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Pathogenesis of endometriosis: the genetic/epigenetic theory

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Objective: To study the pathophysiology of endometriosis.

Design: Overview of observations on endometriosis.

Setting: Not applicable.

Patient(s): None.

Interventions(s): None.

Main Outcome Measure(s): The hypothesis is compatible with all observations.

Result(s): Endometriosis, endometrium-like tissue outside the uterus, has a variable macroscopic appearance and a poorly understood natural history. It is a hereditary and heterogeneous disease with many biochemical changes in the lesions, which are clonal in origin. It is associated with pain, infertility, adenomyosis, and changes in the junctional zone, placentation, immunology, plasma, peritoneal fluid, and chronic inflammation of the peritoneal cavity. The Sampson hypothesis of implanted endometrial cells following retrograde menstruation, angiogenic spread, lymphogenic spread, or the metaplasia theory cannot explain all observations if metaplasia is defined as cells with reversible changes and an abnormal behavior/morphology due to the abnormal environment. We propose a polygenetic/polyepigenetic mechanism. The set of genetic and epigenetic incidents transmitted at birth could explain the hereditary aspects, the predisposition, and the endometriosis-associated changes in the endometrium, immunology, and placentation. 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 cell which may vary from endometrial to stem cells. Subtle lesions are viewed as endometrium in a different environment until additional incidents occur. Typical cystic ovarian or deep endometriosis lesions are heterogeneous and represent three different diseases.

Conclusion(s): The genetic epigenetic theory is compatible with all observations on endometriosis. Implications for treatment and prevention are discussed. (Fertil Steril® 2019;111:327–40. ©2018 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: Endometriosis, pathogenesis, classification, heredity, genetics, epigenetics

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The word endometriosis was introduced by Sampson in 1927 (1, 2) based on the description of endometrium-like tissue in the myometrium by Rokitansky (3), in the rectovaginal septum by Cullen, who called this entity an adenomyoma (4–7), and in "hemorrhagic (chocolate) cysts in the ovaries" (8). Endometriosis was defined as "endometrium-like glands and stroma outside the uterus." Therefore, stromatosis (9) and müllerianosis (10) are not considered to be endometriosis despite similarities.

Endometriosis is an enigmatic disease. Understanding the pathophysiology is important in prevention, diagnosis, and therapy. There is no nonhuman animal model with sufficient similarity to the human myometrium, junctional zone (JZ), endometrium, placentation, and pregnancy disorders, such as preeclampsia. In the absence of experimentation, our views on the pathophysiology of endometriosis are limited to clinical,

histologic, and biochemical observations and to research on endometriotic tissues.

To describe the genetic/epigenetic theory of endometriosis, we will summarize the observations made and review the theories on pathophysiology as they were developed over the last century (Table 1).

OBSERVATIONS IN ENDOMETRIOSIS

Endometriosis has a variable appearance. Reports on endometriosis describe lesions found during surgery which were initially severe lesions in the pelvis (3–7), the ovary (8), and other organs. Although smaller black puckered "powder burn" superficial peritoneal lesions in sclerotic areas had been described, the high prevalence of these typical lesions in women with pain and infertility was realized only after the introduction of laparoscopy in the 1970s. Nonpigmented lesions had been described (8, 11–14), but their high prevalence was realized only in 1986 (15). The observation that retrograde menstruation occurred in almost all women (16, 17) started the search for early and small lesions that were subsequently called subtle lesions (18, 19). Microscopic endometriosis lesions were found in the peritoneum and later in lymphoid glands and in the bowel at a distance from deep endometriosis (20).

"Deep endometriosis" was described in 1990 as deeper lesions with a microscopic appearance of adenomyosis externa, with glands in phase with the endometrium and associated with severe pain (21). These lesions are generally unique, larger than 1 cm in diameter, with frequent invasion into the muscle of the bowel wall, and with occasional nerve invasion (22), a neurotropic effect (23, 24), and some 20% lymph node involvement (25, 26). The definition of deep endometriosis as lesions deeper than 5 mm under the

peritoneum was later suggested because the biphasic frequency distribution of depth of lesions (27) indicated two populations overlapping at 6 mm of depth (Fig. 1). A second argument was that at depths greater than 5 mm, glands were more active (28), which was considered to be compatible with a depth where the effect of the progesterone concentrations in peritoneal fluid was less important (29). This change from a histologic definition to a 5-mm-depth definition remains a cause of confusion, because depth is an inaccurate surgical estimation, permitting some typical lesions to fit the 5 mm definition.

Endometriosis occasionally occurs in women without an endometrium (30, 31) and in men (32, 33). Endometriosis is a hereditary disease. The risk of developing endometriosis is 6%–9% higher in first-degree relatives of women with endometriosis (34, 35) and 15% higher when they had severe disease (36, 37). Familial clustering of endometriosis was demonstrated in humans (38) and other primates (39). In twin sisters, the prevalence (40–43) and the age of onset (44) of endometriosis are similar. More recently, hereditary factors were estimated to account for 50% of endometriosis (45–47).

We are far from understanding the molecular mechanisms (48). Genome-wide scanning and linkage analysis did not identify the genes involved (49). Linkage analysis found two loci but the logarithm of odds scores were low. Genome-wide association studies identified 10 (50) or 15 (51) loci with single-nucleotide polymorphisms (52) associated with severe endometriosis, but located in DNA sequences regulating target genes (53). A recent meta-analysis identified five loci regulating sex steroid hormone pathways, five secondary signals, and 19 single-nucleotide polymorphisms robustly associated with endometriosis (54) All studies that investigated a specific hereditary predisposition as detoxication failed (55).

The natural history of endometriosis is not clear. Endometriosis is considered to be a progressive disease because larger lesions must have developed over some period. However, progression of subtle lesions or progression from typical to cystic or deep lesions has not been observed directly (56). In addition, regression of smaller lesions is common (57). Clinically, endometriotic lesions, especially rectovaginal deep endometriosis lesions do not grow rapidly (58) when surgery is not performed. It is unclear whether endometriosis is a recurrent disease (59). Studies generally describe recurrence of symptoms instead of recurrence of lesions (60). Recurrence rates of cystic ovarian endometriosis after stripping are less than 20% within 6 months (61, 62) but vary with the surgeon (63) and the technique used. Recurrence rates of deep endometriosis lesions after complete excision are rare (personal observations) (60). The recurrence rates of typical lesions and subtle lesions are thought to be higher, although the data are limited.

The epidemiology of endometriosis is unclear. Laparoscopic recognition varies with the expertise of the surgeon. Hospital-based discharge records are therefore hampered by diagnostic uncertainties (64). Clinical observations suggest that the prevalence and severity of deep endometriosis have markedly increased during the past 20 years (58). Subtle endometriosis lesions decrease with age, whereas typical, cystic, and deep lesions increase with age, at least until menopause (58).

TABLE 1

Clinical observations on endometriosis.

1. Variable appearance (subtle-typical-cystic-deep)
2. Occurs also in women without endometrium and in men
3. A hereditary disease and predisposition
4. Natural history:
   - Most subtle lesions do not progress
   - Most typical-cystic-deep lesions are not progressive after diagnosis
   - Most typical-cystic-deep lesions are not recurrent after surgery
5. Epidemiology of endometriosis
6. A heterogeneous disease
7. Endometriosis is associated with:
   - Pain and infertility
   - Adenomyosis
   - Changes in plasma
   - Changes in peritoneal fluid
   - Changes in endometrium
   - Changes in pregnancy outcome
   - Pelvic infections
   - Cancer risk
   - Total body radiation and dioxin intake

The endometriosis lesion:
8. Clonal
9. Altered biology, e.g., estrogen formation and progesterone resistance

Koninckx. Pathogenesis of endometriosis. Fertil Steril 2018.

FIGURE 1
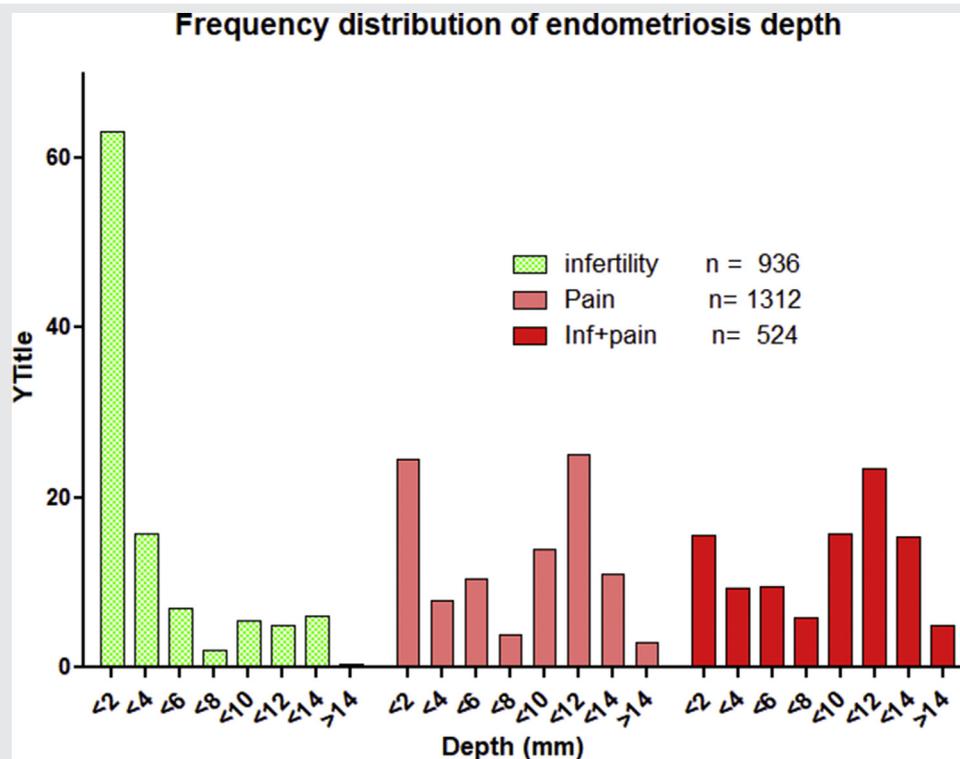
Frequency distribution of the depth of endometriosis lesions in women with infertility, with pain, and with both pain and infertility, as observed during surgical excision. The data, extracted from the Leuven database spanning the years 1990–2010, confirm and extend previous data (27) and illustrate the overlap between the two populations of more superficial (typical lesions) and deeper adenomyosis externa lesions.

Koninckx. Pathogenesis of endometriosis. Fertil Steril 2018.

Endometriosis is a heterogeneous disease. Although most women with deep endometriosis have severe pain, especially during menstruation (65), some large lesions (estimated to be 5%) are not painful. Most deep endometriosis lesions do not (or very slowly) progress over time, but some lesions can be fast progressive (unpublished observations). Estrogens stimulate growth, whereas progestogen therapy and pregnancy stop growth or cause decidualization and decrease endometriosis-associated pain. However, some endometriosis lesions behave differently. Bowel perforations have been reported during pregnancy (66, 67) and estrogen-progestin treatment (68). During pregnancy, polypoid bladder lesions (69), bladder perforations (70), and peritoneal bleeding (71) occur. Growth has been observed in men (32) and in postmenopausal women (72) without increased circulating estrogen concentrations.

OTHER OBSERVATIONS ASSOCIATED WITH ENDOMETRIOSIS

Endometriosis is thought to be associated with pain and infertility. However, it is unclear whether microscopic endometriosis (20) and subtle lesions cause pain or infertility, given the high prevalence in women with infertility only and women with pain only (27). Typical endometriosis is estimated to cause minor pain in 50% of affected women, and in women with infertility only, one-half of them are estimated to have typical lesions (27). Cystic ovarian endometriosis causes pain in more than 80%, and deep endometriosis causes severe pain in the large majority of women (27). Notwithstanding the 30%–50% cumulative pregnancy rates after surgical excision (73), it remains unclear whether and how typical and deep endometriosis cause infertility. That cystic ovarian endometriosis is a cause of infertility is not surprising, because it is associated with adhesions.

Despite the widely held belief of the association of endometriosis with adenomyosis, the data demonstrating this association are limited (74). Focal adenomyotic nodules are more frequent in women with deep endometriosis (75, 76).

In plasma of women with endometriosis, numerous reports have identified changes in immunology (77–85), lymphocytes (86), prostaglandins (87), and insulin-like growth factor I (88). That the low natural killer (NK) cell activity in plasma remains low whereas the elevated CA-125 concentrations return to normal after surgical excision of deep endometriosis suggests that the NK cell defect is a cause and the elevated CA-125 a consequence of endometriosis (89).

Peritoneal fluid of women with endometriosis and the luteinized unruptured follicle syndrome has much lower concentrations of estrogens and progesterone after ovulation (29). The peritoneal fluid exhibits low-grade inflammation with a high number of activated macrophages (90), changes

in cytokines (91–95), growth factors, acylcarnitines, phosphatidylcholines, and sphingomyelins (96), vascular epithelial growth factor (97, 98), and other angiogenic factors (99–118), especially of the transforming growth factor β superfamily (119). The concentrations of CA-125 and glycodelin are greatly elevated (120). More retrograde menstruation (121) would increase the retraction of peritoneal mesothelial cells, thus facilitating the implantation of endometrial cells (122, 123).

In the endometrium of women with endometriosis several hundred minor biochemical changes have been described (124–128). Contractility of the uterus is modified in women with deep endometriosis or adenomyosis (129).

Endometriosis, especially cystic ovarian and deep endometriosis (130, 131), and adenomyosis (132, 133) are associated with abnormal placentation, insufficient physiologic changes in the spiral arteries, and an increased risk of preterm birth, small for gestational age (SGA) babies, and preeclampsia (131).

Endometriosis is associated with higher concentrations of *Escherichia coli* in menstrual blood (134, 135), with vaginal infections (136), and with chronic endometritis (137). The low-grade pelvic inflammation in endometriosis was postulated to be a consequence of an initial infection and subsequent sterile inflammation (78). High-risk papillomavirus infection and Mollicutes are found more frequently in ovaries of women with cystic ovarian endometriosis (138) and in peritoneal fluid, respectively.

Endometriosis seems associated with a higher risk of cancer, as recently reviewed (139, 140). The association with ovarian cancer remains debated (141). Dioxin (142–145) and total body radiation (146, 147) are suggested to be associated with endometriosis. Both can have genomic or epigenetic (148) effects. In addition, the endometriosis that develops after total body radiation in nonhuman primates develops after a delay of 5 years, which suggests a genomic effect.

Endometriosis lesions are clonal, as demonstrated for typical (149), deep (150), and cystic ovarian (151–153) endometriosis. Multifocal, monoclonal lesions in one woman may derive from different progenitor cells (149).

Endometriosis lesions have an altered biology. Local estrogen production (154) and progesterone resistance (155–162) were demonstrated in larger endometriosis lesions (154–163) Numerous biochemical changes exist, such as mitogen-activated protein kinase (164), transcription-3 signaling (165), genetic variants expression (166), the Hoxa10/HOXA10 gene (167), cytokines (168–171), dendritic cells (172), vitamin D (173), mast cells (174, 175), hypoxia-inducible factor (176), high Mobility Group Box 1 and Toll-Like Receptor 4 (177), matrix metalloproteinase promoter polymorphisms (178), galectin-3 expression (179), promoter polymorphisms of matrix metalloproteinases genes (180), progesterone receptor expression (181), GF-I (182), myostatin and activin II receptor expression (183), Smad3/4 (184) or leptin (185) stimulated activation of aromatase activity, and expression of numerous cancer-associated mutations (186, 187). These changes are increasingly viewed as a consequence of genetic or epigenetic polymorphism (154, 188–190). Other epigenetic changes (191–196) comprise methylation, demethylation of DNA and modifications in histone code (193, 197, 198).

THE PATHOGENESIS OF ENDOMETRIOSIS: THE GENETIC/EPIGENETIC THEORY
Historical Background

The pathophysiology of the adenomyomas described by Cullen (4–7) was suggested by Meyer (199) and later by Gruenwald (31) to be due to metaplasia. Another hypothesis was the development from müllerian remnants (200).

Sampson (1, 11, 201) proposed retrograde menstruation as the cause of cystic ovarian endometriosis. Retrograde menstruation is an attractive hypothesis because menstrual fluid contains living cells, demonstrated already in 1927 (202), with implantation and growth potential as demonstrated in 1958 by means of subcutaneous injection (203) and by growth in vitro and on the chicken allantoic membrane (204). For the latter, tissue integrity is important (204). The implantation of endometrial fragments was directly observed (205) in a neonate. Also pelvic endometriosis is more frequently found on the left side of the pelvis (206, 207) and on the right side of the diaphragm, which is compatible with gravity and with the clockwise circulation of peritoneal fluid. Microscopic and subtle lesions are considered to be the initial stages after implantation. Neonatal menstruation (208–211), occurring in some 5% of neonates (208, 212–217), especially in postmature and SGA babies, might explain premenarchal and severe adolescent (218, 219) endometriosis. The behavior of endometriosis lesions and the aromatase activity or progesterone resistance are speculated to be caused by an abnormal environment, by immunology, or by implantation of basal endometrium (163). The retrograde menstruation and implantation theory does not explain all clinical observations (Table 1), such as extragenital endometriosis (220), endometriosis in women without endometrium (31) and in men (33), or the clonal aspect (149).

The mesothelial cell metaplasia theory, proposed in 1942 (31), has been expanded to metaplasia of peritoneal stem cells (215, 221–231), endometrial stem cells (232, 233), and more recently bone marrow cells (221, 225, 234–238), pale cells (239, 240) and embryonic remnants (241–243). These concepts find support in the frequent mesothelial-mesenchymal transitions with a role of platelets (244) and in the role of bone marrow cells in peritoneal repair (245). Metaplasia, unfortunately, is a poorly defined concept. If metaplasia is defined as metaplastic changes without permanent and transmissible genetic or epigenetic changes, the resulting endometriosis cells are genetically and epigenetically similar to endometrium and lesions after retrograde menstruation and implantation. If, on the contrary, metaplasia indicates stable and transmissible genetic or epigenetic changes, this comes close to the genetic/epigenetic theory.

The Genetic/Epigenetic Theory

The endometriotic disease theory (EDT) postulated (246) that genetic incidents are required for the development of typical,

cystic, or deep endometriosis. Microscopic and subtle endometriosis were considered to be early lesions following implantation of endometrium occurring intermittently in all women (247). It was suggested to use "endometriosis" for these "normal" subtle endometriosis cells and "endometriotic disease" for lesions with genetically abnormal cells and clinical symptoms. The development into typical, cystic, or deep lesions was postulated to be the consequence of the type of genetic incidents. Some subtle lesions thus contain "normal" cells that would regress spontaneously, whereas others would progress to more severe disease (20).

The genetic/epigenetic theory (Fig. 2) is an update of the EDT by adding current knowledge of genetic and epigenetic changes and of the redundancy of cellular processes. First, the oxidative stress in the uterus during menstruation and in the peritoneal cavity following retrograde menstruation (248) are recognized as potential causative factors to induce genetic or epigenetic changes. In addition, we recently realized the association of endometriosis with vaginal and pelvic infection (78, 136, 138) and the presence of an important metabolome in the uterine and peritoneal cavities. Second, functional redundancy is a characteristic of many cellular processes. Redundancy means that a similar task can be achieved by several pathways, albeit not with the same efficiency. They can take longer, and the capacity can be

less. Redundant mechanisms explain the cumulative effect of sequential genetic and epigenetic incidents. They also can mask the (phenotypic) effect of genetic and epigenetic changes (249). They explain that effects become visible only when a higher capacity is needed. Today, we can only speculate what combination of and how genetic and epigenetic incidents lead to typical, cystic, or deep or extragenital forms of endometriosis.

The genetic/epigenetic theory is compatible with all observations made on endometriosis. Subtle or microscopic lesions will progress to more severe lesions only if additional incidents happen. The clinical suggestion that typical, cystic, and deep endometriosis are three different diseases seems logical. It is compatible with hereditary aspects and with a predisposition to develop endometriosis, and it explains why dioxin and total body radiation could increase the risk of endometriosis. It is also compatible with the observation that typical, deep and cystic ovarian endometriosis are clonal in origin, with the clinical heterogeneity of endometriosis lesions, and with the molecular changes observed in endometriosis lesions as well as with the observed genetic and epigenetic aspects (49). The many molecular abnormalities in the endometrium of women with endometriosis are explained as an expression of the genetic and epigenetic changes transmitted at birth. Also, the increased risk of

FIGURE 2
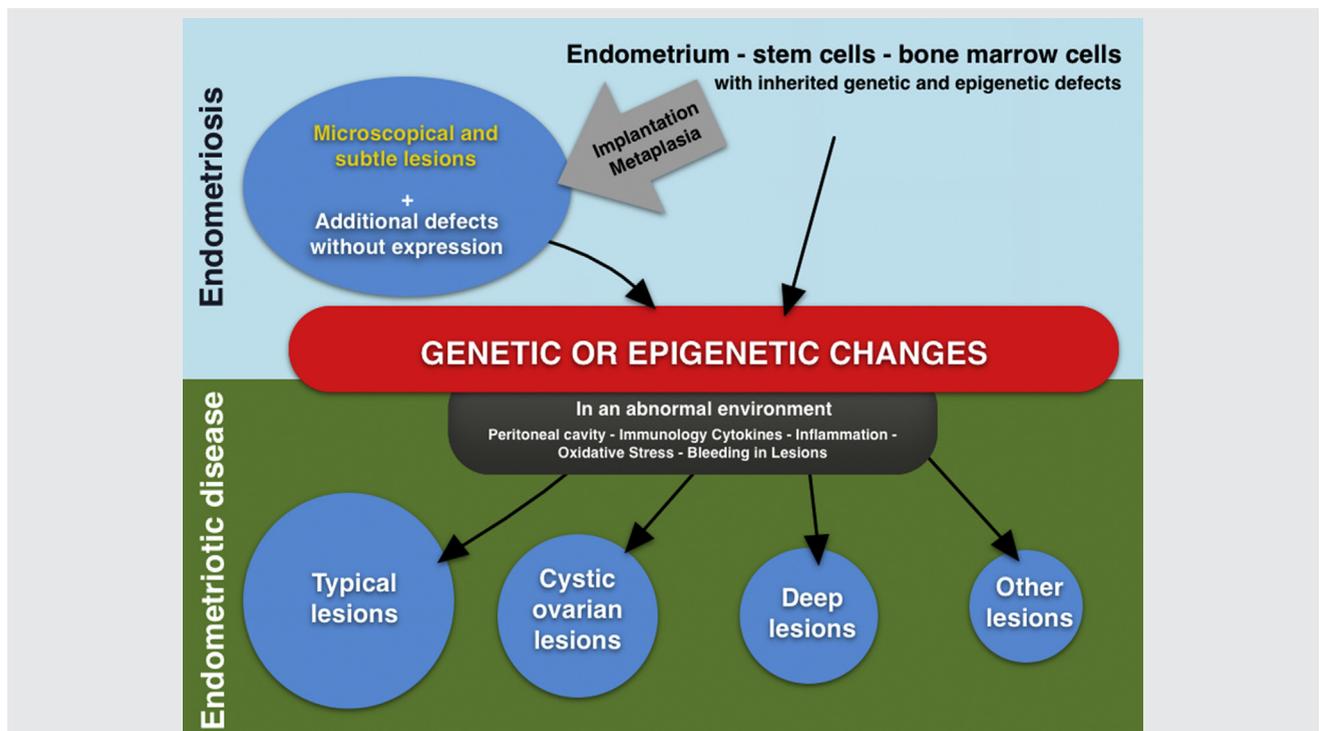
The genetic/epigenetic theory. The original cell can be an endometrial cell, a stem cell, or a bone marrow cell with their inherited genetic and epigenetic defects. These defects, together with additional acquired defects without expression constitute the predisposition. After implantation or metaplasia, defined as stable and transmittable changes, subtle and microscopic lesions occur. Additional genetic or epigenetic changes are required for these cells to change behavior and to progress into typical, cystic, deep, or other lesions.

Koninckx. Pathogenesis of endometriosis. Fertil Steril 2018.

pregnancy complications, the associated infertility, and some immunologic alterations could be viewed as the expression of these changes inherited at birth. Even subtle lesions can be viewed as the expression of inherited changes in an abnormal environment.

It should be stressed that this view does not exclude that some associations are the consequence of endometriosis. The final incidents starting the disease are additive to other incidents that might have occurred previously. It can explain the high prevalence in the peritoneal cavity and the increasing prevalence with increased retrograde menstruation. Bleeding and remodeling in the endometriosis lesions (250) are candidates to trigger additional genetic or epigenetic incidents. That many of the molecular biologic alterations described in endometriosis lesions are increasingly viewed as the result of genetic and epigenetic incidents lends further support to the hypothesis.

Some observations are more difficult to explain although they remain compatible. The induction of deep endometriosis–like lesions that develop in baboons by transplantation of functional and basal endometrium together with myometrium and JZ cells (251) is intriguing. First, it is unclear whether baboons are a useful model, because deep endometriosis has not been observed in nonhuman primates except after dioxin administration (252); second, it is unlikely that intact blocks of myometrium and JZ/myometrium are the cause of deep endometriosis in humans. Also intriguing is the role of the increased nerve density and their modulation over time (253, 254). This interaction with the body can be understood as both a cause and a consequence.

The genetic/epigenetic theory has several clinical implications. First, most subtle or microscopic lesions are normal endometrium-like cells that would likely resolve. Typical, cystic, and deep lesions are benign tumors, which after an initial period of rapid growth stop growing or progress slowly and which do not recur after complete excision. However, new lesions can be formed after new incidents, and the probability that this happens increases with the cumulative genetic and epigenetic abnormalities transmitted at birth and acquired throughout life. Adolescent endometriosis becomes a genetic and epigenetic incident early in life, possibly beginning as early as neonatal retrograde menstruation or during fetal life (191).

The genetic and epigenetic defects transmitted at birth explain the predisposition according to the first hit–second hit hypothesis (255) in oncology. However, these defects might also explain the associated subfertility, with monthly fecundity rates below 10% being similar to women with unexplained infertility, the associated changes in the endometrium, and the associated pregnancy problems. The latter is supported by the observation that pregnancy problems do not improve after deep endometriosis excision (256).

The genetic/epigenetic theory explains that with their specific set of changes, endometriotic lesions may vary in their reaction to estrogens, progestins, and pregnancy. The clinical consequence is that lesions vary, that occasional lesions can be rapidly progressive, and that the effect of medical therapy can be variable between patients. Incidents also occur in lesions, and a clonal origin does not exclude heterogeneity

within a lesion as demonstrated for breast (257) and other (258, 259) cancers.

The genetic/epigenetic theory makes it conceivable that the fibrosis surrounding deep endometriosis lesions and eventually the outer cell layers might be composed of normal cells with reversible "metaplastic" changes induced by the endometriosis lesion through cell-cell interaction (260). This suggestion is based on the observation that recurrence rates after (often incomplete) excision and after large bowel resections for deep endometriosis are not strikingly different. Clinically, it might become an argument to be less radical during surgery.

A classification of endometriosis should reflect that microscopic, subtle, typical, cystic, deep and extra-genital endometriosis need to be considered as four or more different entities. Also, the pathophysiology of adenomyosis and its relationship with endometriosis can be explained by this genetic/epigenetic concept (74).

Prevention of genetic/epigenetic incidents triggering the disease can be a matter of speculation. However, it seems attractive to postulate that reduction of repetitive stress by retrograde menstruation and microtrauma in the lesions and prevention of pelvic inflammatory diseases may be useful in this regard.

GROWTH AND MATURATION OF TYPICAL, CYSTIC, AND DEEP ENDOMETRIOSIS LESIONS

The growth and maturation of lesions varies with the set of genetic and epigenetic changes and with the local environment and thus with the many hormones, immune factors, and growth factors in plasma and the peritoneal cavity. As an example, the high glycodelin concentrations in peritoneal fluid might protect early lesions from NK cell attack (261, 262) and could thus facilitate survival.

Recurrent microbleedings in endometriosis lesions during menstruation can be a cause of pain. These bleeding episodes are also repeated tissue injuries, which are believed to play a role in the maturation of endometriosis (263, 264). In addition, they may trigger additional genetic and epigenetic incidents through inflammation and oxidative stress. Interestingly, microtraumas are also observed in the endometrial-myometrial JZ (239), which is consistent with the Archimetra theory (265, 266).

DISCUSSION

Mistakes in the DNA sequence are chromosomal alterations, and they can occur during cell division or as a consequence of noxious agents. Most DNA mistakes are repaired by the cell, or the cell becomes apoptotic and dies. However, if the cell survives, the changes persist and are transmitted to the next generation of cells. Activation and repression of DNA transcription and the subsequent translation is a complex process. Stable structural changes in these regulatory mechanisms are called epigenetics (267). Unfortunately, different investigators use different definitions (268). Some, such as the National Institutes of Health Epigenomics Mapping Consortium (269), use the term epigenetics to indicate changes in gene expression; others use it to refer to transgenerational

effects and inherited expression (270). We use epigenetics to indicate stable and transmissible non-DNA changes.

Many words in the endometriosis literature are not clear. This confusion stems from the fact that the meanings of words often change over time, especially after new clinical and molecular-biologic observations are added to the initial clinical, macroscopic, and microscopic descriptions. Stem cell research demonstrated that changes during cellular differentiation can be stable and transmitted, though reversible. It is unclear whether "metaplastic" changes preceding the development of cancer are reversible or whether they signal stable changes that increase the risk that another incident will start the development of a malignant tumor. Metaplasia was introduced as a descriptive histologic observation. A better interpretation of metaplasia is that the underlying mechanisms can be reversible or irreversible changes, and both can be transmitted. The term metaplasia is thus used to indicate the (reversible) expression of environmental stress (271) as well as to indicate the expression of stable genetic or epigenetic damage. Epigenetics describes both reversible and stable changes that are transmitted after cleavage. When transmitted at birth, they are called the epigenetic trait (272).

The implantation theory (1, 11, 201) was a reasonable hypothesis when formulated, while the metaplasia theory (31) was a histologic observation that did not consider genetic or epigenetic changes. The poor definition of metaplasia continues to create confusion. The polygenetic/polyepigenetic theory is compatible with observations made up to now. However, it will remain a theory until disproven by new observations. Understanding the genetic or epigenetic incidents involved, the hereditary incidents, and the environmental factors will be important for prevention, diagnosis, and therapy.

Redundancy of biologic processes adds to the difficulty of identifying minor changes that remain without visible clinical effects. Similar to concepts of tumor biology, it is important to distinguish between hereditary changes transmitted between generations and additional local cellular incidents that would either express the disease or facilitate the expression of the disease after additional incidents later. This distinction is especially important when considering the floating mesothelial and stem cells in peritoneal fluid: A first "facilitating" incident together with predisposition could explain the subsequent development of various forms of endometriosis in different locations (273, 274). This might also explain that deep, peritoneal, and ovarian endometriosis often occur simultaneously in the same individual (275). It is suggested that the same mechanisms apply to adenomyosis.

Similarly to uterine myomas, endometriosis lesions can remain dormant without progression for longer periods of time. Although the mechanisms of reactivation are not understood, deep endometriosis seems to be reactivated by trauma, such as by in vitro fertilization–related needle punctures for oocyte pick-up, triggering the subsequent development of more severe lesions and even a frozen pelvis (56), as frequently observed.

The genetic/epigenetic theory is also important for our views on nonhuman models of induced endometriosis in both primates and rodents. These models remain valid to study the effect of abnormal environments on (normal) endometrium. Transplantation of human endometriosis into SCID/nude mice could be a model to study the development of (abnormal) endometriotic tissue in a normal or controlled environment.

In conclusion, the genetic/epigenetic theory permits us to explain and understand all observations of this enigmatic disease called endometriosis from heredity and clonality to inflammation, mutations, progesterone resistance, aromatase, and many other findings associated with the disease by the time typical, deep, or cystic endometriosis has develop. Elucidating the mechanisms and pathways involved will hopefully permit the development of more specific means of prevention and therapy of this common and ravaging disease.

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Patogénesis de la endometriosis: La teoría de la genética/epigenética

Objetivo: Estudiar la fisiopatología de la endometriosis.

Diseño: Resumen de las observaciones sobre endometriosis.

Entorno: No aplicable.

Paciente(s): Ninguno.

Intervenciones: Ninguna.

Principal(es) medida(s) de resultado(s): La hipótesis es compatible con todas las observaciones.

Resultado(s): La endometriosis, tejido similar al endometrio fuera del útero, tiene una apariencia macroscópica variable y una historia natural poco comprendida. Es una enfermedad hereditaria y heterogénea con muchos cambios bioquímicos en las lesiones, que son de origen clonal. Se asocia con dolor, infertilidad, adenomiosis y cambios en la zona de unión, placentación, inmunología, plasma, líquido peritoneal e inflamación crónica de la cavidad peritoneal. La hipótesis de Sampson de la implantación de células endometriales como consecuencia de menstruación retrógrada, la diseminación angiogénica, la diseminación linfogénica o la teoría de la metaplasia no pueden explicar todas las observaciones si la metaplasia es definida como células con cambios reversibles y un comportamiento/morfología anormales debido a un ambiente anormal. Proponemos un mecanismo poligenético/ poliepigenético. El conjunto de incidentes genéticos y epigenéticos transmitidos al nacer podría explicar los aspectos hereditarios, la predisposición, y los cambios asociados a la endometriosis en el endometrio, en la inmunología y en la placentación. Para desarrollar los típicos quistes ováricos o las lesiones de endometriosis profunda, es necesario que ocurra una serie variable de incidentes genéticos y epigenéticos transmisibles en una célula que puede variar desde células endometriales hasta células madre. Las lesiones sutiles se visualizan como endometrio en un entorno diferente hasta que aparecen alteraciones adicionales. Los típicos quistes ováricos o las lesiones de endometriosis profunda son heterogéneos y representan tres enfermedades diferentes.

Conclusión(es): La teoría genética epigenética es compatible con todas las observaciones sobre la endometriosis. Se discuten las implicaciones para el tratamiento y la prevención.