

Endometriomanın IVF sonuçlarına etkisi

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ENDOMETRIOSIS

- Up to 22% of asymptomatic women have endometriosis
- Up to 45% of women with pelvic pain have endometriosis
- 25-50% of infertile women have endometriosis
- 30-50% of women with endometriosis are infertile
- Infertile women are 6 to 5 times more likely to have endometriosis than fertile women

Counsellor VS, Am J Onstet gynecology

Verkauf BS, J Fla Med, 1987

Hart RJ, Cochrane Database of Systematic

Reviews, 2008



ENDOMETRIOSIS

- Mechanisms of infertility associated with endometriosis are controversial
- Although endometriosis impairs fertility, it does not usually completely prevent conception



Pathogenic mechanisms and consequences in endometriosis-associated infertility

Abnormal folliculogenesis

- Impaired follicle growth

Impaired granulosa cell (GC) function:

- Increased GC apoptosis
- Increased oxidative stress in GC
- DNA damages

Abnormal follicular fluid immune function

- Increased B lymphocytes, natural killer cells and monocytes-macrophages
- Changes in ovarian steroid enzymes
- Increased interleukins, cytokines
- Decreased angiogenic factors, e.g., vascular endothelial growth factor (VEGF)

Impaired oocyte maturation

- Chromosomal changes
- Poor oocyte quality

Impaired sperm function

- Increased reactive oxidative species
- Decreased binding of spermatozoa to zona-pellucida

Reduced fertilization rate

- Low embryo quality and implantation potential

Peritoneal fluid immunologic abnormalities

- Altered humoral and cell-mediated immunity
- Presence of autoendometrial antibodies
- Local inflammatory cascade
- Increased cytokines, growth factors, prostaglandins, nitric oxide

Impaired tubal function

- Impaired sperm and endosalpinx interaction

Distorted pelvic anatomy

- Adhesions
- Impaired ovum pickup

ENDOMETRIOSIS DECREASE FECUNDITY

	MODERATE	SEVERE
MILD	7.4	2.8
		0

Olive, Fertil Steril 1985



Indications for treatment of endometriosis

- **Improve the outcome of ART**
- Treat pelvic pain
- Treat dyspareunia

Hart RJ, Cochrane Database of Systematic Reviews, 2008



IMPACT OF ENDOMETRIOSIS ON ART OUTCOMES

- 22 retrospective studies
- Endometriosis patients
 - Fewer oocytes (7.3 vs. 7.8)
 - Lower implantation rate (12.7 vs. 18.1)
 - Lower pregnancy rate (25.4 vs. 29.5)
 - Effect of stage
 - I/II- 21.1% CPR
 - III/IV 13.8% CPR

ART cycles in the presence of an endometrioma

- Difficulty with monitoring ovarian response by ultrasound
- Difficult oocyte aspiration due to pelvic adhesions
- Higher cycle cancellation rates due to poor ovarian response to stimulation
- Rarely postovum pick up infection

Matson PL, fertility and sterility, 1986

Oehinger S, J of In vitro Fertilization and embryo Transfer, 1988

Pellicer A, Human Reproduction, 1995

Dechaud, Gynecol Endocrin, 2009

D'Hoogue, Fertil Steril, 2006



Treatment options for women undergoing ART because of subfertility associated with endometrioma:

- Undergoing ART without treatment (expectant management or placebo)
- Medical treatment of endometrioma prior to ART
- Surgical treatment to remove or destroy the endometrioma prior to ART
- Combination of surgical and medical treatment prior to ART

Benschop L, Cochrane Database of Systematic Reviews, 2010



National survey of the current management of endometriomas in women undergoing assisted reproductive treatment

It is clear from this survey that the majority (95%) of gynaecologists would offer surgery (mostly cystectomy) for endometriomas before ART and 26% would offer surgery even for small endometriomas (<5 cm in diameter). This is despite the available evidence that surgery does not improve outcomes of ART and may damage ovarian reserve. We therefore recommend that clinicians should reconsider the value of surgery, especially in patients who have no or mild symptoms.

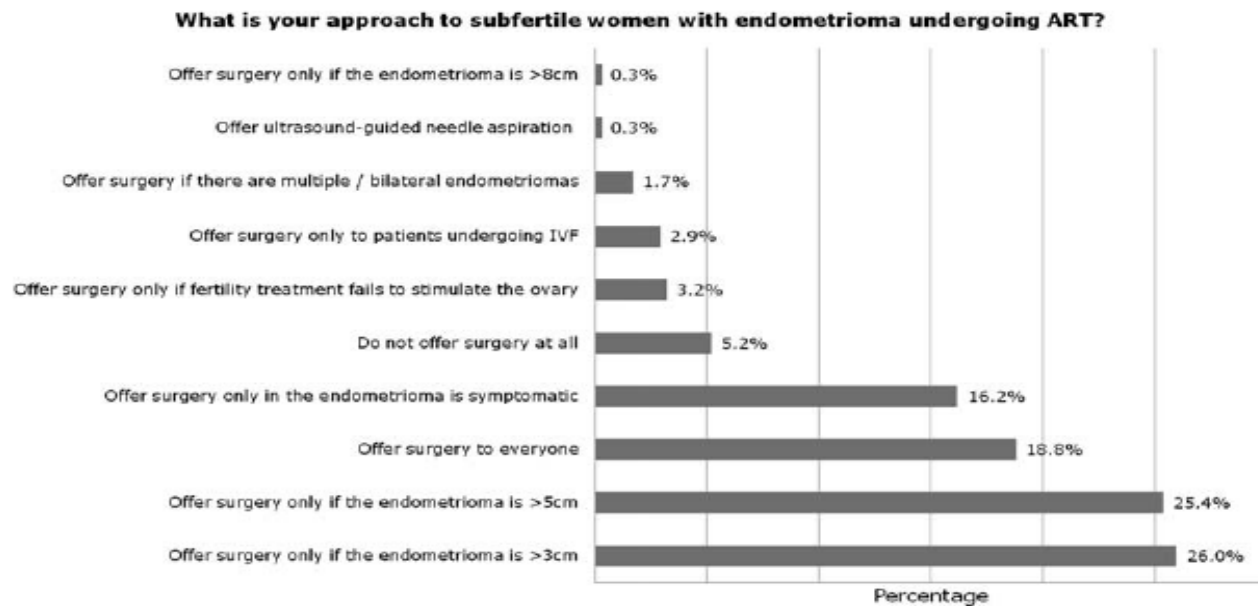


Figure 1 Clinician's approach to subfertile women with endometrioma undergoing ART.

Table I Please give your opinion of the following statements on possible reasons/advantages of surgical treatment of endometriomas before assisted reproductive treatment.

Answer options	Strongly agree	Agree	Not sure	Disagree	Strongly disagree	Response count
Improves ovarian response to stimulation	33 (11%)	149 (48%)	108 (35%)	20 (6%)	0	310
Improves access to ovarian follicles during oocyte retrieval	35 (12%)	211 (69%)	53 (17%)	6 (2%)	0	305
Avoids the risk of infection during oocyte retrieval	33 (11%)	120 (39%)	123 (40%)	27 (9%)	3 (1%)	306
Gives an opportunity to treat other pelvic endometriosis	79 (26%)	184 (60%)	31 (10%)	11 (4%)	1	306
Relieves symptoms	91 (30%)	188 (61%)	26 (8%)	3 (1%)	1	309
Increases the possibility of natural conception	41 (14%)	173 (57%)	80 (26%)	9 (3%)	0	303
Improves patient's satisfaction/gives patients assurance	29 (9%)	180 (59%)	72 (24%)	21 (7%)	2 (1%)	304

Values in bold indicate most common response.

Table II Please give your opinion of the following statements on the possible reasons for not performing surgical treatment of endometriomas before ART.

Answer options	Strongly agree	Agree	Not sure	Disagree	Strongly disagree	Total
Avoid possible damage to ovarian reserve	19 (7%)	175 (59%)	48 (16%)	48 (16%)	5 (2%)	295
Avoid possible risk of oophorectomy	11 (4%)	174 (59%)	28 (10%)	69 (23%)	11 (4%)	293
Unnecessary exposure to surgical and anaesthetic risks	12 (4%)	134 (46%)	33 (11%)	95 (33%)	16 (6%)	290
Unnecessary delay of fertility treatment	6 (2%)	89 (30%)	63 (22%)	121 (41%)	14 (5%)	293
Avoid increasing the patient's stress levels	2 (1%)	53 (18%)	83 (29%)	136 (47%)	16 (5%)	290
Avoid adding to the cost of treatment	4 (1%)	58 (20%)	72 (25%)	129 (45%)	24 (9%)	287

Values in bold indicate most common response.

Table III Comparative analysis for years of experience versus approach to women with endometrioma undergoing ART.

What is your approach to subfertile women with endometriomas undergoing assisted reproductive treatment (ART)?						
Answer options	Number of years of work experience					Total (n = 341) ^a
	<5 years (n = 40)	5–10 years (n = 127)	10–15 years (n = 64)	15–20 years (n = 46)	>20 years (n = 64)	
Do not offer surgery at all	0	5 (4%)	6 (9%)	2 (4%)	5 (8%)	18 (5%)
Offer surgery to everyone	9 (23%)	30 (24%)	9 (14%)	7 (15%)	10 (15%)	65 (19%)
Offer surgery only to patients undergoing IVF	3 (7%)	2 (2%)	1 (2%)	1 (2%)	3 (4%)	10 (3%)
Offer ultrasound-guided needle aspiration	0	0	0	0	1 (2%)	1 (0%)
Offer surgery only if the endometrioma is symptomatic	3 (7%)	18 (14%)	11 (17%)	12 (26%)	11 (17%)	55 (16%)
Offer surgery only if the endometrioma is >3 cm	8 (20%)	32 (25%)	18 (28%)	10 (22%)	19 (30%)	87 (26%)
Offer surgery only if the endometrioma is >5 cm	14 (35%)	32 (25%)	14 (22%)	13 (29%)	14 (22%)	87 (26%)
Offer surgery only if the endometrioma is >8 cm	1 (3%)	0	0	0	0	1 (0%)
Offer surgery only for multiple/bilateral endometriomas	0	3 (2%)	2 (3%)	1 (2%)	0	6 (2%)
Offer surgery only if fertility treatment fails	2 (5%)	5 (4%)	3 (5%)	0	1 (2%)	11 (3%)

^aForty-seven responders skipped this question.

Table IV Comparative analysis for years of experience versus reason for offering surgery

Please explain why you offer surgery (*more than one answer possible)						
Answer options	Number of years of work experience					Total (n = 576) [*]
	<5 years	5–10 years	10–15 years	15–20 years	>20 years	
To improve ovarian response to stimulation	24	56	30	16	23	149 (26%)
To improve access to ovarian follicles during oocyte retrieval	15	46	25	19	26	131 (23%)
To avoid risk of infection during oocyte retrieval	6	27	17	15	16	81 (14%)
To improve symptoms	14	71	34	25	40	184 (32%)
Other (please specify)	2	6	7	8	8	31 (5%)

Values in bold indicate most common response.

Medical treatment

- There is no evidence to support medical treatment use in the treatment of infertility associated with endometriosis

Hughes E, Cochrane Database of Systematic reviews, 1998, 2010

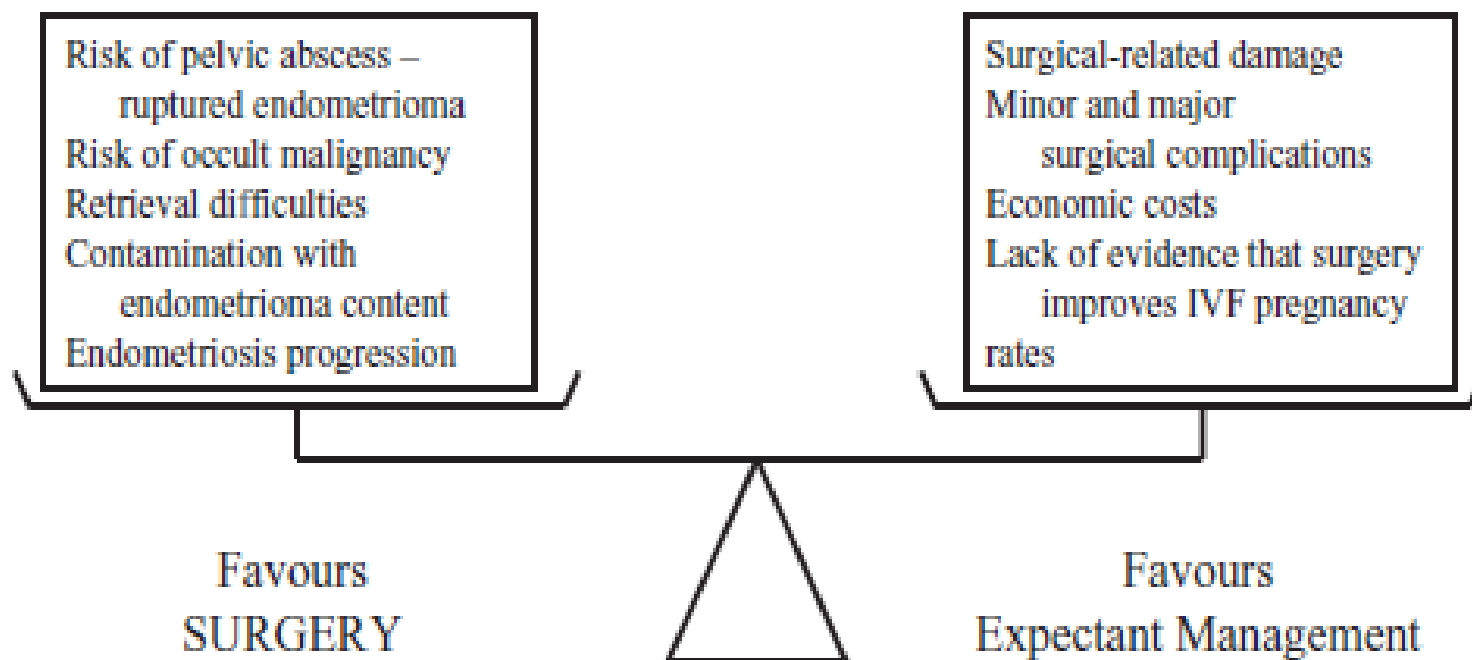
- Suppression of ovarian function to improve fertility in minimal–mild endometriosis is not effective and should not be offered for this indication alone . *There is* no evidence of its effectiveness in more severe disease.

Stephen Kennedy, human reprod 2005

ESHRE guideline for the diagnosis and treatment of endometriosis



IVF vs SURGERY



Edgardo Somigliana

The aim of surgery

- Restore the normal anatomy of the ovaries
- Improve accessibility of fallopian tubes
- Improve spontaneous fertility rates and ART outcomes

Benschop L Cochrane Database of Systematic Reviews, 2010



The resection of endometriomas results in

- Loss of small follicles adjacent to the cyst wall
- Leading to a reduced oocyte pool
- Fewer dominant follicles, oocytes and high quality embryos in operated ovary during hyperstimulation for IVF
- Premature ovarian failure
- Trauma to the ovary and subsequent reduced ovarian response

Exacoustos C, Am J Obstet Gynecol, 2004

Somigliana E, Hum Reprod, 2003

Ragni G, Am J Obstet Gynecol, 2005

Ho HY, J Assist Reprod. Genet, 2002

Busacca M, Am J Obstet Gynecol, 2006



THE POSTOPERATIVE DECLINE IN SERUM ANTI-MÜLLERIAN HORMONE CORRELATES WITH THE BILATERALITY AND SEVERITY OF ENDOMETRIOSIS

Characteristics and variables	Overall (n = 38)	Unilateral (n = 20)	Bilateral (n = 18)	P-value
Age (years)	33.8 ± 4.7	34.0 ± 3.9	33.6 ± 5.4	0.830 ^a
BMI (kg/m ²)	20.1 ± 2.3	20.4 ± 2.7	19.7 ± 1.7	0.781 ^b
Preoperative				
Monocystic/Multicystic (%)	6 (16)/32 (84)	5 (25)/15 (75)	1 (6)/17 (94)	0.184 ^c
Cyst size 1 (cm)	6.4 ± 2.2	6.1 ± 2.5	6.7 ± 1.8	0.125 ^b
Cyst size 2 (cm)	3.9 ± 1.3	NA	3.9 ± 1.3	NA
Cyst size 1 + 2 (cm)	8.2 ± 3.4	6.1 ± 2.5	10.6 ± 2.5	<u><0.001^b</u>
Serum CA125 (IU/ml)	85.4 ± 84.8	99.7 ± 105.1	68.7 ± 46.3	0.915 ^b
Surgery				
Laparoscopy/Laparotomy	33 (87)/5 (13)	18 (90)/2 (10)	15 (83)/3 (17)	0.653 ^c
Blood loss (ml)	249 ± 305	152 ± 216	357 ± 350	0.005 ^b
rASRM score	49.5 ± 28.3	36.7 ± 23.5	63.7 ± 26.3	<u><0.001^b</u>
Number of follicles in specimens	18.1 ± 19.8	16.9 ± 14.8	19.4 ± 24.2	0.763 ^b
Serum AMH (ng/ml)				
Preoperative	3.9 ± 2.5	4.1 ± 2.3	3.6 ± 2.7	0.299 ^b
Post-operative	2.1 ± 1.6	2.9 ± 1.6	1.2 ± 1.0	<u>0.001^b</u>

Surgical excision of endometriomas and ovarian reserve: a systematic review on serum antimüllerian hormone level modifications

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Objective: To evaluate serum antimüllerian hormone (AMH) level modification after surgical excision of ovarian endometriomas.

Design: Systematic review. MEDLINE search from January 1990 to April 2012 using the combination of medical terms endometriosis, endometrioma, endometriotic cyst, and AMH or antimüllerian hormone, MIF or müllerian inhibiting factor. Reference lists of selected studies were checked for additional potential contributions.

Setting: Not applicable.

Patient(s): Women with ovarian endometriomas requiring surgery.

Intervention(s): Serum AMH level assessment.

Main Outcome Measure(s): Serum AMH level modifications.

Result(s): Eleven articles satisfied our selection criteria. Data pooling were deemed inopportune owing to the heterogeneity of the study designs and of the reported parameters. Nine of 11 studies documented a statistically significant reduction of serum AMH level after surgery. The two studies failing to document this decrease were published by the same study group and partly overlapped. The magnitude of the decline was more evident in women operated on for bilateral endometriomas.

Conclusion(s): Evidence deriving from the evaluation of serum AMH level modifications after surgical excision of endometriomas supports a surgery-related damage to ovarian reserve. (Fertil Steril® 2012;98:1531–8. ©2012 by American Society for Reproductive Medicine.)

Key Words: Endometrioma, AMH, surgery, stripping, ovarian reserve

Discuss: You can discuss this article with its authors and with other ASRM members at <http://fertstertforum.com/somiglianae-endometrioma-ovarian-reserve-amh/>



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Laparoscopic stripping of endometriomas negatively affects ovarian follicular reserve even if performed by experienced surgeons

The data show that laparoscopic stripping of endometriomas reduces ovarian reserve. The significant decrease of AMH after surgery confirms that part of the healthy ovarian pericapsular tissue, containing primordial and preantral follicles, is removed or damaged despite all the surgical efforts to be atraumatic. This must be carefully considered when laparoscopic cystectomy surgery is scheduled for patients with no relevant symptoms besides infertility or with already small ovarian reserve.

Table 2 Hormone concentrations before laparoscopic stripping of ovarian endometrioma(s) and after 3 and 9 months.

Hormone	Before LPS	After LPS		P-value
		3 months	9 months	
FSH (IU/l)	6.6 ± 2.0	7.8 ± 3.4	8.0 ± 3.7	NS
LH (IU/l)	5.0 ± 2.0	4.5 ± 1.7	4.2 ± 2.0	NS
Oestradiol (pg/ml)	35.2 ± 24.5	33.5 ± 29.3	32.9 ± 26.6	NS
Inhibin B (pg/ml)	51.6 ± 31.3	47.4 ± 23.0	44.5 ± 26.0	NS
AMH (ng/ml)	3.0 ± 0.4	1.4 ± 0.2	1.3 ± 0.3	<0.0001

Values are mean ± SD. AMH = anti-Müllerian hormone; LPS = laparoscopic stripping; NS = not statistically significant.

Table 3 Ultrasonographic variables before laparoscopic stripping of ovarian endometrioma(s) and after 3 and 9 months for patients with monolateral endometrioma (n = 33).

Ultrasonographic finding	Before LPS	After LPS		P-value
		3 months	9 months	
AFC (affected ovary)	3.3 ± 3.2	6.0 ± 4.5	5.1 ± 3.6	NS
AFC (healthy ovary)	8.4 ± 6.0	9.0 ± 6.2	8.1 ± 4.9	NS
Ovarian volume (affected) (ml)	10.5 ± 0.8	8.5 ± 0.6	8.6 ± 0.9	<0.0001
Ovarian volume (healthy) (ml)	8.1 ± 0.8	8.4 ± 0.6	8.2 ± 0.8	NS

Values are mean ± SD. AFC = antral follicle count; LPS = laparoscopic stripping; NS = not statistically significant.

Effects of excision of ovarian endometrioma on the antral follicle count and collected oocytes for in vitro fertilization

The results of our study suggest that excision of ovarian endometrioma is followed by a reduced number of oocytes and a high percentage of ovaries that are not responsive to gonadotropin stimulation.

TABLE 1

Number of antral follicle count, dominant follicle, and collected oocytes in the operated ovaries and in the nonoperated ovaries among women with previous ovarian endometrioma.

	Operated side (n = 80)	Nonoperated side (n = 80)	P value	95% CI
Antral follicle count	4.5 ± 3.8	7.4 ± 5.2	0.003	1.0–5.0
No. of dominant follicles	4.7 ± 3.9	7.5 ± 4.7	<0.0001	1.5–4.2
No. of dominant follicles ≤ 2 (%)	24 (30%)	10 (12.5%)	0.02	5.1–29.8
No. of collected oocytes	4.3 ± 3.9	7.4 ± 4.8	<0.0001	1.7–4.4
No. of collected oocytes ≤ 2 (%)	32 (40%)	13 (16.2%)	0.008	10.3–37.2
No. of zero oocytes collected (percent)	15 (18.7%)	1 (1.2%)	0.0002	8.6–26.4

Almog. Endometrioma excision, antral follicle count, and retrieved oocytes. Fertil Steril 2010.



OVARIAN RESERVE

Table 1 Studies comparing the number of follicles in the operated and in the contralateral non-operated ovaries during ovarian hyperstimulation for IVF.

Authors	Number of cycles	Operated ovary	Control ovary	P
Loh <i>et al.</i> (1999)	12	4.6 ^a	3.6 ^a	n.s.
Ho <i>et al.</i> (2002)	38	1.9 ± 1.5	3.3 ± 2.1	<0.001
Somigliana <i>et al.</i> (2003)	46	2.0 ± 1.5	4.2 ± 2.5	<0.001
Ragni <i>et al.</i> (2005)	38	1.8 ± 1.8	4.5 ± 2.0	<0.001
Duru <i>et al.</i> (2007) (LPS)	28	3.1 ± 1.8	4.4 ± 1.0	<0.05
Duru <i>et al.</i> (2007) (LPT)	10	2.1 ± 1.4	5.0 ± 2.0	<0.05
Alborzi <i>et al.</i> (2007)	70	3.2 ± 1.1	3.2 ± 1.7	n.s.

Data are expressed as Mean ± SD.

^aSD was not reported.

n.s., not significant; LPS, laparoscopy; LPT, laparotomy.

Only studies referring to surgical excision of endometriomas were included.



Ovarian response after laparoscopic excision of endometrioma compared with contralateral ovary

Study	Oocytes retrieved (n)		Mature follicles (n)	
	S	C	S	C
Loh <i>et al.</i> ²⁴	ND	ND	4.6	3.6
Ho <i>et al.</i> ²⁵	2.9	6.1*	1.9	3.3*
Somigliani <i>et al.</i> ²⁶	ND	ND	2.0	4.2*
Ragni <i>et al.</i> ^{27a}	2.4	5.0*	1.8	4.5*
Duru <i>et al.</i> ²⁸	ND	ND	3.1	4.4*

S, surgical removal of endometrioma; C, contralateral ovary; ND, not documented.

*Significantly increased ($P < 0.05$).

Loh FH, Fertil Steril, 1999

Ho HY, J Assist Reprod. Genet, 2002

Somigliana E, Hum Reprod, 2003

Ragni G, Am J Obstet Gynecol, 2005

Duru NK, J Reprod Med, 2007



*LAPAROSCOPIC SURGERY IN WOMEN WITH MINIMAL AND MILD
ENDOMETRIOSIS*

	<i>no treatment</i>	<i>surgical treatment</i>
Marcoux (1997)	n=177 PR 29%	n=169 PR 28%
Parazzini (1999)	N=54 PR 22%	n=47 PR 17%
Total	PR 27%	PR 18%

LAPAROSCOPIC SURGERY IN WOMEN WITH MINIMAL AND MILD ENDOMETRIOSIS

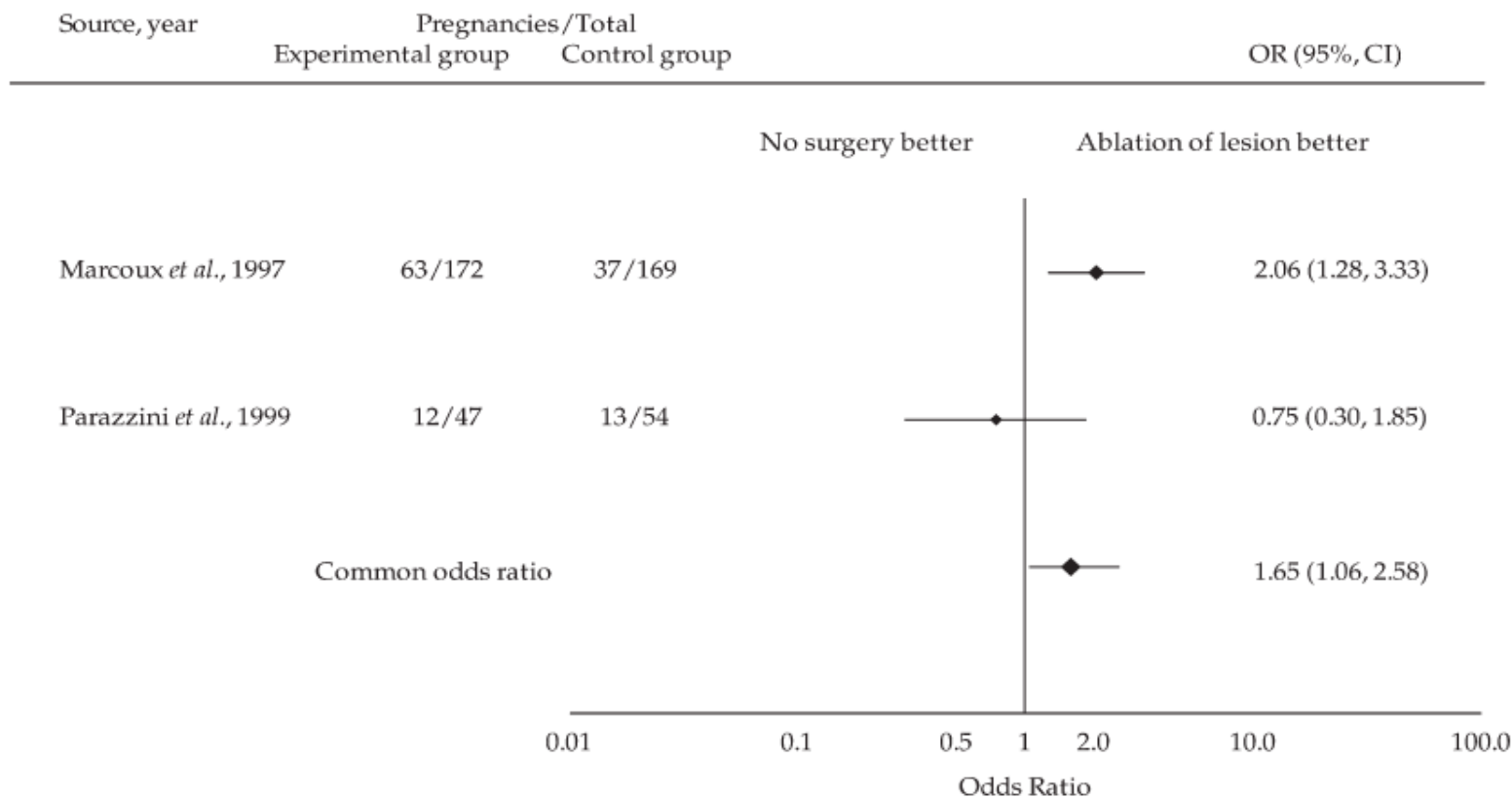


Figure 2 Overview of RCTs comparing laparoscopic ablation of lesions with no surgery in infertile women with minimal or mild endometriosis. Diamonds represent odds ratio of conception and horizontal lines 95% CIs. Breslow-Day test for heterogeneity: $\chi^2 = 13.24$, $P = 0.42$. Data from Al-Inany *et al.* (2000).



CPR AFTER CONSERVATIVE SURGERY IN INFERTILITY ASSOCIATED WITH ENDOMETRIOMA:

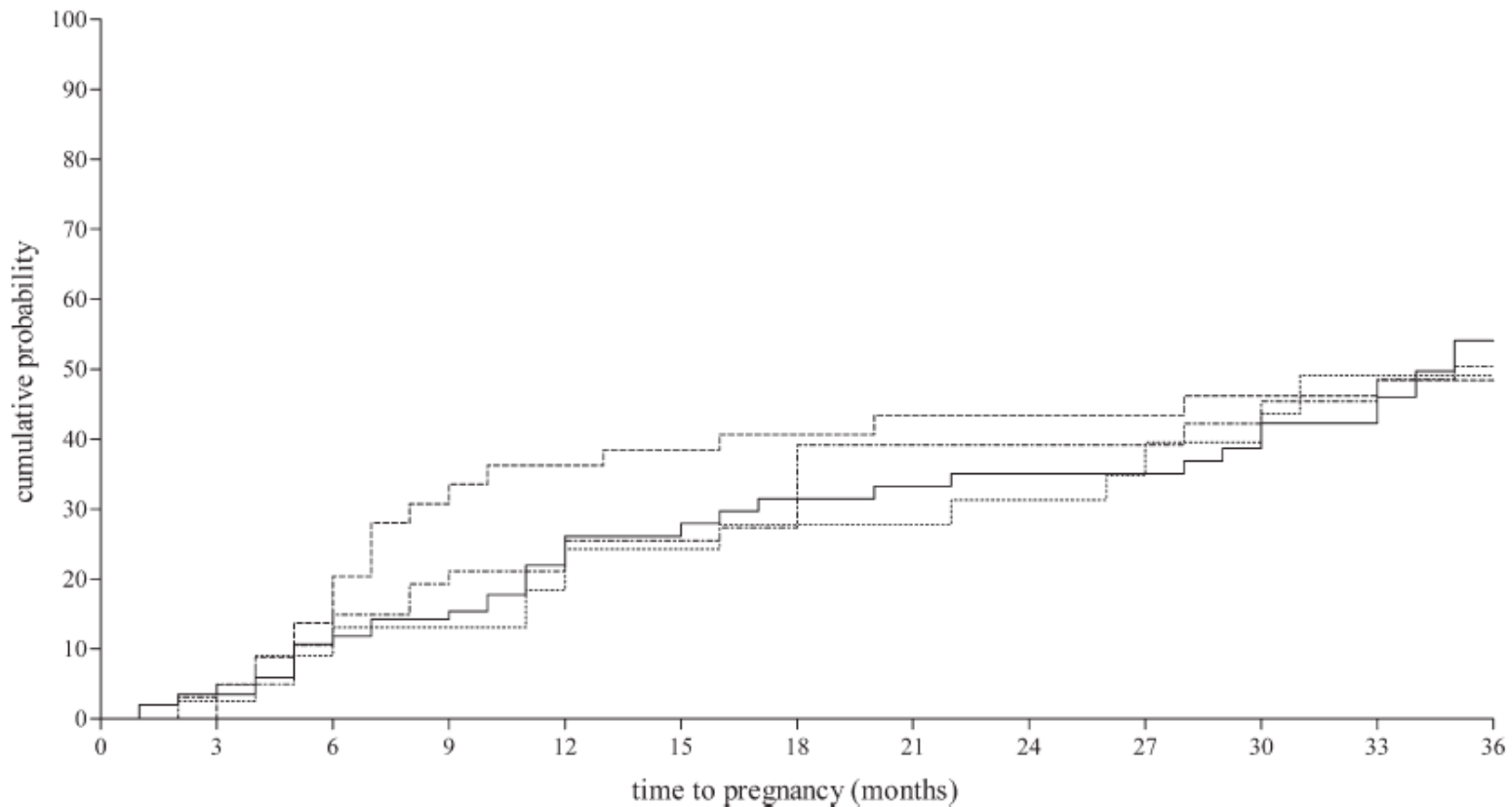


Figure 1 Cumulative 36-month probability of becoming pregnant by disease stage in 222 infertile women who underwent conservative surgery for endometriosis and had no other infertility factor (continuous line, stage I; dotted line, stage II; dashed line, stage III; dash-dotted line, stage IV). From Vercellini *et al.* (2006a), with permission.



IMPACT OF THE REMOVAL OF ENDOMETRIOMA ON ART OUTCOMES

	Surgery (133)	Endometrioma (56)	P value
Cycles	147	63	
Age	34.7 ± 0.3	33.9 ± 0.5	0.158
Gn used	3380 ± 129	3404 ± 162	0.35
Basal FSH	7.5 ± 0.6	7.6 ± 0.8	NS
Basal E2	68.2 ± 10.5	37.8 ± 5.4	0.064
Oocytes	10.8 ± 0.6	11.8 ± 0.9	NS
IR	12.8%	14.1%	NS
MC	3.9%	6.1%	NS

Garcia-Velasco J Fertil Steril 2004

IMPACT OF THE REMOVAL OF ENDOMETRIOMA ON ART OUTCOMES

	<i>Cystectomy (49)</i>	<i>IVF (50)</i>	<i>P</i>
Age	35.2 ± 0.3	34.9 ± 0.2	
<u>Stimulation days</u>	14.0 ± 2.5	10.8 ± 2.6	0.001
<u>Peak E2</u>	1170 ± 417	1680 ± 429	0.001
<u>Mature oocytes</u>	7.8 ± 3.1	8.6 ± 2.8	0.032
IR	16.5	18.5	NS
CPR	34.4	38.2	NS

IMPACT OF THE REMOVAL OF ENDOMETRIOMA ON ART OUTCOMES: BILATERAL ENDOMETRIOMA

Table III. Characteristics of the IVF–ICSI cycles in patients operated for bilateral endometriomas (cases) and controls.

Characteristics	Cases (n = 68)	Controls (n = 136)	p
Cancelled cycle			<0.001
Hyper-response	1 (2%)	20 (15%)	
Poor response	17 (28%)	8 (6%)	
Dosage of rFSH/die	333 ± 133	212 ± 112	<0.001
Duration of stimulation (day) ^a	11.5 ± 2.3	11.8 ± 2.4	0.58
Number of follicles 11–15 mm ^a	3.2 ± 2.8	4.6 ± 3.3	0.009
Number of follicles > 15 mm ^a	5.2 ± 2.8	6.5 ± 2.7	0.006
Number of oocyte retrieved ^a	5.7 ± 4.0	7.2 ± 3.6	0.024
Number of oocyte used ^{a,b}	2.8 ± 2.3	3.8 ± 2.7	0.034
Number of embryos obtained ^{a,b}	2.0 ± 1.9	2.8 ± 2.0	0.024
Number of transfers not performed ^a	14 (28%)	16 (15%)	0.08
Number of embryos transferred ^c	2.0 ± 0.6	2.2 ± 0.7	0.20
Clinical pregnancy rate (PR)			
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)			
Number of deliveries	3	23	
DR per starting cycle	4%	17%	0.013
DR per oocyte retrieval	6%	21%	0.02
DR per embryo transfer	8%	25%	0.049

^aData refer to patients undergoing oocyte retrieval.

^bThe number of oocytes retrieved and oocytes used differ due to the new Italian legislation that since March 2004 bans the use of more than three oocytes.

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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)			
Number of deliveries	3	23	
DR per starting cycle	4%	17%	0.013
DR per oocyte retrieval	6%	21%	0.02
DR per embryo transfer	8%	25%	0.049

^aData refer to patients undergoing oocyte retrieval.

^bThe number of oocytes retrieved and oocytes used differ due to the new Italian legislation that since March 2004 bans the use of more than three oocytes.



IMPACT OF THE REMOVAL OF ENDOMETRIOMA ON ART OUTCOMES: BILATERAL ENDOMETRIOMA

Table III. Characteristics of the IVF–ICSI cycles in patients operated for bilateral endometriomas (cases) and controls.

Characteristics	Cases (n = 68)	Controls (n = 136)	p
Cancelled cycle			<0.001
Hyper-response	1 (2%)	20 (15%)	
Poor response	17 (28%)	8 (6%)	
Dosage of rFSH/die	333 ± 133	212 ± 112	<0.001
Duration of stimulation (day) ^a	11.5 ± 2.3	11.8 ± 2.4	0.58
Number of follicles 11–15 mm ^a	3.2 ± 2.8	4.6 ± 3.3	0.009
Number of follicles > 15 mm ^a	5.2 ± 2.8	6.5 ± 2.7	0.006
Number of oocyte retrieved ^a	5.7 ± 4.0	7.2 ± 3.6	0.024
Number of oocyte used ^{a,b}	2.8 ± 2.3	3.8 ± 2.7	0.034
Number of embryos obtained ^{a,b}	2.0 ± 1.9	2.8 ± 2.0	0.024
Number of transfers not performed ^a	14 (28%)	16 (15%)	0.08
Number of embryos transferred ^c	2.0 ± 0.6	2.2 ± 0.7	0.20
Clinical pregnancy rate (PR)			
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
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^aData refer to patients undergoing oocyte retrieval.

^bThe number of oocytes retrieved and oocytes used differ due to the new Italian legislation that since March 2004 bans the use of more than three oocytes.



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

The baseline characteristics and controlled ovarian hyperstimulation response 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 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/m ²)	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 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 ± 4.1	7.1 ± 2.6 ^a	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 ^a	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

Note: Values are expressed as mean ± SD or n (%). NS = not significant.

^a Statistically different from unilateral cystectomy and control groups.

Esinler. ICSI outcome after endometrioma cystectomy. *Fertil Steril* 2006.



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

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 ^a	11.1 ± 6.1	<.05
<u>No. of metaphase II oocytes</u>	8.1 ± 5.4	5.5 ± 3.2 ^a	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
<u>No. of 2-pronucleated oocytes</u>	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 ± SD, unless stated otherwise. NS = not significant.

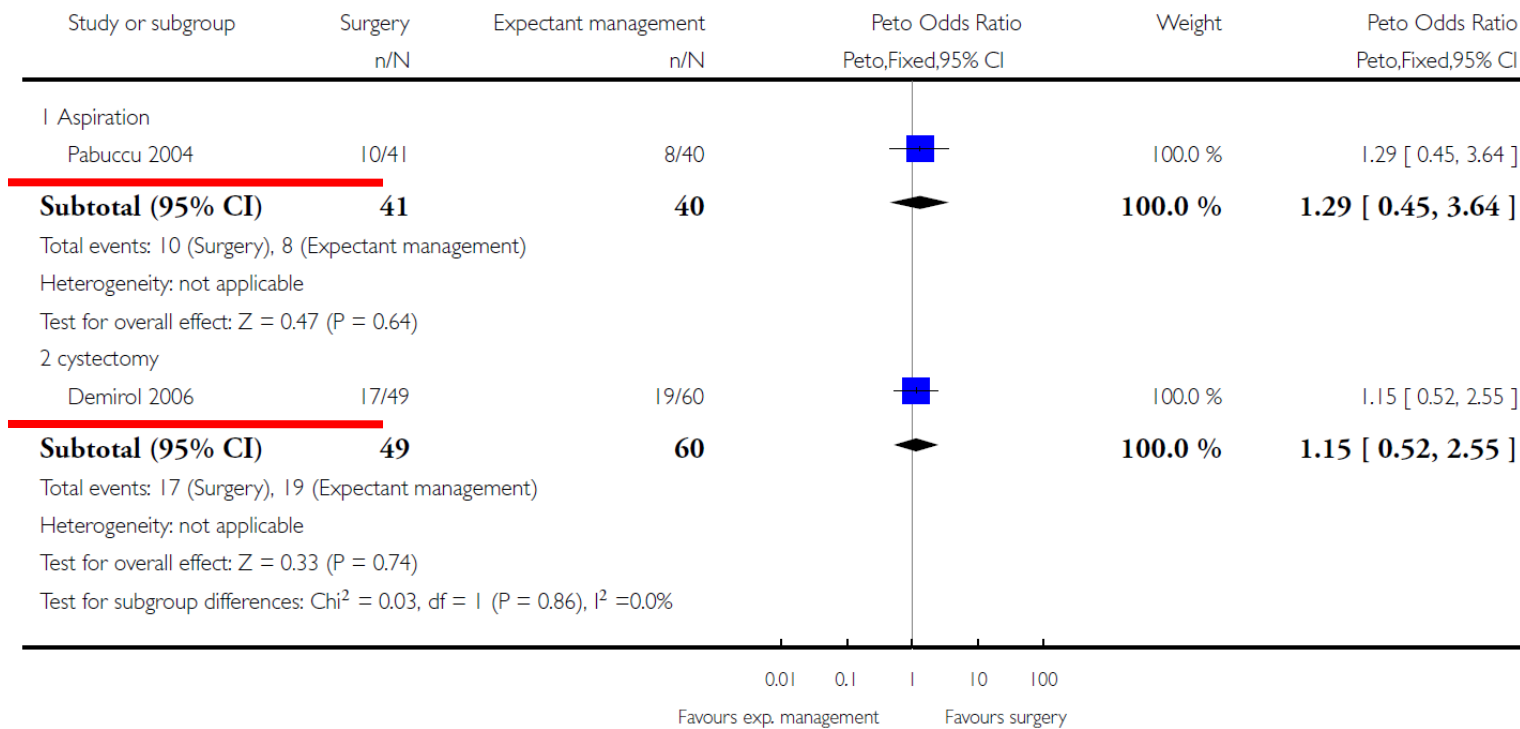
^a Statistically different from unilateral cystectomy and control groups.

^b Mean ± SEM.

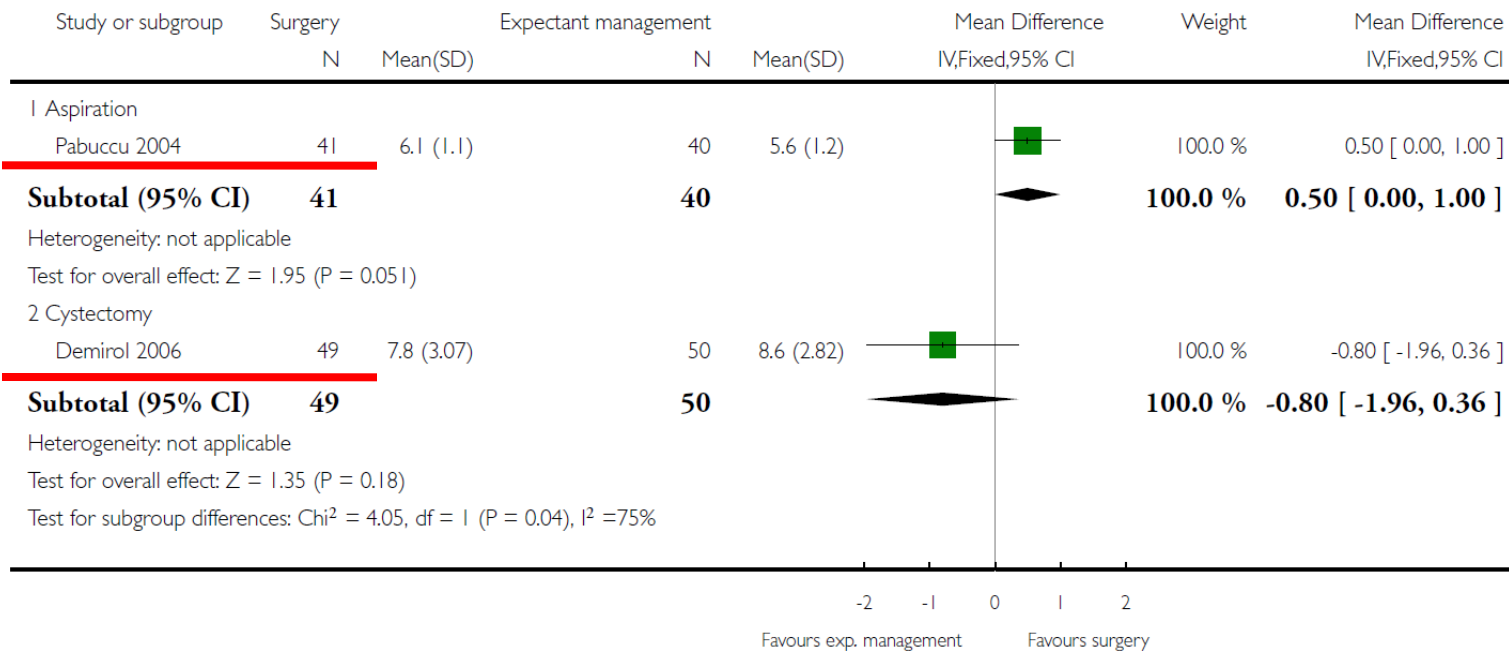
Esinler. ICSI outcome after endometrioma cystectomy. Fertil Steril 2006.



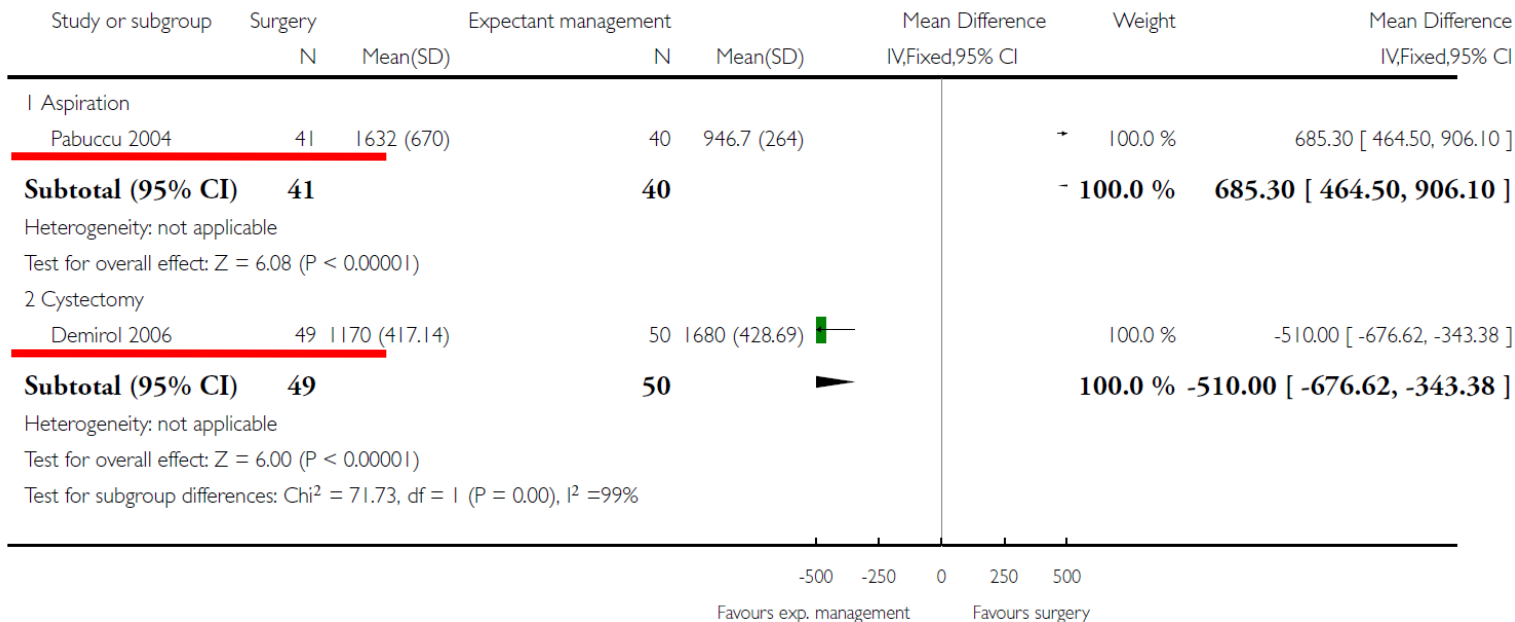
Surgery (aspiration or cystectomy) versus expectant management prior to ART, Outcome I Clinical pregnancy.



SURGERY (ASPIRATION OR CYSTECTOMY) VERSUS EXPECTANT MANAGEMENT PRIOR TO ART, OUTCOME 2 NUMBER OF MATURE OOCYTES RETRIEVED



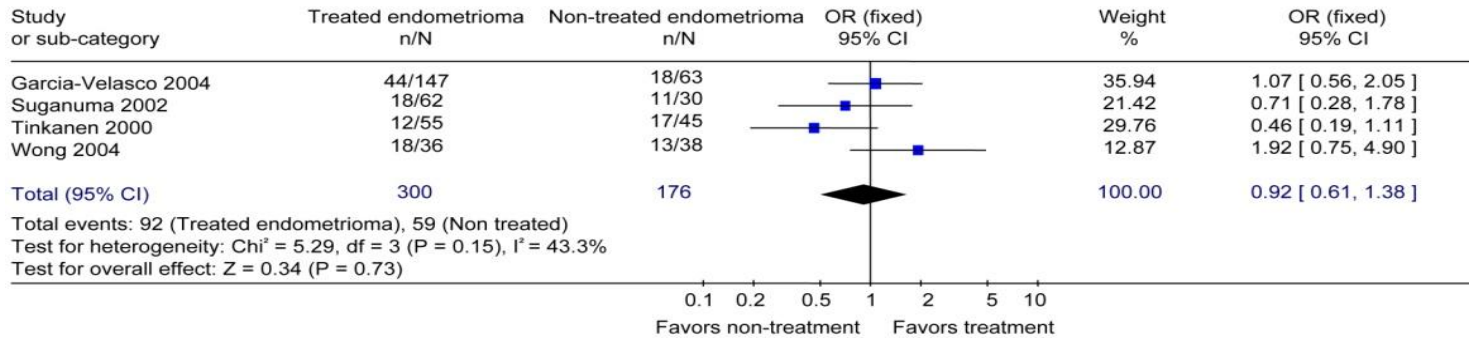
SURGERY (ASPIRATION OR CYSTECTOMY) VERSUS EXPECTANT MANAGEMENT PRIOR TO ART, OUTCOME 3 OVARIAN RESPONSE TO COH



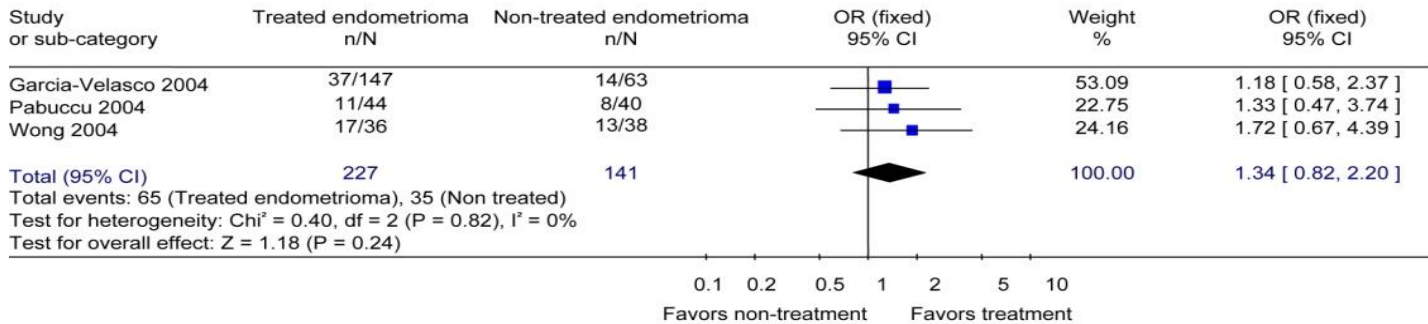
IMPACT OF THE REMOVAL OF ENDOMETRIOMA ON ART OUTCOMES

<i>Cystectomy</i>				<i>No surgery</i>		
Study	N	Oocytes-S	PR-S	N	Oocytes-C	PR-C
Tinkanen 2000	55	6.5	22	45	6.1	38
Suganuma 2002	62	7.2 ± 6.2	29	30	9.7 ± 6.7	37
Garcia-Velasco 2004	147	10.8 ± 7	25*	63	11.8 ± 7	22*
Wong 2004	36		47*	38		34*
Pabuccu 2004	44	5.3 ± 1.3 (MII)	25*	40	5.2 ± 1.1 (MII)	20*

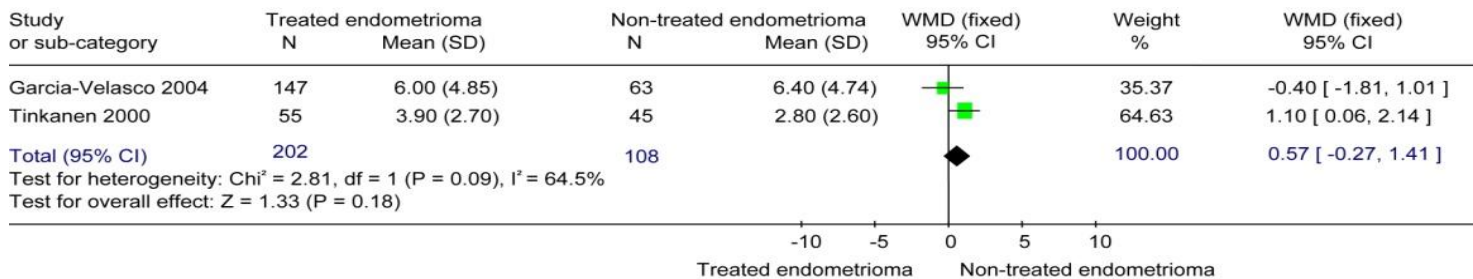
Outcome: a. Pregnancy / cycle



Outcome: b. Clinical pregnancy / cycle



Outcome: c. Number of embryos / cycle



THE COMPLICATIONS OF SURGERY

- The risk of premature ovarian failure after surgery (2.4%- *Busacca, AJOG 2006*)
- 30.4% Recurrens rates (*Koga, Hum Reprod, 2006*)
- Some complications associated risk general anesthesia and surgery



- No RCT or meta-analyses are available to answer the question whether surgical excision of moderate–severe endometriosis enhances pregnancy rates
- There is a negative correlation between the stage of endometriosis and the spontaneous cumulative pregnancy rate after surgical removal of endometriosis, but statistical significance was only reached in one study

Adamson et al. 1993

Guzick et al., 1997

Osuga et al., 2002

ESHRE guideline for the diagnosis and treatment of endometriosis



Endometriomas: clinical variables to be considered when deciding whether to perform surgery or not in women selected for IVF

Characteristics	Favours surgery	Favours expectant management
Previous interventions for endometriosis	None	≥1
Ovarian reserve ^a	Intact	Damaged
Pain symptoms	Present	Absent
Bilaterality	Monolateral disease	Bilateral disease
Sonographic feature of malignancy ^b	Present	Absent
Growth	Rapid growth	Stable

^a Ovarian reserve is estimated based on serum markers or previous hyperstimulation cycles

^b Sonographic feature of malignancy refers to solid components, locularity, echogeniety, regularity of shape, wall, septa, location and presence of peritoneal fluid



Logical decision for surgery prior to ART

- Laparoscopic ovarian cystectomy is recommended if an ovarian endometrioma ≥ 4 cm in diameter:
 - confirm the diagnosis histologically
 - reduce the risk of infection
 - improve access to follicles
 - possibly improve ovarian response
- The woman should be counselled regarding the risks of reduced ovarian function after surgery and the loss of the ovary
- The decision should be reconsidered if she has had previous ovarian surgery.

ESHRE guideline for the diagnosis and treatment of endometriosis



Endometriosis +COH+IUI

- COH+IUI is associated with a higher pregnancy rate in women with minimal/mild endometriosis
- COH+IUI improves fertility in minimal/mild endometriosis
- Treatment with intrauterine insemination (IUI) improves fertility in minimal–mild endometriosis: IUI with ovarian stimulation is effective but the role of unstimulated IUI is uncertain

Tummon IS, fertil steril, 1997

ESHRE guideline for the diagnosis and treatment of endometriosis



ENDOMETRIOSIS-ART



- The history of endometriosis don't endanger the success of IVF and/or outcome of pregnancy. Female age, parity, and duration of infertility appeared as the most accurate predictors for pregnancy outcome.
- Minimal/mild endometriosis have higher live birth rate than women with moderate/severe disease after IVF/ICSI

Templeton A, Lancet, 1996

Kuivasaari P, Human Repro, 2005



ENDOMETRIOSIS-ART

- Ovarian suppression with a gonadotropin –releasing hormone analogue has favorable effect on ART outcome in women with endometriosis
- Pretreatment did not impair the ovarian response to controlled ovarian hyperstimulation.
- Prolonged treatment with a GnRH agonist before IVF in moderate–severe endometriosis should be considered and discussed with patients because improved pregnancy rates have been reported

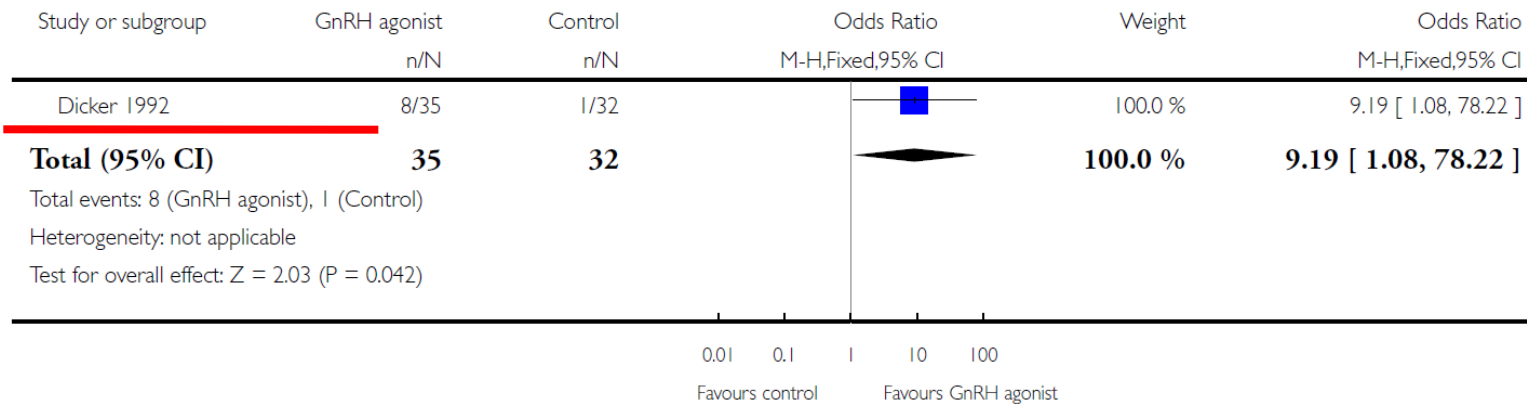
Surrey ES, fertil steril 2002

Rickes et al., 2002;

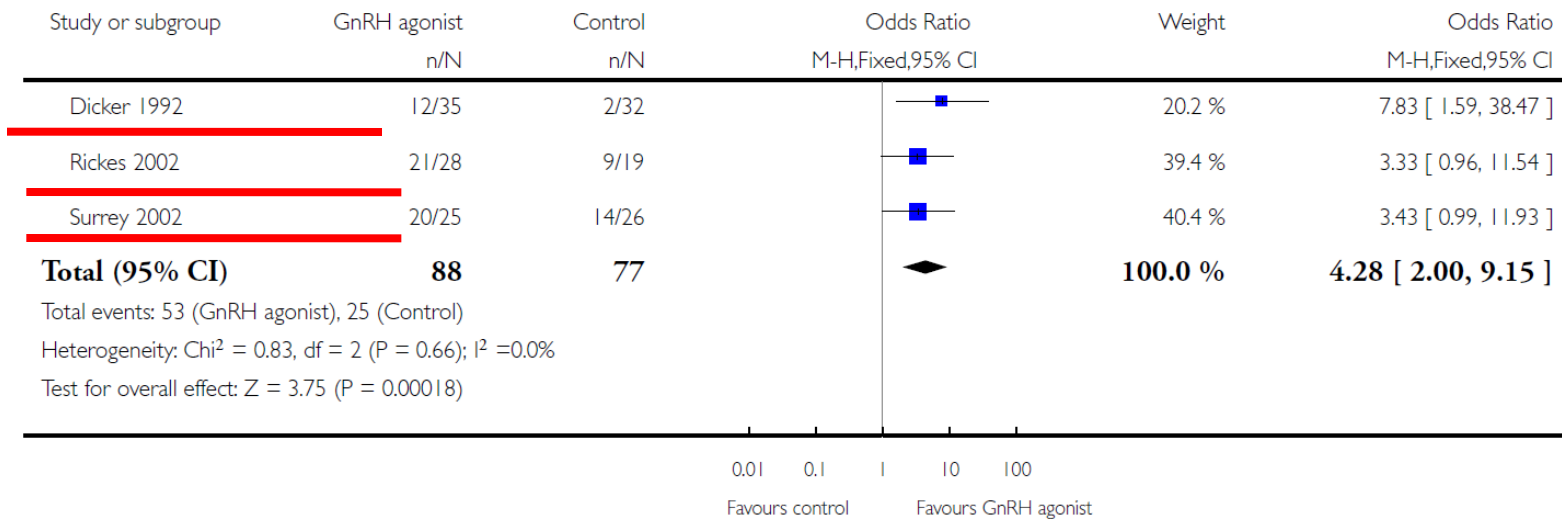
ESHRE guideline for the diagnosis and treatment of endometriosis



GnRH agonist versus no agonist before IVF or ICSI, Outcome I Live birth rate per woman.



GnRH agonist versus no agonist before IVF or ICSI, Outcome 2 Clinical pregnancy rate per woman.



GnRHa PRIOR TO IVF

<u>Intervention</u>	<u>Outcome</u>
○ Loverro 3 months GnRHa (N=30) Immediate IVF (N=30)	No difference
○ Surrey 3 months GnRHa (N=25) Immediate IVF (N=26)	80% CPR 54% CPR
○ Rickes 6 months GnRHa (N=28) Immediate IVF (N=19)	47% CPR 24% CPR
○ Dicker 6 months GnRHa (N=35) Immediate IVF (N=32)	25% CPR 4% CPR

Loverro G. Eur J Obstet Gynecol Repro Biol 2008

Surrey ES. Fertil Steril 2002

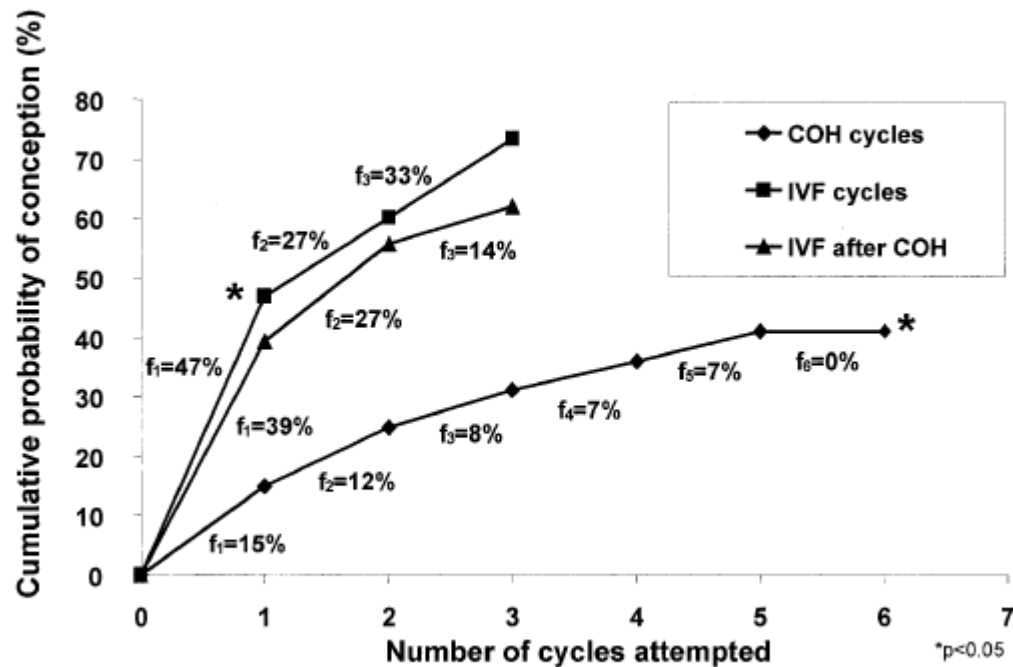
Rickes D. Fertil Steril 2002

Dicker D. Fertil Steril 1992



3 CYCLES CPR IN IVF

Cycle and cumulative fecundity in women with endometriosis undergoing COH-IUI, IVF-ET, or IVF-ET after failed COH-IUI.

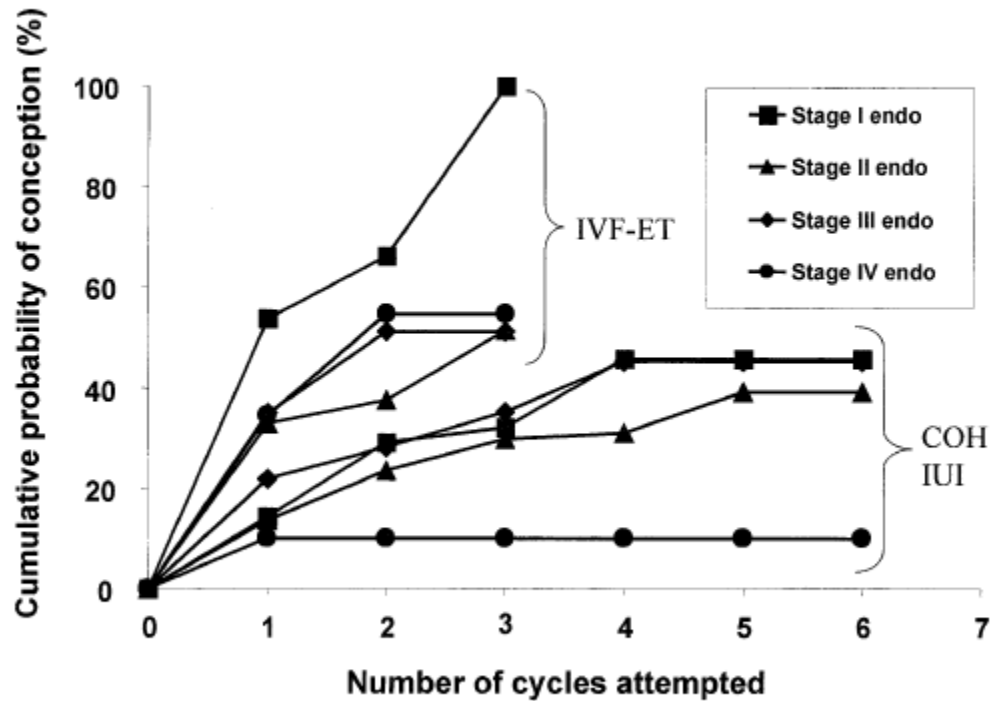


Dmowski. Fecundity with COH or IVF in endometriosis. Fertil Steril 2002.



3 CYCLES CPR IN IVF

Effect of COH-IUI or IVF-ET on fecundity according to the stage of endometriosis.



ESHRE guideline: management of women with endometriosis[†]

In infertile women with endometriosis, clinicians should not prescribe hormonal treatment for suppression of ovarian function to improve fertility (Hughes *et al.*, 2007). A

In infertile women with AFS/ASRM Stage I/II endometriosis, clinicians should perform operative laparoscopy (excision or ablation of the endometriosis lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only, to increase ongoing pregnancy rates (Nowroozi *et al.*, 1987; Jacobson *et al.*, 2010). A

In infertile women with AFS/ASRM Stage I/II endometriosis, clinicians may consider CO₂ laser vaporization of endometriosis, instead of monopolar electrocoagulation, since laser vaporization is associated with higher cumulative spontaneous pregnancy rates (Chang *et al.*, 1997). C

In infertile women with ovarian endometrioma undergoing surgery, clinicians should perform excision of the endometrioma capsule, instead of drainage and electrocoagulation of the endometrioma wall, to increase spontaneous pregnancy rates (Hart *et al.*, 2008). A

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. GPP



ESHRE guideline: management of women with endometriosis[†]

In infertile women with AFS/ASRM Stage III/IV endometriosis, clinicians can consider operative laparoscopy, instead of expectant management, to increase spontaneous pregnancy rates (Nezhat *et al.*, 1989; Vercellini *et al.*, 2006). B

In infertile women with endometriosis, the GDG recommends clinicians not to prescribe adjunctive hormonal treatment before surgery to improve spontaneous pregnancy rates, as suitable evidence is lacking. GPP

In infertile women with endometriosis, clinicians should not prescribe adjunctive hormonal treatment after surgery to improve spontaneous pregnancy rates (Furness *et al.*, 2004). A

The GDG recommends the use of ART for infertility associated with endometriosis, especially if tubal function is compromised or if there is male factor infertility, and/or other treatments have failed. GPP

In infertile women with endometriosis, clinicians may offer treatment with ART after surgery, since cumulative endometriosis recurrence rates are not increased after controlled ovarian stimulation for IVF/ICSI (D'Hooghe *et al.*, 2006; Benaglia *et al.*, 2010; Coccia *et al.*, 2010; Benaglia *et al.*, 2011). C

ESHRE guideline: management of women with endometriosis[†]

In infertile women with AFS/ASRM Stage I/II endometriosis undergoing laparoscopy prior to treatment with ART, clinicians may consider the complete surgical removal of endometriosis to improve live birth rate, although the benefit is not well established (Opoien *et al.*, 2011). C

In infertile women with endometrioma larger than 3 cm there is no evidence that cystectomy prior to treatment with ART improves pregnancy rates (Donnez *et al.*, 2001; Hart *et al.*, 2008; Benschop *et al.*, 2010). A

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

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. GPP

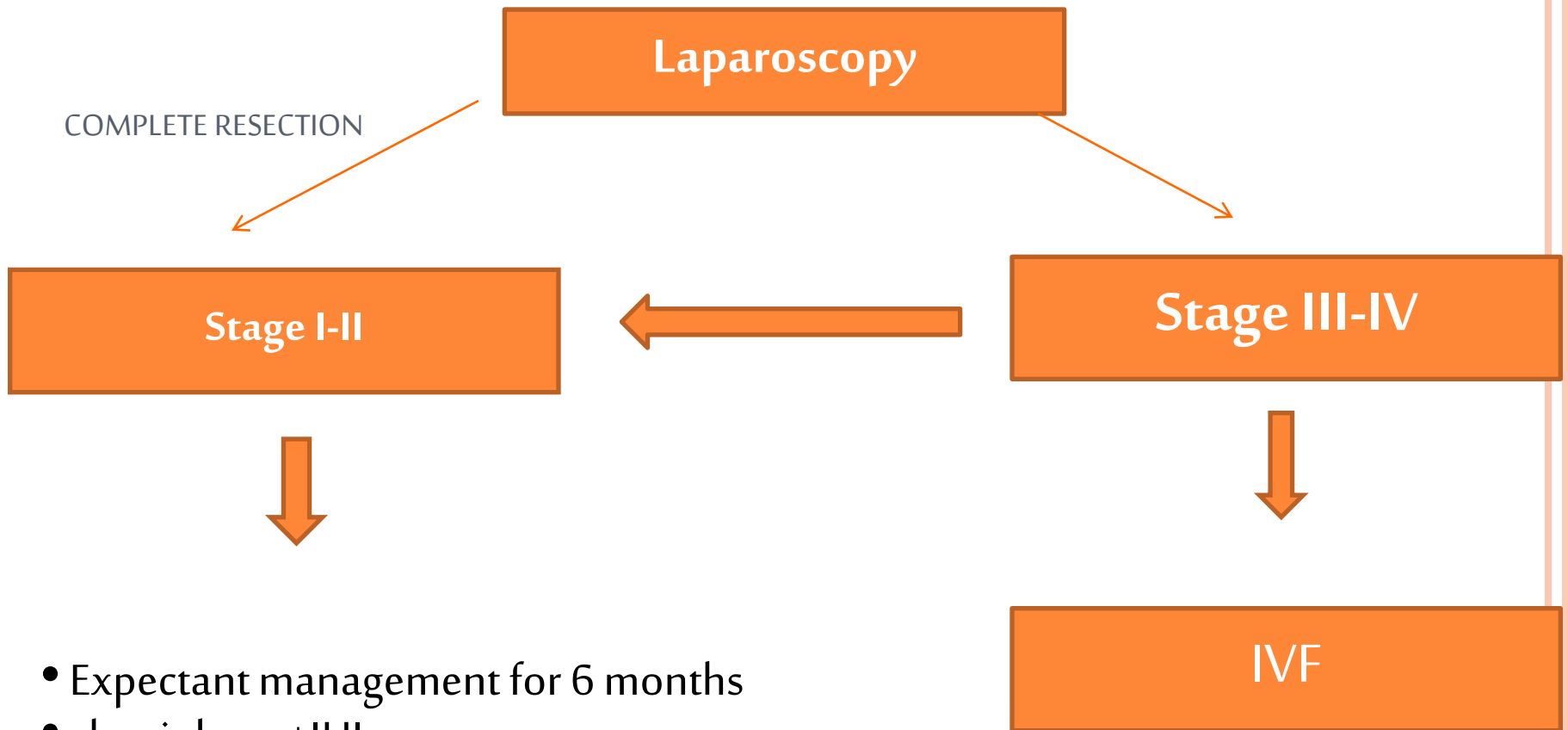
ESHRE guideline: management of women with endometriosis[†]

Clinicians can prescribe GnRH agonists for a period of 3–6 months prior to treatment with ART to improve clinical pregnancy rates in infertile women with endometriosis (Sallam *et al.*, 2006). B

The effectiveness of surgical excision of deep nodular lesions before treatment with ART in women with endometriosis-associated infertility is not well established with regard to reproductive outcome (Bianchi *et al.*, 2009; Papaleo *et al.*, 2011). C



Flow for management of fertility in women with endometriosis



- Expectant management for 6 months
- clomiphene+IUI
- Gonadotropin+IUI
- IVF

Mark DH, 2010 uptodate



- Concurrently with tubal factor
- Combined male factor
- Other treatments have failed

+

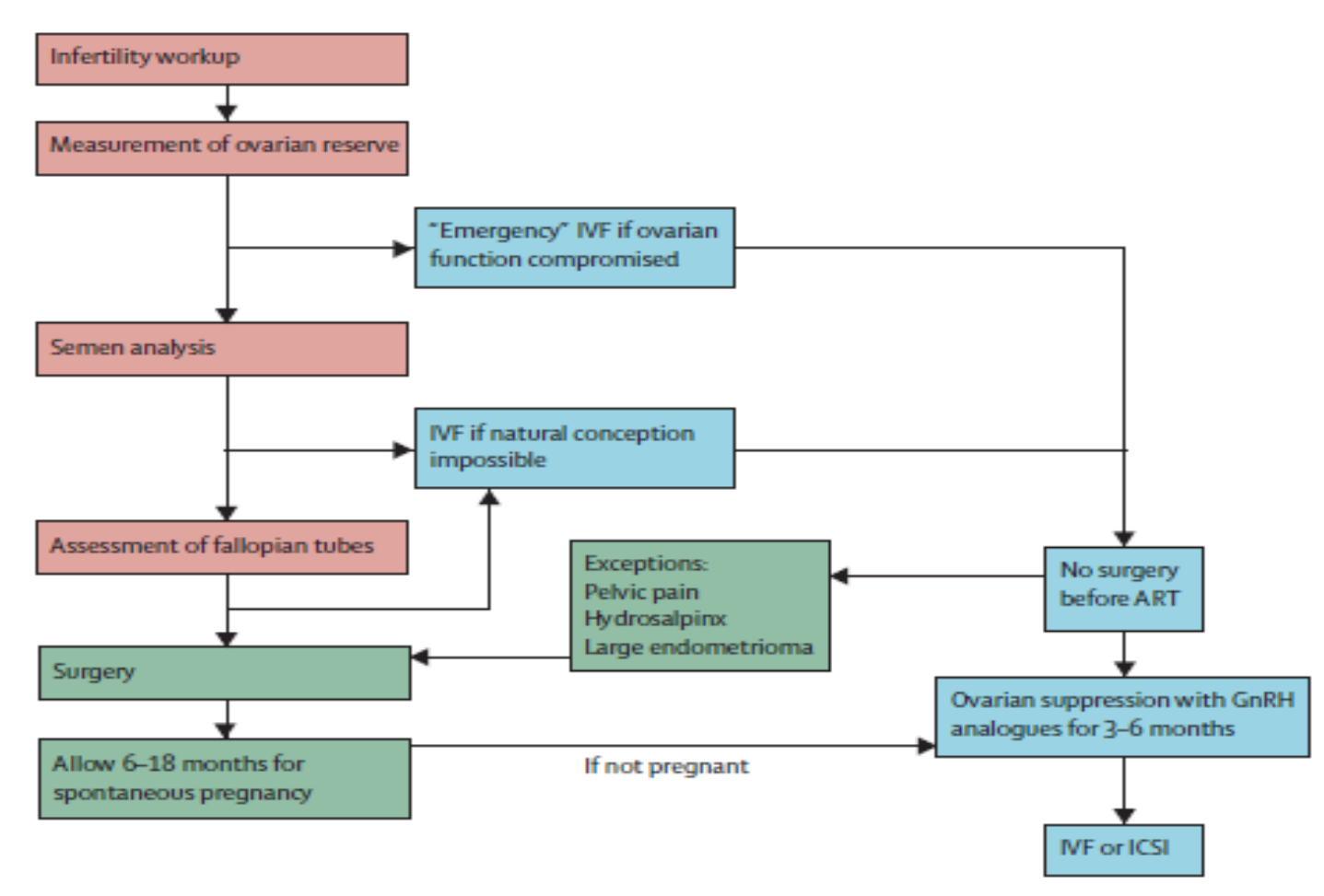
ENDOMETRIOSIS



IVF is appropriate treatment



ALGORITHM FOR MANAGEMENT OF INFERTILITY ASSOCIATED WITH ENDOMETRIOSIS



SUMMARY

- Surgery for ovarian endometriosis failed to augment outcome of ART versus expectant management

Garcia-Velasco JA, fertil steril, 2004

- Surgery for endometriomas could cause harm, particularly in women with bilateral disease, impaired ovarian reserve, or who had previous surgery for endometriomas.

Demirol A, Reprod Biomed Online 2006

Somigliana E, human reprod, 2008

Busacca M, J Minim Invasive Gynecol 2009



SUMMARY

- The need to remove hydrosalpinges, which reduce outcome of ART by about 50%

Daftary GS, fertil steril 2007

- Surgery before ART should also be considered in cases of pain, because pain by itself can be associated with infertility.

fertil steril 2008

- Surgery might be advisable when endometriomas are excessively large or doubts exist about their exact nature.

Garcia-Velasco JA, human reprod 2009



INTERNATIONAL GUIDELINES

Table II. International guidelines on surgical treatment of endometriosis-associated infertility in asymptomatic women.

Clinical condition	Recommendation		
	ESHRE 2005	ASRM 2006	RCOG 2006
Minimal-mild endometriosis (stage I–II disease)	Limited benefit: surgery recommended	Small benefit: surgery recommended	Demonstrated benefit: surgery recommended
Moderate–severe endometriosis (stage III-IV disease)	Possible but unproven benefit: surgery recommended	Possible benefit: surgery recommended	Possible benefit: recommendation uncertain
Post-operative adjuvant treatment	No benefit: not recommended	No benefit: not recommended	No benefit: not recommended
Surgery before IVF	Recommended if endometrioma ≥ 4 cm	Doubtful benefit: no recommendation	Recommended if endometrioma >4 cm
Recurrent endometriosis	No recommendation	Second-line surgery not recommended	No recommendation



SUMMARY

Infertility surgery is dead: only the obituary remains?

Despite the multiple advantages of assisted reproductive technology compared with surgery, there remain several diagnoses for which surgery is still widely performed: distal tubal occlusion, regret of permanent sterilization, and endometriosis. Assisted reproductive technology is superior to surgery and should be offered as first-line treatment. (*Fertil Steril*® 2008;89:232–6. ©2008 by American Society for Reproductive Medicine.)

