재발된 자궁내막증의 처치

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Pathogenesis of ES recurrence

- **Recurrence of ES-associated symptoms** : more complicated

- **Regrowth of residual lesions**
  - DIE : observed in same area of first operation
  - endometrioma : formerly treated ovary (88.7%)
    - satellite lesion with multiple endometriotic foci
    - incomplete removal at first operation
- **De novo lesion formation**
  - retrograde menstruation or ovulation (after hysterectomy)

Koga K et al., Fertil Steril 2015

Recurrence rate of ES

- **21.5% at 2 years / 40%–50% at 5 years**
- **Varies greatly with**
  - *type of ES, methods of surgery, post-op. intervention*
  - *disease severity, type of hospital, surgeon's skills*
  - *presence of recurrence risk factors*
  - **definition of recurrence**

    : subjective pain → 20.5% (3yrs) & 43.5% (5yrs)

    : objective measurements → 9% (3yrs) & 28% (5yrs)

Guo SW. Hum Reprod Update 2009; Koga K et al., Fertil Steril 2015

Management of recurrent ES (I)

- **Recurrence after medical treatment** : other agent or surgical treatment
- **Recurrence after hysterectomy**

  : pain persistence 15% & worsening 3 – 5%

  : repeat surgery, GnRH agonist ?
- **Recurrence after conservative surgery**
  - medical treatment
  - conservative surgery (repetitive)
    - pain recur : 20 – 40% / further surgical procedure 10 – 20%
    - spont. pregnancy rate : 34% (1^{st} surgery) → 19% (repetitive surgery)
    - conception after IVF : 30% (1^{st} surgery) → 20% (repetitive surgery)

Berlanda N et al., Curr Opin Obstet Gynecol 2010; Vercellini P et al., Ferteil Steril 2009

Management of recurrent ES (II)

- *Recurrence of pain* *vs.* *recurrent ovarian mass*
- *Pain* *vs.* *fertility*

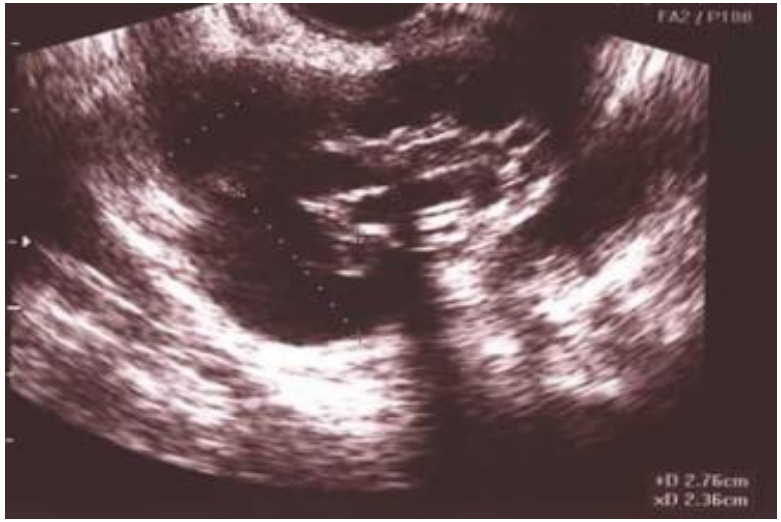
- *Medical treatment* *vs.* *surgical treatment*
- *Conservative treatment* *vs.* *radical treatment*

Individualized approach

Berlanda N et al., Curr Opin Obstet Gynecol 2010

Case 1-1

- **11. 6월**
  - 27세, laparoscopic both ovarian cystectomy : endometriosis
- **11. 7 – 12. 1월 : GnRH agonist 6cycle**
- **12. 11. 21**
  - R/O recurrent endometrioma 소견보여 전원 옴

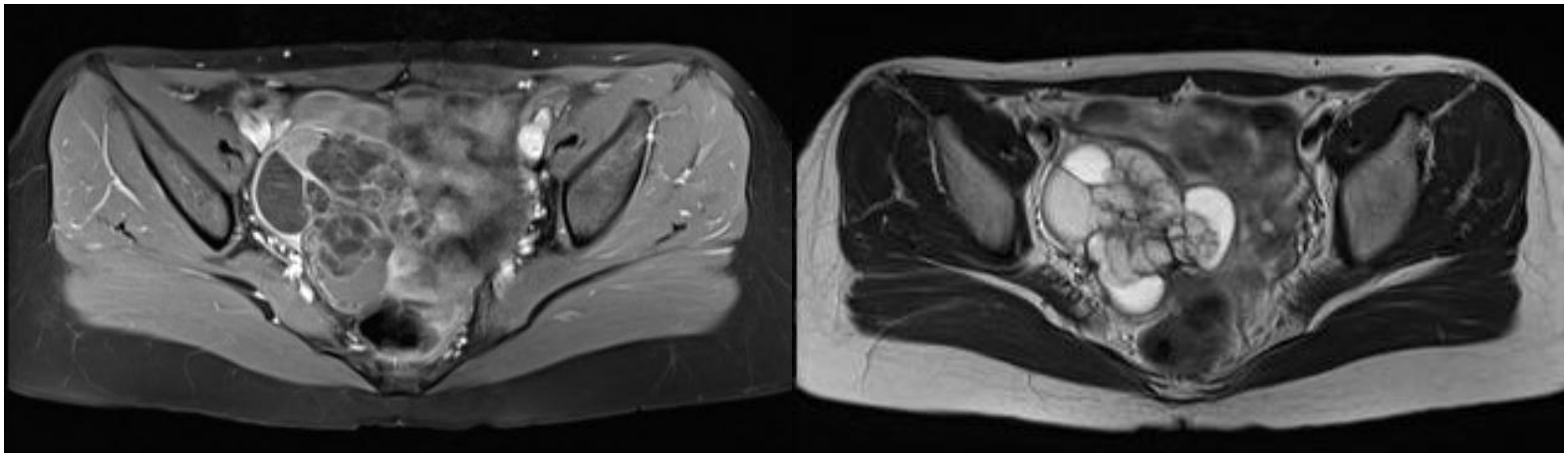


Rt. ovarian cyst (2.3cm & 3cm)

R/O recurrent endometriosis

Case 1-2

- **12. 11월**
  - MR pelvis : mucinous borderline malignancy, more likerly



  - AMH : 1.48 ng/mL
- **12. 12. 21**
  - Rt. salpingo-oophorectomy was done
  - frozen biopsy : normal follicle / permanet : endometriosis

Case 1-3

- **13. 1 – 15. 3월**
  - GnRH agonist – OCs cycling
  - AMH : 0.45 ng/mL (13.3월)
- **15. 3. 24**
  - 임신 계획 중으로 OCs stop & IVF recommend

diagnosis of recurrent ES ??
ovarian cancer & ES ??

Diagnosis of ES : MRI, CA-125 ??

Imaging modalities for the non-invasive diagnosis of endometriosis (Review)

Nisenblat V, Bossuyt PMM, Farquhar C, Johnson N, Hull ML

Authors' conclusions

None of the evaluated imaging modalities were able to detect overall pelvic endometriosis with enough accuracy that they would be suggested to replace surgery. Specifically for endometrioma, TVUS qualified as a SpPin triage test. MRI displayed sufficient accuracy to suggest utility as a replacement test, but the data were too scant to permit meaningful conclusions. TVUS could be used clinically to identify additional anatomical sites of DIE compared with MRI, thus facilitating preoperative planning. Rectosigmoid endometriosis was the only site that could be accurately mapped by using TVUS, TRUS, MRI or MDCT-e. Studies evaluating recent advances in imaging modalities such as TVUS-BP, RWC-TVS, 3.0TMRI and MDCT-e were observed to have high diagnostic accuracies but were too few to allow prudent evaluation of their diagnostic role. In view of the low quality of most of the included studies, the findings of this review should be interpreted with caution. Future well-designed diagnostic studies undertaken to compare imaging tests for diagnostic test accuracy and costs are recommended.

Combination of the non-invasive tests for the diagnosis of endometriosis (Review)

Nisenblat V, Prentice L, Bossuyt PMM, Farquhar C, Hull ML, Johnson N

Authors' conclusions

None of the biomarkers evaluated in this review could be evaluated in a meaningful way and there was insufficient or poor-quality evidence. Laparoscopy remains the gold standard for the diagnosis of endometriosis and using any non-invasive tests should only be undertaken in a research setting.

Nisenblat V et al., Cochrane Database Syst Rev 2016(CD009591, CD012281)

ES & cancer – ESHRE guideline

Recommendations

The GDG recommends that clinicians inform women with endometriosis requesting information on their risk of developing cancer that 1) there is no evidence that endometriosis causes cancer, 2) there is no increase in overall incidence of cancer in women with endometriosis, and 3) some cancers (ovarian cancer and non-Hodgkin's lymphoma) are slightly more common in women with endometriosis.	GPP

The GDG recommends no change in the current overall management of endometriosis in relation to malignancies, since there are no clinical data on how to lower the slightly increased risk of ovarian cancer or non-Hodgkin's lymphoma in women with endometriosis.	GPP

Cancer risk in patient with ES

TABLE 1
Cohort Studies Evaluating Cancer Risk in Patients With Endometriosis

Study	No. of Patients	Follow-up Time, y	Overall Cancer Risk		EOC Risk	
			SIR	95% CI	SIR	95% CI
Brinton et al[29]	20,686	11.4	1.2	1.1–1.3	1.9	1.3–2.8
Melin et al[32]	64,492	12.7	1.0	0.9–1.1	1.4	1.2–1.7
Melin et al[33]	63,630	13.4			1.37	1.14–1.62
Kobayashi et al[34]	6398	12.8	8.95	4.12–5.3	13.2	6.9–20.9
Brinton et al[36]	12,193	18.8			2.48	1.3–4.2
Olsen et al[38]	1392	13			0.78 (RR)	0.25–2.44

RR indicates relative risk.

TABLE 2
Case-Control Studies Evaluating Cancer Risk in Patients With Endometriosis

Study	No. of Patients	No. of Control Subjects	EOC Risk	
			RR	95% CI
Ness et al[39]	767	1367	1.7	1.2–2.4
Ness et al[40]	5207	7705	1.73	1.10–2.71
Modugno et al[41]	2098	2953	1.32	1.06–1.65
Borgfeldt and Andolf[31]	28,163	3 Control Subjects per case	1.34	1.03–1.65
Rossing et al[42]	812	1313	1.5	1.1–2.1
Brinton et al[43]	104,561	99,812	1.69	1.27–2.25

RR indicates relative risk.

Carmen MG. Obstet Gynecol Surv 2015

EAOC diagnosis

- **Relatively low frequency : 0.3 – 0.8%**
- **Clinically,** independent predictors : > 40 years, 9cm ↑

  several years benign-appearing ovarian masses

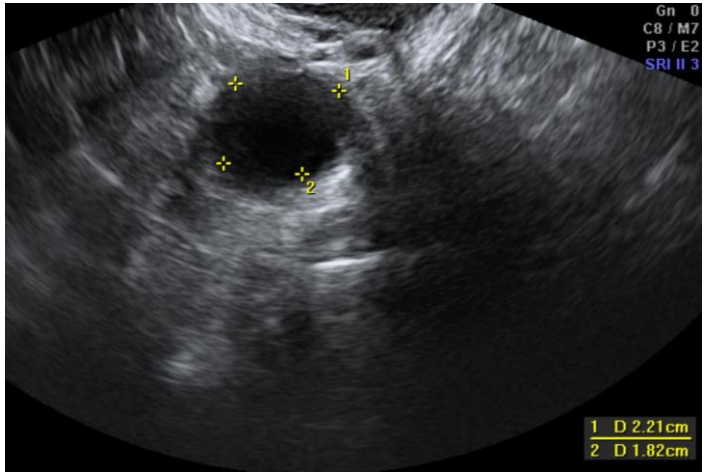
  slightly elevated CA-125 level (sensitivity ↑& specificity ↓)

- **MR finding**
  - contrast-enhanced mural nodule on T1-weighted images
  - sudden enlargement of endometrioma
  - disappearance of shading on T2

Kobayashi H. Int J Clin Oncol 2009
Takeuchi M et al., Radiographics2006

Case 2-1

- **11년**
  - 33세 미혼, Breast cancer patient
  - 월경통으로 local clinic에서 시행한 US상 Lt. ovarian cyst
- **12. 12월**
  - Lt. ovarian cyst 의 size 증가로 수술 권유 받고 본원 내원

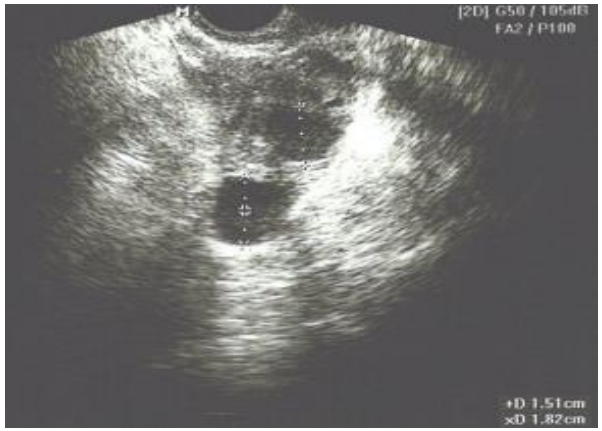


Lt. ovarian cyst 2.2*1.8cm

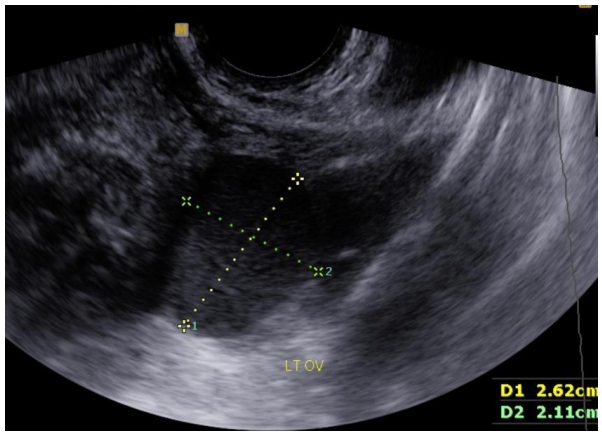
R/O endometrioma

Case 2-2

- **13. 1.10** : laparoscopic Lt. ovarian cystectomy : endometriosis
- **13. 1 – 13. 6월** : GnRH agonist 6cycle (+)
- **15. 12월**
  - 월경통 발생하여 내원
  - US : 1.5cm / 1.8cm Eoma
  - **NSAIDs start**



- **17. 5. 30 follow up visit**
  - **tolerable dysmenorrhea with NSAIDs**
  - US follow up – endometrioma 2.6cm



ES-associated pain

ESHRE guideline

Recommendations

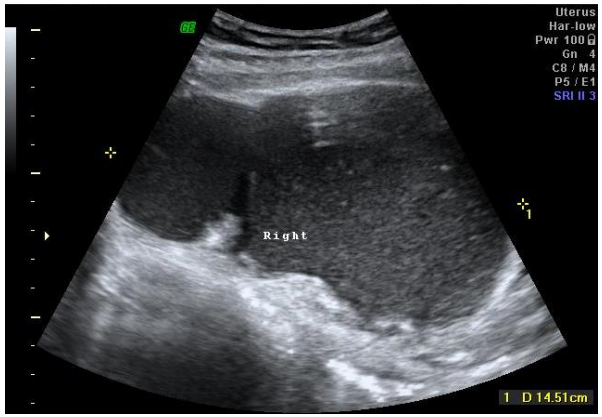
Clinicians are recommended to prescribe hormonal treatment [hormonal contraceptives (level B), progestagens (level A), anti-progestagens (level A), or GnRH agonists (level A)] as one of the options, as it reduces endometriosis-associated pain (Vercellini, et al., 1993, Brown, et al., 2012, Brown, et al., 2010).	A-B
The GDG recommends that clinicians take patient preferences, side effects, efficacy, costs and availability into consideration when choosing hormonal treatment for endometriosis-associated pain.	GPP

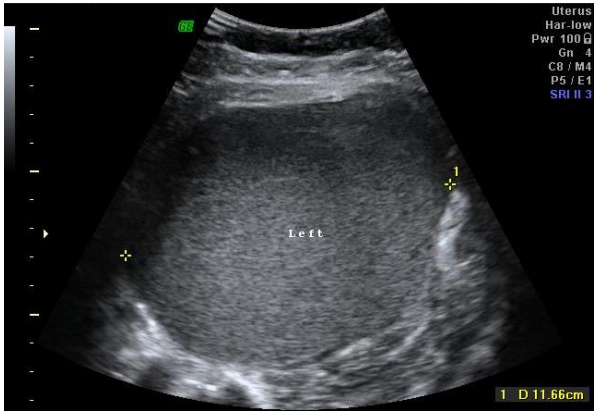
Recommendation

The GDG recommends that clinicians should consider NSAIDs or other analgesics to reduce endometriosis-associated pain.	GPP

Case 3-1

- **13. 1. 21**
  - 21세, 156cm, 73.4kg (BMI 30.1)
  - 월경통과 하복부 통증으로 local clinic 거쳐 내원
  - local clinic MR finding : both ovarian cyst, R/O endometrioma
  - US





  - AMH : 2.0 ng/mL

Case 3-2

- **13.1.31**
  - laparoscopic both ovarian cystectomy

    : combined technique of excisional & ablative surgery
    - right, cystectomy : endometriosis (46.9g / 12.0x4.5x0.9cm)
    - left, cystectomy : endometriosis (20.8g / 13.2x9.5x0.2cm)

- **13.2 – 13.7월** : GnRH agonist 6cycle injection was done
- **13. 10. 30** : 월경재개 & dienogest start

Case 3-3

- **13. 10 – 15. 11월 : dienogest 복용**
  - US finding : both ovaries, none-specific finding
  - CA-125 follow up 13.1.21(preop) : 175.3 U/mL

    14.4.30 : 43.05 U/mL / 15.1.27 : 21.97 U/mL

    15.11.18 : 74.57 U/mL
  - LFT (15.11.18) : AST 64 IU/L / ALT 132 IU/L / LDH 262 IU/L
  - dienogest stop & GI part consult

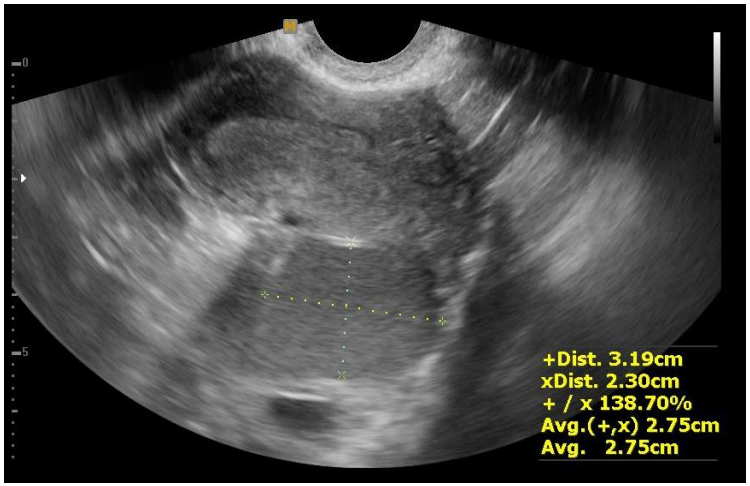
- **15. 12월 liver US – mild fatty liver**
  - LFT follow up
    - AST 34 IU/L / ALT 65 IU/L / LDH 185 IU/L

Case 3-4

- **16. 5. 23**
  - US follow up

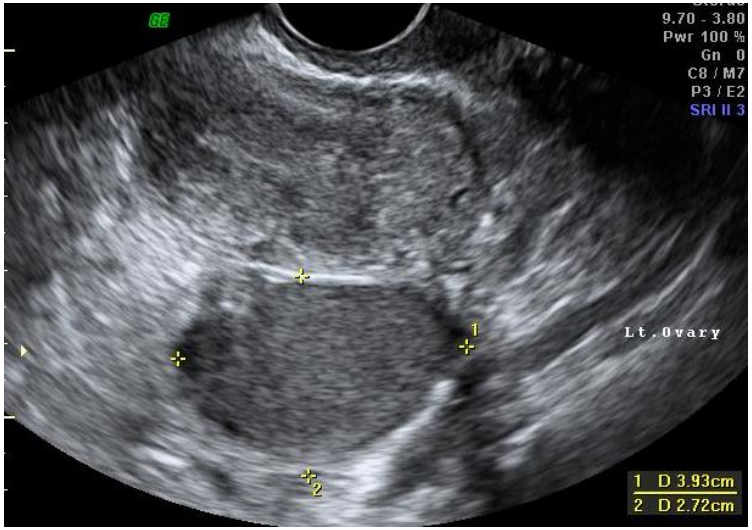
    : R/O Lt. endometrioma

    (3.19*2.30cm)



  - **dienogest re-start**

- **16. 12. 12**
  - **US follow up : NSIC**
  - **no dysmenorrhea**



Combined excisional/ablative technique

- 51 patients with bilateral endometrioma (>3cm)
- One ovary – stripping vs. contralateral ovary – combined technique

- **4 recurrences (7.8%) at 6-month follow-up period**
  - 3 (5.9%) for stripping technique OR 3.00 (95% CI 0.24–157.5; P=0.62)
  - 1 (2.0%) for combined technique

Table II AFC, and OV, for the stripping technique and the combined technique at 1, 3 and 6-month follow-up.

	1 month (n = 51)		3 months (n = 47)		6 months (n = 40)	
	AFC	OV (mL)	AFC	OV (mL)	AFC	OV (mL)
Stripping side	4.5 ± 2.1	8.4 ± 5.1	5.0 ± 2.9	7.7 ± 4.6	4.8 ± 2.9	8.4 ± 5.0
Combined side	4.8 ± 2.4	7.3 ± 4.0	4.6 ± 2.3	7.0 ± 3.7	4.4 ± 2.3	6.5 ± 3.3
P value[a]	0.42	0.24	0.43	0.42	0.57	0.04

Data are presented as mean ± SD.
[a]Paired Student's t-test.

Muzii L et al., Hum Reprod 2016

2nd surgery & ovarian reserve

- Laparoscopic excision of monolat. ovarian endometrioma
- 1st surgery (n=17) vs. recurrence after previous surgery (n=11)
- US evaluation 3mo. after surgery

TABLE 2

Histologic parameters of the endometrioma cyst wall

Specimen thickness and histology grade	PS group (n=17)	RS group (n=11)	P value
Total cyst wall (mm)	**1.1±0.3**	**1.7±0.3**	**0.00003**
Endometriotic tissue (mm)	**0.2±0.1**	**0.3±0.1**	**0.007**
Ovarian tissue (mm)	**0.3±0.2**	**0.6±0.3**	**0.0009**
Histology grade	0.4±0.6	0.7±0.3	0.35

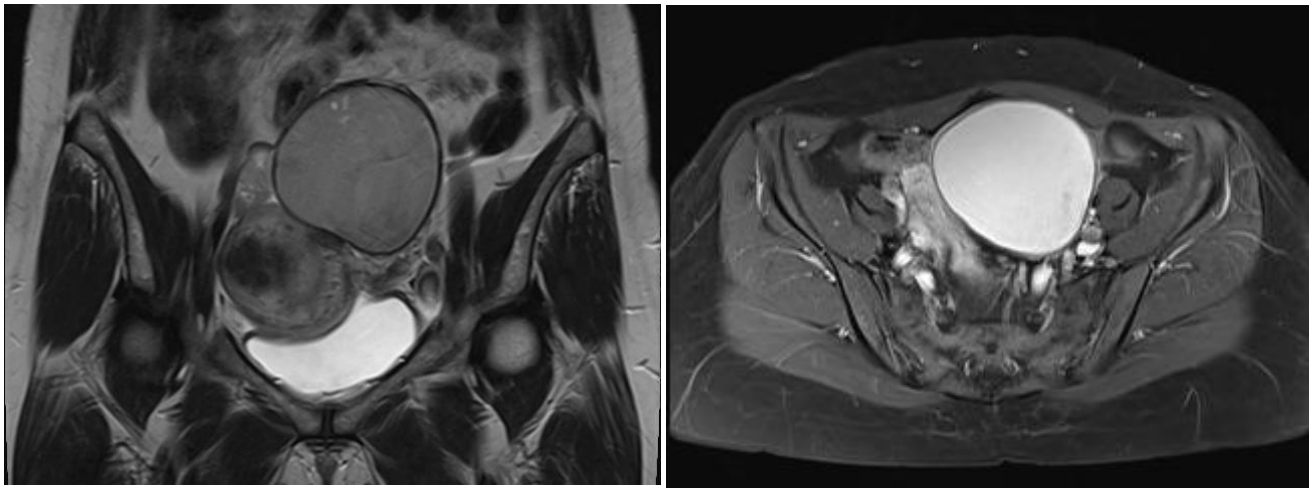
Data are expressed as mean ±SD; PS, primary surgery; RS, recurrent surgery

- **Surgery for recurrence**
  - higher loss of ovarian tissue, more harmful to ovarian reserve

Muzzi L et al., Fertil Steril 2015

Case 4-1

- **16. 1. 25**
  - 41세, 1년 전에 결혼하였으며 난임으로 내원
  - 10년 전 자궁내막증 수술 병력 - both ovarian cystectomy ?
  - AMH 0.08 ng/mL
  - MR pelvis



multiple endometriosis, left adnexa,
rectosigmoid junction, uterine torus & right adnexa

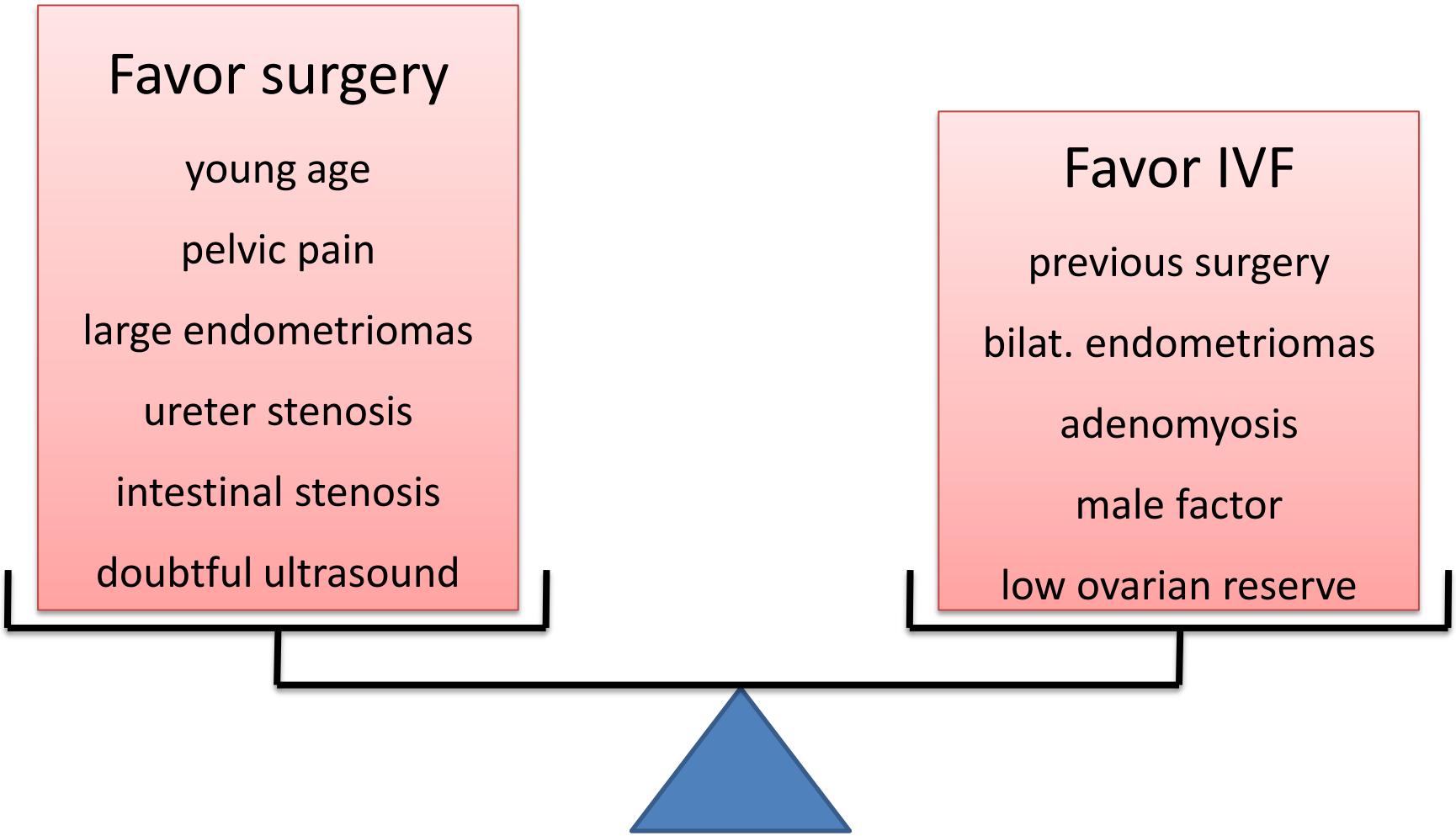
Case 4-2

- **16. 3. 3 transvaginal cyst aspiration was done**
  - liquid based cytology : many hemosiderin-laden macrophage

- **16. 3월 / 6월 : COH with GnRH antagonist protocol**
  - M2, 5 oocytes – 4 blastocyst
- **16. 7월 myomectomy with Lt. ovarian cystectomy was done**
  - uterus, myomectomy : leiomyoma
  - ovary, left, cystectomy : endometriotic cyst

- **16.12.5 / 17.2.3** : frozen ET(2) – hCG < 0.1

Decision-making process for infertile women with advanced endometriosis



Somigliana E et al., Semin Reprod Med 2017

Aspiration without sclerotherapy

- 129 infertile patients (32.6 ±4.3 yrs), followed up for 24 months

: 53 patients had undergone surgical diagnosis of ovarian endometrioma

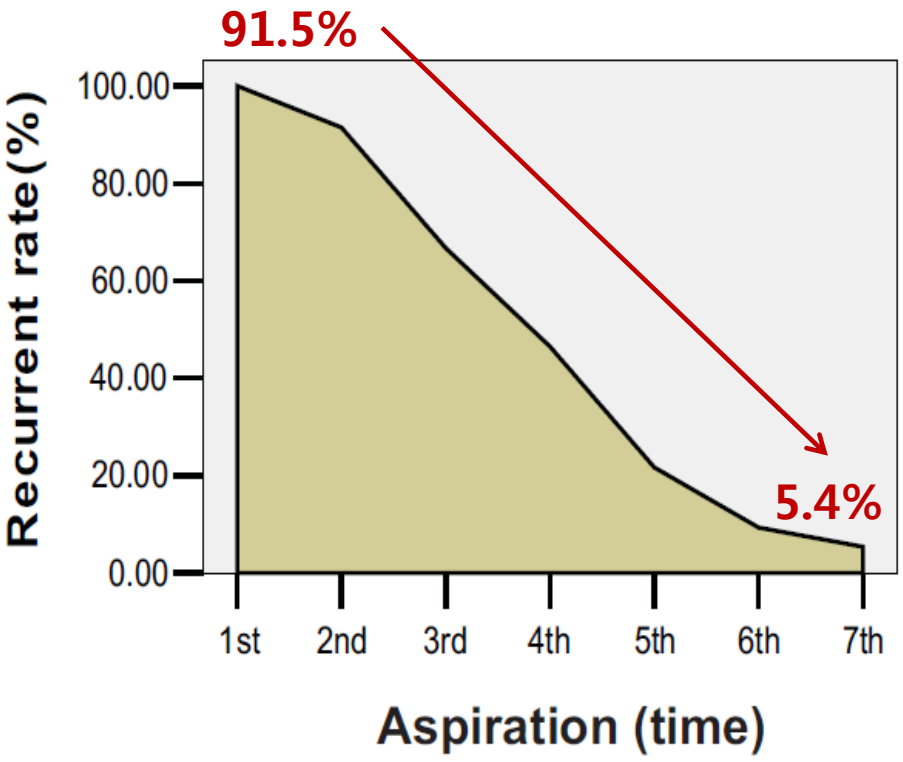


FIGURE
Relationship between times of aspirations and recurrence of cysts

Pregnancy rate in 24mo.

: 56/129 (43.3%-IUI 12 / natural 44)

Recurrence rate in 24mo.

: 36/129(27.9%)

Hormonal Tx. before or after aspiration

: no benefits

in recurrence or ease of aspiration

No complications

Zhu W et al. Am J Obstet Gynecol 2011

Repeat aspiration for endometrioma

- **Recurrence rate reduced by repetitive aspirations**

- **Exfoliation of residual endometriotic tissues**
- **Tissue reaction from mechanical stimulation of aspiration**
  - cyst refilled with much more fluid

    → lining cystic wall, decreased endometrial tissues

⟹ ***Low rate of recurrence & slow growing***

Zhu W et al. Am J Obstet Gynecol 2011

ES diagnosis by cytologic specimens

- 8 FNA, 4 effusion cytology, 5 touch imprint, 1 cervical smear

- Atypia & mitotic figures were rarely encountered
- Ratio of endometrial glandular & stromal cell : similar

- On follow up, none of the patients developed malignancy

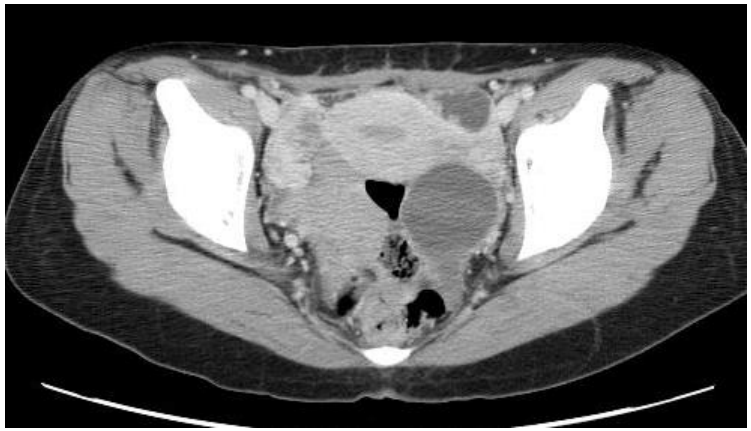
Endometriosis can be reliably & safely diagnosed

in various cytologic materials

Barkan G et al., Diagn Cytopathol 2013

Case 5-1

- **06. 11. 23**
  - 35세, 월경통으로 병원 방문 / previous twice C/section
  - CT abdomen & pelvis

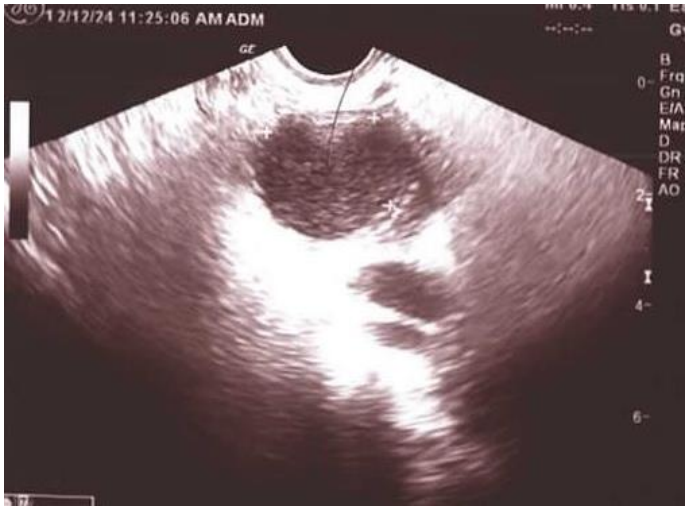


Left ovarian cystic mass
with hydrosalpinx or pyosalpinx
: tubo-ovarian abscess
DDx. endometriosis

- **06. 11. 22 both ovarian cystectomy with appendectomy**
  - right, left, cystectomy / appendix, appendectomy : endometriosis
- **06.12 – 07.5월** : GnRH agonist 6 cycle injection was done

Case 5-2

- **12.12.24**
  - 최근에 다시 발생한 월경통으로 자궁내막증 재발확인을 원해 병원 방문



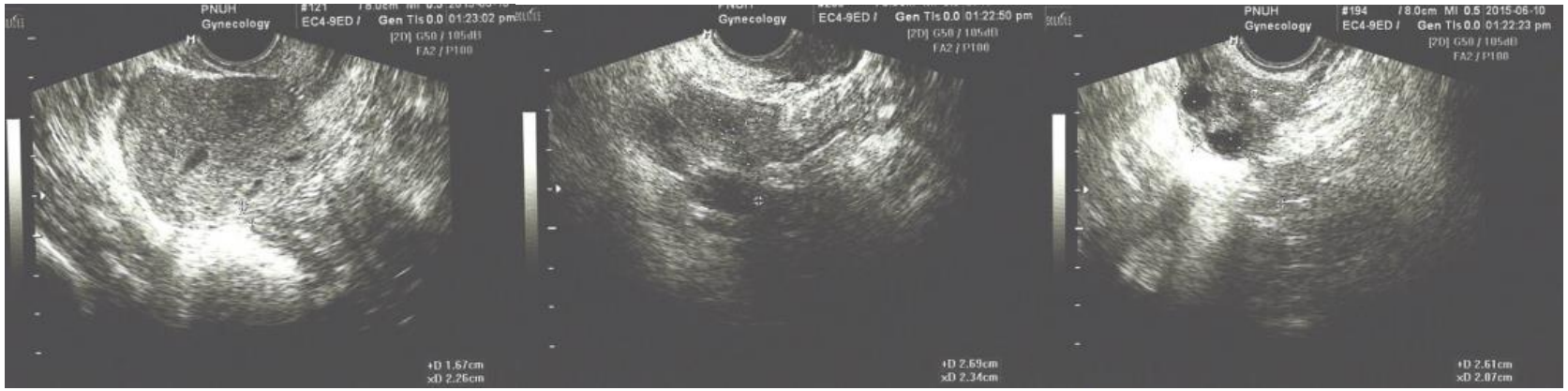
Lt. ovarian cyst 2.6*2.0cm

R/O endometrioma

- **13. 1. 9 transvaginal Lt. ovarian cyst aspiration with alcohol irrigation**
  - cytology : numerous hemosiderin-laden macrophages, c/w endometriosis

Case 5-3

- **13.1.22**
  - GnRH agonist recommend – refused by patient
- **15. 6. 10 follow up visit**
  - US finding – no ovarian cyst, R/O adenomyosis
  - no dysmenorrhea



Aspiration with ethanol sclerotherapy

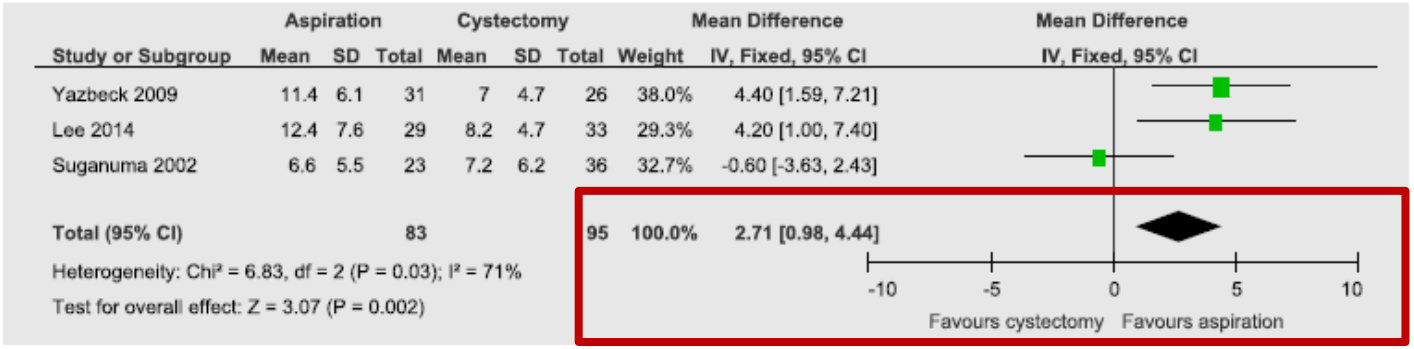
- **Method**
  - ethanol injection (50-80% of aspirated volume or 100mL)
  - left in situ, better outcome than irrigation only
- **Recurrence rate**
  - 0 – 13.3% (left in situ) / 0-62.5% (washing)
  - pain relief : 68 – 96%
- **Adhesion formation, abscess, fever, abdominal pain**
- **Favorable reproductive outcome ???**
  - more oocytes, but similar pregnancy rates

Cohen A et al., Fertil Steril 2017

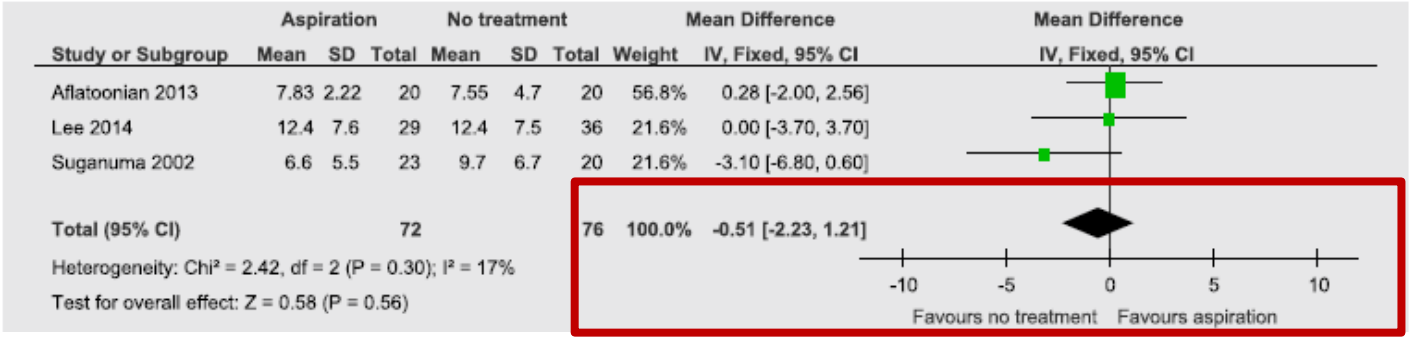
Sclerotherapy & ART outcome

No. of oocytes retrieved

SUPPLEMENTAL FIGURE 2



SUPPLEMENTAL FIGURE 3

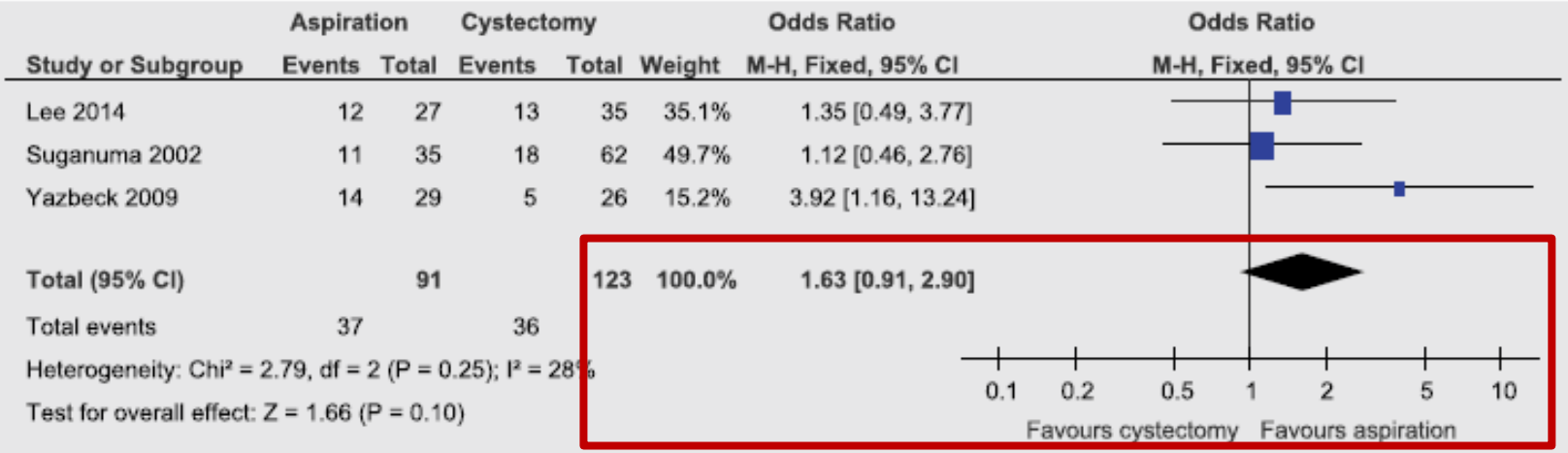


Cohen A et al., Fertil Steril 2017

Sclerotherapy & ART outcome

Pregnancy rate

FIGURE 2



Comparison of clinical IVF pregnancy rate in cystectomy and ethanol sclerotherapy groups. Clinical pregnancy rates of the cystectomy group and the ethanol sclerotherapy group are similar: odds ratio 1.63, 95% confidence interval [CI] 0.91–2.90. M-H = Mantel-Haenszel.

Cohen. Sclerotherapy of ovarian endometrioma. Fertil Steril 2017.

Cohen A et al., Fertil Steril 2017

Sclerotherapy & ART outcome

Post-surgical recurrence : ethanol sclerotherapy vs. repeat surgery

	EST group (n=31)	Control group (n=26)	P-value
Stimulation protocol (%)	ultralong (87.1)	long (50.0)	<0.001
No. of oocytes retrieved	**11.4 ± 6.1**	**7.0 ± 4.7**	**0.03**
No. of mature oocytes	**10.4 ± 5.4**	**6.1 ± 3.8**	**0.02**
No. of transferred embryos	2.1 ± 1.1	1.8 ± 0.6	NS
Implantation rate (%)	38.4	43.1	NS
Ongoing pregnancy rate (%)	**48.3**	**19.2**	**0.04**
Cumulative pregnancy rate (%)	**55.2**	**26.9**	**0.03**

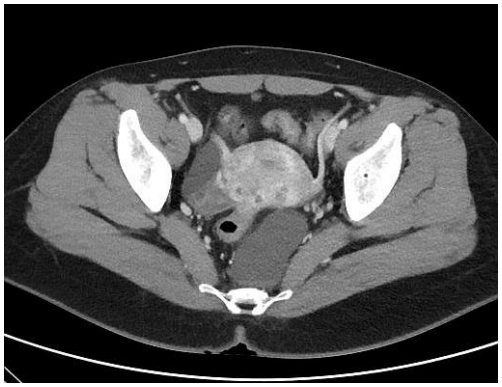
Values are mean ± SD

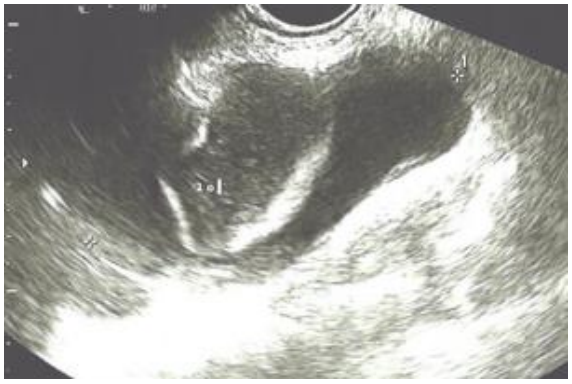
Yazbeck C et al., Reprod Biomed Online 2009

Case 6-1

- **08년**
  - local clinic, laparoscopic Lt. ovarian cystectomy : endometrioma
- **10년, marriage**
- **12년, HSG – Rt. tube : patent / Lt. tube : obstruction**
- **12년, 14년 – 2회 IVF-ET : fail**

- **15. 8. 28**
  - 월경통과 하복부 통증으로 병원 방문





Lt. endometrioma

Lt. hydrosalpinx or
Lt. side pseudocyst

Case 6-2

- **15. 9. 2**
  - laparoscopic Lt. ovarian cystectomy / Lt. salpingectomy / myomectomy
    - salpinx, left, salpingectomy : stromal endometriosis, probably
    - ovary, left, cystectomy & peritoneum, wall, biopsy : endometriosis
- **AMH** : preop. 8.53 ng/mL → postop. 2.42 ng/mL

- **15. 9 – 15. 11월 : GnRH agonist 3 cycle injection was done**
- **15. 12. 11 COH start (ultrolong protocol)**
  - OPU – 19 oocytes
  - 16. 1. 13 fresh ET – hCG < 0.1
  - 16. 2. 6 frozen ET – hCG 2382 mIU/mL

Surgery for severe ES & repeated IVF failure (I)

- Retrospective cohort study with 78 women

- **After surgical treatment 33 women (42.3%) delivered**

  : 3 women (9%) spontaneously & all others after IVF

  - ***younger*** *(32.5 ±4.1 vs. 35.5 ±3.8 years)*
  - ***less often diagnosed with DOR*** *before surgery (6% vs. 28.8%)*
  - *more often diagnosed with* ***normal uterine anatomy***
  - ***performing salpingectomy*** *during surgery (70% vs. 51%)*

Soriano D et al., Fertil Steril 2016

Surgery for severe ES & repeated IVF failure (II)

- **ES is associated with a sterile low-grade inflammatory reaction**

  in the peritoneal cavity as judged by an increased amount of activated macrophages & their secretion products

- **Salpingectomy is associated with improved reproductive outcome**
  - misdiagnosed or left hydrosalpinges (severe pelvic adhesion)
  - development of hydrosalpinges due to repeated IVF cycles

Soriano D et al., Fertil Steril 2016

Summary (I)

Treatment of pelvic pain with ESCurrent ES

- **Surgical therapy**
  - excision of cyst wall, drainage & ablation
  - presacral neurectomy
  - hysterectomy
- **Medical therapy**
  - NSAIDs
  - COCs / progestogens
  - GnRH agonist

individualization !!

pain, fertility

ovarian reserve

IVF ??

Summary (II)

- **Multiple surgical procedures should be avoided**
  - pelvic pain due to adhesion ?
  - decreased ovarian reserve
    - simple aspiration
    - sclerotherapy
    - hormonal suppression
- **EAOC**
  - CA-125 / US follow up / perimenopausal women
  - MR pelvis – mural nodule, disappearance of shading


경청해 주셔서
감사합니다.

Repetitive surgery ???

Before IVF

Characteristics	Favours surgery	Favours expectant management
Previous intervnetions for ES	None	≥ 1
Ovarian reserve	Intact	Damaged
Pain symptoms	Present	Absent
Bilaterality	Monolaterel disease	Bilateral disease
Sono. feature of malignancy	Present	Absent
Growth	Rapid growth	Stable

Garcia-Velasco JA et al. Hum Reprod 2009

2nd surgery & ovarian reserve

- Recurrent endometrioma may represent a **more aggressive form**
- Ovary with the recurrent endometrioma may be **already damaged** by the presence of the **first endometrioma** and/or by the **first surgical procedure**
- **Fibrosis induced by the first surgery** may render the second surgical procedure **more technically challenging**, with the plane of cleavage identifiable with more difficulty
- **Longer cumulative residence of an endometrioma** within the ovary in a patient with a recurrence may cause greater damage on the adjacent ovarian cortical tissue due to the **higher concentrations of free iron, reactive oxygen species, proteolytic enzymes, and inflammatory molecules**

Muzzi L et al., Fertil Steril 2015