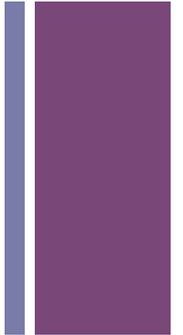


Towards early diagnosis, what would be the best strategy

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2015-May, Paris

Conflicts of interest

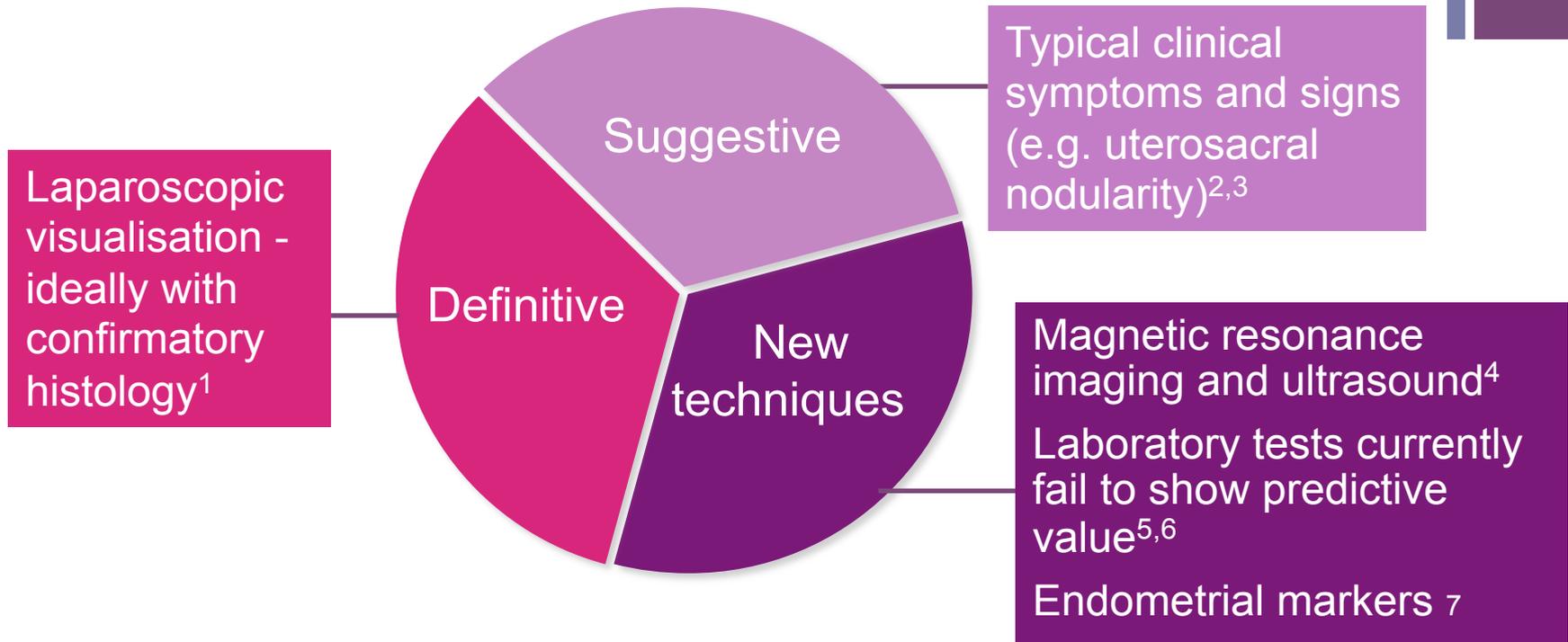


- No conflict

Barriers to early diagnosis

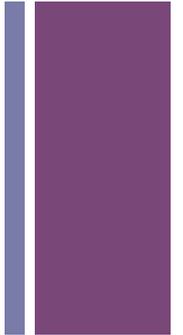
- Lack of awareness
- May be mistakenly dismissed as routine menstrual pain, particularly in younger women
- Lack of nonsurgical markers significantly delay diagnosis
- Typically, women with endometriosis suffer a delay in diagnosis of 7–12 years and may present to 5+ physicians before symptoms are addressed

Current Diagnostic Techniques



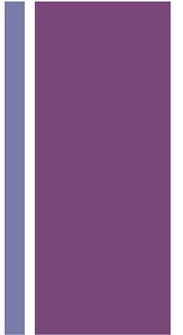
1. Kennedy, et al. *Hum Reprod* 2005;20(10):2698-704; 2. Mounsey, et al. *Am Fam Physician* 2006;74(4):594-600; 3. Matorras, et al. *Am J Obstet Gynecol* 1996;174(2):620-3; 4. Bazot, et al. *J Minim Invasive Gynecol* 2005;12(2):178-85; 5. Bedaiwy, et al. *Clin Chim Acta* 2004;340(1-2):41-56; 6. Matalliotakis, et al. *Arch Gynecol Obstet* 2005;271(1):40-5; 7. Al-Jefout, M, et al. *Hum Reprod* 2009;24(12):3019-24. 7. Bokor, A, et al. *Human Reproduction* 2009;24(12):3025-32.

History and physical examination for diagnosis



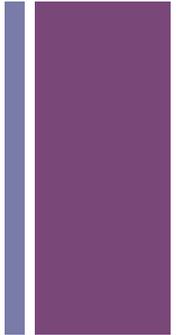
- Clinical history and pelvic examination can highlight the possibility of endometriosis, but have limited value due to heterogeneity in clinical presentation¹⁻³
- Abnormalities on clinical examination correlate with the presence of endometriosis on laparoscopy in 70% to 90% of cases⁴

How do fully comprehensive patient-centered descriptions of EM symptoms



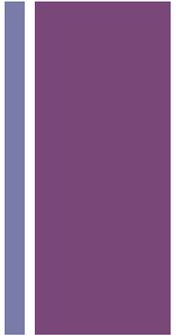
- Detailed knowledge of pelvic pain characteristics was found to be helpful in the pre-operative assessment of patients with suspected EM
- The various existing pain questionnaires and pain scales to assess symptoms related to EM were primarily developed on the clinician's basis
- The qualitative study results indicated :
 - Patients and clinicians identified the same five categories of pain symptoms
Severe pelvic pain and dysmenorrhoea, Dyspareunia, Gastro-intestinal symptoms, Bladder symptoms, Other symptoms
 - Clinicians' description, especially on the severe pelvic pain and dysmenorrhoea, is incomplete

A clinical screening tool: symptom-based predictive model



- Using the clinical information to predict EM before surgery
 - Symptoms
 - Medical history profiles
 - Ultrasound evidence

Surgical diagnosis and staging

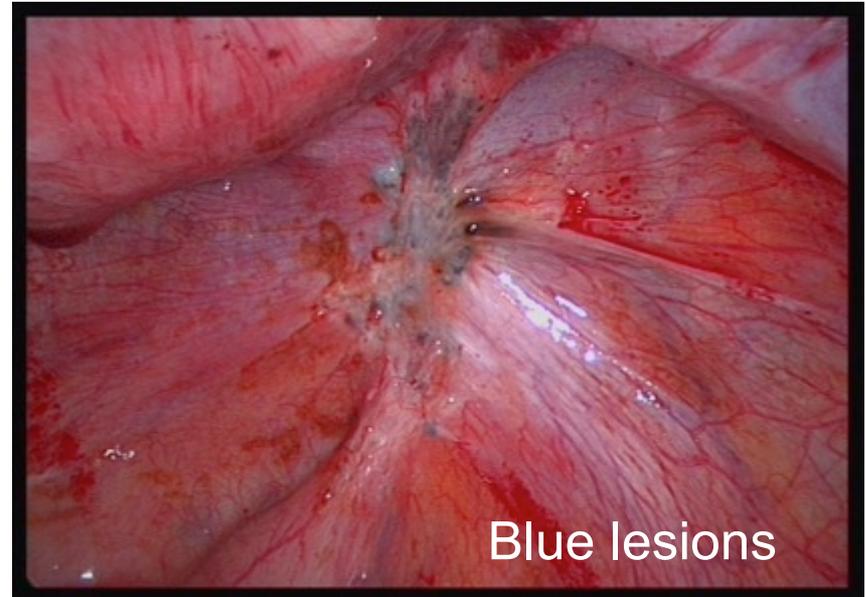
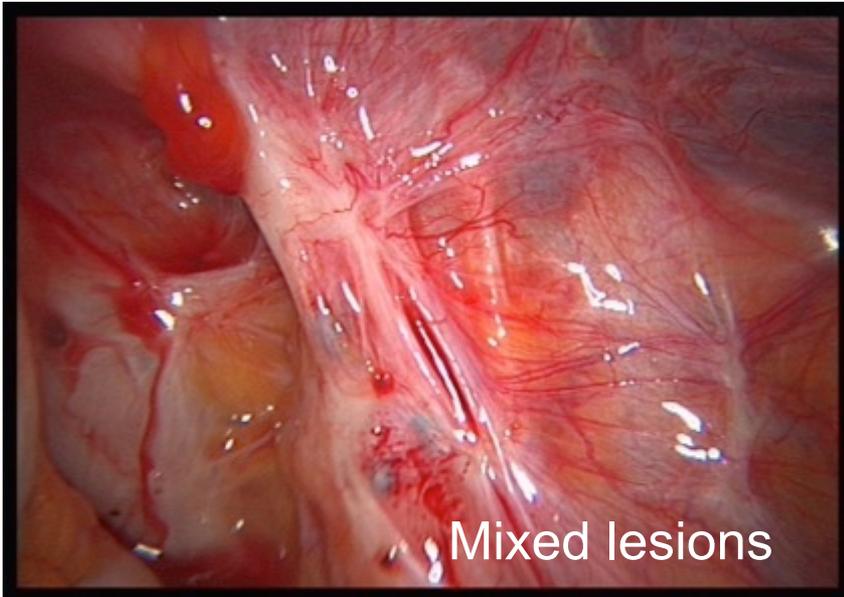
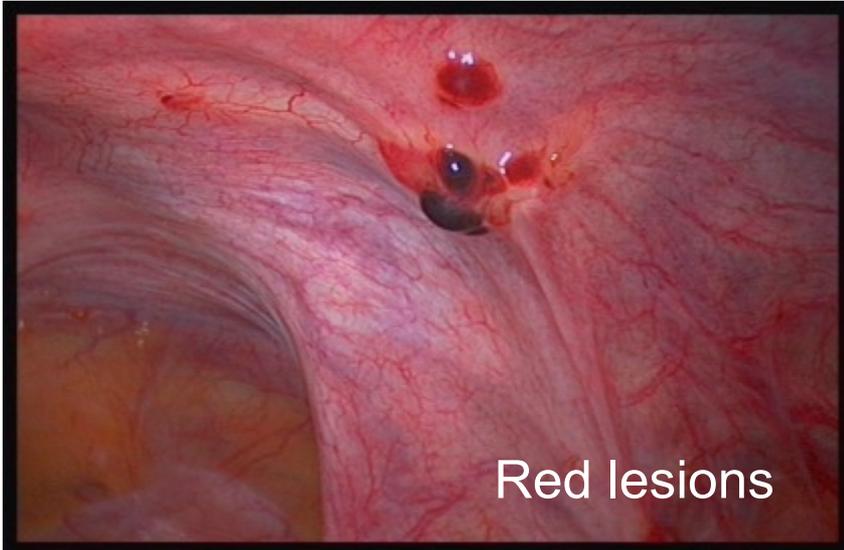


- Laparoscopic intervention is the primary means of definitive diagnosis
- Clinically visualized findings may represent the “tip of the iceberg”
- Glands + stroma = gold standard diagnosis, but fibrosis + hemosiderin-laden macrophages may be sufficient for presumptive diagnosis
- Accuracy of diagnosis depends on ability of surgeon to adequately identify disease

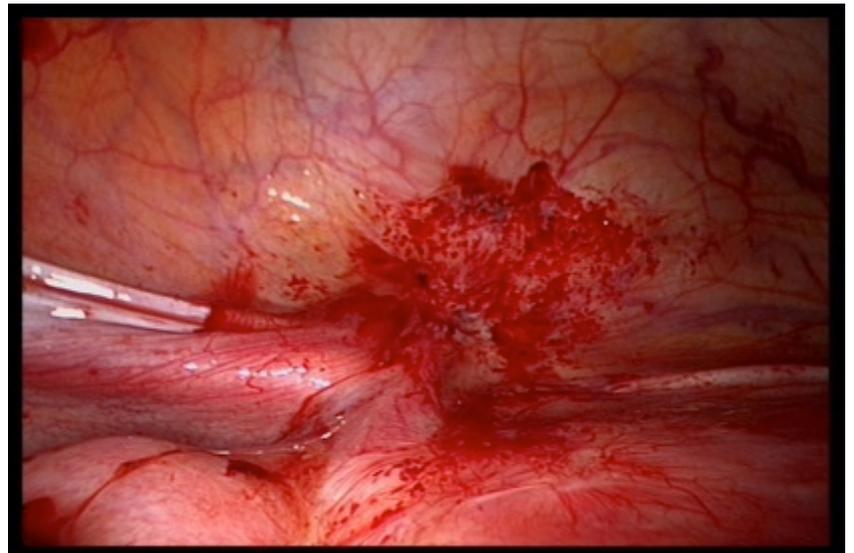
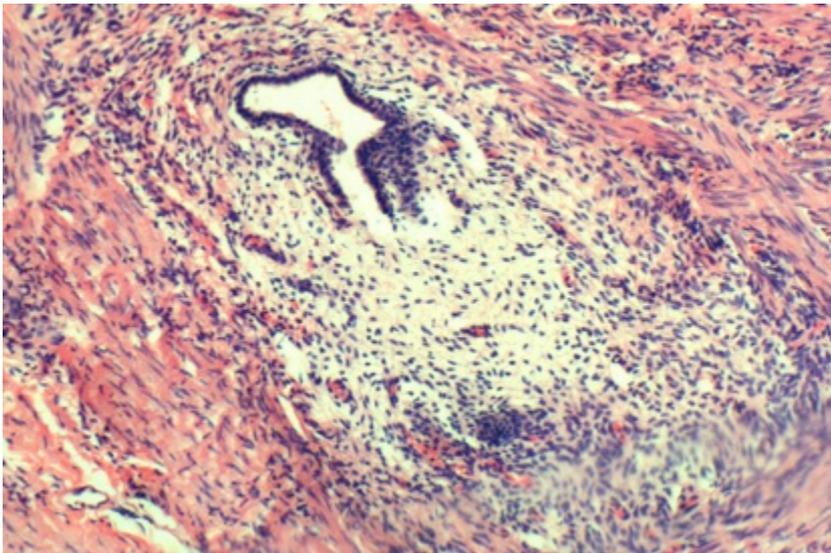
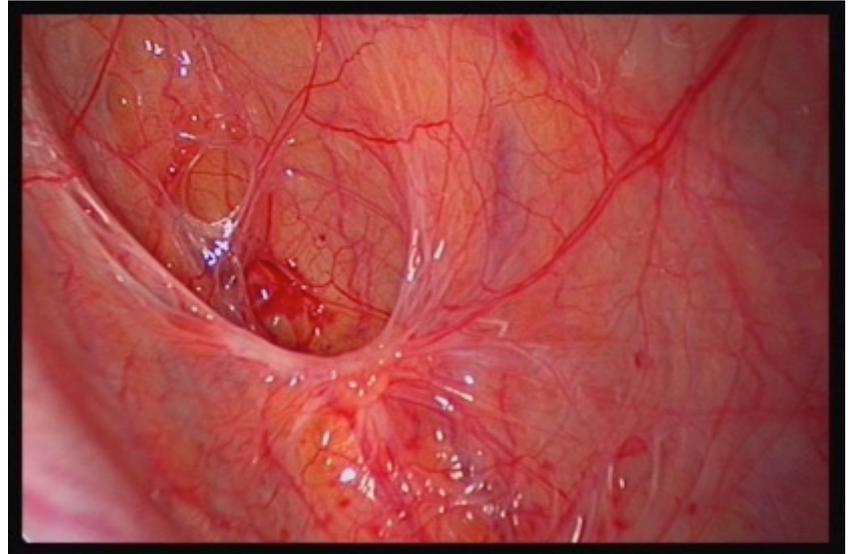
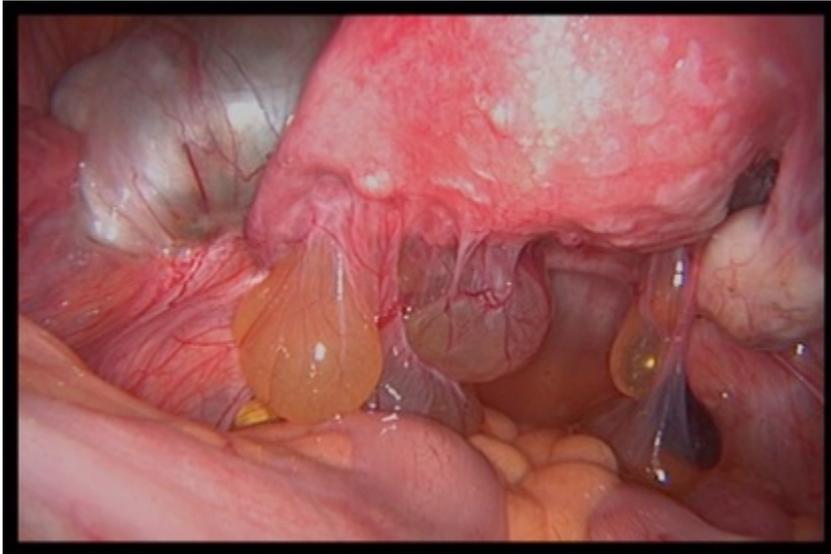
Laparoscopy

Advantages	Disadvantages ^{2,3}
Gold standard investigation technique ¹	Facilities/surgical expertise not universally available
Possibility to diagnose and treat during one procedure	Not all patients are suitable for invasive techniques
	False-positive and false-negative findings
	Risk of major complications (bowel injury and vascular injury)

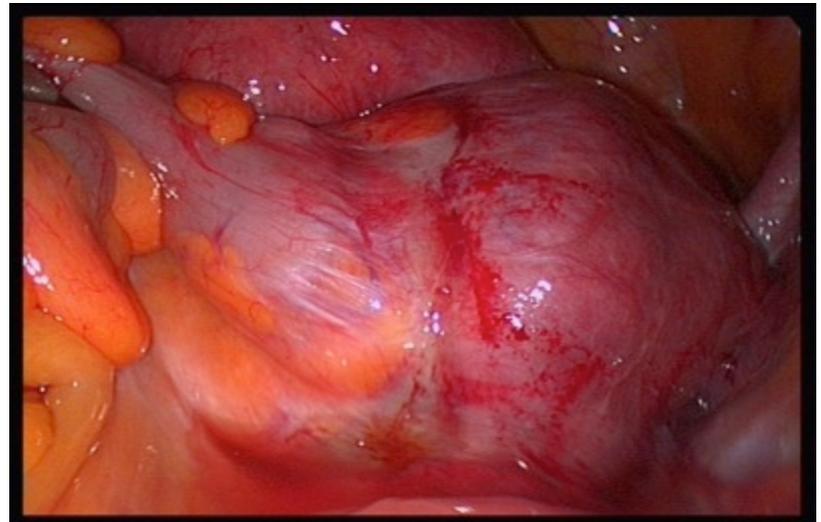
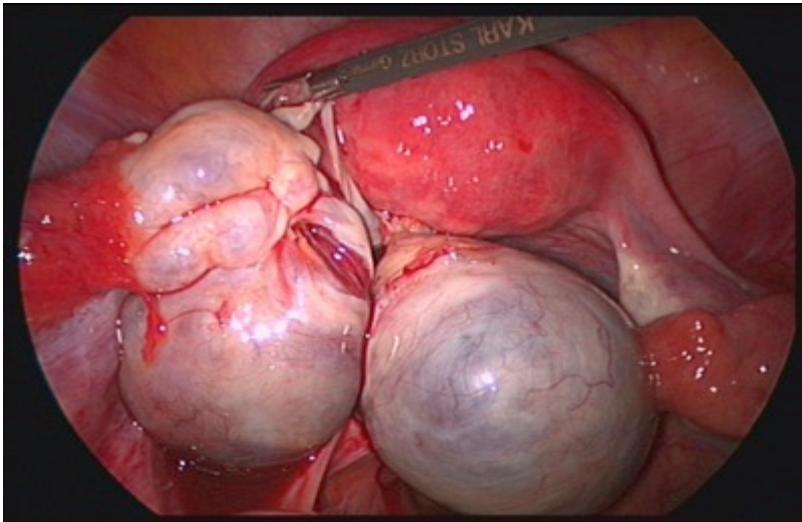
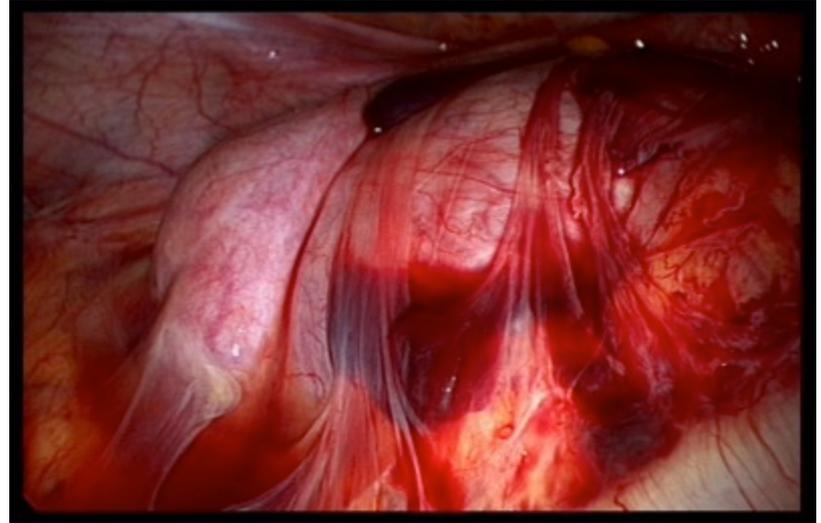
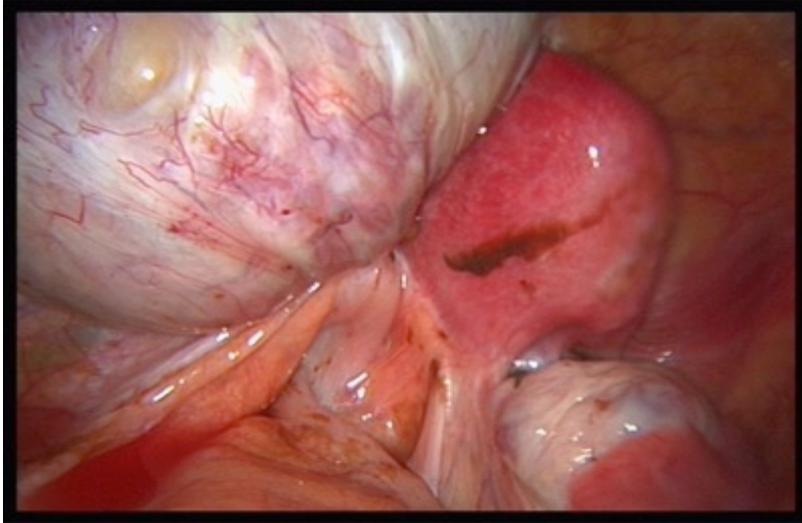
Typical EM lesions



Atypical EM lesions



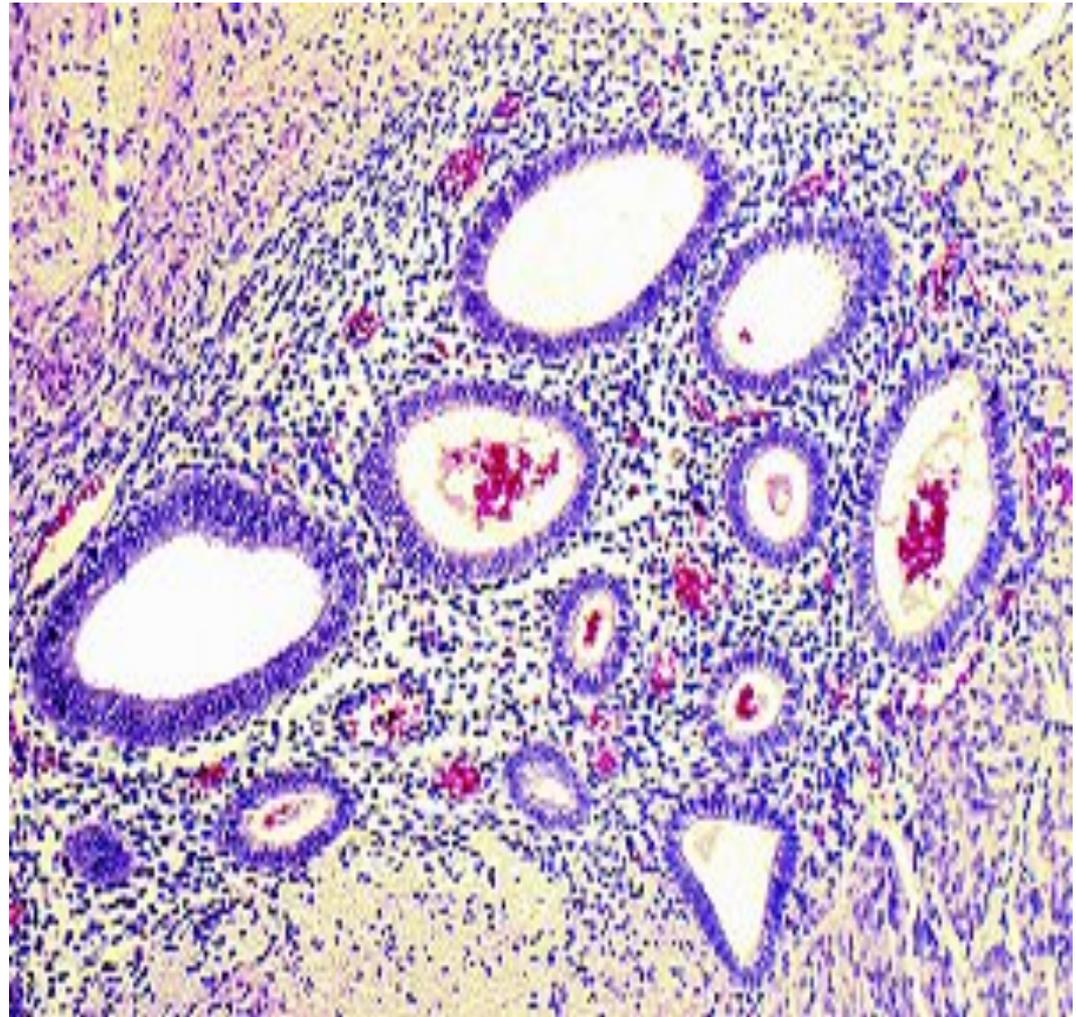
Ovarian endometrioma with adhesion to neighborhood structures



Histological features

2 or more of the following histologic features are criteria for diagnosis:

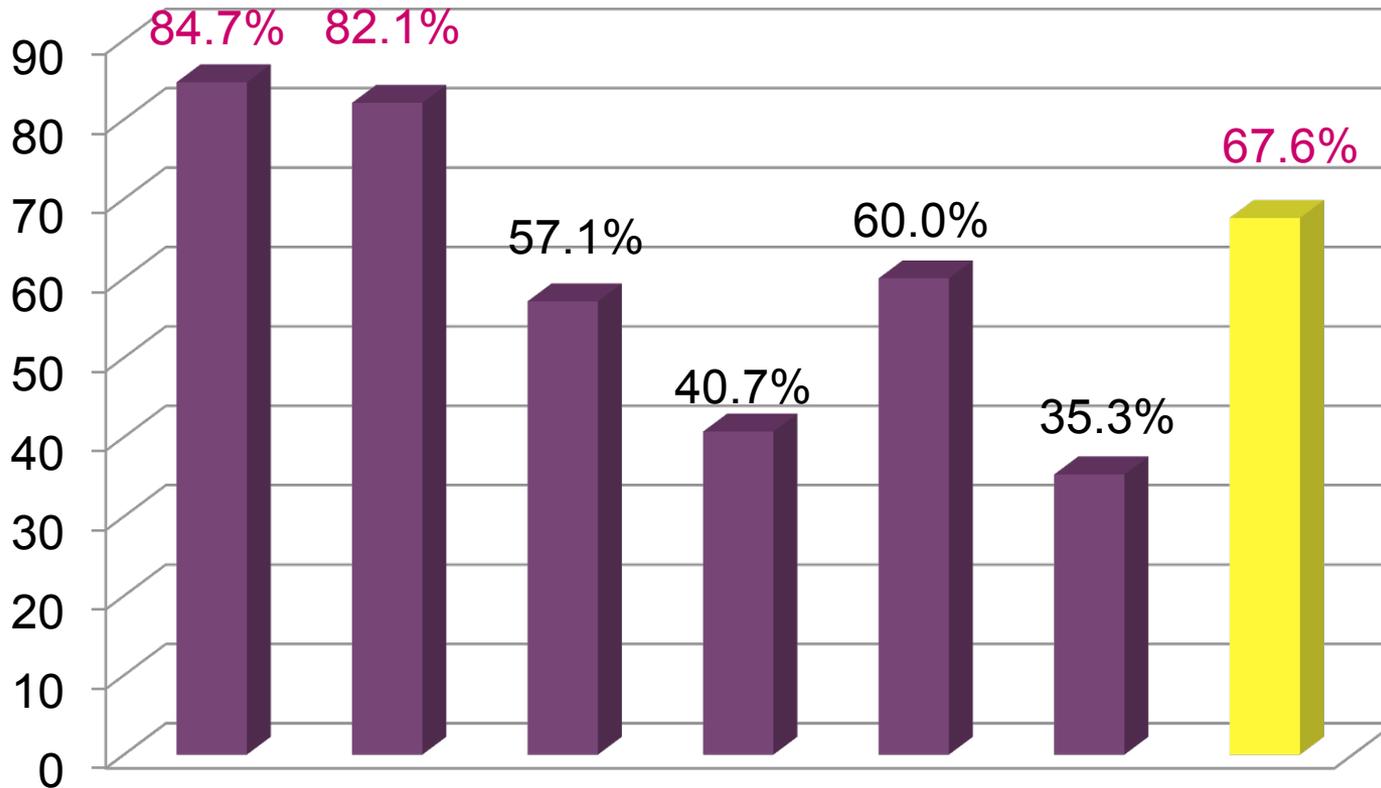
- Endometrial epithelium
- Endometrial glands
- Endometrial stroma
- Hemosiderin-laden macrophages



Study on the correlation between laparoscopic and histologic diagnosis of endometriosis

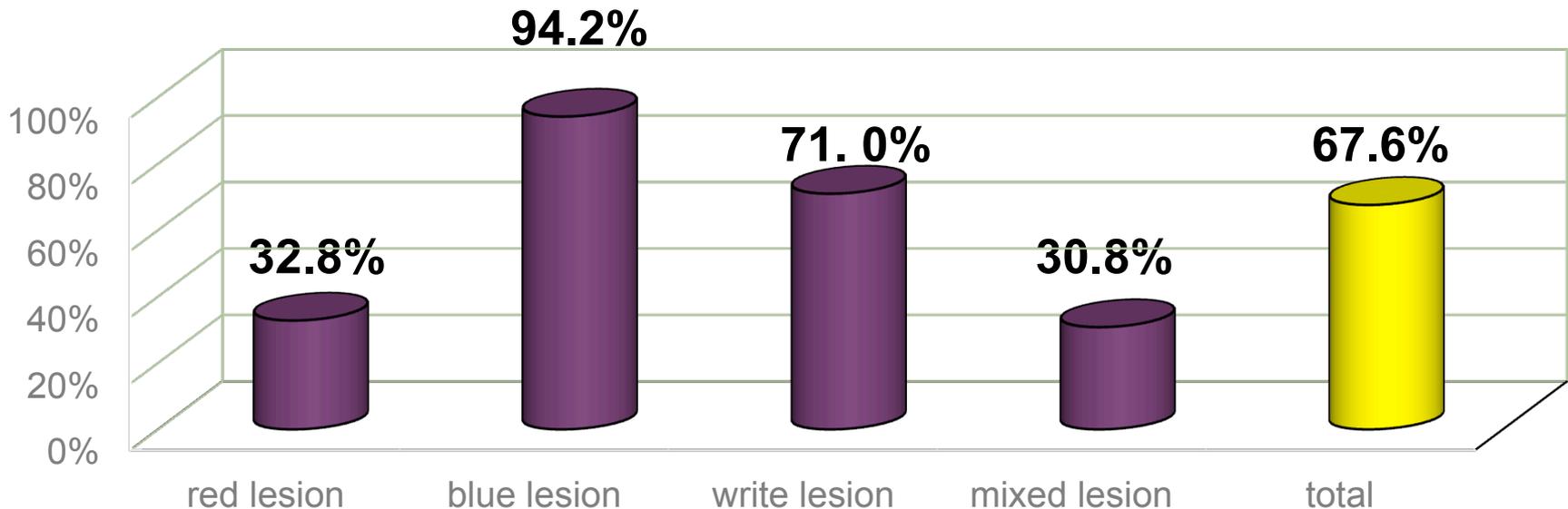
- 62 cases of laparoscopically diagnosed endometriosis performed by one surgeon, locations and colours of different lesions were recorded
- Excision of lesions or biopsy of normal-appearing peritoneum or ovarian cystectomy were performed, 273 specimens
- Histologic evaluation
- Correlation between laparoscopic diagnosis and pathological findings
- Sen, Spe, PPV, NPV of laparoscopic diagnosis

PPVs of lesions for different biopsy sites



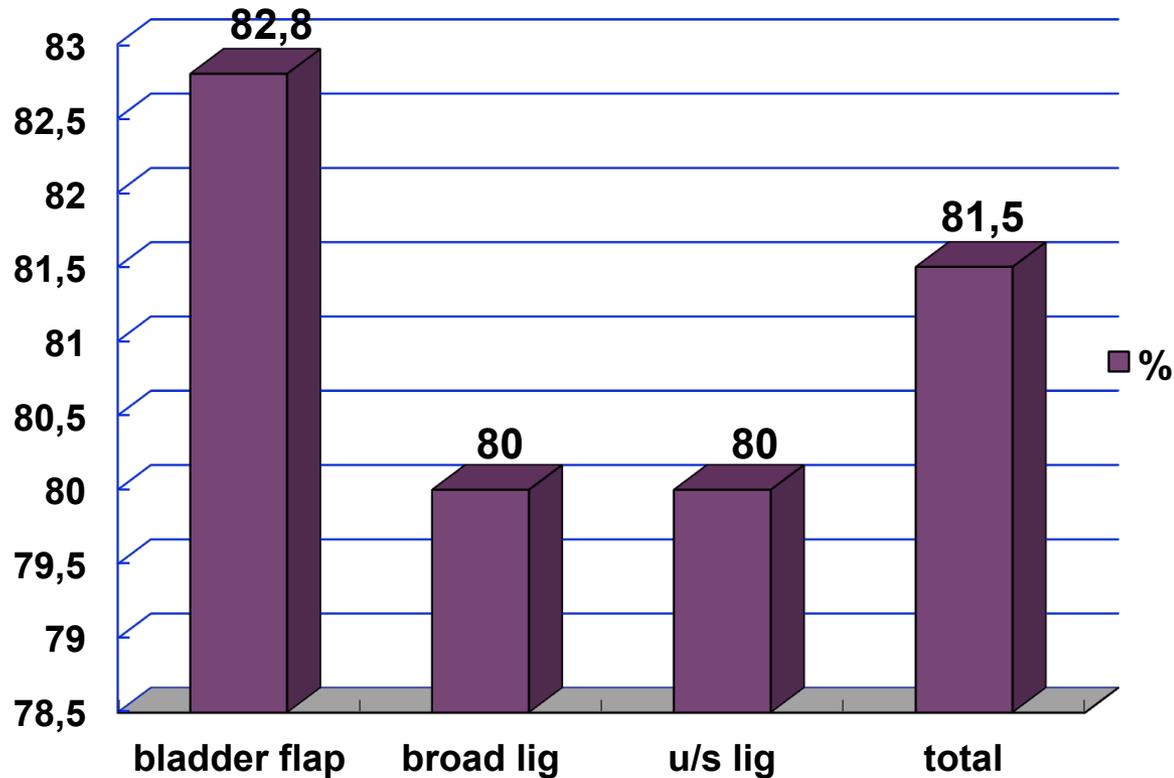
- PPVs varied among sites. The total PPV was 67.6%, with highest of 83% for lesions at u/s lig

PPVs of different colours of lesions



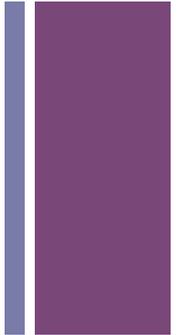
- Highest PPV of 94.2% for black(blue) lesion and lower of about 30% for red or mixed lesions
- The sensitivity 97.3%

NPVs of normal-appearing peritoneal biopsies



- 18.5% of normal-appearing peritoneal biopsies were confirmed to be endometriosis histologically
- Specificity was low (38.3%)

Histologic diagnosis of ovarian endometriosis



- 80.3% (57/71) cysts were histologically confirmed
- Of 55 cases with ovarian endometrioma, each patient had at least one cyst confirmed histologically to be endometriosis

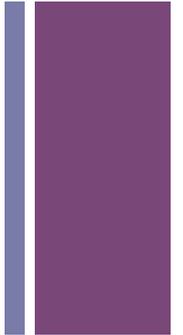
Conclusions of our study

- Laparoscopy might reach 100% diagnostic accuracy with histology for patients with endometriosis.
- Black lesions and deep nodules in U/S ligament are of higher PPV than other colours or locations

Accuracy of visual diagnosis (laparoscopy) of endometriosis

- Positive predictive values vary greatly: 25 – 100%¹
- **Deep lesions are more accurately diagnosed than superficial lesions:**²
 - Odds ratio for deep lesions: 2.50 (1.50 – 4.18; p<0.01)
 - Odds ratio for superficial lesions: 0.16 (0.06 – 0.41; p<0.01)
- Endometriosis was accurately diagnosed in 49.7% of ASRM² stage 1
 - Low accuracy for peritoneal lesions
 - Deep endometriosis was more likely to be diagnosed accurately than superficial endometriosis
 - **Larger lesions diagnosed more accurately than smaller lesions.**

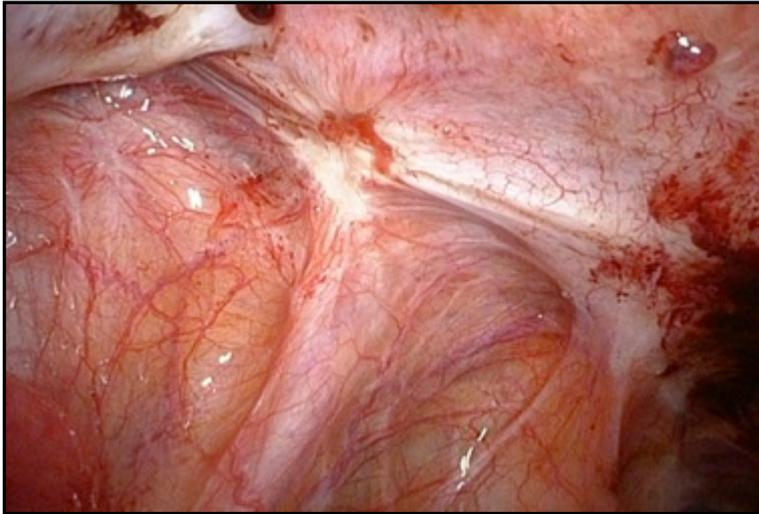
Difficulties in lesion assessment



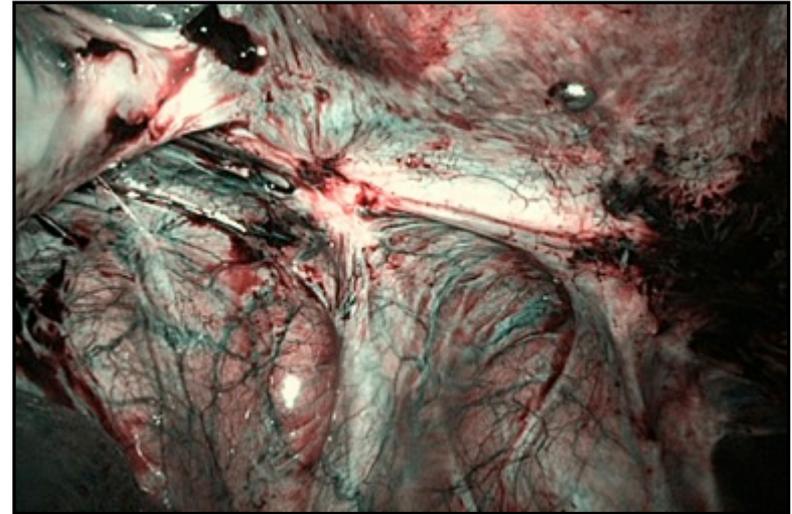
- Lesion inspection
 - Very varied peritoneal lesion appearances
 - Depth and location of lesions
 - Bulk of lesions and tissue distortion; adhesions
 - Inter-observer variability
- Pathology assessment
 - Diathermy artefact, especially small biopsy samples
 - Serial sections
 - Limited tissue amount; stroma only
 - Previous surgery and scarring

Narrow band imaging laparoscopy could more effectively detect peritoneal endometriosis

- Blue and green narrow band lights source using 415 and 540nm filters can be absorbed into the blood, increase the contrast and definition of vascular pattern in mucosa and submucosa, and improve the accuracy of diagnosis



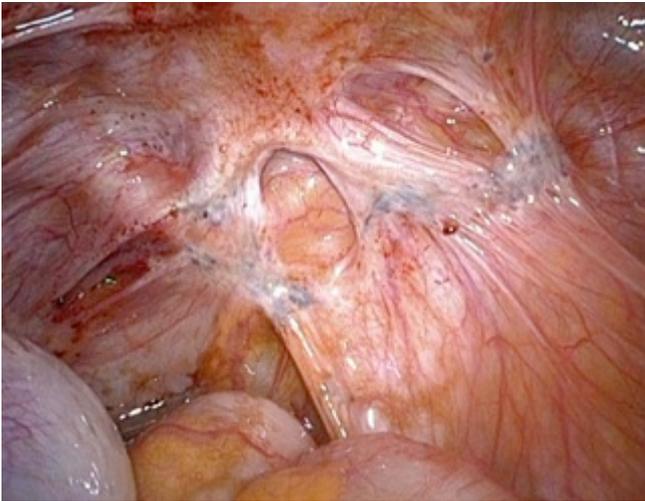
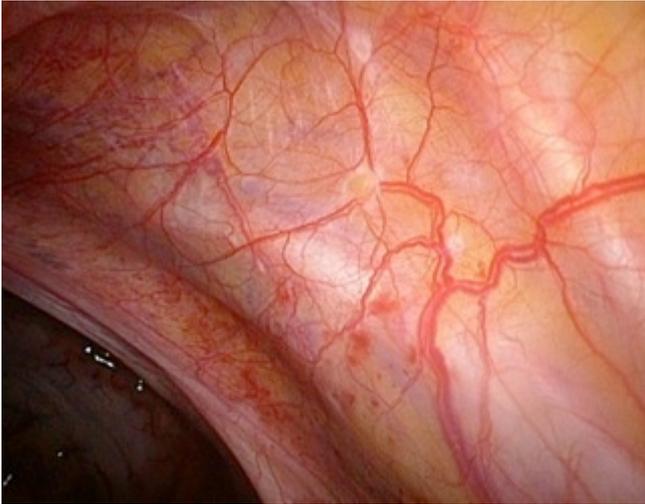
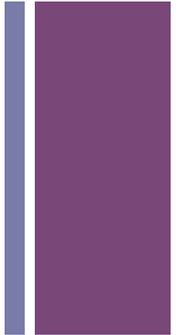
Conventional laparoscopy



NBI

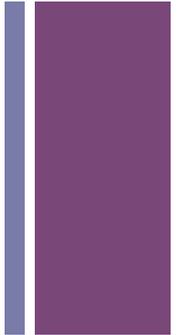
For peritoneal lesions, sensitivity is 92.3%, specificity is 63%, PPV: 68%, higher than that of conventional laparoscopy

Conventional and NBI laparoscopy



- Imaging of different colour lesions:
 - Red and blue lesions show the blue and black
 - White lesions show the white with blue vascular net and clear lesion margin

Ultrasound diagnosis of endometrioma



- Criteria for diagnosis by ultrasound:¹
 - Typical endometrioma: a unilocular cyst with ground glass echogenicity and no to moderate vascularization
 - Atypical endometrioma: a unilocular cyst with ground glass echogenicity and papillary projections (protrusion of solid tissue into the cyst lumen with a height of 3 mm or more), and no flow inside the papillary projection
- Postmenopausal women are less likely to have unilocular cysts and to exhibit ground glass echogenicity²

U/S to detect adhesions in the presence of endometrioma

- The presence of **pelvic fluid, fine septa** (adhesions) can be seen between the ovary, the endometrioma, the uterus, or the peritoneum of the pouch of Douglas (POD)¹
- The **sliding sign**: gentle pressure is placed against the cervix with the transvaginal probe to establish whether the anterior rectum glides freely across the posterior aspect of the cervix (posterior cervical region) and posterior vaginal wall²
- **Kissing ovaries**: The detection of kissing ovaries at TVS is confirmed to be associated with the presence of intestinal deep endometriosis and longer operating time but its diagnostic accuracy in term of sensitivity is poor and it cannot be used in the clinical practice as “soft marker” of rectosigmoid endometriosis³



Endometrioma diagnosis: MRI

- MRI is requested in selected cases if ultrasound outcome is inconclusive, if malignant transformation is suspected, or both¹
- MRI has a high specificity (98%) in diagnosing endometriomas¹
- Owing to its ability to characterize hemorrhage, “shading” is a specific MRI of sign for endometrioma

DIE diagnosis

- DIE is difficult to diagnose, and there is usually a significant delay in diagnosing endometriosis^{1,2}
- Diagnostic delay is longer in more severe cases³
- Specialized radiological assessments may be needed to detect DIE lesions preoperatively: U/S, MRI, rectal endoscopic ultrasonography⁴⁻⁶

A clinical score can predict associated DIE before surgery for an endometrioma

- The first clinical model to determine the likelihood of having DIE from the U/S diagnosis of an ovarian cyst using four clinical symptoms:

Clinical symptom	Coefficient
Dyspareunia VAS score >5 or GI symptoms ≥ 5	18
Duration of pain for over 24 months	13
Prescription of the oral contraceptive pill for severe primary dysmenorrhea or worsening of secondary dysmenorrhea	13
Primary or secondary infertility	9

- Absent = 0; present = 1; then \times coefficient
 - < 13 = low risk; predicted risk = 10% (95% CI: 7–15)
 - ≥ 35 = high risk; predicted risk = 88% (95% CI: 83–92)

MRI signs suggestive of posterior and lateral wall DIE

- Presence of macroscopic endometriosis implants (>5 mm)
- Disappearance of the fat tissue plane separating the different structures
- Direct signs of adhesions are well displayed on T2 -weighted imaging as hypointense bands, with variable thickness
- Uterosacral ligament increased and inhomogeneous thickness
- Presence of specific signs of posterior cul-de-sac obliteration:
 - Retroflexed uterus
 - Tethered appearance of the rectum in direction of the uterus
 - Strands between the uterus and intestine
 - Fibrotic plaque covering the serosal surface of the uterus
 - Elevated posterior cervical fornix

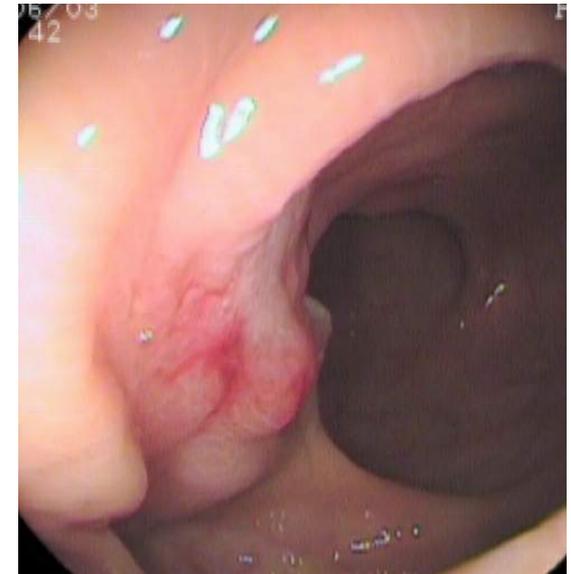
MRI for DIE

- May detect even smallest of lesions and distinguish hemorrhagic signal of endometriotic implants
- Superior to CT scan in detecting limits between muscles and abdominal subcutaneous tissues
- T1-weighted images, hyperintense foci may be visualized; this finding is highly specific for endometriosis

Region	MRI sensitivity ¹	MRI specificity ¹
Retrocervical space	89.4%	92.3%
Rectosigmoid space	86.0%	92.9%
Bladder	23.1%	100%
Ureters	50.0%	100%
Vagina	72.7%	100%

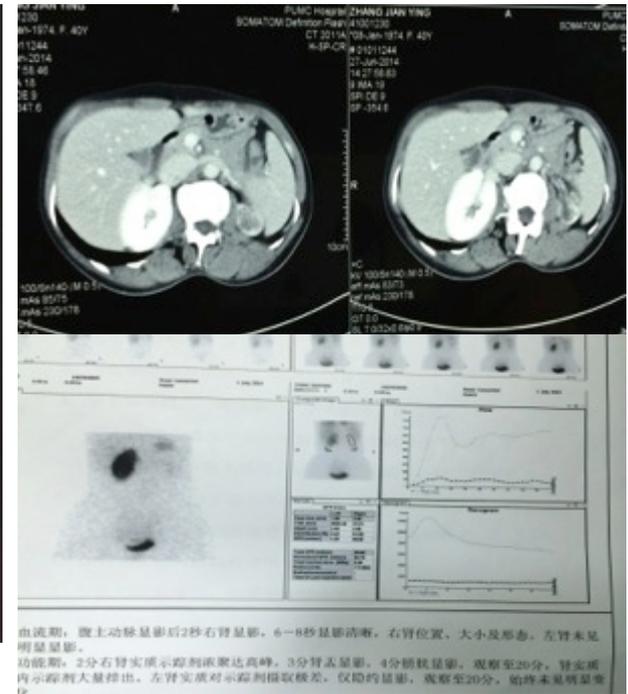
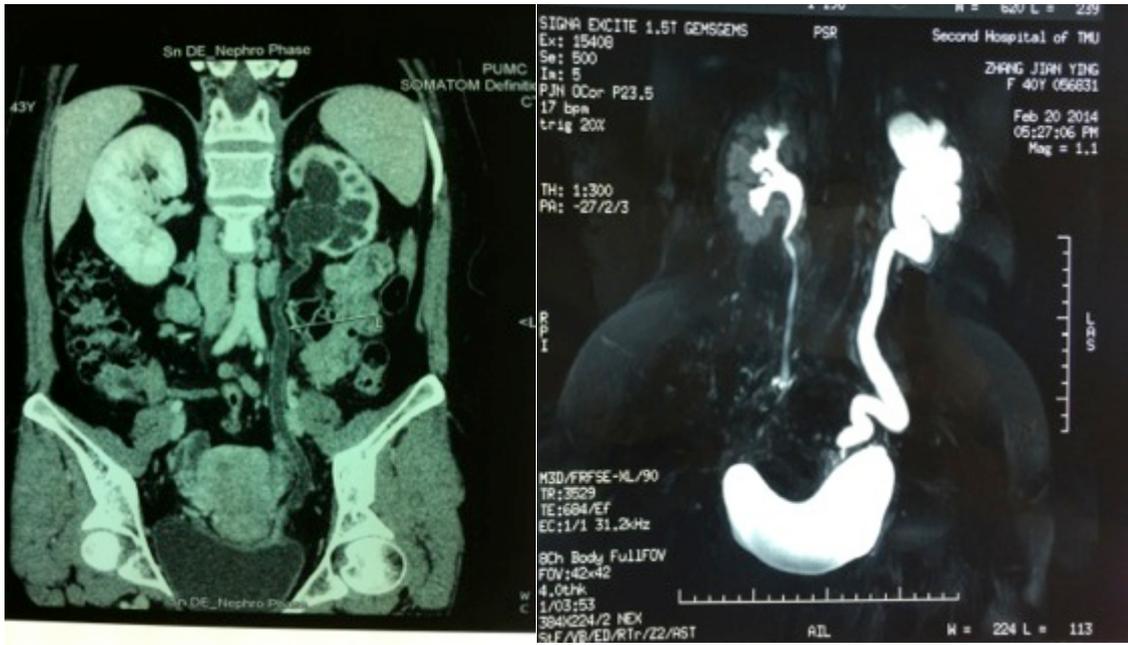
Specific evaluation for bowel involvement

- If rectal nodules was found during pelvic exam, MRI was used to evaluate infiltration depth and rectal stenosis
- If protrusion or stenosis of rectum was found, colonoscopy is suggested to evaluate sigmoid- rectal lumen and biopsy to exclude rectal malignancy



Specific evaluation for ureter involvement

- DIE may affect ureter, leading to hydroureter or hydronephrosis. MRI or CTU are used to evaluate the location and extent of damage of the ureter
- Renogram may be used for evaluation of renal function

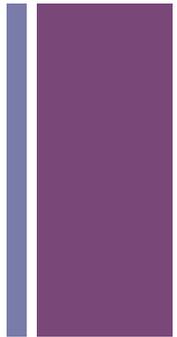


Current leads for “non-invasive” diagnosis

- Multiple publications on biomarker studies in blood, urine, endometrial biopsy, peritoneal fluid or combinations
- Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria; systematic review of >50 potential biomarkers identified in literature

“Have not yet identified a single clinically useful non-invasive diagnostic biomarker or panel of biomarkers. More studies are needed before biomarkers can be introduced into clinical practice”

Diagnostic value of plasma microRNAs in endometriosis



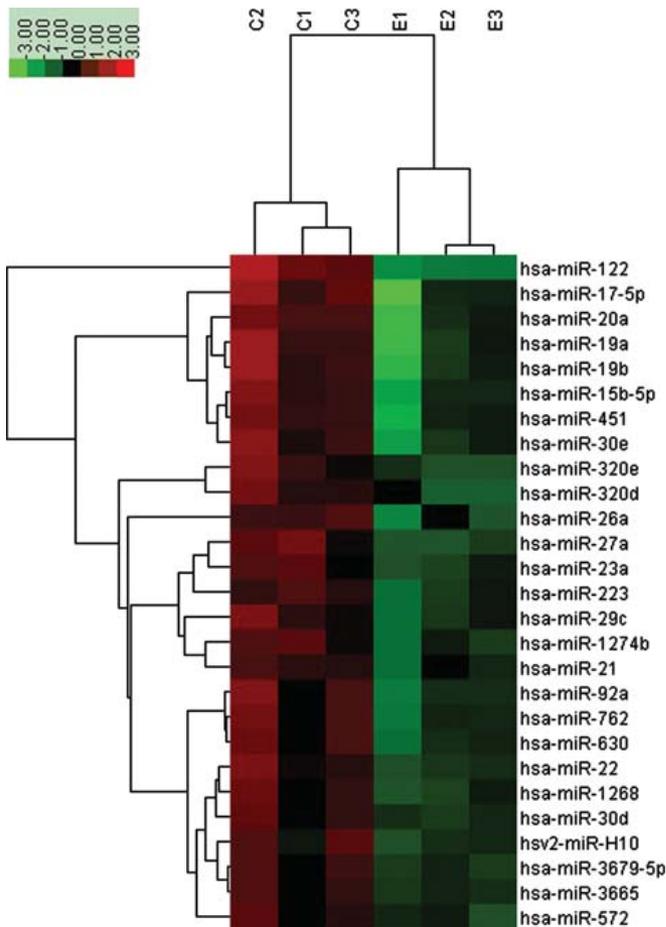
human reproduction ORIGINAL ARTICLE *Gynaecology*

Plasma miR-17-5p, miR-20a and miR-22 are down-regulated in women with endometriosis

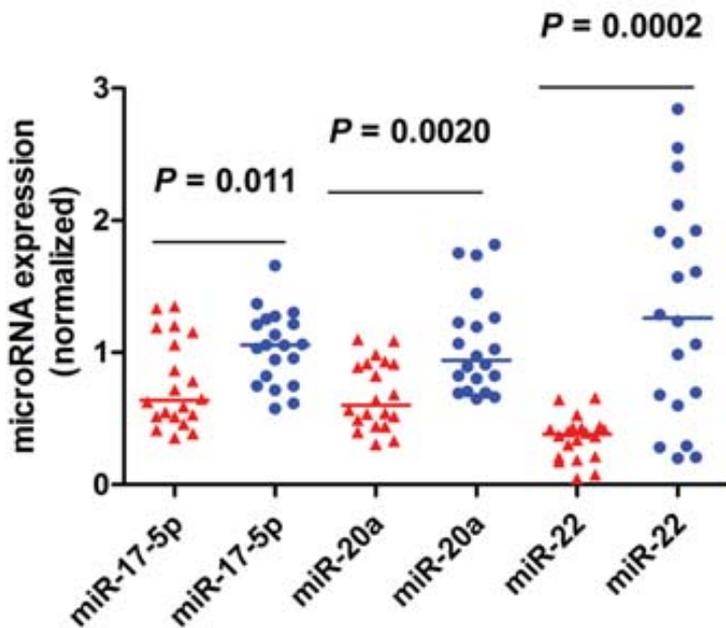
Shuang-zheng Jia[†], Yunpeng Yang[†], Jinghe Lang, Pengran Sun, and Jinhua Leng^{*}

Department of Obstetrics and Gynecology, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, PR. China

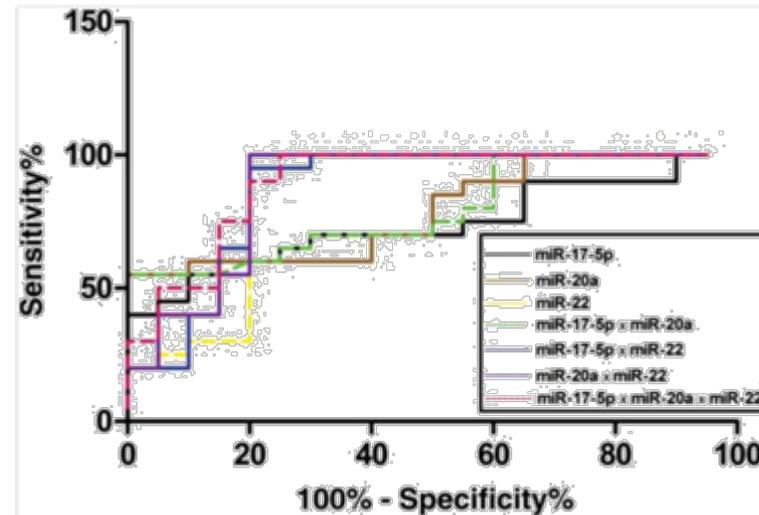
- Heat map showing 27 differentially expressed (fold change = 2) microRNAs from plasma samples of women with endometriosis and controls having uterine leiomyoma but free of endometriosis. Each row represents one microRNA, and each column represents a plasma sample. The legend on the right indicates the microRNA represented in the corresponding row. The relative microRNA expression is depicted according to the color scale. Red indicates up-regulation; green indicates down-regulation. The numbers with E indicate endometriosis; numbers with C indicate controls.



Diagnostic value of plasma microRNAs in endometriosis



- Validation of microRNA expression by qRT-PCR analysis in plasma samples from women with and without endometriosis. Plasma miR-17-5p, miR-20a and miR-22 were significantly down-regulated in women with endometriosis compared with controls. Red indicates women with endometriosis and blue indicates women that are endometriosis-free.



- ROC curve analysis using plasma microRNAs for discriminating endometriosis. ROC curve analyses revealed that the plasma levels of miR-17-5p, miR-20a and miR-22 were useful biomarkers for differentiating women with and without endometriosis, with AUC values of 0.74 (95% CI: 0.58–0.90), 0.79 (95% CI: 0.65–0.93) and 0.85 (95% CI: 0.71–0.98), respectively. When the three microRNAs were combined by multiplication, the AUC values for differentiating women with and without endometriosis were 0.79 (95% CI: 0.65–0.93), 0.87 (95% CI: 0.74–0.99), 0.88 (95% CI: 0.76–1.00) and 0.90 (95% CI: 0.80–1.00), respectively.

Proposed serum, urine and endometrial markers

- Proposed serum biomarkers include:
 - Interleukin (IL)-6 and IL-8
 - Tumor necrosis factor (TNF)- α
 - Macrophage migration inhibitory factor
 - Macrophage chemotactic protein-1
 - Interferon- γ
 - Leptin
 - CA-125
 - Vascular endothelial growth factor (VEGF)
- Other markers
 - Nerve fibre density in the endometrium
 - Neurotrophins in the endometrium or circulation
 - MicroRNA (miRNA) in endometrial biopsies and endometriotic lesions
- Urine markers
 - Urine peptide biomarkers using magnetic beads-based matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS)¹
- Blood (peripheral and menstrual) markers
 - Myeloperoxidase (MPO)
 - N-acetyl- β -D-glucosaminidase (NAG)
 - TNF- α
 - VEGF

However, none of these markers has shown clinical utilization

Take home messages

- Laparoscopy is the gold standard of endometriosis diagnosis
- It is very important to diagnose endometriosis early, especially in young women with primary dysmenorrhea
- A good history taking and thorough clinical examination are still of great value in confirming suspected endometriosis and triaging patients planned for surgery
- Imaging techniques are of great value for advanced endometriosis
- There is yet no valid non-invasive marker for the diagnosis of endometriosis