



# Endometriosis related infertility: Treatment modalities and strategies

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# Endometriosis related infertility

- Specifications and pathogenesis
- What are the therapeutic options ?
- How to choose between the therapeutic options?
- Proposition for a strategy

# Endometriosis related infertility

- **Specifications and pathogenesis**
- **What are the therapeutic options ?**
- **How to choose between the therapeutic options?**
- **Proposition for a strategy**

# Endometriosis: Heterogeneous disease



SUP



OME



DIE

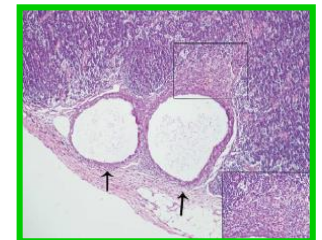
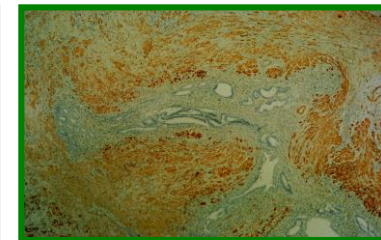
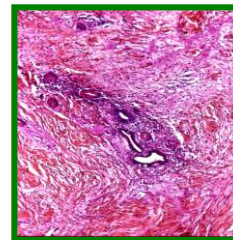


Adenomyosis

Asymptomatic

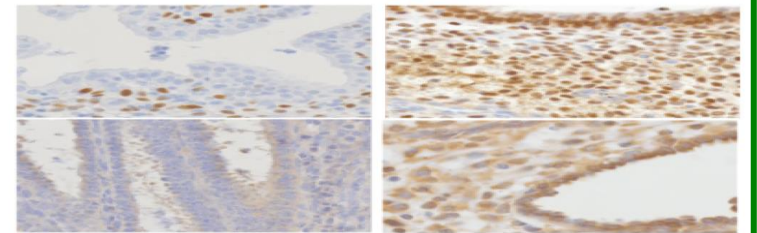
Pain

Infertility



PR-AB

PR-B



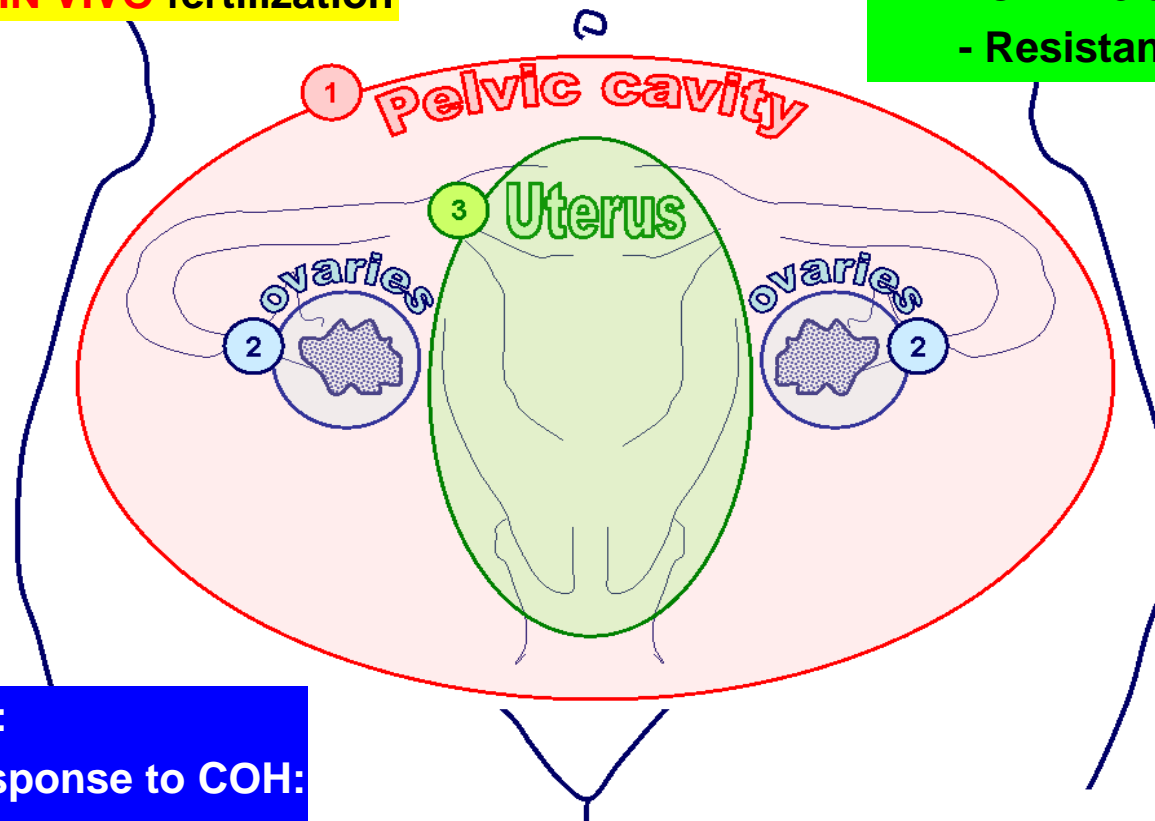
# Endometriosis and infertility: *Pathogenesis*

## Pelvic cavity:

Inflammation-related process interferes with sperm-oocyte interactions:  
Reduced chances of **IN VIVO** fertilization

## Uterus:

Alterations of eutopic endometrium:  
- PTGS2 overexpression  
- CYP-19 and NR5A1 activation  
- Resistance to P4 (PR-D)



## Ovaries:

Decreased ovarian response to COH:  
- More FSH / hMG needed  
- Less oocytes obtained

# Endometriosis related infertility

- Specifications and pathogenesis
- **What are the therapeutic options ?**
- How to choose between the therapeutic options?
- Proposition for a strategy

# Endometriosis related infertility

## *Management options*

- **Medical treatment**
- **Surgery**
- **Assisted Reproductive Technologies**

# Endometriosis related infertility

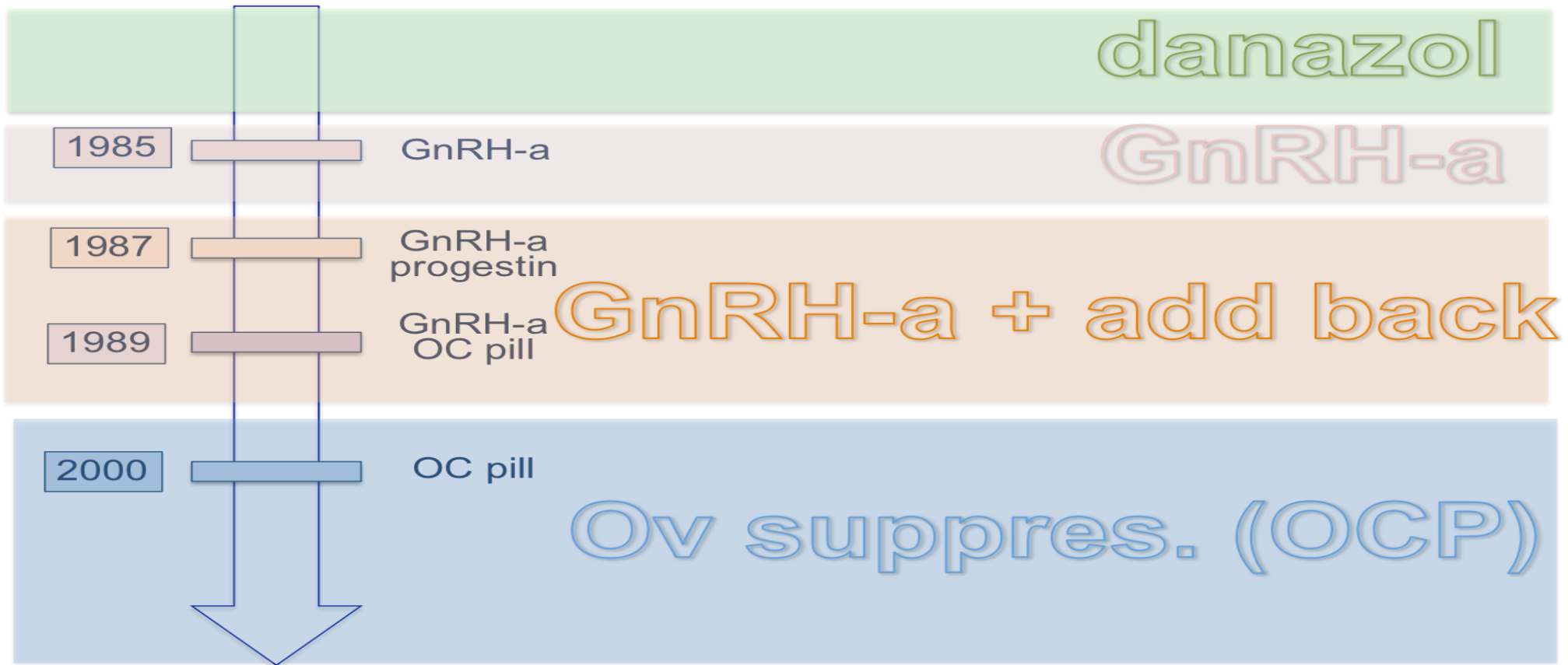
## *Management options*

- **Medical treatment**
- **Surgery**
- **Assisted Reproductive Technologies**



# Endometriosis related infertility

## Medical treatment ?



**All options are contraceptive**

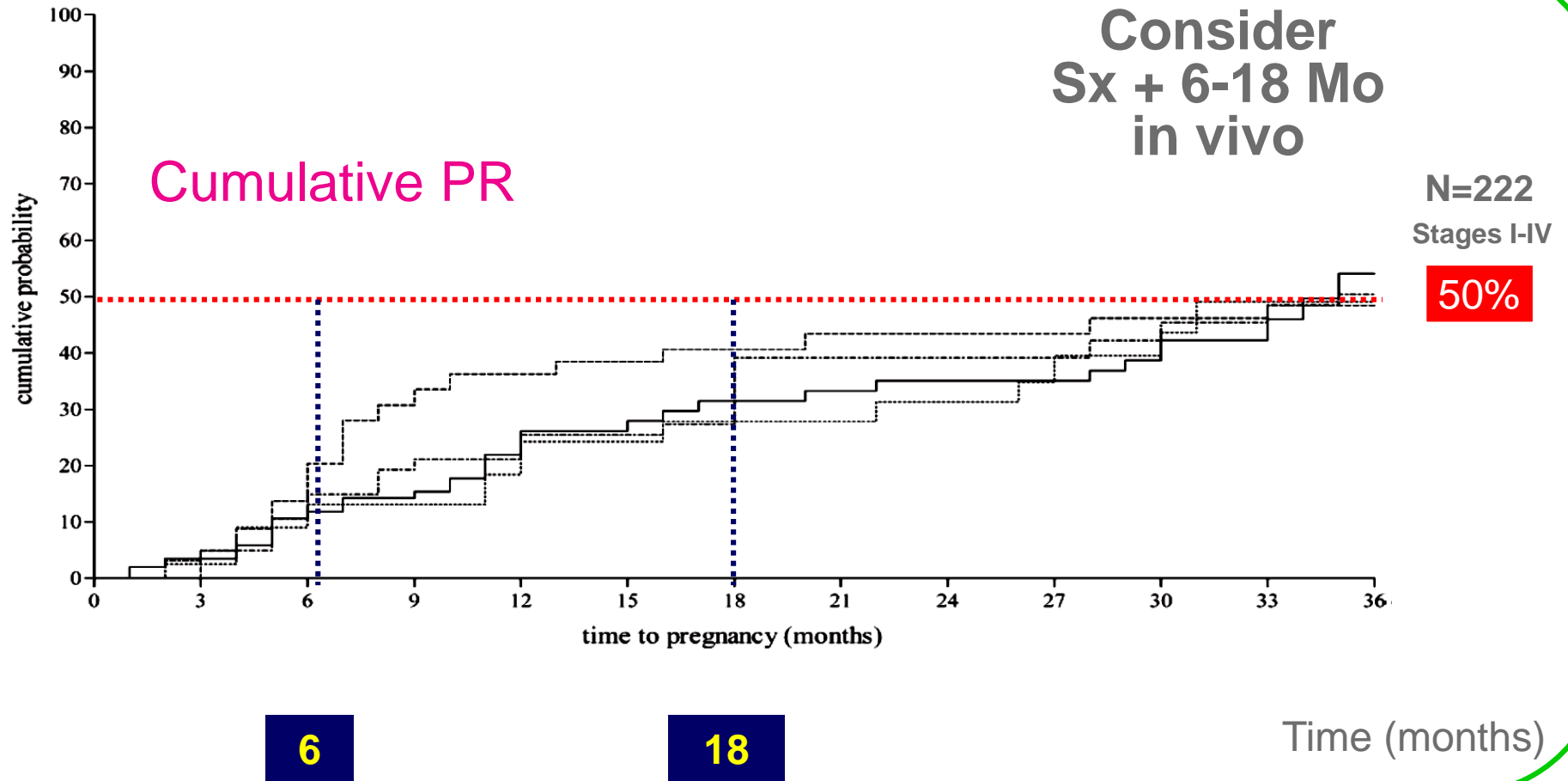
# Endometriosis related infertility

## *Management options*

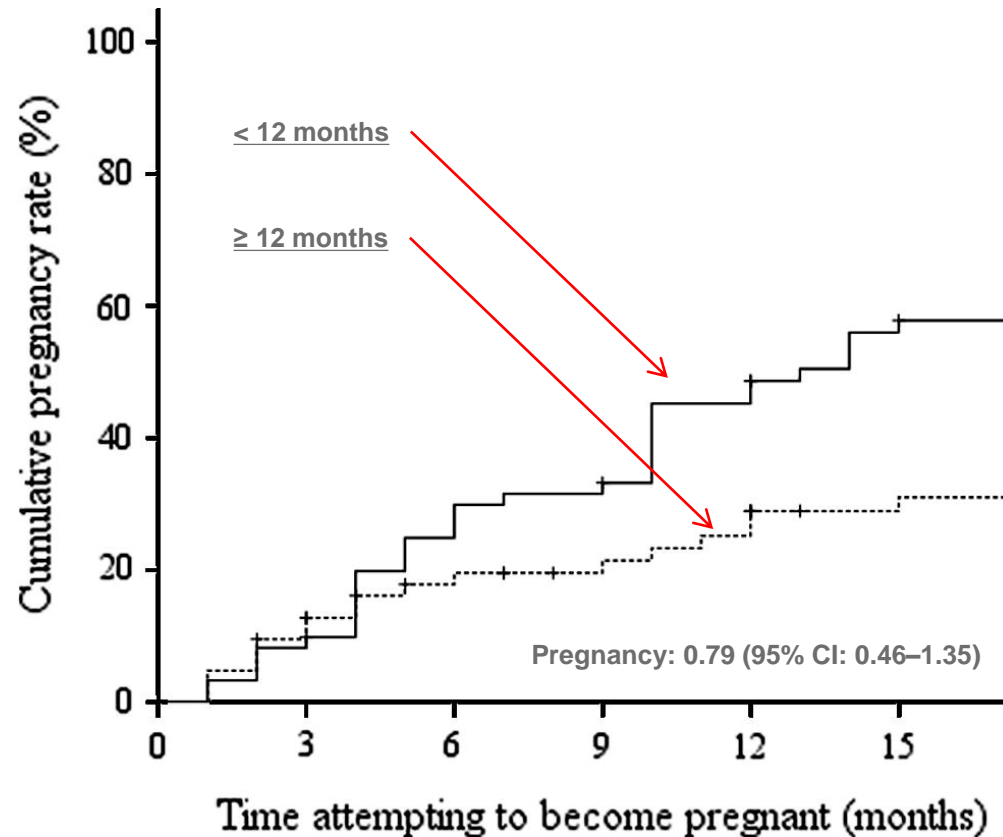
- Medical treatment
- **Surgery**
- Assisted Reproductive Technologies

# Endometriosis related infertility

## *surgery in infertile women*

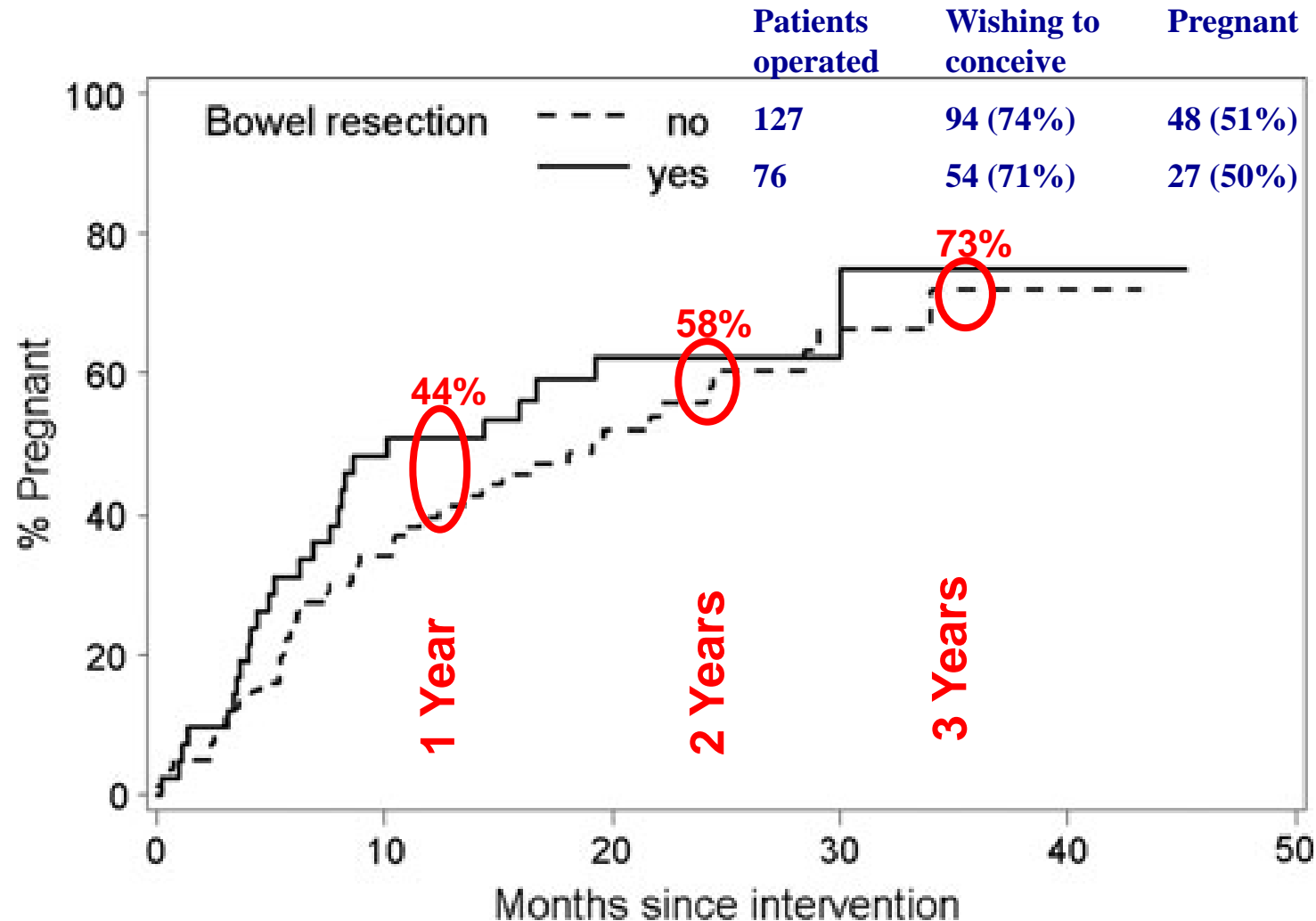


# Endometriosis related infertility : *Postoperative delayed initiation of attempted conception*



# Deep endometriosis related infertility :

## Laparoscopic surgery in women with moderate to severe endometriosis



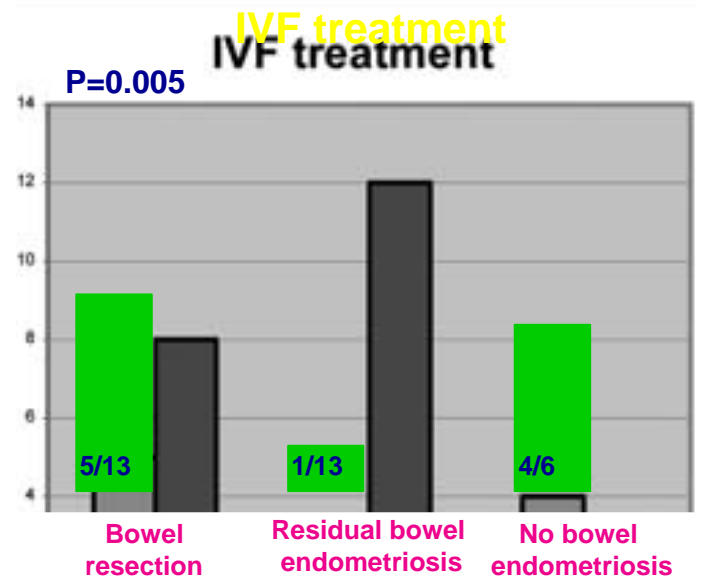
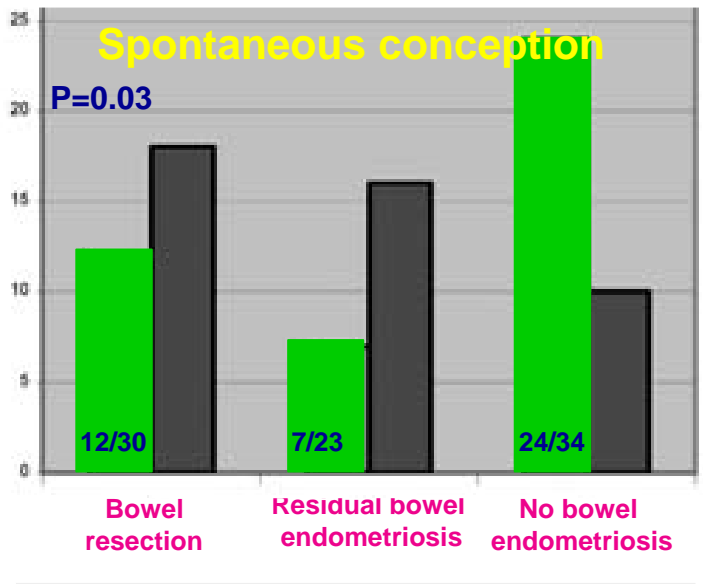
# Deep endometriosis related infertility :

## Laparoscopic surgery in women with moderate to severe endometriosis

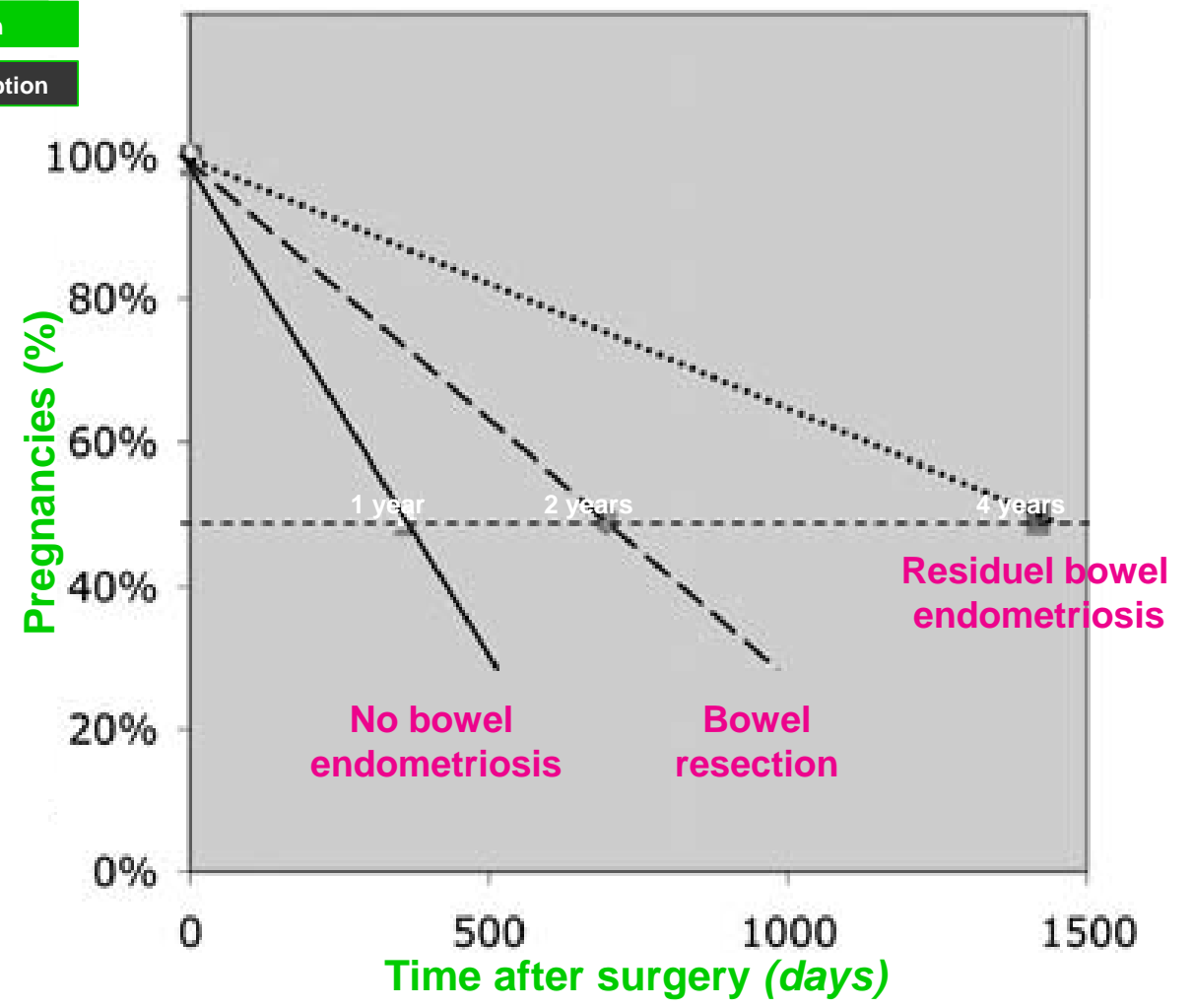
Mode of Conception (First Pregnancy)	Total (n = 75)	Patients With at Least 1 Functional Tuba (n = 66)	Study Group (n = 48)	Control Group (n = 27)
Spontaneous	31 (41%)	30 (45%)	18 (38%)	13 (48%)
Stimulation + HIUI	7 (9%)	7 (11%)	6 (13%)	1 (4%)
IVF	24 (32%)	20 (30%)	14 (29%)	10 (37%)
IVF with donor sperm	1 (1%)	0 (0%)	1 (2%)	0 (0%)
Intracytoplasmic sperm injection	7 (9%)	6 (9%)	6 (13%)	1 (4%)
Cryo	3 (4%)	2 (3%)	1 (2%)	2 (7%)
Oocytes reception	2 (3%)	1 (2%)	2 (4%)	0 (0%)

**20% conceived spontaneously**

# Intestinal DIE: Surgical techniques



Conception  
No Conception



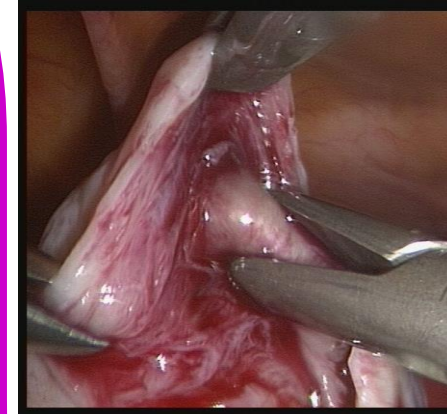
# Deep endometriosis: *Complications*

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

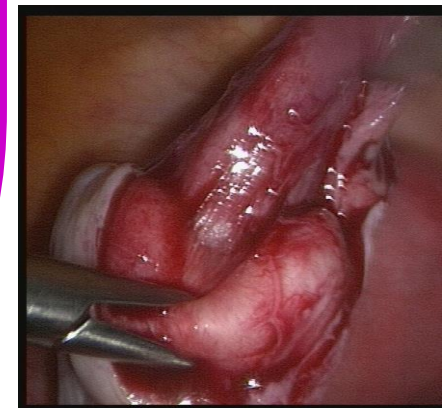


# OMAs: Laparoscopic excision

Laparoscopic excision of endometrioma (OMA)	N	# IUP	% IUP
Daniell et al., 1991	32	12	37.5
Marrset al., 1991	23	7	30.4
Bateman et al., 1994	21	9	42.8
Crosignani et al., 1996	22	6	27.3
Montanino et al., 1996	11	5	45.5
Donnez et al., 1996	814	414	50.8
Sutton et al., 1997	66	30	45.5
Beretta et al., 1998	9	6	66.7
Milingos et al., 1998	32	17	53.1
Busacca et al., 1999	67	39	58.2
Jones and Sutton, 2002	39	15	38.5
Alborzi et al., 2004	32	19	59.4
Fedele et al., 2006	90	29	32.2
Vercellini et al., 2006	237	128	54.0
<b>Total</b>	<b>1495</b>	<b>736</b>	<b>49.2</b>



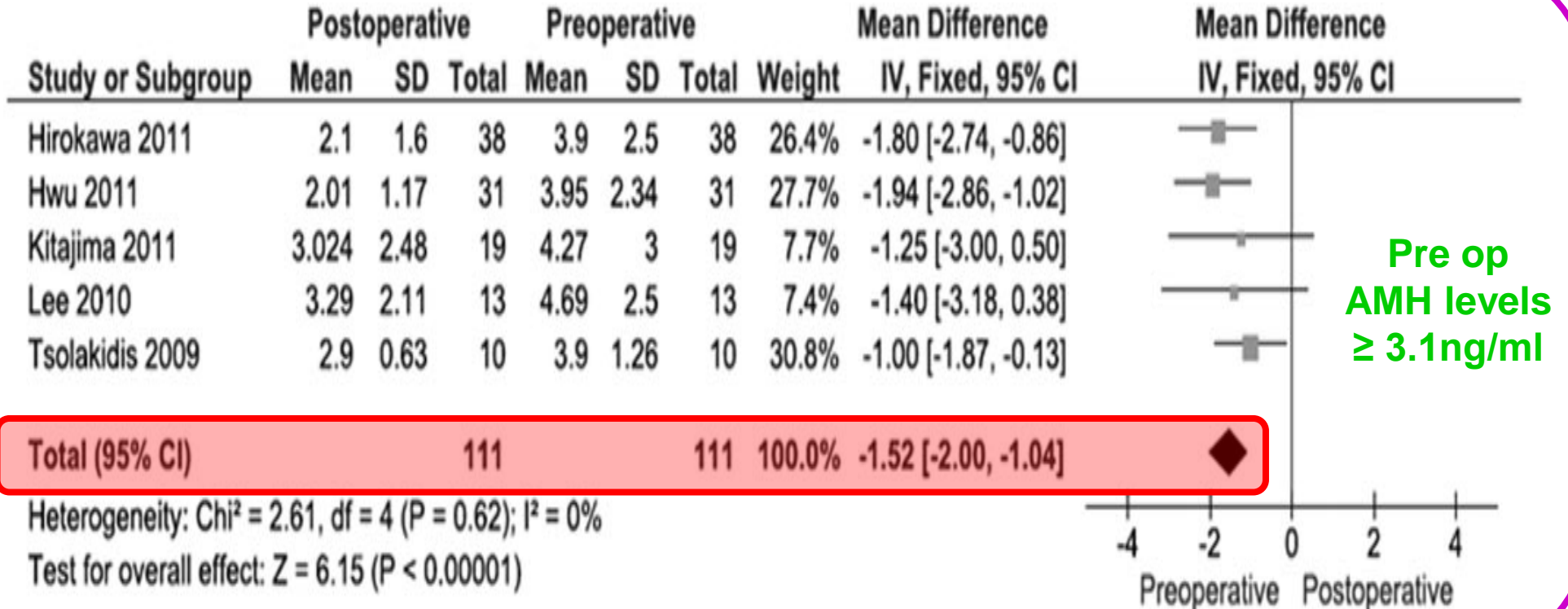
49.2%



## Endometriosis and infertility: pathophysiology and management

# The Impact of Excision of Ovarian Endometrioma on Ovarian Reserve: A Systematic Review and Meta-Analysis

Raffi *et al.*, JCEM (2012)



# Endometriosis and ovarian reserve

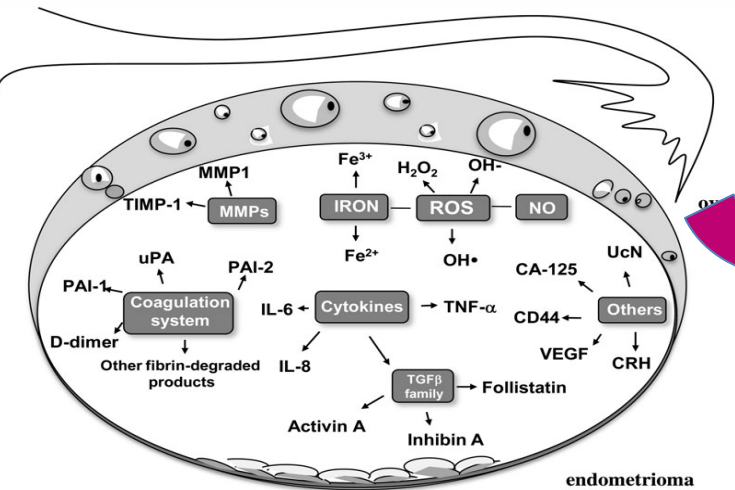
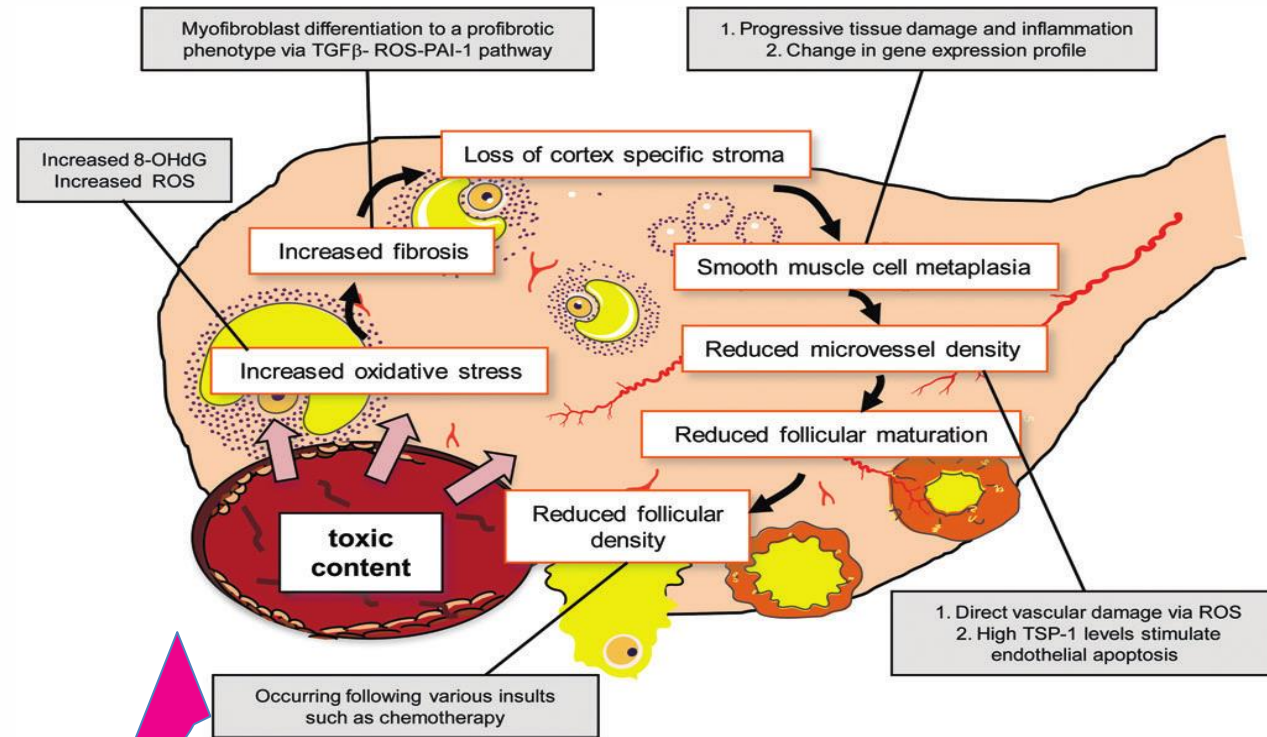
Impact of endometriosis per se on ovarian reserve ?





# Endometriosis and ovarian reserve

## Quality





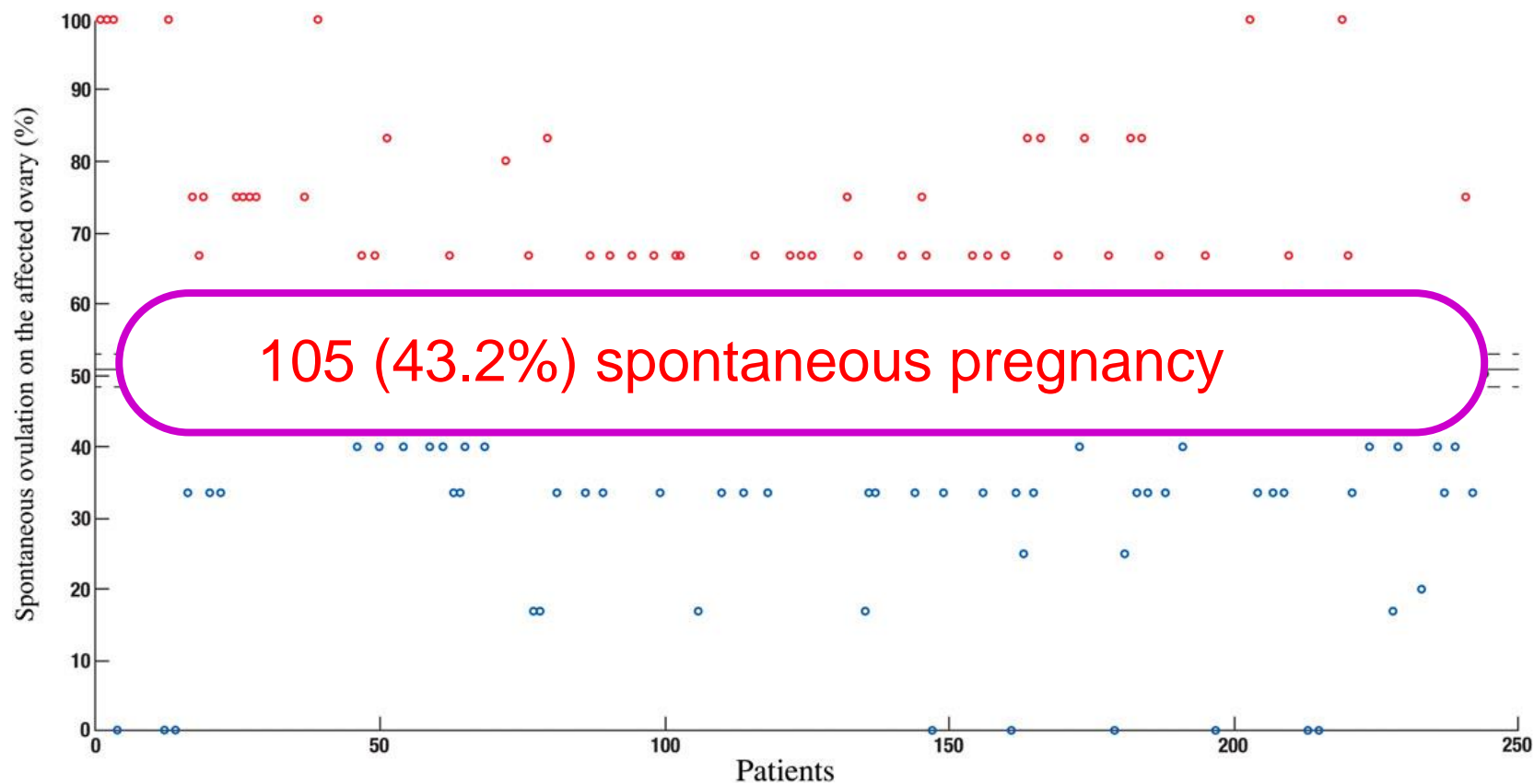
# Endometriosis and ovarian reserve

## Quality

N=244 (183-75% DIE)

Follow up 6 months

1199 cycles of spontaneous ovulation

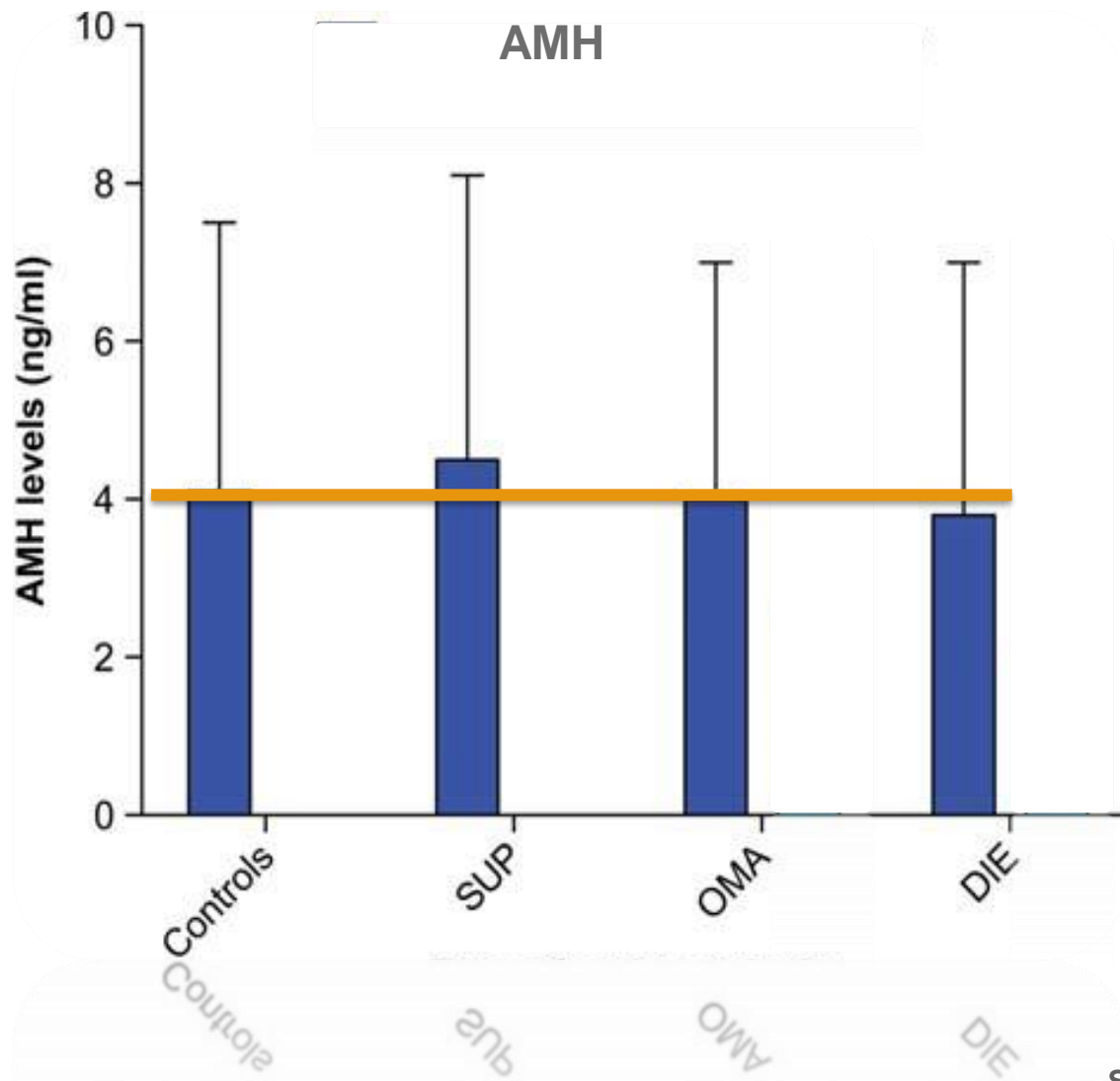




# Endometriosis and ovarian reserve

Quantity

N=726

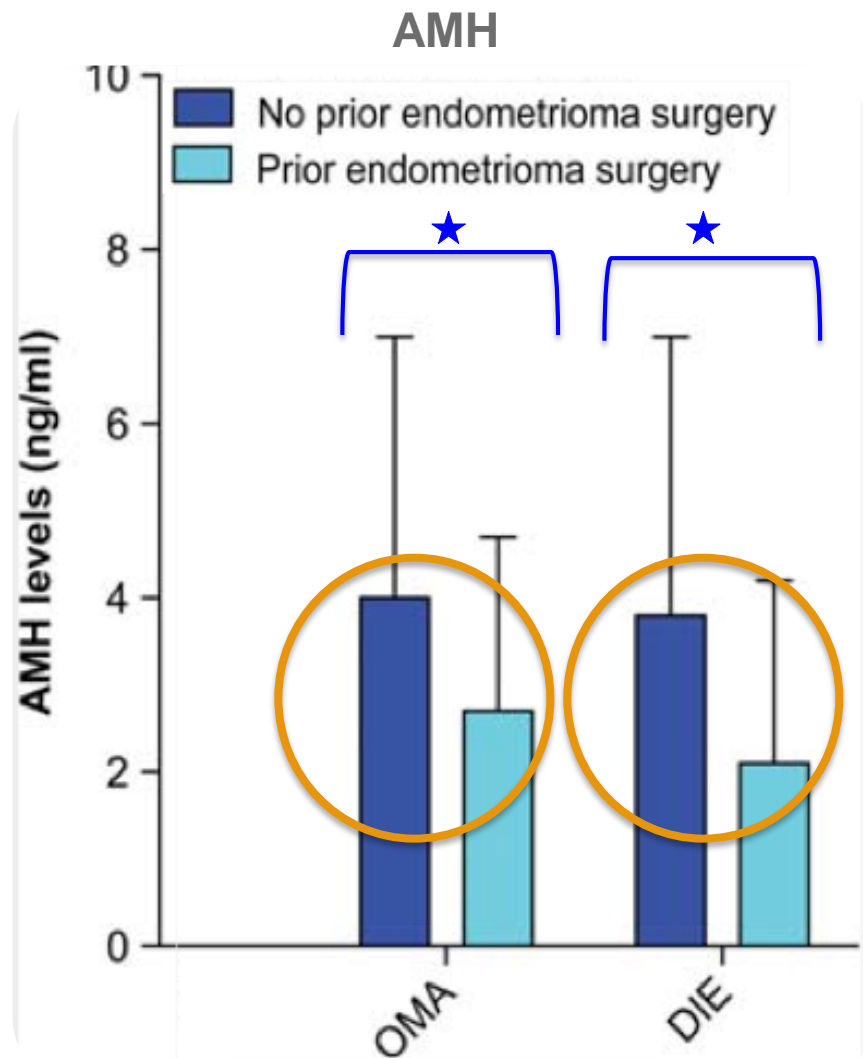




# Endometriosis and ovarian reserve

## Quantity

N=726

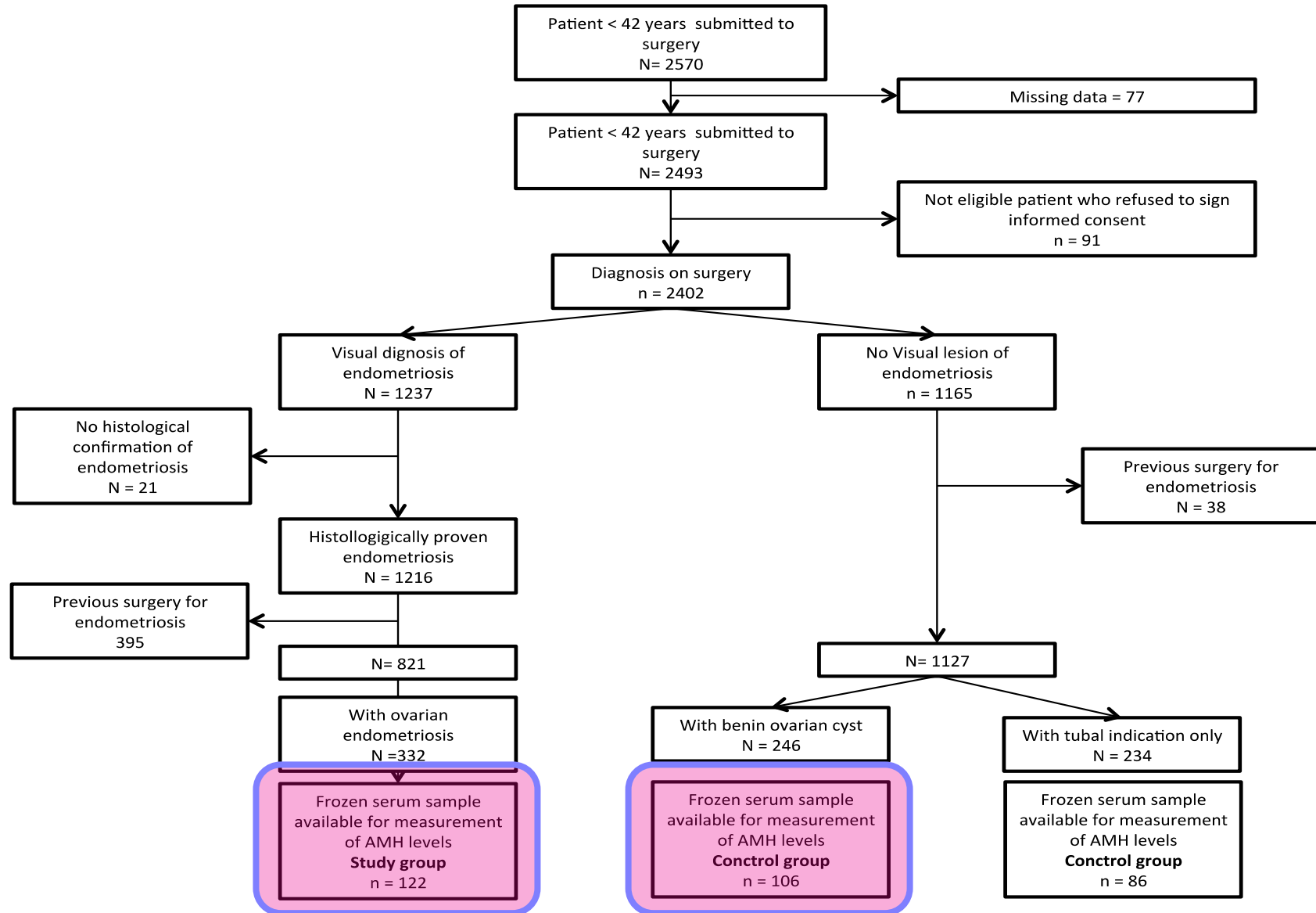


Previous OMA surgery  
OR= 3.0 (1.40-6.41); p=0.01



# Endometriosis and ovarian reserve

## Quantity

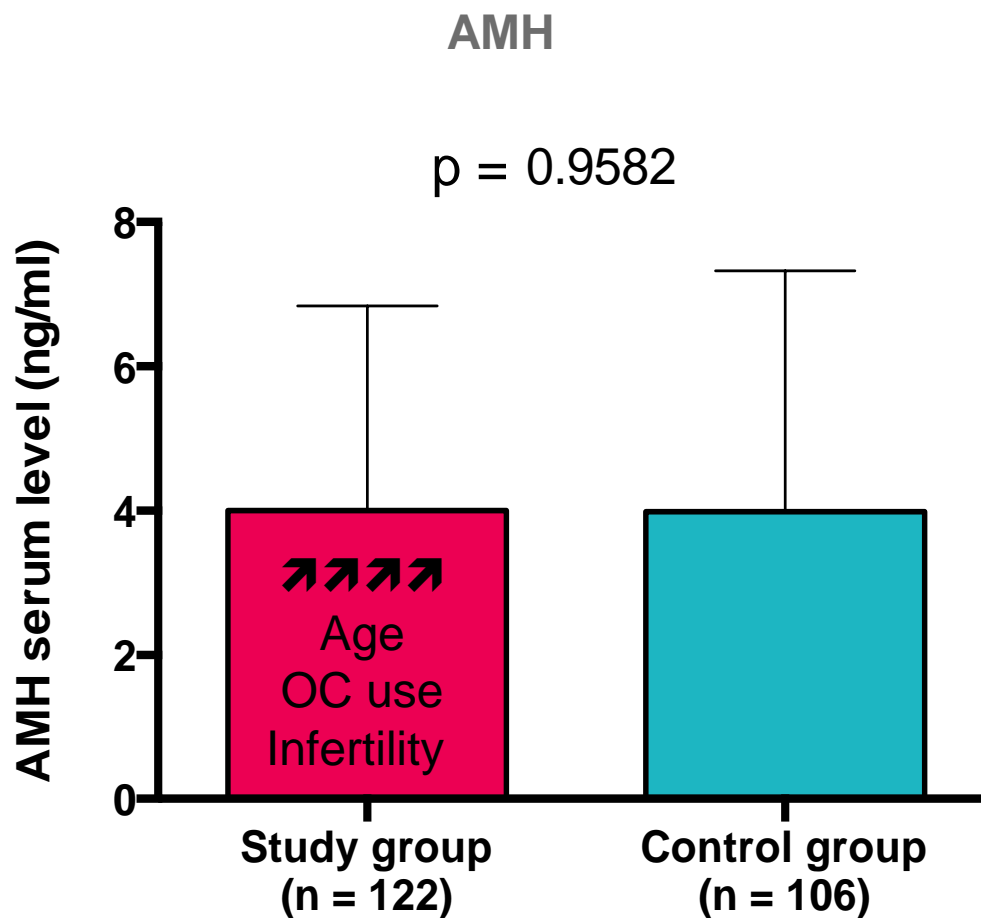






# Endometriosis and ovarian reserve

## Quantity

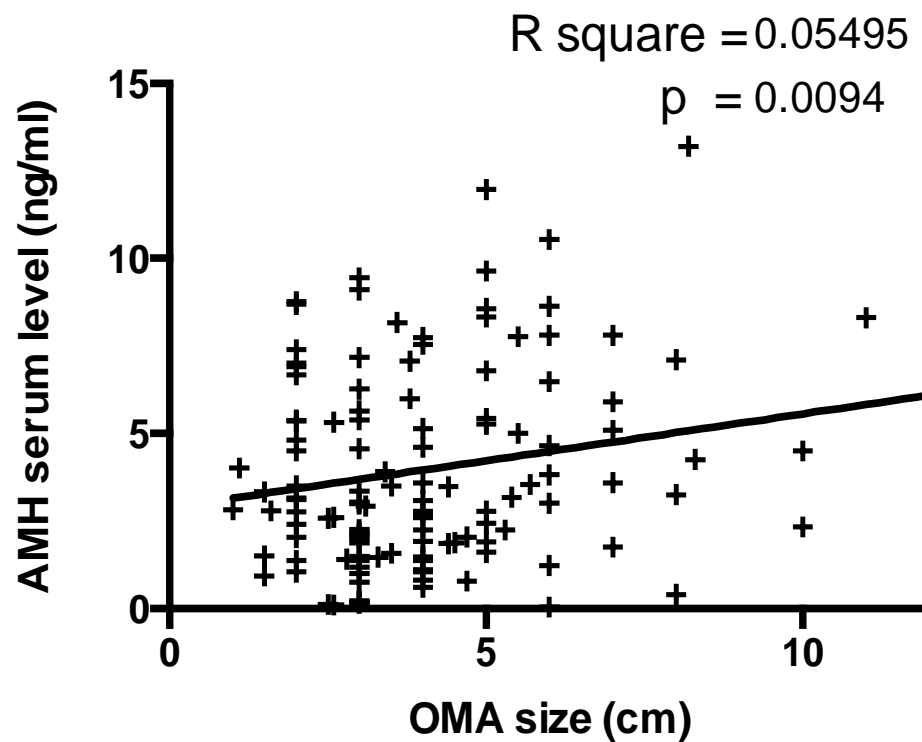
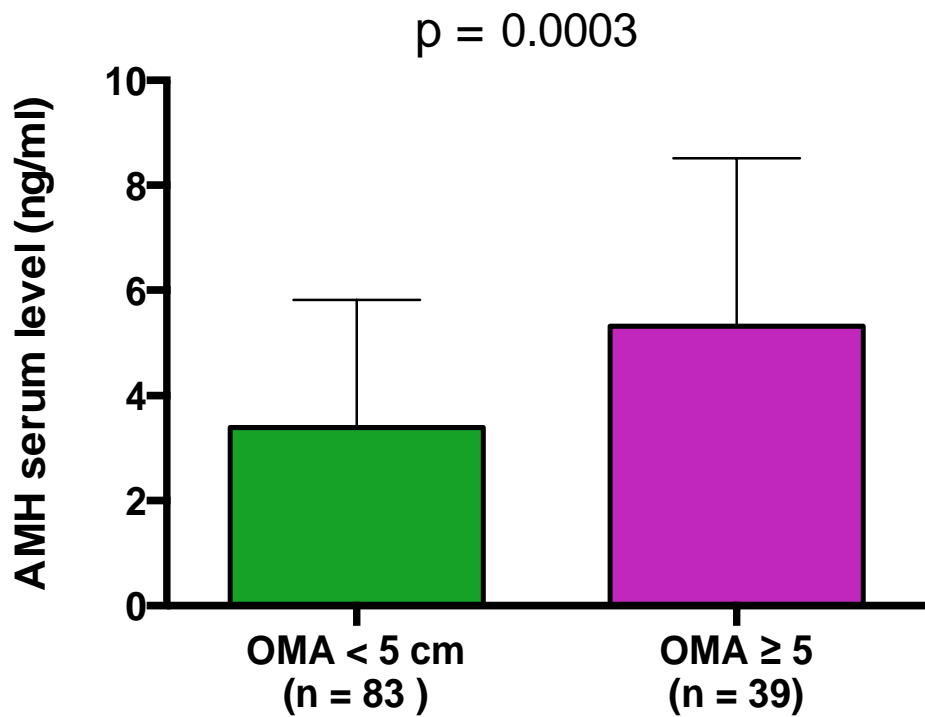




# Endometriosis and ovarian reserve

## Quantity

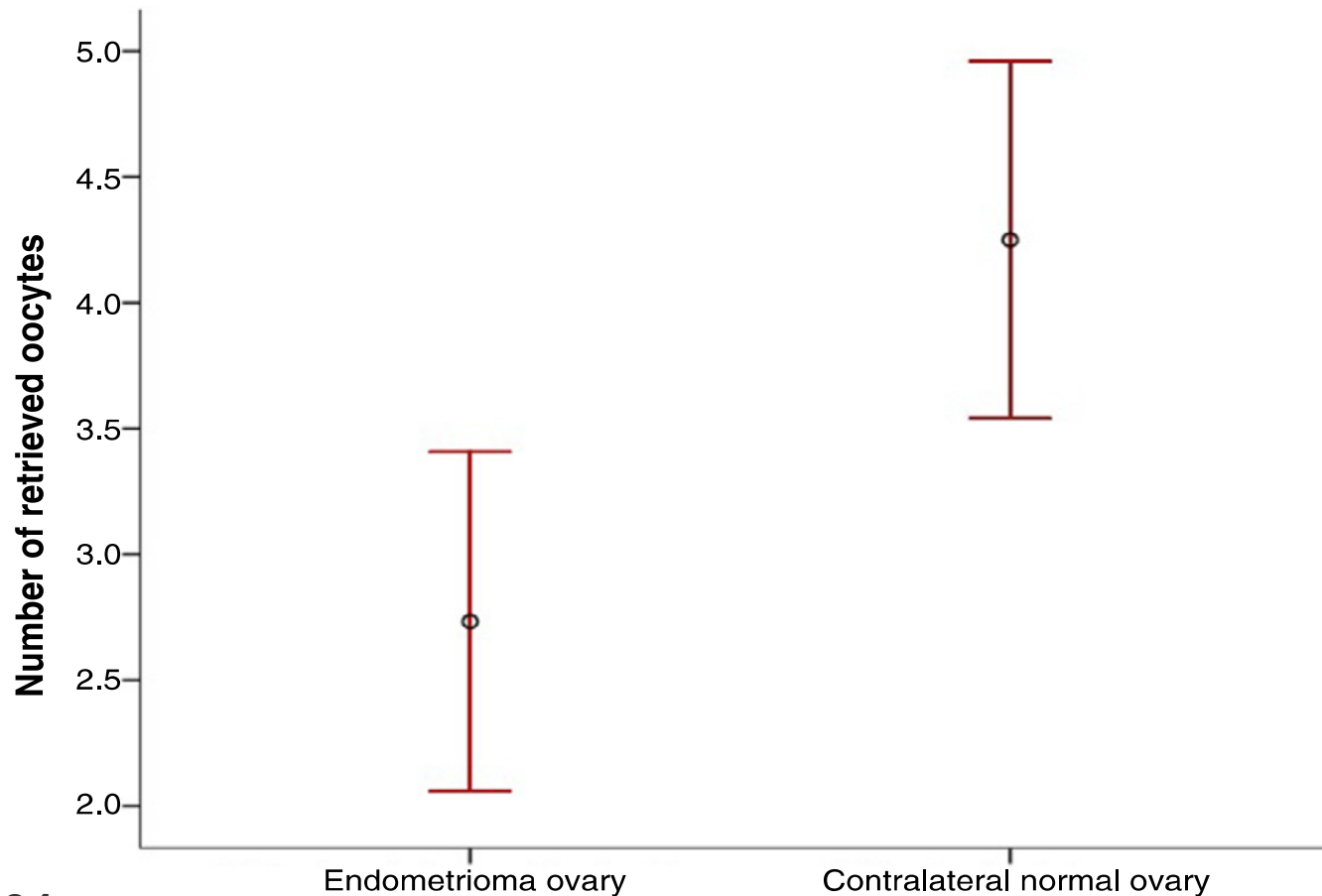
AMH





# Endometriosis and ovarian reserve

## The impact of OMA on IVF outcomes



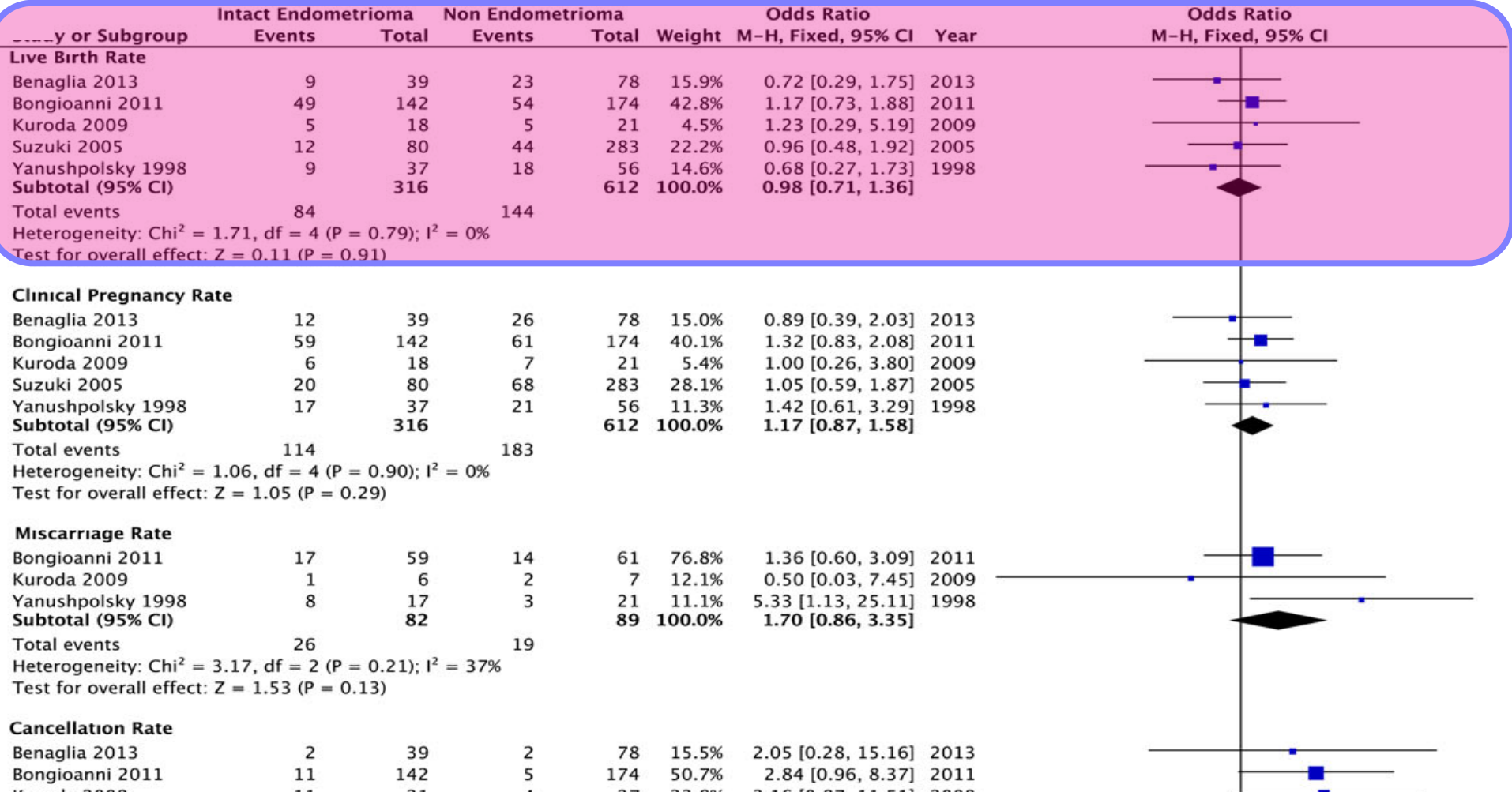
**N=64**

**\*  $P = 0.001$**



# Endometriosis and ovarian reserve

## The impact of OMA on IVF outcomes



# IVF and diminished ovarian reserve: Post OMA cystectomy versus idiopathic

Diminished ovarian reserve  
AMH < 2ng/ml

OMA Cystectomy

Idiopathic

Characteristics	Group A (125 cycles)	Group B (243 cycles)	P-value
Implantation rate (%)	13/181 (7.2%)	49/364 (13.5%)	0.03
Clinical pregnancy rate per cycle (%)	14/125 (11.2%)	50/243 (20.6%)	0.02
Live birth rate (%)			
Per cycle	9/125 (7.2%)	41/243 (16.9%)	0.01
Per transfer	9/104 (8.7%)	41/216 (18.8%)	0.02
Spontaneous abortion rate (%) (before or after 12 weeks of gestation)	4/13 (30.8%)	8/49 (16.3%)	NS
Ectopic pregnancy rate (%)	1/14 (7.1%)	1/50 (2.0%)	NS
Multiple pregnancy rate (%)	2/13 (15.4%)	6/49 (12.2%)	NS

Retrospective study

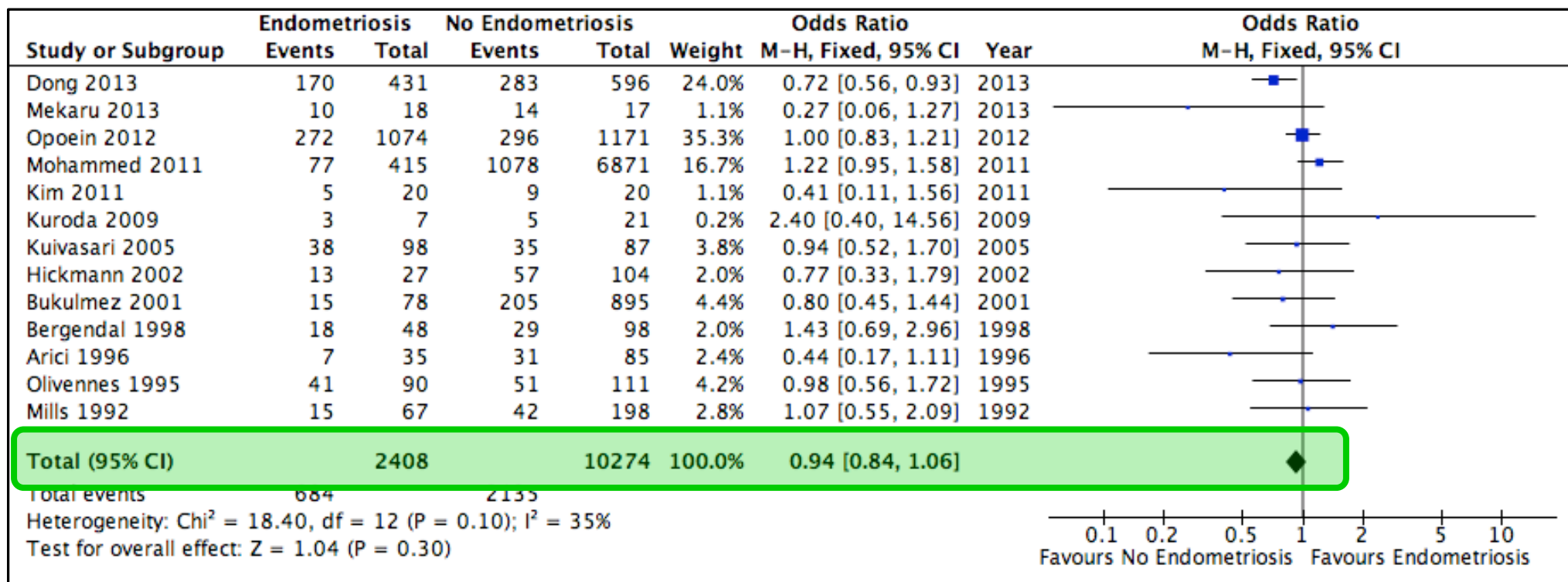
# Endometriosis related infertility

## *Management options*

- Medical treatment
- Surgery
- **Assisted Reproductive Technologies**

# Endometriosis:

## IVF outcome: Life birth rate



# Endometriosis and IVF

## The Phenotype n=359

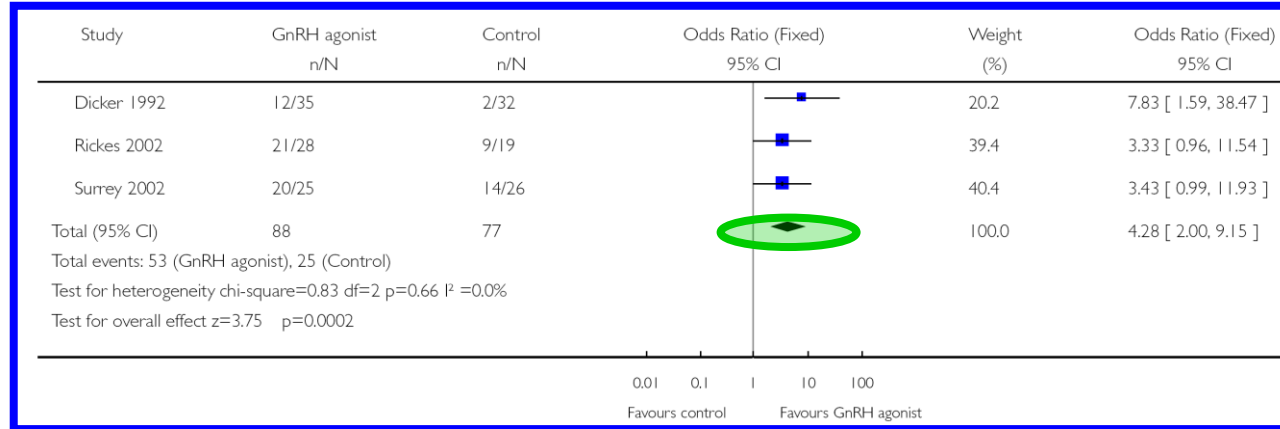
	DIE	Oma	Sup	P value
<b>Patients</b>	212	98	49	
No. of cycles	425	200	95	
No. of ET	282/425 (66.4)	141/200 (70.5)	77/95 (81.1)	<b>0.018</b>
Clinical pregnancy rate per cycle	98/425 (23.1)	55/200 (27.5)	29/95 (30.5)	0.22
<b>Clinical pregnancy rate per ET</b>	98/282 (34.8)	55/141 (39)	29/77 (37.7)	0.67
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)	<b>0.049</b>



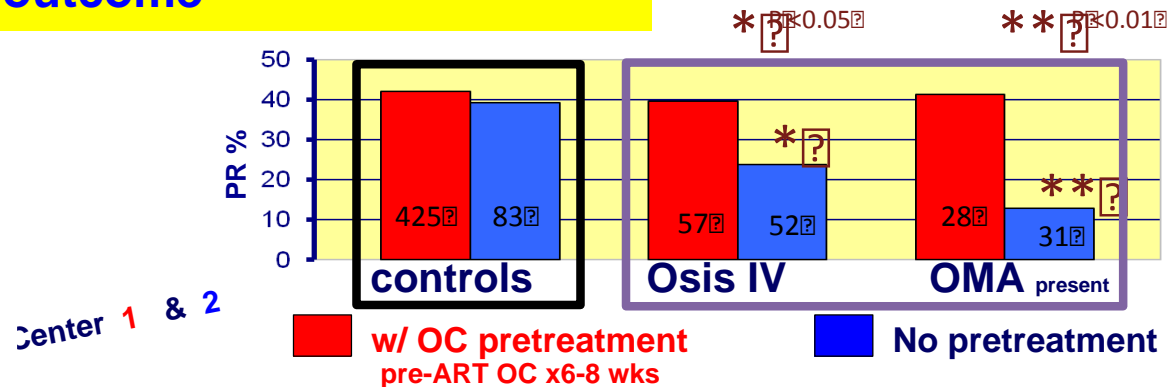


# Ovarian suppression before COH

## Effects of GnRH-a IVF outcome



## Effects of OC IVF outcome



***the administration of GnRH-a or OC prior to IVF/ICSI in women w/ endometriosis increases the odd of pregnancy > 4 fold.***

# Endometriosis related infertility

## *Surgery vs ART*



**Fertility**



**DIE surgery complications**  
**Ovarian reserve damage**

**Limits**

**Post retrieval Infection**  
**Pain ?**

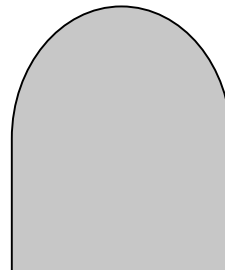
**Pain treatment**

**Advantages**

**OMA surgery not necessary**

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**Surgery**



**ART**

# Endometriosis related infertility

- Specifications and pathogenesis
- What are the therapeutic options ?
- **How to choose between the therapeutic options?**
- Proposition for a strategy

# How to choose between the therapeutic options?

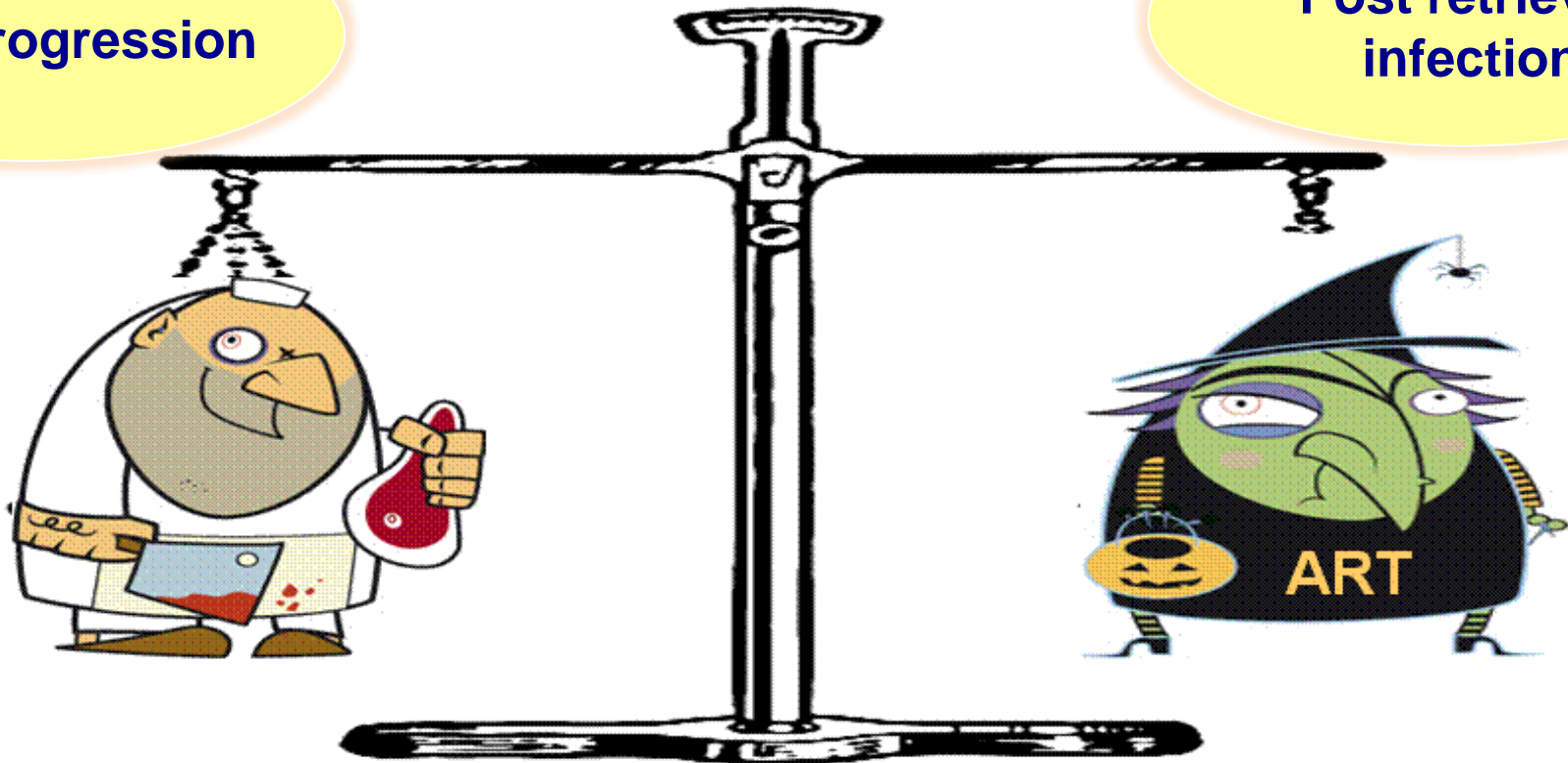
- **Endometrioma: to remove or not ?**
- **Clinical symptoms**
- **Adenomyosis**
- **Iterative Surgery**
- **Large endometrioma**

# Endometrioma and IVF:

*To remove or not to remove  
That is the question*

Pain progression

Post retrieval  
infection

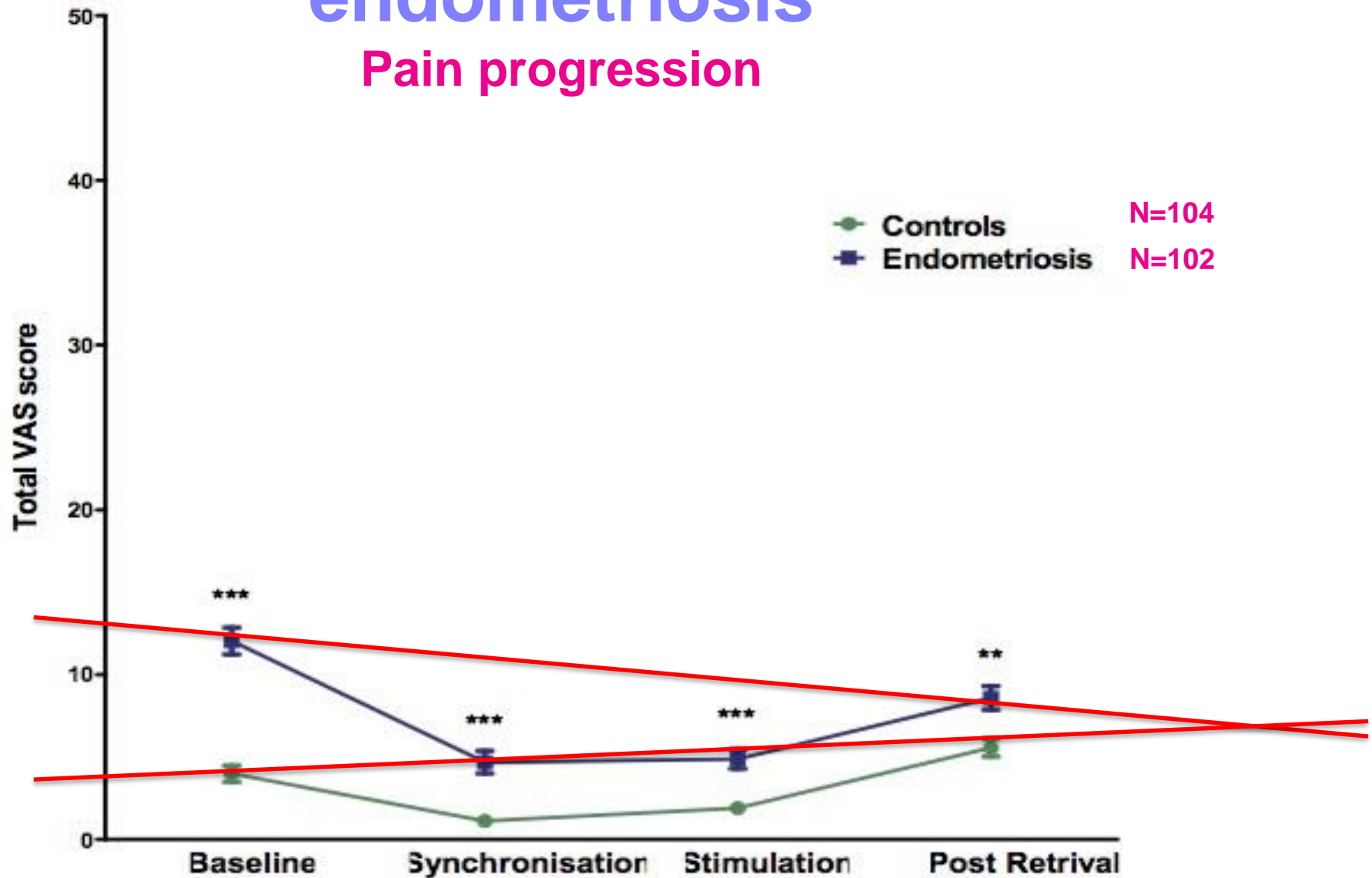


**Surgery**

**ART**

# Fertility preservation in women with endometriosis

Pain progression



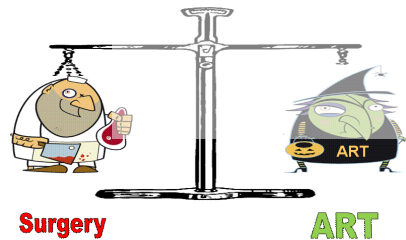
# Fertility preservation in women with endometriosis

## Pelvic infection after oocyte retrieval

ART in global population	Oocyte retrieval	Post procedure infection
Bennett SJ et al. J Assist Reprod Genet (1993)	2 670	18 (0.67%)
Dicker D et al. Fertil Steril (1993)	3 656	9 (0.24%)
Moini A et al. J Assist Reprod Genet (2005)	5 958	10 (0,16%)
<b>TOTAL</b>	<b>12 284</b>	<b>37 (0.30%)</b>

ART in endometriotic women	Oocyte retrieval	Post procedure infection
Tsai YC et al. J Assist Reprod Genet (2005)	108	2 (1.9%)
Benaglia L et al. Fertil Steril (2008)	214	0 (0.0%)
de Ziegler et al. In press (2015)	513	2 (0.38%)
<b>TOTAL</b>	<b>835</b>	<b>4 (0.48%)</b>

# Endometrioma and IVF: To remove or not to remove That is the question



Item	Theoretical relevance	Demonstrated clinical relevance	Effect of prophylactic surgery
Ovarian responsiveness	++	-	Detrimental
Oocytes competence	++	-	Ineffective
Technical difficulties	+	-	Doubtful
Endometrioma rupture	+	-	Effective
Injury to adjacent organs	++	-	Doubtful
Infection of the endometrioma	++	+	Effective
Follicular fluid contamination with the endometrioma content	+	+/-	Effective
Progression of endometriosis	++	-	Effective
Pregnancy complications	++	+/-	Doubtful
Occult malignancy missed	+++	-	Effective
Cancer development after IVF	+++	+	Effective

**✓ No systematic surgery before IVF**



# Endometriosis: $n = 870$ patients

Asymptomatic

	110	12.6%
SUP	25	22.7%
OMA	59	53.6%
DIE	26	23.6%

Pelvic pain

Infertility

453 52.1%

SUP	52	11.5%
OMA	105	23.2%
DIE	296	65.3%

202 23.2%

SUP	21	10.4%
OMA	36	17.8%
DIE	145	71.8%
* Oma +	76	52.4%
* Oma -	69	47.6%

≠

$p < 0.001$

105 120%

SUP	49	46.7%
OMA	29	27.6%
DIE	27	25.7%
* Oma +	9	33.3%
* Oma -	18	66.7%

# Endometriosis related infertility: Pelvic pain

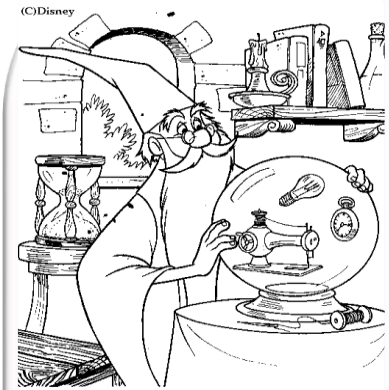
**Determinants for pain  $\geq 7$  in endometriotic women with infertility  
results from multiple logistic regression analysis**

	<b>OR (95%IC)</b>	<b>P value</b>
DIE intestine	3.9 (1.3-11.2)	0.012
Previous endometriosis surgery	2.7 (1.3-5.4)	0.006

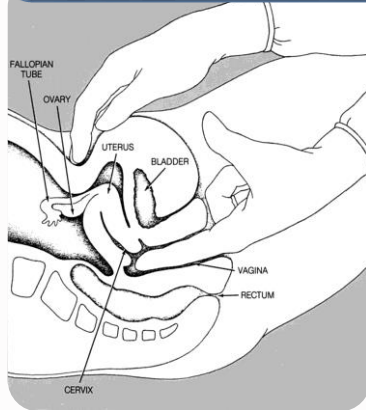
# Endometriosis:

## Preoperative work-up Questioning and Imaging

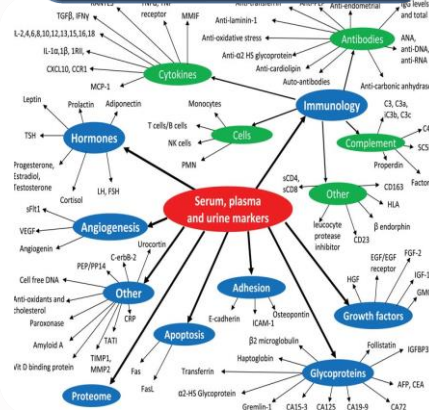
Questioning



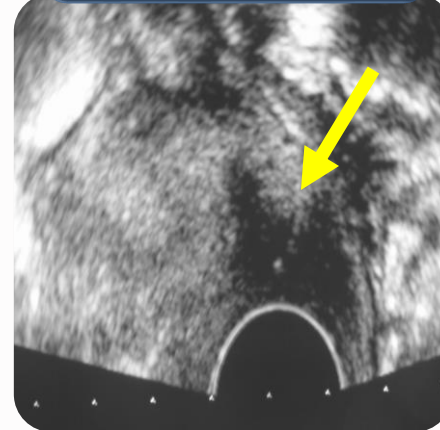
Pelvic examination



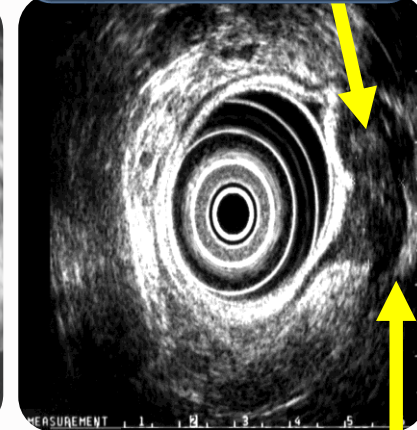
Biochemical markers



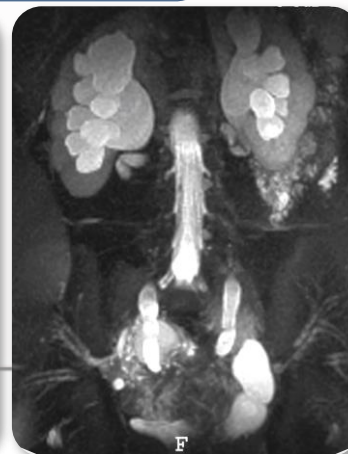
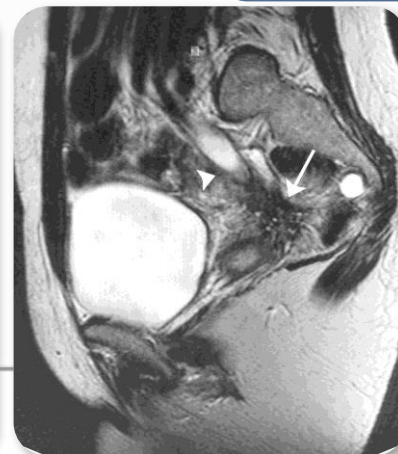
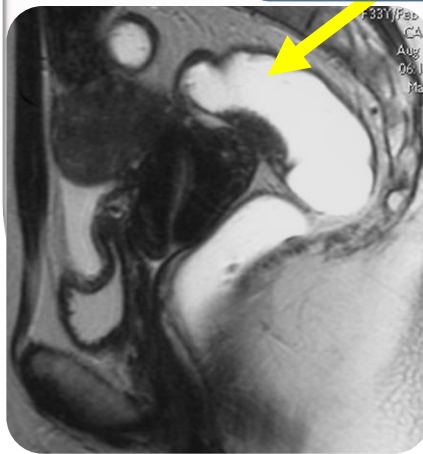
Trans-vaginal US



Trans-rectal US

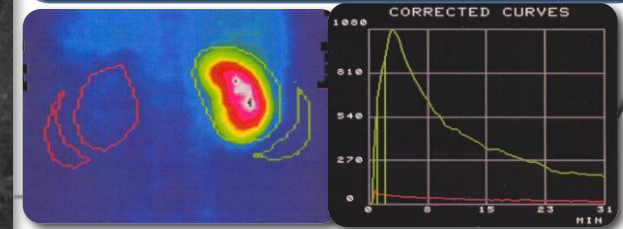


MRI



Uro-MRI

Kidney scintigraphy



# Endometriosis and infertility: Phenotype

## Adenomyosis



SUP



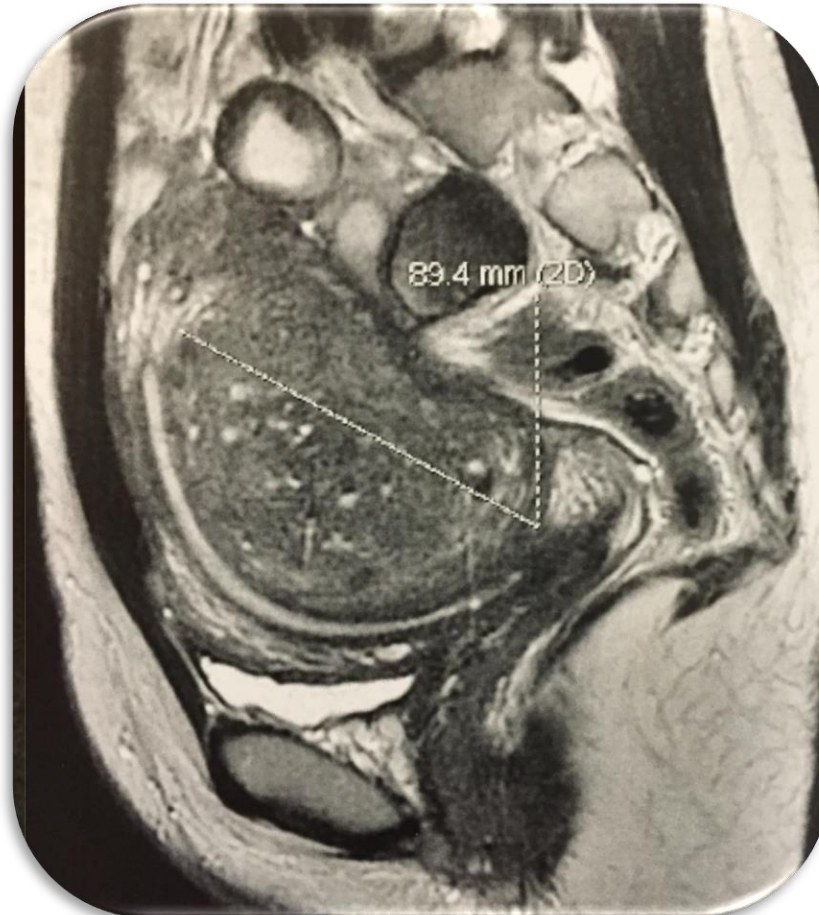
OME



DIE

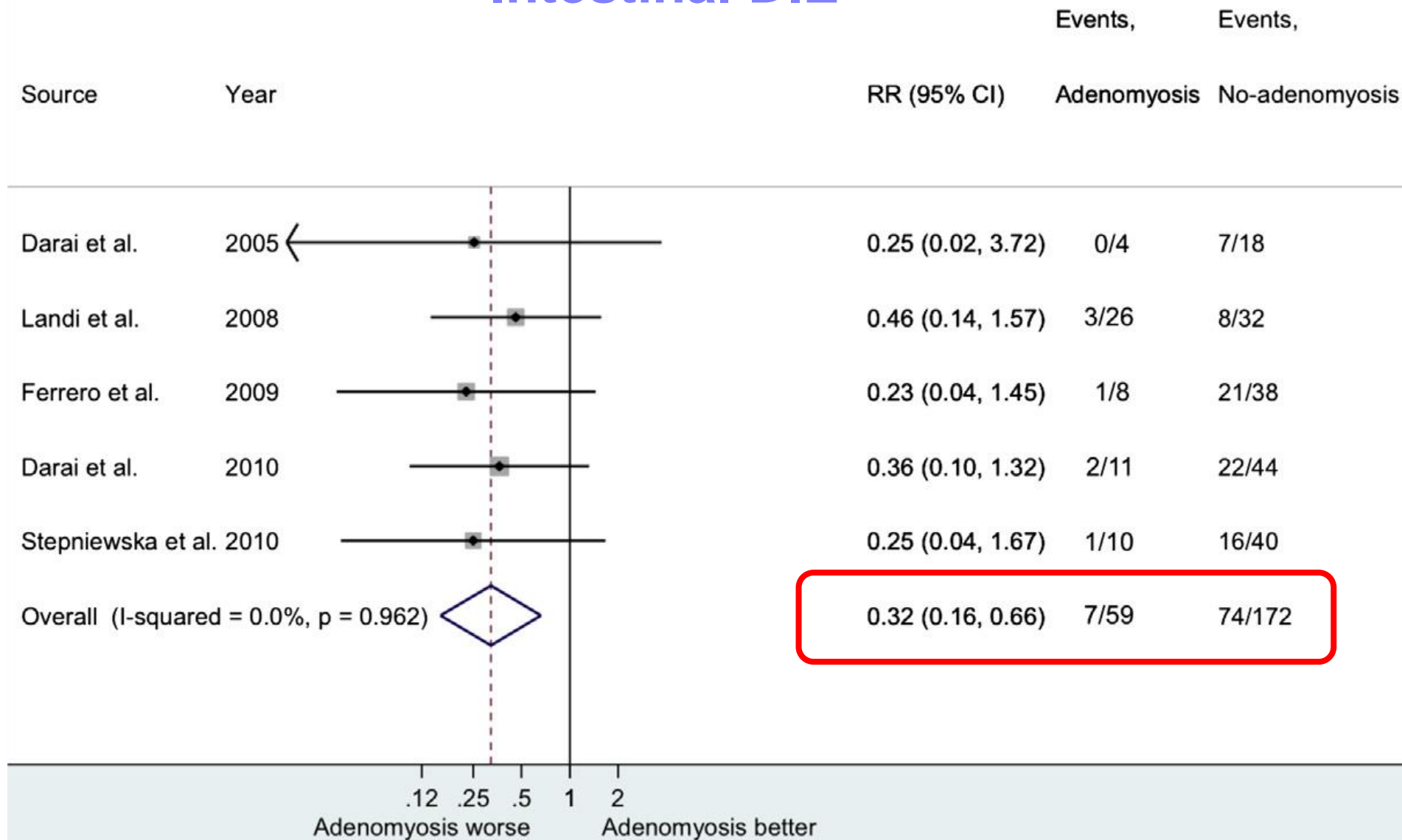


Adenomyosis



# Adenomyosis and infertility

## Intestinal DIE



# Endometriosis: *Surgical management*

**Disease**

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**Progression**

**Recurrence**

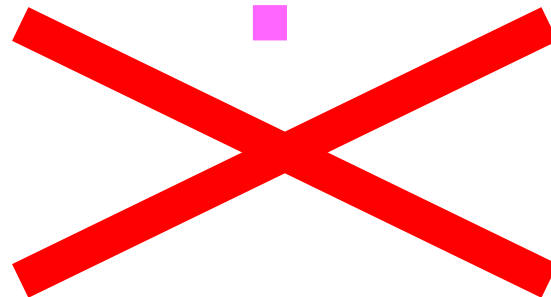
?

**Surgery**

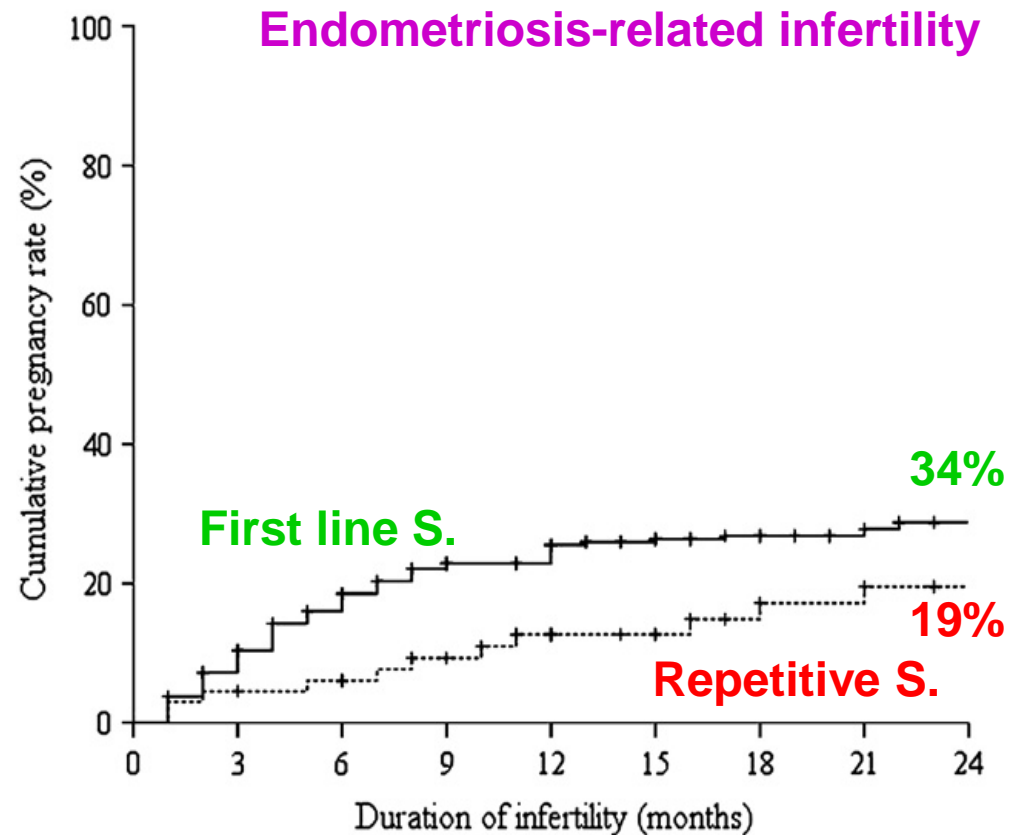
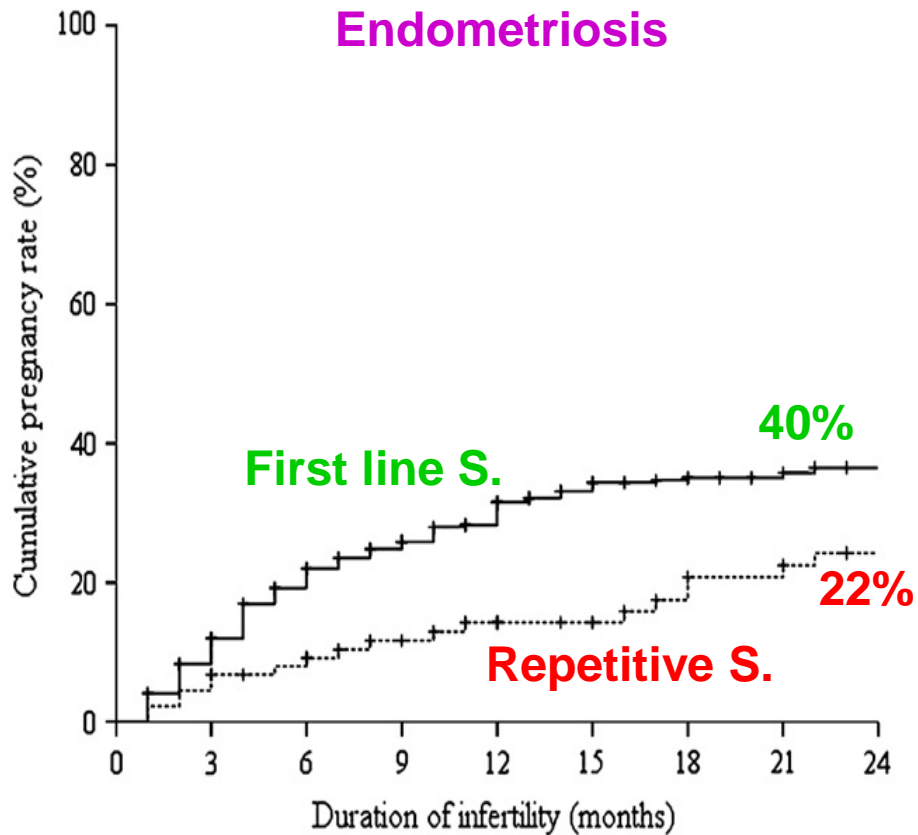
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**Unnecessary**

**Inappropriate**



# Repetitive surgery: 24-month cumulative pregnancy rate



# OMA:

## Ovarian reserve and repetitive cystectomy

Variable	Before second surgery (n = 18)	After second surgery (n = 18)	P value
AMH (ng/mL), mean $\pm$ SD	2.7 $\pm$ 1.9	1.2 $\pm$ 1.2	<.001
Basal FSH (mIU/mL), mean $\pm$ SD	8.7 $\pm$ 3.9	14.9 $\pm$ 6.6	<.001
Total AFC (n), median (range)	8 (4-15)	6.5 (4-13)	.34
AFC in the healthy ovary (n), median (range)	5.5 (3-9)	5.5 (4-12)	.65
AFC in the affected ovary (n), median (range)	2 (1-6)	1 (0-4)	.005
Volume of the affected ovary (cm <sup>3</sup> ), mean $\pm$ SEM	95.0 $\pm$ 22.2	4.7 $\pm$ 0.2	<.001
Volume of the healthy ovary (cm <sup>3</sup> ), mean $\pm$ SEM	6.9 $\pm$ 0.3	6.4 $\pm$ 0.2	.23



# Fertility preservation in endometriosis

## *Validity of fertility preservation*

<b>Conditions</b>	<b>Quality of the fertility preservation program (number/quality of eggs)</b>	<b>Negative effects of new surgery on ovarian reserve</b>	<b>Likelihood that the frozen eggs will be used</b>	<b>Overall validity of the fertility preservation program</b>
Bilateral endometriomas	++	Relevant	High	++
Previous monolateral excision of endometriomas, contralateral recurrence	+	Relevant	Very high	++
Previous surgery for bilateral endometriomas, no endometriomas recurrence	+	None	High	+
Previous surgery for bilateral endometriomas, monolateral recurrence	+/-	Relevant	Very high	+
Previous surgery for bilateral endometriomas, bilateral recurrences	+/-	Relevant	Very high	+
Previous monolateral excision of endometriomas, ipsilateral recurrence	++	Modest	High	+
Unilateral endometriomas	+++	Modest	Low	+
Deep peritoneal endometriosis without endometriomas	+++	None	Low	+

# Large EndometriOMAs :

## *Surgery before ART ?*

Comparative study on the pregnancy outcomes of in vitro fertilization-embryo transfer between long-acting gonadotropin-releasing hormone agonist combined with transvaginal ultrasound-guided cyst aspiration and long-acting gonadotropin-releasing hormone agonist alone

Yi-hong Guo, Na Lu, Yu Zhang, Ying-chun Su, Yang Wang, Yi-le Zhang, Ying-pu Sun\*

*Reproductive Medical Center of the First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China*

### Pre-ART intervention:

GnRH-a + OMA aspiration

vs. GnRH-a

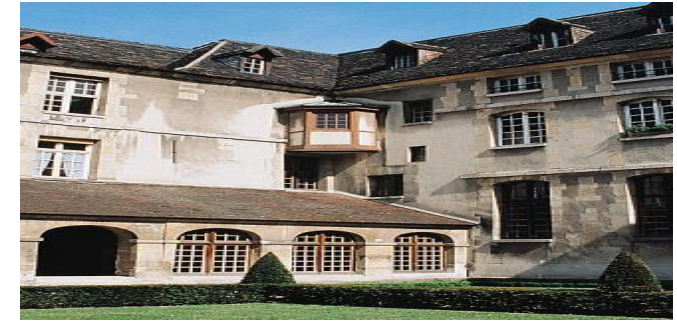
	Experimental group (n = 134)	Control group (n = 102)	P
No. of retrieved oocytes (n)	8.13 ± 4.32	6.46 ± 3.48	0.001
No. of embryos transferred			0.311
1	18	9	
2	93	77	
3	23	16	
2PN fertility rate (%)	87.46	72.46	0.041
Cleavage rate (%)	70.33	74.86	0.092
High-quality embryo rate (%)	62.37	52.32	0.003
Implantation rate (%)	29.35	20.71	0.037
Clinical pregnancy rate (%)	47.76	39.21	0.031
Abortion rate (%)	6.25	22.50	0.049

# Endometriosis related infertility

- Specifications and pathogenesis
- What are the therapeutic options ?
- How to choose between the therapeutic options?
- **Proposition for a strategy**



# Take home messages



## Strategy

- **Global** approach

Endometriosis

*and*

Patients

OMAs

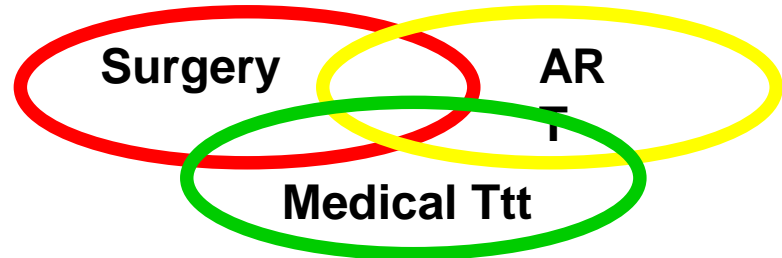
DIE

Adenomyosis

Pelvic pain

Infertility

- **Multidisciplinary** management



# Infertility *Work up*



pre ART

1 Ovarian reserve  
*Time available for in vivo*

2 Semen analysis

3 Fallopian tubes

1 Emergency IVF

2 IVF for severe male factor

3 IVF for tubal factor

# ART

de Ziegler,  
Borghese,  
and Chapron

The Lancet, 2010

# Sx

## Surgery

Provide 6-18 mo  
for spontaneous preg.

*if not pregnant*

**Exceptions for:**

**Surgery if:**

- Pelvic pain
- Hydrosalpinx
- Large oma???

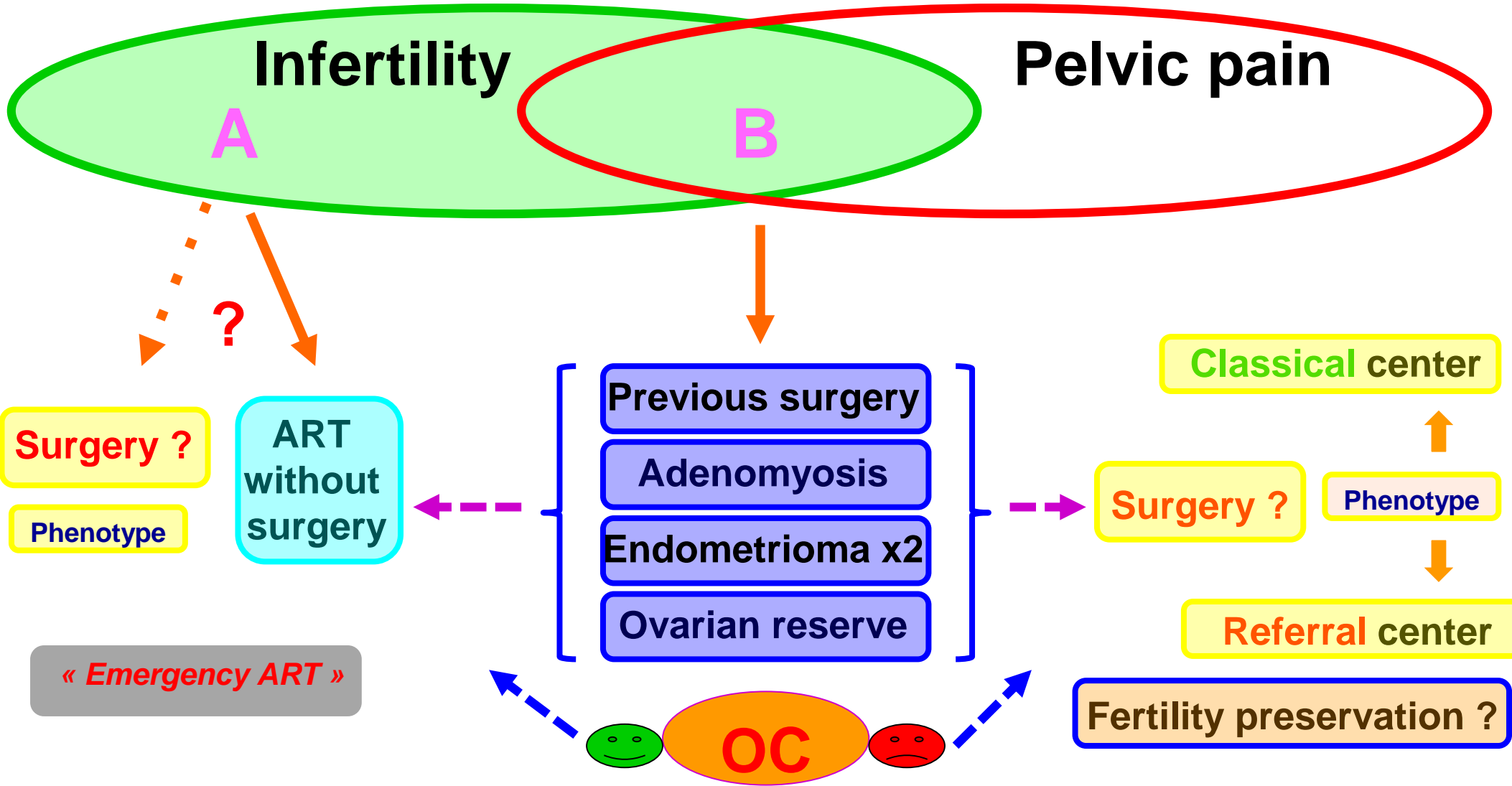
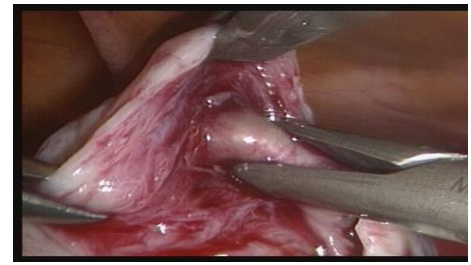
in principle  
NO surgery

ovarian suppression  
*(3 months)*  
IVF / ICSI

# Sx

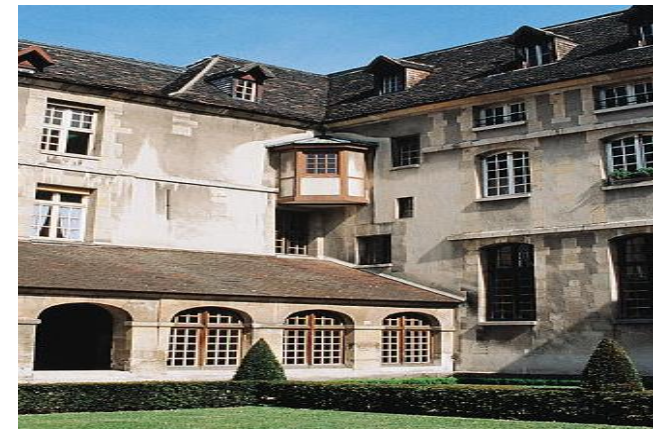


# Infertility: *management*



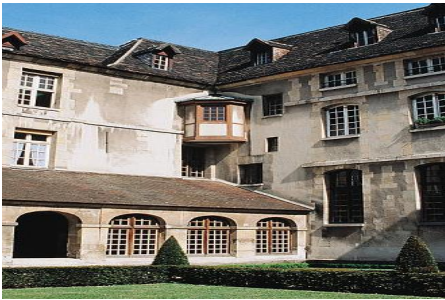


## Take home messages



**Best indication for surgery**  
**in cases of endometriosis**  
**related infertility is**  
***pelvic pain***





# Take home messages



- **DIE surgery should be complete**
- **Risks of DIE surgery**
- **Endometrioma alters the ovarian responsiveness *per se***
- **Endometrioma surgery alters the ovarian reserve**
- **OMA surgery unnecessary before ART**
- **Fertility preservation should be considered as part of preoperative counselling in young women with severe endometriosis**
- **Oocyte vitrification**

*One goal - One surgery  
in « the endometriosis life »*





## Gynecology

### Surgical unit:

C Chapron, B Borghese, P Santulli,  
H Foulot, MC Lafay-Pillet, A Bourret, G

Pierre,

M Even, MC Lamau, L Marcellin, P

Marzouk

### Medical unit:

A Gompel, G Plu-Bureau, L Maitrot

### Reproductive endocrinology unit:

D de Ziegler, P Santulli, V Gayet, P Pirtea,  
FX Aubriot

## Intestinal surgery

B Dousset, S Gaujoux, M Leconte

## Radiology

D de Ziegler, **Professor and Head**, Reproductive Endocrinology and Infertility unit,

AE Millischer, L Maitrot, A Gompel, **Professor and Head**, Medical Gynecological unit,

C Chapron, **Professor and Chair**, Gynecology Obstetrics II and Reproductive Medicine

## Laboratory: Genetic

D Vaiman, F Mondon, S Barbaux

## Laboratory: Immunology

F Batteux, S Chouzenoux, C Nicco,  
C Chéreau, B Weill

## Laboratory: Reproductive biology

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JM Kuntzman, C Chalas

## Statistical unit

F Goffinet, PY Ancel

2<sup>ND</sup> CONGRESS OF THE SOCIETY OF ENDOMETRIOSIS AND UTERINE DISORDERS

SEUD  
CONGRESS  
2016

# ADENOMYOSIS: NEW VISION

• FOR AN **OLD CHALLENGE**

2016 MAY 12, 13, 14  
**BARCELONA**

Location  
Barcelona, Spain

Congress President  
Pr Francisco Carmona, Spain

SEUD President  
Pr Charles Chapron, France