

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

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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%)







## **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

#### A prospective, randomized study comparing laparoscopic ovarian cystectomy versus fenestration and coagulation in patients with endometriomas

Saeed Alborzi, M.D., Mozhdeh Morntahan, M.D., Mohammad Ebrahim Parsanozhad, M.D., Sedigheh Dehbashi, M.D., Jaleh Zolghadri, M.D., and Soroosh Alborzi Division of Intertility and Endoscopy, Department of Obstetrics and Gynecology, School of Medic University of Medical Sciences, Shiraz, Irac

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TABLE 2				TABLE 3					iqožados x neplečen group				
Recurrence of signs and rate of reoperation after	( )	if endometrioma	s and	Recurrence of signs and rate of reoperation after 2		i endometrioma	s and	foymaad Vogel, 191 Thematopid al, 198	87 10	13	from reprisation/ magilation	fivzeciór	
	Cystectorry	Fenestration and coagulation	P		Cystectomy	Fenestration and congulation	Р	lentii, 19	62	12	_		
Recurrence of cyst (%)	362 (5.8)	948 (18.8)	~)))	Recurrence of cyst (%)	9/52 (17.3)	15/48 (31,3)	.16	Seith and Taland, 199	574	101			
Recurrence of symptoms (%)	2/38 (5.3)	650 (20)	~.[]	Recurrence of symptoms (%)	6/38 (15.8)	17/30 (56.7)	.001	Comment adda natio					
Reoperation (%)	152 (1.9)	448 (8.3)	~.[9	Reoperation (%)	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

#### **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

#### 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





#### 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 Khamsi et al.,2001

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

### Toru Hachisuga<sup>1</sup> and Tatsuhiko Kawarabayashi

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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 WHİLE 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 IVF Affected by <u>endometriosis</u>?

FERTILITY AND STERILITY® VOL. 81, NO. 5, MAY 2004 Copyright 62004 American Scolety for Reproductive Maticine Nuclished by Elsevier Inc. Printed on acti-free paper in U.S.A.

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

Juan A. Garcia-Velasco, M.D., <sup>a</sup> Neal G. Mahutte, M.D., <sup>b</sup> José Corona, M.D., <sup>a</sup> Victor Zúriiga, M.D., <sup>a</sup> Juan Gilés, M.D., <sup>a</sup> Aydin Arici, M.D., <sup>b</sup> and Antonio Pellicer, M.D.<sup>cd</sup>

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#### TROLL

Patient characteristics and controlled ovarian hyperstimulation parameters.

	Endometrioma removed (147 cycles)	Endometrioma present (63 cycles)	P value
Age (y)	$34.7 \pm 0.3$	33.9 ± 0.5	.158
Basal FSH (IU)	$7.5 \pm 0.6$	$7.6 \pm 0.8$	.778
Basal E <sub>2</sub> (pg/mL)	$68.2 \pm 10.5$	$37.8 \pm 5.4$	.064
Total FSH/hMG (IU)	3,880 ± 129	$3,404 \pm 162$	.035
Days of stimulation	$10.2 \pm 0.3$	$10.3 \pm 0.3$	.780
Peak E <sub>2</sub> levels (pg/mL)	$1,910 \pm 106$	$2,472 \pm 261$	.018
Note: Data are presented a	as mean ± SEM.		
Endometri	omas >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	$10.8 \pm 0.6$	$11.8 \pm 0.9$	.378
No. of mature oocytes	$8.7 \pm 0.6$	$8.4 \pm 0.8$	.780
Fertilization rate (%)	76.5	69.9	.051
No. of embryos/cycle	$6.0 \pm 0.4$	$6.4 \pm 0.6$	.582
No. of embryos transferred	$2.7 \pm 0.1$	$2.8 \pm 0.1$	.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



#### 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





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

Online - Vol 12 No 5. 2006 639-643 Reproductive BioMedicine Online; www.zbmonline.com/Azticle/2182 on web 17 March 2006

Article

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

Aygül Demirol<sup>1,4</sup>, Suleyman Guven<sup>1</sup>, Cem Baykal<sup>2</sup>, Timur Gurgan<sup>1,3</sup>

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	A	rticle - Endometrioma	cystectory
Table 1. Patient characteri who underwent ovarian en did not (group II).			
Characteristics	Group I (n = 49)	Group II (n = 50)	P-valu
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
	$14.0 \pm 2.5$	$10.3 \pm 2.6$	0.001
Stimulation days (day)			0.001

Demirol A, Guven S, Baykal C, Gurgan T RBM Online, 12(5), 639-43, 2006 Table 2. Comparison of intracytoplasmic sperm injection cycle outcome parameters between patients 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
Number of mature occytes retrieved.	7.8 ± 3.07	8.6 ± 2.82	0.032*
Fertilization rate (%)	86.2	88.3	NS <sup>b</sup>
Number of embryos transferred	3.2 ± 0.84	3.4 ± 0.67	NS*
Implantation rate (%)	16.5	18.5	NS⁰
Clinical pregnancy rate (%)	34.4	38.2	NS⁰

Data are presented as mean ± SD or percentages. NS = not statistically significant. "Student r-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

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oyoteotoniy, bilaterar oyoteoto	my, and control gro	ups.		
Characteristic	Unilateral cystectomy (n = 34)	Bilateral cystectomy (n = 23)	Control (n = 99)	P value
No. of canceled cycles (n, %)	3 (8.8)	5 (21.7)	9 (9.1)	NS
Female age (y)	31.3 ± 3.9	$31.2 \pm 4.4$	$31.9 \pm 4.0$	NS
Body mass index (kg/m <sup>2</sup> )	24.1 ± 2.4	$24.9 \pm 4.6$	$24.8 \pm 3.8$	NS
Duration of infertility (mo)	72.2 ± 40.5	85.3 ± 35	83.6 ± 42	NS
Time interval between cystectomy and ICSI (mo)	34.4 ± 15.6	42.7 ± 22.3	—	NS
Day 3 FSH level (mIU/mL)	7.1 ± 2.2	8.1 ± 2.5	7.3 ± 3.3	NS
Day 3 antral follicle count	$10.0 \pm 4.1$	7.1 ± 2.6 <sup>a</sup>	$11.3 \pm 3.9$	<.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 <sup>a</sup>	2519.4 ± 964.9	<.05
E <sub>2</sub> 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
No. of oocyte-cumulus complexes	4.5±4.0	6.6±3.5	<dj< td=""></dj<>


Characteristic	Unilateral cystectomy (n = 34)	Bilateral cystectomy (n = 23)	Control (n = 99)	P value
No. of oocyte-cumulus complexes	10.8 ± 6.2	$7.1 \pm 4.4^{a}$	11.1 ± 6.1	<.05
No. of metaphase II oocytes	8.1 ± 5.4	5.5 ± 3.2ª	8.7 ± 4.8	<.05
Metaphase II oocytes/total oocytes (%) 2-pronuclei/metaphase II oocytes (%)	76.4 71.9	79.7 68.6	76.6 73.6	NS NS
No. of 2-pronucleated oocvtes	6.6 ± 3.1	3.9 ± 2.3 <sup>a</sup>	6.7 ± 4.4	<.05
No. of transferred grade I embryosb	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 embryosb	$2.0 \pm 0.2$	$2.1 \pm 0.3$	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









urgery p			
bilateral endo	mot	riama	•
<u>piialerai enuv</u>	<u>, mer</u>		1
<b>Table III.</b> Characteristics of the P bilateral endometriomas (cases) an		in patients opera	ted for
Characteristics	Cases	Controls	p
			·
Cancelled cycle		11-130	< 0.001
Hyper-response	1 (2%)	20 (15%)	
Poor response	17 (28%)	8 (6%)	
Dosage of rFSH/die	$333 \pm 133$	$212 \pm 112$	< 0.001
Duration of stimulation (day) <sup>a</sup> Number of follicles 11–15 mm <sup>a</sup>	$11.5 \pm 2.3$ $3.2 \pm 2.8$	$11.8 \pm 2.4$ $4.6 \pm 3.3$	0.58
Number of follicles >15 mm <sup>a</sup>	$\frac{3.2 \pm 2.8}{5.2 \pm 2.8}$	$4.6 \pm 3.3$ $6.5 \pm 2.7$	0.009
Number of follicles > 15 mm" Number of oocyte retrieved"	$5.2 \pm 2.8$ $5.7 \pm 4.0$	$6.5 \pm 2.7$ 7.2 + 3.6	0.006
Number of oocyte retrieved Number of oocyte used <sup>a,b</sup>	$\frac{5.7 \pm 4.0}{2.8 \pm 2.3}$	$7.2 \pm 3.6$ $3.8 \pm 2.7$	0.024
Number of embryos obtained <sup>a,b</sup>	$2.8 \pm 2.3$ $2.0 \pm 1.9$	$\frac{3.8 \pm 2.7}{2.8 \pm 2.0}$	0.034
Number of transfers not performed <sup>a</sup>	14(28%)	16 (15%)	0.08
Number of embryos transferred <sup>e</sup> Clinical pregnancy rate (PR)	$2.0\pm0.6$	$2.2\pm0.7$	0.20
Number of pregnancies	5	26	
PR per starting cycle	7%	19%	0.037
PR per oocyte retrieval	10%	24%	0.051
PR per embryo transfer	14%	28%	0.11
Implantation rate	5 (7%)	33 (16%)	0.048
Delivery rate (DR)	5 (1.47	55 (1010)	
Number of deliveries	3	23	
DR per starting cycle	4%	17%	0.013
	6%	21%	0.02
DR per occyte retrieval			







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

Table 2 IVF parameters in cycles before and after laparoscopic beament of endometrics: (N=30)

	IVF oyole before Surgery	IVF oyole after surgery
Days on OCPs	20.3 ±3.2	18.4±4.6
Days of stimulation	10.5±2.4	$10.9 \pm 1.9$
Amount of gonadotropins in IU	4,950±540	5,025±420
Endometrial lining in mm	$10.0 \pm 1.2$	10.1 +/1 1.8
Number of follicles	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% IVF	68% IVF
	76% ICSI	75% ICSI
Assisted hatching	53%	67%
Number of ET	$2.8 \pm 1.1$	3.3±0.9
Mumber of eight cell day 3 embryos	$2.6 \pm 1.1$	2.3±0.9
NAGEnbel We day 3 embryos six cell Stagenhall & Grade I or II	3.8±1.2	3.3±1.6
Bacturyst (day 5) transfers	13%	20%
Stage III 13% and blastocysts frozen	2.1±13	2.8±2.1









#### 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;AI-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

r not to touch n A. Garcia-Velasco <sup>1,7</sup> and Edgardo Somigliana <sup>2</sup> https://www.com/archivelines.org/archiveling/org/archiveling/org/archiveling/org/archiveling/arc			
Table I Clinical va deciding whether with endometrion Characteristics	to perform surger	y or not in wome	
Previous interventions for endometriosis	None	≥I	
Ovarian reserve <sup>a</sup>	Intact	Damaged	
Pain symptoms	Present	Absent	
Bilaterality	Monolateral disease	Bilateral disease	
Sonographic feature of malignancy <sup>b</sup>	Present	Absent	
	Rapid growth	Stable	

#### **Conclusions and Recommendations**

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





