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Double trouble for fertility: new insight into adenomyosis and endometriosis

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Inserm, Unité de recherche U1016 – équipe Dr D. Vaiman, Institut Cochin, Paris, France

Disclosure



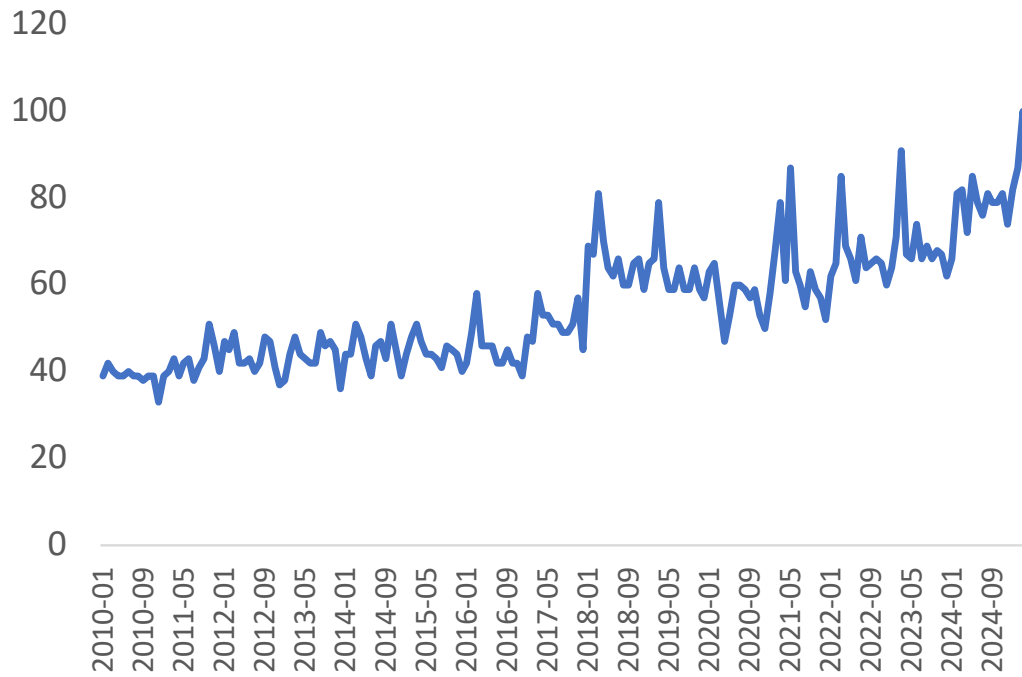
Name of entity	Grant	Personal fees	Non-financial support	Other	Comments
Merck	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Unrestricted research grant and honoraria
Gedeon	<input checked="" type="checkbox"/>	<input checked=""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

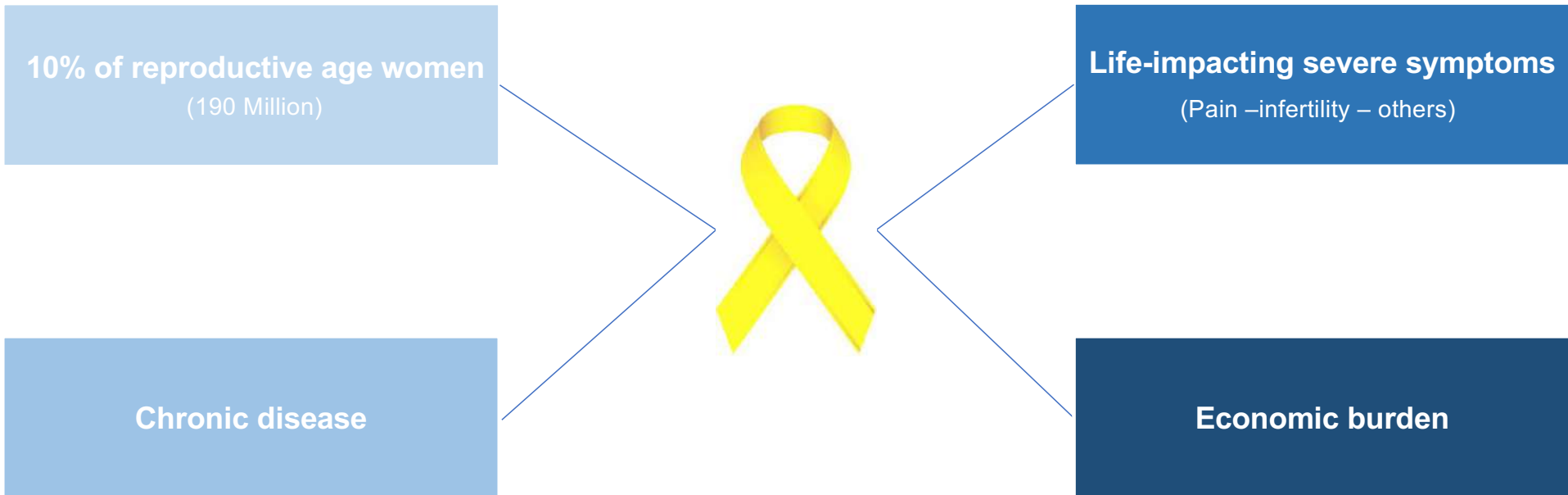


Interest by region



Endometriosis

A major public health concern



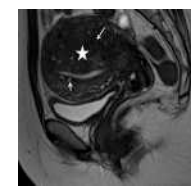
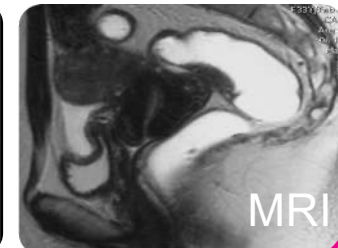
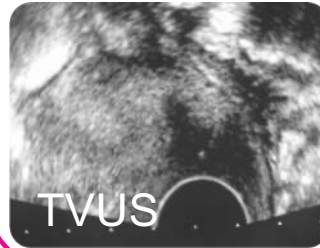
Rethinking endometriosis diagnosis

Heterogenous disease

Questioning



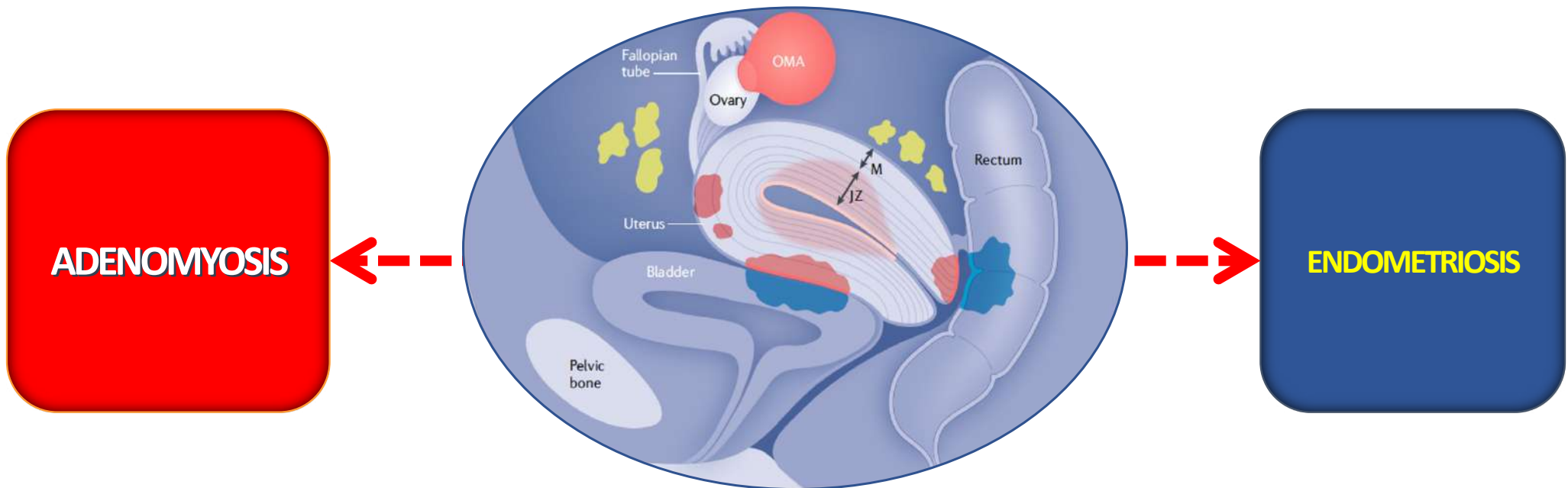
Imaging



Endometriosis
diagnosis

Endometriosis phenotypes

Adenomyosis and endometriosis



Enigmatic relationship
30-60% association

Endometriosis and Adenomyosis: infertility

Mechanisms

Uterus :

- Altered eutopic endometrium
 - Inflammation
 - Oxidative stress
- Lack of adhesion molecules

Abnormal uterotubal transport
Tubal occlusion

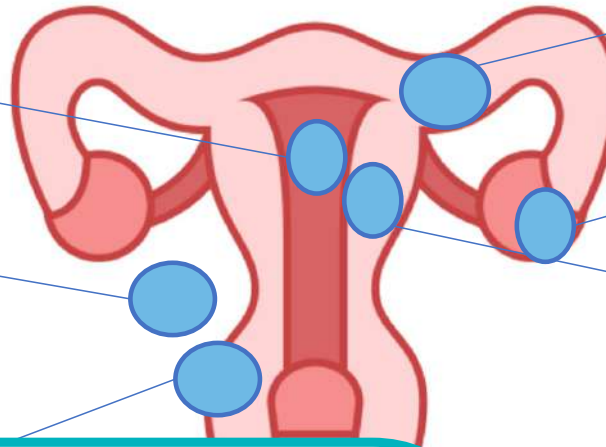
Ovaries:

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

Pelvic cavity:

Proliferation of macrophages
Phagocytic dysfunction
Release of proinflammatory factors

**Anatomical distortion of the
uterine cavity**
Disturbed uterine peristalsis



er

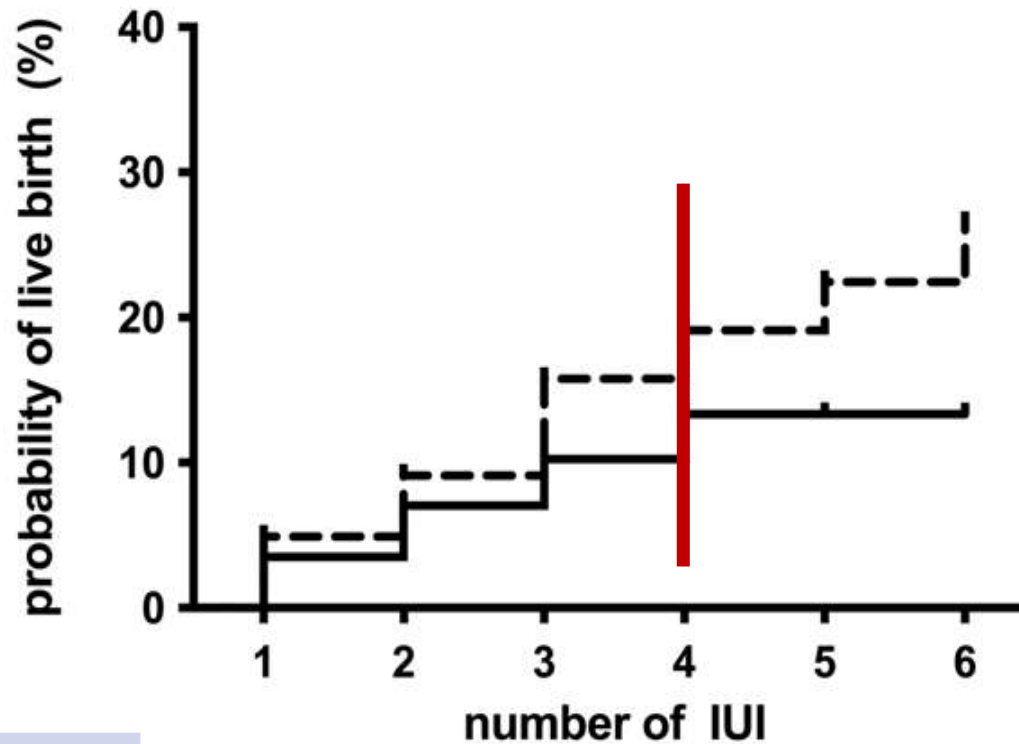
105 (43.2%) spontaneous pregnancy
76 (41.5%) with DIE

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

Santulli et al RBMO 2025
de Ziegler D et al. Lancet 2010

Endometriosis and infertility

Mechanisms: donor sperm intrauterine insemination



--- : control group
 ___ : endometriosis group

Phenotype of endometriosis ^a	
SUP	7 (7.4)
OMA	7 (7.4)
DIE	80 (85.1)

Characteristics	Control group	Endometriosis group
Total number of women	447	94
Total number of IUI	1240	257

submitted

Fertility and endometriosis-adenomyosis



Endometriosis and adenomyosis related infertility: who matters the most ?



What are the available therapeutic options for infertility?



What conclusions can we draw ?

Fertility and endometriosis-adenomyosis



Endometriosis and adenomyosis related infertility: who matters the most ?



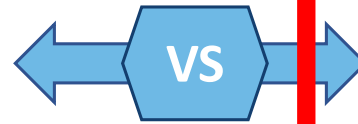
What are the available therapeutic options for infertility?



What conclusions can we draw ?

Endometriosis and infertility

Implantation



OMA ?
DIE ?
Adenomyosis ?
Previous surgery ?

**Endometriosis related
altered ovarian function ?**



QUANTITY



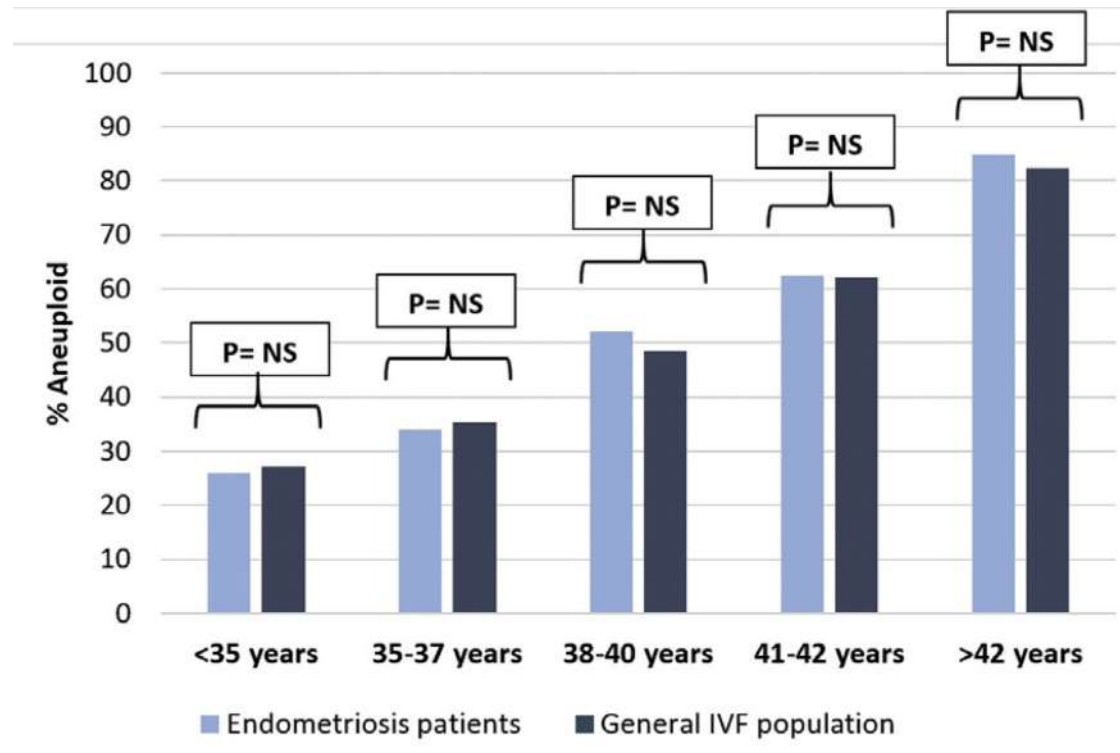
QUALITY



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

Juneau et al., Fertil Steril (2017)



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

Kamath MS et al., HR Open (2022)



Endometriosis and ovarian reserve

Follicular burnout



Altered ovarian reserve *per se* ?

JCEM THE JOURNAL
OF CLINICAL
ENDOCRINOLOGY
& METABOLISM

CLINICAL RESEARCH ARTICLE

Endometriosis Triggers Excessive Activation of Primordial Follicles via PI3K-PTEN-Akt-Foxo3 Pathway

Arisa Takeuchi,¹ Kaori Koga,¹ Erina Satake,¹ Tomoko Makabe,¹ Ayumi Taguchi,¹ Mariko Miyashita,¹ Masashi Takamura,¹ Miyuki Harada,¹ Tetsuya Hirata,¹ Yasushi Hirota,¹ Osamu Yoshino,² Osamu Wada-Hiraike,¹ Tomoyuki Fujii,¹ and Yutaka Osuga¹

¹Obstetrics and Gynecology, University of Tokyo, Hongo Bunkyo Tokyo 113-8655, Japan; and ²Obstetrics and Gynecology, Kitasato University School of Medicine, Kitasato, Minami-ku, Sagami-hara-shi, Kanagawa 252-0374, Japan

ORCID numbers: [0000-0002-5057-4120](https://orcid.org/0000-0002-5057-4120) (K. Koga).

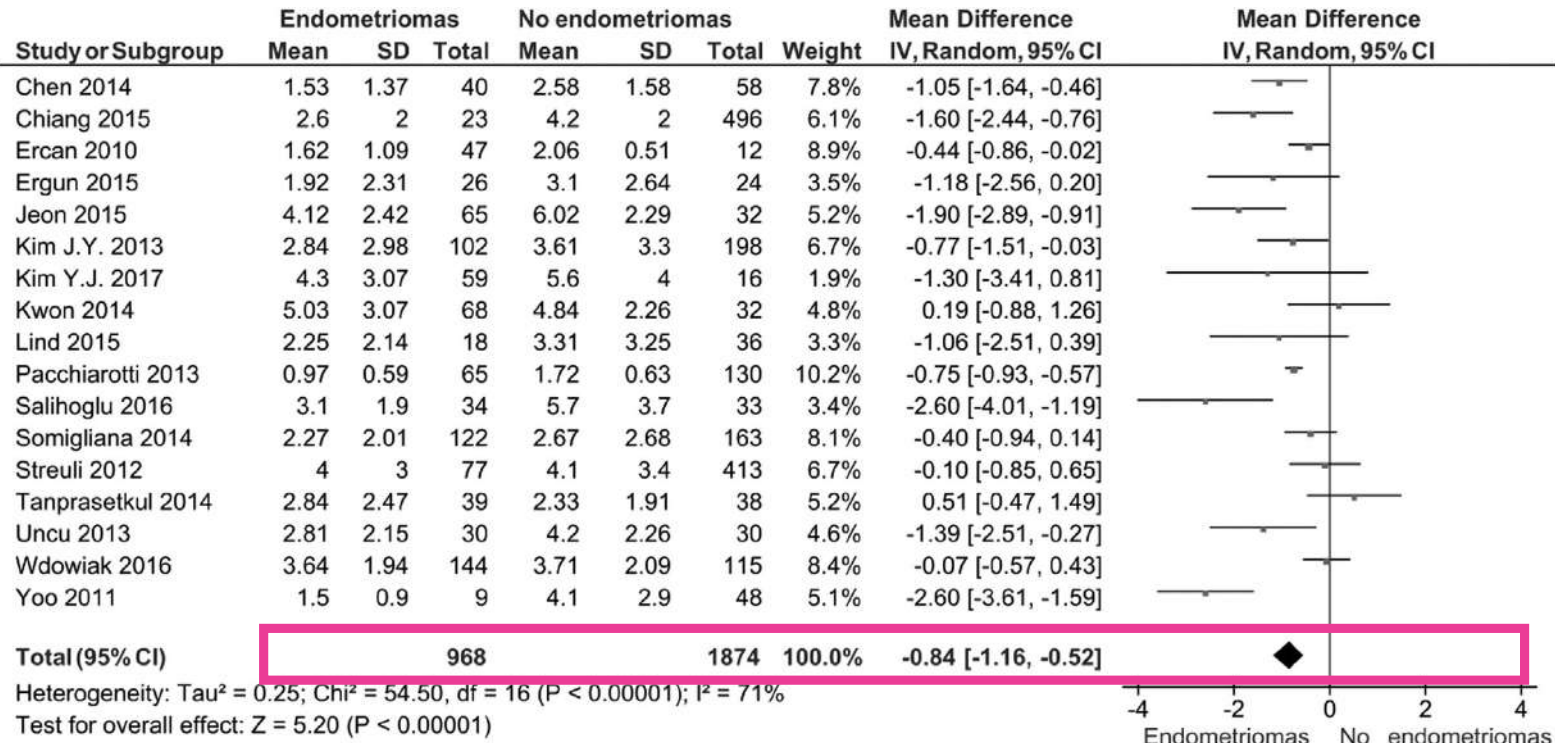
J Clin Endocrinol Metab, November 2019,



Endometriosis and ovarian reserve

Oocyte quantity : AMH levels

Meta-analysis :
 - 39 studies
 - 968 non-operated OMA
 - 1874 controls



OMA+ OMA-



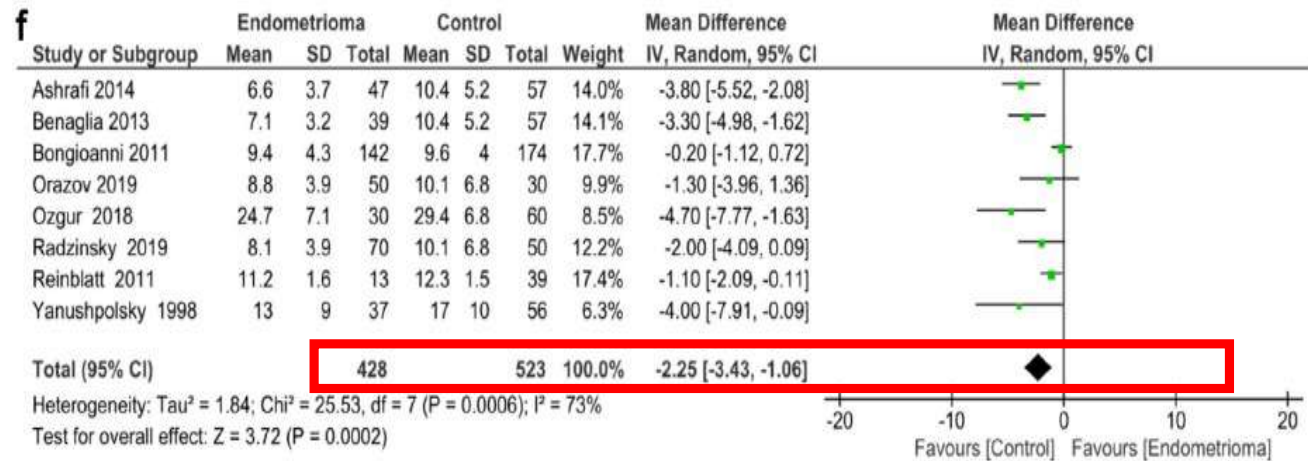
Endometriosis and ovarian reserve

Oocyte quantity : ovarian response to stimulation

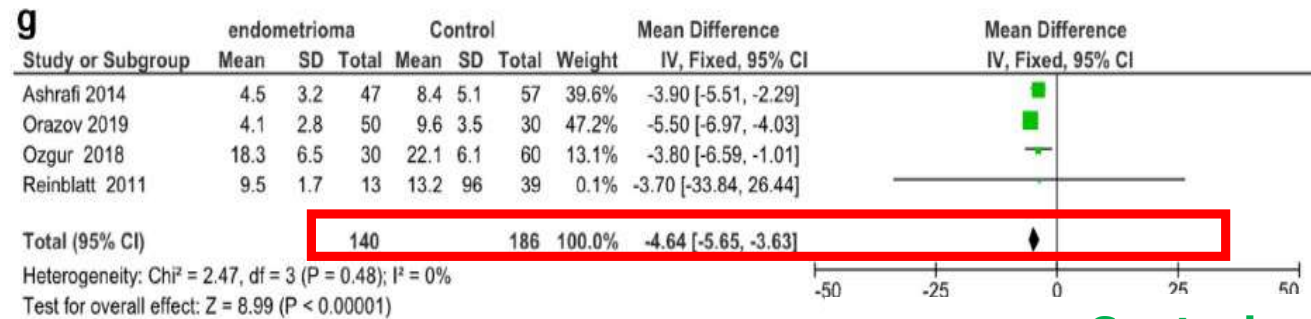
Meta-analysis :

- 8 observational studies
- 428 intact OMA
- 544 controls

Number of oocytes



Number of mature oocytes



OMA + Controls

The studies were not adjusted for dose of Gn and ovarian reserve

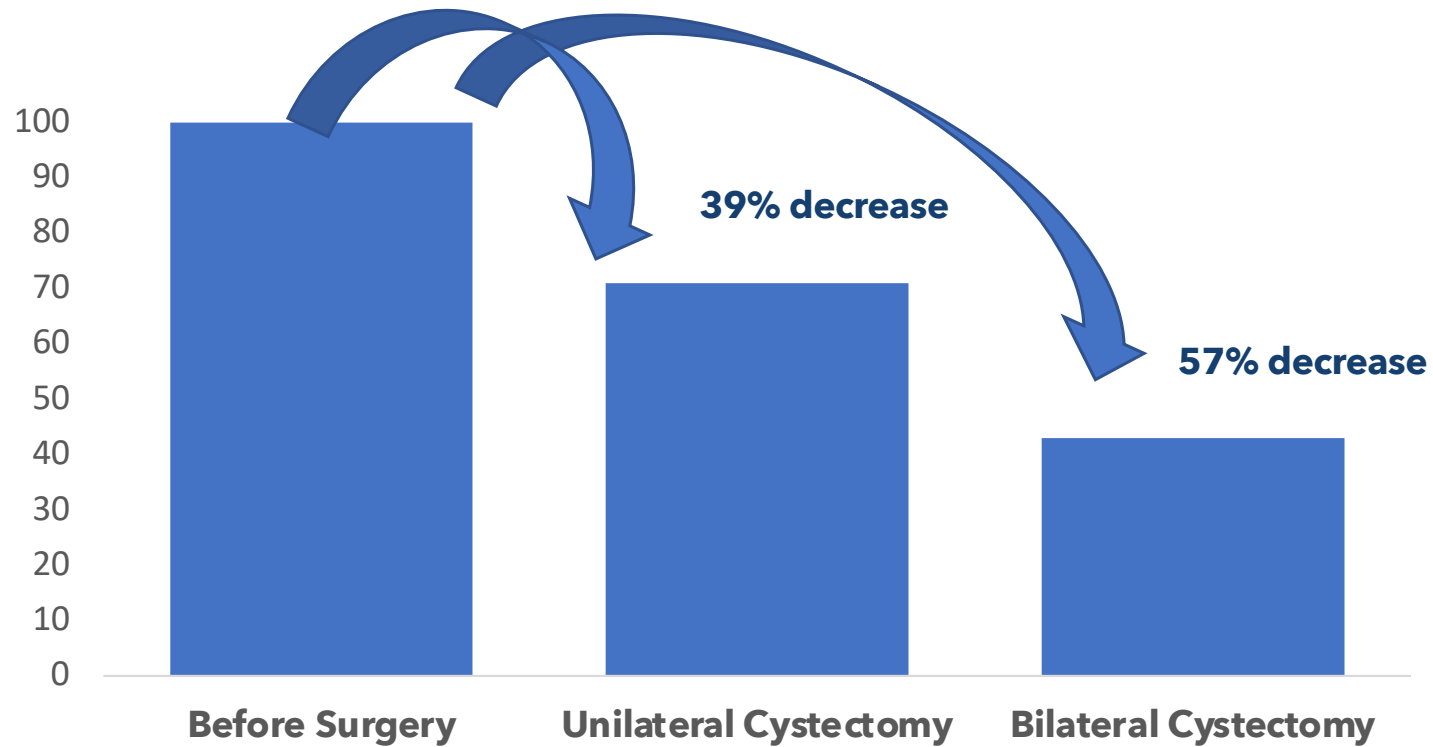
OMA: Ovarian endometrioma



Endometriosis and infertility: surgery

Endometrioma and ovarian reserve

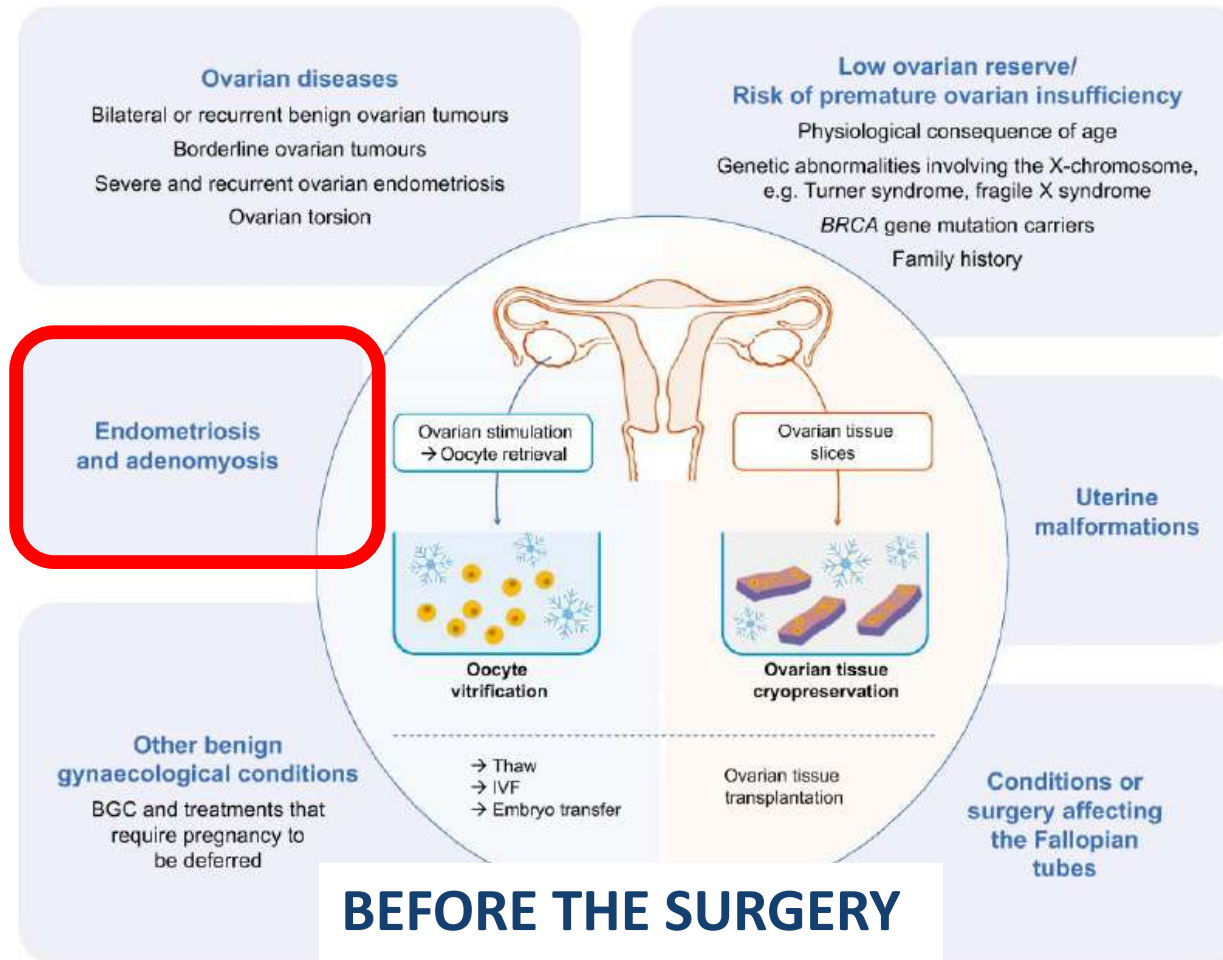
12 months post Operative AMH decrease



Metaanalysis
12 studies

Fertility preservation and BGC

Endometriosis

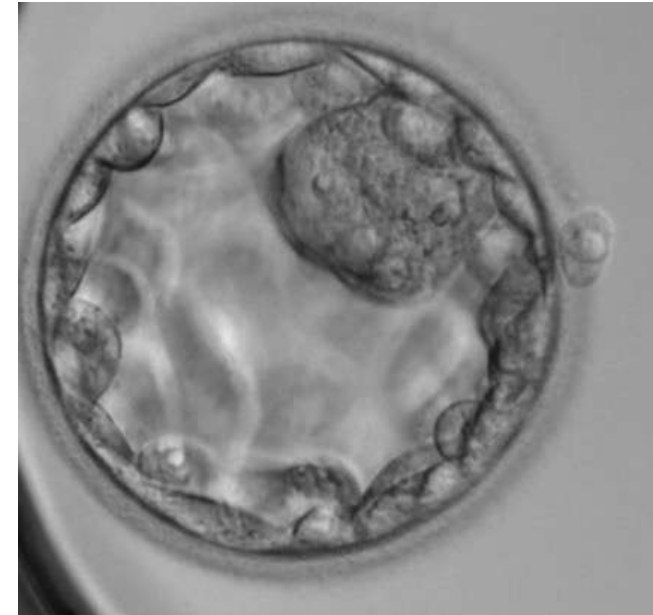


BGC, Benign gynaecological condition

Santulli P, et al. HR Open 2023

Endometriosis and infertility

Implantation



OMA ?
DIE ?
Adenomyosis ?
Previous surgery ?

**Endometriosis related
altered ovarian function ?**



QUANTITY



QUALITY

Endometriosis and infertility: ART

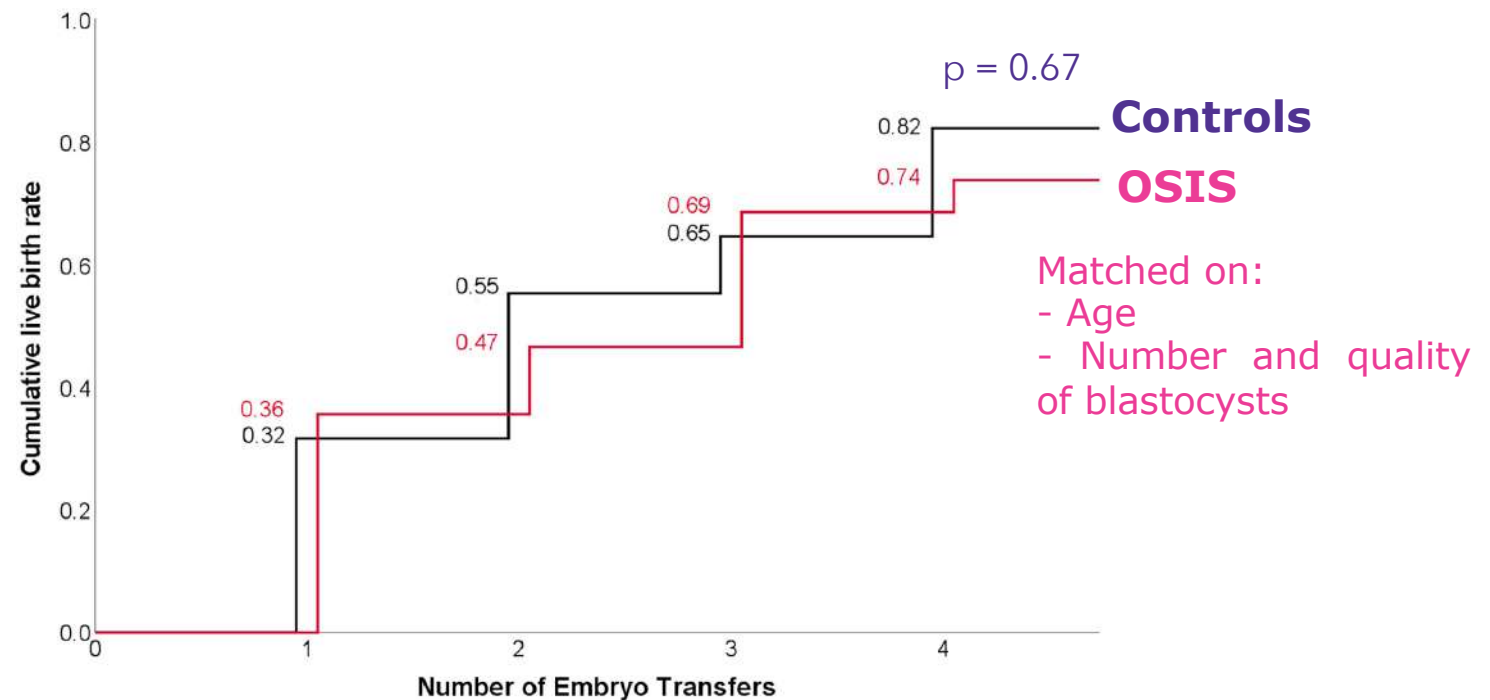
Uterine receptivity: a matched study



Retrospective matched case-control study:

- FET cycles
- 101 OSIS patients
- 101 controls

Cumulative live birth rates based on the number of FET in women with and without OSIS



Endometriosis and infertility: ART

Uterine environnement: 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

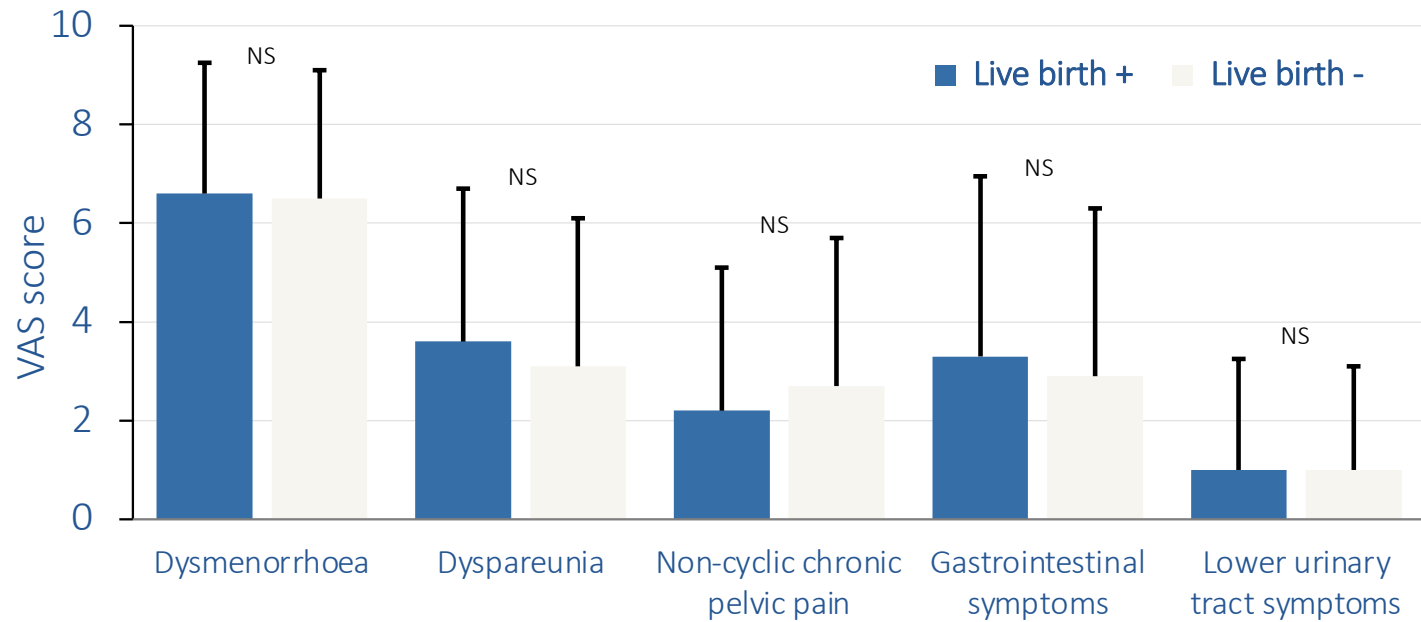
Endometriosis and infertility: ART

Uterine environment: ART results according to pain symptoms

France, 2014 to 2021

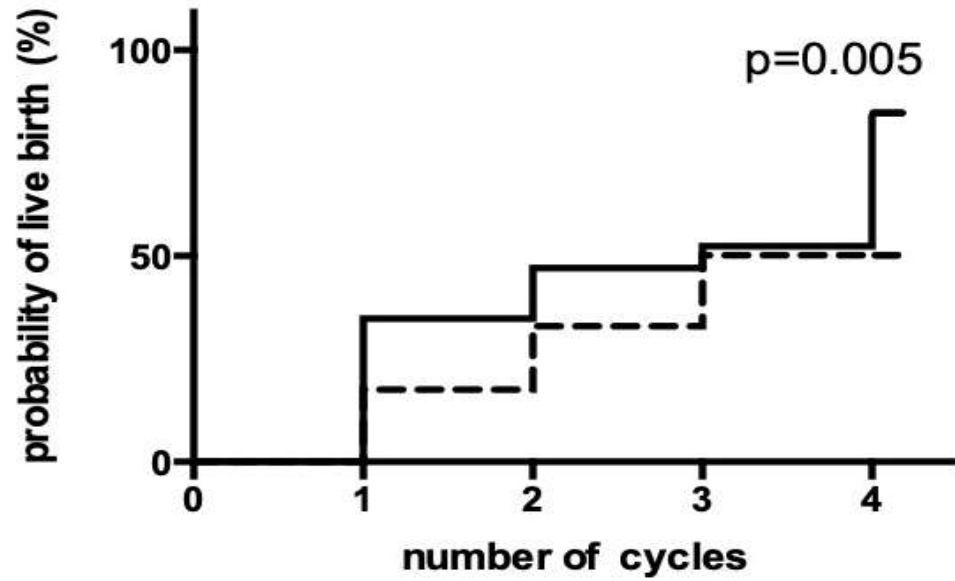
354 endometriosis-
affected women

711 ART cycles



VAS, visual analogue scale

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

Fertility and endometriosis-adenomyosis



Endometriosis and adenomyosis related infertility: who matters the most ?



What are the available therapeutic options for infertility?



What conclusions can we draw ?

Endometriosis and fertility

Therapeutic options

Surgery



Hormones



ART



ART, assisted reproductive technology

Endometriosis and fertility

Therapeutic options

Surgery



Hormones



ART

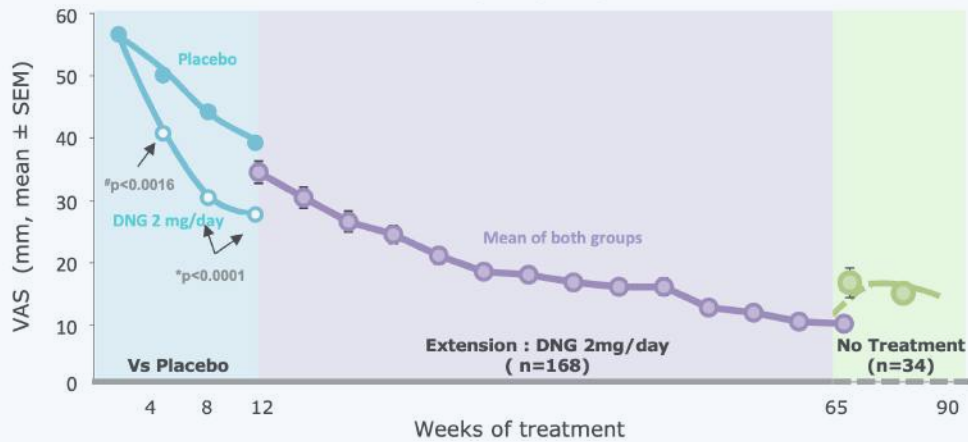


ART, assisted reproductive technology

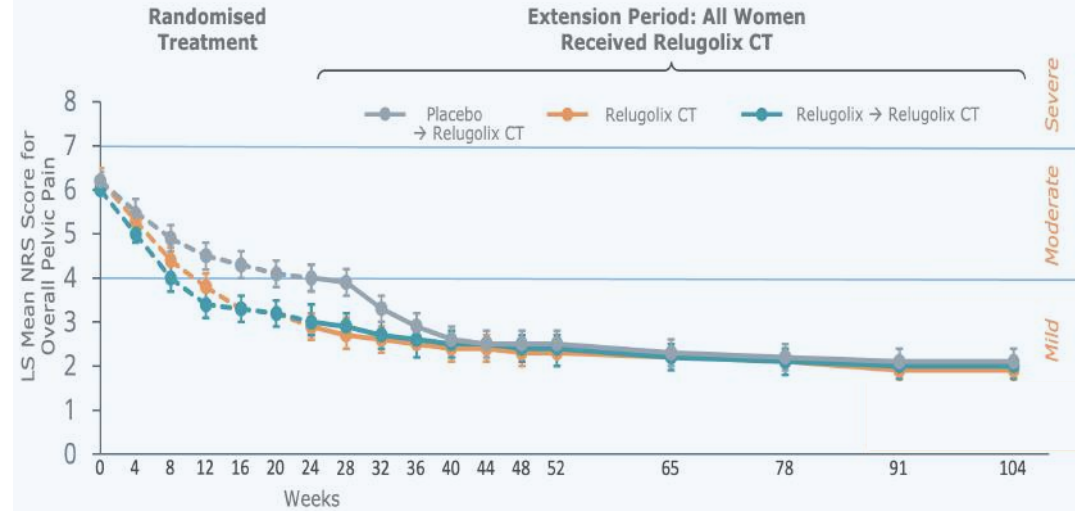
Endometriosis and hormonal treatments

Longer is the medical treatment higher is the pain relief

Dienogest (DNG)



Relugolix CT (RYEQO)

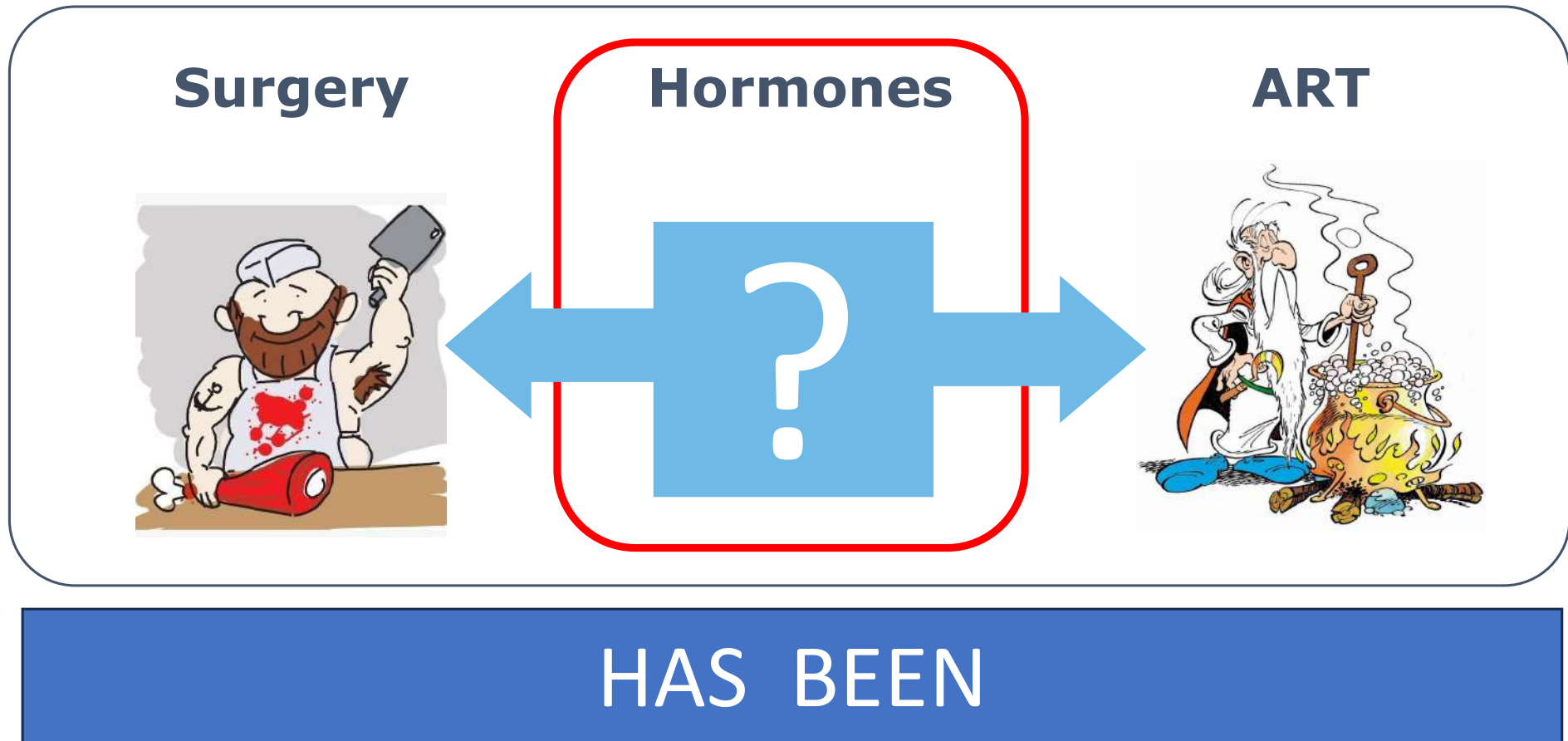


≈ 70% reduction from Baseline

SEM, standard error of the mean; VAS, visual analogue scale
 Strowitzki T, et al. Eur J Obstet Gynecol Reprod Biol. 2010;151:193–198;
 Petraglia F, et al. Arch Gynecol Obstet. 2012;285(1):167–173
 Giudice LC, et al. Lancet 2022;399:2267–79
 Becker CM et al, Hum Reprod. 2024 Jan 18:dead263. doi: 10.1093/humrep/dead263

Endometriosis and fertility

Therapeutic options



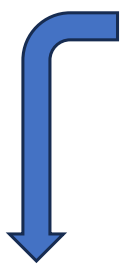
Endometriosis and infertility: Optimized ART

Surgery as pretreatment

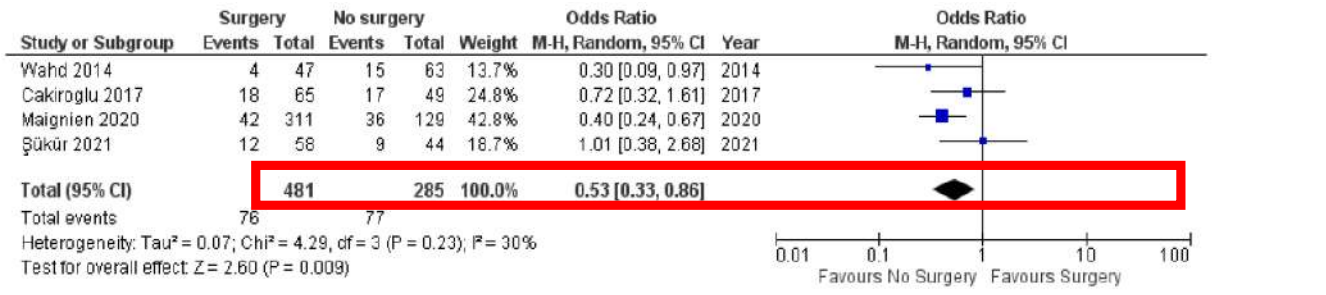
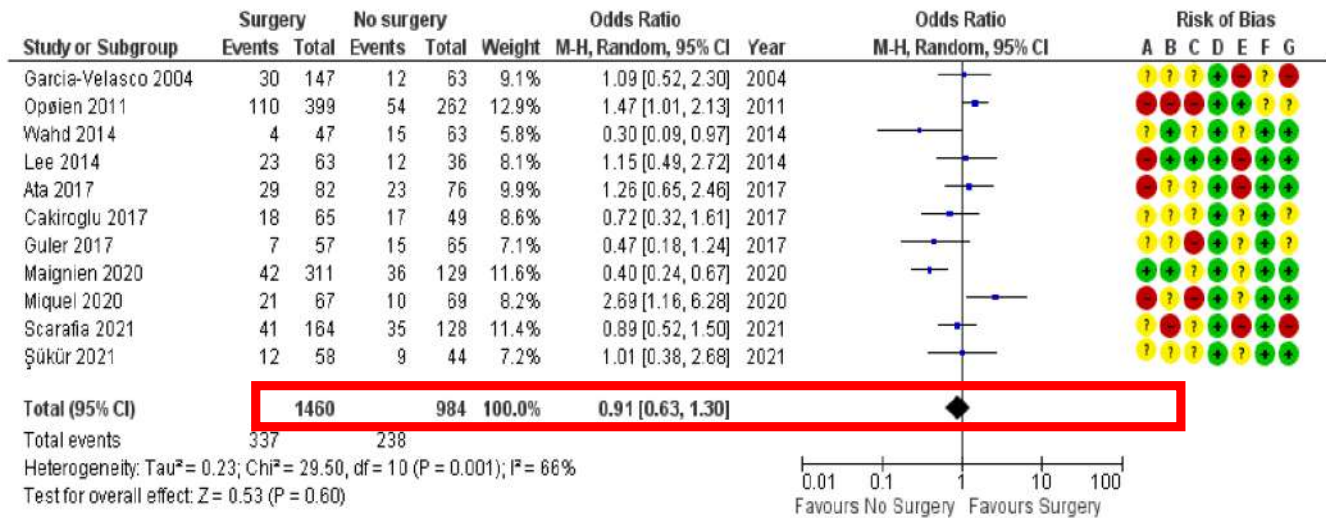
ART live birth rates Surgery before ART vs 1st line ART

Meta-analysis:

- 19 studies
- Infertile OSIS
- 1st line ART vs ART after surgery



Exclusion of studies with high risk of bias



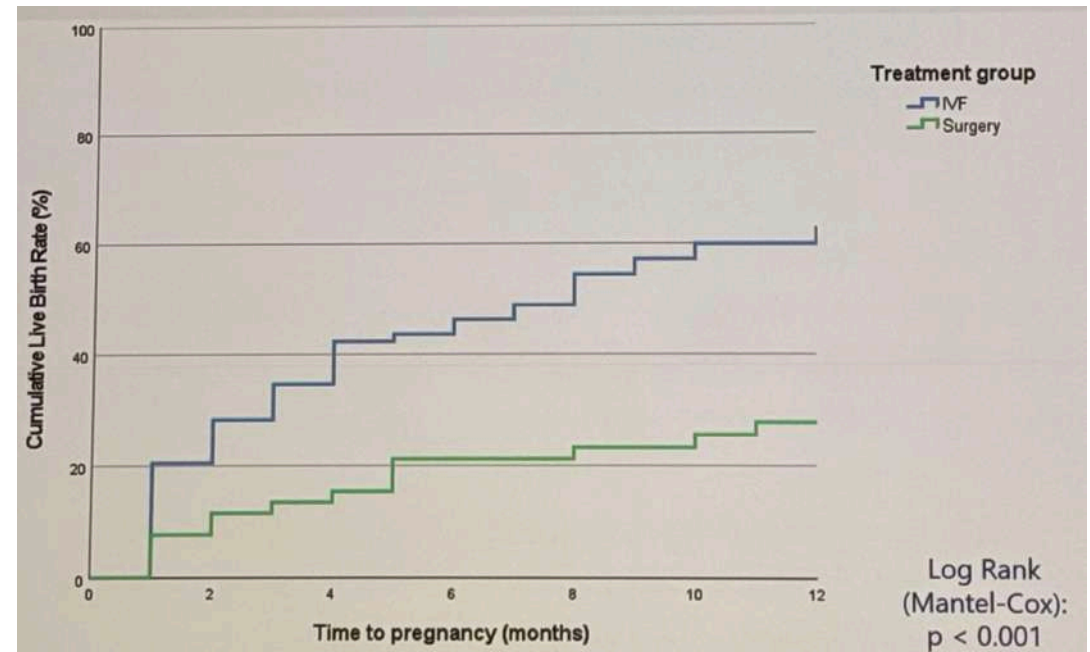
Surgery - **Surgery +**

Endometriosis and infertility:

Surgery vs ART : RCT

LBR

Population	IVF (n/N, %)	Surgery (n/N, %)	p
Randomized N=55	15/28 (54%)	7/27 (26%)	0,0364
PPT` N=75	33/50 (66%)	7/25 (28%)	0,0019
Total N=130	48/78 (62%)	14/52 (27%)	0,0001



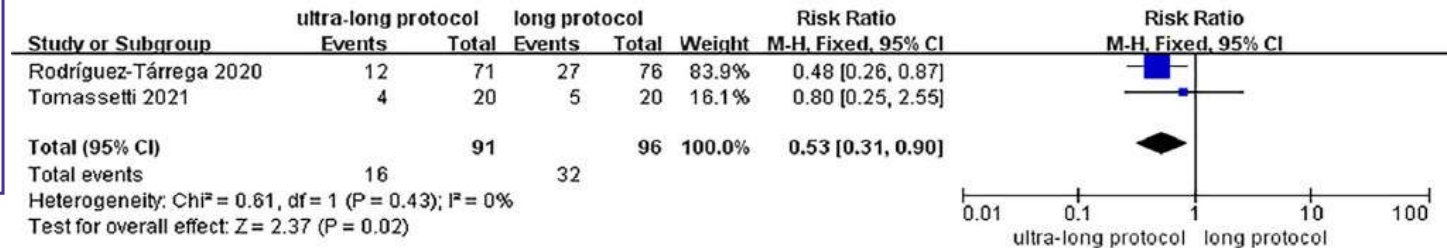
Endometriosis and infertility: Optimized ART

Long-term pituitary down-regulation pretreatment: Impact on efficacy

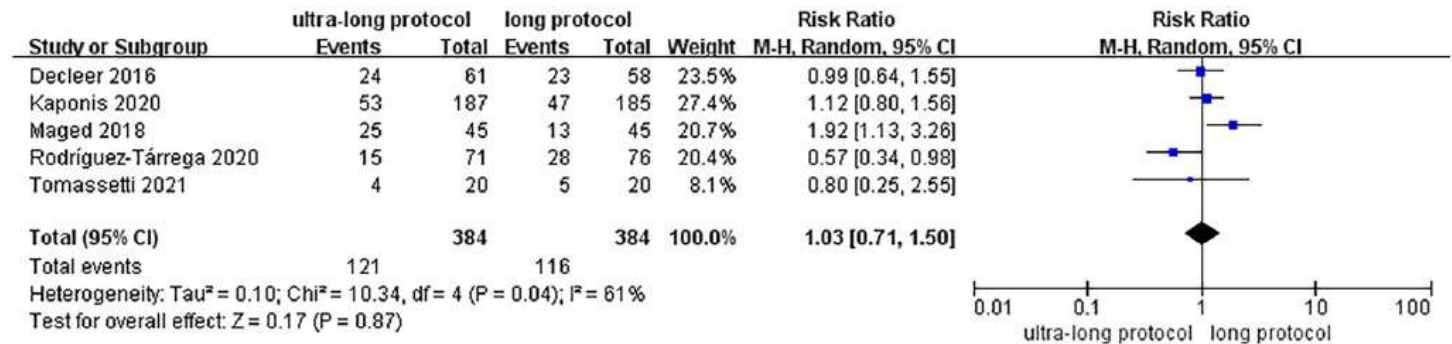
Meta-analysis:

- 7 RCTs
- Ultra-long vs long GnRHa protocols
- Outcome: clinical pregnancy rate

ART outcomes Live birth rates



Clinical pregnancy rates



Ultra-long Long protocol

RCTs: Randomised Controlled Trials; GnRHa: Gonadotropin-releasing hormone agonist;
M-H: Mantel-Haenszel test

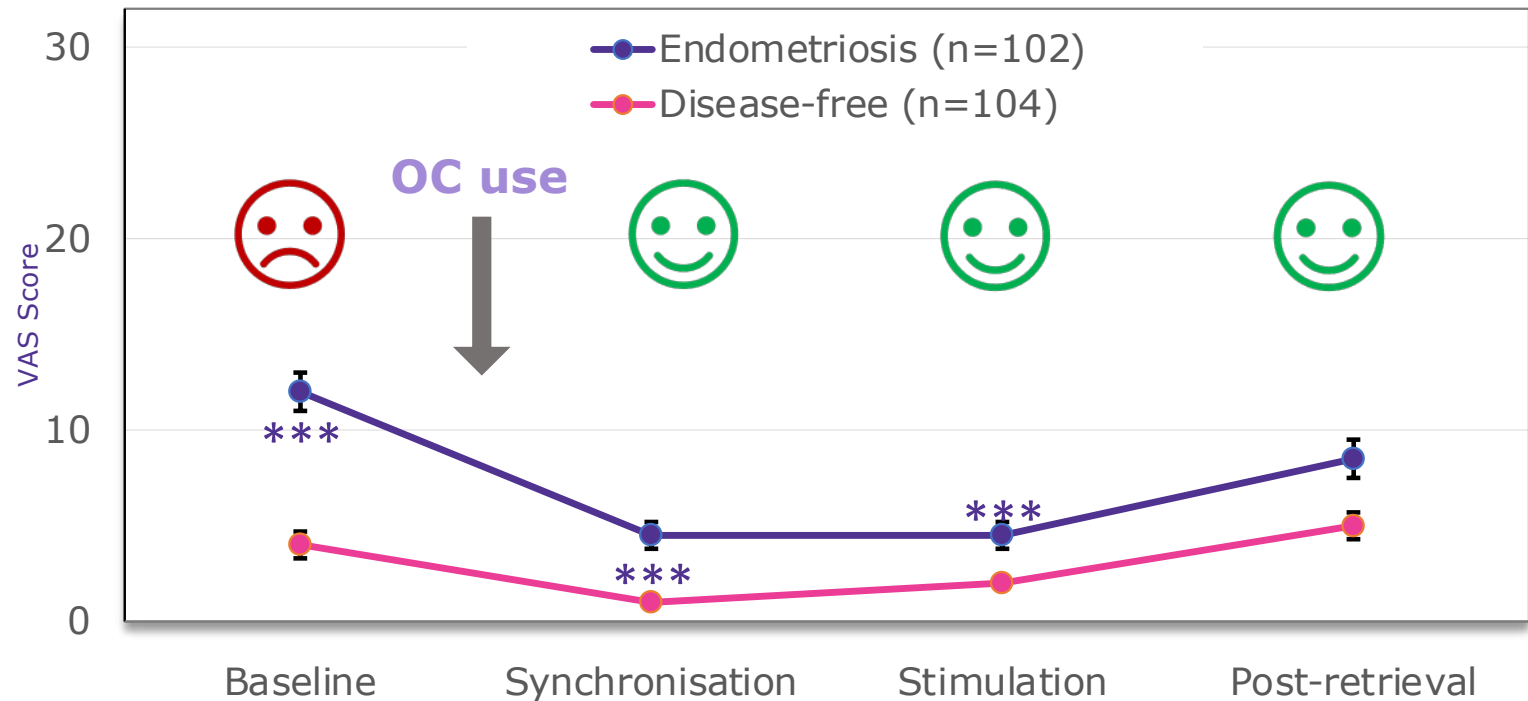
Endometriosis and infertility: Optimized ART

Pituitary down-regulation pretreatment: pain management

Prospective controlled cohort study:

- 102 OSIS patients
- 104 controls
- VAS-score + quality of life assessment

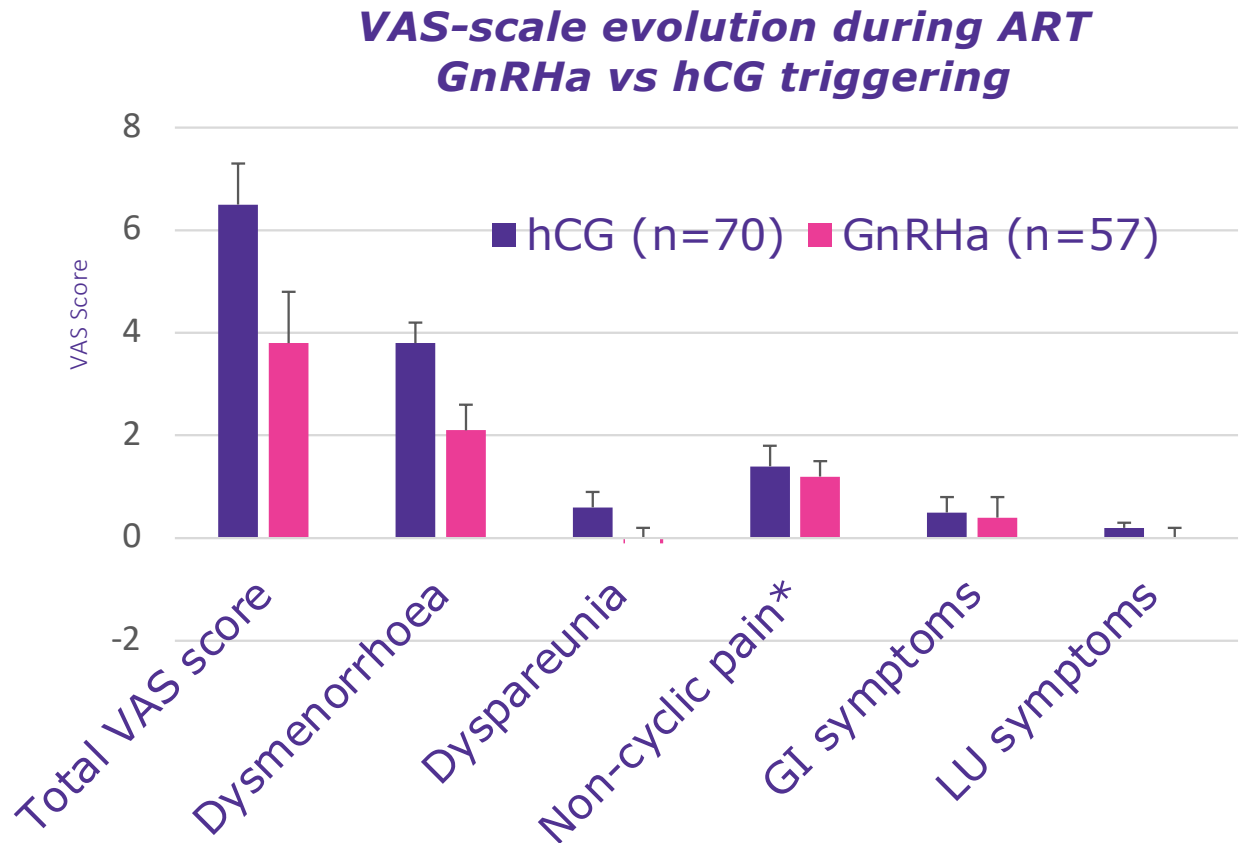
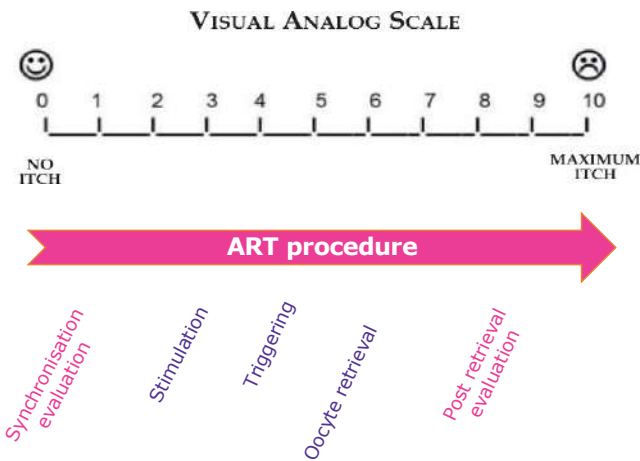
Evolution of pelvic pain during ART women with OSIS versus controls



Endometriosis and infertility: Optimized ART

GnRH agonist triggering : Pain management

Observational cohort:
 - 57 GnRHa triggering
 - 70 hCG triggering



GnRHa: Gonadotropin-releasing hormone agonist; hCG: Human chorionic gonadotropin;
 VAS: Visual analogue scale; GI: Gastrointestinal; LU: Lower urinary tract

Endometriosis and infertility: Optimized ART

Protocols: GnRH agonist vs antagonist



Systematic review:

- 1 RCT + 7 observational studies
- 2761 ART cycles

ART live birth rates Long agonist vs antagonist protocols

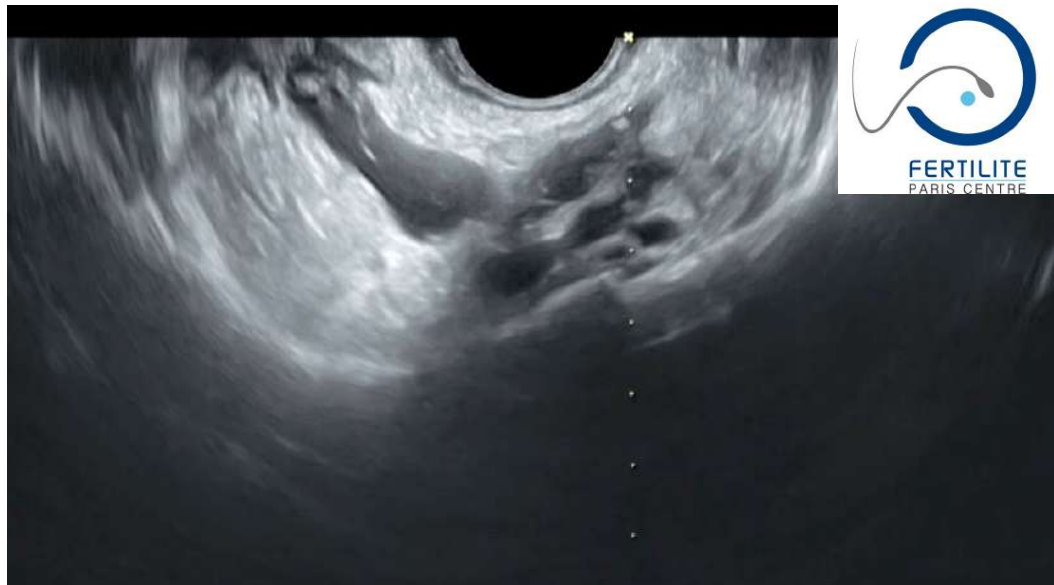
	Method of calculating LBR	GnRH agonist	GnRH antagonist	p-value
Zhao et al., 229 patients	LBR / ET cycle	24.6%	19.5%	NS
Drakopoulos et al., 386 patients	LBR / patient	Stage I/II : 42.8% Stage III/IV : 27.3%	Stage I/II : 26.7% Stage III/IV : 23.8%	NS
Kolanska et al., 218 patients	Cumulative LBR	21%	14%	NS

RCT: Randomised Controlled Trial; GnRH: Gonadotropin-releasing hormone;
LBR: Live birth rate; ET: Embryo transfer; NS: Non-significant

Kuan et al. Ther Adv Endocrinol Metab. (2023)

Large EndometriOMAs

Oocyte yield



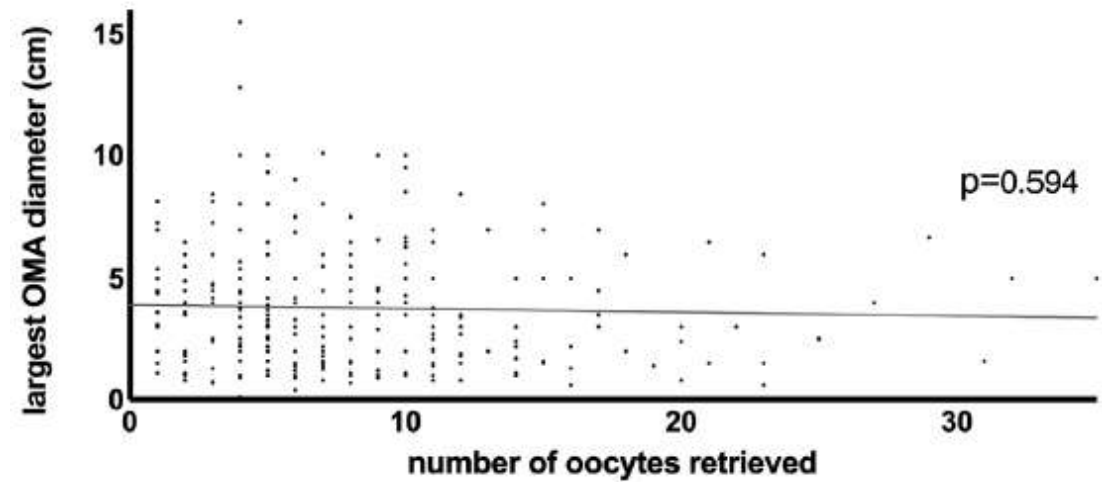
OMA
IVF-ICSI
N=326

RBMO



ARTICLE

Influence of endometrioma size on ART outcomes

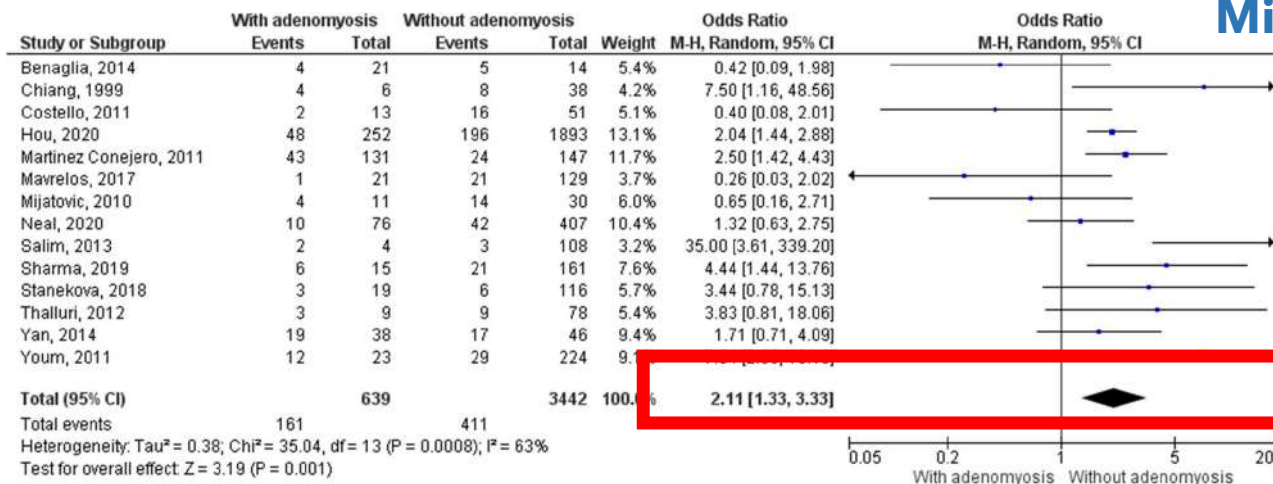
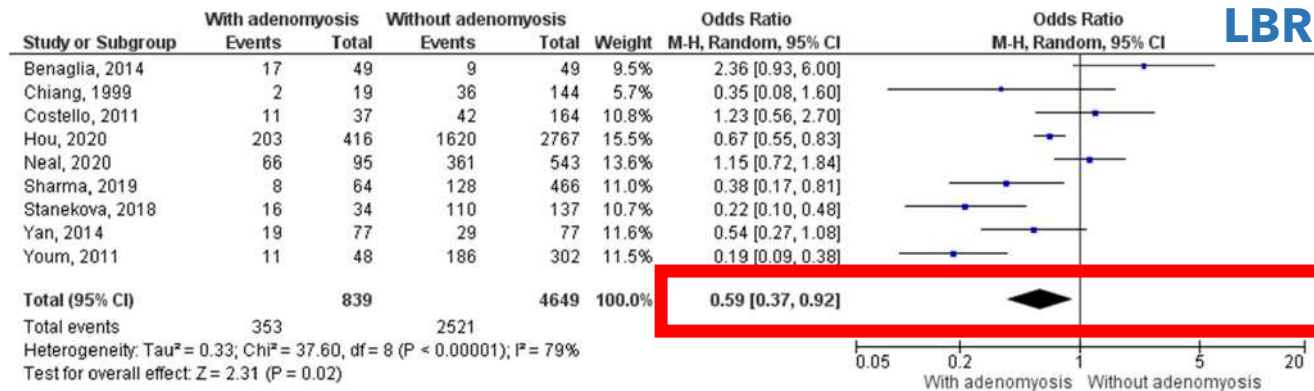


Bourdon - Santulli et al RBMO (2022)



Adenomyosis and infertility : IVF - ICSI

Méta-analysis



Adenomyosis and infertility :

How ART



- When should we transfer : fresh or differed ?
- With or without down regulation ?

ART and differed embryo transfer : Adenomyosis

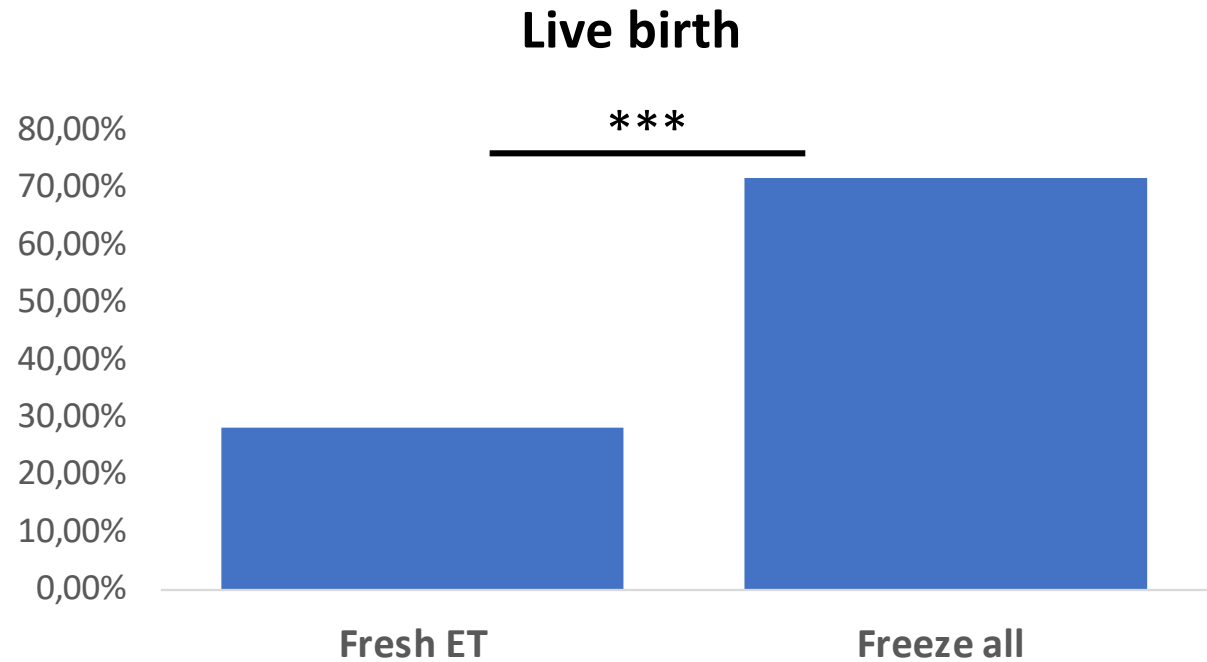
Variables associated with the presence of a live birth: multiple logistic regression analysis.

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.



Adenomyosis and ART :

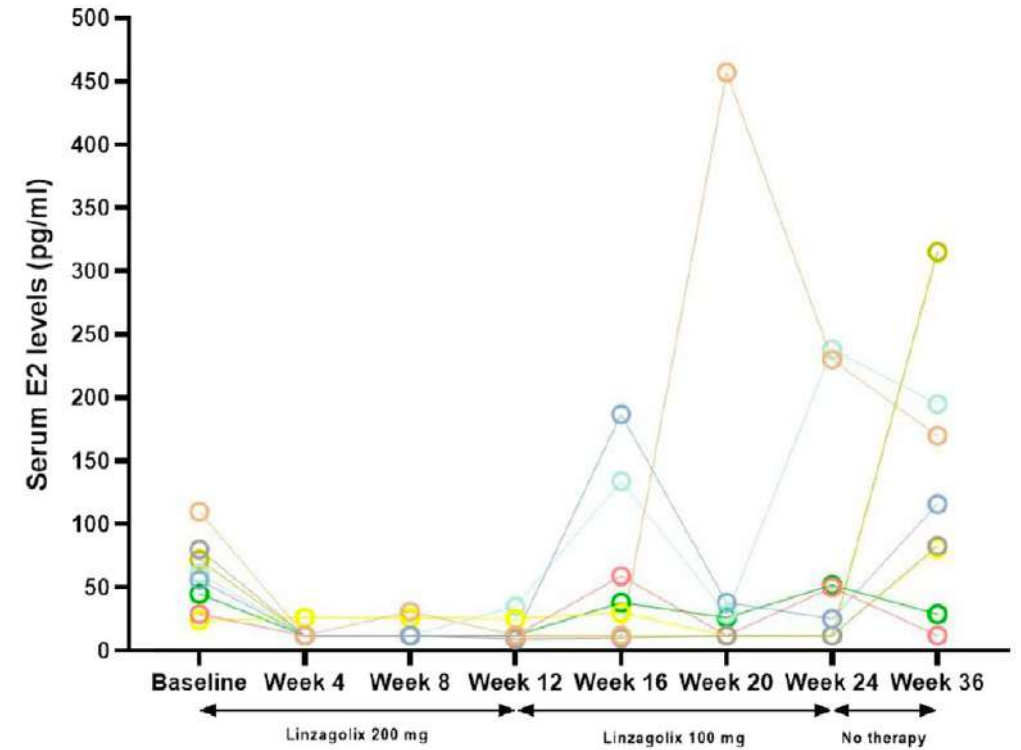
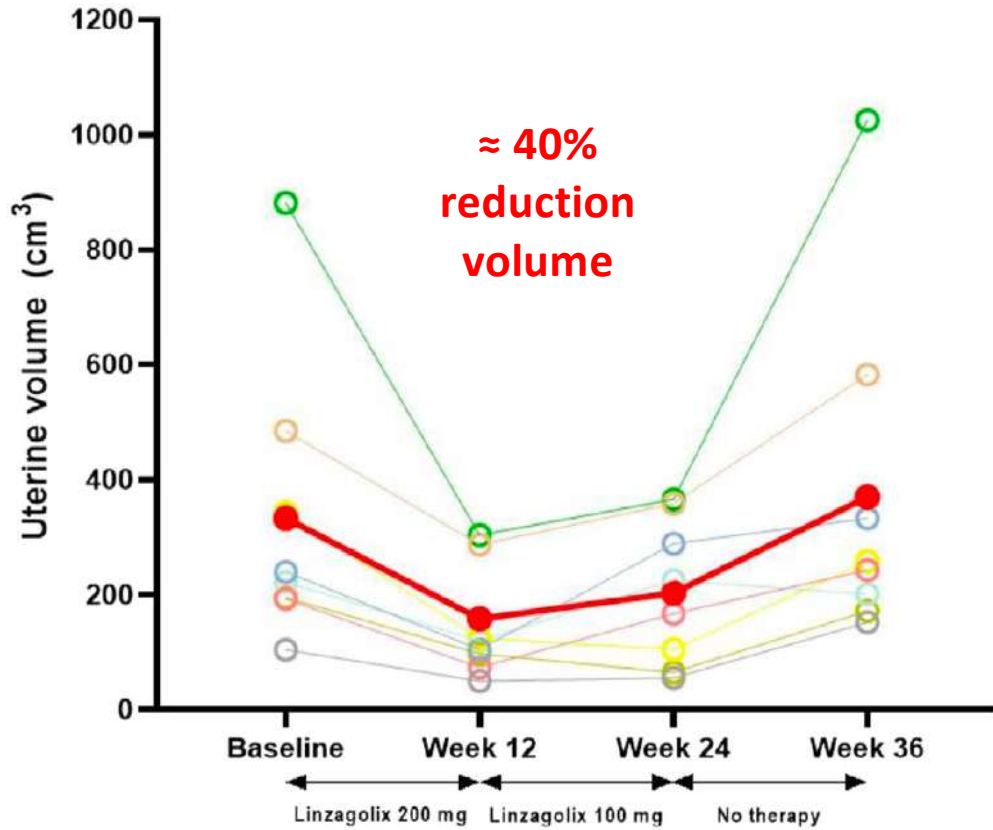
GnRHa downregulation

Effectiveness of prolonged downregulation with gonadotrophin-releasing hormone analogue (GnRHa) in women with adenomyosis undergoing IVF/ICSI

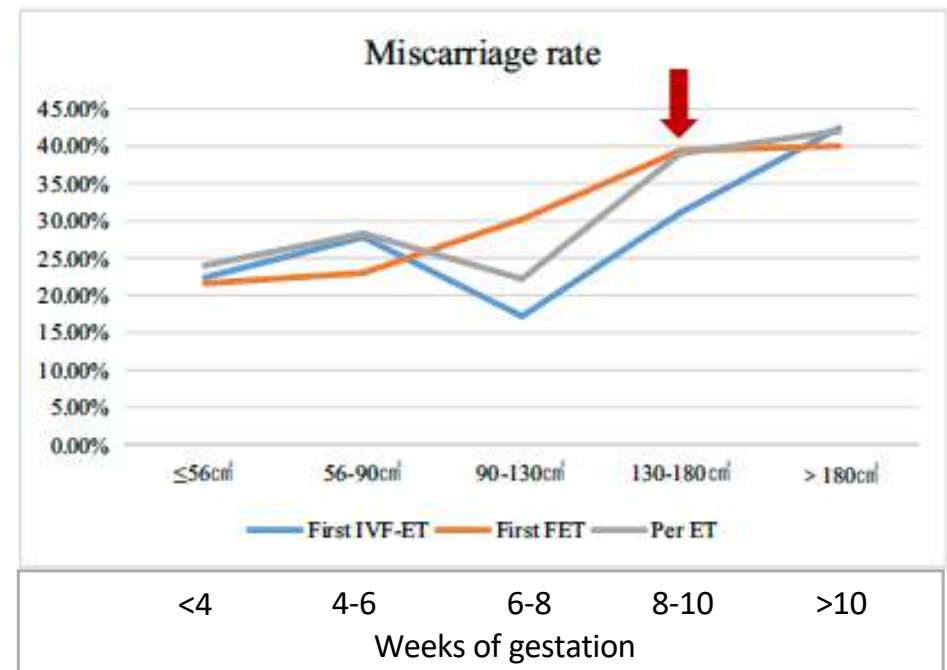
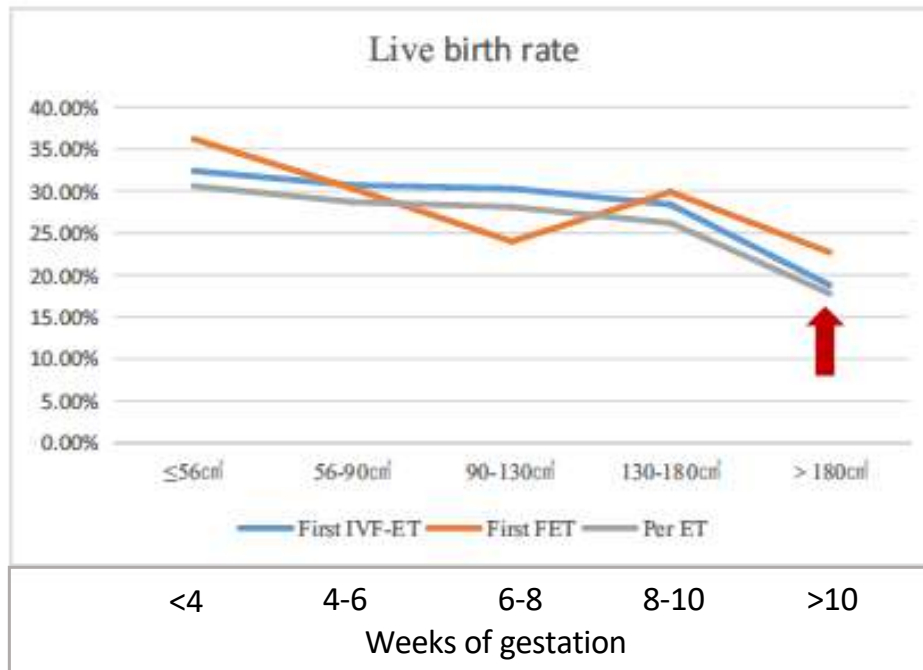
Author	Journal	Inclusion	Studies	Patients	Iplantation	CP	Miscarriage	LBR	
Cozzolino M	Reprod Sci 2022	--> 11/2020	3		≈	≈	≈	≈	Pretreatment with the use of long-term GnRHa could not be beneficial
Latif S	EJOG 2024	--> 03/2023	8 (all from china)	2422 women with adenomyosis	↑	↑	≈	≈	Higher CPR after preTTT (Fresh and frozen mixed)
Ge L	BMJ Open 2024	--> 10/2023	23	4872 cycles with adenomyosis 6289 cycles without adenomyosis	↑	↑	≈	↑	Higher LBR in FET with preTTT/ Fresh LBR in FET with preTTT adenomyosis = controls

Adenomyosis and uterine volume :

Oral antagonists



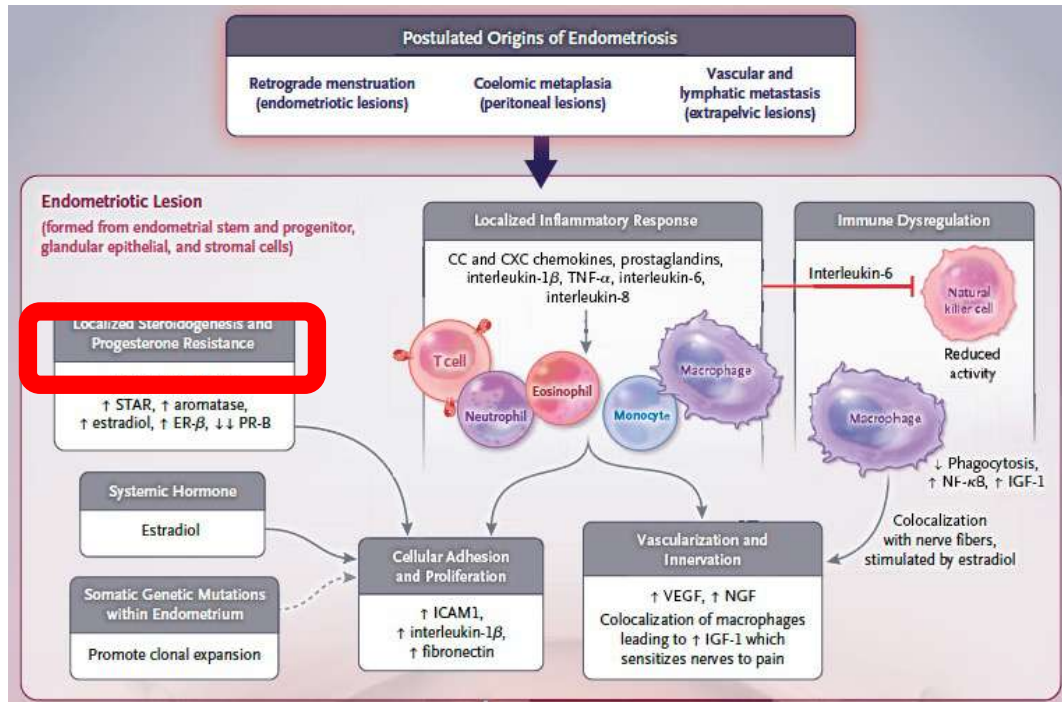
Adenomyosis and ART : Uterine Volume



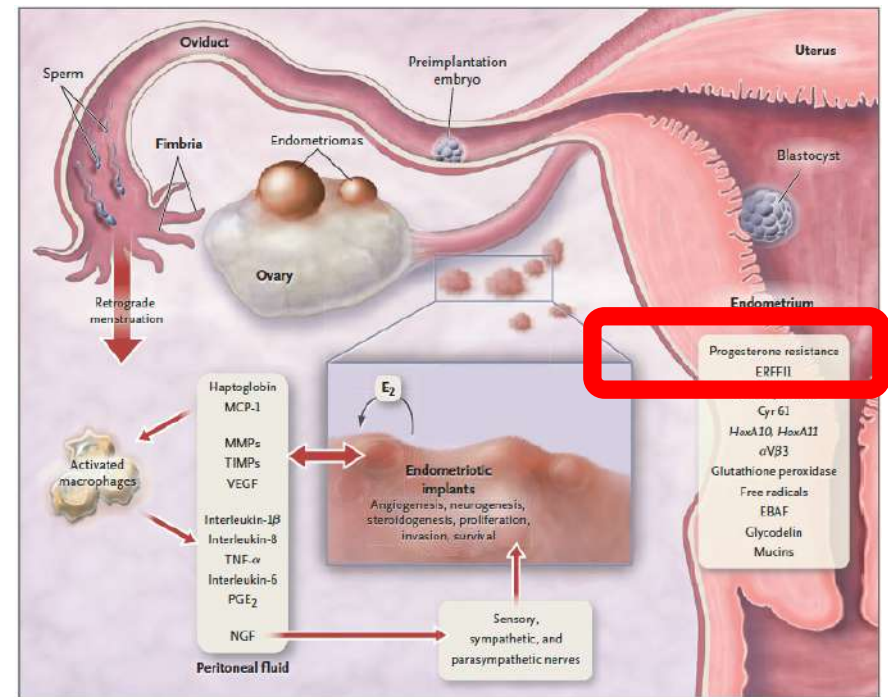
Us based Retro : 1155 patients
 Fresh and subsequent Frozen : 1876 transfers
 China

Endometriosis / Adenomyosis and infertility

Progesterone resistance



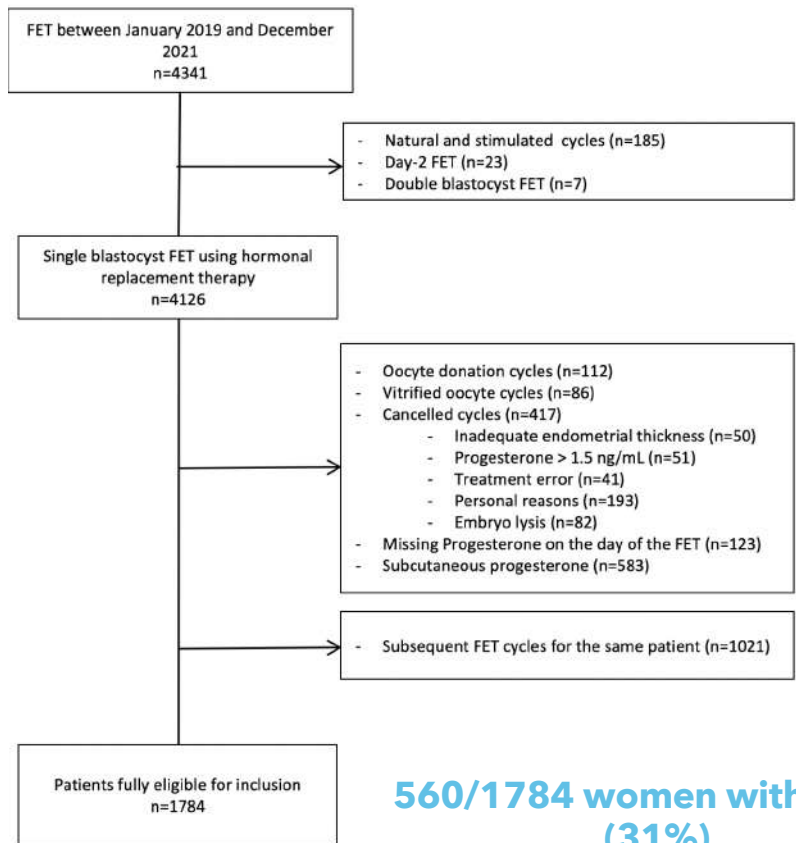
Zondervan KT et al. Nejm 2020



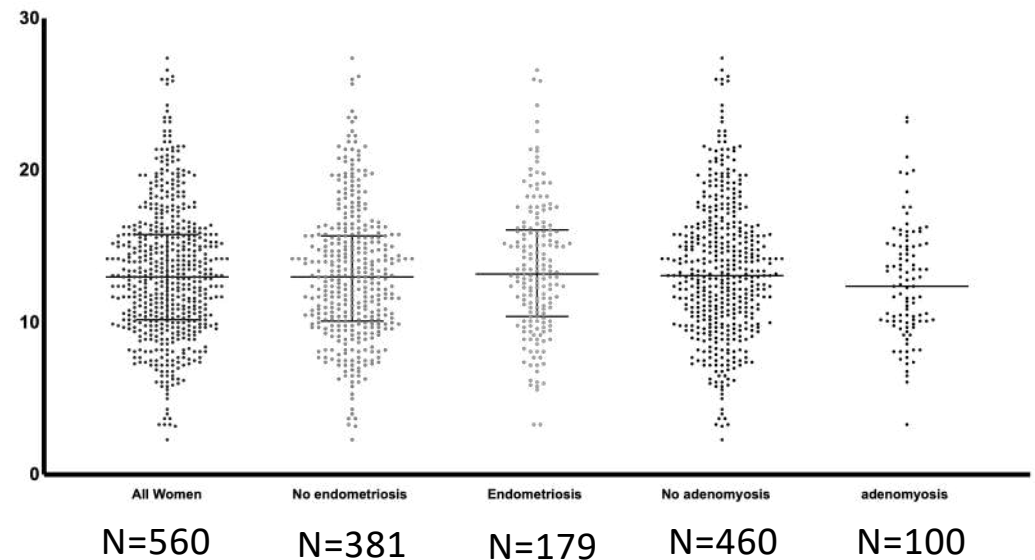
Giudice LC. Nejm 2010

HRT - FET

Progesterone levels and endometriosis



560/1784 women with a LBR (31%)



In endometriosis women, the progesterone level the day of transfer, does not differ with unaffected patients, in case of achieving a LB after HRT-FET.

Fertility and endometriosis-adenomyosis



Endometriosis and adenomyosis related infertility: who matters the most ?



What are the available therapeutic options for infertility?



What conclusions can we draw ?

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 and implantation

Main messages



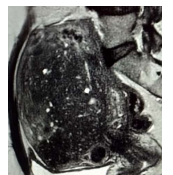
No major impact on the quality of the ovarian reserve



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



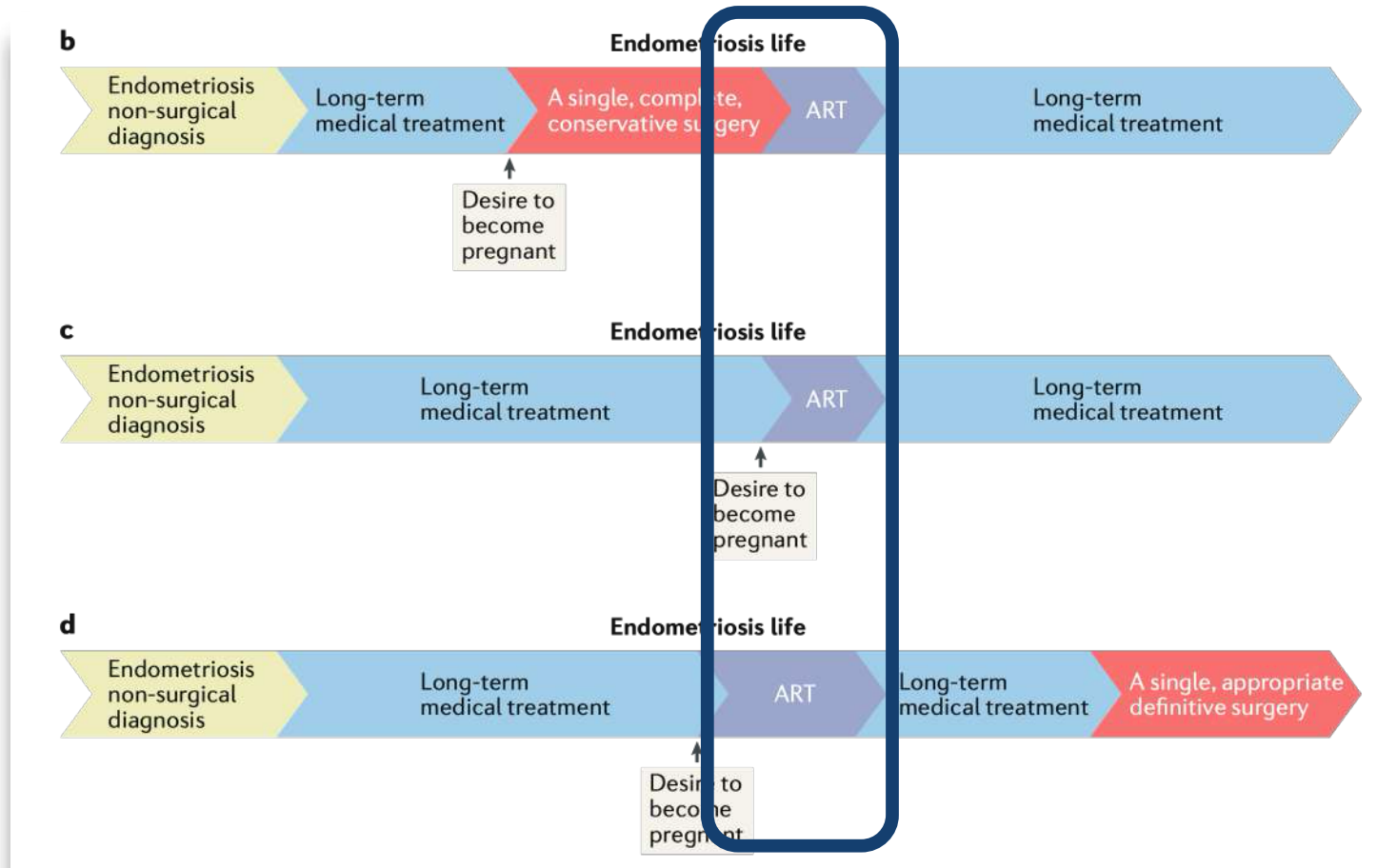
No major impact of endometriosis phenotype on ART outcomes



Adenomyosis decreases (+/-) the chances of LBR

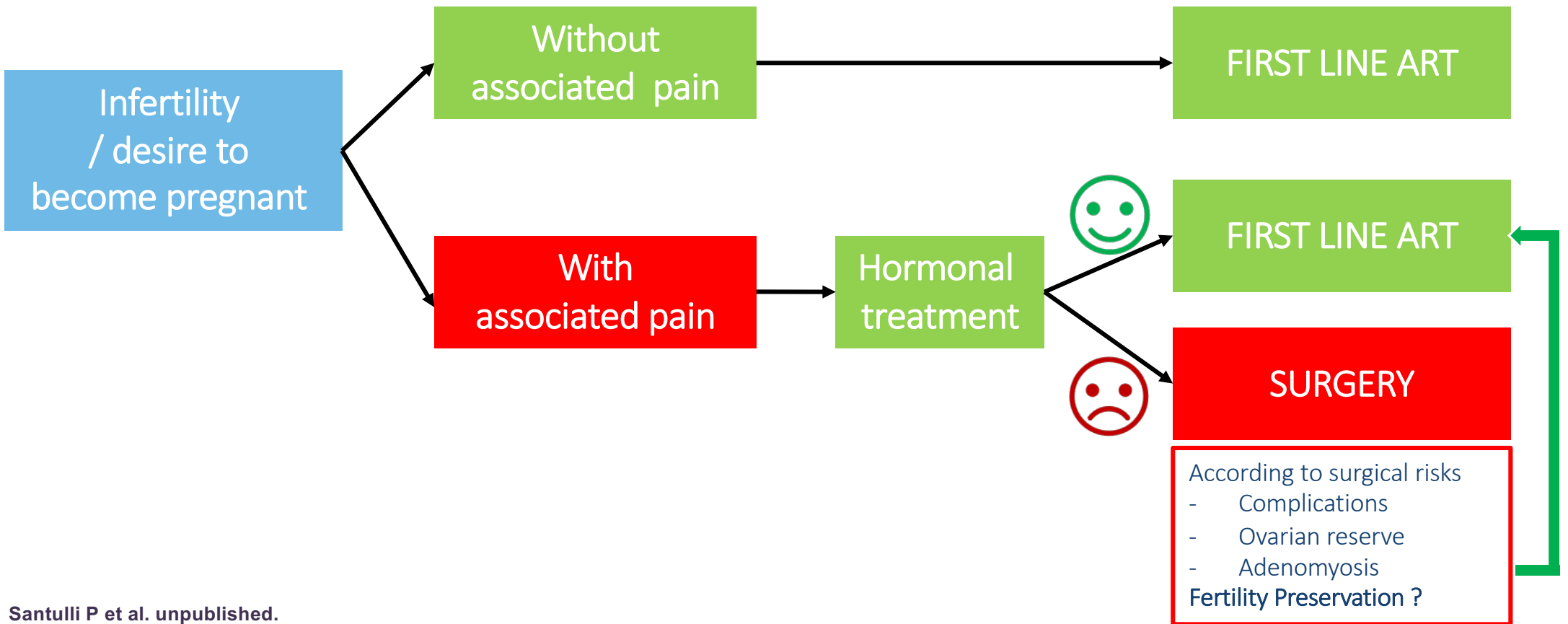
Endometriosis : Primum non nocere

Evolution toward medical treatments



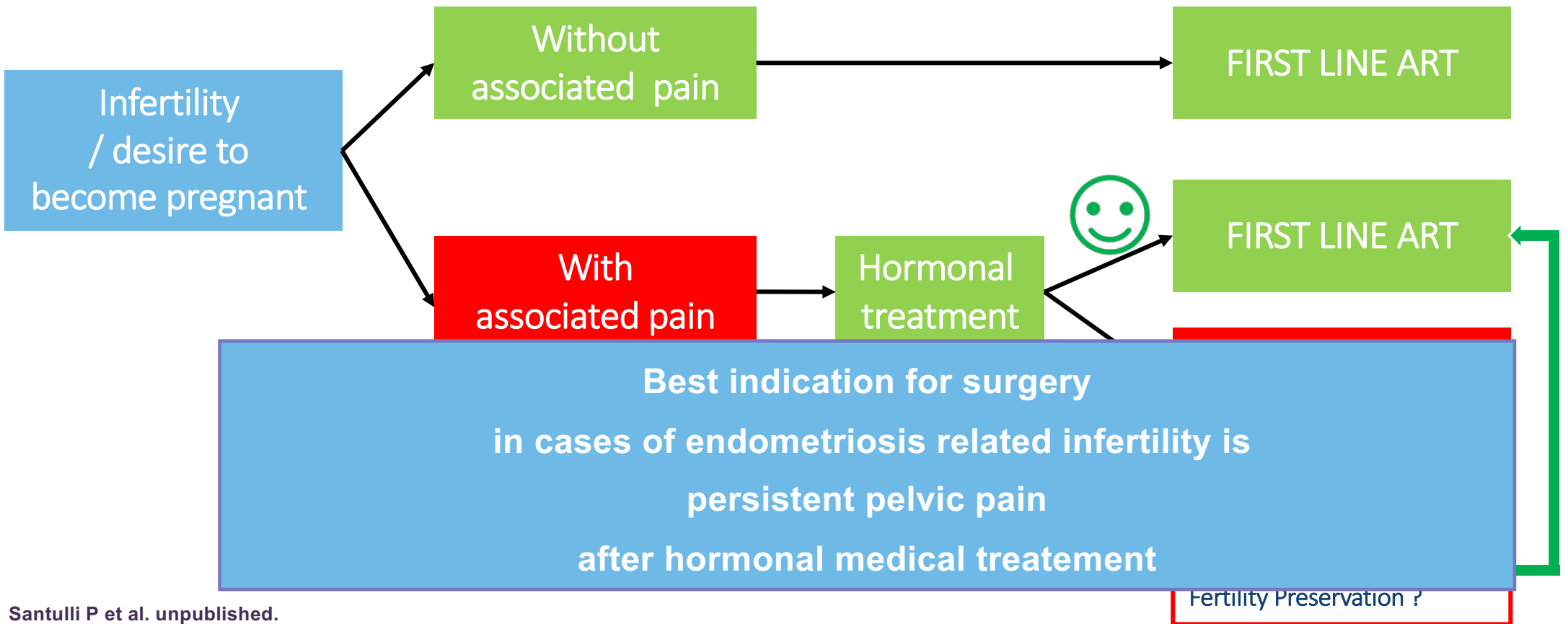
Take Home Message

Modern treatment strategy

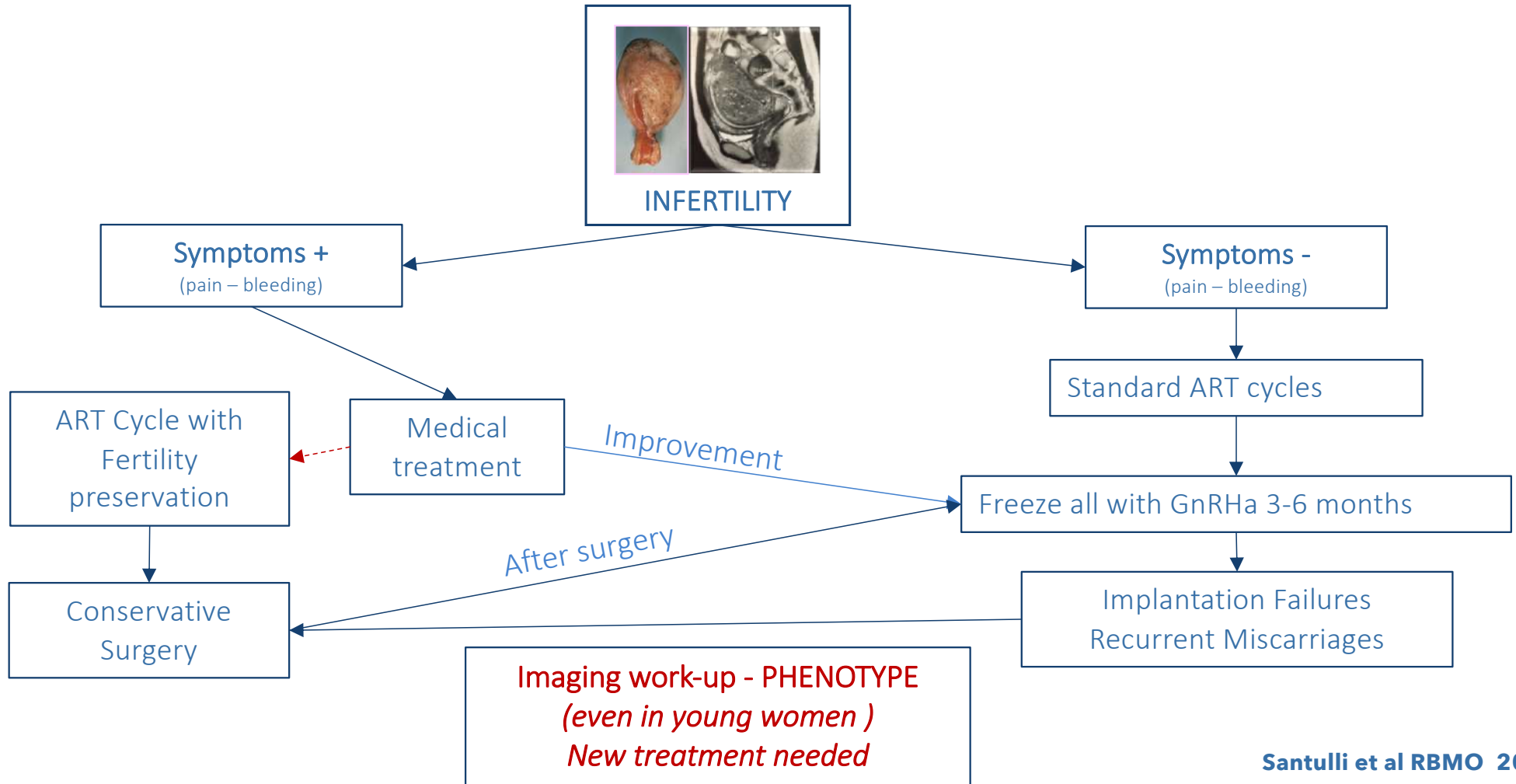


Take Home Message

Modern treatment strategy



Adenomyosis and infertility : Algorithm



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