Adenomyosis in endometriosis—prevalence and impact on fertility. Evidence from magnetic resonance imaging

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BACKGROUND: The hypothesis is tested that there is a strong association between endometriosis and adenomyosis and that adenomyosis plays a role in causing infertility in women with endometriosis. METHODS. Magnetic resonance imaging of the uteri was performed in 160 women with and 67 women without endometriosis. The findings were correlated with the stage of the disease, the age of the women and the sperm count parameters of the respective partners. RESULTS: The posterior junctional zone (PJZ) was significantly thicker in women with endometriosis than in those without the disease (P<0.001). There was a positive correlation of the diameter of the PJZ with the stage of the disease and the age of the patients. The PJZ was thicker in patients with endometriosis with fertile than in patients with subfertile partners. The prevalence of adenomyotic lesions in all 160 women with endometriosis was 79%. In women with endometriosis below an age of 36 years and fertile partners, the prevalence of adenomyosis was 90% (P<0.01) CONCLUSIONS: With a prevalence of up to 90%, uterine adenomyosis is significantly associated with pelvic endometriosis and constitutes an important factor of sterility in endometriosis presumably by impairing uterine sperm transport.

Key words: adenomyosis/disease of archimetra/endometriosis/infertility/magnetic resonance imaging

Introduction
Directed sperm transport into the tube ipsilateral to the dominant follicle provided by uterine peristalsis constitutes one of the fundamental functions of the uterus in the early process of reproduction (Kunz et al., 1996, 2000b; Leyendecker et al., 1998; Wildt et al., 1998). This function is critically dependent upon the architecture of the myometrial wall, particularly on that of the archimyometrium (stratum subvasculare) with its predominantly circular arrangements of muscular fibres and its bipartition at the level of the mid- to upper corporal region as the result of the fusion of the paramesonephric ducts during early ontogeny (Werth and Grusdew, 1898; Wetzstein, 1965; Leyendecker et al., 1998; Noe et al., 1999; Leyendecker, 2000; Leyendecker et al., 2004).

Adenomyosis results from the invasion of basal endometrial gland 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 (Leyendecker et al., 2002). Adenomyosis uteri is a histological diagnosis with certain criteria to be met (Bird et al., 1972; Ferenczy, 1998). Recently, on the basis of correlation studies, imaging criteria have been established, particularly with respect to magnetic resonance imaging (MRI), that allow the diagnosis of adenomyosis in vivo (Hricak et al., 1983; Brosens et al., 1995, Brosens et al., 1998; Reinhold et al., 1998).

Adenomyosis has been shown to be significantly associated with peritoneal endometriosis in infertile patients (Kunz et al., 2000a) and in baboons with lifelong infertility (Barrier et al., 2004). Directed sperm transport is significantly impaired in infertile women with pelvic endometriosis (Leyendecker et al., 1996), which may be caused by the destruction of the myometrial architecture by adenomyotic lesions. Therefore, it was suggested that uterine adenomyosis could constitute a major cause of infertility in pelvic endometriosis (Kunz et al., 2000a; Leyendecker, 2000). The present study was undertaken to extend previous results and to substantiate this notion further.

Patients and methods
Patients
A total of 227 women with regular menstrual cycles (mean 29 days, range 21–28) aged 17–46 years (mean 32.5) entered this study after
of the uterine corpus, respectively (Kunz et al., 2000a) and of the total myometrium on the height of the transition between the upper and lower half of the anterior and the dorsal wall (Werth and Grusdew, 1898; Kunz et al., 1998; Noe et al., 1999; Kunz et al., 2000a). The diameters of all patients were related to their own female infertility could be identified.

In the other 67 women (aged 21–46 years; mean 33.2), no endometriosis or any other pelvic disorder was obtained from laparoscopy. These women were termed the ‘total control’ group.

Since adenomyosis often develops in perimenopausal women with a history of fertility (Parazzini et al., 1997) and might therefore not be associated with a history of endometriosis, the data of this study were also analysed with the exclusion of women older than 36 years of age. The mean age of these women with endometriosis (n = 132) was 30.6 years (range 22–35) and that of those without endometriosis (n = 53) was 31.4 years (range 21–35).

Since all couples that entered the study had a history of infertility, it was not possible to use proven fertility in addition to negative gynaecological findings as a marker of normal reproductive potential of a female patient. Thus, a healthy female was defined as a patient with negative gynaecological findings including absence of endometriosis, with an age under 36 years of age and a male partner with <20% of motile sperm (range 0–15%; mean 5.3%) according to World Health Organization grade A classification (World Health Organization, 1999). It was assumed that under these conditions, the sterility of these women was largely an andrological one (Bundesausschuss, 2002). This group of women (n = 23) was termed the ‘healthy control’ group.

Patients with irregular menstrual cycles, bleeding disorders or abnormalities of the uterine structure such as fibromas or malformations were excluded from the study.

MRI

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

In the mid-sagittal plane, the following diameters and distances were measured: length of the endometrium from the internal os towards the fundus, length of the uterus from the internal os towards the fundal serosa, diameter of the subendometrial myometrium or archimyometrium (junctional zone) (Werth and Grusdew, 1898; Leyendecker et al., 1998, 2002; Noe et al., 1999; Kunz et al., 2000a) and of the total myometrium on the height of the transition between the upper and lower half of the anterior and the dorsal wall of the uterine corpus, respectively (Kunz et al., 2000a).

The diameters as measured by MRI in women with endometriosis were compared with those of the women without endometriosis. Furthermore, the diameters of all patients were related to their own medical history such as age, grade of the endometriotic disease and the intrapelvic distribution of endometriotic implants, and to the sperm quality of their male partners.

Furthermore, all MRI scans comprising all sagittal and transverse sections of the uteri were scrutinized for the existence of focal adenomyosis. In this study, diffuse adenomyosis was defined as the expansion of the posterior junctional zone (PJZ) and/or anterior junctional zone (AJZ) along the whole length of the uterine cavity and focal adenomyosis as expansions of variable shape and size that did not extend over the whole length of the uterine cavity.

Semen analysis

The semen analysis in all male partners was performed according the World Health Organization criteria (World Health Organization, 1999).

Statistical analysis

The statistical analysis was performed using the Student’s t-test and $\chi^2$ test. Significance was assumed when $P < 0.05$.

Results

In all women studied, the zonal anatomy of the uterus could be clearly identified. Figure 1 presents representative MRI scans of a normal uterus and of those with diffuse and focal adenomyosis. Very variable phenotypes of adenomyosis as documented by MRI can be obtained such as enlargement of the AJZ and/or PJZ or focal protrusions of variable size and location into the outer myometrium. When calculating the prevalence of adenomyosis in endometriosis, all these radiological signs, indicative of adenomyosis, were taken into consideration.

The size of the PJZ in patients with and without endometriosis

On a large-scale statistical basis, it is mainly the posterior wall that is affected and only exhibits, with respect to the enlargement of the junctional zone, a statistical difference between women with and without endometriosis (Table I; Figure 2). Therefore, all further statistical analysis, except that of the prevalence of adenomyosis, was based on the data of the PJZ. When patients of an age older than 36 years, who might develop ‘perimenopausal adenomyosis’, were excluded from the analysis, the differences in the thickness of the PJZ between women without and with endometriosis remained significant (Table II).

There is a positive relationship between age and diameter of the PJZ in women with endometriosis (Table II). The control group revealed the same trend, but did not reach statistical significance ($P = 0.07$).

There is also a relationship between the diameter of the PJZ and the stage of the endometriotic disease. Women suffering from minimal or mild endometriosis had a mean diameter of the PJZ of 10.5 ± 4 mm that differed significantly from the mean diameter of 12.5 ± 6.4 mm of those women with moderate and severe endometriosis ($P = 0.02$). However, both groups of women with endometriosis did not differ significantly with respect to their mean age (31.4 ± 5.5 versus 32.8 ± 4.3 years) (Table II).

Women suffering from deep infiltrating recto-vaginal endometriosis in addition to ovarian and pelvic peritoneal endometriotic implants demonstrated the highest mean...
diameter of the PJZ, with 13.1 mm ($n = 11$, SD 5.4 mm) measured in the dorsal mid-sagittal plane. If no recto-vaginal endometriosis but ovarian endometriotic cysts were present, the mean diameter of the PJZ was 12.4 mm ($n = 58$, SD 7 mm). However, this difference failed to reach statistical significance. The mean diameters of the PJZ in women with minimal to mild and moderate to severe endometriosis, respectively, were each significantly more expanded in comparison with the diameter of PJZ of the ‘total control’ group.

### Table 1. Measurements obtained from MRI scans of uteri in the mid-sagittal plane of women with and without endometriosis

<table>
<thead>
<tr>
<th></th>
<th>With endometriosis</th>
<th>Without endometriosis</th>
<th>Significance ($P$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of the uterus</td>
<td>52.1 ± 8.2</td>
<td>52.4 ± 7.0</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Length of the endometrium</td>
<td>38.5 ± 6.7</td>
<td>38 ± 6</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diameter of the anterior junctional zone</td>
<td>10.1 ± 4</td>
<td>9.2 ± 5.1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diameter of the anterior total myometrium</td>
<td>17.1 ± 3.6</td>
<td>18.2 ± 4.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Diameter of the posterior junctional zone</td>
<td>11.5 ± 5.3</td>
<td>8.3 ± 2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diameter of the dorsal total myometrium</td>
<td>19.8 ± 5.3</td>
<td>19 ± 3.1</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Mean values in mm ± SD.

**Figure 2.** Histogram of the data of all patients with ($n = 160$) and without endometriosis ($n = 67$). The comparison of the diameter of the posterior junctional zone and the posterior uterine wall, respectively, in women with and without endometriosis shows that adenomyosis is primarily an infiltrative process (mean ± SEM).

**The PJZ and sperm quality**

We further analysed the thickness of the PJZ in patients with and without endometriosis in relation to the sperm quality of the respective male partners. In 98 male partners of the 160 women with endometriosis and in 50 partners of the 67 women without endometriosis, a recent sperm count was performed in our institution. Women with endometriosis and male partners with a WHO grade A motility >19% had a mean diameter of the PLZ of 14.0 mm (SD 7.9 mm), while those women suffering from endometriosis with partners showing a type A motility <20% (mean 5.8%; range 0–14%) had a mean diameter of the PLZ of 10.2 mm (SD 3.4 mm; $P = 0.001$). No such differences could be observed in the group of women without endometriosis with respect to type A motility (7.2 ± 2.2 versus 8.4 ± 2.4 mm; $P > 0.05$, Figure 3). The mean grade of endometriosis or the mean age did not differ statistically.
Prevalence of focal and diffuse adenomyosis in patients with endometriosis

In the ‘healthy control’ group, the mean diameter of the dorsal PJZ was 7.8 mm with a maximum diameter of 10 mm. Of these 23 women, only two (9%) had minor signs of focal adenomyosis and no enlargement of the AJZ above 10 mm. In the ‘total control’ group, the prevalence of adenomyosis (focal and diffuse) was 28% (19 out of 67). This was due to seven cases with minor focal adenomyosis only, six cases with a thickness of 11 mm, three cases with a thickness of 12 mm and three cases with a thickness of 13 mm, respectively, of the AJZ or PJZ. In the total group of endometriotic patients, the prevalence of adenomyosis (focal and diffuse) was 79% (126 out of 160). This was significantly different (P < 0.05) from the prevalence of adenomyosis in the ‘total control’ and ‘healthy control’ group, respectively.

The prevalence of adenomyosis was also tested in women with endometriosis, aged under 36 years and with presumably fertile partners (WHO type A motility of >19%). It can be assumed that the infertility of these couples is due solely to the endometriotic disease. Thirty women fulfilled these criteria. Twenty of these women had diffuse adenomyosis as indicated by a diameter of the PJZ of >10 mm. In the 10 remaining women with a diameter of the PJZ of up to 10 mm (within the limits of ‘healthy control’), seven showed focal adenomyosis or widening of the AJZ. Thus, 27 of 30 patients with endometriosis at an age of <36 years and fertile male partners had signs of adenomyosis, giving a prevalence of 90%.

Discussion

Most of the major authors of the first half of the past century dealing with the disease considered pelvic endometriosis and uterine adenomyosis as variants of the same disease process (Meyer, 1919; Cullen, 1920; de Snoo, 1942). Also, Sampson (1927), although focusing mainly on the aetiology of the pelvic dissemination of the disease, mentioned uterine adenomyosis and referred to it as ‘primary endometriosis’. It was,
however, mainly his theory of the development of pelvic endometriosis (Sampson, 1927) that caused later authors to distinguish between pelvic endometriosis and uterine adenomyosis and to consider both as different disease entities (Ridley, 1968). Subsequently, this was further enforced by the fact that endometriosis is most frequently encountered by laparoscopy during a sterility work-up and the uterus evades histological examination in these patients for obvious reasons.

With the advent of high-resolution transvaginal sonography and particularly MRI, the morphological structure of the uterus can be assessed in vivo. With respect to both methods, criteria have been established that allow the diagnosis of adenomyosis. While this is, with respect to sonography, sometimes only possible with real-time measurements (Kunz et al., 2000a), MRI provides scans that can be analysed with scrutiny. The mean diameter of the normal junctional zone, representing the innermost myometrial layer, the stratum subvasculare or archimyometrium (Werth and Grusdew, 1898; Noe et al., 1999), has been established to be in the range of 7–8 mm (Reinhold et al., 1998; Kunz et al., 2000a). The diagnosis of adenomyosis by MRI is considered to be established with a thickness of the junctional zone of ≥12 mm. Within a thickness of 8–12 mm, the diagnosis of adenomyosis requires specific secondary criteria such as relative thickening of the junctional zone in a localized area, poor definition of borders or high signal intensity foci (Reinhold et al., 1998, Reinhold et al., 1999). In our study, the maximal diameter of 10 mm that we have obtained in the ‘healthy control’ group was taken as the cut-off value beyond which adenomyosis was assumed. Secondary findings (Reinhold et al., 1999) were always present in cases with a thickness of the junctional zone of 10–12 mm. MRI findings such as local destructions of or hypointense zones within a junctional zone of normal width (up to 10 mm), presumably representing subbasal adenomyosis (Bird et al., 1972), have not been taken into consideration in this study. The diagnosis of focal adenomyosis is usually simple in that these lesions present as hypointense protrusions with variable sizes and locations from the junctional zone into the outer myometrial wall. Peristaltic contractions may cause transient focal thickenings of the junctional zone.

Adenomyosis is a disease of the archimetra (Leyendecker et al., 1998, 2002; Noe et al., 1999). It results from the infiltration of basal endometrium into the underlying myometrium. The lesions are composed of endometrial glands, endometrial stroma and surrounding hyperplastic myometrium (Ferenczy, 1998). Only recently, evidence could be provided that the peristromal muscular tissue of the adenomyotic lesions is paramezonephric in character and homologous to the archimyometrium (Leyendecker et al., 2002). That is why uterine adenomyosis presents in MRI as a hypointense diffuse or focal broadening of the junctional zone (Brosens et al., 1995; Reinhold et al., 1998; Kunz et al., 2000a). In some instances, the expansion of the junctional zone appears to be rather homogenously hypointense; in other cases it appears ‘patchy’ and less hypointense. These differences can be attributed to the variable distribution and amount of glandular structures including stroma within adenomyotic lesions. Expanded junctional zones that are more homogenously hypointense could be considered as diffuse or focal archimyometrial hyperplasia rather than radiological signs of adenomyosis. Real-time transvaginal sonography that was performed in all patients in parallel did not, however, in such cases show just expanded ‘halos’ that were otherwise intact (homogenously hypodense) but rather signs of adenomyotic destruction such as hyperdense inclusions (Kunz et al., 2000a). Furthermore, our data show that, on a large statistical basis, the broadening of the junctional zone was infiltrative rather than expansive (Figure 2).

Statistically, there is a correlation between the stage of endometriosis and the depth of adenomyotic infiltration that becomes particularly apparent in patients with recto-vaginal endometriosis with a more expanded junctional zone than in patients with endometriosis of lower stage (Figure 4). Since the adenomyotic nodules communicate with the uterine cavity (Otto, 1957), pathophysiological a continuous process from initial to deep infiltration must exist. Our data show that endometriosis-associated adenomyosis progresses with age, corroborating previous data (Kunz et al., 2000a) (Table II; Figure 4).

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, as in perimenopausal women (Kaser et al., 1972; Novak and Woodruff, 1979), predominantly affected (Table I). This finding does not exclude a causative factor that involves the whole endometrium, but at least hints at a local and thus most probably mechanical component in the pathophysiology of adenomyosis. No data are available that show an increased mechanical stress of the posterior uterine wall due to chronic uterine peristalsis and hyperperistalsis and a relationship of the site of predilection of adenomyosis with ante- or retroflexion of the uterus.

Our data based on 160 MRI scans in women with and 67 MRI scans in women without pelvic endometriosis support our initial findings of a significant association between uterine adenomyosis and pelvic endometriosis (Kunz et al., 2000a). On the basis of the ‘healthy control’ group, the prevalence of 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%.

Thus, there is a high association between endometriosis and adenomyosis, and vice versa, but no complete coincidence of the two disease varieties. This is not surprising in view of our understanding of the disease process (Leyendecker et al., 2004). There is indirect evidence of an archimetal hyperestrogenism in women with endometriosis (Takahashi et al., 1989; Leyendecker et al., 2002; Absenger et al., 2004) that interferes with the ovarian control of uterine peristaltic activity resulting in uterine hyperperistalsis. Although these phenomena appear to be the common cause for the dislocation of basal endometrium into the uterine wall
and the peritoneal cavity, respectively, it can be assumed that for the manifestation of the two disease varieties, additional and specific as well as time-dependent factors are required.

The aetiology of infertility and subfertility in women with endometriosis and unimpaired tubo-ovarian anatomy and function is still a matter of debate (Akande et al., 2004). Medical and surgical eradication of peritoneal lesions does not improve (Hull et al., 1987; Adamson and Pasta, 1994) or normalize fertility (Marcoux et al., 1997) in women with patent tubes and unaffected ovaries, indicating that peritoneal endometriotic lesions do not constitute a major factor in causing sub- and infertility in these women. Therefore, the most striking finding of our study is the demonstration that the mean diameter of the PJZ was significantly larger in women with endometriosis and fertile partners than those with sub- or infertile partners. It has to be noted that there were no differences with respect to the grades of endometriosis and the age of the patients between these two groups. This, for the first time, indirectly documents that adenomyosis is a condition causing infertility and supports previous results and considerations that uterine pathology and dysfunction constitute factors causing infertility in endometriosis (Leyendecker et al., 1996, 1998). 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 (Kunz et al., 1996; Leyendecker et al., 1996) as a consequence of the destruction of the normal architecture of the archimyometrium. With the peristomal muscular cells of the adenomyotic lesions, a muscular tissue develops that is, in contrast to the archimyometrium with its circular muscle fibres, irregularly arranged. Moreover, this muscular tissue, since it is homologous to the archimyometrium (Leyendecker et al., 2002), is presumably responsive to the endocrine and paracrine stimuli that regulate uterine peristalsis (Kunz et al., 1998a, 2000b). This may result in increased intrauterine pressure (Mäkäräinen, 1988; Bulletti et al., 2002) and in dyserstalsis during the late follicular phase in women with endometriosis (Leyendecker et al., 1996, 1998).

This does, however, not exclude other ‘non-mechanical’ uterine factors leading to infertility in endometriosis such as the increased colonization of the endometrium with macrophages (Leiva et al., 1994) and a possible direct impact of the adenomyotic lesion with its secretory products on ovarian function. A number of studies demonstrated a diminished ovarian reserve, an impaired granulosa cell–oocyte environment and impaired oocyte quality and fertilization rates in patients with endometriosis (Simon et al., 1994; Hull et al., 1998; Pal et al., 1998; Azem et al., 1999). Our own preliminary data from IVF indicate that there is a correlation between the percentage of immature oocytes among those retrieved and the depth of adenomyotic infiltration (G. Kunz and G. Leyendecker, unpublished). The basal endometrium is, by virtue of the expression of P450 aromatase throughout the menstrual cycle (Leyendecker et al., 2002), a tissue capable of converting androgen into estrogen (Takahashi et al., 1989) and producing various substances that are mainly active in a paracrine way such as oxytocin, prostaglandins, growth factors and cytokines. Not only is the eutopic basal endometrium significantly enlarged in women with endometriosis in comparison with controls (Leyendecker et al., 2002), but 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 in both animals (Einer-Jensen, 1988) and humans (Kunz et al., 1998b; Cicinelli et al., 2004).

In conclusion, the data of this study further support our notion that pelvic endometriosis and uterine adenomyosis are
variants of the same disease process, which involves the dislocation of basal endometrium and results from a dysfunction and disease primarily at the level of the architecture. Moreover, uterine adenomyosis is an important factor in causing sub- and infertility in women with pelvic endometriosis by impairing directed sperm transport and possibly by directly affecting ovarian function via the utero-ovarian counter-current system.

References


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