ADENOMYOSIS AND INFERTILITY AN UPDATED REVIEW

Osama M Warda MD
Prof. of OBS/GYN
Mansoura University-EGYPT

Contents

- Background
- Diagnosis ; ultrasound- MRI-Hysteroscopy
- Adenomyosis and infertility.
- Impact of adenomyosis on infertility
- Treatment of adenomyosis in infertility
- Malignant potential of adenomyosis`

Background

- Adenomyosis is defined by ectopic location of endometrial and stromal tissue distal to the endometrial-myometrial junction with associated myometrial smooth muscle hypertrophy.
- Approximately 20% of cases of adenomyosis involve women younger than 40 and 80% are aged 40 to 50.

García-Solares J et al 2018

Background

Adenomyosis can be *asymptomatic* or present with *menorrhagia*, *dysmenorrhea*, and *metrorrhagia* with these symptoms usually occurring in patients aged 35 to 50.

Background

- The most accepted hypothesis for the etiology of adenomyosis stems from the *invagination of the endometrial basalis layer into the myometrium*.

García-Solares J et al 2018

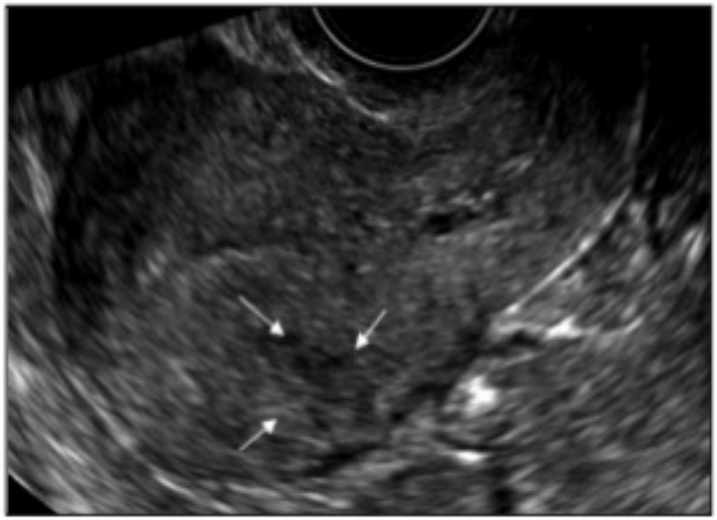


Figure 2. Focal adenomyoma (arrows).

Background

- Adenomyosis can have a *diffuse* (*haphazard* distribution) or more *focal* regions known as adenomyomas.
- Women with the condition, therefore, present with *enlarged*, *boggy* uteri.

DIAGNOSIS-TVS

- ULTASOUND: *Criteria used to define adenomyosis on ultrasound include:*

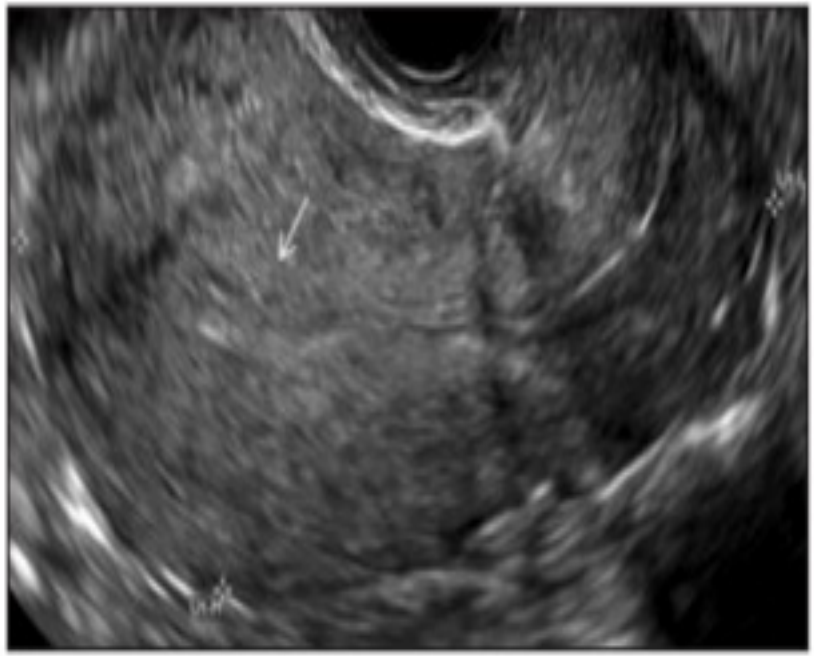
1. Uterine enlargement with focal or diffuse hyperechogeneity in absence of leiomyoma.
2. loss of a normal endo-myometrial interface
3. increased or decreased areas of echogenicity
4. cystic structures within myometrium with increased color Doppler flow.

Luciano DE et al 2013

DIAGNOSIS-TVS

GENERALIZED ADENOMYOSIS

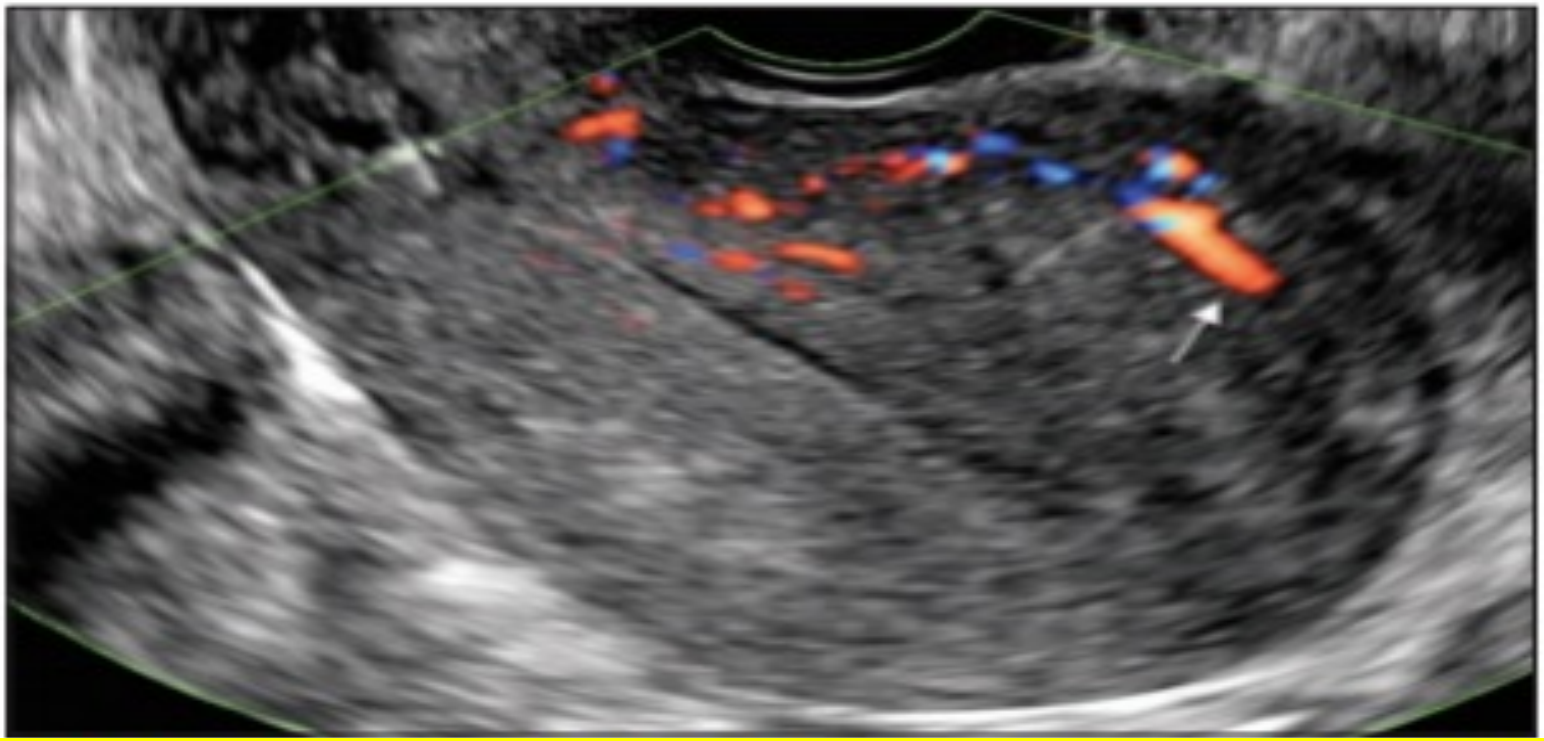
Globular uterine enlargement
With an obscure endometrial -myometrial border (arrow)



DIAGNOSIS-TVS

Sonographic image of a uterus with severe postetrior wall adenomyosis . Dotted blue lines denote focal area of adenomyoma with classic ultrasound features of adenomyosis; myometrial cysts & hyperechoic areas

DIAGNOSIS-TVS

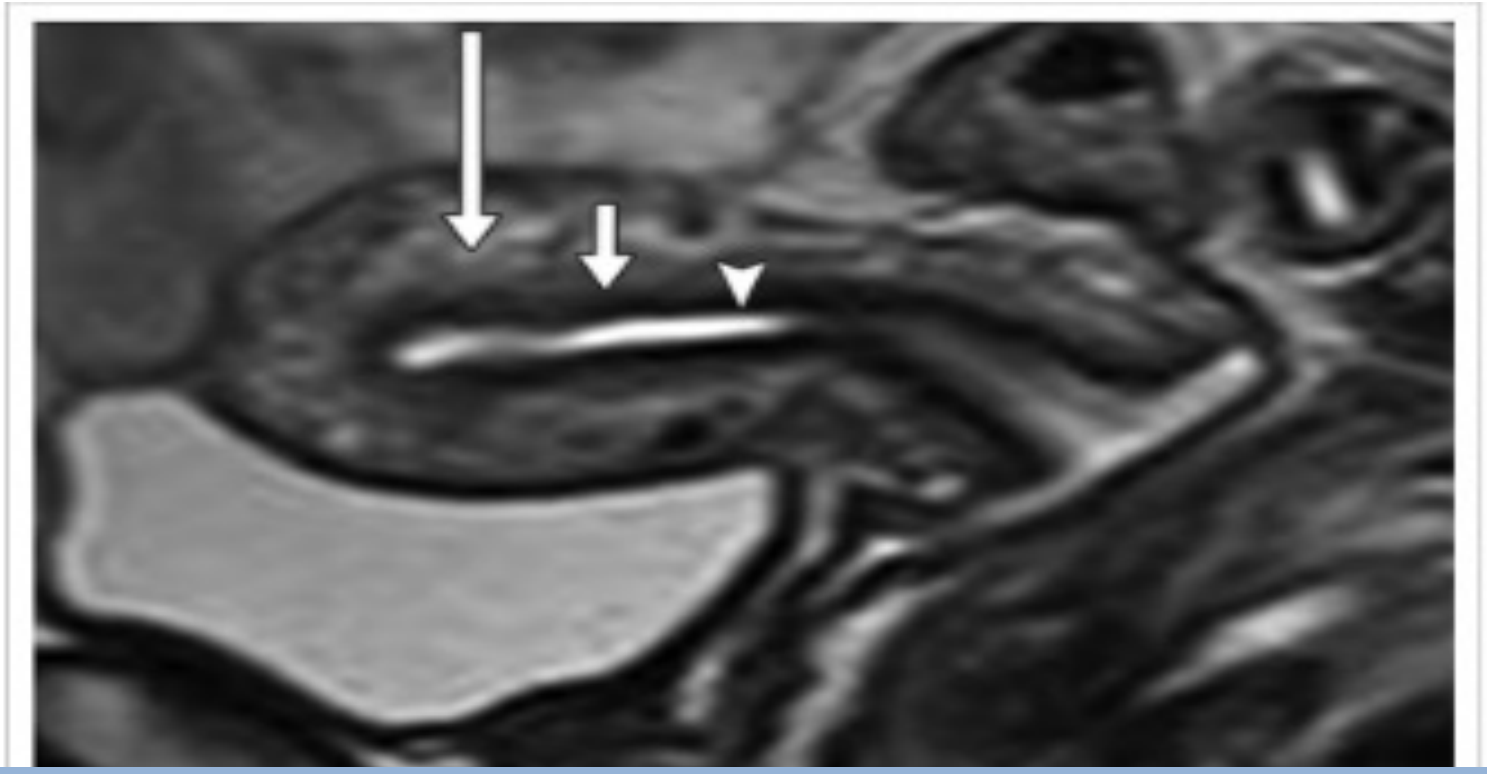


Anechoic cystic lacunae in the posterior uterine wall (arrow) with a heterogenous echo texture.

MRI

- Junctional zone (JZ) is a region representing the inner myometrium and is a very important imaging feature in pelvic MRI for interpretation of various pathologies.
- In its intact state, it is usually visualized as *a low T2 signal layer beneath the endometrium.*
- This low signal intensity is thought to be from *closely packed compact smooth muscle cells with little extracellular matrix and water content*.

MRI-Juctional Zone



Sagittal T2 weighted image of 35 –year-old woman in first part of her menatrual cycle Shows zonal anatomy with endometrium (*arrowhead)* which is hyperdense; junctional zone (*short arrow*) as hypodense band; and outer myometrium (*long arrow*) with intermediate signal.

Significance of JZ : it is disturbed in following conditions:

- **Uterine Adenomyosis**: makes the junctional zone thicker and hazy. JZ of <8 mm is considered unlikely to represent adenomyosis . JZ of >12 mm very likely represents adenomyosis . Other significance include;

1- A feature of myometrial invasion with endometrial cancer.

2- As a feature of myometrial invasion by an invasive mole in the spectrum of gestational trophoblastic disease

3- Uterine lymphoma is not thought to disrupt the JZ.

4- Some research also emphasizes the use of the JZ as a predictor for implantation failure after in vitro fertilization .

(Gordts et al 2018)

DIAGNOSIS-MRI

Magnetic Resonance (MRI):

Assessment of the *thickness of the junctional zone* is the mainstay of diagnosis. The consensus for diagnosis of adenomyosis is when the junctional zone is greater than 12 mm but the disorder can be suspected when the thickness is between 8 and 12 mm.

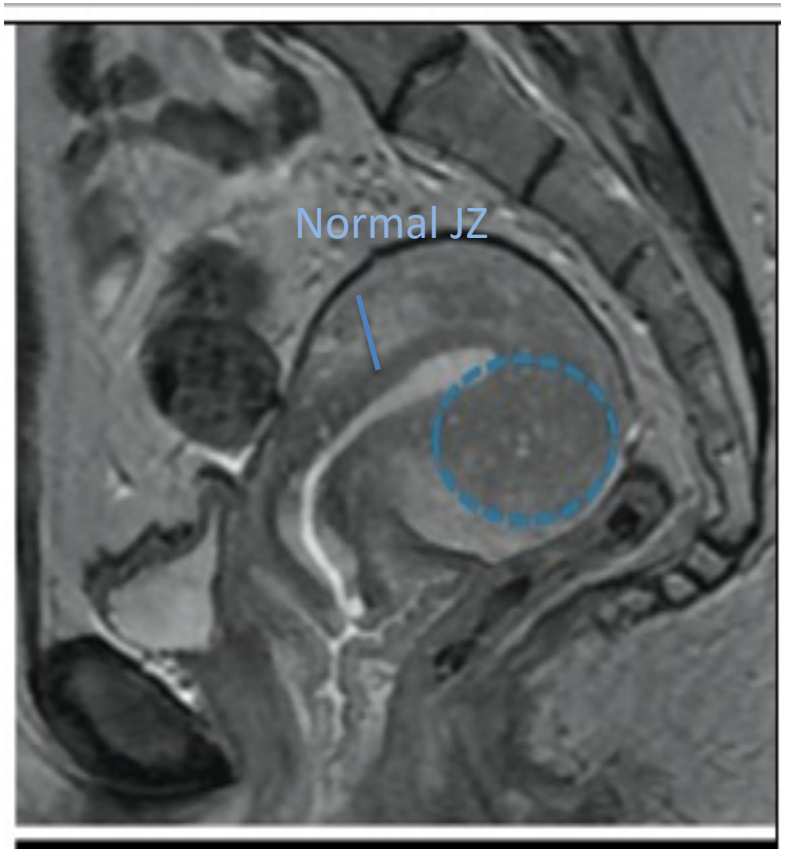
Novellas S et al 2011

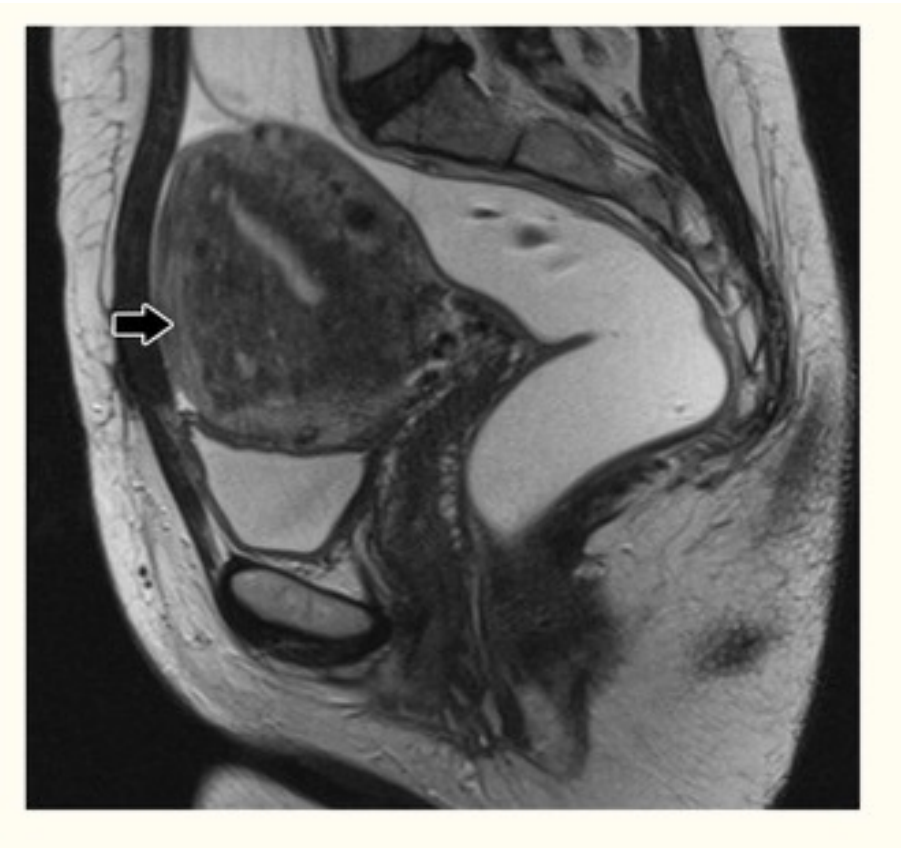
DIAGNOSIS-MRI

1. Focal or diffuse thickening of the JZ.
2. Low signal intensity uterine mass with ill-defined borders.
3. Junctional zone thickness > 12 mm
4. Poor defined JZ borders
5. Localized high signal foci in an area of low signal intensity
6. Linear striations of increased signals radiating out from the endometrium into the myometrium.
7. Bright foci in the endometrium of similar intensity as the myometrium (T1-weighted).
8. Ratio of JZ thickness to myometrium thickness (ratio $_{max}$) >40%.

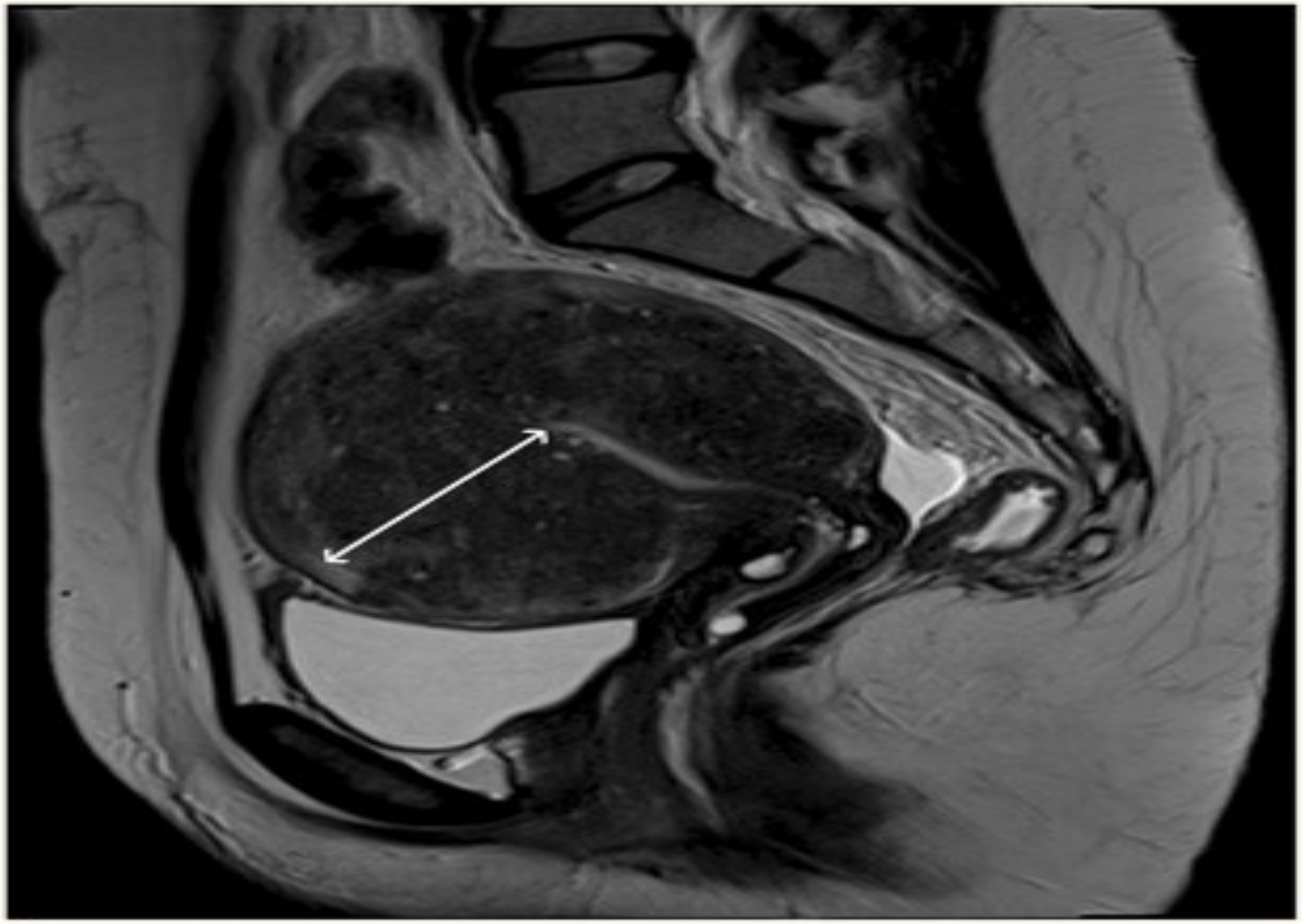
Novellas S et al 2011

DIAGNOSIS-MRI

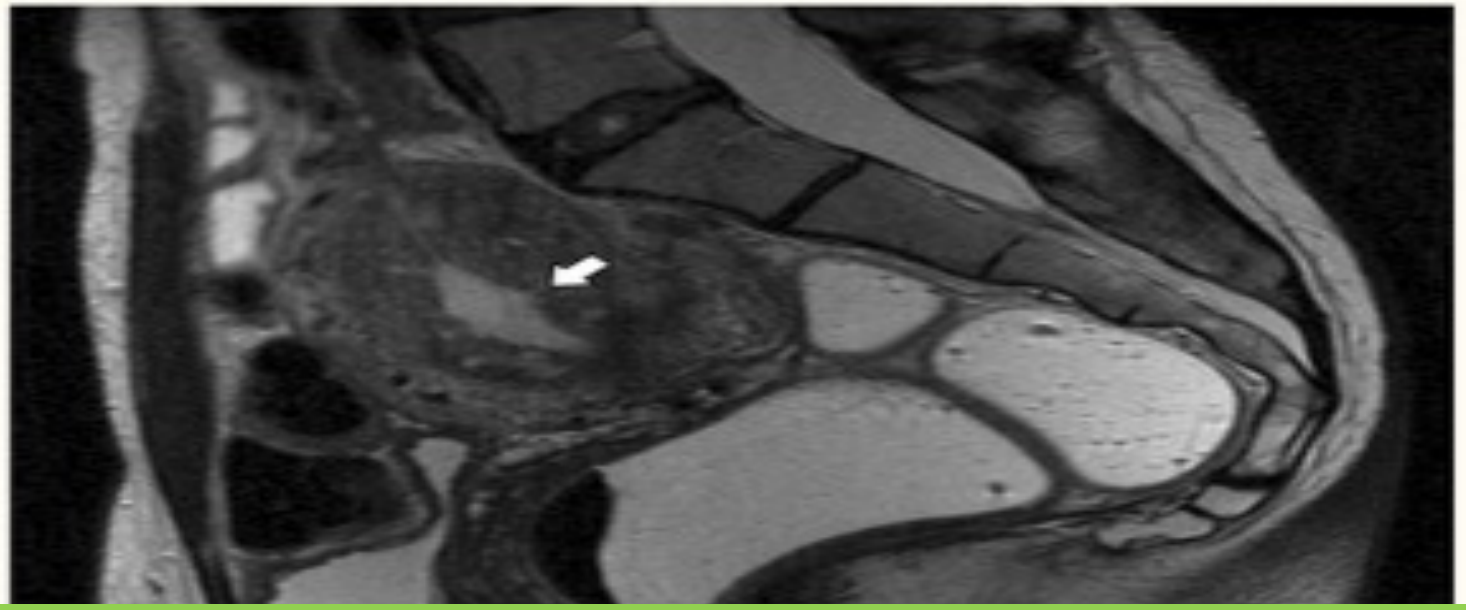




DIAGNOSIS-MRI



DIAGNOSIS-MRI



Pseudo-widening of the endometrium : sagittal T2 weighted images; thickened JZ with striated high signal intensity areas radiating from the endometrium towards the myometrium (white arrow), an appearance that simulates invasion by endometrial carcinoma.

DIAGNOSIS-MRI

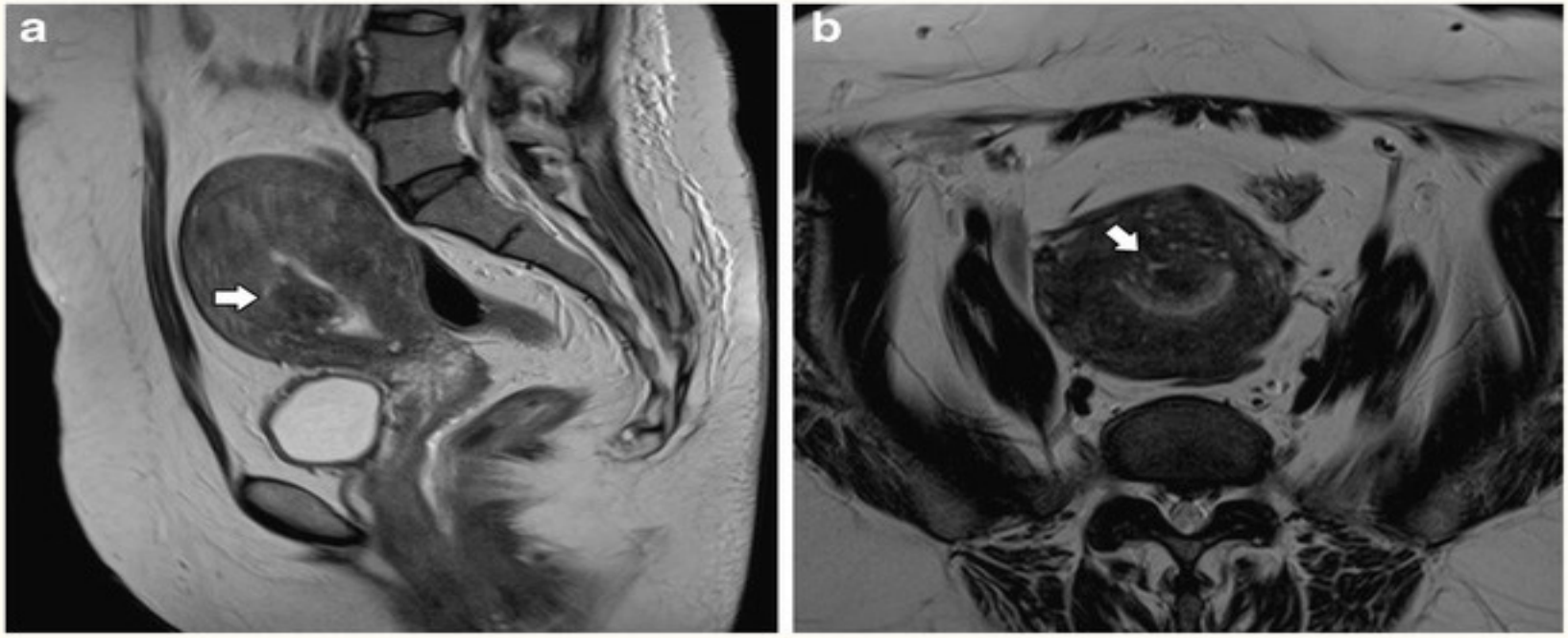


Fig. 8

Polypoid adenomyoma: **a** Sagittal T2- and **b** Axial T2-weighted images; projection of junctional zone into the endometrial cavity with nodular morphology and ill-defined borders (white arrows)

MRI versus ULTRASOUND

- The advantage of MRI ***over*** TVS is that MRI has a greater specificity and can differentiate adenomyomata from leiomyoma.
- When noninvasive diagnosis with MRI and TVS imaging became available, the role of adenomyosis in infertility and early pregnancy was better recognized.

Devlieger R et al, 2003

Diagnosis: Hysteroscopy

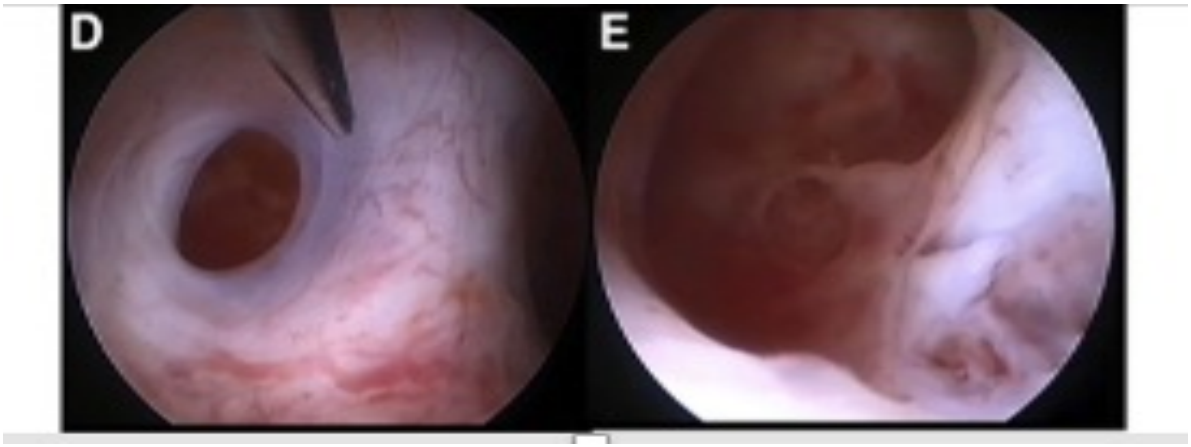
Adenomyotic hysteroscopic images become pathognomic after sub-endometrial exploration: (Gordts et al 2018)

(A) visible endometrial defects on uterine septum;

(B) after incision different cystic structures become visible;

(C) incision of lateral wall of T-uterus reveals the presence of adenomyotic cyst;

Diagnosis: Hysteroscopy

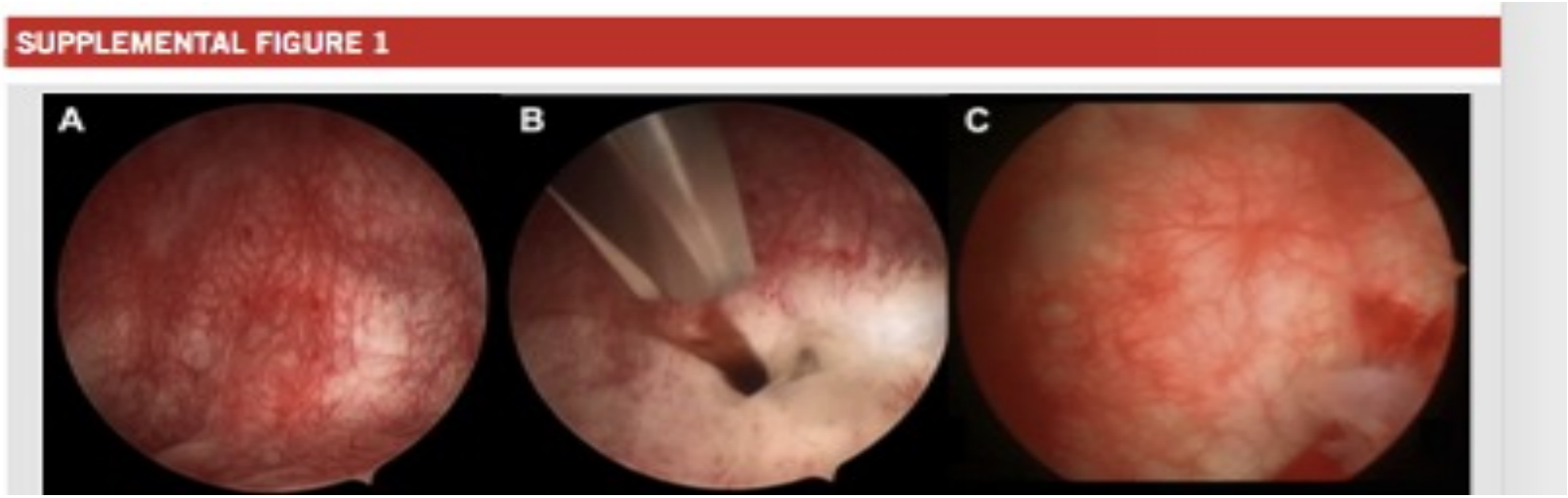


(D) formation of cyst, still small opening is present; and

(E) opening of this defect shows the inner sight of the cyst.

Gordts et al 2018

Hysteroscopy in adenomyosis



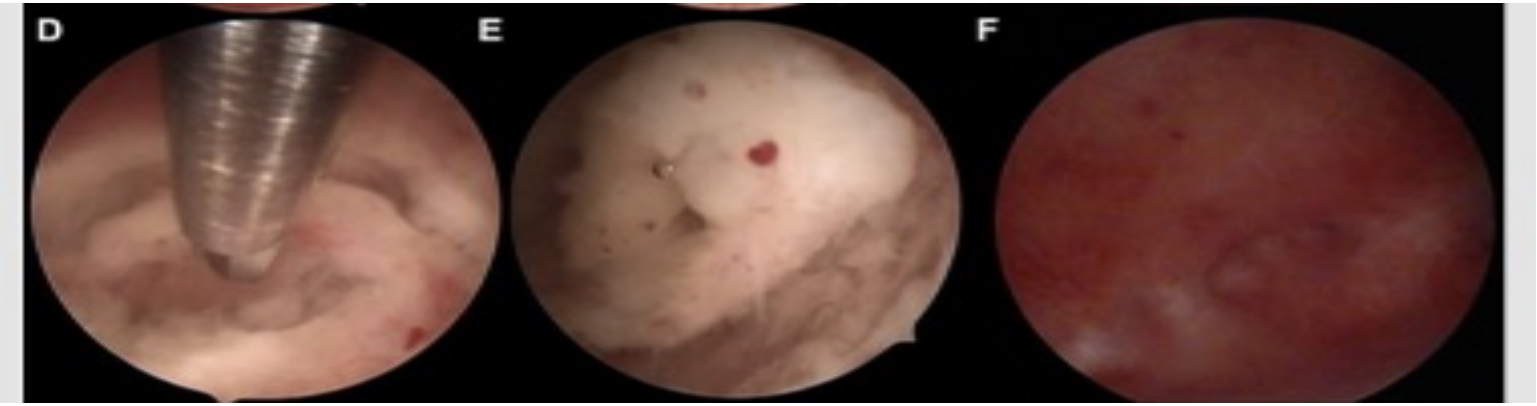
Adenomyosis *(sub-endometrial cystic structures):* [Gordts et al 2018]

(A). by lowering intra-uterine pressure abnormal vascularization and cystic bulging hiding adenomyotic cyst can clearly be identified;

(B) .opening cyst with scissors with outflow of chocolate content;

(C). insight view of adenomyotic cyst;

Hysteroscopy in adenomyosis



Adenomyosis *(sub-endometrial cystic structures):* [Gordts et al 2018]

(D) progressive dissection of cyst with scissors;

(E) view of dissected cyst, arrow showing the opening of initial access with scissors; and

(F) postoperative control after 12 weeks (defect is still visible).

ADENOMYOSIS IN INFERTILITY

- There is a significant association between *pelvic endometriosis and adenomyosis*, with estimates indicating that it occurs in 54% to 90% of cases.
- Because endometriosis is well-known to cause infertility, there is concern that findings of infertility were due to concurrent endometriosis rather than adenomyosis.

Kunz G et al 2005

ADENOMYOSIS IN INFERTILITY

- However, a study in baboons showed a strong association between histological adenomyosis and lifelong infertility (20-fold increased odds) even in cases where coexisting endometriosis was excluded.
- In a study of women who received embryos created through oocyte donation , *rates of miscarriage were significantly higher in those who had adenomyosis alone* versus those with co-existing endometriosis or controls.

Tomassetti C et al 2013

ADENOMYOSIS IN INFERTILITY

- A recent meta-analysis [Younes G, Tulandi T 2017] concluded that *adenomyosis has a detrimental effect on clinical outcomes of in vitro fertilization (IVF)*. In women undergoing IVF, rates of implantation, clinical pregnancy per cycle, clinical pregnancy per embryo transfer, ongoing pregnancy, and live birth among women with adenomyosis were *significantly lower* than in those without adenomyosis.

ADENOMYOSIS IN INFERTILITY

- The miscarriage rate in women with adenomyosis was also higher than in those without adenomyosis. One of the confounding variables in this study was *age*, given that women with adenomyosis were older; however, even after controlling for these confounders using regression analysis, the significant difference still existed.

Younes G, Tulandi T 2017

IMPACT OF ADENOMYOSIS ON INFERTILITY

- Proposed mechanisms of infertility in patients with adenomyosis focus on derangements of three putative pathways:

1- Utero-tubal transport,

2- Endometrial receptivity, and

3-Implantation

Harada T et al 2016

IMPACT OF ADENOMYOSIS ON INFERTILITY

Utero-tubal transport is impaired due to:

1. intrauterine anatomical *distortion that blocks the tubal ostia* and potentially blocks sperm migration and embryo transport.
2. Uterine *hyperperistalsis* has been seen on ultrasound in patients with adenomyosis due to destruction of normal myometrial architecture. These abnormal myometrial contraction waves lead to abnormal sperm transport through the uterine cavity and may also lead to increased intrauterine pressure.

Kissler S et al 2006

IMPACT OF ADENOMYOSIS ON INFERTILITY

Endometrial receptivity and function becomes altered via:

1. increased production of estrogens from aromatization of androgens and altered estrogen receptor/progesterone receptor expression.
2. The inflammatory response in women with adenomyosis has also been shown to be increased.

Tremellen KP , et al 2012

IMPACT OF ADENOMYOSIS ON INFERTILITY

Failed implantation in women with severe adenomyosis may be attributed to:

1. Higher density of macrophages. This increased macrophage density subsequently increases intrauterine inflammatory response and release of reactive oxygen species that are thought to be embryotoxic.
2. impaired implantation results from a lack of adequate expression of adhesion molecules, reduced expression of implantation markers, and altered function of the gene for embryonic development (HOXA10).

Fischer CP , et al 2011

ADENOMYOSIS & OOCYTE FUNCTION

- In contrast to women with endometriosis, adenomyosis has not yet been shown to have an adverse influence on oocyte function or folliculogenesis.
- In patients with endometriosis, levels of activated macrophages, prostaglandins, interleukin (IL)-1β, tumor necrosis factor (TNF)α, and proteases were increased in peritoneal fluid and their high concentrations may adversely affect oocyte function.
- As of yet, there no association has been found between adenomyosis and oocyte quality or function.

Sanchez AM et al 2017

Treatments for Adenomyosis in Infertility

- Treatment with gonadotrophin-releasing hormone agonist **(GnRH-a)** serves to down-regulate the pituitary, exert an anti-proliferative effect, promote apoptosis, and reduce the anti-inflammatory and angiogenesis effect.
- Multiple case reports show conception and live birth in women with infertility and adenomyosis after pretreatment with GnRH-a for 3 to 5 months.
- In other retrospective studies, pretreatment with GnRH-a prior to fresh- or frozen-embryo transfer appears to increase pregnancy rates.

Khan, K.N , et al 2010

Treatments for Adenomyosis in Infertility

- multiple methods of **fertility-sparing surgery** for adenomyosis have been performed, with subsequent pregnancies. These techniques include

1-classical adenomyomectomy,

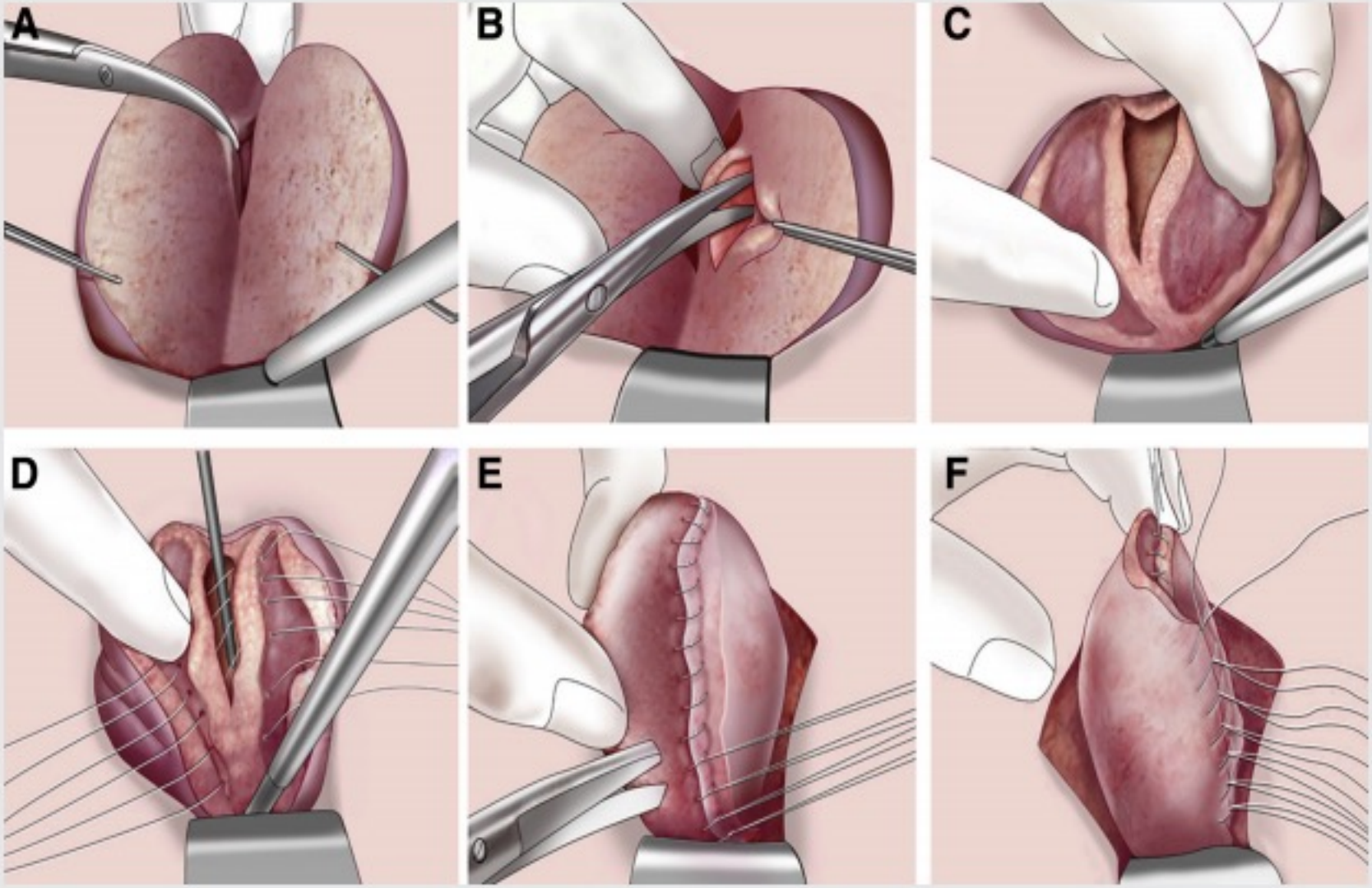
2-H-incision,

3-triple-flap method, and

4-laparoscopic cytoreductive surgery.

Osada H , et al 2011

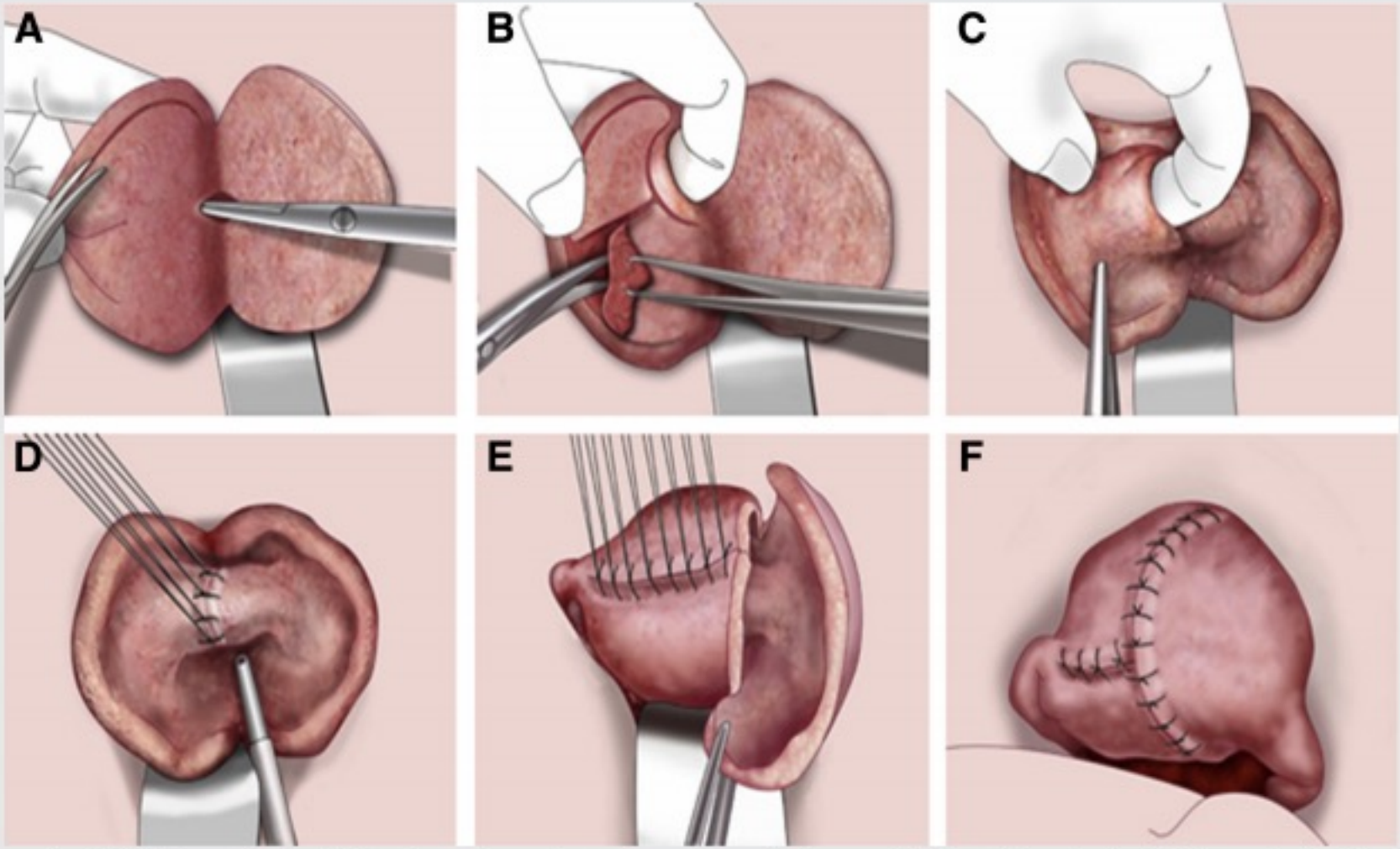
FIGURE 1



Example of Triple-flap method applied to the posterior uterine wall adenomyosis (Adapted from Osada H. Shikyusenkinsho. [Uterine adenomyosis.] In: Osada H. Jissen fujinka fukkukyoka-shujutsu. [Laparoscopy for gynecology: a comprehensive manual and procedure DVD]. Tokyo: Medical View, 2009 [8].).

Osada. Uterine adenomyosis and adenomyoma. Fertil Steril 2018.

FIGURE 2



Example of Triple-flap method applied to the anterior and posterior uterine wall adenomyosis (Adapted from Osada H. Shikyusenkinsho. [Uterine adenomyosis.] In: Osada H. Jissen fujinka fukkukyoka-shujutsu. [Laparoscopy for gynecology: a comprehensive manual and procedure DVD]. Tokyo: Medical View, 2009 [8].).

Osada. Uterine adenomyosis and adenomyoma. Fertil Steril 2018.

Treatment for adenomyosis in infertility

- Surgical management of adenomyomas and adenomyosis can present an operative challenge, especially compared with myomectomy.
- Adenomyomas are less distinct given absence of well-defined borders and given protrusion into the myometrium.
- During dissection, the plane is identified mainly by *recognizing healthy myometrium* rather than simple enucleation as in myomectomies.
- This can lead to increased risk of intraoperative bleeding and weakening of the myometrium, which can increase risk of uterine rupture or abnormal placentation in future.

Treatments for Adenomyosis in Infertility

- Uterine-preserving surgeries have shown benefit for women who have previously experienced IVF treatment failures, especially patients ≤ 39 years old.
- In retrospective studies, conservative surgery or combination surgery with GnRH-a has shown to be more effective in controlling symptoms and also in increasing pregnancy and live birth rates *when compared with GnRH-a alone* in patients with extensive adenomyosis.

Osada H et al 2011

Treatments for Adenomyosis in Infertility

- **HIFU:** High-intensity focused ultrasound ablation (HIFU) has been used for leiomyoma and is now being used for patients with adenomyosis who want fertility.
- HIFU is a *noninvasive thermal ablation technique* in which high-intensity ultrasound energy is focused on a small focal region to increase tissue temperature sufficient to cause irreparable cell damage in the target at a certain depth within the body.

Kishi Y. et al 2014

Treatments for Adenomyosis in Infertility

- **Selection criteria for using HIFU ablation** for adenomyosis vary depending on the center, but very strict selection criteria are required to improve efficacy and decrease risk of thermal injury.
- Patients typically must be age 18 or older,
- premenopausal, have no history of pelvic inflammatory disease or severe pelvic endometriosis,
- symptomatic adenomyosis with junctional zone thickness > 3 cm for diffuse adenomyosis or a lesion diameter between 3 and 10 cm for focal adenomyosis.

Xiong Y . Et al 2015

Treatments for Adenomyosis in Infertility

- A recent retrospective study showed high rates of conception and live birth in HIFU-treated patients with adenomyosis, suggesting that it is a promising noninvasive fertility-sparing treatment option.
- In another study, pregnancies after HIFU resulted in 2 miscarriages and delivery of 4 healthy babies. One delivery was complicated by a major placenta previa and hemorrhage.

Zhou M . Et al 2011

Malignant transformation of adenomyosis

- The malignant transformation of adenomyosis is thought to be due to its *endometrial epithelium transition to monolayer tumor cells before malignant transformation, which eventually develops to varying degrees of cancer.* However, the specific molecular mechanism of adenomyosis is not yet clear.

Yuan H & Zhang S 2019

- .

Malignant transformation of adenomyosis

- Because of its low incidence of malignant transformation, lack of large-sample, multi-center clinical trials, and large heterogeneity of the existing research, the evidence based on the high-risk factors of malignant transformation of adenomyosis is **weak.**

Yuan H & Zhang S 2019

Thank you