



Surgical Removal of Endometrioma: When Is It Worth the Risk?

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Financial Disclosure

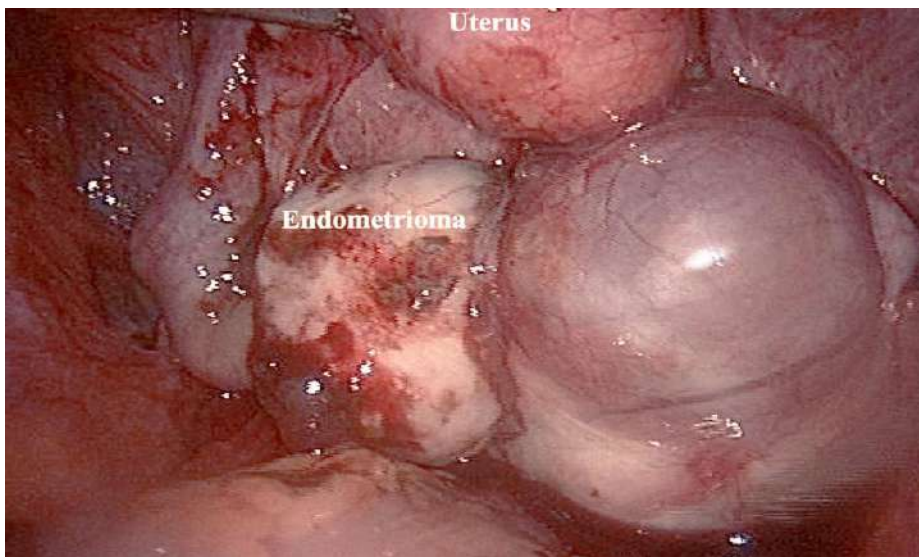
- I have no financial relationships with industry
- Receive honoraria
 - Editor-in-Chief Journal of Minimally Invasive Gynecology (JMIG)
 - Section Editor- Up-To-Date
- Federal research funds
 - MicroRNAs and the MIF System in Uterine Function and Disease (NIH Co PI- R01HD069043)

Learning objectives

At the conclusion of this presentation,
participants should be able to:

- Discuss the impact of endometrioma surgery on fertility outcome
- Discuss the impact of endometrioma surgery on ovarian reserve

Management of Endometriomas



Why remove endometriomas? Relief of pain

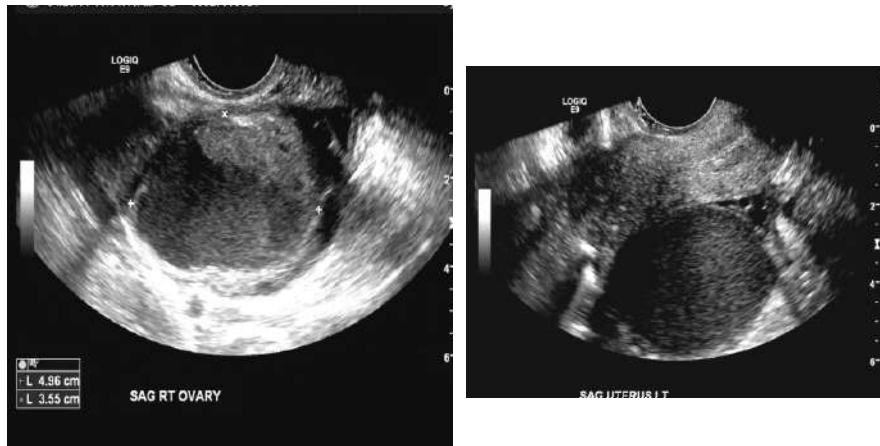
- Clinical presentation: Porpora et al. 2010
 - Dysmenorrhea: 76 %
 - Chronic pelvic pain: 53 %
 - Dyspareunia: 43 %
- Objective endometrioma surgery
 - Histologic confirmation
 - Eliminate all endometriotic tissue but preserve normal tissue

Why remove endometriomas? Possible Malignancy

- Pearce et al Lancet Oncol 2012
 - **Association with ovarian cancer**
 - **clear-cell (odds ratio 3.05, 95% CI 2.43–3.84, $p < 0.0001$), low-grade serous and endometrioid invasive ovarian cancers**
- Buis et al Human Reproduction 2013
 - Dutch nationwide database- subfertile women with endometriosis
 - HR 12.4 (95% CI 2.8-54.2) ovarian cancer
 - HR 5.5 (95% CI 1.6-11.2) Borderline ovarian tumors
- Exclusion of malignancy
 - Risk is small
 - Ultrasound may be confusing

Why remove endometriomas? Exclude malignancy

Recurrent endometrioma- significantly higher rate of unexpected ovarian cancer-in patients older than 40 years



Haraguchi H, Koga K, Takamura M, et al. Development of ovarian cancer after excision of endometrioma. *Fertil Steril* 2016:S0015-0282(16)62507-4

Why remove endometriomas prior to IVF?

- Increases the risk of infection after oocyte retrieval
 - Puncture of endometrioma
 - Ovarian abscess
- Contamination of oocyte obtained with endometriosis cyst contents
- Difficulties in the retrieval

Endometrioma and Fertility

- Does the intrinsic presence of an endometrioma decrease ovarian reserve?
- **Endometrioma removal**: Is there a decrease in ovarian reserve after surgery?
- **How does the endometrioma removal affect pregnancy rates**
 - Spontaneous & ART

Untreated Endometrioma and Ovarian Reserve

- **Unilateral endometriomas-**
- Benaglia et al Human Reproduction 2011
 - Only the first cycle of IVF per patient (N=84)
 - Mean size **21 mm (all less than 4 cm)**
 - No difference in ovarian responsiveness
- Almong et al F&S 2011
 - Only first IVF cycle (N=81)
 - No difference in the number of oocytes retrieved
 - Compared with the contralateral ovary
 - Control group without endometriosis
 - Mean diameter of the endometrioma was **2.8 cm**

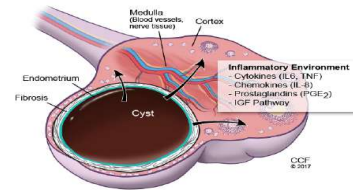
Untreated Endometrioma and Ovarian Reserve

- **Bilateral endometriomas**
- Benaglia et al F&S 2013
 - Case (un-operated bilateral endometrioma N=39) vs. Control (no cysts-N=78)
 - Serum AMH pre-IVF was 2.8 vs. 3.0 (NS)
 - **Mean Diameter 22-23 MM**
 - Total # of oocytes retrieved 7.1 vs. 9.8
 - Implantation & PR similar

Un-operated Ovarian endometrioma: Oocyte quality

- Filippi et al 2014
- The **fertilization rate** in the affected and intact gonads was 64% and 64%, respectively.
- The **cleavage rate** was 58% and 51%, respectively.
- The rate of **high-quality embryos** was 31% and 21%, respectively

Follicular density



- Kitajima et al 2011
- Cortical biopsy specimens
- Follicle density lower in the cortex from ovaries with endometriomas than **unaffected contralateral ovary**
- Maneschi et al 1993 & Schubert et al 2005
 - Lower follicular density in endometrioma than other benign cysts

Ovarian Reserve & Endometriomas:

Cleveland Clinic data- Am J Obstet Gynecol May 2016

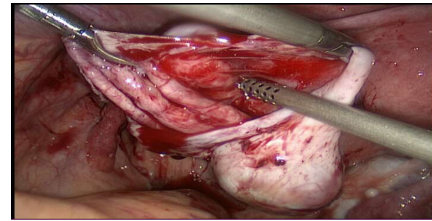
	Endometrioma (n = 58)	Control (n = 58)	P-Value
Baseline AMH ng/ml	1.8 (1.2 – 2.4)	2.8 (2.0 – 3.5)	0.05

Table 3: All values are means (95% Confidence intervals), superscripts are p-values compared with pre-operative values



Mean size 5 cm

Is stripping technique the Gold standard?



- Cochrane database 2008 Hart R et al.
 - Excision of cyst associated with a reduced rate of recurrence; reduced symptom recurrence and increased spontaneous pregnancy rates (OR 5.1) compared with ablative surgery.
- Clinicians can consider performing cystectomy rather than CO2 laser vaporization in women with ovarian endometrioma, because of a lower recurrence rate of the endometrioma (ESHRE Endometriosis Guideline Development Group September 2013).

25 Beretta P, Franchi M, Ghezzi F, Busacca M, Zupi E, Bolis P. Randomized clinical trial of two laparoscopic treatments of endometriomas: cystectomy versus drainage and coagulation. *Fertil Steril* 1998;70(6):1176-1180

26 Alborzi S, Momtahan M, Parsanezhad ME, Dehbashi S, Zolghadri J, Alborzi S. A prospective, randomized study comparing laparoscopic ovarian cystectomy versus fenestration and coagulation in patients with endometriomas. *Fertil Steril* 2004;82(6):1633-1637

27 Carmona F, Martínez-Zamora MA, Rabanal A, Martínez-Román S, Balasch J. Ovarian cystectomy versus laser vaporization in the treatment of ovarian endometriomas: a randomized clinical trial with a five-year follow-up. *Fertil Steril* 2011;96(1):251-254

28 Hart RJ, Hickey M, Maouris P, Buckett W. Excisional surgery versus ablative surgery for ovarian endometriomata. *Cochrane Database Syst Rev* 2008;16(2):CD004992

RCT = randomized controlled trial

Effect on ovarian reserve-

CC experience AJOG 2016

TABLE
Anti-Müllerian hormone, endometrioma, pelvic peritoneal endometriosis, and no endometriosis

Variable	Endometrioma (n = 58), mg/mL ^a	Pelvic peritoneal endometriosis (n = 29), mg/mL ^a	No endometriosis (n = 29), mg/mL ^a	P value
Baseline	1.77 (1.18-2.37)	2.29 (1.34-3.25)	3.20 (1.96-4.43)	.06
1 Month	1.12 (0.81-1.45) ^{<.01}	2.38 (1.26-3.50) ^{.41}	3.22 (2.04-4.49) ^{.78}	<.01
6 Months	1.41 (0.97-1.85) ^{.22}	2.76 (1.58-3.95) ^{.12}	3.14 (1.83-4.43) ^{.67}	.01

Superscripts indicate probability values compared with baseline preoperative values.

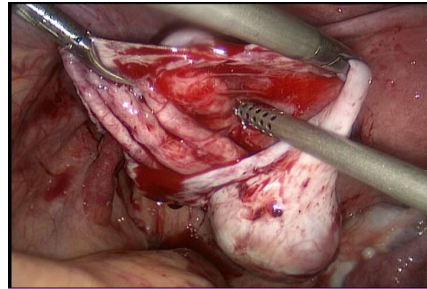
^a Data are given as mean (95% confidence interval).

Goodman et al. Endometriomas and ovarian reserve. *Am J Obstet Gynecol* 2016.



Other markers of decreased ovarian reserve

- Exacoutos et al; 2004
 - Reduction in ovarian volume
- Biacchiardi et al 2011 – Laparoscopic stripping
 - Decreased ovarian volumes & AMH at 9 months
- Does experience matter?



Muzii L, Marana R, Angioli R, et al. Histologic analysis of specimens from laparoscopic endometrioma excision performed by different surgeons: does the surgeon matter? Fertil Steril 2011;95(6): 2116-2119

Operated-Bilateral Endometriomas

- Somigliana et al. HR 2008
- Endometrioma group=68 patients
- Control group (no ovarian surgery)=136 patients
- Day-3 FSH of cases > controls
- Number follicles/oocytes/embryos decreased/implantation rate lower
- PR/DR cases per transfer (14%/8%) vs. controls (28%/25%)
- POF 2.4 % risk

FSH = follicle-stimulating hormone; DR = delivery rate

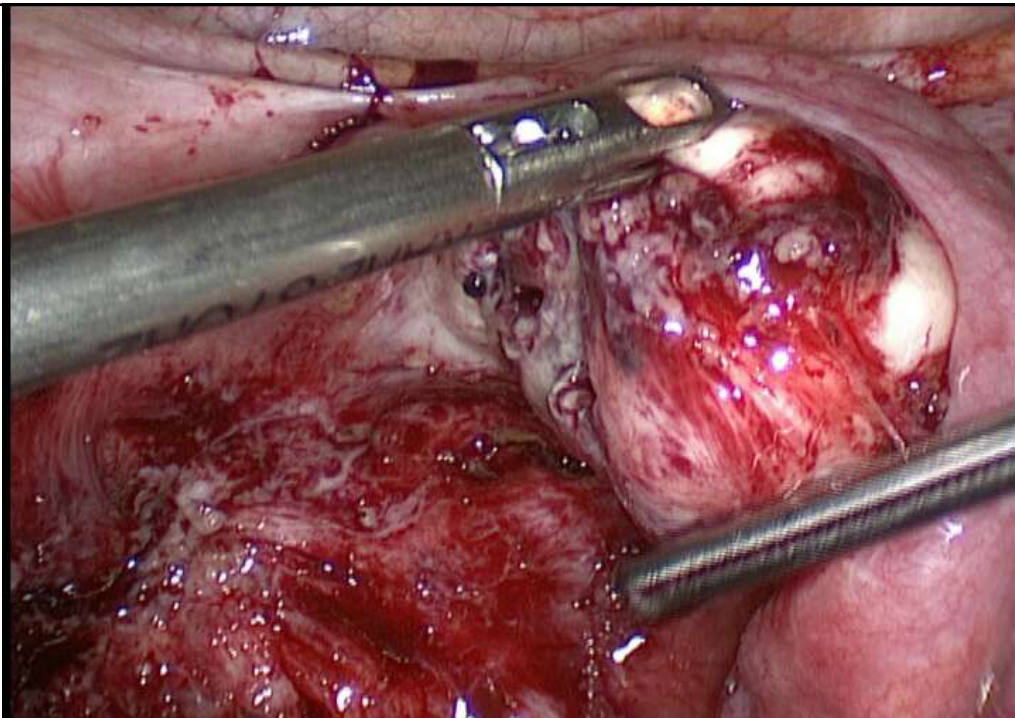
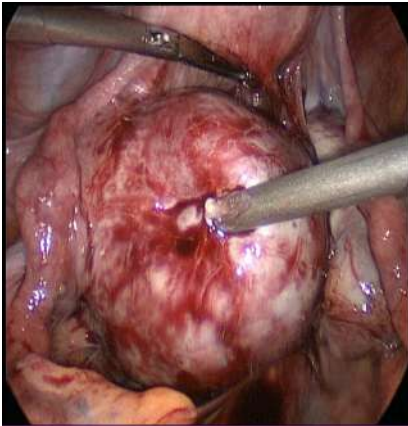
Impact of Excision on Ovarian Reserve

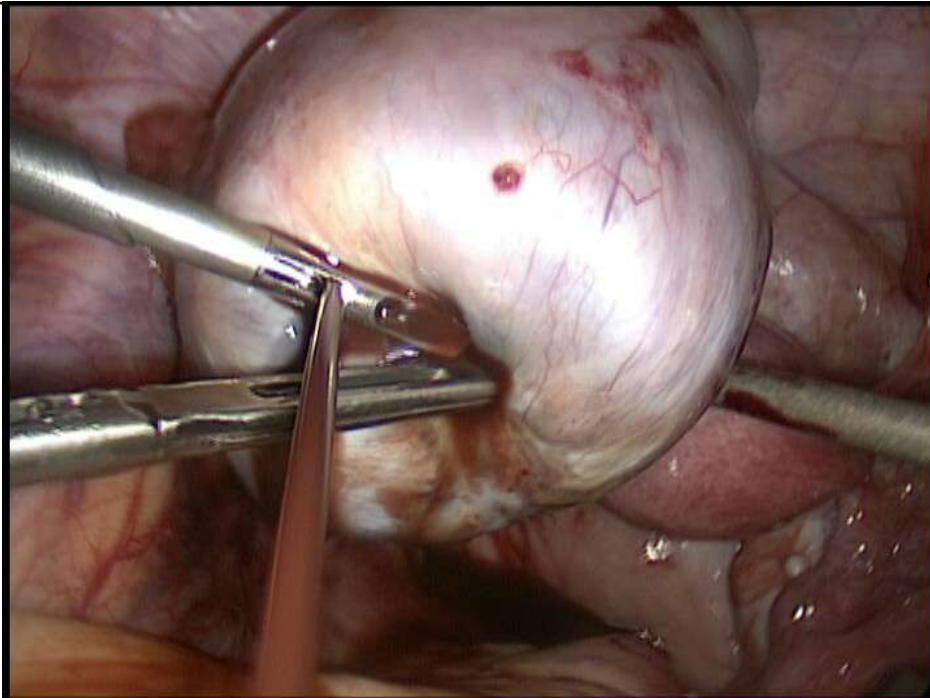
- Raffi et al JCEM 2012
 - Meta-analysis using AMH & AFC
 - 8 studies- excisional surgery
 - Cysts were more than 3-4 cm; mean 4-6 cm
 - Up to a 30 % fall in AMH in unilateral cystectomy & 44% fall in bilateral cystectomy
 - Gradient effect of increasing size of the endometrioma on the magnitude of the fall in AMH
- Muzii L et al HR 2014: meta-analysis= no change in AFC after non-excisional surgery

Second Surgery for recurrent Endometrioma

- Muzii et al F&S 2015
- Prospective- trial-primary vs. secondary surgery
 - Control was the unoperated side
 - Lower AFC & volume vs. unoperated side in the repeat surgery group
 - Histology- more ovarian tissue removed with secondary surgery

Adherent to pelvic side wall- Lysis of adhesions

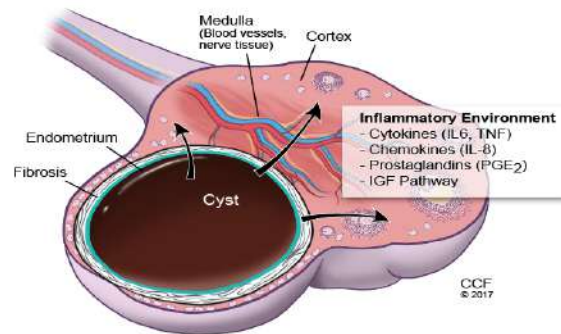




What about the other ovary?

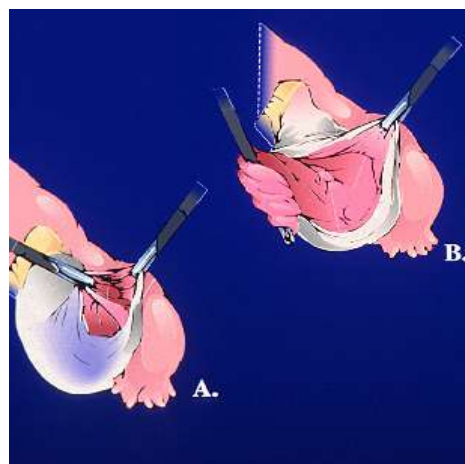


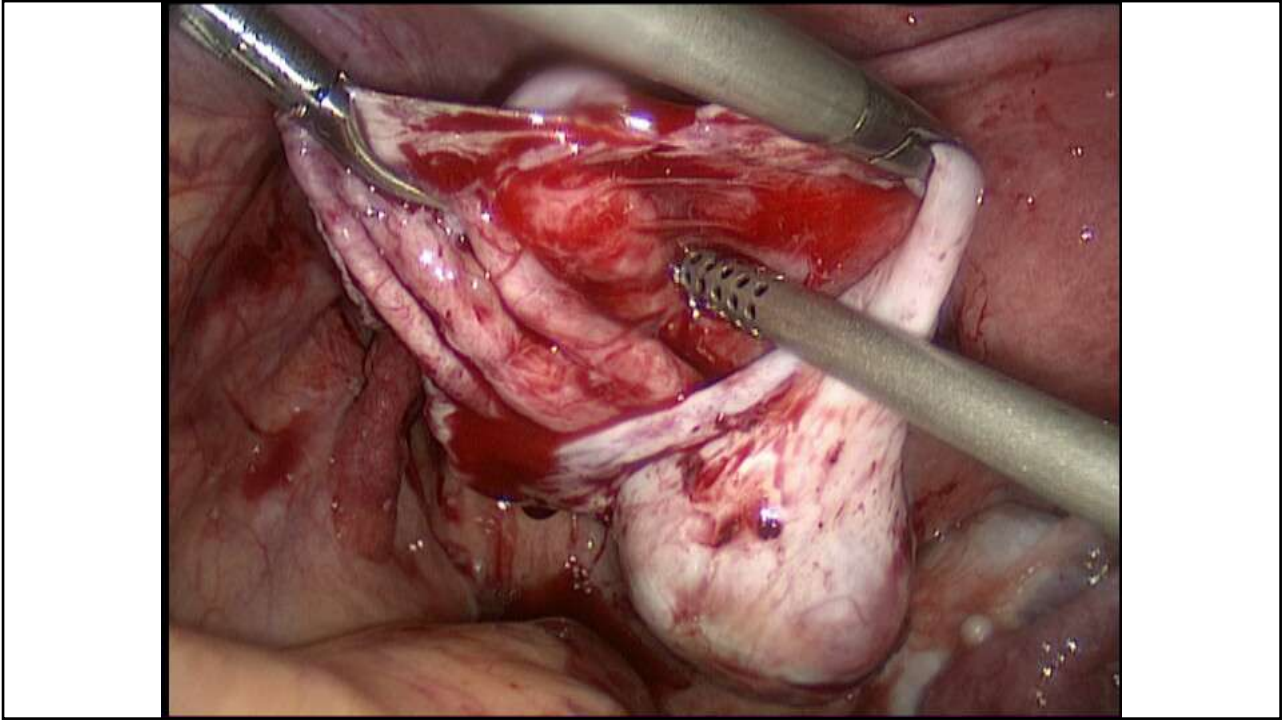
Where is the blood supply in relation to the cyst



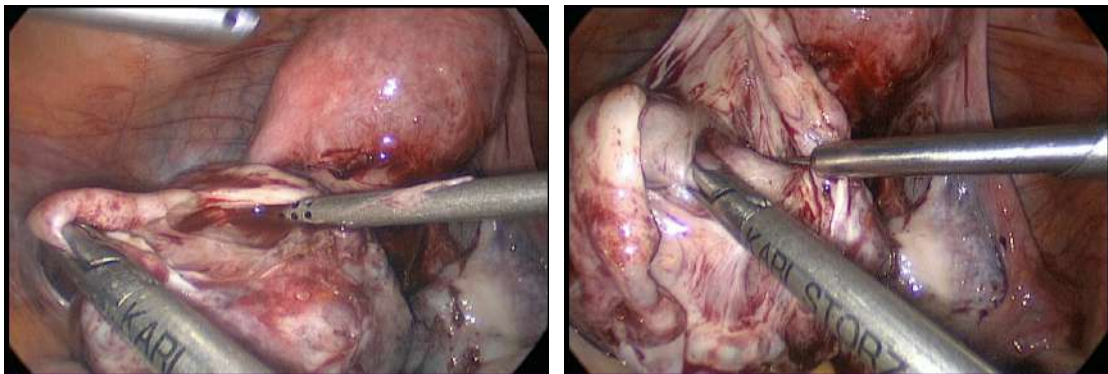
Technical Consideration-cleavage plane

- Muzii et al. 2007 histological analysis
 - **Ovarian tissue removed with the cyst.**
 - Endometriosis of the inner cyst rarely penetrates more than 1.5 mm into the cyst capsule .
- Muzii et al. 2005
 - Circular incision and then stripping vs. simply stripping
 - Circular incision removes more follicles.

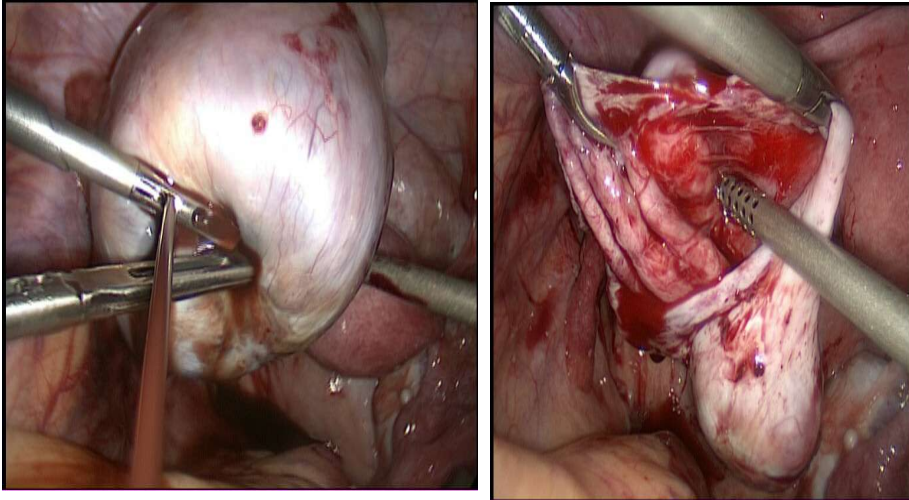




Fibrosis



Risk for ovarian reserve: Technical considerations



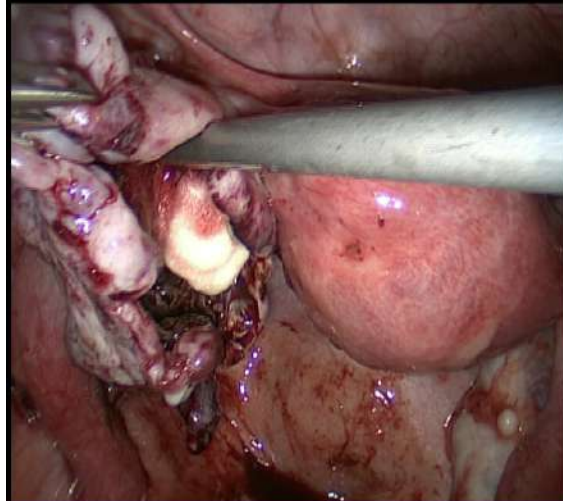
Risk for ovarian reserve: Technical considerations-vasopressin

- RCT – control, saline or vasopressin injection
Vasopressin reduced use of electrocautery
Saeki A et al J Reprod Infertil 2010;17:176-9
- RCT – control, saline or vasopressin injection-
Vasopressin limited tissue damage and prevented postop increase in FSH
Qiong-Zhen R et al J Min Invas Gynecol 2014;21:266-71
- RCT –saline or vasopressin injection
NSD - OR time, electrocautery use, change in FSH or AFC
Ghafarnejad M et al J Reprod Infertil 2014;15:199-204



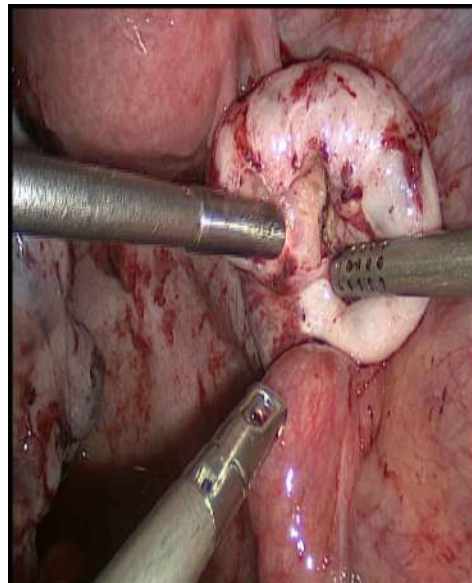
Alternative Techniques to Minimize Damage

- Angioli R et al. JMIG 2009
 - Use of hemostatic agent
- Tsolakidis et al 2010-3 stage procedure
 - surgery 1-drained/GnRHa=3 months/surgery 2-laser vaporization
 - 20% recurrence rate



Ablative Therapy- alternative energy forms

- Partial cystectomy & ablation of the hilum
 - Donnez J et al Fert Steril 2010; 94:28–32
 - Muzii L & Panici PB Reprod Biomed Online 2010;20:300–2
- Roman et al Fert Steril 2011-Plasma energy-coagulation mode-10-40W
 - recurrence 5-9%



Endometrioma removal: alternative technique

Hum. Reprod., 2016 Feb;31(2):339-44. doi: 10.1093/humrep/krv313. Epub 2015 Dec 18.

Comparison between the stripping technique and the combined excisional/ablative technique for the treatment of bilateral ovarian endometriomas: a multicentre RCT.

Muzilli L, Achilli C², Bergamini V³, Candiani M⁴, Garavaglia E⁴, Lazzari L⁵, Lecce E², Malcrana A⁶, Maneschi E⁷, Marana R⁸, Parandini A⁹, Porpora MG², Seracchioli R⁹, Spagnolo E⁹, Vignali M¹⁰, Benedetti Panici P².

- Recurrence rate at 6 months 5.9% vs. 2% (P = 0.62)
 - AFC same- AMH not measured
 - Postop pain recurrence 17%
 - No postop suppression

Electrosurgical approach

- Capsule may be up to 3 mm
- Bipolar can penetrate 10-12 mm
- Deep coagulation may destroy follicles



Technique to Minimize Damage

- Ding W et al RBO 2015: Impact on ovarian reserve of hemostasis by **bipolar coagulation vs. suture** following surgical stripping of ovarian endometrioma: 21 studies- 312 patients
 - Bipolar coagulation did more harm to ovarian reserve than suture hemostasis
- Ata et al JMIG 2015- Systematic reviews-
 - 5/6 studies decrease in ovarian reserve after bipolar electrosurgery
 - In all 3RCT **desiccation** groups had greater loss in AMH than **hemostatic sealant**; in 2 RCT bipolar had a greater loss than suturing groups.



Treatment of endometriomas: uncontrolled studies

- Vercellini et al. 2009
 - 14 studies; approximately 1500 patients; overall weighted mean was 50 %
 - Assume ½ of this observation: **NNT= 4**

NNT = number needed to treat

Systematic Reviews, Meta-analysis & Cochrane review: Intervention for Women with endometrioma prior to ART

- Meta-analysis: Tsoumpou et al. Fertil Steril 2009
 - 5 studies: No treatment versus surgery before IVF
 - No difference in clinical pregnancy rate
 - No significant difference in outcome (PR/oocytes retrieved/ embryos/gonadotropins/estradiol)
- *Cochrane database Syst Rev 2010*: Benschop et al
 - 4 trials-
 - Ovarian cystectomy or aspiration does not yield improved clinical PR

ESHRE consensus

- In infertile women with endometrioma **less** than 3 cm there is no evidence that cystectomy prior to treatment with assisted reproductive technologies improves pregnancy rates. (Benschop, et al., 2010, Donnez, et al., 2001, Hart, et al., 2008).

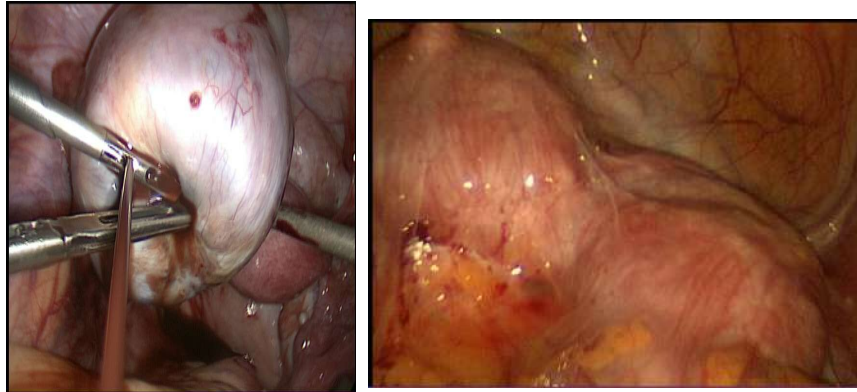
ESHRE consensus

- In women with endometrioma **larger** than 3 cm, the GDG recommends clinicians only to consider cystectomy prior to assisted reproductive technologies to improve endometriosis-associated pain or the accessibility of follicles.

ESHRE consensus

- The GDG recommends that clinicians counsel women with endometrioma regarding **the risks of reduced ovarian function after surgery and the possible loss of the ovary**. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery.

How do you decide: Chance of spontaneous pregnancy vs. need for IVF



Long Term suppression: 18-24 months

- **Recurrence**
 - 2-year follow-up (Seracchioli R et al. Fertil Steril 2010)
 - No suppressive therapy: 29 %
 - Cyclic oral contraceptives (OCs): 15 %
 - Continuous: 8 %
 - Porpora MG et al F&S 2010
 - 9.6 % after 3 years with suppressive therapy
- Vercellini et al meta analysis 2012
 - Endometrioma recurrence
 - 8 % with OC and 34 % control group
- Chen et al AJOG June 2017-RCT post cystectomy- **Mirena vs. control- recurrence at 30 months –pain much better with Mirena but recurrent cyst same (25%vs.37%)**

Dunselman GA, Vermeulen N, Becker C, et al; European Society of Human Reproduction and Embryology. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014;29(3):400–412

Seracchioli R, Mabrouk M, Manuzzi L, et al. Post-operative use of oral contraceptive pills for prevention of anatomical relapse or symptom-recurrence after conservative surgery for endometriosis. Hum Reprod 2009;24(11):2729–2735
 Vercellini P, DE Matteis S, Somigliana E, Buggio L, Frattaruolo MP, Fedele L. Long-term adjuvant therapy for the prevention of postoperative endometrioma recurrence: a systematic review and meta-analysis. Acta Obstet Gynecol Scand 2013;92(1):8–16

 Cleveland Clinic

