

Endometriosis and Adenomyosis. A shared Pathophysiology

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Abstract

The major authors of the last century described endometriosis as ectopic endometrial lesions occurring in both the uterus and in the peritoneal cavity, and the lesions were considered as variants of the same disease process. In the 1920s a theory had been put forward that, although severely and chronically challenged, resulted in the clear cut separation of the two entities. A new understanding of the disease process, however, enables to reunify these two disease entities and to integrate them into a new nosological concept. Circumstantial evidence suggests that endometriosis and adenomyosis share a similar pathophysiology and are caused by trauma. In the spontaneously developing disease chronic uterine peristaltic activity or phases of hyperperistalsis induce, at the endometrial-myometrial interface near the fundus-cornual raphe, microtraumata with the activation of the basal and general

mechanism of 'tissue injury and repair (TIAR). This results in the local production of estrogens. With ongoing peristaltic activity such sites will accumulate and the increasingly produced estrogens interfere via paracrine mode of action with the endocrine ovarian control over uterine peristaltic activity resulting in permanent hyperperistalsis and a self-perpetuation of the disease process. Overt auto-traumatisation of the uterus with dislocation of fragments of basal endometrium into the peritoneal cavity and infiltration of basal endometrium into the depth of the myometrial wall ensues. In most cases of endometriosis/adenomyosis a causal event early in the reproductive period of life must be postulated leading to uterine hyperperistalsis. In late premenopausal adenomyosis such an overt event might not have occurred. However, as indicated by the high prevalence of the disease, it appears to be unavoidable that, with time, chronic normoperistalsis throughout the reproductive period of life may result in events that accumulate to the same extent of microtraumatisation. With the activation of the TIAR mechanism followed by infiltrative growth and chronic inflammation, endometriosis/adenomyosis of the younger woman and premenopausal adenomyosis share in principle the same pathophysiology. In conclusion, endometriosis and adenomyosis result from the physiological mechanism of 'tissue injury and repair' (TIAR) involving local estrogen production in an estrogen-sensitive environment normally controlled by the ovary. It appears that many of the altered endometrial molecular markers described in the context of endometriosis are the consequence rather than the cause(s) of the disease.

Introduction

Endometriosis is a disease that affects women predominantly during the reproductive period of life. With the cardinal symptoms, pelvic pain, bleeding disorders and infertility, the disease has a tremendous impact on women's health. In most of the women affected the first symptoms can be traced back to adolescence [1]. Many women, however, remain free of symptoms or exhibit only minor complaints. Moreover, in cases with the development of the

disease after childbearing, the condition may remain undiagnosed. Not infrequently, at laparoscopy for tubal sterilisation [2] and hysterectomy for fibroids and adenomyosis, endometriotic implants and scars, respectively can be observed. Thus, the current estimates of prevalence are probably too low. The syndrome of dislocated basal endometrium (SDBE), a term that comprises the pathophysiological continuum of endometriosis, endometriosis in association with adenomyosis and premenopausal adenomyosis, thus appears to be a very common phenomenon [3]. We had, therefore, a decade ago, suggested that its cause or causes may be unspectacular and closely related to the physiologic process of reproduction. Trauma followed by tissue specific hyper reactive inflammatory response and repair involving specific, albeit physiological cellular, biochemical and molecular mechanisms may be considered the major events in the development of the disease [4].

Recently we could extend our previous views and to elaborate a comprehensive model of the pathophysiology of endometriosis and adenomyosis [5]. This endeavour was undertaken with the premise that all phenotypes of endometriosis share in principal the same pathophysiology and that no parallel and separate mechanisms of their development do exist. This does, however, not exclude various and different etiologies at the very onset of the disease process including iatrogenic [6], exogenous [7,8] and hereditary [9] factors. With respect to hereditary factors they might be remote from the genuine disease process and thus not easily to disclose.

Historical remarks

The aetiology and pathogenesis of endometriosis, which is the ectopic occurrence of endometrial tissue, has been enigmatic from its first description until today. The theory of dissemination of endometrial tissue by retrograde menstruation, proposed by Sampson in 1927, has remained the presently prevailing pathophysiological concept [10]. However, since retrograde menstruation has later been considered to be a physiological phenomenon other factors such as

menstrual outflow obstruction or immunological defects on the level of the pelvic peritoneum have been additionally proposed to refine Sampson's view (for review: [4]). Also the recent advances that have been made in the understanding of the molecular biology of endometriosis, both on the level of the endometriotic lesions and the eutopic endometrium in affected women, did not result in a principal revision of Sampson's concept. It is suggested that in women with endometriosis fragments of inherently or epigenetically altered endometrium are shed during menstruation and disseminated within the peritoneal cavity [11,12].

From the very beginning Sampson's theory was seriously challenged continuously. While in monkey experiments endometrial tissue from cyclic endometrium could readily grow as autotransplants or in culture this was not the case with menstrual debris. Even experimentally produced utero-peritoneal fistulae in monkeys did not result in peritoneal endometriosis. In contrast and much to the surprise of the investigators, following surgery that was performed to correct for retroflexio uteri by using a thread of silk that was deeply positioned into the fundal part of the uterus severe uterine adenomyosis ensued that penetrated along the thread into the peritoneal cavity to form endometriotic lesions (for review: [13]). Philipp and Huber speculated that retrogradely transported menstrual debris would only cause endometriosis in those rare cases when the necrotic material was mixed with vital tissue fragments detached from the deeper basal layer [13].

We for the first time provided strong circumstantial evidence that, in the human, endometriosis results, in fact, from the dislocation of fragments of basal than opposed to functional endometrium [14]. This was at harmony with findings in the baboon model that inoculation of bioptic material taken from menstrual endometrium was more likely to result in endometriotic lesions than that obtained from secretory endometrium [15]. The possibility was declined by the authors themselves that the higher implantation rate with biopsies from menstrual endometrium was owed to fragments of basal endometrium that could

have been more easily obtained from menstrual than from secretory endometrium. Nevertheless, for the induction of experimental endometriosis in the baboon model, it is now strongly recommended to use material that results from vigorous biopsies during the menstrual period of these animals [16,17]. According to our view such biopsies have a high probability to contain basal endometrium.

In critically analyzing Sampson's data and the available clinical and experimental literature Philipp and Huber in 1939 appreciated Sampson's observation that in nearly all of his patients the tubes were patent, a finding that they thought should be kept in mind and incorporated into a future comprehensive model of the pathophysiology of the disease. They arrived, however, at the conclusion that retrograde menstruation would be, for various reasons, an insufficient model to describe the pathophysiology of a disease that did, in their opinion and that of other authorities at that time, comprise more than just a disease of the pelvic peritoneum [13].



Figure 1. Transvaginal sonography (TVS) and magnetic resonance imaging (MRI) of the uterus of a 29 years old woman unaffected with endometriosis and adenomyosis. Sagittal scans of the uterine midline are shown. The myometrial-endometrial lining is sharp and smooth; the "halo" in TVS and the "junctional zone" in MRI are unaltered; there is symmetry with respect to the anterior and posterior myometrial walls and the texture of the myometrium in TVS appears to be homogenous.

In fact, the major authors of the last century described ectopic endometrial lesions

occurring in both the uterus and in the peritoneal cavity, and the lesions were considered as variants of the same disease process. Robert Meyer, favouring the concept of metaplasia, was the first to hint at the chronic inflammatory character of the lesions in both, the extra- and intrauterine sites [18]. Also Sampson, who introduced the term 'endometriosis', described "primary endometriosis" as the uterine variant of the disease [10]. His scientific interest, however, was nearly exclusively directed towards the development of the peritoneal variety. This and his view of uterine adenomyosis to result from vascular transmission were probably the reasons why he did not report on the parallel presentation of "primary endometriosis" in his cases of peritoneal endometriosis [19]. In fact, it was his theory that laid the basis for considering uterine adenomyosis and external endometriosis as different disease entities [20]. This was later on enforced by the fact that endometriosis was mostly diagnosed by laparoscopy in a sterility work-up and the uterus evades histological, structural and morphological examination for obvious reasons in such cases. Pelvic endometriosis became a topic of research, while the clinical and scientific interest in uterine adenomyosis nearly completely vanished. The definition of endometriosis that is currently in use and propagated by influential societies such as the ASRM and the ESHRE is reflecting this strict separation and present confinement to the peritoneal variety [21, 22]. Much of the research work performed during the last two decades originated from this concept [23-29].

Yet, the issue of endometriosis and adenomyosis whether or not representing distinct disease entities is far from being resolved. A search in PubMed reveals that under the headings of endometriosis and adenomyosis, respectively, rather the same items are displayed. In addition, the recent resurrection of the term 'adenomyoma' does, in our opinion, not contribute to the clarification of the issue. In an attempt to prove the distinctiveness of endometriosis and adenomyosis, respectively, hospital records of surgery were analyzed [30,31]. Given the fact that premenopausal adenomyosis represents the slowly and endometriosis with and without associated

adenomyosis the more rapidly developing form of the disease, respectively, it was to be expected that the former women, given also the fact they represented a study population with a reproductive pattern of attempting early pregnancies, would more likely be parous than the latter. Moreover, it is unlikely, that during routine hysterectomy, the same meticulous search for endometriosis is performed as in work-up for infertility. In our opinion, these studies do not take into account the pleiomorphic character of endometriosis and adenomyosis.

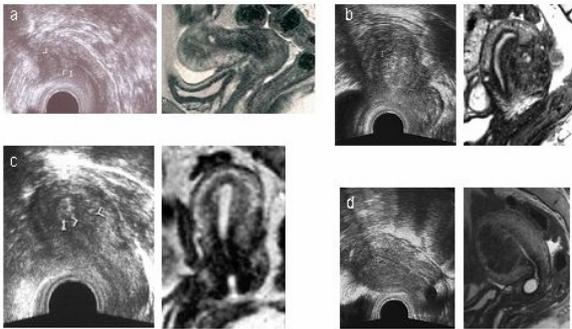


Figure 2. Pleiomorphic appearance of focal and diffuse adenomyosis in women with moderate to severe endometriosis (27 to 31 years of age; a-c). In patient (d) (37 years of age) because of low sperm count of the husband no laparoscopy was performed. She had a curettage at an age of 22. The TVS was apparently normal. Meticulous analysis, however, showed asymmetry of the uterine walls and no “halo” could be demonstrated. MRI revealed focal to diffuse adenomyosis of the anterior wall and beginning adenomyosis of the posterior wall of the uterus. Sagittal scans of the uterine midline are shown.

When we, for the first time, recognized again the frequent association of endometriosis with adenomyosis [32-34], seemingly challenging Sampson’s view, we earned pure disbelief. Fortunately, our German colleagues in contrast to those in other countries are entitled to perform ultrasound in their own offices. Thus, It took only a few weeks after they had seen enough cases on their own and had also performed some MRI scans, until the discussion whether or not endometriosis may be associated with adenomyosis was terminated. Also other groups that incorporated imaging techniques in their set up confirmed in principal the findings [35]. Meticulously performed ultrasound usually reveals in cases of endometriosis characteristic signs of uterine adenomyosis

(“abnormal patterns” of the uterus; Margit Dueholm; personal communication) such as abnormal shapes and sizes of the uterus if fibroids are excluded, asymmetry with respect to the anterior and posterior walls, irregularities of the lining of the endometrium, an unusual texture of the myometrium, and of course a broadened, focally destroyed or completely absent ‘halo’. MRI usually confirms these findings [3] (Fig 1 and 2). Cullen and some of the scientific giants around the turn of the last century were rapidly back [36]. Of course, Sampson was not proven wrong in a strict sense in that tubal dissemination constitutes, without doubt, an important

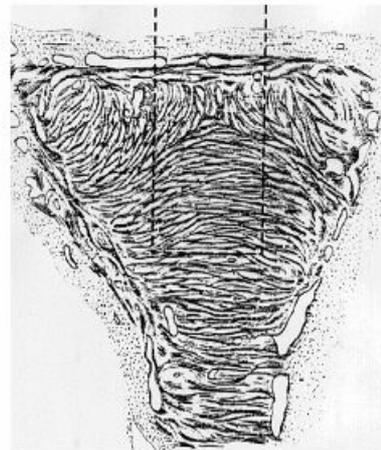


Figure 3. Modified original drawing from Werth and Grusdew [9] showing the architecture of the subendometrial myometrium (archimyometrium) in a human fetal uterus. The specific orientation of the circular fibers of the archimyometrium results from the fusion of the two paramesonephric ducts forming a fundo-cornual raphe in the midline (dashed rectangle). The peristaltic pump of the uterus, which is continuously active during the menstrual cycle, is driven by coordinated contractions of these muscular fibers. Directed sperm transport into the dominant tube is made possible by differential activation of these fibers. The fundo-cornual raphe constitutes a region of increased mechanical strain and tissue injury followed by local estrogen production (TIAR). (From 5)

aspect in the disease process. This aspect, however, has to be more precisely defined in a consistent and comprehensive concept of the pathophysiology of endometriosis and adenomyosis (*vide infra*). In any event, the focus of studying the pathogenesis of endometriosis shifted from the pelvic peritoneum to the archimetra, which is the Müllerian part of the uterus [4]. It became evident that the peritoneal endometriotic

lesion merely constitutes one of the pleiomorphic phenomena rather than the genuine disease itself.

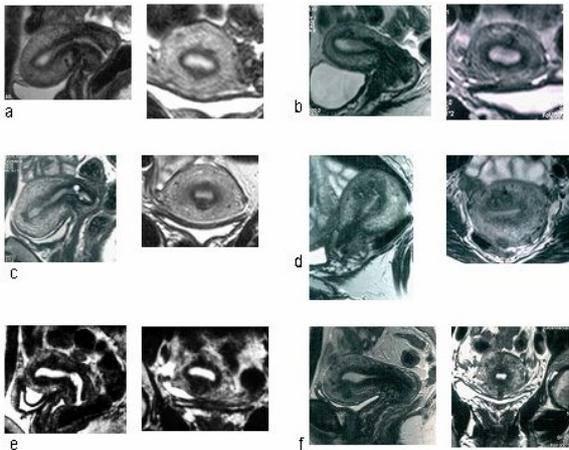


Figure 4. Examples of uterine adenomyosis in six patients as presented by magnetic resonance imaging (MRI). Representative sagittal and coronary scans are shown. In the infertile, non-parous women (a-e) (30 – 32 years of age) pelvic endometriosis of grade I-IV was demonstrated by laparoscopy. In the parous woman (f) (40 years of age) no laparoscopy was performed. In all scans preponderance of the adenomyotic lesions (expanded junctional zone) in the midline close to the fundo-cornual raphe of the archimyometrium can be demonstrated. In the first three scans (a-c) the diagnosis of adenomyosis would not meet the established radiologic criteria for MRI. In a scientific context, however, the irregularities of the junctional zone are characteristic of beginning adenomyosis. (From 5)

The role of the uterus in the disease process

In the understanding of the pathophysiology of endometriosis and adenomyosis a re-analysis of, both, structure and function of the non-pregnant uterus turned out to be of utmost importance [4,37-39]. With uterine peristalsis and directed (sperm) transport a novel uterine function has been discovered [40-47]. It became evident that the non-pregnant uterus is constantly active throughout the reproductive period of life and thereby, like other mechanically active organs of the body such as the skeletal and the cardiovascular systems, respectively, rather inevitably subjected to mechanical strain. Research performed over the last years has demonstrated a crucial role of mechanical strain in normal and pathological function of various tissues. Moreover, it became apparent that the molecular mechanisms associated with mechanical strain, injury and repair displays a pattern that is quite similar in different

tissues and involves the expression of the P450 aromatase and the local production of estrogen [48]. The sequels of tissue injury and repair, however, may become very specific depending on structure and functions of the tissues and organs involved such as tendons and cartilage in the skeletal and the intima in the cardiovascular system, respectively. This is of particular importance, when the tissue, as it is the case with the uterus, is physiologically highly estrogen sensitive and when injury is chronic in character.

There are several lines of evidence for the notion that dysfunctions of the uterus play a crucial role in the pathophysiology of endometriosis.

1. Fragments of basal endometrium were found in the menstrual effluent with a higher prevalence in women with endometriosis than in controls. On the basis of these and other findings it was suggested that pelvic endometriosis results from the transtubal dislocation of fragments of basal endometrium [14].
2. There is a significant association of pelvic endometriosis with uterine adenomyosis in women and in the baboon with life-long infertility. In women, the reported prevalence, however, differs according to the study population chosen and to the criteria applied to the interpretation of MRI findings [4,32,34,49,50].
3. The uterine function of rapid and directed sperm transport into the 'dominant tube' is dysfunctional in women with endometriosis and is characterized by hyper- and dysperistalsis [51-56].

It was suggested that this uterine dysfunction in women with endometriosis and adenomyosis is a result of archimetral hyperestrogenism [3,4,53,57]. There are several lines of evidence that support this notion.

1. In comparison to normal controls and in contrast to peripheral blood estradiol levels are elevated in menstrual blood of women with endometriosis and adenomyosis [58].
2. The expression of the P450 aromatase is increased in adenomyotic tissue and in the ectopic and eutopic endometrium of women with endometriosis [11,12,59-63].
3. A highly estrogen-dependent gene, *Cyr61*, is up-regulated in eutopic

endometrium in women with endometriosis and also in ectopic lesions as well as in experimental endometriosis [64,65].

4. The peristaltic activity of the subendometrial myometrium can be dramatically increased by elevated peripheral levels of estradiol as they are observed during controlled ovarian hyperstimulation. The intensity of uterine peristaltic activity in women with endometriosis resembles that of women during controlled ovarian hyperstimulation although the peripheral estradiol levels are within the normal range [4,53,66].

On the basis of the data presented above we had suggested that auto-traumatisation of the uterus would constitute the critical factor in the development of endometriosis and adenomyosis [3,4,57]. Hyperperistalsis induced by the local production of estrogen would constitute a mechanical trauma resulting in an increased desquamation of fragments of basal endometrium and [14], in combination with an increased retrograde uterine transport capacity [53], in enhanced transtubal dissemination of these fragments. Hyperperistalsis and increased intrauterine pressure would with time, result in myometrial dehiscences that are infiltrated by basal endometrium with the secondary development of peristomal muscular tissue. Diffuse or focal adenomyosis of various extent ensue. Adenomyotic foci are usually localized in the anterior and/or posterior with preference of the posterior but only rarely in the lateral walls of the uterine corpus. Early lesions usually present close to the “fundocornual raphe” of the archimyometrium [3,33,34] (Fig. 3 and 4).

The enigma of archimetral hyperestrogenism

The local production of estrogen both on the level of the eutopic endometrium in women with endometriosis and of the ectopic lesions is, undoubtedly, central to the understanding of the pathophysiology of the disease. The etiology of this increased estrogen-producing “glandular” potential of these tissues, however, is still enigmatic. It was recently suggested that the susceptibility of developing the disease with the potential to locally produce estrogen within the eutopic endometrium would be acquired by an epigenetic mechanisms

during prenatal life that would become manifest not until after puberty [12]. Other authors suggest that the endometrium in women with endometriosis is inherently altered [11]. Clinical and experimental evidence do not support these views. If primary alterations of the endometrium were a prerequisite of the development of the disease it would not be possible, in the primate model, to induce peritoneal endometriosis by inoculation of endometrial fragments that were obtained from endometrial biopsies of healthy animals [15-17,65]. Moreover, abdominal wall endometriosis following caesarean section develops in presumably primarily healthy subjects.

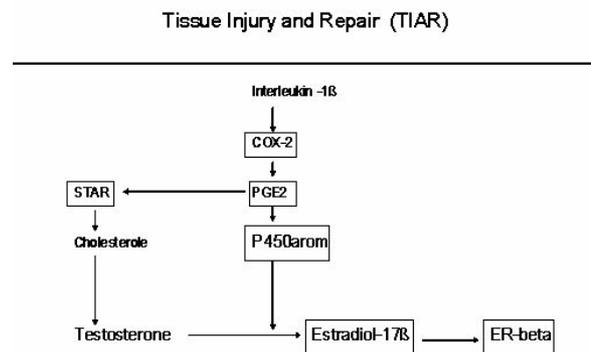


Figure 5. The basic aspects of the molecular biology of the physiological mechanism of ‘tissue injury and repair’ (TIAR) as demonstrates in mesenchymal tissue such as astrocytes, tendons and cartilage (From 5)

Tissue injury and repair (TIAR)

Recent studies have increasingly shown that estradiol is of utmost importance in the process of wound healing [67-69]. This action of estrogens appears to be mainly mediated by the estrogen receptor-beta (ER2). Animal experiments with chemotoxic and mechanic stress to astroglia [48,70,71] and urinary bladder tissue as well as studies with isolated connective tissue such as fibroblasts and cartilage [72-74] have revealed that tissue injury and inflammation with subsequent healing is associated with a specific physiological process that involves the local production of estrogen from its precursors. Interleukin-1 induced activation of the cyclooxygenase-2 enzyme (COX-2) results in the production of prostaglandin E2 (PGE2), which in turn activates STAR (steroidogenic acute

regulatory protein) and the P450 aromatase. Thus, with the increased transport of cholesterol to the inner mitochondrial membrane testosterone can be formed and aromatized into estradiol that exerts its proliferative and healing effects via the ER2. In studies with fibroblast it was surprising that the first steps of this cascade could be activated by seemingly minor biophysical strain [72]. Following termination of unphysiological strain and healing this process is down-regulated and the local production of estrogen or up-regulation of estrogen dependent genes ceases [72,75]. This cascade can even be activated in tissue that normally does not express the P450aromatase indicating the basic physiological significance of the local production of estrogen in tissue injury and repair (TIAR) [76]. The similarity of the molecular biology of TIAR in various tissues with that described in endometriosis [11,12,63-65,77-80] strongly suggests that this represents the common underlying mechanisms of both processes (Fig.5).

Mechanism of disease: Uterine auto-traumatisation

Structure and function of the subendometrial myometrium and the endocrine control of directed sperm transport have been described elsewhere [33,37,43,66,81,82]. It is comprehensible that the myometrial fibers and the fibroblast at the endometrial-myometrial interface near the fundo-cornual raphe are subjected to increased mechanical strain during midcycle, because not only is the ovarian estradiol secretion at its peak at that time, but also additional mechanical strain is imposed on these cells due to estradiol that reaches the uterus via the utero-ovarian counter-current system and controls the direction of the upward transport [81]. Directed sperm transport begins during the mid-follicular phase of the cycle when the dominant follicle becomes visible [43]. The fundo-cornual raphe as a site of predilection of mechanical strain is documented by the observation that early adenomyosis usually evolves in the sagittal midline of the mid-corporal and fundal part of the uterus (Fig. 4). Even in more advanced cases of adenomyosis the expansion of the junctional zone in MRI often shows preponderance at these locations [3].

First step injury: Microtraumatisation

Experiments with cultivated fibroblasts have shown that mechanical strain within certain limits is physiological to such cells. However, even minor increments in mechanical strain resulted and the activation of COX-2 and the production of PGE2, the basic biochemical mechanisms underlying tissue injury [72], and also in the production of interleukin-8 [83]. Thus, with respect to the subendometrial myometrium, deviations from the normal cyclic endocrine pattern with increases or prolongations of estradiol stimulation of uterine peristalsis could impose suprphysiological mechanical strain on the cells near the fundo cornual raphe. It has been attempted to relate irregularities of the menstrual cycle to the development of endometriosis without clear-cut evidence [84]. The irregularities under discussion, however, are not easily disclosed and might escape self-observation and recording of patient history. It is tempting to speculate that events such as prolonged follicular phases, anovulatory cycles or periods of follicular persistency and also the presence of large antral follicles in both ovaries before definite selection of the dominant follicle would impose, by increased or prolonged estrogenic stimulation, stronger mechanical strain to the muscular fibers and fibroblasts. That a prolonged period of estrogenic stimulation might promote the development of endometriosis is documented in a study aiming at examining the hereditary component of endometriosis in colonized rhesus monkeys. Only a history of application of estrogen patches (in addition to a history of trauma by hysterotomy) showed a significant association with endometriosis [85]. The cyclic irregularities discussed above, that might have also a hereditary background, occur frequently during the early period of reproductive life. This concurs with an early onset of endometriosis in most cases. But also other factors should be taken into consideration that might increase the susceptibility to mechanical strain and tissue injury.

In any event, repeated and sustained overstretching and injury of the myocytes and fibroblasts at the endometrial-myometrial interface close to the fundo-

cornual raphe would activate the TIAR system focally with increased local production of estradiol. This process starts on a microscopical level and complete healing might be possible particularly if the mechanical strain with subsequent tissue injury happened to be only a singular event or followed by a longer phase of uterine quiescence such as during pregnancy and breastfeeding.

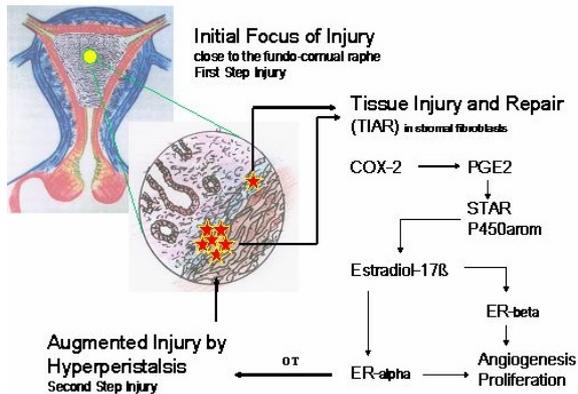


Figure 6. Model of 'tissue injury and repair' (TIAR) on the level of the endometrial-myometrial interface at the fundo-cornual raphe. The mechanisms of first and second step injury are depicted. Persistent uterine peristaltic activity and hyperperistalsis are responsible for perpetuation of injury with permanently increased paracrine estrogen action. (From 5)

During such a singular phase of 'first step' injury transtubal dislocation of fragments of basal endometrium might occur. In addition to the very low probability of transtubal seeding of fragments of basal endometrium in normal women such single events could contribute to the development of asymptomatic pelvic endometriosis [2,3,14]. In case of accidental implantation at an unfavorable site, such as the ovaries, severe intraperitoneal endometriosis could develop without further involvement of the uterus in the disease process as indicated by a completely normal junctional zone in MRI.

With continuing hyperperistaltic activity and sustained injury, however, healing at the fundo-cornual raphe will not ensue and an increasing number of foci are involved in this process of chronic injury, proliferation and inflammation. The expansion or accumulation of such sites with an activated TIAR system renders local areas of the basal endometrium to function as an

endocrine gland that produces estradiol (Fig. 6).

Second step injury: Auto-traumatisation by hyperperistalsis

Focal estrogen production might reach a tissue level that, in a paracrine fashion, acts upon the archimyometrium and increases uterine peristaltic activity presumably mediated by endometrial oxytocin and its receptor [66,86,87]. Hyperperistalsis constitutes a mechanical trauma resulting in an increased desquamation of fragments of basal endometrium and, in combination with an increased retrograde uterine transport capacity, in enhanced transtubal dissemination of these vital fragments [14,53]. The development of peritoneal endometriotic lesions from fragments of basal endometrium is in fact a process of transplantation and represents to a certain extent Sampson's aspect of the disease development [10].

The development of uterine adenomyosis is a continuation of the process that is initiated by the 'first step injury'. With the extension or accumulation of the sites of injury and with the ensuing hyperperistalsis following paracrine estrogen effects this inflammatory process of tissue injury and repair is reinforced and perpetuated resulting in the proliferation of connective tissue with the inherent potential of smooth muscle metaplasia. That is why adenomyotic lesions, in contrast to superficial endometriotic lesions, display a more fibromuscular character. While even short time transtubal seeding might result in peritoneal lesions such as in experimental endometriosis with inoculation of endometrial material in the peritoneal cavity, the development of adenomyosis is a more prolonged process. In any event, the initiation of the TIAR mechanism in the depth of the endometrial stroma and its possible perpetuation constitute the initial events in the development of both, endometriosis and adenomyosis.

Premenarcheal endometriosis

Pelvic endometriosis has been described in adolescent girls prior to menarche and coelomic metaplasia had been suggested as the underlying mechanism [88]. It has,

however to be taken into consideration that with the progression of puberty there is an increasing nocturnal hypothalamo-pituitary activity with secretory bursts of LH and FSH [89]. Such as in low grade hypothalamic amenorrhea large antral follicles are observed in the ovaries of premenarcheal girls that, following the nocturnal gonadotropic stimulation, intermittently secrete estradiol during the morning hours that presumably in turn stimulates uterine peristalsis [90-92]. Thus, detachment and upward transport of fragments of basal endometrium from the more or less unstimulated endometrium in these girls has to be considered as well.

In this respect, the significance of menstruation in the disease process [10] should be more precisely defined. It is not the menstruation *per se* but rather the fact that the basal endometrium is, following the detachment of the functionalis, maximally exposed. This facilitates, in the presence of hyperperistalsis, both, the detachment of fragments of basal endometrium and their upward transport [14,53.56].

Iatrogenic injury

Iatrogenic traumata to the uterus are considered to increase the risk for the development of endometriosis and adenomyosis [93]. A history of hysterotomy in colonized rhesus monkeys showed a significant association with the later development of endometriosis in these animals [85]. The underlying mechanism of induction of endometriosis by iatrogenic trauma such as curettage and other ablative techniques appears to be very similar to those described above. Such surgical interventions might result in extended lesions with an enhanced TIAR reaction. The rapidly increasing local estrogen levels during the process of healing interfere with the ovarian control over uterine peristaltic activity leading rapidly to second step injury with ensuing auto-traumatisation and perpetuation of the disease process. Thus, within the context of our model, iatrogenic lesions that result in the development of endometriosis and adenomyosis can be viewed as strong one-time 'first-step' injuries. In the baboon model experimental endometriosis was induced by inoculation of endometrial fragments that were obtained

by endometrial biopsies during the menstrual phase of the animals. In the endometriotic lesions *Cyr61*, a highly estrogen dependent gene, was soon up-regulated [65]. Surprisingly, *Cyr61* started to be up-regulated also in the eutopic endometrium of these primarily healthy animals. Most probably, the activation of *Cyr61* in the eutopic endometrium resulted from the activation of the TIAR system with local production of estrogen following tissue injury that was caused by the biopsy rather than from a 'cross-talk' between the endometriotic lesions and the eutopic endometrium as suggested by the authors.

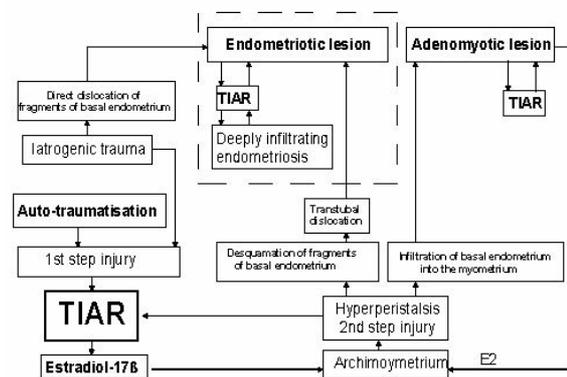


Figure 7. Model of the pathophysiology of endometriosis and adenomyosis. Tissue injury in the depth of the endometrium and the activation of the TIAR system constitute the *primum movens* in the disease development. This pertains to spontaneously developing endometriosis/adenomyosis as well as to that induced by iatrogenic trauma. The dashed rectangle depicts the extra uterine sites of the disease process. (From 5)

The eutopic endometrium in endometriosis and the endometriotic lesions.

In both, the endometriotic lesions and in the eutopic endometrium of women with endometriosis, the cellular and molecular components of the regulatory systems that enable the tissue to produce estradiol have been demonstrated to be expressed. While this has been convincingly shown for peritoneal lesions, data concerning the eutopic endometrium of women with endometriosis are unequivocal in this respect.

The ectopic lesions. Fragments of basal endometrium constitute injured tissue. The expression of acute and inflammatory

cytokines such as interleukin-1 β and interleukin 6 and also interleukin-8 [83,94] facilitate implantation. As auto-transplants, however, the fragments should implant without inflammatory sequels. The endometriotic lesions are, however, as the eutopic endometrium, subjected to cyclic endocrine stimuli and immunological phenomena but devoid the potential of desquamation and externalization of cellular debris. Presumably due to this cyclic strain imposed upon the peritoneal endometriotic lesions the TIAR system is repeatedly and chronically activated. Immunohistochemistry has demonstrated also a dramatic up-regulation of the estradiol receptor alpha [14]. The recent finding of nerve fibers in ectopic lesions and also in the eutopic endometrium of affected women and their regression following gestagen administration is at harmony with the view that chronic strain and healing sustains an inflammatory process [95-99].

Superficial lesions usually display the glandular character of the parent tissue and are surrounded by muscular fibers [14,100] that result from the inherent potential of the basal mesenchym to form muscular tissue [14]. They have, therefore, been described as 'microuteri' or 'microarchimetas'[14]. The unfavourable environment, however, does in most cases not allow for an even truncated simulation of the cyclic events seen in the parent tissue such as proliferation and secretory transformation. Therefore, the glandular epithelium and the stroma of the lesions display the immunohistochemical character of the basalis layer of the eutopic endometrium [14].

In superficial lesions this chronic inflammatory process might calm down and healing might be possible [101]. Deeply infiltrating lesions develop at sites that are in addition subjected to chronic mechanical irritation such as the recto-sigmoid fixed to the pelvic wall or uterus, the sacro-uterine ligaments, the urinary bladder, ovaries fixed to the pelvic wall, the recto-vaginal septum as well as the abdominal wall. It appears that chronic trauma to the ectopic lesions maintains the inflammatory process and results in the same tissue response as seen in uterine adenomyosis [3]. These are in

fact the extra-uterine sites of adenomyoma described by Cullen [36]. The peristromal fibromuscular tissue of endometriotic lesions is homologous to the respective tissue within the archimetra [14]. and probably in the same way susceptible to mechanical strain. Chronic mechanical strain results in proliferation and preponderance of fibromuscular tissue, both characteristic of deeply infiltrating endometriosis and uterine adenomyosis [102]. Deeply infiltrating lesions tend to persist, while superficial lesions might heal. That is why long lasting endometriosis usually presents with deeply infiltrating lesions [101] and also uterine adenomyosis [3,32,34].

The eutopic endometrium. As delineated above, the disease process starts focally in the depth of the basal endometrium. Thus, endometrial biopsies might miss the focus with an activated TIAR system. With the progression of the disease the area of alteration might be expanded. This is in keeping with the observation that the molecular markers associated with endometriosis could be more consistently demonstrated in more advanced stages of the disease [11].

With respect to the molecular biology of the eutopic endometrium in endometriosis it has to be taken into consideration that the endometrium is composed morphologically and functionally of at least two distinct layers, the basalis and the functionalis layers, respectively [14,103-105]. This is not sufficiently taken into account when studies on molecular biology are performed with material taken from more or less random endometrial biopsies [11,12,63,106]. The basal endometrium in women with endometriosis is twice as thick as in healthy women [14,57]. Moreover, while in healthy women the endometrial-myometrial lining is smooth and regular it is irregular and sometimes polypoid in affected women [14,107]. Thus, endometrial biopsies taken from women with endometriosis might, to a variable and unknown extent, be 'contaminated' with basal endometrium. They may even contain basal endometrial stroma of the fundo-cornual region that is altered by the TIAR process, because endometrial biopsies are, for obvious anatomical reasons, mostly taken from the

midline of the anterior and posterior walls of the uterine cavity. This might explain at least in part the finding of 'progesterone resistance' or 'attenuated progesterone response' [11,108,109] and an impaired estradiol metabolism in the endometrium of women with endometriosis [11,106]. Using immunohistochemistry of estradiol receptor alpha and progesterone receptor no progesterone resistance could be observed in the late secretory phase of the *functional* endometrium of affected women. As in healthy women, with the progression of the secretory phase, the ER and PR expression declined in the functionalis and steadily rose in the basalis as well as in the endometriotic lesions [14]. The latter findings suggest physiological progesterone resistance in the basal endometrium and also in the endometriotic lesions as they are derived from implanted fragments of basal endometrium. Moreover, clinical studies with oocyte donation do not support a generally impeded implantation in women with endometriosis [110]. With respect to the expression of the 17 β HSD type 2 no data are available that distinguish between functionalis and basalis as well as endometrial tissue subjected to the chronic TIAR process [111]. In any event, endometriosis and adenomyosis result from the physiological mechanism of 'tissue injury and repair' (TIAR) involving local estrogen production in an estrogen-sensitive environment normally controlled by the ovary. It appears that many of the altered endometrial molecular markers described in the context of endometriosis are the consequence rather than the cause(s) of the disease.

Conclusions

Both, endometriosis adenomyosis may now be integrated into the physiological mechanism and new nosological concept of "tissue injury and repair"(TIAR) and may, in this context, just represent the extreme of a basically physiological, estrogen-related mechanism, that is pathologically exaggerated in an extremely estrogen sensitive, reproductive organ.

Circumstantial evidence suggests that endometriosis and adenomyosis are caused by trauma. In the spontaneously developing disease chronic uterine peristaltic activity or

phases of hyperperistalsis induce, at the endometrial-myometrial interface near the fundus-cornual raphe, microtraumatisations with the activation of the TIAR mechanism. This results in the local production of estrogen. With ongoing peristaltic activity such sites might accumulate and the increasingly produced estrogens interfere in a paracrine fashion with the ovarian control over uterine peristaltic activity resulting in permanent hyperperistalsis and a self-perpetuation of the disease process. Overt auto-traumatisation of the uterus with dislocation of fragments of basal endometrium into the peritoneal cavity and infiltration of basal endometrium into the depth of the myometrial wall ensues. In most cases of endometriosis/adenomyosis a causal event early in the reproductive period of life must be postulated leading rapidly to uterine hyperperistalsis. In late premenopausal adenomyosis such an event might not have occurred. However, as indicated by the high prevalence of the disease, it appears to be unavoidable that, with time, chronic normoperistalsis throughout the reproductive period of life accumulates to the same kind of microtraumatisation. With the activation of the TIAR mechanism followed by chronic inflammation [18] and infiltrative growth endometriosis/adenomyosis of the younger woman and premenopausal adenomyosis share in principal the same pathophysiology. In conclusion, endometriosis and adenomyosis result from the exaggeration of the basically physiological mechanism of 'tissue injury and repair' (TIAR) involving local estrogen production. This is magnified in an estrogen-sensitive environment normally controlled by the ovary.

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