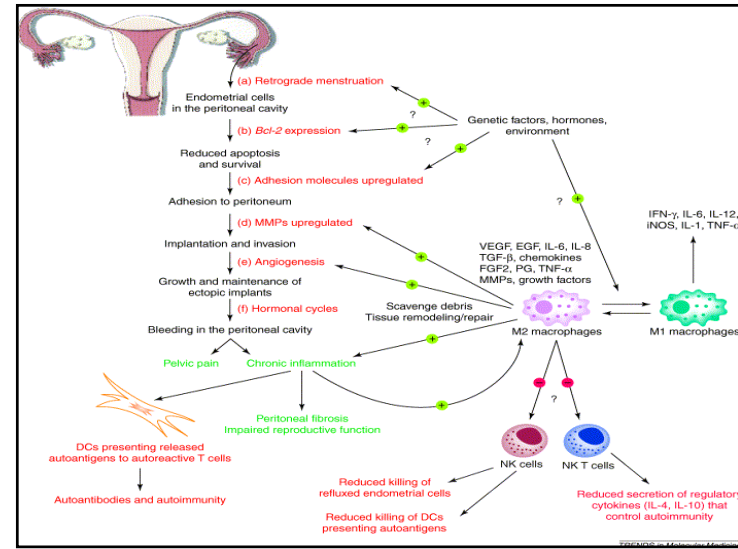
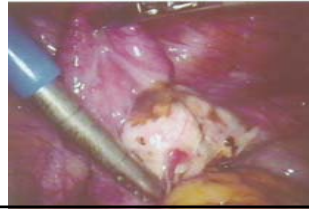
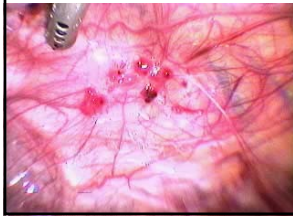


Endometriose og IVF – nyere betraktninger

Tom Tanbo

Reproduksjonsmedisinsk seksjon,
gynekologisk avd, OUS



Endometriosis classification

THE AMERICAN FERTILITY SOCIETY
REVISED CLASSIFICATION OF ENDOMETRIOSIS

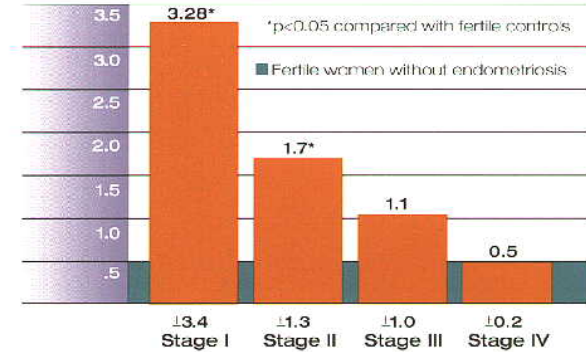
ENDOMETRIOSIS	C (cm)	1 (cm)	2 (cm)	3 (cm)
Superficial	0	2	4	6
Deep	2	4	6	8
A (cm)	1	2	3	4
B (cm)	1	2	3	4
C (cm)	1	2	3	4
D (cm)	1	2	3	4
E (cm)	1	2	3	4
F (cm)	1	2	3	4
G (cm)	1	2	3	4
H (cm)	1	2	3	4
I (cm)	1	2	3	4
J (cm)	1	2	3	4
K (cm)	1	2	3	4
L (cm)	1	2	3	4
M (cm)	1	2	3	4
N (cm)	1	2	3	4
O (cm)	1	2	3	4
P (cm)	1	2	3	4
Q (cm)	1	2	3	4
R (cm)	1	2	3	4
S (cm)	1	2	3	4
T (cm)	1	2	3	4
U (cm)	1	2	3	4
V (cm)	1	2	3	4
W (cm)	1	2	3	4
X (cm)	1	2	3	4
Y (cm)	1	2	3	4
Z (cm)	1	2	3	4

EXAMPLES & SCHEMATA

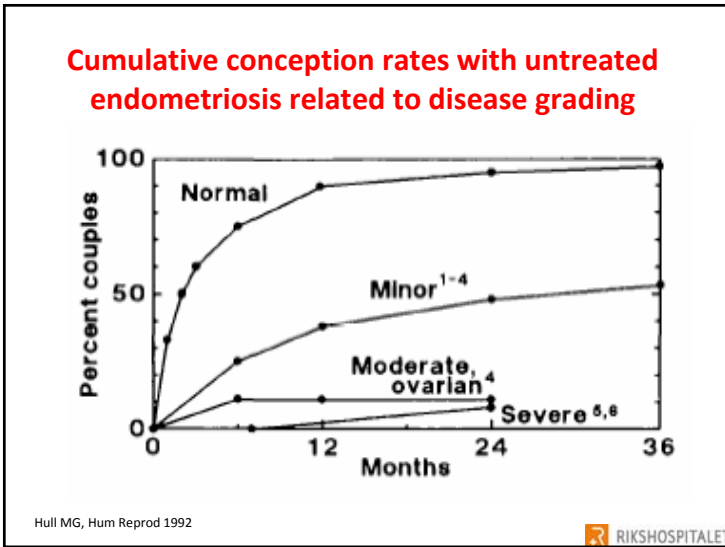
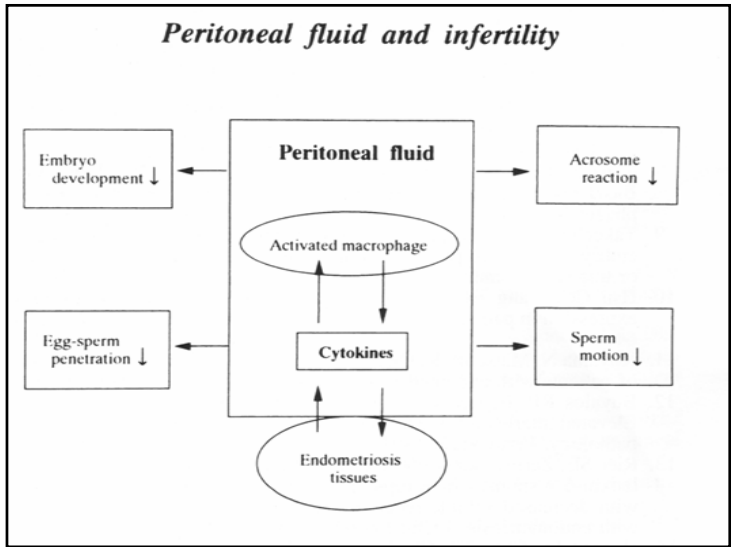
STAGE I (MINOR)	STAGE II (MODERATE)	STAGE III (SEVERE)
<p>PERITONEUM</p> <p>Superficial foci = 1-5 mm</p> <p>Deep foci = 0</p> <p>Adhesions = 0</p> <p>Endometriosis = 0</p>	<p>PERITONEUM</p> <p>Superficial foci = 5-10 mm</p> <p>Deep foci = 0</p> <p>Adhesions = 0</p> <p>Endometriosis = 0</p>	<p>PERITONEUM</p> <p>Superficial foci = 10-15 mm</p> <p>Deep foci = 0</p> <p>Adhesions = 0</p> <p>Endometriosis = 0</p>
<p>STAGE IV (SEVERE)</p> <p>PERITONEUM</p> <p>Superficial foci = 15-20 mm</p> <p>Deep foci = 0</p> <p>Adhesions = 0</p> <p>Endometriosis = 0</p>	<p>STAGE IV (SEVERE)</p> <p>PERITONEUM</p> <p>Superficial foci = 20-25 mm</p> <p>Deep foci = 0</p> <p>Adhesions = 0</p> <p>Endometriosis = 0</p>	<p>STAGE IV (SEVERE)</p> <p>PERITONEUM</p> <p>Superficial foci = 25-30 mm</p> <p>Deep foci = 0</p> <p>Adhesions = 0</p> <p>Endometriosis = 0</p>

ASRM Fertil Steril 1997

Peritoneal Fluid Macrophage Concentrations by Endometriosis Stage¹ (10³ cells/cc)



Hill et al. Fertil Steril 1988;50:216-22



Human Reproduction Vol.20, No.10 pp. 2698-2704, 2005
 Advance Access publication June 24, 2005
 doi: 10.1093/humrep/dei135

ESHRE guideline for the diagnosis and treatment of endometriosis

Stephen Kennedy^{1,10}, Agneta Bergqvist², Charles Chapron³, Thomas D'Hooghe⁴, Gerard Dunselman⁵, Robert Greb⁶, Lone Hummelshoj⁷, Andrew Prentice⁸ and Ertan Saridogan⁹ on behalf of the ESHRE Special Interest Group for Endometriosis and Endometrium Guideline Development Group*

Endometriosis is defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic inflammatory reaction

<http://humrep.oxfordjournals.org/cgi/reprint/20/10/2698>

CONCLUSIONS

ESHRE guidelines – recommendations for assisted reproduction in confirmed endometriosis-associated infertility

<u>Treatment type</u>	<u>Recommendation</u>	<u>Level of evidence</u>	<u>Strength of evidence</u>
IUI	Effective	1b	A
IVF	Effective (but lower than in tubal inf.)	2b (1a)	B (A)
Cystectomy (>4 cm)	Reduce risk of infection Improve access to follicles Improve ovarian response		GPP ?
Long GnRHa pre-treatment	Effective in mod./severe endo.	1b	A

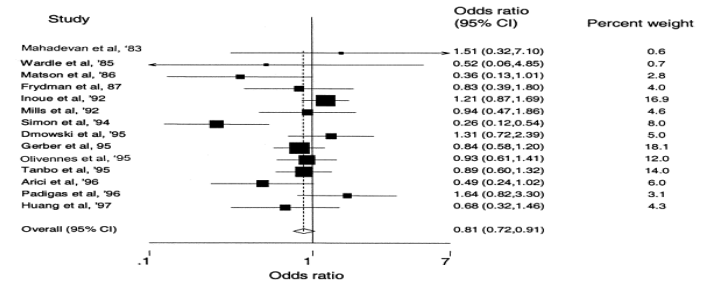
Hum Reprod 2005;20:2698-2704

Prediction of an ongoing pregnancy after intrauterine insemination

	No. cycles	No. ongoing pregnancies	OR	95% CI
Prim. subfertility			1	
Maternal age			0.97	0.96 – 0.99
Dur. of subfertility			0.98	0.94 – 1.00
Cervical factor	1578	140	1.32	1.08 – 1.61
Male factor	5292	322	0.86	0.75 – 0.99
One-sided tubal pathology	775	46	0.85	0.62 – 1.15
Uterine anomaly	156	4	0.37	0.13 – 0.97
Endometriosis	1261	64	0.71	0.54 – 0.92
Cycles 1-6	13885	938	0.92	0.88 – 0.96

Steures et al. Fertil Steril 2004;82:45-51

Odds of pregnancy with IVF in endometriosis patients vs. tubal factor controls.



ESHRE Guidelines
 B Evidence level 2b
 IVF is appropriate treatment especially if tubal function is compromised, if there is also male factor infertility, and/or other treatments have failed.
 A Evidence level 1a
 IVF pregnancy rates are lower in patients with endometriosis than in those with tubal infertility (Barnhart et al., 2002).

Barnhart. Fertil Steril 2002.

Cycle outcome stage I/II versus III/IV endometriosis

	Endo I/II	Endo III/IV	P
Peak E2 (pmol/l)	5813	1448	< 0.001
Mean no. oocytes	8.2	6.7	< 0.001
Fertilization rate	74.5	58.4	< 0.001
Implantation rate	11.3	10.2	< 0.01
Pregnancy rate	21.1	13.8	< 0.001

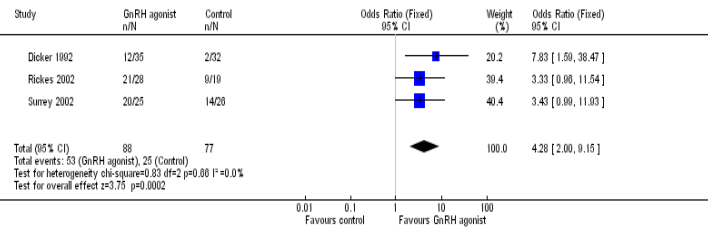
Barnhart. Fertil Steril 2002.

SART - National registry data 2007

Age (Years)	< 35	35 – 37	38 – 40	41 – 42
Endometriosis				
No. started cycles	2249	1161	676	188
Implantation rate (%)	32.2	24.2	17.7	7.1
Pregnancy rate per cycle (%)	46.7	38.9	32.1	17.6
Live birth rate per cycle (%)	41.0	32.2	24.4	10.6
Tubal infertility				
No. started cycles	3608	2224	1658	555
Implantation rate (%)	31.6	24.8	15.9	9.2
Pregnancy rate per cycle (%)	44.7	39.9	29.6	19.8
Live birth rate per cycle (%)	38.7	32.5	21.4	13.0

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

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

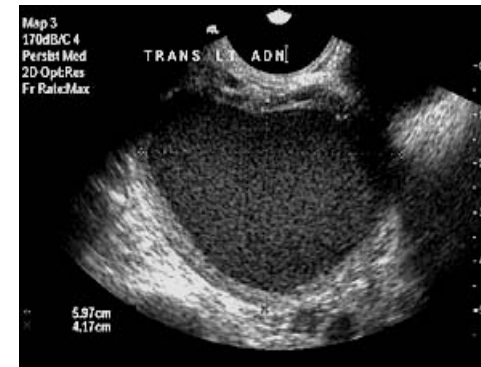


ESHRE Guidelines

A Evidence level 1b
 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 (Rickes et al., 2002; Surrey et al., 2002).

Sallam HN et al. *Cochrane Database of Systematic Reviews* 2006

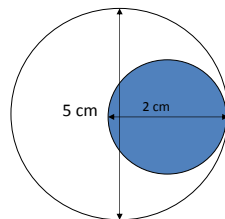
Vaginal ultralyd av et endometriom



To what extent does extirpation of an endometrioma affect the follicle cohort?

Surface of a sphere = $4\pi r^2$

AMH = an indicator of all growing follicles

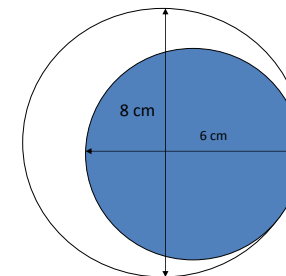


Total surface of the ovary = $4\pi(2.5)^2 + 4\pi(1)^2 = 78.5 + 12.6 = 91.1 \text{ cm}^2$ of which the endometrioma surface accounts for 13.1%

To what extent does extirpation of an endometrioma affect the follicle cohort?

Surface of a sphere = $4\pi r^2$

AMH = an indicator of all growing follicles



Total surface of the ovary = $4\pi(4)^2 + 4\pi(3)^2 = 291 + 113 = 404 \text{ cm}^2$ of which the endometrioma surface accounts for 28 %

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

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^aDepartment of Obstetrics and Gynecology, Royal Lancaster Infirmary, Lancaster, United Kingdom; ^bDepartment of Obstetrics and Gynecology, Lancashire Teaching Hospitals, Preston, United Kingdom; and ^cDepartment of Reproductive Medicine, St. Mary's Hospital, Central Manchester and Manchester Children's University Hospitals, Manchester, United Kingdom

Objective: To investigate the effect of surgical treatment of endometrioma on pregnancy rate and ovarian response to gonadotrophin stimulation in women undergoing IVF.

Design: A systematic review and meta-analysis.

Setting: Tertiary referral center for reproductive medicine.

Patient(s): Subfertile women with endometrioma undergoing IVF.

Intervention(s): Surgical removal of endometrioma or expectant management.

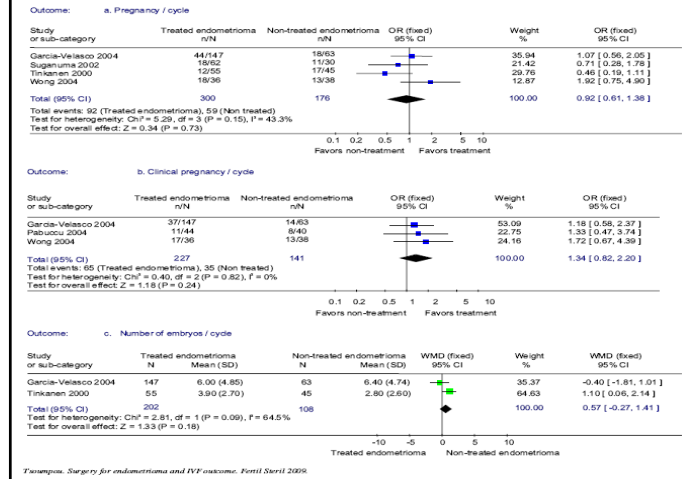
Main Outcome Measure(s): Clinical pregnancy rate and ovarian response to gonadotrophins (number of gonadotrophin ampoules, peak E₂ levels, number of oocytes retrieved, and number of embryos available for transfer).

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.

Conclusion(s): Collectively the available data in the literature show that surgical management of endometriomas has no significant effect on IVF pregnancy rates and ovarian response to stimulation compared with no treatment. Randomized controlled trials are needed before producing best-practice recommendations on this topic. (Fertil Steril® 2009;92:75–87. ©2009 by American Society for Reproductive Medicine.)

Key Words: Endometrioma, surgery, IVF, ovarian response, pregnancy outcome

(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.



AOGS 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

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¹Department of Science for the Woman and Child's Health, University of Florence, Florence, ²Department of Medical

Pathophysiology, Sapienza University of Rome, Rome, ³Unit of Physiopathology of Reproduction, Cattolica General Hospital

and University of Bologna, Bologna, and ⁴Department of Obstetrics, Gynecology and Reproductive Sciences, Second University of Naples, Naples, Italy

Characteristics of patients

	Number of patients	Number of cycles	Age (years; mean±SD)	Primary infertility		Duration of infertility
				n	(Percentage)	(years; mean±SD)
Endometriosis						
All stages	148	164	31.3±2.9	131	(88.5)	3.9±2.6
Stage I–II	54	55	31.8±3.3	45	(83.3)	4.8±2.7
Stage III–IV	94	109	31±2.5	86	(91.5)	3.3±2.4
Tubal factor	72	80	30.7±3.1	27	(37.5)	3.5±2.8

Note: Primary infertility in endometriosis (all stages, I–II and III–IV) vs. tubal factor: p=0.0001.

Comparison of semen characteristics between the endometriosis group and the control group

Semen characteristics	Partners of women with endometriosis	Partners of women with tubal factor	p-Value
Ejaculate volume (ml)	3.7±2.2	3.6±1.7	NS
pH	7.7±0.4	7.5±0.3	NS
Sperm count (10 ⁶ /ml)	97.4±71.3	92.1±66.5	NS
Total sperm count (10 ⁸ per ejaculate)	143.7±47.7	212±67.3	NS
Motility a (%)*	43.5±27.7	37.8±13.3	NS
Motility b (%)*	12.7±7.5	18.1±3.4	NS
Morphologically normal spermatozoa (%)	42.4±24.3	43.3±20.8	NS

*Sperm motility is graded according to World Health Organization guidelines (WHO, 1999) (a): rapidly progressive (>25 µm s⁻¹) (grade 'a'), slowly progressive (5–25 µm s⁻¹) (grade 'b').

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

	Endometriosis	Tubal factor	p-Value
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
Number of oocytes retrieved	7.8±5.4	10.8±6.1	0.001*
Fertilization rate (%)	65.3	71.9	0.101
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 started cycle	(19 of 164) 11.6%	(18 of 80) 22.5%	0.041*
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.

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	p-Value for endometriosis vs. stage III-IV	p-Value for endometriosis vs. stage I-II
Total FSH/hMG (IU)	3 952±1 923.6	4 072±1 754.4	3 301.9±1 421.7	0.45	0.02*	0.05
Cycle cancellation rate	2 of 53 (3.8%)	5 of 116 (4.3%)	3 of 80 (3.7%)	0.68	0.02*	0.55
Number of oocytes retrieved	10±5.5	13.5	10.8±6.1	0.24	0.02*	0.01
Fertilization rate (%)	65	76.5	71.9	0.001*	0.05	0.02*
Mean number of transferred embryos	2±1.5	2.2±1.5	2.3±1.6	0.09	0.02*	0.45
Total number of pregnancies (β-hCG+)	9±5.4	10±5.4	22 of 72	0.71	0.02*	0.02*
Implantation rate (%)	9.1	8.5	10.8	0.45	0.05	0.01*
Clinical pregnancy rate per started cycle	(7 of 53) 13.2%	(8 of 116) 6.9%	(18 of 80) 22.5%	0.05	0.02*	0.02*
Clinical pregnancy rate per embryo transfer	(7 of 44) 15.9%	(8 of 67) 11.9%	(18 of 69) 26.1%	0.02	0.02*	0.04*

Abbreviations: hMG, human menopausal gonadotropin; FSH, follicle-stimulating hormone; β-hCG, β-subunit of human chorionic gonadotropin; β-hCG+ when >5IU/L. *P < 0.05.

IVF in endometriosis versus tubal infertility Rikshospitalet 1996 – 2011 Demographics

	ASRM I - II	ASRM III - IV	Tubal factor
No. couples	724	350	1171
Mean age (years)	33.0 ± 3.3	32.9 ± 3.6	33.2 ± 3.6**
BMI (kg/m ²)	22.8 ± 3.5	22.9 ± 3.5	23.6 ± 3.9***
Gravida 0	70.3 %	70.0%	42.4%***
Duration of infertility (years)	3.7 ± 2.8	3.9 ± 3.0	4.0 ± 3.3**
Treatment period			
1996 - 1999	21.2%	32.9%	35.5%***
2000 - 2005	32.5%	36.2%	36.7%*
2006 - 2011	46.2%	30.9%	27.9%***

*P<0.05,**P< 0.01,***P<0.001

1. cycle

Type of treatment	ASRM I – II (n=724)	ASRM III – IV (n=350)	Tubal factor (n=1171)
IVF	671 (92.7%)	332 (94.9%)	1119 (95.6%)
ICSI	53 (7.3%)	18 (5.1%)	52 (4.4%)*
Dose of FSH	1965 ± 930	2313 ± 1024**	2081 ± 1046
Cancellation rate	1.2%	2.3%	1.2%
No. oocytes	9.3 ± 5.2	8.0 ± 5.3**	9.2 ± 5.6
Mature	90.3%	91.3%	90.4%
sperm conc.	117 ± 89**	123 ± 77	135 ± 90
sperm motility	54 ± 20**	57 ± 19	59 ± 20
Fertilization rate IVF	59.6%**	62.9%	63.5%
Implantation rate	27.8%	25.0%	24.9%
Pregnancy rate/started cycle	36.0%	32.9%	34.7%
Pregnancy rate/embryo transfer	39.4%	36.7%	37.9%
Biochemical pregnancy(<6)	9.6%	8.7%	14.5%
Miscarriage (6-12)	18.8%	17.4%	12.6
Birth	71.6%	73.9%	72.9%
Birth/started cycle	25.8%	24.3%	25.3%

* P < 0.05, ** P < 0.01

Logistic regression

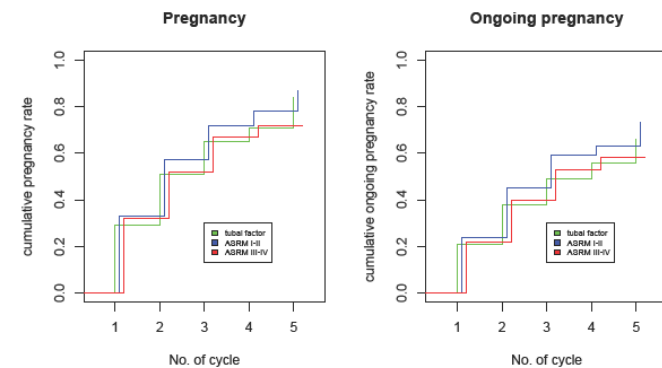
In order to account for the effect on treatment outcomes of baseline differences in age, BMI, previously having been pregnant or not, treatment year and duration of infertility among patients with endometriosis (ASRM I – IV) and tubal infertility in the first treatment cycle, multiple logistic regression analysis was performed. **The presence of endometriosis was not significantly associated with becoming pregnant (OR=1.00, 95% CI 0.87 – 1.16) or having an ongoing pregnancy or birth (OR= 0.97, 95% CI 0.82 – 1.13).** Treatment during the later years of the observation period had a slight, positive impact on having an ongoing pregnancy or birth, (OR=1.03, 95% CI 1.01-1.06).

Stage III – IV endometriosis

	Peritoneal	Endometrioma
No. couples	164	186
Total no. attempts	347	418
Total no pregnancies	118	108
No. ongoing/births	90	75
No. miscarriages < 6 weeks	17	22
No. miscarriages 6 - 12 weeks	9	10
No. Ectopic pregnancies	2	1
Ong/birth rate per couple	54.9%	40.3%*

* P < 0.01

Cumulative pregnancy rate after laparoscopy



Conclusion

In endometriosis, IVF is a highly successful treatment alternative

at least in Rikshospitalet

