial cell properties, are associated with induced differentiation of peritoneal cells into endometrial tissue and support the theory of coelomic metaplasia.

213. Burlev & Ilyasova 2017, Burlev, et al. 2018 – Burlev, et al. concluded that serum and eutopic endometrial vasoactive intestinal peptide (VIP) can be used to assess pain and neuroangiogenesis in endometriosis. They found elevated vasoactive intestinal peptide (VIP) transcript and protein levels in serum, eutopic endometrium, and endometriosis were associated with chronic pain indicated an elevated inflammation in the pelvic microenvironment. See Novella-Maestre 2009 and Laganà 2020.


215. Saare 2017 – The limited overlap between the proposed disease-related miRNAs could be due to the heterogeneity in tissue composition, as some studies have compared highly heterogeneous whole-lesion biopsies with endometrial tissue, some have compared the endometrium from patients and controls, and some have used pure cell fractions isolated from lesions and endometrium. This review concludes that the experimental design should be changed and should move from highly heterogeneous tissues to studies using specific cell populations. See Ohlsson Teague 2009, Burney 2009, Agrawal 2018

216. Agrawal 2018 – Despite numerous studies on circulating miRNAs in endometriosis, no single miRNA or any panel of them seems to meet the criteria of a diagnostic biomarker. The disagreement between the various studies upholds the demand of larger, well-controlled systematic validation studies with uniformity in the research approaches and involving diverse populations. See Ohlsson Teague 2009, Burney 2009, Saare 2017.


218. Guo 2018 – The six driver genes reported to be mutated in endometriosis (the RP set) may play important roles in fibrogenesis but not necessarily malignant transformation. See Guo 2020 for review including mutations in endometriomas and normal tissue.
219. Klemmt 2018 – Other stem cell concerns include lack of apoptosis, evasion of immunosurveillance, angiogenesis, neurogenesis, exosomes, plasticity, stem cell signaling, aberrantly activated signaling pathways, stem cell migration, immunogenicity, peritoneal cavity homeostasis, dysregulation of Wnt and Hox genes, phenotype and microRNA analysis. Free download at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5925869/

220. Brosens 2018 – Progression requires active neo-angiogenesis.

221. Panir 2018 – Non-coding RNA is associated with endometriosis.


223. Matsuzaki 2018 – Using autophagy inhibition may decrease the chance of recurrence.

224. Baranov 2018 – A genetic program governs the origin of stem cells, transition into mesenchymal stem cells, invasion of the peritoneum and progression to late, endometriotic lesions. Baranov discusses the possibility that the stem cells could be disseminated during organogenesis or from the endometrium during retrograde menstruation.

225. Rei 2018 – Male endometriosis is rare. Rei found only 17 cases in men in the world literature from 1971 to 2018. Rei discusses Müllerian embryonal rests, induction, immune dysfunction, and coelomic metaplasia theories. Seven of the most recent eight had markers compatible with Müllerian source. One (see Zamecnik 2013) of the seven had markers compatible with coelomic metaplasia. Even in men, more than one theory may be necessary. Open access at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5833878/

226. Zhang 2018 – Metastasis-associated gene 1 (MTA1) may serve as a prognosis marker. The conclusion that a prognosis marker may be more important than a diagnostic marker was discussed at the 2017 World Congress of Endometriosis in Vancouver.

227. Christofolini 2018 – Differences in allelic genetic distribution between fertile women and women with endometriosis and infertility are seen in the KAZN gene for grades 1 and 2 and LAMA5 gene for grades 3 and 4. Infertility may be genetic.

228. Margatho 2018 – CA-125 decreases more on etonogestrel (ENG) implant than on levonorgestrel-releasing intrauterine system (LNG-IUS). However, the decrease in soluble CD23 and endometrial nerve fiber density were similar. CD23 and nerve fiber density may be a surrogate marker for response to hormonal suppression with implantable progestational devices. See Oosterlynck 1994 for CA-125 and natural killer activity response to excision.

229. Chen 2018 – Women affected by endometriosis have an independently elevated risk of placenta previa in pregnancy.

230. Sui 2018 – Autophagy-related proteins, microtubule-associated protein light chain 3 (LC3) and Beclin1 were lower while matrix metalloproteinase-2 (MMP-2) was higher in women with endometriosis.

231. Nishihara 2018 – Oxidative stress in women with infertility is associated with endometriosis. See Mier-Cabrera 2009 & Samimi 2019

232. Jiang 2018 – IL-37 regulated the biological behavior of ectopic endometrial stromal cells through multiple signaling pathways such as β-catenin, p-p38, p-ERK1/2, and p-JNK, and this signaling was abolished by a Wnt/β-catenin inhibitor.

233. Rekker 2018 – Cell-type-specific analysis revealed differences in miRNA expression patterns between stromal cells isolated from the endometrium and endometriomas. Two molecular mechanisms are involved in endometriosis pathogenesis. First, HOXA9 and HOXA10 genes are regulated by miR-139-5p among other factors and are potentially involved in endometriosis-associated infertility. Second, the aberrant expression of miR-375
in ectopic stromal cells may contribute to higher levels of EDN1 in lesions, which can be associated with pain mechanisms or be involved in the regulation of invasive growth and cell proliferation in endometriosis development

234. Gibson 2018 – ‘Intracrine’ is a 1980s concept based on the ability of cells within non-gonadal tissues to both produce and respond to the same hormone. Intracrinology is the way that tissue such as endometriosis can utilize inactive steroids present in the blood to respond to local physiological demands and ‘fine-tune’ the activation or inhibition of steroid hormone receptor-dependent processes.

235. Flores 2018 – Symptomatic response to progestin has been unpredictable. However, a progesterone receptor status can predict clinical response and, therefore, be useful in clinical management. See Marquardt 2019 for molecular mechanisms.

236. Arosh 2018 – Dual inhibition of ERK1/2 and AKT pathways, that regulate signaling proteins in human endometriotic cells in an epithelial cells and stromal cell specific pattern, can decrease the growth and survival of endometriotic lesions by decreasing proliferation and inducing apoptosis of epithelial cells and stromal cells of the endometriotic lesions.

237. García-Solares 2018 – Endometriotic gland invasion is dominated by collective cell migration. If the lead edge loses contact with the dominant central portion, expansion ceases.

238. Jaeger-Lansky 2018 – There were higher local levels of inflammatory IL-6, IL-8, IL-10 and TNF-α levels in peritoneal lavage fluid of endometriosis patients but not in plasma levels. There was no elevation of tissue damage markers (“Danger signals” HMGB1, IL-32α, and IL-33) associated with cell death in response to strong inflammation.

239. Suda 2018 – Suda et al. identified numerous cancer-associated mutations in epithelial cells from ovarian endometriosis and normal endometrium. They describe a heterogeneous and mosaic-like uterine endometrial epithelium, shaped by endometrial glands with distinct somatic mutations. They suggest clonal expansion of epithelial cells with cancer-associated mutations leads to the development of endometriosis. See Hapangama 2018 for basalis-like cells in the endometrium of endometriosis patients.

240. Hapangama 2018 – Women with endometriosis demonstrated higher number of basalis-like cells (SSEA1+, nSOX9+) in the functionalis layer of the eutopic endometrium compared with the healthy women without endometriosis in the secretory phase of the cycle (P < 0.05). Induction of endometriosis resulted in a similar increase in basalis-like epithelial cells in the eutopic baboon endometrium. See Suda 2018 for cancer-associated mutations.

241. Manavella 2018 – A two-step ovarian tissue transplantation procedure using adipose tissue-derived stem cells in xenografted frozen–thawed human ovarian tissue enhances vascularization in the early post-grafting period. A parallel implication is that the combination of local or hematogenous stem cells combined with retrograde menstruation may be necessary for or may increase the rate of implantation of endometriosis.

242. Marcellin 2018 – Marcellin, Méhats, and Gogusen found histopathological alterations (fibrinoid necrosis and connective tissue accumulation in the amnion, chorion, and decidual layers) in the fetal membranes of women with endometriosis, but none in controls at Cesarean-section. Fifteen (89%) of 19 were previously diagnosed at surgery while 4 (21%) of 19 women were diagnosed using clinical and imaging evaluation.

243. Nirgianakis 2018 – Nirgianakis et al. is a retrospective analysis of the complications of pregnancy after laparoscopic excision of deep infiltrating endometriosis (DIE). They conclude that excision of DIE does not decrease the increased risk of placenta previa, gestational hypertension and intra uterine growth retardation (IUGR) associated with endometriosis.
244. Laganà 2018 – Updated article on molecular and cell biology insights. Open access https://www.mdpi.com/1422-0067/20/22/5615/pdf

245. Miyazaki 2018 – Defective endometrial stromal fibroblasts (EMSFs) contribute to uterine factor infertility, endometriosis, and endometrial cancer. Induced pluripotent stem cells (iPSCs) derived from skin or bone marrow biopsies can provide a patient-specific source that can be differentiated to various cells types.

246. Long 2018 – Perioperative use of a nonspecific b-blocker and/or a nuclear factor-kB (NF-kB) inhibitor can retard the growth of residual endometriotic lesions that are left intact in the primary surgery in mice. Also see Rock 1981, Donnez 1984, Hu & Taylor 2019, Munrós 2017, Munrós 2019, and Guo and Martin 2019.

247. Grund 2018 – Cell contacts (tight junctions, adherens junctions, desmosomes, and gap junctions) exhibit a considerable influence on tissue physiology and homeostasis by controlling paracellular and intercellular transport processes, as well as by affecting signaling pathways. Since they maintain cell polarity, they play an important role in cell plasticity. In contrast to most other tissues, the endometrium undergoes extensive physiological changes and reveals an extraordinary plasticity due to its crucial role in the establishment and maintenance of pregnancy. These complex changes are accompanied by changes in direct cell–cell contacts to meet the various requirements in the respective developmental stage. Impairment of this sophisticated differentiation process may lead to failure of implantation and embryo development and may be involved in the pathogenesis of endometrial diseases. See Regidor 1997 for expression pattern of gap junction connexins in endometriotic tissues.

248. Hu & Taylor 2019 – Decreased miR-370-3p, is associated with an increased risk of endometriosis and was found in the circulation of women with endometriosis, indicating the potential for remote effects far removed from the areas affected by endometriosis. Steroidogenic factor 1 (SF-1), an essential transcriptional regulator of multiple genes involved in estrogen biosynthesis, is aberrantly increased and plays an important role in the pathogenesis of endometriosis. The expression of SF-1 in endometriosis is regulated by miR-370-3p. miR-370-3p levels are decreased in the serum of patients with endometriosis while SF-1 mRNA levels are inversely upregulated in endometriotic lesions compared to respective controls. Overexpression of miR-370-3p inhibits cell proliferation and induces apoptosis in endometriotic cells. miR-370-3p functions as a negative regulator of SF-1 and cell proliferation in endometriotic cells. MiR-370-3p may affect steroidogenesis in multiple organs, altering steroid production in several tissues and effecting the local estrogen effect throughout the body. See Sampson 1918 & 1927b for venous dissemination and Munró 2017 and Munró 2019 for circulating microparticle levels.

249. Konincx 2019 – The genetic/epigenetic theory is a theory of the transition from endometrial or other stem cells to endometriosis. It is not dependent on the cell of origin or method of dissemination. A set of genetic and epigenetic incidents transmitted at birth, some of which occurred during inter-uterine development, include hereditary aspects that predispose to the endometriosis-associated changes in the endometrium, immunology, and placentation. However, to develop typical, cystic ovarian or deep endometriosis lesions, a variable series of additional transmissible genetic and epigenetic incidents are required to occur in a precursor cell. Subtle lesions are viewed as endometrium with a histologic diagnosis of “endometriosis.” After additional genetic and epigenetic incidents, those can transition into “endometriotic disease.” Typical cystic ovarian or deep endometriosis lesions are heterogeneous and represent three different diseases. See Deans 2015 for clarification of definitions of “epigenetics.”
250. Sokalska 2019 – Lipid-soluble statins (simvastatin, lovastatin, atorvastatin) were effective in inhibition of growth and invasiveness of human endometrial stromal cells.


252. Ryu 2019 – Chrysin derived from honey, propolis (bee glue), or passion flowers has anti-inflammatory and anti-angiogenesis effects. Chrysin suppresses the proliferation of endometriosis and induces programmed cell death by activating the endoplasmic reticulum stress response, inactivating the PI3K signaling pathways, increasing the cytosolic calcium level and generating of reactive oxygen species.

253. Donnez 2019 – Adenomyosis externa (a form of deep pelvic endometriosis) may be an extension of uterocervical adenomyosis. Uterocervical adenomyosis could therefore be the cause of deep endometriotic nodules, as is also the case for deep anterior endometriosis, called bladder adenomyotic nodules.

254. Samani 2019 – Samani et al. demonstrated that endometriosis-derived cells are capable of migration to extrapelvic organs including the lung, spleen, liver and brain in a mouse model. They speculate that some of the non-pelvic pain, fatigue, malaise, eating disorders, anthropometric variation, endocrine and metabolic dysfunction, immunologic defects, and sociopsychological issues may be due to undiagnosed, distal cellular infiltration with endometriosis.

255. Chen 2019 – Menstrual blood-derived stem cells (MenSCs) may contribute to endometriosis and be an alternative source for research and application in regenerative medicine. See Meng 2007 for initial recognition of MenSCs.

256. Sun 2019 – Interferon-inducible transmembrane protein 1 (IFITM1) is a highly sensitive marker for endometriotic stromal cells in ovarian and extragenital endometriosis. See Parra-Herran 2014 for high sensitivity and specificity of IFITM1 comparing normal and sarcomatous endometrial samples with leiomyoma, usual type, and cellular leiomyoma.

257. Taylor 2019 – Reviews endometriosis as a complex systemic disease with manifestations including pain, fatigue, powerlessness, social support, emotional well-being and self-image impairment on the Endometriosis Health Profile 30; psychological manifestations; depression and anxiety; multiple organ system involvement; central sensitization; lower average body weight; and cardiovascular abnormalities. These may involve circulating inflammatory cytokines and microRNAs.

258. Bouquet de Joliniere 2019 – Expands the use of multiple inflammatory markers to classify endometriosis and discusses the possibility that these may have individualize care.

259. Forster 2019 – Macrophages are central to the pathophysiology of endometriosis: they dictate the growth and vascularization of endometriosis lesions and promote lesion innervation. Disease-modified macrophages exhibit increased expression of IGF-1 in an in vitro model of endometriosis-associated macrophages. Macrophage-derived IGF-1 promotes sprouting neurogenesis and nerve sensitization in vitro. IGF-1 elevations in peritoneal fluid from women with endometriosis positively correlate with their pain scores. Macrophage depletion in a mouse model of endometriosis can reverse abnormal changes in pain behavior. The Igf-1 receptor inhibitor linsitinib reverses the pain behavior observed in mice with endometriosis. Therapies that modify macrophage phenotype may be attractive therapeutic options for the treatment of women with endometriosis-associated pain.

260. Knox 2019 – Adolescents with dysmenorrhea were followed for an average of 10.2 years during which time 18.6% were diagnosed with endometriosis. All cases of endometriosis were mild. This is contrasted with Brosens’ 2013 conclusion from a tertiary center that endometriosis in adolescents is a hidden, progressive and severe disease. See Brosens 2013
261. Yan 2019 – There is evidence that sensory nerves play an important role in promoting the development and fibrogenesis of endometriosis. This role explains as why deep endometriosis (DE) frequently have higher fibromuscular content than that of ovarian endometriomas (OE), highlights the importance of lesional microenvironment in shaping the lesional fate, gives more credence to the idea that ectopic endometrium is fundamentally wounds that go through repeated tissue injury and repair, and should shed much needed light into the pathophysiology of endometriosis.

262. Zhou 2019 – Women with high pre-operative anti-Müllerian hormone (AMH) had a significantly higher cumulative pregnancy rate than those with low AMH. Preoperative AMH level might be a useful marker to predict the occurrence of natural pregnancy and as part of the consideration of women considering endometriosis surgery for fertility.

263. Akter 2019 – Machine learning using transcriptomics and methylomics data can be used to distinguish endometriosis from non-endometriotic samples.

PMC: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6737999/

264. Mori 2019 – PGC-1a, a transcriptional coactivator-modulating steroid hormone, regulates aromatase expression and activity. Estrogen activities mediated by different types of estrogen receptors abnormally elevated in local tissues could also be involved in the development of endometriosis. The authors demonstrated that the isoflavone aglycone, a partial agonist of the estrogen receptor, suppressed the formation of endometriotic lesions. See Noble 1996 & 1997 1997, Bulun 1999, Attar 2006, Maia 2008, Northnick 2016

265. Samimi 2019 – Molecular signaling pathways can be used to study the roles of inflammation, oxidative stress, angiogenesis, and apoptosis dysregulation. See Mier-Cabrer 2009 and Nishihara 2018.

266. Alio 2019 – The 41 members of the Endometriosis Treatment Italian Club published ten low-value medical interventions, characterized by an unfavorable balance between potential benefits, potential harms, and costs, which should be discouraged in women with endometriosis. PMC: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6560357/


269. Ding 2019 – Women with endometriomas demonstrate a hypercoagulable status due to the inflammatory nature of endometriosis. The combined determination for CA-125 and fibrinogen demonstrate a higher area under the curve than the single detection of CA-125 in those with endometriomas compared to these with benign ovarian cysts. Endometriosis is also associated with increased platelets.

270. Vallvé-Juanico 2019 – Circulating endometrial or endometriotic stromal cells were identified, only in women with endometriosis but not in controls using stromal marker CD10, while endometrial epithelial cells were not identified in the circulation of either group using epithelial marker cytokeratin (CK). Endometrial stromal cells may migrate through circulation and promote the pathophysiology of endometriosis. See Sampson 1927b, Bulun 1999, Bobek 2014, and Kiss 2020.
271. Ścieżyńska 2019 – Endometriosis may be a subject of immunotherapy by blocking NK cell negative control checkpoints including inhibitory NK cell receptors. Immunotherapies with genetically modified NK cells cannot be excluded.

272. Marquardt 2019 – This review focuses on the molecular mechanisms governing progesterone and estrogen signaling supporting endometrial function and how they become dysregulated in endometriosis. Progesterone and estrogen act primarily through their cognate receptors to set off cascades of signaling pathways and enact large-scale gene expression programs. In endometriosis, progesterone and estrogen signaling are disrupted, commonly resulting in progesterone resistance and estrogen dominance. This hormone imbalance leads to heightened inflammation and may also increase the pelvic pain of the disease and decrease endometrial receptivity to embryo implantation. See Flores 2018.

273. Hu 2019 – As a master regulator of steroidogenic enzymes, SF-1 plays a key role in sustained survival of endometrial tissue at the ectopic sites by promoting a hyperestrogenic state in endometriosis. The aberrant presence of SF-1 in endometriosis and its absence in endometrium is the key event for the differential expression of StAR and CYP19A1. SF-1 mRNA levels are upregulated in endometriotic lesions compared to respective controls while miR-370-3p levels are decreased in the serum of patients with endometriosis. miR-370-3p functions as a negative regulator of SF-1 and cell proliferation in endometriotic cells. Decreased miR-370-3p is associated with increased endometriosis and was found in the circulation of women with endometriosis, indicating the potential for remote effects far removed from the areas affected by endometriosis. Overexpression of miR-370-3p inhibits cell proliferation and induces apoptosis in endometriotic cells. Steroidogenic factor 1 (SF-1), an essential transcriptional regulator of multiple genes involved in estrogen biosynthesis, is aberrantly increased and plays an important role in the pathogenesis of endometriosis. See Ohlsson Teague 2009, Burney 2009, and Agrawal 2018.


275. Laganà 2020 – The direct effect of cabergoline on endometriosis implants is through its effect on angiogenesis in a murine model. Indeed, the exposure to cabergoline was associated with decreased number of active lesions, lower cellularity, and a significantly less developed vascularization. Neoangiogenesis is essential for the onset and progression of endometriosis through pathways including increased levels of M2 macrophages as compared to M1 type, the overall dysregulation of inflammatory response, favoring Th2 anti-inflammatory response, and the direct ability of endometrial stem progenitor cells to induce angiogenesis by the production of the vascular endothelial growth factor (VEGF).

276. Peinado 2020 – Endometriosis risk is associated with bisphenol A (BPA) and Σbisphenols but not with BPS or BPF. thiobarbituric acid reactive substances (TBARS) concentrations showed a close-to-significant increased endometriosis risk. Exposure to bisphenols may increase the risk of endometriosis, and oxidative stress may play a crucial role in this association. Bisphenol A (BPA), an endocrine disrupting chemical, is used in the manufacture of polycarbonates and epoxy resins for water bottles, plastic containers, and cans for food or beverages. See Rier 1993, 1995, 2001 & Smarr 2006.

277. Pluchino 2020 – Targeting CXCR4 or CXCR7 receptors reduced bone marrow-derived stem cell recruitment into endometriosis implants. Endometriosis lesion size was not affected when the local effects of CXCL12 were abrogated suggesting an effect primarily on bone marrow cell migration rather than a direct endometrial effect. Antagonist treatment also
decreased hallmarks of endometriosis physiopathology such as pro-inflammatory cytokine production and vascularization.

278. Ghiasi 2020 – Heterogeneity of inclusion and diagnostic criteria and selection bias overwhelmingly account for variability in endometriosis prevalence estimated across the literature. Thus, it is difficult to conclude if the lack of observed change in frequency and distribution of endometriosis over the past 30 years is valid.

279. Lu 2020 – T-cadherin (T-cad), an important cell surface glycoprotein adhesion molecule, is coded by the CDH13 gene. T-cadherin can inhibit cell invasion, migration and proliferation in various cancer cells. T-cadherin overexpression inhibited the invasion and migration of endometrial stromal cells. The expression of T-cadherin was decreased in ectopic endometriotic lesions, but not the normal control endometrium or the endometriotic eutopic endometrium.

280. Jerman 2020 – In bowel endometriosis and pelvic cancer populations with or without endometriosis, endometrial-like cells (CD10) and immune cell populations (T cells (CD3, CD4, CD8, and FoxP3), dendritic cells (DC; DC-Lamp and DC-Sign), B cells (CD20, CD79 and plasma), macrophages (CD68), and natural killer cells (NK; CD57)) were present in all studied nodes. No difference in cancer associated node CD10 with or without endometriosis. None of the studied lymph nodes contained endometriotic lesions. See Sampson 1922, Halban 1924, and Jerman 2015.

281. Alali 2020 – Expression of RPLP1 mRNA and protein were significantly higher in ectopic lesion tissue compared to paired eutopic endometrium and immunohistochemical localization revealed predominant localization to epithelial cells. The ribosomal protein large P1 (RPLP1) is associated with cell proliferation and/or survival and may play a role in the pathophysiology of endometriosis.

282. Angioni 2020 – Genetics are population dependent and require evaluating genetic variants in different populations. In different ethnic groups, it is possible that specific risk alleles could act differently in the pathogenesis of the disease.

283. Hogg 2020 – Hogg explores the paradigm that under disease-modified conditions, macrophages that normally maintain homeostasis become modified such that they promote disease. In health, tissue-resident macrophages are seeded during early embryonic life are vital for development and homeostasis of tissues. In the adult, under inflammatory challenge, monocytes are recruited from the blood and differentiate into macrophages in tissues where they fulfill functions, such as fighting infection and repairing wounds. In endometriosis, Macrophages are critical for the growth, development, vascularization, and innervation of lesions as well as generation of pain symptoms.

284. Guo 2020 – Cancer-associated mutations (CAMs) are found in deep infiltrating endometriosis, endometriomas, and normal appearing tissue. Endometriotic epithelial cells have much higher mutation frequencies than their stromal counterpart. Genes involved in CAMs are likely to be active players in lesional fibrogenesis, and hyperestrogenism and oxidative stress are likely drivers of both CAMs and fibrogenesis. Furthermore, endometriotic lesions harbouring CAMs would conceivably be more refractory to medical treatment, due, in no small part, to their high fibrotic content and reduced vascularity and cellularity.

285. Wei 2020 – This review of inflammation and autonomic nervous system and inflammation interaction in endometriosis-associated pain includes cellular components (macrophages, mast cells, neutrophils), inflammatory mediators (interleukins, transforming growth factor β1, tumor necrosis factor-α, prostaglandin, noninflammatory factors), influence of estrogen, neurotropic and neuroprotective activity of cytokines, sympathetic and sensory nerve...
distribution, neurotrophins, the transition from acute to chronic inflammation, and potential implication in the management of endometriosis.

286. García-Gómez 2020 – Hormonal alterations in endometriosis are related to the inflammatory unbalance in this disease. Steroid hormones (mainly estradiol) promote the expression and release of pro-inflammatory factors. Excessive inflammation in endometriosis contributes to changes of hormonal regulation by modulating sex steroid receptors expression and increasing aromatase activity. Dysregulation of the inflammasome pathway, mediated by an alteration of cellular responses to steroid hormones, participates in disease progression through preventing cell death, promoting adhesion, invasion, and cell proliferation. Inflammation is involved in endometriosis-associated infertility, which alters endometrium receptivity.

287. Kiss 2020 – Women with spontaneous pneumothorax (SP) have gene expression profiling revealed two distinct phenotypes of circulating endometrial cells (CECs) in SP and catamenial pneumothorax CP: one of them refers to the diaphragm openings syndrome and the other to endometrial tissue pleural implantations. Comparisons of the gene expression profiles of CECs in pneumothorax (CECs-SP group) with CECs in pelvic endometriosis (CECs-non-SP group) have revealed significantly higher expression of HER2 in the CECs-SP group compared with the CECs-non-SP group. Identification of CECs in SP could alert endometriosis involvement. See Sampson 1927b, Bobek 2014, Vallvé-Juanico 2019, and Pospisilova 2019.

The Tomato Effect (Theory-Based Medicine)

The tomato effect in medicine occurs when an effective treatment for a specific 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 can interfere with the acceptance of useful remedies. According to Goodwin & Goodwin (1984), the only three issues that matter in picking a therapy are:

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

Goodwin & Goodwin’s three issues can be updated to

- Risks
- Benefits
- Costs
- Alternative treatment
- Acceptability
- Availability
- Insurance coverage
- Preauthorization
- In-network providers
- Out-of-network providers
- Other associated concerns of using a therapy.

Patient’s questions include:

- What do I have?
- How did I get it?
- What can we do about it?
- Will insurance cover it?
• Can I avoid surgery?
• Can I avoid hormones?
• How do I manage my allergies?
• How do I avoid narcotics?
• Can I have access to narcotics?

Discussions of theory are not discussions about the effectiveness of treatment. The results of surgical or medical therapy stand on their therapeutic outcomes, not on an opinion or a theory. Since early endometriosis can be transient or stable in many, if not most cases, observation or symptomatic care, such as hormonal suppression can be reasonable. Superficial endometriosis can respond to observation (Evers 1994, Koninckx 1994, Harrison 2000), medication or coagulation. Deep endometriosis will more likely require excision (Malinak 1979, Semm 1980, Martin 1989). Excision was successful in my practice (DCM), just as it was for Dr. David Redwine. His reoperation rate of 55%, with only 19% having histologic endometriosis, was like mine in the 1980s. (Redwine 1991)

In the later years of my practice, although the persistent pain rate after surgery remained relatively constant, I stopped doing as many repeat laparoscopies. Sutton (1994) noted that three to six months of pain relief after surgery is non-specific and can be a placebo response. Performing a repeat laparoscopy for pain that occurred in the first six months after excision was not commonly useful. I focused more on their questions and concerns, helping them with expectations, considering hormonal suppression, encouraging physical therapy, considering stress therapy, deciding about judicious use of narcotics, and more.

Reversal in Evidence-Based Medicine

Evidence-based medicine, like theory, is dependent on the knowledge available at the time it is applied. When knowledge changes, the approach to a disease and its treatment can also change. “Medical reversal” is a term used to describe the phenomenon when the long-established medical practice changes due to new, emerging evidence. Vinay Prasad’s Ending Medical Reversal: Improving Outcomes, Saving Lives (2015) discusses the problems that can occur with those changes. Although evidence-based medicine is more grounded than theory-based medicine, both are subject to change over time. Both are subject to the seven stages of a medical reversal: 1) promising report, 2) adoption by providers, 3) patients and payors accept the innovation, 4) insubstantial studies that superficially support the innovation, 5) randomized controlled trials, 6) denial if the trials do not support earlier observations and finally 7) acceptance.

These problems can be compounded by delay. Balas (2000) studied the components of delay such as the time needed to do the research, have the research accepted for publication, and have the change accepted by the general medical community. He calculated that it takes an average of 17 years for research evidence to reach clinical practice.

Subtle Inflammatory Lesions (Subtle Peritonitis)

Additional concerns are raised by inflammatory lesions suggestive of endometriosis in adolescents and children. (Marsh and Laufer 2005, Cabana et al. 2010) Endometrial or endometrioid stroma can be challenging to recognize in inflammation (Clement 2007), and the conclusions that these reactive and inflammatory are endometriosis is reasonable. However, neither Marsh and Laufer (2005) nor Cabana et al. (2010) nor Cabana et al. (2010) used stromal markers such as CD10. Nor did they exclude infection, endotoxins, or other causes of inflammation (Khan 2014, Khan 2016, Canis 2017) as the source of the inflammation. If these are infectious, then antibiotics can treat active infection and potentially decrease long-term
morbidity. Conversely, if these are sterile inflammatory lesions or if bacteria are present but part of a healthy microbiome, then antibiotics may interfere with a healthy microbiome (Power 2017).

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Cicinelli et al. (Fertil Steril 2017, 108:289-292) concluded that chronic endometritis might represent a facilitating factor in the development of endometriosis.


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.

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


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


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