X. TÜRK ALMAN JİNEKOLOJİ KONGRESİ

30 Nisan - 4 Mayıs 2014

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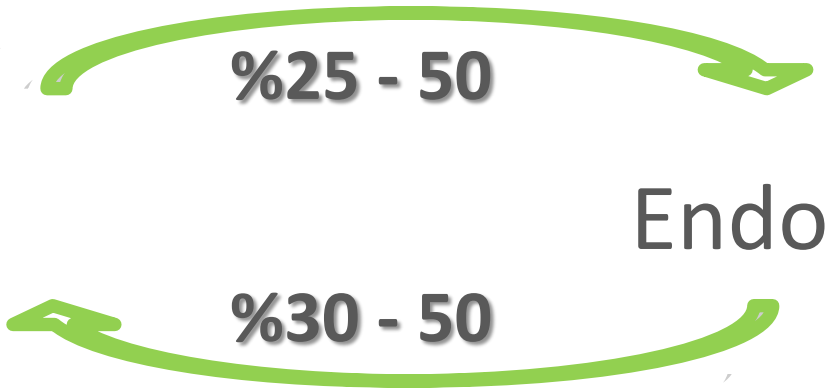
TAJEV

Maniging Patients with Endometriosis Associated Infertility

Prof Dr Bülent Gülekli
Dokuz Eylül Üniversitesi Tıp Fakültesi
Kadın Hastalıkları Doğum Anabili Dalı ve
Üreme Endokrinolojisi Bilim Dalı öğretim üyesi



- **Endometriosis is 6 – 8 times more common in infertilie women comparing women without disease****

- **Decreased fecundity*** 0.15-0.20 vs %0.02-0.10**

* Ozkan S, Murk W, Arici A. Endometriosis and infertility: epidemiology and evidence-based treatments. Ann N Y Acad Sci 2008;1127:92-100

** Verkauf BS. Incidence, symptoms, and signs of endometriosis in fertile and infertile women. J Fla Med Assoc 1987;74:671–675.

*** Hughes EG, Fedorkow DM, Collins JA. A quantitative overview of controlled trials in endometriosis-associated infertility. Fertil Steril 1993;59(5):963-70.

PELVIC ANATOMY

PERITONEAL FUNCTION

⇧ PGL, IL-6, IL-1

IL-8 ve VEGF

ENDOMETRIAL RECEPTIVITY

⇧ Ig G ve A ile lenfosit

Otoantikorlar

MECHANISM ????

IMPLANTATION

⇩ L-Selectin

OVULATORY ENDOCRINE

⇧Follicular phase

⇩E2,

⇩ LH dependent P

LUFS, Luteal faz disfxn,

Premature LH surge

OOCCYTE - EMBRYO QUALITY

ESHRE guideline for the diagnosis and treatment of endometriosis

Stephen Kennedy[1,10], Agneta Bergqvist[2], Charles Chapron[3], Thomas D'Hooghe[4], Gerard Dunselman[5], Robert Greb[6], Lone Hummelshoj[7], Andrew Prentice[8] and Ertan Saridogan[9] on behalf of the ESHRE Special Interest Group for Endometriosis and Endometrium Guideline Development Group*

Human Reproduction Vol.20, No.10 pp. 2698–2704, 2005
Advance Access publication June 24, 2005.

THE COCHRANE COLLABORATION®

Fertility and Sterility® Vol. 98, No. 3, September 2012

Endometriosis and infertility: a committee opinion

The Practice Committee of the American Society for Reproductive Medicine

Human Reproduction, Vol.28, No.6 pp. 1552–1568, 2013

Consensus on current management of endometriosis

Neil P. Johnson[1,2,3,*] and Lone Hummelshoj[1], for the World Endometriosis Society Montpellier Consortium[†]

The European Society of Human Reproduction and Embryology guideline for the diagnosis and treatment of endometriosis: an electronic guideline implementability appraisal

Lotte JEW van Dijk[1], Willianne LDM Nelen[1*], Thomas M D'Hooghe[2], Gerard AJ Dunselman[3], Rosella PMG Hermens[4], Christina Bergh[5], Karl G Nygren[6], Arnold HM Simons[7], Petra de Sutter[8], Catherine Marshall[9], Jako S Burgers[4], Jan AM Kremer[1]

van Dijk *et al. Implementation Science* 2011, **6**:7
http://www.implementationscience.com/content/6/1/7

Human Reproduction, Vol.29, No.3 pp. 400–412, 2014

ESHRE guideline: management of women with endometriosis[†]

G.A.J. Dunselman[1,*], N. Vermeulen[2], C. Becker[3], C. Calhaz-Jorge[4], T. D'Hooghe[5], B. De Bie[6], O. Heikinheimo[7], A.W. Horne[8], L. Kiesel[9], A. Nap[10], A. Prentice[11], E. Saridogan[12], D. Soriano[13], and W. Nelen[14]

- **Endometriosis**
  - Low response to ovarian stimulation
  - Decreased number of oocytes
  - however no change in pregnacy rates

Bergendal, et al. J Assist Reprod Genet 1998

- **Studies showing decrease in ovarian response**

Geber, et al. Reprod Biomed 2002

Pabuçcu R, et al. Fertil Steril 2004

Suzuki, et al. Fertil Steril 2005

Esinler I, et al. Fertil Steril 2006

- **Studies doesn't show any effect**

Canis M, et al. Hum Reprod 2001

Donnez J, et al. Fertil Steril 2001

Marconi, et al. Fertil Steril 2002

Nakagawa, et al. J Obstet Gynecol Res 2007

FERTILITY AND STERILITY® VOL. 77, NO. 6, JUNE 2002

Effect of endometriosis on in vitro fertilization

Kurt Barnhart, M.D., M.S.C.E.,[a,b] Rebecca Dunsmoor-Su, M.D., M.S.C.E.,[a] and Christos Coutifaris, M.D., Ph.D.[a]

Endometriosis – ART Metaanalysis

- 1983 -1999
- 22 studies (2377 vs 4383 cycles)
- Pregnancy rates OR 0.56 (0.44 – 0.70)
- Decreased implantaion and pregnancy rates, approximately 50% decresaed oocyte number
- Decreased pregnancy rates in advanced stages comparing to early stages OR 0.60 (0.42 – 0.87)

Journal of Assisted Reproduction and Genetics, Vol. 20, No. 9, September 2003 (© 2003)

Assisted Reproduction

Does Surgical Management of Endometriosis Within 6 Months of an In Vitro Fertilization–Embryo Transfer Cycle Improve Outcome?[1]

Eric S. Surrey[2,3] and William B. Schoolcraft[2]

What's the optimal time for ART after surgery?

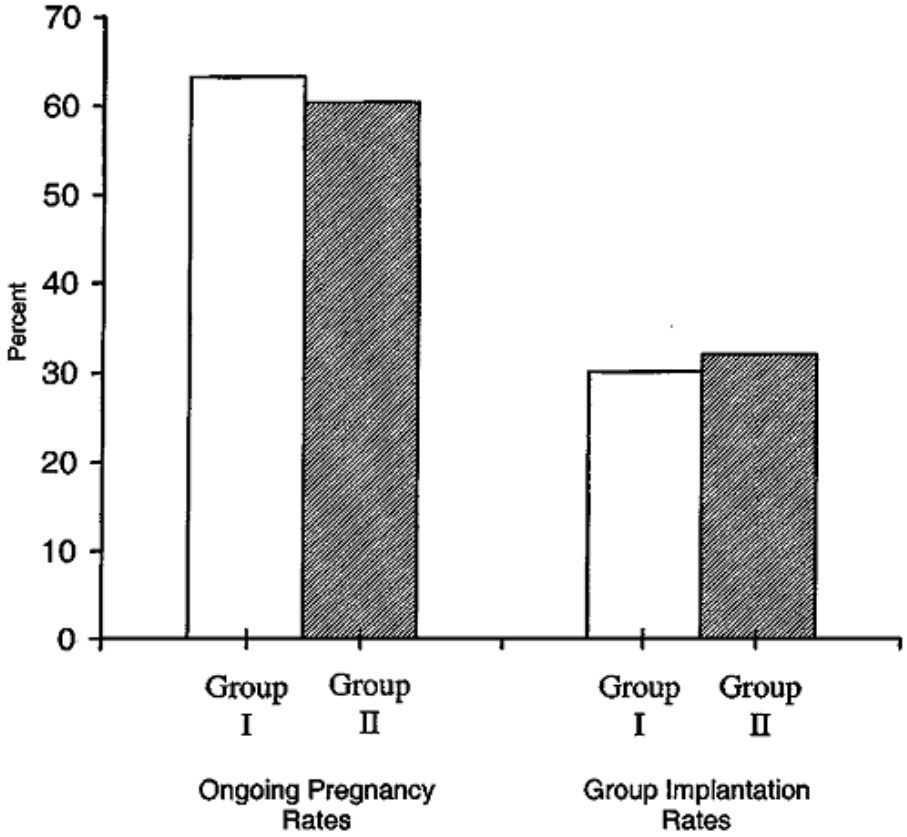


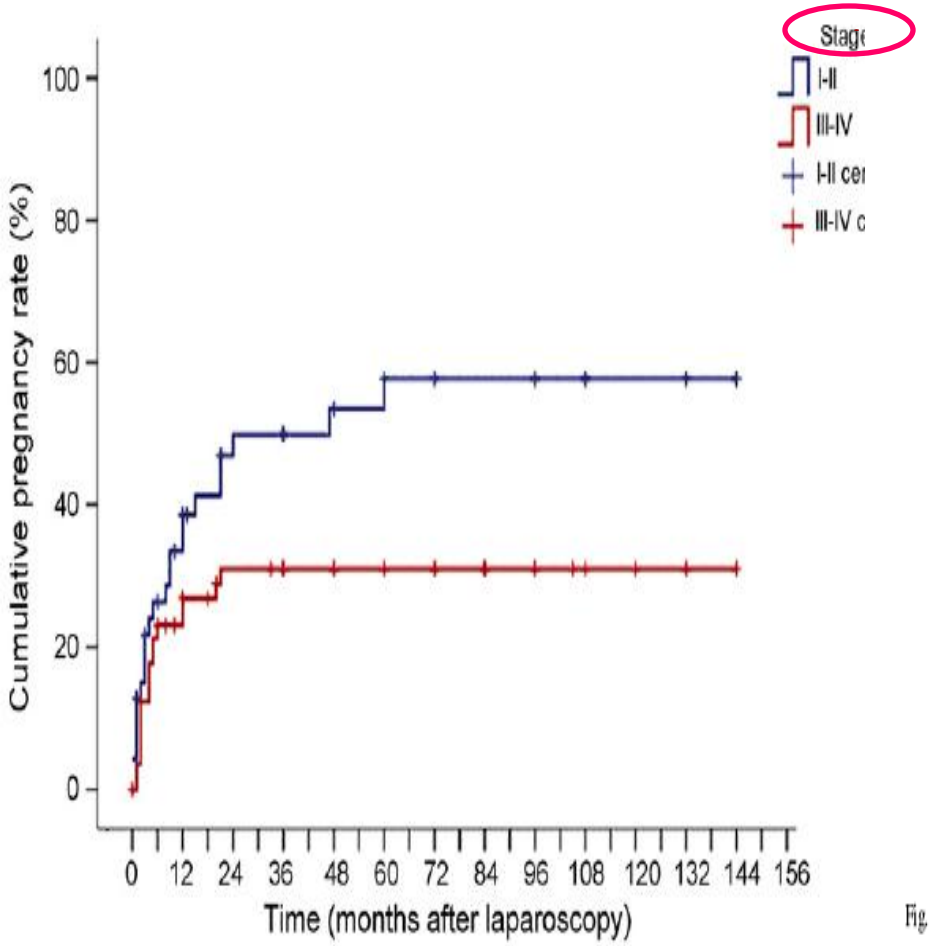
Fig. 1. Ongoing pregnancy and group implantation rates in patients undergoing surgical resection of endometriosis ≤6 months prior (Group I) and >6–60 months (Group II) prior to oocyte aspiration. There were no significant differences between the groups.

European Journal of Obstetrics & Gynecology and Reproductive Biology 138 (2008) 54–59

Endometriosis and infertility

Surgery and ART: An integrated approach for successful management

M. Elisabetta Coccia *, Francesca Rizzello, Fiamma Cammilli, Gian Luca Bracco, Gianfranco Scarselli



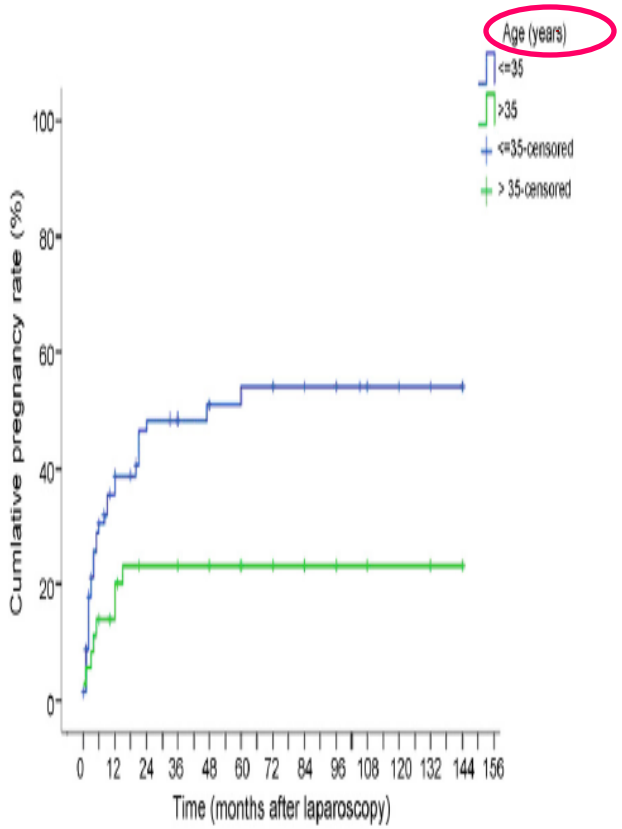
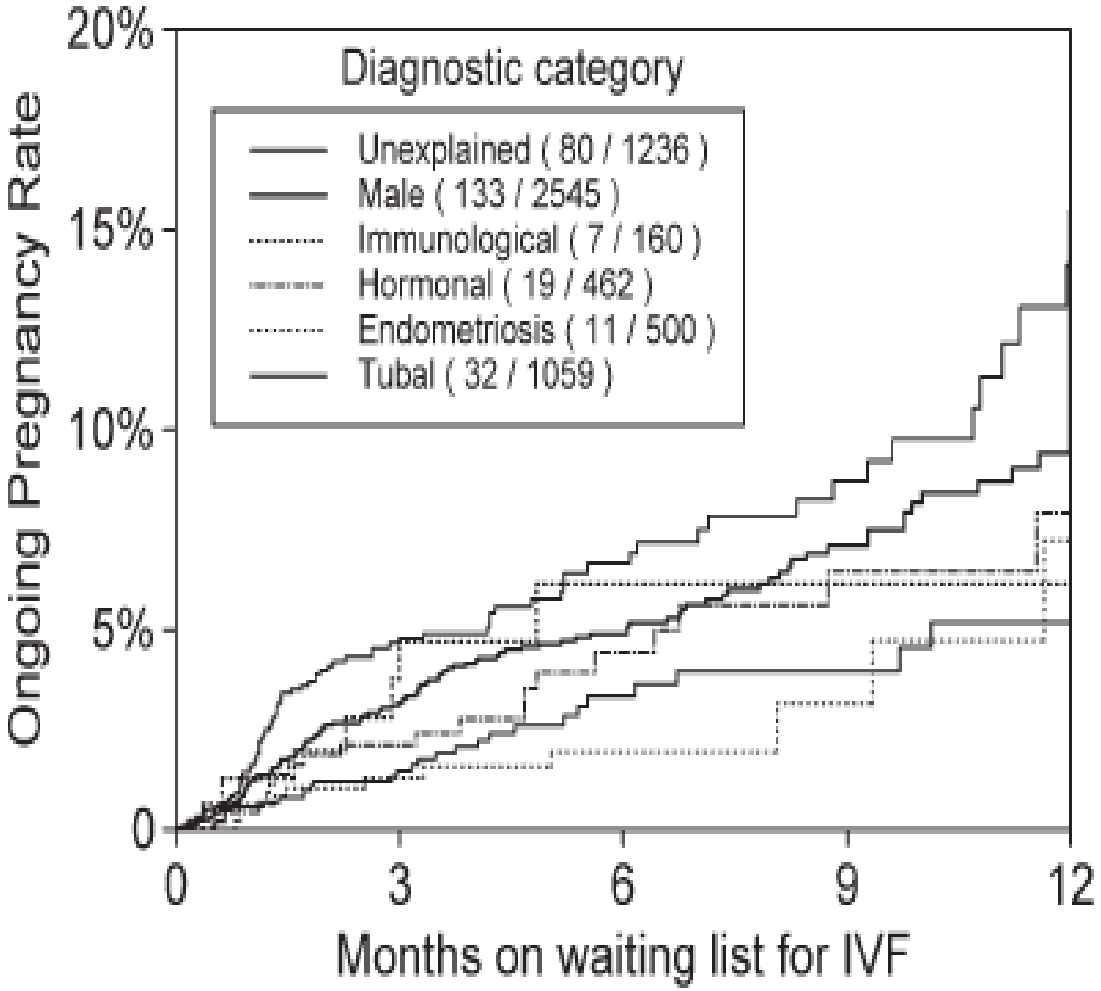


Fig. 3. Effect of endometriosis on fecundity according to the age of the women with endometriosis. Vertical tick marks represent censored observation.

Pregnancy chances on an IVF/ICSI waiting list: a national prospective cohort study

M.J.C. Eijkemans[1,5], A.M.E. Lintsen[2], C.C. Hunault[1,3], C.A.M. Bouwmans[4], L. Hakkaart[4], D.D.M. Braat[2] and J.D.F. Habbema[1]

Human Reproduction Vol.23, No.7 pp. 1627–1632, 2008



The ongoing pregnancy chances differed markedly between diagnostic categories chances with tubal infertility and endometriosis were lowest

Fig. 1. Comparison 01 Ovulation Suppression vs Placebo

01.01 Clinical pregnancy

Review: Ovulation suppression for endometriosis

Comparison: 01 Ovulation Suppression vs Placebo

Outcome: 01 Clinical pregnancy

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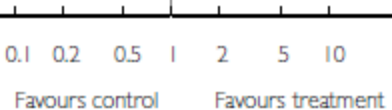
Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Bayer 1988	13/37	17/36		22.3	0.61 [0.24, 1.54]
Bianchi 1999	6/11	8/16		8.4	1.19 [0.26, 5.38]
Fedele 1992	17/35	17/36		22.4	1.05 [0.42, 2.66]
Telimaa 1988a	7/17	3/7		6.3	0.94 [0.16, 5.37]
Telimaa 1988b	6/18	3/7		6.0	0.67 [0.11, 4.00]
Thomas 1987	5/20	4/17		8.7	1.08 [0.24, 4.78]
Vercellini 1999	8/69	17/76		25.9	0.47 [0.20, 1.12]
Total	207	195		100.0	0.74 [0.48, 1.15]

Total events: 62 (Treatment), 69 (Control)

Test for heterogeneity chi-square=2.49 df=6 p=0.87 I^2 =0.0%

Test for overall effect z=1.34 p=0.2



Ovulation suppression for endometriosis for women with subfertility (Review)

Hughes E, Brown J, Collins JJ, Farquhar C, Fedorkow DM, Vanderkerchove P

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 1

http://www.thecochranelibrary.com

Analysis 1.1. Comparison 1 Ovulation suppression versus placebo, Outcome 1 Clinical pregnancy.

Review: Ovulation suppression for endometriosis for women with subfertility

Comparison: 1 Ovulation suppression versus placebo

Outcome: 1 Clinical pregnancy

Study or subgroup	ovarian suppression n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Loverro 2008	5/14	6/13		6.8 %	0.66 [0.15, 2.98]
Bayer 1988	13/37	17/36		18.0 %	0.61 [0.24, 1.54]
Bianchi 1999	6/11	8/16		6.8 %	1.19 [0.26, 5.38]
Busacca 2001	5/15	6/15		7.2 %	0.76 [0.18, 3.26]
Fedele 1992	10/35	11/36		15.0 %	0.91 [0.33, 2.51]
Harrison 2000	0/50	3/50		2.9 %	0.13 [0.01, 1.28]
Parrazzini 1994	7/36	7/39		11.6 %	1.10 [0.35, 3.50]
Shawki 2002	16/34	5/34		14.8 %	4.45 [1.60, 12.36]
Telimaa 1988(a)	7/17	3/7		5.0 %	0.94 [0.16, 5.37]
Telimaa 1988(b)	6/18	3/7		4.9 %	0.67 [0.11, 4.00]
Thomas 1987	5/20	4/17		7.0 %	1.08 [0.24, 4.78]
Subtotal (95% CI)	**287**	**270**		**100.0 %**	**1.02 [0.69, 1.50]**

Total events: 80 (ovarian suppression), 73 (placebo)

Heterogeneity: $Chi^2 = 13.11$, $df = 10$ ($P = 0.22$); $I^2 = 24\%$

Test for overall effect: $Z = 0.08$ ($P = 0.94$)

Test for subgroup differences: $Chi^2 = 0.03$, $df = 1$ ($P = 0.85$), $I^2 = 0.0\%$

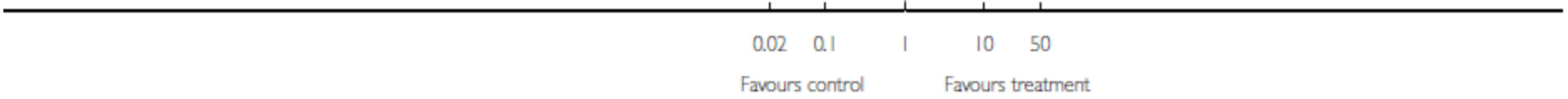


Fig. 4. Comparison 02 Post-surgical medical therapy vs no therapy

02.03 Pregnancy

Review: Pre and post operative medical therapy for endometriosis surgery

Comparison: 02 Post-surgical medical therapy vs no therapy

Outcome: 03 Pregnancy

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bianchi 1999	6/11	8/16		20.2	1.09 [0.53, 2.26]
Busacca 2001	5/15	6/15		18.6	0.83 [0.32, 2.15]
Loverro 2001	5/33	6/29		19.8	0.73 [0.25, 2.15]
Vercellini 1999	8/69	14/76		41.3	0.63 [0.28, 1.41]
Total	128	136		100.0	0.78 [0.50, 1.22]

Total events: 24 (Treatment), 34 (Control)

Test for heterogeneity chi-square=1.12 df=3 p=0.77 I^2 =0.0%

Test for overall effect z=1.10 p=0.3

Human Reproduction, Vol.24, No.2 pp. 254–269, 2009

Surgery for endometriosis-associated infertility: a pragmatic approach

Paolo Vercellini[1,3,4], Edgardo Somigliana[2,3], Paola Viganò[3], Annalisa Abbiati[1,3], Giussy Barbara[1], and Pier Giorgio Crosignani[1]

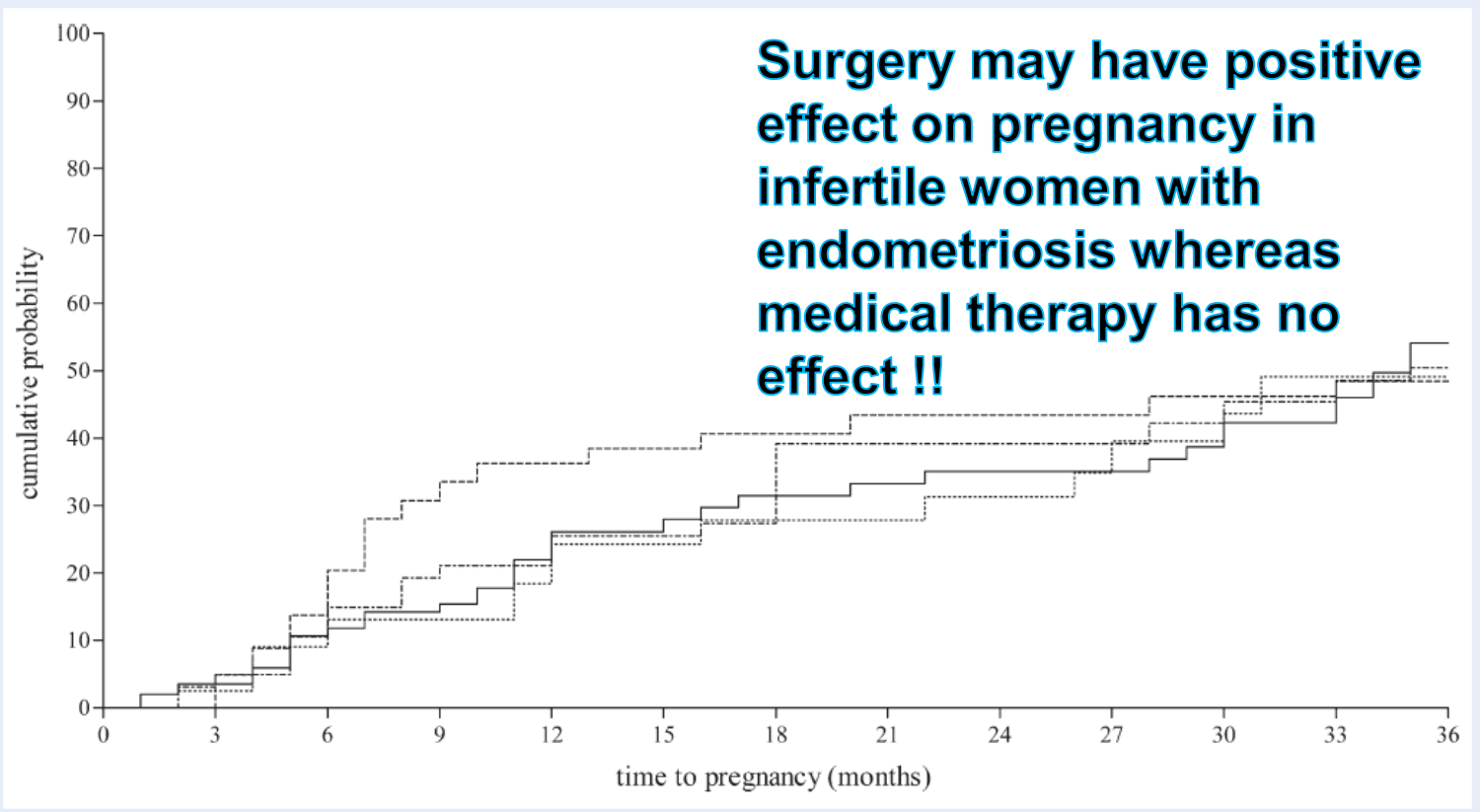


Figure 1 Cumulative 36 month probability of becoming pregnant by disease stage in 222 infertile women who underwent conservative surgery for endometriosis and had no other infertility factor (continuous line, stage I; dotted line, stage II; dashed line, stage III; dash dotted line, stage IV).From Vercellini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

FERTILITY AND STERILITY® Vol. 68, No. 1, July 1997

Randomized controlled trial of superovulation and insemination for infertility associated with minimal or mild endometriosis*

Ian S. Tummon, M.D.†‡
Linda J. Asher, R.N.C.†
James S. B. Martin, M.D.†
Togas Tulandi, M.D.§

There were 30% cumulative live births after four cycles of superovulation with IUI and 10% cumulative live births after four cycles of no treatment

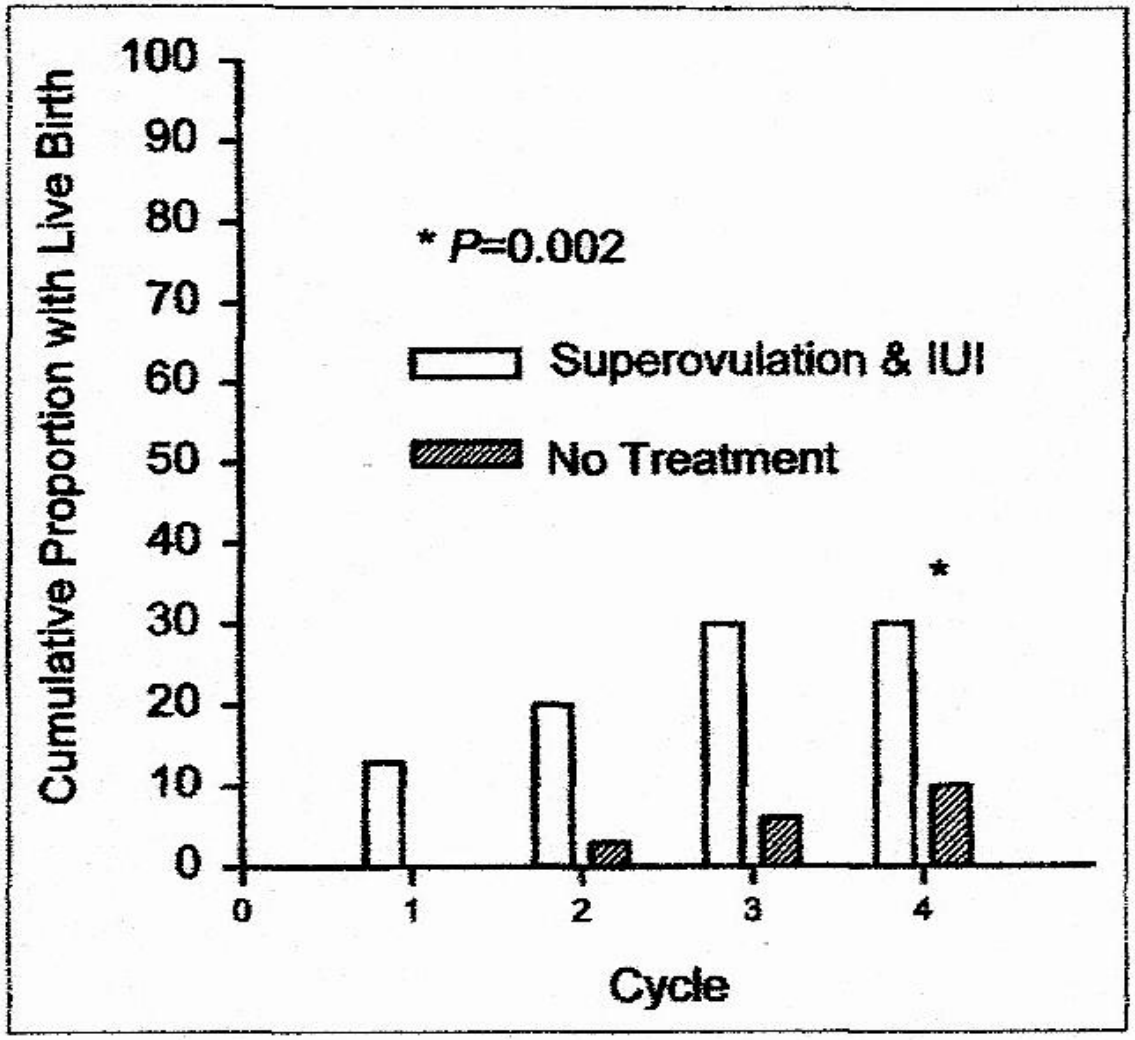


Figure 1 Cumulative proportion of patients with live birth.

Cycle fecundity in women with stage I or II endometriosis, according to treatment.

Group	Unexplained infertility	Endometriosis-associated infertility			
Treatment	**Guzick et al. (27)**	**Deaton et al. (28)**	**Chaffkin et al. (29)**	**Fedele et al. (30)**	**Kemmann et al. (31)**
No treatment or intracervical insemination	0.02	0.033	—	0.045	0.028
IUI	0.05[a]	—	—	—	—
Clomiphene	—	—	—	—	0.066
Clomiphene/IUI	—	0.095[a]	—	—	—
Gonadotropins	0.04[a]	—	0.066	—	0.073[a]
Gonadotropin/IUI	0.09[a]	—	0.129[a]	0.15[a]	—
IVF	—	—	—	—	0.222[a]

[a] $P<.05$ for treatment vs. no treatment.

ASRM Practice Committee. Endometriosis and infertility. Fertil Steril 2006.

FERTILITY AND STERILITY®
VOL. 78, NO. 4, OCTOBER 2002

Published by Elsevier Science Inc.
Printed on acid-free paper in U.S.A.

Cycle-specific and cumulative fecundity in patients with endometriosis who are undergoing controlled ovarian hyperstimulation–intrauterine insemination or in vitro fertilization–embryo transfer

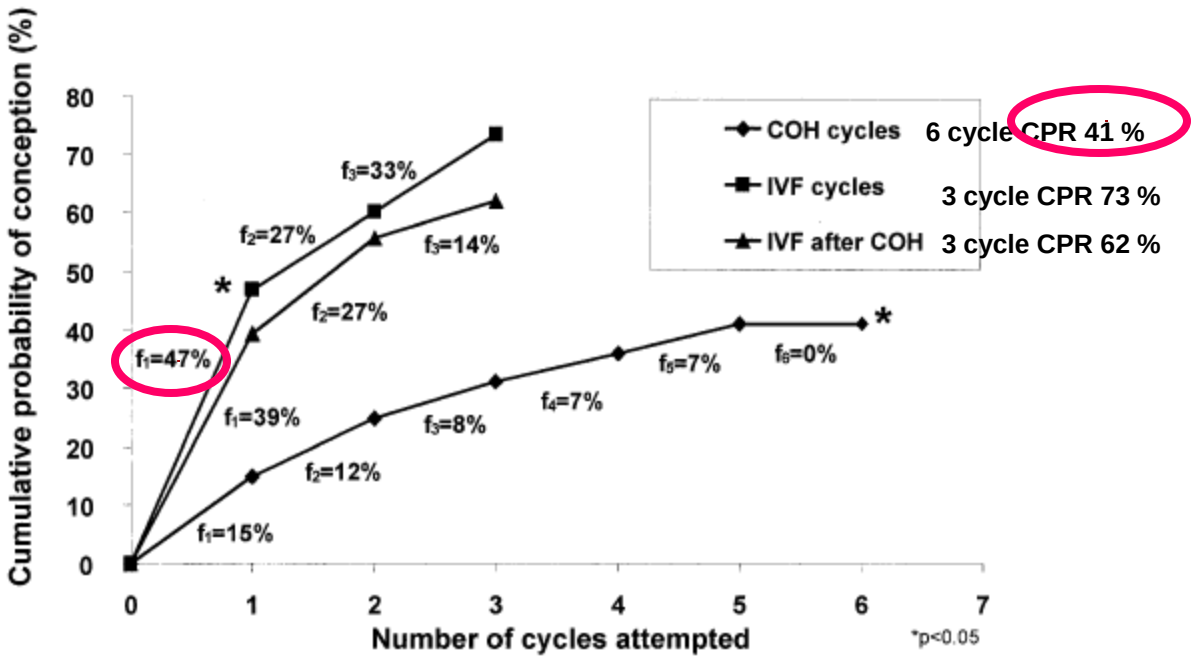
W. Paul Dmowski, M.D., Ph.D., Michelle Pry, M.S.N., Jianchi Ding, Ph.D., and Nasir Rana, M.D., M.P.H.

Institute for the Study and Treatment of Endometriosis, Oak Brook, Illinois

2

FIGURE 1

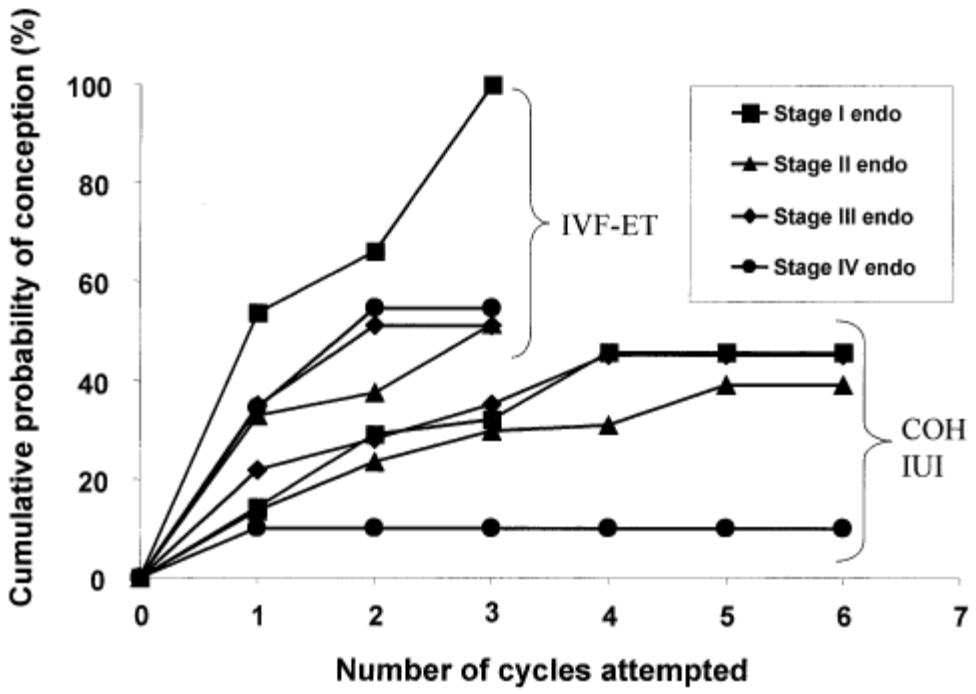
Cycle and cumulative fecundity in women with endometriosis undergoing COH-IUI, IVF-ET, or IVF-ET after failed COH-IUI.



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

FIGURE 2

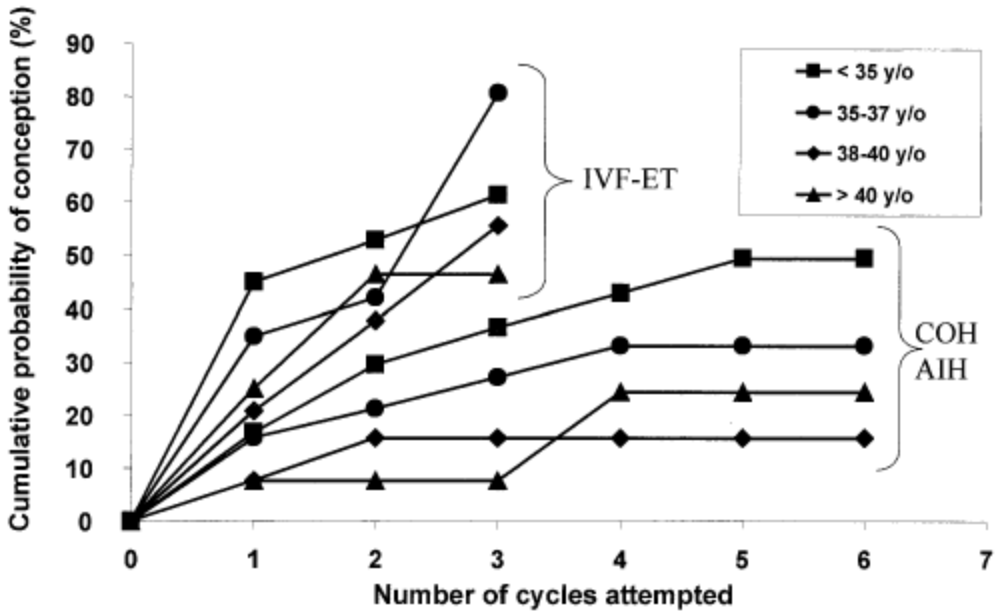
Effect of COH-IUI or IVF-ET on fecundity according to the stage of endometriosis.



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

FIGURE 3

Effect of COH-IUI or IVF-ET on fecundity according to the age of the women with endometriosis.



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

Indications for COH + IUI

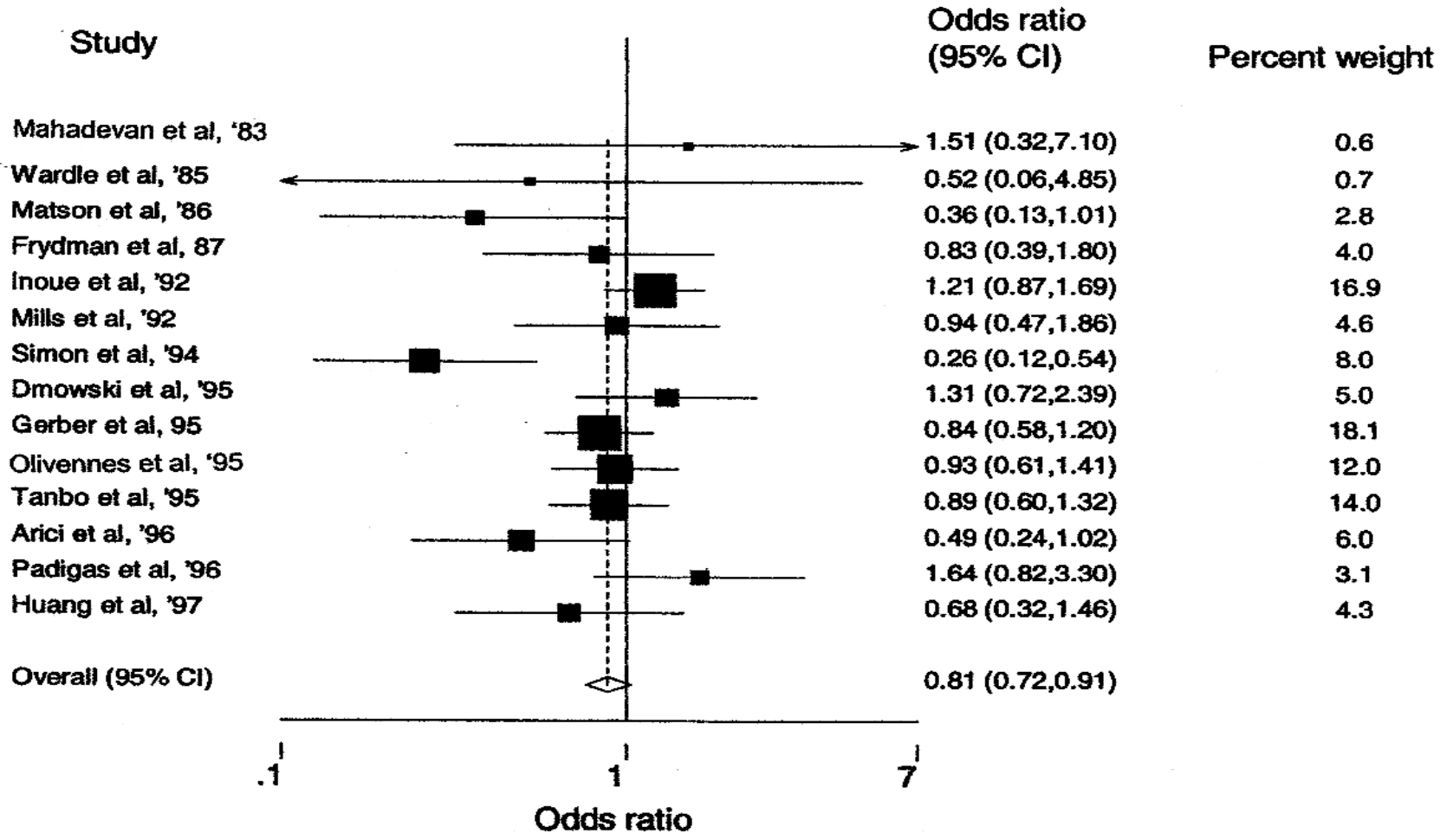
- Early stage (I – II)
- < 38 years
- Max. 4 cycles

FERTILITY AND STERILITY® VOL. 77, NO. 6, JUNE 2002

Effect of endometriosis on in vitro fertilization

Kurt Barnhart, M.D., M.S.C.E.,[a,b] Rebecca Dunsmoor-Su, M.D., M.S.C.E.,[a] and Christos Coutifaris, M.D., Ph.D.[a]

Unadjusted meta-analysis of odds of pregnancy in endometriosis patients vs. tubal factor controls.



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

Lora K. Shahine · Richard O. Burney · Barry Behr · Amin A. Milki · Lynn M. Westphal · Ruth B. Lathi

J Assist Reprod Genet (2009) 26:69–73

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

	IVF cycle before surgery	IVF 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 follicles	15.2±2.6	12.8±1.8
Number of oocytes	11.6±2.3	9.9±3.3
ICSI	17%	23%
Fertilization rate	65% IVF 70% ICSI	68% IVF 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
Number of day 3 embryos six cell or higher & Grade I or II	3.8±1.2	3.3±1.6
Blastocyst (day 5) transfers	13%	20%
Number of blastocysts frozen	2.1±1.3	2.8±2.1

No P-value <0.05

The First Congress on
Controversies In Obstetrics, Gynecology & Infertility

Stages of Endometriosis: Does It Affect the Success of IVF?

B. Gulekli, W.M. Buckett and S.L. Tan

Department of Obstetrics and Gynecology, McGill University, Royal Victoria Hospital Women's Pavilion, Montreal Québec, Canada

AOGS
ACTA Obstetricia et Gynecologica Scandinavica

Acta Obstetricia et Gynecologica Scandinavica © 2011 Nordic Federation of Societies of Obstetrics and Gynecology **90** (2011) 1232–1238

MAIN RESEARCH ARTICLE

Impact of endometriosis on in vitro fertilization and embryo transfer cycles in young women: a stage-dependent interference

MARIA ELISABETTA COCCIA[1], FRANCESCA RIZZELLO[2], GIULIA MARIANI[1], CARLO BULLETTI[3], ANTONIO PALAGIANO[4] & GIANFRANCO SCARSELLI[1]

[1]*Department of Science for the Woman and Child's Health, University of Florence, Florence,* [2]*Department of Medical Pathophysiology, Sapienza University of Rome, Rome,* [3]*Unit of Physiopathology of Reproduction, Cattolica General Hospital and University of Bologna, Bologna, and,* [4]*Department of Obstetrics, Gynecology and Reproductive Sciences, Second University of Naples, Naples, Italy*

Table 3. Results of analysis comparing endometriosis patients (any stage) with control women.

	Endometriosis	Tubal factor	*p*-Value
Mean days on gonadotropins	11.8±1.9	11.7±1.9	0.779
Total FSH/hMG (IU)	3 842.1±1 692.2	3 301.9±1 421.7	0.016*
Cycle cancellation rate	17 of 164 (10.4%)	3 of 80 (3.7%)	0.129
Peak E_2 levels (pg/ml)	1 296.5±948.1	1 470.6±975.3	0.222
Number of follicles on day of hCG	11.6±6.5	14.6±6.5	0.001*
Number of follicles ≥15mm on day of hCG	3.7±2.7	2.8±2.6	0.011*
Number of of oocytes retrieved	7.8±5.4	10.8±6.1	0.001*
Fertilization rate (%)	65.3	71.9	0.101
Total number of embryos	2.7±3.1	5±4	0.001*
Mean number of transferred embryos	2.3±1.6	3.1±1.6	0.001*
Total number of pregnancies (β-hCG+)	24	22	0.015*
Number of clinical pregnancies	19	18	0.048*
Implantation rate (%)	8.6	10.8	0.477
Clinical pregnancy rate per patient	(19 of 148) 12.8%	(18 of 72) 25%	0.038*
Clinical pregnancy rate per started cycle	(19 of 164) 11.6%	(18 of 80) 22.5%	0.041*
Clinical pregnancy rate per retrieval	(19 of 147) 12.9%	(18 of 77) 23.4%	0.070
Clinical pregnancy rate per embryo transfer	(19 of 126) 15.1%	(18 of 69) 26.1%	0.092

Abbreviations: hMG, human menopausal gonadotropins; FSH, follicle-stimulating hormone; β-hCG, β-subunit of human chorionic gonadotropin, β-hCG+ when >5IU/l.

*$P < 0.05$.

Table 4. Results of analysis comparing endometriosis patients (stage I–II and III–IV) with control women.

	Endometriosis stage I–II	Endometriosis stage III–IV	Tubal factor	*p*-Value for endometriosis vs. stage I–II tubal factor	*p*-Value for endometriosis vs. stage III–IV tubal factor	*p*-Value for endometriosis vs. stage I–II stage III–IV
Mean days on gonadotropins	11.9±1.4	11.8±2.1	11.7±1.9	0.300	0.872	0.807
Total FSH/hMG (IU)	3 505.8±1 527.6	4 021.5±1 754.4	3 301.9±1 421.7	0.429	0.003*	0.065
Cycle cancellation rate	2 of 55 (3.6%)	15 of 109 (13.8%)	3 of 80 (3.7%)	0.668	0.039*	0.055
Peak E_2 levels (pg/ml)	1 603.3±954.3	1 108.5±899.6	1 470.6±975.3	0.463	0.019*	0.004*
Number of follicles on day of hCG	14.3±5.6	6.5±0.6	14.6±6.5	0.761	0.001*	0.001*
Number of follicles ≥15mm on day of hCG	3.6±3.1	2.4±2.1	3.7±2.7	0.931	0.0001*	0.003*
Number of oocytes retrieved	9.8±5.5	6.7±5	10.8±6.1	0.347	0.001*	0.001
Fertilization rate (%)	52.6	70.5	71.9	0.0001*	0.805	0.003*
Total number of embryos	2.8±2.9	2.6±3.2	5±4	0.001*	0.001*	0.731
Mean number of transferred embryos	2.4±1.6	2.2±1.6	3.1±1.6	0.016*	0.001*	0.419
Total number of pregnancies (β-hCG+)	14 of 54	10 of 94	22 of 72	0.711	0.002*	0.028*
Implantation rate (%)	14.1	5.3	10.8	0.453	0.055	0.010*
Clinical pregnancy rate per patient	(11 of 54) 20.4%	(8 of 94) 8.5%	(18 of 72) 25%	0.691	0.007*	0.069
Clinical pregnancy rate per started cycle	(11 of 55) 20%	(8 of 109) 7.3%	(18 of 80) 22.5%	0.893	0.006*	0.033*
Clinical pregnancy rate per retrieval	(11 of 53) 20.7%	(8 of 94) 8.5%	(18 of 77) 23.4%	0.890	0.013*	0.062
Clinical pregnancy rate per embryo transfer	(11 of 44) 25%	(8 of 82) 9.7%	(18 of 69) 26.1 %	0.927	0.015*	0.044*

Abbreviations: hMG, human menopausal gonadotropins; FSH, follicle-stimulating hormone; β-hCG, β-subunit of human chorionic gonadotropin, β-hCG+ when >5IU/l.

*$P < 0.05$.

Deep infiltrating endometriosis is a determinant factor of cumulative pregnancy rate after intracytoplasmic sperm injection/in vitro fertilization cycles in patients with endometriomas

Marcos Ballester, M.D.,[a] Anne Oppenheimer, M.D.,[a] Emmanuelle Mathieu d'Argent, M.D.,[a] Cyril Touboul, M.D.,[a] Jean-Marie Antoine, M.D.,[a] Michelle Nisolle, M.D., Ph.D.,[b] and Emile Daraï, M.D., Ph.D.[a]

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Fertility and Sterility® Vol. 97, No. 2, February 2012

TABLE 3

Characteristics of patients who became pregnant and those who did not.

	Women who did not become pregnant (n = 45)	Women who became pregnant (n = 58)	*P* value
Age (y), median (range)	34 (24–42)	33 (25–39)	.03
Duration of prior infertility (y), median (range)	4 (1–12)	3 (1–9)	.2

Using multivariable analysis, associated DIE (odds ratio [OR] 0.2; 95% CI, 0.06–0.6; $P=.008$) and an AMH serum level $\leq$ 1 ng/mL (OR 3.9; 95% CI, 1.1–13.5; $P=.03$) were independent factors associated with a lower pregnancy rate.

Bilateral	20 (44.4)	30 (51.7)	
Size of the largest endometrioma (mm), median (range)	33 (10–88)	32.7 (10–100)	.9
Associated DIE, n (%)	38 (84.5)	35 (60.3)	.01
Prior surgery, n (%)			
Endometriosis	31 (68.9)	42 (72.4)	.9
Endometrioma	22 (71)	32 (76.2)	.6
No. of cycles, median (range)	1 (1–5)	1 (1–4)	.01
AMH >1 (ng/mL), n (%)	28 (62.2)	48 (82.7)	.008
Total AFC (n), median (range)	9 (2–50)	14 (2–60)	.14

Note: AFC = antral follide count; AMH = antimüllerian hormone; BMI = body mass index; DIE = deep infiltrating endometriosis.

Ballester. Cumulative pregnancy rate and endometriomas. Fertil Steril 2012.

The effect of surgical treatment for endometrioma on in vitro fertilization outcomes: a systematic review and meta-analysis

1

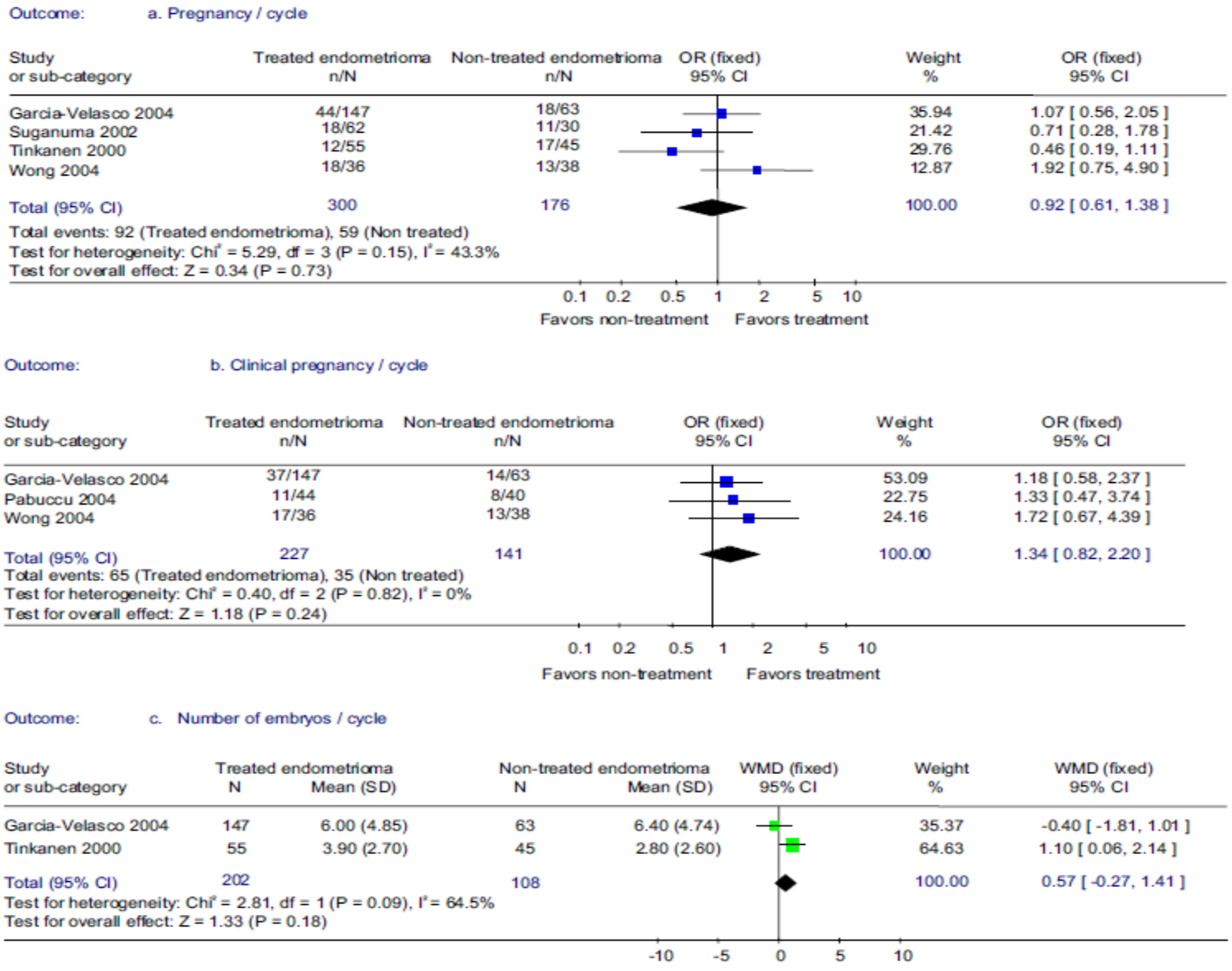
Ioanna Tsoumpou, M.B., Ch.B.,[a] *Maria Kyrgiou, M.D.,*[b] *Tarek A. Gelbaya, M.D.,*[c] *and Luciano G. Nardo, M.D.*[c]

Result(s): A search of three electronic databases for articles published between January 1985 and November 2007 yielded 20 eligible studies. Meta-analysis was conducted for five studies that compared surgery vs. no treatment of endometrioma. There was no significant difference in clinical pregnancy rate between the treated and the untreated groups. Similarly, no significant difference was found between the two groups with regard to the outcome measures used to assess the response to controlled ovarian hyperstimulation with gonadotrophins.

Fertility and Sterility® Vol. 92, No. 1, July 2009

FIGURE 2

(A–F) Forest plots of the meta-analysis on clinical outcomes and on the parameters of ovarian response to gonadotrophin stimulation in women who underwent surgical treatment for endometrioma versus women with non-treated endometrioma.



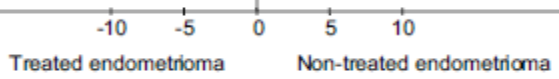
Tsoumpou. Surgery for endometrioma and IVF outcome. Fertil Steril 2009.

FIGURE 2 Continued.

Outcome: d. Oocytes retrieved / cycle

Study or sub-category	Treated endometrioma N	Treated endometrioma Mean (SD)	Non-treated endometrioma N	Non-treated endometrioma Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Garcia-Velasco 2004	147	10.80 (7.30)	63	11.80 (7.10)		64.54	-1.00 [-3.11, 1.11]
Suganuma 2002	62	7.20 (6.20)	30	9.70 (6.70)		35.46	-2.50 [-5.35, 0.35]
Tinkanen 2000	55	6.50 (0.00)	45	6.10 (0.00)			Not estimable
Total (95% CI)	264		138			100.00	-1.53 [-3.23, 0.17]

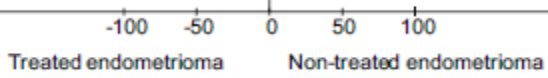
Test for heterogeneity: Chi² = 0.69, df = 1 (P = 0.41), I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)



Outcome: e. Gonadotrophin ampoules / cycle

Study or sub-category	Treated endometrioma N	Treated endometrioma Mean (SD)	Non-treated endometrioma N	Non-treated endometrioma Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
Pabuccu 2004	44	33.20 (8.40)	40	36.80 (9.90)		53.19	-3.60 [-7.55, 0.35]
Wong 2004	36	36.70 (14.00)	38	29.30 (15.50)		46.81	7.40 [0.68, 14.12]
Total (95% CI)	80		78			100.00	1.55 [-9.21, 12.31]

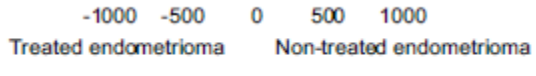
Test for heterogeneity: Chi² = 7.65, df = 1 (P = 0.006), I² = 86.9%
Test for overall effect: Z = 0.28 (P = 0.78)



Outcome: f. Estradiol peak (pg/mL)

Study or sub-category	Treated endometrioma N	Treated endometrioma Mean (SD)	Non-treated endometrioma N	Non-treated endometrioma Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
Garcia-Velasco 2004	147	1910.00 (1285.00)	63	2472.00 (2062.00)		28.80	-562.00 [-1111.92, -12.08]
Pabuccu 2004	44	1196.00 (445.00)	40	946.70 (264.00)		43.32	249.30 [94.44, 404.16]
Wong 2004	36	1956.00 (1290.00)	38	1928.00 (1227.60)		27.88	28.00 [-546.38, 602.38]
Total (95% CI)	227		141			100.00	-46.05 [-535.14, 443.04]

Test for heterogeneity: Chi² = 8.03, df = 2 (P = 0.02), I² = 75.1%
Test for overall effect: Z = 0.18 (P = 0.85)



Tsoumpou. Surgery for endometrioma and IVF outcome. Fertil Steril 2009.

Interventions for women with endometrioma prior to assisted reproductive technology (Review)

Benschop L, Farquhar C, van der Poel N, Heineman MJ

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 11

Main results

Eleven trials were identified of which seven were excluded and four with 312 participants were included.

No trial reported live birth outcomes. One trial compared gonadotropin-releasing hormone (GnRH) agonist with GnRH antagonist. There was no evidence of a difference for clinical pregnancy rate (CPR), however the number of mature oocytes retrieved (NMOR) was greater with GnRH agonists (MD -1.60, 95% CI -2.44 to -0.76) and the ovarian response was increased (estradiol (E2) levels on day of human chorionic gonadotropin (hCG) injection) (MD -456.30, 95% CI -896.06 to -16.54).

Surgery (aspiration or cystectomy) versus expectant management (EM) showed no evidence of a benefit for clinical pregnancy with either technique. Aspiration was associated with greater NMOR (MD 0.50, 95% CI 0.02 to 0.98) and increased ovarian response (E2 levels on day of hCG injection) (MD 685.3, 95% CI 464.50 to 906.10) compared to EM. Cystectomy was associated with a decreased ovarian response to controlled ovarian hyperstimulation (COH) (MD -510.00, 95% CI -676.62 to -343.38); no evidence of an effect on the NMOR compared to EM. Aspiration versus cystectomy showed no evidence of a difference in CPR or the NMOR.

Authors' conclusions

There was no evidence of an effect on reproductive outcomes in any of the four included trials. Further RCTs of management of endometrioma in women undergoing ART are required.

Adenomyosis does not affect implantation, but is associated with miscarriage in patients undergoing oocyte donation

José A. Martínez-Conejero, Ph.D., Maika Morgan, M.D., Manel Montesinos, M.D., Sara Fortuño, M.D., Marcos Meseguer, Ph.D., Carlos Simón, M.D., José A. Horcajadas, Ph.D., and Antonio Pellicer, M.D.

TABLE 3

In vitro fertilization outcomes in recipients of oocytes from donors with and without ultrasound diagnosis of adenomyosis or endometriosis (Fedele [7] and Reinhold [8] criteria of transvaginal ultrasonographic diagnosis of adenomyosis).

	Adenomyosis group		Endometriosis group		Control group		
		95% CI		95% CI		95% CI	*P* value
Donated oocyte	10.8	10.2–11.3	11.2	10.8–11.6	11.2	10.8–11.7	NS
Blastomeres in day 3	7.6	7.5–7.8	7.5	7.3–7.8	7.4	7.2–7.7	NS
ET day							NS
Day 2	4 (1.2%)		3 (1.2%)		6 (1.8%)		
Day 3	232 (70.7%)		164 (67.8%)		255 (77%)		
Day 5	58 (17.7%)		40 (16.5%)		42 (12.7%)		
Day 6	34 (10.4%)		35 (14.5%)		28 (8.5%)		
No. of transferred embryos	1.97	1.90–204	1.93	1.88–1.98	1.90	1.85–1.96	NS
Implantation rate	29.6%	22.5–36.7	33.3%	28.3–38.2	30.8%	26.6–34.9	NS
Clinical pregnancy rate	40.0% (n = 131)	34.6–45.2	44.2% (n = 107)	37.9–50.4	44.4% (n = 147)	39.0–49.8	NS
Clinical miscarriage	13.1% (n = 43)	9.4–16.7	6.1% (n = 15)	3.1–9.2	7.2% (n = 24)	4.4–10.0	< .05
Multiple pregnancy	13.1% (n = 43)	9.5–16.7	15.3 % (n = 37)	10.7–19.8	12.4% (n = 41)	8.8–15.0	NS
Term pregnancy rate	26.8% (n = 88)	22.0–31.6	38.0% (n = 92)	31.9–44.1	37.1% (n = 123)	31.9–42.4	< .05

Note: NS = not significant.

Adenomysosis and outcome of IVF-clinical pregnancy rates

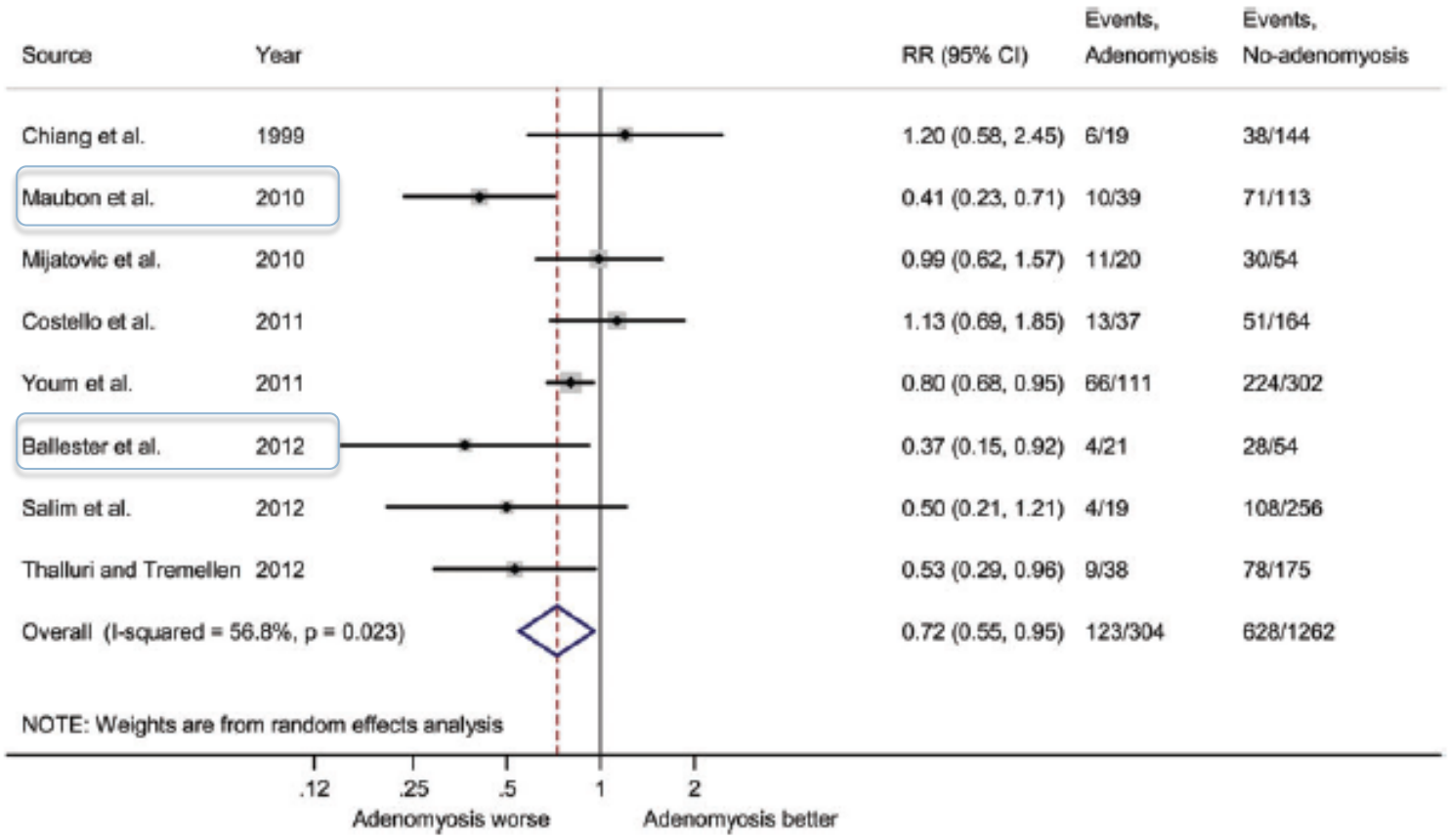


Figure 2 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the likelihood of clinical pregnancy in infertile women with or without adenomyosis undergoing IVF/ICSI. Horizontal lines indicate 95% CIs; boxes show the study-specific weight; diamond represents combined effect size; dashed line indicates the overall estimate. **From Vercellini et al. Hum Reprod 2014**

Adenomysosis and outcome of IVF-miscarriage rates

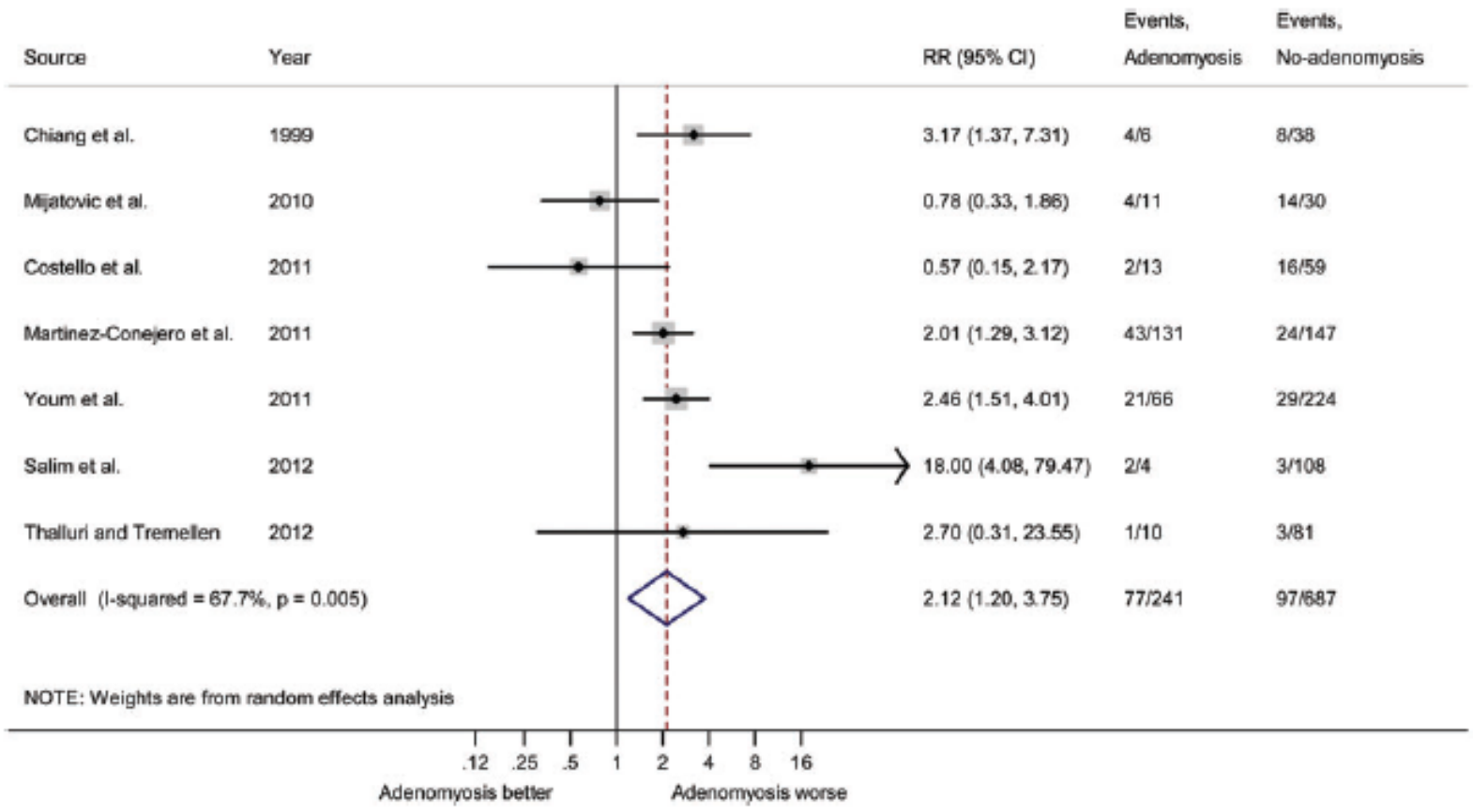


Figure 3 Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the risk of miscarriage in clinical pregnancies obtained at IVF/ICSI in women with or without adenomyosis. Horizontal lines indicate 95% CIs; boxes show the study-specific weight; diamond represents combined effect size; dashed line indicates the overall estimate.

From Vercellini et al. Hum Reprod 2014

Implantation & Endometriosis

Group-I (n=44) **Donors and recipients (without endometriosis)**

Group-II (n=14) **Donors with Endometriosis**
Recipients without the disease

Group-III (n=16) **Donors without Endometriosis**
Recipients with the disease

Pregnancy rates

Group-I : 61.4% **Group-II : 28.6%(*)** **Group-III: 60.0%**

Pellicer A et al Prog in Endometriosis *p177-83*, 2004

Which protocol in IVF ?

GnRH-a

- Ultra-short
- Short
- Long
- Ultra-long
- *Prolonged*

GnRH-ant

Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis (Review)

Sallam HN, Garcia-Velasco JA, Dias S, Arici A, Abou-Setta AM

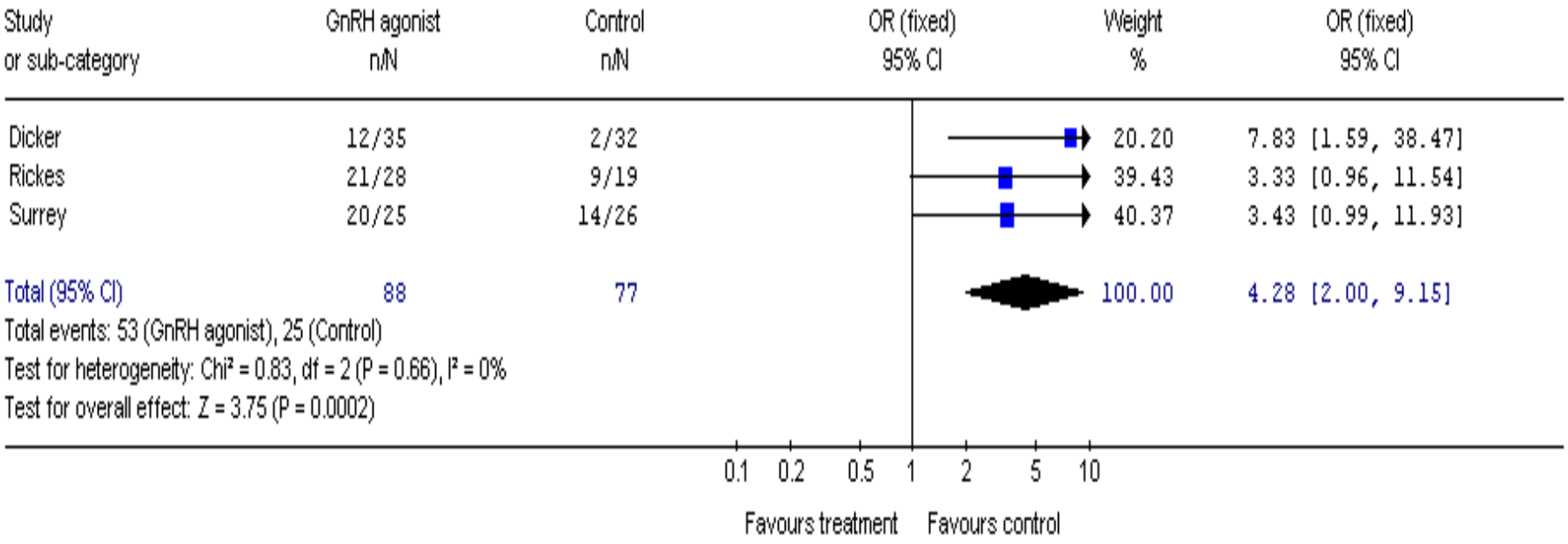
THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 11

Comparison 1. GnRH agonist versus no agonist before IVF or ICSI

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth rate per woman	1	67	Odds Ratio (M-H, Fixed, 95% CI)	9.19 [1.08, 78.22]
2 Clinical pregnancy rate per woman	3	165	Odds Ratio (M-H, Fixed, 95% CI)	4.28 [2.00, 9.15]
3 Miscarriage rate per clinically pregnant woman	1	14	Odds Ratio (M-H, Fixed, 95% CI)	0.5 [0.02, 10.25]
4 Miscarriage rate per woman randomised	1	67	Odds Ratio (M-H, Fixed, 95% CI)	4.0 [0.42, 37.84]
5 Dose of FSH or HMG (ampoules)	2	118	Mean Difference (IV, Fixed, 95% CI)	0.34 [-0.70, 1.38]
6 Duration of FSH administration (days)	1	51	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.90, 0.98]
7 Number of oocytes per woman	2	150	Mean Difference (IV, Fixed, 95% CI)	2.05 [1.27, 2.84]

Review: Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis (Version 03)
Comparison: 01 GnRH agonist versus no agonist before IVF/ICSI
Outcome: 02 Clinical pregnancy rate per woman



3 RCT with 3 – 6 months GnRH agonist treatment increases clinical pregnancy rates ????

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 11

CONCLUSION I

- **No increase in fertility with medical treatment (suppresion of ovulation) of endometriosis.**
- **L/S surgery is effective in early stages, but no enough evidence for severe endometriosis.**
- **COH + IUI is a good choice in early stages (good choice in cases after surgical treatment max 3-4 times).**
- **In severe endometriosis IVF/ICSI should be chosen.**

CONCLUSION II

- **IVF success is lower in endometriosis (especially in severe forms) compared with tubal factor infertility.**
- **Lower implantaion rates is associated with low ovarian reserve rather than poor embryo quality and endometrial receptivity.**
- **Prior to IVF treatment using long term GnRH-a (3-6 months) can improve fertility.**


Thank you

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

Women with advanced-stage endometriosis and previous surgery respond less well to gonadotropin stimulation, but have similar IVF implantation and delivery rates compared with women with tubal factor infertility

Ioannis M. Matalliotakis, M.D., Ph.D.,[a,b] *Hakan Cakmak, M.D.,*[a] *Neal Mahutte, M.D.,*[c] *Yvoni Fragouli, M.D., Ph.D.,*[d] *Aydin Arici, M.D.,*[a] *and Denny Sakkas, Ph.D.*[a]

IVF laboratory parameters in women with endometriosis and previous surgeries compared with women with tubal infertility. Where appropriate, data are expressed as mean ± SD.

	Endometriosis (113 cycles)	Tubal factor (208 cycles)	*P* value
No. of oocytes retrieved	9.4 ± 6.7	12.3 ± 7.1	.001
No. of mature oocytes	5.6 ± 4.4	7.4 ± 5.8	.006
ICSI			
All eggs	18/133 (13.5%)	37/208 (17.8%)	NS
Half eggs	42/133 (31.6%)	62/208 (29.8%)	NS
Total	60/133 (45.1%)	99/208 (47.6%)	NS
Fertilization rate (%)	60.2%	60.1%	NS
Total number of embryos	6.6 ± 4.8	8.9 ± 6.2	.001
No. of cleaved embryos on day 3	6.1 ± 4.6	8.2 ± 5.8	.001
Cleavage rate (%)	92.4%	92.1%	NS
Blastocyst	25/133 (18.8%)	47/208 (22.6%)	NS
Day of transfer	3.5 ± 1.1	3.6 ± 1.1	NS
Mean no. of transfered embryos	3.5 ± 1.4	3.5 ± 1.2	NS

Note: NS = not significant.

Matalliotakis. IVF in women with endometriosis and previous surgery. Fertil Steril 2007.

Women with advanced-stage endometriosis and previous surgery respond less well to gonadotropin stimulation, but have similar IVF implantation and delivery rates compared with women with tubal factor infertility

Ioannis M. Matalliotakis, M.D., Ph.D.,[a,b] *Hakan Cakmak, M.D.,*[a] *Neal Mahutte, M.D.,*[c] *Yvoni Fragouli, M.D., Ph.D.,*[d] *Aydin Arici, M.D.,*[a] *and Denny Sakkas, Ph.D.*[a]

IVF outcomes in women with endometriosis and tubal factor.

	Endometriosis (133 cycles)	Tubal factor (208 cycles)	*P* value
No. of pregnancies	46[a]	81[b]	—
Implantation rate	11.4%	11.8%	NS
Pregnancy sacs	43/133 (34.6%) 1(29), 2(10), 3(3), 5(1)	79/208 (38%) 1(58), 2(10), 3(10), 4(1)	NS
Fetal heartbeat (+)	37/133 (27.8%) 1(23), 2(10), 3(4)	62/208 (29.8%) 1(41), 2(10), 3(10), 4(1)	NS
Deliveries per cycle	35/133 (26.3%)	58/208 (27.9%)	NS
Deliveries per transfer	35/116 (30.1%) 1(21), 2(11), 3(3)	58/196 (22.6%) 1(37), 2(11), 3(9), 4(1)	NS
Miscarriages	9/46 (19.5%)	17/81 (21%)	NS
Ectopic	1/46 (2.1%)	3/81 (3.7%)	NS
Terminal abortion	1/46 (2.1%)	3/81 (3.7%)	NS

Note: NS = not significant.

[a] Three patients conceived twice.

[b] Fifteen patients conceived twice and two three times.

Matalliotakis. IVF in women with endometriosis and previous surgery. Fertil Steril 2007.

2

Impact of ovarian endometrioma on oocytes and pregnancy outcome in in vitro fertilization

Takahiro Suzuki, M.D., Shun-ichiro Izumi, M.D., Ph.D., Hidehiko Matsubayashi, M.D., Ph.D., Hideo Awaji, M.D., Kikuo Yoshikata, M.D., and Tsunehisa Makino, M.D., Ph.D.

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Fertility and Sterility® Vol. 83, No. 4, April 2005

TABLE 1

IVF outcomes for the groups.

endometrioma. "endometriosis without endometrioma," tubal factor,"

	Group A	Group B	Group C
Cycles	80	248	283
Age (y)	34.6 ± 3.3	34.7 ± 3.3	34.0 ± 8.8
BMI (kg/m^2)	22.3 ± 0.5	21.7 ± 0.9	22.1 ± 0.8
No. of oocytes retrieved	4.40 ± 2.99 (P = .0037 vs. group C)	4.48 ± 2.81 (P<.0001 vs. group C)	5.34 ± 2.99
Fertilization rate (%)	77.5 ± 28.1	78.8 ± 27.9	82.0 ± 21.9
Good quality rate[a] (%)	67.2 ± 32.5	63.0 ± 36.8	58.1 ± 35.1
Transferred embryos	2.20 ± 0.86 (P = .0001 vs. group C)	2.35 ± 0.83 (P = .0001 vs. group C)	2.67 ± 0.89
Implantation rate (%)	14.1	11.7	11.3
Pregnancy rate per ET (%)	25.3	22.3	23.9
Live birth rate per ET (%)	14.7	15.0	15.4

Note: Values are mean ± SD. IVF = in vitro fertilization; BMI = body mass index; ET = embryo transfer.

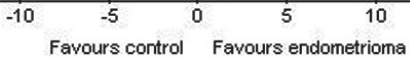
[a] Embryos were graded from 1 to 5 according to the classification of Veeks and defined as "good quality" when the embryo was 1 or 2 grade; 80 cycles had ovarian endometriomas that were aspirated and identified as "chocolate" cyst(s) at the time of oocyte retrieval (group A); 248 cycles did not have cysts at the time of oocyte retrieval, while endometriosis was diagnosed by laparoscopy or laparotomy before IVF (group B); 283 cycles had tubal factor without endometriosis, as diagnosed by previous laparoscopy (group C).

Suzuki. IVF outcomes with endometriomas. Fertil Steril 2005.

Review: Impact of Ovarian Endometrioma on IVF-ET Outcomes
06 # Oocytes
01 Number of ocytes

Study or sub-category	Endometrioma N	Endometrioma Mean (SD)	Control N	Control Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
Canis 2001	39	9.40(6.20)	59	10.90(6.50)		17.70	-1.50 [-4.06, 1.06]
Donnez 2001	187	10.60(4.20)	633	8.60(6.30)		24.82	2.00 [1.22, 2.78]
Marconi 2002	39	7.50(3.90)	39	8.70(5.10)		20.11	-1.20 [-3.21, 0.81]
Suzuki 2005	80	4.40(2.99)	283	5.34(2.99)		24.91	-0.94 [-1.68, -0.20]
Yanushpolsky 1998	37	13.00(9.00)	56	17.00(10.00)		12.45	-4.00 [-7.91, -0.09]
Total (95% CI)	382		1070			100.00	-0.74 [-2.66, 1.17]

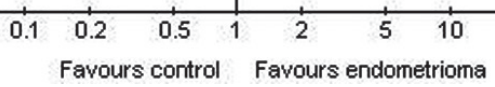
Test for heterogeneity: Chi² = 37.69, df = 4 (P < 0.00001), I² = 89.4%
Test for overall effect: Z = 0.76 (P = 0.45)



Review: Impact of Ovarian Endometrioma on IVF-ET Outcomes
01 Clinical PR (%)
01 Clinical pregnancy rate/all

Study or sub-category	Endometrioma n/N	Control n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
Canis 2001	14/39	18/59		37.45	1.28 [0.54, 3.01]
Marconi 2002	15/39	13/39		32.04	1.25 [0.49, 3.16]
Pabuccu 2004	10/41	14/46		30.51	0.74 [0.29, 1.91]
Total (95% CI)	119	144		100.00	1.07 [0.63, 1.81]

Total events: 39 (Endometrioma), 45 (Control)
Test for heterogeneity: Chi² = 0.86, df = 2 (P = 0.65), I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)



Gupta et al., RBM Online 2006

CONTROVERSY: IS THE OUTCOME OF IVF AFFECTED BY ENDOMETRIOSIS?

FERTILITY AND STERILITY®
VOL. 81, NO. 5, MAY 2004

Published by Elsevier Inc.
Printed on acid-free paper in U.S.A.

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

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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.

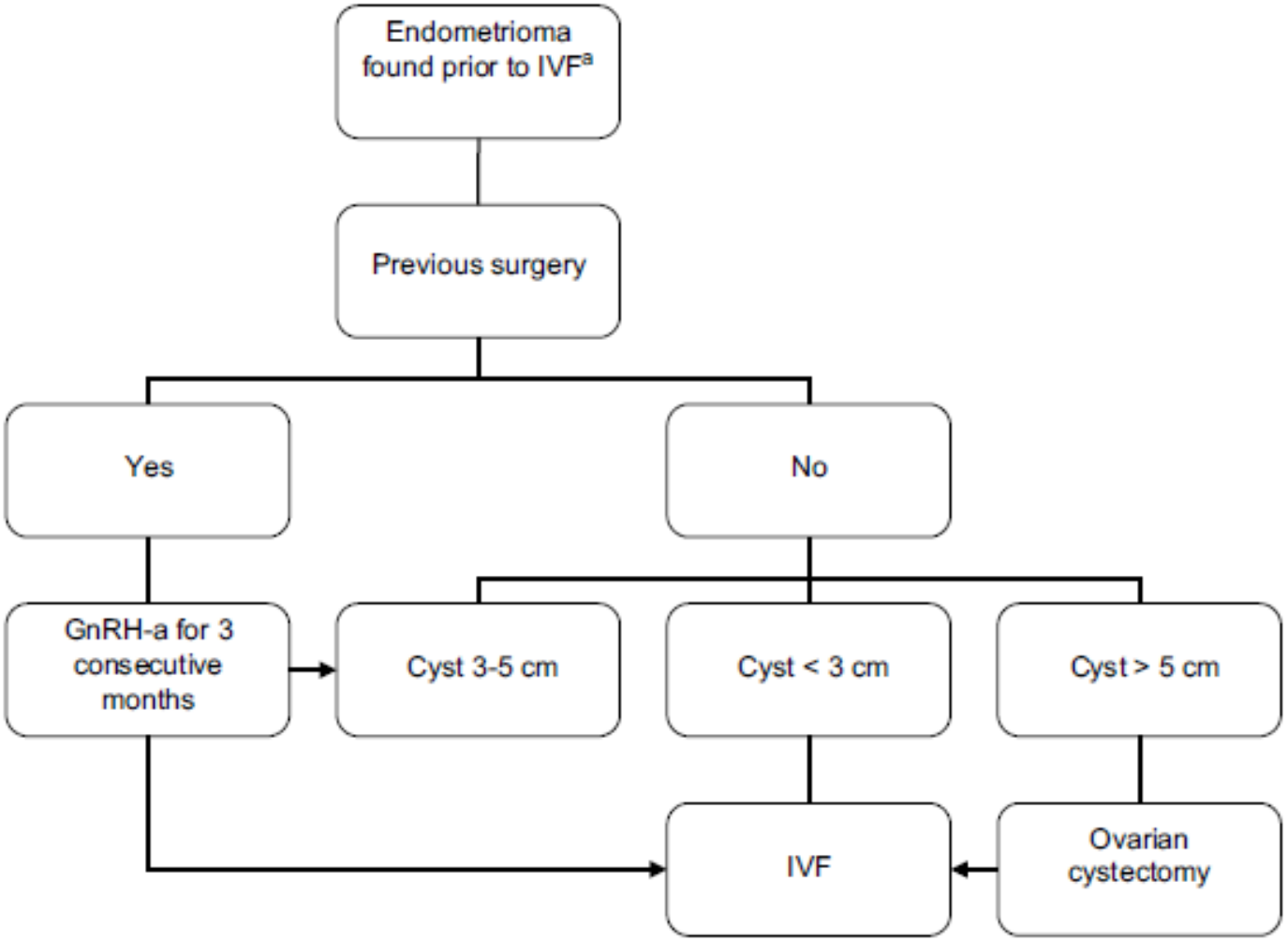
	Endometrioma removed (147 cycles)	Endometrioma present (63 cycles)	*P* value
No. of oocytes retrieved	10.8 ± 0.6	11.8 ± 0.9	.378
No. of mature oocytes	8.7 ± 0.6	8.4 ± 0.8	.780
Fertilization rate (%)	76.5	69.9	.051
No. of embryos/cycle	6.0 ± 0.4	6.4 ± 0.6	.582
No. of embryos transferred	2.7 ± 0.1	2.8 ± 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 %.

Garcia-Velasco. IVF and endometriosis. Fertil Steril 2004.

FIGURE 3

Flow chart for management of endometrioma.



[a]: in vitro fertilization

Tsoumpou. Surgery for endometrioma and IVF outcome. Fertil Steril 2009.