# Pathogenesis of deep endometriosis

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The pathophysiology of (deep) endometriosis is still unclear. As originally suggested by Cullen, change the definition "deeper than 5 mm" to "adenomyosis externa." With the discovery of the old European literature on uterine bleeding in 5%–10% of the neonates and histologic evidence that the bleeding represents decidual shedding, it is postulated/hypothesized that endometrial stem/progenitor cells, implanted in the pelvic cavity after birth, may be at the origin of adolescent and even the occasionally premenarcheal pelvic endometriosis. Endometriosis in the adolescent is characterized by angiogenic and hemorrhagic peritoneal and ovarian lesions. The development of deep endometriosis at a later age suggests that deep infiltrating endometriosis is a delayed stage of endometriosis. Another hypothesis is that the endometriotic cell has undergone genetic or epigenetic changes and those specific changes determine the development into deep endometriosis. This is compatible with the hereditary aspects, and with the clonality of deep and cystic ovarian endometriosis. It explains the predisposition and an eventual causal effect by dioxin or radiation. Specific genetic/epigenetic changes could explain the various expressions and thus typical, cystic, and deep endometriosis become three different diseases. Subtle lesions are not a disease until epi(genetic) changes occur. A classification should reflect that deep endometriosis is a specific disease. In conclusion the pathophysiology of deep endometriosis remains debated and the mechanisms of disease progression, as well as the role of genetics and epigenetics in the process, still needs to be unraveled. (Fertil Steril® 2017;108:872–85. ©2017 by American Society for Reproductive Medicine.)

**Key Words:** Deep endometriosis, pathogenesis, classification, heredity, genetics, epigenetics, neonatal menstruation

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At the turn of the 19th century Cullen (1–3) described 10 different sites in the pelvis where he found the presence of "uterine mucosa." When located in the rectovaginal septum he called it a rectovaginal adenomyoma. Meyer (4) and Gruenwald (5) suggested that this was caused by metaplasia. Later Sampson (6, 7) suggested retrograde menstruation with the tubal transport of endometrial cells as etiology. When retrograde menstruations was found in almost all women (8, 9) speculation started why not all women developed endometriosis. It remains debated whether these lesions should be considered either as initial lesions after implantation or as "a physiologic" phenomenon occurring intermittently in all women (10).

Deep endometriosis was described in the early nineties as adenomyosis externa (11) with endometrial glands and stroma in fibromuscular tissue. Because the glandular activity was more in phase ($\leq$75%) with the menstrual cycle at depths >5 mm deep endometriosis was defined as lesions >5 mm in the peritoneum (12). This definition seemed consistent with the concept that deep endometriosis had escaped from the high steroid concentrations in peritoneal fluid (PF) (13) (Supplemental Fig. 1). At present we realize that this definition was a mistake and should be abandoned. The 5-mm definition permits the inclusion of slightly deeper typical lesions. It would have been preferable to define deep endometriosis as adenomyosis externa. With this latter definition most deep endometriosis lesions are unique (occasionally 2 and rarely 3) and big (mostly >1 cm in diameter). These deep endometriosis lesions seem to develop as a benign tumor, preferentially in the pouch of Douglas, with extension toward the uterine artery or the ureters, with a preferential invasion into the muscle of the bowel wall or the diaphragm, but not into the fat. These adenomyosis externa lesions occasionally invade nerves (14) and have some neurotropic effect (15, 16). In most bowel lesions lymph nodes are invaded (17, 18).

To avoid confusion metaplasia and genetic or epigenetic changes are defined as follows. Metaplasia (19) is the reversible transformation of one differentiated cell type to another differentiated cell type. This may be part of a normal maturation process or caused by some abnormal stimulus. If the stimulus causing metaplasia is removed, tissues return to their normal pattern of differentiation. Genetic and epigenetic changes are permanent heritable changes in DNA sequence or in gene function not associated with changes in DNA sequence (20).

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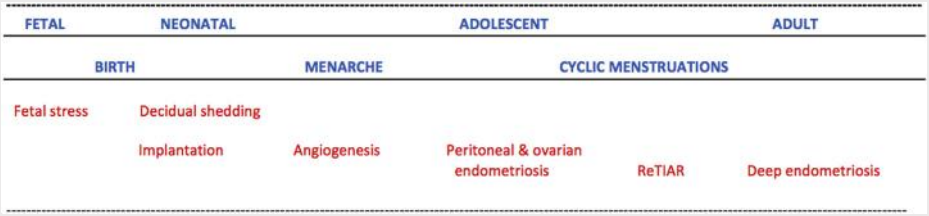
FIGURE 1




Life cycle of early onset endometriosis. ReTIAR = "recurrent tissue injury and repair" leading to adenomyotic and fibrotic changes of deep endometriosis.

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Deep endometriosis as the only form of disease in absence of other endometriotic lesions was present in only 6.5% (21). The high correlation between the presence of deep endometriosis and the presence of peritoneal and ovarian endometriosis raises the question whether they are three different entities with a common or different pathogenesis. That peritoneal, ovarian, and rectovaginal endometriotic lesions represent three clinically separate disease entities with a different pathogenesis had already been suggested 20 years ago (22). Are ovarian endometrioma (OMA) and rectovaginal endometriosis phenotypes of a progressive disease with as main driver recurrent menstrual bleeding causing repeated tissue injury and repair (ReTIAR) or are they caused by (epi)genetic changes? As the pathophysiology of deep endometriosis remains debated and in absence of clear evidence the two visions on pathogenesis were developed separately.

## HYPOTHESIS I: PATHOGENESIS OF EARLY ONSET ENDOMETRIOSIS BY NEONATAL UTERINE BLEEDING WITH THE CYCLIC MENSTRUATION AS DRIVING MECHANISM FOR ADENOMYOTIC FORMATION

### The Forgotten Menstruation

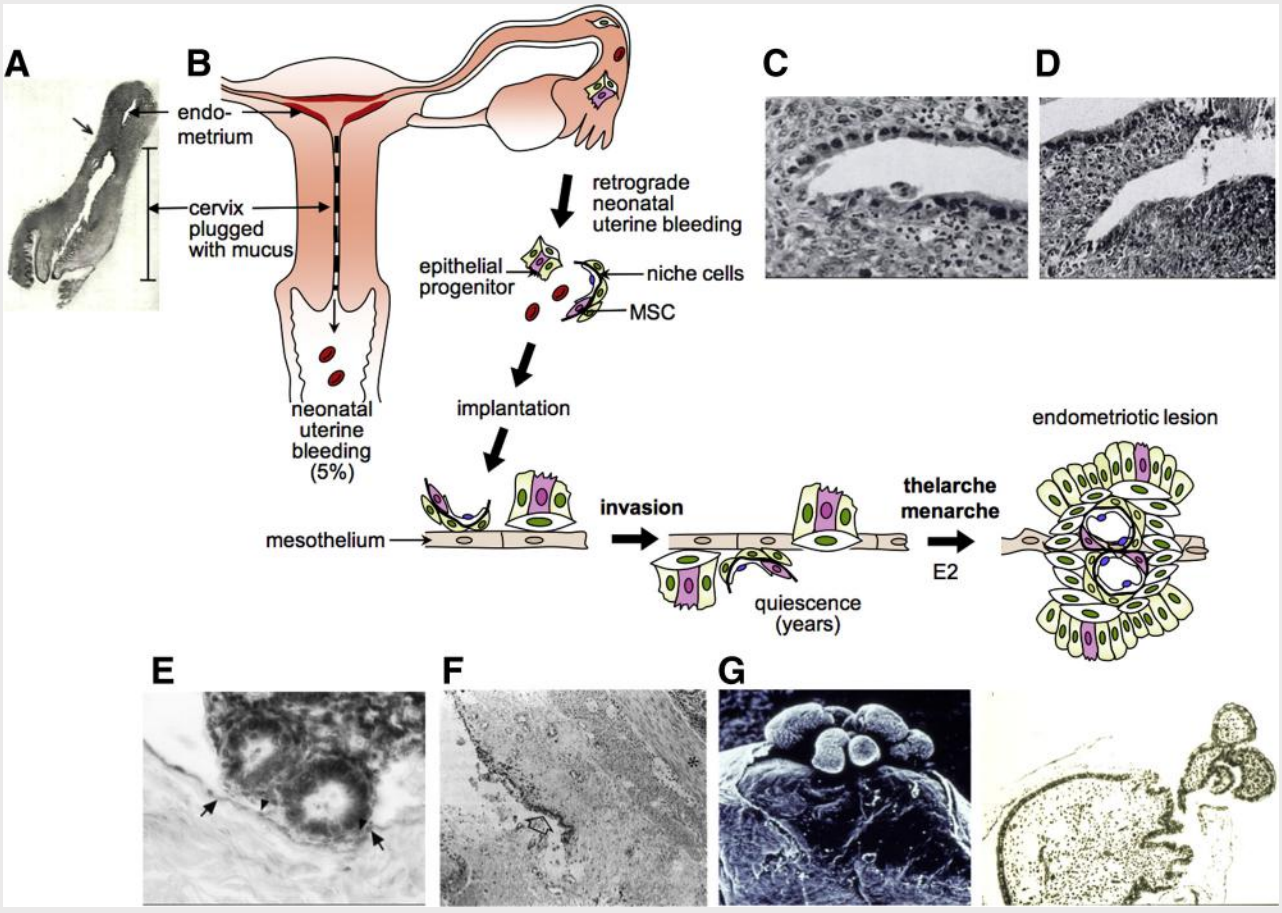
At birth the endometrial cell in the neonatal uterus expresses a variable response to maternal P. In a classic autopsy study of the neonatal endometrium the Harvard pathologists Ober and Bernstein (23) described that in 5% of the neonates the endometrium is P responsive and responds with decidualization and menstrual changes. In 95% of the neonates, however, the endometrium responds with weak proliferation or secretory changes despite the high maternal P levels during pregnancy. These histologic findings are in agreement with the occurrence of neonatal menstruation during the first week after birth in approximately 5% of the neonates (24) (Fig. 1). The discovery of a large European scientific literature on neonatal menstruation and the recent reports on premenarcheal endometriosis, including OMAs, raised the question whether neonatal uterine bleeding is involved in the pathogenesis of endometriosis (Fig. 2) (24–30).

There are three major observations that support the hypothesis of neonatal menstruation and the risk of early onset endometriosis. Arcellana et al. (31) observed in one neonate with the McKusick-Kaufman syndrome not only the presence of tubal regurgitation of menstrual debris, as also observed by Sampson (6, 7), but in addition, for the first time, the serosal implantation of endometrial fragments. It is important to note that although Sampson observed tubal reflux of menstrual shedding (7) at the time of menstruation, but never reported the early stage of endometrial attachment to the mesothelium and invasion as documented by Witz et al. (32) in experimental conditions. Endometriosis, including the rare premenarcheal endometriosis that presents the same phenotype with angiogenic peritoneal implants and the formation of OMA as adolescent endometriosis, is unexplained by Sampson's hypothesis (33, 34). A recent review study (35) on endometriosis in symptomatic adolescents has shown that early onset disease is frequently severe and often involves extensive adhesions and even OMAs. In a study of 368 patients with histologically proven deep infiltrating endometriosis Borghese et al. (36) observed that with low birth weight (defined as birth weight <2,500 g) had a higher risk of endometriosis, especially deep infiltrating endometriosis, compared with the reference group. It has been shown that preeclampsia and placental insufficiency increase significantly the risk of the neonatal menstruation (37). Fourth, and probably most important, is the occurrence of the uterine immaturity in the young adolescent. The recent observation (38) of "ontogenetic" uterine P resistance refers to the observation that the endometrial stromal compartment is not intrinsically P responsive at birth. Thus, functional transition of the endometrium to a fully P responsive tissue may be present at birth in newborns showing neonatal uterine bleeding but, in most girls, full endometrial P response will be achieved during adolescence. Hence, the pathogenesis of endometriosis may start in newborns presenting menstrual shedding at a much earlier stage than suggested by the theory of Sampson (7).

### The Life Cycle of endometriosis

A life cycle approach of endometriosis reveals unexpected aspects of the natural history of the disease throughout a woman's life (33). In premenarcheal and adolescent

**FIGURE 2**




Schematic describing the hypothesis that endometrial stem/progenitor cells may play a role in early onset endometriosis with supporting images from published works. (**A**) Neonatal uterus and vagina showing relatively long cervix in comparison to the uterine body. The *arrow* indicates the corpus–cervical junction. Mucus has been removed from the cervix. (**B**) Schematic showing neonatal uterine bleeding (occurs in 5% of neonates) and hypothesized retrograde neonatal bleeding due to cervical obstruction by thick mucus in the long neonatal cervix. The fragments of shed endometrial tissue are postulated to contain an endometrial epithelial progenitor cell (*pink*) and a perivascular mesenchymal stem/stromal cell (MSC) (*pink*) together with niche cells. These rapidly adhere to the neonatal mesothelium, invade and/or become contiguous with the mesothelial lining where they remain in a quiescent state for 10 years. Increasing estrogen (E2) levels associated with thelarche and menarche reactivate the stem/progenitor cells to initiate the growth of endometriosis lesions on the surface of or below the peritoneal mesothelium. Neonatal (**C**) decidualized and (**D**) shedding endometrium. (**E**) Endometrial attachment to the mesothelium occurs within 1 hour and (**F**) implantation by 18 hours, with endometrial cells becoming contiguous with the mesothelium (*arrow*) before the onset of quiescence. (**G**) Scanning electron microscopy (left) and histologic section (right) of a peritoneal endometriotic implant showing a polypoid lesion extending through the mesothelium in a young girl after a decade of quiescence. (Images reprinted with permission [23, 31, 231-233].)

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endometriosis, two types can be distinguished: a classic form that can occur before menarche and a congenital form that is caused by uterine anomaly and outflow obstruction. The lesions include superficial angiogenic peritoneal implants and adhesions, and OMA can occasionally occur. It is suggested that premenarcheal and possibly adolescent endometriosis develop by activation of resting stem cells shed at the time of neonatal retrograde uterine bleeding (29). In adult life, endometriosis can be related to uterine preconditioning by cyclic menstruations acting as a priming mechanism (39). The typical lesions are peritoneal, ovarian, and deep or adenomyotic endometriosis. In postmenopause, endometriosis can develop or be reactivated in the presence or absence of exogenous estrogens (Es) and can spread to various organs and structures causing obstructive lesions (Supplemental Table 1).

## A Disease Characterized by Recurrent Bleeding

Menstruation is widely viewed as serving no purpose other than to reinitiate the menstrual cycle in the absence of pregnancy. Yet, it is striking that cyclic endometrial decidualization followed by menstrual shedding is confined to few species where placentation is characterized by deep trophoblast invasion and remodeling of the spiral arteries from their origin in the inner myometrium. Uterine immaturity in adolescence is manifested by a higher risk of preeclampsia. Apparently, maturation of the uterus to respond adequately

to ovarian hormones by full decidualization is achieved by cyclic menstruation (38). Thus, the emergence of cyclic menstruation may serve to protect uterine tissues from the profound hyperinflammation and oxidative stress associated with deep placentation, a process known as preconditioning. Menstrual preconditioning implies that P withdrawal bleedings or menstruations evolved in the human because of the need to initiate decidualization in the absence of pregnancy and protect uterine tissues from the profound hyperinflammation and oxidative stress that are associated with deep placentation (39). Endometriosis can be viewed as a disorder of exaggerated menstrual preconditioning that confers protection against placentation-related disorders such as preeclampsia.

Whether superficial peritoneal endometriosis, OMA, and deep infiltrating endometriosis represent three different pathogenetic entities or are phenotypes of endometrial tissue in different topographic environments remains to be elucidated. Recurrent ectopic bleeding, however, occurs as a common feature in all three entities. Therefore, the hypothesis was formulated that endometriosis, an ovarian hormone-dependent disorder, is physiologic unless recurrent bleeding in the implant causes progressive disease and symptoms (40). Based on randomized trials (41) against placebo, endometriosis appears to be responsible for chronic pelvic pain symptoms in more than half of confirmed cases. A causal association between severe dysmenorrhea and endometriosis is very probable. This association is independent of the macroscopic type of the lesions or their anatomical locations and may be related to recurrent cyclic microbleeding in the implants (42).

Deep infiltrating endometriosis is found not only in the rectovaginal septum, but also in all fibromuscular pelvic structures such as the uterosacral and utero-ovarian ligaments and the muscular wall of pelvic organs. Cornillie et al. (11) showed that infiltration by endometrial glands and stroma occurs into adjacent fibromuscular tissue along the loose connective tissue and that penetration is arrested at the border of the underlying fat tissue. Hyperplasia of the surrounding smooth muscle and fibrous tissue results in nodule formation and, important, deep infiltrating endometriosis is focally associated with microendometriomas of 500–2,000 $\mu$m in diameter particularly in the submucosal layer of the vagina, rectum. or bladder. These non-OMAs are also lined, similarly to the OMA, by endometrial surface epithelium with or without stroma or by polypoid endometriotic tissue.

## ReTIAR as Pathogenetic Mechanism of Progressive endometriosis

Whatever the location, the ReTIAR in the formation of both OMA and deep infiltrating endometriosis appears to be the mechanism of progressive endometriosis. The key issue of smooth muscle metaplasia in the pathogenesis of progressive severe endometriosis was first investigated by Hughesdon in 1957 (43). He investigated a series of ovaries with endometrioma in situ and documented the presence of progressive smooth muscle metaplasia (SMM) of the invaginated cortical wall to the extent that in advanced cases the invaginated pseudocyst was mimicking a uterine structure. Fukunaga (44) confirmed the presence of SMM as a focal, microscopic change or an incomplete rim of SMM surrounding the endometriotic cyst in both the endometrial stroma and the endometriotic cyst. The metaplastic phenomenon in the pathogenesis of deep infiltrating endometriosis, whether located in peritoneum, ovary, rectovaginal septum, or uterosacral ligament was at least partially confirmed by immunohistochemical studies (45). Anaf et al. (45) concluded that the definition of distinct endometriotic entities based on the difference in the tissue composition of the lesions (endometriotic nodules vs. adenomyotic nodules) is inconsistent with the very frequent presence of smooth muscle cells in endometriosis irrespective of its localization. In a review of the literature Donnez et al. (46) suggested that metaplastic changes of Müllerian rests into adenomyotic glands involving the rectovaginal septum and the retroperitoneal space are responsible for the striking proliferation of the smooth muscle, creating an adenomyomatous appearance similar to that of adenomyosis in the endometrium. Van Kaam et al. (47) characterized the fibromuscular tissue and showed that the tissue shared characteristics with pathological wound healing, although the process could not be explained by transforming growth factor-$\beta$ (TGF-$\beta$) alone.

Zhang et al. (48) investigated with in vitro experimentations the roles of activated platelets in driving epithelial-to-mesenchymal transition and fibroblast-to-myofibroblast transdifferentiation in endometriosis and concluded that endometriotic lesions and their microenvironment contain all the necessary molecular machinery to promote SMM and fibrogenesis. Their results suggested that endometriotic lesions are wounds that undergo repeated injury and healing, highlighting the importance of platelets in the development of endometriosis.

Therefore, due to the commonality shared with endometriosis (i.e., cyclic bleeding), adenomyotic lesions behave just like endometriotic lesions, which are essentially wounds that undergo ReTIAR. Liu et al. (49) recently explored the difference in the progression of epithelial-to-mesenchymal transition, fibroblast-to-myofibroblast transdifferentiation, SMM, and fibrogenesis within the framework of ReTIAR. They showed that these conditions may share the same pathogenesis/pathophysiology. Proteins that are known to be involved in fibrogenesis, such as THY-1 and PPAR-$\gamma$, were also aberrantly expressed in these conditions. The many similarities between OMA and deep infiltrating endometriosis (DIE) indicate that the two conditions share the same pathophysiology and very likely the same pathogenesis. The differences may result from the different lesional microenvironments and, in addition, from the difference in the aging between both as the OMA is the typical severe lesion in adolescent whereas deep endometriosis is typical in the older adult.

The conclusion by Tosti et al. (50) that the specific pathogenic features, such as apoptosis, neuroangiogenesis, oxidative stress, and inflammation, may explain the more severe symptomatology of deep endometriosis should include that OMA is a most severe reproductive disease with an early onset in reproductive life and with great delay in diagnosis. Fortunately, with the advancement in imaging techniques, the

OMA is increasingly diagnosed at an earlier stage when the endometrioma may be less fibrotic and more responsive to medical treatment, making an evaluation of medical options critically important. The fact that OMA causes ovarian fibrosis is a medical problem that should arouse widespread concern in clinicians worldwide. At present, reliable, noninvasive diagnostic procedures of an OMA are available and should be used to identify at the earliest stage the presence of this type of severe pathology.

In conclusion, the different phenotypes (neonatal, premenarcheal, adolescent, adult, menopausal) as well as locations at different sites (superficial, peritoneal, deep, nonperitoneal) of endometriotic lesions raised the question whether they have a different origin and therefore should be considered as separate entities. In light of the natural history of endometriosis (i.e., epithelial-to-mesenchymal transition, fibroblast-to-myofibroblast transdifferentiation, SMM, and finally fibrosis), a pathology-based endometriosis classification system is within reach (51). The present confusion by superficial, deep, pseudodeep, free, enclosed, invasive, metaplastic, or progressive phenotypes can be avoided (52). The two dominant phenotypes of ectopic endometrium largely depend on the localization and have a different sex steroid hormone response (53). The first phenotype characterized by poor sex steroid hormone response is along the Müllerian tract including the uterus, rectovaginal septum, and, to some extent, the uterine ligaments, and the second phenotype outside the Müllerian tract particularly the ovaries. The differentiation has also therapeutic implications, but the current long delay of diagnosis implicates increasing SMM and fibrosis and loss of sex steroid hormone response in all locations. The critical factor in the progression of endometriosis is aging, but unfortunately the long delay in diagnosis of pelvic endometriosis prevents management at the early stage. The neonatal origin in the pathogenesis of early onset endometriosis remains hypothetical, but the hypothesis is falsifiable by the establishment of a registration of neonatal menstruation. Recently several investigators (26, 54) have made a call for systematic registration of the neonatal uterine bleeding.

## A POSSIBLE EMBRYONIC ORIGIN?

An alternate theory postulates that endometriosis is caused by defects during organogenesis. Aberrant differentiation and migration of Müllerian ducts cause misplaced spreading of endometrial cells during fetal organogenesis called Müllerianosis (55). Metaplasia of Müllerian remnants was suggested as the histopathogenesis of deep endometriosis in 1992 (56). Autopsy of 36 human fetuses of different gestational age (57) showed the presence of misplaced endometrium at five ectopic sites in 11%. This misplaced endometrium was located at sites correlating with the common location and the incidence of endometriosis in women. Misplaced endometrial glands and embryonic-like duct remnants were also described in six of seven fetuses, supporting the theory that some subtypes of endometriosis are related to an abnormal embryogenesis (58). In a case-controlled study (36) of 743 patients with low birth weight the risk of developing deep endometriosis is almost two times more, reflecting the possibility of the influence of placental insufficiency on the embryonic development and also favoring the occurrence of neonatal uterine bleeding. A recent study (59), looking at the anogenital distance, a biomarker of prenatal hormonal environment, suggests that endometriosis and especially deep infiltrating endometriosis might have a prenatal origin. Further studies are necessary to prove the importance of hormonal prenatal environment on the later development of endometriosis. Laganà et al. (60) support the hypothesis that ectopic Müllerian remnants from the endometrium, endocervix, and endosalpinx are items from the genital ridge leaked during organogenesis. Special interest should be given to research focusing on the role of genes with a fundamental role in the development of the urogenital tract.

## HYPOTHESIS II: DEEP ENDOMETRIOSIS IS A SPECIFIC TYPE OF ABNORMAL ENDOMETRIUM-LIKE CELL, A BENIGN TUMOR

Endometriosis is an enigmatic disease "defined as glands and stroma outside the uterus" with many clinical manifestations and variable symptoms. Its natural history is unclear. In the absence of an animal model mimicking specific endometrial functions such as placentation, and permitting the induction of the different clinical manifestations of endometriosis, the pathophysiology remains debated with hypotheses, theories, and speculation. Neither implantation, metaplasia, lymphatic, nor hematologic spread can explain all clinical manifestations including extrapelvic localizations (61). The genetic/epigenetic changes are proposed as a unifying theory. Key in this discussion is whether the endometriotic cell is similar or different from the endometrium. Whether normal or abnormal, these cells develop in an environment different from the uterus with its specific relationship to the junctional zone. For the many associated events the question remains whether these are cofactors in the development of endometriosis, or rather consequences of the disease.

### Clinical Observations

"Endometrial glands and stroma" outside the uterus are not always pathology. As discussed recently (62), microscopic endometriosis in the peritoneum, in the bowel at a distance from a deep endometriotic nodule, and in lymph nodes is not associated with pain or infertility, and there is no evidence so far for their subsequent development.

Endometriosis is—erroneously (63)—considered a progressive disease. However, progression from subtle to more severe lesions, or from typical to cystic or deep, or from cystic to deep has never been observed and remains speculation. In addition, at the moment of clinical diagnosis most lesions are no longer progressive, although they had obviously progressed before. This is a common observation for typical lesions and consistent with their burnt out aspect by pathology. Many cystic lesions can remain unchanged during longer periods of time as evidenced by ultrasound. Most rectovaginal deep endometriosis lesions, which were

followed clinically without surgery, did not progress (clinical observations as acknowledged) (64). However, when traumatized by clinical examination or by puncture for oocyte pick-up, deep endometriosis lesions seem to be activated and might start growing again (63). Deep endometriosis is also an heterogeneous disease. Most lesions are painful, especially during menstruation, but a minority (around 5%) does not cause pain. Some lesions—estimated at <1%—are fast progressive and they do have a different aspect during surgery. Instead of becoming at rest during a pregnancy, some deep lesions do progress and can cause bowel (65, 66), uterus, or bladder perforations. Clinically, typical cystic and deep endometriosis lesions, thus seem to be three different end points as suggested previously (22, 67).

The epidemiology of endometriosis is unclear because of a variable inclusion of subtle lesions and because of diagnostic uncertainties of hospital-based discharge records (64). Clinical observation by surgeons suggests that the prevalence and severity of deep endometriosis is increasing during the past 20 years (64).

## Development of (Deep) Endometriosis: Players and Mechanisms

The growth of endometriosis cells varies with the hormonal and immunologic environment. Estrogen and P concentrations in PF (Supplemental Fig. 1) are much higher than in plasma, especially after ovulation (13). These high P concentrations were speculated to inhibit the development of endometriotic implants. Because concentrations were lower in the luteinized unruptured follicle syndrome, it was even speculated that endometriosis development might be a consequence of infertility (8). For many other factors it remains unclear whether they are the cause or the consequence of endometriosis. Pelvic endometriosis is associated with a low-grade inflammation of the peritoneal cavity with higher concentrations of activated macrophages and thus with higher concentrations of the many different cytokines (68–72) and angiogenic factors (73–91). The many immunologic disturbances were recently reviewed (92–99). Specific attention was given to natural killer cells (95, 100) and recently to the role of platelets in their function (101, 102). The natural killer activity is decreased in PF and in plasma of women with endometriosis (103–105) and after excision of deep endometriosis their activity remains low, whereas elevated CA-125 concentrations return to normal (106). This suggests that the immunologic defect might be preexisting to the development of endometriosis. Interestingly, glycodelins in concentrations as secreted by endometriosis cells in PF (107) decrease the natural killer activity (108), which can be viewed as an autoprotective mechanism of the endometriotic cell. Retrograde menstruation and bleeding in endometriosis lesions generate an iron overload and oxidative stress in the peritoneal cavity (109) and/or in the endometriosis tissue (110). In addition the extremely sensitive mesothelial cells react to retrograde menstruation by mesothelial cell retraction thus facilitating implantation of endometrial cells (111, 112).

## Development of (Deep) Endometriosis: What is the Original Cell?

The endometrium is the candidate because shredded menstrual endometrium is viable, was demonstrated in 1927 (113) and has implantation potential as demonstrated by subcutaneous injection (114) as early as 1958. For development on the chicken allantoic membrane, tissue integrity is important (115). It remains unclear whether endometriosis is composed of functional or basal endometrium. The latter might be suggested by the well-demonstrated P resistance (116–123).

The metaplasia theory (5) was proposed because women without a uterus can develop endometriosis. More recently pluripotent stem cells were found in the endometrium and in the peritoneal cavity. Mesothelial-to-mesenchymal transition in the peritoneal cavity is well known (124, 125) with a specific role of platelets (48). Some of these mesenchymal/mesothelial cells of the peritoneal cavity (48), of the mesothelial repair after surgery (126) and in endometrium and endometriosis (127–131) are directly derived from bone marrow. Endometriosis could develop from stem cells in the endometrium (132, 133) or in the peritoneal cavity (29,134–144), possibly induced by genetic changes (60). Recently a specific cell in the endometrium called pale cell (145, 146), because of their appearance, was speculated to be involved in endometriosis and adenomyosis development.

Cells from neonatal retrograde menstruation (54,147–149) or cells remaining from embryonic development (150, 151) are other candidates. Key is that these are (epi)genetically normal cells, and with the actual knowledge of multipotential stem cells in adult life the concept of embryological remnant has become less important.

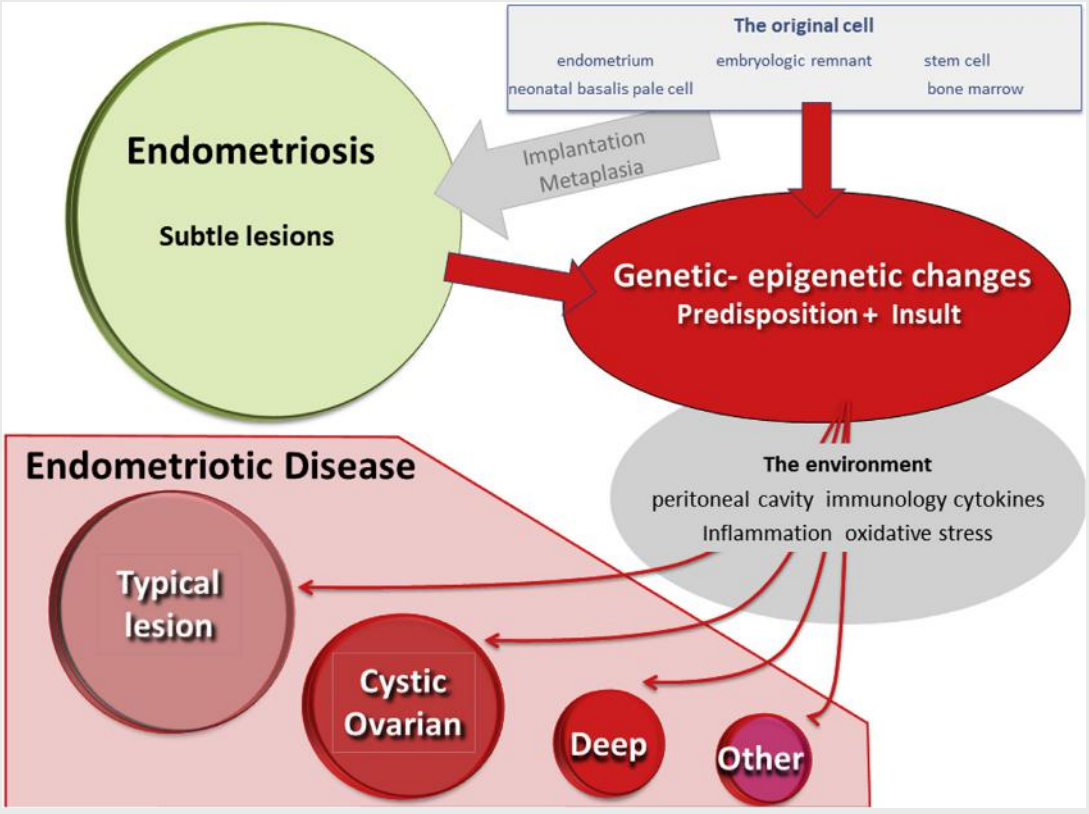
## The Endometriotic Disease Theory or Genetic/Epigenetic Changes

The endometriotic disease theory (Fig. 3) was proposed in 1999 (152). Because microscopic and subtle endometriosis lesions are not associated with pain or infertility and most lesions do not progress to more severe pathology, "endometriosis" was suggested for subtle lesions to stress that this was not a clinical pathology. "Endometriotic disease" indicated that typical, cystic, or deep endometriosis was associated with clinical symptoms. To explain the transition from endometriosis to endometriotic disease, the endometriotic disease theory postulated that some cellular or genomic incident or change must have happened. Key in the endometriotic disease theory is that typical, cystic, and deep endometriosis lesions thus should be composed of slightly abnormal cells, similar to many other benign tumors. These cells develop in an abnormal environment outside the uterus and without the specific relationship with the junctional zone. Whether the original cell comes from the endometrium—a specific endometrial cell such as a pale cell, stem cells, bone marrow, or embryonic cells—is not important.

## Arguments Pointing to Genetic or Epigenetic Changes

Genetic and epigenetic changes in endometriosis were reviewed recently (20). Endometriosis is an hereditary disease

**FIGURE 3**




The updated endometriotic disease theory (152). The original cell is not important. Subtle endometriosis by implantation or metaplasia is not a disease until (epi)genetic changes occur. Key is genetic or epigenetic changes, which will lead to typical, cystic, deep, or other lesions as Müllerianosis and extra pelvic localizations. Each of them are (epi)genetically different endometriotic diseases with eventually clinical symptoms.

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and some 50% of endometriosis lesions can be attributed to hereditary factors (153–155). Well established are familial clustering in humans (156) and primates (157). In twin sisters a prevalence of endometriosis (158–161) and age of onset (162) are similar. Prevalence is increased by 6%–9% in first degree relatives (163, 164) and by 15% for severe disease (165, 166).

Genome-wide scanning and linkage analysis have identified potential genes involved. Linkage analysis found two aberrant loci on 10q26 and 7p13-15 (harboring genes such as CYP2C19, INHBA, SFRP4, and HOXA10), but the logarithm of the odds scores are too low to be compatible with one major gene. Genome-wide scanning resulted in 10 significant loci and a significant association of six of these (167, 168). It is too early, however, to understand the exact mechanisms involved. Also attractive is the loss of heterozygosity or the first hit–second hit hypothesis. If in a carrier with a first hit, a second genomic hit would induce endometriosis, this might explain the hereditary character. The many studies that tried to identify a specific hereditary predisposition, especially those investigating detoxication mechanisms, however, failed.

More than 200 differences between the endometrium of women with and without endometriosis were described (for recent reviews, see Refs. [169–173]). These changes might signal a genetic predisposition. Some differences, however, could be the consequences of endometriosis.

A strong argument is that deep (174, 175) and cystic (176–178) ovarian endometriosis are consistently found to be clonal in origin. This suggests an initial chromosomal or epigenetic change. Typical lesions are too small to be investigated for clonality.

Epigenetic changes, during fetal life (179), have become a focus of interest during the past decade (180–184). They comprise methylation and demethylation of DNA (181, 185, 186), modifications in the histone code in endometriosis tissue in comparison with the endometrium, and experimental modifications of the histone code in cell lines and animal species. Many aberrations have been described, leading to speculation but without a comprehensive view at present.

Dioxin (187–190) and total body radiation (191, 192) might be associated with endometriosis development. Both can have genomic or epigenetic effects (193). In addition the endometriosis developing after total body radiation in primates can have a delay of 5 years, again suggesting a genomic effect.

Taking all elements together we only can speculate why and how some genetic and/or epigenetic changes lead to "abnormal growth of endometrial-like tissue." External

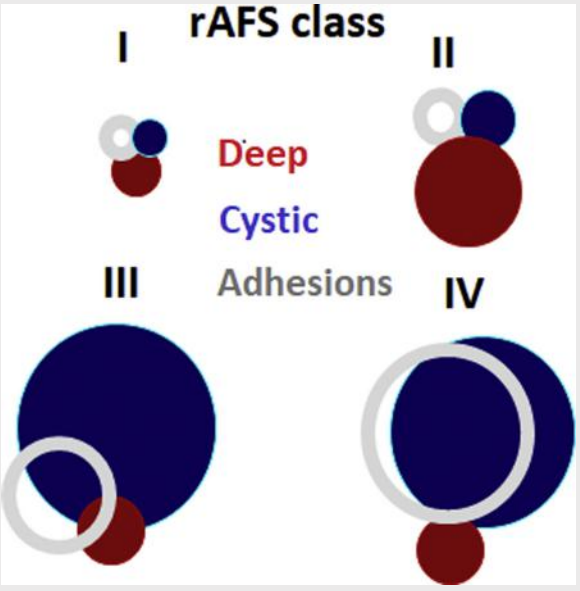
insults and factors, such as oxidative stress in PF (109) or in the tissue because of bleeding, or immunology or cytokines might trigger genetic/epigenetic changes, especially in predisposed cells. This would start the proliferation of endometrium-like tissue into a disease with clinical symptoms. The development into typical, cystic, or deep endometriosis thus will vary with the type of genetic/epigenetic insult. Typical, cystic, and deep endometriosis become three different diseases, which only have endometrium-like tissue in common. Genetic/epigenetic modifications also help to understand the clinical heterogeneity of deep endometriosis.

In conclusion, in the absence of an animal model that permits the induction of severe cystic and deep endometriosis and manipulation of growth, data on pathophysiology are limited to clinical, histologic, and biochemical observations. Whatever the original cell might be, endocrine, immunologic, or biochemical observations cannot explain why some initial lesions will progress and develop into severe endometriosis lesions. The many observations in women with endometriosis can be interpreted as the expression of predisposition and/or as the consequence of endometriosis instead of being the cause. These comprise abundant retrograde menstruation (194) and the recent observations on cellular pathways (195), cytokines (196–199), dentritic cells (200), vitamin D (201), mast cells (202, 203), hypoxia-inducible factor (204), high Mobility Group Box-1 and Toll-Like Receptor 4 (205), matrix metalloproteinase promoter polymorphisms (206), galectin-3 expression (207), promoter polymorphisms of matrix metalloproteinase genes (208), P receptor (PR) expression (209), acylcarnitines, phosphatidylcholines, and sphingomyelins in PF (210), uterine leukocytes (96), vascular epithelial growth factor (211, 212), and other angiogenic factors (213) such as the TGF-$\beta$ superfamily (214), vezatin expression (215), lymphocytes in blood (216), prostaglandins (217), insulin-like growth factor I (IGF-I) (218), repeated micro-trauma (219) or macro-trauma (63), transcription-3 signaling (220), genetic variants expression (221), and the Hoxa10/HOXA10 gene (222).

The baboon model with induction of deep endometriosis-like lesions by transplantation of endometrium and myometrium (223) is difficult to interpret. First, spontaneous deep endometriosis has not been reported in primates. Second, it is hardly conceivable that blocks of myometrium and junctional zone/myometrium are the cause of deep endometriosis in humans. These experiments, however, emphasize the importance of tissue integrity—as for the chicken allantoic membrane experiments (115)—and of the special relationship of endometrium and junctional zone for growth and development. Equally intriguing is the role of the increased nerve density and the modulation with time (224, 225). This points to an interaction with the body and can be understood as a cause and as a consequence. It is unclear whether these lesions do undergo (epi)genetic changes as a consequence of their abnormal pelvic environment. Rodent models of endometriosis including human endometrium in nude and SCID mice are not considered appropriate models.

The interpretation that deep endometriosis is a specific disease is reflected in the distribution of deep lesions in all classes of The Revised American Fertility Society (AFS) classification with little association with cystic ovarian endometriosis (Fig. 4). The hypothesis that genetic or epigenetic changes are a prerequisite for development into typical cystic or deep endometriosis is a unifying theory and compatible with all clinical manifestations of endometriosis. In addition it implies that subtle and microscopic lesions are a physiologic condition and that only after genetic/epigenetic changes into typical, cystic, or deep endometriosis does this occur. It is also attractive to consider that the type of genetic/epigenetic changes will orient further development. Deep endometriosis thus becomes one specific type of endometriotic disease.

**FIGURE 4**




Distribution of deep endometriosis in The Revised American Fertility Society (AFS) classification. The size of the *circles* is proportional to the incidences. The overlap indicates simultaneous presence. Most deep endometriosis lesions were found in class II. (Adapted from Koninckx PR, Meuleman C, Demeyere S, Lesaffre E, Cornillie FJ. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. Fertil Steril 1991;55:759–65 [234].)

*Gordts. Deep endometriosis: Pathogenesis. Fertil Steril 2017.*

## DISCUSSION

To explain the pathophysiology of endometriosis and more specifically of deep endometriosis, the many hypotheses and observations have been critically reviewed. Two opposing visions persist as evidenced in this review. If the endometriosis cell is considered a normal cell then endometriosis is a single disease and the discussion focuses on the original cell, on subtle lesions as early stages, and on the local and immunologic factors that induce growth, transformation, or metaplasia. If typical, cystic, and deep endometriosis are considered the consequence of a genetic or epigenetic modified cell, microscopic and subtle lesions become a physiologic condition until (epi)genetically modified, the various expressions causing a clinical disease become three or more different

pathologies, and the many associated observations become a consequence of proliferation or a signal of predisposition.

On the other hand, in a life cycle approach of endometriosis it can be suggested that early onset endometriosis develops by activation of resting stem cells shed at the time of neonatal retrograde bleeding to cause angiogenic peritoneal and ovarian endometriotic implants (24, 30). In the adult, the adenomyotic changes, whether in the pelvis or in the ovary, can be related to the uterine preconditioning by cycling menstruation (39). Where cyclic menstruations act as a priming mechanism of uterine preconditioning for deep placentation in case of pregnancy, in case of absence of pregnancy, ReTIAR causing epigenetic modifications may act as a mechanism of deep endometriosis. In this way both hypotheses explain not only the pathogenesis from its earliest stage in the adolescent, but also the progession of endometriosis with aging.

Deep endometriosis, defined as adenomyosis externa, and adenomyosis are morphologically very similar. With Sampson's enunciation of "retrograde menstruation" as a cause of endometriosis the disorder was divorced from adenomyosis and research became focused on how the fragments of menstrual shedding could implant and cause endometriotic pelvic lesions. It is time to reconsider the role of the uterus in the pathogenesis of both disorders as suggested already in 1948 (226)—"one cannot resist the feeling that there is some common denominator between endometrial hyperplasia and adenomyosis, and possibly also pelvic endometriosis." The statement of Novak and De Lima (226) was based on the association of adenomyosis and endometriosis, and observation confirmed more recently by the association of deep endometriosis and adenomyosis. The archimetra concept, the role of the junctional zone (227) with tissue injury and ReTIAR (219, 228) and the role of pale cells could become a unifying concept. The key factor is the local (peritoneal) environment that induces the different types of endometriosis. That E receptors (ERs) and PRs are present not only in glands and stroma but also in the smooth muscle component of deep endometriosis (229), and the expression of $\alpha$-smooth muscle actin and collagen I in and around endometriotic lesions support the notion of the metaplastic process (230).

The genetic/epigenetic hypothesis is attractive as it is consistent with heredity and clonality and as it explains why not all women with retrograde menstruation and implantation develop endometriosis. The importance of the original cell is weakened by pluripotent stem cells, some of them originating from bone marrow in adult life and by mesothelial-to-mesenchymal transition. The many associated effects are no longer considered the cause but either the consequence of (epi)genetic changes to endometriotic disease or they are factors signaling predisposition. This predisposition can be existing genetic or epigenetic changes facilitating an insult (e.g., differences in the endometrium of women with endometriosis), or biochemical or immunologic factors facilitating growth of endometriotic disease once initiated into typical, cystic, or deep lesions. It is intriguing to realize that, at present, all observations can be explained with this vision. Abundant retrograde menstruation, for example, will increase peritoneal mesothelial cell retraction and oxidative stress, thus facilitating implantation and subtle lesions and also (epi)genetic changes. Clinically this hypothesis has two consequences. First typical, cystic, and deep endometriosis are three distinct pathologies that only look similar by pathology. Second, although a metaplastic cell will return to normal when the environment changes, (epi)genetically modifications will be transmitted after cell division whatever the environment. Deep endometriosis then becomes a benign tumor.

These complementary views, describing the onset and the further development of (deep) endometriosis lesions are also important to interpret in animal models. They are useful to understand the mechanisms of growth of normal endometrium in an abnormal environment. For the latter reason extrapolation of rodent experiments to the human should be done very carefully. The primate is much closer to the human and thus more appropriate. It cannot be excluded that the induction of deep endometriosis-like lesions by implantation of endometrium and myometrium signals that (epi)genetic modifications did occur (e.g., by the local environment as bleeding with oxidative stress).

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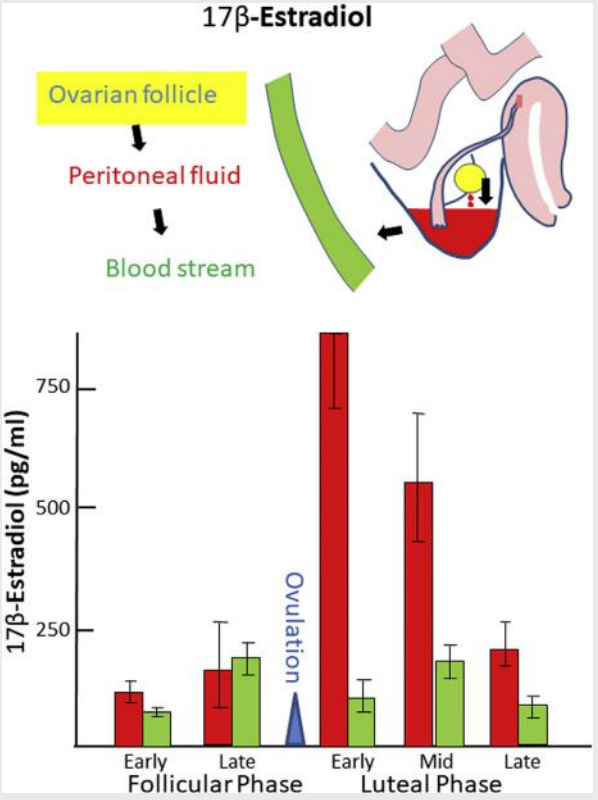
## SUPPLEMENTAL FIGURE 1




Estradiol ($E_2$) concentrations (mean and SD) in plasma (*green*) and in peritoneal fluid (PF) (*red*) during the menstrual cycle. Considering that the sex hormone-binding globulin (SHBG) concentrations in PF are only 65% of plasma concentrations, the free steroid concentrations in PF are even much higher. Progesterone concentration time curves are similar but the relative differences between PF and plasma are even much higher. It was calculated that after ovulation these steroids are secreted predominantly into the PF from where they are resorbed into plasma. (Adapted from Koninckx PR, Heyns W, Verhoeven G, van BH, Lissens WD, de MP, et al. Biochemical characterization of peritoneal fluid in women during the menstrual cycle. J Clin Endocrinol Metab 1980;51:1239-44; Ref. [13].)

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