# A new concept of endometriosis and adenomyosis: tissue injury and repair (TIAR)

**Gerhard Leyendecker[1,*] and Ludwig Wildt[2]**

[1]Kinderwunschzentrum (Fertility Center) Darmstadt, Darmstadt, Germany
[2]Department of Obstetrics and Gynecology, University Clinic of Gynecological Endocrinology and Reproductive Medicine, Medical University Innsbruck, Innsbruck, Austria

## Abstract

Pelvic endometriosis, deeply infiltrating endometriosis and uterine adenomyosis share a common pathophysiology and may 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. The acronym TIAR describes a fundamental and apparently ubiquitous biological system that becomes operative in mesenchymal tissues following tissue injury and, upon activation, results in the local production of estradiol. 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 fundo-cornual raphe, microtraumatisations, with activation of the TIAR mechanism. With ongoing traumatisations, such sites of inflammation might accumulate and the increasingly produced estrogens interfere in a paracrine fashion with ovarian control over uterine peristaltic activity, resulting in permanent hyperperistalsis and a self-perpetuation of the disease process. Overt autotraumatisation 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, rapidly leading to archimetral hyperestrogenism and 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 extent of microtraumatisation. With activation of the TIAR mechanism followed by chronic inflammation and infiltrative growth, endometriosis/adenomyosis of the younger woman and premenopausal adenomyosis share in principal the same pathophysiology.

## Introduction

Endometriosis is a disease that affects many women predominantly during the reproductive period of life [1]. With the cardinal symptoms such as pelvic pain, bleeding disorders and infertility, the disease has a tremendous impact on women's health. Usually, endometriosis is defined as the occurrence of endometrial tissue outside of the uterus, and retrograde menstruation is considered as the main causal event [2]. This pathophysiological concept has resulted in considering endometriosis and adenomyosis as separate disease entities [3–5]. The leading authors of the last century, however, described endometriosis as ectopic endometrial lesions occurring in the uterus (adenomyosis), in the peritoneal cavity and at other sites of the body (endometriosis), and the lesions were considered as variants of the same disease process [6–8]. A new understanding of the disease process enables us to reunify these disease entities and to integrate them into a new nosological concept [9, 10]. Already a decade ago we had suggested that the cause or causes of endometriosis and adenomyosis may be unspectacular and closely related to some of the physiological processes of reproduction. Trauma followed by tissue-specific 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 [11].

This concept will now be extended and recent advances in the understanding of the pathophysiology of endometriosis and adenomyosis will be reviewed. It will be demonstrated that development of the disease results in fact from localised uterine trauma and from the subsequent interaction of two primarily independent physiological processes, both involving the regulatory functions of estradiol: (A) the ovarian endocrine system that is under the control of the hypothalamic-pituitary axis; and (B) a non-organ specific paracrine system that is locally activated in processes of tissue injury and wound healing. We coined the acronym TIAR (tissue injury and repair) to describe this fundamental and apparently ubiquitous biological system [9, 10]. In various mesenchymal tissues, following tissue injury the TIAR mechanism is rapidly activated and results in the local production

*Corresponding author: Gerhard Leyendecker,
Kinderwunschzentrum (Fertility Center) Darmstadt,
Bratustrasse 9, 64295 Darmstadt, Germany
Tel.: +491718505490, Fax: +496151710363,
E-mail: gerhard.leyendecker@t-online.de

of estradiol. TIAR is considered an evolutionarily conserved system independent of steroidal precursors that are usually produced in endocrine glands such as the adrenal gland and gonads. This adds another facet to the largely known fact that the regulatory roles of estrogen extend well beyond the reproductive system. In the TIAR system, estradiol exerts its healing effects mainly via the estradiol receptor β (ER2) and results in upregulation of specific estrogen-dependent genes. In general, wound healing following injury constitutes an inflammatory process that involves cell proliferation and the sprouting of sensory nerve fibers into the site of inflammation. Following healing and termination of the inflammatory process, the TIAR system is downregulated, the activation of estrogen-dependent genes ceases and the nerve fibers regress (vide infra).

The view that trauma, in particular autotraumatisation of the uterus with subsequent involvement of the mechanism of TIAR, plays a fundamental role in the development of both endometriosis and adenomyosis requires, first of all, a detailed delineation of the structure and function of the normal non-pregnant uterus.

## Role of the uterus in the disease process

In the understanding of the pathophysiology of endometriosis and adenomyosis, re-analysis of both the structure and function of the non-pregnant uterus and in particular the functional architecture of the archimyometrium with the formation of the fundo-cornual raphe during ontogeny turned out to be of utmost importance [11–14]. With uterine peristalsis and directed (sperm) transport, a novel uterine function has been discovered [15–22]. It became evident that the non-pregnant uterus is constantly active throughout the reproductive period of life and, thus, like other mechanically active organs of the body such as the skeletal and cardiovascular systems, inevitably becomes subjected to mechanical strain. Research performed over the last years has demonstrated a crucial role of mechanical strain in normal and pathological functions of various tissues. Moreover, it became apparent that the molecular mechanisms associated with mechanical strain, injury and repair display a pattern that is quite similar in different tissues and involves expression of P450 aromatase and the local production of estrogen [23]. The sequelae of TIAR, however, may become very specific depending on the structure and functions of the tissues and organs involved, such as tendons and cartilage in the skeletal system as well as the intima of the cardiovascular system. Normally, healing is supported by avoiding further strain to the organ involved. The mechanisms of TIAR, however, may be perpetuated in an organ that is autonomously regulated and highly estrogen-sensitive as is the case with the uterus. The locally produced estrogen may interfere with that of ovarian origin and may increase its stimulatory function with respect to the peristaltic activity of the non-pregnant uterus, thus both re-enforcing and chronifying mechanical strain that in turn sustains the inflammatory process.

Meyer has already hinted at the inflammatory character of the ectopic endometrial lesions [6].

## Structure and function of the non-pregnant uterus

The uterus is composed of two different organs, the inner archimetra and the outer neometra [11, 14] (Figure 1A). Phylogenetically and ontogenetically, the archimetra or endometrial-subendometrial unit, constitutes the oldest part of the uterus (hence its denomination) and is composed of the epithelial and stromal endometrium and the underlying stratum subvasculare of the myometrium (archimyometrium [12]) with a predominantly circular arrangement of muscular fibers. Whilst both the endometrium and the subendometrial myometrium display a marked cyclic pattern of steroid hormone receptor expression, the two other layers of the myometrium, the outer stratum supravasculare with a predominantly longitudinal arrangement of muscular fibers and the stratum vasculare consisting of a three-dimensional mesh of short muscular bundles [12, 13], show a more or less continuously high receptor expression throughout the cycle [14, 24]. Only the archimetra is of paramesonephric origin, whilst the outer layers, the neometra, are of non-Müllerian origin [12].

**The archimyometrium**    The archimyometrium extends from the lower part of the cervix through the uterine corpus into the cornua, where it continues as the muscular layer of the Fallopian tubes [13]. In high resolution sonography and magnetic resonance imaging (MRI), the archimyometrium can be visualised as a hypodense 'halo' and a hypointense 'junctional zone', respectively, with 4–8 mm of width encircling the endocervix as well as the endometrium (Figure 1D and 1E). The anlage of the archimyometrium can already be identified during the first trimester of gestation [12, 14]. Circular mesenchymal layers surround the fused paramesonephric ducts and develop into muscular fibers during mid-gestation. Short longitudinal fibers branch off from the circular ones [12], presumably providing coherence of the circular fibers in a longitudinal direction and thereby adding physical strength to the archimyometrium. In the adult, coordinated contractions of the circular and short longitudinal fibers result in a thickening of the archimyometrium that moves from the cervix to the fundal part of the uterus and that can be visualised in cine MRI as a wave of focal and symmetric enlargements of the junctional zone.

The ontogenetically early formation of the archimyometrium is pertinent to its function and is in particular documented by the fundo-cornual raphe that results from fusion of the two paramesonephric ducts and their mesenchymal elements to form the primordial uterus [12, 25]. Bipartition of the circular subendometrial myometrium in the upper part of the uterine corpus and its separate continuation through the cornua into the respective tubes is the morphological basis of directed sperm transport into the tube ipsilateral to the dominant follicle (Figure 2).

Production of smooth muscle cells by stromal metaplasia occurring during the first trimester of gestation [12] is a property of the basal endometrial stroma that is also retained
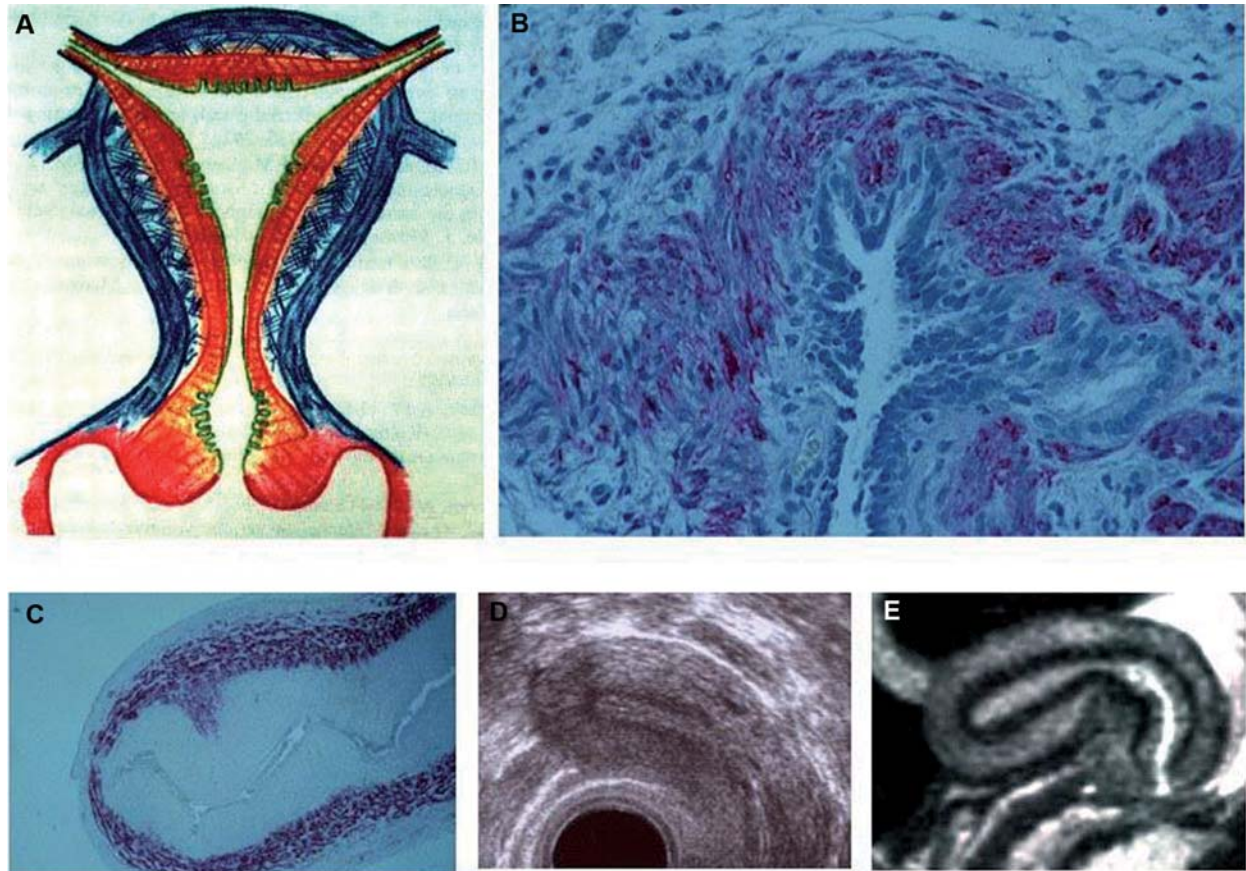
**Figure 1** (A) Schematic representation of the endometrial-subendometrial unit ('archimetra') within the human uterus based on immunocytochemical results as well as morphological and ontogenetic data, respectively. The endometrial-subendometrial unit is composed of the glandular part (green) and the stromal part of the endometrium and the stratum subvasculare of the myometrium with predominantly circular muscular fibers (yellow). Ontogenetically, the endometrial-subendometrial unit is derived from the paramesonephric ducts (green) and their surrounding mesenchyme (yellow). The bulk of the human myometrium does not originate from the paramesonephric ducts (blue). It consists of the stratum vasculare with a three-dimensional meshwork of short muscular bundles, and the stratum supravasculare with predominantly longitudinal muscular fibers. The stratum vasculare is the phylogenetically most recent acquisition and, in contrast to the endometrial-subendometrial unit, both the stratum vasculare and supravasculare develop late during ontogeny. The stratum vasculare and supravasculare surround the uterine corpus and extend caudally only to the uterine isthmus. There is a transitory zone within the stratum vasculare adjacent to the stratum subvasculare where muscular fibers of the two layers blend (yellow margin of the stratum vasculare). The endocervical mucosa is the most caudal structure derived from the paramesonephric ducts. The underlying circular muscular fibers, which are progressively diminishing in the caudal direction, and the accompanying connective tissue blend with vaginal tissue elements (red) to form the vaginal portion of the cervix. (B) Peritoneal endometriotic lesion (×400) as an ectopic 'micro archimetra'. With endometrial glands, endometrial stroma and peristromal muscular tissue, the lesion is composed of all elements of the archimetra. (C) The primordial uterus of the 23rd week of pregnancy (×50) is composed of the elements of the archimetra, such as the endometrium and archimyometrium (specific actin staining) (top right). The archimetra is essentially the adult representation of the primordial uterus. (D) The 'halo' on transvaginal sonography (TVS) represents the archimyometrium, as does (E) the 'junctional zone' on magnetic resonance imaging (MRI). TVS and MRI of the uterus of a 29-year-old woman unaffected by endometriosis and adenomyosis. Sagittal scans of the uterine midline are shown. The myometrial-endometrial lining is sharp and smooth; the 'halo' on TVS and the 'junctional zone' on magnetic resonance imaging are unaltered; there is symmetry with respect to the anterior and posterior myometrial walls and the texture of the myometrium on TVS appears to be homogenous. (Modified from Leyendecker et al. Ann NY Acad Sci 2004;1034:338–55 [26].)

in the adult. Cyclic metaplasia of the basal endometrial stromal cells into myofibroblasts and back into stromal cells is constantly taking place at the endometrial-myometrial junction [27, 28]. This metaplastic potential of the basal endometrial mesenchym is of particular importance with respect to the metaplastic production of smooth muscle cells in endometriotic lesions and their possible further development in deeply infiltrating foci (Figure 1B). There is indirect evidence derived from immunohistochemical studies that the archimyometrium and the muscular fibers of ectopic endometrial lesions constitute homologous tissues [24].

**Functional versus basal endometrium** Improved immunostaining techniques could extend previous data about the cyclic pattern of ER and progesterone receptor (PR) expression in the endometrium during the menstrual cycle [24]. In
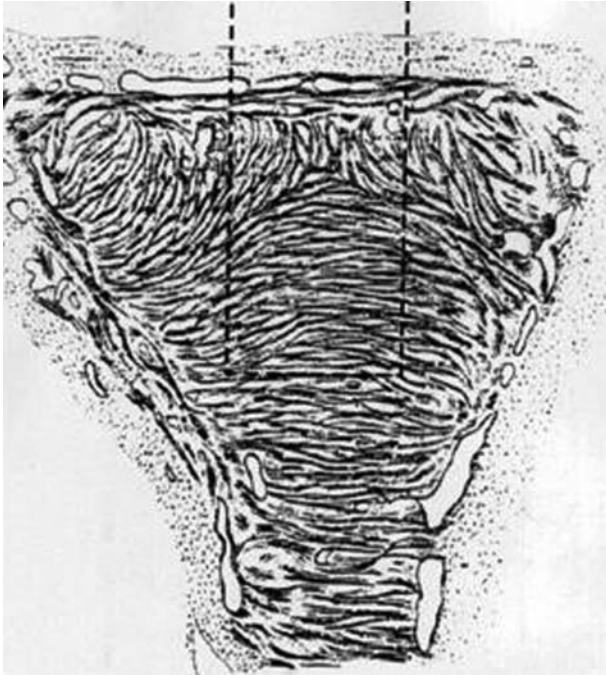
**Figure 2** Modified original drawing from Werth and Grusdew showing the architecture of the subendometrial myometrium (archimyometrium) in a human fetal uterus. The specific orientation of the circular fibers of the archimyometrium results from the fusion of the two paramesonephric ducts forming a 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 co-ordinated contractions of these muscular fibers. Directed sperm transport into the dominant tube is made possible by differential activation of these fibers. The region of the fundo-cornual raphe is considered the predominant site of mechanical strain. (Modified from Werth and Grusdew. Arch Gynäkol 1898;55:325–409 [12].)

both the functional and basal layer, there is a cyclic pattern of ERα and PR expression. Whilst within the functionalis receptor expression of both steroids is steadily declining during the secretory phase, with immunoreactive scores (IRS) tending virtually towards zero immediately prior to menstruation, there is in the basal endometrium, after an intermediate fall parallel to a rise in mitotic activity, a steady increase of the IRS of ERα and PR during the secretory phase that extends into the next proliferative phase (Figure 3). This is of importance in characterising the tissue fragments that are shed during menstruation and potentially seeded within the peritoneal cavity by retrograde transport. Judged from cytomorphological criteria, tissue fragments devoid of receptor expression (functional endometrium) are destined to cellular death, whilst those with positive staining (basal endometrium) appear to be highly vital [24].

The archimetra and the outer layers of the uterus have different functions during the process of reproduction. Whilst the stratum supravasculare and the stratum vasculare, sequentially acquired during evolution in meeting the requirements for the appropriate forces during parturition [13], only subserve the expulsion of the conceptus, the archimetra has extra fundamental functions in the very early processes of reproduction. These functions may be summarised as proliferation and differentiation of the endometrium for implantation, uterine peristalsis for directed rapid and sustained sperm transport, and inflammatory defence [11]. To meet these functions, the components of the archimetra, the epithelial and stromal endometrium as well as the subendometrial myometrium, constantly undergo fundamental structural and biochemical changes throughout the cycle [14, 28].

**Uterine peristalsis** Peristaltic activity of the non-pregnant uterus is a fundamental function in the early process of reproduction [18, 19, 29]. Uterine peristalsis only involves the stratum subvasculare of the myometrium and exhibits cyclic changes in direction, frequency and intensity [15, 16, 18]
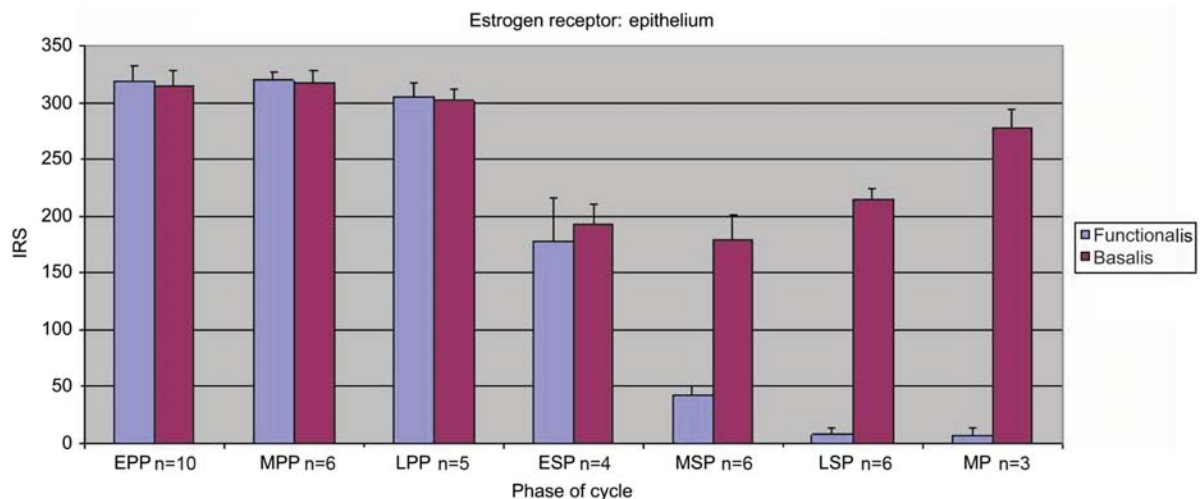


**Figure 3** Immunoreactive scores of estradiol receptor α expression in the functionalis (blue) and basalis (red), respectively, during the menstrual cycle. (Modified from Leyendecker et al. Hum Reprod 2002;17:2725–36 [24].)

(Figure 4). Only during menstruation are the contraction waves with low frequency directed towards the cervix, whilst during the other phases of the cycle, with highest frequency and intensity during the periovulatory phase, cervico-fundal peristalsis prevails [30]. Rapid as well as sustained sperm transport [16, 18, 29] constitutes the predominant reproductive function of uterine peristalsis. In addition, high fundal implantation of the embryo is considered a function of uterine peristalsis during the luteal phase [15]. Vaginal discharge of the menstrual debris may be effected by fundo-cervical peristalsis and additional contractile activity of the stratum vasculare that increases the tone of the uterus during this phase of the cycle. Retrograde menstruation is probably scant and may just constitute a 'side effect' of the low cervico-fundal contractile activity during this phase of the cycle. Retrograde shedding of blood might, however, be significant under the pathological conditions of cervico-fundal uterine hyperperistalsis, such as in endometriosis, and of juvenile dysfunctional bleeding, helping to preserve the iron content of the body in the latter situation [31]. During the follicular phase, cervico-fundal peristalsis is controlled by the rising tide of follicular estradiol [32], which induces, within the archimetra, a cascade of transcriptional events such as the expression of endometrial oxytocin (OT) and oxytocin receptor (OTR) mRNA [33, 34]. OT has been shown to increase uterine peristaltic activity [32]. As soon as a dominant ovarian structure can be visualised by ultrasound, sperm transport is directed preferentially into the tube ipsilateral to the dominant follicle [18]. Directed sperm transport by uterine peristalsis is made possible by the specific structure of the stratum subvasculare in the fundal and cornual regions [12, 25, 26, 31] as well as by the specific endocrine stimuli that

reach the upper part of the uterus by means of the utero-ovarian countercurrent system [35] and are superimposed on those reaching the uterus via the systemic circulation [31, 36]. This enables the uterus, although having become an unpaired organ during evolution and embryogenesis, to function asymmetrically as a paired one.

During the luteal phase, the contractile activity of the archimyometrium decreases and changes in character. This results in a zone of relative quiescence in the fundal region of the uterine cavity. The cyclic functions of the archimetra can be completely mimicked by the sequential administration of estradiol and estradiol plus progesterone that yields physiological blood levels of these hormones, thus underlining the ovarian role in the control of normal archimetral function [30].

## Evidence of the involvement of uterine structure, functions and dysfunctions in the disease process

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

i.  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 [24].
ii. 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 preva-
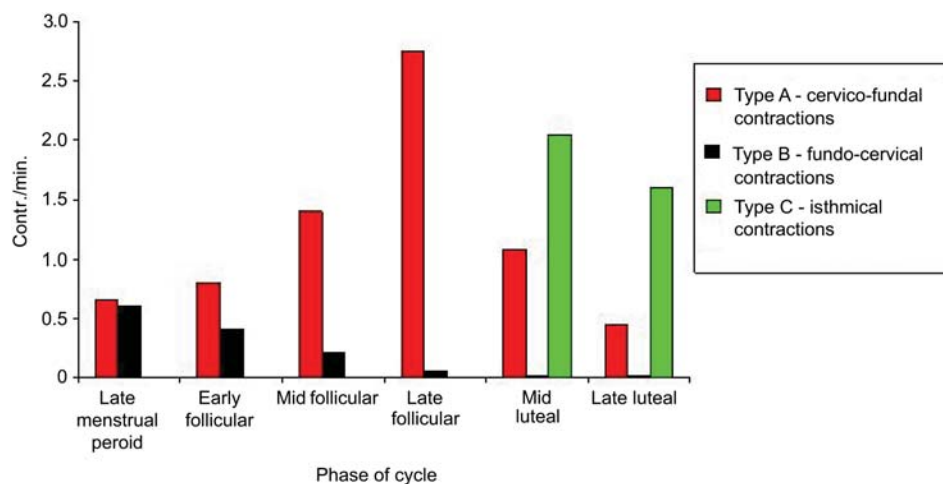


**Figure 4** Histogram demonstrating the frequency of uterine peristaltic waves during menstruation, the early, mid and late follicular phase, and the mid and late luteal phase of the cycle, respectively, as obtained from video sonography of uterine peristalsis (VSUP) in healthy women. The relative distribution of cervico-fundal (type A) versus fundo-cervical (type B) and isthmic (type C) contractions is also shown. The graph clearly demonstrates the increase in frequency of type A contractions with progression of the follicular phase, reaching a maximum during the late follicular phase, and the decrease during the luteal phase of the cycle. With the progression of the menstrual cycle, type B contraction waves almost disappear. Type C contractions prevail during the luteal phase. These contractions do not extend beyond the isthmic or lower corporal parts of the uterus, rendering the fundo-cornual part of the uterus a zone of relative peristaltic quiescence during the period of embryo implantation. (Modified from Kunz et al. In: Filicori M, editor. Endocrine basis of reproductive function. Bologna, Italy: Monduzzi Editore, 2000 [30].)

lence, however, differs according to the study population chosen and to the criteria applied to the interpretation of MRI findings [11, 37–41] (Figure 5).

iii. The uterine function of rapid and directed sperm transport into the 'dominant tube' is dysfunctional in women with endometriosis and is characterised by hyperperistalsis and dysperistalsis [26, 27, 42–46] (Figure 6).

Dysperistalsis with the convulsive pattern of contractions in endometriosis presumably results from adenomyotic proliferations that destroy, with their irregular arrangement of smooth muscle fibers, the functional architecture of the archimyometrium. This may contribute to infertility by impairing directed sperm transport [38]. Uterine hyperperistalsis results most certainly from archimetral hyperestrogenism [11, 26, 29, 31]. There are several lines of evidence that support this notion.

i. In comparison with normal controls and in contrast to peripheral blood, estradiol levels are elevated in menstrual blood of women with endometriosis and adenomyosis [47].

ii. Expression of P450 aromatase is increased in adenomyotic tissue and in the ectopic and eutopic endometrium of women with endometriosis [48–54].

iii. A highly estrogen-dependent gene, *Cyr61*, is upregulated in eutopic endometrium in women with endometriosis and also in ectopic lesions as well as in experimental endometriosis [55, 56].

iv. 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 [11, 29, 30] (Figure 7).

On the basis of the data presented above, we had suggested that autotraumatisation of the uterus would constitute the critical factor in the development of endometriosis and adenomyosis [11, 26, 31]. Hyperperistalsis induced by the local production of estrogen would constitute a mechanical trauma resulting in increased desquamation of fragments of basal endometrium [24] and, in combination with an increased retrograde uterine transport capacity [29], in enhanced transtubal dissemination of these fragments. On the basis of a new interpretation of the available data, our initial view that hyperperistalsis and increased intrauterine pressure would, with time, result in myometrial dehiscences that are infiltrated by basal endometrium with the secondary development of peristromal muscular tissue and the formation of diffuse or focal adenomyosis of various extent will be now be extended and modified (vide infra). Adenomyotic foci are usually localised in the anterior and/or posterior, with preference for the posterior, but only rarely in the lateral walls of the uterine corpus. Early lesions usually present close to
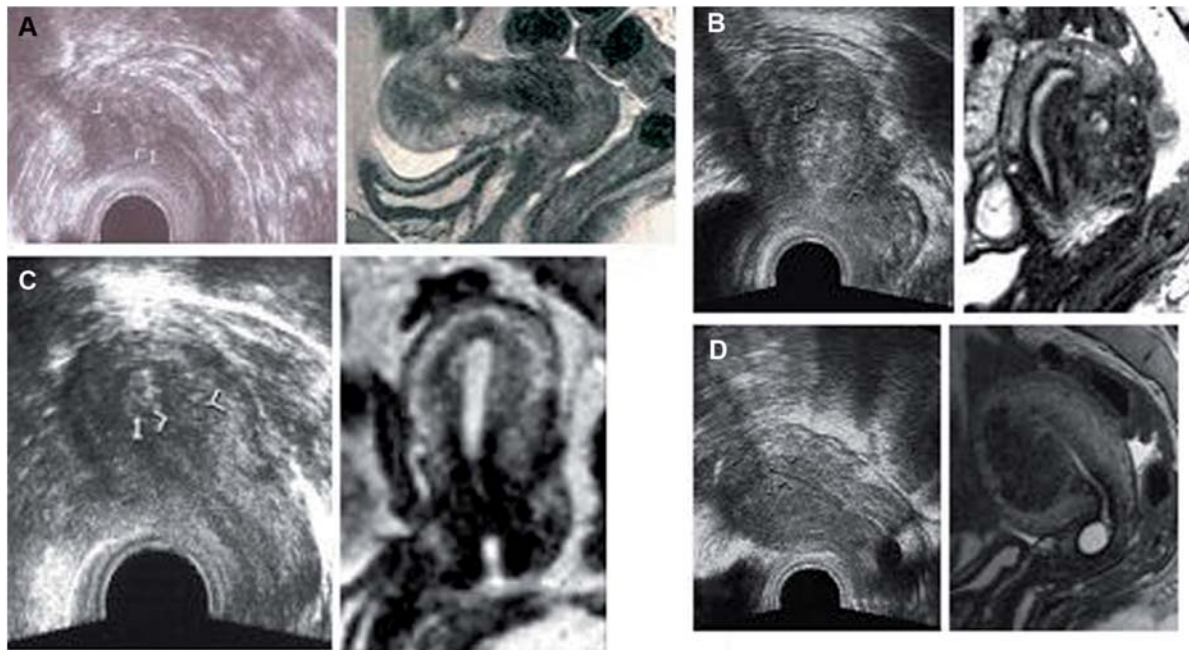


**Figure 5**  Pleiomorphic appearance of focal and diffuse adenomyosis in women with moderate to severe endometriosis (27–31 years of age; A–C). In patient (D) (37 years of age), because of a low sperm count of the husband no laparoscopy was performed. She had a curettage at the age of 22 years. Transvaginal sonography (TVS) was apparently normal. Meticulous analysis, however, showed asymmetry of the uterine walls and no 'halo' could be demonstrated. Magnetic resonance imaging (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. (Courtesy of Prof. Dr P. Huppert, Department of Radiology, Klinikum Darmstadt, Academic Teaching Hospital, Darmstadt, Germany.)
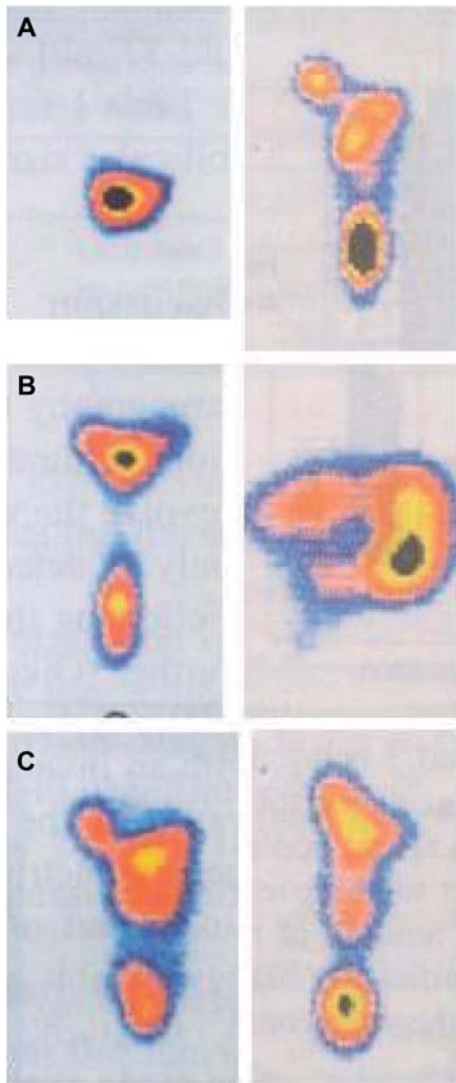
**Figure 6** Representative scans obtained from hysterosalpingoscintigraphy in women without (left panel) and with endometriosis (right panel) 32 min following application of technetium-labelled macrospheres of sperm size in the posterior fornix of the vagina in six different women in (A) early follicular phase, (B) mid follicular phase and (C) late follicular phase of the menstrual cycle. In normal women with normoperistalsis the particles usually remain at the site of application during the early follicular phase (left panel A). In women with endometriosis and hyperperistalsis there is in this phase already a massive transport of the particles through the uterine cavity in one of the tubes (right panel A). In the mid follicular phase, normal women show only an ascension of the particles into the uterine cavity and sometimes a trend of ascension into the tube ipsilateral to the dominant follicle (left panel B). In women with endometriosis the ascension dramatically increases and in this example the particles are transported through the tube into the peritoneal cavity. This was, however, the contralateral tube to the dominant follicle (right panel B). During the pre-ovulatory phase of healthy women the particles are rapidly transported into the 'dominant' tube (left panel C), whilst, owing to dysperistalsis, there is a breakdown of directed sperm transport in women with endometriosis (right panel C). These scans show the enormous power of the uterine peristaltic pump during the early and mid follicular phase of the cycle in women with hyperperistalsis and endometriosis. Continuous hyperperistalsis results in autotraumatisation of the uterus. (Modified from Kunz et al. Hum Reprod 1996;11:627–32 [18]; and from Leyendecker et al. Hum Reprod 1996;11:1542–51 [29].)

the 'fundo-cornual raphe' of the archimyometrium [9, 25, 31, 38] (Figures 8 and 9).

## The enigma of archimetral hyperestrogenism

The local production of estrogens 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 potential of these tissues, however, is still enigmatic. It was recently suggested that the susceptibility of developing the disease with the potential to produce estrogen locally within the eutopic endometrium would be acquired by an epigenetic mechanisms during prenatal life that would not become manifested until after puberty [49]. Other authors suggest that the endometrium in women with endometriosis is inherently altered [48]. Clinical and experimental evidence does not support these views. If primary alterations of the endometrium were a prerequisite for development of the disease it would not be possible, in the primate model, to induce peritoneal endometriosis by

inoculation of endometrial fragments obtained from endometrial biopsies of healthy animals [56–59]. Moreover, abdominal wall endometriosis following cesarean section develops in presumably primarily healthy subjects.

## Tissue injury and repair (TIAR)

As already pointed out in the introductory section, recent studies suggest that estradiol plays a ubiquitous central role in the process of wound healing [60–62]. This is probably an evolutionary old function of the hormone that appears to be mainly mediated by ER$\beta$ (ER2). Animal experiments with chemotoxic and mechanical stress to astroglia [23, 63, 64] and urinary bladder tissue as well as studies with isolated connective tissue such as fibroblasts and cartilage [65–67] 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 (IL-1)-induced activation of the cyclo-oxygenase-2 enzyme (COX-2) results in the production of prostaglandin $E_2$ (PGE$_2$), which in turn activates STAR (steroidogenic acute regulatory protein) and P450 aromatase. Thus, with increased transport of cholesterol to the inner mitochondrial membrane, testosterone can be formed and aromatised into estradiol that exerts its proliferative and healing effects via ER2. In studies with fibroblasts, it was demonstrated that the first steps of this cascade could be activated by seemingly minor biophysical strain [65]. Following termination of strain and healing, this process is
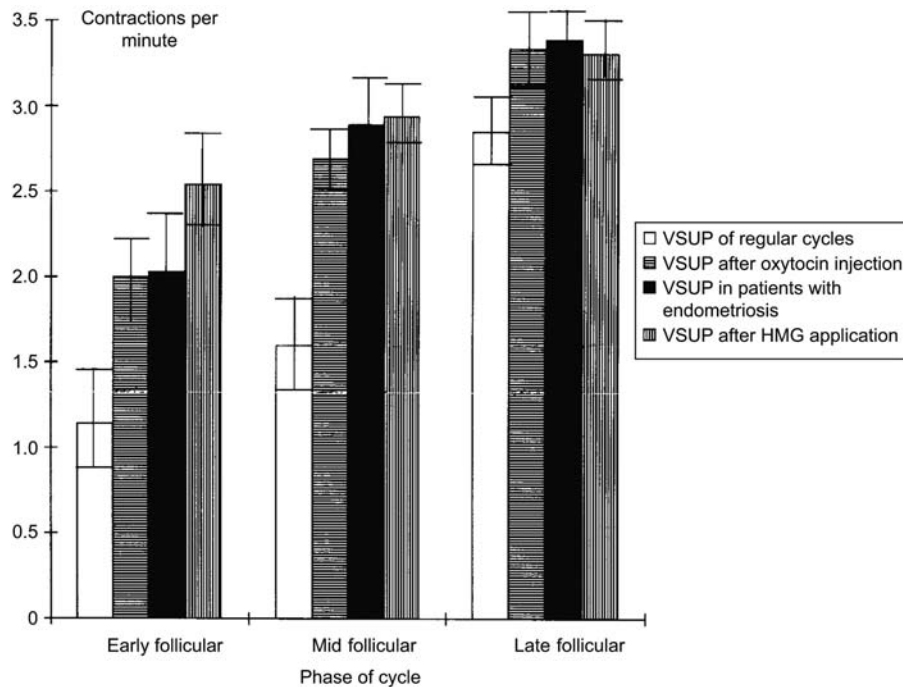
**Figure 7** Frequency of uterine peristaltic contractions during the follicular phase of the menstrual cycle in healthy women, in those with endometriosis, in those treated with human menopausal gonadotropins (HMG) resulting in unphysiologically high levels of estradiol in serum, and in normal women treated with an intravenous bolus of oxytocin. The data show that high estradiol levels and bolus injections of oxytocin simulate the significantly increased uterine peristalsis in patients with endometriosis in comparison with healthy women. Values are mean ± standard error of the mean (SEM). Vaginal sonography of uterine peristalsis (VSUP). (From Leyendecker et al. Hum Reprod Update 1998;4:752–62, with permission [11].)

downregulated and the local production of estrogen or upregulation of estrogen-dependent genes ceases [65, 68]. This cascade can even be activated in tissue that normally does not express P450 aromatase, indicating the basic physiological significance of the local production of estrogen in TIAR [69]. The similarity of the molecular biology of TIAR in various tissues with that described in endometriosis [48, 49, 54–56, 70–73] strongly suggests that this represents the common underlying mechanisms of both processes (Figure 10).

### Mechanism of disease: uterine autotraumatisation

It is comprehensible that the myometrial fibers and the fibroblasts at the endometrial-myometrial interface near the fundo-cornual raphe are subjected to increased mechanical strain during mid-cycle, not only because ovarian estradiol secretion peaks at that time but also because additional mechanical strain is imposed on these cells owing to estradiol that reaches the uterus via the utero-ovarian countercurrent system and controls the direction of the upward transport [35, 36]. Directed sperm transport begins during the mid-follicular phase of the cycle when the dominant follicle becomes visible [18]. The significance of the fundo-cornual raphe as a site of predilection for mechanical strain is documented by the observation that early adenomyosis usually evolves in the sagittal midline of the mid-corporal and fundal parts of the uterus. Even in more advanced cases of adenomyosis the

expansion of the junctional zone on MRI often shows a preponderance at these locations [9, 31, 38] (Figures 8 and 9).

### 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 in the activation of COX-2 and the production of $PGE_2$, the basic biochemical events underlying tissue injury [64], and also in the production of IL-8 [74]. 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 supraphysiological 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 [75]. The irregularities under discussion, however, are subtle and may not easily be disclosed by recording of patient history or even by conventional hormone determination and might escape self-observation. It is tempting to speculate that events such as prolonged follicular phases, anovulatory cycles or periods of follicular persistency as well as 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 mus-
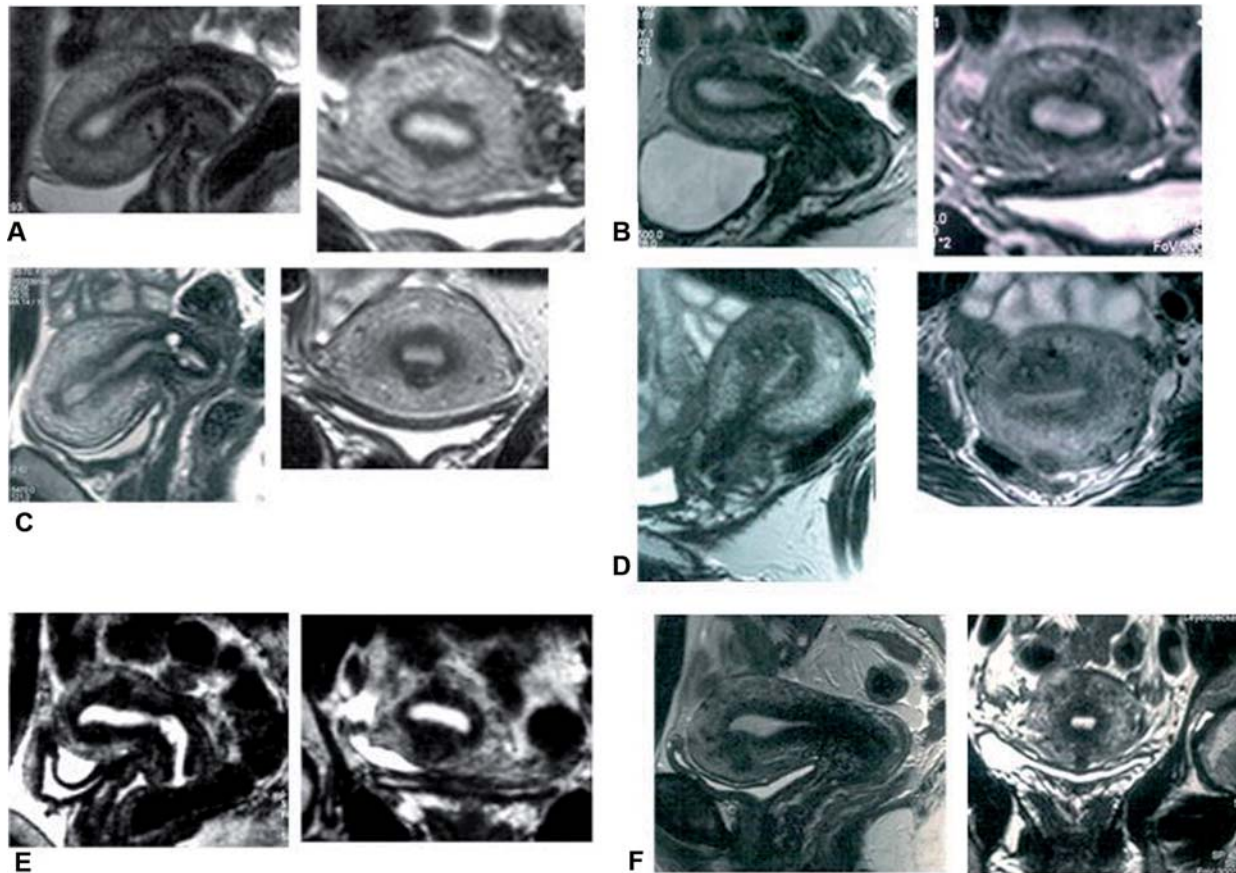
**Figure 8** Examples of uterine adenomyosis in six patients as shown by magnetic resonance imaging (MRI). Representative sagittal and coronary scans are shown. In the infertile, non-parous women (A–E) (30–32 years of age), pelvic endometriosis of grade I–IV was demonstrated by laparoscopy. In the parous woman (F) (40 years of age) no laparoscopy was performed. In all scans, a 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 radiological criteria for MRI. In a scientific context, however, the irregularities of the junctional zone are characteristic of beginning adenomyosis. (From Leyendecker et al. Arch Gynecol Obstet 2009;280:529–38, with permission [9].)

cular fibers and fibroblasts. That a prolonged period of estrogenic stimulation might promote the development of endometriosis is documented in a study aimed at examining the hereditary component of endometriosis in colonised 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 [76]. The cyclic irregularities discussed above, which might also have a hereditary background, occur frequently during the early period of reproductive life. This concurs with an early onset of endometriosis in most cases [1]. However, other factors should also 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 will activate the TIAR system focally with increased local production of estradiol. This process starts on a microscopic 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 breast-feeding.

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 [24, 77]. In case of accidental implantation at an unfavourable 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 on MRI.

With continuing hyperperistaltic activity and sustained injury, however, healing at the fundo-cornual raphe will not ensue and an increasing number of foci will be 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 endo-
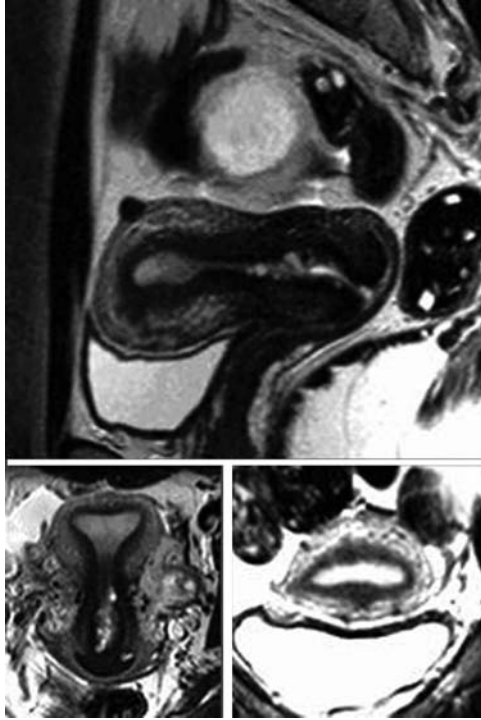
**Figure 9**   Magnetic resonance imaging (MRI) scans of a 33-year-old infertile woman with normal sperm count of husband. Within 3 months she developed severe dysmenorrhea and chronic pelvic pain. Vaginal ultrasound revealed the formation of a growing endometrioma of the left ovary. The sagittal MRI scan (top) shows the endometrioma and focal adenomyosis with a preponderance in the fundal part of the anterior junctional zone. The frontal scan of the uterus (bottom left) shows completely unaffected lateral parts of the junctional zone. The coronary scan of the uterus (bottom right) shows a preponderance of focal expansion of the junctional zone in the midline (fundo-cornual raphe). (Courtesy of Prof. Dr. P. Huppert, Department of Radiology, Klinikum Darmstadt, Academic Teaching Hospital, Darmstadt, Germany.)



**Figure 10**   Basic aspects of the molecular biology of the physiological mechanism of 'tissue injury and repair' (TIAR) as demonstrated in mesenchymal tissue such as astrocytes, tendons and cartilage. (From Leyendecker et al. Arch Gynecol Obstet 2009;280:529–38, with permission [9].)

metrium to function as an endocrine gland that produces estradiol (Figure 11).

### Second-step injury: autotraumatisation 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 OT and its receptor OTR [32–34, 78]. Hyperperistalsis constitutes a mechanical trauma resulting in increased desquamation of fragments of basal endometrium and may, in combination with increased retrograde uterine transport capacity, result in enhanced transtubal dissemination of these vital fragments [24, 29]. Development of peritoneal endometriotic lesions from fragments of basal endometrium is in fact a process of transplantation and reflects to a certain extent Sampson's view of the disease development [2].

Although there is a significant increase of fragments of basal endometrium in the menstrual blood effluent in women with endometriosis in comparison with controls [24], it cannot be expected that in affected women at the end of each cycle a dissemination of endometrial fragments within the peritoneal cavity takes place. Recently, it could be shown that the reflux of red blood cells is increased but there was no difference found with respect to endometrial cells in women with endometriosis and controls [79]. The concentration of OTRs within the neometra is highest at the end of the luteal phase and there is an increasing gradient of these receptors in a longitudinal direction with the highest density in the fundal region [32, 80]. The decrease of progesterone at the end of the cycle results in fundo-cervical contractions [30] (Figure 4) that might at the same time occlude the transmural part of the tubes to a certain degree allowing only the reflux of small cellular elements. Some of the relatively large fragments of basal endometrium observed in the menstrual effluent [24] might be retained in the uterine cavity and eventually transported into the peritoneal cavity in a later phase of the cycle when retrograde transport is increased in combination with a relaxation of the tone of the neometra. In fact, the finding of endometrial tissue in the tubes of women with endometriosis was highest during the luteal phase [81]. It has probably to be envisaged that retrograde transport of whole tissue fragments constitutes a more or less accidental event rather than a continuous cyclic phenomenon in women with endometriosis. In the extreme, one event might suffice to result in peritoneal endometriosis as shown in experimental endometriosis. In a cycle with follicular persistency, for example with strong breakthrough bleeding, maximal retrograde transport and little neometral muscular tone such an event is likely to happen.

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 sites of injury and with the ensuing hyperperistalsis following paracrine estrogen effects this inflammatory process of TIAR is reinforced and perpetuated resulting in the proliferation of stromal fibroblasts with
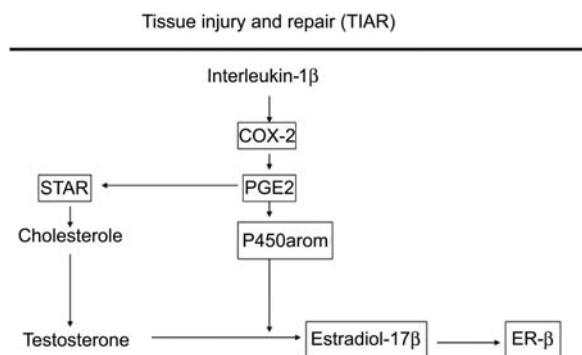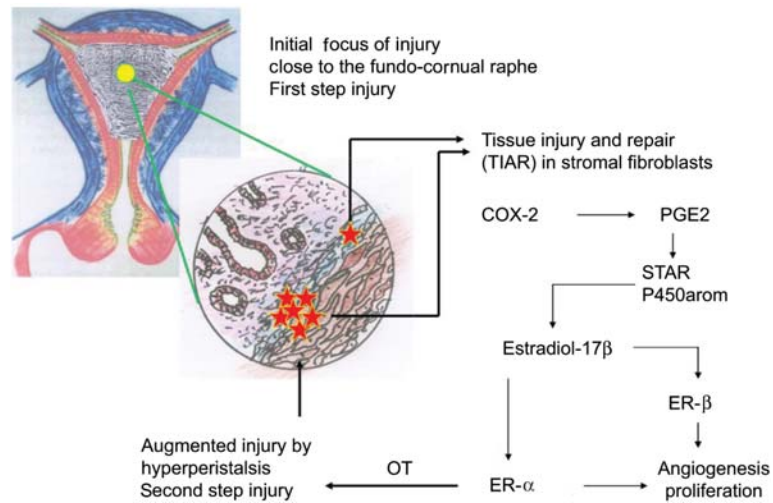
**Figure 11**  Model of 'tissue injury and repair' (TIAR) at the level of the endometrial-myometrial interface at the fundo-cornual raphe. The mechanisms of first- and second-step injury are depicted. Persistent uterine peristaltic activity and hyperperistalsis are responsible for perpetuation of injury with permanently increased paracrine estrogen action. (From Leyendecker et al. Arch Gynecol Obstet 2009;280:529–38, with permission [9].)

the inherent potential of smooth muscle metaplasia. Therefore, adenomyotic lesions, in contrast to superficial endometriotic lesions, display a more fibromuscular character. Whilst 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 (Figure 12).

## Premenarcheal endometriosis

Pelvic endometriosis has also been described rarely in adolescent girls prior to menarche, and coelomic metaplasia has been suggested as the underlying mechanism [82]. However, it has to be taken into consideration that with the progression of puberty there is an increasing nocturnal hypothalamic-pituitary activity with secretory bursts of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [83]. Such as in low-grade hypothalamic amenorrhea, large antral follicles are observed in the ovaries of premenarcheal girls that, fol-
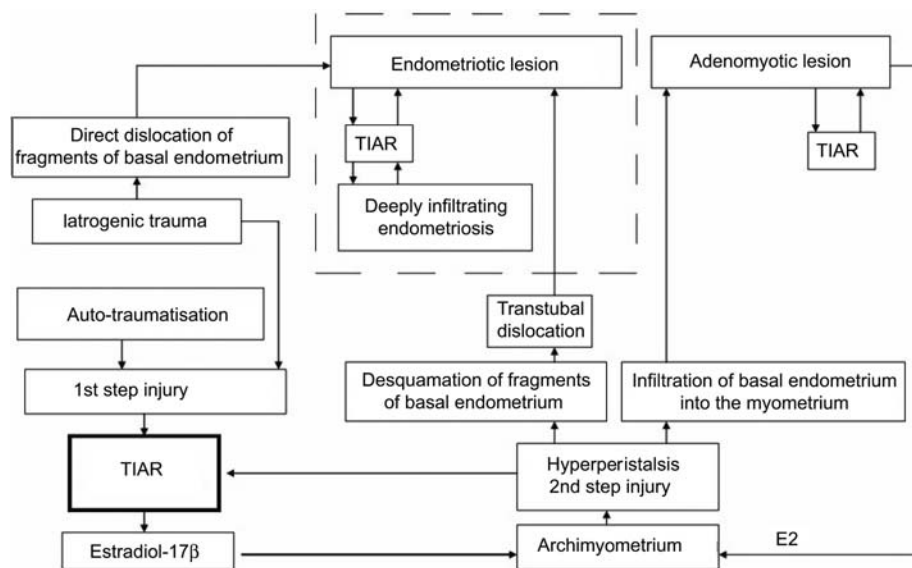


**Figure 12**  Model of the pathophysiology of endometriosis and adenomyosis. Tissue injury in the depth of the endometrium and activation of the 'tissue injury and repair' (TIAR) system constitute the primum movens in the disease development. This pertains to spontaneously developing endometriosis/adenomyosis as well as to that induced by iatrogenic trauma. The dashed rectangle depicts the extra uterine sites of the disease process. (From Leyendecker et al. Arch Gynecol Obstet 2009;280:529–38, with permission [9].)

lowing the nocturnal gonadotropic stimulation, intermittently secrete estradiol during the morning hours that presumably in turn stimulates uterine peristalsis [83–86]. 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 [2] should be more precisely defined. It is not the menstruation per se but rather the fact that the basal endometrium is, following detachment of the functionalis, maximally exposed. This facilitates, in the presence of hyperperistalsis, both the detachment of fragments of basal endometrium and, possibly, their upward transport [24, 29].

### Iatrogenic injury

Iatrogenic traumata to the uterus are considered to increase the risk for the development of endometriosis and adenomyosis [87]. A history of hysterotomy in colonised rhesus monkeys showed a significant association with the later development of endometriosis in these animals [76]. 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 (Figure 12). The rapidly increasing local estrogen levels during the process of healing interfere with ovarian control over uterine peristaltic activity leading rapidly to second-step injury with ensuing autotraumatisation 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 upregulated [56]. Surprisingly, *Cyr61* started to be upregulated also in the eutopic endometrium of these primarily healthy animals. Most probably, activation of *Cyr61* in the eutopic endometrium resulted from 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.

### 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. Whilst this has been convincingly shown for peritoneal lesions, data regarding the eutopic endometrium of women with endometriosis are unequivocal in this respect.

**The ectopic lesions** Fragments of basal endometrium constitute injured tissue. Expression of acute and inflammatory cytokines such as IL-1β and IL-6 and also IL-8 [74, 88] facilitate implantation. As autotransplants, however, the fragments should implant without inflammatory sequelae. The endometriotic lesions are, however, as the eutopic endometrium, subjected to cyclic endocrine stimuli and immunological phenomena but devoid of the potential of desquamation and externalisation 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 also demonstrated a dramatic upregulation of the ER [24].

Superficial lesions usually display the glandular character of the parent tissue and are surrounded by muscular fibers [24, 89] that result from the inherent potential of the basal mesenchym to form muscular tissue [24]. They have therefore been described as 'micro uteri' or 'micro archimetras' [24]. The unfavourable environment, however, in most cases does 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 basal layer of the eutopic endometrium [24].

In superficial lesions this chronic inflammatory process might calm down and healing might be possible [90]. Deeply infiltrating lesions develop at sites that are in addition subjected to chronic mechanical irritation such as the rectosigmoid fixed to the pelvic wall or uterus, the sacrouterine ligaments, the urinary bladder, ovaries fixed to the pelvic wall, the rectovaginal 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 [31]. These are in fact the extrauterine sites of adenomyoma described by Cullen [7]. The peristromal fibromuscular tissue of endometriotic lesions is homologous to the respective tissue within the archimetra [24] 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 [91]. Deeply infiltrating lesions tend to persist, whilst superficial lesions might heal. That is why long-lasting endometriosis usually presents with deeply infiltrating lesions [90] and also uterine adenomyosis [31, 37, 38] (Figure 13).

**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 [48].

With respect to the molecular biology of the eutopic endometrium in endometriosis, it has to be taken into consider-
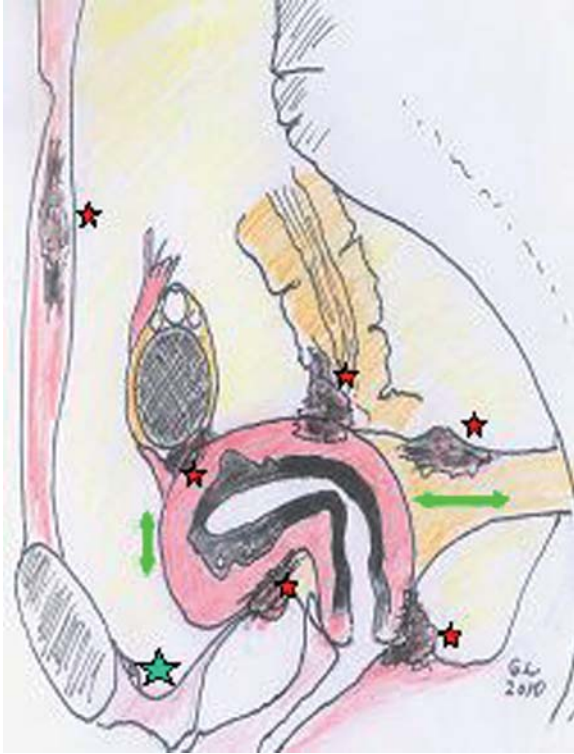
**Figure 13** This is a schematic demonstration of the sites of the development of deeply infiltrating adenomyosis (red asterix). These sites are characterized by chronic mechanical strain and correspond with the locations of adenomyoma as described by Cullen [7]. The superficial lesion (green asterix) is not subjected to mechanical strain.

ation that the endometrium is composed morphologically and functionally of at least two distinct layers, the basalis and the functionalis layers [24, 92–94]. This is not sufficiently taken into account when studies on molecular biology are performed with material taken from more or less random endometrial biopsies [48, 49, 54, 95]. The basal endometrium in women with endometriosis is twice as thick as in healthy women [24, 26]. Moreover, while in healthy women the endometrial-myometrial lining is smooth and regular, it is irregular and sometimes polypoid in affected women [24, 96]. Endometrial biopsies taken from women with endometriosis might, therefore, to a variable and unknown extent, be 'contaminated' with basal endometrium. Because endometrial biopsies are, for obvious anatomical reasons, mostly taken from the midline of the anterior and posterior walls of the uterine cavity, they may even contain basal endometrial stroma and fibroblasts of the fundo-cornual region that are altered by the TIAR process. Thus, changes in the molecular biology observed in these biopsies, such as progesterone resistance or 'attenuated progesterone response' [48, 97, 98] and impaired estradiol metabolism, might not be representative of the whole endometrium in women with endometriosis [48, 95].

Using immunohistochemistry of ERα and PR, no progesterone resistance could be observed in the late secretory phase of the functional endometrial epithelium and stroma 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 [24]. The latter findings suggest a differential regulation of PRs as well as ERs in the functional and basal endometrium and also in the endometriotic lesions as they are derived from implanted basal fragments. Full equipment of the basal endometrium with ERs and also PRs at the end of the luteal phase allows both in healthy and affected women the prompt proliferative response of the endometrium to rising estradiol levels with the beginning of the follicular phase. Moreover, earlier clinical studies with oocyte donation do not support a generally impeded implantation in women with endometriosis [99] as has been suggested earlier.

In a stricter sense, however, 'progesterone resistance' or 'attenuated progesterone response' was defined by some authors as a reduced response of the stromal fibroblast to differentiate into decidual cells with a parallel reduced expression of decidual molecular markers such as prolactin (PRL) and insulin-like growth factor binding protein 1 (IGFBP-1) [48, 97, 98, 100]. In fact, in endometrial biopsies of women with endometriosis the expression of decidual markers such as PRL and IGFBG-1 in stromal fibroblasts is reduced concomitant with a defective morphological differentiation into epithelioid-like, secretory decidual cells. As delineated above, in endometriosis, close to the fundo-cornual raphe, stromal fibroblasts are subjected to the TIAR process thereby undergoing dramatic biochemical changes that enable them to produce estradiol de novo and to proliferate in response to chronic strain. This re-programming might at the same time impede their physiological potential to change completely into decidual cells in response to progesterone. In 'attenuated progesterone response' the stromal fibroblasts enter the process of decidualisation but retain to a certain degree the expression of α-smooth muscle actin (SMA) and their contractility [101].

With respect to the expression of 17β hydroxysteroid dehydrogenase (17βHSD) type 2 in the endometrium of women with endometriosis, no data are available that distinguish between functionalis and basalis as well as basal endometrial tissue in the vicinity of the fundo-cornual raphe subjected to the chronic TIAR process [102].

## Nerve fibers in the disease process

The recent finding of nerve fibers in ectopic lesions and also in the eutopic endometrium has prompted some to postulate a mechanism of 'neuromodulation' in the disease process. Initially, it was assumed that the lesions would grow in the direction of adjacent nerve fibers [103]. Recent studies, however, suggest that it is the inflammatory process itself that induces the sprouting of sensory nerve fibers into the ectopic lesions as well as into the endometrium of affected women [104–108]. They regress following gestagen administration [109]. The sprouting of nerve fibers and their regression following healing is also observed in other inflammatory processes such as in tendovaginitis [110]. It therefore appears that the sprouting of nerve fibers is not specific to endo-

metriosis but is rather an integral part of TIAR processes. There is no doubt that the sensory nerve fibers in endometriotic lesions and in the endometrium of affected women, as in other inflammatory processes, transmit the pain associated with the disease. In animal experiments it was shown that denervation impedes healing. Thus, physiologically, the sprouting of nerve fibers apparently subserves tissue reconstruction in addition to nociception [111, 112].

### The aryl hydrocarbon (AhR)-CYP1A1 system

There is no doubt that the TIAR process with the production of estradiol and the subsequent synthesis of growth factors and other regulatory proteins has to be tightly controlled in order to result in a physiological process of healing. The AhR-CYP1A1 system, an evolutionary old and well preserved system [113, 114], could be operative in this respect. It is encountered in a plethora of physiological processes and is observed to be upregulated under various pathological conditions associated with inflammation and proliferation [115–120]. AhR acts as a ligand-activated transcription factor and exhibits a strong binding of dioxin [tetrachlorodibenzodioxin (TCDD)] and other xenobiotics. The AhR-CYP1A1 system has been shown to be upregulated in ectopic and eutopic endometrium of women with endometriosis. In view of the strong TCDD-AhR binding, the AhR-CYP1A1 system is therefore mostly discussed whether or not xenobiotics such as dioxin (TCDD) may stimulate the development of endometriosis [121–124].

With respect to the TIAR concept, it is of interest to note that mechanical stress (fluid shear stress) to vascular endothelium rapidly resulted in the expression of COX-2 and CYP1A1 [125, 126]. On the basis of the data reviewed before, we assume that the rapid expression of CYP1A1 [125] in response to shear stress is preceded by activation of the TIAR system with the production of $PGE_2$ [125] and estradiol. Eicosanoids and steroids are, among other substances, considered endogenous ligands of the constitutive AhR [119]. It is therefore reasonable to assume that the AhR-CYP1A1 system is, possibly also by means of cross-talk between the AhR and ERs [120], involved in the regulation of homeostasis within TIAR processes. The significance of this system with respect to endometriosis needs to be explored in further studies.

### Conclusions

As shown in this review, a detailed consideration of the functional architecture of the non-pregnant uterus, in particular of the archimetra, its endocrine regulation, the biological significance of the mechanism of TIAR as well as the sites of possible unphysiological mechanical strain within the structure of the archimetra are of outmost importance for a better understanding of the pathophysiology and, by inference, for treatment of endometriosis and adenomyosis. In conclusion, endometriosis, deeply infiltrating endometriosis and uterine adenomyosis share a common pathophysiology and result from localised uterine trauma and from the subsequent inter-action of two primarily independent physiological processes, both involving the regulatory functions of estradiol: (A) the ovarian endocrine system that is under the control by the hypothalamic-pituitary axis; and (B) a non-organ specific paracrine system, which is locally activated in processes of tissue injury and wound healing. We coined the acronym TIAR (tissue injury and repair) to describe this fundamental and apparently ubiquitous biological system. In various mesenchymal tissues, following tissue injury this mechanism is rapidly activated and results in the local production of estradiol and the involvement of ERβ. Furthermore, it appears that many of the altered endometrial molecular markers and phenomena described in the context of endometriosis, such as the expression of growth factors and other proteins, are the consequences of the chronic TIAR process rather than the cause(s) of the disease.

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