



Review imaging diagnosis of adenomyosis
how this impacts therapy

Discuss new investigation in adenomyosis
how it changes our conception of the
disease

Discuss medical therapies for adenomyosis

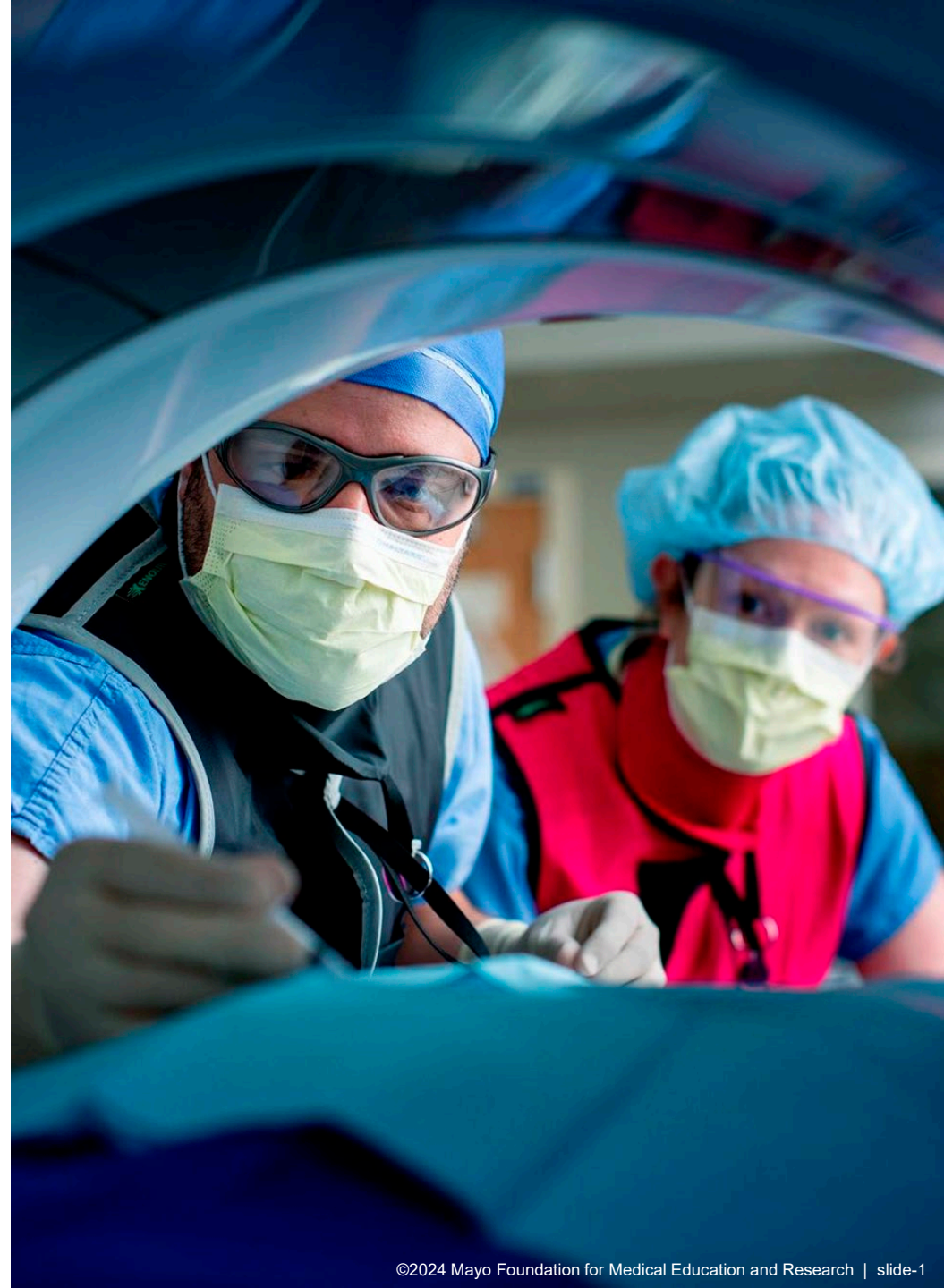
Review surgical and interventional therapies

ADENOMYOSIS

CURRENT AND FUTURE TREATMENTS

Elizabeth A. (Ebbie) Stewart M.D.

Society for Reproductive Investigation
March 17, 2022 Denver CO



DISCLOSURES (24 MONTHS)

- **Consulting Fee (e.g., Advisory Board):**
Analyn, AbbVie

LEARNING OBJECTIVES

- To review imaging diagnosis of adenomyosis and how this impacts therapy
- To discuss new investigation in adenomyosis and how it changes our conception of the disease
- To discuss medical therapies for adenomyosis
- To review surgical and interventional therapies



1

**IMAGING GIVES US AN
ALTERNATE WAY TO DIAGNOSE
ADENOMYOSIS**

Adenomyosis is like Weeds: Once you start looking, it is everywhere

IN THE GARDEN

The Dirty Secret About Weeding

The most experienced gardeners know that you just have to keep doing it. They know something else, too: It's easier if you can identify the enemy.

NY Times May 8, 2020



Image based diagnosis changes everything

If we require surgical diagnosis, it will be difficult to understand the role of adenomyosis in:

- Young women with chronic pelvic pain
- Infertility
- Recurrent pregnancy loss
- Recurrent implantation failure

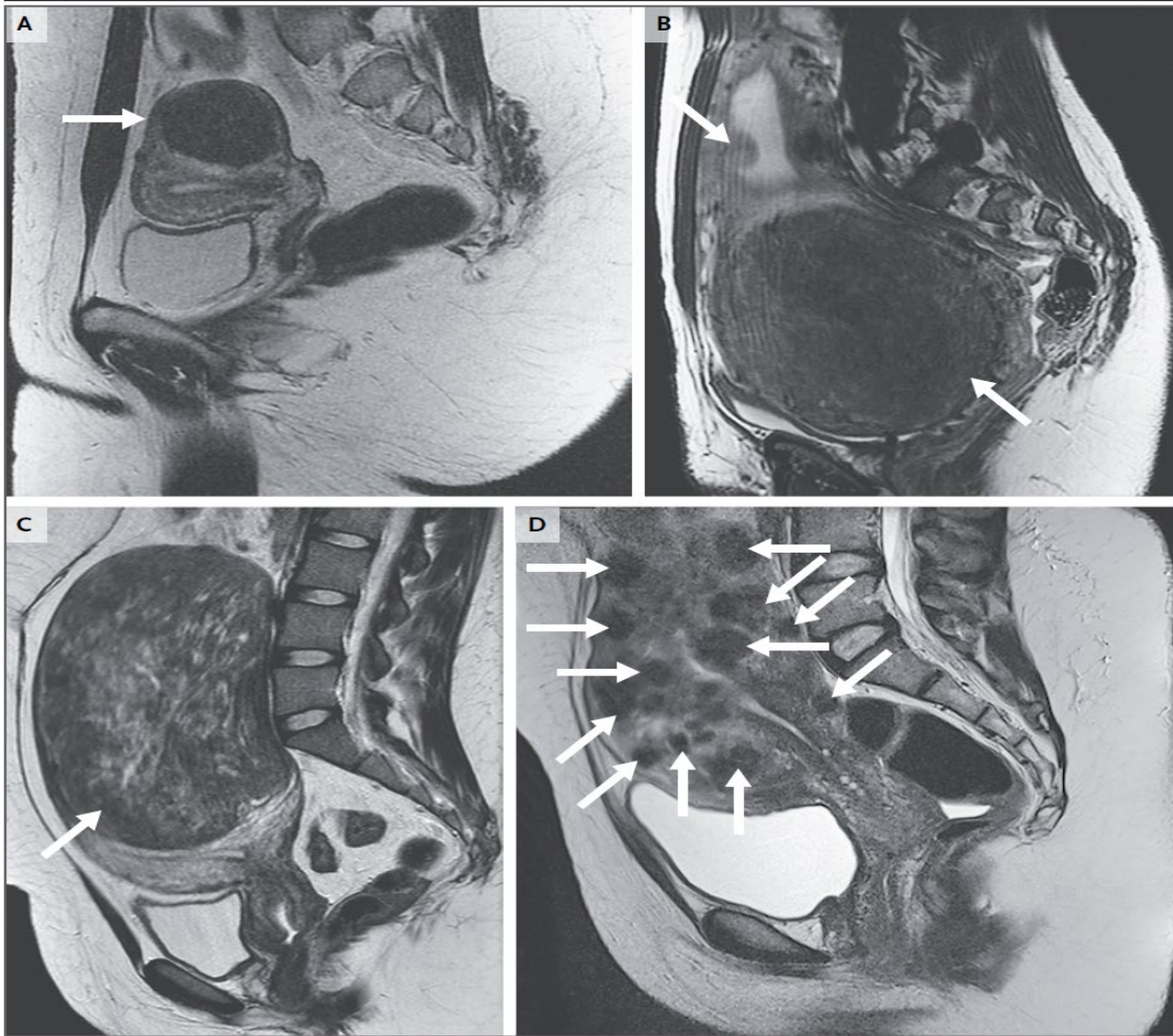


Figure 1. Magnetic Resonance Images of Fibroids.

Stewart E.A.: NEJM 372:17 1646-55, 2015

We don't say that any of these women have "presumed fibroids." We say they have uterine fibroids and proceed to treat them in a variety of ways knowing that in a small number of cases there will be other pathology.

Why can't we adopt the same approach to adenomyosis?

MUSA CRITERIA FOR ADENOMYOSIS

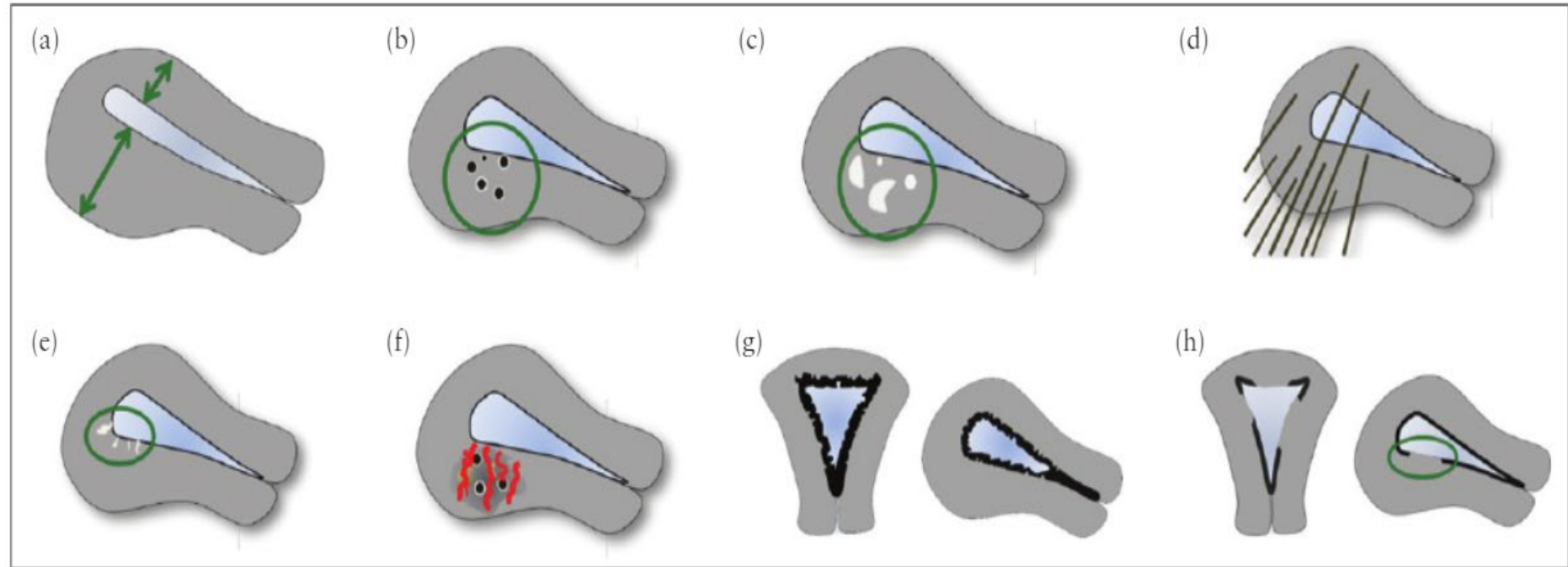
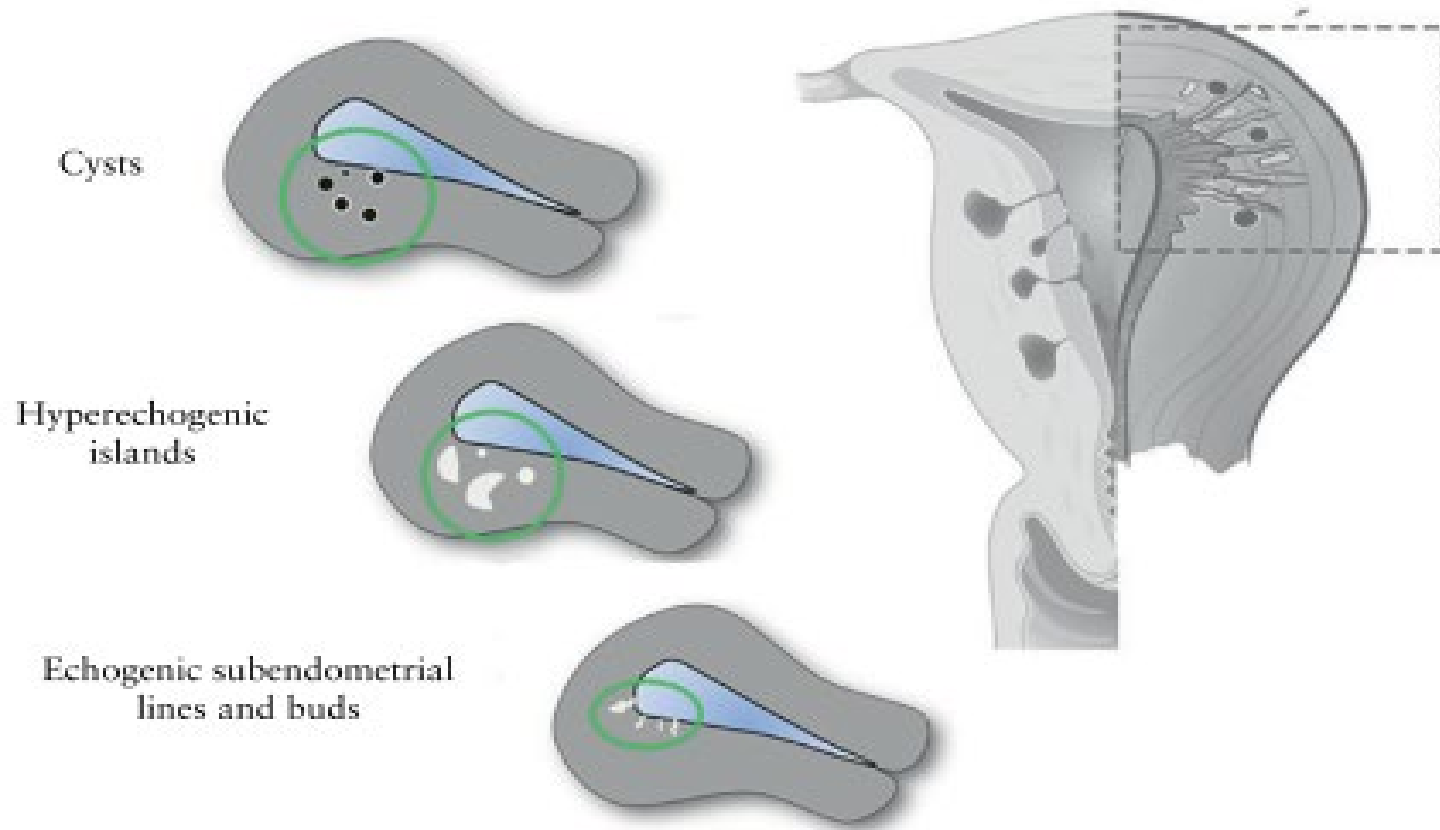


Figure 10 Schematic drawings illustrating the ultrasound features considered currently to be typical of adenomyosis: asymmetrical thickening (a), cysts (b), hyperechoic islands (c), fan-shaped shadowing (d), echogenic subendometrial lines and buds (e), translesional vascularity (f), irregular junctional zone (g) and interrupted junctional zone (h).

Van den Bosch *et al.* US Obs Gyn 46: 284-98 2015

Direct features



Indirect features

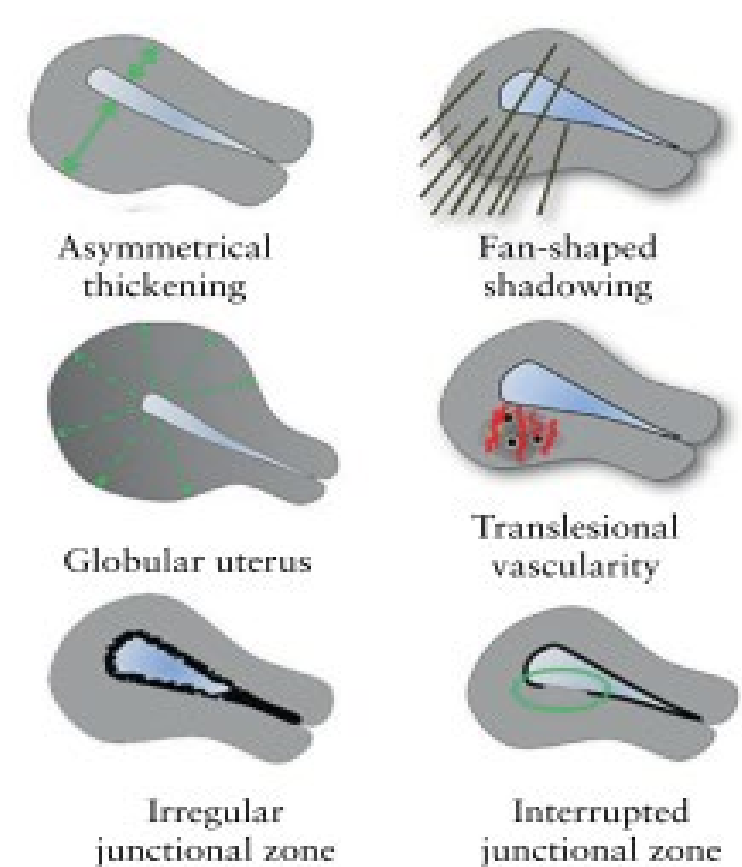
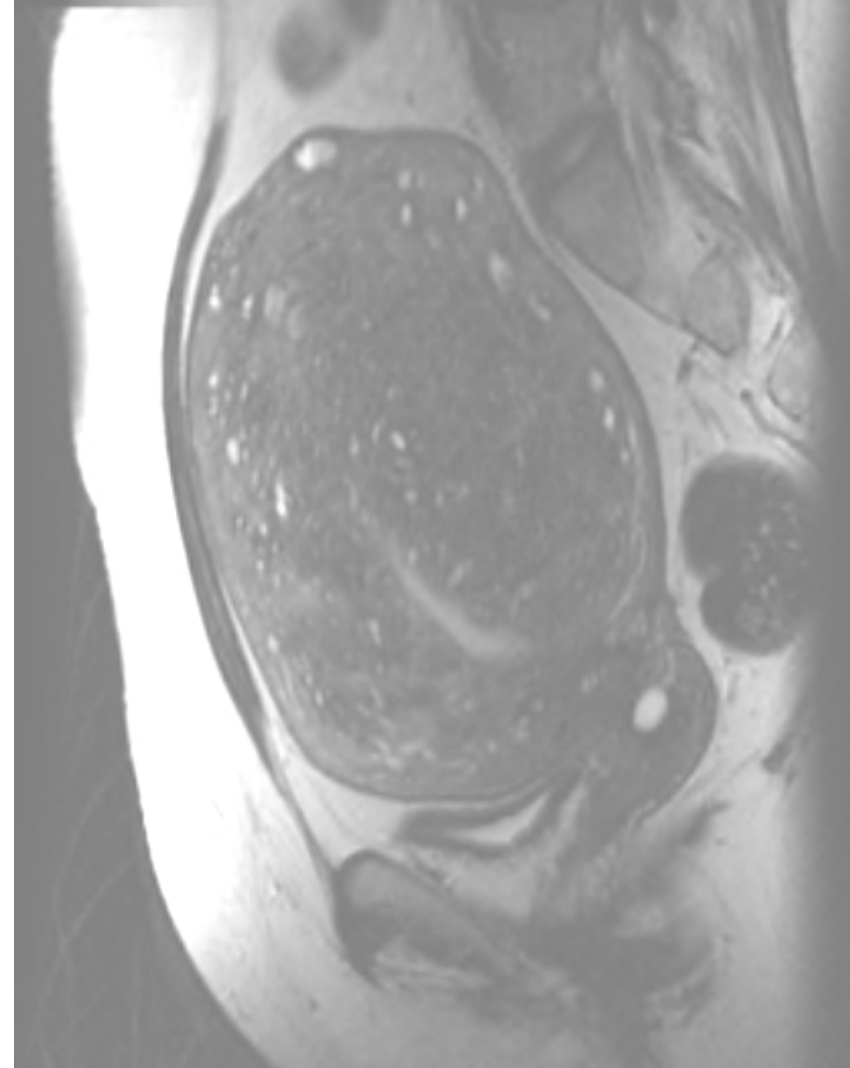


Figure 5 Schematic representation of direct and indirect Morphological Uterus Sonographic Assessment (MUSA) features of uterine adenomyosis (not endometriosis), according to modified Delphi procedure. Adapted from Van den Bosch *et al.*⁶.

Harmsen *et al.* US Obs Gyn 60: 118-31 2022

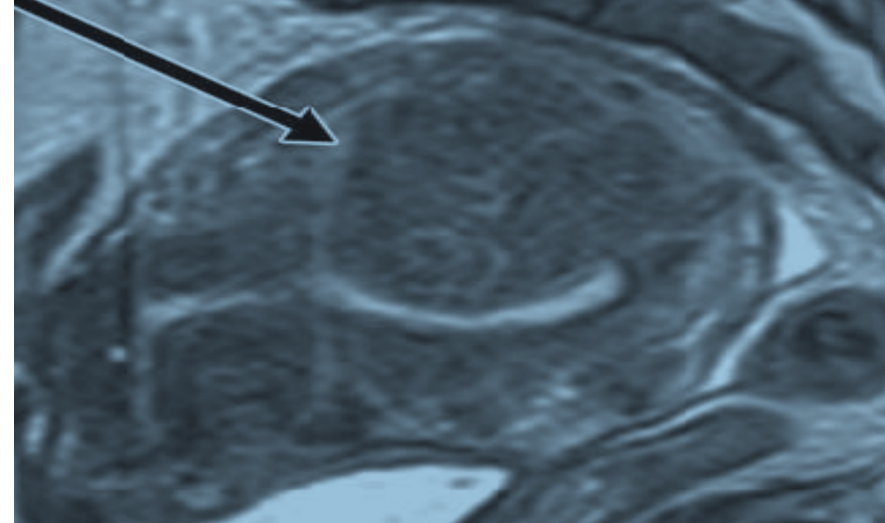
MYOMETRIAL IMAGING: CHARACTERISTICS OF ADENOMYOSIS

- Global uterine enlargement
- Cystic spaces in myometrium
- Asymmetric wall thickening
- Heterogeneity
- Obscuring of endometrial/ myometrial border

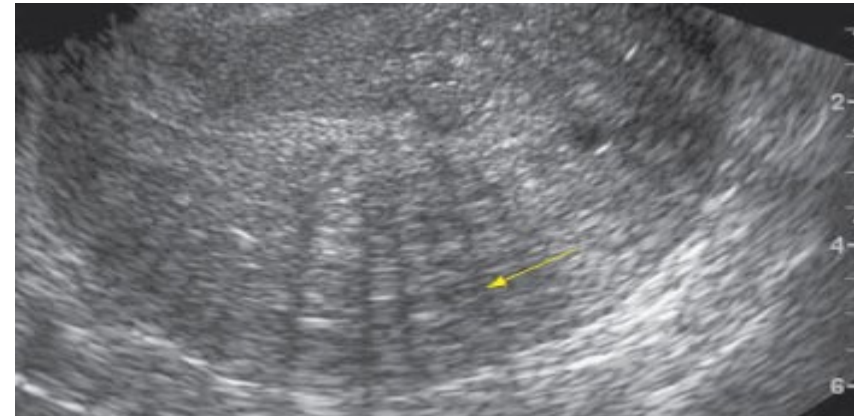


OTHER IMAGING CHARACTERISTICS OF ADENOMYOSIS

- Thickening of junctional zone



- Subendometrial linear striations





2

NEW INVESTIGATION

ADENOMYOSIS: SYMPTOMS

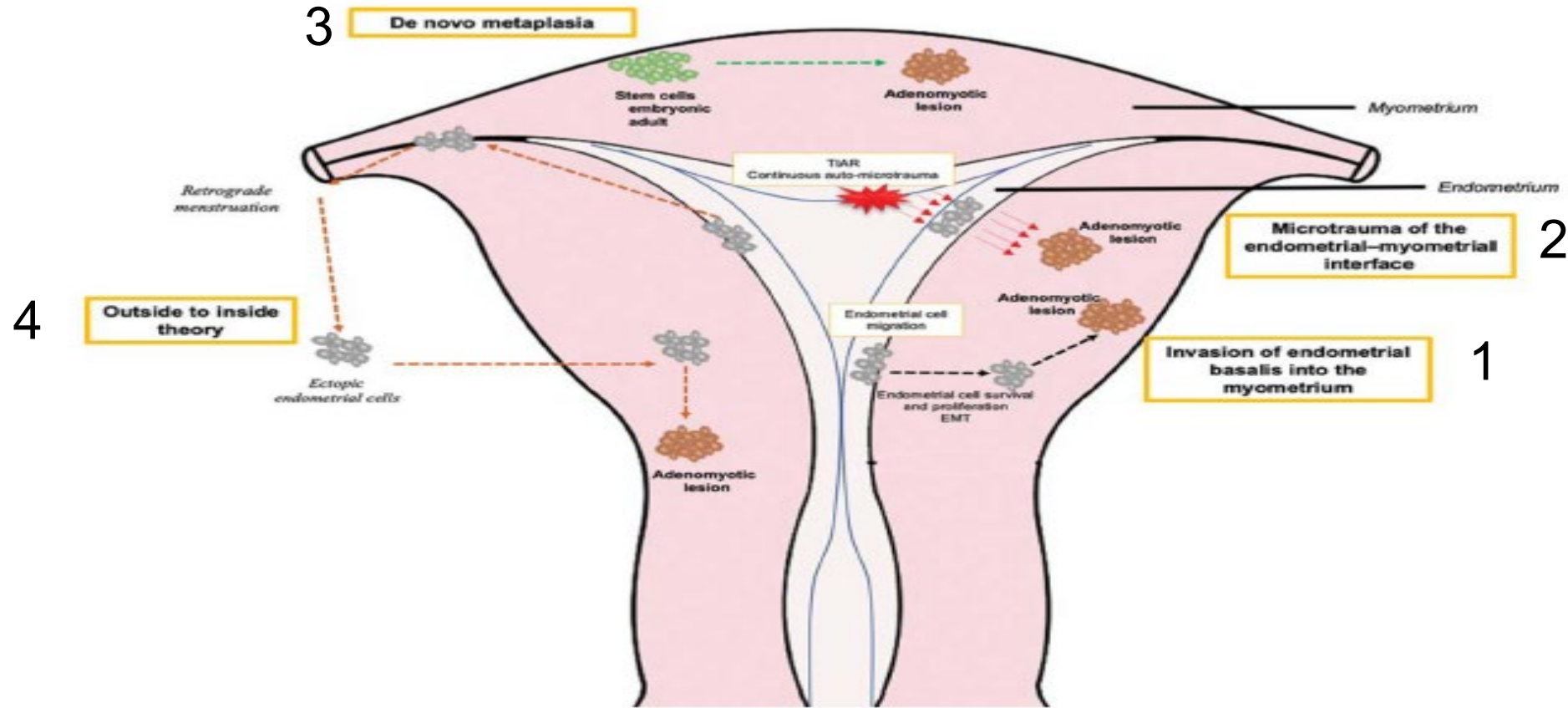
- Heavy Menstrual Bleeding
- Pelvic Pain
- Possible Fertility Impairment

ADENOMYOSIS: CLASSIC RISK FACTORS

- Parity
- Uterine Surgeries

If adenomyosis is only diagnosed by hysterectomy, are we just describing the group of women willing to undergo hysterectomy?

THEORIES OF MECHANISMS OF ADENOMYOSIS



Zhai et al. Semin Repro Med 2020: 38:129-143

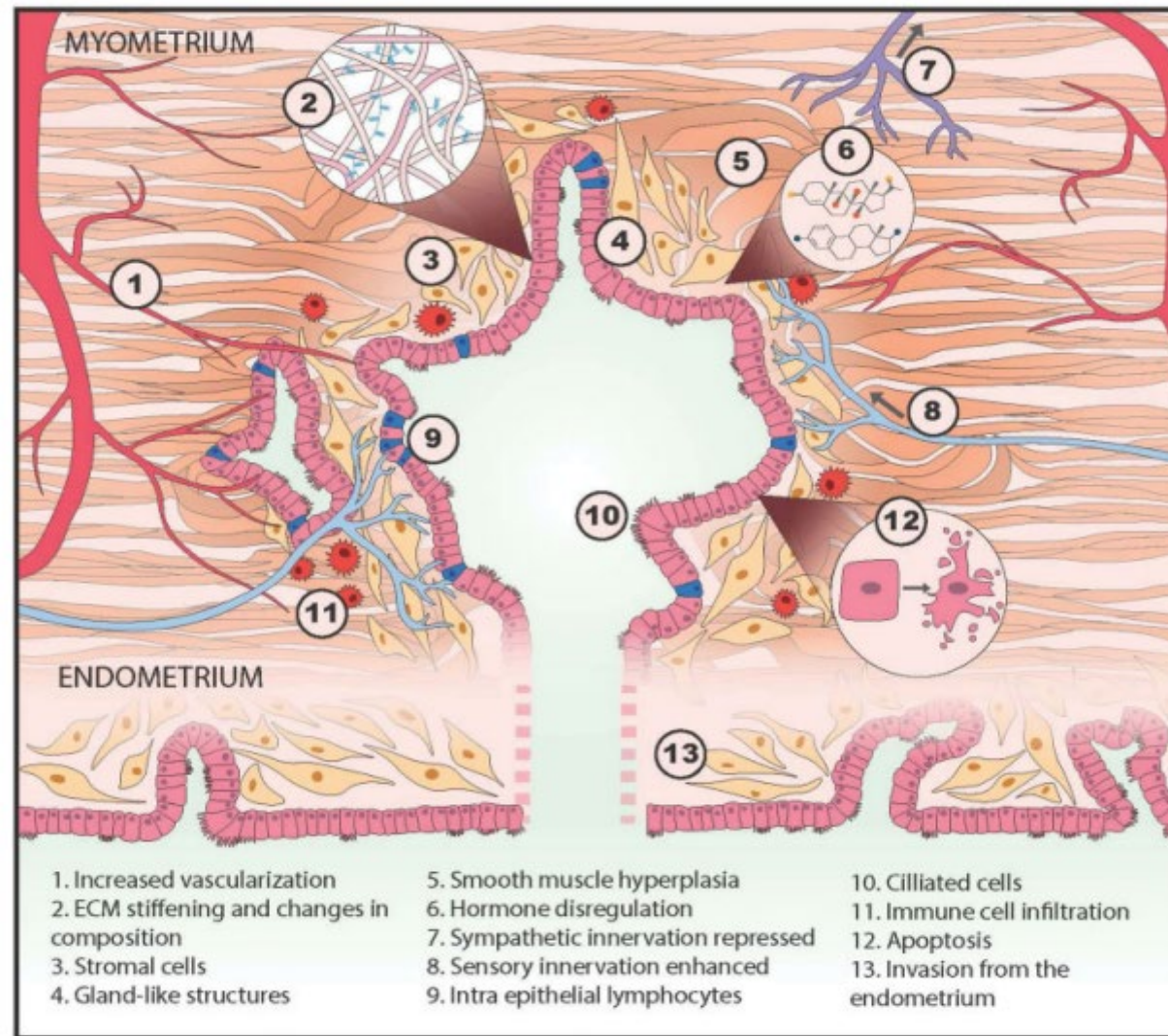


Fig. 2 Conceptualization of an adenomyosis lesion, showing the biological components and pathological processes to consider in building an in vitro model.



2

MEDICAL THERAPIES FOR ADENOMYOSIS

CAVEATS RELEVANT TO THERAPY

- There are few high-quality studies of adenomyosis
- Of studies of adenomyosis, many participants have long-standing disease that may be more resistant to therapy
- Much data comes from studies of other diseases where concomitant adenomyosis is not an exclusion
- There is little phenotyping of adenomyosis

WE NEED CLINICAL TRIALS FOR ADENOMYOSIS

Hormonal Therapies Especially the Levonorgestrel IUDs are Effective for HMB and Pain



Contraceptive Steroids, PRMs and GnRH analogs are all effective treatments for Bleeding and Pain

Table 1 Summary of efficacy of medical treatments for adenomyosis

Class of agent	HMB	PM or PP	Fertility	General comments
Treatments that modulate gonadal steroids				
Contraceptive steroids	LNG-IUS most effective, PBAC score reduced in all patients to <100, amenorrhea rate 25% ^{10,13}	LNG-IUS most effective, 45–77.4% reduction in mean VAS ^{9–14}	No available efficacy data	Also provides contraception
Aromatase inhibitors	Subjective improvement in 60% of those with HMB ²³	Subjective improvement in 57.1% with PM and 83.3% with PP ²³	No available efficacy data	
Progesterone receptor modulators	Reduction from “heavy” PBAC to “controlled” PBAC in 90.2% ²⁶	56–92% reduction in mean VAS ^{26,28}	No available efficacy data	Not available currently in the United States and treatment halted in rest of the world as of this writing
Gonadotropin-releasing hormone receptor analogs	Subjective improvement in 100% of those with HMB and amenorrhea rate of 94.4% ¹⁸	52–100% reduction in mean VAS ^{18,34,35}	26.7% spontaneous pregnancy rate after treatment ³⁹	Current data primarily on depot formulations, new studies underway for oral agents
Other therapeutic agents				
Dopamine agonists	33% reduction in mean PBAC ⁴⁹	50% reduction in mean VAS ⁴⁹	No available efficacy data	
Oxytocin antagonists	No available efficacy data	No available efficacy data	No available efficacy data	

Abbreviations: HMB, heavy menstrual bleeding; LNG-IUS, levonorgestrel-releasing intrauterine system; PBAC, pictorial bleeding assessment calculator; PM, painful menses; PP, pelvic pain; VAS, visual analog scale.

PAIN IMPROVED IN RCT OF DINOGEST

Demographic and efficacy data (full analysis set).

Characteristic	Dienogest (n = 34)	Placebo (n = 33)	P value
Age (y) ^a	37.3 ± 7.9	37.4 ± 6.6	.816
Weight (kg) ^a	56.9 ± 7.7	54.2 ± 7.1	.132
BMI (kg/m ²) ^a	22.2 ± 3.2	21.4 ± 2.4	.415
Menstrual cycle length (d) ^a	28.4 ± 4.1	28.1 ± 4.7	.835
Hemoglobin level (g/dL)			
Baseline ^a	12.8 ± 1.3	12.3 ± 1.6	.177
At EOT	13.2 ± 0.7	12.8 ± 1.4	
Number of partus ^a	1.2 ± 1.2	1.2 ± 1.1	.845
Pain score			
Baseline ^a	4.6 ± 1.1	4.8 ± 1.0	.298
Change at 16 wk ^b	-3.8 ± 1.9	-1.4 ± 1.8	<.001
Pain severity score			
Baseline ^a	2.4 ± 0.5	2.5 ± 0.5	.397
Change at 16 wk ^b	-1.9 ± 1.0	-0.6 ± 0.8	<.001
Analgesics usage score			
Baseline ^a	2.1 ± 1.0	2.3 ± 0.8	.470
Change at 16 wk ^b	-1.9 ± 1.2	-0.8 ± 1.3	<.001
Visual analogue scale (mm)			
Baseline ^a	66.3 ± 19.1	69.0 ± 20.6	.518
Change at 16 wk ^b	-58.4 ± 23.6	-20.6 ± 23.6	<.001
Uterine size			
Baseline (cm ³) ^a	96.5 ± 60.3	93.3 ± 68.3	.749
Reduction at EOT (%) ^b	20.0 ± 28.8	9.6 ± 23.0	.103

Osuga *et al.* Fert Steril 108: 673-8, 2017

Contraceptive Steroids, PRMs and GnRH analogs are all effective treatments for Bleeding and Pain

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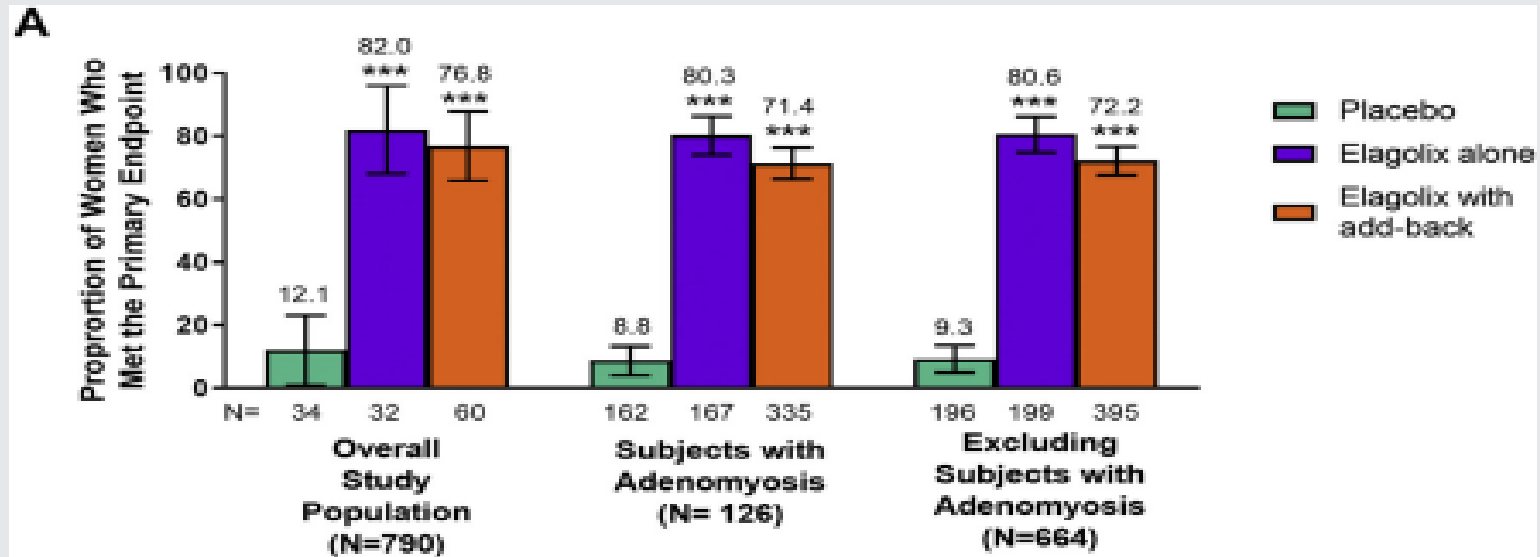
Abbreviations: HMB, heavy menstrual bleeding; LNG-IUS, levonorgestrel-releasing intrauterine system; PBAC, pictorial bleeding assessment calculator; PM, painful menses; PP, pelvic pain; VAS, visual analog scale.

FDA APPROVAL OF ORAL GNRH ANTAGONISTS COMBINATION THERAPY FOR TREATMENT OF FIBROID-RELATED HMB

- Elagolix 300 mg/Estradiol 1 mg/ NETA 0.5 mg q AM and elagolix 300 q PM -Approved May 2020
- Relugolix 40 mg/Estradiol 1 mg/ NETA 0.5 mg qd -Approved May 2021

CONCOMITANT ADENOMYOSIS DOES NOT DECREASE EFFICACY FOR HMB OF ELAGOLIX

FIGURE 1



Odds Ratios (95% CI) for Women Who Met the Primary Endpoint

	Subjects with Adenomyosis	Excluding Subjects with Adenomyosis
Elagolix alone	33.7 (8.0, 139.9)	43.1 (21.5, 86.7)
Elagolix with Add-back	24.4 (7.2, 82.2)	26.3 (14.0, 49.4)

PROLACTIN AND UTERUS

- Animal model of adenomyosis with pituitary graft
- Both ligand and receptor in human uterus
- PRL acts as smooth muscle mitogen
- Regulation of uterine prolactin with Ru486 and gonadotropins

TWO MULTIVARIATE MODELS FOR ADENOMYOSIS VS. FIBROIDS SUGGEST LINKAGE TO PROLACTIN

	Model 1: Symptoms OR (95% CI)	Model 2: Uterine weight >150 g OR (95% CI)
Age	1.4 (1.02–1.9)	0.9 (0.4–1.7)
History of Depression	3.3 (1.7–6.4)	3.8 (1.2–12.2)
History of Endometriosis	2.8 (0.8–10.1)	8.8 (1.4–56.1)
History of Uterine Surgery	1.4 (0.7–2.6)	0.7 (0.2–2.1)
Pelvic Pain	2.8 (1.4–5.6)	2.3 (0.7–7.6)

Taran *et al.* Fertil Steril 94: 1223-8, 2010

MENSTRUAL BLEEDING, PAIN AND QOL IMPROVES WITH VAGINAL BROMOCRIPTINE: PILOT STUDY

	Baseline	3 Mo	6 Mo	9 Mo (3 Mo after Rx)
PBLAC	349 (292- 645)	264* (181-324)	242* (76-384)	233* (149- 515)
AMCOQ	51 (40-61)	38* (25-52)	35* (21-48)	35* (24-47)
VAS	5 (4, 8.3)	3* (1.6, 4)	2.2* (0.4, 6.3)	2.5 * (0.4, 5)
UFS-QOL SSS	60 (44, 72)	44* (19, 59)	44* (28, 59)	44 * (25, 56)
UFS-QOL HR	57*	72*	66*	72*
QOL Total	(37, 63)	(45, 88)	(52, 85)	(51, 85)

Andersson *et al.* Acta ObGyn Scand 2019.10:1341-50

Full length article

Vaginal bromocriptine for treatment of adenomyosis: Impact on magnetic resonance imaging and transvaginal ultrasound

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^b Department of Abdominal Radiology, Karolinska University Hospital, Stockholm, Sweden

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^d Department of Clinical Science and Education Karolinska Institutet, and Department of Obstetrics and Gynecology, Sodersjukhuset, Stockholm, Sweden

^e Division of Reproductive Endocrinology and Infertility, Department of Obstetrics & Gynecology, Mayo Clinic, Rochester, MN, USA

^f Department of Women's and Children's Health, Karolinska Institutet, and Karolinska University Hospital, Stockholm, Sweden

2020.254:38-43

Significant decrease in junctional zone thickness and wall symmetry following bromocriptine therapy

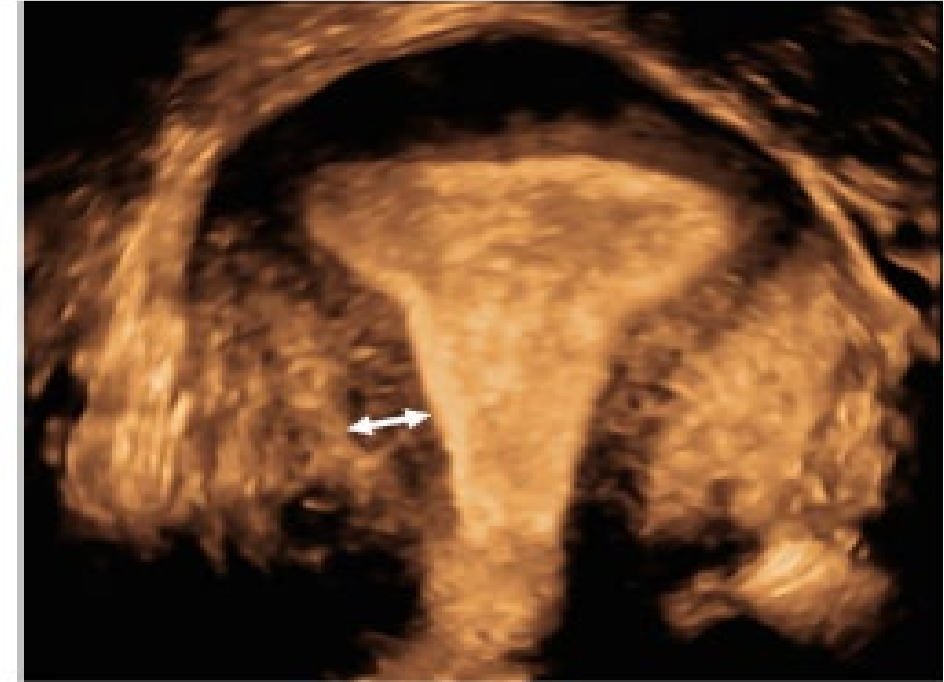


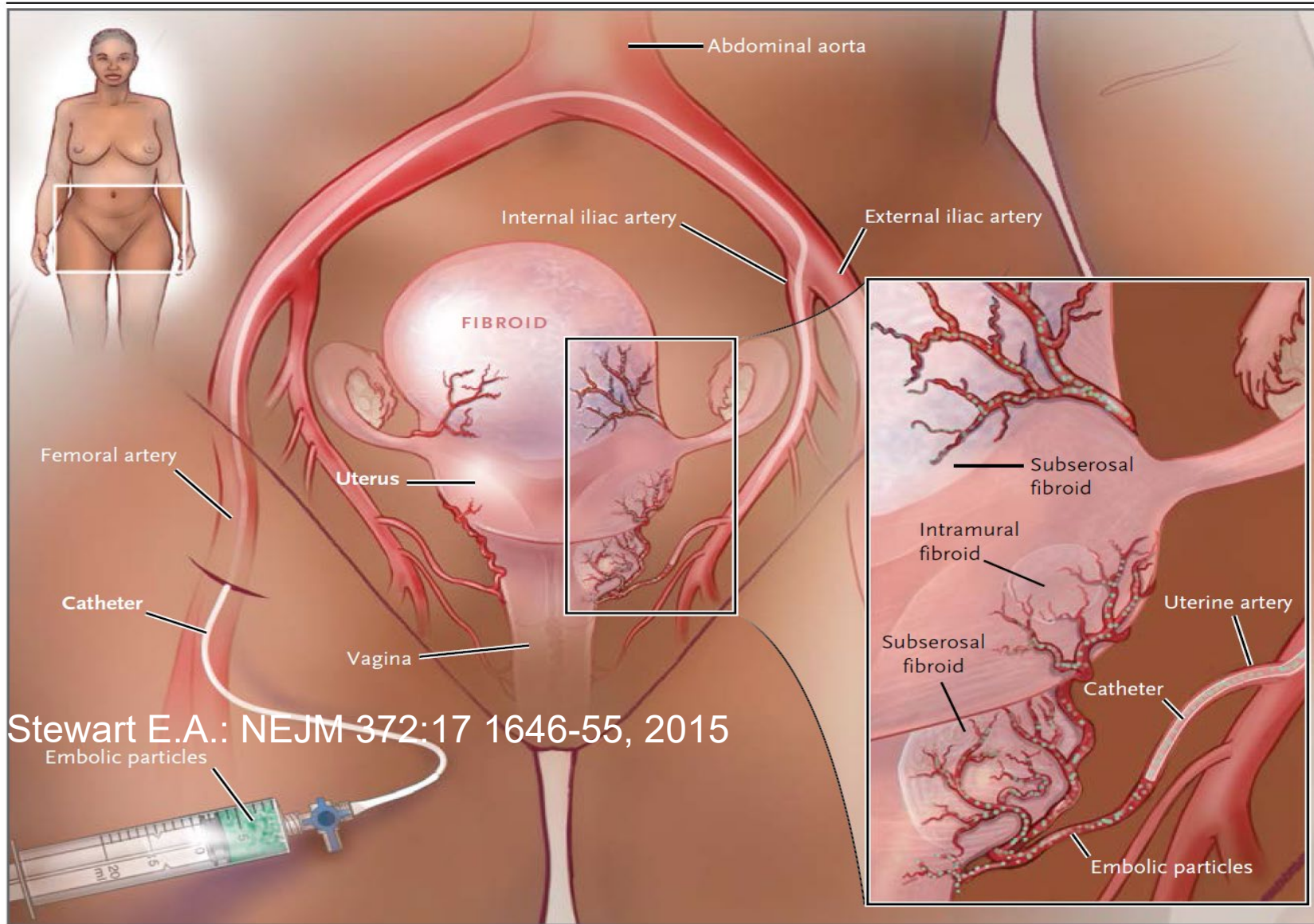
Fig. 4. Measurement of 3 D Junctional Zone.



3

SURGICAL AND INTERVENTIONAL THERAPIES FOR ADENOMYOSIS

UTERINE ARTERY EMBOLIZATION



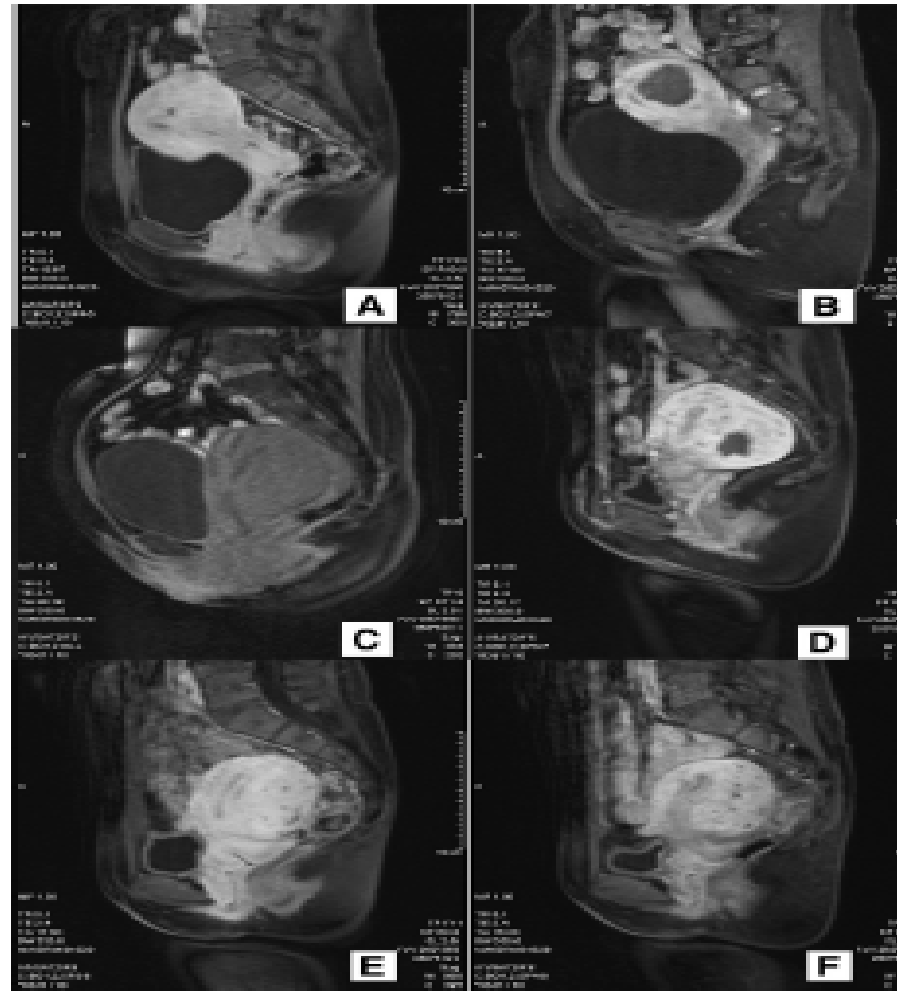
UTERINE ARTERY EMBOLIZATION FOR ADENOMYOSIS: OUTCOMES AT 5 YEARS

- 264 women treated, 195 followed for 5 years
- 70% women had improved painful menses and heavy menses
- Improvement greatest when there were hypervascular lesions

Zhou *et al.* PLoS One, 11 (11)2016

FIGURE 1

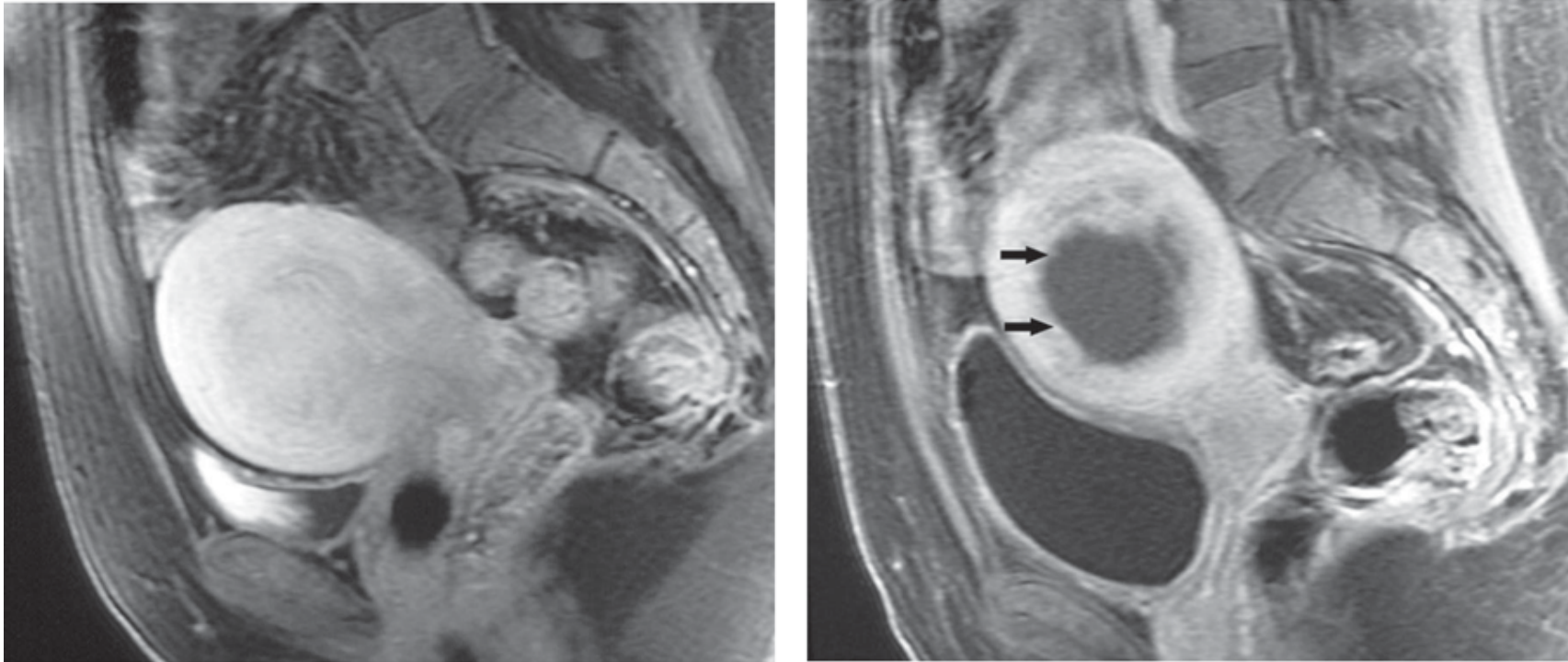
Sagittal T1-weighted gadolinium-enhanced magnetic resonance images of the patient's pelvis. (A) Before treatment. (B) Three months after treatment, showing a non-perfused region over 50% of the lesion. (C) Before treatment. (D) Three months after treatment, showing a non-perfused region below 50% of the lesion. (E) Before treatment. (F) Three months after treatment; no significant non-perfused region showing.



Reprinted with permission from the copyright holder. *Fert Steril* 2011.

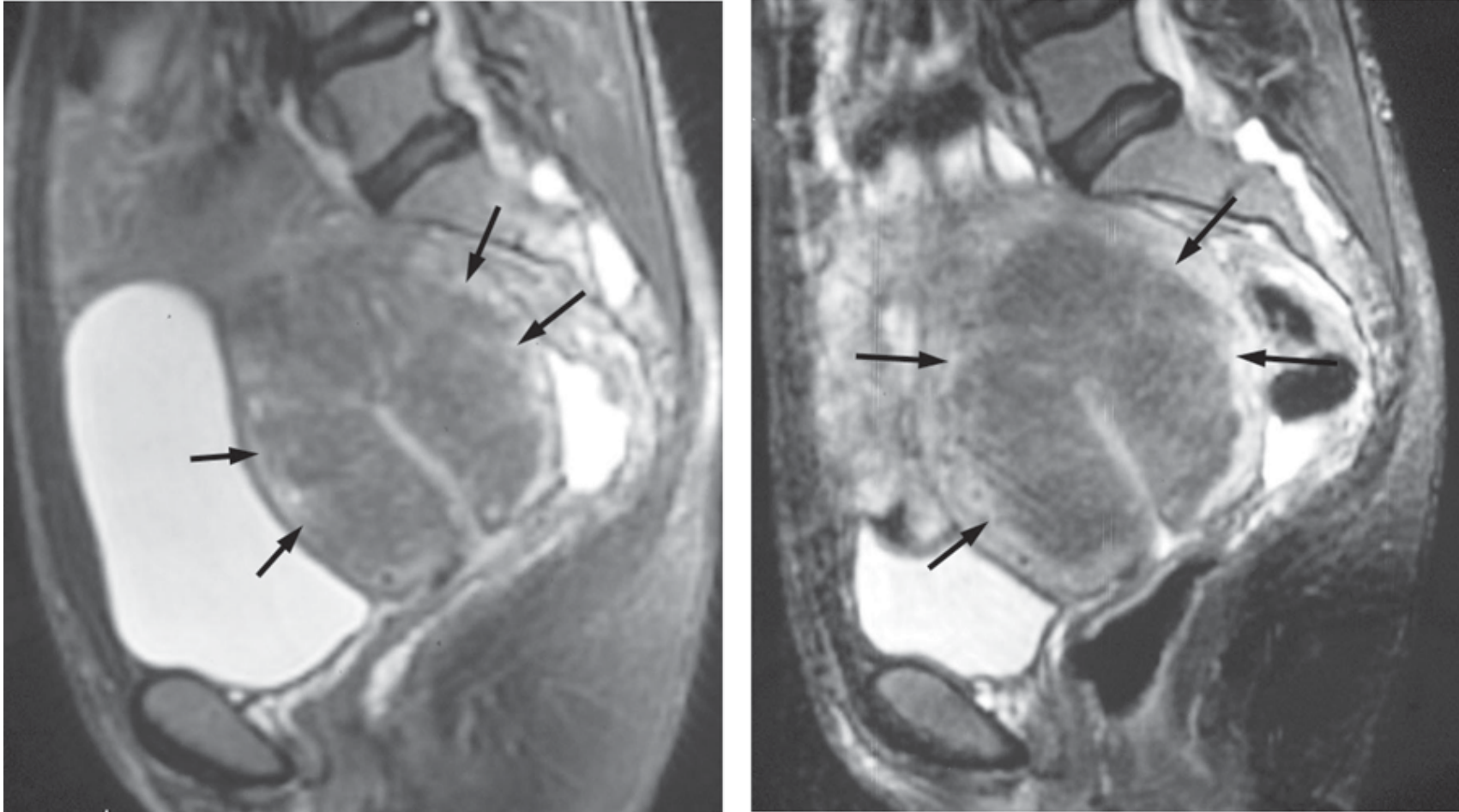
Zhou et al: *Fert Steril* 95:900-5, 2011

Devascularization Day 4 following UAE



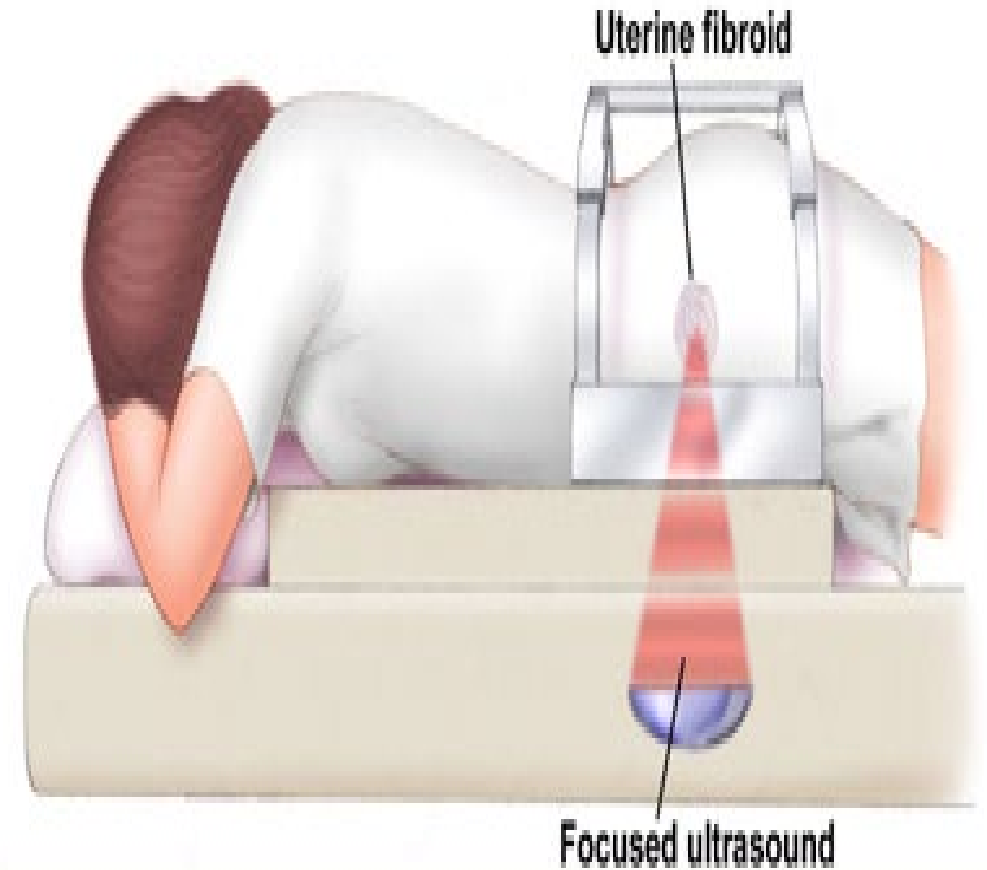
Pelage et al.: Radiology 234: 948-53, 2005

Junctional zone unchanged at 6 months



Pelage et al.: Radiology 234: 948-53, 2005

IMAGE-GUIDED FOCUSED ULTRASOUND TREATMENT



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US-Guided HIFU

- 208 women followed median 40 mo
- 82 % had decreased dysmenorrhea and 71% were asymptomatic
- More complete treatment, older age and lower BMI predicted success

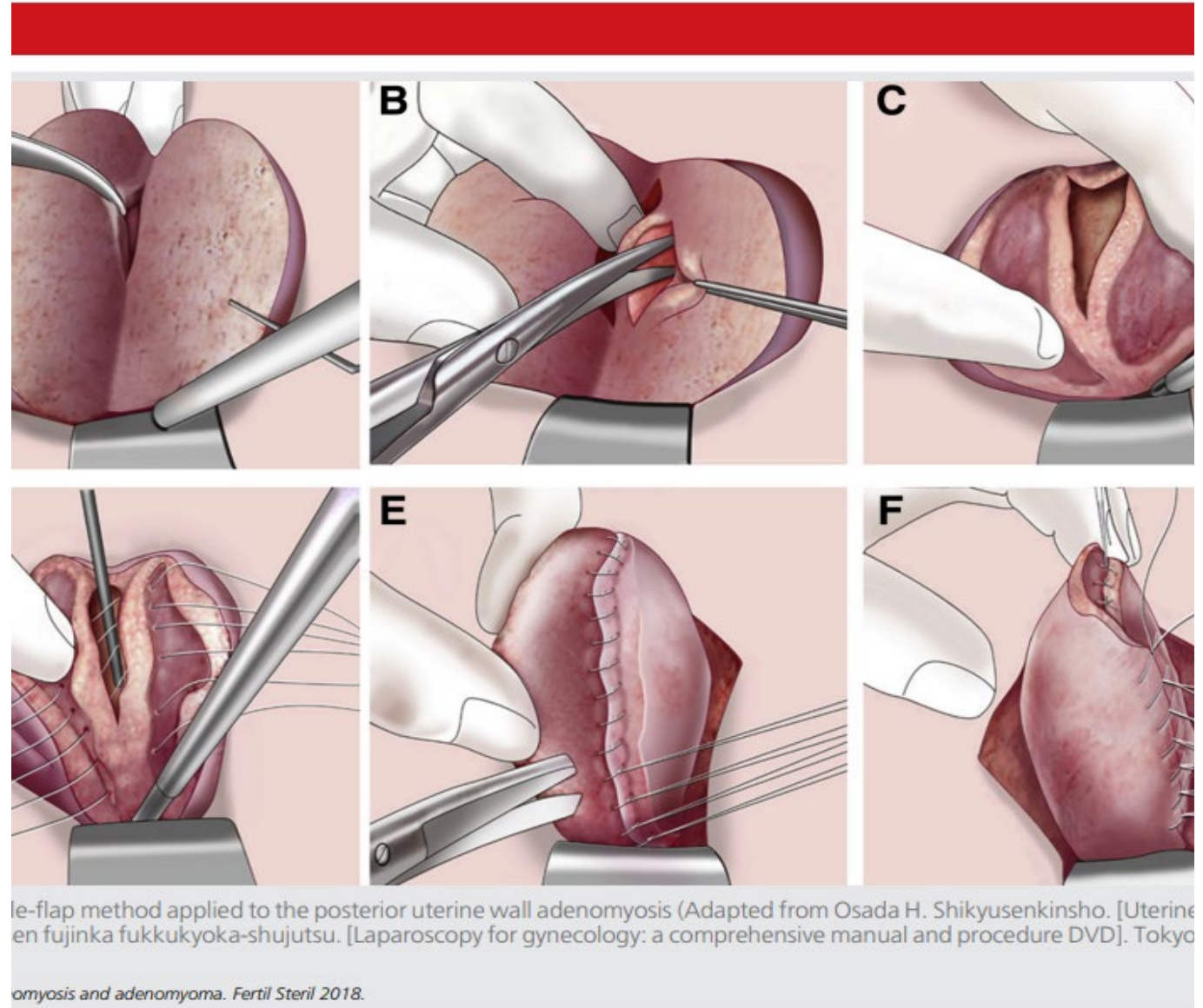
Liu et al.: Medicine 95 (3) e2443, 2016

Adenomyosis: Case series 6 months following MRgFUS

	Pre Rx	6 months	P
SSS of UFS-QOL	48.4 ± 12.1	26.7 ± 13.5	0.0001
Uterine volume (cc³)	445 ± 296	417 ± 315	.0029
Junctional zone (mm)	45.9 ± 12.2	41.4 ± 15.3	0.0111

Fukunishi et al. JMIG 2008:15:571-9.

CONSERVATIVE SURGERY FOR FOCAL ADENOMYOSIS



The risk of uterine rupture following surgical resection is high

Even when performed by expert surgeons, the rate of **uterine rupture in a future pregnancy appears to be 4%** and has been reported to occur **between 12 and 35 weeks of gestation**. The rate of uterine rupture rate following classical cesarean section with labor is 2%.

TABLE 2

Published cases of uterine ruptures after laparotomic and laparoscopic adenomyomectomy.

Author, year (ref.)	Patient age (y)	Operative method	Uterine incision	Contraceptive period (mo)	Modes of conception	Uterine rupture (wk)	Fetal number	Surgical treatment	Volume of bleeding (ml)	Fetal weight (g)	Fetal survival	Maternal survival
Yoshiki et al., 2004 (35)	NR	Laparotomic	Monopolar	NR	NR	26	Singleton	Preservation	NR	NR	Live	Live
Wada et al., 2006 (50)	33	Laparoscopic	Monopolar	12	IVF-ET	30	Twin	Preservation	2,600	1,585/1,545	Live	Live
Morimatsu et al., 2007 (46)	35	Laparoscopic	Monopolar	1	Spontaneous	28	Singleton	Preservation	2,560	1,356	Live	Live
Suginami et al., 2008 (11)	NR	NR	Laser knife	NR	NR	NR	Singleton	NR	NR	NR	NR	Live
Suginami et al., 2008 (11)	NR	NR	Laser knife	NR	NR	NR	Singleton	NR	NR	NR	NR	Live
Kasama et al., 2010 (51)	33	Laparotomic	Laser knife	36	IVF-ET	28	Singleton	Hysterectomy	6,130	1,274	Live	Live
Ukita et al., 2011 (52)	39	Laparotomic	NR	60	Spontaneous	29	Singleton	Hysterectomy	3,943 ^a	1,614	Death	Live
Yazawa et al., 2011 (53)	37	Laparoscopic	NR	5	IVF-ET	33	Singleton	Preservation ^b	NR	1,956	Live	Live
Onishi et al., 2011 (54)	40	Laparotomic	NR	NR	IVF-ET	31	Singleton	Hysterectomy	5,200	1,700	Live	Live
Kishi et al., 2014 (14)	NR	Laparoscopic	Laser knife	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tanaka et al., 2014 (36)	33	Laparo. assist. adeno.	Monopolar	36	IVF-ET	34	Singleton	Preservation	1,900	2,100	Live	Live
Kodama et al., 2015 (30)	41	Laparoscopic	Monopolar	4	Spontaneous	34	Singleton	Hysterectomy	5,150	2,032	Live	Live
Sato et al., 2015 (55)	35	Laparoscopic	NR	3	IVF-ET	28	Singleton	Preservation	NR	1,484	NR	Live
Nagao et al., 2016 (56)	42	Laparoscopic	NR	12	Spontaneous	35	Singleton	Preservation	NR	2,283	Live	Live
Nishida et al., 2016 (29)	38	Laparotomic	High-frequency	16	IVF-ET	31	Singleton	Hysterectomy	NR	NR	NR	Live
Nishida et al., 2017 (29)	35	Laparotomic	High-frequency	1	Spontaneous	27	Singleton	Preservation	NR	1,106	Live	Live
Nishida et al., 2018 (29)	31	Laparotomic	High-frequency	6	IVF-ET	30	Singleton	Preservation	NR	1,373	Live	Live
Nishida et al., 2019 (29)	34	Laparotomic	High-frequency	NR	Spontaneous	16	Singleton	Preservation	NR	NR	NR	Live
Nishida et al., 2020 (29)	32	Laparotomic	High-frequency	24	IVF-ET	19	Singleton	Preservation	NR	NR	NR	Live
Iwahashi et al., 2017 (57)	37	Laparotomic	High-frequency	72	IVF-ET	22	Singleton	Preservation	2140	NR	Death	Live
Yamaguchi et al., 2017 (58)	38	Laparotomic	NR	36	IVF-ET	33	Singleton	Preservation	759 ^a	1,850	Live	Live
Wood et al., 1998 (59)	NR	Laparoscopic	Monopolar	24	NR	12	Singleton	NR	NR	NR	Death	Live
Saremi et al., 2014 (27)	NR	Laparotomic	Scalpel, monopolar	NR	NR	NR	Singleton	NR	NR	NR	NR	NR
Saremi et al., 2015 (27)	NR	Laparotomic	Scalpel, monopolar	NR	NR	NR	Singleton	NR	NR	NR	NR	NR

Note: High-frequency = high-frequency cutter; IVF-ET = in vitro fertilization-embryo transfer; Laparo. assist. adeno. = laparoscopy-assisted adenomyomectomy; Laparoscopic = laparoscopic surgery; Laparotomic = laparotomic surgery; Monopolar = monopolar cautery; NR = no record.

^a Includes amniotic fluid.

^b Adenomatoid tumor.

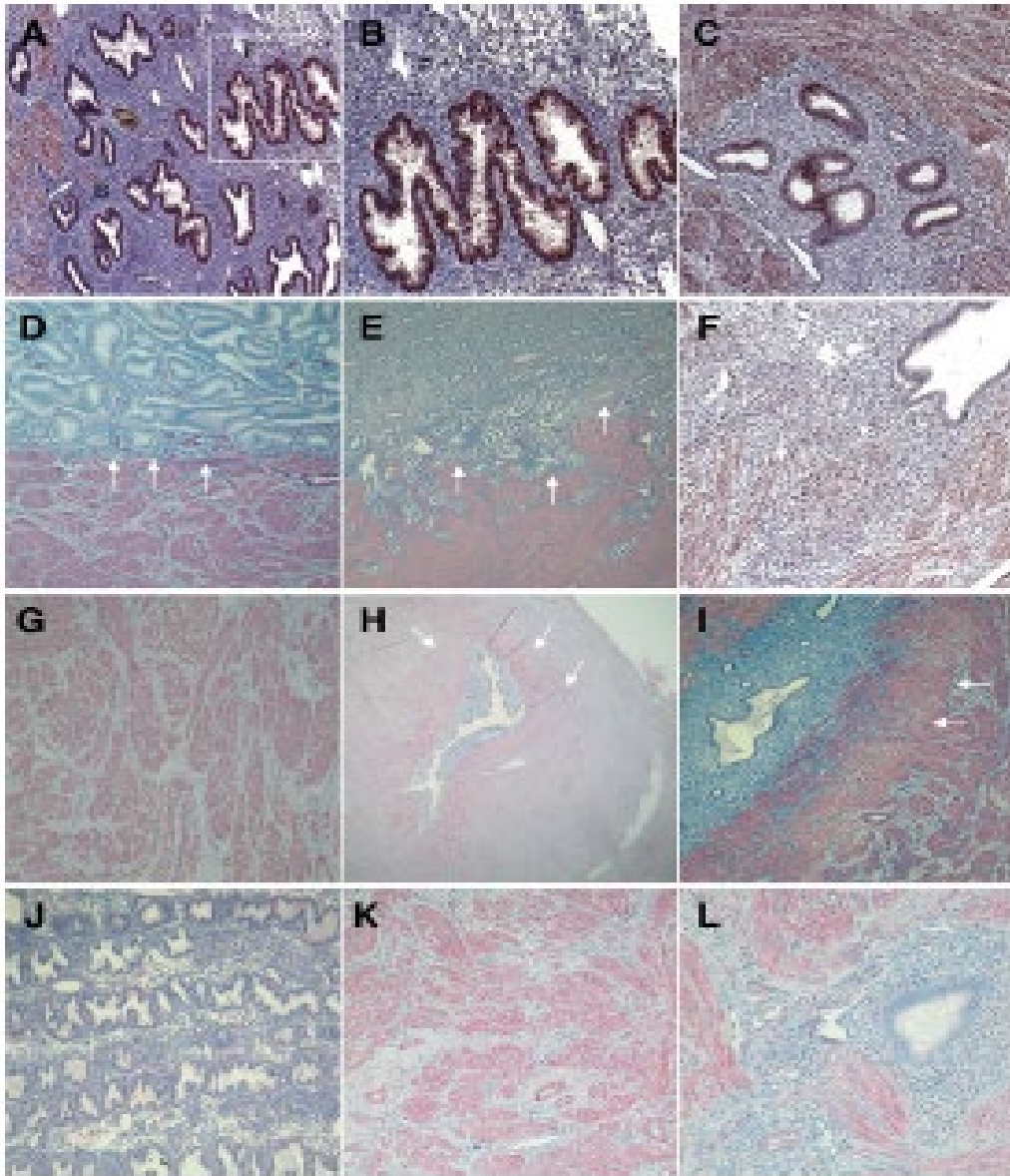
Osada. Uterine adenomyosis and adenomyoma. *Fertil Steril* 2018.



3

FUTURE THERAPIES FOR ADENOMYOSIS

Oxytocin Receptor Overexpressed In Adenomyotic Uteri



Mechsner. OTR and VP-1aR in adenomyosis uteri. Fertil Steril 2010.

[Home](#) > Study Record Detail

Save this study

Saved Studies (0)

Placebo-controlled Proof of Concept Study of Epelsiban in Women With Adenomyosis

This study has been withdrawn prior to enrollment.

(Study was prematurely discontinued due to GSK's change in prioritization for the portfolio and is not due to any safety concerns or regulatory interaction.)

Sponsor:

GlaxoSmithKline

ClinicalTrials.gov Identifier:

NCT02794467

First Posted: June 9, 2016

Last Update Posted: January 18, 2017

Epelsiban- selective oxytocin receptor antagonist

REST/NRSF, miRNAs, and tissue remodeling in adenomyosis pathophysiology

Project Number

1R01HD105714-01

Contact PI/Project Leader

NOTHNICK, WARREN B

Awardee Organization

UNIVERSITY OF KANSAS MEDICAL
CENTER

Description

Abstract Text

Project Summary Adenomyosis is a nonmalignant uterine disease characterized by endometrial stroma and glands found within the myometrium. Adenomyosis has been associated with heavy and painful menstrual periods, pelvic pain, pain with intercourse, and reproductive dysfunction. However, now that imaging is identifying adenomyosis in younger and more varied women than those electing hysterectomy where pathological diagnosis occurred, many of our assumptions about the clinical disease are changing. Additionally, the only widely accepted and effective treatments for adenomyosis, hysterectomy and hormonal suppression, are unacceptable for this wider group of women. Much of our uncertainty on diagnosis and treatment for adenomyosis stem from our uncertainty on its' pathogenesis. The most common theory of adenomyosis development centers on the involvement of tissue injury and repair mechanisms with resulting adenomyosis development from invagination of the endometrial basalis into the myometrium (the invasion/invagination theory). While