Nouveau paradigme de prise en charge thérapeutique de l'endométriose

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Laboratory: *Imunulogy*

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Professor Charles Chapron,
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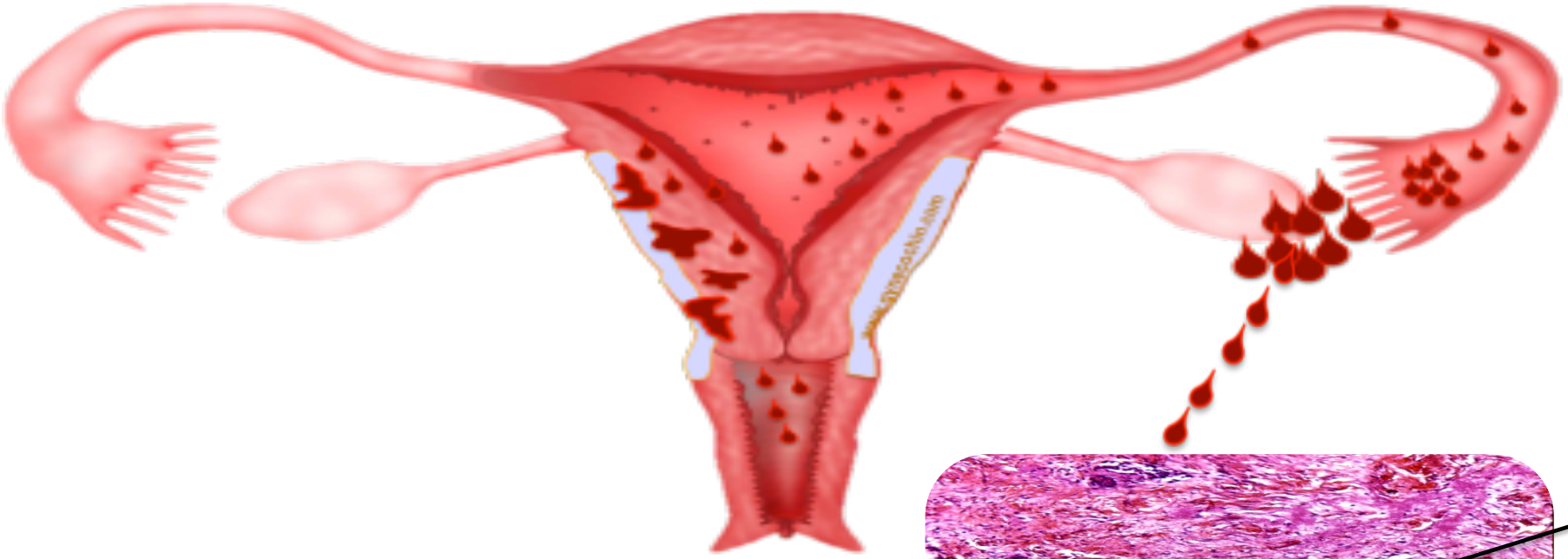
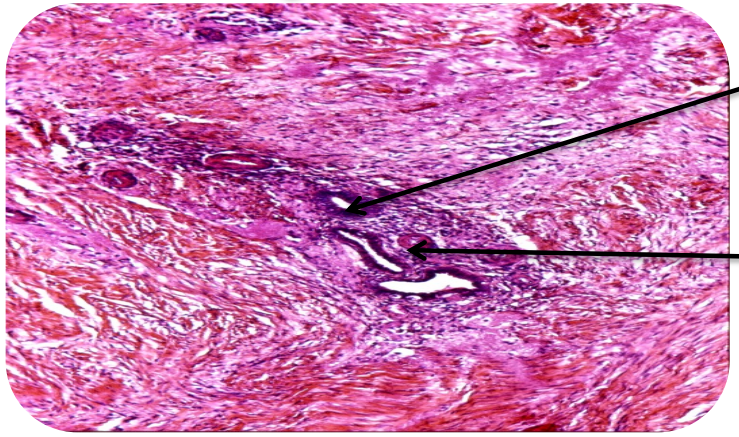
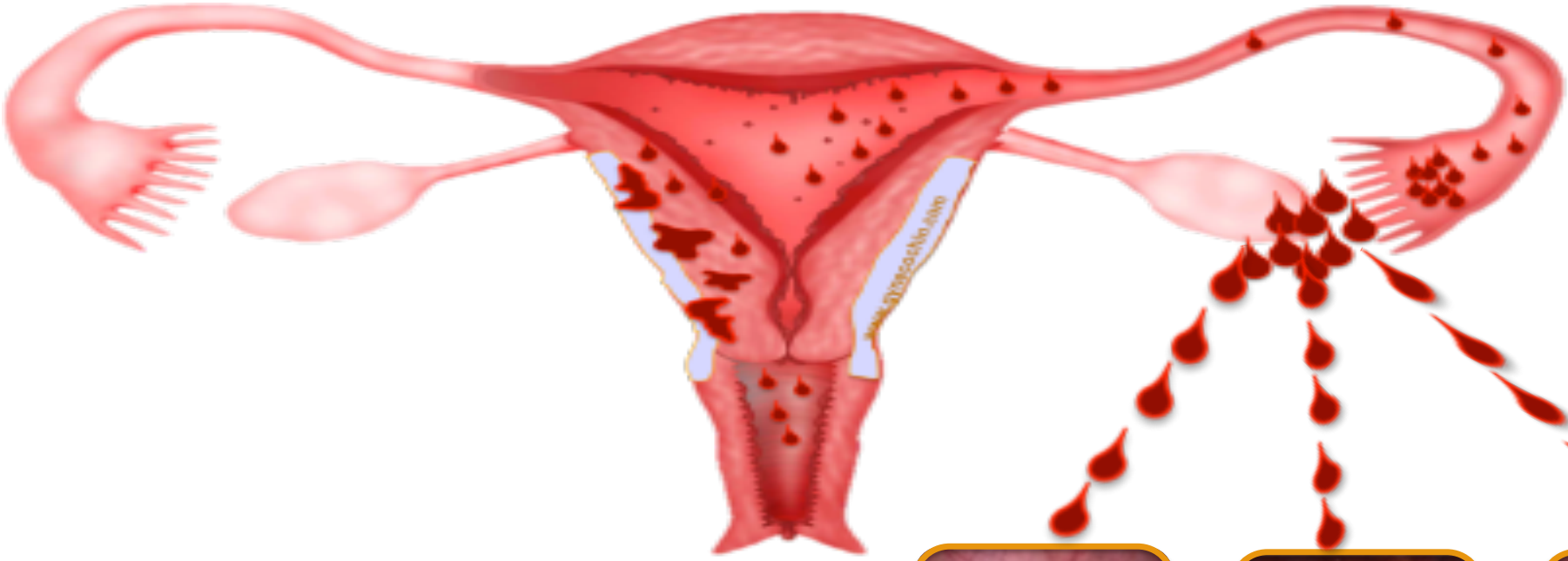
Endometriosis: *The implantation theory*





Sampson JA AJOG (1927)

Endometriosis: *The implantation theory*

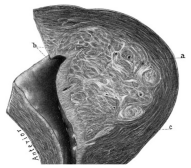


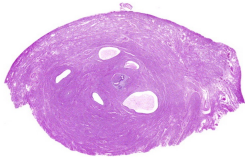
Three phenotypes

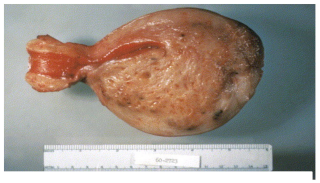
- SUP: Superficial peritoneal endometriosis
- OMA: Ovarian endometrioma
- DIE: Deep infiltrating endometriosis

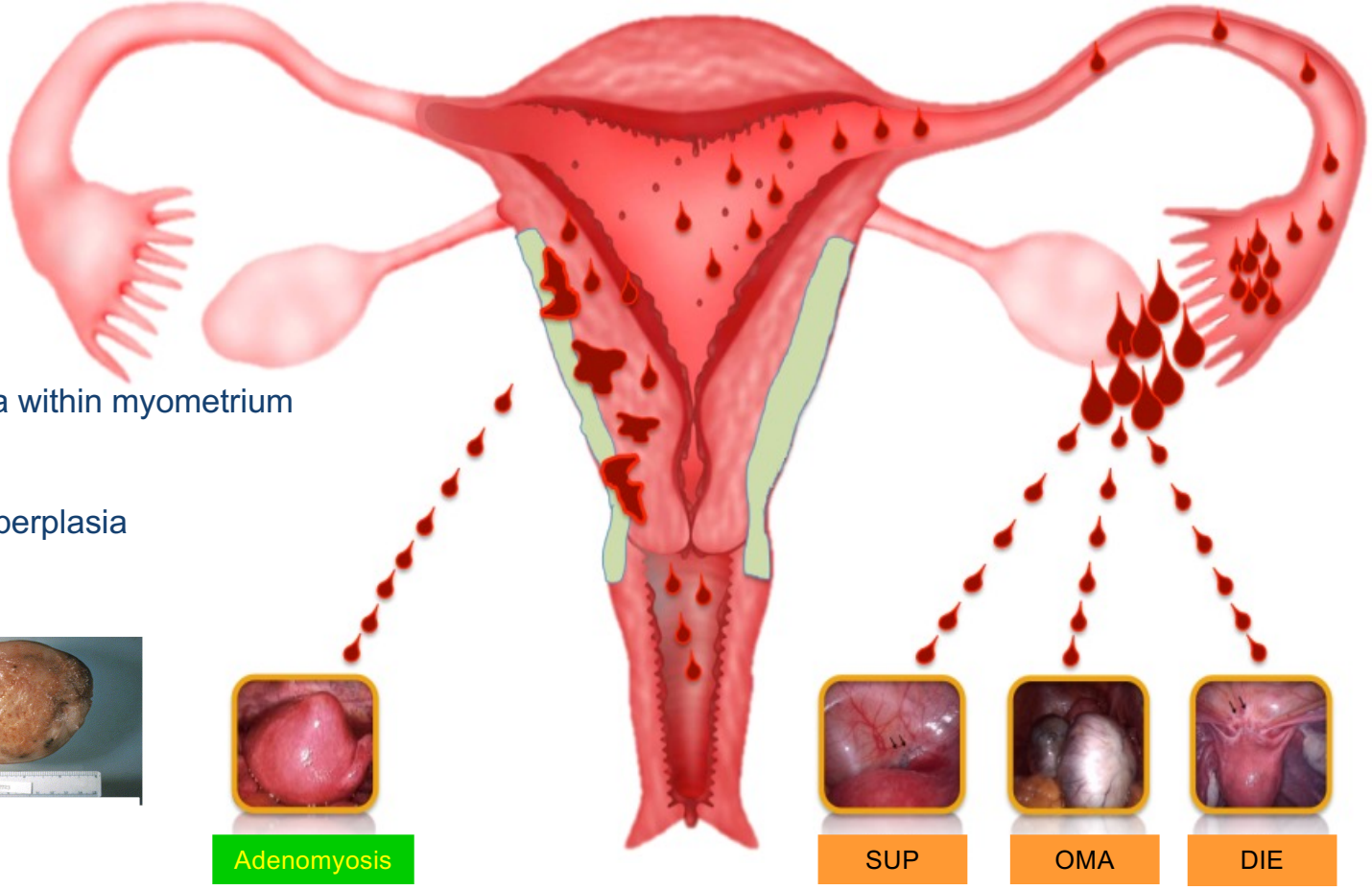
Endometriosis: The implantation theory

- Heterotopic endometrial glands and stroma within myometrium
- Local inflammatory response
- Variable degree of adjacent myometrial hyperplasia



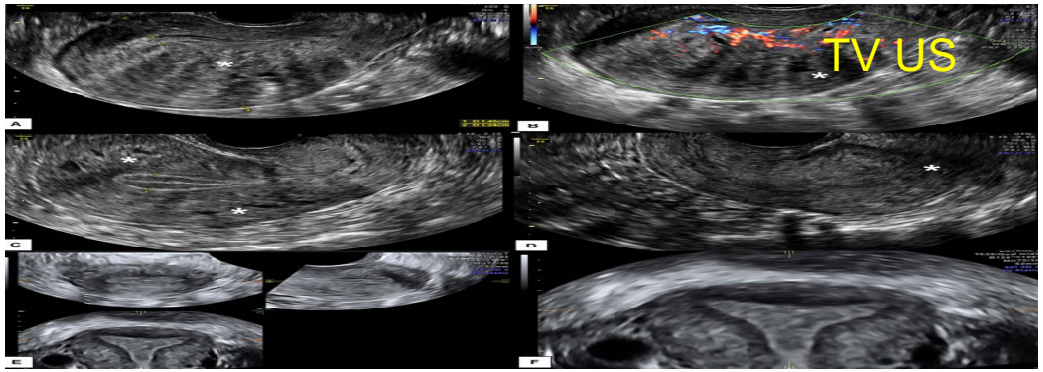


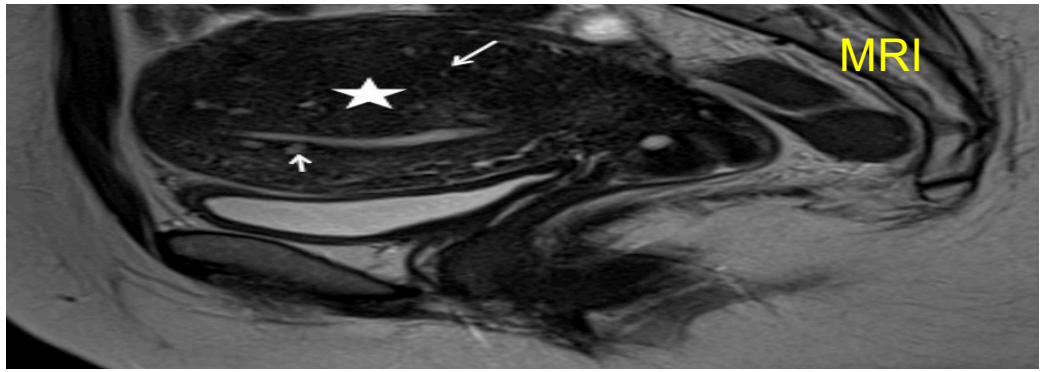




SUP: superficial lesion; OMA: endometrioma; DIE: deep infiltrating endometriosis

Adenomyosis: Prevalence





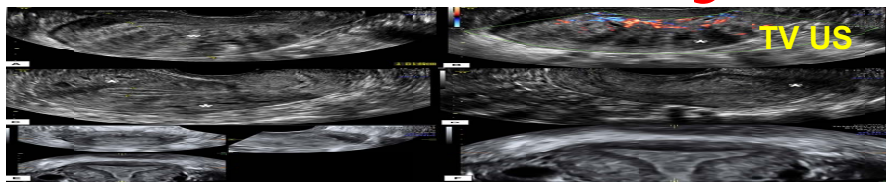
Mean age	N	DIFFUSE Adenomyosis
24 years (range 23-27 years)	156	53 (33.9%)

Pinzauti *et al.,* Ultrasound Obstet Gynecol (2015)

Mean age	N	DIFFUSE Adenomyosis
31.5 ± 5.5 *(range 17 to 41 years)*	292	101 (34.6%)

Chapron *et al.,* Hum Reprod (2017)

Adenomyosis: clinical impacts



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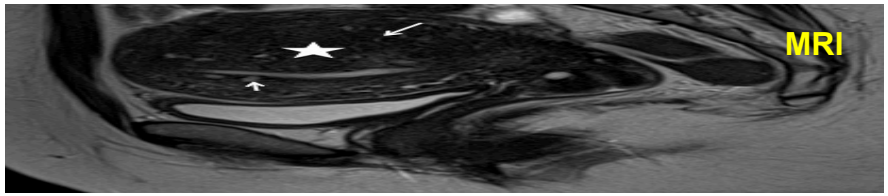

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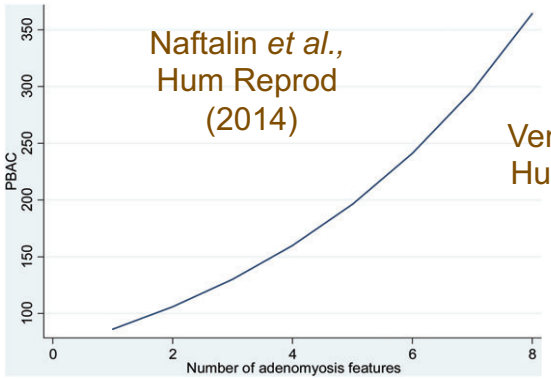
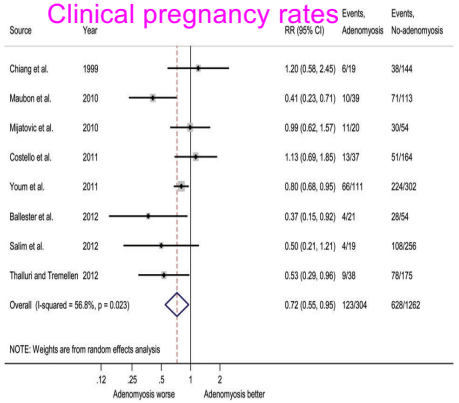
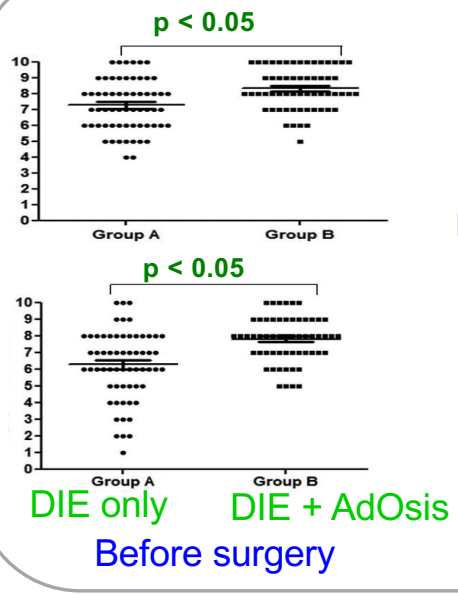


Naftalin *et al.*, Hum Reprod (2014)

Vercelllini *et al.*, Human Reprod (2014)

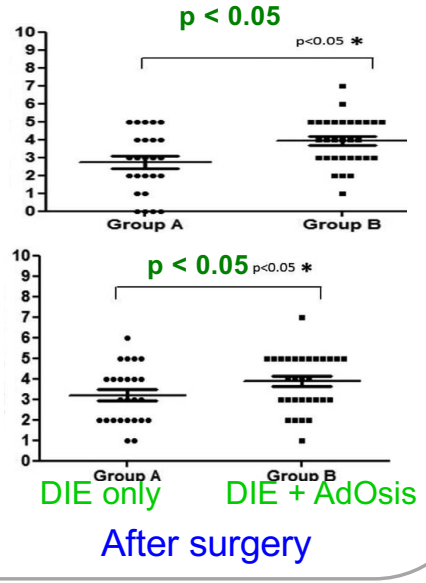




VAS DM

Lazzeri *et al.*, Reprod Sci (2014)

VAS DP



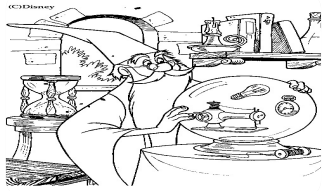
Endometriosis *and* adenomyosis: Relationship

Osis patients' phenotype	N	DIFFUSE Adenomyosis	FOCAL Adenomyosis
Controls	55	20 *(36.4%)*	3 *(5.4%)*
Endometriosis	237	81 *(34.2%)*	119 *(50.2%)*
SUP	40	8 *(20.0%)*	3 *(7.5%)*
OMA	31	14 *(45.2%)*	6 *(19.3%)*
DIE	166	59 *(35.5%)*	110 *(66.3%)*

Chapron *et al.*, Hum Reprod (2017)

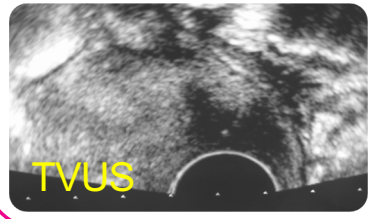
Rethinking endometriosis diagnosis

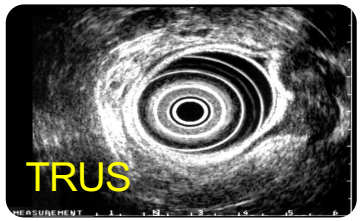
Questionning

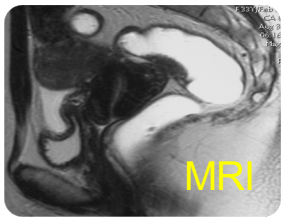


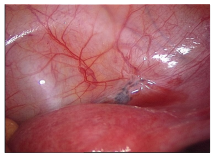
Patients with a high risk of endometriosis

Imaging

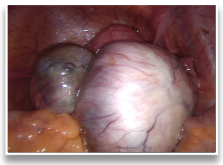






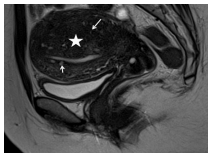


SUP



OMA

DIE



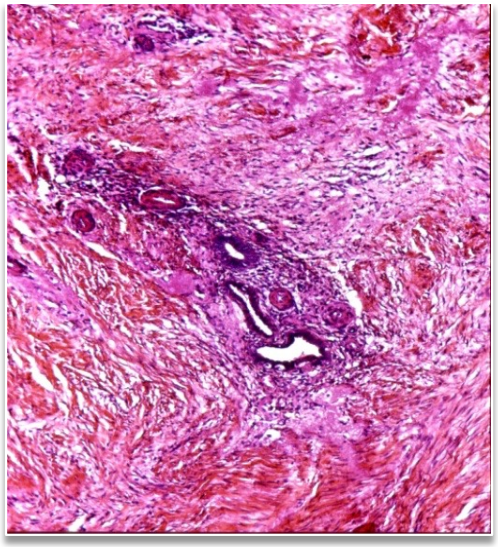
AdOsis

Endometriosis phenotypes + cartography

Chapron C *et al.,* Nat Rev Endocrinol (2019)

The shift towards clinical diagnosis

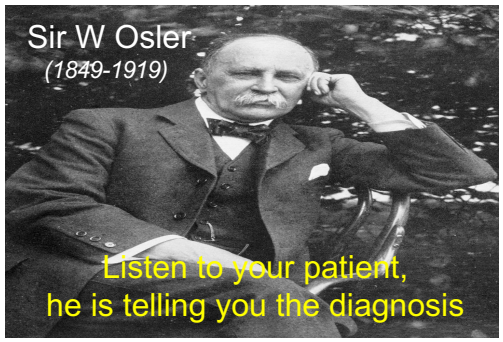
Surgical diagnosis

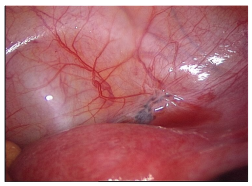


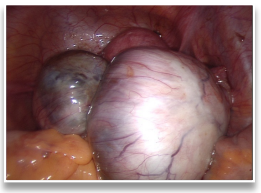
Histology

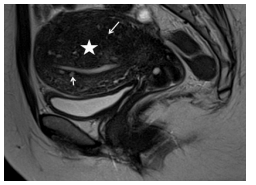
Questionning

Imaging









SUP OMA DIE AdOsis

Endometriosis phenotypes

"Moving from a histological to a clinical definition opens the door to an approach that emphasizes symptoms and their origins."

Chapron C *et al.*, Nat Rev Endocrinol (2019)

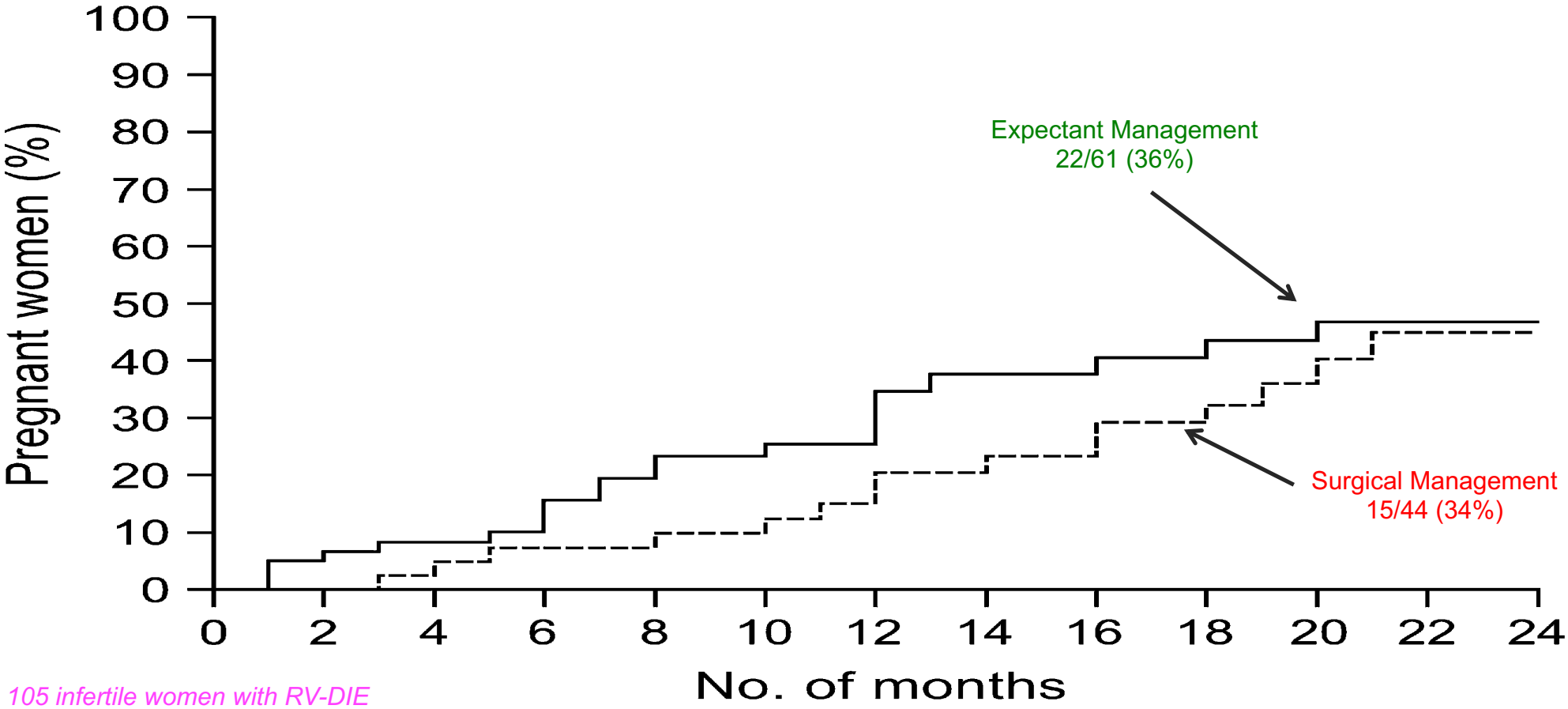
Isolated Superficial Endometriosis

Dependent variable	Prevalence in the SUP group ($n = 203$)	Prevalence in the control group ($n = 1292$)	Crude prevalence ratio (95% CI)	Adjusted prevalence ratio (95% CI)
Primary infertility	67/202 (33%)	236/1292 (18%)	1.82 (1.45–2.28)	1.83 (1.46–2.24)
Dysmenorrhea (moderate or severe)	164/203 (81%)	720/1286 (56%)	1.44 (1.33–1.57)	1.43 (1.31–1.52)
Deep dyspareunia (moderate or severe)	92/198 (47%)	369/1234 (30%)	1.55 (1.31–1.85)	1.50 (1.25–1.75)

Reis - Chapron *et al.*, Reprod Sci (2020)

Endometriosis and infertility:

Conservative versus surgical management in DIE

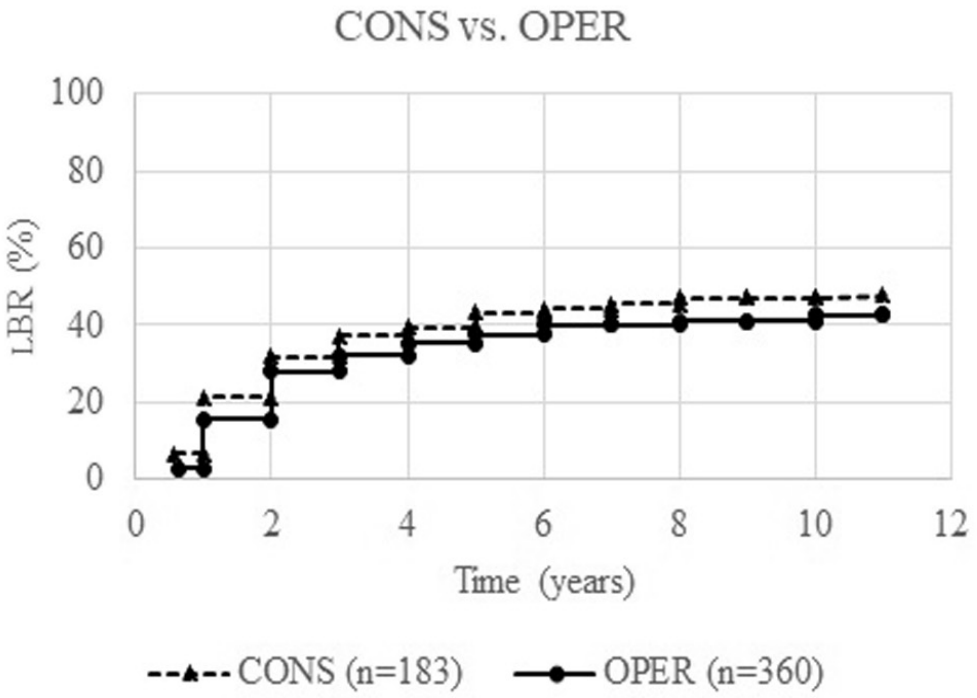


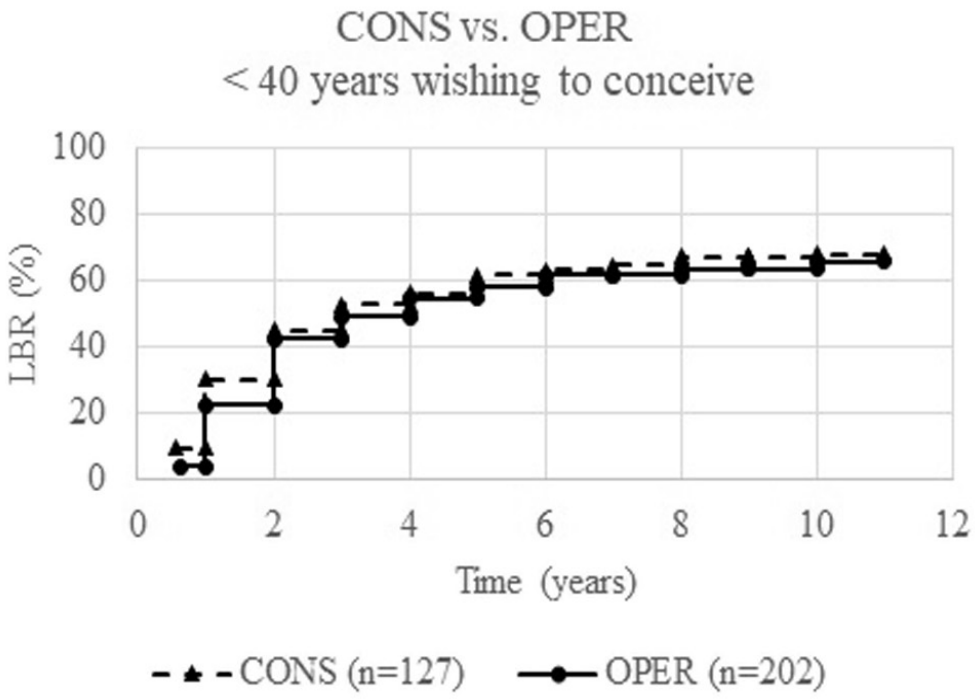
N = 105 infertile women with RV-DIE
Follow up 24 months

Vercellini *et al.*, AJOG (2006)

Endometriosis and infertility:

Conservative versus surgical management in DIE





Finland Retrospective N =5 43 Rectovaginal endometriosis
Surgery vs conservative

Tuominen, *et al.,* Fertil Steril (2021)

Endometriosis and infertility:

Conservative versus surgical management in DIE

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

	CONS (n = 183)		OPER (n = 360)		
Outcome	**n**	**%**	**N**	**%**	**OR (95% CI)**
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)

Finland Retrospective N = 543
Rectovaginal endometriosis
Surgery vs conservative

Patients with spontaneous LBR
34/183 = 18.6%

Patients with spontaneous LBR
82/360 = 22.8%

Tuominen, *et al.,* Fertil Steril (2021)

OMA: Determinant for painful symptoms severity

(Multiple logistic regression analysis)

Dysmenorrhoea	Main DIE lesion: intestine[a]	5.2 (2.7–10.3)
	Bilateral endometrioma	2.8 (1.4–5.6)
Deep dyspareunia	Main DIE lesion: USL[a]	2.0 (1.1–3.5)
Non-cyclic chronic pelvic pain	Main DIE lesion: USL[a]	2.1 (1.1–4.3)
	Left sided endometrioma	3.5 (1.7–7.1)
	Previous surgeries for endometriosis	2.2 (1.1–4.5)
Gastrointestinal symptoms	Main DIE lesion: intestine[a]	7.1 (3.3–15.3)
LU symptoms	Main DIE lesion: vagina[a]	13.4 (3.2–55.8)
	Hematuria	10.0 (1.3–77.6)

Chapron *et al.*, Hum Reprod (2012)

Endometriosis and Pelvic Pain

	Osis WITH chronic pain	Osis WITHOUT chronic pain	p
	N = 248	N = 224	
Endometrioma	114 (46%)	126 (56%)	0.032

Leuenberger *et al.*, Eur J Pain (2022)

Deeply infiltrating endometriosis

Results according to the presence of OMA *(n = 500 patients)*

Main DIE lesion	R	OR	95% CI	p - value
USL	0.118	-	-	NS
Vagina	5.98	1.70	1.1 - 2.6	.014
Bladder	0.137	-	-	NS
Intestine	34.5	3.59	2.3 - 5.6	< 0.0001
Ureter	8.6	3.91	1.4 – 10.’	.003

Chapron *et al.,* Fertil Steril (2009)

Deeply infiltrating endometriosis

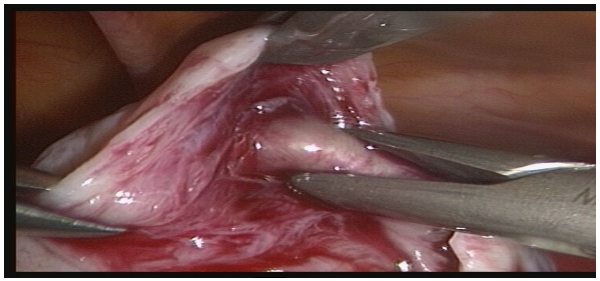
Results according to the presence of OMA *(n = 500 patients)*

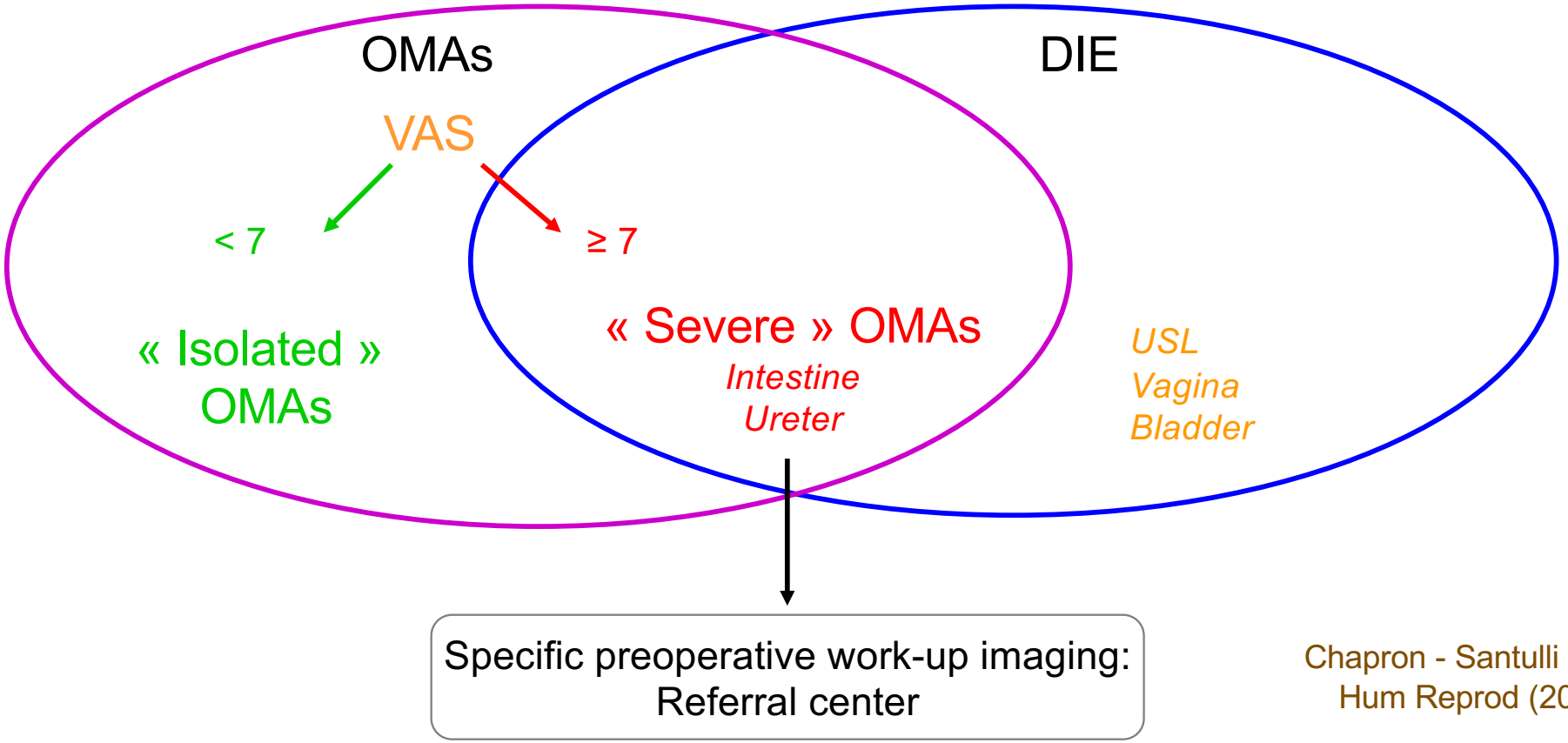
	OMA : No	OMA : Yes	p - value
Mean number of DIE lesions	1.64 ± 1.0	2.51 ± 1.72	< 0.0001
rAFS scores			
Implants	6.7 ± 4.9	28.1 ± 10.1	< 0.0001
Adhesions	16.5 ± 23.7	36.2 ± 28.7	< 0.0001
Total	23.6 ± 25.7	65.6 ± 33.1	< 0.0001

Chapron *et al.*, Fertil Steril (2009)

Painful OMAs

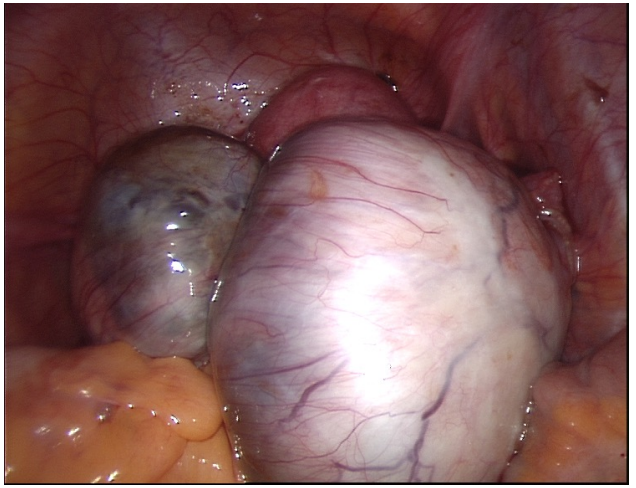
Modern management

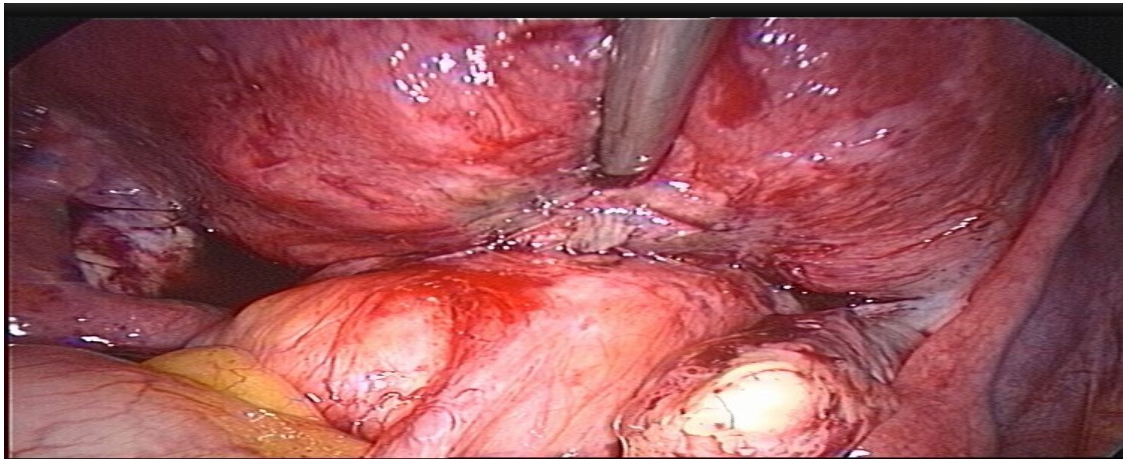




Chapron - Santulli *et al.*,
Hum Reprod (2012)

Painful ovarian endometrioma





OMA: Spontaneous ovulation rate *(n = 244)*

Number of patients conceiving during the study protocol (*n*, %)	105 (43.0%)
Patients conceiving during the study protocol (*n*, %)*	
without concomitant deep endometriosis	29 (47.5%; 35.0–60.0%)
with concomitant deep endometriosis	76 (41.5%; 34.4–48.6%)
Last cycle evaluated before conceiving (median, median, 25th–75th percentiles)	4 (3–5)
Side of ovulation when conceiving (*n*, %; 95% CI)**	
Healthy ovary	56 (53.3%; 43.3–63.1%)
Affected ovary	49 (46.7%; 36.9–56.7%)

Maggiore *et al.*, Hum Reprod (2015)

Ovarian reserve and OMA recurrence

	Homolateral OMA recurrence	No OMA recurrence	
AMH (ng/mL), mean ± SD	2.7 ± 1.9	3.1 ± 1.9	.59
Basal FSH (mIU/mL), mean ± SD	8.7 ± 3.9	8.4 ± 3.7	.85
Total AFC (n), median (range)	8 (4–15)	9 (5–15)	.37
AFC in the healthy ovary (n), median (range)	5.5 (3–9)	6 (2–12)	.54
AFC in the affected ovary (n), median (range)	2 (1–6)	3 (1–5)	.24
Volume of the affected ovary in case subjects and of the previously operated ovary in control subjects (cm^3), mean ± SEM	95.0 ± 22.2	6.8 ± 0.4	<.001
Volume of the healthy ovary (cm^3), mean ± SEM	6.9 ± 0.3	6.6 ± 0.3	.44

Ferrero *et al.*, Fertil Steril (2015)

Endometriosis: Risk factors associated with infertility

infertility—multiple logistic regression model. (N = 870)

Variable	OR (95% CI)	*P*
Age >32 years[a]	1.9 (1.4–2.5)	<0.001
Gravidity >0	0.7 (0.6–0.9)	<0.001
Peritoneal superficial endometriosis	3.1 (1.9–4.9)	<0.001
Previous history of surgery for endometriosis	1.9 (1.3–2.2)	<0.001

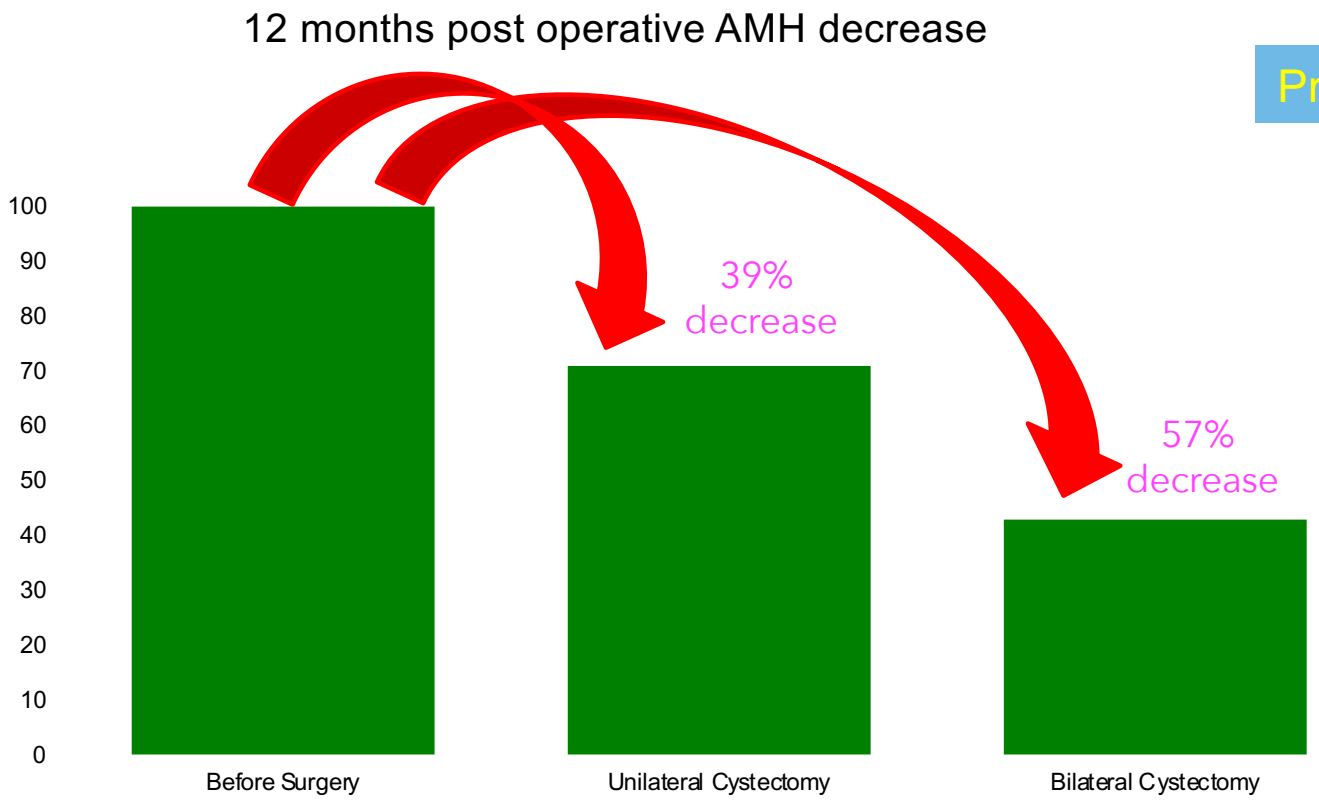
CI, confidence interval; OR, odds ratio; ASRM: American Society for Reproductive Medicine classification.

OMA *per se* is not associated with presentation for infertility

Santulli - Chapron *et al.*, Hum Reprod (2016)

Endometriosis *and* infertility: Impact of surgery

Endometrioma and ovarian reserve



Metaanalysis
12 studies

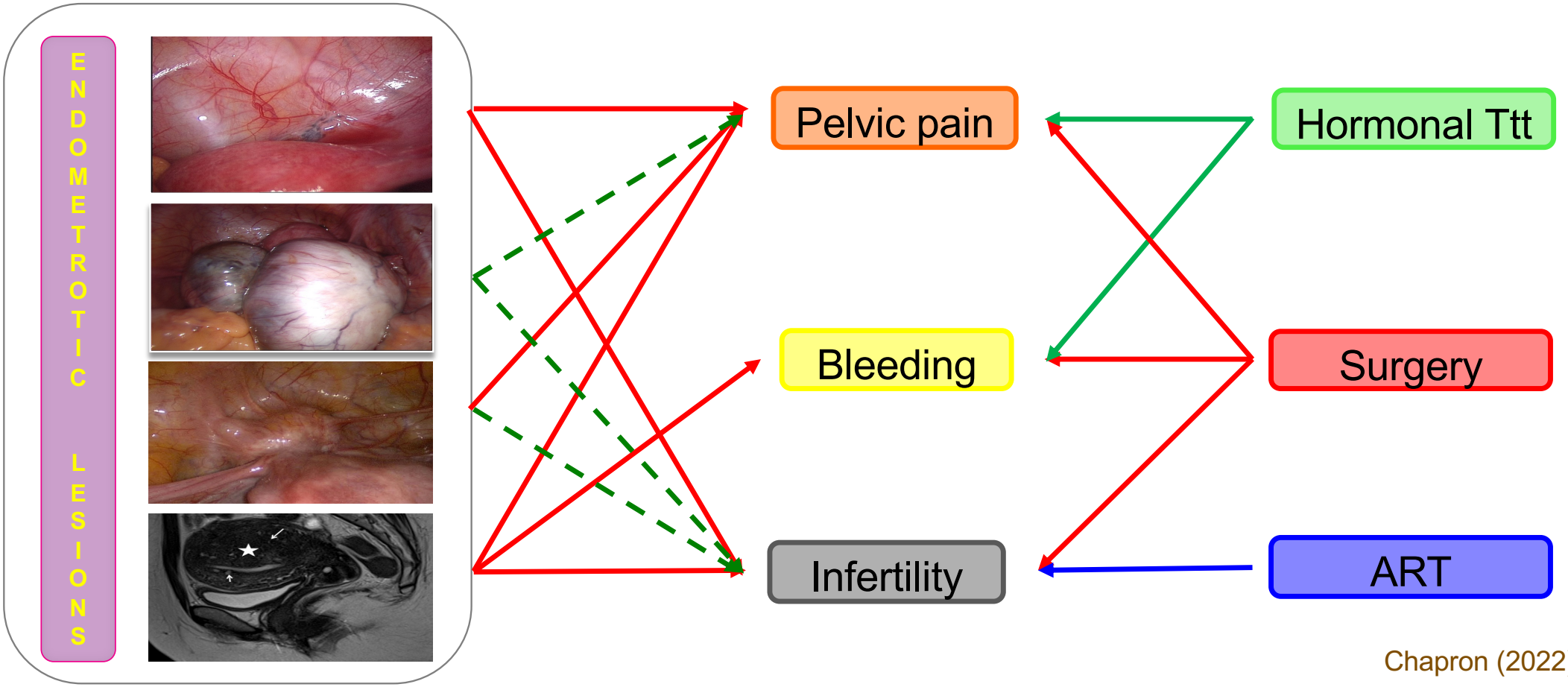
Younis YS *et al.*, HRU (2019)

Rethinking endometriosis management

Clinical impact of endometriotic lesions

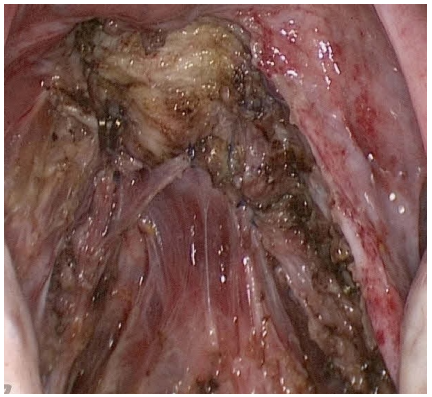
Pain	Endometriotic lesions	Infertility
YES	SUP	YES
Controversial	OMA	Controversial
YES	DIE	Controversial
YES	Adenomyosis	Yes

Endometriosis - Adenomyosis: Management



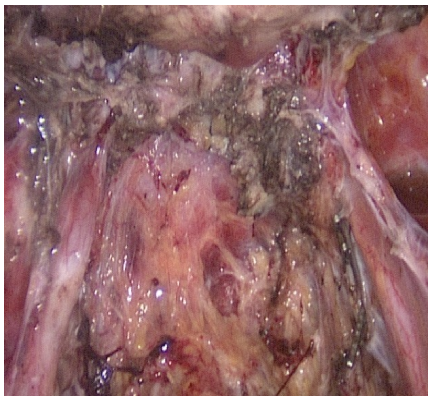
Chapron (2022)

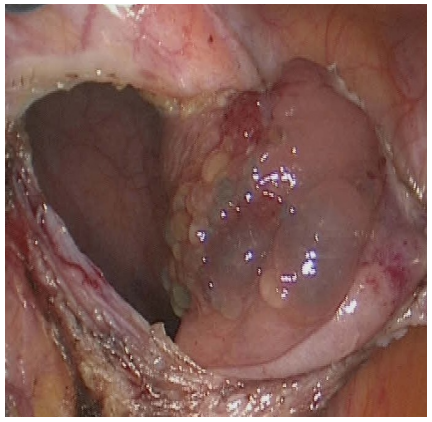
Symptomatic endometriosis:
Limitations for surgical treatment

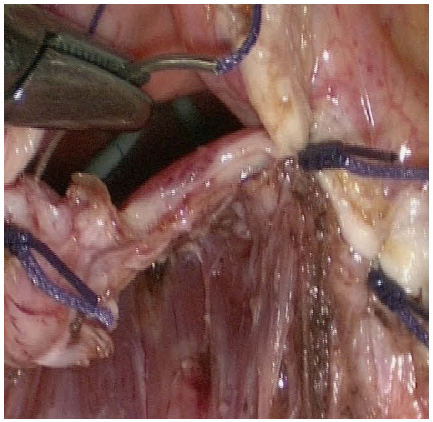


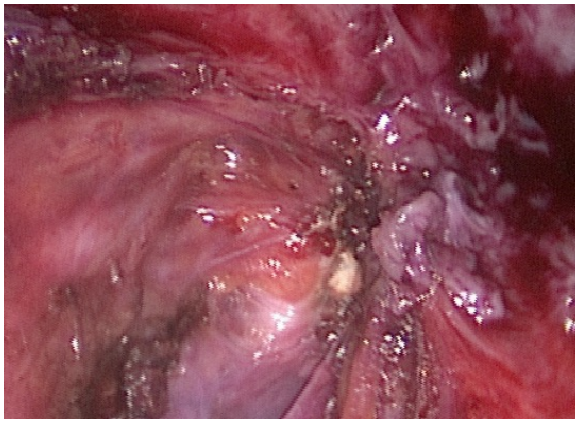
Althought surgery allows
for exeresis of endometriotic lesions,

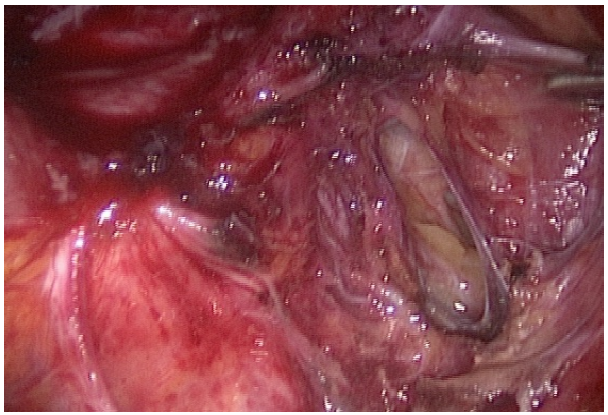
it does not treat
the underlying cause of the disease











Chapron *et al.,* Nat Rev Endocrinol (2019)

Symptomatic endometriosis:
Rationale for medical treatment

- Endometriosis is a chronic inflammatory disease and it requires lifelong management

- Surgical exeresis of endometriotic lesions has no effect on retrograde menstruation

- Medical treatments decrease inflammation, which is a key aspect of endometriosis pathogenesis

- Surgery is inefficient for treating pain due to central sensitization

- Numerous inadequate unecessary surgical procedures are performed for endometriosis

- High rates of symptoms and lesions recurrences after surgical treatment only

- Coexisted adenomyosis conservative surgery is difficult and controversial

Chapron *et al.,* Nat Rev Endocrinol (2019)

Endometriosis: Guidelines

Leyland N, Casper R, Laberge P, Singh SS, SOGC Endometriosis: diagnosis and management. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 2010; 32 (7 Suppl 2): S1-32.

American College of Obstetricians and Gynecologists. ACOG: Practice bulletin no. 114: Management of endometriosis. Obstet Gynecol 2010; 116 (1): 223-36.

Johnson NP, Hummelshoj L, World Endometriosis Society Montpellier C. Consensus on current management of endometriosis. Human reproduction 2013; 28 (6): 1552-68.

Dunselman GA, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. Human Reproduction 2014; 29 (3): 400-12.

National Institute for Health and Care Excellence (NICE): Diagnosis and management of endometriosis: summary of NICE guidance. BMJ 2017; 358: 4227.

Endometriosis-related pelvic pain: Hormonal treatments: a STEPWISE approach

- First line: Low cost drugs
  - Oral contraceptives: *cyclic, continuous*
  - Progestogens: *oral, IUD*

- Second line: High cost drugs
  - Dienogest
  - GnRH analogues: *IM*
  - GnRH antagonist

Vercellini *et al.,* Fertil Steril (2016)

Endometriosis: is it a progressive disease ?

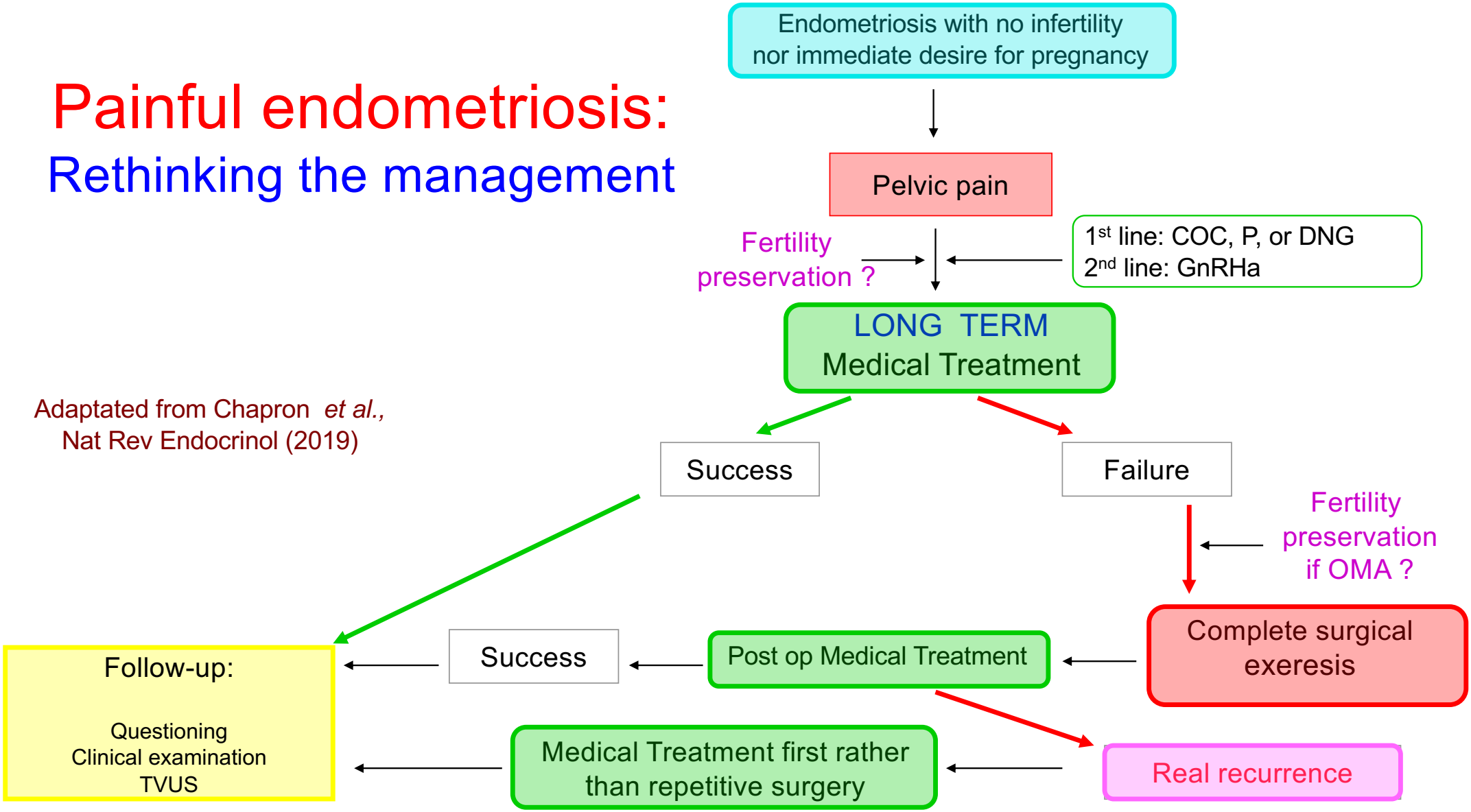
Evolution of recto-sigmoid DIE nodules between two MRI (38.2 ± 21.1 months)	%	Mean duration of amenorrhea
Stability	60.5	8.5 months
Regression	11.6	21 months
Progression	27.9	7.5 months
		p < 0.001

Progression of recto-sigmoid DIE lesion	%
Never amenorrhea	39
No continuous amenorrhea	34
Continuous amenorrhea	0

Netter *et al.*, Hum Reprod (2019)

Painful endometriosis:

Rethinking the management



Adaptated from Chapron *et al.*,
Nat Rev Endocrinol (2019)

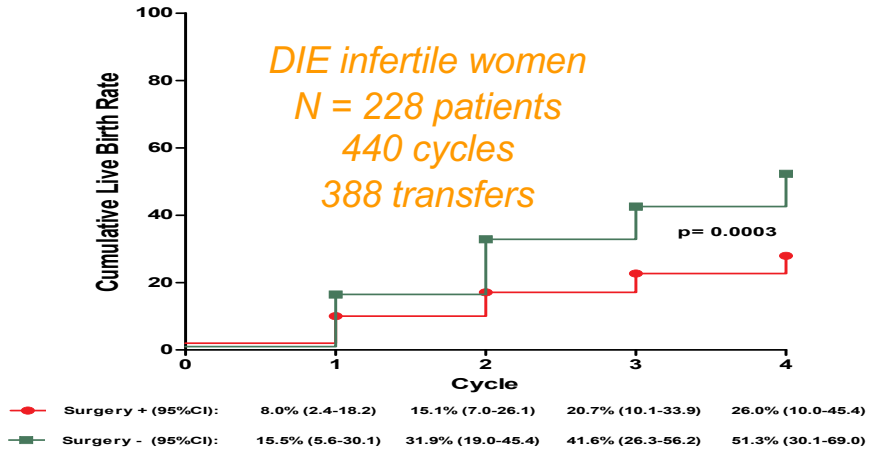
Endometriosis-related infertility

CONTROVERSY: IS THE OUTCOME OF IVF AFFECTED BY ENDOMETRIOSIS?

	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

Garcia-Velasco *et al.*, Fertil Steril (2004)

Pregnancy	N	Previous surgery for Osis		p
		YES (*n* = 167)	No (*n* = 61)	
DIE patients	228	49 (29.3%)	34 (55.7%)	0,0002
Intestinal +	137	20 (19.6%)	16 (45.7%)	0,0002
Intestinal -	91	29 (44.6%)	18 (69.2%)	



Maignien, Santulli, Chapron Reprod Sci (2020)

Endometriosis and infertility: ART

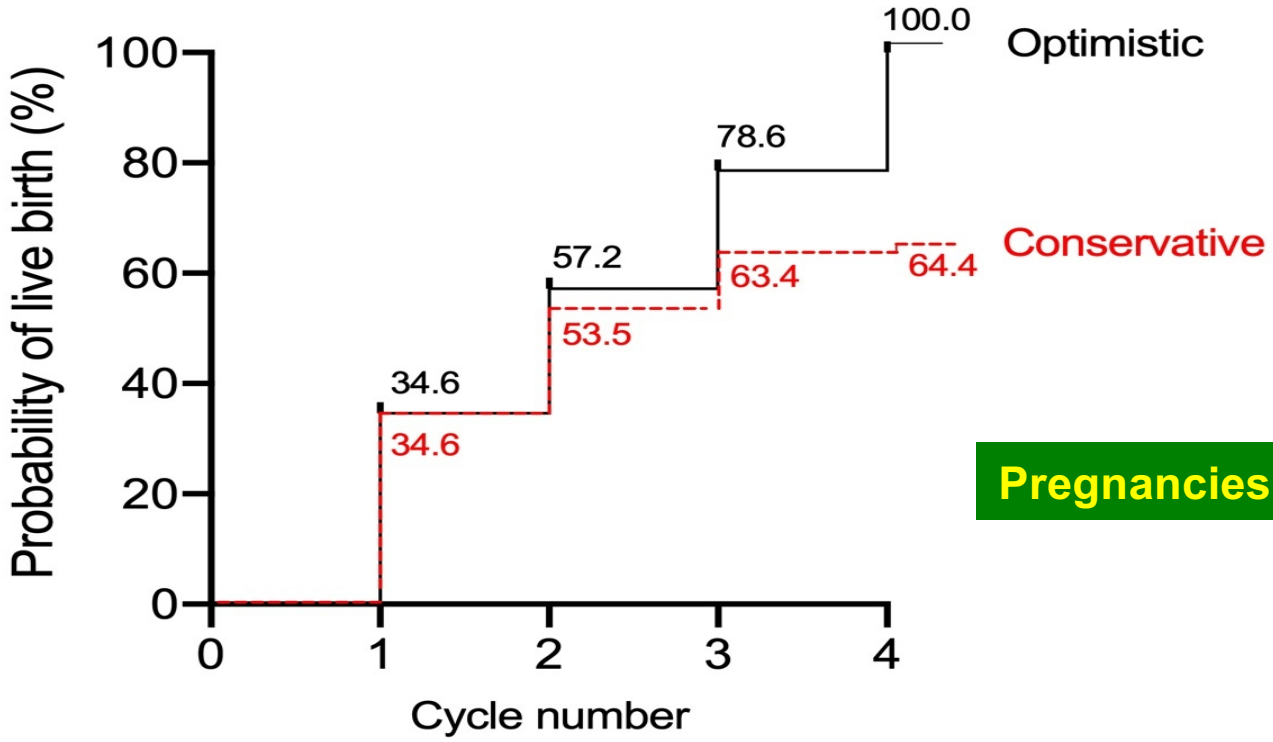
LBR in case of unoperated bowel deep endometriosis

N = 101

LBR = 65/101 (64%)

Associated OMA: 74 (73%)

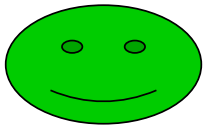
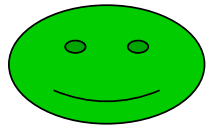
Associated Adenomyosis: 89 (88%)



Pregnancies rates

Maignien C, Santulli P, Chapron C *et al., Fertil Steril* (2021)

Surgery *versus* ART

	Surgery	ART
Fertility results		
Limits 	Negative impact on ovarian reserve Reduced responsivenessto COS Ineffectiveness of IUI Major complications (DIE) Recurrences of Osis and pain Incomplete repetitive surgeries	Low risk of TOA Low risk of disease progression Multiples pregnancies Obstetrical and perinatal outcomes No suitable for pain management
Advantages 	Treatment of painful symptoms Avoid very low risk of ovarian cancer	Exeresis of OMA and DIE lesion does appear to be necessary before ART

My personal approach

+ Endometriosis pathogenesis: infammation
+ Non surgical endometriosis diagnosis
+ Efficiency of medical treatments
+ ART results without previous surgery
+ Limits and risks of surgery
+ Rapid onset of pregnancy after surgery

Surgery must be performed when the patient want to be pregnant

Chapron *et al.*, Nat Rev Endocrinol (2019)

My personal approach

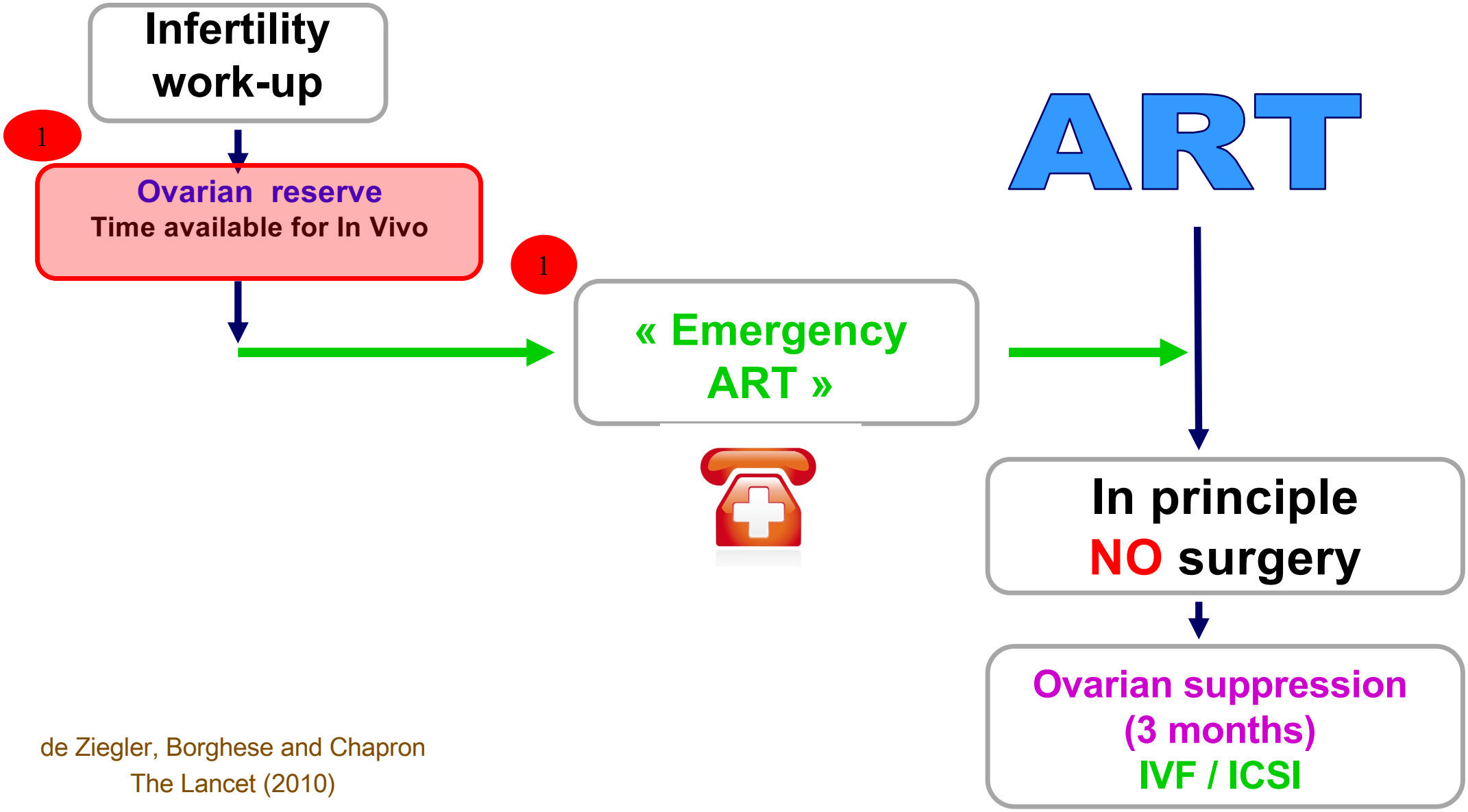
New strategy for endometriosis management:

To plan **the best moment**
to perform the surgery

Chapron *et al.*,
Nat Rev Endocrinol
(2019)

Long term
Medical
treatment

Once only in *« the endometriosis life »*



de Ziegler, Borghese and Chapron
The Lancet (2010)

Rethinking endometriosis

Chapron *et al.*,
Nat Rev Endocrinol (2019)

Ovarian reserve
Patients' desire and priorities
Age
Infertility duration
Associated infertility factors
Previous surgery for Osis (specifically OMA)
Pelvic pain intensity
Ovarian endometrioma
Associated adenomyosis

Rethinking endometriosis

Ovarian reserve	Satisfactory
Patients' desire and priorities	Patient choice
Age	Young
Infertility duration	Short
Associated infertility factors	No
Previous surgery for Osis (specifically OMA)	No
Pelvic pain intensity	Intense
Ovarian endometrioma	No
Associated adenomyosis	No

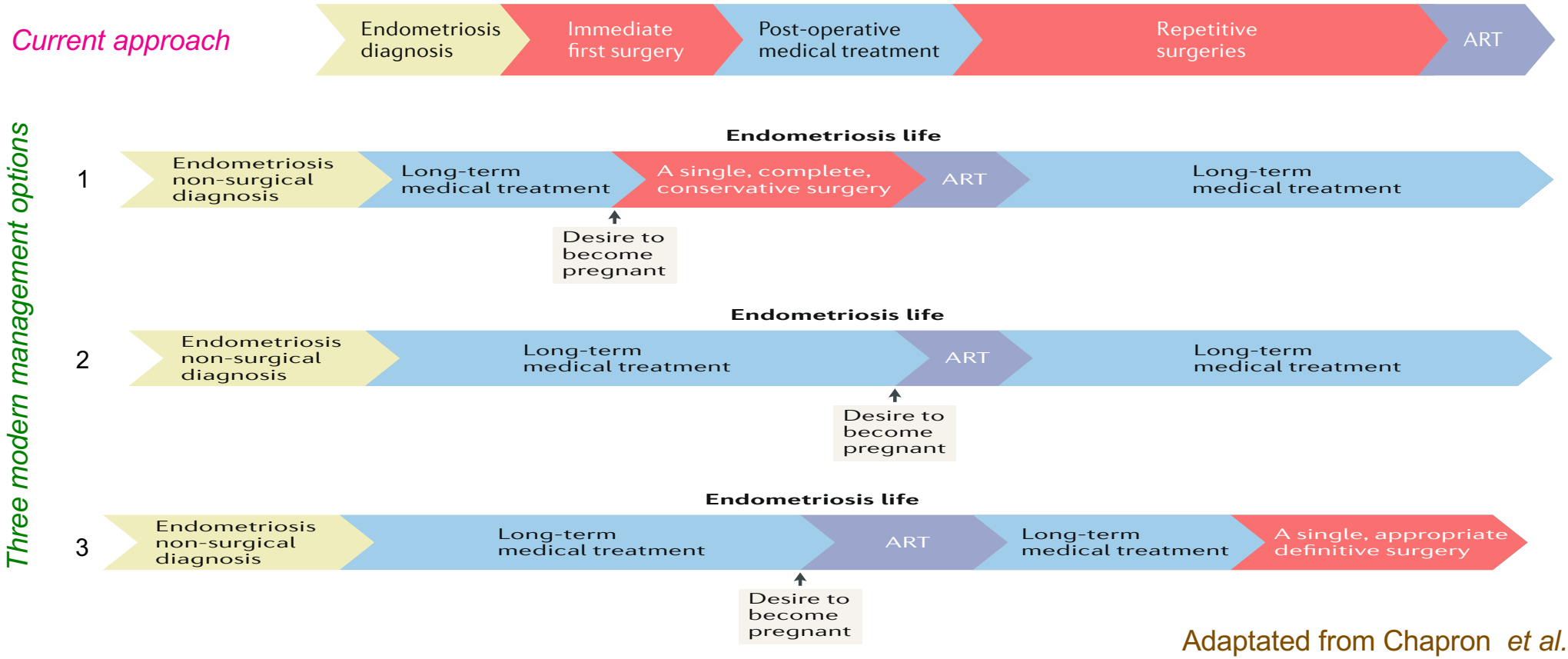
Chapron *et al.*,
Nat Rev Endocrinol (2019)

Rethinking endometriosis

Chapron *et al.*,
Nat Rev Endocrinol (2019)

Ovarian reserve	Satisfactory	Decreased
Patients' desire and priorities	Patient choice	Patient choice
Age	Young	Old
Infertility duration	Short	Long
Associated infertility factors	No	Yes
Previous surgery for Osis (specifically OMA)	No	Yes
Pelvic pain intensity	Intense	Low
Ovarian endometrioma	No	Yes
Associated adenomyosis	No	Yes

Rethinking endometriosis management

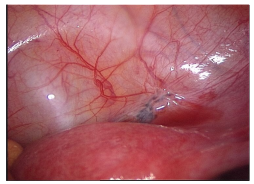


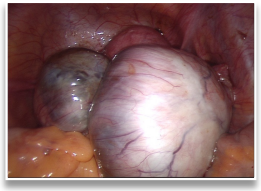
Adaptated from Chapron *et al.*,
Nat Rev Endocrinol (2019)

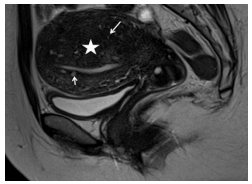
Rethinking endometriosis management

Multi - disciplinary patient approach

ENDOETRIOTIC LESIONS







Surgery

ART

Medical treatments

Multidisciplinary surgical team:

- *Gynecological*
- *Intestinal*
- *Urologists*
- *Thoracic*

- Analgesics drugs
- Hormonal treatments

Laboratory techniques:

- *IVF and ICSI*
- *Frozen transfers*
- *Fertility preservation (3)*

CELEC: *Cochin Endometriosis Life Center of Excellence*

ENDOMETRIOSIS AND UTERINE DISORDERS:

STRATEGIC MANAGEMENT AND CHALLENGES IN THE NEW MILLENNIUM

MARCH 15-18
ABU DHABI, UAE

Society of Endometriosis and Uterine Disorders

Congress President:
Pr. Ghassan Lotfi, UAE

SEUD President:
Dr Francisco Carmona, Spain

Location:
Abu Dhabi

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LUNA
Veille sur vous, votre cycle menstruel
et votre endométriose