Article

Adenomyosis as a disorder of the early and late human reproductive period

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Abstract

Magnetic resonance imaging (MRI) allows the diagnosis of adenomyosis *in vivo* with a high sensitivity and specificity. Usually the diagnosis of adenomyosis is obtained from women in their fourth to fifth decade of life. However, recent data suggest that adenomyosis may develop much sooner in life, particularly in women with endometriosis. In order to test these suggestions, MRI of the uterus in 227 women with and without endometriosis was performed and the results were related to the age of the subjects (age groups: 17–24, 25–29, 30–34 and >34 years). The study revealed that the process of the development of adenomyosis, represented by an increased diameter of the dorsal junctional zone of the uterus as the imaging correlative of the invasion of basal endometrium into the junctional zone, had already commenced early in the third decade of life and progressed steadily during the fourth decade in women with endometriosis. Women without endometriosis showed almost no signs of adenomyosis up to the age of 34 years. Surprisingly, parallel in both groups of women, a marked increase in the incidence of adenomyosis could be observed beyond the age of 34 years, thus representing a common phenomenon in the age-related pathophysiological continuum of adenomyosis.

Keywords: *adenomyosis, archimetra, endometriosis, reproduction*

Introduction

Recently, on the basis of correlation studies, imaging criteria have been established with respect to magnetic resonance imaging (MRI) that allows the diagnosis of adenomyosis *in vivo* (Hricak *et al*., 1983; Brosens *et al*., 1995, 1998; Reinhold *et al*., 1998; Kunz *et al*., 2005). When compared with histology, MRI represents an accurate technique for the detection of uterine adenomyosis with a high sensitivity of 53–89% and a high specifity of 65–98% (Ascher *et al*., 1994; Reinhold *et al*., 1996; Bazot *et al*., 2001; Dueholm *et al*., 2001). Uterine adenomyosis itself presents in MRI as a hypo-intense diffuse broadening of the predominantly dorsal (Zaloudek and Norris, 1987; Ferenczy, 1998) junctional zone (Brosens *et al*., 1995; Kang *et al*., 1996; Reinhold *et al*., 1998; Kunz *et al*., 2000, 2005; Tamai *et al*., 2006). This is because adenomyosis itself results from the invasion of basal endometrium into the underlying myometrium (Bazot *et al*., 2001) as a disease of the archimetra, the latter consisting of the endometrium and the subendometrial myometrium or archimyometrium (Leyendecker *et al*., 2002, 2006; Noe *et al*., 1999; Bazot *et al*., 2001). This assumption is supported by the finding that the peristromal muscular tissue of the adenomyotic lesions is paramesonephric in character and homologous to the archimyometrium or junctional zone (Leyendecker *et al*., 2002).

Adenomyosis is diagnosed either by means of MRI or by histological means in uteri predominantly obtained from women in their fifth or sixth decade of life (Parazzini *et al*., 1997). However, during recent years substantial evidence has

suggested that adenomyosis may already develop during the early reproductive phase of life, frequently in association with pelvic endometriosis (Kunz *et al.*, 2000, 2005; Vercellini *et al.*, 2006; Zacharia *et al.*, 2006; Kissler *et al.* 2007a,b). This study used MRI with a large study group of 227 women with and without endometriosis aged from 17 to 46 years, in an attempt to evaluate whether the process of the invasion of the basal endometrium into the adjacent myometrium, resulting in adenomyosis as presented by an enlargement of the junctional zone, might develop earlier in the reproductive phase of life than commonly known, and whether its prevalence can be related to different age groups. The rationale to perform the study was to present a comprehensive view of adenomyosis as a disease possibly affecting women all of ages during the reproductive phase of life.

Materials and methods

Patients

A total of 227 women with regular menstrual cycles (mean 28 days, range 21–29 days) aged 17–46 years (mean 32.5 years) entered this study after giving informed consent. Together with their male partners, they had a history of infertility prompting them to have a sterility work-up and subsequent treatment in the study clinic.

Of these patients, 160 women (mean 32.3 years, range 17–46 years) with a history of infertility of 1–13 years (mean 3.6 years) were suffering from endometriosis as demonstrated by laparoscopy. Almost half of these patients presented with minimal or mild endometriosis (n = 81) and the rest with moderate or severe endometriosis (n = 79), according to the revised classification of the American Society of Reproductive Medicine (American Fertility Society, 1985). No additional factors responsible for their female infertility could be identified.

In the other 67 women (mean 33.2 years, range 21–46 years), no endometriosis or any other pelvic disorder was obtained from laparoscopy. These women were termed the healthy controls.

Patients with irregular menstrual cycles, bleeding disorders or abnormalities of the uterine structure such as fibroids or malformations were excluded from the study. MRI was never performed during menstruation, thus excluding a selection bias with respect to the measurement of the junctional zone (Tamai *et al.*, 2006).

Magnetic resonance imaging (MRI)

In all 227 women, the uteri were examined by means of MRI using the same techniques as previously published (Kunz *et al.*, 2000, 2005). All diameters were documented by electronic calipers and expressed in millimetres and were obtained from the uteri in a mid-sagittal plane. All quantitative measurements were performed separately and independently by two investigators (GK, DB) who were unaware of the clinical symptoms, clinical data, diagnosis or data from other observers and there was always consensus with respect to the placement of the calipers.

In the mid-sagittal plane, the diameters of the subendometrial myometrium or archimyometrium (Werth and Grusdew, 1898; Leyendecker *et al.*, 1998; Noe *et al.*, 1999; Kunz *et al.*, 2000, 2005; Leyendecker *et al.*, 2002) and of the total myometrium on the height of the transition between the upper and lower half of the dorsal wall of the uterine corpus (Kunz *et al.*, 2000, 2005) were measured. Originally (Kunz *et al.*, 2000, 2005), the length of the endometrium from the internal os towards the fundus and the length of the uterus from the internal os towards the fundal serosa, as well as the diameters of the total myometrium and of the archimyometrium of the anterior uterine wall, were also obtained from MRI. However, they revealed no differences.

The diameters as measured by MRI in women with endometriosis were compared with those of the women without endometriosis.

Statistical analysis

The statistical analysis was performed using Student's t-test and significance was assumed when $P < 0.05$ (Microsoft Excel; Werner, 1989). Prior to the use of the Student's t-test, a test was performed (for further details, see Riffenburgh, 2005) that revealed a normal distribution of the data.

Results

The results are presented in **Figure 1**. **Table 1** lists the mean ages and standard deviations for each age group of women, revealing no significant differences between the endometriosis patients and the healthy control in each age group.

No differences were obtained with respect to the diameters as measured, except the diameter of the dorsal archimyometrium as published in all this group's previous studies (Kunz *et al.*, 2000, 2005). Apparently, MRI revealed that women with pelvic endometriosis exhibited an increased diameter of the dorsal archimyometrium representing adenomyosis (Kunz *et al.*, 2000, 2005) very soon in their lives as compared with the healthy controls. Healthy women aged between 30 and 34 years showed no further increase of the diameter of the dorsal archimyometrium. In the corresponding age group of women with endometriosis, such an increase could be observed, consequently yielding a highly significant difference ($P < 0.001$, **Figure 1**). It appears tempting to speculate that the process of invasion of basal endometrial glands into the adjacent myometrium, i.e. adenomyosis, appeared as a pathophysiological continuum presumably starting during the second decade of life up to the mid-30s only in women with endometriosis.

However, beyond the age of 34 years, a surprisingly parallel and steep pattern of the curves could be observed. In this age group, both the endometriosis group and the control group increasingly developed an enlargement of the dorsal junctional zone representing adenomyosis (**Figure 1**). The difference between the women with endometriosis to those without endometriosis in this age group with regard to the diameter of the dorsal archimyometrium or junctional zone remained quite stable and highly significantly different ($P < 0.008$).

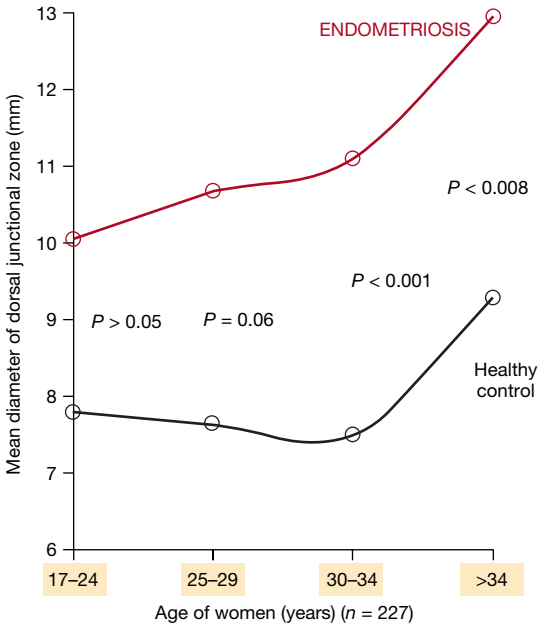

Figure 1. This graph depicts the results of magnetic resonance imaging obtained from women with endometriosis (upper red line) and without endometriosis (lower black line). Apparently the mean diameter of the dorsal junctional zone in women with endometriosis was already increased in very young women as compared with healthy controls; however, the difference only reached statistical significance in women of 30 years and older. Note that starting from an age of >34 years, both groups of women demonstrated a parallel and sharp increase of the diameter of the junctional zone representing adenomyosis.

Table 1. Characteristics of the women in the study groups.

Age (years)	*Endometriosis* n	*Age (years) (mean ± SD)*	*Control* n	*Age (years) (mean ± SD)*
17–24	11	21.4 ± 2.5	2	22.0 ± 1.0
25–29	26	27.6 ± 1.5	12	27.6 ± 1.2
30–34	71	31.7 ± 1.3	28	31.9 ± 1.4
>35	52	37.8 ± 3.3	25	37.9 ± 3.6

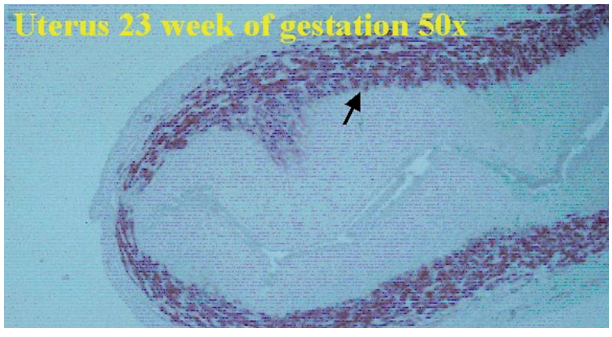

Figure 2. This primordial uterus of the 23rd week of pregnancy is composed of the endometrium and the adjacent myometrium or archimyometrium (actin staining, ×50). Note that the border between the basal endometrium and the adjacent junctional zone (indicated by arrow) is clearly defined with no protrusions. (Photograph provided by courtesy of M Herbertz.)

Discussion

Hitherto, adenomyosis is mostly diagnosed from hysterectomy specimens usually obtained from women in their fifth decade of life (Parazzini *et al*., 1997). Although Vercellini and co-workers (2006) assumed that the incidence of adenomyosis seems to rise from the mid-thirties, there is compelling evidence that adenomyosis is also present in even younger women and then is predominantly associated with pelvic endometriosis and infertility (Kunz *et al*., 2000, 2005; Leyendecker *et al*., 2006; Zacharia *et al*., 2006; Kissler *et al*. 2007a,b). Adenomyosis and endometriosis constitute, as a disease of the archimetra, a pathophysiological and nosological entity (Werth and Grusdew, 1898; Wetzstein, 1965; Leyendecker *et al*., 2002, 2006; Kunz *et al*., 2005; Kitawaki, 2006). Both endometriotic and adenomyotic lesions form peristromal muscular tissue that has characteristics of the archimyometrium (Leyendecker *et al*., 2002, 2006). The observation of an ovarian adenomyoma with thick muscular bundles corresponds with previous findings (Bayar *et al*., 2006). The archimetra itself, consisting of the endometrium and the adjacent archimyometrium or junctional zone, is the organ responsible for basic reproductive procedures in human such as directed sperm and embryo transport and implantation of the blastocyst (Kunz *et al*., 1996, 1998, 2006, 2007).

The advent of high resolution imaging techniques allows the documentation of and correlation with adenomyosis *in vivo* (Bazot *et al*., 2001), and thus offers the possibility to elucidate adenomyosis in younger women. It is generally agreed that MRI of the uterus represents the best means *in vivo* of documenting the different layers of the uterine wall, particularly for adenomyosis (Hricak *et al*., 1983; Ascher *et al*., 1994; Brosens *et al*., 1995, 1998; Reinhold *et al*., 1996, 1998; Bazot *et al*., 2001; Dueholm *et al*., 2001; Dueholm, 2006; Tamai *et al*., 2006). The purpose of the study was to increase the reliability of the results by including a high number of women with endometriosis. Obviously, the relation between the number of women with endometriosis and those without the disease in this study does not represent the real percentages.

This study revealed the development of adenomyosis in all women as a life-long process. It seems reasonable to assume that, in women with endometriosis, this process starts earlier in life and even appears to accelerate (as shown by the increasingly significant difference) as compared with women without endometriosis and as related to the diameter of the dorsal archimyometrium representing adenomyosis (Kunz *et al*., 2000, 2005; Leyendecker *et al*., 2002, 2006). In healthy women, the development of adenomyosis usually appears to be restricted to an age of older than 34 years.

Diffuse adenomyosis was found in the posterior as well as the anterior wall of the uterus. On a large statistical basis, however, the posterior wall of the uterus was predominantly affected (Kunz *et al*., 2000, 2005), confirming previously published data (Zaloudek and Norris, 1987; Ferenczy, 1998; for overview see Vercellini *et al*., 2006). However, early adenomyosis, i.e. sub-basal adenomyosis (Bird *et al*., 1965), might evade radiological diagnosis on the basis of presently established criteria.

The archimyometrium, as the innermost of three myometrial layers, surrounds the whole endometrium and is characterized by a predominantly circular arrangement of the muscular fibres (Werth and Grusdew, 1898; Wetzstein, 1965; Noe *et al*., 1999; Kunz *et al*., 2000). The ontogenetically early formation of the archimyometrium is pertinent to its function that results from the fusion of the two paramesonephric ducts and their mesenchymal elements to form the primordial uterus (Werth and Grusdew, 1898; Noe *et al*., 1999). 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 transport mechanisms in the physiology of reproduction (Kunz *et al*., 1996, 1998, 2006, 2007). In women with endometriosis, hyperperistaltic contractions of the uterine musculature, predominantly of the archimyometrium, and an increased intrauterine pressure could be documented (Mäkäräinen, 1988; Salamanca and Beltran, 1995; Leyendecker *et al*., 1996; Bulletti *et al*., 2002). This process of muscular hyperactivity might start very early in the reproductive period of life in women with endometriosis. As a result, a uterine auto-traumatization further sustains an infiltration of basal endometrium into the myometrium, predominantly where the paramesonephric ducts have fused (Kunz *et al*., 2005; Leyendecker *et al*., 2006). That traumatization might induce the development of adenomyosis is supported by the notion that intrauterine operative procedures such as hysteroscopically performed endometrial ablations or Caesarean sections provoke the development of severe adenomyosis (Vercellini *et al*., 2006). Furthermore, a mouse model suggested that physical disturbance to the normal myometrium or the myometrial–endometrial junction in early life is also an important factor that predisposes to the development of adenomyosis in adulthood (Greaves and White, 2006). It appears reasonable to assume that, in women with endometriosis, this process of auto-traumatization may initiate the development of adenomyosis early in life and further support its progressive growth.

In all women beyond 34 years of age, the development and progressive growth of adenomyosis might be the result of a natural and quite physiological course of events with regard to the human menstrual cycle such as menstruation and uterine peristalsis. It is tempting to speculate that adenomyotic growth in women beyond 34 years of age represents a more or less physiological ageing progress of the uterus, which, however, aggravates the situation in women with endometriosis. Thus, it can be seen from microscopical and immunohistochemical observations of uteri, from fetuses to post-menopausal women,that the transition or junction between the basal endometrium and the adjacent subendometrial myometrium develops from confines that are as sharp as a blade to a structure that is characterized by multiple focal protrusions of the basal endometrium into the archimyometrium (M Herbertz, unpublished; **Figure 2**). The older the uterus, the higher is the probability that adenomyosis will occur. However, this age-related progress of adenomyosis was paralleled by the women with endometriosis starting from the second half of the fourth decade of life.

There is evidence that adenomyosis causes infertility by impairing directed sperm transport and possibly oocyte maturation in younger women (Kunz *et al*., 2005; G Kunz *et al*., unpublished). As shown by this and other recent studies, the chance of developing adenomyosis is increased in all women starting from their mid-30. Add to this the fact that, in highly developed countries, reproduction is often postponed to the fourth or even fifth decade of life. As a consequence,

it appears reasonable to assume that, generally, adenomyosis may significantly contribute to the decreased conception rates as observed in this age group of women.

References

American Fertility Society 1985 Revised American Fertility Society classification of endometriosis. *Fertility and Sterility* **43**, 351–352.

Ascher SM, Arnold LL, Patt RH *et al*. 1994 Adenomyosis: prospective comparison of MR imaging and transvaginal sonography. *Radiology* **190**, 803–806.

Bayar U, Demirtas E, Usubütün A *et al*. 2006 Ovarian adenoma following gonadotrophin treatment for infertility. *Reproductive BioMedicine Online* **13**, 676–679.

Bazot M, Cortez A, Darai E *et al*. 2001 Ultrasonography compared with magnetic resonance imaging for the diagnosis of adenomyosis: correlation with histopathology. *Human Reproduction* **16**, 2427–2433.

Bird CC, Willis RA 1965 The production of smooth muscle by the endometrial stroma of the adult human uterus. *Journal of Pathology and Bacteriology* **90**, 75–81.

Brosens JJ, Barker FG, de Souza NM 1998 Myometrial zonal differentiation and uterine junctional zone hyperplasia in the non pregnant uterus. *Human Reproduction Update* **4**, 496–502.

Brosens JJ, de Souza NM, Barker FG 1995 Uterine junctional zone: function and disease. *Lancet* **346**, 558–560.

Bulletti C, De Ziegler D, Polli V *et al*. 2002 Characteristics of uterine contractility during menses in women with mild to moderate endometriosis. *Fertility and Sterility* **77**, 1156–1161.

Dueholm M 2006 Transvaginal ultrasound for diagnosis of adenomyosis: a review. *Best Practice and Research in Clinical and Obstetrical Gynaecology* **20**, 569–582.

Dueholm M, Lundorf E, Hansen ES *et al*. 2001 Magnetic resonance imaging and transvaginal ultrasonography fort he diagnosis of adenomyosis. *Fertility and Sterility* **76**, 588–594.

Ferenczy A 1998 Pathophysiology of adenomyosis. *Human Reproduction Update* **4**, 312–322.

Greaves P, White INH 2006 Experimental adenomyosis. *Best Practice and Research in Clinical and Obstetrical Gynaecology* **20**, 503–510.

Hricak H, Alpers C, Crooks LE, Sheldon PE 1983 Magnetic resonance imaging of the female pelvis: initial experience. *American Journal of Radiology* **141**, 119–1128.

Kang S, Turner DA, Foster GS *et al*. 1996 Adenomyosis: specificity of 5 mm as the maximum normal uterine junctional zone thickness in MR images. *American Journal of Roentgenology* **166**, 1145–1150.

Kissler S, Zangos S, Kohl J *et al*. 2007a Duration of dysmenorrhea and extent of adenomyosis visualised by magnetic resonance imaging. *European Journal of Obstetrics and Gynecology and Reproductive Biology*, Mar 28; [epub ahead of print], PMID: 17397990.

Kissler S, Zangos S, Wiegratz I *et al*. 2007b Utero-tubal sperm transport and its impairment in endometriosis and adenomyosis. *Annals of the New York Academy of Science* **1101**, 38–48.

Kitawaki J 2006 Adenomyosis: the pathophysiology of an oestrogen-dependent disease. *Best Practice and Research in Clinical and Obstetrical Gynaecology* **20**, 493–502.

Kunz G, Beil D, Huppert P, Leyendecker G 2007 Oxytocin – a stimulator of rapid sperm transport in human. *Reproductive BioMedicine Online* **14**, 32–39.

Kunz G, Beil D, Huppert P, Leyendecker G 2006 Control and function of uterine peristalsis during the human luteal phase. *Reproductive BioMedicine Online* **13**, 528–540.

Kunz G, Beil D, Huppert P *et al*. 2005 Adenomyosis in endometriosis – prevalence and impact on fertility. Evidence from magnetic resonance imaging. *Human Reproduction* **20**, 2309–2316.

Kunz G, Beil D, Huppert P, Leyendecker G 2000 Structural abnormalities of the uterine wall in women with endometriosis and infertility visualized by vaginal sonography and magnetic resonance imaging. *Human Reproduction* **15**, 76–82.

Kunz G, Herbertz M, Noe M, Leyendecker G 1998 Sonographic evidence of a direct impact of the ovarian dominant structure on uterine function during the menstrual cycle., *Human Reproduction Update* **4**, 667–672.

Kunz G, Beil D, Deininger H *et al*. 1996 The dynamics of rapid sperm transport through the female genital tract. Evidence from vaginal sonography of uterine peristalsis (VSUP) and hysterosalpingoscint igraphy (HSSG). *Human Reproduction* **11**, 627–632.

Leyendecker G, Kunz G, Kissler S, Wildt L 2006 Adenomyosis and reproduction. *Best Practice and Research in Clinical and Obstetrical Gynaecology* **20**, 523–546.

Leyendecker G, Herbertz M, Kunz G, Mall G 2002 Endometriosis results from the dislocation of basal endometrium. *Human Reproduction* **17**, 2725–2736.

Leyendecker G, Kunz G, Wildt L *et al*. 1996 Uterine hyperperistalsis and dysperistalsis as dysfunctions of the mechanism of rapid sperm transport in patients with endometriosis and infertility. *Human Reproduction* **11**, 1542–1551.

Mäkäräinen L 1988 Uterine contractions in endometriosis: effects of operative and danazol treatment. *Obstetrics and Gynecology* **9**, 134–138.

Noe M, Kunz G, Herbertz M *et al*. 1999 The cyclic pattern of the immunocytochemical expression of oestrogen and progesterone receptors in human myometrial and endometrial layers: characterization of the endometrial-subendometrial unit. *Human Reproduction* **14**, 101–110.

Parazzini F, Vercellini P, Panazza S *et al*. 1997 Risk factors for adenomyosis. *Human Reproduction* **12**, 1275–1279.

Reinhold C, Tafazoli F, Wang L 1998 Imaging features of adenomyosis. *Human Reproduction Update* **4**, 337–349.

Reinhold F, McCarthy S, Bret PM *et al*. 1996 Diffuse adenomyosis: comparison of endovaginal US and MR imaging with histopathologic correlation. *Radiology* **199**, 151–158.

Riffenburgh RH 2005 *Statistics in Medicine*. *A Process Oriented Approach*. 2nd edition. Academic Press.

Salamanca A, Beltran E 1995 Subendometrial contractility in menstrual phase visualized by transvaginal sonography in patients with endometriosis. *Fertility and Sterility* **64**, 193–195.

Tamai K, Koyama T, Umeoka S *et al*. 2006 Spectrum of MR features in adenomyosis. *Best Practice and Research in Clinical and Obstetrical Gynaecology* **20**, 583–602.

Vercellini P, Vigano P, Somigliana E *et al*. 2006 Adenomyosis: epidemiological factors. *Best Practice and Research in Clinical and Obstetrical Gynaecology* **20**, 465–477.

Werner J 1989 *Medizinische Statistik*. Urban and Schwarzenberg, Vienna, Austria, 167–171. [In German.]

Werth R, Grusdew W 1898 Untersuchungen über die Entwicklung und Morphologie der menschlichen Uterusmuskulatur. *Archiv der Gynäkologie* **55**, 325–409.

Wetzstein R 1965 Der uterusmuskel: morphologie. *Archives of Gynecology* **202**, 1–13.

Zacharia TT, O'Neill MJ 2006 Prevalence and distribution of adnexal findings suggesting endometriosis in patients with MR diagnosis of adenomyosis. *British Journal of Radiology* **79**, 303–307.

Zaloudek C, Norris HJ 1987 Mesenchymal Tumors of the Uterus. In: Kurman RJ (ed.) *Blaustein's Pathology of the Female Genital Tract* 3rd edition. Springer Verlag, New York, pp. 374–528.

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