



Patient Management and Outcome of IVF/ICSI in Patients with Endometriomas

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The Goals of ART

- To minimize the risk of ART (complications,psycological,economical etc.)
- O To optimize pregnancy rates
- O To produce healthy, genetically normal, singleton full-term deliveries















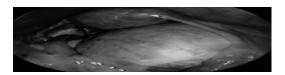


Surgery Before Assisted Reproduction Uterine pathologies Endometriomas Tubal diseases To achieve pregnancy To increase the success of the IVF/ICSI

• Cost • Complication(s) • Increase the sucess rate ? Which patients ? Which opereration ? Timing ?

Surgery Before Assisted Reproduction

Endometriomas :
Remove or not to Remove ?



Endometriomas

- Adnexeal mass (14%-44%)
- · Pelvic pain
- Infertility

Treatment Options

- Expectant management
- Surgery

Aspiration

Fenestration

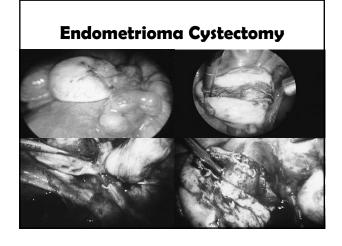
Ablation,coagulation

Cystectomy

Recurrence of the endometriomas is an important issue! (18%-30%)



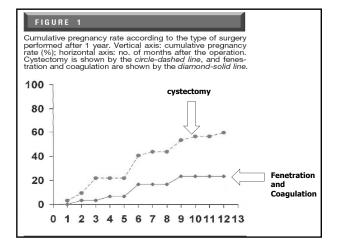
Endometrioma Tx L/T vs L/S



Treatment of Endometriomas

- Medical therapy alone has a limited role
- Operative laparoscopy represents the first-line treatment Chapron et al.,2002; Jones and Sutton,2002
- Better PR and a lower rate of recurrences after laparoscopic ovarian cystectomy
- PR after surgey vary between 23%-67% Elsheikh et al.,2003;Alborzi et al.,2004
- PR significantly influenced by patients charasteristics,length of follow – up, selection criteria, adhesion score and surgical technics (40%-50%)
- USG guided aspiration associated with high rate of recurrances

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TABLE 2				TABLE 3					Neprission or magalaism group		From recription/	- function
Recurrence of signs and rate of reoperation after	/ /	of endometrioma	s and	Recurrence of signs and rate of reoperation after 2	/ 1	f endometriomas	and	System (spt. 19)	87*	13	mgários	
Tallo of Toopolatori and	. you.		_	rate of resperation after a	L yours.			honispid., 98	18	136	_	
	Cystectomy	Fenestration and coagulation	P		Cystectomy	Fenestration and congulation	P	Betari, 98	62	131	-	
Recurrence of cyst (%)	3/52 (5.8)	948 (18.8)	~.09	Recurrence of cost (%)	9/52 (17.3)	15(10/212)	.16	Skirk and Taland, 1999	STR.	101		
Recurrence of symptoms (%)	2/38 (5.3)	6/30 (20)	~.13	Recurrence of symptoms (%)	638 (15.8)	15/48 (31.3) 17/30 (56.7)	.10	Common robbs so				
Reoperation (%)	152 (1.9)	448 (8.3)	~.[9	Remeration (%)	3/52 (5.8)	11/48/22.9)	.003					



Is Laparoscopic Surgery less commonly employed today?

- It is generally agreed that laparoscopic surgery can improve Pregnancy rates!
- · Higher sucess rates with IVF
- Fewer highly skilled laparoscopic surgeons
- Relatively poor managed care insurance reimbursement for surgery



There was a significantly lower pregnancy rate per fresh embryo transfer after pooled cycles (1–4) among women with stage III/IV endometriosis (22.6%) compared to stage I/II group (40.0%) or tubal infertility (36.6%). After 1–4 IVF/ICSI treatments, including frozen embryo transfer, 56.7% of the women with stage III/IV endometriosis were pregnant and 40.3% gave birth. Kuivasaari et al, Hum Reprod, 2005	
	1
IVF/ICSI in Endometriomas	
Laparoscopic ovarian cystectomy is recomended if an ovarian endometrioma larger than 4 cm in diameter is present to confirm diagnosis, reduce risk of	
infection,improve access to follicles and possibly improve the ovarian response (??).	
The women should councel regarding the risks of reduced ovarian function after surgery!	
ESHRE Guideline for diagnosis and treatment of Endometriosis:Human Reproduction,2005	
	1
Endometriomas and IVF : Alternative Treatment Options	
Ultrasound Guided Aspiration: Significant improvement in number of oocytes retrieved in women who failed to conceive a previous IVF cycle (Dicker et al.,1991)	
- LT-L/S , no treatment vs aspiration : a higher fertilization rate in the group of treated with aspiration	

(Suganuma et al.2002)

Aspiration of Ovarian Endometriomas Before ICSI

- Randomized study
- 41 women randomized for aspiration at the begining of ovarian stimulation, whereas 40 women who did not undergo aspiration were used as controls
- Number of oocytes retrieved, fertilization rate,implantation rate and pregnancy rate resulted similar

(Pabuccu et al., Fertil Steril,2004)

Endometrioma Cystectomy and IVF/ICSI

The average time between laparoscopic cystectomy and IVF cycle (6-24 m)

Whether cystectomy reduces response to COH and/or ART outcome?

What is the impact of endometriosis on the results of ART?

- 1. Number of oocytes
- 2. Oocyte quality
- 3. Fertilisation
- 4. Implantation
- 5. Miscarriage rates

Should endometriomas be treated before IVF-ICSI cycles? Risk of pelvic abscess – ruptured endometrioma Surgical-related damage Minor and major Risk of occult malignancy surgical complications Economic costs Retrieval difficulties Lack of evidence that surgery Contamination with endometrioma content improves IVF pregnancy Endometriosis progression Favours Favours SURGERY **Expectant Management** Edgardo Somigliana, 2006

Endometriomas and Ovarian Reserve

Mechanical streching

Meneschi et al.,1993

May cyst per se damage the the surrounding ovarian tissue?

Yes! Maneschi et al.,1993- Using pathological sections of the ovarian cortex found reduced number of follicles Need for clinical studies in human comparing follicular growth in the affected and contralateral intact gonad!

- Biochemical negative influence
 Magnetical 2004
- Adhesions which typically surround affected ovaries. In a rabbit model of endometriosis endometrial implants in the gonads decreased ovulation points

 Kaplan et al. 1989

Damage Machanisms

 Surgery-mediated damage **Negative effect of SURGERY!?**

Presence of healthy ovarian tissue adjacent to removed the cyst wall

Muzzi et al.,2002;Hachisuga and Kawarabayashi,2002 Excission of healthy ovarian cortex with follicles Brosens et al.,2004

Surgery related local inflamation and electrocoagulation during haemostasis

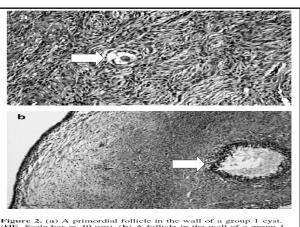
La Torre et al.,1998; Marconi et al.,2002; Fedele et al.,2004

Histopathological analysis of laparoscopically treated ovarian endometriotic cysts with special reference to loss of follicles

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Human Reproduction Vol.17, No.2 pp. 432-435, 2002



Endometrioma Cystectomy

- Recognizable ovarian tissue inadvertently removed 54% of the cases
- Close to the ovarian hilus ovarian tissue remove by endometriomas consisted of mostly primary and secondary follicles

GREAT CAUTION SHOULD BE UNDERTAKEN TO AVOID OVARIAN DAMAGE WHILE STRIPPING THE CYST CAPSULE AND HEMOSTASIS NEAR THE HILUS!

Muzzi et al. Fertil Steril 2002; Human Reprod, 2005

IVF/ICSI:Endometriomas, Endometriosis and Tubal Factor Infertility

Ovarian response during IVF-embryo transfer cycles after laparoscopic ovarian cystectomy for endometriotic cysts of >3 cm in diameter.

Canis et al., Hum Reprod 2001

- The number of oocytes and embryos obtained was not significantly decreased by laparoscopic cystectomy.
- In experienced hands this procedure may be a valuable surgical tool for the treatment of large ovarian endometriomas.
- However, great care must be taken to avoid ovarian damage!!!

Before IVF Should be removed endometriomas?

- Follicular reserve
- Decraesed ovarian response to COH
- Cycle cancel rate

Loh FH. Fertil Steril 1999

-	

CONTROVERSY: IS THE OUTCOME OF IVE AFFECTED BY ENDOMETRIOSIS?

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Removal of endometriomas before in vitro fertilization does not improve fertility outcomes: a matched, case-control study

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INDLL

Patient characteristics and controlled ovarian hyperstimulation parameters.

	Endometrioma removed (147 cycles)	Endometrioma present (63 cycles)	P value
Age (y)	34.7 ± 0.3	33.9 ± 0.5	.158
Basal FSH (IU)	7.5 ± 0.6	7.6 ± 0.8	.778
Basal E ₂ (pg/mL)	68.2 ± 10.5	37.8 ± 5.4	.064
Total FSH/hMG (IU)	3,880 ± 129	3,404 ± 162	.035
Days of stimulation	10.2 ± 0.3	10.3 ± 0.3	.780
Peak E ₂ levels (pg/mL)	1,910 ± 106	2,472 ± 261	.018

Note: Data are presented as mean ± SEM.

Endometriomas >3 cm

TABLE 2

In vitro fertilization/intracytoplasmic sperm injection cycle outcomes in women with an endometrioma present at the beginning of the stimulation compared with women with a previously removed ovarian endometrioma by laparoscopic cystectomy.

	Endometrioma removed (147 cycles)	Endometrioma present (63 cycles)	P value
No. of oocytes retrieved	10.8 ± 0.6	11.8 ± 0.9	.378
No. of mature oocytes	8.7 ± 0.6	8.4 ± 0.8	.780
Fertilization rate (%)	76.5	69.9	.051
No. of embryos/cycle	6.0 ± 0.4	6.4 ± 0.6	.582
No. of embryos transferred	2.7 ± 0.1	2.8 ± 0.1	.281
Implantation rate (%)	12.8	14.1	.958
Positive β-hCG (%)	30.2	28.8	.480
Clinical pregnancy rate (%)	25.4	22.7	.776
Multiple pregnancy rate (%)	7.9	12.1	.545
Biochemical pregnancy (%)	3.9	3.0	.817
Miscarriage rate (%)	3.9	6.1	.636
Cancellation rate (%)	6.3	7.6	.844

Note: Data are presented as mean ± SEM or %.

Influance of Endometrioma Cytectomy on Ovarian reserve

- Low peak E2 levels and higher gonadotropin requrements were documented in the operated patients
- Number of oocytes retrieved, number of embryos obtained and pregnancy rates were similar in both groups !!

The Presence of Ovarian Endometriomas is Associated with Reduced Responsiveness to Gonadotropins?

- 36 patients (56 IVF cycles)
- Endometrioma(s) in one ovary, intact contralateral ovary
- The median between diagnosis and the IVF cycle - 10 months
- · Duration of infertility- 4.3-2.2 yrs
- Dimeters of endometriomas (which are mainly small!)
- Histological confirmation of the diagnosis is missing in most of the patients

Somigliana et al.,FS,2006

Values are mean \pm SD. *P < 0.001

Does laparoscopic excision of endometriotic ovarian cysts significantly affect ovarian reserve? Insights from IVF cycles E.Somigliana¹, G.Ragni, F.Benedetti, R.Borroni, W.Vegetti and P.G.Crosignani Table III. Ovarian response in previously operated and in contralateral ovaries according to cyst diameter Variable Cyst diameter Variable Cyst diameter Variable Cyst diameter No. of cases* No. of folicles >15 mm Control ovary* A 2.1 ± 1.7 Operated ovary* 2.1 ± 1.7 Operated ovary* 2.1 ± 1.7 Operated ovary* Basal volume (cm²)* Basal volume (cm²)*

Control ovary* Operated ovary* P

8.3 ± 7.0 0.12

The Presence of Ovarian Endometriomas is Associated with Reduced Responsiveness to Gonadotropins?

- The number of condominant follicles developing in the affected gonad reduced
- In women with larger endometriomas follicle number decrease more significantly
- Poorer response with more than one cyst
- The differance between healthy and affected gonads was particularly relavent in women who were more responsive to gonadotropin stimulation ??

Somigliana et al.,FS,2006

http://online - Vol 12 No 5, 2006 639-643 Reproductive BioMedicine Online; www.rbmonline.com/Article/2182 on web 17 March 2006

Article

Effect of endometrioma cystectomy on IVF outcome: a prospective randomized study

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Article - Endometrioma cystectomy and IVF - All

Table 1, Parient characteristics and ovarian stimulation parameters for those who underwent ovarian endometrioma cystectomy (group I) and those who did not (group II).

Characteristics	Group $I(n = 49)$	Group II (n = 50)	P-value
Age (years)	35.2 ± 0.3	34.9 ± 0.2	NS
Basal FSH (mIU/ml)	8.2 ± 0.38	7.9 ± 0.36	NS
Total FSH dose (IU)	4575 ± 530.54	3675 ± 792.58	0.001
Stimulation days (day)	14.0 ± 2.5	10.8 ± 2.6	0.001
Peak oestradiol (pg/ml)	1170 ± 417.14	1680 ± 428.69	0.001

Data are presented as mean \pm SD. NS = not statistically significant. The Student t-text was used for statistical analysis.

Demirol A, Guven S, Baykal C, Gurgan T RBM Online, 12(5), 639-43, 2006

Table 2. Comparison of intrac	cytoplasmic sperm injection cycle outcome parameters
between patients who underwe	ent ovarian endometrioma cystectomy (group I) and those
who did not (group II).	

Characteristics	<i>Group I</i> (n = 49)	Group II $(n = 50)$	P-value
Number of mature oocytes retrieved.	7.8 ± 3.07	8.6 ± 2.82	0.03:24
Fertilization rate (%)	86.2	88.3	NS ^b
Number of embryos transferred	3.2 ± 0.84	3.4 ± 0.67	NS*
Implantation rate (%)	16.5	18.5	NS°
Clinical pregnancy rate (%)	34.4	38.2	NS°

Data are presented as mean \pm SD or percentages. NS = not statistically significant. "Student i-test, "Yates corrected chi-squared test, and "Fisher's exact test were used for statistical analysis.

Demirol A, Guven S, Baykal C, Gurgan T RBM Online, 12(5), 639-43, 2006

Conclusion

- In the ovarian surgery group stimulation period was significantly longer, total rec-FSH dose was significantly higher and peak E2 levels and mean number of mature oocytes were significantly lower
- There was no difference in terms of fertilization, implantation and pregnancy rate
 Demirol et al., RBM Online,2006

Outcome of in vitro fertilization/intracytoplasmic sperm injection after laparoscopic cystectomy for endometriomas

lbrahim Esinler, M.D., ^a Gurkan Bozdag, M.D., ^a Funda Aybar, M.D., ^b Ulku Bayar, M.D., ^c and Hakan Yarali, M.D. ^a

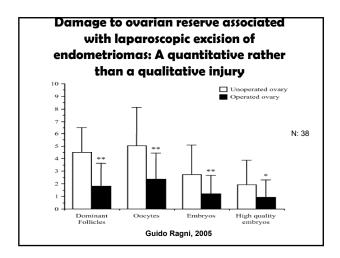
*Department of Obstetrics and Gynecology, Hacettepe University Faculty of Medicine and b Anatolia Women and IVF Health Center, Ankara; and Department of Obstetrics and Gynecology, Zonguldak Karaelmas University Faculty of Medicine, Zonguldak, Turkey

	Unilateral cystectomy	Bilateral cystectomy	Control	
Characteristic	(n = 34)	(n = 23)	(n = 99)	P valu
No. of canceled cycles (n, %)	3 (8.8)	5 (21.7)	9 (9.1)	NS
Female age (y)	31.3 ± 3.9	31.2 ± 4.4	31.9 ± 4.0	NS
Body mass index (kg/m²)	24.1 ± 2.4	24.9 ± 4.6	24.8 ± 3.8	NS
Duration of infertility (mo)	72.2 ± 40.5	85.3 ± 35	83.6 ± 42	NS
Time interval between	34.4 ± 15.6	42.7 ± 22.3	_	NS
cystectomy and ICSI (mo)				
Day 3 FSH level (mIU/mL)	7.1 ± 2.2	8.1 ± 2.5	7.3 ± 3.3	NS
Day 3 antral follicle count	10.0 ± 4.1	7.1 ± 2.6°	11.3 ± 3.9	<.05
Duration of stimulation (d)	11.3 ± 3.1	10.7 ± 1.5	10.3 ± 2.1	NS
Total dose of FSH used (IU)	2655.8 ± 1449.1	3423.4 ± 1682.3°	2519.4 ± 964.9	<.05
E ₂ level on the day of hCG administration (pg/mL)	2536.4 ± 1514.7	1730.6 ± 1060.8	1949.4 ± 1323.2	NS
Endometrial thickness at hCG administration (mm)	10.3 ± 2.4	11.2 ± 2.2	9.9 ± 2.1	NS

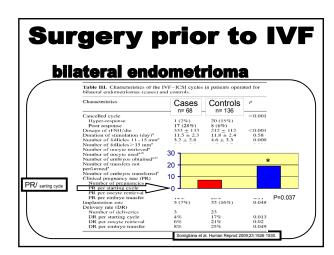
Variable	Operated Ovary (n=33)	Contralateral Normal ovary (n=33)	<i>P</i> value
Vo. of oocyte-cumulus omplexes	4.5±4.0	6.6±3.5	<.05

The embryological data and pregnancy outcome of the unilateral cystectomy, bilateral cystectomy, and control groups. $ \\$					
Characteristic	Unilateral cystectomy (n = 34)	Bilateral cystectomy (n = 23)	Control (n = 99)	P value	
No. of oocyte-cumulus complexes	10.8 ± 6.2	7.1 ± 4.4°	11.1 ± 6.1	<.0₺	
No. of metaphase II oocytes	8.1 ± 5.4	5.5 ± 3.2°	8.7 ± 4.8	<.05	
Metaphase II oocytes/total oocytes (%)	76.4	79.7	76.6	NS	
2-pronuclei/metaphase II oocytes (%)	71.9	68.6	73.6	NS	
No. of 2-pronucleated oocytes	6.6 ± 3.1	3.9 ± 2.3 ^a	6.7 ± 4.4	<.05	
No. of transferred grade I embryos ^b	0.6 ± 0.2	0.4 ± 0.2	0.9 ± 0.1	NS	
No. of transferred grade I embryos/No. of embryos transferred (%)	22.1	14.6	25.5	NS	
No. of transferred grade 2 embryos ^b	2.0 ± 0.2	2.1 ± 0.3	1.9 ± 0.1	NS	
No. of embryos transferred	2.9 ± 1.3	2.7 ± 1.2	3.0 ± 1.3	NS	
Clinical pregnancy/embryo transfer (%)	45.2	44.4	47.8	NS	
Implantation rate (%)	23.2	27.0	19.1	NS	
Multiple pregnancy rate (%)	36	38	38	NS	
Twin (%)	29	26	31	NS	
Triplet (%)	7	12	7	NS	
Miscarriage rate (n, %)	2 (14.2)	1 (12.8)	6 (13.9)	NS	

Note: Values are expressed as mean \pm SD, unless stated otherwise, NS = not significant a Statistically different from unilateral cystectomy and control groups. b Mean \pm SEM.



Surgery prior to IVF bilateral endometrioma Human Reproduction Vol.23, No.7 pp. 1526-1530, 2008 Advance Access publication on April 26, 2008 IVF-ICSI outcome in women operated on for bilateral endometriomas Edgardo Somigliana¹, Mariangela Arnoldi^{1,2}, Laura Benaglia^{1,2,3}, Roberta Iemmello^{1,2}, Anna Elisa Nicolosi^{1,2} and Guido Ragni¹ Somigliana et al. Human Reprod 2008.23 1526-1530.



Embryo quality before and after surgical treatment of endometriosis in infertile patients

Table 2 IVF parameters in cycles before and after laparoscopic treatment of endometriosis (N=30)

	IVF cycle before surgery	TVF cycle after surgery
Days on OCPs	20.3 ±3.2	18.4±4.6
Days of stimulation	10.5 ± 2.4	10.9 ± 1.9
Amount of gonadotropins in IU	4,950±540	5,025±420
Endometrial lining in mm	10.0 ± 1.2	10.1 +/1 1.8
Number of follioles	15.2 ± 2.6	12.8±1.8
Number of occytes	11.6±2.3	9.9±3.3
ICSI	17%	23%
Fertilization rate	63% TVF	68% IVF
	70% ICSI	75% ICSI
Assisted hatching	53%	67%
Number of ET	2.8±1.1	3.3±0.9
Number of eight cell day 3 embryos	2.6±1.1	2.3±0.9
Mumber of eight cell day 3 embryos SAUmber of day 3 embryos six cell	3.8±1.2	3.3±1.6
Stagenlian & Grade Ior II		
State the 13% (day 5) transfers	13%	20%
Stage III 13/0 Shanker of blastocysts frozen	2.1±13	2.8±2.1

Lora K. Shahine, 2009

Surgery prior to IVF

			1	
	n, Vol.24, No.3 pp. 496–501, 2009 ian on December 4, 2008 dai:10.1093/humrep.	/der398		
human reproduction	OPINION			
	Management	of endometr	iomas	
	in women red	quiring IVF: t	o touch	
	or not to tou			
		* and Edgardo Somiglia		

Table I Clinical variables to be considered when deciding whether to perform surgery or not in women with endometriomas selected for IVF Characteristics Favours surgery Favours expectant management Previous interventions for endometriosis Ovarian reserve¹ Intact Damaged Pian symptoms Present Sonographic feature of malignancy¹* Report Monolateral disease Absent Growth "Ovarian reserve is estimated based on serum markers or previous hyperstimalision cycles." Sonographic feature of malignancy¹* Carowth Stable "Ovarian reserve is estimated based on serum markers or previous hyperstimalision cycles." Sonographic feature of malignancy¹* Carowth Stable "Ovarian reserve is estimated based on serum markers or previous hyperstimalision cycles." Sonographic feature of malignancy refers to solid components, locularity,

Endometriomas and Ovarian Reserve: Insigths from IVF-ICSI Cycles in Women with Endometriomas

- Contralateral gonad may adequately compansate for the reduced function of the affected gonad
- The number of follicles developed in the cystectomized ovary significantly reduced when compared to the contralateral intact gonad!
- Bilateral cysts may elevated risk of ovarian function impairement (19%-28% bilaterality)
 Prefumo et al.,2002; Al-Fozan and Tulandi,2003. Esiner et al.2006

Ovarian Endometriomas

- Ovarian endometriosis is unilateral in the vast majority of the cases- 72%-82%
- The contralateral intact ovary adequately compansate the ovarian function!
- Overall, studies suggest that surgery does not benefit asymptomatic women preparing to undergo IVF-ICSI who are found to have endometrioma

Endometriomas and IVF/ICSI Individualized treatment plan can be developed, executed and modified as necessary based on: Bilaterality Number of endometriomas · Size of the endometrioma Surgical technic · Previous ovarian surgery · Ovarian reserve · Other factor(s) which contribute(s) to infertility Management of endometriomas in women requiring IVF: to touch or not to touch Juan A. Garcia-Velasco^{1,*} and Edgardo Somigliana² Medicid Rev Juan Carlos University. Av. del Talen 68. Medicid 28023. Scale ²Infectitive Univ. Care Table I Clinical variables to be considered when deciding whether to perform surgery or not in women with endometriomas selected for IVF Favours surgery Favours expectant management Previous interventions None ≥1 for endometriosis Ovarian reserve^a Intact Damaged Pain symptoms Present Absent Monolateral disease Bilateral disease Bilaterality Sonographic feature of malignancy^b Present Absent Rapid growth Growth ^aOvarian reserve is estimated based on serum markers or previous hyperstimulation cycles; ^bsonographic feature of malignancy refers to solid components, locularity, echogeniety, regularity of shape, wall, Human Reproduction, Vol.24, No.3 pp. 496–501, 2009

Conclusions and Recommendations

 Recommend generally proceeding directly to IVF to reduce time to pregnancy, to avoid potential surgical complications and to limit patient costs.

