The pathophysiology of uterine adenomyosis: an update

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Brief

- Adenomyosis:
  - 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

- During the second half of the nineteenth and the first part of the twentieth century
  - "adenomyoma" was used to represent such lesions
  - The origin of these mucosal invasions was debated for decades before their endometrial nature became accepted
- In 1925, Frankl used the term "adenomyosis"
  - it does not imply an inflammatory process to the situation where "the direct connection of the endometrium with the islands of mucosa located in the musculature can be established in serial sections"
  - At this point, adenomyosis came to be identified as an entity

- The first attempt at a noninvasive diagnosis of adenomyosis
  - On 1979, with gray-scale ultrasound
- The real advance came in the mid-1980s with the advent of magnetic resonance imaging (MRI) and transvaginal ultrasound (TVU)

PROGRESS IN DIAGNOSIS

- Diagnosis of adenomyosis today
  - based on differences in appearance of smooth muscle
  - the inner myometrium (IM; the “myosis” component) and the identification of endometrial glands within the myometrium (the “adeno” component)
- With the advances in imaging techniques
  - it became clear that adenomyosis is not confined to older women but can be diagnosed in young symptomatic patients

PROGRESS IN DIAGNOSIS

- MRI
  - Able to identify a region in the IM with distinct signal density on T2-weighted images compared with the endometrium and the outer myometrium (OM)
    - Uterine junctional zone (JZ), archimyometrium, IM, endometrial-myometrial interphase, transitional zone, or subendometrial myometrium
  - Definable JZ is absent in 20% of premenopausal normal women
  - Longitudinal studies have shown that the JZ increases in thickness from the early proliferative to the late secretory Phase

PROGRESS IN DIAGNOSIS

- Uterine JZ
  - MRI: distinct low-intensity myometrial band
  - high-resolution ultrasound: subendometrial halo
- The reason for the distinct appearance
  - Different water content or differences in blood flow
  - The latter explanation seems unlikely
    - “zonation” is noted also in hysterectomy specimens
- The percentage of nuclear area is higher at JZ(size and number)

PROGRESS IN DIAGNOSIS

- Normal JZ and adenomyotic uterine JZ
  - Both has higher cell density and total nuclear area compared with the OM
  - Adenomyotic JZ –
    - distinct zonation seen on MRI
    - JZ measuring >12 mm and hemorrhagic high-signal myometrial spots – highly predictive
  - Normal JZ –
    - the change in cell density and nuclear area is gradual
    - The decrease in the extracellular matrix component elastin from the OM to the IM is also gradual

PROGRESS IN DIAGNOSIS

- (2D) TVU introduced in the 1980s
  - enabled affordable nonoperative diagnosis of adenomyosis.
  - highly observer dependent
  - experienced investigators have reported satisfactory accuracy in clinically suspected cases but not in unselected premenopausal women with myomas

PROGRESS IN DIAGNOSIS

- On TVU, adenomyosis appears as heterogeneous and hypoechogenic, poorly defined areas in the myometrium
- TVU has a predictive likelihood ratio of 4.67 (95% confidence interval [CI], 3.13–6.17)
  - A meta-analysis of reports published between 1966 and 2007 included papers starting in 1992
- The overall prevalence of adenomyosis was 27.9% (95% CI, 25.5–30.3), and the probability with an abnormal TVU was 66.2% (95% CI, 61.6–70.6)

PROGRESS IN DIAGNOSIS

- The probability of adenomyosis with a normal TVU was 9.1% (95% CI, 7.3–11.1).
- The most specific 2D TVU feature (specificity,98%; accuracy, 78%) is the presence of myometrial cysts, and the most sensitive is the finding of a heterogeneous myometrium (sensitivity, 88%; accuracy, 75%).

PROGRESS IN DIAGNOSIS

- 3D ultrasound
  - enables assessment of the lateral and fundal aspects of the JZ
  - provides clearer visualization of endometrial protrusion into the yometrium
- The best markers
  - A difference (JZdi) of $>$ 4 mm between the area of maximum thickness (JZmax) and the area of minimum thickness (JZmin) and its distortion and infiltration had high sensitivity (88%) and best accuracy (85% and 82%, respectively).

PROGRESS IN DIAGNOSIS

- Overall, for 2D TVU and 3D TVU, respectively, the accuracy was 83% and 89%; sensitivity was 75% and 91%; specificity was 90% and 88%; positive predictive value was 86% and 85%; and negative predictive value was 82% and 92% .
- Diagnosis of adenomyosis can be made when one or more of the following sonographic findings are present:
  - a globular uterine configuration;
  - poor definition of the endometrial-myometrial interface;

PROGRESS IN DIAGNOSIS

- There are several studies that suggest comparable diagnostic accuracy between MRI and TVU.
- A systematic review and a meta-analysis of data obtained with TVU and/or MRI with histological confirmation of adenomyosis (Table 1) concluded that both techniques showed high levels of accuracy.
- The advantage of MRI is that images produced are standard and unaffected by the presence of fibroids .

PROGRESS IN DIAGNOSIS

TABLE 1

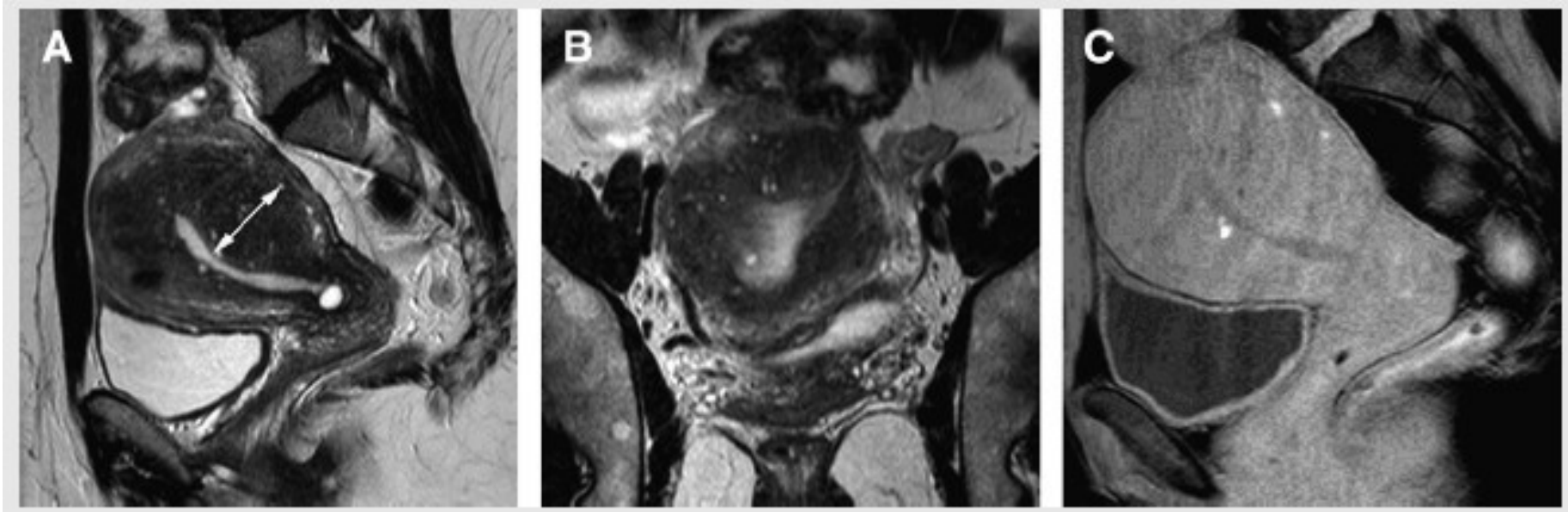
TVU and MRI for the diagnosis of adenomyosis (32).

	TVU	MRI
Sensitivity	72 (95% CI, 65%–79%)	77 (95% CI, 67%–85%)
Specificity	81 (95% CI, 77%–85%)	89 (95% CI, 84%–92%)
Positive likelihood ratio	3.7 (95% CI, 2.1–6.4)	6.5 (95% CI, 4.5–9.3)
Negative likelihood ratio	0.3 (95% CI, 0.1–0.5)	0.2 (95% CI, 0.1–0.4)

Benaglano. The pathophysiology of uterine adenomyosis. Fertil Steril 2012.

PROGRESS IN DIAGNOSIS

FIGURE 1



- A 42-year-old woman with increasing dysmenorrhea and unclear sonographic findings at endovaginal ultrasound.
- Pathology of hysterectomy specimen–diagnosed adenomyosis. Preoperative MRI of the pelvis.

PROGRESS IN DIAGNOSIS

- True-cut transhysteroscopic device – 1997
  - to obtain basal endometrium and JZ biopsies
- TVU-guided biopsy – 2003
- Laparoscopy-guided myometrial biopsies
  - A study involving 100 patients with symptoms suggestive of adenomyosis reported 98% sensitivity, 100% specificity, and 100% positive and 80% negative predictive value for laparoscopy-guided myometrial biopsies

PROGRESS IN DIAGNOSIS

- Adenomyosis
  - lack of agreed-upon terminology or consensus on the classification of the lesions
  - irregularity at the endometrial-myometrial interface is common and that some basal glands can be seen within the superficial myometrium raises the question of the appropriate cutoff point for defining adenomyosis

PROGRESS IN DIAGNOSIS

- Recently, an Italian group argued that not all JZ abnormalities identified by imaging should be equated to histological adenomyosis .
- They therefore proposed that the existence of a "subendometrial myometrium unit" be recognized as a new nosological entity distinct from adenomyosis and that disruption of that unit is linked to infertility and pregnancy complications.

VIEWS ON PATHOGENESIS

- Traditionally describtion of adenomyosis
  - abnormal in-growth and invagination of the basal endometrium into the myometrium
- First theory of the pathogenesis
  - During periods of regeneration, healing, and reepithelization, the endometrium invades a predisposed myometrium or a traumatized endometrial-myometrial interface
    - Repeated sharp curettage during pregnancy greatly increase the risk of adenomyosis by disrupting the endometrial-myometrial border and facilitating implantation, embedding, and survival of endometrium

VIEWS ON PATHOGENESIS

- Building on this hypothesis, a staged process was suggested
  - Disruption of the normal boundary between the endometrium and the myometrium -> Invasion of endometrial glands into the myometrium -> resulting ectopic intramyometrial glands -> cause myometrial hypertrophy and hyperplasia
- Against this hypothesis are experiments on neonatal mice demonstrating that disruption of the myometrium is not necessarily followed by the appearance of adenomyosis
- In addition, a recent study found no statistically significant association between adenomyosis and previous cesarean section, endometrial curettage, or evacuation of the uterus

VIEWS ON PATHOGENESIS

- There is some evidence for familial predisposition
  - hormonal, genetic, immunological, and growth factors may play a role
- Association of adenomyosis with tamoxifen treatment
  - suggest a role for hormonal imbalances, if hyperestrogenism is involved, it is probably through increased local estrogen
- Hyperestrogenism may also account for the hypertrophy/hyperplasia in the surrounding myometrium and overlying endometrium

VIEWS ON PATHOGENESIS

- Experimental data in rodent models
  - in utero or neonatal exposure to tamoxifen or diethylstilbestrol
    - induce adenomyosis and marked myometrial disruption
  - raising the possibility of in utero developmental events leading to adenomyosis.
- Studies in animal models also support a role for hyperprolactinemia (either induced by pituitary transplantation or drug therapy) , although there is no evidence for a similar mechanism in humans

THE ENDOMETRIUM

- The observed histological continuity between the basal endometrium and underlying adenomyosis lends itself to the hypothesis of an origin from invaginating endometrium basalis.
  - increased invasiveness of endometrial cell be these external or mechanical forces or innate properties of the endometrium
  - the similarities between the endometrium basalis and adenomyotic nodules

THE ENDOMETRIUM

- There is evidence of increased invasiveness of endometrial cells in endometriosis
  - endometrial cells from endometriosis nodules had an invasive potential in a collagen invasion assay comparable to that of a metastatic bladder carcinoma cell line (EJ28), exceeding that of a nonmetastatic bladder cell line (RT112)
- Invasive cells were identified as E-cadherin negative epithelial cells
- loss of cohesion of myometrial bundles influenced by enzymes such as matrix metalloproteinases (MMPs)
- Endometrial stromal fibroblasts produce tenascin

THE ENDOMETRIUM

- Adenomyosis seems to be associated with the presence of a more invasive endometrium
  - Stromal cells from adenomyosis exhibit greater invasiveness compared with normal stromal cells when grown on a plain collagen matrix or in double culture with myocytes from normal or adenomyosis-affected uteri
  - At the same time, myocytes from adenomyosis enhance invasion of stromal cells when compared with normal myocytes.
- This suggests that both the stromal and the myometrial components may have a role in the etiology of adenomyosis

THE MYOMETRIUM

- There are ultrastructural differences between smooth muscle cells from adenomyosis and normal myometrium
  - Myocytes of adenomyosis
    - exhibit cellular hypertrophy
    - With differences in cytoplasmic organelles, nuclear structures, and intercellular junctions
    - rER and Golgi apparatus in adenomyosis are more prominent, denoting active protein synthesis, consistent with the observed cellular hypertrophy

THE ENDOMETRIUM

- Recent observation that myocytes from adenomyosis enhance stromal cell invasion and the presence of similar peak cluster patterns for secreted proteins when adenomyosis stromal and muscle cells grown in culture are compared with normal stromal and muscle cells, respectively, suggests that both stromal and muscle cells have a role and reflect a panuterine abnormality.

THE ENDOMETRIUM

- Gene expression profile demonstrated differences between mRNA expression in the IM and the OM in women with adenomyosis and the corresponding layers in unaffected uteri.
- WNT5A mRNA
  - down-regulated in adenomyosis, both in the secretory and the proliferative phases
- WNT5A is a conserved homolog of Wingless, a key regulator of Drosophila melanogaster embryonic segmentation and patterning.

THE ENDOMETRIUM

- Studies in rodents are indicative of a role for neurotrophins such as nerve growth factor (NGF), which was significantly up-regulated in endometrial luminal epithelium in the CD-1 mouse model of adenomyosis
- Thus, neurotrophins may affect myogenic differentiation through paracrine mechanisms. The pattern of neurotrophin (NGF, BDNF) and neurotrophin receptor (trkB, trkC and p75NTR) expression in the human myometrium also points to a possible role .

THE ENDOMETRIUM

- Videosonography and experimental data indicate altered myometrial contractility in endometriosis
- Uterine hyperperistalsis and dysperistalsis (contractions that have one or more ectopic origins and/or abnormal or incomplete propagation) may be linked to the pathogenesis of endometriosis
  - although there are no direct studies on contractility in adenomyosis, estrogen-mediated paracrine mechanisms were hypothesized to perpetuate a cycle of uterine autotraumatization leading to the genesis of adenomyosis.

HORMONAL ABNORMALITIES

- Adenomyosis is influenced by steroids
  - Distribution of estrogen (ER) and progesterone (PR) receptors and their isoforms in the endometrium.
  - Some studies have reported receptor distribution in the inner but not the OM.

HORMONAL ABNORMALITIES

- Cyclical changes in the JZ as seen by MRI, together with the peristaltic waves seen by videosonography, directly demonstrate that this layer is influenced by steroids .
- Steroid hormones have also been implicated in the pathogenesis of uterine adenomyosis, and local rather than systemic hyperestrogenism may be implicated .
- This may be through the action of aromatase on androgen precursors or estrone sulphatase acting to convert estrone-3-sulphate to estrone; mRNA for

HORMONAL ABNORMALITIES

- These findings may account for the higher E2 level detected in menstrual but not in peripheral blood in women with adenomyosis .
- There is also evidence of altered 17b-hydroxysteroid dehydrogenase type-2 in the endometrium in women with adenomyosis resulting in increased conversion of E2 to estrone during the secretory phase of the cycle .
- ER-a expression is reduced in a CD-1 neonatal mouse model for adenomyosis, but a similar reduction is noted after tamoxifen administration to C57/BL6J

HORMONAL ABNORMALITIES

- In the adenomyotic functionalis glands and stroma, there is a statistically significant ($P<.001$) decrease in ER-a expression during the midsecretory phase of the menstrual cycle, but the expression of ER-a in the IM and OM is not statistically significantly different .

HORMONAL ABNORMALITIES

- The ER-b expression is statistically significantly elevated in the adenomyotic functionalis gland during the proliferative phase and throughout the myometrium across the entire menstrual cycle.
- Expression of PR-A is similar to that of PR-B, with reduced expression in the basalis stroma and the IM and OM in adenomyosis .
- The pattern of ER-b, PR-A, and PR-B expression is similar in the endometrium basalis and adenomyotic foci.

HORMONAL ABNORMALITIES

- Studies using the neonatal mouse model and the PRL-induced adenomyosis mouse model suggested that disruption and/or “permissiveness” of the IM could play a role in the development of adenomyosis .
- However, abnormalities of the IM cannot on their own explain the development of adenomyosis .
- Stromal and myometrial cells from adenomyosis have a distinct proteomic profile compared with controls.

HORMONAL ABNORMALITIES

- Furthermore, some of the distinct features of adenomyosis-derived cells are shared between stromal and myometrial cells.
- This suggests that adenomyosis may be characterized by a soluble secreted protein profile, at least in coculture, supporting the hypothesis that adenomyosis is a manifestation of an affection of both myometrium and stroma.
- This is perhaps not surprising given the common paramesonephric duct origin of the stroma and the IM

HORMONAL ABNORMALITIES

- Myometrial smooth muscle cells originate from undifferentiated mesenchymal cells .
- The presence in the basal endometrium of cells with some of the features seen in smooth muscles has been shown .
- These cells resembled myofibroblasts in the proliferative phase and immature smooth muscle cells in the secretory phase and early pregnancy.
- This suggests some plasticity at the endometrialmyometrial interphase. In the

POSSIBLE LYMPHATIC INVASION ABNORMALITIES

- The occasional finding of endometrial tissue in the intramyometrial lymphatics suggests a possible route for invagination of the basal endometrium, since isolated nodules of endometrial stromal cells without endometrial glands (type 1 nodules) along blood or lymphatic vessels were described , suggesting that the new stroma may serve as "new soil" for proliferative endometrial glands.
- However, this expansion and growth may represent a type of stromatosis or endometrial stromal sarcoma (endo1 lymphatic stromal myosis), which are

NEOANGIOGENESIS

- A marked increase in vascularization of the endometrium in adenomyosis was reported with the total surface area of capillaries up to 11.6 times that of the controls in the proliferative phase .
- This has not been confirmed in a subsequent study, although microvessel density in adenomyotic tissue was increased compared with the endometrium of the same patient .
- A recent molecular study found an elevation of MMP-2 and -9 expressions in eutopic and ectopic endometria with a good correlation with increased

NEOANGIOGENESIS

- On the other hand, an analysis of MMP-2, -9, TIMP-1, and -2 in endometrial stromal cells (ESCs) of adenomyosis indicates that the formation of adenomyosis does not result from altered invasiveness of ESCs , therefore other enzymes should be considered.
- The role of the MMPs and TIMPs in the development of adenomyosis was further investigated through genetic studies; there was an association between adenomyosis and MMP-2 -1306C/T polymorphism in North Chinese women (91).

NEOANGIOGENESIS

- The same investigators also suggested that the presence of the 2578A or 1154A allele of the vascular endothelial growth factor (VEGF) gene might be protective , and that polymorphisms of two angiogenic factors, fibroblast growth factor (FGF) -1 and -2, might play a role in the initiation of angiogenesis in endometriosis or adenomyosis .

LINKS BETWEEN ADENOMYOSIS AND ENDOMETRIOSIS

- An important contribution of MRI is the ability to correlate JZ thickness with the degree of infiltration and stage of endometriosis .
- One study reported that 27% of women with endometriosis had concomitant adenomyosis .
- The percentage with adenomyosis in a group of infertile women with endometriosis was 70% (96). More recently 34.6% of 153 women with suspected deeply infiltrating endometriosis compared with 19.4% from a reference group of women who underwent hysterectomy for benign (n =100) or

LINKS BETWEEN ADENOMYOSIS AND ENDOMETRIOSIS

- In addition, 39.9% of the women with endometriosis had an irregular JZ, compared with 22.5% in the reference group (P<.01) .
- Nevertheless, the investigators could not conclude that their study supported a common pathogenesis of adenomyosis and endometriosis because the invasive potential of endometrial cells in the uterus and peritoneum corresponded only to a limited extent.
- A 42.76% prevalence of adenomyosis in patients with endometriosis has been recently identified in patients reporting severe or incapacitating

LINKS BETWEEN ADENOMYOSIS AND ENDOMETRIOSIS

- A common pathogenesis for adenomyosis and endometriosis has been hypothesized , and it was argued that endometrial stroma being in direct contact with the underlying myometrium allows communication and interaction,thus facilitating endometrial invagination or invasion of a structurally weakened myometrium during periods of regeneration, healing, and reepithelization.
- Mechanical damage to and/or physical disruption of the endometrial-myometrial interface may be due to dysfunctional uterine hyperperistalsis and/or

LINKS BETWEEN ADENOMYOSIS AND ENDOMETRIOSIS

- Expression of the motility-related molecule Cdc42 in eutopic endometrium was higher in patients with ovarian endometriotic cysts compared with in patients with adenomyosis , suggesting that Cdc42 may not be involved in the pathogenesis of adenomyosis but may play a role in the process of endometrial cell migration; this could contribute to the pathogenesis of ovarian endometriosis supporting the process of adhesion of endometriotic cells on the ovarian surface followed by invagination and pseudocyst formation .

LINKS BETWEEN ADENOMYOSIS AND ENDOMETRIOSIS

- The question therefore arises whether the pathogenesis of adenomyosis is more associated with deep rectovaginal endometriosis than with cystic ovarian endometriosis.
- On the other hand, FGF-1 polymorphism has been linked to risk of endometriosis but not adenomyosis, while FGF-2 754C/G polymorphism was associated with a decreased susceptibility to developing endometriosis (odds ratio [OR],0.575; 95% CI, 0.387–0.854) and adenomyosis (OR, 0.577;95% CI, 0.367–0.906).

LINKS BETWEEN ADENOMYOSIS AND ENDOMETRIOSIS

- Our understanding of the clinical significance of adenomyosis has changed markedly during the last decade.
- Pathophysiological studies of adenomyosis were until recently exclusively performed in older women with symptoms of abnormal uterine bleeding and/or dysmenorrhea, severe enough to justify hysterectomy.
- Since it became possible to assess the structure and function of the JZ by imaging techniques, an increasing number of studies were performed on

LINKS BETWEEN ADENOMYOSIS AND ENDOMETRIOSIS

- Obstetric risks after endometriosis and/or adenomyosis have recently been described and suggest a defective role of the JZ in deep placentation (105–109).
- It is clear that laparoscopy and imaging are today complementary techniques that provide new opportunities for research and clinical management of the disease that has manifestations related to a defective uterine function.

CONCLUSION

- Several hypotheses have been proposed for the pathogenesis of the disease:
  - The origin from the endometrium basalis invaginating deep within the myometrium
  - Local hyperestrogenism and mechanical forces manifesting as hyper- or dysperistalsis may facilitate the process
- While the innate properties of the endometrium may be a factor, recent observations also point to a role of the myometrium
  - Smooth muscle cells from uteri with adenomyosis are ultrastructurally different from smooth muscle cells of normal

CONCLUSION

- The concomitant presence of endometriosis and adenomyosis in a range of clinical conditions, such as infertility and obstetrical syndromes, supports the possibility of a common uterine etiology and can be advanced to support the proposition that both diagnostic laparoscopy and uterine imaging be offered in suspected cases.