Reproductive BioMedicine Online (2012) 24, 35–46

www.sciencedirect.com
www.rbmonline.com

REVIEW

Adenomyosis and infertility

Sebastiano Campo [a], Vincenzo Campo [a,*], Giuseppe Benagiano [b]

[a] *Institute of Obstetrics and Gynaecology, Catholic University of Sacred Heart, Rome, Italy;* [b] *Department of Obstetrics, Gynaecology and Urology, Sapienza, University of Rome, Rome, Italy*
[*] Corresponding author. *E-mail address:* vincecampo76@gmail.com (V Campo).

Prof Sebastiano Campo has been associate professor in the Department of Obstetrics and Gynecology at the Catholic University of the Sacred Heart in Rome since 1984. His special interests include ovarian physiology, infertility, endometriosis and polycystic ovary syndrome.

Abstract Today an accurate diagnosis of adenomyosis can be made thanks to progress in imaging techniques: sonography and magnetic resonance imaging (MRI). This has made it possible to clinically correlate the presence of adenomyosis to infertility. At the same time, a series of pathogenetic hypotheses have been presented to explain this correlation. First, the identification of the myometrial junctional zone (JZ) and of its disruption and thickening has been linked to poor reproductive performance mainly through perturbed uterine peristalsis, a phenomenon that originates exclusively from the JZ in the nonpregnant uterus. In addition, a number of biochemical and functional alterations in both eutopic and heterotopic endometrium in women with adenomyosis have now been found to lead to lower receptivity, indicated by the presence of 'implantation marker' defects. In these patients there is also an altered decidualization and abnormal concentrations of intrauterine free radicals. All these abnormalities in the endometrial environment seem to contribute to subfertility. Several attempts have been made to restore fertility in adenomyosis patients, the oldest being gonadotrophin-releasing hormone agonists coupled to conservative surgery. Also, uterine artery embolization and MRI-assisted high-intensity focused ultrasound ablation have been tried with some degree of success.

KEYWORDS: adenomyosis, infertility, junctional zone, myometrium, uterine environment, adenomyosis treatment

Introduction

Adenomyosis has been defined by Bird et al. (1972) as the 'benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic, non-neoplastic, endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium'. The disease has been recognized since the end of the 19th century, but during the first quarter of the 20th century, all mucosal invasions in the peritoneal cavity or within the uterine walls were labelled 'adenomyomas'. It is noteworthy that the recognition that they were nests of endometrial cells and stroma took time to be accepted by all (Benagiano and Brosens, 2011). Then, in 1925, Frankl separated 'true adenomyoma', which he considered a very rare condition, from the simple invasion of uterine mucosa into the myometrium that he defined 'adenomyosis', stressing the fact that it was not a situation

1472-6483/$ - see front matter
doi:10.1016/j.rbmo.2011.10.003

caused by an inflammatory reaction (Frankl, 1925). Two years later, Sampson described the endometrial invasion of the peritoneal cavity through retrograde menstruation and called this condition 'endometriosis' (Sampson, 1927). From that moment on these two entities were considered separate pathologies, developing through different mechanisms. This separation became even more striking in the 1960s when laparoscopy was introduced, revolutionizing the diagnosis and management of endometriosis but leaving behind adenomyosis, which continued to be identified only with hysterectomy specimens. Soon after, the presence of even mild forms of endometriosis was linked to a condition of subfertility and a series of medical and surgical treatment options were attempted (De Ziegler et al., 2010). This in turn, caused a relative neglect of adenomyosis, with its only retrospective diagnosis. The situation, however, changed dramatically in the mid-1980s, when noninvasive, imaging techniques became available, enabling a preoperative diagnosis also for adenomyosis (Dueholm, 2006; Meredith et al., 2009; Tamai et al., 2006). This elicited new interest by the scientific community, in turn providing a better understanding of the disease and its pathophysiology and creating the basis for new treatment modalities (Benagiano et al., 2009). As a consequence, evidence began to accumulate also linking adenomyosis to a condition of subfertility and prompting the design of new treatment modalities.

This review briefly reports: (i) the new imaging techniques that have made possible a noninvasive diagnosis of adenomyosis; (ii) clinical and epidemiological evidence pointing to the possibility that adenomyosis can cause infertility; (iii) pathophysiological mechanisms through which adenomyosis can cause infertility; and (iv) modern treatment modalities that have been successfully applied over the last decade.

New imaging techniques and their impact on noninvasive diagnosis and pathophysiology studies

Some 25 years ago, the application of magnetic resonance imaging (MRI) to the study of the female reproductive tract resulted in the identification of a new functional uterine zone: the junction between the endometrium and the inner myometrium (Hricak et al., 1983). This zone, known as the junctional zone (JZ) myometrium, possesses a specific characteristic that distinguishes it from other similar junctions in the human body: it lacks a recognizable protective layer or membrane, a true submucosa. This means that endometrial glands lie in direct contact with the myometrium (Fusi et al., 2006). Today, through MRI T2-weighted images, in the uterus of healthy women of reproductive age, three distinct layers can be displayed (Tamai et al., 2006): (i) the innermost zone with a high signal intensity, corresponding to the endometrial stripe; (ii) an intermediate inner low-signal-intensity area adjacent to the basal endometrium, the JZ myometrium, or subendometrial layer, measuring in healthy young women $\leq$5 mm in thickness; and (iii) an outer medium-signal-intensity zone extending all the way to the serosal layer, or outer myometrium. An early study by Wiczyk et al. (1988) indicated the existence of cyclical changes in the thickness of the JZ, mimicking those of the endometrium and characterized by maximum growth between days 8 and 16. In a more recent study by Hoad et al. (2005), the thickness of a normal JZ was found to be around 4 mm on average and can vary during the cycle by 0.9 mm on average. Finally another recent MRI study did not find a significant difference in JZ thickness between the two phases of the menstrual cycle in 100 healthy women (Hauth et al., 2007). The consensus today is that using MRI adenomyosis can be strongly suspected when the JZ thickness is $\geq$12 mm, although in approximately 20% of premenopausal women there is an absence of a definable JZ on imaging (Novellas et al., 2011). A diagnosis can be made even when thickness is $<$12 mm, if other signs (such as high-signal spots or an irregularly bounded JZ) are present (Reinhold et al., 1998) (**Figure 1**).

Adenomyosis can also be diagnosed through three-dimensional (3D) ultrasonography. In a very recent paper, Exacoustos et al. (2011) have correlated 2D and 3D transvaginal ultrasound imaging (TVS) with histopathological features of adenomyosis in a total of 72 premenopausal patients. The most specific 2D-TVS feature for the diagnosis of adenomyosis was presence of myometrial cysts (98% specificity; 78% accuracy), whereas a heterogeneous myometrium was most sensitive (88% sensitivity; 75% accuracy). On 3D-TVS, the best markers were JZ difference $\geq$4 mm and JZ infiltration and distortion (both 88% sensitivity; 85% and 82% accuracy, respectively).

As a consequence of these investigations, the JZ has emerged as a hormone-dependent structure that governs uterine peristalsis outside pregnancy. Suppression of ovarian activity, for example during hormonal contraception or

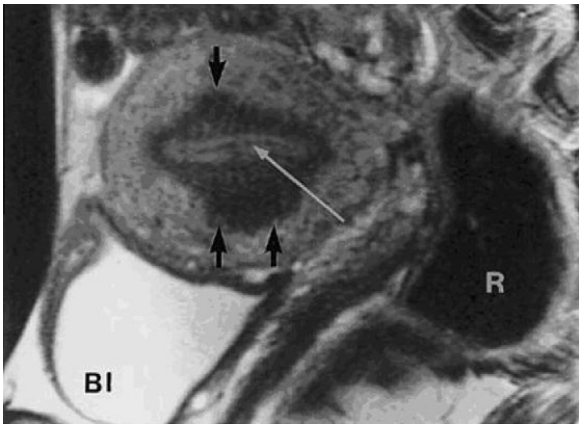

Figure 1 Adenomyosis as identified through focal thickening of the myometrial junctional zone (JZ). Sagittal T2-weighted magnetic resonance image demonstrates focal thickening of the JZ (short arrows) both ventrally and dorsally, consistent with adenomyosis. Although the maximal thickening of the JZ ventrally was $<$12 mm, the focal nature of the thickening suggests adenomyosis. Note the absence of mass effect on the endometrial cavity. The linear area of low signal within the endometrial cavity (long arrow) represents menstrual blood. Bl = bladder; R = rectum.

following administration of a gonadotrophin-releasing hormone analogue, results in an indistinct appearance on MRI of the myometrial layers, a feature observed in postmenopausal women in whom use of hormone replacement therapy results in the reappearance of the typical zonal anatomy (McCarthy et al., 1986).

Birnholz (1984) has documented the presence in the myometrium of distinct contraction waves: using transabdominal ultrasound, he showed that uterine peristaltic activity originates exclusively from the JZ, while the outer myometrium remains quiescent. During the follicular and periovulatory phases, contraction waves have a cervico-fundal orientation and their amplitude and frequency increase significantly towards the time of ovulation. These waves seem implicated in many aspects of physiological reproductive processes, from endometrial differentiation (Bulletti and De Ziegler, 2006) and menstruation (Oki et al., 2002) to sperm transport (Ijland et al., 1997) and implantation (Turnbull et al., 1995).

Subsequently, Kunz et al. (1996), using technetium-labelled inert albumin microspheres placed in the cervix during late follicular phase, showed that myometrial contractions can quickly transport and preferentially direct these microspheres towards the tubal ostium on the side of the dominant follicle. Then, during the luteal phase, uterine activity decreases under the influence of progesterone and myometrial contraction waves become short and asymmetrical, often running in opposing directions. This reduced activity may help the blastocyst to implant near the fundus and perhaps facilitates local supply of nutrients and oxygen (Ijland et al., 1997). In addition, in humans, interstitial and intravascular trophoblast invasion goes beyond the endometrium and involves the JZ, but not the outer myometrium (Brosens et al., 2002). Finally, MRI during a conception cycle shows, 7 days post-ovulation (a time coinciding with embryo implantation), focal disruption of the JZ signal intensity (Turnbull et al., 1995).

These physiological phenomena are altered in the presence of adenomyosis, and therefore it seems logical to assume that the condition may cause hypo- or infertility in affected women.

Clinical and experimental evidence of association between adenomyosis and infertility

The fact that until two decades ago the diagnosis of adenomyosis could only be made at surgery, usually in women in their late thirties and forties (Lee et al., 1984), made it impossible to evaluate its effects on fertility. Even today a preoperative diagnosis of adenomyosis remains sporadic and limited to a relatively small number of centres. Although in the event of the rare adenomyoma, myomectomy can successfully treat the associated infertility (Honorè et al., 1988), the situation only began to change after the advent of high-resolution imaging techniques.

The hypothesis of a possible link between adenomyosis and infertility is becoming more and more plausible thanks to the observation that adenomyosis is present even in younger women and can be associated with pelvic endometriosis and infertility (Kissler et al., 2007; Kunz et al., 2005; Leyendecker et al., 2006; Zacharia and O'Neill, 2006). Kunz et al. (2007) have found that an increase in the diameter of the dorsal JZ of the uterus (a sign of invasion of basal endometrium into the JZ) is already evident early in the third decade of life and that in women with endometriosis the mean thickness of the JZ is increased even in young women when compared with healthy controls.

Unfortunately, it is difficult to evaluate the incidence of adenomyosis even in the general population, since — until recently — data were obtained only at hysterectomy, obviously referring only to the most severe forms. In summarizing available evidence, Benagiano et al. (2009) mention that new information is beginning to appear; de Souza et al. (1995) detected MR pattern consistent with a diagnosis of adenomyosis in 54% of young women with infertility, dysmenorrhoea and/or menorrhagia, but as of today it is impossible to draw conclusions valid for the general population. In addition, evidence is accumulating of a relationship between adenomyosis and endometriosis. Bazot et al. (2004) found that 27% of women with endometriosis concomitantly had adenomyosis. This percentage rose to 70% in a study conducted by Kunz et al. (2005).

Although clinical data are scarce and epidemiological information simply doesn't exist, some experimental evidence is available. Observations in knock-out mice indicate that their gestational capacity is impaired if these animals are deprived of perforin (a protein produced by lymphocytes that induces apoptosis in target cells) and treated with interleukin (IL) 2 that induces a thickening of the subendometrial myometrium in the absence of perforin (Kusakabe et al., 2005). Furthermore, it has been shown that in baboons, endometriosis is statistically significantly associated to adenomyosis and the latter is strongly associated with lifelong primary infertility (Barrier et al., 2004).

As pointed out by Soares et al. (2008), a good model for the study of possible influences of adenomyosis on fertility is represented by women requesting oocyte donation followed by IVF. Unfortunately, no data exist in the literature showing what impact, if any, the presence of adenomyosis might have on endometrial receptivity in oocyte donation cycles. What is known is that, in IVF cycles, an increased uterine JZ activity just before embryo transfer is associated with a reduced pregnancy rate and an increase in the frequency of ectopic pregnancy (Lesny and Killick, 2004). Piver (2005) investigated JZ thickness and implantation failure in IVF cycles concluding that MRI evaluation of JZ thickness is the best negative predictive factor of implantation failure. In fact, they observed that in patients with JZ $<$10 mm the pregnancy rate was 45% per transfer, while rates as low as 16% and 5% were observed with JZ thicknesses 10—12 mm or $>$12 mm, respectively.

Recently, the same group (Maubon et al., 2010) in a prospective investigation involving 152 patients studied the influence of the uterine JZ thickness, measured by means of MRI, on implantation rates during IVF. They found that the increase in JZ can be significantly correlated with implantation failure at IVF: implantation failure rate was 95.8% in patients with an average JZ of 7—10 mm versus 37.5% in all other subjects ($P < 0.0001$), independently of the cause of infertility or patient age.

Pathophysiology of adenomyosis-associated infertility

As already mentioned, today adenomyosis is defined as the 'benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic, non-neoplastic endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium' (Bird et al. (1972). Bergeron et al. (2006) mention three pathogenetic theories formulated to explain the formation of adenomyosis: the first two involve an origin from the invagination of the deepest portion (basalis) of the endometrium between bundles of smooth muscle fibre of the myometrium or along the intramyometrial lymphatic system. The third theory is based on the common origin of the JZ myometrium and endometrium from Müllerian ducts, composed of pluripotent cells, and postulates that adenomyosis may originate and ultimately develop through metaplasia from ectopic intramyometrial endometrial tissue produced *de novo*.

Irrespective of its origin, recently a simple classification for adenomyosis has been proposed by Gordts et al. (2008) based on MRI analysis of the uterine JZ: (i) simple JZ hyperplasia (zone thickness $\geq$8 mm but $<$12 mm on T2-weighted images, in women aged 35 years or less); (ii) partial or diffuse adenomyosis (thickness $\geq$12 mm; high-signal-intensity myometrial foci; involvement of the outer myometrium: $<$1/3, $<$2/3, $>$2/3); and (iii) adenomyoma (myometrial mass with indistinct margins of primarily low-signal intensity on all MRI sequences).

Evidence is accumulating that there is a close relationship between the occurrence of adenomyosis and structural and functional defects in eutopic endometrium and myometrial uterine JZ; in turn, these abnormalities may cause implantation failure and infertility.

What follows is an analysis of factors that may contribute to subinfertility or infertility in women with adenomyosis.

Gene dysregulation

Recently, Liu et al. (2008) carried out a proteomic analysis of the adenomyotic tissue in women with adenomyosis and found 12 dysregulated proteins compared with the protein profiling of normal uterine muscle. The study identified 10 of them, suggesting that biomarkers might be utilized for diagnostic purposes.

Altered uterine peristaltic activity

One of the plausible explanations for the impact of adenomyosis on fertility is an impairment of the rapid, sustained and accurately directed sperm transport through the uterus as a consequence of the destruction of the normal architecture of the 'archimyometrium' (the JZ myometrium) (Kunz and Leyendecker, 2002).

Quinn (2007) has recently found that adenomyosis is associated with loss of nerve fibres at the endometrium–myometrium interface and absence of nerve fibres in the adenomyosis, although focal proliferation of small-diameter nerve fibres was observed at the margins of adenomyosis in some uteri. Subserosal nerve fibres were still present in those sections that extended to include this region. In addition, in the presence of adenomyosis, myocytes exhibited cellular hypertrophy, leading Mehasseb et al. (2010) to conclude that smooth muscle cells from uteri with adenomyosis are ultrastructurally different from smooth muscle cells of normal uteri.

In 2005 Kunz et al. postulated that adenomyosis interfered with fertility by impairing uterine sperm transport and a year later assessed the impact on fertility of adenomyosis associated with endometriosis and proposed that the threshold value for a diagnosis of adenomyosis be set at 10 mm (Kunz et al., 2005, 2007).

In an elegant experiment, Kissler et al. (2006) placed into the posterior vaginal fornix 99m-Tc-labelled macro-albumin aggregates (with a size of 5–20 μm mimicking sperm size) and scanned with a gamma camera immediately after application and at various time intervals up to 30 min. They were able to show in fertile women a positive, uni- and ipsilateral transport of radionuclides to the side bearing the dominant follicle. In contradistinction to this, in women with diffuse adenomyosis and primary infertility no uterotubal transport could be detected and radionuclides remained in the uterine cavity in 70% of the cases. In an additional 22% of the women transport was contralateral, whereas it was ipsilateral in only 8% of the cases. Interestingly, studying 41 subjects with endometriosis, they detected signs of adenomyosis in 85% of them; this has been taken as an indication that infertility in at least some cases with endometriosis may be explained by the contemporary presence of adenomyotic foci. In this regard, Kido et al. (2007), using cine-MRI, have shown that uterine peristalsis appears to be suppressed during the periovulatory phase also in patients with endometriosis.

Altered endometrial function and receptivity

Following ovulation, corpus luteum secretion produces a receptive endometrium creating the so-called 'implantation window' believed to occur between 7 to 10 days following the LH surge. Implantation is a delicate process beginning with the attachment of the blastocyst to the decidualized maternal endometrium and can be considered as a controlled invasion of the trophectoderm promoted by complex networks of interrelated receptors and signalling molecules. Thus, nidation involves multiple communications between the early embryo and the decidualized endometrium, with signalling back to the corpus luteum.

Although a proper secretory endometrium is a key factor for implantation and therefore 'secretory-phase defects' are to be considered as a cause of infertility (Liu et al., 1995), Bromer et al. (2009) have now introduced the concept of 'proliferative-phase defect' in subfertile patients, making proper proliferation of the endometrium an equally important factor. They have documented how, in subjects with polycystic ovary syndrome, as well as in women affected by endometriosis, the so-called 'endometrial plateau' thickness is significantly lower than in control patients. Indeed, endometrial growth begins from a nadir of approximately 4.5 mm on day 4 of the cycle and proceeds

linearly 1 mm per day to a plateau of approximately 10 mm by day 9.

An aberrant endometrial development throughout the proliferative phase has not been documented in women with adenomyosis, although there is altered endometrial vascularization as well as changes in endometrial molecular markers of inflammation (Ulukus et al., 2006). This early phenomenon may lead to abnormalities of the secretory phase and ultimately to impairment of implantation. Indeed, vascular distribution of both eutopic and heterotopic endometrium in adenomyosis is different from that of normal fertile patients. In normal women, mean and total surface area and total number of capillaries significantly increases during the secretory phase of the cycle. In contrast, in cases of adenomyosis, the above parameters are increased in both the proliferative and secretory phase compared with fertile women. In particular, the total surface area of capillaries per mm^2 can rise by more than 10 times compared with the proliferative phase in fertile women, suggesting that, in cases with adenomyosis, regulatory factors involved in the endometrial vascular proliferation are exaggerated (Ota and Tanaka, 2003). Clinically, the abnormal vascularization of the endometrium is closely related to hypermenorrhoea.

A whole series of functional abnormalities at the molecular level have been described in the eutopic as well as heterotopic endometrium of women with adenomyosis (**Table 1**). Li et al. (2006) evaluated the expression of two matrix metalloproteinases (MMP2 and MMP9), enzymes expressed in the human endometrium as a consequence of cellular events during the menstrual cycle that require extracellular matrix remodelling. They also studied a major mediator of angiogenesis and vascular permeability, the vascular endothelial growth factor (VEGF) and microvessel density (MVD). In both eutopic and ectopic endometrium of subjects with adenomyosis they found a significantly greater activity than in normal endometrium. Specifically, MVD was higher in ectopic than in eutopic endometrium, with or without adenomyosis. In adenomyosis, a positive correlation was observed between the expression of VEGF and that of MMP2, as well as MMP9. A positive correlation was also found between expression of MVD and MMP2 or MMP9. These findings indicate that the elevation of MMP2 and MMP9 expression may represent an important factor in the development of the disease, contributing to invasion of endometrial tissues into the myometrium and angiogenesis in adenomyotic implants. Similar results for MMP2 were obtained by Tokyol et al. (2009). Subsequently, Goteri et al. (2009) compared in the same women the expression of VEGF and hypoxia-inducible factor-1α (HIF-1α) by heterotopic versus normotopic endometrium in women with adenomyosis and found that both were increased, particularly in epithelial cells. Furthermore, Kang et al. (2009) investigated four VEGF polymorphic alleles and found significant differences between adenomyosis patients and a control group in the allele frequencies and genotype distributions. It seems that the presence of two alleles of the VEGF gene may significantly decrease the risk of adenomyosis, potentially representing protective factors for its development.

Finally, 15 years ago, it was suggested that endometriotic tissue may actively contribute to the biological changes observed in the peritoneal fluid of endometriosis patients (Akoum et al., 1996), through changes in IL-6 secretion, and indeed Yang et al. (2006), studying eutopic endometrium in women with adenomyosis, found an improper secretion of IL-6. In addition, IL-8 may be involved. This is a cytokine that acts as an endometrial autocrine and paracrine factor and regulates many physiological processes at the time of menstruation, including remodelling of the endometrium (Garcia Velasco and Arici, 1999). Two specific receptors for IL-8 have been identified on the surface of human neutrophils — CXCR1 (IL-8RA) and CXCR2 (IL-8RB) — and Ulukus et al. (2006) have observed that, in eutopic endometrium of women with adenomyosis, proliferative-phase samples have higher epithelial IL-8 receptors CXCR1 and CXCR2 immunoreactivity compared with normal

Table 1 Implantation factors with altered concentrations in adenomyosis-associated infertility.

Publications	*Factors affected*	*Effect*
Goteri et al. (2009)	Hypoxia-inducible factor-1α (HIF-1α)	Increased
Yang et al. (2006)	Interleukin-6	Increased
Ulukus et al. (2006)	Interleukin-8 receptor CXCR1—CXCR2	Increased
Wang et al. (2009)	Interleukin-10	Increased
Li et al. (2006), Tokyol et al. (2009)	Matrix metalloproteinases (MMP2 and MMP9)	Increased
Li et al. (2006), Goteri et al. (2009)	Vascular endothelial growth factor	Increased
Li et al. (2006)	Microvessel density (MVD)	Increased
Yen et al. (2006), Xiao et al. (2010)	Leukaemia inhibitory factor (LIF)	Decreased
Yen et al. (2006)	Interleukin-11	Decreased
Yen et al. (2006)	LIF-receptor α	Decreased
Fischer et al. (2011)	*HOXA10*	Decreased
Wicherek (2009)	RCAS1	Decreased
Lessey et al. (2006)	Cytochrome P450	Increased
Ota et al. (1999)	Nitrogen oxide synthase, xanthine oxidase, superoxide dismutase	Increased
Igarashi et al. (2002)	Catalase	Increased

proliferative-phase samples. IL-10 is one of the major anti-inflammatory cytokines and plays an important role in several chronic inflammatory diseases and cancers. Recently in eutopic and ectopic endometrium of women with adenomyosis, epithelial cells have shown higher staining intensity for IL-10 than normal controls (Wang et al., 2009). These findings suggest that an abnormal inflammatory response may be present in eutopic and ectopic endometrium of women with adenomyosis and this may impair fertility, and in this connection Yen et al. (2006) have demonstrated that, during the implantation window, a number of implantation markers are decreased in the endometrium of women with adenomyosis, suggesting that a significant decrease in the expression of leukaemia inhibitory factor (LIF), LIF receptor α and IL-11 may be one of the molecular mechanisms associated with the decreased implantation rate observed in these women.

Impaired implantation

A lack of expression of specific proteins, such as cell-adhesion molecules can lead to implantation failure. Numerous cell-adhesion molecules (including integrins, selectins and cadherins) are expressed by the endometrium and appear to be necessary for the successful interaction between embryo and endometrium (Lessey et al., 1994a,b). These have been called 'implantation markers' and their evaluation has been proposed as a means of distinguishing between receptive and nonreceptive endometria in clinical practice. The expression of α-4,β-3 integrin and the formation of pinopodes are the two best-known markers postulated to frame the window of implantation and in this context integrins are perhaps the best-studied markers of endometrial receptivity. The α-4,β-3 integrin appears on the surface of epithelial cells of both embryo and endometrium and on maternal surfaces around cycle days 19–20 and continues to be expressed during pregnancy (Lessey et al., 1994a). This integrin is present in normal fertile patients but is missing in a subset of women with unexplained infertility and endometriosis (Lessey et al., 1994b). Indeed, aberrant endometrial expression of the integrin subtype α-5,β-3 occurs with high frequency in patients with prior IVF failure despite good embryo quality (Surrey et al., 2007). In the endometrium, osteopontin binds to integrin α-5,β-3 (vitronectin) and α-4,β-1, giving rise to speculation that it may mediate trophoblast-endometrial interactions during implantation.

Very little is known on changes in implantation markers in women with adenomyosis and knowledge is almost exclusively based on observations in women with endometriosis and on similarities in the endometria of subjects with the two conditions. For instance, it has been found that glycodelin and osteopontin are down-regulated in women with endometriosis (Wei et al., 2009) and, although it is not yet known whether the same situation exists in the case of adenomyosis, it is possible that also in this condition these acidic extracellular matrix glycoproteins, regulated by progesterone and determinant in embryo attachment, may be down-regulated. Since glycodelin is secreted by endometrial glands during the secretory phase and suppresses the maternal immune response supporting the implantation of the blastocyst (Seppälä et al., 2000), its down-regulation may impair implantation.

An important factor that seems to be involved in impairing implantation in women with adenomyosis involves the HOXA10 gene, the expression of which is necessary for implantation. Satokata et al. (1995) have shown that Hoxa10-deficient mice ovulate normally, but implantation does not occur. However, when their embryos are transferred to wild-type mice, implantation is restored. Conversely, wild-type embryos do not implant in Hoxa10 (−/−) mice. In the human it has been shown that a cyclical endometrial expression of Hoxa10/HOXA10 (with a peak expression occurring during the window of implantation) is observed in response to oestrogen and progesterone stimulation (Taylor et al., 1998). The activity of this gene is diminished in women with endometriosis, as well as other conditions associated with abnormal implantation (Taylor et al., 1999) and recently it has been shown that in women with adenomyosis HOXA10 gene expression is significantly lower during the midsecretory phase compared with fertile controls and diminished expression of HOXA10 is therefore a potential mechanism to explain the decreased implantation observed in women with adenomyosis (Fischer et al., 2011). Another factor associated to endometrial receptivity that has been proposed as an 'implantation marker' (Aghajanova, 2004) is the already-mentioned LIF, which during the mid–late secretory phase is expressed predominantly in the glandular and luminal epithelium (Dimitriadis et al., 2005). Mikolajczyk et al. (2006) found that LIF concentrations in uterine flushing fluid during the implantation window are lower in women with infertility compared with healthy controls. A recent study by Xiao et al. (2010) has shown that LIF expression is decreased in the endometrium of women with adenomyosis during the midsecretory phase. In addition, women with adenomyosis and a history of infertility showed significantly lower LIF concentrations in uterine flushing fluid, compared with fertile controls.

Altered decidualization

The successful establishment and maintenance of pregnancy requires decidualization, an extensive remodelling of maternal endometrium, followed by a co-ordinated trophoblast invasion (Brosens et al., 1999). Klemmt et al. (2006) has now suggested that in women with endometriosis the signalling cascade leading to decidualization might be impaired, potentially decreasing the biochemical maturation required for successful implantation. In addition, women with endometriosis display progesterone resistance (Burney et al., 2007) and their eutopic endometrium shows an impaired decidualization, a fact with important implications for uterine receptivity (Minici et al., 2007, 2008). The decidualization is associated with an increase in endometrial expression of proteins involved in the suppression of immune cell activity. One of them, RCAS1, is responsible for the inhibition of growth and activation of NK cells and T lymphocytes and also for their apoptosis. Recently, Wicherek (2009) showed that in normal women the highest serum concentrations of RCAS1 are found during the secretory phase and the lowest during the proliferative phase, while in patients with adenomyosis the concentration of

sRCAS1 remain almost constant. Lessey et al. (2006) have studied the relationship between expression of oestrogen receptor α and defective uterine receptivity in humans. In fertile patients the pattern of expression for oestrogen receptor α changes throughout the menstrual cycle: it is increased in glandular, luminal and stromal compartments in the proliferative and early secretory phases in response to oestrogen; subsequently, there is a decline in the mid- and late-secretory phases in response to progesterone. In the endometrium, decline in expression during the secretory phase may be a critical event, exercising an inhibitory influence on specific genes and providing a signal for the establishment of endometrial receptivity under the influence of progesterone. In patients with endometriosis, oestrogen receptor α is constantly higher and does not decrease in the midluteal phase, thus, its continued expression in mid-luteal endometrium may represent the best biomarker of a dysfunctional endometrium.

As already mentioned, in adenomyosis IL-6 is overexpressed (Yang et al., 2006) and this could lead to increased oestrogen receptor-α expression since IL-6 can activate oestrogen receptor in breast cancer cells (Fontanini et al., 1999).

Another cause of implantation failure may be represented by an altered intraendometrial steroid metabolism due to overexpression of cytochrome P450 (Kitawaki et al., 1997) and, indeed, significantly lower clinical pregnancy rates (with similar numbers of retrieved oocytes and replaced embryos with respect to controls) in IVF/embryo transfer have been reported in women with an overexpression of endometrial aromatase (Brosens et al., 2004).

According to Lessey et al. (2006), overexpression of P450 aromatase in women with adenomyosis increases local oestrogen production within the endometrium. This condition, associated with defects in progesterone receptors and loss of its action, might alter the balance between oestrogen and progesterone and result in the persistence of oestrogen receptor α, given that down-regulation of this receptor is one of the primary functions of progesterone. The overexpression of oestrogen receptor α in mid-secretory phase reduces the secretion of β-3 integrins negatively regulated by oestrogens thereby altering uterine receptivity.

Very recently, Mehasseb et al. (2011) have postulated that oestrogen receptor-β expression and the lack of PR expression may be related to the development and/or progression of adenomyosis and might explain the poor response of adenomyosis-associated menstrual symptoms to progestational agents.

Abnormal concentrations of intrauterine free radicals

Another possible cause for infertility in adenomyosis patients is the presence of abnormal concentrations of intrauterine free radicals, because a low-oxygen environment in the uterus is a prerequisite for implantation. An excessive free radical environment damages fertilized eggs and inhibits embryo development and pregnancy. Some of the enzymes producing or eliminating free radicals are xanthine oxidase (XO), superoxide dismutase (SOD), glutathione peroxidase (GPx) and nitric oxide synthase (NOS). XO produces superoxide, whereas SOD eliminates superoxide by converting it to hydrogen peroxide that is then converted to water and oxygen by glutathione, simultaneously producing hydroxyl radicals, which are powerful free radicals and can be eliminated by GPx. Enzymes associated with free radicals are present in the glandular epithelium of the endometrium in humans and their concentration varies dynamically depending on the menstrual phase. In normal women, concentrations of SOD and NOS in the endometrium are low during the proliferative phase and increase during the early and mid-secretory phases (Narimoto et al., 1990; Telfer et al., 1995). In women with endometriosis and adenomyosis, NOS, XO and SOD concentrations do not fluctuate during the menstrual cycle and are overexpressed (Ota et al., 1999). Finally, expression of catalase, an enzyme that directly catalyses the decomposition of hydrogen peroxide into water and oxygen, also fluctuates during the menstrual cycle in the glandular epithelium of fertile patients. In contradistinction to this, in women with adenomyosis, catalase scores not only do not fluctuate but are consistently higher (Igarashi et al., 2002).

Thus, available evidence strongly suggests that generation of nitric oxide, superoxide and other free radicals is heightened in women with adenomyosis. Since low concentrations of free radicals are believed to create an ideal environment for embryonic development during the period in which fertilized eggs divide (Noda et al., 1991), alterations in the expression of these enzymes may impair early embryo development. In fact, in the presence of abnormal concentrations of free radicals, the embryo may be attacked by activated macrophages or T cells or be exposed to an excess of nitric oxide, which results in early miscarriage (Ota et al., 1998).

Treatment of adenomyosis-associated infertility

As already mentioned, an increasing volume of information is becoming available on new modalities for the management of infertility-associated endometriosis (de Ziegler et al., 2010). In contrast to this, data available on treatment of infertility associated with adenomyosis are still fairly limited and mostly confined to case reports or uncontrolled small series. An early report on the possibility of surgically treating adenomyosis-associated infertility was published by Honorè et al. (1988), although in the three reported cases the disease presented itself in the less common form of adenomyoma.

A new conservative technique to be employed in women with adenomyosis wishing to become pregnant has just been published (Osada et al., 2011). Indications for surgery were based on size and extent of lesions. They had 38 cases of anterior (36.5%), 44 of posterior (42.3%) and 22 (21.2%) involving both anterior and posterior sides of the uterus. With the new technique of 'adenomyomectomy', adenomyotic tissues are radically excised and the uterine wall is reconstructed by a triple-flap method, without overlapping suture lines. This should effectively prevent uterine rupture in subsequent pregnancies. Of 26 women who wished to

conceive, 16 became pregnant and 14 (53.8%) carried their pregnancy to term, delivering a healthy infant, with no cases of uterine rupture. Obviously, before the new technique can be widely accepted, this uncontrolled study should be confirmed and validated by others.

Medical and combined medico-surgical treatment

No systematic study of any medical regimen aimed at treating infertility associated with adenomyosis has ever been attempted, although a variety of drugs have been employed over the last 20 years (Fedele et al., 2008). The first agents utilized for this purpose were gonadotrophin-releasing hormone agonists (GnRHa) (Grow and Filer, 1991) and several case reports or small series have been published of successful treatment of adenomyosis-associated infertility with GnRHa, given alone or in combination with surgery. In this respect it is noteworthy that aromatase cytochrome P450, the enzyme that catalyses the conversion of androgens to oestrogens, is overexpressed in women with endometriosis and adenomyosis, and that therapy with GnRHa decreases expression of aromatase cytochrome P450 in the eutopic endometrium of women with adenomyosis and endometriosis (Ishihara et al., 2003). This effect has been recently confirmed in women with endometriosis by Kim et al. (2009).

It has also been shown that GnRHa do not significantly influence the extent of decidualization of endometrial stromal cells derived from fertile women during the implantation window; furthermore, they seem to have no adverse effect on human blastocyst invasion (Klemmt et al., 2009). In addition, GnRHa can suppress the expression of nitric oxide synthases and, as a consequence, the generation of peroxynitrite in women with adenomyosis. This compound is known for causing tissue injury (Kamada et al., 2000). Finally, prolonged pretreatment with GnRHa before IVF has been reported to improve clinical pregnancy rates in infertile women with endometriosis (Tavmergen et al., 2007). Although, no data are available on women with adenomyosis, it seems reasonable to infer that also in this case pretreatment may be beneficial.

It seems therefore that GnRHa can have specific effects in women with adenomyosis (and endometriosis), over and above the suppression of ovarian oestrogen production.

In 1993 the group of Moghissi (Hirata et al., 1993) was the first to obtain a pregnancy after a 6-month course of nafarelin acetate; following discontinuation of treatment, the patient conceived quickly, but later experienced a spontaneous abortion. The following year Silva et al. (1994) published the first term pregnancy in a patient with a 10-year history of secondary infertility, after 5 months of therapy with GnRHa. These early reports were followed by small series of successful combined (GnRHa plus surgery) treatment in women with adenomyosis seeking pregnancy. The first report came from Taiwan (Huang et al., 1998) and described the case of a woman with long-term secondary infertility that had a successful pregnancy after treatment with cytoreductive surgery and a subsequent 6-month course of GnRHa therapy. From their case, authors concluded that early combined GnRHa treatment immediately after cytoreductive surgery and a delay of 4–6 months before attempting to become pregnant promises to become a novel method for women with adenomyosis who wish to conceive. The following year a Japanese group (Ozaki et al., 1999) published a case of a successful term pregnancy delivered by Caesarean section, following conservative surgery for severe adenomyosis and preoperative therapy with GnRHa. The woman had a 5-year history of secondary infertility and received a first course of leuprolide acetate for 16 weeks to control severe dysmenorrhoea; because symptoms re-appeared upon discontinuation of treatment, GnRHa therapy was reinstated. After 24 weeks of the second course, her uterus decreased to a normal size and an MRI revealed a localized low-signal-intensity myometrial mass with well-defined borders, which was easily resected. The patient became pregnant after 12 weeks of additional danazol therapy. The same year, a Chinese group (Lin et al., 1999) treated four symptomatic patients with infertility and enlarged uteri. The report mentions that 'adenomyosis was diagnosed under laparoscopy' and that 'coexisting endometriosis, pelvic adhesion and adenomyoma were treated by surgery and endocoagulator in 4 and 2 cases respectively'. GnRHa therapy was instituted for 6 months before laparoscopic surgery in one case and after laparoscopic surgery in three cases.

The enlarged uteri decreased to normal or near normal size in all four patients and menstruation returned within 3 months of cessation of treatment. Three cases conceived within 4 months; the first woman gave birth to a healthy baby at 38 weeks by Caesarean section; the second pregnancy was terminated by emergency Caesarean section at 30 weeks gestation because of threatened rupture of uterus. The third was still ongoing (28 weeks) at the time of writing the report. Their report, originally published in Chinese, was re-presented 1 year later in English (Lin et al., 2000).

In 2000, another Chinese group (Wang et al., 2000) treated a series of patients with microsurgical resection of the visible adenomyotic areas followed by treatment of GnRHa and reported pregnancies in three patients. Notwithstanding these positive outcomes, Farquhar and Brosens (2006) warned that the role of the combination of cytoreductive surgery and GnRHa treatment in managing infertile women with adenomyosis is, still far from clear, because of possible surgical and obstetrical risks.

No published reports are available on pregnancies following treatment with either oestrogen/progestin combinations or orally administered danazol. At the same time, a Japanese group (Igarashi et al., 2000) have published interesting results following insertion of an intrauterine system releasing danazol. In a series of 14 women with symptomatic adenomyosis that had relapsed after previous medical therapy, the insertion of the system provided relief from the symptoms and, in particular, three of the four infertile women conceived after removal.

More recently the levonorgestrel-releasing intrauterine system known as Mirena has been utilized for the relief of symptoms associated with adenomyosis (Fedele et al., 1997; Sheng et al., 2009), but it is not yet known whether the system may be useful in infertile patients.

Uterine-artery embolization

Several studies have been published on the effect of uterine artery embolization on symptoms associated with adenomyosis (Kim et al., 2004, 2007; Pelage et al., 2005) and the topic has been reviewed by Rabinovici and Stewart (2006a). Although there is a report of age-related impairment of ovarian function following uterine artery embolization leading to amenorrhoea (Pron et al., 2003), several authors have concluded that pregnancies are possible — at least after uterine artery embolization for fibroids — although women may be a risk of complications, possibly due to abnormal placentation (Goldberg, 2005; Goldberg et al., 2004). Both pregnancy and vaginal delivery seem possible after uterine artery embolization for adenomyosis. A first uncontrolled series of 94 subjects treated for adenomyosis or fibroids was reported by a Korean group (Kim et al., 2005). Among them, six women desired to become pregnant and five succeeded, with one becoming pregnant twice. In addition, two pregnancies occurred after contraception failed, with one terminated upon request of the woman. Of the remaining seven pregnancies, five were delivered vaginally and two by elective Caesarean. In one case, there was a premature rupture of membrane followed by preterm labour and delivery of a small-for-gestational-age infant. Although these data cannot be considered definitive, they are nonetheless encouraging.

Endometrial ablation/resection

Results with this procedure have been recently reviewed (Mc Causland and Mc Causland, 2008) and, once again, no data exist on possible effects on infertility.

MRI-assisted high-intensity focused ultrasound (HIFU) ablation

HIFU utilizes an external ultrasound energy source to induce thermal ablation at a given depth through the intact skin. Ablation through HIFU is a new technique utilized in the treatment of patients with a variety of malignancies and its application to adenomyosis has recently been reviewed (Dong and Yang, 2010). It appears that this novel technique, mostly investigated in China, offers advantages over current conservative treatments, at least in patients with localized adenomyosis, where the main histological changes are coagulative necrosis of the targeted localized adenomyosis, associated to vascular damage. This was already evident at macroscopic observation that also indicated that there was no haemorrhage in treated lesions. Microscopic examination confirmed a typical coagulation necrosis within the treated tissue in all patients (Yang et al., 2009).

Only one case of successful treatment of adenomyosis-associated infertility with HIFU has been published. Rabinovici and colleagues (Rabinovici et al., 2006b) presented the case of a 36-year-old woman who had difficulty conceiving because of profuse menometrorrhagia. A diagnosis of focal adenomyosis was made at MRI and focused ultrasound surgery destroyed a significant part of the ectopic endometrium and stroma. At 6 weeks, the patient experienced a significant reduction in menometrorrhagia and a marked decrease in the size of the uterus. She conceived spontaneously and, after an uneventful pregnancy, gave birth at term to a healthy infant via normal vaginal delivery.

Conclusions

Much progress in the understanding of adenomyosis has been made over the last two decades and new theories for its pathogenesis and relationship to endometriosis have been advances. Progress has been possible thanks to the introduction of new imaging techniques: sonography and MRI. The latter in particular has greatly facilitated early noninvasive diagnosis and the evaluating of the uterine JZ thickness. An increasing body of detailed investigations of eutopic and ectopic endometrium in women with adenomyosis is beginning to clarify mechanisms through which the condition can impair fertility, first and foremost an impairment of the process of implantation. In this connection, it has been shown that the thickening, infiltration or disruption of the JZ myometrium is probably linked to poor reproductive performance, mainly through perturbed uterine peristalsis.

References

Aghajanova, L., 2004. Leukemia inhibitory factor and human embryo implantation. Ann. N. Y. Acad. Sci. 1034, 176—183.

Akoum, A., Lemay, A., Paradis, I., Rheault, N., Maheux, R., 1996. Secretion of interleukin-6 by human endometriotic cells and regulation by proinflammatory cytokines and sex steroids. Hum. Reprod. 11, 2269—2275.

Barrier, B.F., Malinowski, M.J., Dick Jr., E.J., Hubbard, G.B., Bates, G.W., 2004. Adenomyosis in the baboon is associated with primary infertility. Fertil. Steril. 82, 1091—1094.

Bazot, M., Darai, E., Hourani, R., Thomassin, I., Cortez, A., Uzan, S., Buy, J.N., 2004. Deep pelvic endometriosis: MR imaging for diagnosis and prediction of extension of disease. Radiology 232, 379—389.

Benagiano, G., Brosens, I., 2011. Who identified endometriosis? Fertil. Steril. 95, 13—16.

Benagiano, G., Brosens, I., Carrara, S., 2009. Adenomyosis: new knowledge is generating new treatment options. Women's Health 5, 297—311.

Bergeron, C., Amant, F., Ferenczy, A., 2006. Pathology and physiopathology of adenomyosis. Best Pract. Res. Clin. Obstet. Gynaecol. 20, 511—521.

Bird, C.C., McElin, T.W., Manalo-Estrella, P., 1972. The elusive adenomyosis of the uterus. Am. J. Obstet. Gynecol. 112, 583—593.

Birnholz, J.C., 1984. Ultrasonic visualization of endometrial movements. Fertil. Steril. 41, 157—158.

Bromer, J.G., Aldad, T.S., Taylor, H.S., 2009. Defining the proliferative phase defect. Fertil. Steril. 91, 698—704.

Brosens, J.J., Hayashi, N., White, J.O., 1999. Progesterone receptor regulates decidual prolactin expression in differentiating human endometrial stromal cells. Endocrinology 140, 4809—4820.

Brosens, J.J., Pijnenborg, R., Brosens, I.A., 2002. The myometrial junctional zone spiral arteries in normal and abnormal pregnancies: a review of the literature. Am. J. Obstet. Gynecol. 187, 1416—1423.

Brosens, J.J., Verhoeven, H., Campo, R., Gianaroli, L., Gordts, S., Hazekamp, J., Hägglund, L., Mardesic, T., Varila, E., Zech, J., Brosens, I., 2004. High endometrial aromatase P450 mRNA expression is associated with poor IVF outcome. Hum. Reprod. 19, 352—356.

Bulletti, C., De Ziegler, D., 2006. Uterine contractility and embryo implantation. Curr. Opin. Obstet. Gynecol. 18, 473–484.

Burney, R.O., Talbi, S., Hamilton, A.E., Vo, K.C., Nyegaard, M., Nezhat, C.R., Lessey, B.A., Giudice, L.C., 2007. Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. Endocrinology 148, 3814–3826.

de Ziegler, D., Borghese, B., Chapron, C., 2010. Endometriosis and infertility: pathophysiology and management. Lancet 376, 730–738.

de Souza, N.M., Brosens, J.J., Schwieso, J.E., Paraschos, T., Winston, R.M., 1995. The potential value of magnetic resonance imaging in infertility. Clin. Radiol. 50, 75–79.

Dimitriadis, E., White, C.A., Jones, R.L., Salamonsen, L.A., 2005. Cytokines, chemokines and growth factors in endometrium related to implantation. Hum. Reprod. Update 11, 613–630.

Dong, X.-J., Yang, Z., 2010. High-intensity focused ultrasound ablation of uterine localized adenomyosis. Curr. Opin. Obstet. Gynecol. 22, 326–330.

Dueholm, M., 2006. Transvaginal ultrasound for diagnosis of adenomyosis: a review. Best Pract. Res. Clin. Obstet. Gynaecol. 20, 569–582.

Exacoustos, C., Brienza, L., Rienza, A., Di Giovanni, A., Szabolcs, B., Romanini, M.E., Zupi, E., Arduini, D., 2011. Adenomyosis: three-dimensional sonographic findings of the junctional zone and correlation with histology. Ultrasound Obstet. Gynecol. 37, 471–479.

Farquhar, C., Brosens, I., 2006. Medical and surgical management of adenomyosis. Best Pract. Res. Clin. Obstet. Gynaecol. 20, 603–616.

Fedele, L., Bianchi, S., Raffaelli, R., Portuese, A., Dorta, M., 1997. Treatment of adenomyosis-associated menorrhagia with a levonorgestrel-releasing intrauterine device. Fertil. Steril. 68, 426–429.

Fedele, L., Bianchi, S., Frontino, G., 2008. Hormonal treatments for adenomyosis. Best Pract. Res. Clin. Obstet. Gynaecol. 22, 333–339.

Fischer, C.P., Kayisili, U., Taylor, H.S., 2011. HOXA10 expression is decreased in endometrium of women with adenomyosis. Fertil. Steril. 95, 1133–1136.

Fontanini, G., Campani, D., Roncella, M., Cecchetti, D., Calvo, S., Toniolo, A., Basolo, F., 1999. Expression of interleukin 6 (IL-6) correlates with oestrogen receptor in human breast carcinoma. Br. J. Cancer 80, 579–584.

Frankl, O., 1925. Adenomyosis uteri. Am. J. Obstet. Gynecol. 10, 680–684.

Fusi, L., Cloke, B., Brosens, J.J., 2006. The uterine Junctional Zone. Best Pract. Res. Clin. Obstet. Gynaecol. 20, 479–491.

Garcia Velasco, J.A., Arici, A., 1999. Chemokines and human reproduction. Fertil. Steril. 71, 983–993.

Goldberg, J., 2005. Pregnancy after uterine artery embolization for leiomyomata: the Ontario Multicenter Trial. Obstet. Gynecol. 106, 195–196.

Goldberg, J., Pereira, L., Berghella, V., Diamond, J., Daraï, E., Seinera, P., Seracchioli, R., 2004. Pregnancy outcomes after treatment for fibromyomata: uterine artery embolization versus laparoscopic myomectomy. Am. J. Obstet. Gynecol. 191, 18–21.

Gordts, S., Brosens, J.J., Fusi, L., Benagiano, G., Brosens, I., 2008. Uterine adenomyosis: a need for uniform terminology and consensus classification. Reprod. Biomed. Online 17, 244–248.

Goteri, G., Lucarini, G., Montik, N., Zizzi, A., Stramazzotti, D., Fabris, G., Tranquilli, A.L., Ciavattini, A., 2009. Expression of vascular endothelial growth factor (VEGF), hypoxia inducible factor-1α (HIF-1α), and microvessel density in endometrial tissue in women with adenomyosis. Int. J. Gynecol. Pathol. 28, 157–163.

Grow, D.R., Filer, R.B., 1991. Treatment of adenomyosis with long-term GnRH analogues: a case report. Obstet. Gynecol. 78, 538–539.

Hauth, E.A., Jaeger, H.J., Libera, H., Lange, S., Forsting, M., 2007. MR imaging of the uterus and cervix in healthy women: determination of normal values. Eur. Radiol. 17, 734–742.

Hirata, J.D., Moghissi, K.S., Ginsburg, K.A., 1993. Pregnancy after medical therapy of adenomyosis with a gonadotropin-releasing hormone agonist. Fertil. Steril. 59, 444–445.

Hoad, C.L., Raine-Fenning, N.J., Fulford, J., Campbell, B.K., Johnson, I.R., Gowland, P.A., 2005. Uterine tissue development in healthy women during the normal menstrual cycle and investigations with magnetic resonance imaging. Am. J. Obstet. Gynecol. 192, 648–654.

Honorè, L.H., Cumming, D.C., Dunlop, D.L., Scott, J.Z., 1988. Uterine adenomyoma associated with infertility. A report of three cases. J. Reprod. Med. 33, 331–335.

Hricak, H., Alpers, C., Crooks, L.E., Sheldon, P.E., 1983. Magnetic resonance imaging of the female pelvis: initial experience. Am. J. Roentgenol. 14, 1119–1128.

Huang, W.H., Ynag, T.S., Yuan, C.C., 1998. Successful pregnancy after treatment of deep adenomyosis with cytoreductive surgery and subsequent gonadotropin-releasing hormone agonist: a case report. Zhonghua Yi Xue Za Zhi (Taipei) 61, 726–729.

Igarashi, M., Abe, Y., Fukuda, M., Ando, A., Miyasaka, M., Yoshida, M., Shawki, O.A., 2000. Novel conservative medical therapy for uterine adenomyosis with a danazol-loaded intrauterine device. Fertil. Steril. 74, 412–413.

Igarashi, S., Sato, N., Tanaka, H., Tanaka, T., 2002. Involvement of catalase in the endometrium of patients with endometriosis and adenomyosis. Fertil. Steril. 78, 804–809.

Ijland, M.M., Evers, J.L., Dunselman, G.A., Volovics, L., Hoogland, H.J., 1997. Relation between endometrial wavelike activity and fecundability in spontaneous cycles. Fertil. Steril. 67, 492–496.

Ishihara, H., Kitawaki, J., Kado, N., Koshiba, H., Fushiki, S., Honjo, H., 2003. Gonadotropin-releasing hormone agonist and danazol normalize aromatase cytochrome P450 expression in eutopic endometrium from women with endometriosis, adenomyosis, or leiomyomas. Fertil. Steril. 79, 735–742.

Kamada, Y., Nakatsuka, M., Asagiri, K., Noguchi, S., Habara, T., Takata, M., Kudo, T., 2000. GnRH agonist suppressed expression of nitric oxide synthases and generation of peroxynitrite in adenomyosis. Hum. Reprod. 15, 2512–2519.

Kang, S., Zhao, J., Liu, Q., Zhou, R., Wang, N., Li, Y., 2009. Vascular endothelial growth factor gene polymorphisms are associated with the risk of developing adenomyosis. Environ. Mol. Mutagen. 50, 361–366.

Kido, A., Togashi, K., Nishino, M., Miyake, K., Koyama, T., Fujimoto, R., Iwasaku, K., Fujii, S., Hayakawa, K., 2007. Cine MR imaging of uterine peristalsis in patients with endometriosis. Eur. Radiol. 17, 1813–1819.

Kim, M.D., Won, J.W., Lee, D.Y., Ahn, C.-S., 2004. Uterine artery embolization for adenomyosis without fibroids. Clin. Radiol. 59, 520–526.

Kim, M.D., Kim, N.K., Kim, H.J., Lee, M.H., 2005. Pregnancy following uterine artery embolization with polyvinyl alcohol particles for patients with uterine fibroid or adenomyosis. Cardiovasc. Intervent. Radiol. 28, 611–615.

Kim, M.D., Kim, S., Kim, N.K., Lee, M.H., Ahn, E.H., Kim, H.J., Cho, J.H., Cha, S.H., 2007. Long-Term Results of Uterine Artery Embolization for Symptomatic Adenomyosis (UAE) in the management of symptomatic adenomyosis. Am. J. Rad. 188, 176–181.

Kim, Y.A., Kim, M.R., Lee, J.H., Kim, J.Y., Hwang, K.J., Kim, H.S., Lee, E.S., 2009. Gonadotropin-releasing hormone agonist reduces aromatase cytochrome P450 and cyclooxygenase-2 in ovarian endometrioma and eutopic endometrium of patients with endometriosis. Gynecol. Obstet. Invest. 68, 73–81.

Kissler, S., Hamscho, N., Zangos, S., Wiegratz, I., Schlichter, S., Menzel, C., Doebert, N., Gruenwald, F., Vogl, T.J., Gaetje, R., Rody, A., Siebzehnruebl, E., Kunz, G., Leyendecker, G.,

Kaufmann, 2006. Uterotubal transport disorder in adenomyosis and endometriosis — a cause for infertility. Br. J. Obstet. Gynaecol. 113, 902—908.

Kissler, S., Zangos, S., Wiegratz, I., Kohl, J., Rody, A., Gaetje, R., Doebert, N., Wildt, L., Kunz, G., Leyendecker, G., Kaufmann, M., 2007. Uterotubal sperm transport and its impairment in endometriosis and adenomyosis. Ann. N. Y. Acad. Sci. 1101, 38—48.

Kitawaki, J., Noguchi, T., Amatsu, T., Maeda, K., Tsukamoto, K., Yamamoto, T., Fushiki, S., Osawa, Y., Honjo, H., 1997. Expression of aromatase cytochrome P450 protein and messenger ribonucleic acid in human endometriotic and adenomyotic tissues but not in normal endometrium. Biol. Reprod. 57, 514—519.

Klemmt, P.A.B., Liu, F., Carver, J.G., Jones, C., Brosi, D., Adamson, J., Mardon, H.J., McVeigh, E., 2009. Effects of gonadotrophin releasing hormone analogues on human endometrial stromal cells and embryo invasion in vitro. Hum. Reprod. 24, 2187—2192.

Klemmt, P.A., Carver, J.G., Kennedy, S.H., Koninckx, P.R., Mardon, H.J., 2006. Stromal cells from endometriotic lesions and endometrium from women with endometriosis have reduced decidualization capacity. Fertil. Steril. 85, 564—572.

Kunz, G., Beil, D., Deininger, H., Wildt, L., Leyendecker, G., 1996. The dynamics of rapid sperm transport through the female genital tract: evidence from vaginal sonography of uterine peristalsis and hysterosalpingoscintigraphy. Hum. Reprod. 11, 627—632.

Kunz, G., Leyendecker, G., 2002. Uterine peristaltic activity during the menstrual cycle: characterization, regulation, function and dysfunction. Reprod. Biomed. Online 4, 5—9.

Kunz, G., Beil, D., Huppert, P., Noe, M., Kissler, S., Leyendecker, G., 2005. Adenomyosis in endometriosis prevalence and impact on fertility. Evidence from magnetic resonance imaging. Hum. Reprod. 20, 2309—2316.

Kunz, G., Herbertz, M., Beil, D., Huppert, P., Leyendecker, G., 2007. Adenomyosis as a disorder of the early and late human reproductive period. Reprod. Biomed. Online 15, 681—685.

Kusakabe, K., Li, Z.L., Kiso, Y., Otsuki, Y., 2005. Perforin improves the morphogenesis of mouse placenta disturbed by IL-2 treatment. Immunobiology 209, 719—728.

Lee, N.C., Dicker, R.C., Rubin, G.L., Ory, H.W., 1984. Confirmation of the preoperative diagnoses for hysterectomy. Am. J. Obstet. Gynecol. 150, 283—287.

Lesny, P., Killick, S.R., 2004. The junctional zone of the uterus and its contractions. Br. J. Obstet. Gynecol. 111, 1182—1189.

Lessey, B.A., Castelbaum, A.J., Buck, C.A., Lei, Y., Yowell, C.W., Sun, J., 1994a. Further characterization of endometrial integrins during the menstrual cycle and in pregnancy. Fertil. Steril. 62, 497—506.

Lessey, B.A., Castelbaum, A.J., Sawin, S.J., Buck, C.A., Schinnar, R., Bilker, W., Strom, B.L., 1994b. Aberrant integrin expression in the endometrium of women with endometriosis. J. Clin. Endocrinol. Metab. 79, 643—649.

Lessey, B.A., Palomino, W.A., Apparao, K.B.C., Young, S.L., Lininger, R.A., 2006. Estrogen receptor-alpha (ER-alpha) and defects in uterine receptivity in women. Reprod. Biol. Endocrinol. 4, S9.

Leyendecker, G., Kunz, G., Kissler, S., Wildt, L., 2006. Adenomyosis and reproduction. Best Pract. Res. Clin. Obstet. Gynaecol. 20, 523—546.

Li, T., Li, Y.-G., Pu, D.-M., 2006. Matrix metalloproteinase-2 and -9 expression correlated with angiogenesis in human adenomyosis. Gynecol. Obstet. Invest. 62, 229—235.

Lin, J., Sun, C., Li, R., 1999. Gonadotropin releasing hormone agonists in the treatment of adenomyosis with infertility. Zhonghua Fu Chan Ke Za Zhi 34, 214—216 (article in Chinese).

Lin, J., Sun, C., Zheng, H., 2000. Gonadotropin-releasing hormone agonists and laparoscopy in the treatment of adenomyosis with infertility. Chin. Med. J. (Engl.) 113, 442—445.

Liu, H.C., Pyrgiotis, E., Davis, O., Rosenwaks, Z., 1995. Active corpus luteum function at pre-, peri- and postimplantation is essential for a viable pregnancy. Early Pregn. 1, 281—287.

Liu, H., Lang, J., Wang, X., Wu, S., 2008. Comparative proteomic analysis of human adenomyosis using two-dimensional gel electrophoresis and mass spectrometry. Fertil. Steril. 89, 1625—1631.

Maubon, A., Faury, A., Kapella, M., Pouquet, M., Piver, P., 2010. Uterine junctional zone at magnetic resonance imaging: a predictor of in vitro fertilization implantation failure. J. Obstet. Gynaecol. Res. 3, 611—618.

McCarthy, S., Tauber, C., Gore, J., 1986. Female pelvic anatomy: MR assessment of variations during the menstrual cycle and with use of oral contraceptives. Radiology 160, 119—123.

Mc Causland, V., Mc Causland, A., 2008. The response of adenomyosis to endometrial ablation/resection. Hum. Reprod. Update 4, 350—359.

Mehasseb, M.K., Bell, S.C., Pringle, J.H., Habiba, M.A., 2010. Uterine adenomyosis is associated with ultrastructural features of altered contractility in the inner myometrium. Fertil. Steril. 93, 2130—2136.

Mehasseb, M.K., Panchal, R., Taylor, A.H., Brown, L., Bell, S.C., Habiba, M., 2011. Estrogen and progesterone receptor isoform distribution through the menstrual cycle in uteri with and without adenomyosis. Fertil. Steril., March 26 [Epub ahead of print].

Meredith, S., Sanchez-Ramos, L., Kaunitz, A., 2009. Diagnostic accuracy of transvaginal sonography for the diagnosis of adenomyosis: systematic review and metanalysis. Am. J. Obstet. Gynecol. 201, 1—6.

Mikolajczyk, M., Wirstlein, P., Skrzypczak, J., 2006. Leukaemia inhibitory factor and interleukin 11 levels in uterine flushings of infertile patients with endometriosis. Hum. Reprod. 21, 3054—3058.

Minici, F., Tiberi, F., Tropea, A., Miceli, F., Orlando, M., Gangale, M.F., Romani, F., Catino, S., Campo, S., Lanzone, A., Apa, R., 2007. Paracrine regulation of endometriotic tissue. Gynecol. Endocrinol. 23, 574—580.

Minici, F., Tiberi, F., Tropea, A., Orlando, M., Gangale, M.F., Romani, F., Campo, S., Bompiani, A., Lanzone, A., Apa, R., 2008. Endometriosis and human infertility: a new investigation into the role of eutopic endometrium. Hum. Reprod. 23, 530—537.

Narimoto, K., Noda, Y., Shiotani, M., Tokura, T., Goto, Y., Takakura, K., Mori, T., Fujimoto, K., Ogawa, K., 1990. Immunohistochemical assessment of superoxide dismutase expression in the human endometrium throughout the menstrual cycle. Acta Histochem. Cytochem. 23, 487—497.

Noda, Y., Matsumoto, H., Umaoka, Y., Tatsumi, K., Kishi, J., Mori, T., 1991. Involvement of superoxide radicals in the mouse two-cell block. Mol. Reprod. Dev. 28, 356—360.

Novellas, S., Chassang, M., Delotte, J., Toullalan, O., Chevallier, A., Bouaziz, J., Patrick Chevallier, J.P., 2011. MRI characteristics of the uterine junctional zone: from normal to the diagnosis of adenomyosis. Am. J. Roentgenol. 196, 1206—1213.

Oki, T., Douchi, T., Maruta, K., Nakamura, S., Nagata, Y., 2002. Changes in endometrial wave-like movements in accordance with the phases of menstrual cycle. J. Obstet. Gynaecol. Res. 28, 176—181.

Osada, H., Silber, S., Kakinuma, T., Nagaishi, M., Kato, K., Kato, O., 2011. Surgical procedure to conserve the uterus for future pregnancy in patients suffering from massive adenomyosis. Reprod. Biomed. Online 22, 94—99.

Ota, H., Tanaka, T., 2003. Stromal vascularization in the endometrium during adenomyosis. Microsc. Res. Tech. 60, 445—449.

Ota, H., Igarashi, S., Hatazawa, J., Tanaka, T., 1998. Is adenomyosis an immune disease? Hum. Reprod. 4, 360—367.
Ota, H., Igarashi, S., Hatazawa, M., Tanaka, T., 1999. Immunohistochemical assessment of superoxide dismutase expression in the endometrium in endometriosis and adenomyosis. Fertil. Steril. 72, 129—134.
Ozaki, T., Takahashi, K., Okada, M., Kurioka, H., Miyazaki, K., 1999. Live birth after conservative surgery for severe adenomyosis following magnetic resonance imaging and gonadotropin-releasing hormone agonist therapy. Int. J. Fertil. Womens Med. 44, 260—264.
Pelage, J.-P., Jacob, D., Fazel, A., Namur, J., Laurent, A., Rymer, R., Le Dref, O., 2005. Midterm results of uterine artery embolization for symptomatic adenomyosis: initial experience. Radiology 234, 948—953.
Piver, P., 2005. Uterine factors limiting ART coverage. J. Gynecol. Obstet. Biol. Reprod. (Paris) 34, 5S30—5S33.
Pron, G., Bennett, J., Common, A., Wall, J., Asch, M., Sniderman, K.Ontario Uterine Fibroid Embolization Collaboration Group, 2003. The Ontario uterine fibroid embolization trial: Part 2. Uterine fibroid reduction and symptom relief after uterine artery embolization for fibroids. Fertil. Steril. 79, 120—127.
Quinn, M., 2007. Uterine innervation in adenomyosis. J. Obstet. Gynaecol. 27, 287—291.
Rabinovici, J., Stewart, E.A., 2006a. New interventional techniques for adenomyosis. Best Pract. Res. Clin. Obstet. Gynaecol. 20, 617—636.
Rabinovici, J., Inbar, Y., Eylon, S.C., Schiff, E., Hanane, A., Freundlich, D., 2006b. Pregnancy and live birth after focused ultrasound surgery for symptomatic focal adenomyosis: a case report. Hum. Reprod. 21, 1255—1259.
Reinhold, C., Tafazoli, F., Wang, L., 1998. Imaging features of adenomyosis. Hum. Reprod. Update 4, 337—349.
Sampson, J.A., 1927. Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. Am. J. Obstet. Gynecol. 14, 422—469.
Satokata, I., Benson, G., Maas, R., 1995. Sexually dimorphic sterility phenotypes in Hoxa10-deficient mice. Nature 374, 460—463.
Seppälä, M., Taylor, R.N., Koistinen, H., Koistinen, R., Milgrom, E., 2000. Glycodelin: a major lipocalin protein of the reproductive axis with diverse actions in cell recognition and differentiation. Endocr. Rev. 23, 401—430.
Sheng, J., Zhang, W.Y., Zhang, J.P., The, D.L., 2009. LNG-IUS study on adenomyosis: a 3-year follow-up study on the efficacy and side effects of the use of levonorgestrel intrauterine system for the treatment of dysmenorrhea associated with adenomyosis. Contraception 79, 189—193.
Silva, P.D., Perkins, H.E., Schauberger, C.W., 1994. Live birth after treatment of severe adenomyosis with a gonadotropin-releasing hormone agonist. Fertil. Steril. 61, 171—172.
Soares, S.R., Velasco, J.A., Fernandez, M., Bosch, E., Remohí, J., Pellicer, A., Simón, C., 2008. Clinical factor affecting endometrial receptiveness in oocyte donation cycles. Fertil. Steril. 89, 491—501.
Surrey, E.S., Minjarez, D.A., Schoolcraft, W.B., 2007. The incidence of aberrant endometrial alpha-beta(3) vitronectin expression in a high risk infertility population: could prolonged GnRH agonist therapy play a role? J. Assist. Reprod. Genet. 24, 553—556.
Tamai, K., Koyama, T., Umeoka, S., Saga, T., Fujii, S., Togashi, K., 2006. Spectrum of MR features in adenomyosis. Pract. Res. Clin. Obstet. Gynaecol. 20, 583—602.
Tavmergen, E., Murat Ulukus, M., Goker, E.N., 2007. Long-term use of gonadotropin-releasing hormone analogues before IVF in women with endometriosis. Curr. Opin. Obstet. Gynecol. 19, 284—288.
Taylor, H.S., Arici, A., Olive, D., Igarashi, P., 1998. HOXA10 is expressed in response to sex steroids at the time of implantation in the human endometrium. J. Clin. Invest. 101, 1379—1384.
Taylor, H.S., Bagot, C., Kardana, A., Olive, D., Arici, A., 1999. HOX gene expression is altered in the endometrium of women with endometriosis. Hum. Reprod. 14, 1328—1331.
Telfer, J.F., Lyall, F., Norman, J.E., Cameron, I.T., 1995. Identification of nitric oxide synthase in human uterus. Hum. Reprod. 10, 19—23.
Tokyol, C., Aktepe, F., Dilek, F.H., Sahin, O., Arioz, D.T., 2009. Expression of cyclooxygenase-2 and matrix metalloproteinase-2 in adenomyosis and endometrial polyps and its correlation with angiogenesis. Int. J. Gynecol. Pathol. 28, 148—156.
Turnbull, L.W., Manton, D.J., Horsman, A., Killick, S.R., 1995. Magnetic resonance imaging changes in uterine zonal anatomy during a conception cycle. Br. J. Obstet. Gynaecol. 102, 330—331.
Ulukus, M., Ulukus, E.C., Seval, Y., Cınar, O., Zheng, W., Arici, A., 2006. Expression of interleukin-8 receptors in patients with adenomyosis. Fertil. Steril. 85, 714—720.
Wang, P.H., Yang, T.S., Lee, W.L., Chao, H.T., Chang, S.P., Yuan, C.C., 2000. Treatment of infertile women with adenomyosis with a conservative microsurgical technique and a gonadotropin-releasing hormone agonist. Fertil. Steril. 73, 1061—1062.
Wang, F., Li, H., Yang, Z., Du, X., Cui, M., Wen, Z., 2009. Expression of interleukin-10 in patients with adenomyosis. Fertil. Steril. 91, 1681—1685.
Wei, Q., St Clair, J.B., Fu, T., Stratton, P., Nieman, L.K., 2009. Reduced expression of biomarkers associated with the implantation window in women with endometriosis. Fertil. Steril. 91, 1686—1691.
Wicherek, L., 2009. Alterations in RCAS1 serum concentration levels during menstrual cycle in patients with uterine leiomyoma and lack of analogical changes in adenomyosis. Gynecol. Obstet. Invest. 67, 195—201.
Wiczyk, H.P., Janus, C.L., Richards, C.J., Graf, M.J., Gendal, E.S., Rabinowitz, J.G., Laufer, N., 1988. Comparison of magnetic resonance imaging and ultrasound in evaluating follicular and endometrial development throughout the normal cycle. Fertil. Steril. 49, 969—972.
Yang, J.H., Wu, M.Y., Chang, D.Y., Chang, C.H., Yang, Y.S., Ho, H.N., 2006. Increased interleukin-6 messenger RNA expression in macrophage co-cultured endometrial stromal cells in adenomyosis. Am. J. Reprod. Immunol. 55, 181—187.
Yang, Z., Cao, Y.-D., Hu, L.N., Wang, Z.B., 2009. Feasibility of laparoscopic high-intensity focused ultrasound treatment for patients with uterine localized adenomyosis. Fertil. Steril. 91, 2338—2343.
Yen, C.F., Basar, M., Kizilay, G., Lee, C.L., Kayisli, U.A., Arici, A., 2006. Implantation markers are decreased in endometrium of women with adenomyosis during the implantation windows. Fertil. Steril. 86, P550.
Xiao, Y., Sun, X., Yang, X., Zhang, J., Xue, Q., Cai, B., Zhou, Y., 2010. Leukemia inhibitory factor is dysregulated in the endometrium and uterine flushing fluid of patients with adenomyosis during implantation window. Fertil. Steril. 94, 85—89.
Zacharia, T.T., O'Neill, M.J., 2006. Prevalence and distribution of adnexal finding suggesting endometriosis in patients with MRI diagnosis of adenomyosis. Br. J. Radiol. 79, 303—307.

Declaration: The authors report no financial or commercial conflicts of interest.

Received 26 October 2010; refereed 30 September 2011; accepted 4 October 2011.