

Endometriosis Pathology Outline

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ABSTRACT

Endometriosis is the presence of tissue estrogen-dependent endometrial outside the uterine cavity. The two main symptoms are pain and infertility. It is a common disease, but the whole pathological mechanisms remain poorly understood. However, in addition to the two main pathological theories (implantation and metaplasia), new data have been added: inflammation and perinervous infiltration appear to be two major elements in the mechanism of pain. The basis of infertile process is not dependent on a mechanic cause, but also on disturbances in follicular generation and in fluid abnormality in the peritoneum.

Keywords: Endometriosis, pathology, pain, infertility, urinary.

INTRODUCTION

Endometriosis is defined by the presence of ectopic foci of hormone-dependent endometrial tissue that is, having glandular endometrial epithelium and stroma outside the uterine cavity and uterine muscle (*Dastur, 2010*). This pathology, very common in gynecology, has an estimated prevalence of 10-15% (*Nezhat, 2012*). It mainly affects women of childbearing age, but it can also affect women during adolescence or menopause (*Agarwal, 2010*). It is a very polymorphic condition with a wide variety of symptoms. The main elements recognized today as suggestive of endometriosis are chronic pelvic pain, dysmenorrhea, dyspareunia, pain during defecation and infertility (*Panel, 2007*). There are three types of endometriotic disease in practice: superficial endometriosis which only affects the pelvic peritoneum, endometriomas (endometriotic ovarian cysts) and deep endometriosis defined by infiltration of the subperitoneal space by endometrial tissue over 5 mm thick (*Charles, 2003*). Today, the etiology and pathology of endometriosis have not yet been fully elucidated. Many theories have been proposed, but none can explain on its own the different forms of endometriosis. It is likely that several mechanisms intervene. Another explanation could be that endometriosis is not just a single disease: superficial peritoneal lesions, deep lesions, endometriomas and extrapelvic endometriosis are different diseases, each with its own pathology (*Nisolle, 1997*).

LITERATURE REVIEW

I. History of the various pathology outline theories

Most of gynecological pathologies are described since antiquity. This is not the case with endometriosis. The earliest writings of endometriosis are those of a German physician (*Shroen, 1690*). In his book, he describes very precisely "ulcers" which, in their initial forms, distribute themselves over the peritoneum and are located near the bladder, intestines, large ligaments and outside the uterus. Shroen already believes this pathology is typically female and only affects women of childbearing age. It is the reference for several authors of the 17th and 18th centuries. (*Vassiliadis, 2011*) It was only from the end of the 19th century that the first pathological theories appeared. It is very surprising that unlike so many diseases, endometriosis is a recent onset. (*Sutton, 2019*) evokes a social and conjunctural cause. The women being pregnant very young and having successive pregnancies, endometriosis did not have time to set in. This pathology has become more frequent with longer life expectancy and later and less frequent pregnancies. At the end of the 19th century, the first pathological theories appeared thanks to the work carried out by others (*Knapp, 1999*). Two main theories have been proposed to explain endometriotic lesions:

- *The implantation theory* in which endometrial tissue originates in the uterine cavity and flows back to the abdominal cavity via the tubes during menstrual cycles and;

▪ *The theory of metaplasia* in which the endometriotic tissue differentiates in situ from preexisting tissue.

The implantation theory, proposed by (*Sampson, 1927*), involves the dissemination of viable endometrial stromal and epithelial cells via the fallopian tubes to the abdominal cavity. The implantation of these cells in the peritoneum would then lead to endometriotic lesions. According to this theory, the three main stages in the formation of endometriosis are: menstrual reflux of endometrial cells, adhesion of these cells to the peritoneum and invasion of the latter by these cells with local proliferation and angiogenesis. *Several arguments are in favor of this theory:*

I. Reflux of endometrial cells during menstruation is a physiological phenomenon. (*Halme, 1984*) demonstrated that blood was habitually and physiologically present in the peritoneal fluid in 90% of women with healthy tubes;

a. The anatomical distribution of the lesions corresponds to the path of tubal reflux (*Bricou, 2008*);

b. Pelvic malformations that increase reflux increase the incidence of endometriosis;

c. The endometrial cells found in the abdominal cavity are viable and able to proliferate;

d. Endometrial cells carry many molecules adhesion allowing them to attach to the peritoneum;

e. The endometrial fragments found in the peritoneal fluid express numerous metalloproteases capable of degrading the extracellular matrix and the basement membrane of the peritoneum;

f. The endometrium also produces angiogenic factors essential for local neovascularization;

g. Microscopic analysis of the macroscopically healthy peritoneum frequently identifies endometrial implants (*Balash, 1996*).

However, not all endometriotic disorders can be explained by this theory. How to explain the cases of endometriosis in men or extrapelvic involvement?

The theory of coelomic metaplasia is proposed by (*Meyer, 1919*). It is based on embryological data: the Müllerian ducts and the pelvic peritoneum derive from the same epithelium. The coelomic cavity is thought to contain cells capable of differentiating into endometrial tissue under the influence of factors still poorly understood. This theory would explain the case of

endometriosis without menstrual reflux, especially the rare cases of endometriosis in men.

There are other more debated theories such as induction or the metastatic model. The theory of induction corresponds to the endometrial differentiation of undifferentiated cells under the effect of endogenous, biochemical and immunological factors. This theory is supported by experiments in rabbits. Authors have shown that metaplasia of the mesothelium is possible if the endometrium and ovarian epithelium are placed in high concentrations of estrogen (*Thomas, 2015*). The metastatic theory is based on the dissemination of endometrial cells through lymphatic or blood vessels. This theory would explain extrapelvic endometriosis: pulmonary, cerebral, muscular, etc. The role of the environment is also increasingly studied to explain the mechanisms of this disease. Currently, there are several animal studies that primarily assess the effect of dioxins. In his study using a simian model, (*Rier, 2002*) demonstrated a significant dose-dependent increase in the incidence and severity of endometriosis in exposed monkeys. There are fewer data in the human species, as they most often correspond to studies of environmental disasters. Few significant results emerge from these studies. Some authors support the idea of genetic transmission of endometriosis. Numerous cytogenetic studies have shown alterations affecting several chromosomes. Some candidate genes are being explored. Thus, individual susceptibility to various external aggressions could be explained by the existence of genetic polymorphisms.

II. Pathology outline of the main symptoms

A. Pathology outline of pain

Pain is one of the main symptoms in endometriosis, and especially chronic pelvic pain (CPP). The CPPs pose a problem of definition; rare are the studies which use the same one. Some authors differentiate dysmenorrhea and profound dyspareunia from CPP (*Martin, 2020*), while others use a broader definition by including the first two in CPP (*Vercellini, 1990*). This is responsible for bias, which makes studies on the subject difficult to compare. To date, there is no consensus on the definition and characterization of CPP. Some patients, despite significant endometriosis are asymptomatic. Others, on the contrary, will present with very rich symptoms even though they have minimal lesions of endometriosis. The presence of severe dysmenorrhea (VAS \geq 8) is suggestive

of endometriosis (*Mahmood, 1991*). Several studies have shown that there is no correlation between the revised classification of the American Fertility Society (rAFS) of endometriosis and the intensity or frequency of pain (*Leyland, 2010*). In contrast, there is a correlation between the existence of severe dysmenorrhea and the extent of adhesions or the depth of involvement (*Fauconnier, 2005*). Other studies have shown a relationship between pain symptoms and the location of deep endometriosis lesions (*Chapron, 2003*). Therefore, not all forms of endometriosis are painful. To date, no single mechanism can explain this phenomenon on its own. The different mechanisms explaining the pain are essentially based on the inflammation linked to repeated cyclical bleeding, on perinervous infiltration and on adhesions. In deep endometriosis, the implants will penetrate the adjacent organs and increase the inflammatory phenomena. Endometrial tissues differentiate as the infiltration progresses, becoming more glandular and more active (*Joao, 2017*). (*Anaf, 2009*) showed that nerve and perinervous invasion of the subperitoneal nerves was correlated with the severity of CPP including dyspareunia and dysmenorrhea. Adhesions, sequelae of chronic inflammation, will be responsible for pain via a traction phenomenon but also by their own innervation (*Macer, 2012*).

B. Pathology of infertility

Infertility is the second leading cause for patients to consult. The more severe the endometriosis, the more severe the fertility problems. Thus, in stage IV patients of the AFS (American Fertility Society) score, the spontaneous pregnancy rate is 3%, 22% for stages III and 37% for stages I and II (*Parasar, 2017*). The simplest mechanisms to explain this poor fertility rate are mechanical.

First of all at the tubal level, acute and chronic inflammations will be at the origin of alteration of tubal function by obstruction, mobility disorder, morphological abnormality of the pinna and peritubo-ovarian adhesions hindering the both ovulation and oocyte uptake. All of these phenomena are quite similar to those observed in cases of chronic pelvic infections. New data complements our knowledge. They come from research on folliculogenesis and more recently on abnormalities of the peritoneal fluid and its potential antispermatozoid effect. (*Mansour, 2009*) studied the effect of peritoneal fluid on sperm morphology and sperm DNA. Two populations

were compared: healthy women and women with endometriosis. Semen samples were incubated with peritoneal fluid from these two populations. In women free from any pathology, there was no significant increase in DNA damage unlike in patients with endometriosis.

Second: Cytokines also appear to play a role in modifying peritoneal fluid not only through their proinflammatory action, but also through toxic action on gametes. In vitro, TNF α is believed to be responsible for reduced oocyte quality, reduced sperm mobility and their interaction with the zona pellucida oocyte. This cytokine, secreted by macrophages and by granulosa cells, is particularly abundant in endometriotic patients (*Lornage, 2002*).

Thus, as with pain, multiple pathologic mechanisms are involved in infertility.

C. Pathology of functional urinary disorders and digestive system

Urinary disorders, although secondary, are common in endometriosis. During a well-conducted interview, one often finds a rich symptomatology such as pollakiuria (idiopathic urinary frequency), urgency, urination burns, urinary incontinence and dysuria. These voiding disorders can be found both preoperatively and postoperatively. Their pathological mechanism is probably not the same before and after surgery. The study of bladder innervation allows us to understand the different possible mechanisms. It is a complex system. Two levels of innervation can be described: the central nervous system and the peripheral nervous system. Peripheral innervation is mixed with participation the cholinergic system, the adrenergic system via the hypogastric plexus, somatic pudendal system and NANC (non-adrenergic-non-cholinergic) system (*Azaïs, 2014*). Apart from any surgery, the symptoms are based probably on two mechanisms: nerve infiltration by endometriosis lesions in the bladder and / or hypogastric plexus and contractures associated with chronic inflammation. Postoperatively, functional disorders are explained first of all by the existence of intraoperative lesions. Postoperatively, the functional disorders are explained first of all by the existence of intraoperative lesions of the hypogastric plexuses, particularly during the resection of uterosacral ligaments. The technique of preserving these nerves (the nerve sparing surgery) significantly reduces postoperative complications (*Baader, 2003*).

The most common digestive symptoms are dyschezia, constipation, painful cravings, and non-cyclical

abdominal pain. Digestive disorders can be explained by two main mechanisms:

- *Mechanical damage*: endometriosis infiltrates the digestive wall and blocks more or less stenosing the lumen of the digestive tract. This easily explains the functional intestinal disorders including constipation, pain on defecation for low located lesions and painful cravings, etc. But this mechanism is insufficient, because after resection surgery, not all patients are improved, and moreover, not all digestive damage is obstructive;
- *Functional impairment*: endometriosis affects the nervous command. The nerves responsible for digestive function, and in particular for defecation, will also be affected by endometriotic infiltration and local inflammation. Again, surgery can also cause digestive

symptoms or their aggravation by intraoperative nerve plexus damage.

CONCLUSION

The pathology of endometriosis remains today still poorly known. The oldest theories, based on menstrual reflux or metaplasia, are still relevant today. Modern studies allow this knowledge to be refined. Many factors are involved, including environmental and genetic. Molecular biology studies have made it possible to highlight numerous mediators that can intervene at all stages of the disease. By refining our understanding of the pathological phenomena, we can hope for new therapeutic approaches and thus obtain better patient care.

REFERENCES

1. Agarwal, Neha & Subramanian, Arulselvi. (2010). Endometriosis – Morphology, Clinical Presentations and Molecular Pathology. *Journal of laboratory physicians*. 2. 1-9. 10.4103/0974-2727.66699.
2. Anaf V, Simon P, El Nakadi I, et al (2000) Relationship between endometriotic foci and nerves in rectovaginal endometriotic nodules. *Hum Reprod*. 15(8):1744–50
3. Azais, Henri & Rubod, Chrystèle & Ghoneim, Tarek & Vassilief, Maud & Bailly, Emmanuel & Boileau, Laurent & Villet, Richard & Collinet, Pierre. (2014). Persistent urinary retention after surgery for deep infiltrating endometriosis: a multi-center series of 16 cases. *Archives of gynecology and obstetrics*. 291. 10.1007/s00404-014-3588-7.
4. Baader B, Herrmann M. (2003) Topography of the pelvic autonomic nervous system and its potential impact on surgical intervention in the pelvis. *Clin. Anat*. Mar; 16(2):119-30. doi: 10.1002/ca.10105. PMID: 12589666.
5. Balasch, Juan & Creus, Montserrat & Fabregues, Francisco & Carmona, Francisco & Ordi, Jaume & Martinez-Román, Sergio & Vanrell, Juan. (1996). Visible and non-visible endometriosis at laparoscopy in fertile and infertile women and in patients with chronic pelvic pain: A prospective study. *Human reproduction* (Oxford, England). 11. 387-91. 10.1093/HUMREP/11.2.387.
6. Bricou A, Batt RE, Chapron C. (2008) Peritoneal fluid flow influences anatomical distribution of endometriotic lesions: why Sampson seems to be right. *Eur J Obstet Gynecol Reprod Biol*. Jun; 138(2):127-34. doi: 10.1016/j.ejogrb.2008.01.014. Epub 2008 Mar 11. PMID: 18336988.
7. Chapron, Charles & Fauconnier, Arnaud & Dubuisson, Jean-Bernard & Barakat, Habib & Vieira, Marco & Bréart, Gérard. (2003), Deep infiltrating endometriosis: Relation between severity of dysmenorrhoea and extent of disease. *Human reproduction* (Oxford, England). 18. 760-6. 10.1093/humrep/deg152.
8. Charles Chapron, Arnaud Fauconnier, Jean-Bernard Dubuisson, (2003) Deep infiltrating endometriosis: relation between severity of dysmenorrhoea and extent of disease, *Human Reproduction* Vol.18, No.4 pp. 760±766, DOI: 10.1093/humrep/deg152
9. Dastur, A. E., & Tank, P. D. (2010). John A Sampson and the origins of Endometriosis. *Journal of Obstetrics and Gynaecology of India*, 60(4), 299–300. <https://doi.org/10.1007/s13224-010-0046-8>
10. Fauconnier, Arnaud & Chapron, C. (2005). Endometriosis and pelvic pain: Epidemiological evidence of the relationship and implications. *Human reproduction* update. 11. 595-606. 10.1093/humupd/dmi029.
11. Halme J, Hammond MG, Hulka JF, et al (1984) Retrograde menstruation in healthy women and in patients with endometriosis. *Obstet Gynecol* 64(2):151–4

12. Joao Paulo Leonardo-Pinto, Cristina Laguna Benetti-Pinto, Kleber Cursino, Daniela Angerame Yela, (2017), Dienogest and deep infiltrating endometriosis: The remission of symptoms is not related to endometriosis nodule remission, *European Journal of Obstetrics & Gynecology and Reproductive Biology* 211: 108–111
13. Knapp VJ. (1999) How old is endometriosis? Late 17th- and 18th-century European descriptions of the disease. *Fertil Steril*. Jul; 72(1):10-4. doi: 10.1016/s0015-0282(99)00196-x. PMID: 10428141.
14. Leyland, Nicholas & Casper, Robert & Laberge, Philippe & Singh, Sukhbir. (2010). Endometriosis: Diagnosis and management. *Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstétrique et gynécologie du Canada : JOGC*. 32. S1-32.
15. Lornage J. (2003) Particularités biologiques de la reproduction en cas d'endométriose [Biological aspects of endometriosis in vitro fertilization]. *J Gynecol Obstet Biol Reprod* (Paris). Dec; 32(8 Pt 2):S48-50. French. PMID: 14968070.
16. Macer, M. L., & Taylor, H. S. (2012). Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. *Obstetrics and gynecology clinics of North America*, 39(4), 535–549. <https://doi.org/10.1016/j.ogc.2012.10.002>
17. Mahmood TA, Templeton AA, Thomson L, Fraser C. (1991) Menstrual symptoms in women with pelvic endometriosis. *Br J Obstet Gynaecol*. Jun; 98(6):558-63. doi: 10.1111/j.1471-0528.1991.tb10370.x. PMID: 1873245.
18. Mansour G, Aziz N, Sharma R, et al (2009) The impact of peritoneal fluid from healthy women and from women with endometriosis on sperm DNA and its relationship to the sperm deformity index. *Fertil Steril* 92(1):61–7
19. Martin, Dan. (2020). Endometriosis Concepts and Theories. At: https://www.researchgate.net/publication/339461010_Endometriosis_Concepts_and_Theories
20. Meyer R (1919) Über den Stand der frage der Adenomyositis und Adenomyome in allgemeinen und Insbesondere über Adenomyositis seroepithelialis und Adenomyometritis sacromatosa. *Zentralbl Gynakol* 43:745–50
21. Nezhat C, Nezhat F, Nezhat C: (2012) Endometriosis: ancient disease, ancient treatments. *Fertil Steril* 98(suppl 6):S1-S62.
22. Nisolle M, Donnez J. (1997) Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. *Fertil Steril*. Oct; 68(4):585-96. doi: 10.1016/s0015-0282(97)00191-x. PMID: 9341595.
23. Panel P, Renouvel F. (2007) Prise en charge de l'endométriose: évaluation clinique et biologique [Management of endometriosis: clinical and biological assessment]. *J Gynecol Obstet Biol Reprod* (Paris). Apr; 36(2):119-28. French. doi: 10.1016/j.jgyn.2006.12.020. Epub 2007 Feb 2. PMID: 17276015.
24. Parasar, P., Ozcan, P., & Terry, K. L. (2017). Endometriosis: Epidemiology, Diagnosis and Clinical Management. *Current obstetrics and gynecology reports*, 6(1), 34–41. <https://doi.org/10.1007/s13669-017-0187-1>
25. Rier SE (2002), The potential role of exposure to environmental toxicants in the pathophysiology of endometriosis. *Ann N Y Acad Sci* 955:201–12
26. Sampson J (1927), Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. *Am J Obstet Gynecol* 14:422–69
27. Shroen D. (1690) Disputatio inauguralis medica de ulceritus ulceri. *Jena, German Democratic Republic: Krebs*,
28. Sutton; Christopher G. David Adamson, Kevin D. Jones (2019) The history of endometriosis. Modern management of endometriosis, CRC Press
29. Thomas, Viju & Prince, Deborah. (2015). The Pathogenesis of Endometriosis: Still searching for answers. *Obstetrics and Gynaecology Forum*. 25. 31-38.
30. Vassiliadis, Simon. (2011). The Endometriotic Stem Cell and known immunological processes as stepping stones for the onset of Endometriosis: A novel theory. At: https://www.researchgate.net/publication/277331732_The_Endometriotic_Stem_Cell_and_known_immunological_processes_as_stepping_stones_for_the_onset_of_Endometriosis_A_novel_theory
31. Vercellini P, Fedele L, Molteni P, Arcaini L, Bianchi S, Candiani GB. (1990) Laparoscopy in the diagnosis of gynecologic chronic pelvic pain. *Int J Gynaecol Obstet*. Jul; 32(3):261-5. doi: 10.1016/0020-7292(90)90355-o. PMID: 1972119.

Endometriosis is a common, chronic gynecological condition defined as the presence of functional endometrial glands and stroma-like lesions outside the uterus. It manifests in three ways; superficial (peritoneal) disease, ovarian disease (endomet...⁴ Epidemiology. Typically endometriosis presents in young women, with a mean age of diagnosis of 25-29 years, although it is not uncommon among adolescents. Up to 5% of cases are diagnosed in postmenopausal women. Cite this page: Gonzalez R. Endometriosis. PathologyOutlines.com website. <https://www.pathologyoutlines.com/topic/colonendometriosis.html>. Accessed January 29th, 2021. Definition / general. Endometriosis arising within colon. Epidemiology. Up to 1/3 with endometriosis have involvement of large or small intestine. Sites. Usually rectosigmoid or rectovaginal septum (Med Sci Monit 2000;6:787); can involve any portion of colonic wall, from mucosa to serosa. PathologyOutlines.com website. <https://www.pathologyoutlines.com/topic/cervixendometriosis.html>. Accessed January 26th, 2021. Definition / general. May cause abnormal uterine bleeding, postcoital bleeding. Mean age 37 years, range 20 to 51 years.⁴ Similar to endometriosis elsewhere. Two of three present - endometrial glands with basal nuclei, spindled stroma, hemorrhage. Usually involves superficial third of cervical wall, not deep wall. The lining is called the endometrium. Learn the causes, complications, and outlook.⁴ Endometriosis occurs when endometrial tissue grows on your ovaries, bowel, and tissues lining your pelvis. It's unusual for endometrial tissue to spread beyond your pelvic region, but it's not impossible. Endometrial tissue growing outside of your uterus is known as an endometrial implant. Original Editors - Rebecca Clark from Bellarmine University's Pathophysiology of Complex Patient Problems project. Top Contributors - Rebecca Clark , Kim Jackson , Elaine Lonnemann , Laura Ritchie and Wendy Walker One Page Owner - Anthonia Abraham as part of the One Page Project. Related online courses on Physioplus. Online Course: Chronic Ankle Instability Risk Identification Online Course: Chronic Ankle Instability Risk Identification How to identify and prevent chronic ankle instability after an