Pathogenesis of deep endometriosis

Stephan Gordts, M.D.,[a] Philippe Koninckx, M.D., Ph.D.,[b,c] and Ivo Brosens, M.D., Ph.D.[a]

[a] Leuven Institute for Fertility& Embryology; [b] Department of Obstetrics and Gynecology, Catholic University Leuven, University Hospital, Gasthuisberg, Leuven, Belgium; and [c] Gruppo Italo Belga, Villa del Rosario and Gemelli Hospitals Università Cattolica, Rome, Italy

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;■:■–■. ©2017 by American Society for Reproductive Medicine.)

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

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/19718-24761

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).

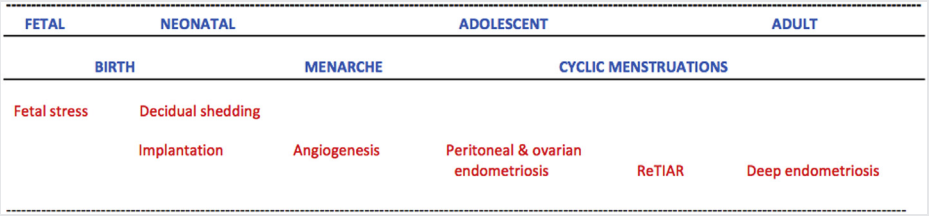
To avoid confusion metaplasia and genetic or epigenetic changes are defined as follows. Metaplasia (19) is the reversible transformation of one differentiated cell type to another differentiated cell type. This may be part of a normal maturation process or caused by some abnormal stimulus. If the stimulus 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).

Received July 27, 2017; revised August 22, 2017; accepted August 28, 2017.
S.G. has nothing to disclose. P.K. has nothing to disclose. I.B. has nothing to disclose.
Reprint requests: Stephan Gordts, M.D., Life Expert Centre, Schipvaartstraat 4, 3000 Leuven, Belgium (E-mail: stephan.gordts@lifeexpertcentre.be).

Fertility and Sterility® Vol. ■, No. ■, ■ 2017 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2017.08.036

FIGURE 1



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

Gordts. Deep endometriosis: Pathogenesis. Fertil Steril 2017.

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