Best Practice & Research Clinical Obstetrics and Gynaecology
Vol. xx, No. xxx, pp. 1–24, xxxx
doi:10.1016/j.bpobgyn.2006.01.008
available online at http://www.sciencedirect.com

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Adenomyosis and reproduction

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Evidence has been provided that pelvic endometriosis is significantly associated with uterine adenomyosis and that the latter constitutes the major factor of infertility in such conditions. Furthermore, it has become evident that both adenomyosis and endometriosis constitute a pathophysiological and nosological entity. Mild peritoneal endometriosis of the fertile woman and premenopausal adenomyosis of the parous and non-parous woman, as well as adenomyosis in association with endometriosis of the infertile woman, constitute a pathophysiological continuum that is characterized by the dislocation of basal endometrium. Due to the postponement of childbearing late into the period of reproduction, premenopausal adenomyosis might increasingly become a factor for infertility in addition to adenomyosis associated with endometriosis of younger women. In any event, the presence or absence of uterine adenomyosis should be examined in a sterility work-up.

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Key words: adenomyosis; endometriosis; dislocation of basal endometrium; uterine peristalsis; directed sperm transport; uterine dysperistalsis; hyperperistalsis; uterine auto-traumatization; archimetra; endometrial oestrogens.

Adenomyosis results from the invasion of basal endometrial glands and basal endometrial stroma into the underlying myometrium. The surrounding myometrium results from stromal metaplasia forming peristromal muscular tissue that is homologous to the archimyometrium.[1,2] Adenomyosis is generally considered a uterine pathology of premenopausal women. It does, however, also present in younger women, and in such cases is associated — more often than the premenopausal variety — with pelvic endometriosis.[3–6] Because premenopausal adenomyosis and the variants in younger women with and without endometriosis do not differ from each other with respect to sites of predilection within the uterine wall, gross anatomical shape and histology,[6] a similar pathophysiology may be assumed.

Recently, it became evident that adenomyosis is an important factor in infertility. This has been shown in infertile women with endometriosis and in baboons with life-long infertility.[6,7] Because of the change in the pattern of reproductive behaviour during recent decades, with the postponement of childbearing towards the end of the reproductive period of life, premenopausal adenomyosis — in addition to that associated with endometriosis — may increasingly become a factor causing infertility. Thus, adenomyosis in general should become a concern in reproductive medicine, rendering its diagnosis or exclusion mandatory in a sterility work-up.

HISTORICAL REMARKS

The association of endometriosis with adenomyosis and vice versa has often been discussed in the literature.[8,9] 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.[3,10–12] Also Sampson, who introduced the term 'endometriosis', described 'primary endometriosis' as the uterine variant of the disease.[13] His scientific interest, however, was directed towards the development of the peritoneal variety. This and his view that uterine adenomyosis resulted 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.[8] In fact, it was his theory that laid the basis for considering uterine adenomyosis and external endometriosis as different disease entities.[14] This was later reinforced by the fact that endometriosis was mostly diagnosed by laparoscopy in a sterility work-up, and the uterus evades histological examination for obvious reasons in such cases. Pelvic endometriosis became a topic of research, while the clinical and scientific interest in uterine adenomyosis almost completely vanished.

UTERINE TRAUMA AS A RISK FACTOR FOR THE DEVELOPMENT OF ADENOMYOSIS

Counseller had already suggested that trauma could induce the development of 'endometriosis', a term that he used for both the extra- and intrauterine variants of the disease.[3] In a study that aimed to demonstrate a genetic background for the development of endometriosis, a history of hysterotomy showed a significant association with the development of the lesions in colonized rhesus monkeys.[15] Particularly with respect

to uterine adenomyosis, it was frequently demonstrated that the risk of developing adenomyosis is dramatically increased in parous women as well as following abortion, curettage and other uterine surgical procedures.[16–19]

A considerable number of non-parous women without a history of iatrogenic uterine trauma, however, do also develop uterine adenomyosis.[6] A new understanding of the pathophysiology of such cases became possible when cyclic peristaltic activity of the non-pregnant uterus was discovered.[20–22] It was, however, chiefly the aspect of retrograde utero-tubal transport of this function that suggested, in view of Sampson's theory, an association with the development of endometriosis.[23,24] When the peristaltic activity was studied in more detail,[22,25–29] it became evident that continuous cyclic uterine peristaltic activity throughout the whole period of reproductive life could constitute a chronic trauma to the uterus responsible for the development of both endometriosis and adenomyosis.[2,5,6,30]

In this article an attempt will be made to delineate and discuss the association of adenomyosis with reproduction from both pathophysiological and clinical points of view. It will become apparent that a discussion on the development of uterine adenomyosis is not possible without frequent reference to pelvic endometriosis. This requires, first of all, a review of the data on peristaltic activity of the non-pregnant uterus. Evidence will be summarized that uterine peristalsis and its dysfunction constitute very early steps in the events that finally lead to pelvic endometriosis and uterine adenomyosis. Moreover, it will be shown that pelvic endometriosis of the fertile woman, endometriosis/adenomyosis of the infertile woman, and premenopausal adenomyosis constitute a pathophysiological continuum that is characterized by the dislocation of basal endometrium and can, therefore, be considered as a syndrome of dislocated basal endometrium (SDBE) with bleeding disorders, pain and infertility as the symptoms of the severest forms. Finally, the impact of adenomyosis on fertility will be discussed.

THE PERISTALTIC ACTIVITY OF THE NON-PREGNANT UTERUS

Rhythmic contractions of the non-pregnant uterus as well as rapid sperm transport within minutes from the vagina to the Fallopian tubes have long been recognized in many species, including man. Since the velocity of spermatozoal movement could not account for covering such a long distance through the female genital tract within a few minutes, rapid sperm transport was considered a passive phenomenon and had been ascribed to uterine contractile activity. Recently, the availability of videosonography of uterine peristalsis (VSUP)[20–22] and hysterosalpingoscintigraphy (HSSG)[22,31] using technetium-labelled albumin macrospheres of spermatozoal size made it possible to study uterine peristaltic activity and utero-tubal transport in vivo without stress and injury.

Characterization of uterine peristaltic activity

Three major types of contractions may be distinguished from each other (Figure 1). Cervico-fundal contractions (type A), fundo-cervical contractions (type B), and isthmical contractions (type C). While contractions of type A and B travel as peristaltic waves over the whole distance from the cervix to the fundal region and from the fundus to the cervical region, respectively, isthmical peristaltic waves (type C) only extend from the uterine isthmus to the lower mid-corporal region.[32]

In general, cervico-fundal contraction waves (type A) prevail during the follicular as well as the luteal phase of the cycle (Figure 1). The frequency of these contractions is

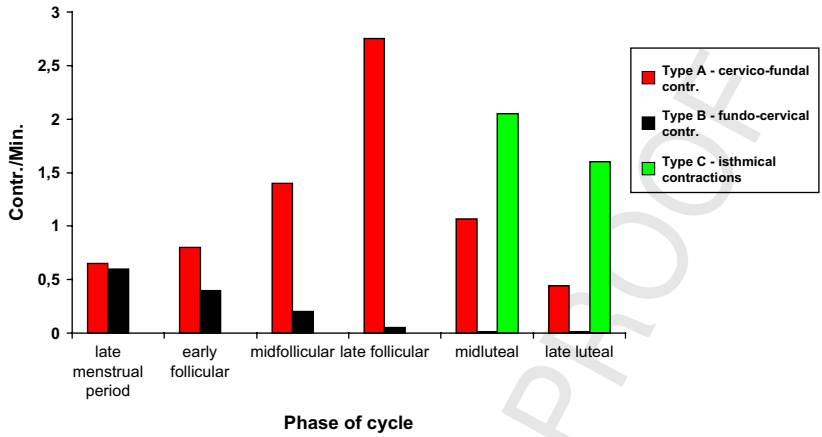

Figure 1. Histogram demonstrating the frequency of the uterine peristaltic waves during menstruation, the early-, mid- and late follicular and mid- and late-luteal phases of the cycle, respectively, as obtained from video sonography of uterine peristalsis in healthy women. The relative distribution of cervico-fundal (type A) versus fundo-cervical (type B) and isthmical (type C) contractions is also shown. The graph clearly demonstrates the increase in the frequency of type A contractions with the progression of the follicular phase, reaching a maximum during the late follicular phase, and the decrease during the luteal phase of the cycles, respectively. 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 isthmical or lower corporal part of the uterus, rendering the fundo-cornual part of the uterus a zone of relative peristaltic quiescence during the period of embryo implantation.

low during the late menstrual period and increases gradually during the proliferative phase, with a maximum frequency during the preovulatory phase. In parallel, type B contraction waves (fundo-cervical peristalsis) decrease progressively during the late menstrual period and almost completely disappear at mid-cycle. Thus, practically all peristaltic activity around ovulation is cervico-fundal in character.

During the luteal phase uterine peristaltic activity is composed of type A and type C contraction waves. The frequencies of type A and type C, respectively, decrease from the mid- to the late-luteal phase. This renders the fundal part of the uterus a region of relative peristaltic quiescence (Figure1).

The morphological basis of uterine peristalsis

Videosonography reveals that the uterine peristaltic waves are confined to the subendometrial myometrium. Anatomically, this is the *stratum subvasculare* of the myometrium or *archimyometrium* and is characterized by a predominantly circular arrangement of the muscular fibres. The other two layers of the myometrium are the *stratum supravasculare*, with a predominantly longitudinal arrangement of the muscular fibres, and the *stratum vasculare* as the middle layer, composed of a three-dimensional mesh of short muscular bundles that constitute the bulk of the human myometrium.[29,33]

The archimyometrium is the muscular component of the archimetra, of which the others are the epithelial and stromal endometrium.[28,29,33,34] It 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. In high-resolution sonography and MRI the

archimyometrium can be visualized 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 2).[4]

Unlike the two outer layers of the myometrium that develop late during ontogeny and are therefore termed neomyometrium, the anlage of the archimyometrium can already be identified during the first trimester of gestation (hence its denomination).[33,28,33] Circular mesenchymal layers surround the fused paramesonephric ducts and develop into muscular fibres during mid-gestation. The ontogenetically early formation of the archimyometrium is pertinent to its function and is in particular recognized by a kind of a fundo-cornual raphe that results from the fusion of the two paramesonephric ducts and their mesenchymal elements to form the primordial uterus.[30,33] The 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 3).[34]

Endocrine control of uterine peristalsis

Uterine peristaltic activity is controlled by the rising tide of oestradiol and progesterone secreted from the dominant ovarian structures, the preovulatory follicle and the corpus luteum that corresponds to the cyclically changing oestradiol and progesterone receptor expression in the archimetrial layers.[25,29] In agonadal women the cyclic pattern of uterine peristalsis can be completely mimicked by the sequential administration of oestradiol and oestradiol plus progesterone simulating the respective peripheral blood levels. Within certain limits, there is a dose–response relationship between the blood levels of these steroids and the frequency of the peristaltic contractions.[25]

Although the cellular, autocrine and paracrine mechanisms within the archimetra that control uterine peristalsis and are modulated by ovarian oestradiol and progesterone remain to be elucidated, there is circumstantial evidence that oxytocin constitutes one of the components of the stimulatory cascade since bolus injections of oxytocin increase the frequency of cervico-fundal contractions during the follicular phases of the cycle and enhance directed sperm transport.[25,31] Endogenous oxytocin that is operative in this respect is probably not of hypothalamic origin but rather synthesized locally by endometrial cells. Oxytocin receptors have been identified in the human and rat endometrium.[35]

Functions of uterine peristalsis

Directed sperm transport

It has been shown using dynamic HSSG that changes in utero-tubal flow velocity occur at the same frequency as the peristaltic contractions.[36] It is therefore reasonable to assume that the uterine peristaltic activity with cervico-fundal contraction waves provides the forces that are required for the transport of spermatozoa from the external os of the cervix into the tubes within minutes. According to the data obtained by applying hysterosalpingoscintigraphy with labelled albumin macrospheres of sperm size, the following concept of the dynamics of rapid sperm ascension within the female genital tract could be developed.[22] Rapid sperm ascent occurs immediately following deposition of the ejaculate at the external os of the cervix. As early as 1 minute thereafter spermatozoa have reached the intramural and isthmical part of the tube.

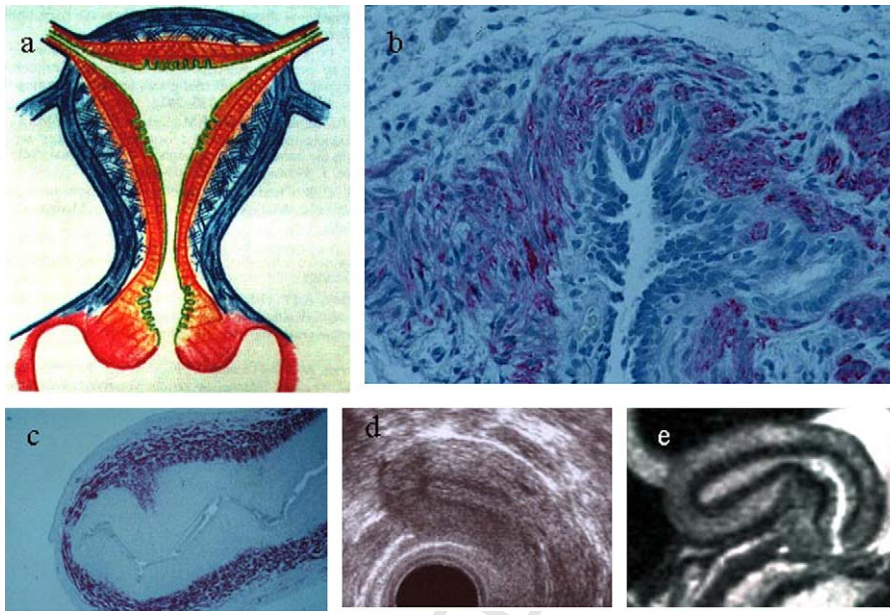

Figure 2. (a) A schematic representation of the endometrial–subendometrial unit ('archimetra') within the human uterus based on immunocytochemical results and morphological and ontogenetic data, respectively. The endometrial–subendometrial unit is composed of the glandular (green), the stromal part of the endometrium, and the stratum subvasculare of the myometrium, with predominantly circular muscular fibres (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 fibres. The stratum vasculare is phylogenetically the 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 fibres 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 muscle fibres, which progressively diminish in caudal direction, and the accompanying connective tissue blend with vaginal tissue elements (red) to form the vaginal portion of the cervix. (b) A peritoneal endometriotic lesion (×400) as an ectopic 'microarchimetra'. With endometrial glands, endometrial stroma and peristromal muscular tissue the lesion is composed of all the 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 endometrium and archimyometrium (specific actin staining) (top right). The archimetra is essentially the adult representation of the primordial uterus. (d) The 'halo' in transvaginal sonography represents the archimyometrium, as does (e) the 'junctional zone' in MR imaging. Modified from Leyendecker et al (2004, *Annals of the New York Academy of Sciences* **1034:** 338–355) with permission.

Quantitatively, however, the extent of ascent increases with the progression of the follicular phase. While only a few spermatozoa enter the uterine cavity, and even fewer the tubes, during the early follicular phase, the proportion of spermatozoa entering the uterine cavity increases dramatically during the mid-follicular phase, with still a limited entry into the tube. During the late follicular phase there is a considerable ascent of spermatozoa into the tubes.

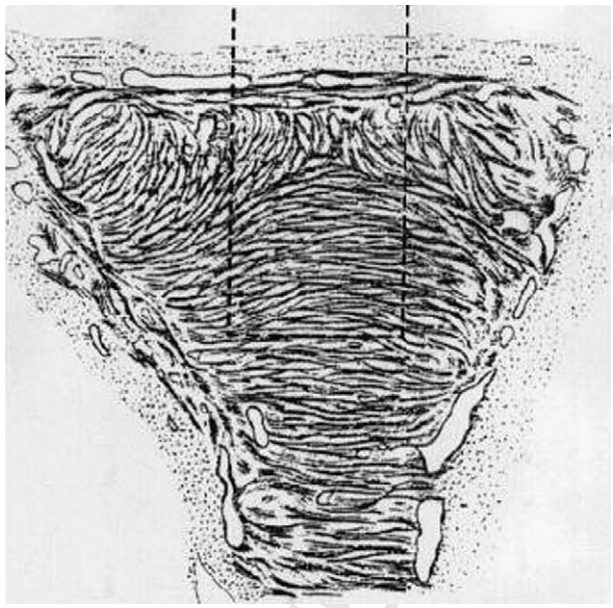

Figure 3. Modified original drawing from Werth and Grusdew[33] showing the architecture of the subendometrial myometrium (archimyometrium) in a human fetal uterus. The specific orientation of the circular fibers of the archimyometrium results from the fusion of the two paramesonephric ducts forming a 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. By the time muscular distensions at the fundo-cornual raphe result in the formation of gaps that results in endometrial proliferation into these dehiscencies. Modified from Werth and Grusdew (1898, *Archiv für Gynäkologie* **55:** 325-409) with permission.

Furthermore, HSSG revealed the preferential direction of rapid sperm transport into the tube ipsilateral to the dominant follicle, which corresponds with findings during surgery that the number of sperm around ovulation was higher in the tube ipsilateral to the dominant follicle than on the other side.[22,37] This directed passive transport of sperm (macrospheres) into the 'dominant' tube constitutes a genuine uterine function and results from both the specific structure of the archimyometrium, with its fundo-cornual bipartition of the circular fibres, and the effects of the utero-ovarian counter-current system that provide a higher input of stimulatory signals from the ovary into the uterine cornual region ipsilateral to the dominant ovarian structure.[26,33]

Fundo-cornual implantation

The uterine peristaltic pump is significantly active also during the luteal phase of the cycle. The specific quality of the contractile activity, however, renders the fundo-cornual region a zone of relative peristaltic quiescence, presumably minimizing mechanical irritation of the process of implantation.[32] The contractions that reach the fundal part of the uterine cavity might ensure high fundal implantation of the embryo.

Retrograde menstruation

Towards the end of the luteal phase the number of oxytocin receptors increases within the neometral myometrium, with highest expression in its fundal part.[38] The discharge of menstrual debris might be facilitated by contractions of the neometra induced by the activation of these receptors by endometrial oxytocin.[35] Anterograde menstruation may be further supported by archimyometrial fundo-cervical peristaltic contractions that decrease with the progression of the early follicular phase.

Retrograde menstruation has been observed in menstruating women with patent tubes and may be caused by the increased uterine tone during menstruation and also by cervico-fundal peristalsis that is already present during the menstrual period and increases further during the early follicular phase.[39,27] Because cervico-fundal peristalsis constitutes a potential risk of infection of the genital tract, and sperm transport that early during the proliferative phase is unlikely to result in pregnancy, retrograde menstruation must provide a significant evolutionary benefit.[40] It had been suggested that cervico-fundal contractions increasing in number with the progression of the menstrual period enable, by retrograde menstruation, the preservation of iron content of the body.[41] This might be of particular importance in cases of juvenile dysfunctional bleeding with persistent follicles and high endogenous oestradiol levels that stimulate the uterine peristaltic pump.

Auto-traumatization of the uterus and dislocation of basal endometrium to intra- and extra-uterine sites

Hyperperistalsis

Women with endometriosis show a significant increase in uterine peristaltic activity in comparison to women free of disease (Figure 4).[27,41] During the early- and mid-follicular phases of the cycle the frequency of the peristaltic waves is doubled in comparison to normal.[27] The cyclical pattern of peristaltic activity in women with endometriosis is similar to that obtained in normal women with high endogenous oestrogen levels during controlled ovarian hyperstimulation and with intravenous bolus injections of oxytocin.[28] At mid-cycle, in women with endometriosis, the peristaltic activity becomes dysperistaltic. The regular contractions are replaced by a more convulsive uterine activity.[27] Moreover, in women with endometriosis the intrauterine pressure is increased in comparison to women without the disease.[42,43]

This change in the contractile activity of the uterus in women with endometriosis has a profound effect on the uterine retrograde transport capacity. In HSSG the transport of labelled inert particles is dramatically increased during the early- and mid-follicular phases of the cycle. Within a few minutes the particles are transported into the tubes and even into the peritoneal cavity, demonstrating the enormous power of the peristaltic pump. Directed transport of the particles into the tube ipsilateral to the dominant follicle, however, is absent in the periovulatory phase. With respect to the fundamental mechanisms in the early processes of reproduction, these findings allow the conclusion that in women with endometriosis directed sperm transport is severely impaired.[27] Astonishingly, this aspect is not recognized as a possible mechanism of subfertility in women with endometriosis and patent tubes.[44] In any event, hyperperistalsis with increased intrauterine pressure constitutes a considerable auto-traumatization of the uterus (Figure 5).

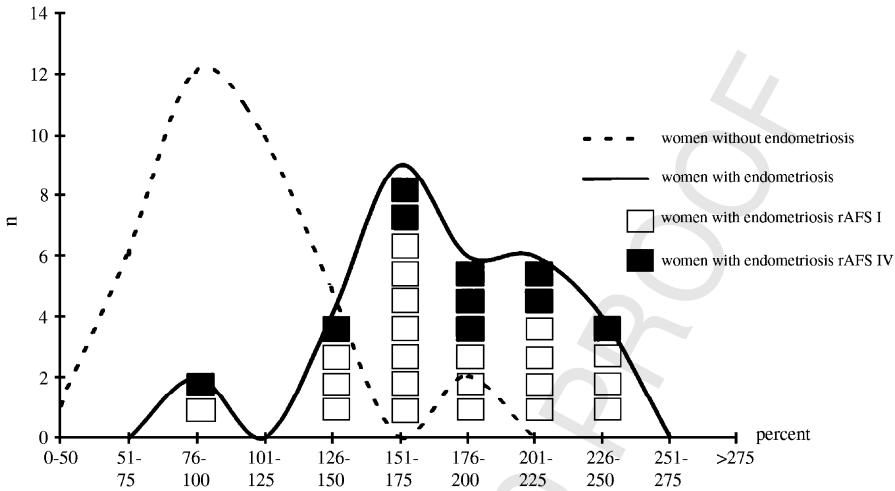

Figure 4. The distribution pattern of uterine peristalsis with respect to the absence (dotted line; n = 36) or presence (solid line; n = 31) of endometriosis. Data from the mid-follicular and the mid-luteal phases of the cycle, respectively, were used. The peristaltic frequency was normalized to the mean frequency in women without endometriosis as 100%. In women with endometriosis the grade according to the revised American Society for Reproductive Medicine (AFS) classification is indicated in addition. From Leyendecker et al (1996, *Human Reproduction* **11:** 1542–1551) with permission.

Dislocation of basal endometrium

Hyperperistalsis that is already present during the menstrual period of the cycle in women with endometriosis abrades fragments of basal endometrium, which is not the normal case. Immunohistochemical studies revealed that immunostaining for the oestradiol receptor (ER), progesterone (PR) receptor, and P450 aromatase (P450A) becomes negative in all of the functionalis and spongiosa but not in the basalis towards the end of the cycle. This discrepancy of the immunostaining between basalis and functionalis at the end of the cycle was utilized to identify endometrial fragments of the basalis and the functionalis, respectively, in menstrual blood. It could be shown that in 80% of women with endometriosis, and in only 10% of women without endometriosis, fragments of basal endometrium could be detected in the respective menstrual blood specimen ($P < 0.05$).[2]

It is reasonable to assume that it is the retrograde transport of fragments of basalis rather than of functionalis that lead to pelvic endometriosis. Currently there is no direct proof available for this assumption. Evidence, however, may be derived from the fact that at the end of the cycle the basal layer of the endometrium constitutes a very active tissue with an increasing mitotic rate and increasing expression of ER and PR, both in the epithelium and stroma, and with the persistent expression of P450 aromatase, while the functionalis is destined for cell death. Moreover, all endometriotic lesions form peristromal muscular tissue. The potential to form Müllerian muscular tissue fibres by stromal metaplasia, however, is – during ontogeny and during the menstrual cycle – confined to the basal stroma.[2,33,45,46]

Immunostaining of the whole uterine wall for ER, PR and P450 showed no differences in the cyclical immunoreactive scores (IRS) for the different uterine layers,

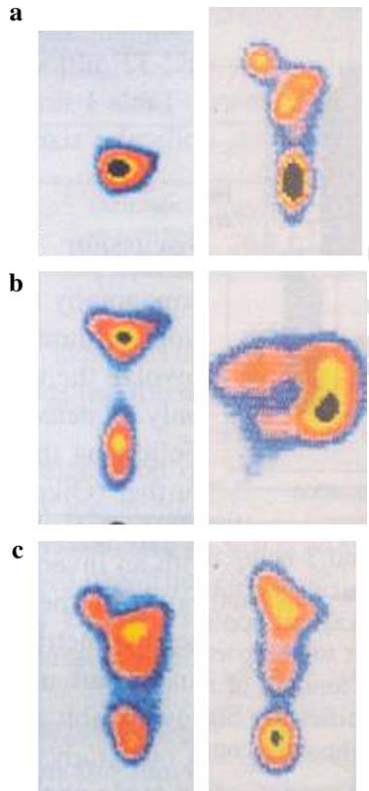

Figure 5. Representative scans obtained from hysterosalpingoscintigraphy in women without (left panel) and with (right panel) endometriosis 32 minutes after application of technetium-labelled macrospheres of sperm size in the posterior fornix of the vagina in six different women in (a) the early follicular, (b) the mid-follicular, and (c) late follicular phases, respectively, 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 ascent of the particles into the uterine cavity, and sometimes a trend of ascent into the tube ispsilateral to the dominant follicle (left panel b). In women with endometriosis the ascension dramatically increased 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 preovulatory phase of healthy women the particles are rapidly transported into the 'dominant' tube (left panel c), while, due 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 auto-traumatization of the uterus. Modified from Leyendecker et al (1996, *Human Reproduction* **11:** 1542–1551) with permission.

including the basalis, in women with and without endometriosis. However, it was observed that the basal endometrium was significantly thicker in women with endometriosis than in those without the disease (0.8 mm versus 0.4 mm) (Figure 5).[2]

Parallel development of adenomyosis

During the studies on uterine peristalsis in women with and without endometriosis, significant structural abnormalities of the uterine wall became apparent in women with endometriosis. As judged from the data of transvaginal sonography (TVS) and MRI, respectively, there was a significant association between uterine adenomyosis and peritoneal endometriosis (Figure 6).[4] In a more recent extended study with MRI scans of the uterus in 227 infertile patients or couples, respectively, including 160 women with endometriosis and 67 controls, these results could be confirmed. The posterior junctional zone (JZ) was significantly thicker in women with endometriosis (11.5 mm) than in the controls (8.5 mm). On the basis of a 'healthy control' group that was defined as the patients younger than 37 years without endometriosis, with an infertile partner and a maximum diameter of the posterior junctional zone of 10 mm, the prevalence of diffuse and focal adenomyosis in all patients with endometriosis was 79%, and reached 90% in those women younger than 36 years and with a fertile partner. In the 'total control' group of women without endometriosis, the prevalence of adenomyosis was 28% and in the 'healthy control' group only 9%.[6]

A unifying concept of the development of endometriosis and adenomyosis

The data presented above provide strong circumstantial evidence that endometriosis results from the transtubal dislocation and implantation of basal endometrium. Likewise, from a mere topographical point of view, it is evident that uterine adenomyosis results from the infiltration of basal endometrium into the underlying myometrium. Both endometriotic and adenomyotic lesions form peristromal muscular tissue that has, with respect to the ER and PR expression, the immunohistochemical characteristics of the archimyometrium. Both lesions with all their components — such as glandular and stromal endometrium and peristromal muscular tissue — mimic with respect to the cyclical pattern of the IRS of ER and PR expression the respective cyclical pattern of the basal endometrium and the archimyometrium. It was therefore suggested that dislocated fragments of basal endometrium have 'stem-cell potential', and when implanted on e.g. peritoneal surfaces, or when they infiltrate into the deeper myometrium, they resume their embryonal growth programme to form all components of the archimetra, including muscular tissue.[2] The ectopic endometrial lesions can therefore be considered as micro-primordial uteri or 'microarchimetras' (Figure 2b).

THE PATHOPHYSIOLOGY OF THE DEVELOPMENT OF ENDOMETRIOSIS AND ADENOMYOSIS

The basal endometrium as an endocrine gland: archimetral hyperoestrogenism

Uterine hyperperistalsis is one of the predominant uterine findings in endometriosis and associated adenomyosis. Since the extent of peristaltic activity is independent of the disease (Figure 4), it was suggested that hyperperistalsis constitutes the primary and endometriosis the secondary phenomenon.[27]

Hyperperistalsis can be induced by increased peripheral levels of oestradiol in blood. In women with endometriosis and hyperperistalsis, however, the mean

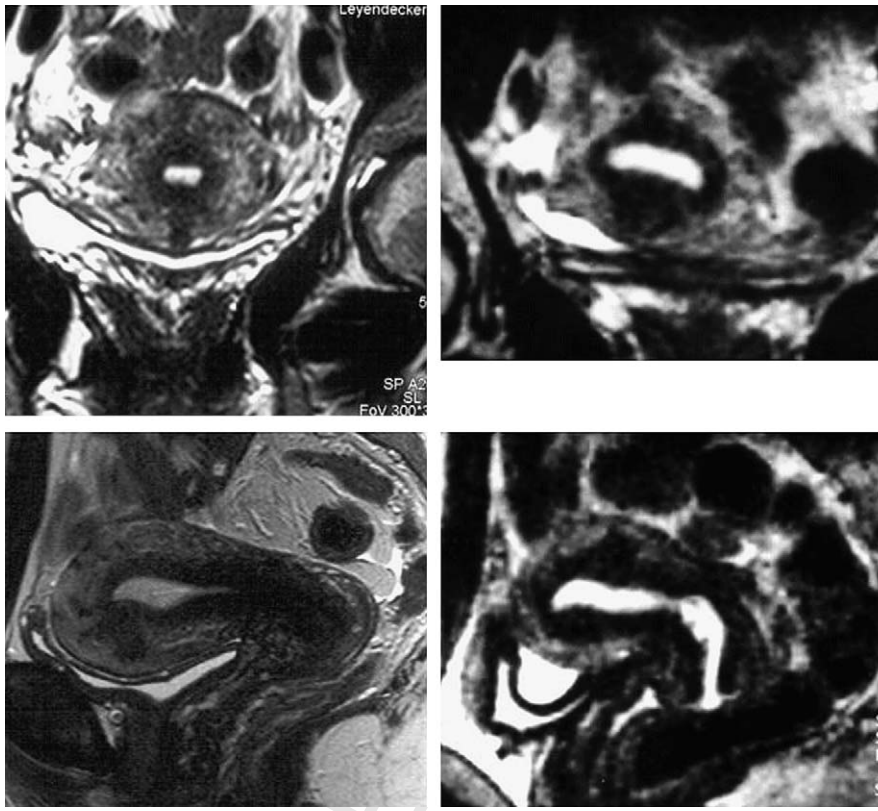

Figure 6. Transverse (top) and sagittal (bottom) MRI scans in two women with adenomyosis. Left panel: 40-year-old parous woman with secondary infertility. Focal adenomyosis was suspected by transvaginal sonography and verified by MRI. No laparoscopy was performed. Right panel: 30-year-old woman with primary infertility, grade IV endometriosis, and focal to diffuse adenomyosis. In both women the transverse scans show a preponderance of the development of adenomyosis in the uterine midline (fundo-cornual raphe).

peripheral oestradiol and also progesterone levels during the menstrual cycle did not differ from those without the disease.

Oestradiol inducing hyperperistalsis might come from the endometrium itself. By virtue of the expression of the P450 aromatase that also persists during the whole luteal phase within the basalis, the basal endometrium constitutes an endocrine gland that produces oestrogen from androgenic precursors.[2] In women with endometriosis and adenomyosis the concentration of oestradiol in menstrual blood was higher than in healthy women, while the respective peripheral levels were the same.[47] In a study applying micro-array technology an endometrial gene, Cyr61, was identified that is oestrogen-dependent and highly upregulated in endometria of women with endometriosis in comparison to controls and also in endometriotic lesions.[48] In our recent study the basalis, as measured during the luteal phase and distant from adenomyotic lesions, was twice as thick as the basal endometrium in healthy women, probably increasing dramatically the amount of oestrogen in the endometrium with its paracrine effects in the chain of events that result in

hyperperistalsis.[2] It remains to be shown whether there is an increased production of oestrogen in the basal endometrium per volume tissue of women with endometriosis in comparison to controls.

This concept of non-ovarian archimetrial hyperoestrogenism as one of the initial events in the development of endometriosis may be pertinent to the ongoing discussion of the role of environmental factors such as endocrine disruptors and food intake.[49–51] In the animal experiment dioxin increased the tubal peristaltic activity, and it was active via the oestrogen receptor.[52] In a study aiming at examining the hereditary component of endometriosis in colonized rhesus monkeys only a history of treatment with oestrogen patches (in addition to a history of trauma by hysterotomy) showed a significant association with endometriosis.[15] Taken together, our own data and data from the literature strongly suggest that the principal mechanism of endometriosis/adenomyosis is the paracrine interference of endometrial oestrogen with the cyclical endocrine control of archimyometrial peristalsis exerted by the ovary.

In Figure 7 an attempt is made to summarize our present concept of the development of endometriosis and adenomyosis, which is an extension of the concept proposed earlier.[28] The archimyometrium is stimulated by locally increased levels of oestradiol and by a cascade of events that may include the endometrial oxytocin and its receptor. The primary event or events that lead to an archimetral hyperoestrogenism are currently not known. The P450 aromatase system seems to play a fundamental role. The activation of the P450 aromatase and the increased local production of oestrogen appears to constitute a general principle in tissue repair.[53] Archimetral hyperoestrogenism results in uterine hyperperistalsis and increased uterine pressure.

In any event 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 fragments. By chance, these fragments might implant somewhere in the peritoneal cavity, with certain sites of predilection dependent on the pelvic topography. After the process of implantation spontaneous healing might be possible, but also proliferation and infiltrative growth, depending upon the proliferative potential of the seeded basal fragments. The pleiomorphic appearance of pelvic endometriosis is largely due to the long causal chain between the primary disturbance on the level of the archimetra and the eventually established individual endometriotic lesion.

In adenomyosis this chain of events is shortened. Hyperperistalsis and increased intrauterine pressure might result in myometrial dehiscencies that are infiltrated by basal endometrium with the secondary development of peristromal muscular tissue. Diffuse or focal adenomyosis of varying extent ensues. Adenomyotic foci are usually localized in the anterior and/or posterior walls, with preference for the posterior wall, and practically never in the lateral walls of the uterine corpus. Early lesions usually present close to the 'fundo-cornual raphe' of the archimyometrium (Figures 3 and 6), underlining the primarily mechanical or traumatic character of their development. With their muscular component, the adenomyotic lesions might contribute to the increased intrauterine pressure.

As ectopic archimetras endometriotic as well as adenomyotic lesions possess the biochemical potential of the parent basal endometrium. Thus, the lesions are able to produce oestrogen and may therefore be able to sustain their benign proliferative

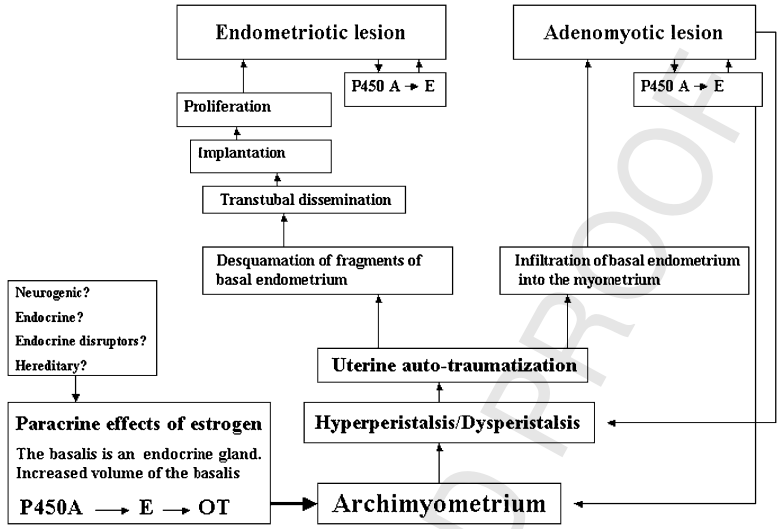

Figure 7. A schematic representation of the pathophysiology of endometriosis and adenomyosis. From Leyendecker et al (2004, *Annals of the New York Academy of Sciences* **1034:** 338–355 with permission.

potential. That is why infiltrative endometriosis and adenomyosis may constitute progressive diseases – in rare cases even beyond the menopause.[54]

'EXTERNAL' ADENOMYOSIS

The development of 'deeply infiltrating endometriosis' or 'external adenomyosis' is enigmatic and still a matter of debate.[55] The paradigm of chronic traumatization and increased tissue concentrations of oestrogen in consequence of the activation of the repair system that involves the expression or hyperexpression of P450A might also be pertinent to the understanding of the development of such lesions. Characteristically, these lesions are located at sites of chronic mechanical irritation such as the bowel, the recto-vaginal septum, the bladder, as well as the sacro-uterine ligaments. It appears that chronic trauma to the ectopic 'microarchimetras' results in the same tissue response as seen in uterine adenomyosis. While superficial endometriotic lesions distant from mechanical irritation might heal, those accidentally located at sites of chronic mechanic irritation develop into deeply infiltrative foci. This might explain the frequent finding of severe uterine adenomyosis with a 'frozen' pouch of Douglas due to recto-vaginal endometriosis and a pelvic peritoneum otherwise free of endometriotic lesions.[56]

The syndrome of dislocated basal endometrium (SDBE): a pathophysiological continuum

According to our understanding of the disease process, minimal and mild endometriosis of the fertile woman, endometriosis in association with adenomyosis of the infertile woman, and premenopausal adenomyosis, respectively, constitute a pathophysiological continuum that could be summarized with the term 'syndrome of dislocated basal endometrium' (SDBE). Pelvic pain, bleeding disorders and infertility constitute

the cardinal symptoms of this syndrome. The presentation of the various forms of SDBE is determined by the strength and temporal occurrence of the uterine autotraumatization and also iatrogenic trauma.

Normoperistalsis

Women without endometriosis and proven fertility desquamate fragments of basal endometrium during menstruation, although at a significant lower rate than infertile women with endometriosis.[2] Moreover, in the presence of normoperistalsis the uterine retrograde transport capacity during menstruation is low in these women (Figure 5).[27] Nevertheless, retrograde menstruation, though limited, might cause incidental dissemination of fragments of basal endometrium within the peritoneal cavity. The probability that implantation might occur increases with age.[57,58]

Premenopausal adenomyosis occurs in parous and non-parous women. Bird et al[9] reported on a prevalence of 69% of adenomyosis in uterine specimen of 200 consecutive hysterectomies in mostly parous women, which is close to prevalence estimates of adenomyosis in the range of 54% based on uteri removed at autopsy.[8] In our recent study, 28% of the non-parous women of our control group without endometriosis had signs of adenomyosis according to MRI, with the majority of the women with adenomyosis being older than 37 years of age.[6]

Presumably, chronic normoperistalsis throughout the reproductive period of life constitutes the principal factor that induces the development of premenopausal adenomyosis by causing continuous traumatization of the archimetra at the fundocornual raphe (Figure 6). Parity and iatrogenic trauma are additional factors. As soon as adenomyotic foci have developed, local oestrogen levels permanently increase, stimulating the further progression of the disease.[59] The slow development of premenopausal adenomyosis, with the uterus becoming increasingly rigid, prevents major dissemination of endometrial tissue into the peritoneal cavity. Thus, the association of premenopausal adenomyosis with endometriosis is low. This observation, however, does not justify the conclusion that these two conditions are different clinical and nosological entities with no shared aetiological mechanisms (Figure 8).[17]

Hyperperistalsis

In infertile women, due to an abnormal stimulation of archimetral oestrogen receptors that results in *hyperperistalsis*, the process of the development of adenomyosis is intensified and advanced.[5] In this dynamic process of disease development endometriosis usually comes first and is followed by adenomyosis. Therefore, no static value for the prevalence of adenomyosis in endometriosis can be expected. This value varies depending on the study population chosen. In our study, a prevalence of adenomyosis in endometriosis in the range 79–90% was observed. The patients were suffering from long-standing infertility and seeking treatment by assisted reproduction, increasing the probability that both the peritoneal and the uterine variant of the disease had developed in these women.

ADENOMYOSIS AND INFERTILITY

In young couples with proven fertility the chance of achieving a pregnancy is around 35% per menstrual cycle.[40] About 85% become pregnant after 6 months.[60]

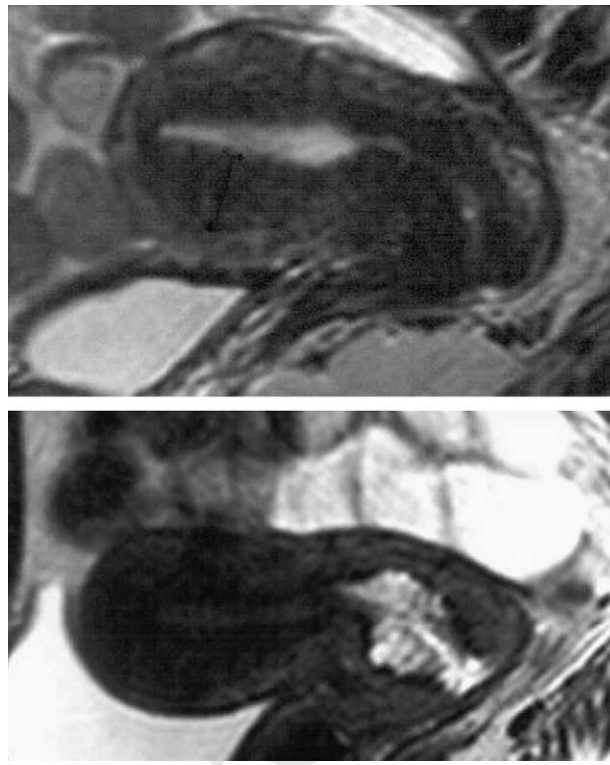

Figure 8. The uteri of two women of 37 years of age with diffuse uterine adenomyosis as presented by MRI in sagittal scans. Top: the parous woman with two children aged 12 and 14 years presented with increasing pelvic pain and bleeding disorders. During laparoscopy-assisted vaginal hysterectomy a minor endometriotic lesion at the peritoneum of the urinary bladder could be documented and excised. Histology confirmed the diagnosis of both adenomyosis and endometriosis. Bottom: the patient presented with longstanding primary infertility. Upon query she reported increasing pelvic pain and premenstrual spotting. A previously performed laparoscopy had revealed minor endometriosis of the peritoneum of the urinary bladder. The condition of the parous woman would be considered as premenopausal adenomyosis associated with mild adenomyosis. Prior to the diagnosis of diffuse adenomyosis, the condition in the infertile patient would have been considered as unexplained infertility. Apart from parity, the clinical and pathological conditions in these two women are the same. These cases illustrate the pathophysiological continuum of the syndrome of dislocated basal endometrium (SDBE).

Women with mild to moderate endometriosis have a reduced chance of becoming pregnant, with only about a 25% and 50% chance of achieving a spontaneous pregnancy after 6 and 18 months, respectively.[61] The remaining 50% of patients do not become pregnant at all. Surgical and medical eradication of the endometriotic lesions does not improve or normalize fertility in such patients, suggesting that peritoneal endometriotic lesions without tubo-ovarian involvement do not constitute a major cause of infertility in such patients.[61,62] Infertility in these patients is often considered as unexplained.

On the basis of the significant association of uterine adenomyosis in infertile women with endometriosis, it was suggested that adenomyosis could constitute this

hitherto unidentified factor.[4,30] This notion was recently substantiated in a larger study.[6] The most plausible explanation for the impact of adenomyosis on fertility is the impairment of the uterine mechanism of rapid and sustained directed sperm transport in consequence of the destruction of the normal architecture of the archimyometrium.[22,27] With the peristromal muscular cells of the adenomyotic lesions, a muscular tissue develops that is irregularly arranged, in contrast to the archimyometrium with its circular muscle fibres. Moreover, this muscular tissue is presumably – since it is homologous to the archimyometrium – responsive to the endocrine and paracrine stimuli that regulate uterine peristalsis.[2,25,32] This may result in increased intrauterine pressure and in dysperistalsis during the late follicular phase in women with endometriosis.[27,42,43]

This does not, however, exclude other 'non-mechanical' uterine factors leading to infertility in endometriosis, such as the increased colonization of the endometrium with macrophages and a possible direct impact of the adenomyotic lesions with their secretory products on ovarian function.[63] A number of studies have demonstrated a diminished ovarian reserve, an impaired granulosa cell–oocyte environment, and an impaired oocyte quality and fertilization rate, respectively, in patients with endometriosis.[64–67] Our own preliminary data from in-vitro fertilization indicate that there is a correlation between the percentage of immature oocytes among those retrieved and the depth of adenomyotic infiltration (G. Kunz, G. Leyendecker, unpublished). Also the rate of blastocyst formation is reduced in the presence of extended adenomyosis (W. Bernart, U. Mischeck, A. Bilgicyildirim, G. Leyendecker, unpublished). The basal endometrium is, by virtue of the expression of P450 aromatase throughout the menstrual cycle, a tissue capable of converting androgen into oestrogen and producing various substances that are mainly active in a paracrine way, such as oxytocin, prostaglandins, growth factors and cytokines.[2,47] Not only is the eutopic endometrium significantly enlarged in women with endometriosis in comparison to controls, the adenomyotic lesions with their basal endometrium further increase the size of this intrauterine 'gland' in women with endometriosis, which could affect ovarian function via the utero-ovarian counter-current system that has been shown to be of physiological significance both in the animal and the human.[2,26,68, 69]

PRACTICAL CONSEQUENCES AND SUGGESTIONS FOR FURTHER RESEARCH

Adenomyosis is encountered in infertile women with endometriosis and constitutes, in addition to the possible impairment of utero-tubal function by adhesions and endometrioma, the major cause of infertility in these women. Adenomyosis is also observed in non-parous women without endometriosis, and the development of this variety usually takes place in the last third of the reproductive period of life. Due to the postponement of childbearing, however, it has increasingly become a factor in sterility. Thus, in a sterility work-up the uterus has not only to be studied with respect to alterations such as fibroids, malformations and endometrial polyps but also with respect to the presence or absence of adenomyosis. In addition to the clinical examination that will eventually show an enlarged or irregularly shaped uterine corpus with 'sourness' upon palpation, transvaginal sonography constitutes the method of choice in the outpatient clinic. 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' are indicative of the presence of adenomyosis (Figure 9).

In cases of adenomyosis the probability of a spontaneous pregnancy occurring is low, suggesting assisted reproduction as the appropriate mode of treatment. This is pertinent to patients with and without endometriosis. In younger women with endometriosis and a short history of complaints and infertility, the absence of adenomyosis might warrant an expectant attitude or minor treatment modalities such as ovarian stimulation with and without insemination. The results, however, are usually limited in comparison to IVF.[70]

Because of poorer results of IVF in women with endometriosis in comparison to women without the disease, prolonged pretreatment with gonadotrophin-releasing hormone (GnRH) analogues has been suggested, and an improved pregnancy rate in patients with endometriosis could be demonstrated.[71,72] This improvement was significant, however, only in severe grades of the disease that are more likely to be associated with extended adenomyosis.[72] It is very possible that a longer period of down-regulation by GnRH analogues reduces, at least temporarily, the detrimental effects of adenomyosis on the cohort of follicles that is recruited in the subsequent cycle of ovarian stimulation.

In view of the fact that endometriosis and adenomyosis might develop very early in the reproductive period of life and rapidly lead to destruction of the reproductive organs, with infertility and disabling pain as the major sequels, an early diagnosis with the possibility of hindering further progression of the disease appears to be desirable. There is no doubt that early onset and severe dysmenorrhoea, and even intermittent attacks of pelvic pain prior to menarche, might be early clinical signs.[73] Methods should become available that allow us to distinguish between functional dysmenorrhoea and those menstrual pains that are symptoms of a beginning disease process. We suggested that menstrual blood could be examined for the presence of fragments of desquamated basal endometrium.[74] Using real-time polymerase chain reaction (PCR) the usefulness of examining menstrual blood could be confirmed. It was shown that patients with endometriosis had significantly increased levels of oestrogen receptor-β and progesterone receptor in menstrual blood samples, whereas no differences were recognized between women with endometriosis and the controls in peripheral blood samples.[75]

The theory presented here does not conflict with other theories such as that of Sampson and those that consider immunological phenomena, growth factors, integrins and cytokines as essential pathophysiological factors. Many of these phenomena — such as the increased expression of factors of angiogenesis and wound healing — can be considered as secondary to archimetral hyperoestrogenism. With respect to immunological factors it has to be kept in mind that inflammatory defence is one of the fundamental functions of the endometrium in the early process of reproduction.[28] Endometriotic and adenomyotic lesions display, as ectopic 'microarchimetras', the same immunological potential as the parent tissue. While immunoreactive cells such as 'bone-marrow-derived white blood cells' and macrophages are cyclically shed with menstruation, they cannot be externalized, at least from extrauterine ectopic lesions. They remain in situ and cause immunological and inflammatory processes that result in cyclical pain.

CONCLUSIONS

Adenomyosis and endometriosis constitute, as diseases of the archimetra, a pathophysiological and nosological entity. They both result from the dislocation of basal

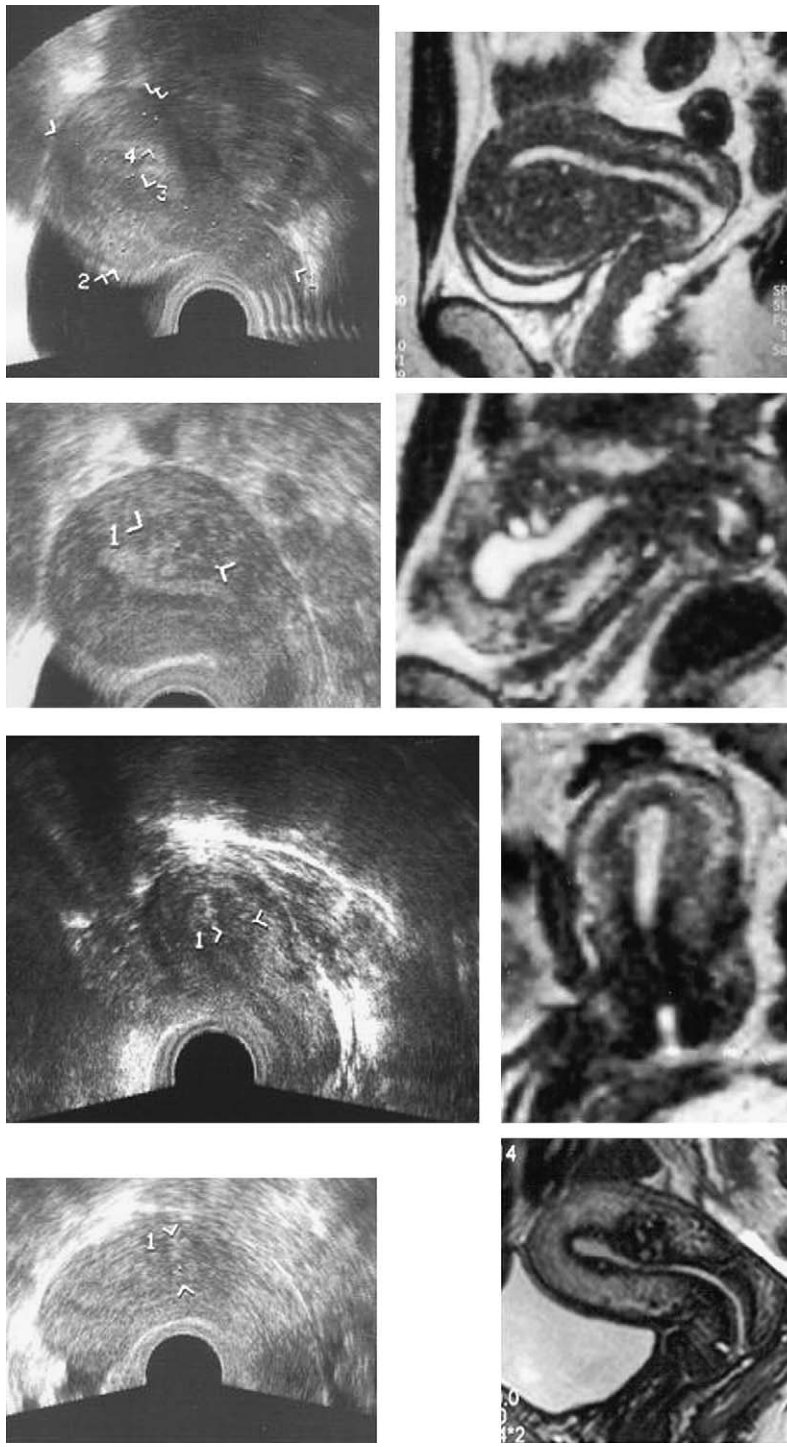

Figure 9. Examples of uterine adenomyosis as presented by transvaginal sonography (left panel) and confirmation by MRI (right panel).

endometrium into uterine and extrauterine sites, respectively, in consequence to uterine auto-traumatization by chronic uterine peristalsis and hyperperistalsis. Iatrogenic trauma might constitute an additional cause. In uterine hyperperistalsis that is caused by a pathological stimulation of archimetral oestrogen receptors, the traumatization is drastically intensified, resulting in an advancement of the disease process with a high association of both adenomyosis with endometriosis and vice versa. The adenomyotic component of the disease constitutes the principal factor of infertility in patients with endometriosis. Premenopausal adenomyosis that was formerly mostly associated with parity and iatrogenic trauma as special risk factors now emerges as a cause of infertility because today not infrequently women postpone childbearing into the last years of their reproductive period of life.

Practice points

- the uterus is composed of two phylogenetically and ontogenetically different structures
- the inner structure, the endometrial–subendometrial unit, is phylogenetically and ontogenetically old and is therefore termed the 'archimetra'. Ontogenetically, the archimetra is of paramesonephric ('Müllerian') origin. The outer structures of the uterus, the stratum vasculare and supravasculare of the myometrium are phylogenetically and ontogenetically younger and not of Müllerian origin ('Neometra'). They are derived from the serosal mesenchyme covering the primordial uterus
- the archimetra is composed of the endometrial glands, the endometrial stroma and the subendometrial myometrium also termed the 'archimyometrium'

Research agenda

- what morphologically and functionally indicates that the archimetra is a paired organ in character?
- what is the basis for considering endometriosis and adenomyosis as diseases of the archimetra?
- elucidation of the endocrine and paracrine regulation of the peristaltic function of the archimyometrium
- aetiology of archimetral hyperoestrogenism and hyperperistalsis
- early diagnosis of the beginning of the disease process of endometriosis/adenomyosis in young women
- definition and development of preventive measures

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