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Diagnosing adenomyosis: an integrated clinical and imaging approach

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Introduction

- Adenomyosis (ectopic endometrial glands and stroma)

Diagnose: has turned from histopathological entity into a clinical condition by imaging techniques (MRI, TVUS),

Has been considered

- multiparous women
- heavy menstrual bleeding (HMB)
- more than 40 years
- undergone hysterectomy

Recently: by non-invasive techniques in young wemen with

AUB

infertility or pelvic pain

asymptomatic women

- gynecological comorbidities (endometriosis and uterine fibroids)

Cont.

review aims to collect all of the available evidence for an accurate diagnosis, considering symptoms (i.e. history) and clinical signs as well as imaging features of adenomyosis.

Imaging diagnostic criteria are lacking

Previous study Heterogeneous date and not fully comparable

Advancements in imaging techniques

controversies on pathogenic theories, classifications and imaging diagnostic criteria

Methods

- PubMed and Google Scholar were searched for all peer-reviewed original and review articles related to diagnosis of adenomyosis published in English until October 2018.
- all of the diagnostic criteria and techniques

Pathogenic correlates of diagnostic features of adenomyosis

- Still poorly understood and there are several theories
- Involvment of

sex steroid hormone receptors

inflammatory molecules

extracellular matrix enzymes

growth factors and neuroangiogenic factors

as pathogenic mediators of adenomyosis

Cont.

- The Most accepted theories:

1) down growth and invagination of the endometrium basalis into the myometrium through an altered or absent junctional zone (JZ)

- JZ: MRI → subendometrial halo, no histological correlate → poor traction among pathologists

  US → hypoechoic tissue, beyond the endometrial basal layer

No uniform terminology: inner myometrium, archimyometrium or endomyometrial junction

structurally and functionally different tissue from the outer myometrium

The endometrial-myometrial interface: particular histological feature ✖

Cont.

2) uterine auto-traumatisation and the mechanism of tissue injury and repair (TIAR) as the primary event in the initiation process of adenomyosis

- auto-traumatization → chronic proliferation and inflammation → JZ → tissue repair

Peristaltic myometrial contractions= ↑ repeated cycles of autotraumatisation damaging the JZ

Uterine Peristalsis : universal → unclear why some women

- TIAR mechanism: hypercontractility → ↑ intrauterine pressure → migration of fragments of basal endometrium into the myometrium

Cont.

3) embryonic or adult stem cells which may undergo metaplasia into the myometrium, as a de-novo process

- adenomyotic foci: metaplastic changes of intramyometrial embryonic pluripotent Müllerian remnants → *de novo* ectopic endometrial tissue
- adult stem cells in endometrial basalis: cyclic repair of endometrium

↓

tissue injury at level of JZ

↓

possibility of uncontrolled growth beyond the endometrial–myometrial interface

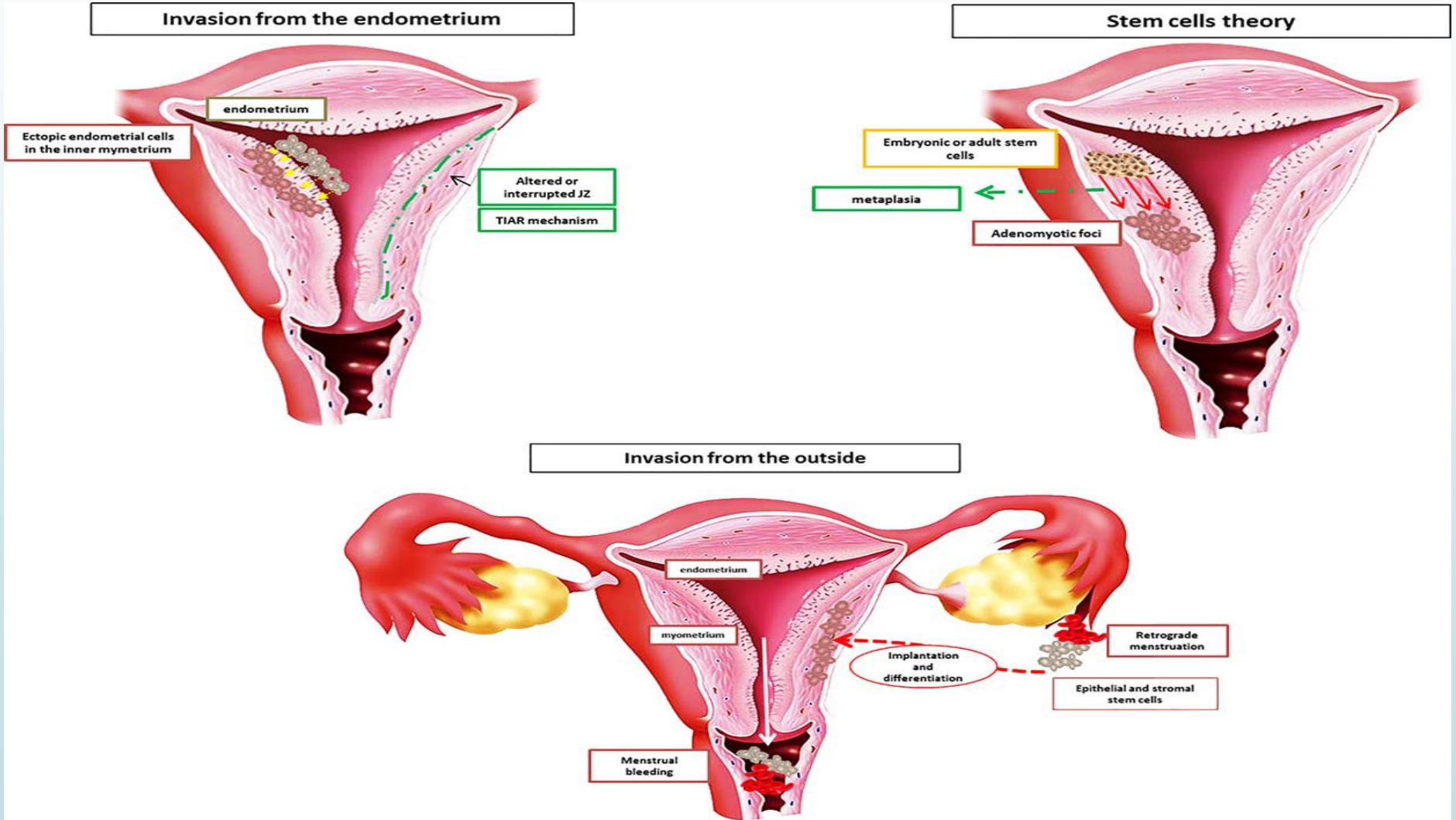
Cont.

- retrograde menstruation → adult endometrial and stromal stem cells cellular differentiation → adenomyotic islands
- Chapron *et al*.: migration of ectopic endometrial cells from deep infiltrating endometriosis (DIE) nodules into the myometrium ('from outside to inside invasion' theory).

- Retrograde menstruation → ectopic endometrial cells infiltrate pelvic organs and uterine walls → posterior focal adenomyosis of the outer myometrium (FOAM) in patients with endometriosis noduls in the posterior compartment (MRI)
- invasion of the vesicouterine pouch → bladder nodule and anterior FOAM

(50% association between anterior FOAM and endometriosis bladder nodules at MRI evaluation)

Pathophysiology of adenomyosis, different theories and potentialmechanisms involved



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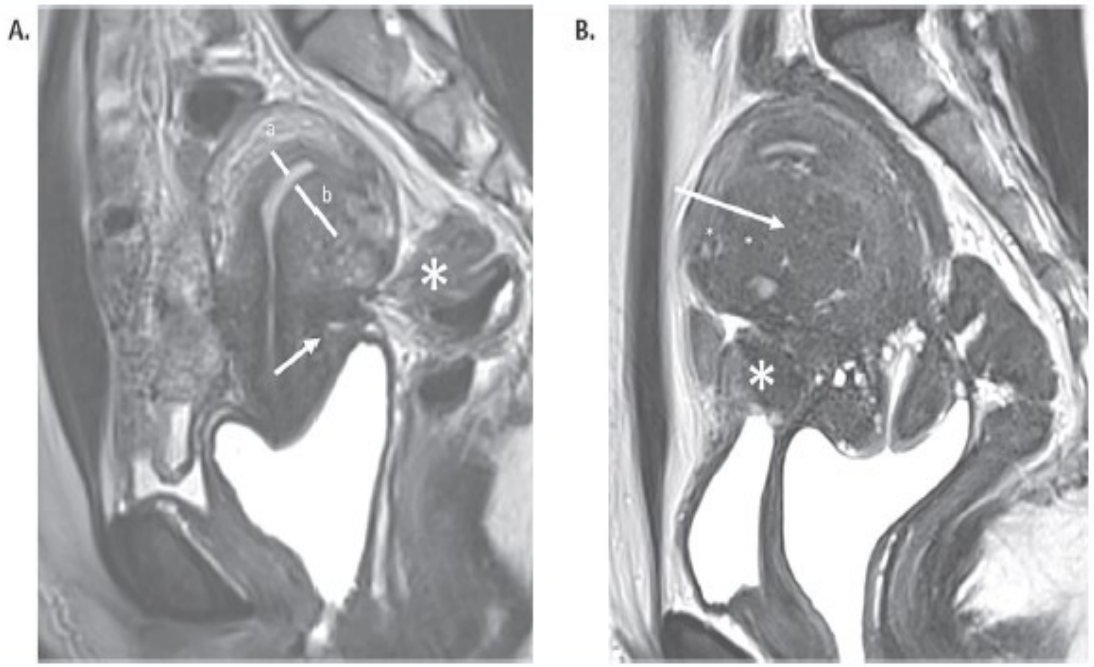


Figure 2 MRI sagittal T2-weighted images of focal adenomyosis and endometriosis. (**A**) posterior focal adenomyosis of the outer myometrium (FOAM) (white arrow). The lesion is contiguous to a deep infiltrating endometriosis (DIE) nodule affecting the uterine torus and the rectal wall (white star). Significant increased focal thickness of posterior junctional zone (b) (JZ) compared to the anterior JZ (a), suggesting a diffuse internal adenomyosis. (**B**) Anterior FOAM (white arrow) with the presence of intramyometrial cysts (small white stars). The lesion is contiguous to a bladder nodule of deep infiltrating endometriosis (DIE) (big white star).

Histopathological aspects of adenomyosis

- severe adenomyosis: diagnosis is straightforward, grossly apparent, uterine corpus is enlarged (globular, may be diffuse, may predominate in one uterine wall, usually the posterior wall), more focal → ill-defined intramural nodule(s)

enlargement mainly: myometrial smooth-muscle hyperplasia/hypertrophy, accompanies adenomyosis foci, grossly as areas of hyperfasciculation, swirl trabeculated pattern

Deferrence with uterine fibroid: smoothmuscle hyperplasia has indistinct limits without bulging at cutting

ectopic endometrium: may grossly unapparent, gray-white foci, hemorrhagic dots or petechial, Small glandular cysts in younger patients

- more limited disease: diagnosis may be difficult

extreme variations in the prevalence of adenomyosis (10-88%)

Cont.

- The smooth muscle hyperplasia/hypertrophy= nodules around the ectopic endometrial foci= hyperfasciculation, with ill-defined borders with the adjacent myometrium

  enlarged when compared to the adjacent myometrial cells

  Smooth muscle hyperplasia minimal or lacking in post-menopausal women

Figure 3 Histopathological images of adenomyosis. (**A**) Microscopic features: presence of ectopic endometrial tissue (endometrial stroma and glands) (white arrow) within the myometrium. (**B**) Gross features of severe adenomyosis: diffuse enlargement of uterine corpus with smooth-muscle hyperplasia/hypertrophy appearing as hyperfasciculation of the myometrium with a swirl trabeculated pattern and indistinct limits. Note also the presence of haemorrhagic cysts within the myometrium (white arrows). Black arrows indicate the eutopic endometrium. (**C**) Microscopic features of early adenomyosis. The adenomyotic process (arrows) originates from the endometrial-myometrial interface (dotted line), extending into the myometrium from 'inside to outside'.

Histopathological classification:

- (According to the origin):

invasion from within the uterus

The invasion from outside the uterus

growth of misplaced endometrial tissue in the uterine wall

- Vercellini *et al.* (2006): (i) depth of penetration (up to one-third, mild disease; between one- and two-thirds, moderate disease; more than two thirds, severe disease), (ii) degree of spread defined by the number of foci per low-power field (1–3 islets, grade I; 4–10 islets, grade II, >10 islets, grade III), and (iii) configuration (diffuse versus nodular/focal).
- If the number of foci per slide appeared to be associated to the depth of penetration, it remains unclear whether this classification is correlated to the clinical severity of the disease.

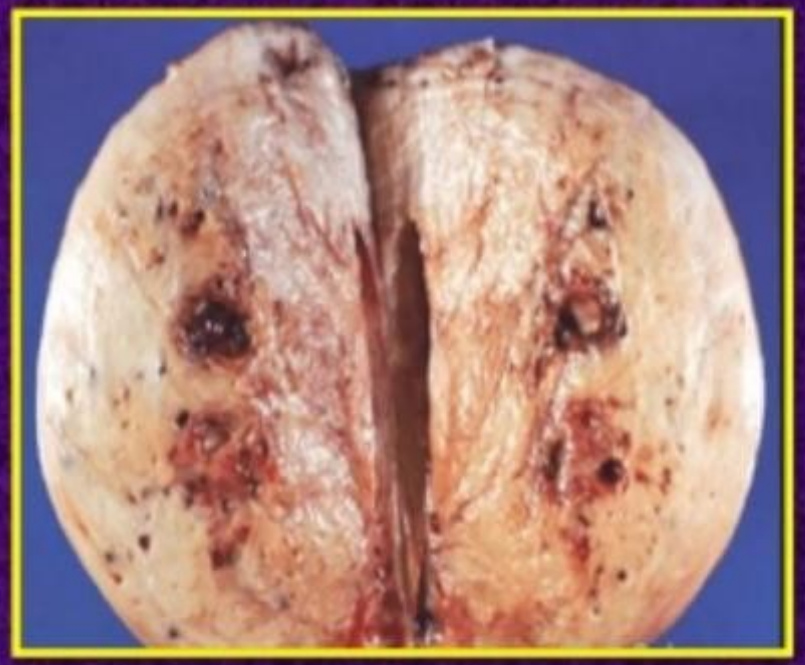
Diagnostic process for adenomyosis

- wide variety of symptoms (Common symptoms include pelvic pain in the forms of dysmenorrhea, dyspareunia and chronic pelvic pain, AUB and impaired reproductive potential)=in other benign gynecological conditions
- approximately 30% of women are asymptomatic.
- Mechanisms of symptoms generation, differences in the histology or pathogenesis in these asymptomatic women → not well known
- imaging and pathology data uterine and pelvic comorbidities (uterine fibroids, endometriosis, endometrial polyps, endometrial hyperplasia) are very common in women with adenomyosis (60–80%)

Diagnosis

If you do not think "adenomyosis",

you will not find "adenomyosis"



Cont.

- suspicion of disease, supported by the clinical presentation of relevant symptoms and signs, and their impact on quality of life ➡ complaint to a health professional
- Interpretation of the presence of AUB and/or chronic pelvic pain
- possible combination with other benign gynecological pathologies
- Confirmation of the presence of adenomyosis ➡ imaging techniques, identifying a range of agreed and acceptable features and assessing the extent of the adenomyosis process (also presence of comorbidities).
- the heterogeneity of the disease and non-specificity of symptoms often make the accurate diagnosis more challenging.

Risk factors profile

- directly associated with the number of births and tended to be higher in cases of miscarriages and induced abortions
- A crosssectional study: adenomyosis as a typical disease of parous middle-aged women (40–50 years)
- ultrasound study on women aged from 18 to 30 years: adenomyosis features were present in more than 30% of young women, correlating with dysmenorrhea and AUB
- an MRI study on women aged less than 42 years: isolated diffuse adenomyosis occurred in one third of the study population (34.6%)
- Previous uterine surgical trauma (dilatation and curettage) ⇑ odds for adenomyosis, through the mechanical endometrial invasion of the myometrium, ⇑ number of abortions → ⇑ risk
- history of a previous cesarean section

Clinical symptoms

- Abnormal uterine bleeding (AUB)

a. Heavy menstrual bleeding (with hysterectomy and adenomyosis= 50%)

b. Prolonged menstrual bleeding

c. Inter-menstrual bleeding

d. pre-menstrual spotting

- Comorbidities (60 to 80%)= great controversy about which symptoms were attributable to adenomyosis per se and which to the comorbidity

Cont.

- Benson series (1958): a correct preoperative diagnosis of adenomyosis based solely on symptoms of HMB, with or without pelvic pain, in 9.3% of women undergoing hysterectomy at a later date

AUB may be due to increased uterine volume, increased vascularisation, improper uterine contractions and/or increased production of estrogen and prostaglandins

- recent study: menstrual symptoms in a large prospective case series of 714 women attending a general gynecology clinic and undergoing a transvaginal ultrasound (TVUS).

The semi-quantitative assessment of HMB: no significant association between the presence of adenomyosis and HMB

strongly significant correlation between the severity of adenomyosis on US and a complaint of HMB.

- a study of hysterectomy specimens which correlated with symptoms: no significant association between the presence of adenomyosis and HMB or other AUB.
- no symptoms which are pathognomonic of adenomyosis

Cont.

- common occurrence of a complaint of HMB by women who are later found to have adenomyosis → the simultaneous presence of another pathology (uterine fibroids)
- Can not exclude that in a proportion of women with adenomyosis, HMB or any other symptoms of AUB is caused exclusively by the adenomyosis itself.

Cont.

- Gynecological pain symptoms controversial
- Two recent prospective studies analysed a group of women attending a gynecology clinic: positive correlation between two specific US features of adenomyosis and the pain score
- an MRI study of women with severe dysmenorrhea lasting more than 11 years: a significantly higher frequency of adenomyosis, chronic pelvic pain was significantly more likely to persist after urgical removal of endometriotic lesions if the JZ thickness was more than 11 mm on preoperative MR imaging
- A study: severity of dysmenorrhea worsened as the depth and degree of invasion of adenomyosis into the myometrium increased
- two studies on women undergoing hysterectomy: the histopathological features of adenomyosis, including the depth and the number of adenomyotic foci, correlated with the severity of dysmenorrhea

Cont.

- 15–57% of the cases: uterine fibroids and adenomyosis coexist in the same uterus and women with both conditions are more likely to experience pelvic pain.
- case–control study on women undergoing hysterectomy: women with uterine fibroids and adenomyosis were more likely to report various types of pain compared to women with fibroids only.

In the presence of coexisting adenomyosis, pain with menses, pain during intercourse and non-cyclic pelvic pain were significantly more frequent than in cases of uterine fibroids alone.

DIE is associated with the presence of adenomyosis.

A preoperative and postoperative evaluation of clinical symptoms and a TVUS evaluation of women with DIE: the coexistence of adenomyosis in around 40% of women (In such cases, bladder and gastrointestinal pain symptoms, such as dysuria and dyschezia, should also be considered)

in those with DIE and adenomyosis, dysmenorrhea, dyspareunia and AUB remained significantly higher after surgical treatment than in those without adenomyosis.

Thus, the presence of adenomyosis explains in part the persistence of pain symptoms and heavy bleeding after surgical treatment

Cont.

- *Reproductive failure:*

The presence of adenomyosis is discovered at a high frequency in patients consulting with fertility problems.

Dysregulation of the myometrial structure and altered endometrial function= expectation of a negative impact of adenomyosis on fertility

- patients with dysmenorrhea, HMB and infertility = 50% incidence of adenomyosis
- Lower pregnancy rates after colorectal surgery for endometriosis in the presence of adenomyosis
- oocyte donation: Genes involved in implantation → not altered, higher miscarriage rate in adenomyosis patients
- Negative impact of uterine adenomyosis in patients after *in vitro* fertilization
- Results after IVF= controversial

Cont.

- Conflicting results ⟶ the heterogeneity of the ovarian stimulation protocols used + mixing up of the different forms of adenomyosis without proper description of the type of adenomyosis.
- meta-analysis: a negative impact of adenomyosis on pregnancy and miscarriage rates.
- Another recent meta-analysis: a negative effect of adenomyosis on IVF clinical outcomes with a reduction of pregnancy rates, a 41% decrease in live birth rates and an increased miscarriage rate (OR 2.2, 95% CI 1.53–3.15).
- the negative impact of diffuse adenomyosis was more pronounced compared with the focal forms.

Cont.

- retrospective study: the impact of adenomyosis in patients with endometriosis on perinatal outcome was evaluated.

The incidence of small for gestational age (SGA) babies in women with endometriosis alone was 10.8% as compared to 40% in patients with endometriosis and diffuse adenomyosis,

no statistically significant difference in comparison with those affected by focal adenomyosis.

- Another study, looking at pre-pregnancy images of ultrasound and/or MRI:

1.84-fold risk increase for preterm delivery in patients with adenomyosis and a 1.98-fold risk increase for preterm premature rupture of membranes (PPROM).

Cont.

- impact of adenomyosis on adverse late pregnancy outcomes, such as preterm birth, SGA babies, cesarean section and postpartum hemorrhage.
- mechanisms seem to be implicated in the link between adenomyosis and obstetric complications:

activation of local and systemic inflammatory pathways

increased myometrial prostaglandin production

altered uterine contractility

defective myometrial spiral artery remodelling at the basis of an altered placentation

- There is need for a comprehensive, clear and user-friendly, categorisation of adenomyosis including the pattern, location, histological variants and the myometrial zone.

Clinical examination

- Bimanual examination of the pelvis:

1) help to estimate uterine or pelvic pain, pain localisation, uterine size and mobility and adnexal masses.
2) raise the suspicion of the presence of DIE in the retrocervical region

✓ Uterine size by bimanual pelvic examination to correlate well

✓ Preoperative ultrasound assessment in women undergoing hysterectomy

- next step → combined with imaging
- clinical examination alone cannot adequately detect uterine adenomyosis

Benign gynecological comorbidities:

- **uterine fibroids and endometriosis** (commonly associated with pelvic pain and HMB).
- Retrospective review of a consecutive cohort of 710 premenopausal women with adenomyosis + hysterectomy:

adenomyosis alone= 343 (48.3%)

adenomyosis and endometriosis= 158 (22.3%)

adenomyosis and uterine fibroids= 129 (18.2%)

and all three conditions combined= 80 (11.3%)

complained of dysmenorrhea= 580 (81.7%, 95% CI = 78.8–84.6%)

Complained of AUB= 352 (49.6%, 95% CI =45.8–53.3%)

Complained of chronic pelvic pain= 116 (16.3%, 95% CI =13.5–19.1%)

- ✓ it is important to differentiate adenomyosis-related symptoms from those caused by other conditions

reported results are biased because of non-homogeneous sampling, diagnosis based on clinical findings is very poor.

Cont.

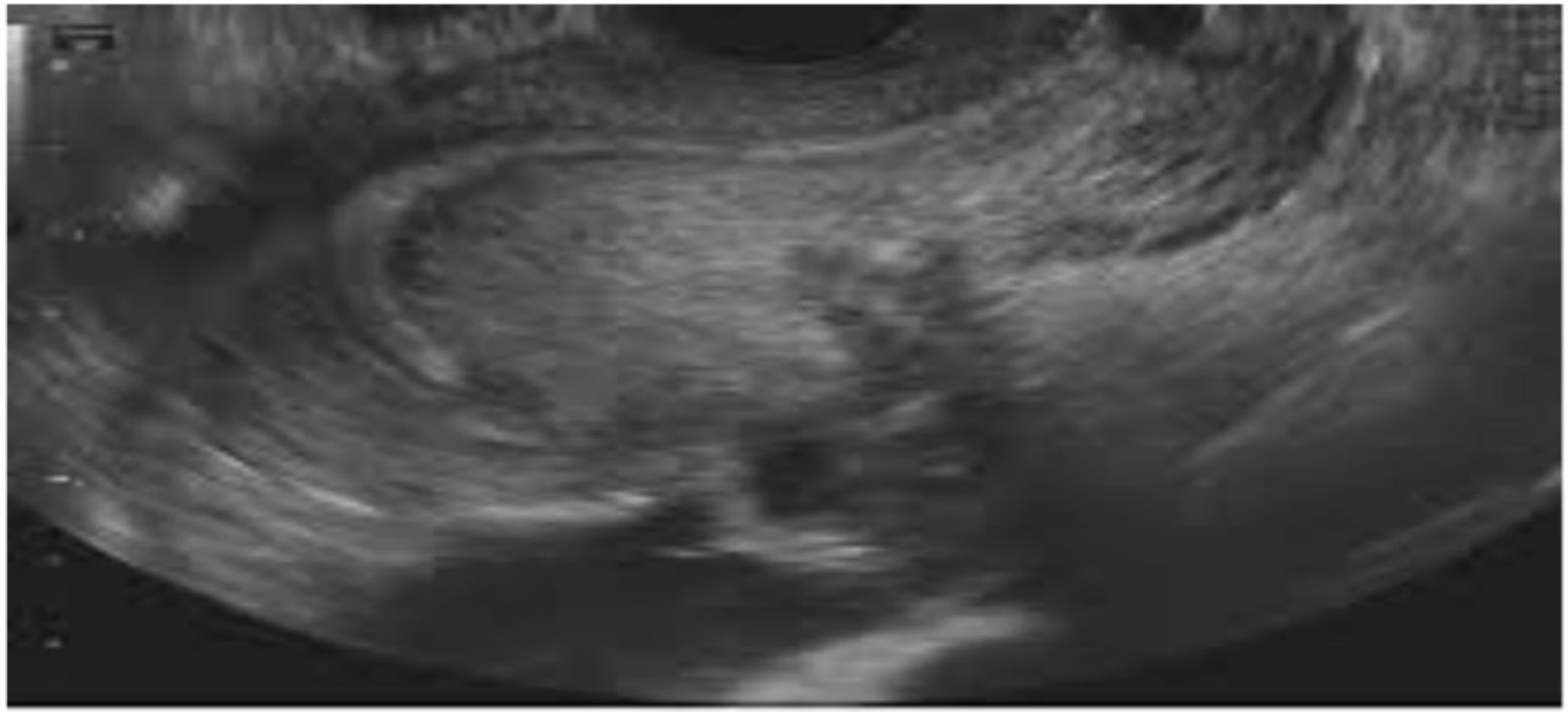
- A concomitant diagnosis of adenomyosis and uterine fibroids was encountered in 22.8% of women attending a gynecological clinic and undergoing a TVUS.
- Women undergoing hysterectomy with both adenomyosis and uterine fibroids compared to those with only fibroids:

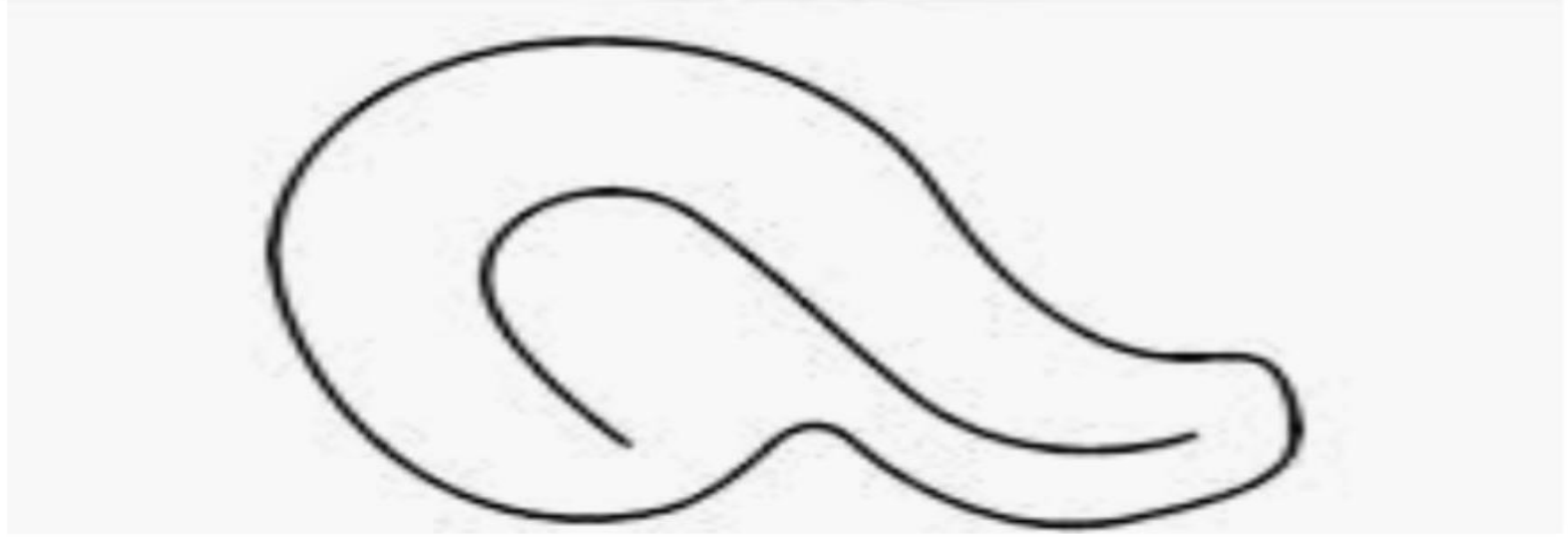
more pelvic pain, less fibroid burden, higher parity and lower body mass index

In women with both adenomyosis and fibroids: severe forms of pelvic pain (dysmenorrhea, dyspareunia, chronic pelvic pain) and higher scores of distress

Cont.

- the presence of endometriosis in patients with adenomyosis= 80.6%
- adenomyosis was present in 79% of patients with endometriosis diagnosed by MRI, with a clear relationship between the thickness of the JZ and the severity of endometriosis.
- an US sign,'question mark sign', commonly found in women with adenomyosis and endometriosis, in particular those with posterior compartment involvement: the corpus uteri is flexed backwards, the fundus of the uterus faces the posterior compartment, and the cervix is directed frontally toward the bladder.
- The dynamic evaluation of the pelvis and the negative sliding sign raise the suspicion of adenomyosis due to invasion from outside, particularly if it is associated with posterior compartment nodules.





Cont.

- in women with DIE, focal adenomyosis of the outer myometrium (FOAM) was significantly more frequent, supporting the hypothesis of a different pathogenesis between the inner and outer myometrium forms of adenomyosis
- the inconsistencies in term of prevalence of adenomyosis and gynecological comorbidities → need to identify uniform diagnostic criteria in imaging.

imaging

- non-invasive diagnosis
- Accurate diagnosis and a tailored management
- enable future studies (assessing changes in adenomyosis appearance during the menstrual cycle, hormonal therapies, fertility treatment and pregnancy)
- the first-line diagnostic tool for diagnosing adenomyosis: 2D (and eventually 3D) TVUS
- while more expensive techniques: MRI, (more complementary role)

US (Ultrasound)

- first-line technique in the gynecological patient work-up
- easily available in the outpatient setting
- relatively less expensive than other imaging techniques
- allows a dynamic examination (exploring organ mobility and site specific tenderness)
- very accurate in the diagnosis of gynecological pathologies, if performed by a trained sonographer

➢ transvaginal ultrasonography (TVUS) → optimal view of the uterus, by using a 2-dimensional (2D) and 3D setting and Power/Colour Doppler.

Cont.

- Transabdominal ultrasonography ⟶ limited value (may be of use when the vaginal route is not possible or in case of grossly enlarged uteri)

a large uterus, regular external contour, asymmetrical myometrial walls and a heterogeneous myometrium, with intramyometrial cysts (specificity of greater than 95%, sensitivity is very poor, around 30%).

- the sensitivity of TVUS to detect adenomyosis ranges from 65% to 81%, and the specificity ranges from 65% to 100% ⟶ comparable to MRI

Cont.

- **ultrasonographic criteria for the diagnosis of adenomyosis:** uterine enlargement, asymmetry of anterior and posterior uterine wall thickness, presence of heterogeneous myometrial areas, findings of anechoic areas in the myometrium (known as myometrial cysts), the presence of echogenic striations in the sub-endometrium, sub-endometrial echogenic nodules, irregular endometrial–myometrial interface, poor definition and thickening of the JZ.
- sign to identify the condition:

1980s= an enlarged uterus

1990s= the improvement of TVUS techniques → better performance in detecting diffuse adenomyosis, diagnosis was mainly based on the presence of ill-defined myometrial heterogeneity.

Also the peak systolic velocity and the resistance index of intralesional vessels were proposed to differentiate between adenomyosis and fibroids.

In women undergoing TVUS, MRI and hysterectomy, the presence of myometrial cysts was the most sensitive and specific TVUS diagnostic criterion.

Cont.

2007= subendometrial linear striations were the most specific sonographic feature (95.5%) with the highest PPV (80.0%) for the diagnosis of adenomyosis.

- Colour flow Doppler imaging:

assessing the location, amount and type of vascular flow

Differentiate adenomyosis from uterine fibroids

the overall diagnostic accuracy of the use of TVUS with colour Doppler for adenomyosis is 93.8%

- 'translesional flow' is seen in adenomyosis
- circular flowis is seen in fibroids
- power Doppler US displays vessels perpendicular to the endometrial interface
- in cases of posterior adenomyosis associated with DIE, the outer posterior myometrial border appears heterogeneous and myometrial cysts and radial vessels can be seen.

Cont.

- 3D TVUS → high frequencies probes and more advanced modalities, such as volume contrast imaging (VCI), increase visibility of Jzon US.
- The main advantage of 3D TVUS: enables assessment of the lateral and fundal aspects of the JZ, clearer visualization of endometrial protrusions into the myometrium ,allowing the rendering of the coronal plane of the uterus, so that the physician can evaluate the JZ.
- JZdif ≥4 mm and JZ infiltration and distortion had a high sensitivity (88%) and the best accuracy (85% and 82%, respectively) for the diagnosis of adenomyosis.
- 3D TVUS demonstrated high diagnostic accuracy in detection of site and position of adenomyosis in the uterine walls.
- Overall, the sensitivity= 88.9 and specificity=56.0%
- when fibroids were present, the sensitivity of TVUS= 33% (in particular when the volume of the uterus was greater than 300 mL)

Cont.

2012= prevalence of US signs of adenomyosis of 20.9% in symptomatic women seeking medical attention.

adenomyosis was independently and significantly associated with the severity of menstrual pain, the higher the number of US features, the higher was the pain score.

severity of adenomyosis on US correlated also with the amount of menstrual loss.

2015= significant association between the number of 2D-TVUS adenomyosis features and the score for dysmenorrhea and HMB in a cohort of nulliparous women, aged 18–30 years.

In this population the prevalence of diffuse adenomyosis was 34%, of whom 83% were symptomatic.

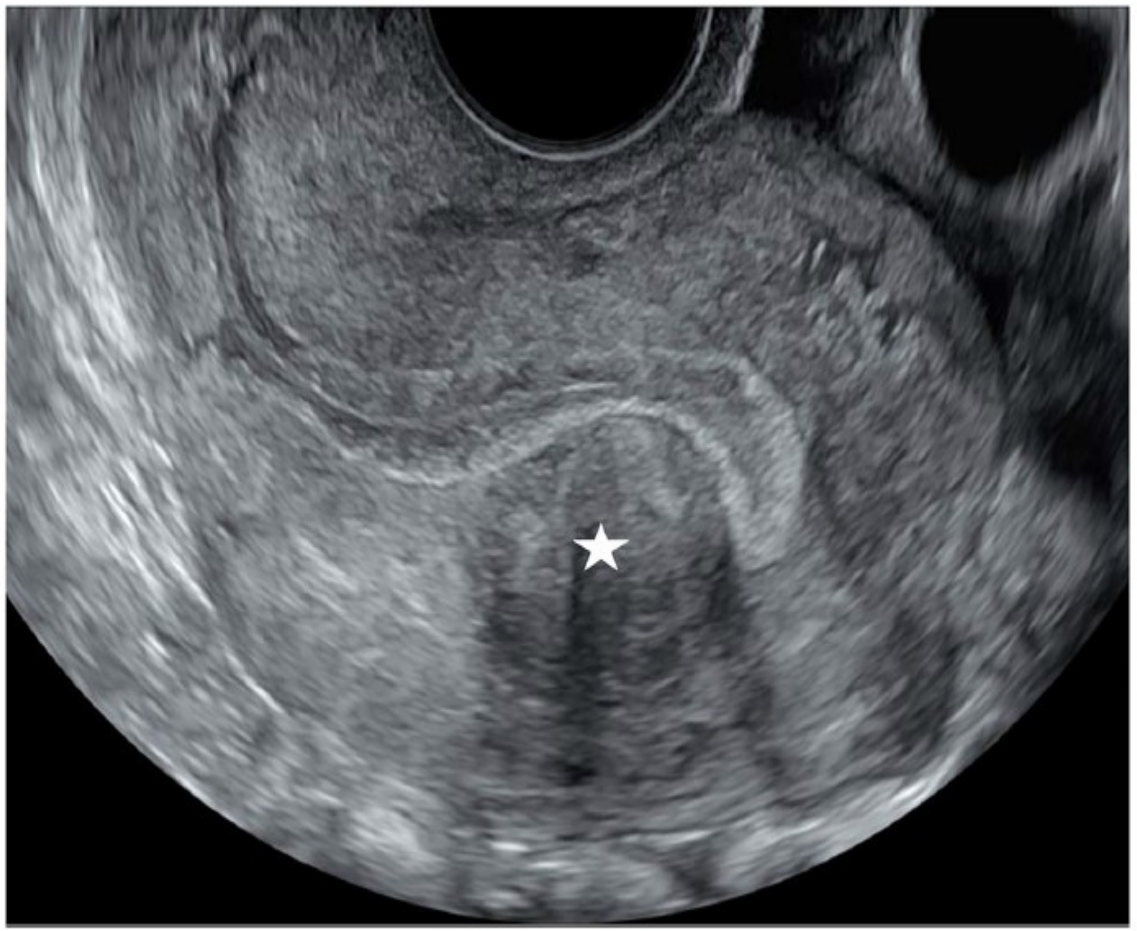


Figure 4 TVUS image of coexistence of uterine adenomyosis and fibroid. The area of coexistence is indicated (white star).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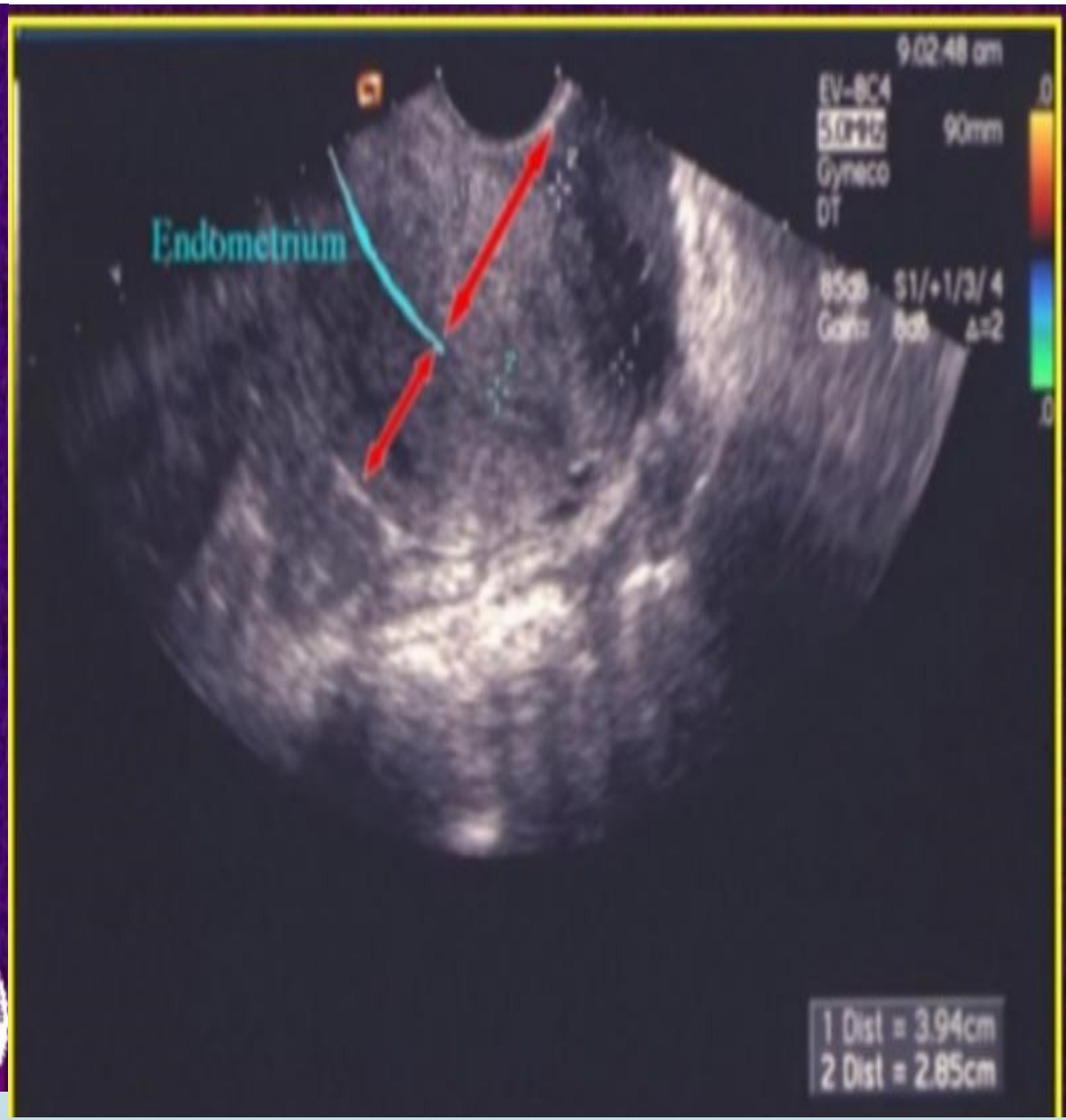
E
E
Sub endometrial stripes
www.marwanalhalabi.com


9:02:48 am
EV-8C4
90mm
Gyneco
OT
Endometrium
1 Dist = 3.94cm
2 Dist = 2.85cm

MUSA terminology and a new reporting system for adenomyosis:

- Morphological Uterus Sonographic Assessment (MUSA) consensus published in 2015, standardised terminology for describing ultrasound images of normal and pathological myometrium.
  - minimise interoperator variability during myometrial evaluation
  - optimise diagnostic accuracy for uterine pathology
  - evaluate myometrial changes after medical or surgical treatments
  - comparison between different studies
- provides a list of 2D and 3D US features associated with adenomyosis

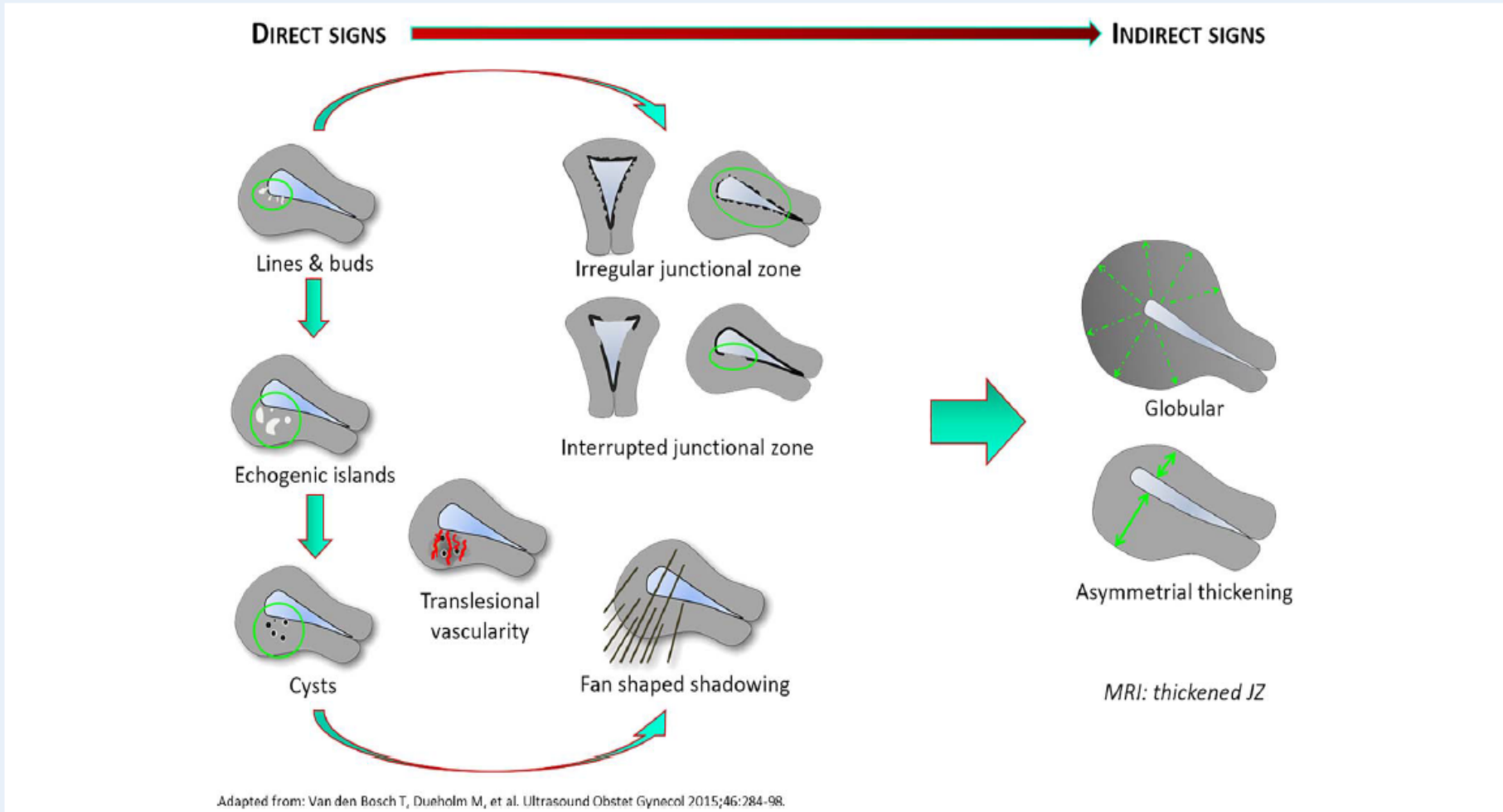


Figure 5 Two-dimensional (2D) and three-dimensional (3D) transvaginal ultrasound sonography (TVUS) features of adenomyosis, according to Morphological Uterus Sonographic Assessment (MUSA) protocol. Direct signs and indirect signs. Adapted from: Van den Bosch T, Dueholm M, *et al*. Ultrasound Obstet Gynecol 2015;46:284–98.

Cont.

- start with a 2D scan with measurements of the uterus, especially the anterior and posterior uterine walls in sagittal view
- An asymmetry of uterine walls thickness (ratio above or below 1 or subjective impression) is considered a 2D US feature of possible adenomyosis .Similarly, an enlarged globular uterus with a regular contour shape is suggestive of adenomyosis
- exclude the presence of transient uterine contractions → may modify the uterine walls thickness and change the myometrial echotexture, making the uterus appearing more globular.

Cont.

- evaluation of myometrial appearance: defining the presence of intramyometrial cysts, hyperechoic islands, fan-shaped shadowing, echogenic subendometrial lines and buds.

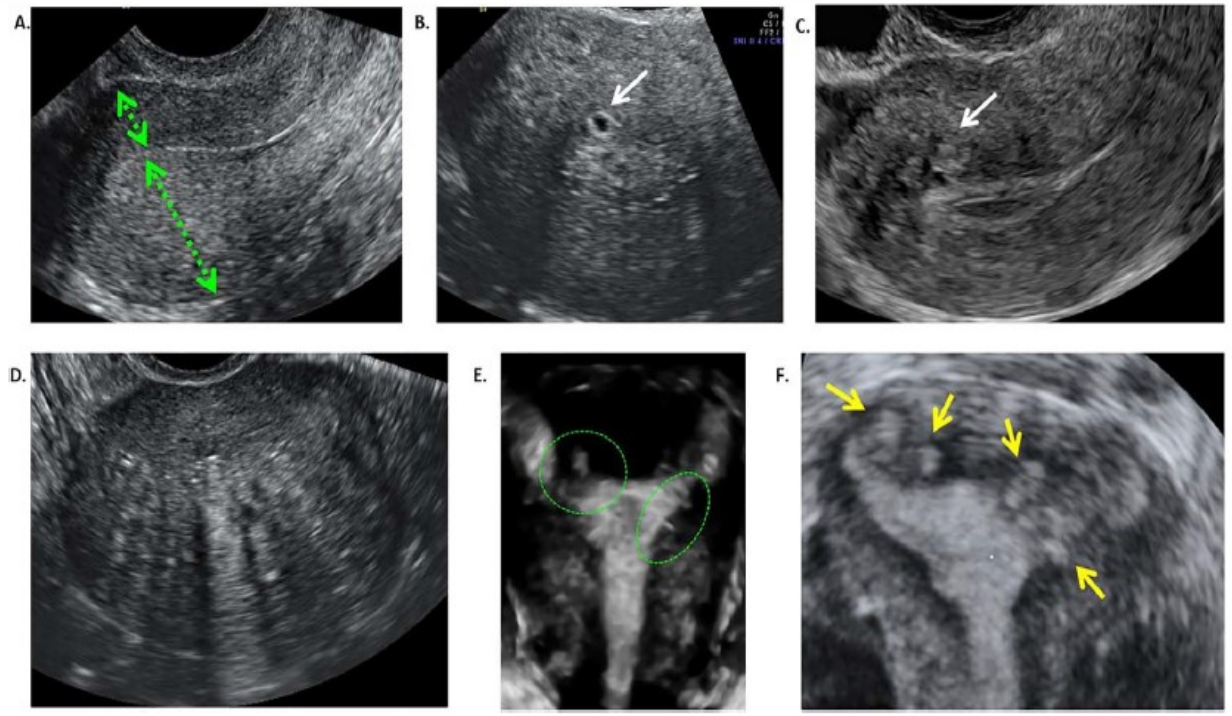


Figure 6 **Two-dimensional (2D) and three-dimensional (3D) transvaginal ultrasound sonography (TVUS) signs of adenomyosis.** (**A**) asymmetry of uterine walls thickness; (**B**) intramyometrial cysts; (**C**) intramyometrial hyperechogenic islands; (**D**) myometrium with fan-shaped shadowing; (**E**) hyperechogenic sub-endometrial lines of buds in 3D coronal view of the uterus, as signs of junctional zone (JZ) interruption; (**F**) JZ interruption in multiple sites visible at 3D coronal view.

Cont.

- The JZ = dark subendometrial brim visible both on 2D and 3D US.

Table II Sensitivity and specificity of different 2D TVUS for the diagnosis of adenomyosis.

TVUS feature	Sens	Spec
Asymmetry myometrial wall	57.2	71.9
Myometrial cysts	72.0	62.7
Hypoechoic linear striations	71.3	79.7
Heterogeneous myometrium	86.0	61.3
Poor definition junctional zone	58.6	71.5
Globular uterus	55.0	80.2
Question mark sign	75.0	92.3

TVUS: transvaginal ultrasonography; Spec: specificity (%); Sens: sensitivity (%)
Adapted from Andres *et al*, Transvaginal Ultrasound for the Diagnosis of Adenomyosis: Systematic Review and Meta-Analysis. J Minim Invasive Gynecol. 2018;25:257–264.

Table III Sensitivity and specificity of different 3D TVUS for the diagnosis of adenomyosis.

TVUS feature	Sens	Spec
Asymmetry myometrial wall	59.2	53.4
Myometrial cysts	58.2	54.3
Hypoechoic linear striations	52.8	61.1
Heterogeneous myometrium	82.7	41.4
Poor definition junctional zone	87.8	56.0

TVUS: transvaginal ultrasonography; Spec: specificity (%); Sens: sensitivity (%)
Adapted from Andres *et al*, Transvaginal Ultrasound for the Diagnosis of Adenomyosis: Systematic Review and Meta-Analysis. J Minim Invasive Gynecol. 2018;25:257–264.

a more detailed uniform reporting system of US findings of adenomyosis:

- adenomyosis should be described in its location (anterior, posterior, lateral left, lateral right or fundal), differentiating between the focal and diffuse types.
- Focal adenomyosis= when more than 25% of the lesion is surrounded by normal myometrium

completely surrounded by hypertrophic myometrium= adenomyoma

focal and diffuse lesions= mixed type adenomyosis

- adenomyosis as 'cystic' or 'non-cystic'

Cont.

- Adenomyosis typing

type 1= when only the JZ is involved

type 2= the middle myometrium (the layer between the JZ and the vascular arcade) is involved

type 3= adenomyotic lesions are found in the outer myometrium

- severity of adenomyosis: extent (percentage of affected myometrium: mild <25%; moderate 25–50%; severe >50%).

MRI

- Accurate, non-invasive technique, second line examination for the diagnosis of adenomyosis.
- sensitivity and specificity= 88 to 93% and 67 to 91%
- overlap in the features used for adenomyosis diagnosis between TVUS and MRI
- MRI diagnosis of adenomyosis:

The thickening of the JZ at least 8–12 mm

the ratio of junctional zone maximum/ total myometrium over 40%

- the difference between the maximum and the minimum thickness of the JZ (JZmax−JZmin) more than 5 mm (> 12 mm highly predictive of adenomyosis, <8 mm generally allows the presence of adenomyosis to be excluded, between 8 and 12 mm identifies the condition of adenomyosis only if other criteria are fulfilled)

Cont.

- JZ thickness varies with: the phase of the menstrual cycle (thickest between Day 8 and Day 16 and variable during menstruation), reproductive status (thinner or possibly absent during menopause and during pregnancy), use of medication (thinning with oral contraceptives or GnRHa) and age (thickens up to the age of 50 and then thins).
- transient uterine contractions causes JZ thickness variation → repeat MRI acquisition

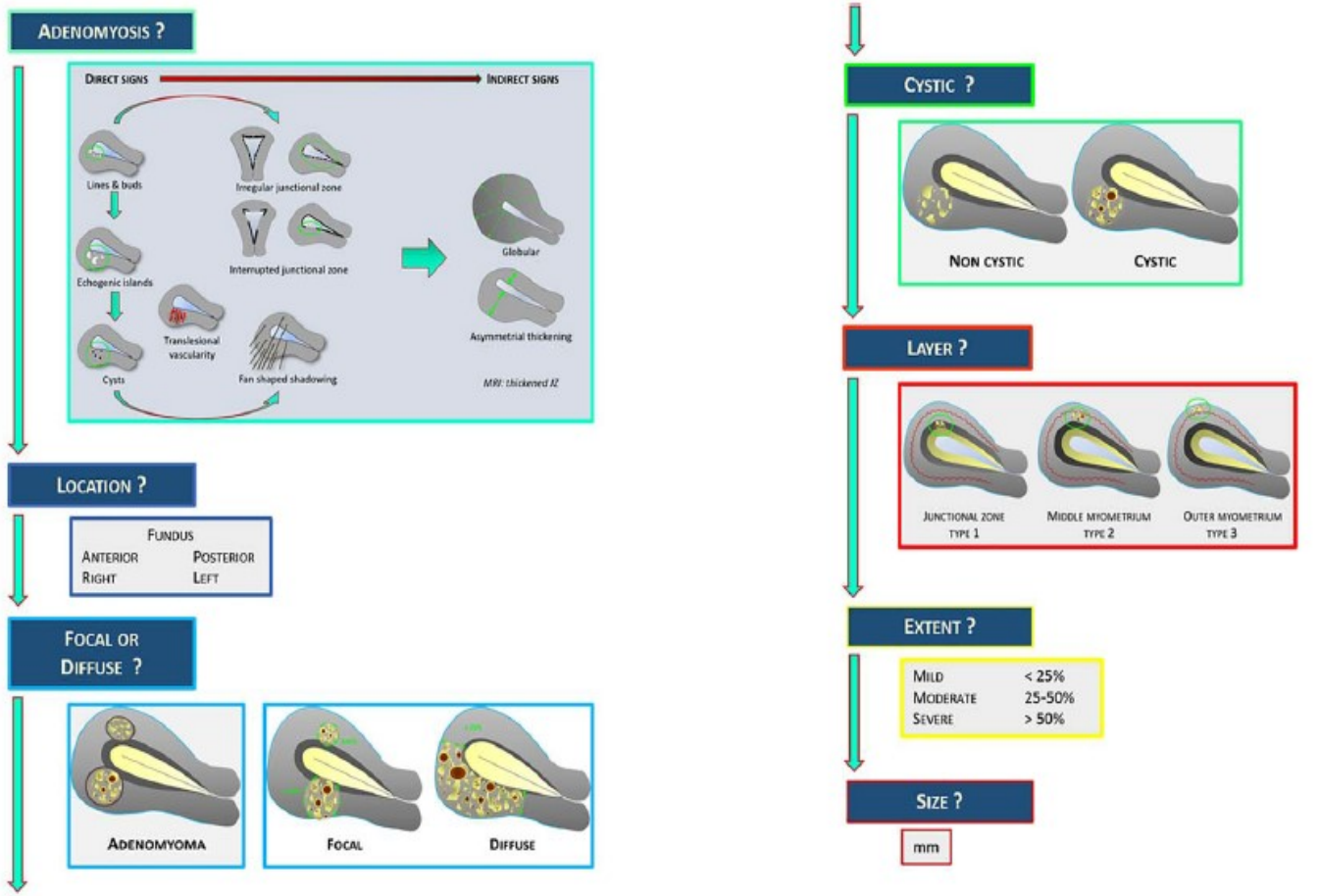


Figure 7 Reporting system of ultrasound findings of adenomyosis, considering also location, type, involved layer, extent and size of the adenomyotic lesions. Adapted from: Van den Bosch T, Dueholm M, *et al*. Ultrasound Obstet Gynecol 2015;46:284–98 and adapted from Van den Bosch T, de Bruijn AM, *et al*. Ultrasound Obstet Gynecol 2019;53:576–582.

Cont.

- Typical adenomyosis appears as an ill-demarcated low-signalintensity area on T2-weighted images, representing the smooth muscle hyperplasia and the heterotopic endometrial tissue.
- intramyometrial cysts and small high-signal-intensity areas referring to ectopic endometrium may also be detected on T2-weighted MRI.
- T1-weighted sequences contribute to the diagnosis of high-signal intensity foci adenomyosis, representing areas of hemorrhage, that has a high positive predictive value (95%), however, with a low sensitivity (47.5%).

Cont.

- classified adenomyosis in four subtypes (by localization of MRI lesions): intrinsic, extrinsic, intramural and indeterminate.
- Subtypes 1 and 2 occur in the uterine inner and outer myometrial layer, respectively and, according to their theory, they originate from direct endometrial invasion and endometriotic invasion from the outside, respectively. Subtype 3 arises from de novo metaplasia and it has no relationship with structural components, subtype 4 is a heterogeneous mixture of advanced disease. (2012)

Cont.

- four types of adenomyosis according to laparoscopic and histological findings: diffuse, sclerotic, nodular and cystic, and these correlated with clinical presentation. (2014)
- a clinical histological classification, identifying

(i) diffuse adenomyosis, with inner myometrium thickening and outer myometrium extensive disease;

(ii) focal adenomyosis, including adenomyomas and cystic adenomyosis;

(iii) polypoid adenomyomas, including typical and atypical forms;

(iv) some special categories, like those of adenomyomas of the endocervical type and retroperitoneal adenomyosis. (2014)

Cont.

- classification of adenomyosis according to MRI features:

internal adenomyosis (may be focal, superficial or diffuse, specifying the symmetry of the lesion)

external adenomyosis (may be anterior or posterior)

Adenomyoma (there are subtypes according to the localisation of the lesion and the content)

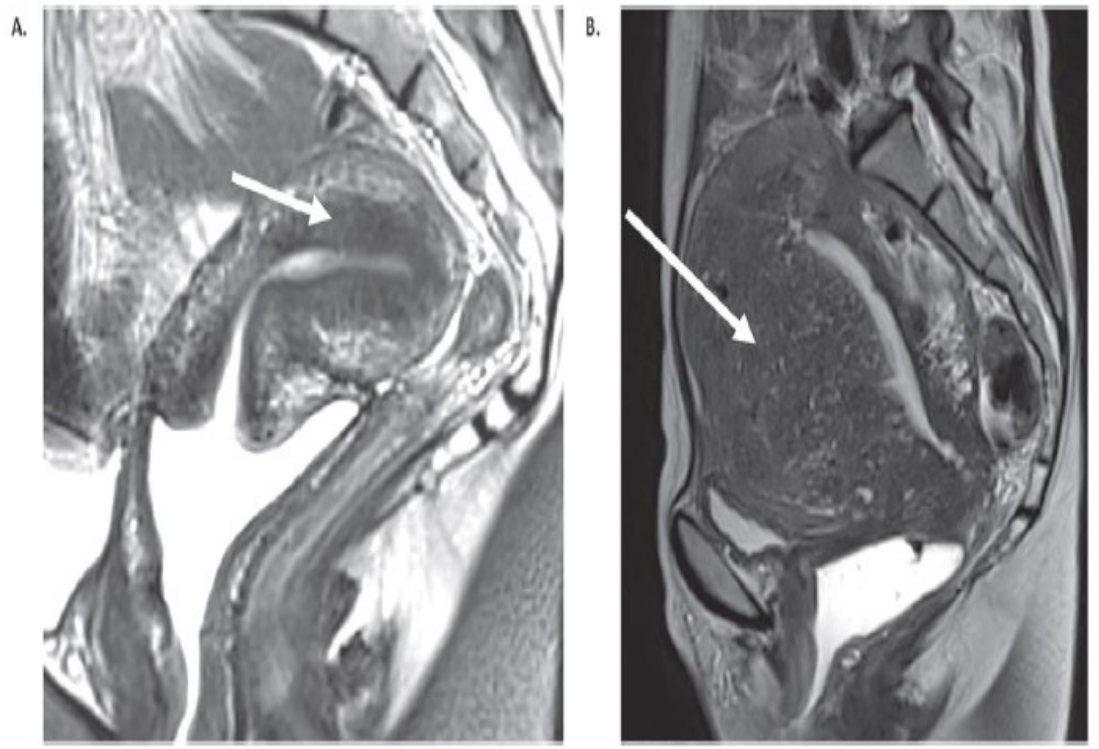


Figure 8 MRI sagittal T2-weighted images of adenomyosis. (**A**) Thickening of the junctional zone (JZ) (white arrow). Ratio of JZ maximum/total myometrium over 40%. (**B**) Severe adenomyosis of the anterior uterine wall (white arrow), with intramyometrial cysts (hyperechoic in T2 sequences).

Other techniques and emerging technologies:

- ***Sonohysterography***

installation of a saline infusion into uterine cavity for a sonohysterography → continuity between the subendometrial cystic spaces characteristic of the disease and the endometrial cavity.

Flame-shaped or lollipop diverticula extending from the endometrium layer to the myometrial wall may be demonstrated.

Cannot depict the overall uterine condition → not a single complete diagnostic method for adenomyosis

provide proof of the loss of continuity between the endometrium and the myometrium in those phenotypes of adenomyosis where the JZ is involved.

Cont.

- ***Hysteroscopy:***

direct visualisation of the uterine cavity

list of endometrial signs suggestive of adenomyosis (endometrial hyper-vascularisation, strawberry pattern, endometrial defects and submucosal hemorrhagic cysts).

not allow a definitive diagnosis of adenomyosis.

not considered as one of the standard methods to identify the disease.

some recent evidence describes the use of hysteroscopy to assess also the inner myometrium.

Hysteroscoy of the sub-endometrial myometrial area may help to identify signs of adenomyosis, such as neovascularisation or chocolate dye filled cysts with endometrial implants.

Cont.

- a new fusion technique:

integrating US and hysteroscopy,

offers the possibility of obtaining endometrial and/or myometrial biopsies by using a utero-spirotome device under US guidance ⟶ histologically evaluate suspicious area for adenomyosis.

specificity of 78.5%, low sensitivity of 54.3%

- use of a utero-spirotome device under US guidance certainly increases costs and patient distress, and it is an invasive technique

Utero-Spirotome mounted in outer sheet of Trophy° hysteroscope

Cont.

- ***Elastography:***

light external tissue compression that produces strain or displacement within the tissue, similar to palpation.

Algorithms calculating the strain profile along the axis of compression produce the elastography image.

The stiffness of the tissues examined by elastography is displayed in a range of false colours from red (components with the greatest strain or displacement in strain elastography; in shear-wave elastography it would be the hardest component i.e. the softest components) to green (components with average strain) to blue (components with no strain, or the hardestcomponents).

Cont.

- when applied to TVUS: discriminate fibroids from adenomyosis.
- The findings as to the lesion stiffness reflected by elastography are conflicting.
- Superior to conventional TVUS in the differential diagnosis of adenomyosis and uterine fibroids.
- lesional stiffness correlated closely with both the extent of lesional fibrosis, and with the severity of symptoms in patients with adenomyosis and expression levels of hormonal receptors

Future perspective for diagnosis

- There are still many controversies in terms of diagnostic criteria
- Most of imaging features have not been correlated yet with the clinical presentation of adenomyosis ➡ their diagnostic and prognostic value is still unknown.
- suspicious signs and symptoms reported by the patient ✖
- a third of adenomyosis patients are asymptomatic or have a gynecological comorbidity.
- classification system
- **ideal imaging technique: diagnose adenomyosis accurately + deciding the best treatment modality**

Thanks for your attention