Adenomyosis

EBM
Definitions and pathophysiology
Diagnosis
A cause of Infertility & Pain ?
Treatment
Conclusions

Gruppo Italo Belga
www.mondoginecologico.it

Philippe R. Koninckx
Anastasia Ussia
Evidence

- Real Evidence $\leftrightarrow$ statistical evidence
  - Real evidence = Mechanism eg law of physics
    = 1 rule explains all
  - Statistical evidence = a probability
    - Of association
    - Of difference
    - Of effect
- Research = statistical evidence with the aim to find the mechanism
- Rare events
Clinical decisions are multifactoreal based upon non-multifactoreal research data

• Clinical decisions are multifactoreal
  • Eg Ovarian cyst
    Size
    Appearance
    Imaging: Ultrasound
    Age
    Duration of presence
    Other pathology

..................................................
EBM 1

• Clinical decisions are multifactoreal.
• Research data are not and cannot be multifactoreal
  ........ because of numbers
  
• Statistical rule of thumb: minimally 30 events
  If less “statistical correction” eg bonferoni
• Also for rare events 1%= 3000 patients for 30 events
• Multivariate analysis: 30 events / each variable
  also the least frequent
• \textit{RCT infection & Hysterectomy}: 1%-> 0.5% \( n =6000 \)
  + 3\textsuperscript{rd} ... 4\textsuperscript{th} variable

*The theoretical solution: the RCT*
Problem : 2  EBM and RCT

Shotgun marriage : who wears the pants?  Trudy Bush
Epidemiological and preventive medicine, Baltimore

Although the RCT is mathematically correct

Dilemma 1  of RCT
• if evidence of benefit exist .......... unethical to perform
• if expected benefit is so little........ No need to perform

Dilemma 2
• The population : inclusion and exclusion criteria
  Strict criteria are needed for clear results since randomisation
corrects for other variables (instead of versus multivariate analysis)
But more strict means more limited extrapolation

Dilemma 3 : not suited for rare events
  a 1% event needs a RCT of 6000 in order to have 30 events each group
Also Meta-analysis is not the solution

Selection of articles

- Ignore all evidence other than RCT’s
- Ignore when not all requirements for an RCT are met such as blinding and randomisation

Not 1 valid RCT for medical treatment of pain in endometriosis
Randomised Clinical Trial: conclusion

- Randomised controlled trial is useful
  - for large trials eg 1% rare event needs 6000
  - Provided the rules are followed eg blinding

- Otherwise I would put my money on Observational studies ... more realistic and more powerful

- Too much: evidence based manipulation:
  how to lie with statistics
How to lie with statistics?

- Statistical significant $\iff$ clinically relevant
  - Clinical decisions = population
  - Statistical significance = sample size

- Sensitivity - specificity $\iff$ predictive value
- Mutivariate worse
- Not Different $\iff$ Identical
RCT: Conclusions

- RCT and meta-analysis are mathematically perfect
  - But feasibility is low
  - Cost is high
  - Information is slow
  - Extrapolation is questionable
  - 1 of the many valid statistics

- Observational medicine
  - Is powerful
  - Is the basis for logistic regression, cluster analysis, case control etc

- Use statistics in a correct way, use the most suitable statistics, without religion
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Anastasia Ussia
Adenomyosis-Endometriosis definition

• Described in 1860 by Rokitanski as

Heterotopic endometrial glands and stroma in the myometrium with adjacent smooth muscle hyperplasia

• Defined morphologically as

Invasion of glands and stroma’ in the myometrium, deeper than 2.5 mm from the EJZ. Associated with smooth muscle hyperplasia

• 1900 1940 Cullen-Sampson : Endometriosis : endometrial glands and stroma outside the uterus `
Adenomyose definition

**Pathology**

Invasion of glands and stroma' in the myometrium, deeper than 2.5 mm from the EJZ. Smooth muscle hyperplasia

**Imaging: US MRI**

JZ >12mm
Focal thickening of JZ
Adenomyotic nodule

After Hysterectomy Non invasive

Thus all articles on treatment are biased since 20% did not have adenomyosis, and 20% were missed
Adenomyose definition

- muscle
- stroma
- glands
Adenomyosis
Adenomyosis
Diagnosis: MRI: 2 types

- Adenomiotic nodule
- Hyperintensive zone
- Thickened JZ
Diagnosis: ultrasound
The Endometrium

- Glands & stroma
  - during menstrual cycle = dating
  - Pregnancy -> decidualisation
- Functionalis and basalis
  - Different hormonal control
- Junctional zone & spiral arteries
The Endometrial function

- The most regenerative tissue
- Hormonal sensitivity
- Peristalsis
- Pregnancy
  - Invasion
  - Immunology

Leyendecker 85
Archimetra
Brosens 68
Pathophysiology: Theories

Sampson

- Viable cells in menstruation

- Retrograde menstruation

- Viable cells in PF

- Implantation potential
  In humans, in primates, in nude mice, in vitro

We see

We Imagine
The Endometriotic Disease Theory

Genetic mutation cause a cell to become tumorous

Koninckx P.R., Kennedy S., Barlow D.,
Gyn Obstet Invest 1999, 47, 1-10
The Endometriotic Disease Theory

Koninckx P.R., Kennedy S., Barlow D., Gyn Obstet Invest 1999, 47, 1-10

Endometriosis

- Subtle lesions
  - Retrograde menstruation,
  - Remodeling,

Endometriotic disease

- Deep

- Cystic Ovarian Adhesions

- Typical

Genetic mutation favorised by heredity immunology volume environment

Sampson-Metaplasia
EDT: Clinical importance 1

**Sampson/Metaplasia**
- Implantation is key
  - Subtle ++
- Why Progression ??

**Endometriotic Disease Theory**
- Implantation occurs in all women
  - Subtle is a normal condition
- Genomic incident -> Progression
  - Explains heredity, dioxin, irradiation
  - ... predisposition
  - ... clonality
  - ... big deep lesions as soon as 1 year after menarche

A normal cell

In an abnormal environment

An abnormal cell

A benign tumour
Genetic predisposition

- Clonality
- Loss of heterozygosity
- Germ cell predisposition
Clonality in endometriosis

Genetic damage to single progenitor cell

Clonal expansion

Monoclonal neoplasm

- **Cystic ovarian endometriosis** Yes
  - Jimbo et al (1997) *Am J Pathol* 150, 1173; 21 samples from 11 endometriomas; Marker = X-linked *HUMARA* gene
    - 21/21 samples monoclonal
  - Tamura et al (1998) *Lab Invest* 78, 213; 25 epithelial cells from 25 archival endometriomas; Controls = 25 matched ovarian stroma tissue; Marker = X-linked *PGK* gene
    - 10/25 samples informative (all 10 monoclonal)

- **Deep endometriosis**
Loss of Heterozygocity

Germline Mutation
= Heredity

First Hit
Second Hit

Somatic Mutation

Where should we look for a first hit?
in the endometrium of women with & without endometriosis
Endometrium in Endometriosis and in adenomyosis

• > 300 articles


EDT : Clinical importance 2

- Microscopical and subtle endometriosis is not pathology
  - Lymph nodes
  - Peritoneum
  - Bowel
SHOULD WE REVISE THE DEFINITION OF ENDOMETRIOSIS?

Clinical evidence strongly suggests that the mere presence of endometrial glands and stroma outside the uterus should no longer be considered to be a clinical pathology by definition. Unfortunately, we cannot distinguish between glands and stroma that have no clinical importance and may disappear spontaneously and those that will develop into endometriosis causing pain and infertility. Hopefully, immunohistochemistry and/or molecular biology one day will allow us to define specific activities or processes causing the endometriosis pathology and therefore to distinguish between normal and pathologic “endometrial-like tissue outside the uterus.”

ENDOMETRIOSIS SURGERY AND ERADICATION OF ALL ENDOMETRIAL CELLS AND STROMA

Philippe R. Koninckx, M.D., Ph.D. a
Jacques Donnez, M.D., Ph.D. b
Ivo Brosens, M.D., Ph.D. a

a Katholieke Universiteit Leuven, Leuven; and b Catholic University of Louvain, Brussels, Belgium
Pathophysiology Adenomyosis

- Myoproliferative disease of the inner myometrium, with an altered local paracrine and immune microenvironment (J Brosens & I Brosens 1998)
- Morphologically similar to deep endometriosis
- Increased incidence after simultaneous disruption of endometrium and myometrium (Parazini 95, Curtis 2002, Levgra 2000)
  - C section
  - Endometrial ablation
  - Spontaneous abortion  OR 1.7-4.4
  - D&C  OR 2.2-15.5
  - Pregnancy terminations
Adenomyosis and endometriosis. Re-visiting their association and further insights into the mechanisms of auto-traumatisation. An MRI study

G. Leyendecker · A. Bilgicyildirim · M. Inacker · T. Stalf · P. Huppert · G. Mall · B. Böttcher · L. Wildt

- Prevalence of
  - adenomyosis → 80% endometriosis
  - endometriosis → 90% adenomyosis
The Archimetra Concept

  - Pelvic endometriosis is significantly associated with uterine adenomyosis and the latter constitutes the major factor of infertility eg by altered contractions
  - According to this concept both adenomyosis and endometriosis constitute a pathophysiological and nosological entity ie a continuum from mild endometriosis to adenomyosis
  - Both are characterized by the dislocation of basal endometrium.

- Mehasseb, M. K., Bell, S. C., Pringle, J. H., and Habiba, M. A. Uterine adenomyosis is associated with ultrastructural features of altered contractility in the inner myometrium. Fertility and Sterility 93(7), 2130-2136. 1-5-2010
Fig. 9 The longitudinal extension of adenomyotic lesions in a percent of the cases in the upper third (a), middle third (b) and lower third (c) of the uterus. Adenomyotic lesions were localized predominantly in the upper two-thirds of the uterine corpus and extended also over the whole length of the uterine corpus (a+b+c). They rarely presented in the lower two-thirds (b+c) and never in the lower third (c).
Fig. 5 The course of a peristaltic wave of the archimyometrium as shown by a sequence of MRI scans obtained from cinematographic MRI scan in a healthy woman in the late follicular phase. Initially, the archimyometrium appears to be relaxed, indicated by a thin JZ with a less marked hypointensity (a). The peristaltic wave starts with tension of the archimyometrium in the lower half of the uterine corpus, indicated by marked hypointensity of the JZ (b). The zone of increased tension (marked hypointensity) moves in a fundal direction. A muscular package is built up, indicated by the rapid increase of the JZ as the wave moves in a fundal direction (c–e) followed by a rapid relaxation (f).
Fig. 8 Six examples of cystic cornual angle adenomyosis. These women suffered from extreme primary dysmenorrhea.
Fig. 10 Schematic representation of the mechanism of uterine auto-traumatization by uterine peristalsis and hyperperistalsis at the fundo-cornual raphe. Green arrows direction of sperm transport. Red arrows distraction of basal stromal cells and archimyo-vascular myocytes at the fundo-cornual raphe by uterine peristalsis. With the development of an early adenomyotic lesion in the midline of the upper uterine corpus, a chronic process of proliferation and inflammation is established that facilitates the detachment of the basal endometrium. Fragment of detached functionalis (a) and a fragment of detached basalis (b) in menstrual blood (modified from [2, 4, 7]).

Table 2 The diameters of the junctional zone in 143 patients with suspected adenomyosis as summarized in three groups of age

<table>
<thead>
<tr>
<th>Age</th>
<th>AW (±SD)</th>
<th>PW (±SD)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 years</td>
<td>9.20 (±3.21)</td>
<td>11.42 (±4.87)</td>
<td>33</td>
</tr>
<tr>
<td>30–35 years</td>
<td>11.31 (±5.87)</td>
<td>11.71 (±5.66)</td>
<td>68</td>
</tr>
<tr>
<td>&gt;35 years</td>
<td>12.43 (±7.39)</td>
<td>14.46 (±7.95)</td>
<td>42</td>
</tr>
</tbody>
</table>

There is an increase in the JZ with age and a trend of the preponderance of an enlarged JZ in the posterior wall of the uterus. The differences were not significant due to the large standard deviation.
Fig. 11 Recording of intrauterine pressure in an adolescent girl with extreme primary dysmenorrhea on the second day of the cycle (Courtesy L. Wildt and B. Böttcher)
Fig. 12 Schematic representation of uterine autotraumatization by the mechanism of 'archimetal compression due to neometral contraction' at the onset of menstruation. N neometra; E endometrium; A archimyometrium (a). Due to the high intrauterine pressure in consequence of the contraction of the neometra, the archimyometrium ruptures in the cornual angles and fragments of basal endometrium are dislocated into the myometrial wall, where they develop into endometriotic cysts (b and c). At the same time, basal stromal cell at the fundo-cornual raphe are chronically overstretched resulting in the initiation of the TIAR mechanism and the development of an adenomyotic lesion.
Conclusions: pathophysiology

- Endometrium and JZ have the same origin, and are both hormonaly responsive
- Adenomyosis increases after disruption of endometrium/myometrium
- Basal endometrium is different from functional endometrium
- Are the cells of adenomyosis abnormal?
  - Fits with the endometriotic disease theory
  - Behaviour of these cells eg Biochemical observations
  - A common pathological basis: susceptibility genes or archimetra, or stem cells
Structural and molecular features of the endomyometrium in endometriosis and adenomyosis

Giuseppe Benagiano¹, Ivo Brosens²*, and Marwan Habiba³

RESULTS: A number of similarities exist between adenomyosis and endometriosis and, by using magnetic resonance and laparoscopy, it was found that, at least in some subgroups, the two conditions often coexist. In both situations the inner myometrium (or junctional zone) is altered, although alterations are much more marked in adenomyosis where a thickness > 12 mm is today considered sufficient for diagnosis. Research has shown differences between the eutopic endometrium of women with both diseases when compared with controls. There is an immune dysfunction and there are alterations of adhesion molecules, cell proliferation and apoptosis. An increase in cytokines and inflammatory mediators has also been observed. Finally, the presence of oxidative stress and anomalies in free-radical metabolism may alter uterine receptivity. When the two conditions were compared, dissimilarities were also observed in the extent of apoptosis inhibition and in the expression of some inflammatory mediators. It is not clear if observed differences are primarily related to presenting symptoms. Finally, both conditions are steroid dependent and
Ultramicro-trauma in the endometrial-myometrial junctional zone and pale cell migration in adenomyosis

Fertility and Sterility® Vol. 104, No. 6, December 2015

Mohamed G. Ibrahim, M.Sc., a Vito Chiantera, M.D., a Sergio Frangini, M.D., a Shadi Younes, M.Sc., a Christhardt Köhler, M.D., b Eliane T. Taube, M.D., c Johanna Plendl, M.D., d and Sylvia Mechsner, M.D. a

Conclusion(s): The myofiber disarray in the inner myometrium, and the nuclear membrane irregularities in adenomyosis, are evidence for ultramicro-trauma in adenomyosis. The migrating nonleukocytic pale cells may be involved.

Van Gieson staining. Collagen fibers stain red; cytoplasm stains brown. (A) The inner myometrium in a nonadenomyosis patient. The smooth muscle fibers are parallel to the basal endometrial glands. (B) The endometrial-myometrial interface in adenomyosis: The basal endometrium clips down (circle) into the inner myometrium, disrupting the regular interface (magnification outside of inset: ×100). (C) The inner myometrium in adenomyosis: The smooth muscle fibers are arranged in diverse directions. Magnifications are ×200, unless otherwise noted.

Adenomyosis

(Ultradicro-trauma in the endometrial-myometrial junctional zone and pale cell migration in adenomyosis)

Mohamed G. Baziz, MD, PhD, * Vita Charters, MD, ** Sergio Francozi, MD, ** Shahid Younes, MD, ** Christof Kühler, MD, ** Elane T. Taube, MD, ** Jostiana Perni, MD, ** and Sylvia Mehner, MD, **

(A–L) Ultrastructure of the EMJZ in (A–D) nonadenomyosis vs. (E–J) adenomyosis groups, using TEM. (A) The interface between stromal cells in basal endometrium and smooth muscle cells (SMCs) in inner myometrium is regular and uninterrupted; magnification: ×2,500. (B) Smooth nuclear membranes (arrows) of epithelial cells in basal endometrium; magnification: ×2,000. (C) Desmosomes (circles) at the lateral borders of the epithelial cells in the basal endometrial glands; magnification: ×5,000. (D) Smooth muscle cells in inner myometrium are parallel, magnification: ×2,500. (E) Epithelial cells in basal endometrial glands show infolding of their nuclear membranes. The desmosomes are seen on the lateral cell borders; magnification: ×4,000. (F) A magnification of 2(E), showing 2 desmosomes between the cell membranes of 2 neighboring glandular epithelial cells (circles); magnification: ×10,000. (G) Inner myometrial smooth muscles in diverse directions; magnification: ×2,500. (H) A vesiculated cell (arrow) situated eccentrically in the basal endometrial gland. The cytoplasm is full of multiple heterogeneously electron-dense vesicles of various sizes; magnification: ×2,500. (I) A tight junction (arrow) can be seen on the upper lateral borders of the basal glandular epithelial cells; magnification: ×10,000. (J) A pale cell (arrow); Its cytoplasm is rich in mitochondria and ribosomes and appears more electron-lucent than the surrounding glandular epithelial cells; magnification: ×5,000. (K) The eccentric position of the pale cells (arrows) in the basal endometrial gland, away from the gland lumen (star); magnification: ×1,600. (L) The pale cell (arrow) is seen close to the endometrial gland lumen (star); magnification: ×1,600. (M–R) Migration steps of the pale cells in adenomyosis. (M) Desmosomes are lacking on the cell border of the pale cell; magnification: ×8,000. (N) The pale cell (arrow) is enclosed by 2 glandular epithelial cells; thick cellular interdigitations separate the basal part of the pale cell from the endometrial stroma (star). A narrow extracellular channel (arrowhead) runs from the pale cell compartment to the stromal compartment. The pale cell border is partially detached from the surrounding epithelial cells; magnification: ×12,500. (O) Marked thinning of the cellular interdigitations (arrow) at the basal border of the pale cell. The pale cell...
Immune-expression of (A, B) CD45 and (D, E) CD68 in the basal endometrium in adenomyosis. The glandular epithelial cells could not show any positive staining. (C and F) Positive controls: (C) CD45 positive immune cells in spleen and (F) CD68 positive macrophages among intestinal crypts. (A and D) Dapi stain. (G and H) E-cadherin immune-expression in the basal glands at the EMZ in adenomyosis. (G) magnification: x200, (H) x400. (I) Diagrammatic illustration of the pale cells’ (shown in yellow) role in the common pathogenesis of endometriosis and adenomyosis. Because they are located eccentrically in the basal endometrial glands, the pale cells can migrate into the myometrium (lower section), where they develop into adenomyotic lesions. Those in close contact with the glandular lumen (concentric position) can migrate through the uterine cavity into the peritoneal cavity, where they develop into peritoneal endometriosis.
Pale Cells Seem to Be Mobile

For the first time, and based on TEM, we were able to describe a cell population found among the epithelial cells of the basal glands at the EMJZ in both groups. Their position varied be-

The Pathogenesis of Adenomyosis: New Insight

To date, retrograde menstrual blood was believed to contain basal endometrial fragments, with a stem cell–like character, that could translocate into the myometrium to develop into adenomyosis (28). Our results provide novel insight into the pathogenesis of adenomyosis: The pale cells—rather than the whole basal endometrial gland—may migrate (under certain conditions) into the stroma of the basal endometrium and subsequently into the myometrium. Pale cells probably

New Insight Into a Common Pathogenesis of Endometriosis and Adenomyosis

Based on the previous findings, we could support the assumption of the common pathogenesis of endometriosis and adenomyosis depending on the following observations:
Corroborating evidence for platelet-induced epithelial-mesenchymal transition and fibroblast-to-myofibroblast transdifferentiation in the development of adenomyosis

Xishi Liu¹,²,*, Minhong Shen¹,*, Qiuming Qi¹, Hongqi Zhang³, and Sun Wei Cui¹,²,*
Myostatin, follistatin and activin type II receptors are highly expressed in adenomyosis

Patrizia Carrarelli, Ph.D., a Chih-Fen Yen, M.D., b,c Felice Arcuri, Ph.D., a Lucia Funghi, Ph.D., a Claudia Tosti, M.D., a Tzu-Hao Wang, M.D., b,o Joseph S. Huang, M.D., Ph.D., e and Felice Petraglia, M.D. a

Fertility and Sterility® Vol. 104, No. 3, September 2015
Myostatin, follistatin and activin type II receptors are highly expressed in adenomyosis

Patrizia Carrarelli, Ph.D., Chih-Fen Yen, M.D., Felice Arcuri, Ph.D., Lucia Fasana, Ph.D., Claudia Tosti, M.D., Tzu-Hao Wang, M.D., Joseph S. Huang, M.D., Ph.D., and Felice Petraglia, M.D.
The disturbance of $T_{H17}$-Treg cell balance in adenomyosis

Additive effects of inflammation and stress reaction on Toll-like receptor 4-mediated growth of endometriotic stromal cells

Khaleque Newaz Khan$^1$, Michio Kitajima$^1$, Tsuneo Inoue$^1$, Seiko Tateishi$^1$, Akira Fujishita$^2$, Masahiro Nakashima$^3$, and Hideaki Masuzaki$^1$

Long Xiaoyu, Ph.D.,$^{a,b}$ Zhang Weiyuan, M.D., Ph.D.,$^a$ Jiang Ping, M.D.,$^b$ Wan Anxia, M.D.,$^b$ and Zhou Liane, M.D.$^b$
Research

Clinical medicine
Diagnosis: ultrasound

- Asymmetrical uterine enlargement
- Ill defined hyperechoic & hypoechoic areas
- Small anechoic cysts
- Indistinct endometrial-myometrial border

Courtesy D. Timmerman
Diagnosis

**Junctional zone (JZ) and Adenomyosis**

- Normal JZ: \( \leq 5 \text{ mm} \)
- Adenomyosis: Thickening of JZ.
  
  \[ JZ \geq 12 \text{ mm highly predictive of histological adenomyosis.} \]


- Focal
- Diffuse

<table>
<thead>
<tr>
<th>23 yrs</th>
<th>Normal JZ</th>
<th>37 yrs</th>
<th>Abnormal JZ</th>
</tr>
</thead>
</table>

Thickening of JZ seen on MRI is related to inordinate myocyte proliferation. (JZ hyperplasia).

Adenomyosis: MRI

- Excellent soft tissue differentiation
- Less operator dependent
- Low intensity area on T2 weighted images
- Focal widening of junctional zone

- High cost
- Limited availability
- 2\textsuperscript{nd} stage test; TVS for initial evaluation
Diagnosis

• By pathology on hysterectomy specimens

• Punch biopsies: not reliable and abandoned
  • Wood et al 1993 (Med J Aust) Percutaneous biopsy in 10 patients
  • Brosens et al 1995 (Fertil Steril) (in vitro) → High specificity, very low sensitivity
  • S Gordts: hysteroscopic guided ?? Too early

• Ultrasound

• MRI
Incidence in the human

Based upon Pathology

- Overall in some 1%
- Found in 5 to 70% of hysterectomy specimens (Aziz 1989)
  - 31% in 3 sections, 61% in 6 sections (Bird 1972)
- Increases with age especially after 30 years

By imaging: TVS and MRI

- By TVS 30-60% in symptomatic women
  
  J Brosens, lancet 1995: in infertility, dysmenorrhoea, menorrhagia   28/56 = 50%
Prevalence by JZ thickness

**Fig. 2** Percentage of patients with the diagnosis of adenomyosis using limits of detection based on the thickness of the junctional zone ranging from ≥6 to ≥12 mm in the sagittal plane of the anterior or posterior wall of the uterus in 143 patients.
Diagnosis: ultrasound

The vasculature of the myoma typically circumscribes the mass.

In patients with diffuse or focal adenomyosis the vascular architecture appears unremarkable, with the vessels following their normal course perpendicular to the endometrial interface even if the vessels are slightly more dilated than the radial artery of a normal uterus.

Courtesy D. Timmerman
Adenomyosis: presenting symptoms

• Diffusely enlarged uterus
• Bleeding problems
  • menorrhagia  (40-50%)
  • Metrorrhagia  (10-12%)
• pain
  • dysmenorrhoea  (10-30%)
  • dyspareunia  (typically 1 wk prior menstruation)
  • dyschezia  (typically 1 wk prior menstruation)

• Thus not useful for diagnosis
Adenomyosis

• Associated with endometriosis
  • Especially with deep endometriosis
  • 54% (De Souza 1995) to 80% (Kunz 2005)

• Different types of adenomyosis
  • Diffuse thickening of JZ
  • Focal thickening with high IS
  • Adenomyotic nodule
Conclusion: diagnosis

- Clinical symptoms are not useful
- US and MRI have a sensitivity-specificity of 80-90%
  - MRI less operator dependent
  - US first line investigation

the focal adenomyotic nodule

JZ thickening
Clinical characteristics indicating adenomyosis coexisting with leiomyomas: a retrospective, questionnaire-based study

Fertility and Sterility® Vol. 101, No. 1, January 2014

Sara Y. Brucker, Prof., a Markus Huebner, M.D., a Markus Wallwiener, M.D., b Elizabeth A. Stewart, Prof., c Sandra Ebersoll, Cand. Med., a Birgitt Schoenfisch, Ph.D., a and Florin A. Taran, M.D. a

Comparison of the Uterine Leiomyoma and Adenomyosis Symptom Questionnaire Scores between patients with adenomyosis and leiomyoma(s) (n = 159) and patients with leiomyoma(s) alone (n = 401).

<table>
<thead>
<tr>
<th>Before surgery, how distressed were you by ...</th>
<th>Adenomyosis and leiomyoma(s)</th>
<th>Leiomyoma(s) alone</th>
<th>P value (Wilcoxon rank sum test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Heavy bleeding during your menstrual period</td>
<td>4.2 (1.3)</td>
<td>3.8 (1.5)</td>
<td>.005</td>
</tr>
<tr>
<td>2. Passing blood clots during your menstrual period</td>
<td>3.5 (1.5)</td>
<td>3.1 (1.5)</td>
<td>.005</td>
</tr>
<tr>
<td>3. Fluctuation in the duration of your menstrual period compared with your previous cycle</td>
<td>3.0 (1.5)</td>
<td>2.8 (1.4)</td>
<td>.081</td>
</tr>
<tr>
<td>4. Fluctuation in the length of your monthly cycle compared with your previous cycles</td>
<td>2.9 (1.5)</td>
<td>2.5 (1.4)</td>
<td>.015</td>
</tr>
<tr>
<td>5. Pelvic pain during your menstrual period</td>
<td>3.5 (1.4)</td>
<td>3.1 (1.4)</td>
<td>.008</td>
</tr>
<tr>
<td>6. Pelvic pain not associated with your menstrual period</td>
<td>2.1 (1.2)</td>
<td>1.9 (1.2)</td>
<td>.049</td>
</tr>
<tr>
<td>7. Intermenstrual bleeding</td>
<td>2.2 (1.2)</td>
<td>2.0 (1.2)</td>
<td>.056</td>
</tr>
<tr>
<td>8. Spotting</td>
<td>2.0 (1.3)</td>
<td>1.8 (1.2)</td>
<td>.162</td>
</tr>
<tr>
<td>9. Feeling tightness or pressure in your pelvic area</td>
<td>2.1 (1.2)</td>
<td>2.1 (1.3)</td>
<td>.568</td>
</tr>
<tr>
<td>10. Frequent urination during the daytime hours</td>
<td>2.1 (1.3)</td>
<td>2.1 (1.3)</td>
<td>.803</td>
</tr>
<tr>
<td>11. Frequent nighttime urination</td>
<td>1.8 (1.0)</td>
<td>1.8 (1.1)</td>
<td>.564</td>
</tr>
<tr>
<td>12. Feeling fatigued</td>
<td>2.9 (1.5)</td>
<td>2.6 (1.4)</td>
<td>.011</td>
</tr>
<tr>
<td>13. Painful sexual intercourse</td>
<td>1.7 (1.1)</td>
<td>1.7 (1.1)</td>
<td>.538</td>
</tr>
</tbody>
</table>
Is adenomyosis associated with menorrhagia?

J. Naftalin, W. Hoo, K. Pateman, D. Mavrelos, X. Foo, and D. Jurkovic*

MAIN RESULTS AND THE ROLE OF CHANCE: A diagnosis of adenomyosis was made in 157/714 women [22.0% (95% CI: 19.1–25.2%)]. Multivariable analysis showed significant associations between submucous fibroids [OR 5.60 (95% CI: 2.69–11.6)], any fibroids [OR 1.53 (95% CI: 0.91 – 2.58)] and endometrial polyps [OR 2.81 (95% CI: 1.15–11.7)] and menorrhagia. There were also significant associations between increasing gravidity and BMI and menorrhagia (P < 0.01). There was no significant association between adenomyosis and menorrhagia in the study population, when adenomyosis was assessed as a binary outcome. When severity of adenomyosis was assessed by counting the number of morphological features of adenomyosis in each woman, we found a significant 22% increase in menstrual loss for each additional feature of adenomyosis [OR 1.21 (95% CI: 1.04–1.40)].
Adenomyosis and infertility


Diagnosis of adenomyosis by ultrasound

• Model: IVF with oocyte donation (to avoid an influence of associated endometriosis with oocyte quality)
• Conclusion: No effect upon fertility


Uterine adenomyosis and *in vitro* fertilization outcome: a systematic review and meta-analysis

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**Main Results and the Role of Chance:** The clinical pregnancy rate achieved after IVF/ICSI was 123/304 (40.5%) women with adenomyosis versus 628/1262 (49.8%) in those without adenomyosis. The RR of clinical pregnancy ranged from 0.37 (95% CI, 0.15–0.92) to 1.13 (95% CI, 0.58–2.45), with a significant heterogeneity among studies (\(I^2 = 56.8\%, P = 0.023\)). Pooling of the results yielded a common RR of 0.89 (95% CI, 0.55–0.95). A funnel plot showed no indication of asymmetry among studies (Egger’s test, \(P = 0.696\)). In a meta-regression model,
Uterus-sparing operative treatment for adenomyosis

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Result(s): A quality assessment tool was used to assess the scientific value of each study. In total, 64 studies dealing with 1,049 patients were identified. After complete excision, the dysmenorrhea reduction, menorrhagia control, and pregnancy rate were 82.0%, 68.8%, and 60.5%, respectively. After partial excision, the dysmenorrhea reduction, menorrhagia control, and pregnancy rate were 81.8%, 50.0%, and 46.9%, respectively.

1. Complete excision of adenomyosis.
   a. Adenomyomectomy. Preferably used in cases of localized adenomyosis (adenomyoma) but also in selected cases of more diffuse adenomyosis with reconstruction of the uterine wall. This includes the complete removal of all clinically recognizable non-microscopic lesions. The integrity of uterine wall is maintained (20).
   b. Cystectomy. Used in cases of cystic focal adenomyosis, including the entire removal of the adenomyotic cyst (17, 21).

2. Cytoreductive surgery/partial adenomyomectomy. Used in cases of diffuse adenomyosis, including the partial removal of the clinically recognizable non-microscopic lesions because complete removal of the lesion would lead to the concomitant excision of critical amount of healthy myometrium, which could lead to “functional” hysterectomy (13, 22).

3. Nonexcisional techniques. Used in interventions where removal of adenomyotic tissue is not included (22–24).
1. **Diffuse adenomyosis.** The extensive form of the disease, characterized by foci of endometrial mucosa (glands and stroma) scattered throughout the uterine musculature (14).

2. **Focal adenomyosis.** A restricted area of hypertrophic and distorted endometrium and myometrium, usually embedded within the myometrium (14, 15). The histologic characteristics of focal adenomyosis may differ from patient to patient, from almost solid to only cystic (adenomyotic cysts); thus, this form could be subdivided to:
   a. **Adenomyoma.** Any disease that infiltrates a restricted area of the myometrium with more or less clear border and with mainly solid characteristics. Practically, the term adenomyoma seems to be used for grossly circumscribed adenomyotic masses (15, 16).
   b. **Cystic adenomyosis.** An extreme form of adenomyosis characterized mainly by the presence of a single adenomyotic cyst within myometrium (8).

   I. In women younger than 30 years old, focal cystic adenomyosis is described as juvenile cystic adenomyosis (JCA). For this variant, Takeuchi et al. (17) proposed the following diagnostic criteria: age less than 30 years, cystic lesion >1 cm clearly independent of the endometrium and severe dysmenorrhea.

3. **Polypoid adenomyomas.** Circumscribed endometrial masses composed of predominantly endometrioid glands and a stromal component predominantly of smooth muscle (15).
   a. Typical polypoid adenomyomas. Polypoid adenomyomas without architectural or cellular atypia (15).

4. **Other forms.**
   a. Adenomyomas of the endocervical type. Rare forms of adenomyomatous polyps in the uterine cervix that contain epithelial component of endocervical type. These lesions are important because they must be differentiated from adenoma malignum (19).
   b. Retroperitoneal adenomyomas. Adenomyotic nodules that are thought to arise from metaplasia of müllerian remnants beneath the peritoneum and in the area of upper rectovaginal septum (7).
Conclusion

Does adenomyosis cause infertility
????
Today we do
not know yet

Surgery seems (unexpectedly) useful
Beyond infertility: obstetrical and postpartum complications associated with endometriosis and adenomyosis

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TABLE 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Type of study</th>
<th>Pregnancy outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juang et al., 2006 (81)</td>
<td>104 women with preterm labor vs. 208 women who delivered after 37 weeks' gestation</td>
<td>Nested case-control</td>
<td>Increased risk for preterm birth (adjusted OR 1.84, 95% CI 1.32–4.31) and preterm premature rupture of membranes (adjusted OR 1.98, 95% CI 1.39–3.15)</td>
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<tr>
<td>Mochimaru et al., 2015 (82)</td>
<td>36 women with adenomyosis diagnosed by ultrasound or MRI before pregnancy vs. 144 women without adenomyosis</td>
<td>Retrospective cohort</td>
<td>Increased risk for preterm birth (OR 5.0, 95% CI 2.2–11.4), preterm premature rupture of membranes (OR 5.5, 95% CI 1.7–17.7), cesarean delivery (OR 4.5, 95% CI 2.1–9.7), SGA (OR 4.3, 95% CI 1.8–10.3), postpartum hemorrhage (OR 6.5, 95% CI 2.2–19.0), and malpresentation (OR 4.2, 95% CI 1.6–10.8)</td>
</tr>
</tbody>
</table>

Note: Abbreviations as in Table 1.

Treatment: embolisation

Adenomyosis and Fibroids

- First application of uterine embolization was in combined disease.
- Most experience to date suggests that when fibroids dominant or co-dominant compared to adenomyosis, results similar to fibroids alone.
- Some cases of failure to improve attributed to adenomyosis
Current Consensus

- Fibroids and adenomyosis
  - UAE effective particularly if fibroids dominant.

- Adenomyosis without fibroids
  - Focal adenomyosis/adenomyoma
    - UAE likely effective
  - Diffuse adenomyosis
    - UAE uncertain effectiveness long-term
    - Anticipate recurrence of 40% at 2-3 yrs.
Medical treatment


• N=25 women with adenomyosis-associated menorrhagia
  • Diagnosed by TVS
  • levonorgestrel-releasing intrauterine device (IUD)
  • Effective in reducing blood loss
  • Decrease in uterine volume
Medical treatment

DANAZOL INTRAUTERINE SYSTEM
(300-400 mg Danazol)

- 14 patients
- Inserted for several months
- No systemic side effects
- Normal ovulatory cycles
- Complete remission of dysmenorrhea in 9 patients

(Igarashi et al., FS, 74, 412-413, 2000)
Medical treatment

  - N=4  3 with focal adenoma
  - LH-RH 6 months
    - All uteri decreased in size
    - ¾ became pregnant within 4 months

  - N=2 with enlarged uteus
  - Nasal LH-RH for 3 months
  - Both conceived within 6 months
Medical treatment


- LH-RH agonist therapy in 30 women with diffuse adenomyosis
  - 12 symmetric
  - 18 asymmetric with focal high IS (intensity signal) foci

  - Decrease in JZ thickness  P<0.0001
  - Disappearance of high IS foci
  - Asymmetric *adenomyosis* with high SI foci appears to be the most sensitive to hormonal therapy
Medical treatment

- Oral contraceptives
- Progestins

The future?

- antiprogestins
Focused Ultrasound

- Ultrasound for energy – MRI for integration and temperature feedback
  - Experimental but promising

84 ml adenomyoma; menometrorrhagia


Zhou, M., Chen, J. Y., Tang, L. D., Chen, W. Z., and Wang, Z. B. Ultrasound-guided high-intensity focused ultrasound ablation for adenomyosis: the clinical experience of a single center. Fertility and Sterility 95(3), 900-905. **1-3-2011 Clinical effectiveness of the treatment was observed in 62 women (89.9%) with varying degrees of symptomatic relief of dysmenorrhea. Eight patients had relapses. Twenty-two patients (28.6%) had 27 complications.**
Conclusions

- There is no EBM to guide us in treatment of adenomyosis
  - Most data are observations in therapies for other conditions as fibroids or bleeding
  - There is no agreed imaging definition of adenomyosis
  - Thus there is no gold standard when the uterus is not excised.
- Emerging evidence for effectivity of
  - Intrauterine medicated IUD
  - Embolisation
  - Focused ultrasound
Overall Conclusions

• Adenomyosis is clearly defined by pathology
• Clinical symptoms are vague and variable
  • menorrhagia (40-50%) dysmenorrheoa (10-30%)
  • metrorrhagia (10-12%) dyspareunia, dyschezia
  • Association with infertility unclear
• Pathophysiology?
• 3 entities:
  • Hyperplasia of JZ
  • Focal hyperplasia
  • Adenomyotic nodule
• Therapy
  • Hormone responsive: OC, LNG IUD
  • Surgery
  • embolisation