هوالعلیم

UTERINE ADENOMYOSIS AND INFERTILITY

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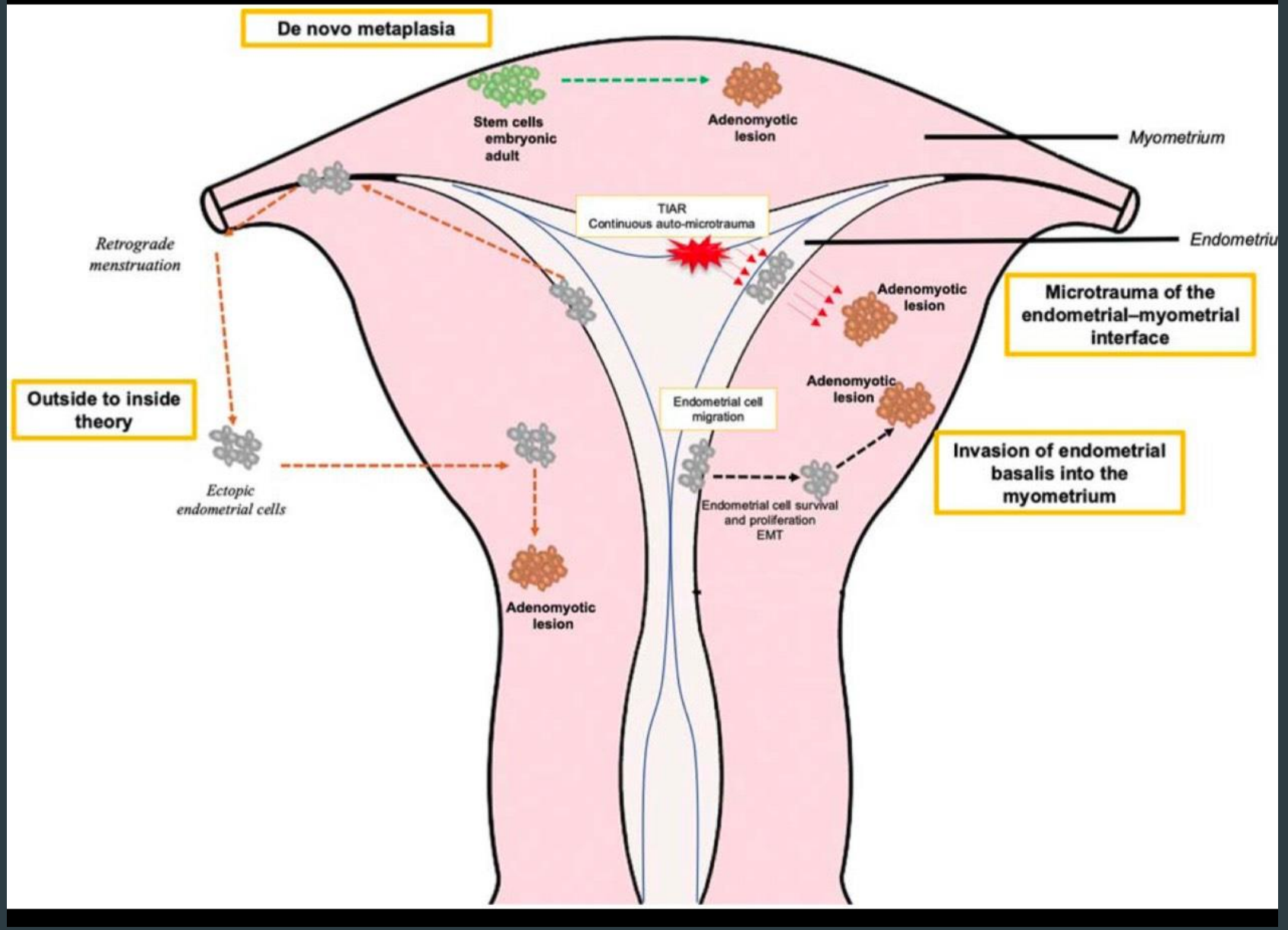
INTRODUCTION

- disorder in which endometrial glands and stroma are present within the myometrium
- the endometrial tissue invading the myometrium at a depth of at least 2.5 mm below the basal layer of the endometrium, typically surrounded by hyperplastic tissue.
- coexist with uterine leiomyoma 35–55% of cases
  and/or endometriosis 65–70% of cases
- lymphatic and vascular channels penetrate the normal myometrium

PATHOGENESIS

- Is not known.
- 'auto-traumatisation' of the uterus which leads to the TIAR (Tissue Injury And Repair) mechanism as the main cause of adenomyosis
- theories suggest that adenomyosis occurs
- Endomyometrial invagination of the endometrium.
- The development from adult stem cells or displaced embryonic müllerian remnants.
- Invagination of the myometrial basalis proceeds along the myometrial lymphatic system, leading to adenomyosis
- Infiltration of endometrial cells in retrograde menstrual into the uterine wall from serosal "invasion from outside to inside".
- Estrogen and progesterone also contribute to adenomyosis pathophysiology


De novo metaplasia
Stem cells
embryonic
adult
Adenomyotic
lesion
Myometrium
TIAR
Continuous auto-microtrauma
Endometriu
Retrograde
menstruation
Adenomyotic
lesion
Microtrauma of the
endometrial–myometrial
interface
Outside to inside
theory
Adenomyotic
lesion
Endometrial cell
migration
Invasion of endometrial
basalis into the
myometrium
Ectopic
endometrial cells
Endometrial cell survival
and proliferation
EMT
Adenomyotic
lesion

Endomyometrial invagination of the endometrium

- This can be related to the weakening of the myometrium
- previous trauma, allowing endometrial growth into the injured mucosa and stromal invasion into the inner layer of the myometrium with glandular invasion
- Abnormal immune phenomenon involving the local production of estrogen by adenomyotic tissue, activation of macrophages and B and T cells, and production of antibodies and stimulation of cytokines.
- Aromatase and estrogen enzymes are present in adenomyotic tissue leading to the local production of estrogens, which might enhance the growth and expansion of the endometriotic glands and stroma into the affected myometrium.

De novo from müllerian remnants

- De novo origin of adenomyosis from misplaced pluripotent Müllerian remnants
- the proliferative and biological properties of ectopic and eutopic endometrium that demonstrate distinct characteristics.
- Ectopic endometrium does not have the same response in hormonal changes. Secretory changes are limited, and cyclic properties are not similar with eutopic endometrium.
- All these support the theory that adenomyosis has a different origin from eutopic endometrium other than basal endometrium

PATHOGENESIS

- Other animal models suggest that pituitary protein hormones (eg, prolactin, follicle-stimulating hormone, oxytocin) may also have roles in the pathogenesis adenomyosis
- Expression of other key molecules (eg, BCL2 gene expression, superoxide dismutase, granulocyte macrophage colony-stimulating factor, *KRAS*) in adenomyotic cells may also differ from eutopic endometrial glands
- Stem cells and immune and inflammatory mediators also appear to play a role

Genetic and Epigenetic Alterations in Adenomyosis

- Adenomyosis shares genetic and epigenetic mechanisms with endometriosis, common pathogenic background.
- Aberrant gene expression promotes **estrogen excess**, **ER-ß-driven inflammation**, and **progesterone resistance** due to reduced progesterone receptor expression.
- Genetic variants in **CYP450 genes (CYP1A1, CYP1A2, CYP19)** and catechol-O-methyltransferase **(COMT)** increase susceptibility to this estrogen-dependent disease.
- Epigenetic changes, including **increased DNA methyltransferase activity**, **PR-B promoter hypermethylation**, and altered **histone deacetylase (HDAC) expression**, further contribute to abnormal hormone signaling and chronic inflammation in adenomyotic tissue.

Risk Factors

- Multiparity
- previously dilation and curettage
- previous uterine surgery is still unclear
- intrinsic adenomyosis in patients with a history of previously induced abortions
- earlier age at menarche (≤10 years)
- shorter menstrual cycle duration (≤25 days)
- use of menopausal hormone therapy

EPIDEMIOLOGY

- The epidemiology of adenomyosis is uncertain because data regarding adenomyosis has often relied on the assessment of the uterus following hysterectomy.
- More common in women between 40 and 50 years old (70–80%).
- Women under 39 years old varies from 5% to 25%
- postmenopausal woman, percentages of the disease drop down to 5–10%
- diffuse type of adenomyosis is more common than the focal type
- develops more often in the posterior than in the anterior wall of the uterus and quite rare in the cornua or in areas close to cervical os

CLINICAL FEATURES

- heavy menstrual bleeding (abnormal uterine bleeding-adenomyosis (AUB-A) in FIGO or PALM-COEIN in 50 to 60 % of patients
- painful menses in 25 to 80 %of patients
- chronic pelvic pain
- infertility
- one-third of patients were asymptomatic

Associated conditions

- **Endometriosis**
- **Leiomyoma**
- **Adverse pregnancy outcomes(** miscarriage, preterm birth, and small-for-gestational-age (SGA) infants)
- **Infertility**
- **Cancer** – Adenomyosis may be associated with an increase in some cancers : ovarian cancer, endometrial cancer , colorectal cancer, thyroid cancer. (Confirmation of these findings in appropriately controlled studies would likely impact screening for these diseases.)

Author	Year of Publication	Classification According to the Depth of Invasion
Bird et al.	1972	• Grade I (sub-basal lesions) • Grade II (up to mid-myometrium) • Grade III (beyond mid-myometrium)
Levgur et al.	2000	• Grade I (sub-basal lesions) • Grade II (up to mid-myometrium) • Grade III (beyond mid-myometrium)
Hulka et al.	2002	• Category I: inner third of the myometrium • Category II: focal lesions • Category III: affecting the outer two-thirds of the myometrium
Sammour et al.	2002	• Group A: up to 25% • Group B: 26–50% • Group C: 51–75% • Group D: >75% of myometrial thickness
Vercellini et al.	2006	• >2.5 mm from endometrial junction • Mild: one-third of the uterine wall • Moderate: two-thirds of the uterine wall • Severe: more than two-thirds of the uterine wall

EVALUUATION

- Medical history
- Pelvic examination (a mobile uterus that is diffusely enlarged ("globular"), soft ("boggy"), and tender
- Pelvic imaging
- Laboratory testing is not needed to diagnose adenomyosis.

Pelvic imaging

- **TVUS** first-line imaging
- **MRI**

Sonographic features of diffuse and focal adenomyosis.

Diffuse Adenomyosis	Focal Adenomyosis
globally enlarged uterus asymmetric thickness anterior and posterior wall = pseudo-widening sign cystic myometrium (cystic anechoic spaces) junctional zone not clearly visible, thickening of the JZ heterogeneous echogenicity of the myometrium	focal disturbances in myometrium layer sometimes focal form diagnosed as intramural myoma anechoic cysts

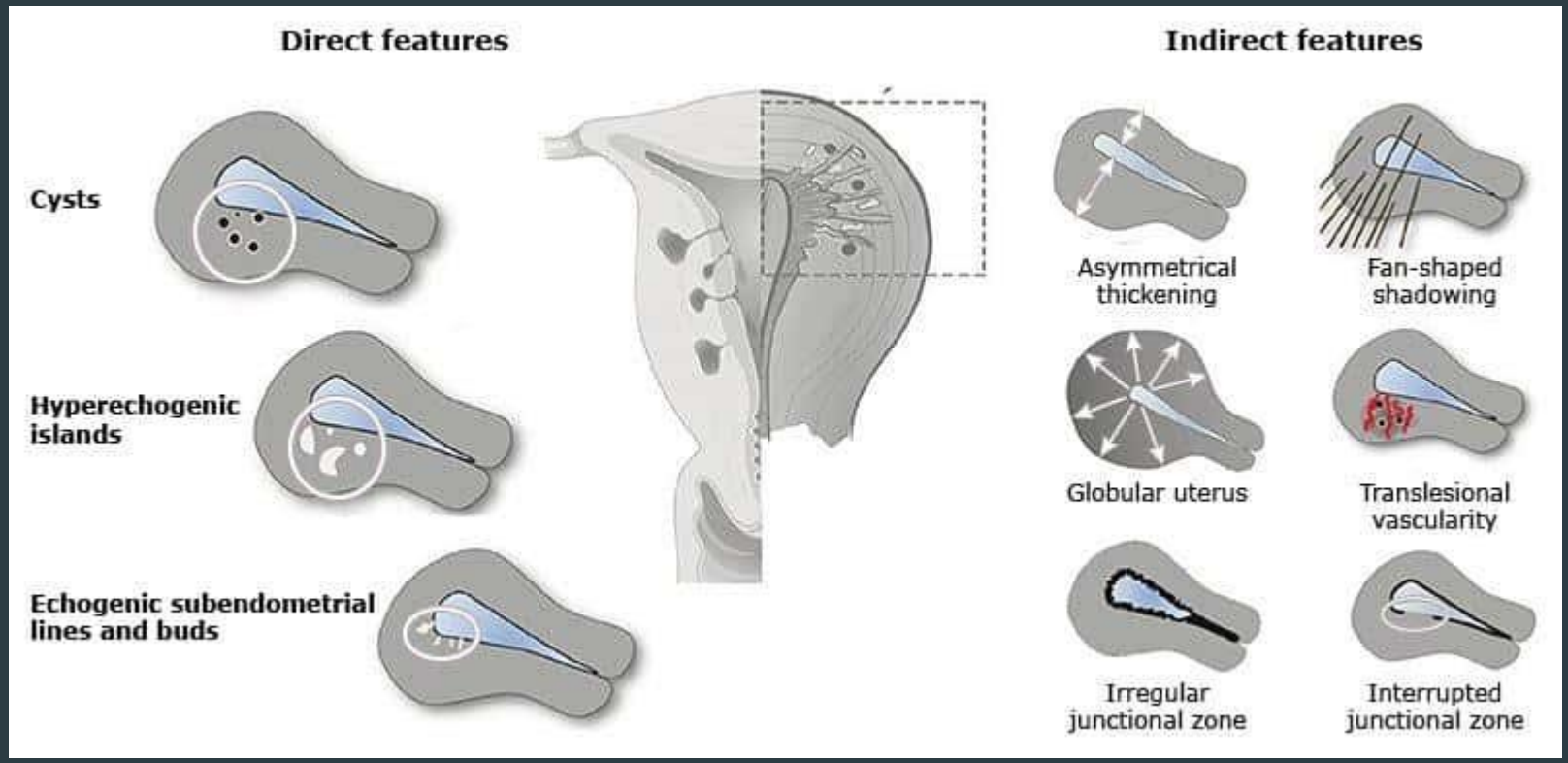
TVUS

- MUSA (morphological uterus sonographic assessment)
- Direct features:
- -Myometrial cysts (eg, 2 to 5 mm), and for histologic diagnosis, the cysts must be separated from the endometrium by at least 2 low-power fields.
- -Hyperechoic islands in the myometrium.
- -Echogenic subendometrial lines and buds.

TVUS

- •Indirect features:
- -An enlarged, globular uterus.
- -Asymmetric thickening of the myometrium
- -Linear striations radiating out from the endometrium . fan-shaped shadowing and appears as alternating bands of shadowing and hyperechogenicity on ultrasound.
- caused by the small cysts in the myometrium allowing for increased transmission and shadowing caused by the surrounding compact myometrium.
- -Increased translesional vascularity in adenomyomas. By contrast, peripheral vascularity is seen in leiomyomas.
- -A junctional zone (JZ; the subendometrial layer of myometrium) that is irregular or interrupted.

2022 MUSA criteria for diagnosis of adenomyosis



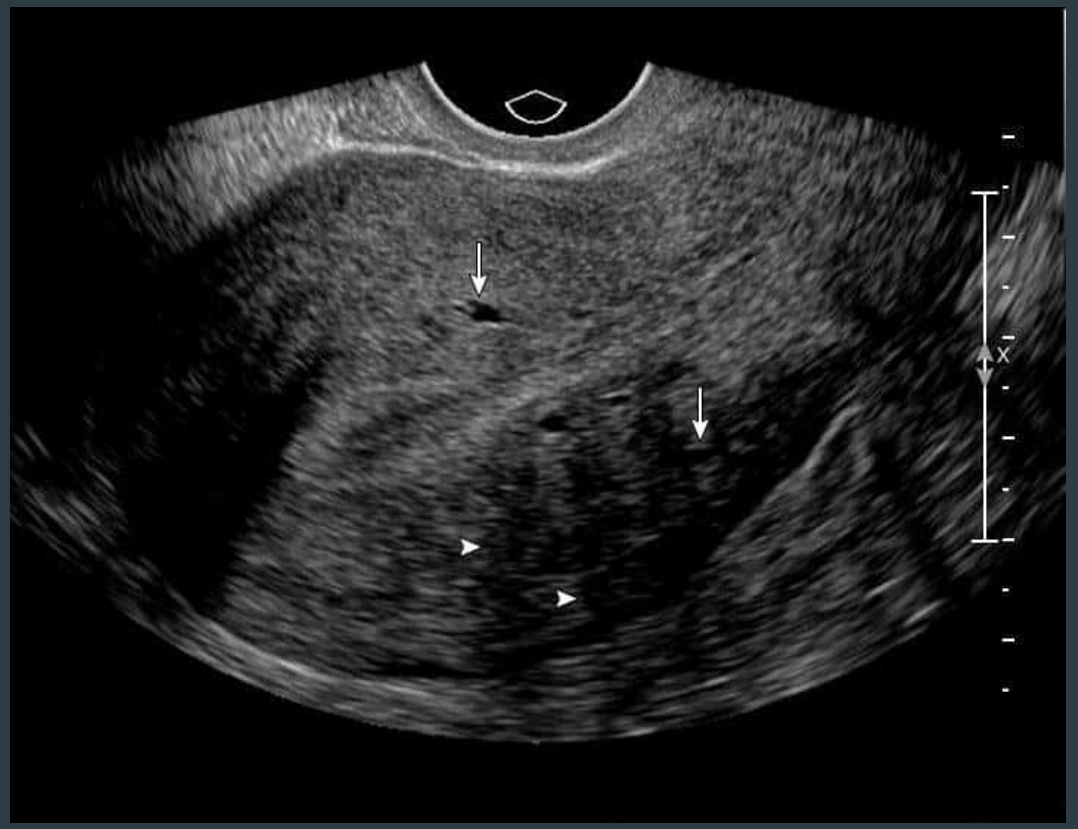
TVUS

- a sign called ‘the question mark form of the uterus’ (when the uterine corpus is flexed backwards, and the cervix is directed anteriorly towards the urinary bladder) high sensitivity and specificity (92% and 75%, respectively) of US

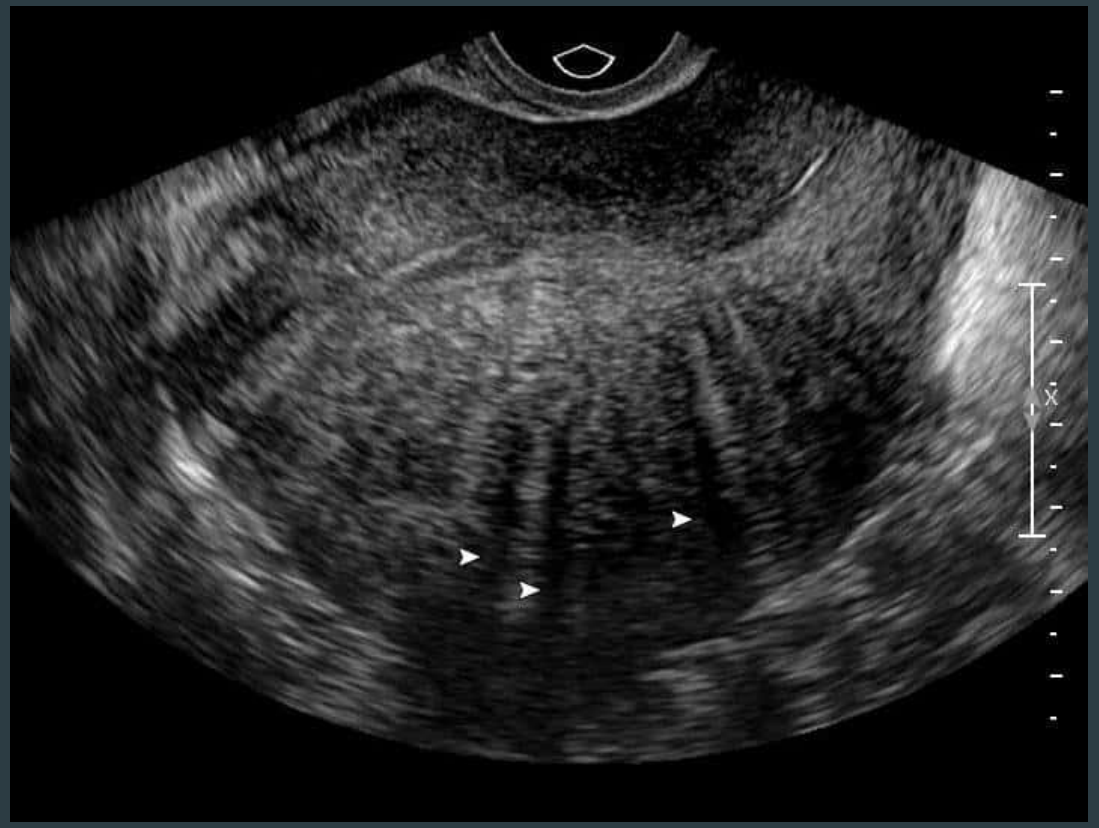
TVUS

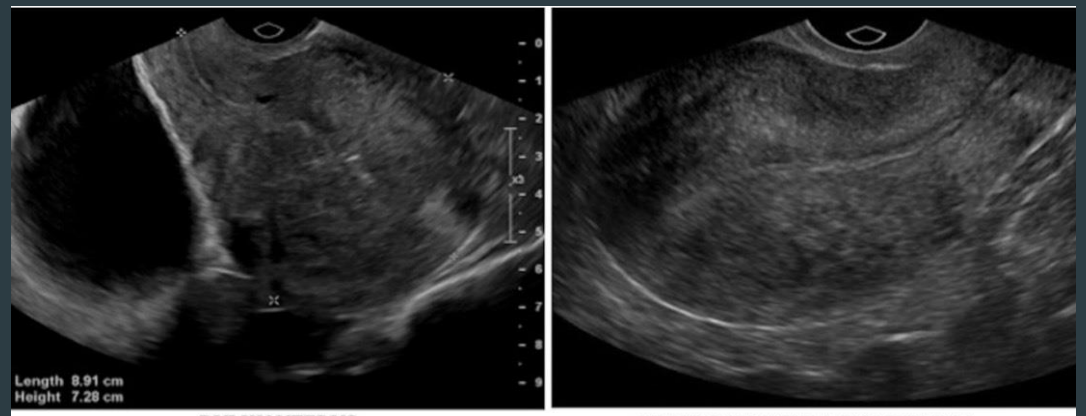
- features of adenomyosis can change with the menstrual cycle.
- For example, cysts may become larger and echogenic masses within the myometrium may change in echogenicity during the menstrual cycle.

Sagittal transvaginal sonogram shows a uterus with multiple myometrial cysts (arrows). Also note the multiple bands of alternating bright and dark echoes (arrowheads).



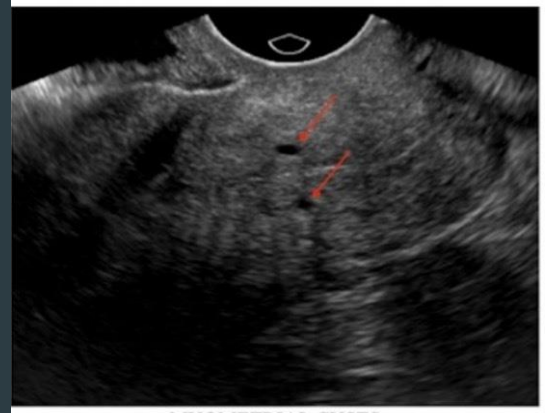
Sagittal transvaginal sonogram shows an enlarged uterus where the posterior wall is thicker than the anterior wall. Note the multiple bands of alternating bright and dark echoes (arrowheads).



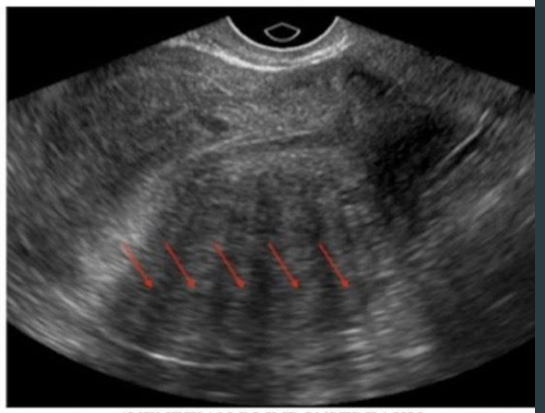


BULKY UTERUS

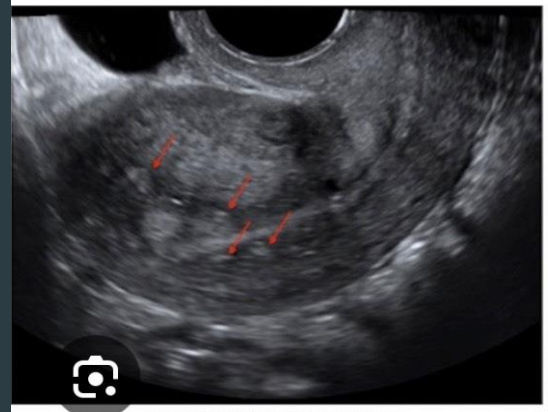
HETEROGENEOUS MYOMETRIUM



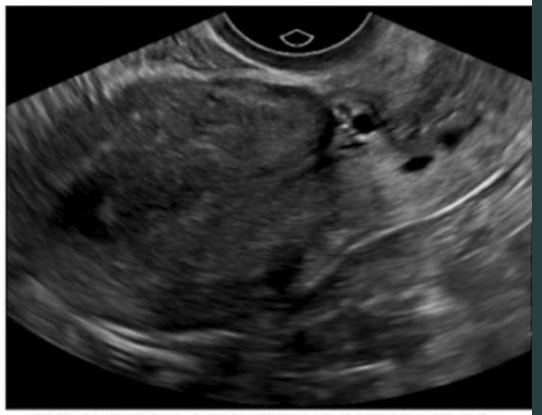
MYOMETRIAL CYSTS



'VENETIAN BLINDS'/STREAKY



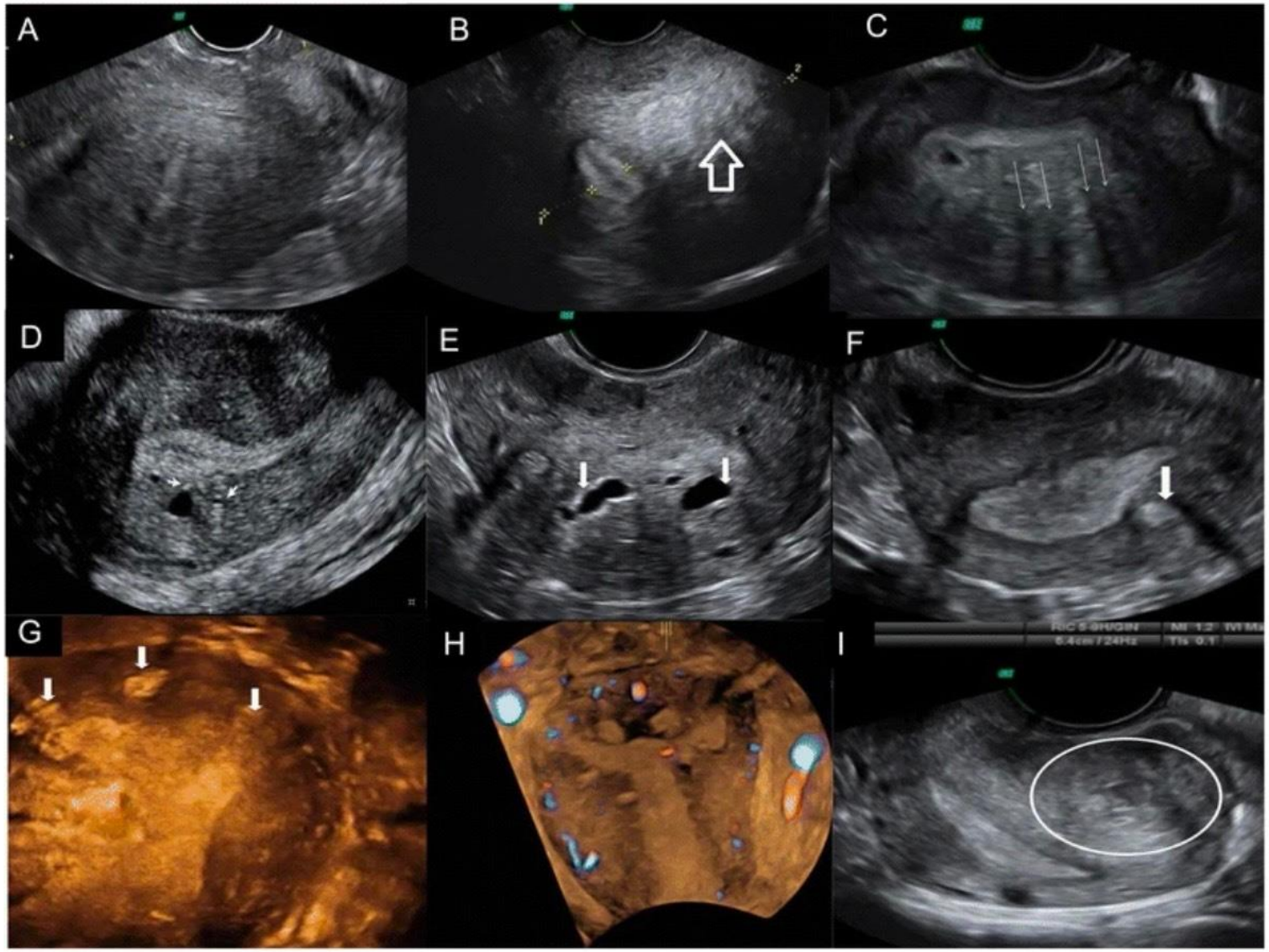
ECHOGENIC STRIATIONS



ENDOMETRIAL-MYOMETRIAL INTERFACE ILL-DEFINITION

Three-dimensional (3D) TVUS

- specificity of 81% and sensitivity of 85% irregular, interrupted junctional zone, a junctional zone thickness > 8 mm
- a significant difference between maximum and minimum thickness measurements of the junctional zone > 4 mm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I

Vannuccini, S et al. Recent advances in understanding and managing adenomyosis. *F1000Research* **2019**.

- Meta-analysis
- two-dimensional TVUS had a sensitivity and specificity of 83.8% and 63.9%, respectively
- Three-dimensional TVUS had a pooled sensitivity and specificity for all combined imaging characteristics of 88.9% and 56.0%, respectively .
- The accuracy and sensitivity of TVUS decreases to as low as 33% when a coexisting pathology such as fibroids is present, especially when the volume of the fibroid is significantly increased.

MRI

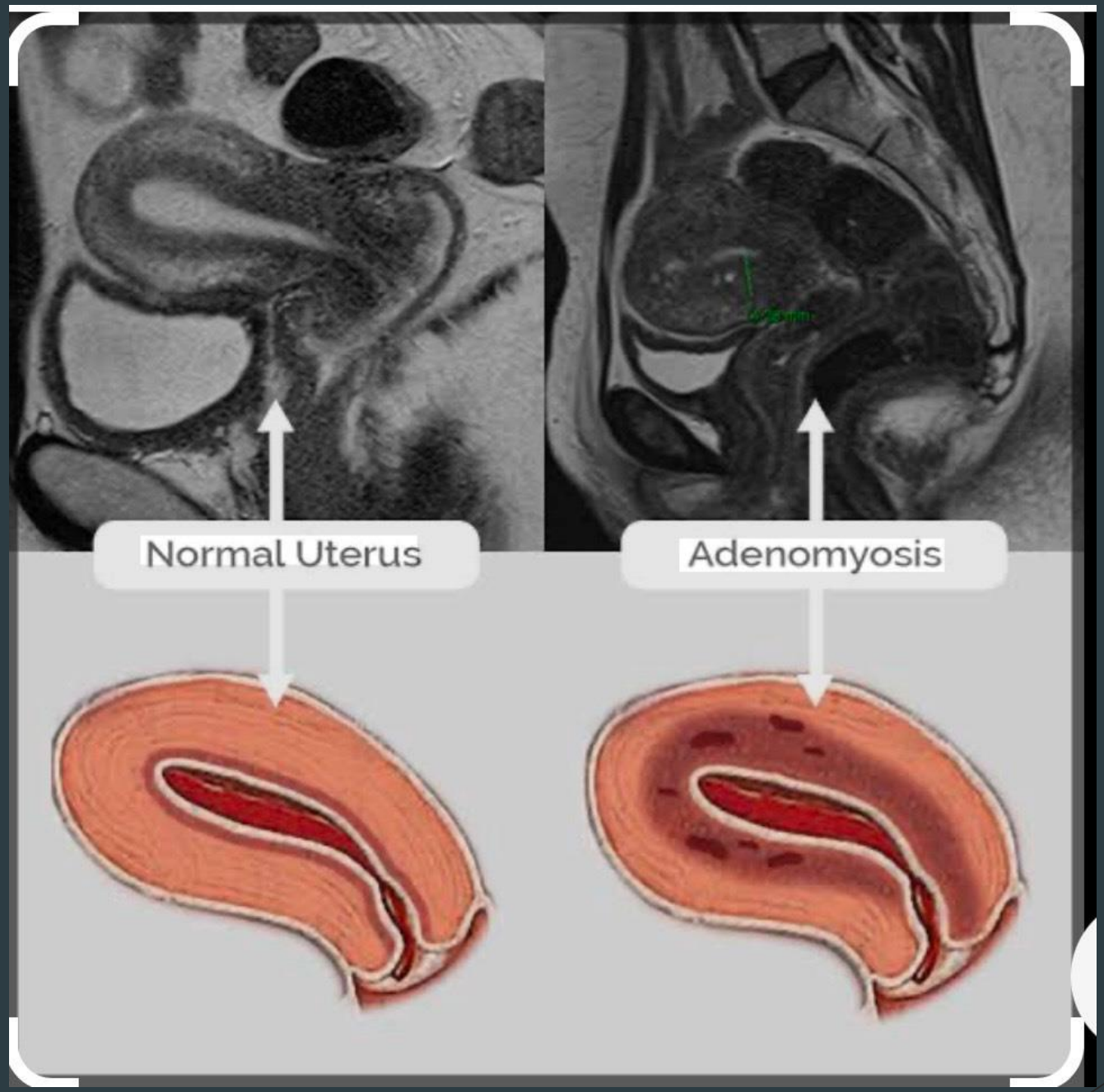
- sensitivity of 77% and a specificity of 89%
- When other uterine abnormalities such as fibroids are present,sensitivity of 67% and a specificity of 82%
- Improves diagnostic by reducing rates of false positive diagnoses
- Intravenous gadolinium contrast is not necessary

MRI

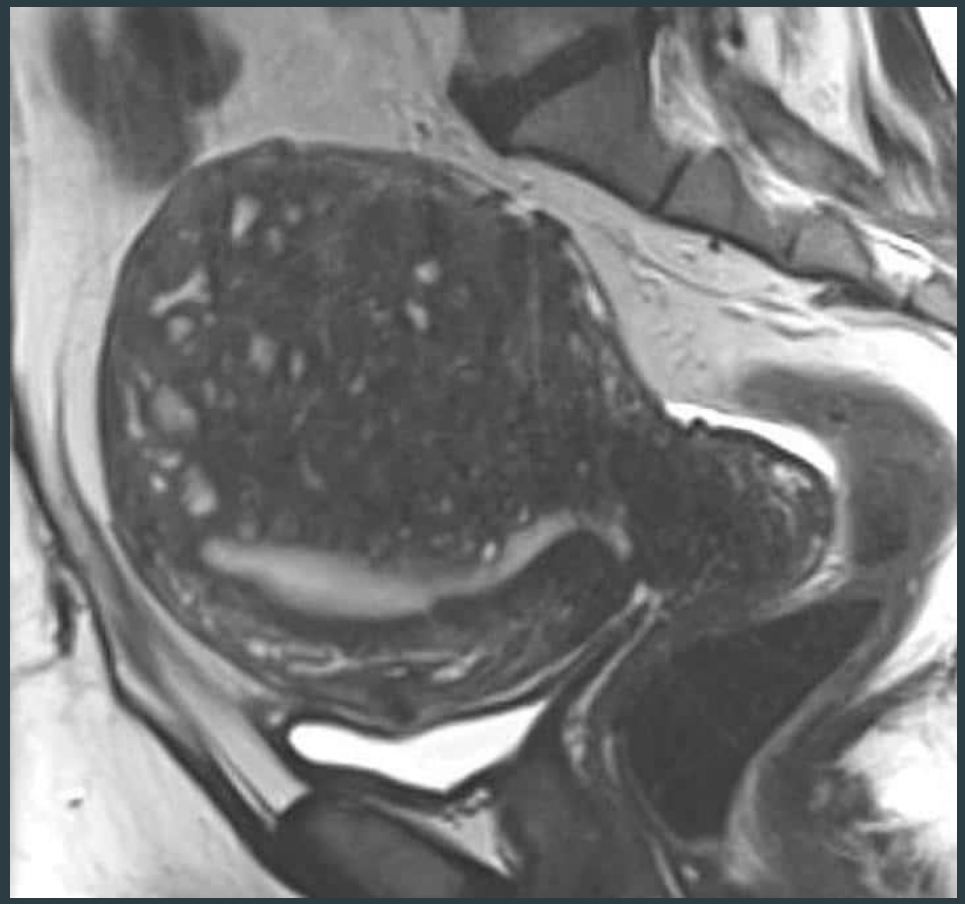
- An abnormal junctional zone to myometrial thickness ratio of more than 40%
- A JZ thickness (visualized as a hypointense signal on T2-weighted images) of >12 mm is a sign of adenomyosis
- thickness of <8 mm indicates the diagnosis unlikely
- While thickening, discontinuity, and interruption of the JZ can be clearly visible on MRI ,its use as a histologic marker of adenomyosis is limited.
- JZ thickness between 8 and 12 mm typically requires additional supportive features for the diagnosis of adenomyosis.
- •Heterotopic endometrial tissue seen as hyperintense foci in the myometrium on T2-weighted images.
- •Hemorrhage within the heterotopic endometrial tissue seen as hyperintense foci in the myometrium on T1-weighted images.
- •Echogenic subendometrial lines or buds extending from the JZ.

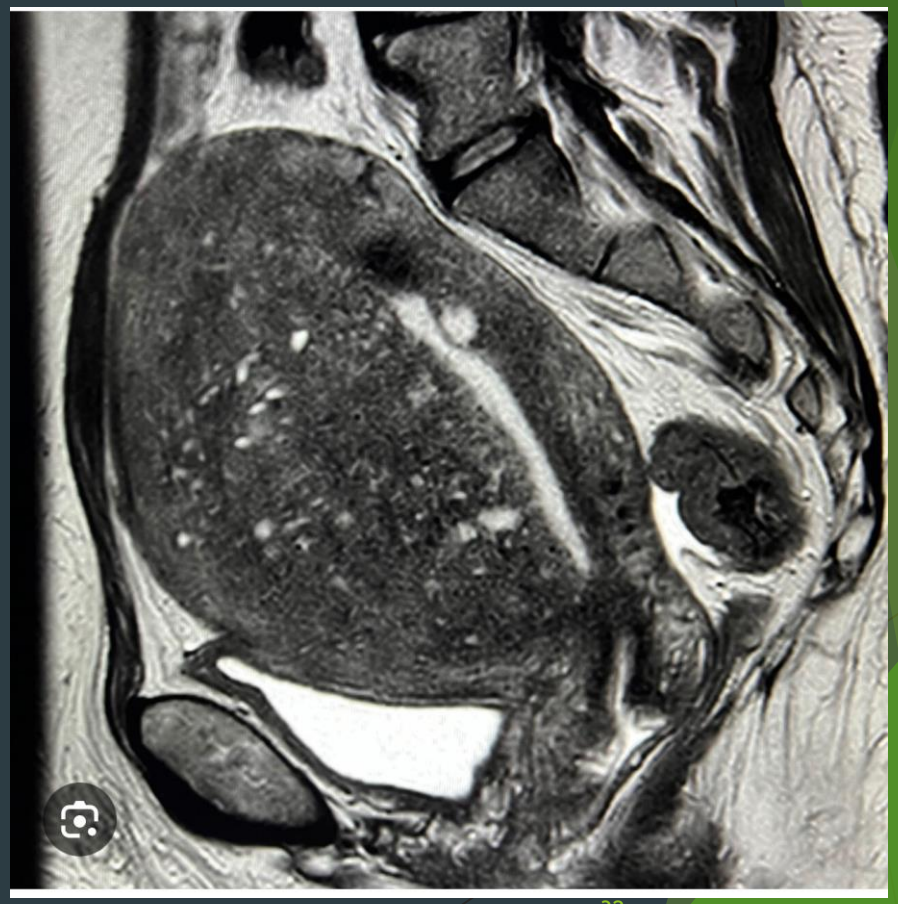
MRI

- Features of adenomyosis can change with the menstrual cycle.


Normal Uterus
Adenomyosis

Sagittal T2-weighted MRI. Note the asymmetric myometrium, thicker posteriorly than anteriorly. There are multiple myometrial cysts.

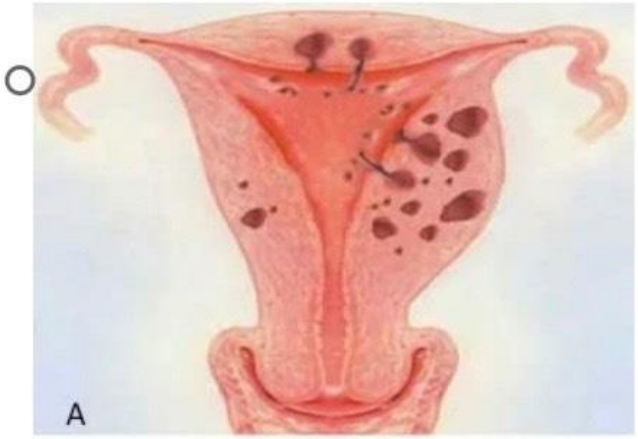




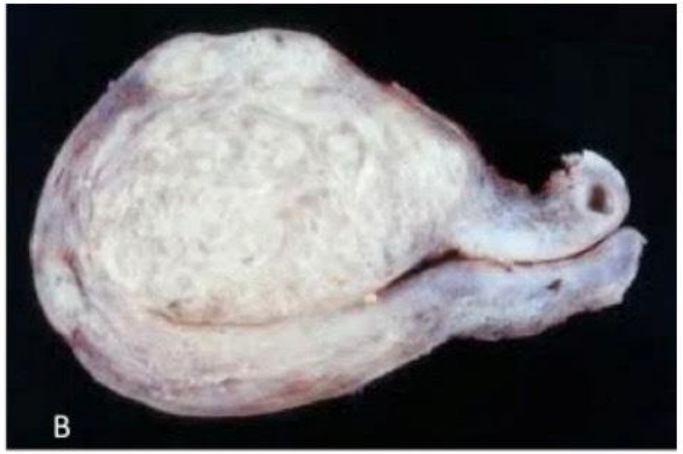
Author	Year of Publication	MRI or TVUS	Classification
Gordts et al.	2008	MRI	•JZhyperplasia • Adenomyosis • Adenomyoma
Kishi et al.	2012	MRI	• Intrinsic • Extrinsic • Intramural • All others
Grimbizis et al.	2014	MRI	• Diffuse • Focal • Polypoid • Other
Bazot and Darai	2018	MRI	• Internal • Adenomyoma • External
Lazzeri L. et al. Van den Bosch et al. Exacoustos et al.	2018 2019 2020	TVUS	• Diffuse of outer myometrium • Diffuse of the inner myometrium or JZ • Focal of the outer myometrium • Focal of the inner myometrium • Adenomyoma

Hysteroscopy

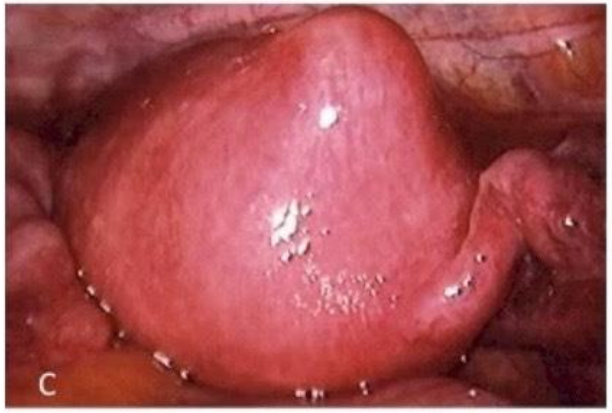
- In patients with AUB valuable diagnostic technique
- Direct visualisation of the uterine cavity
- Collecting of material for histopathological examination.
- Number of features :
- hypervascularisation on the endometrial surface
- An irregular endometrium with small openings,called strawberry pattern
- Fibrous and haemorrhagic cystic lesions.
- More information can be obtained from the behaviour of the uterine muscle during the biopsy with a diathermy loop resectoscope.



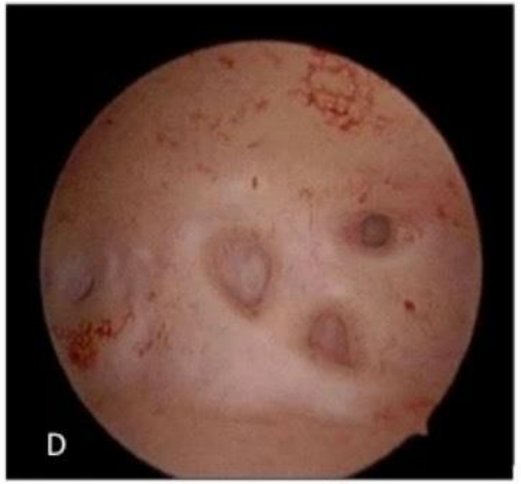
Adenomyosis. Note thickened wall of uterus which can be mistaken for fibroids.



Gross appearance of diffuse adenomyosis



Laparoscopic view of adenomyosis

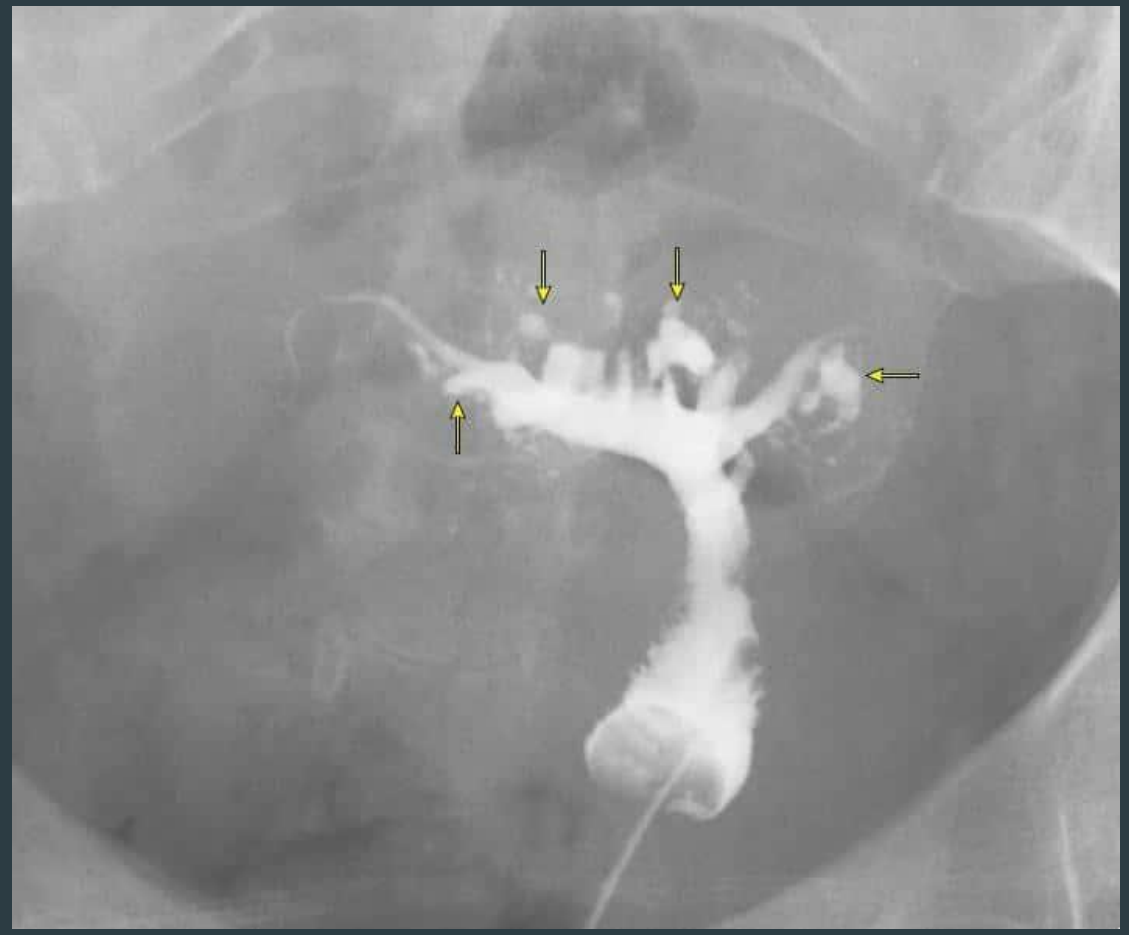


Hysteroscopic view of adenomyosis

hysterosalpingogram (HSG)

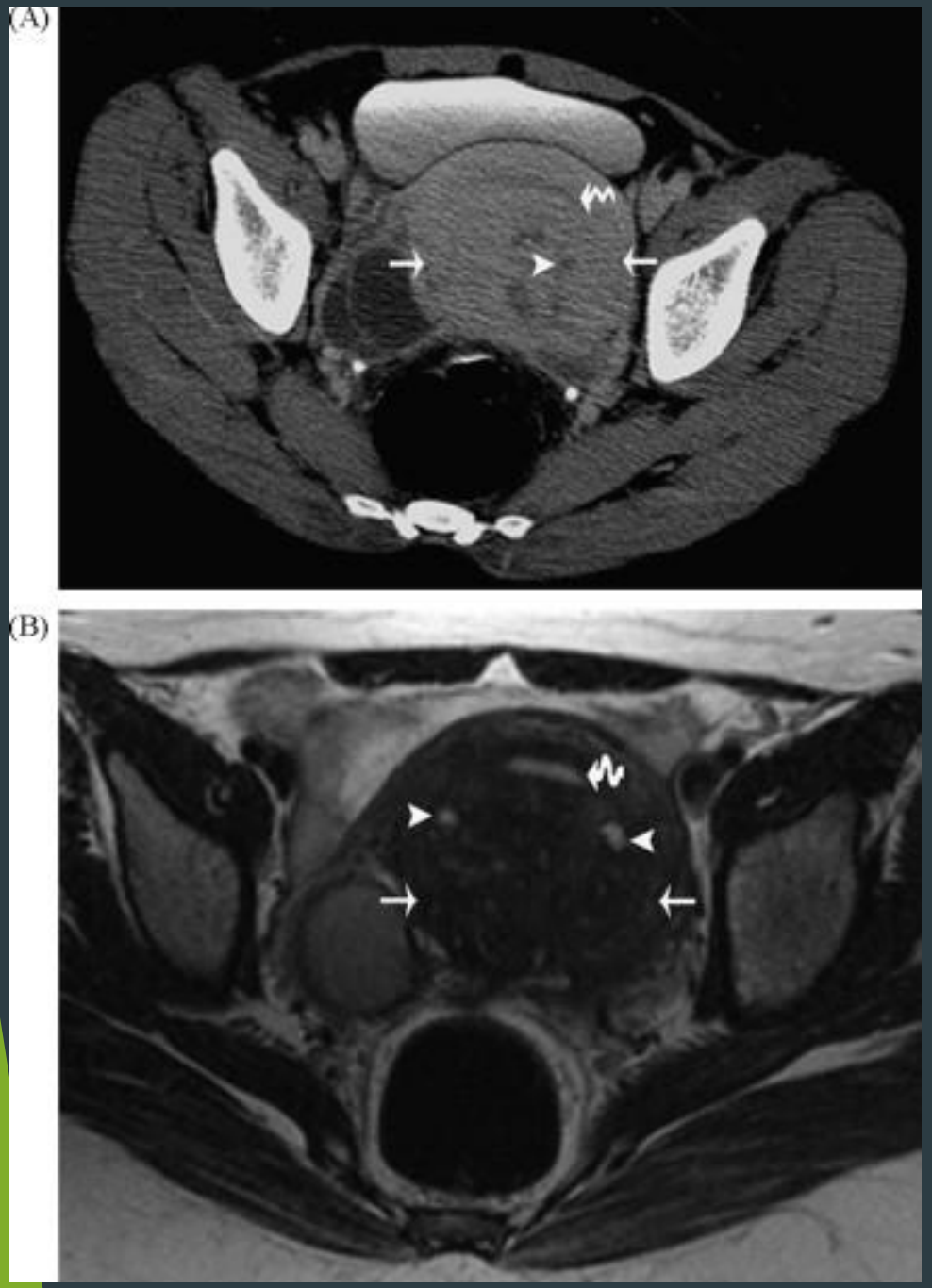
- Enlarged cavity
- Multiple saccular contrast collections that extend beyond the expected endometrial contour into the myometrium

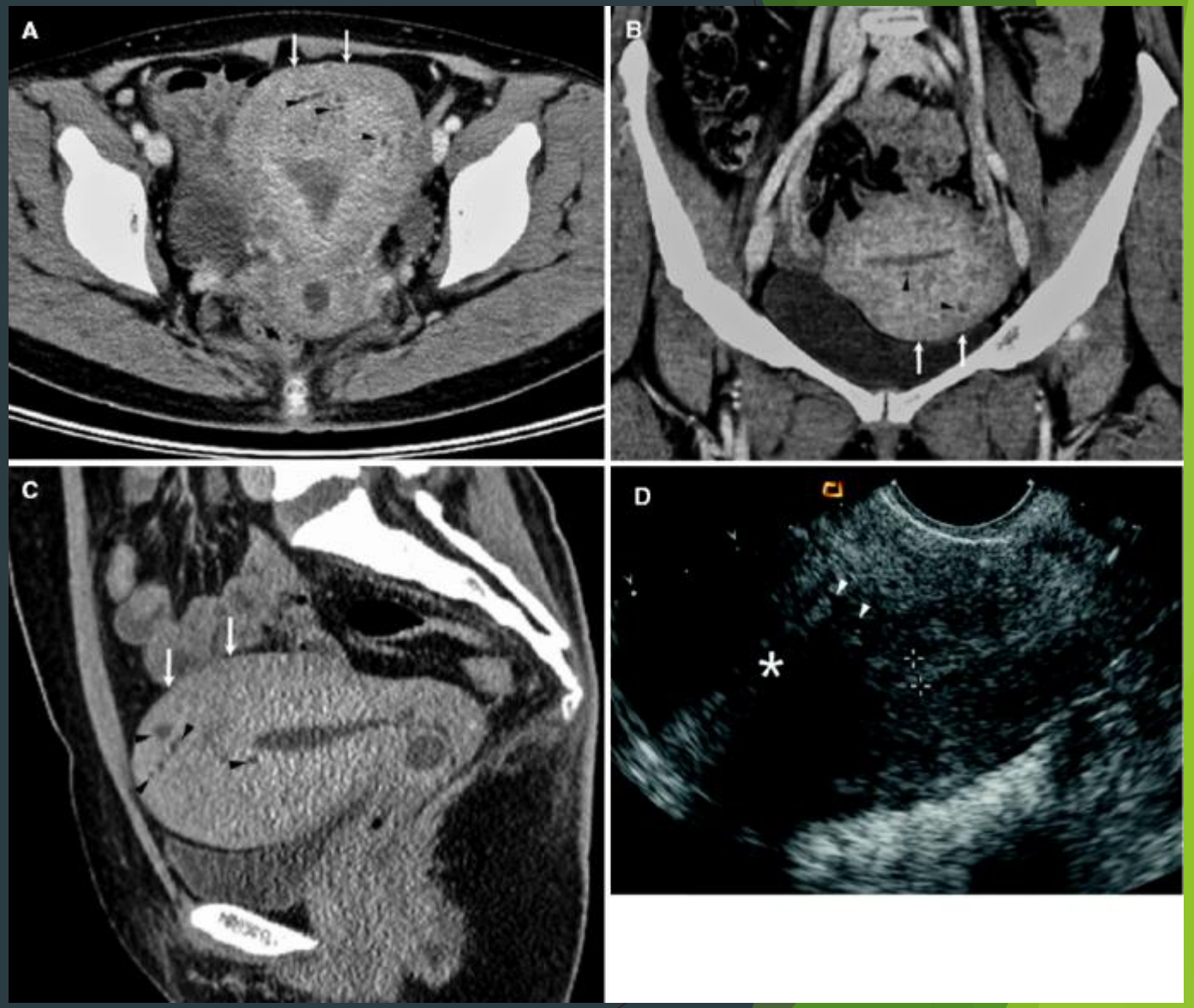
hysterosalpingogram (HSG)



Computed tomography (CT)

- uterine enlargement
- Thickened inner myometrium
- Myometrial cysts.


(A)
(B)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other tests

- **Urine or serum hCG** –to exclude pregnancy in reproductive-age patients with uterine enlargement, AUB, or pelvic pain.
- **Hemoglobin or hematocrit** : patients with AUB or when anemia is suspected.
- **Chlamydia and/or gonorrhea** – If pelvic pain is present, tests to exclude infection
- **Endometrial biopsy** –is not informative in the diagnosis , it is a myometrial disease. required for exclude endometrial hyperplasia or carcinoma
- ●**Needle biopsy** – is not common practice

DIAGNOSIS

- Characteristic clinical manifestations (eg, heavy menstrual bleeding and dysmenorrhea in a patient with an enlarged uterus)
- Imaging findings

HISTOPATHOLOGY

- ●**Diffuse adenomyosis** – uterus enlarged and boggy.
- The average uterine weight is usually between 80 and 200 grams .
- Sectioning the uterus, the myometrial wall appears thickened and small hemorrhagic or chocolate-colored areas (representing islands of endometrial bleeding) without well-demarcated borders are dispersed throughout the myometrium .

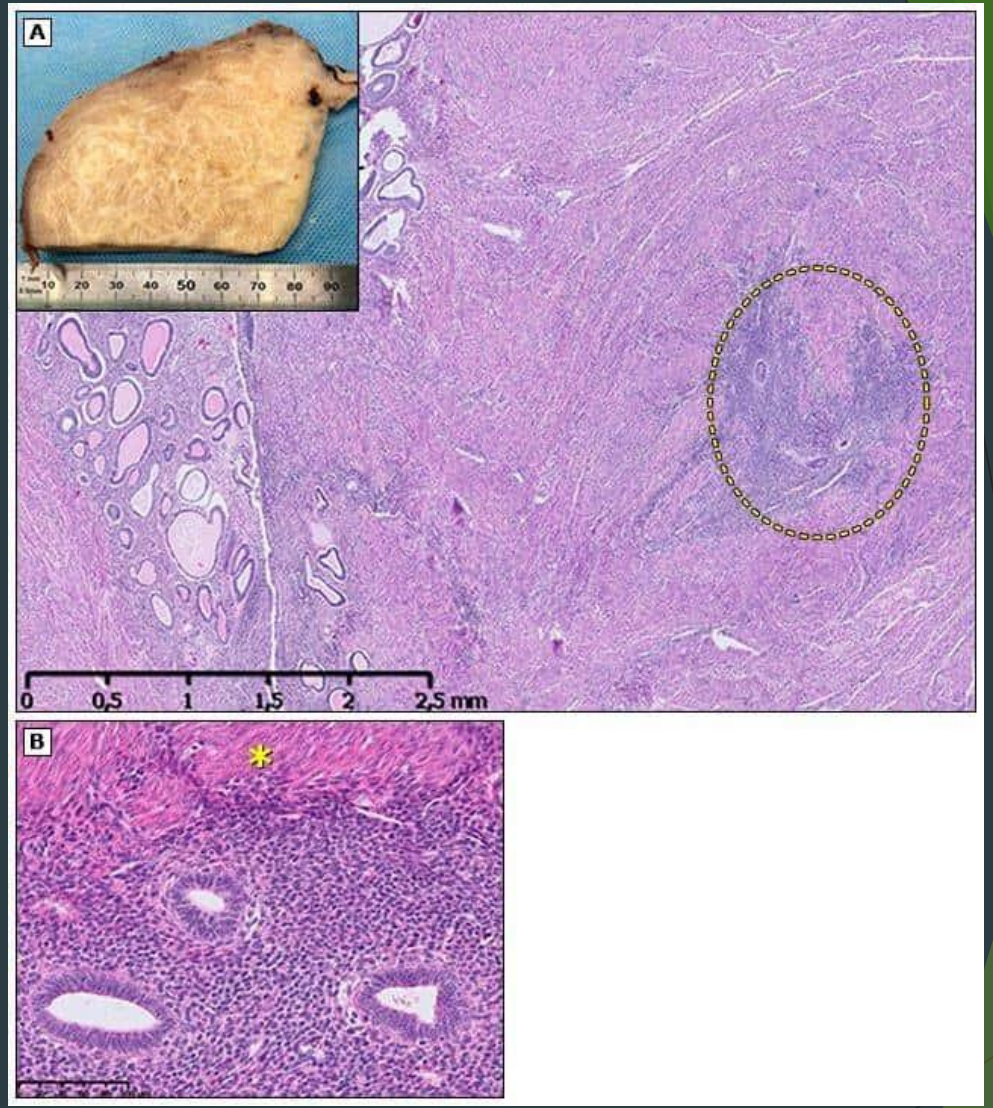
HISTOPATHOLOGY

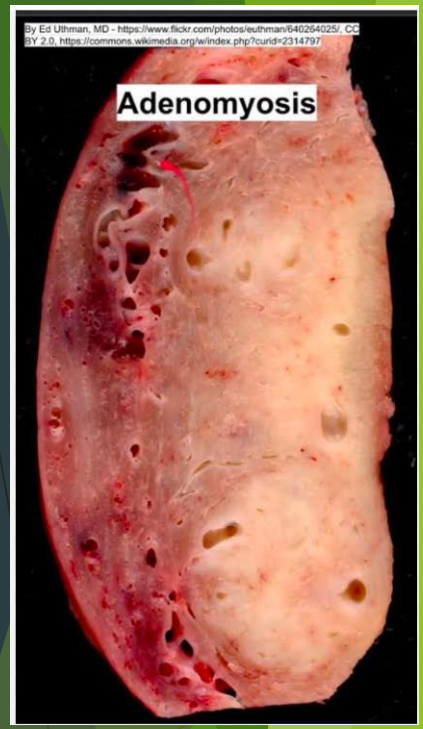
- ●**Focal adenomyosis (also called adenomyoma)**
- GROSS :focal adenomyosis can resemble a leiomyoma without its characteristic pseudocapsule which allows for easy enucleation during surgical resection.
- Sectioning the uterus, circumscribed, nodular aggregates of hemorrhagic or chocolate-colored areas are visualized in only one part of the myometrium.

HISTOPATHOLOGY

- **Junctional zone disease** – The JZ is the border between the endometrium and myometrium
- The presence of endometrial tissue within the myometrium at a distance of at least two low-power fields
- The distance requirement is to preclude mistaking the normal endometrium between muscle fibers at the mucosa for adenomyosis when the specimen is transected for slide preparation.
- The ectopic endometrium has an immature proliferative pattern.

Macroscopic and microscopic appearance of adenomyosis





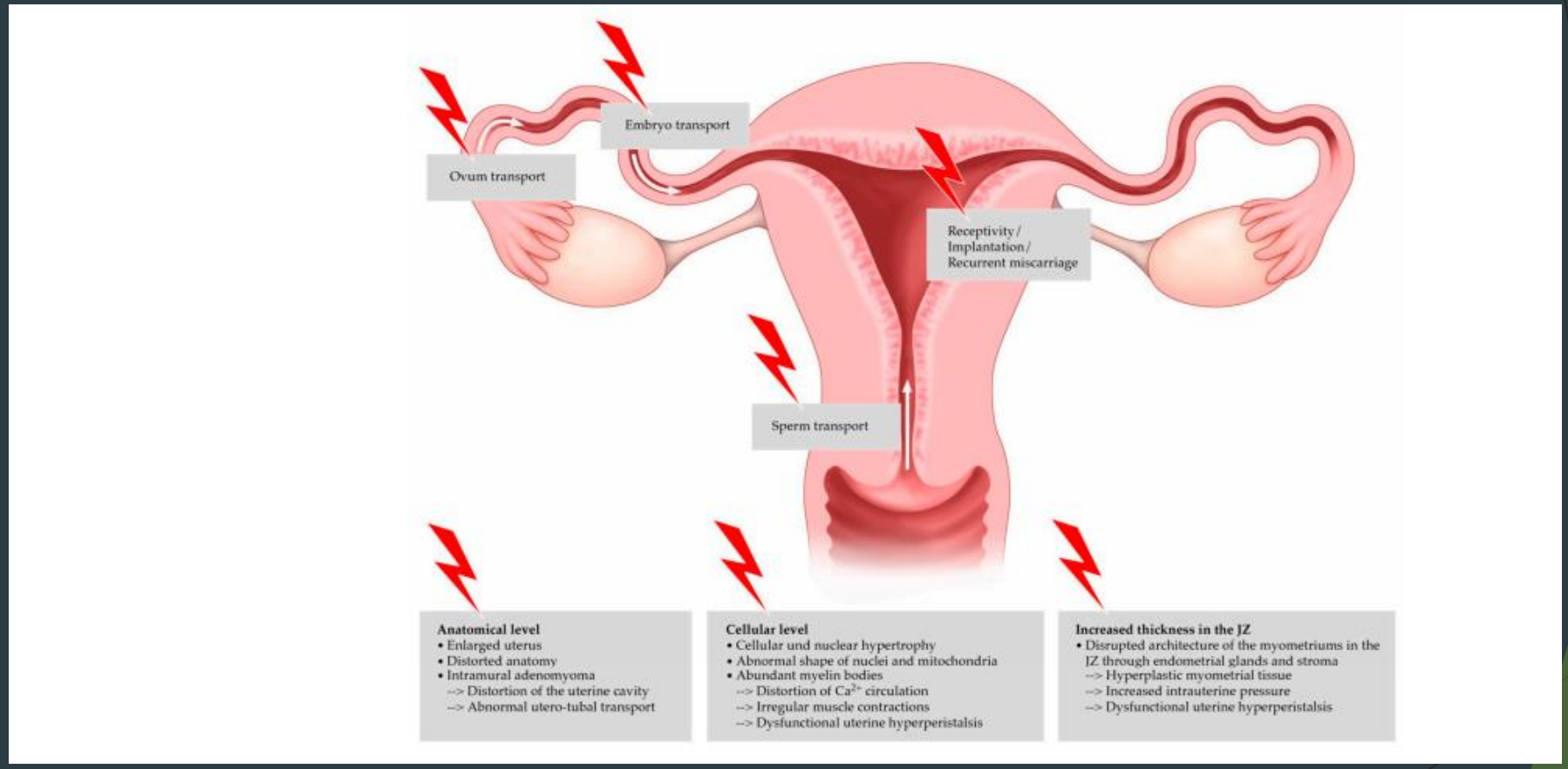
Biological Influence of Adenomyosis on Fertility—Possible Mechanisms

- negatively affects in vitro fertilisation, pregnancy and the live birth rate
- Increases the risk of miscarriage, obstetric complications, such as premature birth and preterm rupture of membranes

Biological Influence of Adenomyosis on Fertility—Possible Mechanisms

- anatomical distortion of the uterine cavity
- disturbed uterine peristalsis and sperm transport
- dysfunctional hyperperistalsis of the inner myometrium
- increased intrauterine pressure
- disturbance in normal myocyte contractility with a subsequent loss of normal rhythmic contraction
- altered sex steroid hormone pathways
- increased inflammatory markers and oxidative stress
- the reduced expression of implantation markers
- a lack of expression of adhesion molecules
- altered function of the gene for embryonic development (the HOXA 10 gene)

Negative impact of adenomyosis on the individual steps of reproduction



endometrial receptivity

- Endometrial receptivity is defined as physiological molecular and histological phenomena occurring during a restricted time of the menstrual cycle, making the uterus exclusively receptive to blastocyst attachment and implantation (so-called implantation window).
- Reduced endometrial receptivity and impaired decidualisation in adenomyosis was found at the molecular level.
- Abnormal function of the implantation-associated molecules such as HOXA10, LIF, MMP, IL-6, IL -10, cytochrome P450 and RCAS1 has been described.
- The decreased expression level of HOXA10 genes in the secretory phase endometrium appears to be involved in impaired implantation
- Leukemia inhibitory factor (LIF) has been demonstrated to be dysregulated thus impairing implantation
- down-regulation of the NR4A receptor and FOXO1A in adenomyotic tissue, which leads to incorrect decidualisation
- P450 (P450arom) and mRNA expression, which seem to be present in women with adenomyosis, leading to lower clinical pregnancy rates.

Biological Influence of Adenomyosis on Fertility—Possible Mechanisms

- Abnormal expression of both integrin ß-3 (adhesion molecules)and OPN mRNA (osteopontin, responsible for the trophoblast-endometrium interaction) related to uterine receptivity.

- Be responsible for in vitro fertilisation (IVF) failure despite good embryo quality
- adenomyotic patients, the levels of ß3 and OPN were statistically lower compared to nonadenomyotic controls.

Biological Influence of Adenomyosis on Fertility—Possible Mechanisms

- chronic inflammation has a negative impact on fertility .
- Increased expression of IL-1b and CRH (corticotrophin-releasing hormone) in the eutopic endometrium was observed
- presence of a higher expression of pro- and anti-oxidative cytokines like Cu, Zn-SOD and Mn-SOD
- The nitric oxide (NO) concentration in endometrium, macrophage activation, Il-6 and neurotrophins .
- NO is involved in modulating uterine contractility during pregnancy and relaxing vascular smooth muscles.
- An abnormal high level of free radicals such as nitric oxide has a negative impact on sperm transport, implantation and decidualisation .

Author Year	Study Design	Sample Size	Results	Limits
Vercellini et al. 2014 Italy	Meta-analysis (4 prospective cohort studies and 5 retrospective cohort studies)	1865 women, 306 of which diagnosed with AD	Lower clinical pregnancy rate (PR) of 0.72 (40.5% vs. 49.8%) 2.12% higher risk of miscarriage (31.9% vs. 14.1%) Live birth rate of 0.70 (26.8% vs. 37.1%)	Qualitative and quantitative heterogeneity among studies was high
Younes and Tulandi 2017 Canada	Meta-analysis (11 observational studies on clinical outcome of IVF and 4 retrospective studies evaluating the effects of surgical or medical treatment of adenomyosis on fertility)	519 patients with and 1535 without adenomyosis	Lower clinical pregnancy rate (PR) of 0.75 2.2% higher risk of miscarriage Live birth rate of 0.59	Differences in the participants' age, duration of infertility, type of down-regulation protocol used, number and quality of the transferred embryos, number of IVF cycles performed, and the clinical outcomes assessed in the studies. In addition, the infertility diagnosis differed among studies

Author Year	Study Design	Sample Size	Results	Limits
Dueholm and Aagaard 2018 Denmark	Meta-analysis (4 case–control studies and 7 cohort studies)	1597 infertile women undergoing IVF/ICSI 782 infertile women with adenomyosis undergoing IVF/ICSI	Lower clinical pregnancy rate (PR) of 0.73 2.12% higher risk of miscarriage Live birth rate of 0.69	Only heterogeneric studies of moderate quality are available
Nirgianakis et al. 2020 Switzerland	Meta-analysis (4 prospective studies and 13 retrospective studies)	841 women with adenomyosis undergoing ART versus 2198 women without adenomyosis undergoing ART	Lower clinical pregnancy rate (PR) of 0.69 2.17% higher risk of miscarriage No significant difference in live birth rate was found	Studies heterogeneity Diagnostic accuracy of the non-invasive imaging techniques for adenomyosis
Zhang et al. 2021 China	Retrospective cohort study	A total of 5087 divided into two groups: adenomyosis with tubal factor infertility (study group, *n* = 193) and only tubal factor infertility (control group, *n* = 4894).	Clinical pregnancy rate 42.8% vs. 42.2% Miscarriage rate 13.3% vs. 5.6% Live birth rate 33.3% vs. 22.8%	Study design No adenomyosis classification (the severity of the disease may affect pregnancy outcomes) Diagnosis of adenomyosis by TVS is not the gold standard

Author Year	Study Design	Sample Size	Results	Limits
Cozzolino et al. 2022 China	Meta-analysis (7 prospective cohort studies, 15 retrospective cohort studies)	7738 patients (1277 women with adenomyosis and 6461 without adenomyosis)	Lower live birth rate (OR 0.59, 95% CI 0.37–0.92, p = 0.02) Lower clinical pregnancy rate (OR 0.66, 95% CI 0.48–0.90) Lower ongoing pregnancy rate (OR 0.43, 95% CI 0.21–0.88) Higher miscarriage rate (OR 2.11, 95% CI 1.33–3.33)	Studies heterogeneity (women's age, duration of infertility, type of downregulation protocol used, number and quality of the transferred embryos, number of IVF cycles performed, and the clinical outcomes assessed in the studies) heterogeneity of the patients with different degrees of the disease (no division between focal and diffuse adenomyosis)
Liang et al. 2022 Italy	Retrospective cohort study	1146 patients with adenomyosis and 1146 frequency-matched control women in a 1:1 ratio based on age, BMI, and basal follicle-stimulating hormone (FSH) level	No significant difference in clinical pregnancy rate (38.1% vs. 41.6%; p = 0.088) Lower implantation rate (25.6% versus 28.6%, p = 0.027) Lower live birth rate (26% versus 31.5%, p = 0.004) Higher miscarriage rate (29.1% versus 17.2%, p = 0.001)	Study design Diagnostic accuracy of non-invasive imaging technology for adenomyosis Inability to exclude certain pathologies, such as peritoneal endometriosis

Adenomyosis Treatment on Fertility

- highly dependent upon a woman's age, other fertility factors, and symptomatology
- The pharmacological treatment of adenomyosis is similar to that of endometriosis
- Final treatment hysterectomy most effective way of achieving symptoms control
- It is unacceptable for women wishing to have children.
- Fertility-saving treatment has variable success rates for both pain and bleeding.
- Some of the available nonsurgical management methods severely interfere with fertility.

Adenomyosis Treatment on Fertility

Pharmacological	Surgical
• Anti-inflammatory drugs • Oral contraceptives • GnRH • progestins	• Endo-myometrial ablation • High-intensity focused ultrasound Ablation • Electrocoagulation of adenomyosis foci • Resection of adenomyosis foci • Hysterectomy

MANAGEMENT

- **First-line therapies**
- **NSAIDs** — first-line therapy includes nonsteroidal anti-inflammatory drugs (NSAIDs; ibuprofen, naproxen, mefenamic acid), effective for the treatment of heavy menstrual bleeding and dysmenorrhea
- impact on fertility is negative
- Cause a delay in ovarian follicle rupture, but there is some evidence that NSAIDs can be used as a co-treatment in the IVF procedure

MANAGEMENT

- **52 mg levonorgestrel IUD** — first-line therapy , direct action on the uterus, low systemic levels of steroid hormones, and long-acting user-independent administration.
- An antiproliferative and anti-inflammatory effect of progestins
- Effective in controlling pain symptoms
- Reduce uterine volume and affect abnormal uterine bleeding, but their influence on fertility
- pre-treatment with the LNG-IUD for 3 months before embryo transfer has been proposed to improve the reproductive outcomes of patients undergoing in vitro fertilization with a significantly increased ongoing pregnancy rate (41.8% versus 29.5%).

MANAGEMENT

- **Oral contraceptive pills** –primary treatments for heavy menstrual bleeding and dysmenorrhea by decidualisation and subsequent endometrial atrophy.
- OCs enables satisfactory, long-term pain control in two-thirds of women with symptomatic endometriosis or adenomyosis.
- No data on the impact on the subsequent fertility improvement

MANAGEMENT

- **GnRH agonists and antagonists** –induce a constant hypoestrogenic state

GnRH agonists

- Recent data shown only GnRHa treatment with add-back estrogen therapy can be beneficial for infertile women, leading to improved implantation rates
- The long-term preparation of the endometrium with GnRH-a therapy for 2 to 4 months, before frozen embryo transfer is associated with significantly higher clinical pregnancy, implantation, and ongoing pregnancy rates .

- In one small case series published by Huang et al., authors did not show an improvement in fertility after the GnRH analogue management combined with conservative microsurgery

MANAGEMENT

- Progestins, danazol, aromatase inhibitors, selective progesterone receptor modulators : Improvement of symptoms
- No clear data on the success of reproduction

MANAGEMENT

- **Later line: Surgical procedures**
- The surgical treatment of adenomyosis-related infertility remains a highly controversial issue

- **Patients who have completed childbearing**
- **Hysterectomy**
- **Uterine artery embolization**

Surgical procedures

- Endo-myometrial resection is effective and indicated in patients with the disease limited to the endo-myometrial junction and allows the reduction of heavy menstrual bleeding .
- In patients who desire pregnancy, endo-myometrial resection is contraindicated .
- Destruction of the endometrium together with JZ can cause serious complications in patients who managed to conceive, such as miscarriage, preterm labour and placentation complications, abdominal and intrauterine adhesions and uterine rupture, especially during the second and third trimester of pregnancy.

Surgical procedures

- optimum surgical technique for adenomyosis is difficult
- Operative options (open or laparoscopic), surgical techniques (complete or partial adenomyomectomy), and modified surgical techniques (U-shaped suturing, overlapping flaps, the triple-flap method, and transverse H-incisions)
- Factors like the extent of excision of the myometrial defect, the reconstruction technique, postoperative infection and the surgeon's experience are quite important.
- Even the use of electrodiathermy instead of a cold knife during the operation might affect the wound healing and integrity of the myometrium.

Uterine Artery Embolization

- Embolisation effective treatment of symptoms
- This endovascular procedure causes the closing of vessels that supply the uterus.
- Premature ovarian insufficiency (POI) is mentioned as a consequence of embolisation
- affect both hormone production and ovarian reserve, leading to premature and iatrogenic amenorrhoea and infertility.
- Endometrial receptivity is also diminished after this procedure.
- It should be contraindicated in women planning pregnancy but is useful in the post-reproductive age

The high-intensity focused ultrasound method (HIFU)

- The high-intensity focused ultrasound method (HIFU) uses the thermal effect of the ultrasound beam, which causes coagulative necrosis within the targeted adenomyotic lesion.
- The lesion should be clearly visible in ultrasound or under MRI so that the beam could be precisely directed.
- unsuitable for the diffuse form
- After the procedure, patients can attempt to conceive much earlier than after surgical treatment, but the exact time of delay in conception is unknown.

Author Year	Study Design	Sample Size	Treatment	Results
Zhou et al., 2016 China	Retrospective cohort	**68 women** with adenomyosis desiring pregnancy	high-intensity focused ultrasound method (HIFU)	**Pregnancy rate:** 79.4% (54/68) **Live birth:** 38.9% (21/54) **Spontaneous abortion:** 37.0% (20/54) **Uterine rupture:** 0 cases Significant improvement in dysmenorrhea and menorrhagia
Otsubo et al., 2016 Japan	Retrospective observational study	**23 pregnancies** after surgery	Uterine-sparing surgery for diffuse adenomyosis	**Delivery rate:** 56.5% (13/23) **Early miscarriage:** 43.5% (10/23) **Uterine rupture:** 2 cases (associated with residual myometrial thickness <7 mm) Optimal pregnancy outcomes observed when uterine wall thickness was **9-15 mm**

Electrocoagulation

- fOR focal or diffuse disease.

- Younes et al. concluded in the recent meta-analysis that conservative surgery in adenomyosis could improve fertility in some patients, but the rate of resulting successful pregnancies varied between surgical centres.

IVF Outcome in Adenomyosis

- The results of studies devoted to the efficacy of assisted reproductive techniques, such as in vitro fertilisation and embryo transfer (IVF-ET) and intracytoplasmic sperm injection (ICSI), on pregnancy rates in patients with adenomyosis showed conflicting results.

Author (Year)	Country	Study Design	Study Population	Intervention / Protocol	Comparator	Main Outcome	Key Findings
Mijatovic et al. (2010)	Netherlands	Cohort study	Infertile women with proven endometriosis and adenomyosis	Long-term GnRH-agonist pretreatment	Controls without adenomyosis	Clinical pregnancy rate (CPR)	No significant difference in CPR between groups
Costello et al. (2011)	Australia	Cohort study	IVF-ICSI patients with adenomyosis	GnRH administration during IVF-ICSI	Controls	Fertility outcomes / CPR	No evidence of impaired fertility in adenomyosis patients
Thalluri & Tremellen (2012)	Australia	Observational study	IVF-ET patients with adenomyosis	GnRH stimulation protocol	Patients without adenomyosis	Clinical pregnancy rate	Significantly lower CPR in patients with adenomyosis
Vercellini et al. (2014)	Italy	Meta-analysis	IVF-ICSI studies	—	—	CPR, implantation rate, early pregnancy loss	Adenomyosis reduced CPR and implantation rates and increased early pregnancy loss

Fertility outcomes and impact of different procedures on adenomyosis symptoms.

Author	Treatment	Patients N	Results		
			Fertility	Bleeding	Pain
Kwack et al. 2018 South Korea	conservative adenomyomectomy with TOUA (transient occlusion of uterine arteries)	116	5/116 conception by natura l5/116 conception by ART 7 live births	menorrhagia: 52/116 complete remission 53/116 partial remission	dysmenorrhea: 98/116 complete remission 18/116 partial remission
Al Jama et al. 2016 Saudi Arabia	treatment with Gn-RH agonist surgery and Gn-RHa therapy	22 18	3/22 pregnancies 1/22 live birth 8/18 pregnancies 6/18 live births	improvement in dysmenorrhea and menorrhagia was noted at the 6- and 12-month follow-up visits in combined conservative both groups	
Saremi et al. 2014 Iran	resection of adenomatosis lesions with a thin margin after sagittal incision in the uterine body	103	49/70 conception by ART 21/70 conception by natural 16/70 live births	decrease of 65% in the number of patients with a heavy bleeding pattern;	decrease of 41% in the number of patients with dysmenorrhoea symptoms;
Kishi et al. 2014 Japan	laparoscopic adenomyomectomy with laser	102	conception by natural: 16/75 (<40 y) and 0/27 (40 or more y) conception by ART: 15/75 (<40 y) and 1/27 (40 or more y) delivery: 26/75 (<40 y)	no data	no data

THANK YOU FOR YOUR ATTENTION