ADENOMYOSIS AND INFERTILITY

Adenomyosis

- Definition in 1972 :
  - Benign invasion of endometrium into the myometrium
  - Which 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.

Introduction

- Diagnosis of adenomyosis can be identified only with hysterectomy specimens
- In the mid-1980s, noninvasive imaging techniques enabling a preoperative diagnosis also for adenomyosis

  -Dueholm, 2006; Meredith et al., 2009; Tamai et al., 2006

Introduction

- Evidence showed link of adenomyosis to a condition of subfertility and prompting the design of new treatment modalities

This review briefly reports

- (i) noninvasive diagnosis of adenomyosis by the new imaging techniques
- (ii) clinical and epidemiological evidence pointing to the possibility that adenomyosis can cause infertility
- (iii) pathophysiological mechanisms through which adenomyosis can cause infertility
- (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, MRI identified
  - A new functional uterine zone -- the junction between the endometrium and the inner myometrium

    -Hricak et al., 1983
- Junctional zone (JZ) myometrium
  - possesses a specific characteristic
  - Lacks a recognizable protective layer or membrane, a true submucosa

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

- Three distinct layers can be displayed through MRI T2-weighted images, in the uterus of healthy women of reproductive age
  - Tamai et al., 2006
  - Innermost zone -- endometrial stripe
    - high signal intensity
  - Intermediate inner -- the JZ myometrium, or subendometrial layer
    - low-signal-intensity area adjacent to the basal endometrium, measuring 5mm in thickness in healthy young women
  - Outer layer – outer myometrium
    - medium-signal-intensity zone extending all the way to the serosal layer

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

- There are cyclical thickness changes in the thickness of the JZ, mimicking those of the endometrium and characterized by maximum growth between days 8 and 16

  - Wiczyk et al. (1988)

- 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.

  - recent study by Hoad et al. (2005)

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

- 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

- Adenomyosis is suspected when JZ thickness is 12 mm by MRI
  - Approximately 20% of premenopausal women absent a definable JZ on imaging

  - Novellas et al., 2011

- Diagnosis can be made even when thickness is <12 mm, if other signs
  - high-signal spots or an irregularly bounded JZ

  - Reinhold et al., 1998

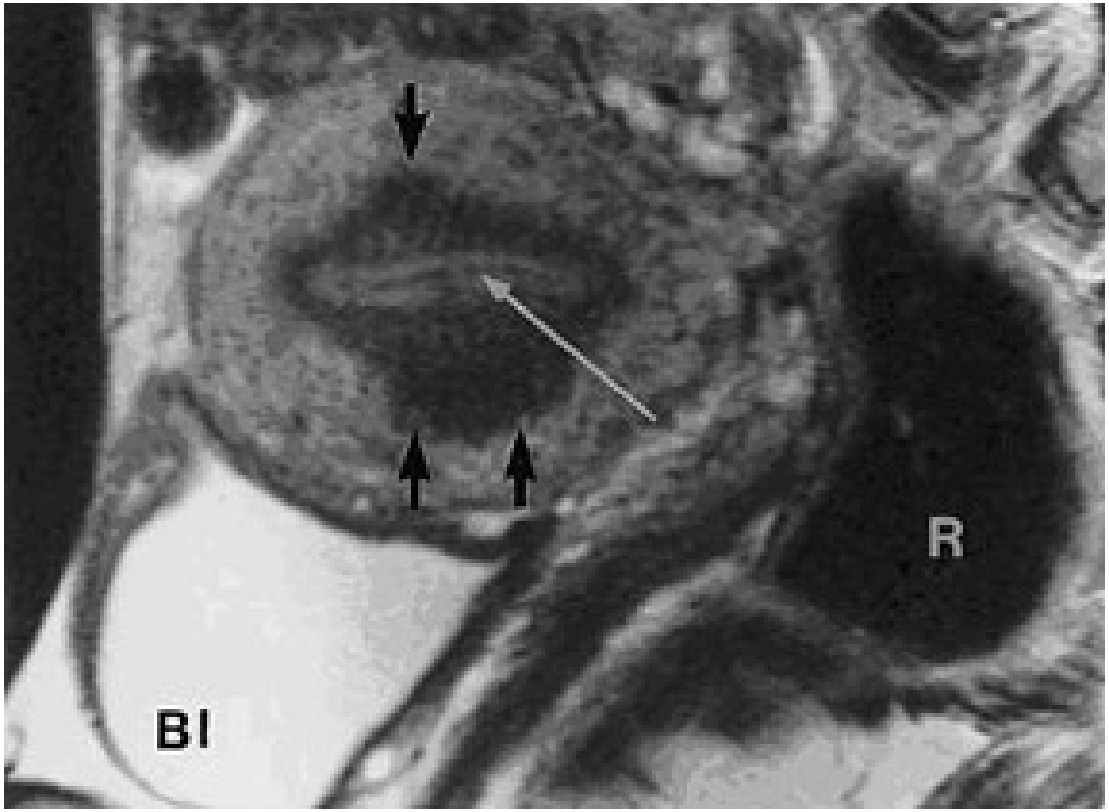

Figure 1 Adenomyosis as identified through focal thickening of the myometrial junctional zone (JZ). Sagittal T2-weighted magnetic resonance image demonstrates focal thickening of the JZ (short arrows) both ventrally and dorsally, consistent with adenomyosis. Although the maximal thickening of the JZ 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.

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

- Adenomyosis can also be diagnosed through 3D ultrasonography
  - The report correlated 2D and 3D TVS with histopathological features of adenomyosis in a total of 72 premenopausal patients

- Exacoustos et al. (2011)

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

- The most specific 2D-TVS feature for the diagnosis of adenomyosis
  - Most specificity if presence of myometrial cysts (98% specificity; 78% accuracy)
  - Most sensitive if presence of heterogeneous myometrium (88% sensitivity; 75% accuracy)
- The best markers on 3D-TVS
  - JZ difference 4 mm and JZ infiltration and distortion (both 88% sensitivity; 85% and 82% accuracy, respectively)

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

- The JZ has emerged as a hormone-dependent structure that governs uterine peristalsis outside pregnancy as a consequence of investigations

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

- Suppression of ovarian activity results in an indistinct appearance on MRI of the myometrial layers, such as
  - during hormonal contraception
  - administration of a gonadotrophin-releasing hormone analogue
- use of hormone replacement therapy in postmenopausal women results in the reappearance of the typical zonal anatomy

- McCarthy et al., 1986

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

- Birnholz (1984) has documented the presence in the myometrium of distinct contraction waves
  - Under transabdominal ultrasound, he showed that uterine peristaltic activity originates exclusively from the JZ, while the outer myometrium remains quiescent.

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

- During the follicular and periovulatory phases
  - Contraction waves have a cervico-fundal orientation
  - The amplitude and frequency increase significantly towards the time of ovulation
- These waves seem implicated in many aspects of physiological reproductive processes
  - Endometrial differentiation - Bulletti and De Ziegler, 2006
  - Menstruation - Oki et al., 2002
  - Sperm transport - Ijland et al., 1997
  - Implantation - Turnbull et al., 1995

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

- 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.

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

- During the luteal phase
  - uterine activity decreases under the influence of progesterone
  - 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

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

- The involvement of interstitial and intravascular trophoblast invasion goes beyond the endometrium and involves the JZ, but not the outer myometrium
  - Brosens et al., 2002
- MRI during a conception cycle 7 days post-ovulation (a time coinciding with embryo implantation) showed focal disruption of the JZ signal intensity
  - Turnbull et al., 1995

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

- Adenomyosis altered these physiological phenomena
  - may cause hypo- or infertility in affected women
- Two decades ago the diagnosis of adenomyosis could only be made at surgery
  - usually in women in their late thirties and forties
  - Made it impossible to evaluate its effects on fertility

Clinical and experimental evidence of association between adenomyosis and infertility

- Myomectomy for adenomyoma can successfully treat the associated infertility
  - Honore` et al., 1988
- The hypothesis of a possible link between adenomyosis and infertility is becoming more and more plausible
- The observation of adenomyosis in younger women
  - It 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

Clinical and experimental evidence of association between adenomyosis and infertility

- Evidence is accumulating of a relationship between adenomyosis and endometriosis.
- 27% of women with endometriosis concomitantly had adenomyosis.
  - Bazot et al. (2004)
- This percentage rose to 70% in a study conducted by Kunz et al. (2005).

Clinical and experimental evidence of association between adenomyosis and infertility

- Although clinical data are scarce and epidemiological information simply doesn't exist, some experimental evidence is available.
- Observations in knock-out mice without perforin and treated with interleukin-2 that showed impairment of gestational capacity
  - Perforin: a protein produced by lymphocytes that induces apoptosis in target cells
  - IL-2: induces a thickening of the subendometrial myometrium in the absence of perforin

- Kusakabe et al., 2005

Clinical and experimental evidence of association between adenomyosis and infertility

- Endometriosis is statistically significantly associated to adenomyosis and the latter is strongly associated with lifelong primary infertility in baboons

  - Barrier et al.,2004

Clinical and experimental evidence of association between adenomyosis and infertility

- One study pointed out of possible influences of adenomyosis on fertility is represented by women requesting oocyte donation followed by IVF.

  - Soares et al. (2008)

- 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.

Clinical and experimental evidence of association between adenomyosis and infertility

- 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

Clinical and experimental evidence of association between adenomyosis and infertility

- MRI evaluation of JZ thickness is the best negative predictive factor of implantation failure in IVF cycle
  - JZ <10 mm -> pregnancy rate was 45% per transfer
  - JZ thicknesses 10–12 mm or >12 mm -> pregnancy rates as low as 16% and 5%

- Piver (2005)

Clinical and experimental evidence of association between adenomyosis and infertility

- Recently, a prospective investigation by MRI involving 152 patients showed
  - increase in JZ -> significantly correlated with implantation failure at IVF
  - implantation failure rate was 95.8% in patients with an average JZ of 7–10 mm
  - all other subject was 37.5% ($P < 0.0001$), independently of the cause of infertility or patient age

- Maubon et al., 2010

Pathophysiology of adenomyosis-associated infertility

- Bergeron et al. (2006) mention three pathogenetic theories
  - first two theories:
    - deepest portion (basalis) of the endometrium invaginated between bundles of smooth muscle fibre of the myometrium or along the intramyometrial lymphatic system
  - The third theory:
    - There are pluripotent cells(from Mu¨llerian ducts) in JZ myometrium and endometrium
    - adenomyosis may originate and develop through metaplasia from ectopic intramyometrial endometrial tissue produced de novo.

Pathophysiology of adenomyosis-associated infertility

- There is a simple classification for adenomyosis recently by MRI analysis of the uterine JZ
  - simple JZ hyperplasia
    - zone thickness 8 mm but <12 mm on T2-weighted images
    - in women aged 35 years or less
  - partial or diffusec adenomyosis
    - thickness 12 mm
    - high-signal-intensity myometrial foci
    - involvement of the outer myometrium: <1/3, <2/3, >2/3) and adenomyoma
      - PS. adenomyoma: myometrial mass with indistinct margins of primarily low-signal intensity on all MRI sequences

- Gordts et al. (2008)

Pathophysiology of adenomyosis-associated infertility

- Evidence is accumulating
  - There is a close relationship between the occurrence of adenomyosis and structural and functional defects in eutopic endometrium and myometrial uterine JZ
  - These abnormalities may cause implantation failure and infertility

Gene dysregulation

- A study carried out a proteomic analysis of the adenomyotic tissue in women with adenomyosis recently
  - Identified 10 of 12 dysregulated proteins compared with the protein profiling of normal uterine muscle
  - Suggesting that biomarkers might be utilized for diagnostic purposes.

- Liu et al. (2008)

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

Altered uterine peristaltic activity

- Recent study of adenomyosis has found that
  - adenomyosis is associated with loss of nerve fibres at the endometrium–myometrium interface
  - 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.

- Quinn (2007)

Altered uterine peristaltic activity

- Myocytes exhibited cellular hypertrophy in the presence of adenomyosis
- Smooth muscle cells from uteri with adenomyosis are ultrastructurally different from smooth muscle cells of normal uteri

- Mehasseb et al. (2010)

Altered uterine peristaltic activity

- Adenomyosis interfered with fertility by impairing uterine sperm transport
  - 2005 Kunz et al.
- The threshold value for a diagnosis of adenomyosis has been set at 10mm

  - Kunz et al., 2005, 2007

Altered uterine peristaltic activity

- In an elegant experiment of Kissler et al. (2006)
  - They placed into the posterior vaginal fornix 99m-Tc-labelled macro-albumin aggregates (with a size of 5–20 lm 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.

Altered uterine peristaltic activity

- 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.

Altered uterine peristaltic activity

- 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.

Altered uterine peristaltic activity

- 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.

Altered endometrial function and receptivity

- Thus, nidation involves multiple communications between the early embryo and the decidualized endometrium, with signalling back to the corpus luteum.

Altered endometrial function and receptivity

- 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.
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Altered endometrial function and receptivity

- 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.

Altered endometrial function and receptivity

- 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.

Altered endometrial function and receptivity

- 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

Altered endometrial function and receptivity

- 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.

Altered endometrial function and receptivity

- 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.

Altered endometrial function and receptivity

- In particular, the total surface area of capillaries per mm2 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.

Altered endometrial function and receptivity

- 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.

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

Altered endometrial function and receptivity

- 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.

Altered endometrial function and receptivity

- 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.

Altered endometrial function and receptivity

- 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).

Altered endometrial function and receptivity

- Subsequently, Goteri et al. (2009) compared in the same women the expression of VEGF and hypoxia-inducible factor-1a (HIF-1a) 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.

Altered endometrial function and receptivity

- 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.

Altered endometrial function and receptivity

- 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.

Altered endometrial function and receptivity

- 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).

Altered endometrial function and receptivity

- 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 proliferative-phase samples.

Altered endometrial function and receptivity

- 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).

Altered endometrial function and receptivity

- 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
- 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 a 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 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

Impaired implantation

- These have been called ‘implantation markers’
  - distinguishing between receptive and nonreceptive endometria in clinical practice
- The expression of a-4,b-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.

Impaired implantation

- a-4,b-3 integrin
  - appears on the surface of epithelial cells of both embryo and endometrium and on maternal surfaces around cycle days 19–20
  - continues to be expressed during pregnancy
    - Lessey et al., 1994a
  - Present in normal fertile patients but is missing in a subset of women with unexplained infertility and endometriosis

    - Lessey et al., 1994b

Impaired implantation

- Indeed, aberrant endometrial expression of the integrin subtype a-5,b-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 a-5,b-3 (vitronectin) and a-4,b-1, giving rise to speculation that it may mediate trophoblast-endometrial interactions during implantation.

Impaired 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.

Impaired implantation

- For instance, it has been found that glycodelin and osteopontin are down-regulated in women with endometriosis (Wei et al., 2009)
- It is possible that acidic extracellular matrix glycoproteins, regulated by progesterone and determinant in embryo attachment, may be down-regulated in the case of adenomyosis

Impaired implantation

- Since glycodelin is secreted by endometrial glands during the secretory phase and suppresses the maternal immune response supporting the implantation of the blastocyst (Seppa¨la¨ et al., 2000), its down-regulation may impair implantation.

Impaired 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.

Impaired implantation

- 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).

Impaired implantation

- 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).

Impaired implantation

- 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.

Impaired implantation

- 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.

Altered decidualization

- 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.

Altered decidualization

- 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.

Altered decidualization

- Lessey et al. (2006) have studied the relationship between expression of oestrogen receptor a and defective uterine receptivity in humans.
- In fertile patients the pattern of expression for oestrogen receptor a 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 midand late-secretory phases in response to progesterone.

Altered decidualization

- 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 a 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.

Altered decidualization

- As already mentioned, in adenomyosis IL-6 is overexpressed (Yang et al., 2006) and this could lead to increased oestrogen receptor-a 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).

Altered decidualization

- 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 a, given that down-regulation of this receptor is one of the primary functions of progesterone.
- The overexpression of oestrogen receptora in mid-secretory phase reduces the secretion of b-3 integrins negatively regulated by oestrogens thereby altering uterine receptivity.

Altered decidualization

- Very recently, Mehasseb et al. (2011) have postulated that oestrogen receptor-b 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 regnancy.
- Some of the enzymes producing or eliminating free radicals are xanthine xanthine oxidase (XO), superoxide dismutase (SOD), glutathione peroxidase (GPx) and nitric oxide synthase (NOS).

Abnormal concentrations of intrauterine free radicals

- 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.

Abnormal concentrations of intrauterine free radicals

- 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).

Abnormal concentrations of intrauterine free radicals

- 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).

Abnormal concentrations of intrauterine free radicals

- 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

- In contrast to the management of infertility-associated endometriosis
- 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 Honore` et al. (1988), although in the three reported cases the disease presented itself in the less common form of adenomyoma.

Treatment of adenomyosis-associated infertility

- One study showed new conservative technique to be employed in women with adenomyosis wishing to become pregnant

  - (Osada et al., 2011).

  - Indications for surgery were based on size and extent of lesions.
  - 38 cases of anterior (36.5%), 44 of posterior (42.3%) and 22 (21.2%) involving both anterior and posterior sides of the uterus.
- New technique - '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.

Treatment of adenomyosis-associated infertility

- Of 26 women who wished to conceive
  - 16 became pregnant, 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

Medical and combined medico-surgical treatment

- 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.
- 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

  - Kim et al. (2009)

Medical and combined medico-surgical treatment

- 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

- 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

Medical and combined medico-surgical treatment

- 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.

Medical and combined medico-surgical treatment

- Combination of cytoreductive surgery and GnRHa treatment
  - Several successful case in recent year

    - Ozaki et al., 1999; Lin et al., 1999; Lin et al., 2000; Wang et al., 2000

Medical and combined medico-surgical treatment

- Farquhar and Brosens (2006) warned
  - Combination of cytoreductive surgery and GnRHa treatment in managing infertile women with adenomyosis
    - The role is still far from clear, because of possible surgical and obstetrical risks
- Oestrogen/progestin combinations or orally administered danazol
  - No published reports are available

Medical and combined medico-surgical treatment

- Use of Mirena?
  - 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
  - Reviewed by Rabinovici and Stewart (2006a).
- One 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

Endometrial ablation or resection

- Results with this procedure have been recently reviewed
  - no data exist on possible effects on infertility

- Mc Causland and Mc Causland, 2008

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

- HIFU - external ultrasound energy source to induce thermal ablation at a given depth through the intact skin
  - For treatment of malignancies
  - application to adenomyosis has recently been reviewed

    - Dong and Yang, 2010
  - It offers advantages over current conservative treatments, at least in patients with localized adenomyosis
  - 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

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

- “Only one case” of successful treatment of adenomyosisassociated infertility with HIFU has been published.
  - A 36-year-old woman who had difficulty conceiving because of profuse menometrorrhagia
  - Diagnosis of focal adenomyosis was made at MRI
  - 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

    - Rabinovici and colleagues (Rabinovici et al., 2006b)

Conclusions

- Much progress in the understanding of adenomyosis has been made over the last two decades
- 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.

Conclusions

- 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.
- The thickening, infiltration or disruption of the JZ myometrium is probably linked to poor reproductive performance, mainly through perturbed uterine peristalsis.