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Tempistiche per trattamento dell'endometriosi e adenomiosi nelle pazienti della PMA

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Disclosure

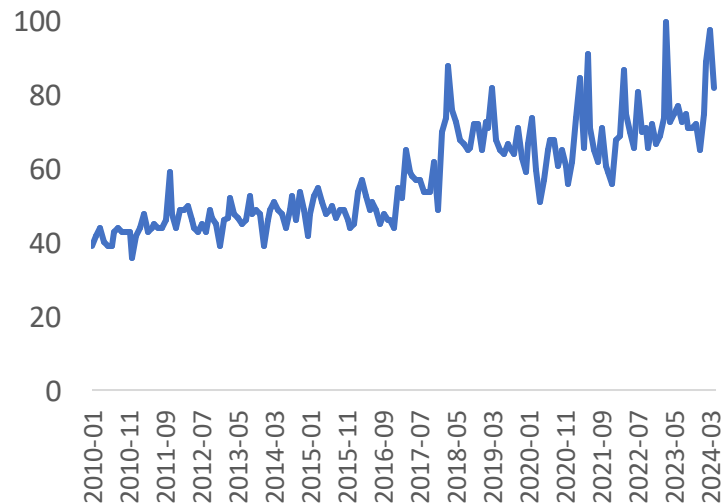
Name of entity	Grant	Personal fees	Non-financial support	Other	Comments
Merck	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Unrestricted research grant and honoraria
Gedeon	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Unrestricted research grant and honoraria
Ferring	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Unrestricted research grant and honoraria
Besins	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Honoraira
Ipsen	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Honoraira
Theramex	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Unrestricted research grant and honoraria

Endometriosis

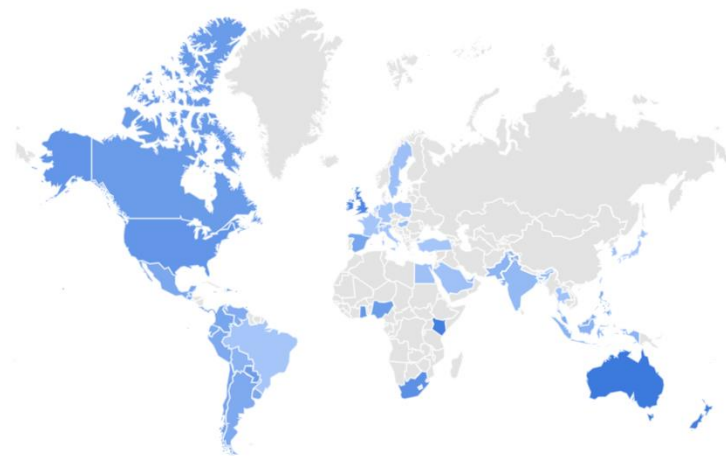
Google trends Worldwide: An important social issue



Interest over time

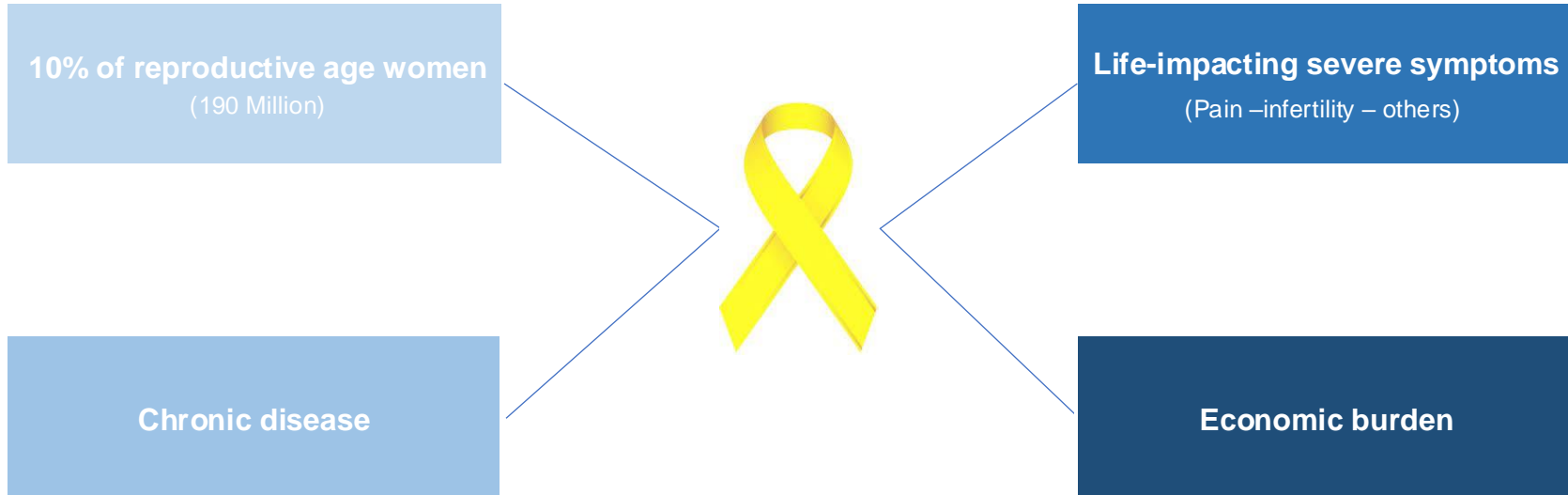


Interest by region



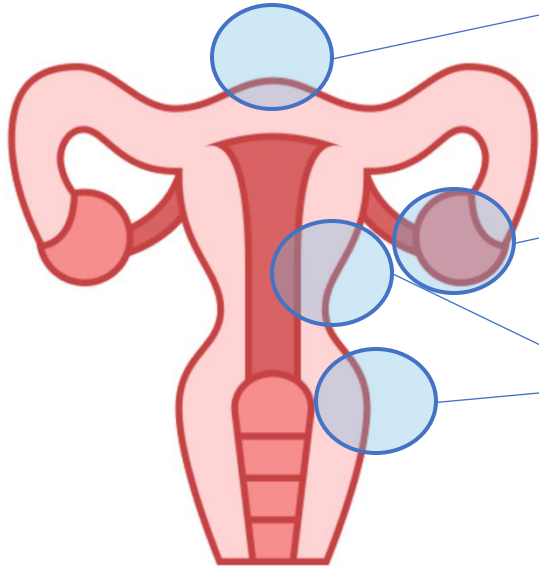
Endometriosis

A major public health concern



Endometriosis

Heterogeneity of phenotypes



SUP
(Superficial)



OMA
(Endometrioma)



DIE
(Deep endometriosis)

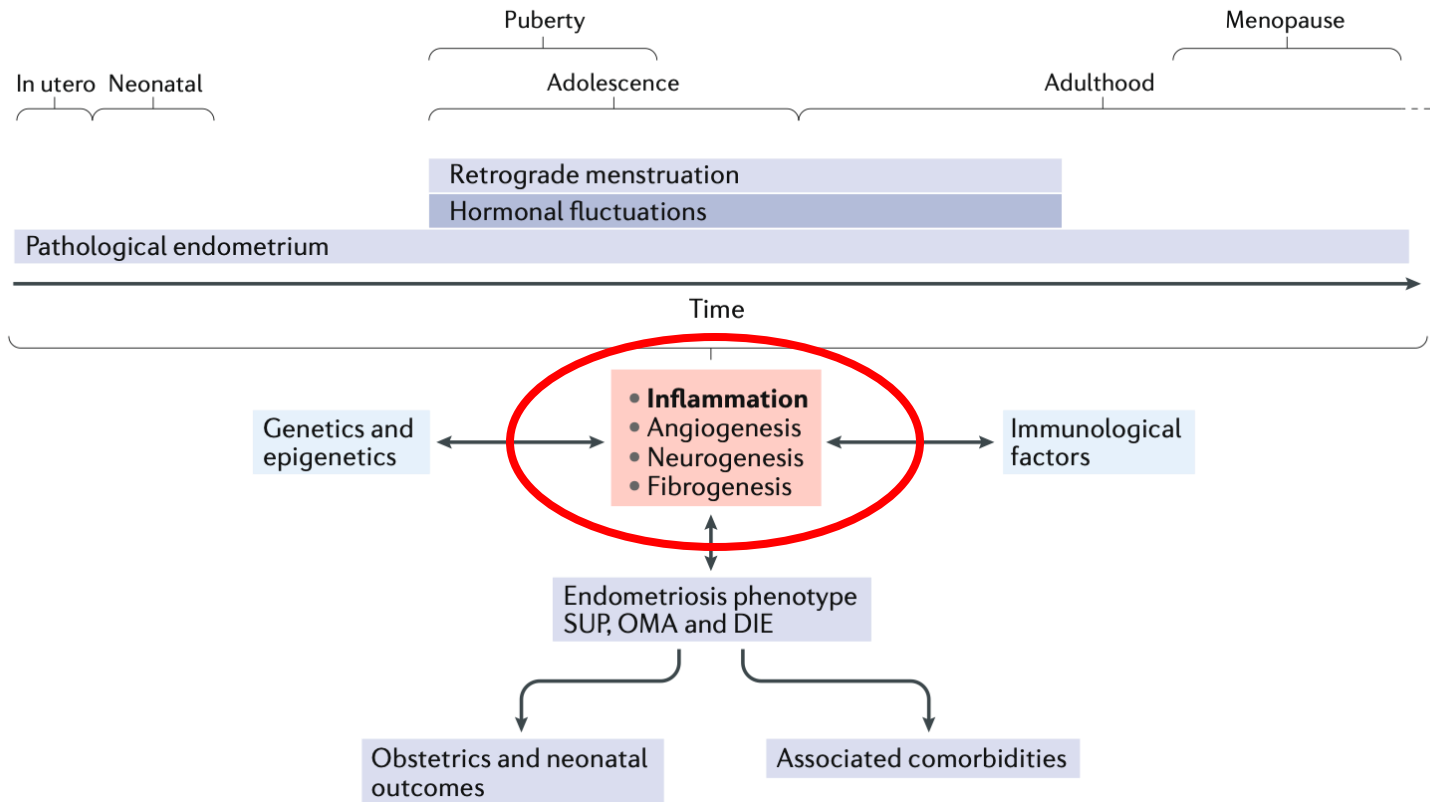


ADOSIS
(Adenomyosis)



« Endometriosis Life »

A lifelong disease

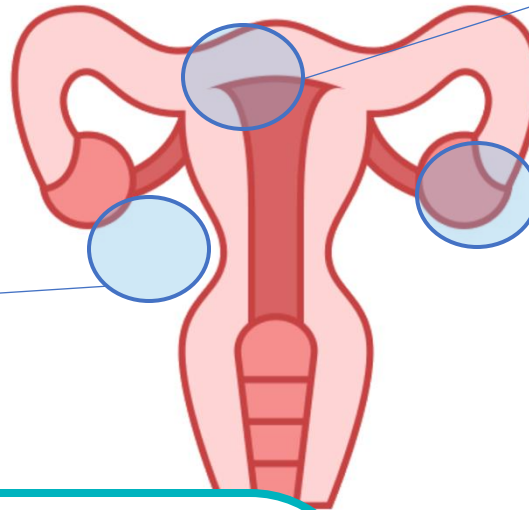


Endometriosis and infertility

Mechanisms

Uterus:

- Increased synthesis of prostaglandin & altered receptivity
- Production of estrogens *in situ* and resistance to progestogen



Pelvic cavity:

- Proliferation of macrophages
- Phagocytic dysfunction
- Release of proinflammatory factors

Ovaries:

- Decreased ovarian response
- Altered oocyte quality?
- Iron overload (proinflammatory factors)

105 (43.2%) spontaneous pregnancy
76 (41.5%) with DIE

Leone Roberti Maggiore *et al.*, Hum Reprod (2014)

Fertility and endometriosis



Implantation



Therapeutics options



Risks



Conclusion

Fertility and endometriosis



Implantation



Therapeutics options



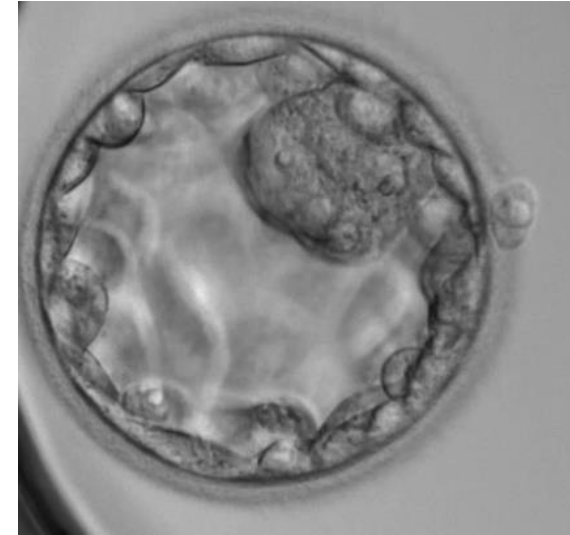
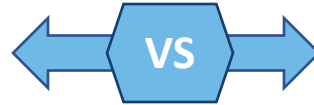
Risks



Conclusion

Endometriosis and infertility

Implantation



OMA ?
DIE ?
Adenomyosis ?
Previous surgery ?

**Endometriosis related
altered ovarian function ?**



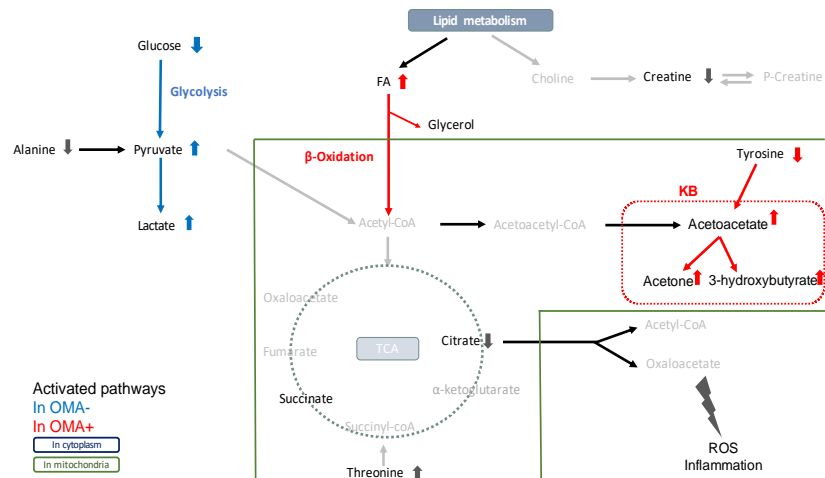
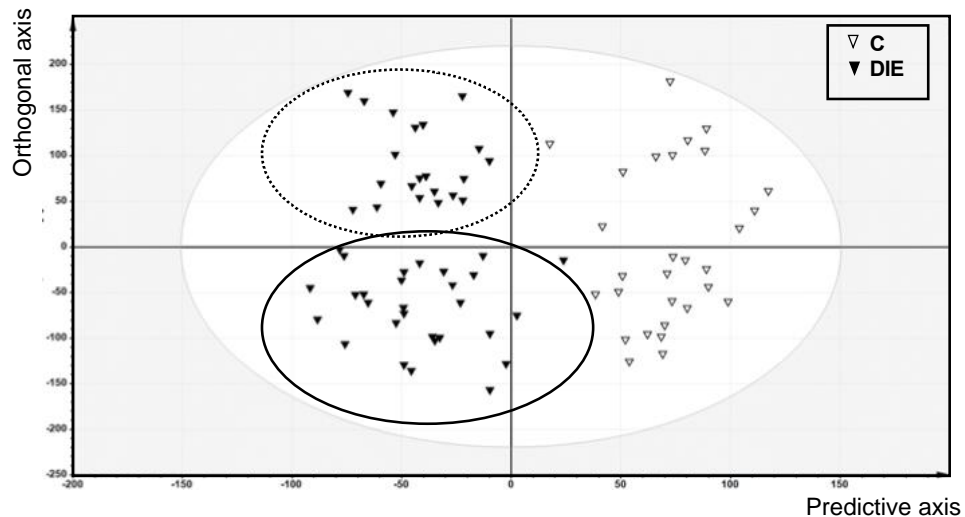
QUANTITY



QUALITY



RMN Follicular Fluid Metabolomics

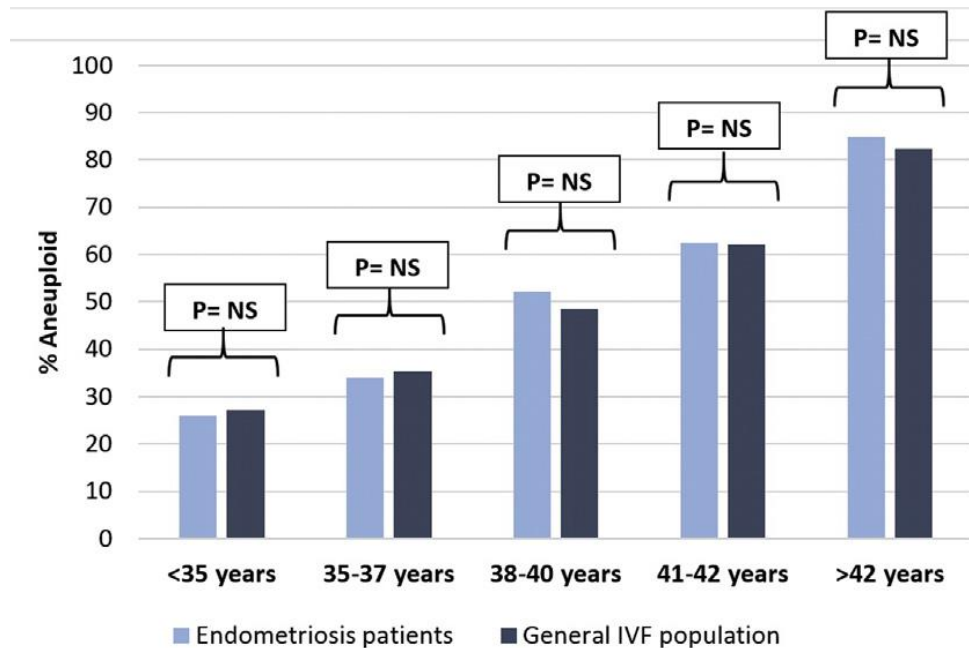




Endometriosis and ovarian reserve

Quality : OSIS and Aneuploid

ART results according to Aneuploid: a PGS study



Endometriosis: 1880 blastocysts from 305 patients

Controls: 23054 blastocysts from 3798



Endometriosis and ovarian reserve

Quality : OSIS and ART outcomes

Table II Live birth rate in women with endometriosis following donor oocyte recipient versus autologous ART cycles.

	Donor oocyte recipient cycle	Autologous ART cycle	Unadjusted OR (99.5% CI)	Adjusted OR (99.5% CI)*
Fresh and frozen LBR per cycle	212/758 (28.0%)	3830/12 856 (29.8%)	0.92 (0.72, 1.16)	1.0 (0.78, 1.28)
Fresh ART	167/528 (31.6%)	3295/10 628 (31.0%)	1.03 (0.79, 1.35)	1.05 (0.79, 1.41)
Frozen ART	45/230 (19.6%)	535/2228 (24.0%)	0.77 (0.47, 1.25)	0.85 (0.51, 1.41)

*Adjustment for confounders (number of previous IVF cycles, previous live birth, year of treatment, day of embryo transfer, number of embryo transferred, fresh and frozen cycle for combined fresh/frozen).

LBR, live birth rate; OR, odds ratio.

Little/No effect on oocyte quality !!

UK: Human Fertilization and Embryology Authority (HFEA)

From 1996 to 2016

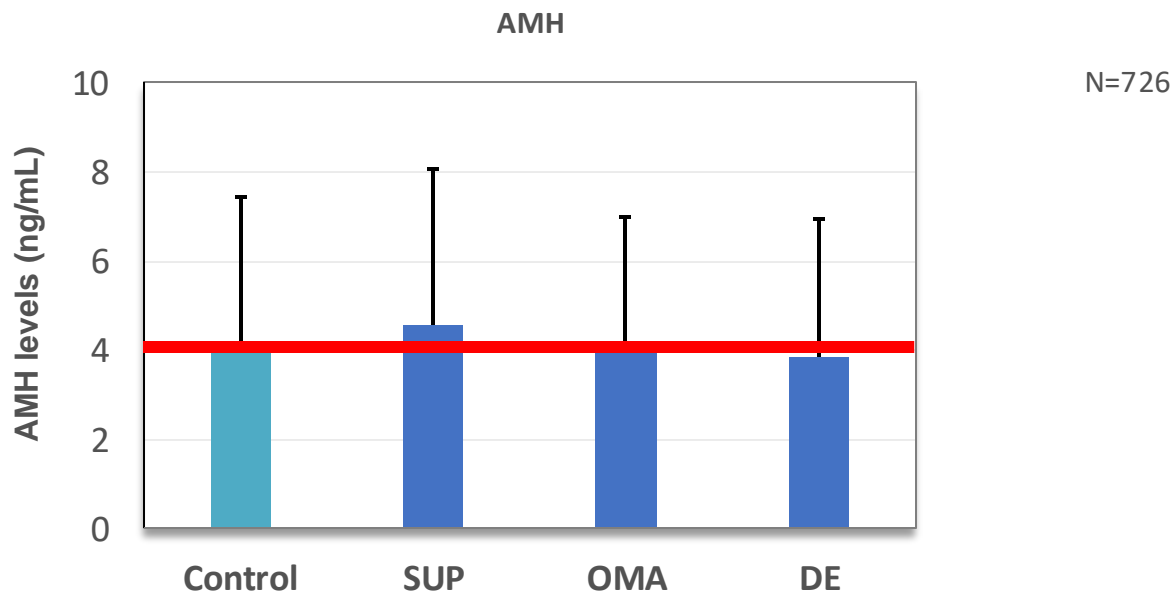
758 donor oocyte recipients, where the recipients with endometriosis

12 856 autologous IVF cycles with endometriosis as the sole cause of infertility



Endometriosis and ovarian reserve

Quantity

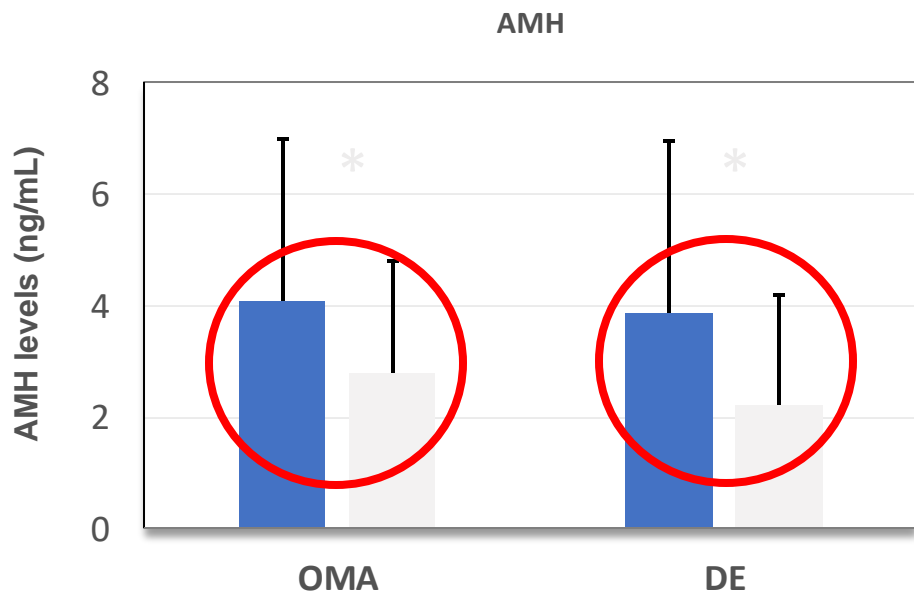


AMH, anti-Müllerian hormone; DE, deep endometriosis; OMA, ovarian endometrioma; SUP, superficial peritoneal endometriosis



Endometriosis and ovarian reserve

Quantity



N=726

- No prior OMA...
- Prior OMA...

Previous OMA surgery
OR= 3.0 (1.40-6.41); p=0.01

AMH, anti-Müllerian hormone; DE, deep endometriosis; OMA, ovarian endometrioma; SUP, superficial peritoneal endometriosis



Endometriosis and ovarian reserve

Quantity: ovarian response to stimulation

Logistic regression analysis of the risk factors for poor response to hyperstimulation (≤ 3 oocytes retrieved or cycle cancelled)

OMA status	Univariate logistic regression analysis			Multiple logistic regression analysis ^a		
	OR	95% CI	P-value	OR	95% CI	P-value
Presence of OMA and no previous surgery for OMA versus no OMA	1.3	0.8–2.0	0.211	1.5	0.9–2.2	0.147
Presence of OMA with previous history of surgery for OMA versus no OMA	2.4	1.3–4.6	0.004	2.1	1.1–4.0	0.033

^aVariables included in multiple logistic regression analysis: age, AMH, dose of gonadotrophin
AMH, anti-Müllerian hormone; CI, confidence interval; OMA, endometrioma; OR, odds ratio

Endometriosis and infertility: ART

ART results according to phenotype

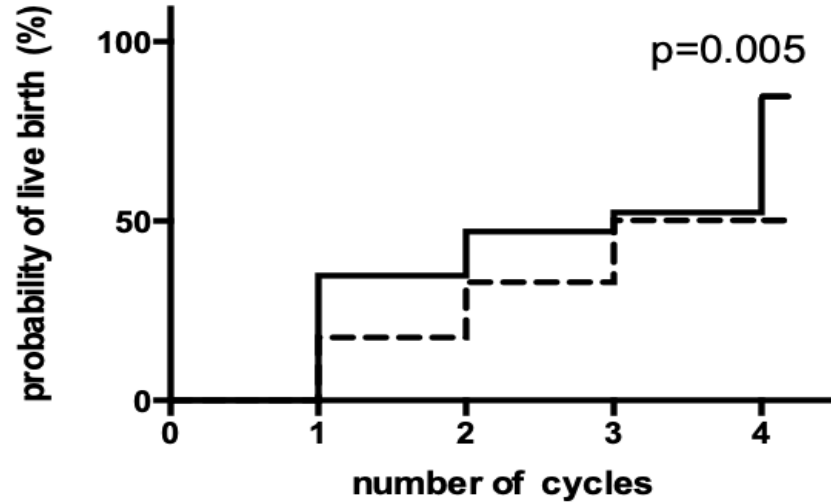
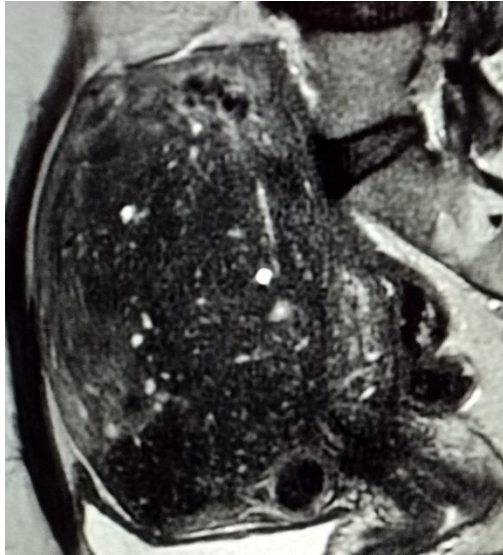
*N=359 endometriosis infertile women
(720 cycles - 500 transfers)*



	DIE	OMA	SUP	P value
Patients	212	98	49	
No. of cycles	425	200	95	
No. of ET	282/425 (66.4)	141/200 (70.5)	77/95 (81.1)	0.018
Clinical pregnancy rate per cycle	98/425 (23.1)	55/200 (27.5)	29/95 (30.5)	0.22
Clinical pregnancy rate per ET	98/282 (34.8)	55/141 (39)	29/77 (37.7)	0.67
Implantation rate	111/513 (21.6)	62/265 (23.4)	35/140 (25.0)	0.66
Abortion rate	30/98 (30.6)	22/55 (40.0)	16/29 (55.2)	0.049

Adenomyosis and infertility :

ART



- Adenomyosis	17,6	33,7	50,7	50,7
- No adenomyosis	31,8	46,8	55,7	85,2

202 patients with endometriosis
IVF
Adenomyosis vs no adenomyosis

Endometriosis and implantation

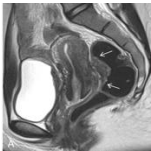
Main messages



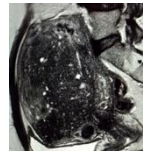
No major impact on the quality of the ovarian reserve



Altered quantity of the ovarian reserve (surgery +++)



No major impact of endometriosis phenotype on ART outcomes



Adenomyosis decreases the chances of LBR

Fertility and endometriosis



Implantation



Therapeutics options



Risks



Conclusion

Endometriosis and fertility

Therapeutic options

Surgery



Hormones



ART



ART, assisted reproductive technology

Endometriosis

Endometriosis natural history

REVIEWS

NATURE REVIEWS | ENDOCRINOLOGY

Rethinking mechanisms, diagnosis
and management of endometriosis

Endometriosis
diagnosis

Immediate
first surgery

Post-operative
medical treatment

Repetitive
surgeries

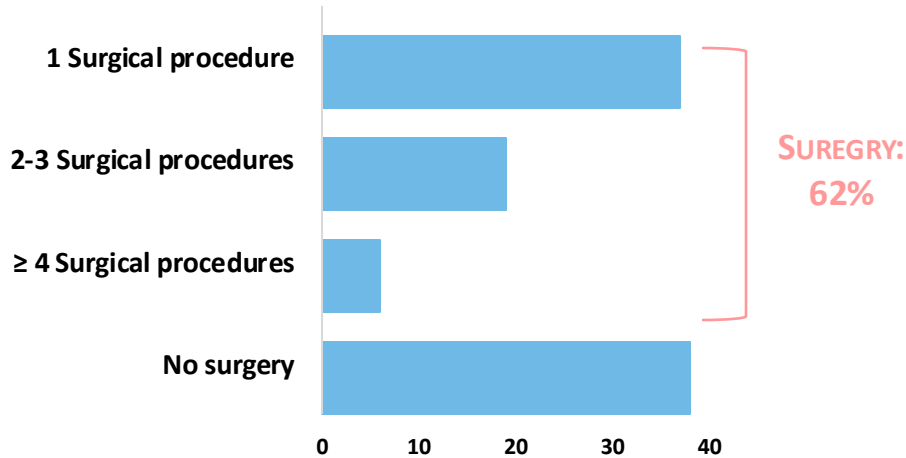
ART

Endometriosis

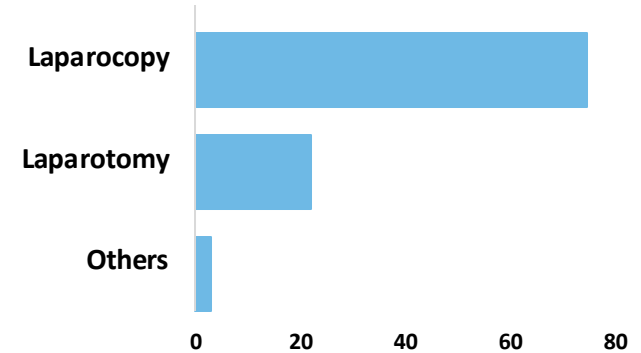
Surgical procedures



PATIENTES
N = 1 557



PATIENTES
AMONG SURGERY
N = 957



Endometriosis and infertility: surgery

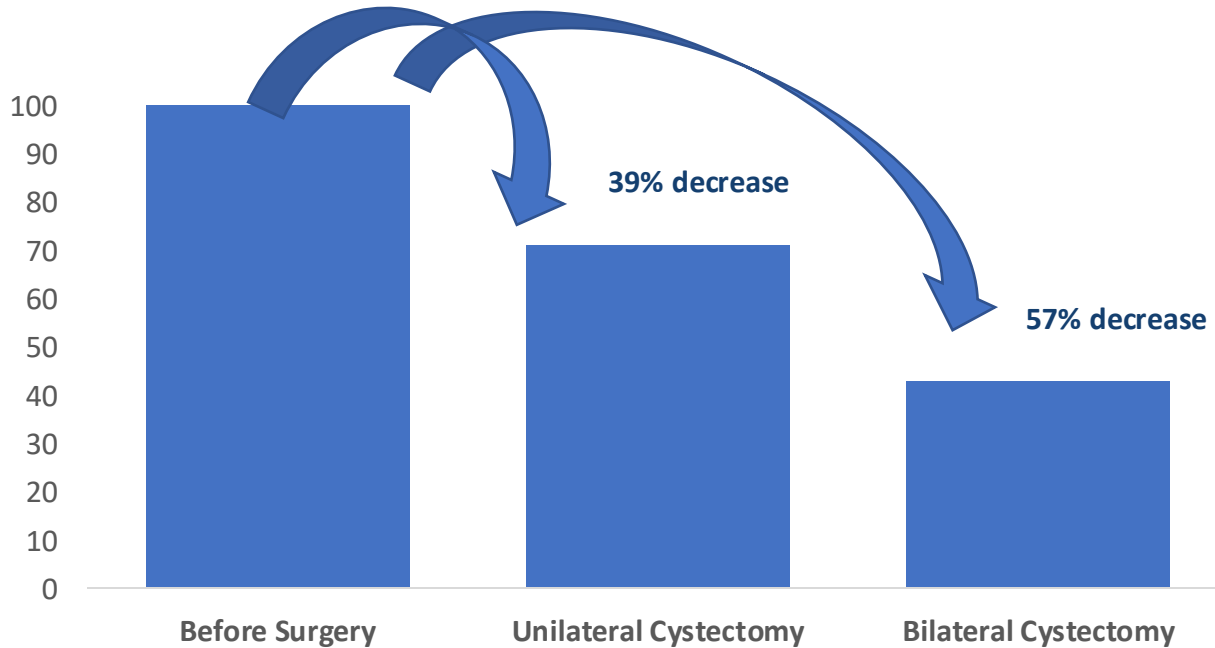
Complications

Complication	Observed incidence (%)
Neurogenic bladder dysfunction	4–10
Rectovaginal fistula formation	2–10
Blood transfusion	2–6
Inadvertent rectal perforation	1–3
Anastomotic leakage	1–2
Pelvic abscess	1–2
Temporary diverting loop ileostomy/ colostomy	0.5–1.5
Intraoperative ureteral lesion	0.5–1
Post-operative ureteral fistula formation	0.5–1
Post-anastomotic rectal stenosis	0.5–1
Post-anastomotic ureteral stenosis	0.5–1

Endometriosis and infertility: surgery

Endometrioma and ovarian reserve

12 months post Operative AMH decrease

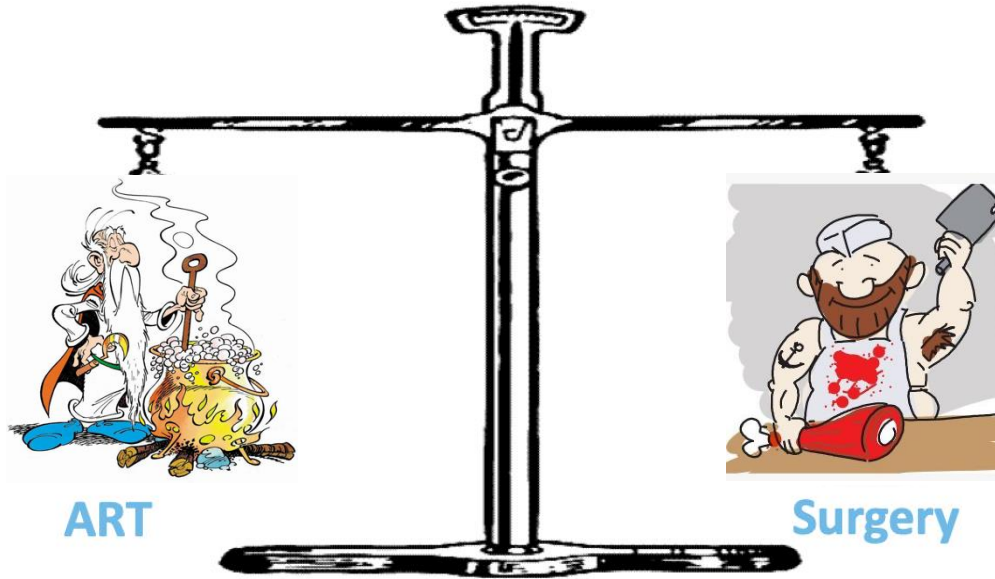


Metaanalysis
12 studies

Endometriosis and infertility

Therapeutic options

Pregnancies rates



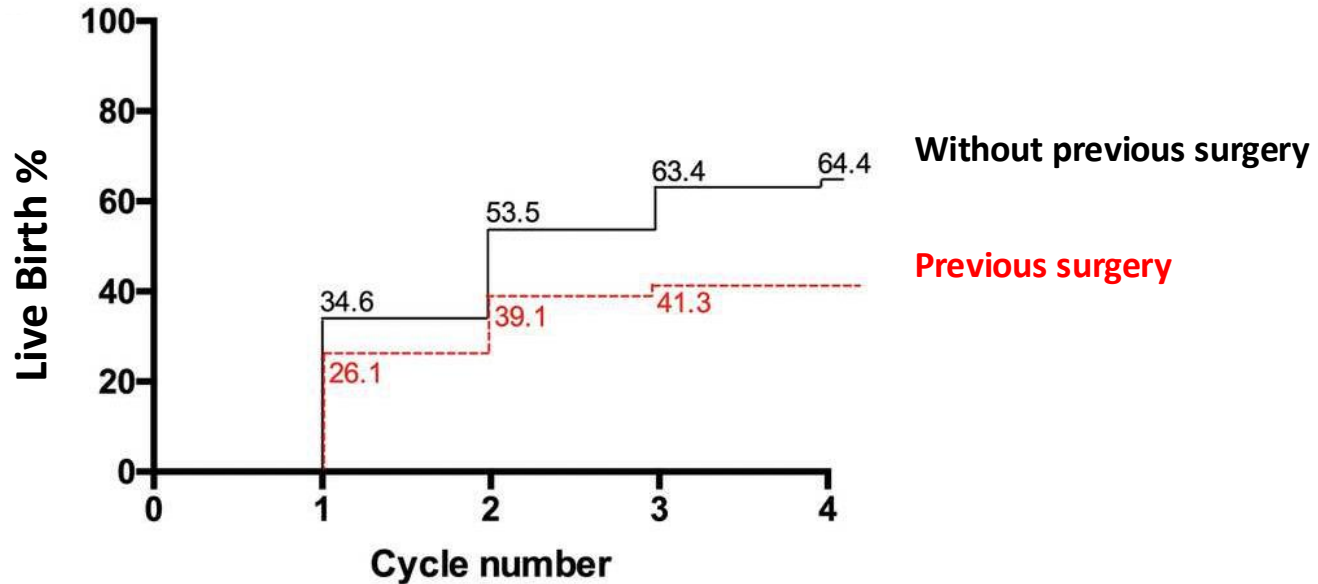
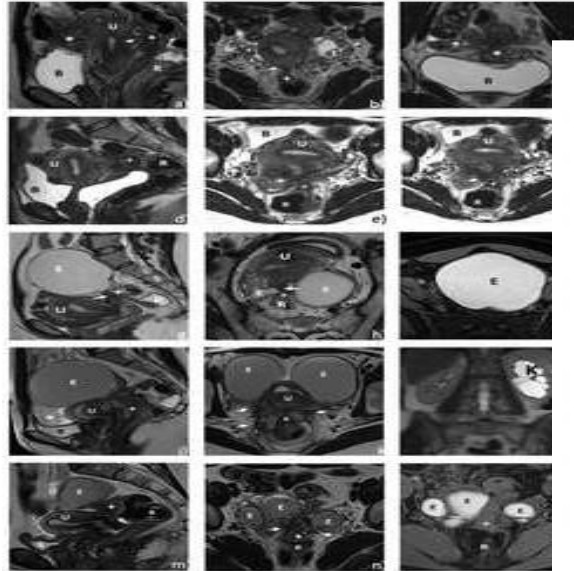
Endometriosis and infertility: ART

Previous history of surgery (OMA)

	Endometrioma removed (147 cycles)	Endometrioma present (63 cycles)	<i>P</i> 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

Endometriosis and infertility: ART

Previous history of surgery – Bowel DIE



*N=101 Bowel DIE infertile women
(88% Associated Adenomyosis)
(73 % Associated OMA)*

Endometriosis and infertility: ART

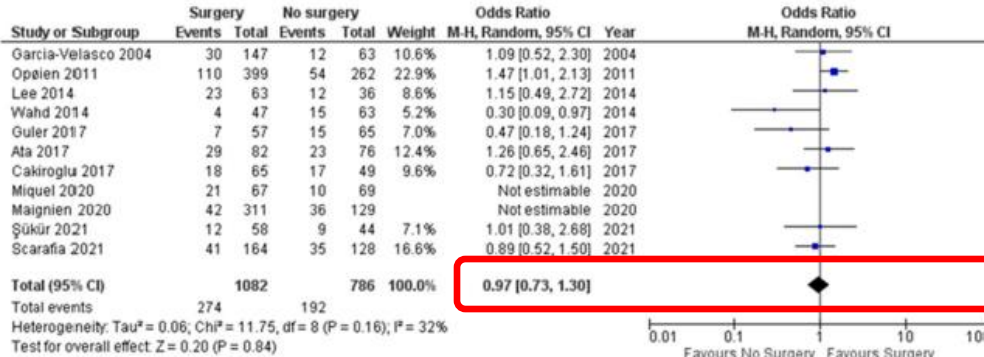
Surgery before ART results according to a metaanalysis

Reproductive Sciences
<https://doi.org/10.1007/s43032-023-01421-7>

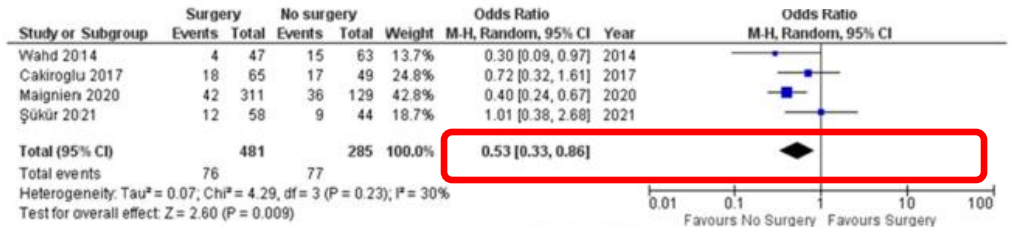
INFERTILITY: REVIEW



Impact of Endometriosis Surgery on In Vitro Fertilization/ Intracytoplasmic Sperm Injection Outcomes: a Systematic Review



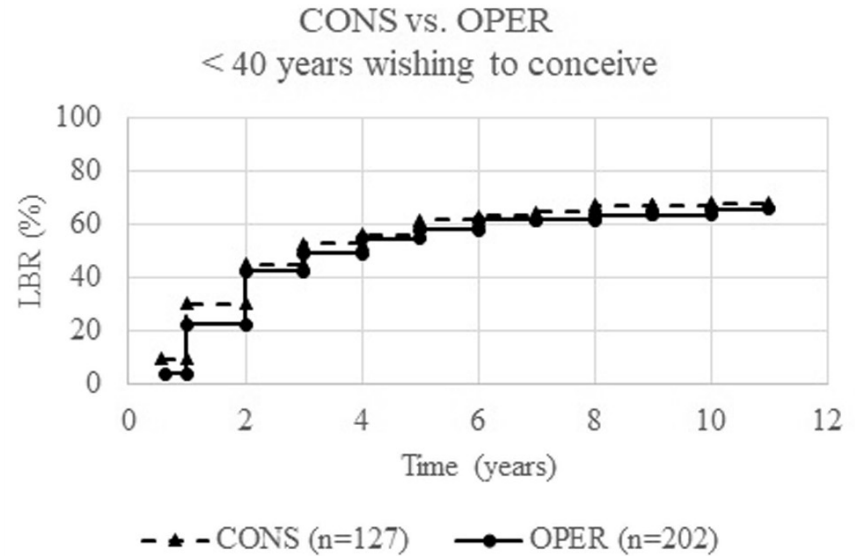
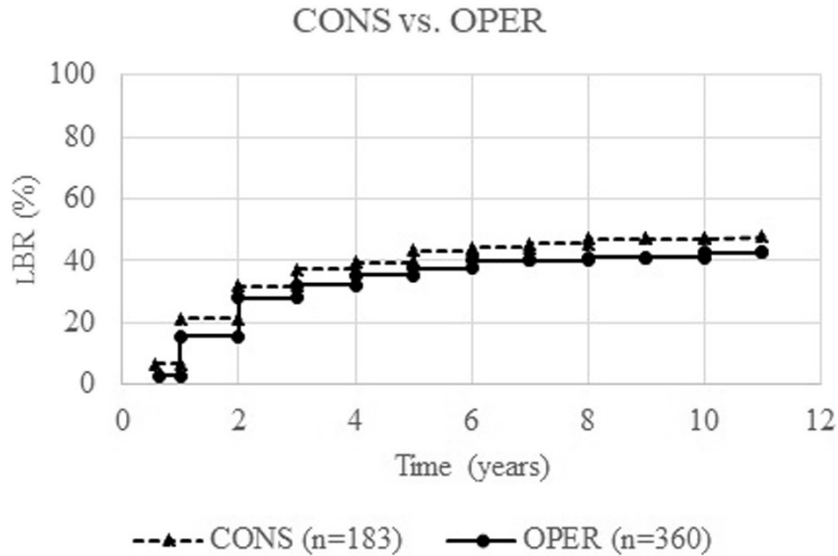
Exclusion of studies with high risk of bias



No surgery Surgery

Endometriosis and infertility

Conservative versus surgical management in DIE



	CONS N=183	OPER N=360	OR (95% CI)
CPR Total	102/183 (55.7%)	181/360 (50.3%)	1.25 (0.87-1.78)

Restrospective - Finland
Rectovaginal endometriosis
Survey vs conservative

Endometriosis and infertility

Surgery in DIE : Bias in pregnancy rates

Outcomes of pregnancy and the first delivery of the women with rectovaginal endometriosis treated either conservatively or operatively.

Outcome	CONS (n = 183)		OPER (n = 360)		OR (95% CI)
	n	%	N	%	
MAR during follow-up	89/183	48.6	149/360	41.4	1.34 (0.94–1.92)
CPR					
Total	102/183	55.7	181/360	50.3	1.25 (0.87–1.78)
Spontaneous	37/102	36.3	92/181	50.8	0.55 (0.34–0.91)
LBR ^a					
Total	87/183	47.5	153/360	42.5	1.23 (0.86–1.75)
Spontaneous	34/87	39.1	82/153	53.6	0.56 (0.33–0.95)
Time to delivery (y), median (IQR)	2.2 (2.3)		2.4 (2.3)		−0.11 (−0.29 to 0.06)
Follow-up time (y), mean ± SD	4.9 ± 3.3		5.6 ± 3.6		−0.74 (−1.36 to −0.11)
LBR (Spontaneous)	34/183 (19%)		82/360 (23%)		Surgery : + 4%
LBR (ART)	53/183 (29%)		71/360 (20%)		Surgery : - 9%

*Restrospective - Finland
Rectovaginal endometriosis
Survery vs conservative*

Endometriosis and infertility: surgery

EFI



LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score	Description		Left	Right
4	= Normal	Fallopian Tube	<input type="text"/>	<input type="text"/>
3	= Mild Dysfunction	Fimbria	<input type="text"/>	<input type="text"/>
2	= Moderate Dysfunction	Ovary	<input type="text"/>	<input type="text"/>
1	= Severe Dysfunction			
0	= Absent or Nonfunctional			
To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the			Lowest Score	<input type="text"/> + <input type="text"/> = <input type="text"/>

80% of the score is endometriosis independent

ENDOMETRIOSIS FERTILITY INDEX (EFI)

Adenomyosis ?

Ovarian Reserve ?

Complete surgery ?

Total Historical Factors	<input type="text"/>	Total Surgical Factors	<input type="text"/>
EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS:		<input type="text"/> + <input type="text"/>	= <input type="text"/>
		Historical	Surgical
			EFI Score

Adamson. Endometriosis fertility index. Fertil Steril 2010.

Endometriosis and fertility

Therapeutic options

Surgery



Hormones



ART



ART, assisted reproductive technology

Endometriosis and hormonal treatments

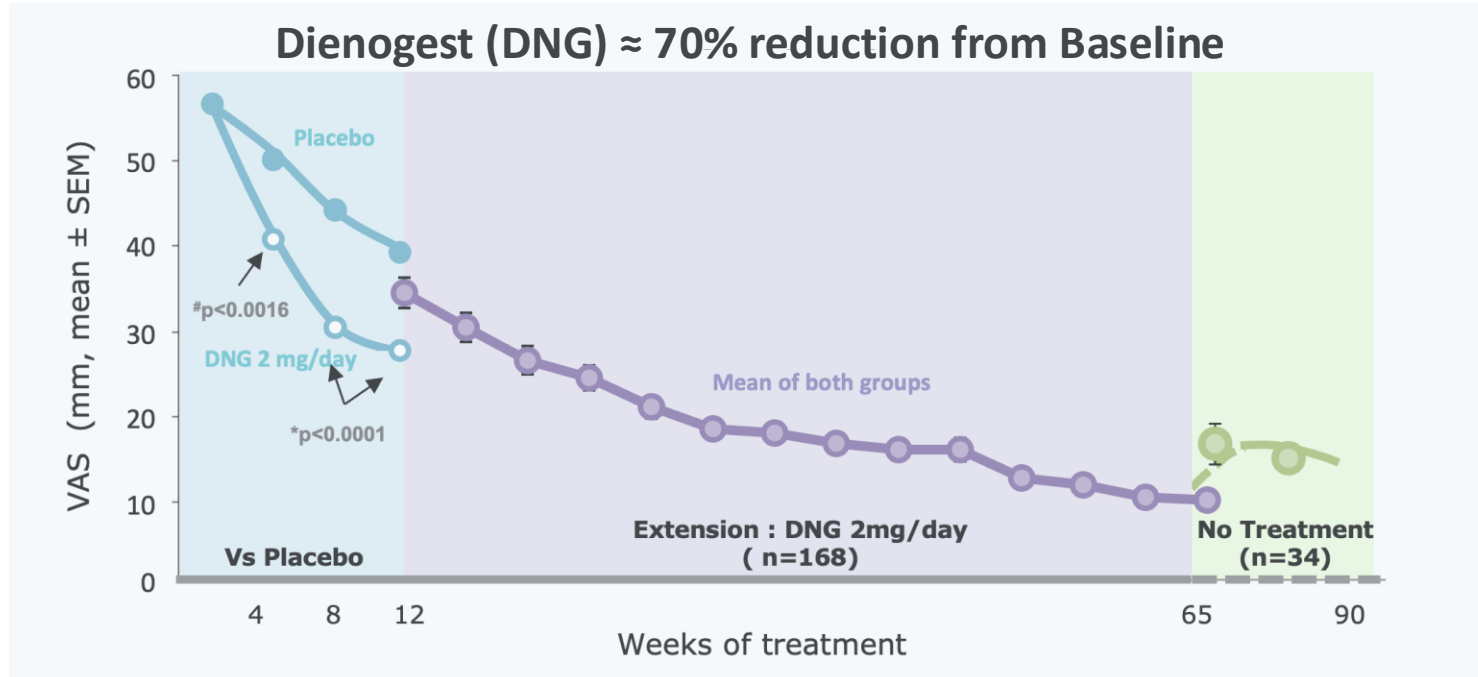
Limitations



All options are contraceptive

Endometriosis and hormonal treatments

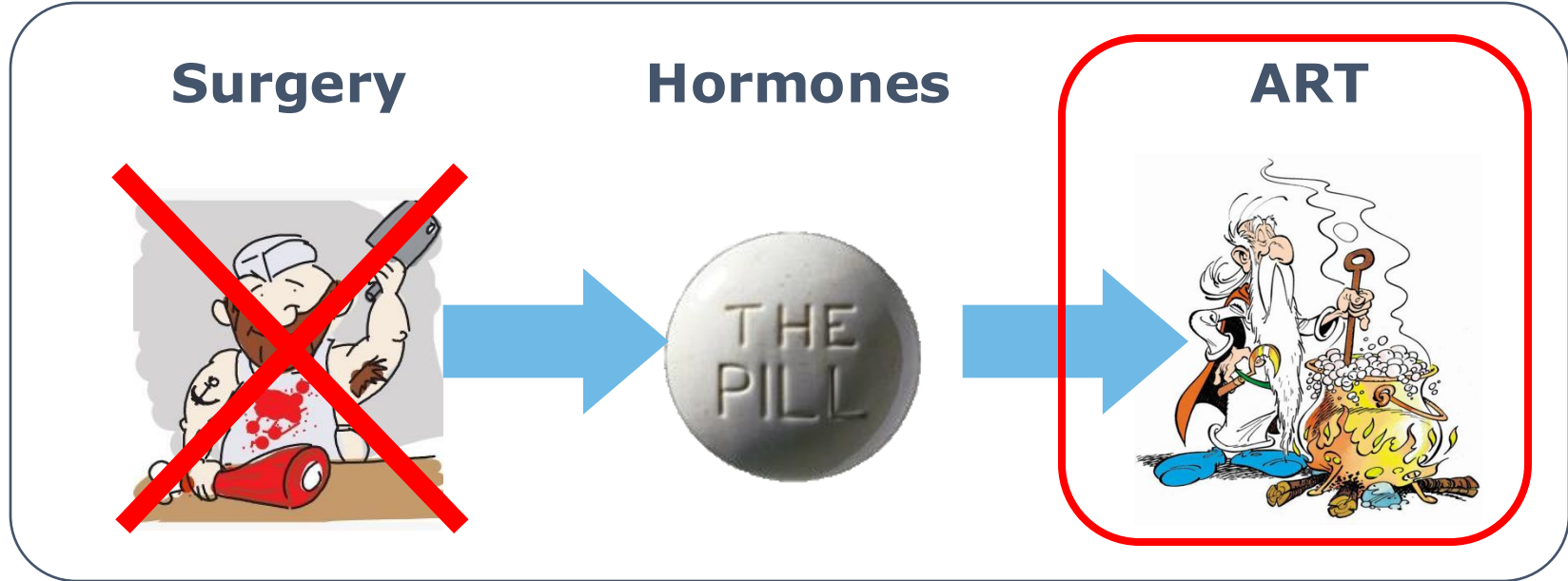
Longer is the medical treatment higher is the pain relief



VAS, visual analogue scale; SEM, standard error of the mean

Endometriosis and fertility

Therapeutic options



ART, assisted reproductive technology

Endometriosis and infertility: ART

Eggs Donation



Original Investigation | Obstetrics and Gynecology

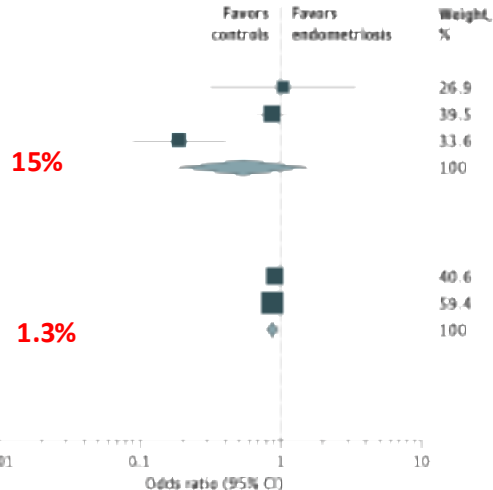
Live Birth After Oocyte Donation In Vitro Fertilization Cycles in Women With Endometriosis

A Systematic Review and Meta-Analysis

Alessio Paffoni, PhD; Maira Casalechi, PhD; Dominique De Ziegler, MD, PhD; Ettore Cicinelli, MD, PhD; Edgardo Somigliana, MD, PhD; Paola Viganò, PhD; Amerigo Vitagliano, MD, PhD

Live birth rate for adjusted analysis between women with and without a history of endometriosis

Study or subgroup	Total endometriosis	Total controls	Odds ratio (95% CI)
Published studies			
Diaz et al, ¹⁴ 2000 ^a	25	33	1.04 (0.32-3.38)
Kamath et al, ¹⁶ 2022	758	5917	0.86 (0.67-1.10)
Prapas et al, ¹³ 2012	120	120	0.19 (0.09-0.40)
Subtotal (95% CI)	903	6070	0.54 (0.19-1.57)
Heterogeneity: $\tau^2 = 0.72$; $\chi^2 = 14.42$, $P < .001$; $I^2 = 86\%$			
Test for overall effect: $z = 1.12$; $P = .26$			
Unpublished data			
HFEA	931	23969	0.91 (0.79-1.04)
SART ^a	1149	136033	0.87 (0.78-0.98)
Subtotal (95% CI)	2080	160002	0.89 (0.81-0.97)
Heterogeneity: $\tau^2 = 0$; $\chi^2 = 0.16$; $P = .69$; $I^2 = 0\%$			
Test for overall effect: $z = 2.65$; $P = .008$			
Test for subgroup differences: $\chi^2 = 0.80$; $P = .37$; $I^2 = 0\%$			



ART and differed embryo transfer : Endometriosis

Journal of Assisted Reproduction and Genetics (2022) 39:1033–1043
<https://doi.org/10.1007/s10815-022-02460-w>

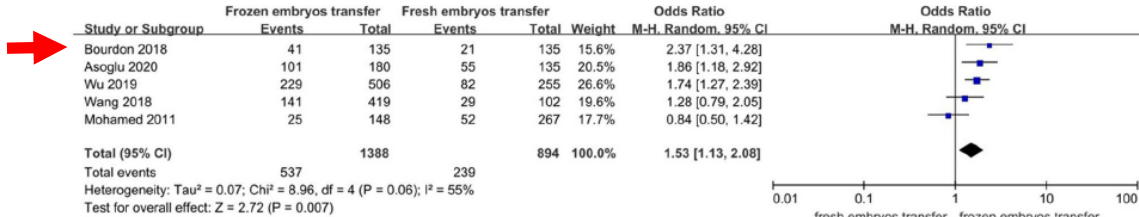
REVIEW



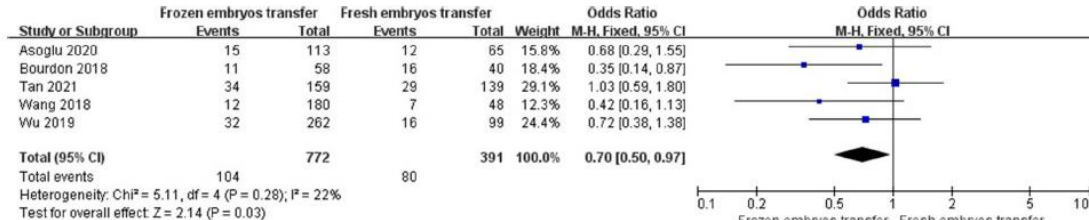
Association of embryo transfer type with infertility in endometriosis: a systematic review and meta-analysis

Yanan Chang¹ · Minghong Shen^{1,2} · Sha Wang¹ · Xiao Li¹ · Hua Duan¹

Received: 22 November 2021 / Accepted: 10 March 2022 / Published online: 24 March 2022
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LBR



MISCARRIAGE

ART and differed embryo transfer : Adenomyosis

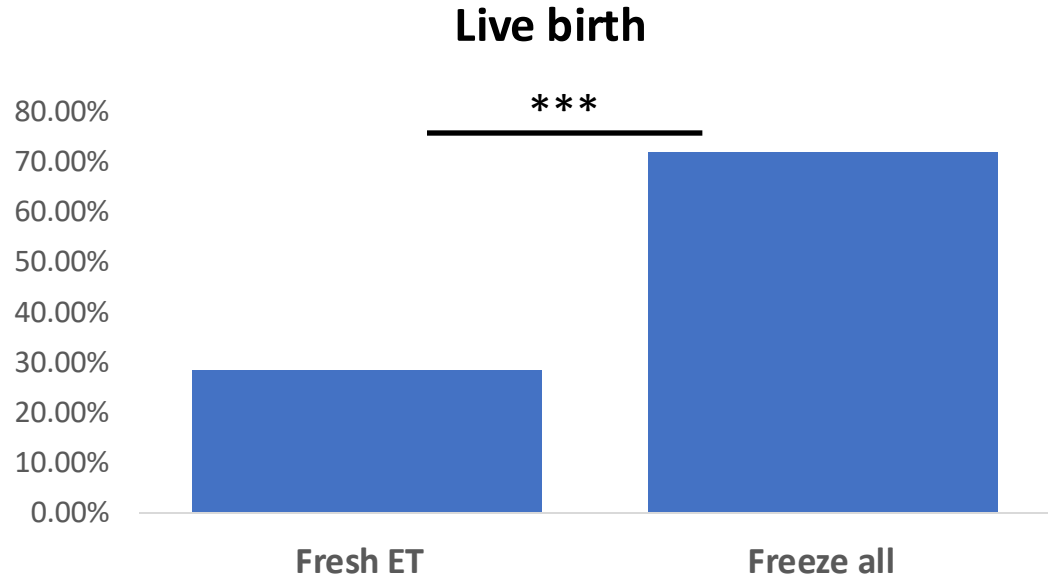
Variables associated with the presence of a live birth: multiple logistic regression analysis.

Parameters ^a	Odds ratio (95% CI)
Freeze-all vs. fresh embryo transfer strategy	1.80 (1.02–3.16)
AMH level	1.12 (0.99–3.56)
Having at least one transfer of a top-quality blastocyst	2.08 (1.22–3.56)
Age (y)	0.88 (0.81–0.95)
Estradiol level at triggering day	1.00 (0.99–1.01)
ICSI vs. IVF	0.88 (0.52–1.50)
Number of previous IVF/ICSI cycles	0.81 (0.64–1.04)
Year of retrieval	1.07 (0.84–1.36)

AMH = antimüllerian hormone; CI = confidence interval; ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization.

^a Freeze-all vs. fresh embryo transfer strategy, the AMH level, having at least one transfer of a top-quality blastocyst, the women's age, the estradiol level at triggering day, the technique of fertilization (ICSI vs. IVF), and the number of previous IVF and ICSI cycles and the year of retrieval were variables included in the analysis.

Bourdon. "Freeze-all" strategy and adenomyosis. *Fertil Steril* 2023.



Impaired ART outcomes : Adenomyosis or endometriosis

TABLE 2 PREGNANCY OUTCOME PARAMETERS

Pregnancy outcome	Tubal (controls)	Endometriosis (group A)	Endometriosis + adenomyosis (group B)	Adenomyosis (group C)
Clinical pregnancy rate, n (%)	161/466 (34.55)	130/355 (36.62)	20/88 (22.72)	15/64 (23.44)
Miscarriage rate/pregnancy, n (%)	21/161 (13.04)	19/130 (14.62)	7/20 (35)	6/15 (40)
Live birth rate, n (%)	128/466 (27.47)	94/355 (26.48)	10/88 (11.36)	8/64 (12.5)

Non-viable severe preterm and intrauterine demise for controls; group B and C were 12, 3 and 1, respectively; for group A, out of 19 such cases, two severe preterm babies survived.

Us based

Retro

IVF

India

Agonist : leuprolide acetate 3.75 mg

Fertility and endometriosis



Implantation



Therapeutics options



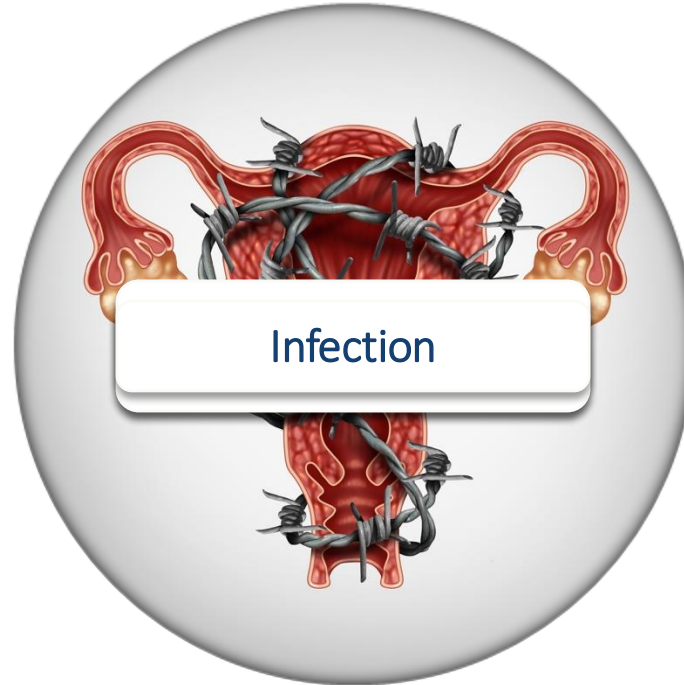
Risks



Conclusion

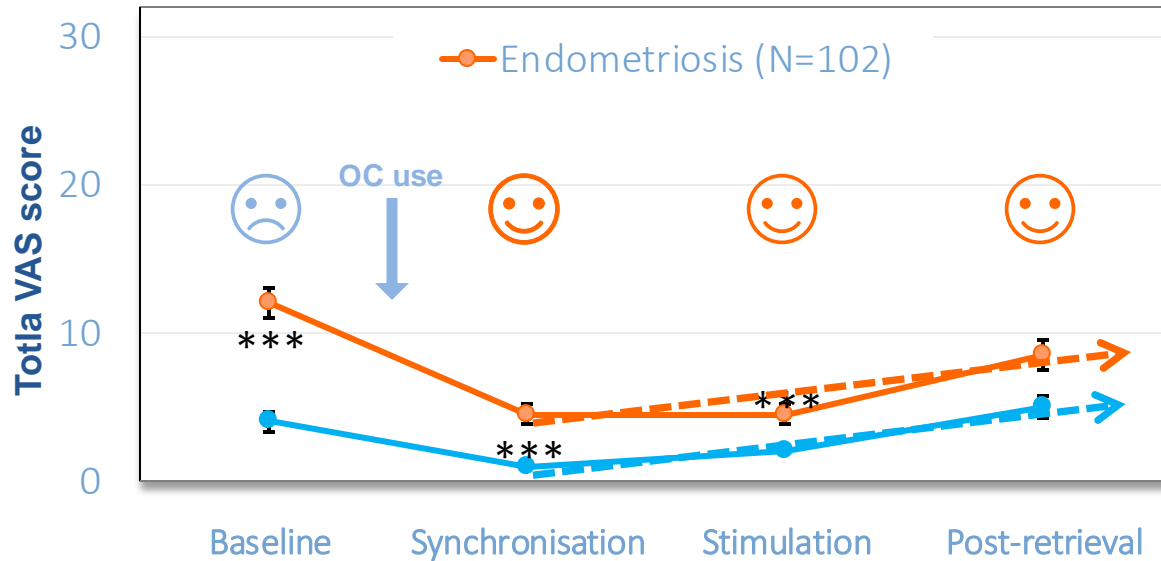
Fertility preservation and endometriosis

Safety issues



Fertility preservation and endometriosis

Pain progression during stimulation



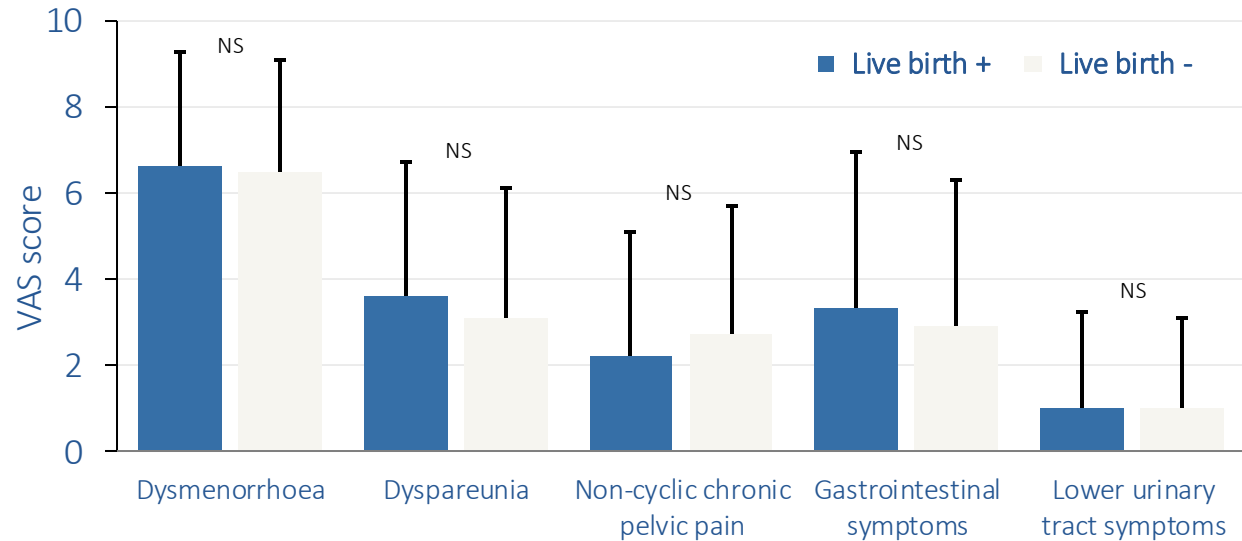
Fertility preservation and endometriosis

Outcomes according to pain symptoms

France, 2014 to 2021

354 endometriosis-
affected women

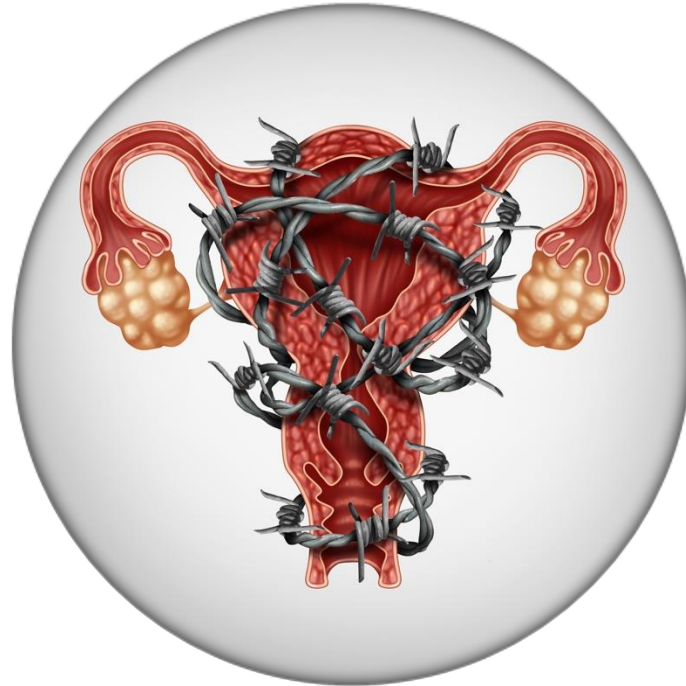
711 ART cycles



VAS, visual analogue scale

Fertility preservation and endometriosis

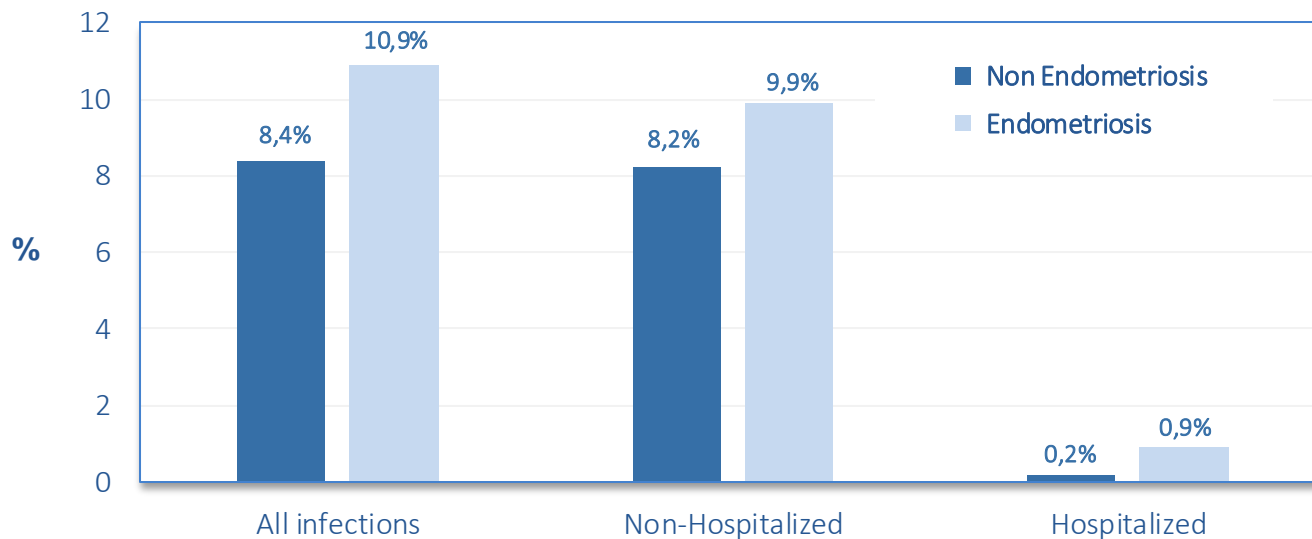
Safety issues



Infection

Fertility preservation and endometriosis

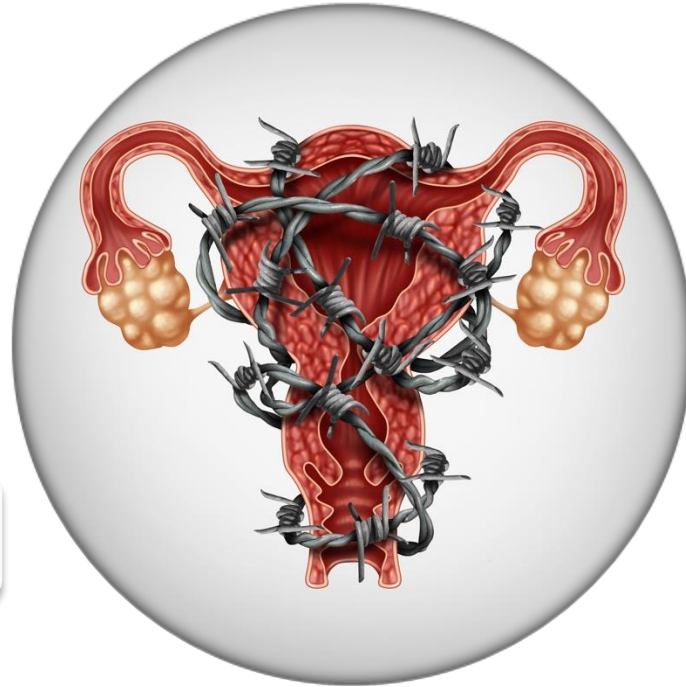
Pelvic infection after oocyte retrieval



2019 – 65948 retrieval – 31 hospitalized infection in endometriosis affected women
Endometriosis and risk of infection --> aOR=1.35 CI 95%[1.20–1.51]

Fertility preservation and endometriosis

Safety issues



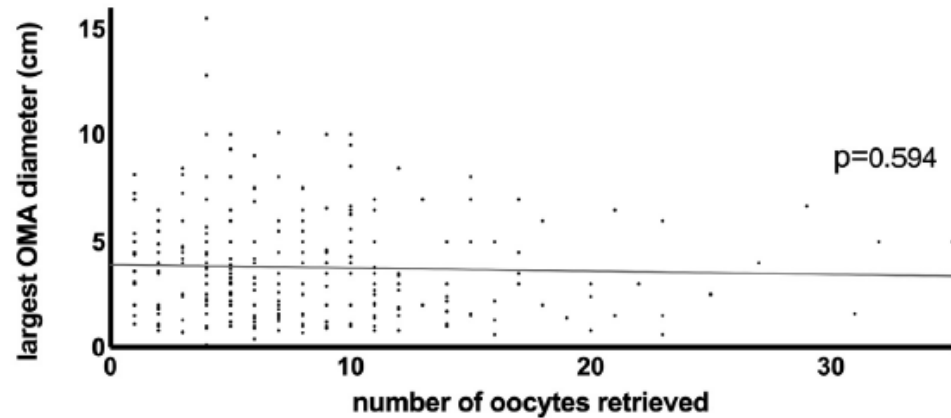
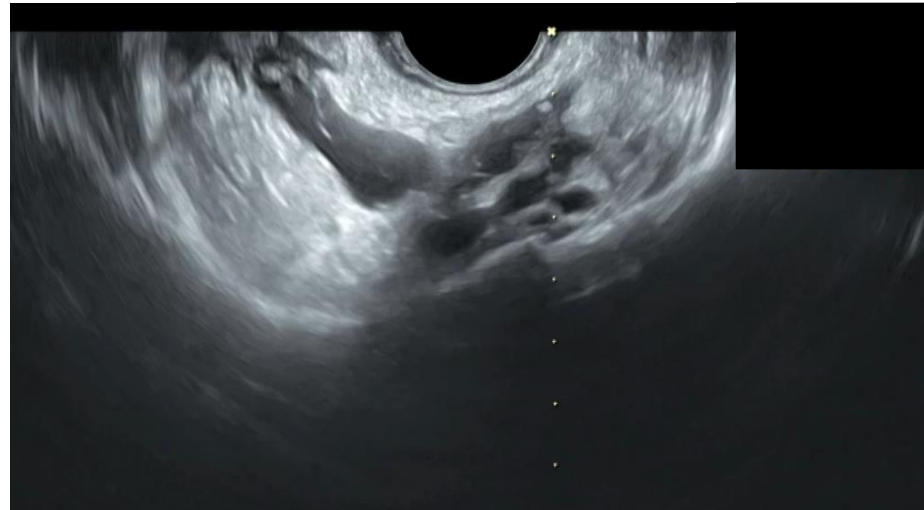
Large endometrioma

Large EndometriOMAs

Oocyte yield

Large Endometriomas

Influence of endometrioma size on ART outcomes



Fertility preservation and endometriosis

Safety issues



Progression of lesions

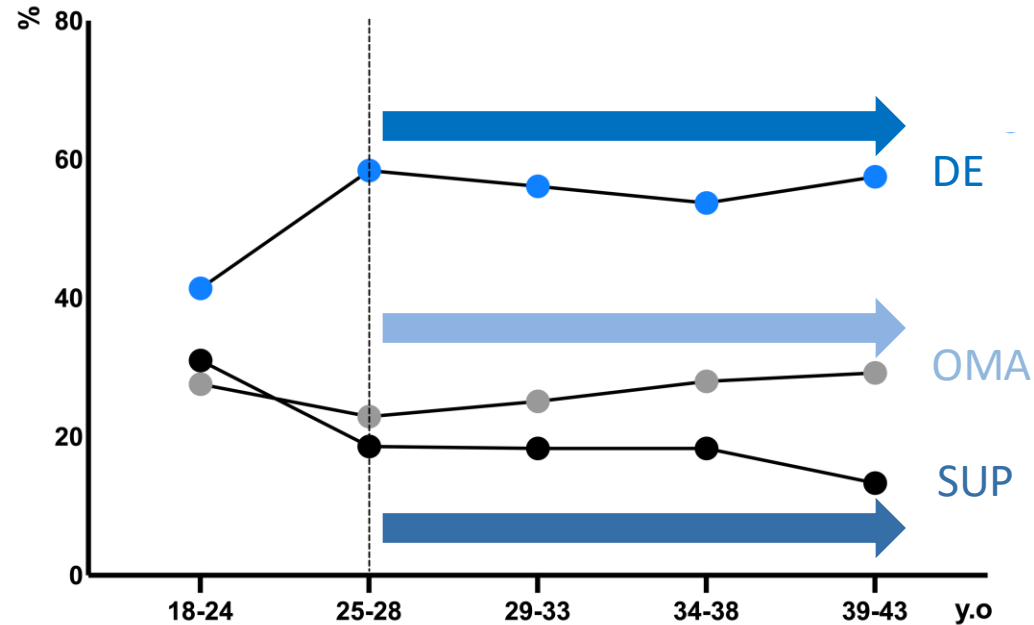
Endometriosis and ART

Disease progression

Endometriosis phenotypes distribution according to age

Cohort study:

- 1311 OSIS patients
- Histological diagnosis



Fertility and endometriosis



Techniques



Outcomes



Risks



Conclusion

Endometriosis and infertility

Take Home Message

Uterus:

- Increased synthesis of prostaglandin & altered receptivity
- Production of estrogens *in situ* and resistance to progestogen

Endometriosis is not synonymous of infertility

Pelvic cavity:

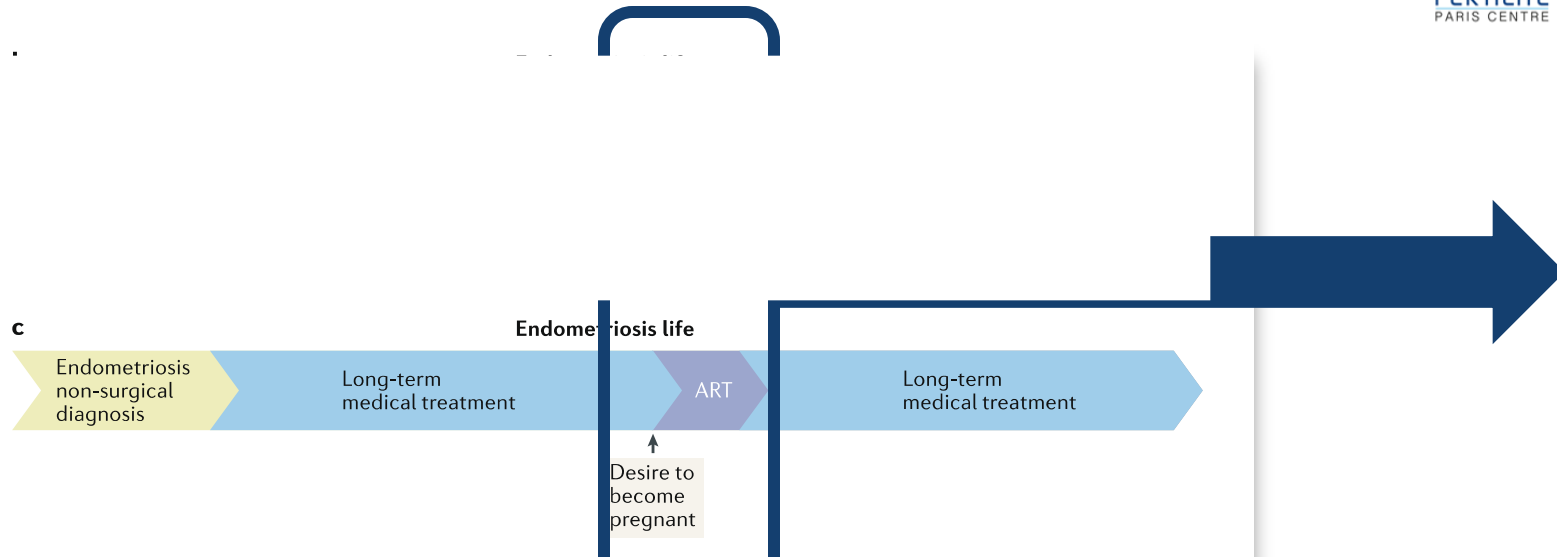
- Proliferation of macrophages
- Phagocytic dysfunction
- Release of proinflammatory factors

Ovaries:

- Decreased ovarian response
- Altered oocyte quality?
- Iron overload (proinflammatory factors)

Endometriosis Life : Primum non nocere

Evolution toward medical treatments

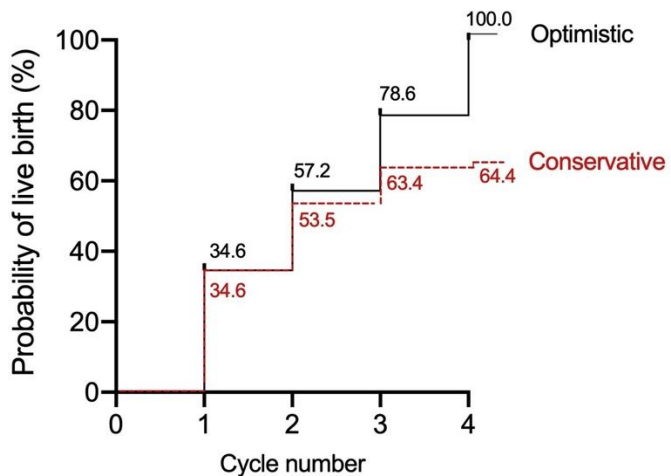


**Best indication for surgery
in cases of endometriosis related infertility is
persistent pelvic pain
after hormonal medical treatment**

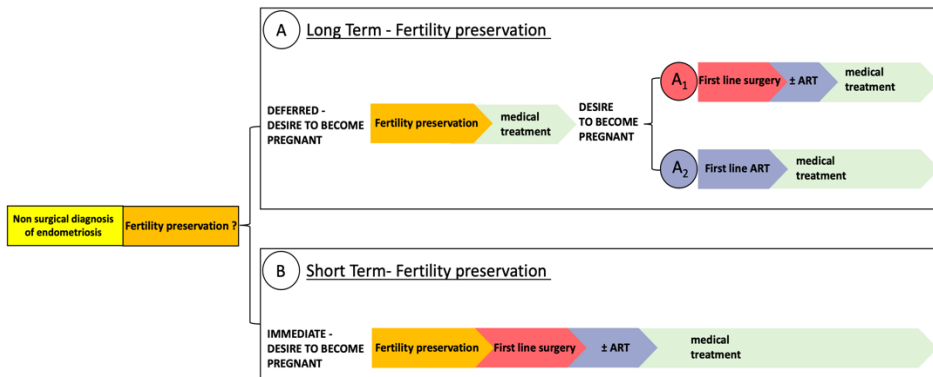
Endometriosis

ART

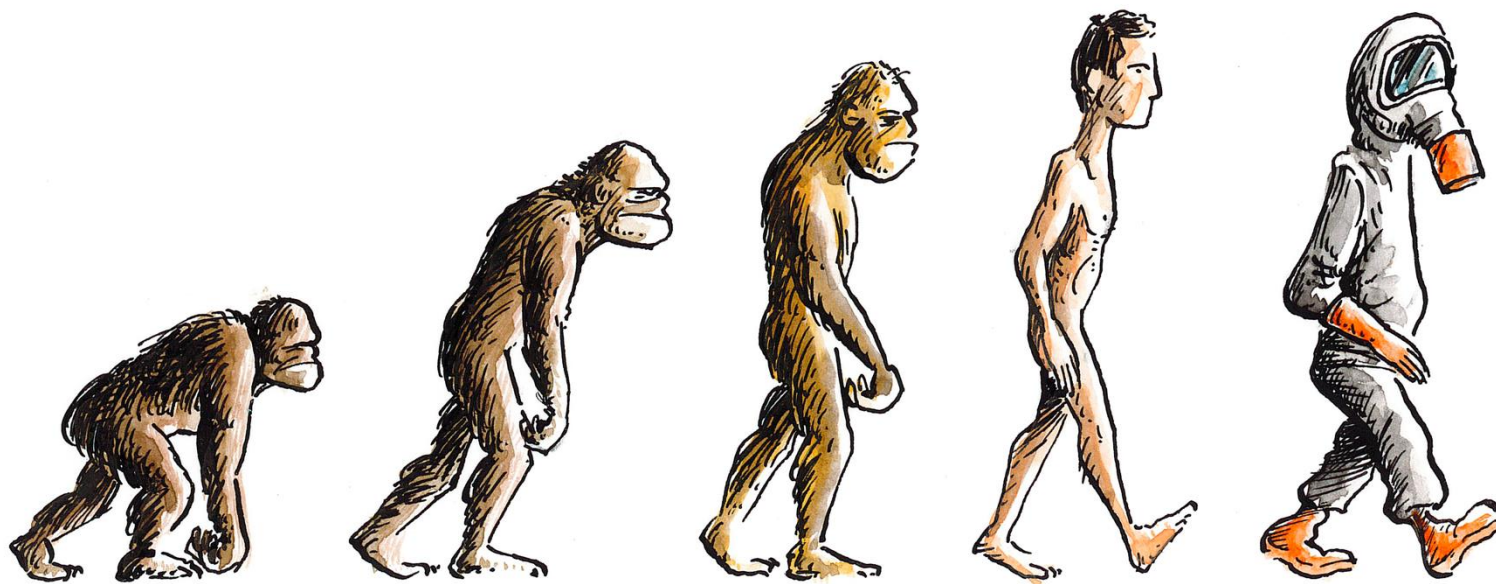
IVF – ICSI Bowel endometriosis



Fertility preservation Short and Long term strategy



Evolution



LARDON

Take Home Message

Modern treatment strategy

Surgery



Hormones



ART



IVF
ICSI

FERTILITY
PRESERVATION

Associated treatments

- Pain specialists: Pelvic Pain Centre
- Psychologists
- Nutritionists
- Complementary therapies: Acupuncture, osteopathy, physiotherapy, sophrology, sexology, hypnosis
- Patient support groups

ART, assisted reproductive technology

Gynecology

Surgical unit:

C Chapron, B Borghese, L Marcellin, P Santulli, G Parpex,
A Bourret, G Pierre, P Marzouk, A Gaudet, F Decuyperre, L Campin

Medical unit:

G Plu-Bureau, A Gompel, L Maitrot, S Perol

Reproductive endocrinology unit:

P Santulli, M Bourdon, C Maignien, L Melka, A Garcia, M Sorel, F Kefelian,
S Koutchinsky, D Stroe, M Boudes,
V Blanchet, C Cervantes, J Gonnot, E Laviro, A Houliat

Intestinal surgery

B Dousset, M Leconte

Radiology

AE Millischer, L Maitrot, C Bordonne

Laboratory: Genetic

D Vaiman, S Barbaux

Laboratory: Immunology

F Batteux, S Chouzenoux,, L Doridot

Laboratory: Reproductive biology

C Patrat, P Fauque, JP Wolf, K Pocate, V Lange, C Chalas, A Chargui,

L Ferreux, B Eraud

Statistical unit

F Goffinet, PY Ancel



P Santulli,

Professor and Head, Reproductive ART and Infertility unit,

C Chapron,

Professor and Chair, Gynecology Obstetrics II and Reproductive Medicine





From adolescence to menopause:

Modern management of
endometriosis and uterine disorders

APRIL 24TH / 26TH

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11TH CONGRESS
OF THE SOCIETY OF ENDOMETRIOSIS
AND UTERINE DISORDERS

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2025**

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Dr. Lubomir Mikulasek

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Dr Francisco Carmona

Contact & Organization COM&CO@SEUD.ORG



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