Adenomyosis

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Clinical manifestations

- Heavy menstrual bleeding
- Dysmenorrhea – 25% of women
- Chronic pelvic pain
- Symptoms develop between 40 - 50 years
- Menorrhagia may be related to the increased endometrial surface of the enlarged uterus
- Pain may be due to bleeding and swelling of endometrial islands confined by myometrium
- Approximately 1/3 of women are asymptomatic

Risk factors

- Advanced age
- Multiparity
- Early menarche
- Obesity
- Previous uterine surgery or intervention
- Endometriosis
- Now known to occur early. Why?

Prevalence of adenomyosis

- Prevalence varies widely (5-70%) depending on the definitions and the population studies
- Frequency of diagnosis of adenomyosis at hysterectomy 12% - 58% among 15 hospitals, and 10% - 88% among 25 pathologists
- Recent study showed adenomyosis in 25% of hysterectomies
- Associated with DIE
- 33.9% in young nullips 18-30 (Pinzauti 2015 doi: 10.1002/uog.14834)
- 88% in women with endometriosis vs. controls

Associated with

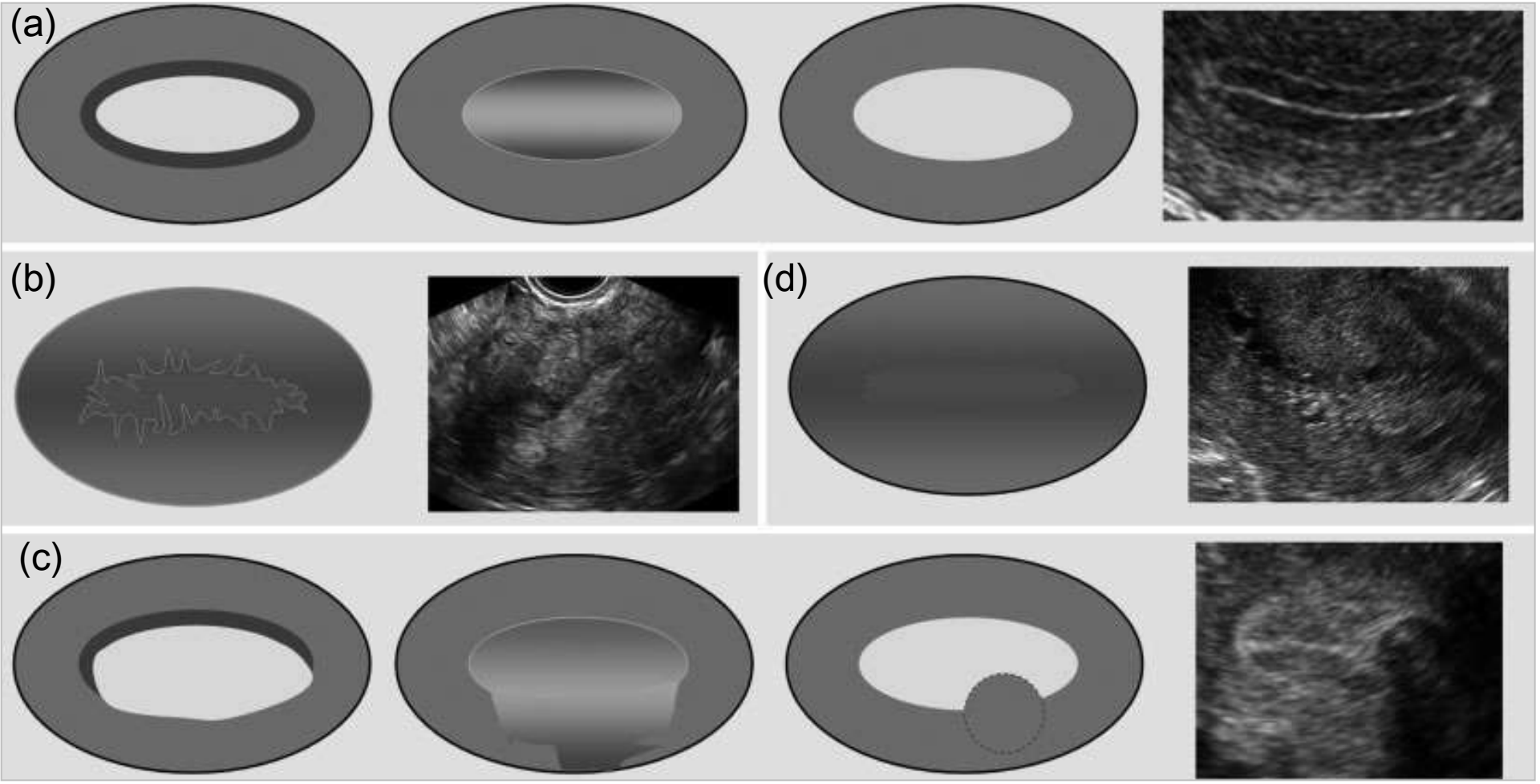
- Endometriosis – 70%
- Myomas – 50%
- Endometrial hyperplasia – 35%
- Endometrial polyps – 2%
- Endometrial carcinomas - rare

Pathogenesis

Endometrial–myometrial junction: EMJ –

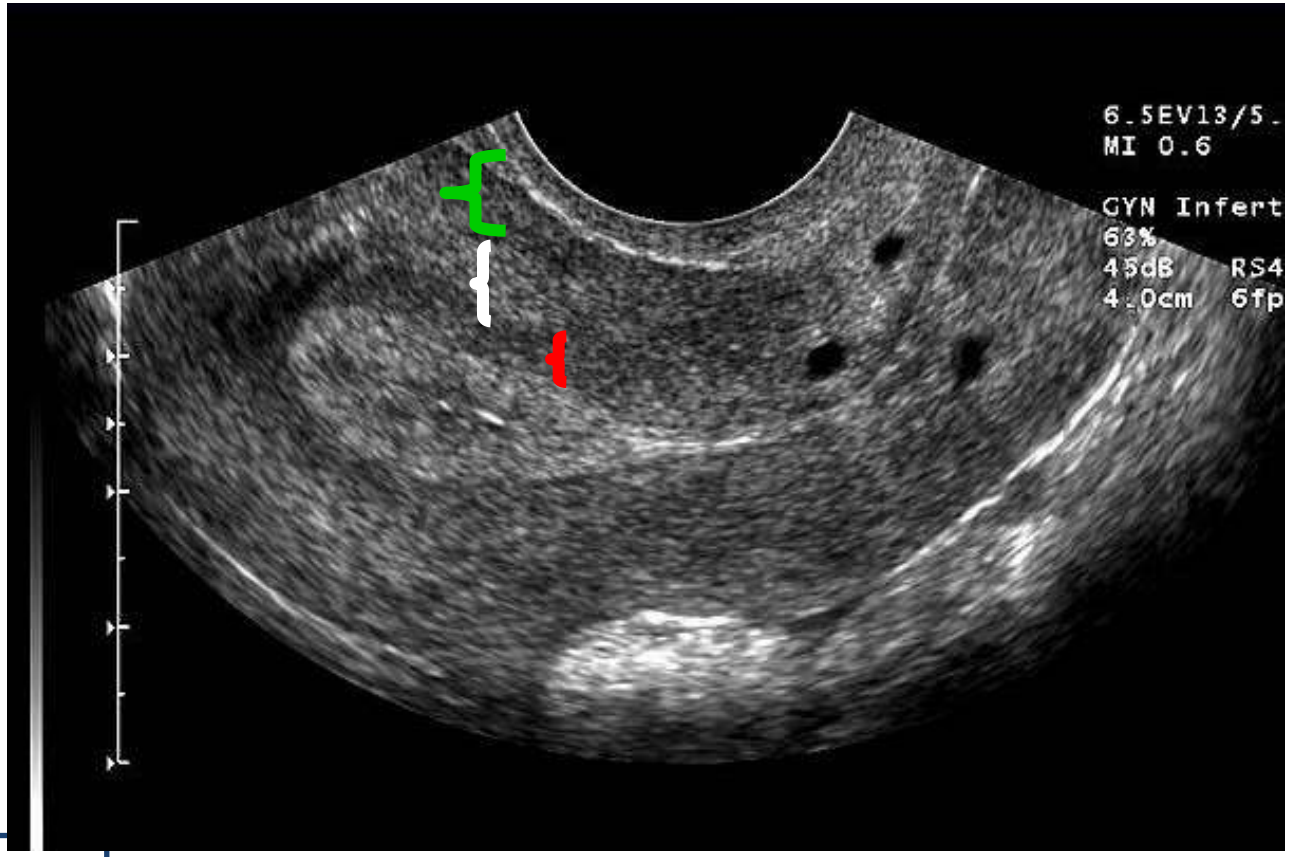
‘regular’ (a), ‘irregular’ (b), ‘interrupted’ (c), not defined (d)

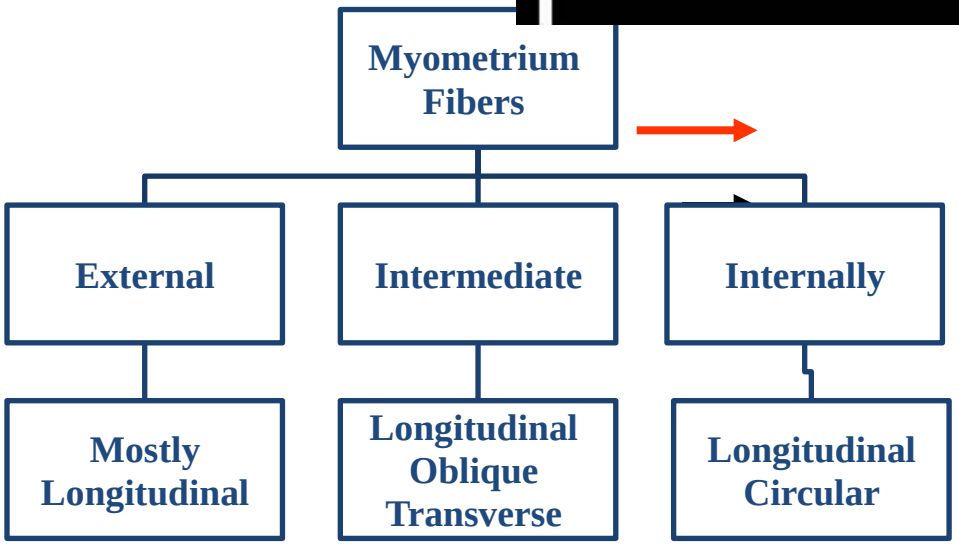
Ultrasound Obstet Gynecol 2010; 35: 103–112



The myometrium

- The myometrium has three distinct sonographic layers: the **outer, middle and inner layers**
- The inner layer (the sub endometrial halo) is composed of longitudinal and circular closely packed smooth muscle fibers
- The inner layer is hypoechogenic on TVS
- On MRI is seen as a low-signal-intensity band referred to as the junctional zone (JZ)





Blood vessels mid-outer zone
More echoic middle zone
Hypoechoic inner zone

Pathogenesis of adenomyosis

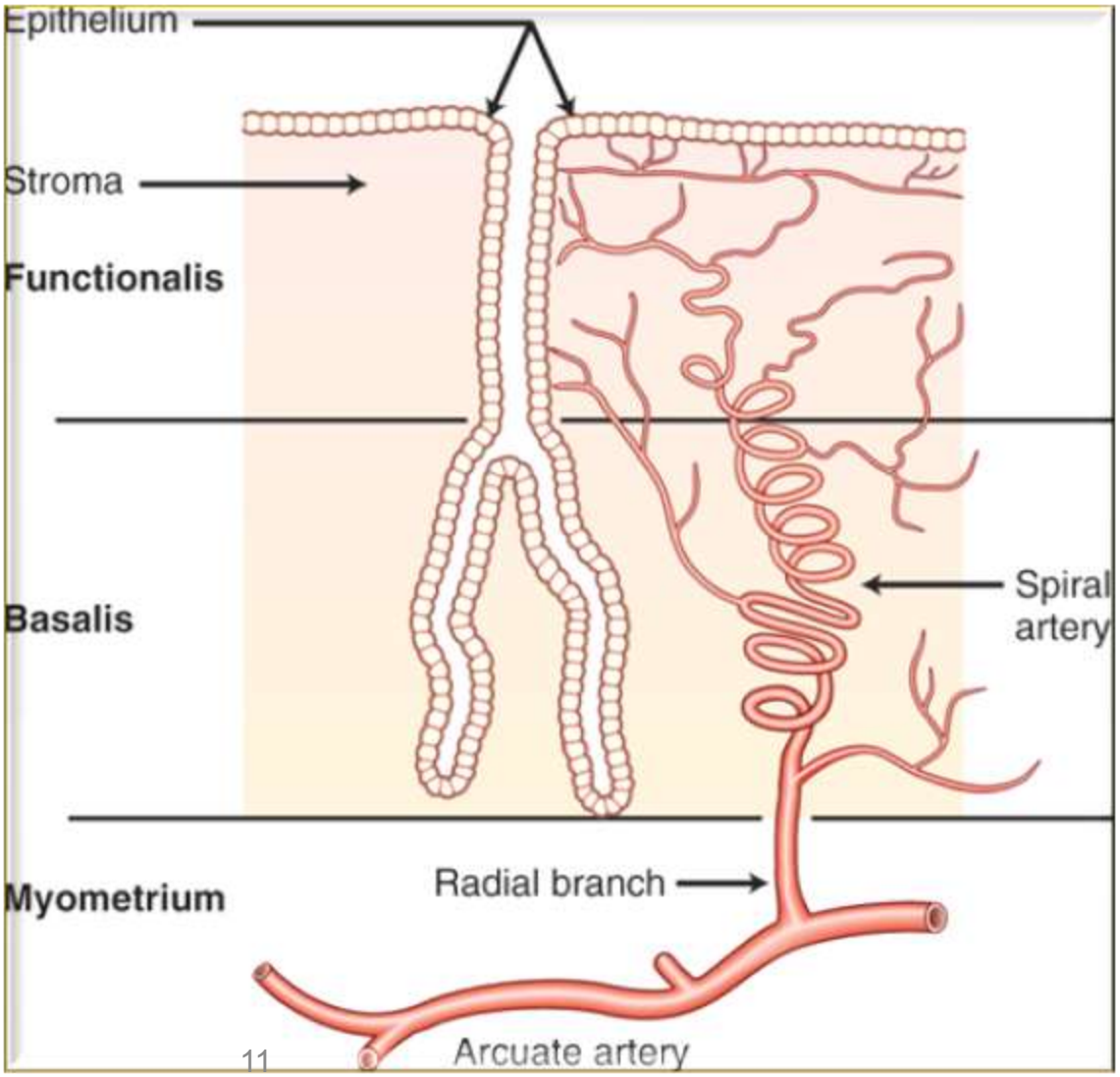
- Uncoordinated proliferation of the inner myometrial cells
- JZ hyperplasia - focal or diffuse, thickened sub endometrial halo (muscular hypertrophy seen in adenomyosis)
- Adenomyosis characterized primarily by disruption of the inner myometrial architecture and function
- Secondary infiltration of endometrial elements into the myometrium under certain circumstances of altered sex steroid milieu or altered local immunity

Endometrial adenogenesis in the uterine wall

Following invagination of stromal cells, invasion of glandular cells

Abnormal growth and differentiation

These cells are surrounded by hypertrophic and hyperplastic myometrium

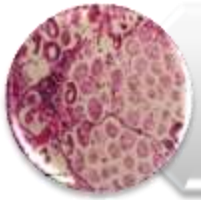


Histogenesis of adenomyosis

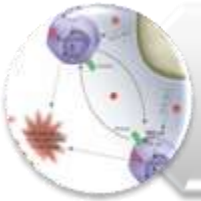
Several key steps are required to establish an adenomyosis:

Epithelial-mesenchymal transition (EMT)

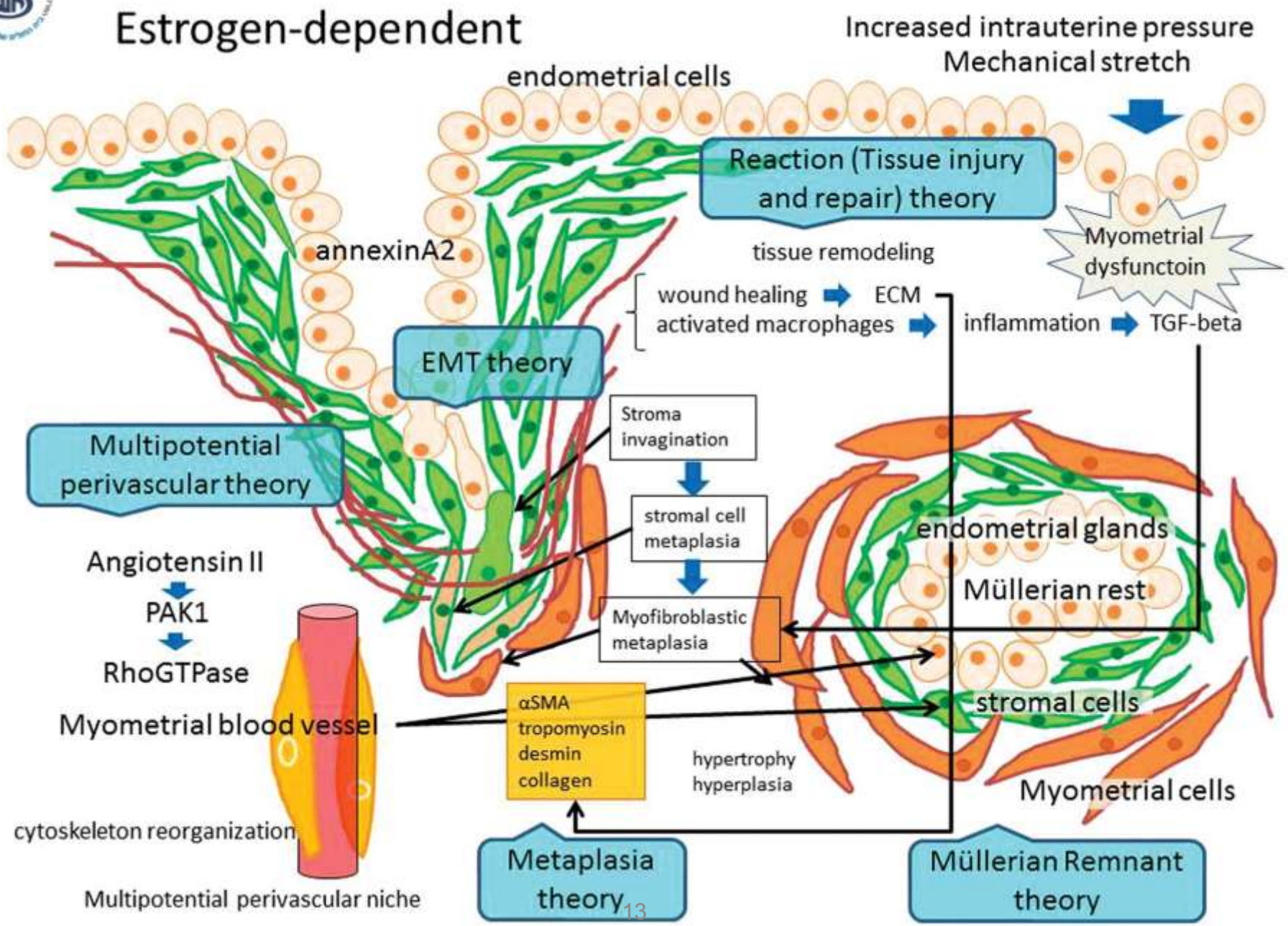
Survival and growth of the ectopic tissue within the myometrium



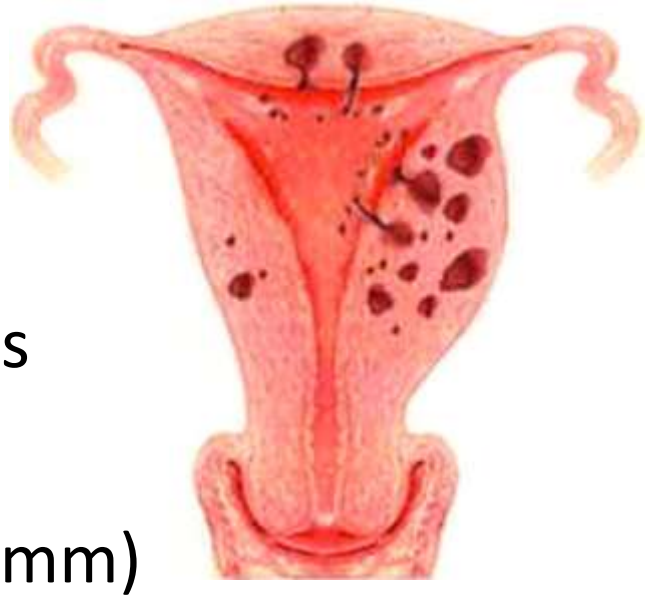
Myometrial hypertrophy and hyperplasia



Induction of an immunosuppressive microenvironment


Estrogen-dependent
Increased intrauterine pressure
Mechanical stretch
endometrial cells
Reaction (Tissue injury and repair) theory
annexinA2
tissue remodeling
Myometrial dysfunctoin
wound healing
ECM
activated macrophages
inflammation
TGF-beta
EMT theory
Multipotential perivascular theory
Stroma invagination
stromal cell metaplasia
endometrial glands
Müllerian rest
Angiotensin II
PAK1
RhoGTPase
Myofibroblastic metaplasia
Myometrial blood vessel
αSMA
tropomyosin
desmin
collagen
stromal cells
hypertrophy
hyperplasia
Myometrial cells
cytoskeleton reorganization
Multipotential perivascular niche
Metaplasia theory
Müllerian Remnant theory

Sonographic criteria of adenomyosis



- Globular shaped uterus
- Mottled inhomogeneous myometrium
- Indistinct borders to a myometrial mass
- Indistinct endometrial stripe
- Subendometrial myometrial cysts (2-6 mm)
- Subendometrial echogenic nodules
- Subendometrial echogenic linear striations
- Asymmetric thickening of the anterior/posterior wall
- Mimimal mass effect on the endometrium or serosa
- Irregular endometrial-myometrial junction (EMJ)

Junctional zone

A normal junctional zone 5 mm in thickness or less

Junctional zone

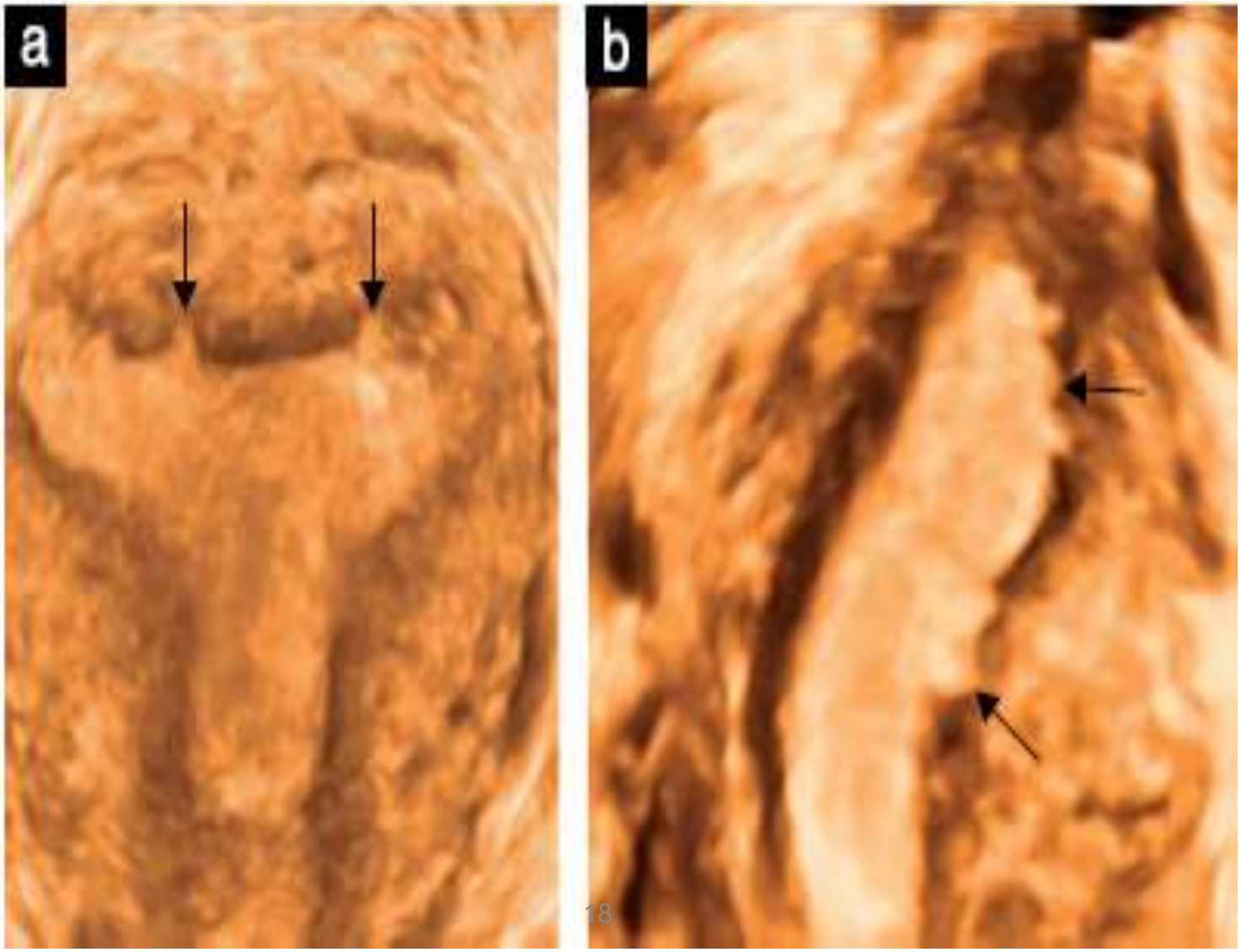
Figure 1 Multiplanar view of the uterine corpus obtained by three-dimensional ultrasound. The junctional zone (JZ) can be seen as a dark line just beneath the endometrium (arrows and dashed lines). The JZ of the anterior and posterior wall is visualized in the A- and B-planes and the JZ of the left and right lateral walls and of the fundus in the C-plane.

Table 2 Reporting the junctional zone (JZ) on ultrasound examination

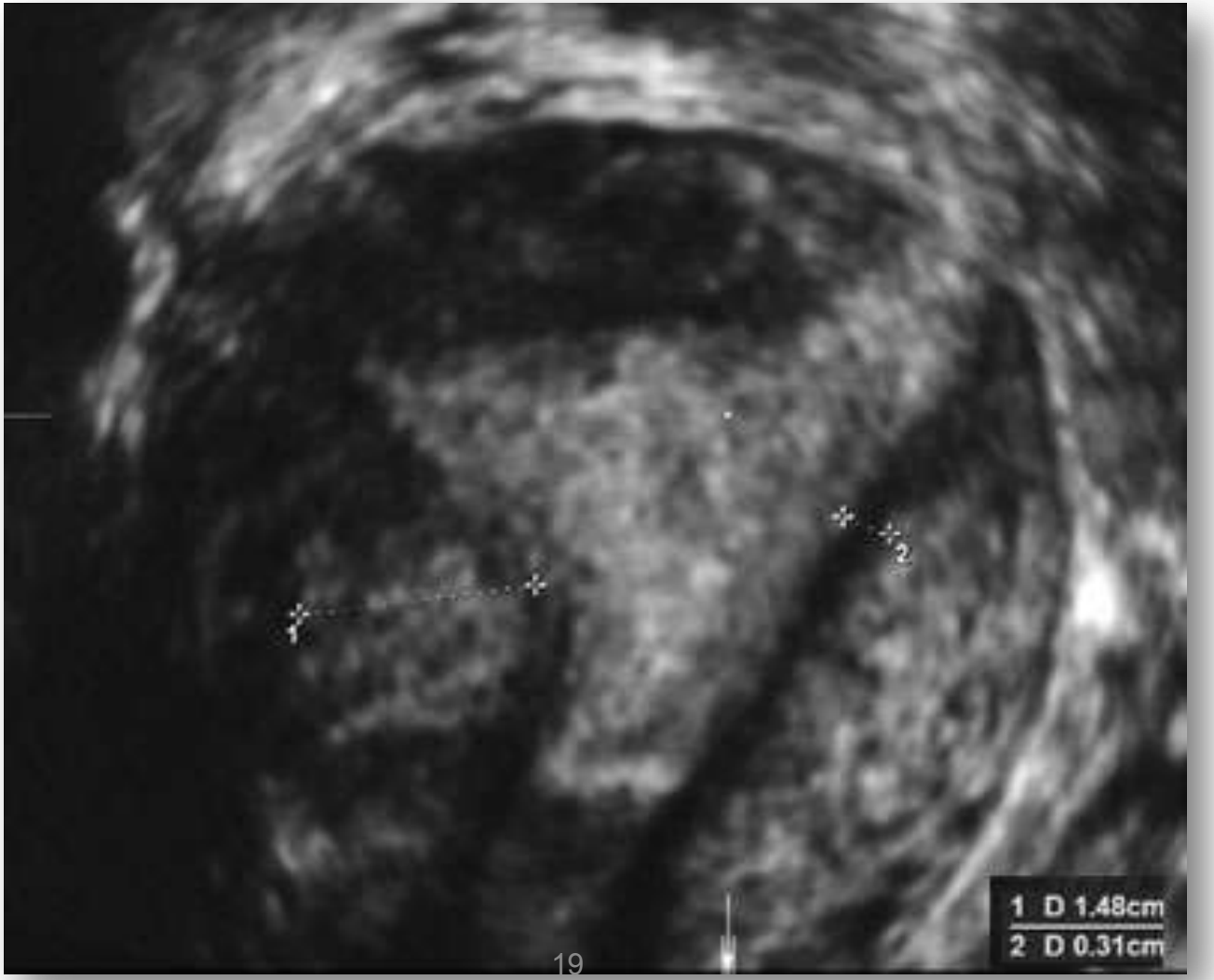
Structure	*Description*	*Measurement*
JZ*†	Regular, irregular, interrupted, not visible, not assessable*	Maximum (JZ_{max}) and minimum (JZ_{min}) JZ thickness in mm or ratio JZ/total myometrial wall thickness†
Irregular or interrupted JZ†	Location: anterior, posterior, fundus, lateral right, lateral left, or global†	Magnitude of irregularity: $(JZ_{max}) - (JZ_{min}) = JZ_{dif}$; extent of irregularity: proportion (%) of JZ that is irregular ($< 50\%$ or $\geq 50\%$)†
Interrupted JZ†	Location: anterior, posterior, fundus, lateral right, lateral left, or global†	Interruption of JZ: proportion (%) of JZ not visualized ($< 50\%$ or $\geq 50\%$)†
Irregularity in JZ†	Cystic areas, hyperechogenic dots, hyperechogenic buds and lines (in each location)†	—

Measurement of the junctional zone

Early adenomyosis



Lateral infiltration of the junctional zone



Three-dimensional (3D) transvaginal ultrasound (TVS) according to histological diagnosis of adenomyosis

	Adenomyosis on histology	
3D-TVS finding	*Yes (n = 32)*	*No (n = 40)*
JZmax (mm)*	15.4 ± 8.6 (12.4–18.4)	8.0 ± 4.1 (6.7–9.3)
JZmin (mm)	6.0 ± 4.5 (4.4–7.5)	5.6 ± 3.0 (4.9–6.5)
JZdif (mm)*	9.4 ± 5.2 (7.7–11.2)	2.8 ± 2.7 (1.9–3.6)
JZmax/myom. thickness (%)*	59.3 ± 17.6 (53.2–65.4)	41.5 ± 18.2 (35.8–47.1)
Presence of:		
JZ alteration*	87.5 (28)	22.5 (9)
Myometrial cysts*	62.5 (20)	5.0 (2)
Asymmetrical myom.*	59.4 (19)	27.5 (11)
Heterogeneous myom.*	90.6 (29)	47.5 (19)

Three-dimensional (3D) transvaginal ultrasound (TVS) according to histological diagnosis of adenomyosis

TVS finding	*Sens. (% (95% CI))*	*Spec. (% (95% CI))*	*PPV (% (95% CI))*	*NPV (% (95% CI))*	*LR+ (95% CI)*	*LR− (95% CI)*	*Accuracy (% (95% CI))*
2D-TVS							
Myometrial cysts	53 (35–70)	98 (85–100)	94 (70–100)	72 (58–83)	21.3 (3.0–151.2)	0.48 (0.33–0.69)	78 (67–86)
Asymmetrical myom.	47 (30–65)	80 (64–90)	65 (43–83)	65 (50–78)	2.3 (1.1–4.8)	0.66 (0.47–0.93)	65 (54–75)
Hypoechoic striations	50 (32–68)	90 (75–97)	80 (56–93)	69 (55–81)	5.0 (1.9–13.5)	0.56 (0.39–0.79)	72 (61–81)
Heterogeneous myom.	88 (70–95)	65 (48–79)	67 (50–80)	87 (68–96)	2.5 (1.6–3.9)	0.19 (0.08–0.49)	75 (64–84)
3D-TVS							
JZmax ≥ 8 mm	84 (67–94)	75 (58–87)	73 (56–86)	86 (69–95)	3.4 (1.9–5.9)	0.21 (0.09–0.47)	79 (68–87)
JZmax − JZmin ≥ 4 mm	88 (70–96)	83 (67–92)	80 (63–91)	89 (74–97)	5.0 (2.5–9.9)	0.15 (0.06–0.38)	85 (75–91)
JZ ratio ≥ 50%	78 (60–90)	65 (48–79)	64 (47–78)	79 (61–90)	2.2 (1.4–3.5)	0.34 (0.17–0.66)	71 (60–80)
JZ alteration	88 (70–96)	78 (61–89)	76 (58–88)	89 (72–96)	3.9 (2.2–7.0)	0.16 (0.06–0.41)	82 (72–89)
Myometrial cysts	63 (44–78)	95 (82–99)	91 (69–98)	76 (62–87)	12.5 (3.1–49.6)	0.40 (0.25–0.62)	81 (70–88)
Asymmetrical myom.	59 (4–76)	73 (56–85)	63 (44–80)	69 (53–82)	2.2 (1.2–3.9)	0.56 (0.36–0.87)	67 (55–76)
Heterogeneous myom.	91 (74–98)	53 (36–68)	60 (45–74)	88 (67–97)	1.9 (1.4–2.7)	0.18 (0.06–0.55)	69 (58–79)
Overall*							
2D-TVS	75 (56–88)	90 (75–97)	86 (66–95)	82 (66–91)	7.5 (2.9–19.4)	0.28 (0.15–0.51)	83 (73–90)
3D-TVS	91 (74–97)	88 (72–95)	85 (68–94)	92 (78–98)	7.3 (3.2–16.6)	0.11 (0.03–0.31)	89 (80–94)

*Overall 2D- and 3D-TVS diagnosis was based on the presence of any two or more of the individual ultrasonographic features. JZ, junctional zone; JZmax, maximum thickness of the junctional zone; JZmin, minimum thickness of the junctional zone; JZ ratio, JZmax/total maximum myometrial thickness, expressed as %; LR+, positive likelihood ratio; LR−, negative likelihood ratio; myom., myometrium; NPV, negative predictive value; PPV, positive predictive value; Sens., sensitivity; Spec., specificity.

Prevalence

	Endometriosis (N=94)	Control (N=60)	P
Asymmetrical myometrial thickening (%)	64 (68.1)	38 (63.3)	0.602
Myometrial cysts (%)	80 (85.1)	47 (78.3)	0.287
Parallel shadowing (%)	54 (57.5)	22 (36.7)	0.014*
Hyperechoic islands (%)	76 (80.9)	46 (76.7)	0.547
Linear striations (%)	25 (26.6)	27 (45.0)	0.023*
Irregular EMJ (%)	81 (86.2)	26 (43.3)	<0.001*
Focal adenomyomas (%)	36 (38.3)	7 (11.7)	<0.001*
Number of features, mean ± SD	4.4 ± 2.0	3.5 ± 2.3	0.009*
Any feature (%)	84 (89.4)	47 (78.3)	0.068
Number of features ≥ 3 (%)	82 (87.2)	41 (68.3)	0.004*
Number of features ≥ 5 (%)	54 (57.4)	21 (35)	0.007*

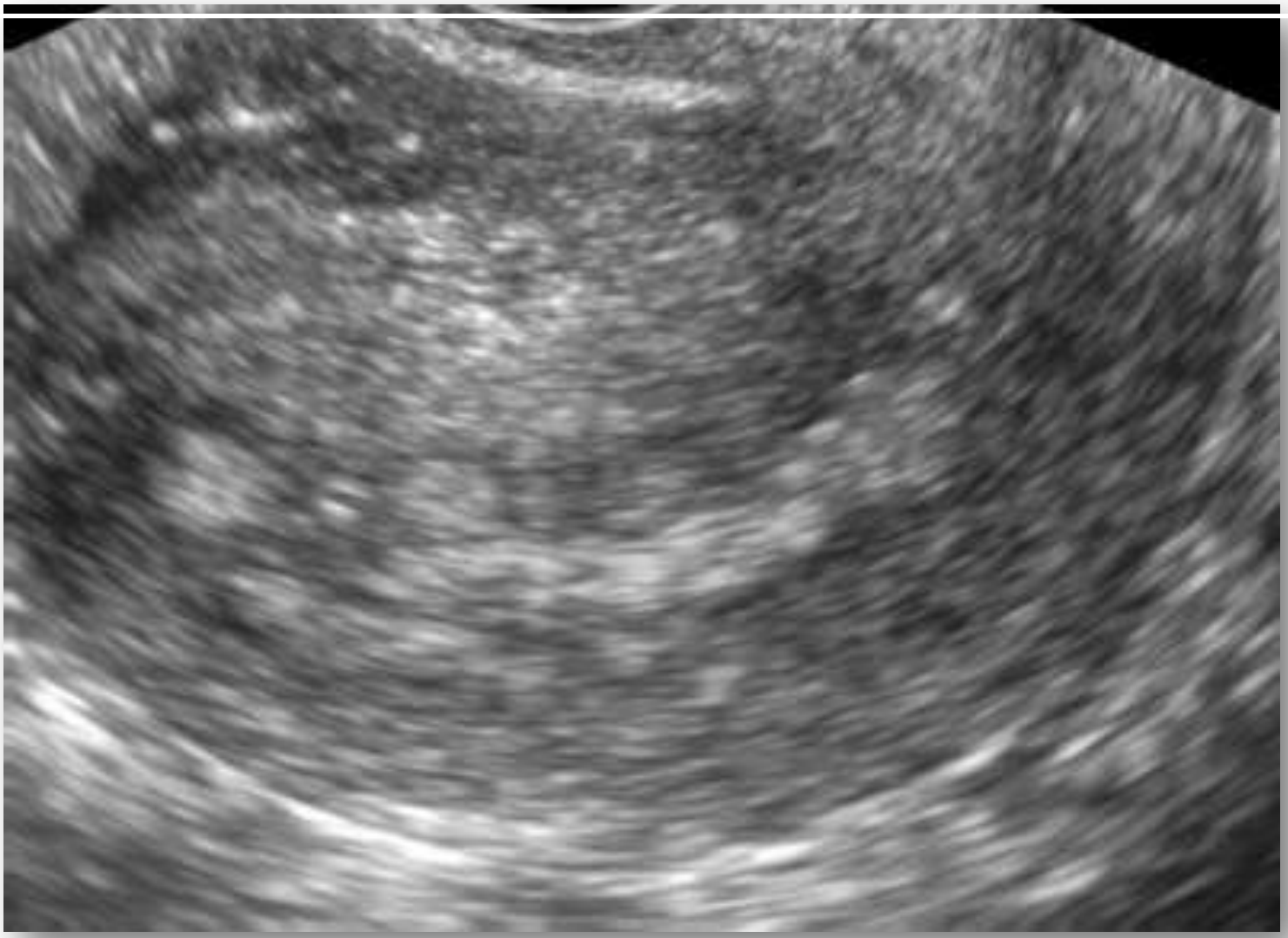
EMJ – Endometrial-myometrial junction; SD – Standard deviation.

* Statistically significant finding.

Progression of adenomyosis

Well-defined myometrial cysts

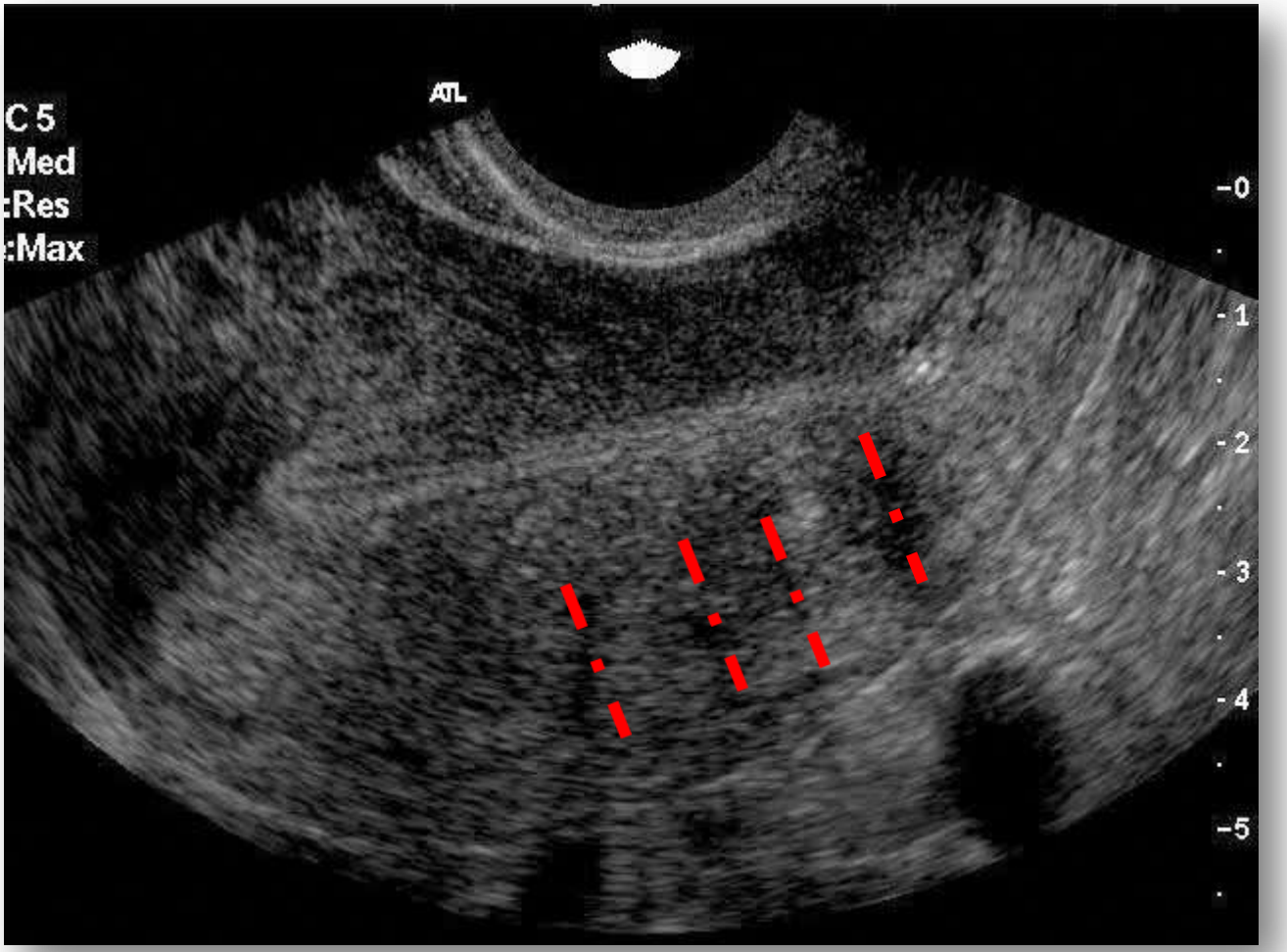
Irregular border



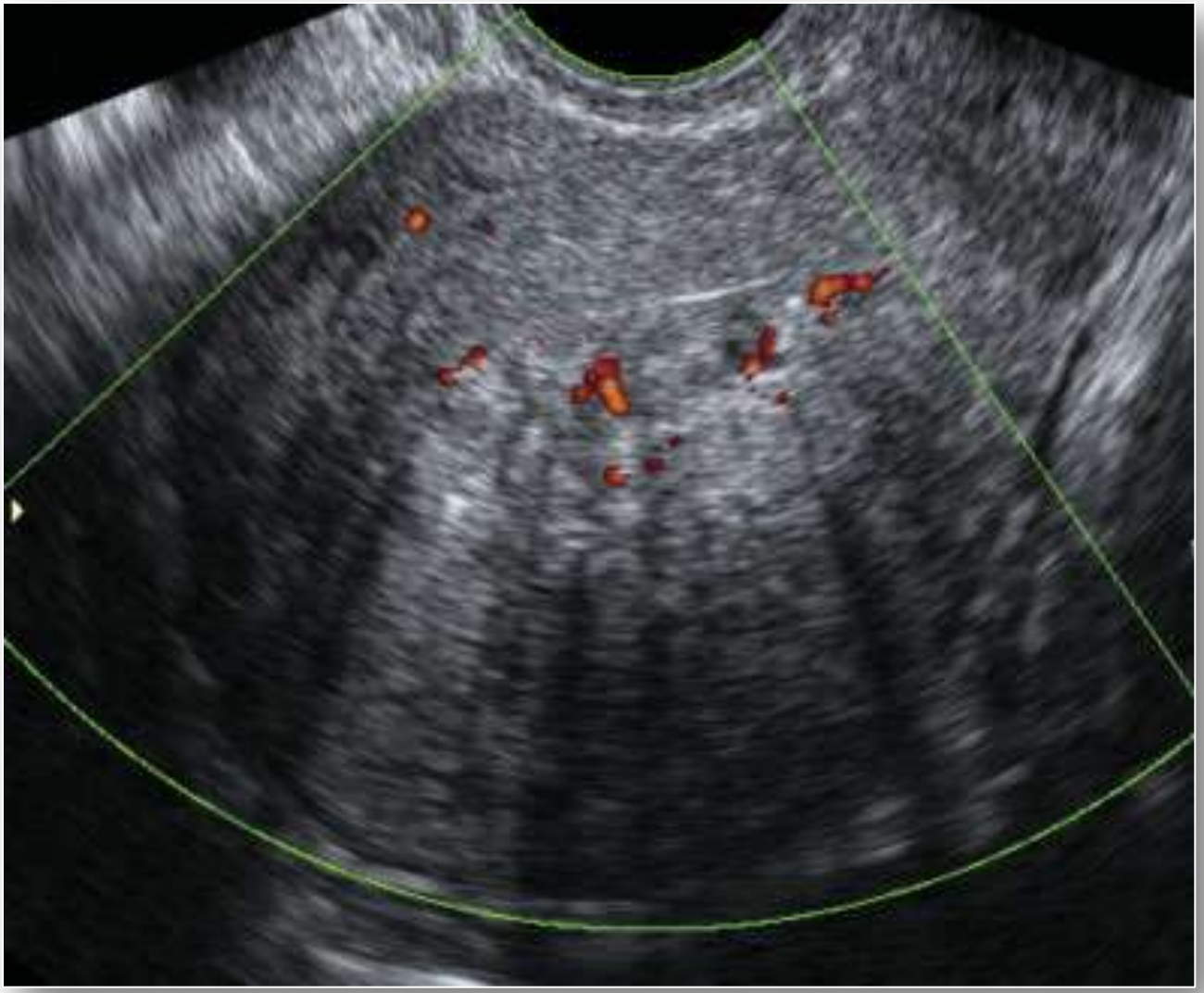
Hyperechoic endometrial tissue penetrating into the inner myometrium

Echogenic linear striations

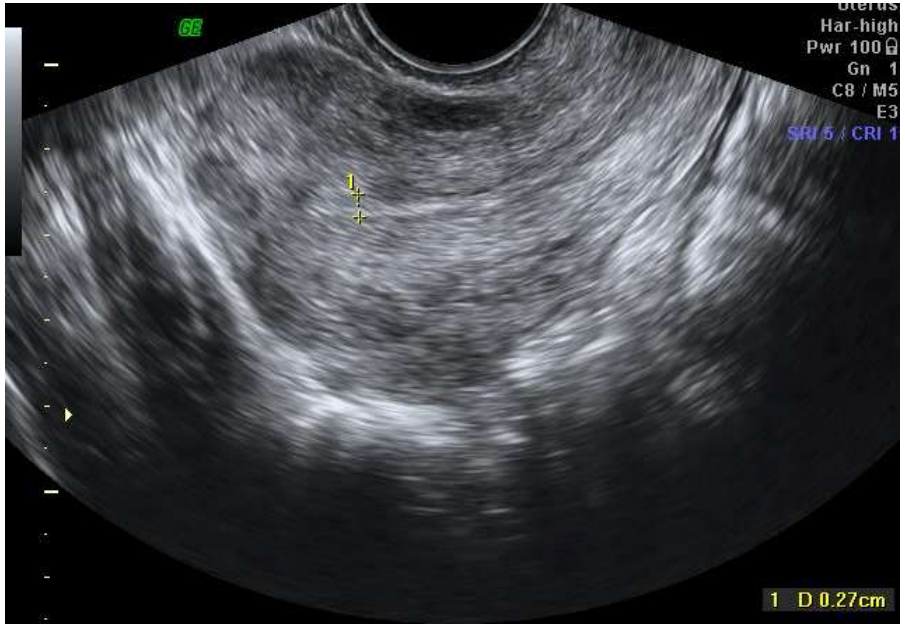
Linear shadows

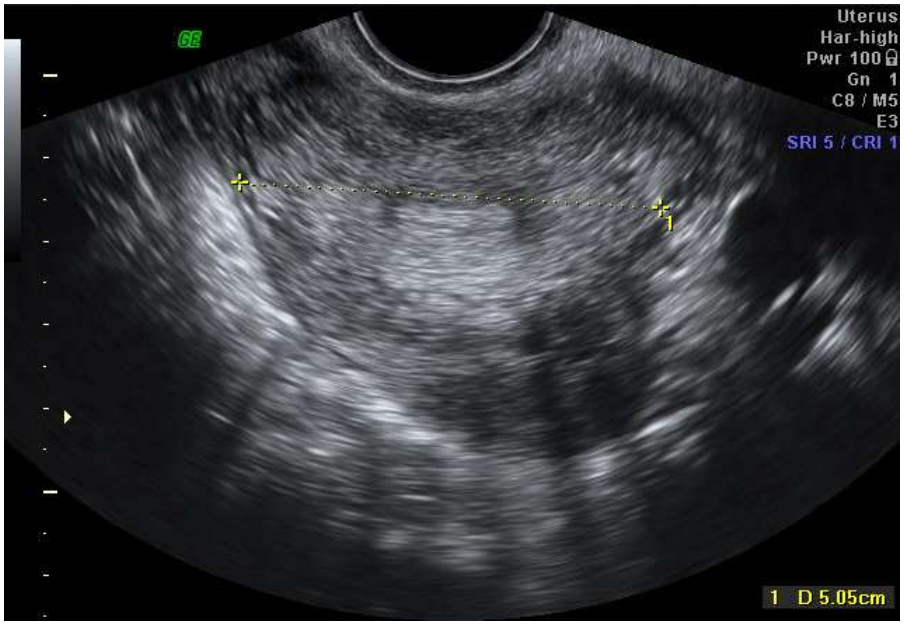


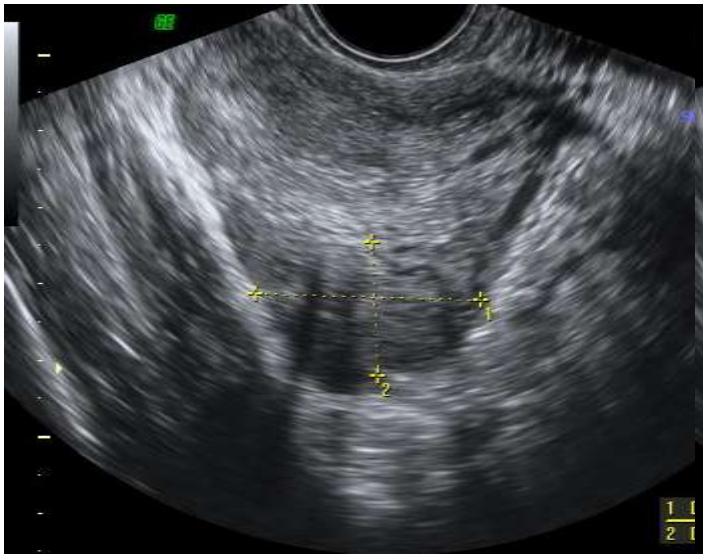
Few diffuse vessels

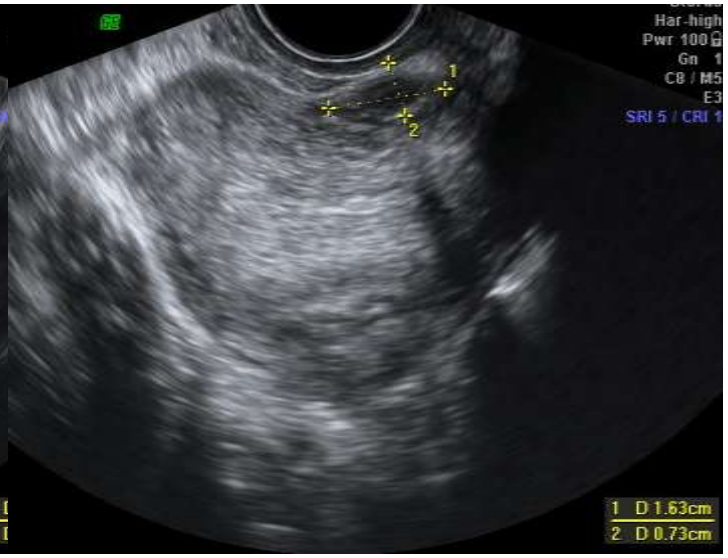


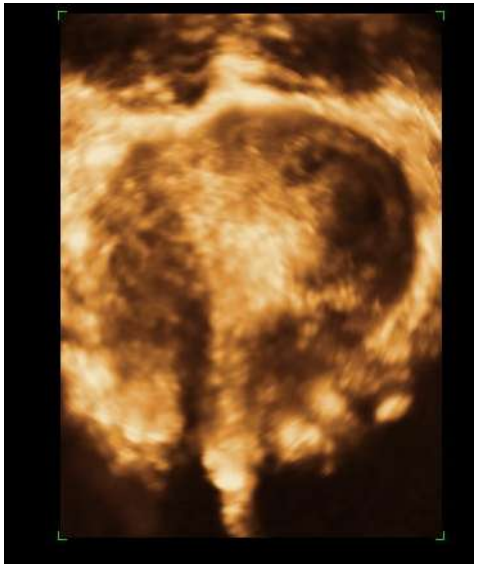
Diffuse and focal adenomyosis



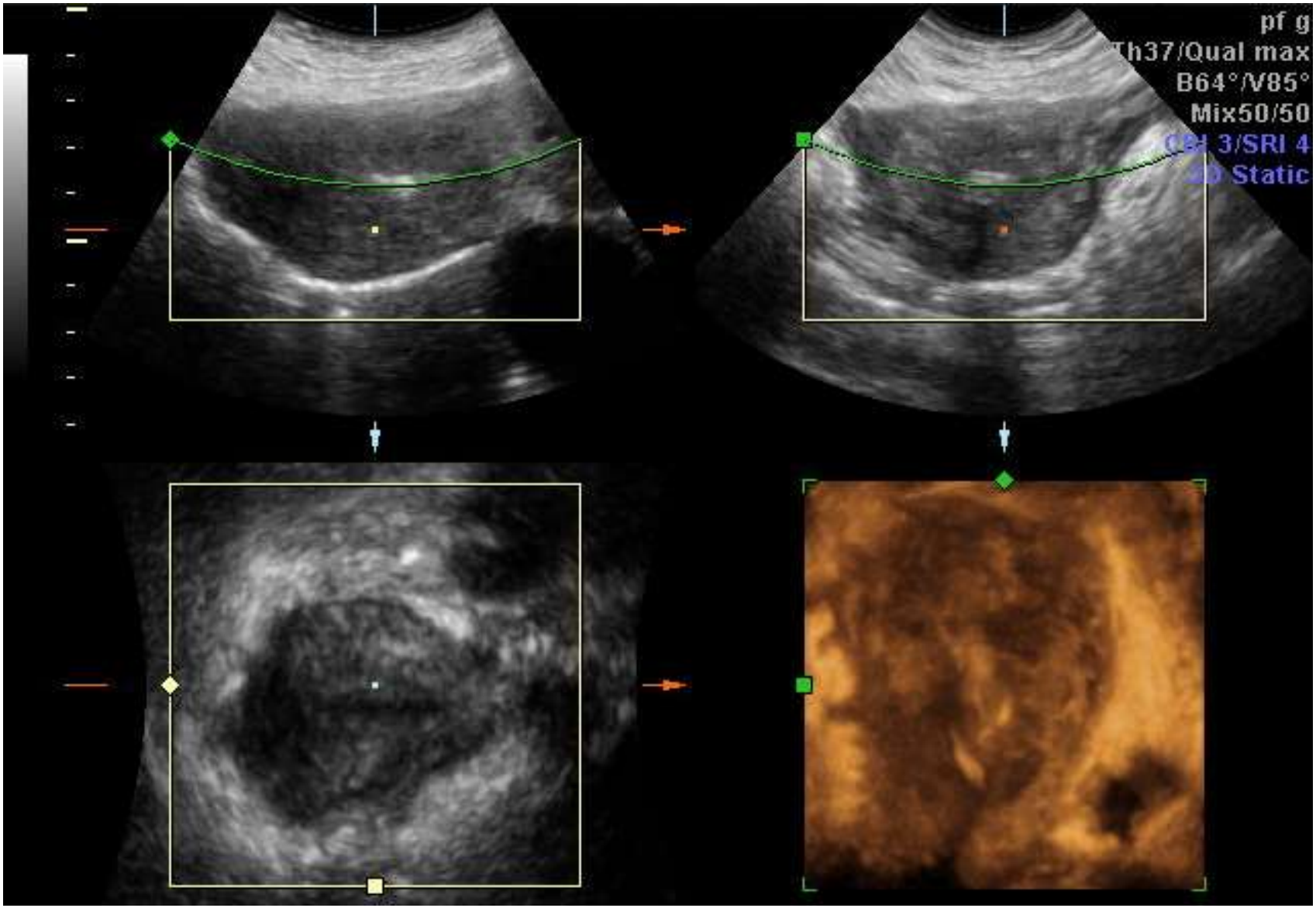




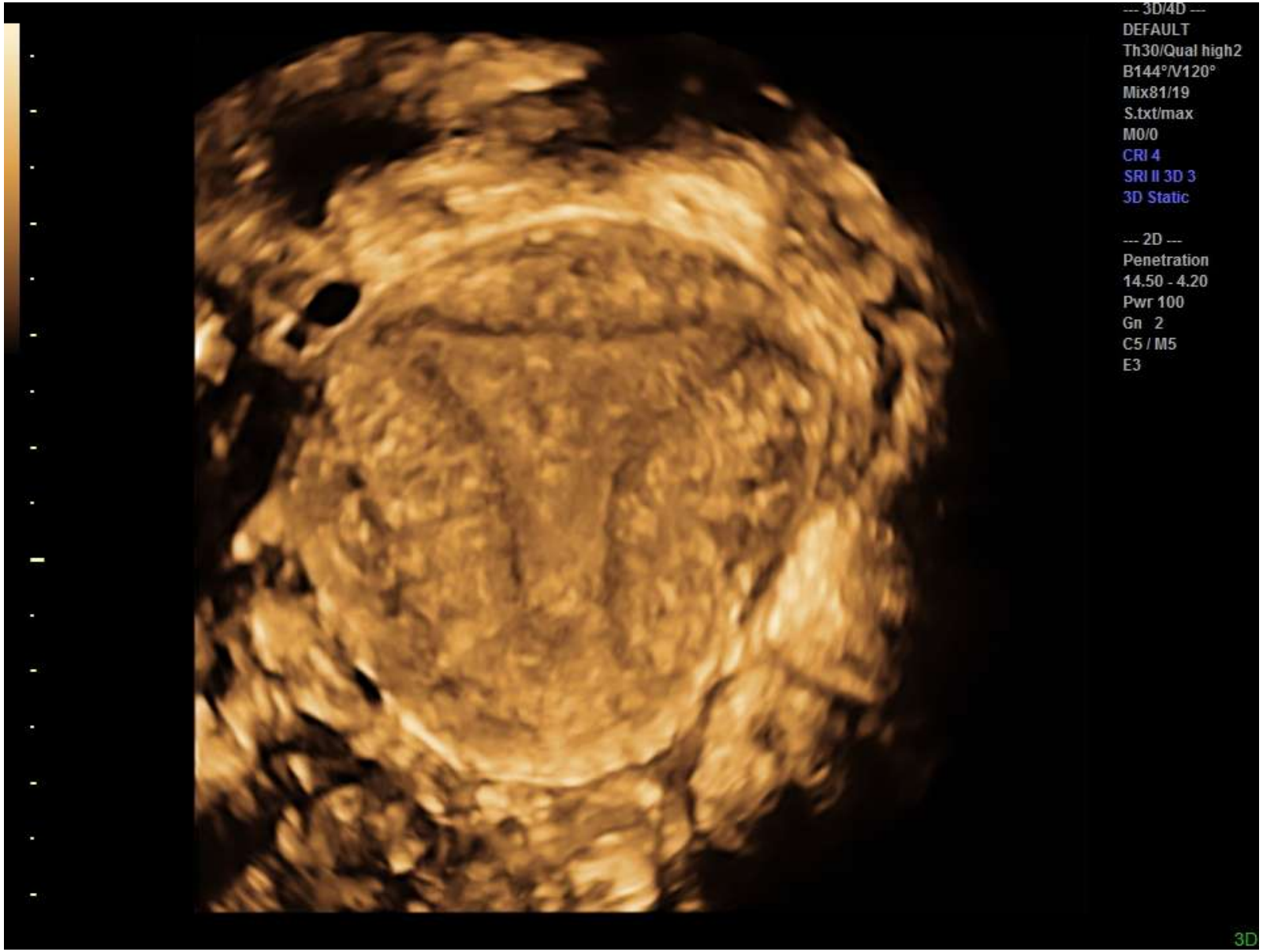




Adenomyosis



Diffuse adenomyosis



MUSA consensus

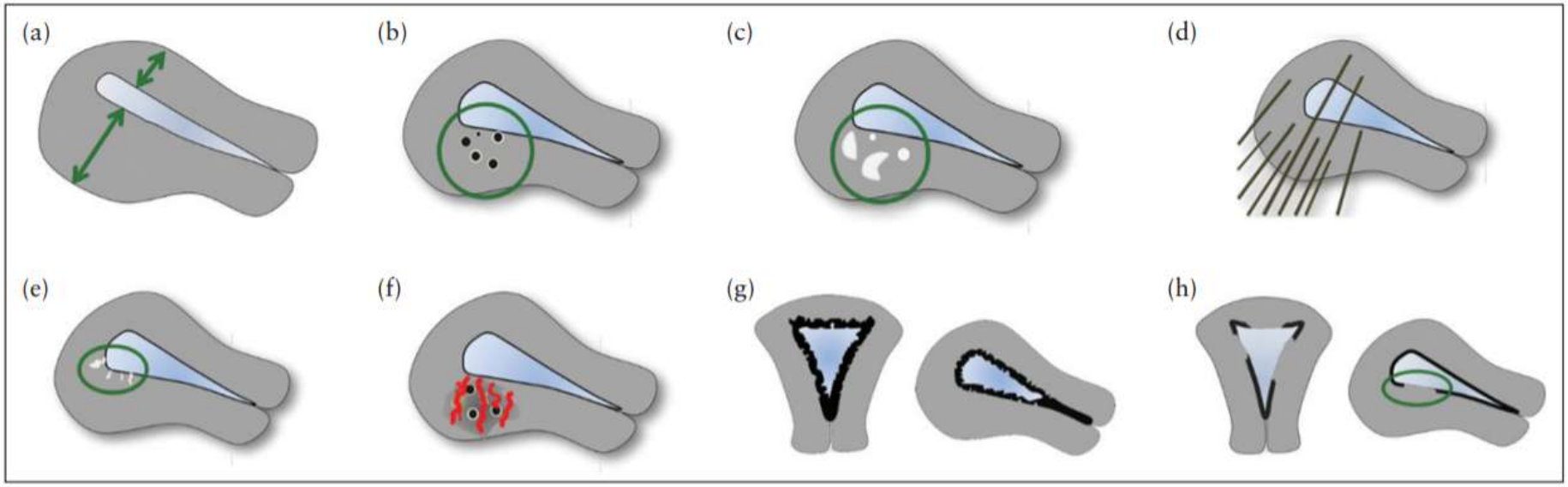


Figure 10 Schematic drawings illustrating the ultrasound features considered currently to be typical of adenomyosis: asymmetrical thickening (a), cysts (b), hyperechoic islands (c), fan-shaped shadowing (d), echogenic subendometrial lines and buds (e), translesional vascularity (f), irregular junctional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

Accuracy of transvaginal ultrasound (TVS) and magnetic resonance imaging diagnosis of adenomyosis

	Reinhold et al[50] % (95%CI)	Bazot et al[71] % (95%CI)	Dueholm et al[70] % (95%CI)	Total % (95%CI)
TVS:				
Sensitivity	89 (71–97)	65 (48–79)	68 (44–86)	74 (63–82)
Specificity	89 (80–94)	98 (90–100)	65 (50–77)	87 (81–91)
Positive predictive value	71 (54–85)	93 (75–99)	42 (25–61)	68 (58–77)
Negative predictive value	96 (89–99)	85 (75–91)	85 (69–94)	89 (84–92)
MRI:				
Sensitivity	86 (66–95)	78 (61–89)	70 (46–87)	78 (68–86)
Specificity	86 (76–92)	93 (84–97)	86 (76–93)	88 (83–92)
Positive predictive value	65 (47–79)	84 (67–93)	58 (37–77)	70 (60–79)
Negative predictive value	95 (87–98)	89 (80–95)	91 (81–96)	92 (87–95)

Accuracy of transvaginal ultrasound (TVS) and magnetic resonance imaging diagnosis of adenomyosis

Sensitivity and Specificity of Transvaginal Sonography in Diagnosing Adenomyosis

Study	Prevalence	Sensitivity (%)	Specificity (%)
Fedele et al., 1992[22]	23/405	87	99
Fedele et al., 1992[23]	22/43	80	74
Ascher et al., 1994[19]	17/20	53	75
Reinhold et al., 1995[24]	29/100	86	86
Brosens et al., 1995[20]	28/56	86	50
Atzori et al., 1996[25]	13/58	87	96
Reinhold et al., 1996[26]	29/119	89	89
Koçak et al., 1998[27]	18/95	89	88
Vercellini et al., 1998[28]	29/102	83	67
Bromley et al., 2000[29]	51/?	84	84
Atri et al., 2000[30]	30/102	81	71
Bazot et al., 2001[31]	40/120	65	97
Bazot et al., 2002[5]	21/23	81	100
Bazot et al., 2002[5]	26/106	38	97

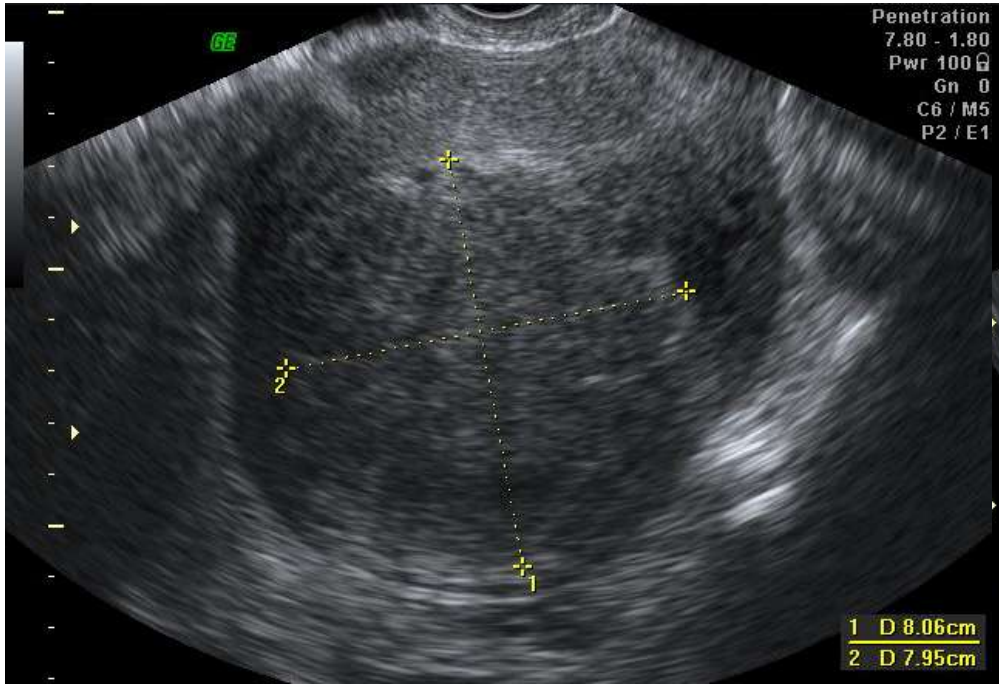
Adenomyosis and myomas

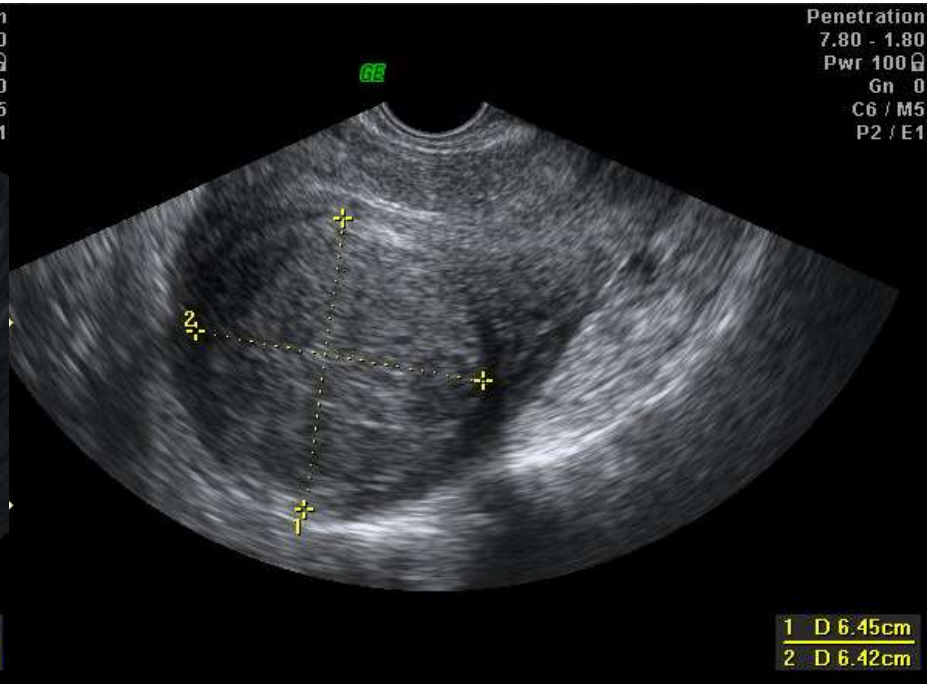
Table 5 Features considered important in diagnosis of fibroids and adenomyosis

Feature	*Typical fibroid*	*Adenomyosis*
Serosal contour of uterus	Lobulated or regular	Often globally enlarged uterus
Definition of lesion	Well-defined	Ill-defined in diffuse adenomyosis (adenomyoma may be well-defined)
Symmetry of uterine walls	Asymmetrical in presence of well-defined lesion(s)	Myometrial anteroposterior asymmetry
Lesion		
Outline	Well-defined	Ill-defined
Shape	Round, oval, lobulated	Ill-defined
Contour	Smooth	Irregular or ill-defined
Rim	Hypo- or hyperechogenic	No rim
Shadowing	Edge shadows, internal shadows (often fan-shaped shadowing)	No edge shadows, fan-shaped shadowing[67]
Echogenicity	Uniform: hyper-, iso-, hypoechogenic Non-uniform: mixed echogenicity	Non-uniform: mixed echogenicity[67,68] Cysts[20–24,62], hyperechogenic islands, subendometrial lines and buds[24,63]
Vascularity	Circumferential flow	Translesional flow[69]
Junctional zone (JZ)		
JZ thickness, regularity	Not-thickened; regular or not visible	Thickened; irregular or ill-defined[9,61–63]
JZ interruption	Interrupted or overstretched JZ in areas with lesions of FIGO types 1–3 (Figure 3)	Interrupted JZ (even in absence of localized lesions)[9]

FIGO, International Federation of Gynecology and Obstetrics[2].

Adenomyoma vs. myoma



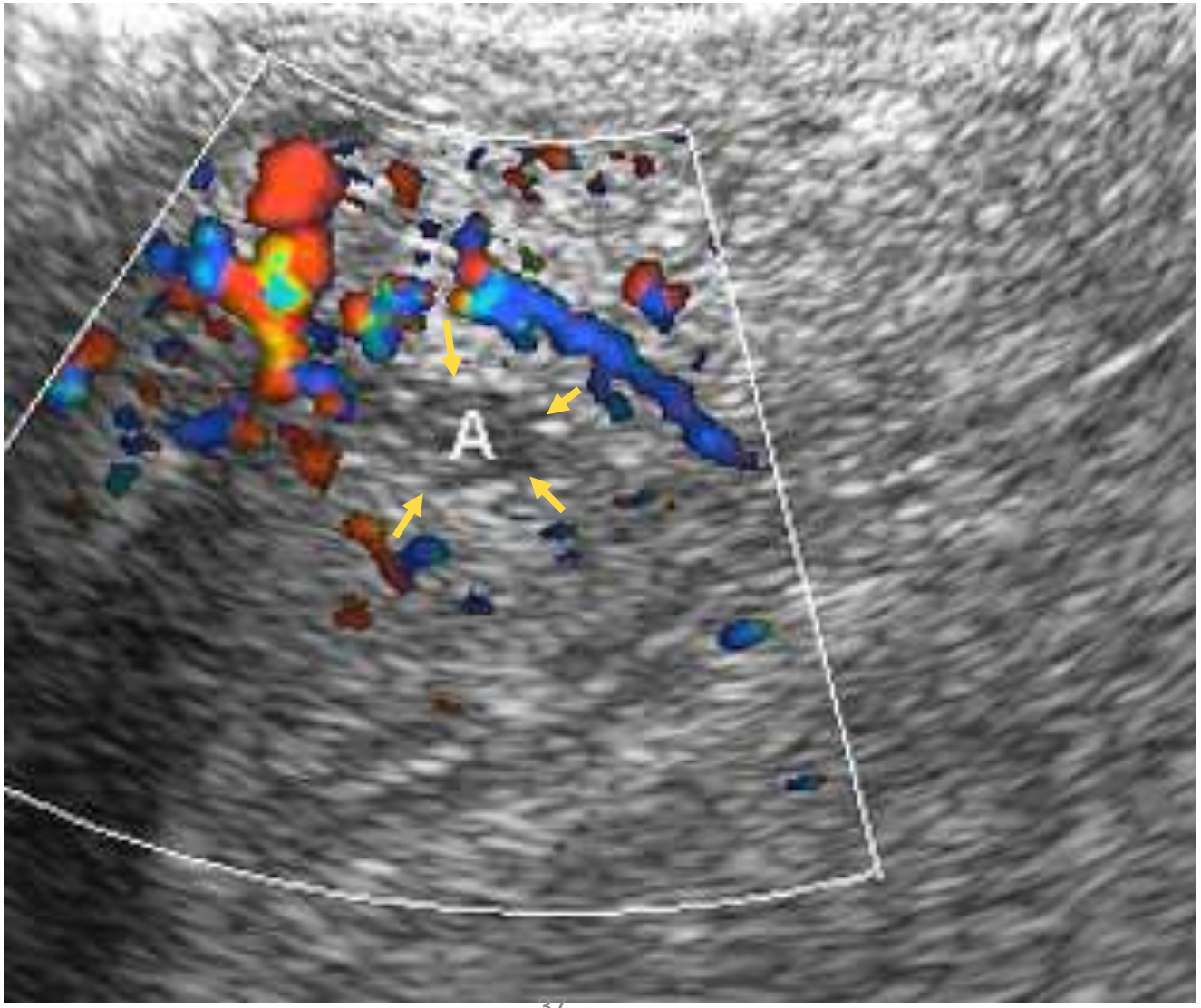


Differentiation between leiomyoma and adenomyosis by color Doppler sonography

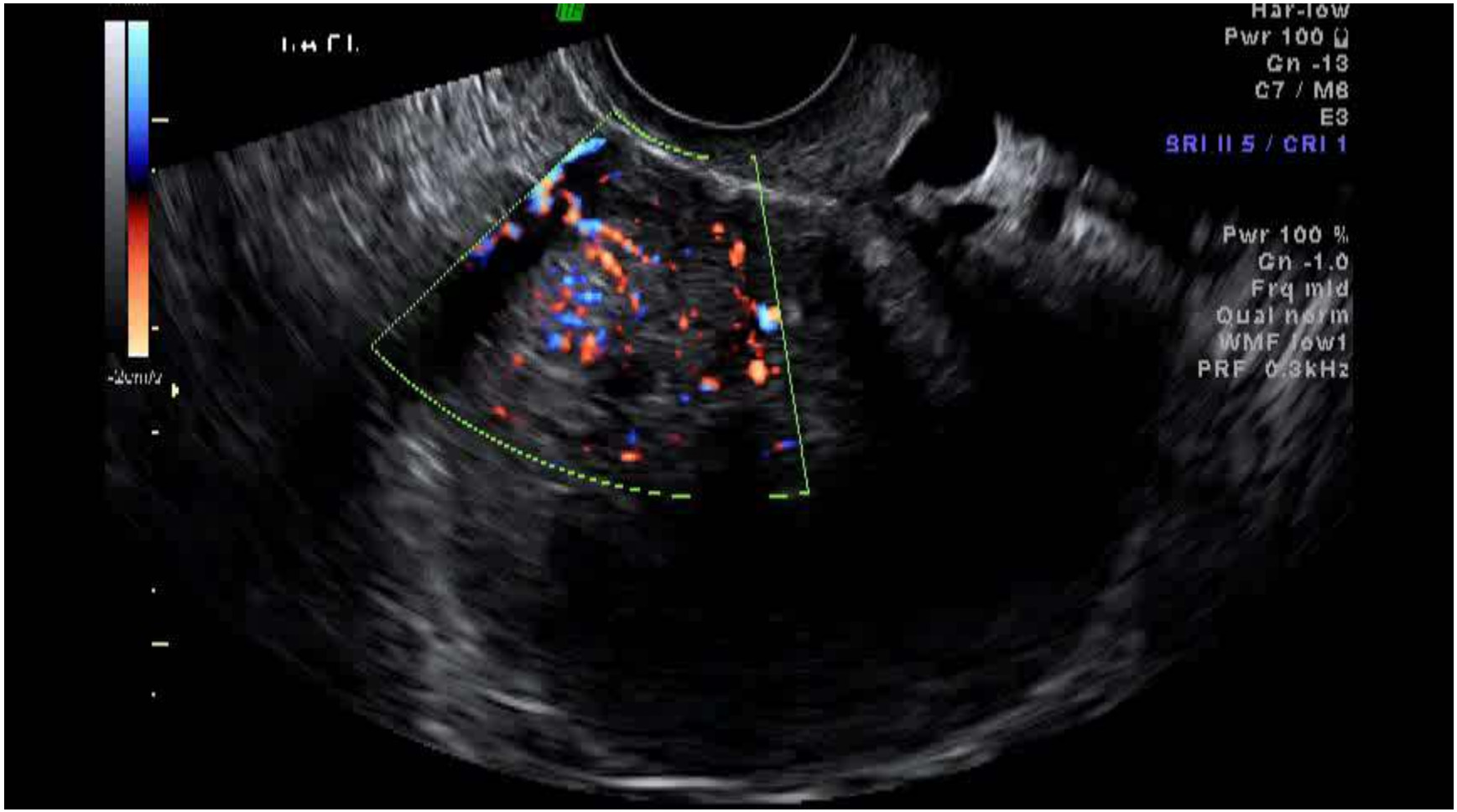
	adenomyosis	leiomyoma
Morphologic criteria sonography detection	79%	84%
Vessels	87% randomly scattered vessels or intramural signals	88% of leiomyomas showed peripheral scattered vessels or outer feeding vessels
Pulsatility index (PI)	82%(PI) of arteries within or around uterine tumors > 1.17	84% of leiomyomas had a PI < or = 1.17

J Assist Reprod Genet. 1999 May; 16(5): 268-75.

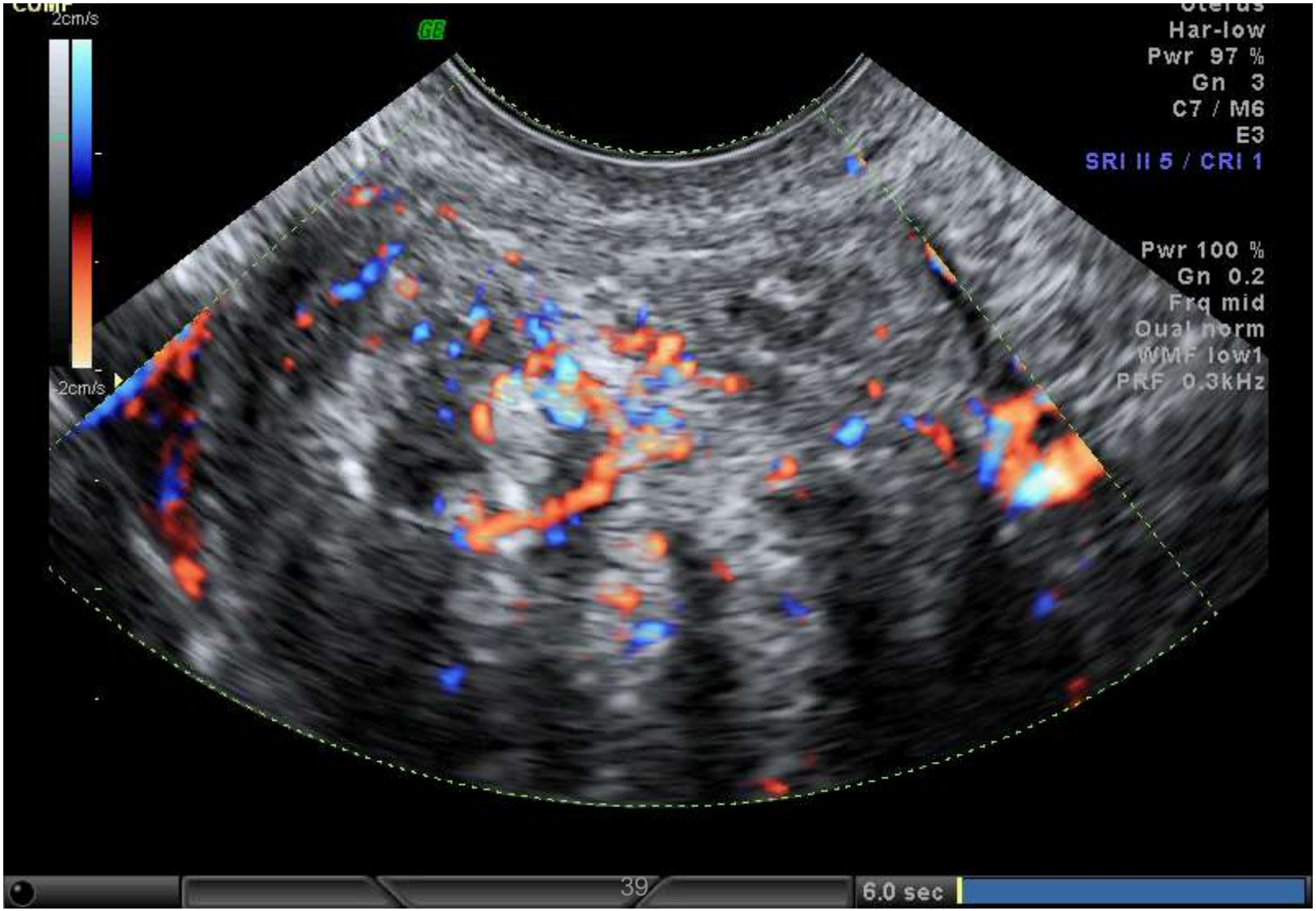
Adenomyosis with Doppler



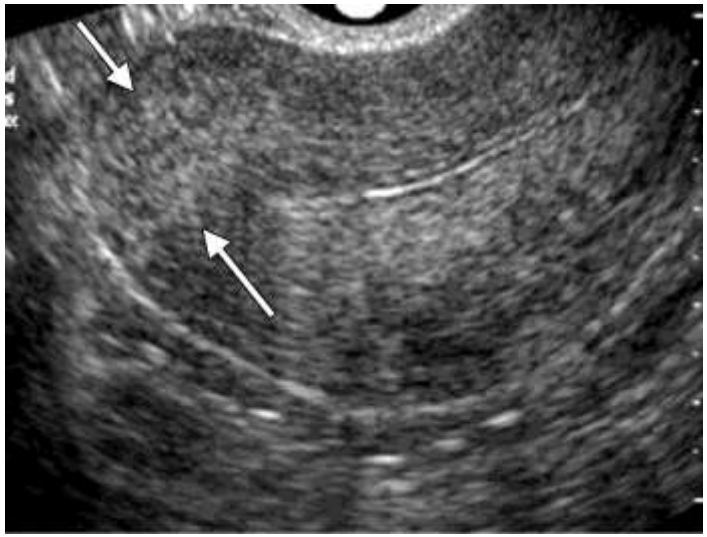
Adenomyosis with Doppler

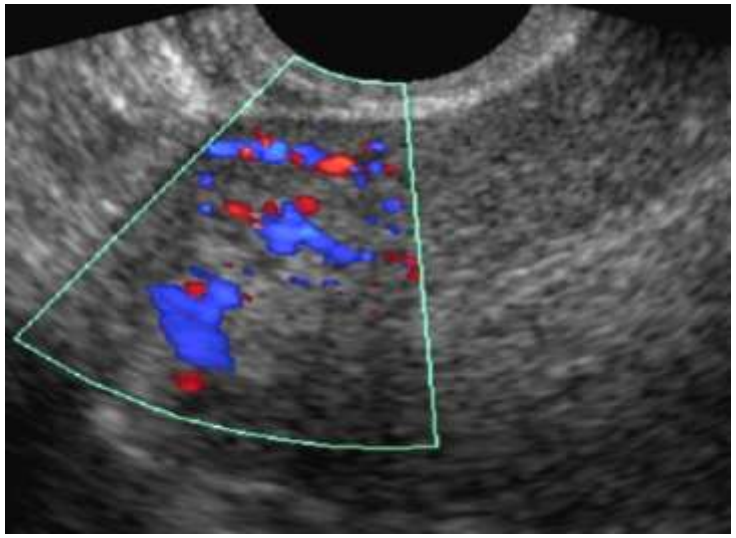


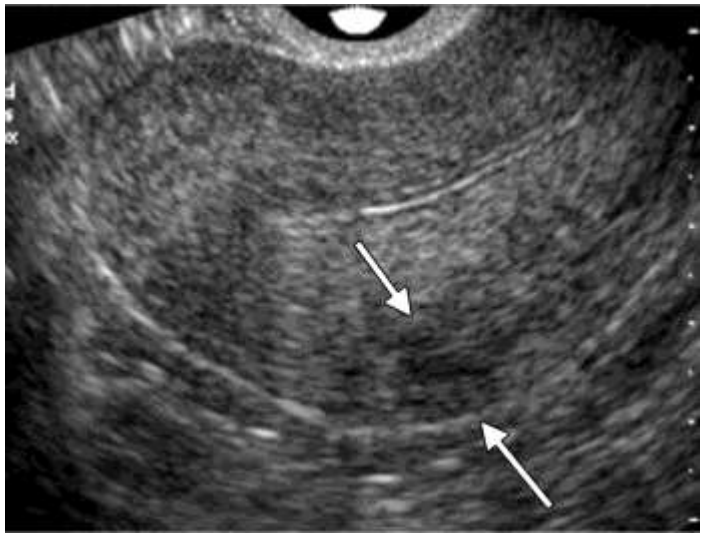
Adenomyosis with Doppler

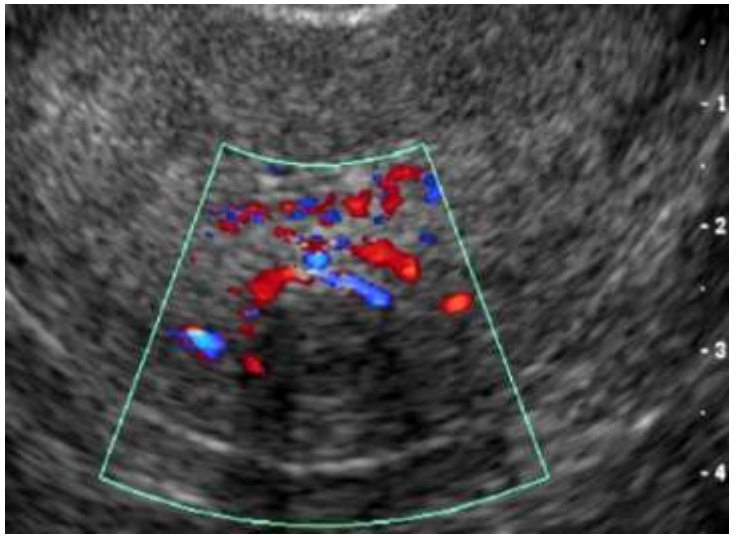


Focal adenomyosis and myoma





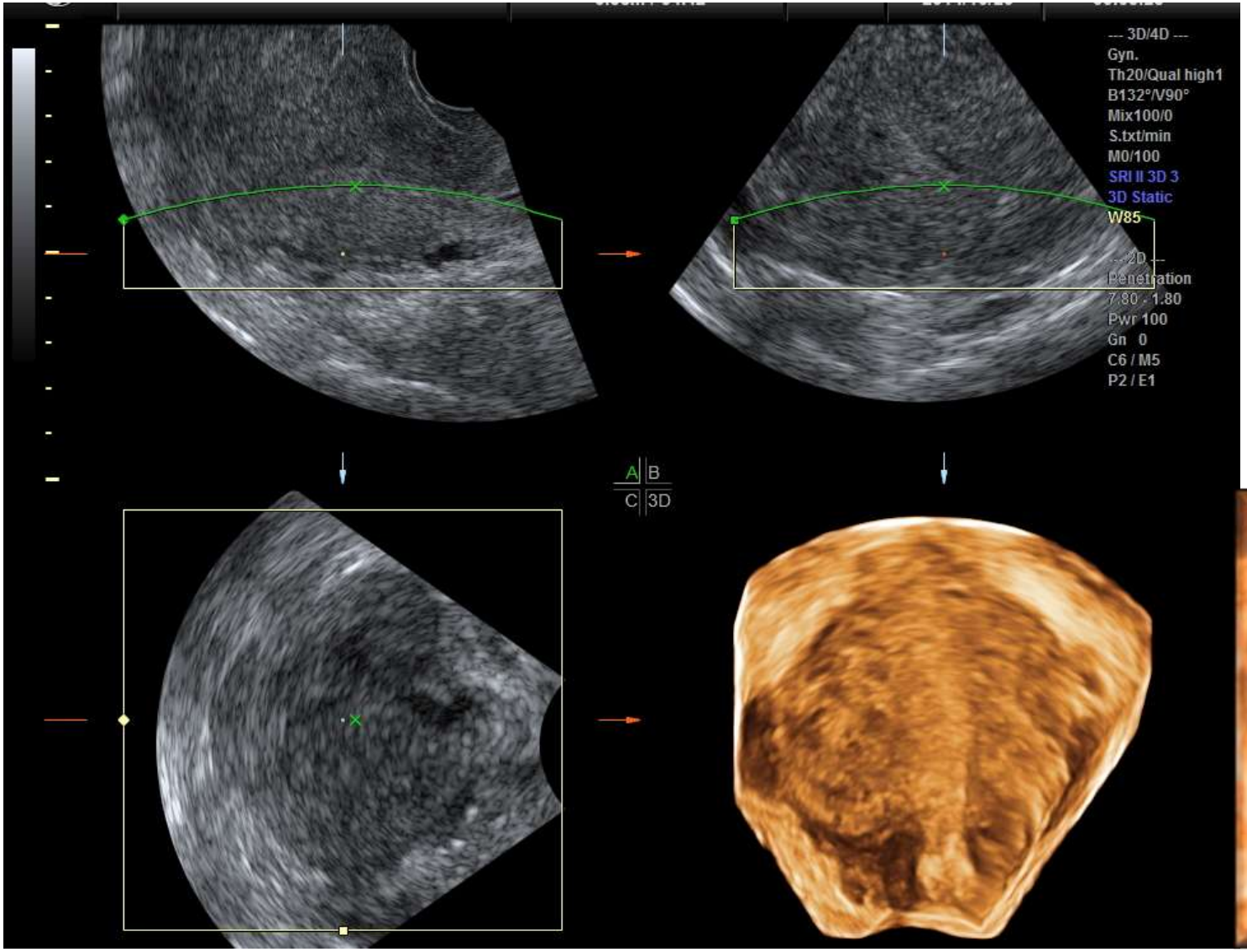




Kuligowska E et al. Radiographics 2005;25:3-20

Severe case

Severe case


--- 3D/4D ---
Gyn.
Th20/Qual high1
B132°/V90°
Mix100/0
S.txt/min
M0/100
SRI II 3D 3
3D Static
W85
--- 2D ---
Penetration
7.80 - 1.80
Pwr 100
Gn 0
C6 / M5
P2 / E1
A
B
C
3D

Adenomyosis signs and menstrual pain

- ✓Gynecologic clinic
- ✓17-55 years
- ✓Quantification of menstrual pain
- ✓US features
- ✓22% adenomyosis

- Statistically significant positive correlation between the severity of menstrual pain and the number of ultrasound features of adenomyosis seen.

Naftalin et al, UOG in press

Malignant transformation of adenomyosis

- **The pathological criteria used for case identification are:**
- i) evidence of pre-existing adenomyosis at the site of the malignant lesion
- ii) presence of glandular cells and/or endometrial stromal cells supporting a diagnosis of adenomyosis
- iii) evidence of transitions between benign and malignant glandular structures
- iv) carcinoma must be absent from invasion or metastasis from another source
- v) carcinoma must be absent from the eutopic endometrium

Malignant transformation of adenomyosis

- Malignant changes in adenomyosis - 6.8% of patients with endometrial cancer
- A majority of cases with adenocarcinoma arising in adenomyosis were associated with adjacent endometrial adenocarcinomas
- Adenocarcinomas developing within adenomyosis often originate from endometrial carcinomas which arise from the eutopic endometrium, then invade into pre-existing adenomyosis

Adenomyosis and infertility

- Adenomyosis may have the potential to impair the implantation of good quality embryos transferred during IVF treatment
- A recent observational study clearly linked adenomyosis diagnosed on magnetic resonance imaging (MRI) with an increase in macrophage and natural killer cells in the endometrium of women experiencing infertility

Human Reproduction, Vol.27, No.12 pp. 3487–3492, 2012

Adenomyosis and infertility

- Macrophages are known to release chemicals which may be detrimental to embryos, such as cytokines tumour necrosis factor a (TNFa) and interferon g (IFNg), plus harmful reactive oxygen species (‘free radicals’)
- Earlier studies have linked the presence of adenomyosis with increased ‘free radical’ concentrations in the endometrium , providing a possible mechanism by which adenomyosis may impair implantation and cause miscarriage.

Human Reproduction, Vol.27, No.12 pp. 3487–3492, 2012

Adenomyosis and IVF outcome

- Metaanalysis 9 papers 1865 women
- Heterogeneity of studies
- Adenomyosis was associated with a 28% (95% CI, 5–45%) reduction in the likelihood of clinical pregnancy in infertile women who underwent IVF/ICSI
- Adenomyosis was associated with a more than doubled risk of early pregnancy loss
- Adenomyosis appears to impact negatively on IVF/ICSI outcome owing to reduced likelihood of clinical pregnancy and implantation, and increased risk of early pregnancy loss
- Screening for adenomyosis before embarking on medically assisted reproductive procedures should be encouraged

Vercellini et al, Human Reproduction, Vol.29, No.5 pp. 964–977, 2014

Adenomyosis and infertility

- Local hyperestrogenism affects implantation
- Hyperperistalsis
- Autoimmune
- Excess free radicals

Adenomyosis and infertility

Table 4: Univariate analysis of the associations between demographic data, clinical symptoms, disease severity and number of sonographic features of adenomyosis in the study group.

	Any adenomyosis feature				Five or above features			
	OR	95% CI for OR LL	UL	P	OR	95% CI for OR LL	UL	P
Age	1.14	1.01	1.29	0.031	1.04	0.97	1.11	0.291
BMI	1.18	0.95	1.46	0.123	1.03	0.94	1.13	0.520
Previous delivery	3.64	0.73	18.15	0.115	0.67	0.3	1.57	0.373
Previous cesarean	1.36	0.16	11.77	0.782	1.04	0.3	3.56	0.947
Dysmenorrhea	1.43	0.15	13.22	0.755	0.99	0.21	4.71	0.993
Dyspareunia	0.41	0.08	2.06	0.280	0.63	0.26	1.52	0.305
GI complaints	0.46	0.11	1.91	0.286	1.32	0.57	3.03	0.515
Urinary complaints	1.68	0.33	8.52	0.529	0.88	0.35	2.2	0.789
Infertility	1.21	0.28	5.21	0.800	**3.19**	**1.25**	**8.17**	***0.015**
ASRM score	1	0.98	1.02	0.873	**1.01**	**1**	**1.02**	***0.046**
ASRM stage	0.91	0.5	1.68	0.772	1.32	0.91	1.9	1.32

ASRM - American Society for Reproductive Medicine; BMI – body mass index; OR – odd's ratio; GI – gastrointestinal; OR – odd's ratio; LL – lower limit; UL – upper limit.

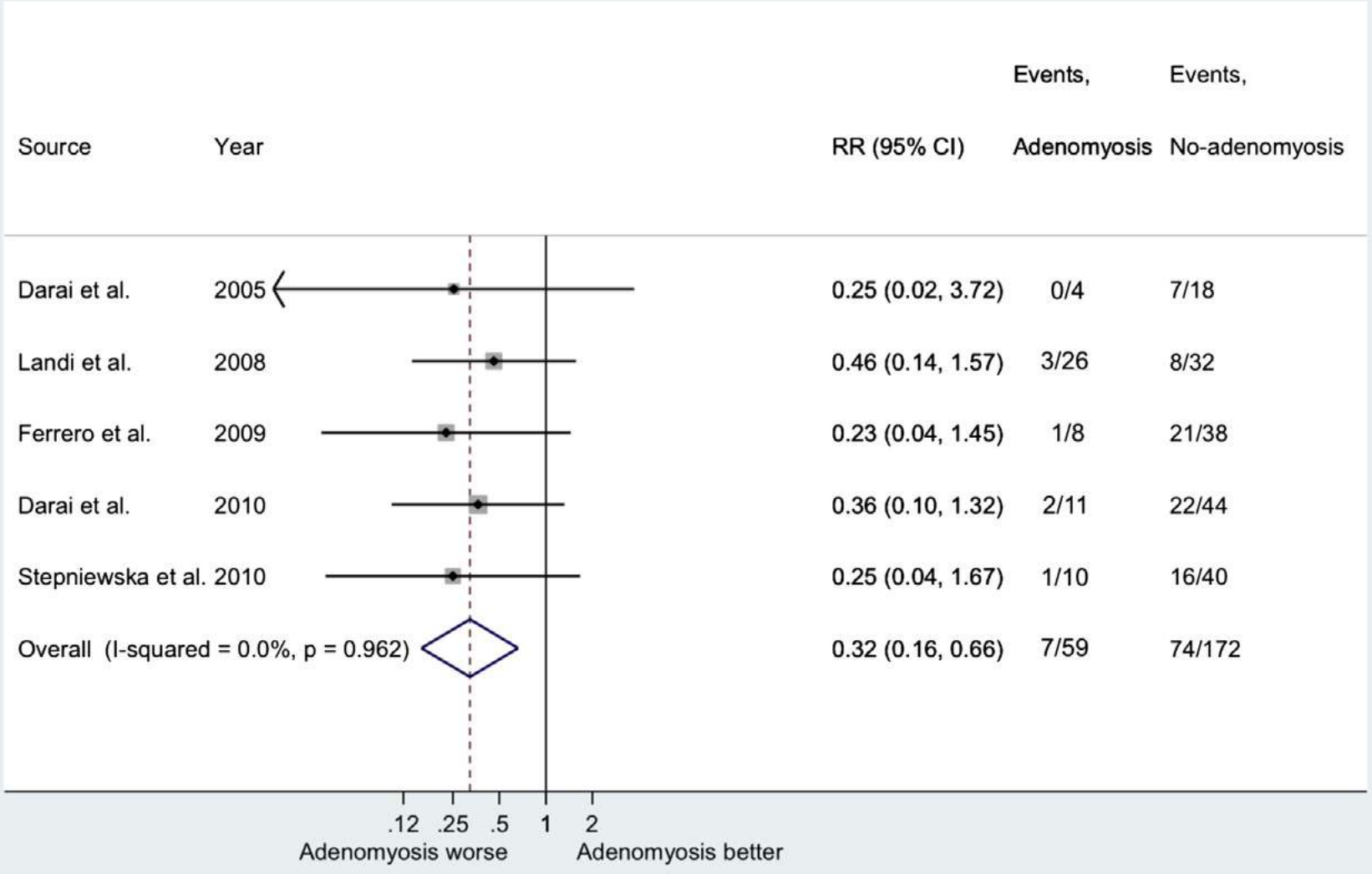
* Statistically significant finding.

What happens after surgery?

- Metaanalysis:
- 5 observational studies, women seeking pregnancy, 7/59 (11.9%) with concomitant adenomyosis conceived, compared with 74/172 (43.0%) in those without adenomyosis
- Adenomyosis was never excised
- RR of clinical pregnancy ranged from 0.23 to 0.46
- Pooling of the results yielded a common RR of 0.32 (95% confidence interval 0.16 to 0.66).
- Screening for adenomyosis before suggesting difficult and risky procedures may allow identification of a subgroup of patients at particularly worse prognosis for which surgery would have a marginal effect on the likelihood of conception

Vercellini et al, Reproductive BioMedicine Online (2014) 28, 704– 713

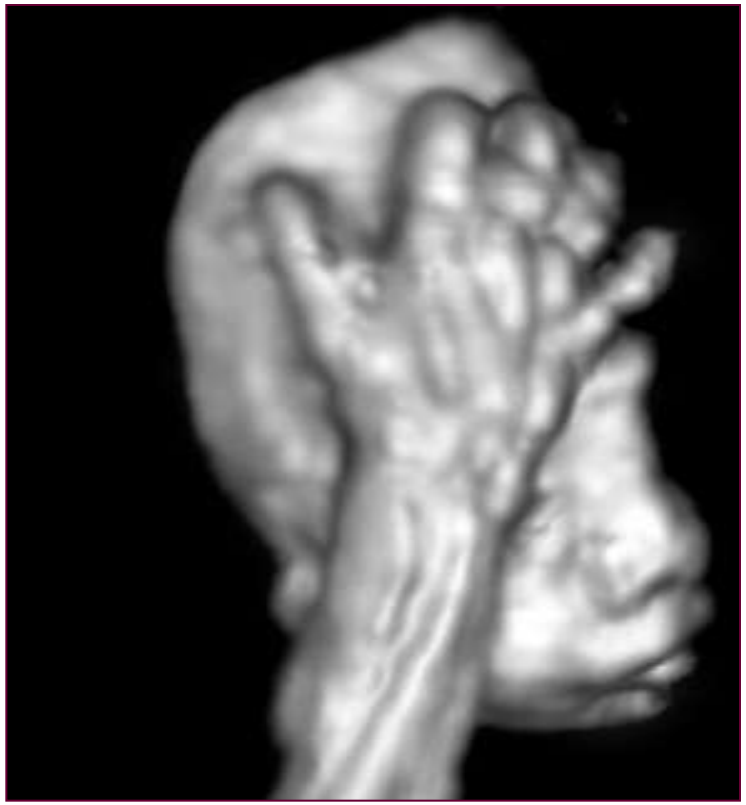
What happens after surgery?



Summary

- ✓Adenomyosis is more common than previously thought
- ✓Can be reliably diagnosed on TVUS
- ✓Is associated with endometriosis
- ✓Possibly similar pathogenesis
- ✓Associated with poor reproductive outcome on IVF and early pregnancy loss
- ✓Even after surgery for endometriosis
- ✓TVUS is imperative for diagnosis and to tailor management

Thank you



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