Endometriosis Concepts and Theories

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This document is updated periodically. An update may be available at http://www.danmartinmd.com/files/endotheory.pdf


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Introduction

“Please don’t refer to endometriosis, adenomyosis, or fibroids as “benign disease” – nope, not benign, they are “common and morbid”.”

Linda G Griffith, Ph.D., 2020

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

Donna Vogel, MD, Ph.D., 2000

Symptoms suggesting endometriosis were reported in 1855 BC (Egyptian Papyrus). Hippocrates (400 BC) noted that “part of the vagina hardens.” Intraabdominal lesion and history compatible with endometriosis were noted in 1690 (Shroen). The histology of endometriosis and adenomyosis was described in 1860 (Rokitansky) and theory reported in 1870 (Waldeyer). The difficulty of recognition was documented in 1899 (Russell).

A theory may be useful at several levels including guiding research, acting as a framework for education, understanding possibilities in endometriosis, explaining changes that occur in endometriosis, and explaining why treatment might work. In contrast, the Tomato Effect discusses how some theories have interfered with treatment. Medical Reversal is a parallel concern that can interfere with useful treatment.

No concept or theory is entirely adequate. I needed only Sampson’s retrograde theory in 1970 (Sampson 1921 & 1927, Ridley 1961) and added Müllerian remnants in 1992 (Batt
1985, Koninckx and Martin 1992). The number I needed increased to five by 2017. Now it takes eighteen to introduce what I saw in patients or published and more to discuss what I have read.

**Summary**

- Endometriosis is heterogenous with more than 65 published, overlapping, visual and anatomic phenotypes and many microscopic, biochemical, histochemical, immunological, genetic, and epigenetic phenotypes. It presents with heterogenous signs, symptoms, and behaviors and has a non-uniform response to hormonal, surgical, and anti-inflammatory therapy. It can regress, progress, or remain stable. There is debate of whether a diagnosis is dependent on a transition from endometrium or Müllerian rests to an endometriotic cell, vascularization, fibrosis, or only the presence of a combination endometrial-like glands or stoma, positive CD10 or BER-Ep4, or other characteristics.
- There are age-dependent, diagnosis, symptom, sign, and imaging differences in appearances, depth of infiltration, and volume of lesions.
- The diffuse locations of endometriosis may be explained by retrograde menstruation, peritoneal dispersion, attachment, infiltration, and growth; peritoneal or pleural metaplasia; and hematogenous or lymphatic dissemination of Müllerian or non-Müllerian stem cells.
- Nodular rectovaginal lesions of 4 cm can be asymptomatic while 0.08 mm lesions have been associated with pain. Tenderness can be 27 mm from a visible lesion.
- Endometriosis can be hidden deep or in plain sight. Clinically unrecognized endometriosis was described as early as 1899 and nodules as large as 5 cm have been discovered beneath adhesions or scar and in ovaries, the retroperitoneum, tubes, lymphatics including nodes, open pockets, cryptic pockets, large and small bowel, appendices, epiploic fat, mesentery, and omentum. It may not be visualized on the peritoneum when it is microscopic; microscopic includes organoid foci and stem cells.
- 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 of the pleura.
- Retroperitoneal, retrocervical, and cul-de-sac endometriosis may be a) Müllerian remnants, b) pelvic lymphatics, c) retrograde with retraction, or d) hematogenous.
- Hematogenous sites may include pulmonary, spinal, dermal, and other distal sites.
- Early endometriosis may start with normal Müllerian (endometrium or remnants) cells or non-Müllerian (bone marrow/peritoneal) stem cells. These undergoes reactive, biochemical, hormonal, immunologic, and genetic changes in developing later and more severe 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 (fibrogenesis) with muscular metaplasia starts as part of a local inflammatory reaction.
- Immunologic maturation, immunocompetence, apoptosis, autolysis, and autophagy limit infiltrative or expansive growth.
Retropertoneal, rectovaginal, and retrocervical endometriosis may be Müllerian remnants (Konincx 1992, Donnez 2001, Signorile 2009, 2010 & 2012), lymphatic metastasis, the result of retrograde with retraction, or hematogenous metastasis. However, hidden, retropertoneal endometriosis in women and any endometriosis in men are rarely reported and, until Badescu et al. (2016), found unrecognized endometriosis in 100% of 26 bowel endometriosis cases, hidden endometriosis was considered as uncommon or rare. That series was recently updated to clarify that nonvisualized nodules as small as 2 mm can be palpated at laparotomy in 25% of bowel resections (Roman 2021).

Rei (2018) found only 17 cases in men in the world literature from 1971 to 2018. The 17 male cases and retropertoneal 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. Furthermore, Rei (2018) reported one case compatible with coelomic metaplasia. 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 retropertoneal, can also be explained with retrograde, hematogenous, lymphatic, or extensional dissemination. Furthermore, various forms of trauma such as delivery, uterine curettage, intraabdominal surgery, retropertoneal menstruation, intraperitoneal hemorrhage, or occult pelvic inflammatory diseases may mitigate the ongoing course and chance of recurrence. That might even include surgical treatment of endometriosis may cause inflammation and increase implantation.

This review covers the source of the cell of origin; methods of dissemination (metastasis) if not in situ: the stimulus or stimuli for the induction or activation of the transition; why, how, and when the cell of origin (early endometriosis) transitions to late endometriosis; and the opposing mechanisms of inactivation and clearance. Some theories combine some or all the components. 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)
      - Mülleriosis (non-organoid and projected to include dissemination and transition)
  - Non-Müllerian metaplastic (differentiation) theories
    - Peritoneal or pleural mesothelial coelomic metaplasia (in situ)
    - Mesenchymal stem cells
    - Bone marrow stem cells
    - Mesoderm
• **Dissemination (Metastasis) or In Situ Location**
  - Retrograde menstruation, implantation, and infiltration
  - Hematogenous dissemination
  - Lymphatic dissemination
  - Uterocervical extension
  - Surgical transplantation
  - Growth (expansion or infiltration)
  - Embryonic Rests
    - In situ - The normal 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)
    - In situ – coelomic metaplasia and Müllerian remnants in normal Müllerian area.

• **Stimulus or Stimuli of Induction or Activation**
  - Estrogen
  - Inflammation
  - Infection
  - Trauma
    - Surgery, delivery
    - TIAR
    - ReTIAR

• **Transition and Growth**
The transition from normal Müllerian or non-Müllerian stem cells to later forms of endometriosis such as infiltrating endometriosis or ovarian endometrioma appears to hold the most potential for future research and therapeutic options. Transition involves the cellular, histological, biochemical, reactive, angiogenic, 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 can involve the local environment, implantation, infiltration, growth, expansion, exposure to endocrine-disrupting chemicals, inflammation, intracellular aromatase, metaplasia, differentiation, transdifferentiation, transcommitment, paligenosis, progesterone resistance, environmental gene regulation, immune system maturation, immune system competence, endotoxins, oxidative stress, progenitor cell differentiation, proliferation, biochemical changes immunologic changes, apoptosis, anti-apoptosis, autophagy, reactive oxygen species, fibrinogenesis, fibrosis, muscular metaplasia, fibroblast to myofibroblast transdifferentiation, macrophage migration inhibitory factor, clonality, microRNA, signaling, nerve activation, cancer-associated driver mutations, neurogenesis, angiogenesis, genetic dysregulation and more that are covered in this document.

• **Inactivation and Stabilization or Clearance**
  Growth is opposed by immunology, inactivation, apoptosis, epigenetic reversibility, and scavenging mechanisms including autophagy/clearance.
The articles listed in this review are only a small part of what is published. A PubMed search for endometriosis 11/16/20 listed 28,744 articles that include many parts of the endometriosis story. That included 1,381 in 2019 (3.7 articles daily) and 1,601 in 2020 (5.0 articles daily). In addition, scholar.google.com lists 363,000 articles 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, histology, histochemistry, spontaneous resolution of endometriosis, stages, phenotypes, aromatase production, hormonal levels, miRNA, embryology, neonatal development, genetics, environmental gene regulation (non-heritatary epigenetics), organoid development, stromal type endometriosis, endometriosis in men, bone marrow stem cells in endometriosis, differentiated stem cells, primordial germ cells, programmed death (apoptosis), autolysis, oxidative stress, angiogenesis, neuroangiogenesis, transitions into mesenchymal cells, fibroblast-to-myofibroblast transdifferentiation, smooth muscle metaplasia, vascularization, hormonal receptors, and proteins involved in epigenetic modifications.

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.

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, Konincx 1994, Harrison 2000), medication or coagulation. Deep endometriosis will more likely require excision (Malinak 1979, Semm 1980, Martin 1989b). Redwine’s (Redwine 1991) reoperation rate of 55%, with only 19% having endometriosis recognized suggested that for many women (65% in that study) endometriosis may not be the cause of their pain.

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. That was one reason that, in the later years of my practice, although the persistent pain rate after surgery remained relatively constant, I stopped doing many repeat laparoscopies. 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.

According to Goodwin & Goodwin (1984), the 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 include:

- Risks
- Benefits
- Costs
- Acceptability
- Availability
Medical Reversal

“Medical reversal” is a companion to the “tomato effect.” The difference is that medical reversal occurs after treatment that is initially accepted based on positive but inadequately studied information is reversed. That contrasts with the initial rejection of a treatment due to the tomato effect because of a negative theory.

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 and create a new standard of care. This commonly happens when new knowledge updates and improves older but effective treatment. But, medical reversal describes when medical practices that were initially thought to be beneficial are found to be inadequate or detrimental. (Prasad 2012, Prasad 2019, Herrera-Perez 2019) The seven stages of medical reversal are: 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.

Both changing to a new standard of care and the recognition of medical reversal 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 broad based, clinical practice.
For endometriosis, perhaps no medical reversal is more distressing for physicians trained in the late 1900s than that regarding the use of diethylstilbestrol (DES). DES was touted as a treatment for endometriosis in the 1940s (Karnaky 1948) but was found to cause vaginal adenosis associated vaginal cancer (Herbst 1971) as the daughters born in the late 1940s and 50s matured. Other significant problems in the daughters of DES exposed mothers include endometriosis, infertility, miscarriage, preterm delivery, loss of second-trimester pregnancy, ectopic pregnancy if pregnant, stillbirth, early menopause, grade 2 or higher cervical precancerous changes, and breast cancer at 40 years of age or older. For most outcomes, the risks among exposed women were higher for those with vaginal epithelial changes than for those without such changes (Senekjian 1988, Wilson 2011, Upson 2015, Ottolina 2020). Medical reversal, in addition to the tomato effect, can have serious consequences.

Can we Recognize Endometriosis?


Moreover, nonvisualized but palpable retroperitoneal nodules as large as 4 cm (Moore 1988) have been found in the retroperitoneum (Moore 1988, Konincx 1993, and Konincx 1996), large and small bowel (Martin 1990c, Roman 2021), appendix (Martin 1990b, Martin 1990c), epiploic fat (1989b), and mesentery (Martin 1995). Hidden endometriosis has also been found during dissection (Martin 1992, Possover 2015, Stuparich 2020). Furthermore, Possover (2015) recognizes deep sciatic involvement based on history, exam, and MRI.

Hollis’s (1984) three steps for nodules or focal tenderness on office exam can aid in recognition. 1) Palpation on exam under anesthesia (EUA) for localization,
2) Use a finger or probe to push the nodule up for better recognition/visualization and excision when needed.
3) After excision, repeat palpation to confirm that the nodule was removed.
4) Continue excision if the nodule is still present and then repeat palpation.

Arrington (2020) uses a rectal probe at laparoscopy to better recognize rectal and sigmoid endometriosis.

As recognition is not always possible, the finding of tenderness 27 mm from the closest visually recognized endometriosis (Demco 1998) may be related to an unrecognized lesion, inflammation, nerve sensitization, or other causes.
In addition to the expected difficulty recognizing endometriosis, there are technical problems that can interfere with recognition. Those include failing to mark the margins, inadequate magnification, lack of palpation for 2 mm lesions, no looking in unusual locations, inadequate power density, bleeding, use of standard histology processing, coexistent fibroids, coexisting cancer, and tunnel vision.

When does the cell of origin become endometriosis?

The question of when a cell of origin, whether retrograde endometrium, congenital rest, peritoneal stem cell, venous disseminated bone marrow stem cell, or other cell, becomes endometriosis or when in development they should be considered as a disease is unanswered. Small lesions can be associated with pain and large lesions may be asymptomatic. The limits of small are not defined. Another asymptomatic woman had a 4 cm, deep infiltrating, rectovaginal nodule that was seen in the posterior upper vagina on yearly exam by a primary care. She remained asymptomatic with no change in size on exam and or MRI for seven years before she moved to another state.

My smallest lesion (0.08 mm) was seen on 35mm film but not during surgery. As the 0.08 mm lesion was not seen in real time, the specimen was not processed to look for lesions that small. Neither David Redwine (personal communications), Paul Raas (1997), nor I (1988 & 1990) saw lesions smaller than 0.18 mm at the time of surgery. Moreover, these small lesions were associated with larger lesions. That is also true of the 0.1 mm bowel lesions in Badescu et al. (2016). Because of the association of smaller and larger lesions, it cannot be determined if it is larger lesions, smaller lesions, a combination, an associated inflammatory reaction, nerve stimulation, or other cause that may be the source of pain.


Evers (2005) concluded that glands and stroma, at a location outside the uterine cavity, must persist and progress to be considered pathologic.

Evers, JLH, Dunselman GAJ, & Groothuis P. Now you see them, now you don’t. Fertil Steril, 2005, 84:31-32. doi: 10.1016/j.fertnstert.2005.01.122. PMID: 16009150


Moen (2002) concluded that asymptomatic lesions seen at tubal ligation are not likely to become symptomatic with 12 to 14 years follow-up.

Martin (1988, revised 2020) documented endometriotic lesions as small as 0.2 mm histologically. Although these were the smallest seen at the time of surgery, lesions as small as 0.08 mm were found on close examination of the 35mm films. Those lesions have not been anticipated and the specimen was not processed to look at that size lesion. Martin DC. Laparoscopic Appearance of Endometriosis. 1988, Resurge Press, Richmond, revised 2020. https://www.danmartinmd.com/files/lae1988.pdf.


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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) 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).

Cabana MD, Foster-Barber AE, Hong T, Martin DC, Shenkin B. Teen troubled by a trembling leg. Contemporary Pediatrics. 27(6):22-27, 201

Canis et al. (J Gynecol Obstet Hum Reprod. 2017, 46(3):219-227) considered “occult pelvic inflammatory disease” as a potential initiating event for endometriosis.”

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.


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.
Koënicx et al (Facts Views Vis Obgyn. 2019b, 11(3):209-216) found that women with endometriosis have a significantly increased risk of lower genital tract infection, chronic endometritis, severe PID and surgical site infections after hysterectomy.

Leonardi et al (BJOG. 2020, 127(2):239–249) found that endometriosis appears to be associated with an increased presence of Proteobacteria, Enterobacteriaceae, Streptococcus spp. and Escherichia coli across various microbiome sites.

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


Concepts and Theories (chronological)

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 scirrhous 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 1990a) 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/1UlBmdgddjD5eO1TxW0mpky_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. Shroen’s “ulcers” were a female disorder, characteristic of those who are sexually maturing. The lesions were in the bladder, intestines, broad ligament, and outside of the uterus and the cervix. They were inflammatory and tended to form adhesions that linked organs together. They expanded in size, were vacuolated, and were susceptible to hemorrhaging. 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 was likely endometriosis. See Knapp 1999 for Shroen and 18th century reference. Discussions are in Knapp 1999, Batt 2000, Brosens 2000, and Batt 2011a.
4. von Reitzenstein c1769 – Leopoldine von Reitzenstein, the Countess of Reitzenstein, had coexistent malignancy and ovarian pathology supporting the diagnosis of an endometriotic ovarian cyst. Reported in van der Weiden 2020.


6. Cruveilhier 1835 – Cruveilhier published a gross description of “the existence of cysts of the adenexa, uterus, and vagina, forming along the course of the Wolffian (mesonephric) and Mullerian paramesonephric remnants. Although lacking accurate descriptions, both gross and microscopic, it is plausible to think that such "cysts" were probably of an endometrial nature.” Quoted in Breus 1894, Ridley 1968, Batt 2011a, Redwine 2016.

7. Rokitansky 1860 – Rokitansky published the first description of the histology of what we now call endometriosi and adenomyosis in addition to endometrial polyps, intracavitary myomas, and either a papillary serous cystadenofibroma with psammoma bodies or an ovarian malignancy in a malnourished 68-year-old. In the time of Rokitansky and Virchow, almost every connective tissue proliferation, whether neoplastic or reactive, with or without epithelial component was also referred to as "sarcoma." Interpretations by Dr. Franz Glasauer, Prim. Dr. Günter Alpi, Prof. Dr. Jörg Keckstein, and Dr. Ken Groshart.

8. Waldeyer 1870 – Waldeyer concluded that epithelial ovarian cysts were from metaplasia (metamorphosis) developing in nests of cells in the germinial epithelium of an ovary. This might be the first recognition of a progenitor cell for epithelial cells. The germinial 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. See Que 2019 for recent concepts of metaplasia, paligenosis, differentiation, transdifferentiation and transcommitment.

9. Marchand 1879 – Marchand’s theory of the extension of tubal epithelium is quoted in Russell 1899. Marchand believed that the epithelium of the tube could extend out over the surface of the ovary, and by penetrating the stroma of the ovary produce tubules like Pflüger ducts. From these, he argued, cysts might arise with a histological resemblance between the mucous membrane of the tube and papillary tumors of the ovary.


11. Iwanoff 1898, Meyer 1903, Lockyer 1918a, Sampson 1921, Suginami 1991, Matsuura 1999 – Coelomic metaplasia of ovarian serosa may be the same concept as Waldeyer’s metaplasia from the germinial epithelium. See Zamecnik 2013 and Rei 2018 for metaplasia in men. See Que 2019 for recent concepts of metaplasia, paligenosis, differentiation, transdifferentiation and transcommitment.
12. Von Recklinghausen 1896 (discussed by Cullen in 1896 and Casler 1919) – The Wolffian theory proposes that adenoma (later called endometriosis) result from intermingling when the Wolffian and Müllerian ducts cross in fetal development.


15. Füth 1903 – A retrouterine, recto-corporal endometriotic mass, labeled as being in the rectovaginal septum, is illustrated in Lockyer 1918a, page335.


17. Clark 1908 (quoted in Kelly 1931) – Clark developed useful electrosurgery.

18. 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.

19. Klages 1912, Huetler 1918, Lockyer 1918a, Meyer 1919, Meyer 1924, Redwine 1988b, Alifano 2006 – Inflammatory induction of coelomic metaplasia of mesoderm or “endothelium” may include both peritoneum and pleura. Lockyer (1918a) quotes Klages (1912) as discussing the earlier work on metaplasia with illustrations of the transition from flat to cylindrical peritoneum by Opitz and Meyer with no citations listed. See Que 2019 for recent concepts of metaplasia, paligenosis, differentiation, transdifferentiation and transcommitment.

20. 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.

21. 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.

22. Sampson 1918, Sampson 1927b, Yovich 2020 – Discusses venous dissemination (metastasis) of intrauterine contents. See Sampson 1927b for endometrial dissemination and Yovich 2020 for review of Sampson 1927b with Sampson’s illustrations. See Bobek 2014 and Pospisilova
2019 for circulating endometrial cells as an endometriosis marker and Vallvé-Juanico 2019 for circulating stromal cells. See Samani 2017 for endometriosis-derived cells migrating to extrapelvic organs including the lung, spleen, liver, and brain in a mouse model.

23. Lockyer 1918b – This first classification was of the anatomic location of adenomyomas that were later called endometriosis.

24. Casler 1919 – Report of cyclic bleeding from ovarian adenoma (later called endometriosis) through a vaginal fistula after hysterectomy. Batt (2100) referred to this as a “menstruating ovary” Casler also discusses Von Recklinghausen’s Wolffian theory of intermingling when the Wolffian and Müllerian systems cross in fetal development.

25. Sampson 1921a, Sampson 1921b – 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. The 1921a Archives of Surgery version is duplicated and expanded with meeting discussion in the 1921b Transactions of the American Gynecological Society version. The discussion includes Sampson first mention of his retrograde theory.

26. Sampson 1921b, Sampson 1926, Sampson 1927a, Nap 2004a, Nap 2004b, Nap 2012 – Sampson suggested retrograde menstrual as “a,” not “the,” source of endometriosis. His 1927a publication expanded of his 1921b introduction of retrograde dissemination and invasion (implantation). He also discussed endometriosis within the adhesions of hemorrhagic cysts. He had previously discussed vascular dissemination, lymphatic dissemination, transplantation endometriosis, differentiation of celomic epithelium, direct extension from perforating ovaries, tubal epithelium as the origin, metaplasia of peritoneal epithelium due to the stimulus of menstrual blood from perforating ovaries, metaplasia of the mesothelial lining of the processus vaginalis peritonei or of the endothelial lining of dilated vessels, extraperitoneal endometriosis remnants from Wolffian bodies, developmentally misplaced endometrial (Müllerian) tissue, and why endometriosis was a better designation than Müllerianosis. In 1921b, Sampson introduced, in the Transactions of the American Gynecological Society, the possibility of “implantation of epithelium escaping from the tube during menstruation and its subsequent invasion of the ovary.” Joseph V. Meigs (1922) heard a subsequent presentation at Peter Bent Brigham Hospital, Boston, February 14, 1922, and discussed Sampson’s theory that ovarian “hematomas” are “due to the implantation of endometrium reaching the ovary by way of the Fallopian tube.” In 1927a, Sampson expanded this theory and 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 can be expanded with current knowledge to include:
- The cell of origin - Endometrial fragments or cells
- Dissemination - Retrograde menstruation of tissue fragments or cells
- Peritoneal dispersion
- Attachment
- Inflammation
- Infiltration
- Growth
  o Fibrosis
  o Entrapment
  o Muscular metaplasia

Theories of dispersion (retrograde menstruation, lymphatic, hematogenous, traumatic, surgical), congenital Müllerian remnants, secondary Müllerian system and metaplasia have been expanded to include the role of stem cells, replacement of endometrial cells by endometriotic cells, differentiation of stem cells into endometriotic cells, differentiation of stem cells into endometrial cells, and other concerns reviewed in the references that follow. See Wang 2020 for retrograde menstruation model.


28. 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

29. 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.”

30. Jacobson 1925 – Experimental induction of endometriosis by intraperitoneal autotransplantation of endometrium during oestrus was successful in sixteen (84%) of 19 rabbits. Early discussion of “Sampson’s syndrome” and “endometriosis.” He rejected metaplasia of mesothelium.

31. AGS Society Transactions 1925 – The American Gynecological Society held a t in a “Symposium on Misplaced Endometrial Tissue” in Washington, DC, May 4, 5, and 6, 1925. Drs. Ewing and Sampson used the term “endometriosis” while Drs. Cullen, Brady, Graves, Danforth, and Heaney used the term “adenomyoma.” and Dr. Keene discussed Sampson’s “perforating ovarian cysts” and Dr. DeWitt Casler (1919) discussed his menstruating ovarian “chocolate cyst containing about a dozen typical uterine polypi” that was a “a tumor of Müllerian origin.”


33. Sampson 1927a – See Sampson 1921b for discussion of his several theories and the development of his landmark retrograde menstruation theory paper (1927a).

34. 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.

35. Hunter 1927 – Early research on grafting of endometrial fragments.


needle tract or traumatic vaginal tears may be from denuded surface, trauma, or inflammation.

38. Novak 1931 – Metaplasia due to hormonal stimulation. See Que 2019 for recent concepts of metaplasia, paligenosis, differentiation, transdifferentiation and transcommitment.


40. Sampson 1940 – Discusses the detail needed for research including attention paid to small implants, sketches, selection 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.

41. 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/

42. Karnaky 1948, Karnaky 1969 – Karnaky proposed the use of the synthetic estrogen diethylstilbestrol (DES) to produce amenorrhea and suppress endometriosis. See section on Reversal in Evidence-Based Medicine. See Upson 2015 and Ottolina 2020 for increase in endometriosis with in-utero DES exposure.

43. Fallon 1946 – 13 to 19-year-old with endometriosis. See Clark 1948 for 11 years old and Marsh 2005 for 8.5 to 15 years old.

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


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

48. Scott 1953, Evers 1994, Koninckx 1994, Evers 1999, 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 cause pain, some do not, pimples hidden behind the skin can cause pain, ugly pimples did not always cause pain, some respond to hormonal therapy (estrogens), some respond to anti-inflammatory medication (tetracycline) some get worse, some come and go (Hoshiai 1993 and Martin 1999), some cause significant scarring, some require dermabrasion (surgery), and some are chronic and nonresponsive. Scott (1953) was the first to propose that if serial sections of all pelvic tissue were feasible, all women might have endometriosis. Evers (1999) calculated that if >16 blind biopsies were taken, then Nisolle et al. would have found endometriosis in all women. 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.”

49. Meigs 1953 – Meigs recommended early and frequent childbearing as prophylaxis.
50. Brews 1954 – Brews reported a woman with ascites and right pleural effusion with diffuse abdominal and diaphragmatic with a small communication through the right side of the diaphragm between the peritoneal and right pleural cavities. See Ṣuginami 1991 for cribriform fenestrations and Maniglio 2018 for perforations.


53. 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.

54. Ridgley 1958 and 1961 – Menstrual endometrium was implanted in the abdominal wall laparotomy sites in 15 women. Abdominal wall endometriosis was induced in two of the 15 with gross and microscopic glands and stroma compatible with endometriosis at the sites of implantation. An additional four had scarring, hemosiderin-laden macrophages, and an occasional small gland ascinus with an atypical epithelium compatible with endometriosis or tissue reaction to the material that had been injected.

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

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

57. Merrill 1966 – “Merrill factor” (quoted in Sugimami 1991) is a metaplasia-inducing substance such as estrogen and a factor liberated from degenerating menstrual endometrium. Also, see Thomas 1996. See Que 2019 for recent concepts of metaplasia, paligenosis, differentiation, transdifferentiation and transcommitment.


59. 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.

60. 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. See Que 2019 for recent concepts of metaplasia, paligenosis, differentiation, transdifferentiation and transcommitment.

61. Karnaky 1969, Jansen 1986, Redwine 1987, Stripling 1988a, Stripling 1988b, Davis 1988, Martin 1989a, Koninckx 1991, Albee 2008 – Any abnormality of the pelvic peritoneum, irrespective of size, the ease of visualization, the subtleness, the color, or the age of the patient may be endometriosis.

for male pseudohermaphroditism. Seventeen reports of endometriosis or endometrial cancer were summarized in Rei 2018. Most were older and on estrogen therapy.

63. Lauchlan 1972 – Differentiation of precursor tissue in a secondary Müllarian system may be responsible for endometriosis outside the normal Müllarian 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 Müllarian area including ileum, appendix, cecum, lateral gutters, and diaphragm.) See Que 2019 for recent concepts of metaplasia, paligenosis, differentiation, transdifferentiation and transcommitment.

64. Schifrin 1973 – Reported endometriosis in 15 teenagers. See Fallon 1946 for 13 to 19 years old, Clark 1948 for 11 years old, and Marsh 2005 for 8.5 to 15 years old.

65. 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.”


68. 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%.

69. 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. Semm was Mettler’s chairman at the University of Kiel.


71. 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.

72. Simpson 2003 – Genetic predisposition is generally seen as an observation, not a theory. This risk indicates that polygenic and multifactorial etiology is far more likely to be the cause than Mendelian inheritance. This conclusion parallels the genetic basis of most adult-onset conditions, including many in reproductive medicine (e.g., polycystic ovarian disease, leiomyomata, endometrial or serous ovarian epithelial cancer).

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

74. 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 Dorién 2017 for update.

76. Dmowski 1981 – Dmowski proposed that the immune system was involved in the development of endometriosis and that endometrial cells translocated from their normal location may implant only in women with specific alteration in cell-mediated immunity. See Koninckx 1980, Badawy 1983, Halme 1983, Halme 1984, Halme 1988, and Dorien 2017.

77. 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.

78. Rock 1981, Donnez 1984 – There is an increased risk of tubal endometriosis, especially after coagulation. Tubal surgery may be the surface disruption, traumatic or inflammatory event that facilitated the growth of endometriosis. See Munrós 2017, Long 2018, Hu & Taylor 2019, Munrós 2019, Guo and Martin 2019.

79. Daniell 1982, Daniell 1984, Tadir 1984, Martin 1985, Martin 1987 – The development of CO2 laser vaporization for endometriosis began with vaporization and progressed to excision. Vaporization was continued until healthy tissue was seen. High power density vaporization was needed to avoid carbonization, excess plume, and distortion at the base of a crater. Building on Semm’s (1980) techniques, excision was found to be easier for excision than vaporization for deep lesions. See Martin 1985 for development of CO2 laser excision.

80. Zinsser 1982 – Two of 128 patients’ omenta had endometriosis and 16 endosalpingiosis. All with endosalpingiosis had inflammatory tubal disease.


82. 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.

83. Wheeler 1983 – Recurrence rates are likely higher than published due to asymptomatic recurrence.

84. Hollis 1984 – Post-resection palpation is needed to confirm that palpable nodules have been removed. These can be too deep for visualization. Hollis’s three steps for nodules or focal tenderness on office exam:
1) Palpation on exam under anesthesia (EUA) for localization,
2) Use a finger or probe to push the nodule up for better recognition/visualization and excision when needed.
3) After excision, repeat palpation to confirm that the nodule was removed.
4) Continue excision if the nodule is still present and then repeat palpation. See Martin 1986a for use and Martin 1988a for acknowledgement.
85. 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 Koninckx 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 stem cells rather than 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.

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


88. Martin 1985, 1986b, 1986c, 1986d, 1987 – Development of laparoscopic excision resulted in confusion regarding the terms as they were different than those used in colposcopy. The general colposcopy terms were adopted. Initially, CO₂ laser vaporization was called ablation. This was used in colposcopy for cryotherapy. The terms evolved so that ablation included electrosurgical coagulation, cryotherapy, and focused sonogram. Although some still use ablation as synonymous with vaporization, these are two different tissue techniques. Wide zone (low power density) vaporization is using a laser to turn tissue into a lab plume. Thin zone vaporization (high power density) is using a laser as a hot knife to remove an intact tissue specimen.

89. Batt 1985 – There are two types of endometriosis: the congenital and the acquired forms. The human female may harbor endometriosis from embryonic life until death, the disease being active or inactive at various times. See Batt 1989 and 2013.

90. 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

91. Taylor 1986 – Clarifies that CO₂ laser secondary 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.


93. 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.

94. 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.

95. 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.

96. Moore 1988 – Five patients had deep retroperitoneal involvement and rectovaginal lesions as large as 4 cm with little or no intraabdominal disease. Three of these patients had either complete ureteral obstruction, hydronephrosis or full thickness involvement of the rectum. The disease was severely symptomatic, difficult to diagnose, and challenging at surgery. Four of the patients were over 40 years old and this appeared a late onset disease. See Griffiths 2007 for rectovaginal endometriosis retrospectively missed at first laparoscopy in only 14 (88%) of 16 cases. See Roman 2021 for nonvisualized but palpable bowel endometriosis prospectively missed at laparoscopy.

97. 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.”

98. 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. See Redwine 1990 for microscopic lesions. See Roman 2021 for nonvisualized but palpable bowel endometriosis missed at laparoscopy.

99. Redwine 1988b – Redwine proposed the term Müllerosis for a model that included a Müllerian cell of origin and any observed defects in the differentiation, transition, or position of those cells. He also discussed metaplasia as a second model. See Redwine 2019.

100. Batt 1989 – Batt considered pockets to be congenital Müllerian remnants and not acquired lesions. He considered the acquired pockets in Martin’s 1988 slide set were due to surgical trauma. [https://www.danmartinmd.com/files/lae1988.pdf] This is later expanded into a theory of congenital Müllerosis and acquired Müllerian diseases. Both include adenomyosis, endometriosis, endosalpingiosis, and endocervicosis. Medial ureteral position was due to an attenuated uterosacral ligament or as the medial border of a large fossa associated with endometriosis is congenital. See Batt 2013.
101. Martin 1989a – 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. See Roman 2021 for lesions missed at laparoscopy.

102. Martin 1989b, 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).

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

104. Martin 1990a – 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.

105. Nisolle 1990 – Nisolle et al. focused on the multiple appearances documented in Jansen (1986), Martin (1989) and Stripling (1988a & 1988b). Despite this focus, histology confirmed endometriosis was found in the normal peritoneum of 13% of women with other areas of endometriosis and 6% of women with no evidence of endometriosis. The size of endometriotic lesions 88 µ to 720 µ. See Murphy 1986, Redwine 1990, and Nezhat 1993.

106. Redwine 1990 – Three visually normal study biopsies had glandular structures identified histologically. Two of these study biopsies appeared to be mesothelial inclusions with one of 30 µ. The third gland had no obvious endometrial stroma, but a pathologist suggested that this might be endometriosis. The diameter was 120 µ. “Visually normal peritoneum does not harbor a high prevalence of invisible microscopic endometriosis.”

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


109. 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.

110. 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.

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

112. Suginami 1991 – Suginami concluded that the multiple sites or endometriosis were most compatible with coelomic metaplasia. Pulmonary implants may be from dissemination through cribriform fenestrations (called communication in Brews 1954 and perforations in
Maniglio 2017) See Que 2019 for recent concepts of metaplasia, paligenosis, differentiation, transdifferentiation and transcommitment.

113. 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.

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

115. 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 Müllerian rest origin. Also see Donnez 1997 and Nisolle 1997.

116. 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 for a tendency for endometriosis to worsen over time if untreated.


118. 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)


120. 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.

121. Nezhat 1993 – Nonvisualized endometriosis included a 1 mm retroperitoneal nodule, too large to be called microscopic, and two surface stromal lesions of 200 μ and 300 μ. See Murphy 1986, Nisolle 1990, and Redwine 1990

122. 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.


124. Adamson 1994. – Surgery or no treatment is better than medical therapy for fertility.

125. Oosterlynck 1994 – CA 125 levels, but not natural killer (NK)-mediated cytotoxicity, are decreased 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 and Margatho 2018 for response to etonogestrel (ENG) implant and levonorgestrel-releasing intrauterine system (LNG-IUS); review in Gavzani 2002; and Moss 2005 for comments on overuse of CA 125.

126. 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.

127. 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.

128. 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.

129. Tran 1994, 2012 – Inflammatory appearance added to staging. Also see review in Bouquet de Joliniere 2019.


131. Lessey 1995 – Abnormal endometrial integrin expression was a frequent finding in women with unexplained infertility. These data suggest that defective uterine receptivity may be an unrecognized cause of infertility in this population of women.

132. Perper 1995 – Menstrual cramps (dysmenorrhea) are related to the number of implants.


134. 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.

135. Khare 1996 – Differences in collagen types suggest that ovarian endometriosis may be metastatic while pelvic wall-infiltrating endometriosis is metaplastic.

136. 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.


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

141. 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.

142. Leyendecker 1998, 2009, 2015 – Uterine dysfunction in women with endometriosis and adenomyosis is a result of archimetral hyperestrogenism. Intrauterine tissue injury and repair (TIAR) at the endometrial-muscularis interface due to intrauterine trauma produces estrogens that interfere in a paracrine fashion with the ovarian control over uterine peristaltic activity, resulting in permanent hyperperistalsis and a self-perpetuation of the disease process. Uterine peristalsis is part of directed sperm transport and occurs during menstruation in the non-pregnant uterus.

143. 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.

144. 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.

145. 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).

146. Evers 1999 – In an article that generally discussed infertility, Evers and Dunselman noted that Balasch et al.’s (1996) 5.5% positive biopsy rate in normal women without endometriosis confirmed Nisolle et al. (1990), who “found 6% positive biopsies in non-endometriosis patients. These investigators only took one biopsy per patient. This means that, if they had taken > 16 biopsies per patient, and if sufficient sections had been studied, then all women would have had endometriosis.” See Scott 1953, Evers 1994, Koninckx 1994, Evers 1999, Koninckx 1999, Harrison 2000, Nap 2004a, Koninckx 2018.

147. Ling 1999, Jenkins 2008, and Momoeda 2014 – The decreased pain on hormonal suppression with estrogen/progestin or GnRHa (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.

148. Knapp 1999 – Knapp concluded that 17th and 18th century reports of “ulcerated” inflammatory lesions were compatible with endometriosis. Although histology was in its infancy and was not discussed, Shroen’s 1690 descriptions of the occurrence in maturing women, symptomatology, distribution, and hemorrhage are more consistent with endometriosis than what we would now call a ulcerative disease. If the term “ulcer” in the 17th century can also mean any lesion, then the description was likely endometriosis. His review includes Shroen 1690 and five 18th century references. Discussions are in Batt 2000, Brosens 2000, and Batt 2011a.

149. 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-year old had a second laparoscopy at age 15, suppression for four years, a miscarriage at age 20, a son at age 21, and was doing well at age 22. See Roman 2021 for nonvisualized but palpable bowel endometriosis.

150. 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.

151. Vigano 1999 – Cell adhesion molecules can engage and transduce a signal that leads to cellular events to change “the phenotype, movement, gene expression or activation state of the cell. On the other hand, cytoplasmic signals regulate the functional activity and surface expression of these receptors.” These molecules transfer information in both directions across cell membranes to influence developmental and immune characteristics.

152. Treloar 1999 – Tetrachoric twin pair correlations for self-reported endometriosis suggest that 51% of the variance of the latent liability to endometriosis may be attributable to additive genetic influences.


154. 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.

156. 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.

157. Redwine 2002 – Thirty-eight differences between eutopic endometrium and endometriosis in humans are reviewed.

158. 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. See the “Subtle Inflammatory Lesions” section of this document.

159. 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.

160. Sumathi 2002 – CD10 is a useful immunohistochemical marker of normal endometrial stroma and of endometrial stromal neoplasms. Endometriotic stromal cells were positive for CD10 in 22 of 25 cases.

161. Tosh 2002 – See Tosh 2014 for metaplasia as replacement by differentiation of stem cells rather than the transdifferentiation of differentiated cell types. See Que 2019 for recent concepts of metaplasia, paligenosis, differentiation, transdifferentiation and transcommitment.

162. 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.

163. Giudice 2004 – A growing body of evidence indicates that a combination of genetic, hormonal, environmental, and immunologic factors play 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).


165. Chan 2004 – Endometriosis is clonal


167. 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.
168. 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). Also, some are inflammatory, some get better on medication (estrogenic BCPs, Accutane, antibiotics including tetracycline possibly more for its anti-inflammatory than its antibacterial properties), some cause pain, others do not, pain is not always related to the appearance, some cause scarring, some are treated with surgery (dermabrasion), and some are chronic and nonresponsive.


169. 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 2010, Khan 2014, Khan 2016, Canis 2017, Leonardi 2020) as the source of the inflammation.

170. 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.


171. Moss 2005 – Moss reviewed the high false positive rate and poor sensitivity and specificity associated with CA 125 screening. The substantial inappropriate usage of CA 125 has led to results that are useless to the clinician, have cost implications, and add to patient anxiety and clinical uncertainty. In female patients having a CA125 for suspicion of malignancy/ovarian cancer, only 39 (20%) of the abnormal results were caused by ovarian cancer. Transvaginal ultrasonography has a greater sensitivity and specificity than CA125 for diagnosing ovarian cancer. Open Access: [https://jcp.bmj.com/content/58/3/308.long](https://jcp.bmj.com/content/58/3/308.long). See Sasamoto 2020.


173. 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.

174. 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.

175. 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.
176. **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 1990a, Martin 1991, and Muzii 2013.

177. **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.

178. **Markovic 2008** – Normalization of menstrual pain by young women, their families and health professionals results in delay to diagnosis and long-term exposure to biomedical treatments. The main characteristics of endurance of pain are delayed presentation to a health professional and women’s initial acceptance of health professionals’ advice about the lack of any abnormality. Women who contest the normalization believe they are experiencing unusually painful periods, reject health professionals’ assessments that the cause of pain was psychosomatic rather than pathological, and once diagnosed with endometriosis, while receiving biomedical care, also explored complementary and alternative treatments. Sachedina (2020) adds the missed educational, social and vocational opportunities due to normalization of dysmenorrhea.

179. **Nair 2008** – Whole explants of human peritoneum, as well as peritoneal mesothelial cell (PMC) monolayer cultures, demonstrate that whole fragments of proliferative, secretory, and menstrual phase endometrium, as well as cultured endometrial stromal cells (ESC) and endometrial epithelial cells (EEC), adhere to intact PMCs within 1 hour. After attachment to PMCs, endometriotic cells begin to invade PMCs and the basement membrane within 6 hours. By 24 hours, PMC growth over the invaded endometrial cells is well established. These studies strongly suggest that PMC attachment and transmesothelial invasion are the initial steps in the genesis of peritoneal endometriotic lesions. The transition from attachment to invasion likely occurs too rapidly to permit observation of endometrial cell attachment to peritoneal mesothelium in vivo. Disruption of the peritoneal mesothelium, and exposure of the basement membrane, is not required. Invasion by endometrial cells (both ESCs and EECs) is increased through MTGL (modeled basement membrane) when the MTGL is covered by PMCs. These results suggest that PMCs are not a barrier to peritoneal invasion. Rather, PMCs play a significant role in enhancing endometrial invasion into the peritoneal extracellular matrix. PMC-endometrial attachment leads to signal transduction resulting in this altered transcription. Also, ESCs from patients without endometriosis can invade through PMCs.

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


182. **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.

183. **Noël 2008** – Lymph node involvement by endometriosis was observed in 42.3% of deep infiltrating rectosigmoid endometriosis cases and correlated with the size of the lesions, the
number of lymph nodes retrieved, and the presence of lymphovascular invasion. Lymphovascular invasion was observed in 36.3% of cases. See Taussig 1906, Sampson 1926, Javert 1949, and Lenz 2020


185. 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

186. 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

187. 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


189. Griffiths 2007 – Rectovaginal endometriosis was identified at first laparoscopy in only two (12%) of 16 cases. This is likely due to scarring of the rectum to the posterior uterus creating a pseudo-pouch of Douglas and obscuring the nature of the disease. Griffiths et al. suggest using a rectal probe to determine the degree of obliteration of the pouch of Douglas and increase diagnostic accuracy.

190. 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; Koninckx 2019b for a review of microbiome, infection, and bacterial endotoxin; and Leonardi 2020 for a review of the microbiome.

191. 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%).

192. Signorile 2010 & 2012 – Fetal tissue compatible with endometriosis on H&E, H&VG and immunohistochemistry stains (CD10, Era, CA 125, 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 Koninckx (1992) with Type III being the most suggestive of a congenital rest and Donnez (2001) on metaplasia from Müllerian remnants.

193. 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

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

195. 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.

196. 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

197. Umezawa 2010 – Prenatal in utero 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. See Upson 2015 and Ottolina 2020 for human in utero and postnatal exposures.

198. Coccia 2011 – Menopause occurred earlier in women who had bilateral cystectomy than those with unilateral endometrioma (42.1 versus 47.1 years of age). Primary ovarian insufficiency was more common after bilateral cystectomy. The relationship between the preoperative ovarian endometriomas total diameter and menopausal age was significant in case of surgery for bilateral endometriomas.

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

200. 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.

201. Batt 2013, Laganà 2017 – Müllerianosis is an organoid remnant of Müllerian tissue in the native area of embryologic Müllerian development. Remnants include adenomyosis, endometriosis, endosalpingiosis, and endocervicosis. The four developmental Müllerian diseases complement the four acquired Müllerian diseases. See Batt 1985. He did not discuss organoid remnants such as accessory and cavitated uterine masses [Acién 2012].

202. Batt 2013 – Hamartoma is a neoplastic Müllerian growth in the native Müllerian area.

203. 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.

204. Raposo 2013 – Extracellular vesicles involved in intercellular communication (signaling)
205. 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.

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

207. Gazvani 2013 – C. albicans may contribute to the pathogenesis of endometriosis by modulating cytokine production. See the “Subtle Inflammatory Lesions” section.

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

209. 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/.


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

213. 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 thee 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). See the “Subtle Inflammatory Lesions” section. Also see Martin 1989a for increase with awareness of subtle appearances, Khan 2010 for endotoxins, Hopton 2014 for “near-contact” laparoscopy, Khan 2016 for crosstalk between inflammation and ovarian steroids or the stress reaction, and Leonardi 2020 for a review of the microbiome.

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


216. 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.

217. 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.

218. 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 thee 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 Khan 2010 for endotoxins, Khan
2016 for crosstalk between inflammation and ovarian steroids or the stress reaction, and Leonardi 2020 for a review of the microbiome.

219. Leconte 2014 – Chemokines and growth factors are found in elevated levels in the peritoneal fluid of women with endometriosis, and these may contribute to the proliferation and implantation of endometriotic implants and neoangiogenesis in the peritoneal cavity. CXCR-4, an alpha-chemokine receptor, and its target chemokine protein CXCL12 have chemotactic activity for lymphocytes produced in the inflammatory peritoneal environment. CXCL12 is higher in DIE peritoneal fluids than in controls. CXCR4 was downregulated in deep infiltrating endometriotic stromal cells. The CXCL12-CXCR4 axis plays a role in the attraction of eutopic endometrial cells into the peritoneal cavity, and the downregulation of CXCR4 in resident endometriotic cells could cause their arrest in situ.

220. Tosh 2014 – Tosh and Slack (2002) and Tosh and Horb (2014) discussed the versatility of adult stem cells and possibly differentiated cells. They discuss metaplasia as both the conversion of one cell type to another including conversions between tissue-specific stem cells and theoretically transdifferentiation or the conversion of differentiated cells types to another cell type. They concluded that some past examples of transdifferentiation (e.g., cervical squamous metaplasia seen as transdifferentiation would be mature columnar cells changing into mature squamous cells) may have been artifact. See Liu 2017 for fibroblast-to-myofibroblast transdifferentiation and different lesional microenvironments. See Tosh 2002 and Tosh 2014 for phenotypic metaplasia compared with transdifferentiation. See Que 2019 for recent concepts of metaplasia, paligenosis, differentiation, transdifferentiation and transcommitment.


222. 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

223. 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.

224. Guo 2015 – Repeated tissue injury and repair (ReTIAR) due to cyclic bleeding in endometriosis. Also see Canis 2016, Canis 2017

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

226. Deans 2015 – Deans and Maggett 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.

227. Upson 2015 – This analysis of 310 women in western Washington State observed that women who were regularly fed soy formula as infants had over twice the risk of endometriosis compared to unexposed women. There was also an increased endometriosis risk with prematurity and maternal use of diethylstilbestrol (DES, a synthetic estrogen). This
is confirmed in Ottolina 2020. See Karnaky 1948 and Karnaky 1969 for mid-1900s use of DES to treat endometriosis.


229. Hughes 2015 – Markers for diagnosis, response to treatment, and disease progression are needed. See Guo 2009 for recurrence marker and Zhang 2018 for prognosis marker.

230. 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.

231. 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.

232. Canis 2016, Canis 2017 – Endometriosis may not be a chronic, recurrent disease. The extent or the surgical phenotype of the disease may be related to the initial anatomic localization, type, and severity of the trauma. Various traumas including delivery, uterine curettage or incision, intraperitoneal hemorrhage, or occult pelvic inflammatory diseases could be involved. The healing process, particularly growth factors and the associated estrogen production, may facilitate the implantation and the growth of ectopic endometrial cells. Also see Guo 2015.

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

234. 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.

235. 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. Crosstalk 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.


237. 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.
238. 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.”

239. Smarr 2016 – Endocrine disrupting chemicals (EDCs), such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), dioxin-like polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), polybrominated diphenyl ethers (PBDEs), perfluoroalkyl and polyfluoroalkyl substances (PFASs), 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.

240. Badescu 2016 and 2018 – Badescu et al. documented histologically positive but clinically unrecognized bowel lesions in all 26 patients (100%) studied. The lesions were up to 5 cm from the primary nodule and were 1 mm to 1 cm in size. Four patients (15%) had nodules at the margins.

241. 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, Mullerian 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.

242. Gordts 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 endometrial cells is not as important as the genetic and epigenetic changes associated with the specific phenotypes of endometriosis. See Deans 2015 for clarification of definition of “epigenetics.” See Wang 2020 stem cells.

243. 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 reviewed 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. See Wang 2020.

244. 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. See Que 2019 for recent concepts of metaplasia, paligenosis, differentiation, transdifferentiation and transcommitment.

245. Makiyan 2017 – Congenital primordial germ cells remnants can be the source.


247. 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

248. 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.


250. 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. See Que 2019 for recent concepts of metaplasia, paligenosis, differentiation, transdifferentiation and transcommitment.

251. 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.


253. 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

254. Power 2017 – Review of microbiome interactions. See the “Subtle Inflammatory Lesions” section of this document.

255. Samani 2017 – 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.

256. Surrey 2017 – GnRHa before embryo transfer in freeze-all cycles resulted in implantation and ongoing pregnancy rates that were similar among the three groups and compared favorably to Group 4 (all transfers after comprehensive chromosomal screening (CCS) for descriptive comparison only). A non-significant trend towards improved outcomes was
noted in Group 1 (+ CCS +endometriosis) Prolonged GnRHa after freeze-all in these patients avoids excessive ovarian suppression and results in excellent outcomes.

257. Turco 2017 – Human adult stem-cell-derived organoid cultures can be used to generate three-dimensional cultures of normal and decidualized human endometrium. These organoids expand long-term, are genetically stable and differentiate following treatment with reproductive hormones. Single cells from both endometrium and decidua can generate a fully functional organoid. Transcript analysis confirmed great similarity between organoids and the primary tissue of origin. Although limited and having no stroma, blood vessels, innervation, and immune cells, these may be useful in studying endometriosis etiology, modeling, and therapeutics. See Boretto 2019 for organoids from endometriosis.

258. 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.

PMC Open Access: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5855821/


260. 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.

261. 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/

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

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


265. Matsuzaki 2018 – Autophagy may be required for regrowth of endometriosis. Autophagy inhibition with MK2206 (an AKT inhibitor) and chloroquine may decrease the chance of recurrence.

266. 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.

267. 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/
268. 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. See Guo 2009 for recurrence markers and Hughes 2015 for markers of diagnosis, response to treatment, and disease progression.

269. 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.

270. 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. See Sasamoto 2020 for lack of discrimination.

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

272. 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.


274. 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.

275. 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.

276. 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.

277. 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.

278. 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.

279. 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.
280. 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.

281. 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.

282. 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.

283. 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.

284. Marcellin 2018 – Marcellin, Méhats, and Gogusev 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.

285. 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.


287. 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.

288. 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, Munró 2017, Munró 2019, and Guo and Martin 2019.

289. 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 endometriotic diseases. See Regidor 1997 for expression pattern of gap junction connexins in endometriotic tissues.

290. Warren 2018 – Flow cytometry analysis of cell subsets within the CD45+ fraction of menstrual effluent (ME) revealed a significant decrease in the number of uterine NK cells in endometriosis patients compared with controls. Menstrual effluent can be useful for investigating the pathobiology of endometriosis and for developing a non-invasive diagnostic for endometriosis. See Leyendecker 1998, 2009, 2015 and Canis 2016, 2017

291. 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.

292. Yin & Taylor 2019 – Yin et al. discusses CD34+KLF4+ stromal stem cells contribution to endometrial regeneration and repair. CD34 is a marker for bone marrow derived, hematopoietic progenitor, vascular endothelial progenitors, mesenchymal (MSCs) and epithelial progenitor stem cells. Also see Fernandez 1995 for endometriosis, Starzinski-Powitz 2001 & 2003 for differentiation, Meng 2007 & Chen 2019 for menstrual blood-derived stem cells, Hufnagel 2015 and Wang 2020 for BMD stem cells in endometriosis, Miyazaki 2018 for pluripotent stem cell, and Yin 2019 for CD34 (bone marrow derived stem cell marker) in endometrium. Search file for “stem cell” for others.

293. Koninckx 2019a – 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.”

294. Koninckx 2019b – Women with endometriosis have a significantly increased risk of lower genital tract infection, chronic endometritis, severe PID and surgical site infections after hysterectomy. They have more colony forming units of Gardnerella, Streptococcus, Enterococci and Escherichia coli in the endometrium. In the cervix Atopobium is absent, but
Gardnerella, Streptococcus, Escherichia, Shigella, and Ureaplasma are increased. They have higher concentrations of Escherichia Coli and higher concentrations of bacterial endotoxins in menstrual blood. A Shigella/Escherichia dominant stool microbiome is more frequent. The peritoneal fluid of women with endometriosis contains higher concentrations of bacterial endotoxins and an increased incidence of mollicutes and of HPV viruses. Endometriosis lesions have a specific bacterial colonization with more frequently mollicutes (54%) and both high and medium-risk HPV infections (11%). They contain DNA with 96% homology with Shigella. In mice transplanted endometrium changes the gut microbiome while the gut microbiome influences the growth of these endometriosis lesions

295. Sokalska 2019 – Lipid-soluble statins (simvastatin, lovastatin, atorvastatin) were effective in inhibition of growth and invasiveness of human endometrial stromal cells.


297. 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.

298. 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.

299. 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.

300. Sun 2019 – Interferon-inducible transmembrane protein 1 (IFITM1) is a 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.

301. 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.

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

303. 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.
304. 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

305. 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 the fibromuscular content of deep endometriosis is frequently higher than in ovarian endometriomas, 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 shed much needed light into the pathophysiology of endometriosis.

306. 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.

307. 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/

308. 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

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

310. 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/

311. Liang 2019 – A pro-endometriotic niche can be established by an existing lesion as a supportive micro-environment for the progression of endometriosis. Reduction of estradiol can decrease chemokine CXCL12 and reduce BMSC accumulation and constrict angiogenesis. Targeting the components involved in pro-endometriotic niche formation and consequently preventing the progression of endometriosis may be a promising strategy for the treatment of endometriosis. See Liang 2016, Smarr 2016, Liang 2018, Peinado 2020.


313. Ding 2019 – Women with endometriomas demonstrate a hypercoagulable status due to the inflammatory nature of endometriosis. The combined determination for CA 125 and fibrinogen demonstrates a higher area under the curve than the single detection of CA 125 in those with endometriomas compared to those with benign ovarian cysts. Endometriosis is also associated with increased platelets. See Sasamoto 2020 for lack of discrimination.
314. 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.

315. 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.

316. 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.

317. 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.


319. Wu 2019 – Recent molecular genetic findings suggest that circulating epithelial progenitor/stem cells which are intended to regenerate uterine endometrium after menstruation may become over-reacted (increase in number and adhesiveness) and can be trapped outside the uterus where the epithelium clonally expands and recruit polyclonal stromal cells to establish endometriosis. The epithelial progenitor cells may likely come from endometrium and circulate in the blood with highest amount during the proliferative phase. Analyzing the evolutionary history of multiple tubal lesions in the same four patients with concurrent ovarian carcinoma indicated distinct evolution trajectories. See Wang 2020.

320. Yilmaz 2019 – Nuclear receptors (NRs) are related to mechanisms responsible for (i) excessive estrogen biosynthesis, (ii) estrogen-dependent inflammation, (iii) defective differentiation due to progesterone resistance and (iv) enhanced survival due to deficient retinoid production and action in endometriosis. There are our distinct abnormalities in the intracavitary endometrium and extra-uterine endometriotic tissue that will underlie
endometriosis progression: dysregulated differentiation of endometrial mesenchymal cells, abnormal epigenetic marks, inflammation activated by excess estrogen and the development of progesterone resistance. Steroid- and other NR-related abnormalities exert genome-wide biologic effects via interaction with defective epigenetic programming and enhance inflammation in endometriotic stromal cells.

321. Bulun 2019 – The underlying pathologic mechanisms in the intracavitary endometrium and extraterine endometriotic tissue involve defectively programmed endometrial mesenchymal progenitor/stem cells. Populations of endometrial and endometriotic epithelial cells also harbor multiple cancer driver mutations, such as KRAS, which may be associated with the establishment of pelvic endometriosis or ovarian cancer.

322. Vercellini 2019 – Serial ultrasonographic scans demonstrated transition from a hemorrhagic corpus luteum to an endometriotic cyst in 11 (85%) of 13 women. Bleeding from a corpus luteum appears to be a critical event in the development of endometriomas.

323. Chapron 2019 – A diagnosis of endometriosis should not lead to immediate surgery. Gynaecologists should consider the patient’s ‘endometriosis life’. Modern endometriosis management should be individualized with a patient-centered, multi-modal and interdisciplinary integrated approach.

324. As-Sanie 2019 – “Delays in diagnosis can degrade the patient-provider relationship, cause physical and emotional damage, impair quality of life, and add to the significant personal and societal costs associated with the disease.” “Due in part to the societal normalization of women’s pain and stigma around menstrual issues, there is also a lack of disease awareness among patients, health care providers, and the public.” About 95% of women with endometriosis have at least one or more comorbid disorders.

325. Steiner 2019 – In patients with recurrent implantation failure (RIF), treatment with a GnRH agonist plus letrozole, an aromatase inhibitor (AI), may improve live birth rates in subsequent cycles. We hypothesize that this improvement is due to alterations in the endometrium receptivity or treatment of undiagnosed endometriosis.

326. Likes 2019 – In patients testing positive for endometrial BCL6 expression and treated with either GnRHa for two months or surgery (ablation or excision), there was a 64% live birth rate achieved on the next IVF transfer. Of 21 patients who had laparoscopy had endometriosis. Prior published studies have shown untreated BCL6 positive patients had a less than a 12% live birth rate on subsequent transfers.

327. Berlanda 2019 – Women with deep endometriosis nodules had a non-significant decrease in nodule size from 19±6 mm before IVF and18±7 mm after failed IVF. One woman had an enlarged ovary with multiple corpora lutea associated with transient renal ectasia.

328. Bas-Esteve 2019 – The association of ovarian epithelial tumors and endometriosis is a factor for good prognosis for ovarian cancer and that this association might correspond in many cases to an intermediate stage in the development of endometriosis to endometrioid, clear cell, or other invasive carcinomas. In addition, endometriosis can evolve to borderline endometrioid carcinoma or clear cell carcinoma.


330. Redwine 2019 – Metaplasia-capable mesodermal tracts with undifferentiated stem cells are what lead to local (superficial) recurrence after visible endometriosis has been excised.

331. Que 2019 – Concepts of metaplasia and transdifferentiation continue to evolve. Recently the concepts of paligenosis and transcommitment have been added to differentiation and
transdifferentiation. This may apply not only to stem and precursor cells, but also to differentiated cells. Transdifferentiation is a process of reprogramming that can include fully differentiated squamous cells changing “into fully differentiated columnar cells—either directly (without undergoing a cell division) or indirectly (via cell division).” Paligenosis is “a process that starts with dedifferentiation of mature cells into progenitor-like cells before they re-differentiate abnormally.” Transcommitment involves the reprogrammed of immature progenitor cells so that they "alter their normal pattern of differentiation" and "proliferate and differentiate into different cell types."

332. 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).

333. 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.

334. 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.

335. 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.

336. 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.

337. 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.

338. 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.

339. 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.

340. 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.

341. 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 harboring CAMs would conceivably be more refractory to medical treatment, due, in no small part, to their high fibrotic content and reduced vascularity and cellularity.

342. 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.

343. 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.

344. 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.
345. Leonardi 2020 – A systemic review found that laboratory and clinical studies demonstrate that there are differences in the microbiome composition of hosts with and without endometriosis. Endometriosis appears to be associated with an increased presence of Proteobacteria, Enterobacteriaceae, Streptococcus spp. and Escherichia coli across various microbiome sites. The phylum Firmicutes and the genus Gardenerella also appear to have an association; however, this remains unclear. Also see Khan 2010 for bacterial endotoxins; Khan 2016 for crosstalk between inflammation and ovarian steroids or the stress reaction; Koninckx 2019 for a review of microbiome, infection, and bacterial endotoxin, and “Subtle Inflammatory Lesions.”

346. Friedman 2020 – Several studies on measured peripheral miRNAs in women with and without endometriosis report disparate findings regarding which plasma miRNAs are altered. Interstudy inconsistencies may be attributed to disparities between study populations, variable specimens, specimen handling, different stages of the menstrual cycle, and variation in plasma miRNA detection platforms. Despite the inconsistent reports, an optimist might discern an emerging consensus regarding altered plasma expression of several miRNAs (miR-17-5p?, miR-20a-5p?, miR-125b?) in patients with endometriosis. However, there remains no consensus on which plasma miRNAs, if any, will predict the presence of in the clinical setting. But there is evidence that miRNAs play a direct role in the pathogenesis of the endometriosis by regulating essential processes such as inflammation and angiogenesis. Whether plasma miRNAs contribute to pathogenesis or are simply markers of existing disease and whether peripheral miRNAs correlate with severity of disease or the degree of pelvic pain remains unknown.

347. Ottolina 2020 – This meta-analysis aims to offer a general picture of the available data regarding the effects of early-life factors and risk to develop endometriosis in adult life. Six studies that included a total of 2,360 women affected by endometriosis were analyzed. The pooled results showed that the risk to develop endometriosis in adult life was significantly increased by being born prematurely, having a low birth weight, being formula-fed, and having been exposed to diethylstilbestrol (DES, a synthetic estrogen) in utero. Among intrauterine and early neonatal exposures, prematurity, birth weight, formula feeding, and DES were risk factors for the development of endometriosis in adult life. See Karnaky 1948, Karnaky 1969 for mid-1900s use of DES to treat endometriosis and medical reversal.

348. Long 2020 – Long et al. (2020) studies the adverse effects of neonatal maternal separation as a form of early-life adversity with subsequent adult development of abnormalities including activation of adrenergic receptor signaling pathways, increased angiogenesis, altered neuronal wiring, hyperactivity of the hypothalamic pituitary adrenal axis, anxiety and depressive symptoms. Open Access https://doi.org/10.1186/s12958-020-00600-4 See Upson 2015 and Ottolina 2020 for increase in endometriosis within utero DES exposure.

349. Matsuzaki 2020 – Anti-inflammatory treatment may prevent growth of endometriotic tissues in excessive inflammatory stages, whereas it may have deleterious effects on fibrotic endometriotic tissues in a low-grade inflammation setting. Patients with inflammatory-stage fibrotic disease are most likely to respond, while patients with noninflammatory fibrosis might experience deleterious effects. Administration of COX-2 inhibitors in the early phase of inflammation yields an anti-inflammatory effect. However, inhibition of COX-2 by nonsteroidal anti-inflammatory drugs (NSAIDs), if used for more than 48 h, causes inhibition of anti-inflammatory mediators, and thus prolongs chronic inflammation and activates fibrosis of the kidneys, lungs, intestines, and muscles, as COX-2 is an important anti-fibrotic enzyme. PMC: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7289797/
350. Song 2020 – Forty-four (51.8% of 85) adolescents had genital tract malformations. 6 (7.1%) were rASRM stage I, 6 (7.1%) were Stage II, 41 (48.2%) were Stage III and 32 (37.6%) were Stage IV. These represent 85 (0.8%) of 11,236 surgically treated endometriosis patients 2008-2018. See Fallas 1956, Marsh & Laufer 2005, and Brosens 2013.

351. Sasamoto 2020 – CA125 did not discriminate endometriosis cases with pain from controls. CA125 values were low in adolescents and young women in both endometriosis cases and controls, suggesting cautious interpretation may be needed when measuring CA125 in this population.

352. Buggio 2020 – Alterations in the anogenital distance (AGD) (i.e., the distance measured from the anus to the genital tubercle) are associated with reproductive health in adult males and females. Studies suggest that a shorter AGD seems to be related to the presence of endometriosis, whereas a longer AGD seems to be associated with an increased risk of PCOS. Scientific evidence is limited, and further well-designed studies are needed to corroborate the findings.


354. Hirata 2020 – All catamenial hemoptysis (CH) patients experienced symptomatic improvement with hormone therapy, no recurrence during hormone therapy, and consequently no surgical therapy, unlike catamenial pneumothorax or endometriosis-related pneumothorax (CP/ERP), patients. The authors proposed that hormonal or conservative treatment was an adequate first-line treatment for most patients with CH. This contrasts with CP/ERP, which has a high recurrence rate both after surgery and hormonal therapy. Accordingly, CP/ERP and CH are suggested to be distinct entities, although both are types of thoracic endometriosis.

355. Esfandiari 2020 – The methylation pattern of human homeobox (HOX) clusters (A–D) and HOX cofactors in normal, eutopic, and ectopic endometrial tissues with ectopic and eutopic endometriosis organoids were determined in epithelial organoids. A conserved pattern of methylation alterations in endometriosis tissues and organoids was observed for 56 of 84 investigated genes. It can be concluded that endometriosis organoids maintain epigenetic changes. They are limited as they have no stroma, blood vessels, innervation, or immune cells. See Turco 2017 & Boretto 2019.

356. Leonardi 2020 – Superficial endometriosis can be seen on sonoPODography (saline-infusion ultrasound of the Pouch of Douglas).

357. Sachedina 2020 – Most adolescents will experience discomfort during menstruation. Due to normalization of dysmenorrhea, there is delay to diagnosis and treatment. Health care providers should avoid normalization of dysmenorrhea, as young women are missing out on educational, social and vocational opportunities. Non-steroidal anti-inflammatories (NSAIDs) are a first line treatment. Menstrual suppression with combined estrogen and progestin hormones such as oral contraceptives or progestin-only options are also first line. Transabdominal ultrasound is indicated when first line treatments do not improve symptoms. When first line treatments do not improve symptoms, gonadotropin releasing hormone agonists with add back treatment or laparoscopy can be considered. If laparoscopy is performed and endometriosis visualized, it should be treated with either excision or ablation. Women with endometriosis should be counselled on menstrual suppression until fertility is desired. Management of chronic pain requires the involvement of a multidisciplinary team. Also see Markovic 2008 for normalization of menstrual pain by young women, their families and health professionals resulting in delay to diagnosis and long-term exposure to biomedical treatments.
358. Matsuzaki 2020 – Primordial follicle activation initiates follicle growth and development and this irreversible process is the primary mode of primordial follicle depletion. Primordial follicle density is lower in the ovarian cortex surrounding endometriomas than in contralateral, unaffected ovaries and in the tissue surrounding non-endometriotic benign cysts. Uncontrolled inflammation, such as that of endometriomas and surgery, may adversely affect ovarian reserve. The inflammation can cause hyperactivation of dormant primordial follicles through the local microenvironment of ovarian endometrioma (mechanical and/or chemical cues). Both conservative management and surgical injury of ovarian endometrioma might decrease ovarian reserve over time.


360. Chen 2020 – Relaxin/relaxin family peptide receptor 1 (RXFP1) signaling is important for both normal physiology and disease. Strong preclinical evidence supports relaxin as a potent antifibrotic molecule. However, relaxin-based therapy failed in clinical trial in patients with systemic sclerosis. Aberrant expression of RXFP1 may contribute to the abnormal relaxin/RXFP1 signaling in different diseases. Reduced RXFP1 expression and alternative splicing transcripts with potential functional consequences have been observed in fibrotic tissues. A relative decrease in RXFP1 expression in fibrotic tissues—specifically lung and skin—may explain a potential insensitivity to relaxin. In addition, receptor dimerization also plays important roles in relaxin/RXFP1 signaling.

361. Yoshino 2020 – Relaxin (RLX)-2, produced by the corpus luteum and placenta, is known to be potentially effective in fibrotic diseases of the heart, lungs, kidneys, and bladder. In the endometriosis mouse model, administration of RLX-2 significantly decreased the area of the endometriotic-like lesion with decreasing fibrotic component compared to non-treated control.

362. Zhang 2021 – The PPARγ agonist rosiglitazone (RSG) (Avandia) is an antidiabetic drug in the thiazolidinedione class that decreases the development and progression of endometriosis in rats likely by inhibiting angiogenesis and inducing apoptosis.

363. Wang 2020 – Molecular genetic findings on endometriosis and normal endometrium suggest a modified model in which circulating epithelial progenitor or stem cells intended to regenerate uterine endometrium after menstruation become overreactive and trapped outside the uterus. These trapped epithelium-committed progenitor cells glands and recruit polyclonal stromal cells, leading to the establishment of endometriosis. The ectopic tissue is subject to immune surveillance, resulting in chronic inflammation in which nuclear factor-κB signaling is exacerbated by aberrations in the estrogen receptor-β and progesterone receptor pathways. This results in a dysregulated inflammation-hormonal loop.

364. Plavnik 2020 – Sixteen female patients with biopsy-confirmed endometriosis had ultrasound-guided pelvic-floor trigger-point injections and peripheral nerve hydrodissection performed once a week for 6 weeks. Pretreatment, the mean VAS score was 6, and posttreatment was 2.9. The mean total FPPS score before treatment was 14.4 and posttreatment it was 9.1. The improvement was statistically significant for intercourse, sleeping, and working. For intercourse, sleeping, and working, the mean change in scores after treatment were 1.3, 1.2, and 0.9, respectively.

365. Surrey 2020 – Endometriosis-related medical, surgical, or both treatments were used 61%, 35%, and 73% of patients, respectively, in the 16 months before the use of the GnRH antagonist elagolix. Opioids were used by 57.3% of the patients. Pelvic pain, dysmenorrhea, and dyspareunia were coded for 71.5%, 30.4%, and 19.3% of the patients, respectively.
366. Lenz 2020 – The immunophenotype in cases with and without node involvement was similar in the proliferative phase with strong nuclear ER and PR expression in more than 90% of endometrial glandular and stromal cells. In the late secretory phase, significant decrease of ER expression occurred only in those without nodal involvement. Perineural spread of endometriosis with significant neural hypertrophy, hyperplasia and involvement of the ganglia of the autonomic nervous system was detected in 5 cases. From a histological and immunohistochemical point of view, deep infiltrating endometriosis and lymph node endometriosis appear to represent the same entity. The marked endometriosis-associated neural changes (endometriotic neuropathy) could be one of the causes of impaired function of the affected organs after debulking surgery with macroscopic negative resection margins as well as pain symptomatology in macroscopic inapparent endometriotic lesions. See Taussig 1906, Sampson 1926, Javert 1949, Noël 2008


368. Le 2020 – Endometriosis patients on hormonal suppression had improvement with less systemic and local inflammation as measured by higher iTregs (tolerant), lower Th17 (inflammatory), and an increased in Treg/Th17 ratio. The imbalance within immune populations of inflammation in patients with endometriosis was improved on monophasic hormonal suppression with oral contraceptive pills. There were decreased inducible Treg cells and inflammatory Th17 cells in the blood, eutopic endometrium, and endometriosis, suggesting decreased systemic and local inflammation.

369. Persoons 2020 - A model for endometriosis-associated pain was induced in rats and resulted in neuro-angiogenesis and endometriotic lesions like humans. Significant differences were noted between control and endometriosis animals concerning bodyweight and posture changes, indicating the presence of ongoing pain in animals with endometriosis.

370. Tuominen 2020 – Women with rectovaginal endometriosis have similar pregnancy and live-birth rates. Cesarean delivery and complications were also similar.

371. Roman 2021 – Seven (14%) of 51 patients having bowel resection for endometriosis had laparoscopically nonvisualized palpable satellite lesions at or past the planned stapler site. A total of 13 (25.5%) had any palpable satellite lesions as small as 2 mm. Although reported success rates for all bowel endometriosis is 1-16%, recurrence after unrecognized endometriosis at the margins is 7-38.5%. See Moore 1988 for retroperitoneal endometriosis and Griffiths 2007 for rectovaginal endometriosis retrospectively missed at first laparoscopy in only 14 (88%) of 16 cases.
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1) Palpation on exam under anesthesia (EUA) for localization,
2) Use a finger or probe to push the nodule up for better recognition/visualization and excision when needed.
3) After excision, repeat palpation to confirm that the nodule was removed.
- Continue excision if the nodule is still present and then repeat palpation.


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