

# *Endometrioma Surgery and Fertility Preservation : A Vital Combination*

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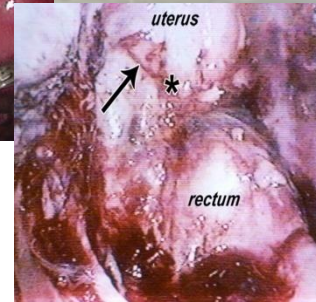
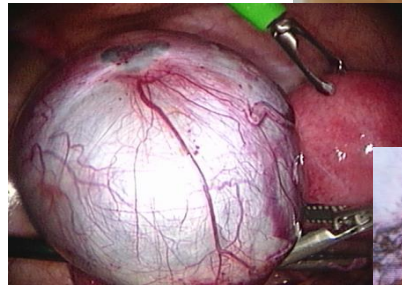
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# Ovarian Endometriomas

## Why/When to Operate ?

- Excessive Pain
- Adnexal Mass
  - Number
  - Unilateral/bilateral
  - Size
- Rupture
- Suspicion of Cancer
  
- To improve the pregnancy rate
- **Prior IVF/ICSI**



# There are some questions

- Does endometrioma decrease ovarian reserve ?
- Does ovarian surgery impair fertility outcomes by damaging healthy ovarian tissue ?
- Does ovarian cystectomy improve fertility outcomes ?

## Surgical treatment of ovarian endometriomas: state of the art?

# Endometriomas and IVF/ICSI

Individualized treatment plan can be developed, executed and modified as necessary based on :

- Bilaterality
- Number of endometrioma(s)
- Size of the endometrioma(s)
- Previous ovarian surgery

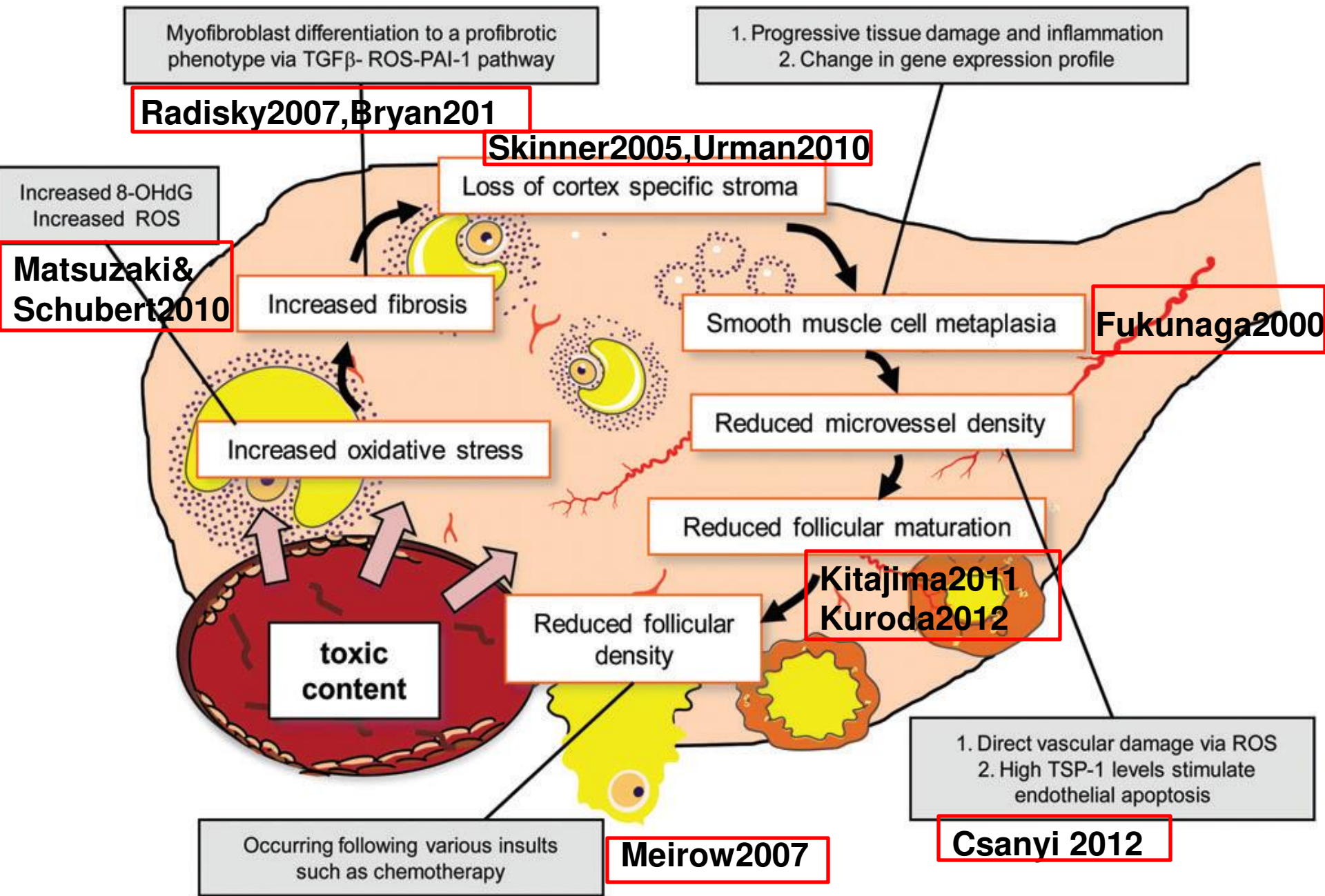


**Recurrence of the endometriomas is an important issue !  
(18%-30%)**

- Ovarian reserve
- Age
- If she wishes to conceive ASAP
- Her symptoms
- Other factor(s) which contribute(s) to infertility



# The mechanism of endometrioma mediated damage to the ovary is explained by several studies



The rate of spontaneous ovulation appears to be lower in ovaries containing endometriomas

human  
reproduction

ORIGINAL ARTICLE *Infertility*

## Endometriotic ovarian cysts negatively affect the rate of spontaneous ovulation

Laura Benaglia<sup>1,2,3</sup>, Edgardo Somigliana<sup>1</sup>, Paolo Vercellini<sup>1,2</sup>,  
Annalisa Abbiati<sup>1,2</sup>, Guido Ragni<sup>1</sup>, and Luigi Fedele<sup>1,2</sup>

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**BACKGROUND:** A growing body of evidence suggests that ovarian reserve is damaged after excision of ovarian endometriomas. However, it may not be excluded that gonadal damage is at least partly caused by the very presence of an endometrioma *per se*, thus preceding surgery. To clarify this aspect, we set up a prospective study in women with monolateral endometriomas in order to assess the rate of ovulation in affected ovaries.

**MATERIALS AND METHODS:** Seventy women with monolateral endometriomas who had not undergone previous adnexal surgery underwent serial ecographic examinations to determine the side of ovulation.

**RESULTS:** Ovulation occurred in the affected ovary in 22 cases (31%; 95% CI: 22–43%). Assuming that the expected rate of ovulation in both ovaries in healthy women is similar, this difference is statistically significant ( $P = 0.002$ ).

**CONCLUSION:** The physiological mechanisms leading to ovulation are deranged in ovaries with endometriomas.

This was illustrated in a 2009 study by Benaglia, who prospectively tracked the laterality of ovulation in 70 women with intact endometriomas and found a lower than expected ovulation rate on the affected side

# The presence of ovarian endometriomas is associated with a reduced responsiveness to gonadotropins

*Edgardo Somigliana, M.D.,<sup>a</sup> Mirco Infantino, M.D.,<sup>a,b</sup> Francesca Benedetti, M.D.,<sup>a,b</sup> Mariangela Arnoldi, M.D.,<sup>a,b</sup> Graziella Calanna, M.D.,<sup>a,b</sup> and Guido Ragni, M.D.<sup>a</sup>*

**Number of codominant follicles according to the characteristics of the endometrioma(s) and the responsiveness to ovarian hyperstimulation.**

	No. of cycles	Intact ovary	Ovary with endometrioma(s)	<i>P</i>
No. of cysts				
1	49	3.9 ± 2.0	3.2 ± 1.7	.08
2	7	5.1 ± 3.1	2.0 ± 1.5	.06
Diameter of the cysts <sup>a</sup>				
≤20 mm	31	3.7 ± 2.1	3.0 ± 1.4	.16
>20 mm	25	4.5 ± 2.2	3.2 ± 2.1	.03
Total IU of rFSH used				
≤2,700 <sup>b</sup>	29	4.6 ± 2.1	3.1 ± 1.7	.01
>2,700 <sup>b</sup>	27	3.4 ± 2.1	3.0 ± 1.8	.42
No. of oocytes retrieved				
≤5	27	3.6 ± 2.2	2.9 ± 1.8	.22
>5	29	4.5 ± 2.1	3.2 ± 1.7	.03

The presence of in this study, the number of codominant follicles developing in affected gonads was reduced when compared with the contralateral intact ovaries of the same patients

This conclusion is further supported by the observation that this effect is dependent on the size and number of the cysts

# Number of retrieved oocytes

Suzuki compared the impact of ovarian endometrioma in three groups: patients with endometrioma, patients with endometriosis and patients with tubal factor

## Impact of ovarian endometrioma on oocytes and pregnancy outcome in in vitro fertilization

	Endometrioma	Endometriosis	Tubal faktör (kontrol)
	Group A	Group B	Group C
Cycles	80	248	283
Age (y)	34.6 ± 3.3	34.7 ± 3.3	34.0 ± 8.8
BMI (kg/m <sup>2</sup> )	22.3 ± 0.5	21.7 ± 0.9	22.1 ± 0.8
No. of oocytes retrieved	4.40 ± 2.99	4.48 ± 2.81	5.34 ± 2.99
	( <i>P</i> = .0037 vs. group C)	( <i>P</i> < .0001 vs. group C)	
Fertilization rate (%)	77.5 ± 28.1	78.8 ± 27.9	82.0 ± 21.9
Good quality rate <sup>a</sup> (%)	67.2 ± 32.5	63.0 ± 36.8	58.1 ± 35.1
Transferred embryos	2.20 ± 0.86	2.35 ± 0.83	2.67 ± 0.89
	( <i>P</i> = .0001 vs. group C)	( <i>P</i> = .0001 vs. group C)	
Implantation rate (%)	14.1	11.7	11.3
Pregnancy rate per ET (%)	25.3	22.3	23.9
Live birth rate per ET (%)	14.7	15.0	15.4

Suzuki T. Et al. Fertil Steril 2005

The number of oocytes retrieved and the number of embryos transferred were significantly lower in endometriosis and endometrioma groups than control

RESEARCH

Open Access

# Ovarian reserve markers and assisted reproductive technique (ART) outcomes in women with advanced endometriosis

Safiya A Wahd<sup>1\*</sup>, Shahla K Alalaf<sup>1</sup>, Talha Al-Shawaf<sup>2,3</sup> and Namir G Al-Tawil<sup>4</sup>

This study compares AFC and levels of AMH in women with stage III-IV endometriosis receiving their first ICSI cycle

Serum AMH levels were significantly low only in women with a previous history of endometrioma surgery, whereas AFC was significantly lower in both groups

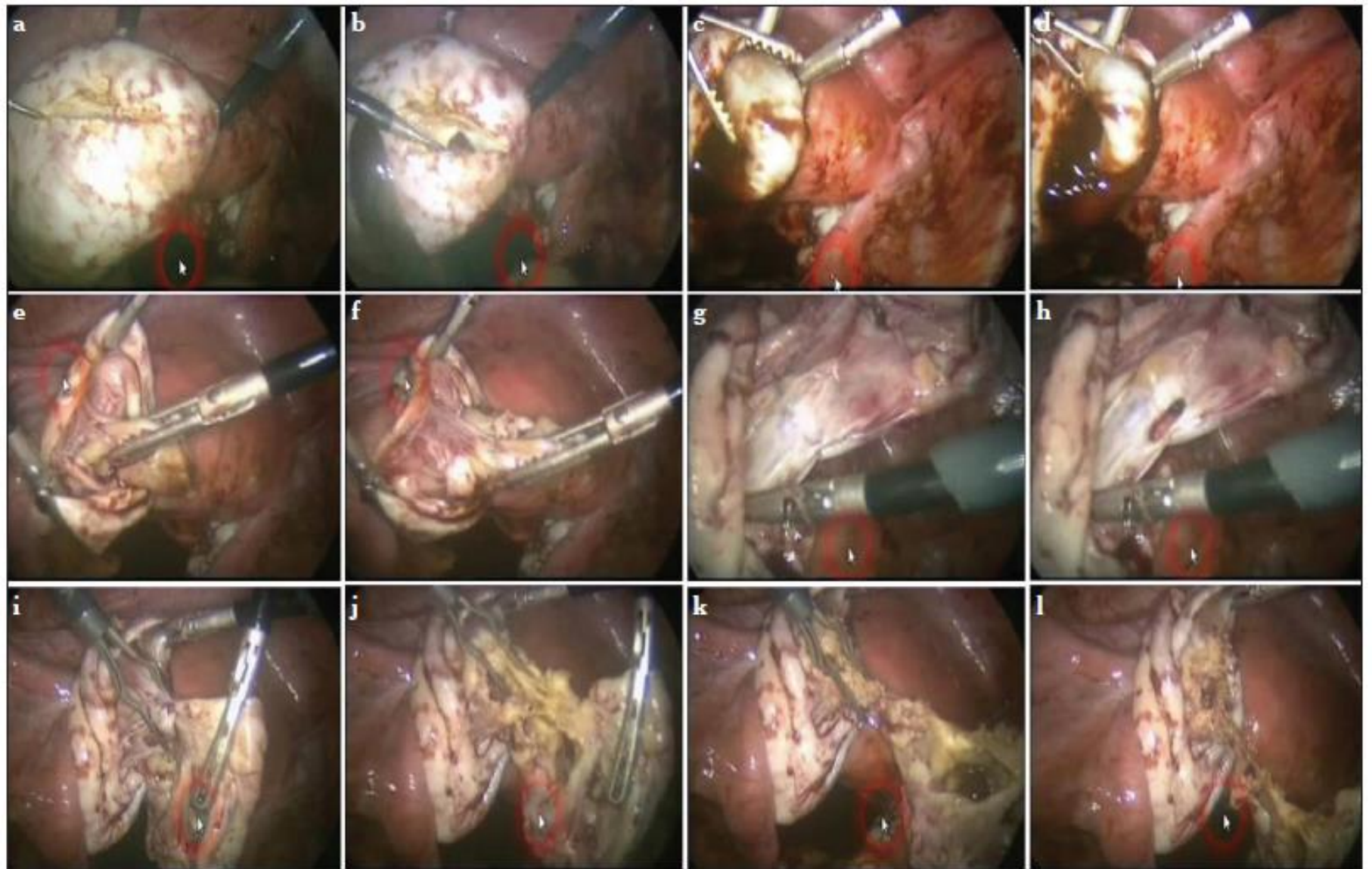
**Table 1 Clinical characteristics of women with endometriosis stage III-IV, previous endometrioma surgery and infertility without endometriosis**

Parameters	Stage III and IV endometriosis, n = 110		II-No endometriosis n = 175	Overall P value	P IaXIb	P IaXII	P IbXII
	Ia-No previous surgery, n = 63	Ib-Previous endometrioma surgery, n = 47					
Age (years)	32.67 ± 5.27	32.62 ± 5.63	32.77 ± 5.99	0.983			
Duration (years)	8.62(4.86)	7.32(5.05)	8.32(5.15)	0.381			
AFC	10.75 ± 3.07	9.09 ± 3.07	12.39 ± 4.17	<0.001	0.24	0.003	<0.001
AMH (ng/mL)*	1.86 ± 1.03	1.06 ± 0.85	2.19 ± 1.57	<0.001	0.003	0.103	<0.001
FSH (mIU/mL)	6.61 ± 2.56	6.97 ± 2.75	6.42 ± 2.51	0.422			
E2 (pg/mL)	38.98 ± 17.34	35.93 ± 16.01	40.13 ± 18.44	0.357			
BMI (kg/m <sup>2</sup> )	25.74 ± 4.27	26.25 ± 4.11	29.66 ± 4.86	<0.001	0.571	<0.001	<0.001

# Endometriomas

The presence of endometrioma has important effects on the ovary

- Impaired folliculogenesis and oocyte quality
- Less spontaneous ovulation (1:2)
- Decreased ovarian response to COH
- Oocyte number and peak serum estradiol (↓)
- Decreased fertilization and implantation
- Increased cancellation rates
- Increased risk of abscess formation during OR

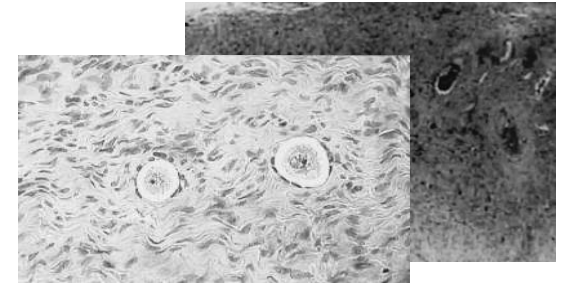


**Figure 6. a-l.** Modified combined technique for the removal of endometrioma. Cleavage plane is revealed with a fine-tip needle electrode (a, b). Countertraction is accomplished to strip the cyst wall from the ovarian cortex (c-f). When the base of the cyst is reached, a white plane is seen (g). With more traction, the tissue usually starts to tear (h). Cyst wall is coagulated using bipolar forceps and cut from the base with scissors (i-l)

# Damage Mechanisms

- **Surgery-mediated damage**

**Negative effect of SURGERY !?**



**Presence of healthy ovarian tissue adjacent to removed the cyst wall**

**Muzzi et al.,2002;Hachisuga and Kawarabayashi,2002**

**Excission of healthy ovarian cortex with follicles**

**Brosens et al.,2004**

**Surgery related local inflammation and electrocoagulation during haemostasis**

**La Torre et al.,1998;Marconi et al.,2002;Fedele et al.,2004**




## The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis

M. Hamdan<sup>1,2,3</sup>, G. Dunselman<sup>4</sup>, T.C. Li<sup>5</sup>, and Y. Cheong<sup>1,3,\*</sup>

**RESULTS:** We included 33 studies for the meta-analysis. The majority of the studies were retrospective (30/33), and three were RCTs. Compared with women with no endometrioma undergoing IVF/ICSI, women with endometrioma had a similar LBR (odds ratio [OR] 0.98; 95% CI [0.71, 1.36], 5 studies, 928 women,  $I^2 = 0\%$ ) and a similar CPR (OR 1.17; 95% CI [0.87, 1.58], 5 studies, 928 women,  $I^2 = 0\%$ ), a lower mean number of oocytes retrieved (SMD  $-0.23$ ; 95% CI  $[-0.37, -0.10]$ , 5 studies, 941 cycles,  $I^2 = 37\%$ ) and a higher cycle cancellation rate compared with those without the disease (OR 2.83; 95% CI [1.32, 6.06], 3 studies, 491 women,  $I^2 = 0\%$ ). Compared with women with no surgical treatment, women who had their endometrioma surgically treated before IVF/ICSI had a similar LBR (OR 0.90; 95% CI [0.63, 1.28], 5 studies, 655 women,  $I^2 = 32\%$ ), a similar CPR (OR 0.97; 95% CI [0.78, 1.20], 11 studies, 1512 women,  $I^2 = 0\%$ ) and a similar mean number of oocytes retrieved (SMD  $-0.17$ ; 95% CI  $[-0.38, 0.05]$ , 9 studies, 810 cycles,  $I^2 = 63\%$ ).

**CONCLUSIONS:** Women with endometrioma undergoing IVF/ICSI had similar reproductive outcomes compared with those without the disease, although their cycle cancellation rate was significantly higher. Surgical treatment of endometrioma did not alter the outcome of IVF/ICSI treatment compared with those who did not receive surgical intervention. Considering that the reduced ovarian reserve may be attributed to the presence of endometrioma *per se*, and the potential detrimental impact from surgical intervention, individualization of care for women with endometrioma prior to IVF/ICSI may help optimize their IVF/ICSI results.

## Surgery versus conservative management of endometriomas in subfertile women. A systematic review

JACOB BRINK LAURSEN<sup>1</sup> , JEPPE B. SCHROLL<sup>2</sup>, KIRSTEN T. MACKLON<sup>3</sup>  & MARTIN RUDNICKI<sup>4</sup> 

**Conclusion.** The very low quality evidence suggests no difference in odds ratio of live birth between women who underwent surgery for endometriomas before IVF/ICSI compared with conservative management. Further high quality studies are needed, but due to a lack of convincing evidence favoring surgery, we recommend considering conservative treatment if the only indication is subfertility.

# Influence of Endometriosis on Assisted Reproductive Technology Outcomes

## A Systematic Review and Meta-analysis

Mukhri Hamdan, *MOBGyn*, Siti Z. Omar, *MOBGyn*, Gerard Dunselman, MD, PhD, and Ying Cheong, MD, *MRCOG*

**CONCLUSION:** Women with and without endometriosis have comparable ART outcomes in terms of live births, whereas those with severe endometriosis have inferior outcomes. There is insufficient evidence to recommend surgery routinely before undergoing ART.

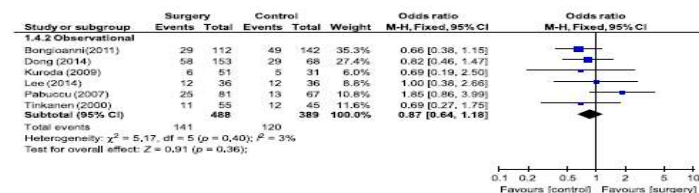


Figure 2. Forest plot for live birth - after sensitivity analysis. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

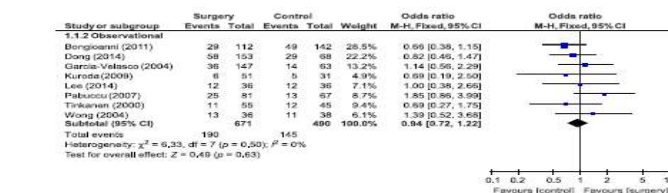
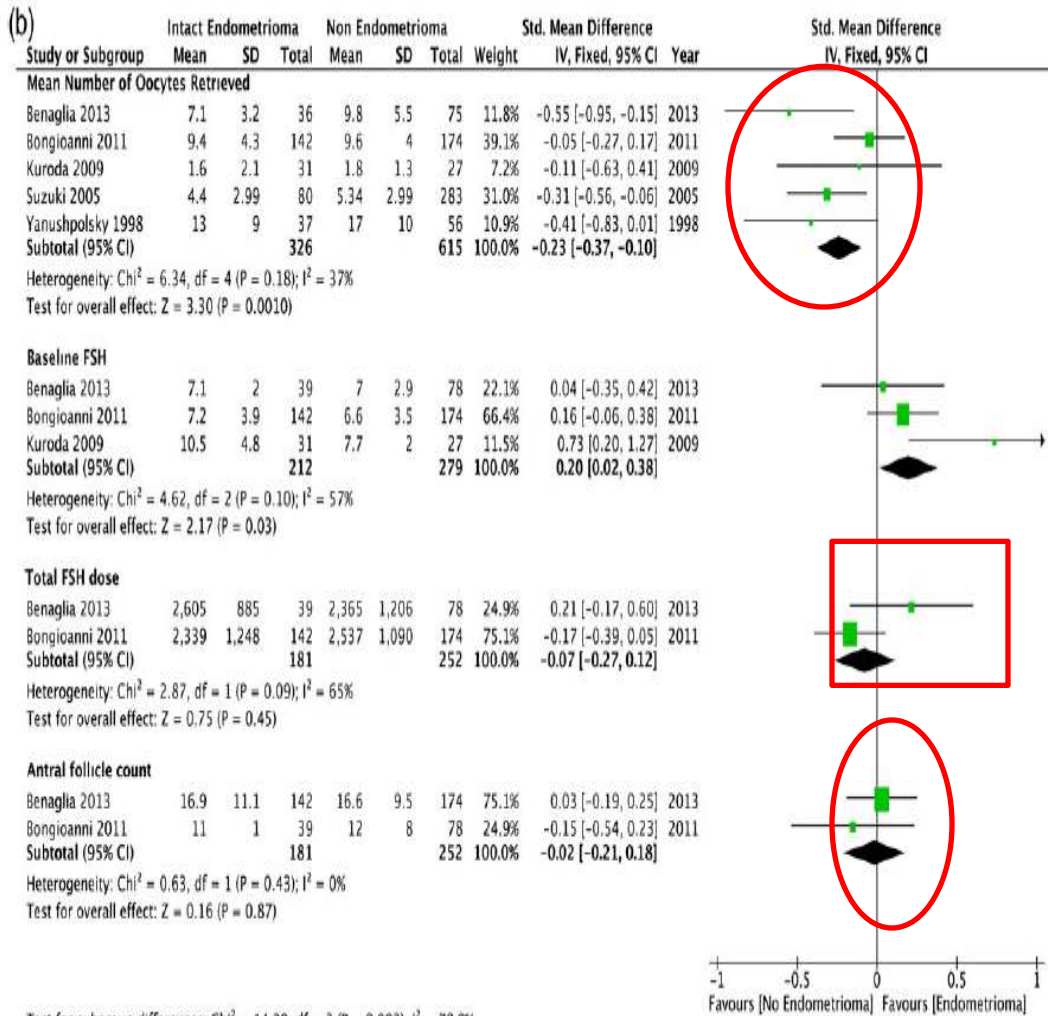


Figure 3. Forest plot for live birth. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

# The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis

M. Hamdan<sup>1,2,3</sup>, G. Dunselman<sup>4</sup>, T.C. Li<sup>5</sup>, and Y. Cheong<sup>1,3,\*</sup>



Also they had stated that, compared with women without the disease, women with endometrioma

- ▶ have a lower mean number of oocyte retrieved,
- ▶ require higher FSH dosage for ovarian stimulation and have a lower AFC,
- ▶ **suggesting that their ovarian reserve is diminished prior to IVF/ICSI**

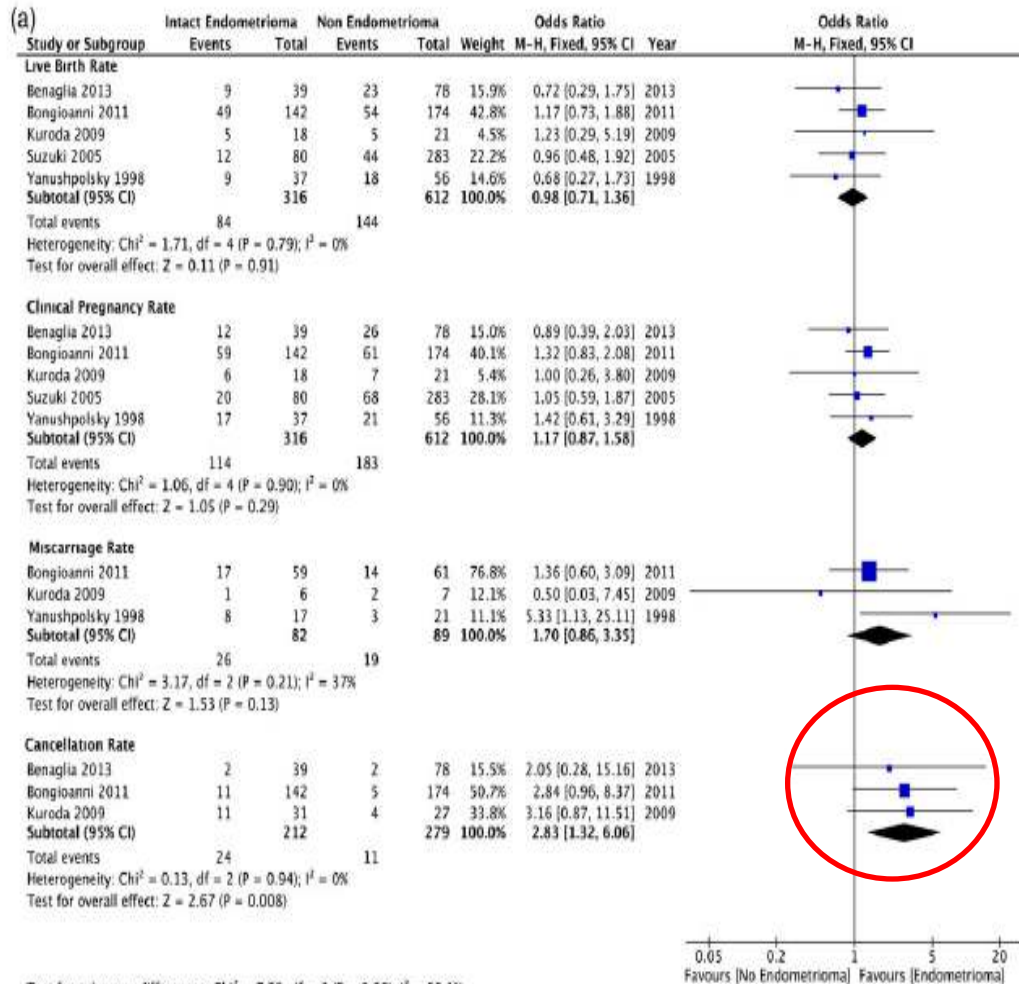
# 4- Clinical Pregnancy Rates in ART cycles

Human Reproduction Update, Vol.21, No.6 pp. 809–825, 2015  
 Advanced Access publication on July 12, 2015 doi:10.1093/humupd/dmw035

human  
reproduction  
update

## The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis

M. Hamdan<sup>1,2,3</sup>, G. Dunselman<sup>4</sup>, T.C. Li<sup>5</sup>, and Y. Cheong<sup>1,3,\*</sup>



In a recent 33 studies for the meta-analysis, Hamdan et al. concluded about the impact of endometrioma on IVF/ICSI outcomes

### AS A RESULT :

Compared with women without the disease, women with endometrioma had a similar LBR, CPR and MR although their cycle cancellation rate was significantly higher

# Laparoscopic stripping of endometriomas negatively affects ovarian follicular reserve even if performed by experienced surgeons

Chiara Perono Biacchiardi <sup>a</sup>, Luisa Delle Piane <sup>b</sup>, Marco Camanni <sup>a</sup>, Francesco Deltetto <sup>a</sup>, Elena Maria Delpiano <sup>a</sup>, Gian Luigi Marchino <sup>b</sup>, Gianluca Gennarelli <sup>b</sup>, Alberto Revelli <sup>b,\*</sup>

**Table 3** Ultrasonographic variables before laparoscopic stripping of ovarian endometrioma(s) and after 3 and 9 months for patients with monolateral endometrioma (n = 33).

Ultrasonographic finding	Before LPS	After LPS		P-value
		3 months	9 months	
AFC (affected ovary)	3.3 ± 3.2	6.0 ± 4.5	5.1 ± 3.6	NS
AFC (healthy ovary)	8.4 ± 6.0	9.0 ± 6.2	8.1 ± 4.9	NS
Ovarian volume (affected) (ml)	10.5 ± 0.8	8.5 ± 0.6	8.6 ± 0.9	<0.0001
Ovarian volume (healthy) (ml)	8.1 ± 0.8	8.4 ± 0.6	8.2 ± 0.8	NS

Values are mean ± SD. AFC = antral follicle count; LPS = laparoscopic stripping; NS = not statistically significant.

**Table 2** Hormone concentrations before laparoscopic stripping of ovarian endometrioma(s) and after 3 and 9 months.

Hormone	Before LPS	After LPS		P-value
		3 months	9 months	
FSH (IU/l)	6.6 ± 2.0	7.8 ± 3.4	8.0 ± 3.7	NS
LH (IU/l)	5.0 ± 2.0	4.5 ± 1.7	4.2 ± 2.0	NS
Oestradiol (pg/ml)	35.2 ± 24.5	33.5 ± 29.3	32.9 ± 26.6	NS
Inhibin B (pg/ml)	51.6 ± 31.3	47.4 ± 23.0	44.5 ± 26.0	NS
AMH (ng/ml)	3.0 ± 0.4	1.4 ± 0.2	1.3 ± 0.3	<0.0001

Values are mean ± SD. AMH = anti-Müllerian hormone; LPS = laparoscopic stripping; NS = not statistically significant.

Overall, the data show that laparoscopic stripping of endometriomas reduces ovarian reserve.

The significant decrease of AMH after surgery confirms that part of the healthy ovarian pericapsular tissue, containing primordial and preantral follicles, is removed or damaged despite all the surgical efforts to be atraumatic.

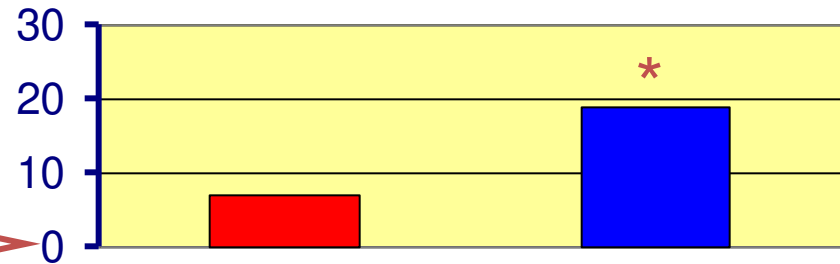
**This must be carefully considered when laparoscopic cystectomy surgery is scheduled for patients with no relevant symptoms besides infertility or with already small ovarian reserve.**

# Surgery prior to IVF

## bilateral endometrioma

**Table III.** Characteristics of the IVF–ICSI cycles in patients operated for bilateral endometriomas (cases) and controls.

Characteristics	Cases n= 68	Controls n= 136	<i>P</i>
Cancelled cycle			<0.001
Hyper-response	1 (2%)	20 (15%)	
Poor response	17 (28%)	8 (6%)	
Dosage of rFSH/die	333 ± 133	212 ± 112	<0.001
Duration of stimulation (day) <sup>a</sup>	11.5 ± 2.3	11.8 ± 2.4	0.58
Number of follicles 11–15 mm <sup>a</sup>	3.2 ± 2.8	4.6 ± 3.3	0.009
Number of follicles > 15 mm <sup>a</sup>	2.2 ± 2.2	2.2 ± 2.7	0.002
Number of oocyte retrieved <sup>a</sup>	11.5 ± 2.3	11.8 ± 2.4	
Number of oocyte used <sup>a,b</sup>	11.5 ± 2.3	11.8 ± 2.4	
Number of embryos obtained <sup>a,b</sup>	11.5 ± 2.3	11.8 ± 2.4	
Number of transfers not performed <sup>a</sup>	11.5 ± 2.3	11.8 ± 2.4	
Number of embryos transferred <sup>c</sup>	11.5 ± 2.3	11.8 ± 2.4	
Clinical pregnancy rate (PR)			
Number of pregnancies	5	33	
PR per starting cycle	7%	16%	0.048
PR per oocyte retrieval	17%	28%	0.11
PR per embryo transfer	5%	16%	0.11
Implantation rate	5 (7%)	33 (16%)	0.048
Delivery rate (DR)			
Number of deliveries	3	23	
DR per starting cycle	4%	17%	0.013
DR per oocyte retrieval	6%	21%	0.02
DR per embryo transfer	8%	25%	0.049



*P*=0.037

PR/ starting cycle

# Second surgery for recurrent endometriomas is more harmful to healthy ovarian tissue and ovarian reserve than first surgery

Ludovico Muzii, M.D.,<sup>a</sup> Chiara Achilli, M.D.,<sup>a</sup> Francesca Lecce, M.D.,<sup>a</sup> Antonella Bianchi, M.D.,<sup>b</sup> Silvia Franceschetti, M.D.,<sup>a</sup> Claudia Marchetti, M.D.,<sup>a</sup> Giorgia Perniola, M.D.,<sup>a</sup> and Pierluigi Benedetti Panici, M.D.<sup>a</sup>

**Result(s):** The cyst wall specimen was significantly thicker in the recurrent endometrioma group than in the first surgery group ( $1.7 \pm 0.3$  mm vs.  $1.1 \pm 0.3$  mm). Both main components of the cyst specimen (i.e., endometriosis tissue and ovarian tissue) were more represented in the recurrent endometrioma group than in the first surgery group. At sonographic follow-up, the operated ovary had a significantly lower AFC and volume than the contralateral nonoperated ovary in the recurrent endometrioma group, but not in the primary surgery group.

**Conclusion(s):** Surgery for recurrent endometriomas is associated with evidence of a higher loss of ovarian tissue and is more harmful to the ovarian reserve evaluated by AFC and ovarian volume, if compared with endometriomas operated for the first time. Indications to surgery for recurrent endometriomas should be reconsidered with caution. (*Fertil Steril*® 2015;103:738–43. ©2015 by American Society for Reproductive Medicine.)

**Key Words:** Endometrioma, laparoscopic surgery, ovarian cyst excision, ovarian reserve, recurrence

**Discuss:** You can discuss this article with its authors and with other ASRM members at <http://fertstertforum.com/muziil-excisional-surgery-recurrent-endometriomas-harmful/>



Use your smartphone to scan this QR code and connect to the discussion forum for this article now.\*

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**TABLE 3**

Ovarian reserve evaluation by antral follicle count after surgical excision of ovarian endometriomas.

Antral follicle count	PS group (n = 17)	RS group (n = 11)	P value (PS vs. RS group)
Operated ovary	5.1 ± 2.8	3.5 ± 1.4	.07
Contralateral ovary	5.7 ± 2.2	4.6 ± 1.5	.17
P value (operated vs. contralateral ovary)	.2	.002	

Note: Data are expressed as mean ± SD. PS = primary surgery; RS = recurrent surgery.

Muzii. Surgery for recurrent endometriomas. *Fertil Steril* 2015.

**TABLE 4**

Ovarian reserve evaluation by ovarian volume after surgical excision of ovarian endometriomas.

Ovarian volume	PS group (n = 17)	RS group (n = 11)	P value (PS vs. RS group)
Operated ovary (mL)	7.0 ± 2.0	5.3 ± 1.7	.03
Contralateral ovary (mL)	7.5 ± 1.9	6.6 ± 1.7	.23
P value (operated vs. contralateral ovary)	.08	.001	

Note: Data are expressed as mean ± SD. PS = primary surgery; RS = recurrent surgery.

Muzii. Surgery for recurrent endometriomas. *Fertil Steril* 2015.

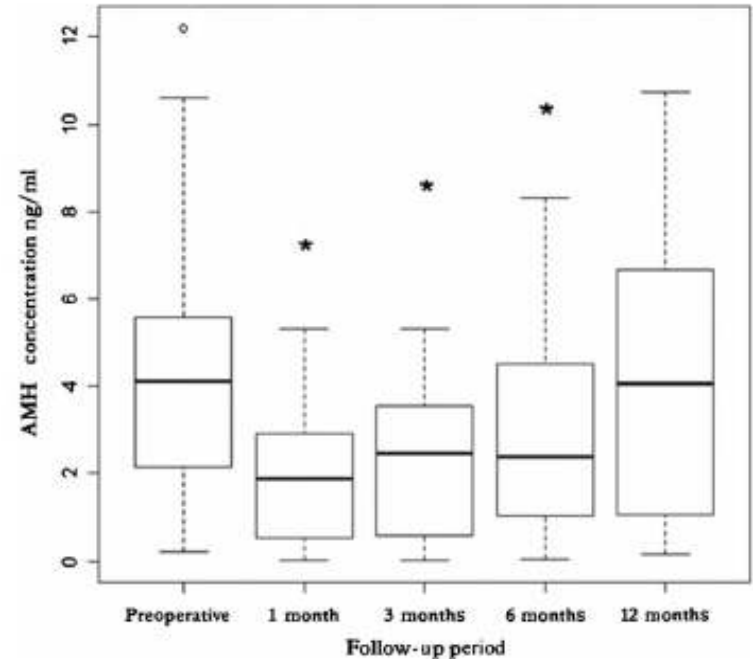
# Surgical excision of ovarian endometriomas: Does it truly impair ovarian reserve? Long term anti-Müllerian hormone (AMH) changes after surgery

Michele Vignali<sup>1</sup>, Mohamed Mabrouk<sup>2</sup>, Erika Ciocca<sup>1</sup>, Giulia Alabiso<sup>1</sup>, Allegra Barbasetti di Prun<sup>1</sup>, Davide Gentilini<sup>3</sup> and Mauro Busacca<sup>1</sup>

**Methods:** A total of 22 patients undergoing laparoscopic cystectomy for unilateral endometrioma (n=10) and bilateral endometriomas (n=12) were included in the study.

**Result(s):** Serum anti-Müllerian hormone (AMH) levels significantly decreased from the baseline value ( $3.98 \pm 3.27$  ng/mL) one ( $1.67 \pm 1.56$  ng/mL), three ( $2.01 \pm 1.70$  ng/mL), and six months ( $2.43 \pm 2.39$  ng/mL) postoperatively. There was no difference between preoperative and 12 month postoperative AMH levels ( $4.01 \pm 3.39$  ng/mL) ( $P > 0.05$ ). Patients with bilateral endometriomas had a significantly higher rate of decline in AMH levels 12 months after surgery than patients with monolateral endometriomas ( $P = 0.035$ ), but in both groups there was no difference in AMH levels at one and 12 months postoperatively ( $P > 0.05$ ).

**Conclusion(s):** AMH levels temporarily decreased after laparoscopic cystectomy for ovarian endometriomas, with complete recovery of preoperative AMH values at 12 months postoperatively. This pattern was equal in patients with bilateral and unilateral ovarian involvement. Patients with bilateral cysts have higher rates of decline of AMH levels compared to patients with unilateral affection.



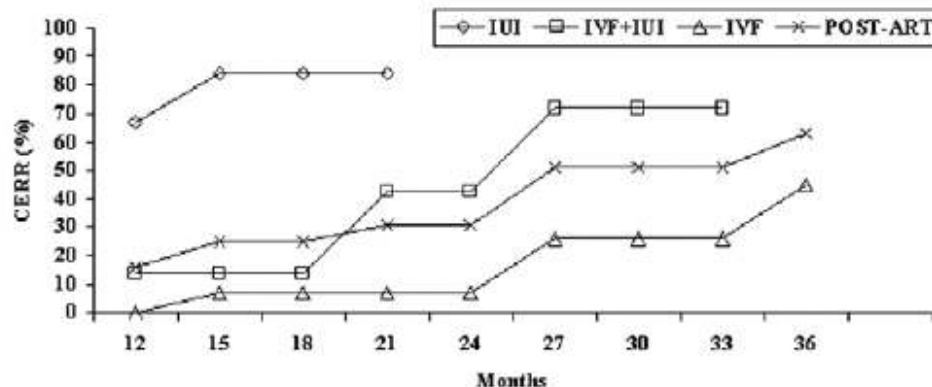
**Figure 1** There was a statistically significant difference between median anti-Müllerian hormone (AMH) levels before surgery and at one, three and six months ( $P < 0.01$ ). However, no significant difference was detected between preoperative and 12 months after surgery ( $P > 0.05$ ).

# Is the endometriosis recurrence rate increased after ovarian hyperstimulation?

*Thomas M. D'Hooghe, M.D., Ph.D., Bénédicte Denys, M.D., Carl Spiessens, Ph.D., Christel Meuleman, M.D., and Sophie Debrock, Ph.D.*

Leuven University Fertility Center, Department of Obstetrics and Gynecology, University Hospital Gasthuisberg, Leuven, Belgium

Post-ART recurrence study: CERR after treatment with IUI, IVF, or a combination of IUI and IVF.



**Conclusion(s):** In contrast to our hypothesis, the results from this study showed that the CERR is lower after ovarian hyperstimulation for IVF than after lower-dose ovarian stimulation for IUI, suggesting that temporary exposure to very high E<sub>2</sub> levels in women during OH for IVF is not a major risk factor for endometriosis recurrence in women treated with assisted reproductive technology. (Fertil Steril® 2006;86:283–90. ©2006 by American Society for Reproductive Medicine.)

# **Endometriomas and Ovarian Reserve: Insights from IVF-ICSI Cycles in Women with Endometriomas**

- **Contralateral gonad may adequately compensate for the reduced function of the affected gonad**
- **The number of follicles developed in the cystectomized ovary significantly reduced when compared to the contralateral intact gonad!**
- **In women with larger endometriomas follicle number decrease more significantly**
- **Poorer response with more than one cyst**

**Somigliana et al.,FS,2006,2010**

- **Bilateral cysts may elevated risk of ovarian function impairment (19%-28% bilaterality)**

**Prefumo et al.,2002;Al-Fozan and Tulandi,2003.Esiner et al.2006**

# Conclusions

- **Ovarian reserve is decreased with ovarian surgery**
- **The rate of ovarian injury is higher in endometrioma compared to other benign cysts**
- **No positive effect of endometrioma removal is expected on IVF outcome**
- **The risk of ovarian injury is increased with the number of endometriomas and bilateral endometrioma**
- **Data is limited on the impact of different surgical techniques**

# Management of endometriomas in women requiring IVF: to touch or not to touch

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**Table I** Clinical variables to be considered when deciding whether to perform surgery or not in women with endometriomas selected for IVF

Characteristics	Favours surgery	Favours expectant management
Previous interventions for endometriosis	None	$\geq 1$
Ovarian reserve <sup>a</sup>	Intact	Damaged
Pain symptoms	Present	Absent
Bilaterality	Monolateral disease	Bilateral disease
Sonographic feature of malignancy <sup>b</sup>	Present	Absent
Growth	Rapid growth	Stable

<sup>a</sup>Ovarian reserve is estimated based on serum markers or previous hyperstimulation cycles; <sup>b</sup>sonographic feature of malignancy refers to solid components, locularity, echogeniety, regularity of shape, wall,



# Cryopreservation of oocytes in a young woman with severe and symptomatic endometriosis: a new indication for fertility preservation

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Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, McGill Reproductive Center, McGill University Health Center, Montreal, Quebec, Canada

**Objective:** To report a new indication for fertility preservation.

**Design:** Case report.

**Setting:** Academic teaching hospital.

**Patient(s):** A 25-year-old nulliparous woman with severe and symptomatic endometriosis and low antral follicular count.

**Intervention(s):** Oocyte cryopreservation.

**Main Outcome Measure(s):** Number of cryopreserved oocytes.

**Result(s):** After three cycles of ovarian stimulation, we cryopreserved 21 oocytes.

**Conclusion(s):** We recommend fertility preservation as part of preoperative counseling in young women with severe endometriosis. (Fertil Steril® 2009;91:293.e1–e3. ©2009 by American Society for Reproductive Medicine.)

**Key Words:** Fertility preservation, endometriosis, endometrioma, premature ovarian failure, oocyte vitrification



human reproduction ORIGINAL ARTICLE *Embryology*

## Vitrification of cleavage stage day 3 embryos results in higher live birth rates than conventional slow freezing: a RCT

S. Debrock\*, K. Peeraer, E. Fernandez Gallardo, D. De Neubourg, C. Spiessens, and T.M. D’Hooghe

Human Reproduction Update, Vol.18, No.5 pp. 536–554, 2012  
 Advanced Access publication on April 25, 2012 doi:10.1093/humupd/dmu016

human reproduction update

## A critical appraisal of cryopreservation (slow cooling versus vitrification) of human oocytes and embryos

David H. Edgar<sup>1,2</sup> and Debra A. Gook<sup>1,2,\*</sup>

		Survival	IR
Smith <i>et al.</i> (2010), slow	1.5 M PROH, 0.3 M sucrose	65	13 <sup>a,b</sup>
Smith <i>et al.</i> (2010), vit	15% EG, 15% DMSO, 0.5 M sucrose	75	38 <sup>a,b</sup>
Noyes <i>et al.</i> (2010), slow	1.5 M PROH, 0.3 M sucrose	85	NR (mixed transfers)
Noyes <i>et al.</i> (2010), vit	15% EG, 15% DMSO, 0.5 M sucrose	88	NR (mixed transfers)
Fadini <i>et al.</i> (2009), slow	1.5 M PROH, 0.3 M sucrose	57.9	4.3
Fadini <i>et al.</i> (2009), vit	EG, PROH, sucrose (Medicult)	78.9	9.3

## Cryopreservation of day 2–3 embryos by vitrification yields better outcome than slow freezing

Jacob Levron, Oshrit Leibovitz, Masha Brengauz, Hila Gitman, Gil M. Yerushalmi, Eldad Katorza, Itai Gat & Shai E. Elizur

**Table III Reproductive outcome data in FET cycles.**

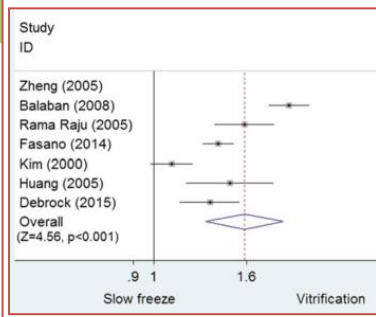
	Slow freezing	Vitrification	P-value	95% CI
N FET cycles	95	121		
N transfer (%/N FET cycles)	70 (73.7)	109 (90.1)	0.0024	
N transfer with 1 embryo (%/N transfer)	40 (57.1)	41 (37.6)	0.0218	
N transfer with 2 embryos (%/N transfer)	30 (42.9)	68 (62.4)		
N clinical pregnancies with IU FHB (%/N transfer)	13 (18.6)	30 (27.5)	0.1984	
N ectopic pregnancies/miscarriages	1/2	0/7		
N pregnancies with 1/2/3 IU implantations	13/1 <sup>a</sup> /0	25/10 <sup>a</sup> /1 <sup>b</sup>		
N multiple IU pregnancies (%/N clinical IU pregnancies)	1 (7.1)	11 (30.6)	0.14	
N LB deliveries (%/N transfer)	10 (14.3) <sup>c</sup>	29 (26.6)	0.0862	
N LB deliveries (%/N FET cycle)	10 (10.5)	29 (24.0)	0.0396	
N embryos transferred (mean ± SD)	100 (1.43 ± 0.50)	177 (1.62 ± 0.49)	0.0106	
N implantations (IU-EU) (%/N embryos transferred) <sup>d</sup>	15 (15.0)	45 (25.4)	0.0778	
N implantations (IU + FHB) (%) <sup>d</sup>	13 (13.0)	38 (21.5)	0.1455	
N live births (%) <sup>d</sup>	10 (10.0)	35 (19.8)	0.0596	
N embryos thawed/warmed	200	217		
N implantations (IU-EU) (%/N embryos thawed/warmed) <sup>e</sup>	15 (7.5)	45 (20.7)	0.0012	1.59–4.81
N implantations (IU + FHB) (%) <sup>e</sup>	13 (6.5)	38 (17.5)	0.0044	
<b>N live births (%)<sup>e</sup></b>	<b>10 (5.0)</b>	<b>35 (16.1)</b>	<b>0.0022</b>	<b>1.64–6.35</b>

Human Reproduction Update, Vol.23, No.2 pp. 139–155, 2017  
 Advanced Access publication on November 4, 2016 doi:10.1093/humupd/dmw038

human reproduction update

## Oocyte, embryo and blastocyst cryopreservation in ART: systematic review and meta-analysis comparing slow-freezing versus vitrification to produce evidence for the development of global guidance

Laura Rienzi<sup>1,\*</sup>, Clarisa Gracia<sup>2</sup>, Roberta Maggiulli<sup>1</sup>, Andrew R. LaBarbera<sup>3</sup>, Daniel J. Kaser<sup>4</sup>, Filippo M. Ubaldi<sup>1</sup>, Sheryl Vanderpoel<sup>5,6</sup>, and Catherine Racowsky<sup>4</sup>



J Assist Reprod Genet (2015) 32:1371–1377  
 DOI 10.1007/s10815-015-0545-8

EMBRYO BIOLOGY

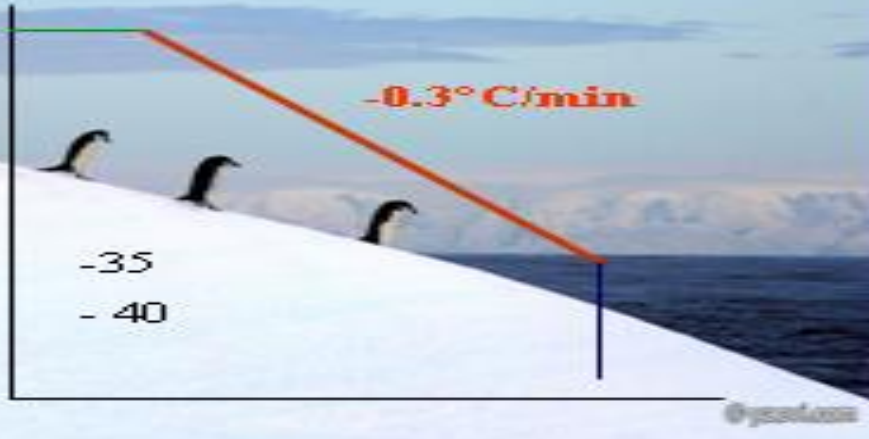
## Slow freezing should not be totally substituted by vitrification when applied to day 3 embryo cryopreservation: an analysis of 5613 frozen cycles

Hai-Yan Zhu<sup>1</sup> · Ya-Mei Xue<sup>1</sup> · Ling-Yun Yang<sup>1</sup> · Ling-Ying Jiang<sup>1</sup> · Chao Ling<sup>1</sup> · Xiao-Mei Tong<sup>1</sup> · Song-Ying Zhang<sup>1,2</sup>

Variable	Slow freeze	Vitrified	P value
No. of cycles	526	485	
Maternal age (years)	32.3±4.8	32.3±4.7	>0.05 <sup>a</sup>
No. of transferred embryos	526	485	
No. of good quality embryos transferred	366 (69.6 %)	400 (82.5 %)	<0.001 <sup>b</sup>
Pregnancy rates			
Overall embryos	184 (35.0 %)	198 (40.8 %)	>0.05 <sup>b</sup>
Good quality embryos	167 (45.6 %)	186 (46.6 %)	>0.05 <sup>b</sup>
Implantation rates			
Overall embryos	182 (34.6 %)	174 (35.9 %)	0.671 <sup>b</sup>
Good quality embryos	165 (45.1 %)	162 (40.5 %)	0.200 <sup>b</sup>

## slow cooling rate

(Whittingham et al., Science; 1972;  
Wilmot, Life Sci, 1972)

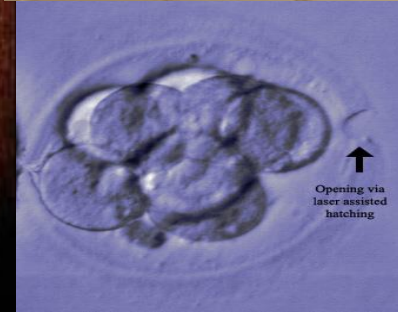


## Vitrification

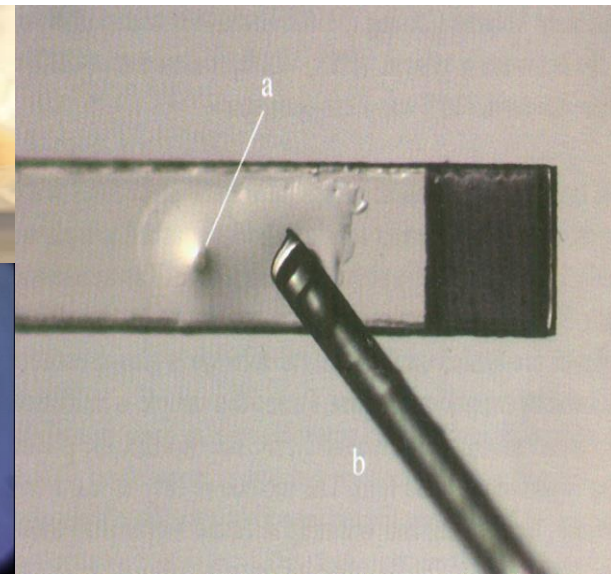
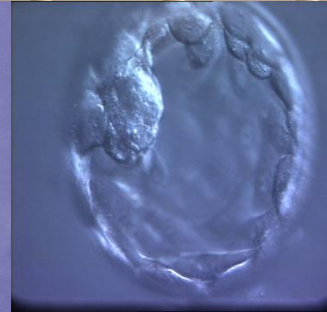
(Rall and Fahy 1985)



Solidification of a solution to a state similar to that of glass



↑  
Opening via  
laser-assisted  
hatching



# Prospective randomized comparison of human oocyte cryopreservation with slow-rate freezing or vitrification

Oocyte survival and functionality following cryopreservation by slow-rate freezing/thawing or vitrification/warming.

	Slow-rate freezing/thawing	Vitrification/ warming	P value
Thaws/liquefactions cycles	30	48	NA
Oocytes thawed/warmed	238	349	NA
Oocyte thawed/warmed per treatment (mean ± SE)	7.9 ± 0.5	7.3 ± 0.3	NS (P= .3)
Survival T0 (%)	159/238 (67%)	281/349 (81%)	P< .001
Survival T4 (%)	155/238 (65%)	260/349 (75%)	P< .01
Patients with no oocytes for ICSI (#)	3	0	NA
Fertilization (%)	104/155 (67%)	200/260 (77%)	P< .03
Patients with no fertilization (n)	2	1	NA
Cleavage D1 to D2 (%)	74/104 (71%)	168/200 (84%)	P< .01
Patients with no cleavage (n)	5	0	NA
Patients with embryos arrest D2 (n)	1	0	NA
Patients with no ET (n)	11	1	NA
Biochemical pregnancies/thaw or warming cycle (%)	5/30 (17%)	22/48 (46%)	P< .01
Clinical pregnancies/thaw or warming cycle (%)	4/30 (13%)	18/48 (38%)	P< .02
Clinical pregnancies/oocytes thawed or warmed (%)	4/238 (1.7%)	18/349 (5.2%)	P< .03

Note: NA = not applicable; NS = nonsignificant; Survival T0 = number of oocytes surviving cryopreservation immediately after thaw/warming solution exposure; Survival T4 = number of oocytes surviving cryopreservation after 4 hours of incubation at 37°C following thaw/warming; ICSI = intracytoplasmic sperm injection; D1 = day 1 (day 0 = day of insemination); D2 = day 2; ET = embryo transfer.

Smith. Freezing and vitrification of oocytes. Fertil Steril 2010.

# Five years' experience using oocyte vitrification to preserve fertility for medical and nonmedical indications

Juan A. Garcia-Velasco, M.D.,<sup>a,d</sup> Javier Domingo, M.D.,<sup>b</sup> Ana Cobo, Ph.D.,<sup>c</sup> Maria Martinez, M.D.,<sup>a</sup> Luis Carmona, M.D.,<sup>b</sup> and Antonio Pellicer, M.D.<sup>c</sup>

<sup>a</sup> IVI-Madrid, Madrid; <sup>b</sup> IVI-Las Palmas, Las Palmas; <sup>c</sup> IVI-Valencia, Valencia; and <sup>d</sup> Rey Juan Carlos University, Madrid, Spain

**Objective:** To evaluate the results of controlled ovarian hyperstimulation (COH) for oocyte vitrification to preserve fertility for medical and nonmedical indications.

**Design:** A retrospective, multicenter, observational study performed between March 2007 and June 2012.

**Setting:** University-affiliated infertility clinics.

**Patient(s):** Of 560 nononcological patients and 475 oncological patients, we performed 1,080 oocyte vitrification cycles, 725 for nonmedical reasons and 355 in patients affected with cancer. Cycle outcome is presented, including 30 women who returned to use their frozen eggs with, 20 pregnancies obtained, 6 newborns, and 8 ongoing pregnancies.

**Intervention(s):** Controlled ovarian hyperstimulation, oocyte retrieval, warming of oocytes, and ET in those who already came back.

**Main Outcome Measure(s):** Days of stimulation, total dose of gonadotropins, estrogen (E) and P levels, number of oocytes retrieved and vitrified, pregnancy rate (PR).

**Result(s):** Comparable results were obtained in both groups of patients, with lower total dose of gonadotropins used and lower serum E<sub>2</sub> levels in patients affected with cancer. Frozen/thawed oocytes performed similarly in both groups.

**Conclusion(s):** Patients who vitrify eggs for medical or nonmedical reasons perform similarly, as observed in this large series. This technique offers realistic expectations to both groups of patients to have a child with their own eggs. These data could be used to adequately counsel our patients. (Fertil Steril<sup>®</sup> 2013;99:1994-9. ©2013 by American Society for Reproductive Medicine.)

**Key Words:** Fertility preservation, oocyte vitrification, cancer, social freezing, newborns

**Discuss:** You can discuss this article with its authors and with other ASRM members at <http://fertstertforum.com/garcia-velascoj-oocyte-vitrification-fertility-preservation-cancer/>



Use your smartphone to scan this QR code and connect to the discussion forum for this article now.\*

\* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

**TABLE 1**

Summary of findings and methods used in the studies included.

Parameter	Authors/year (reference)				
	Smith et al. 2010 (34)	Renzi et al. 2010 (10)	Cao et al. 2009 (33)	Cobo et al. 2008 (5)	Cobo et al. 2010 (6)
Study period	Jan 2005–Apr 2009	Sep 2008–Mar 2009	Not stated	Dec 2006–Nov 2007	Nov 2008–Sep 2009.
Country	Brazil	Italy	China	Spain	Spain
Intervention	Vitrification vs. SF	Vitrification vs. fresh	Vitrification vs. SF	Vitrification vs. fresh	Vitrification vs. fresh
Patients (oocytes) undergoing vitrification	48 (349)	40 (124)	(292)	30 (231)	295 (3,286)
Patients (oocytes) undergoing SF	30 (238)	—	(123)	—	—
Patients (oocytes) undergoing fresh cycles	—	40 (120)	—	30 (219)	289 (3,185)
Ovarian stimulation protocol	rFSH + antagonist	rFSH + antagonist; rFSH + agonist (long protocol)	hMG + agonist (long protocol) <sup>a</sup>	rFSH or hMG + agonist (long protocol)	rFSH or hMG + agonist (long protocol)
Ovulation triggering	rhCG (250 µg)	rhCG (10,000 UI)	???	rhCG (10,000 UI)	rhCG (10,000 UI)
Vitrification protocol	7.5% EG + 7.5% DMSO + 12% SSS. Cryotip	15% EG + 15% DMSO + 0.5 M sucrose. Cryotop	15% EG + 15% PROH + 0.5 M sucrose. Cryoleaf	15% EG + 15% DMSO + 0.5M sucrose. Cryotop	15% EG + 15% DMSO + 0.5 M sucrose. Cryotop
Slow freezing protocol	1.5 M PROH + 0.3 M sucrose + 12% SSS	—	1.5 M PROH + 0.3 sucrose + 30% SSS	—	—
Oocyte assessment	ZP, cytoplasm, oolema	ZP, cytoplasm, oolema	Membrane morphology	ZP, cytoplasm, oolema	ZP, cytoplasm, oolema
Embryo assessment	Number, size, and fragmentation degree of blastomeres	Number, size, and fragmentation degree of blastomeres	Number, size, and fragmentation degree of blastomeres	Number, size, and fragmentation degree of blastomeres	Number, size, and fragmentation degree of blastomeres
Day of ET	3	2	—	3	3
Oocyte survival rate (%)	VT: 74.5; SF: 65.1	96.8	VT: 91.8; SF: 61.0	96.9	92.5
Clinical pregnancy rate (%)	VT: 38.3; SF: 21.0	VT: 38.5; FRESH: 43.5	—	VT: 65.2; FRESH: 100	VIT: 55.4; FRESH: 55.6

Note: DMSO — dimethyl sulfoxide; ZP — zona pellucida; VIT — vitrification; EG — ethylene glycol; SSS — synthetic serum substitute; PROH — propanediol.

<sup>a</sup>The authors of the original manuscript refer to "a long protocol" and to "down-regulation with a GnRH antagonist," which is probably a typographic mistake, although we were unable to check this point with the authors.

Cobo. Meta-analysis of the use of oocyte vitrification. Fertil Steril 2011.

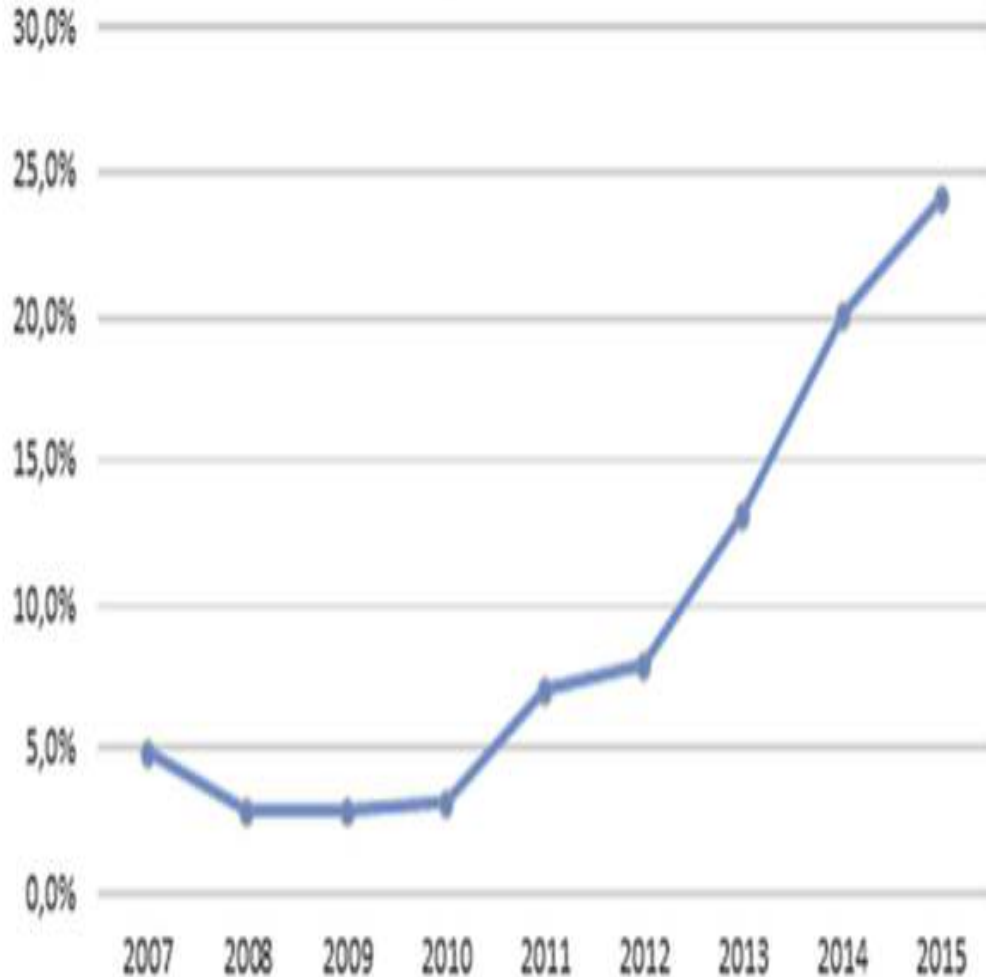
**Table II Clinical outcomes of fresh, and warming cycles according to female age.**

	Overall	≤34 years	35–37 years	38–40 years	41–43 years
Fresh cycles: clinical outcomes					
No. of cycles	182	72	48	41	21
No. of ET	172/182 (94.5)	66/72 (91.6)	46/48 (95.8)	40/41 (97.6)	20/21 (95.2)
Clinical pregnancy rate per cycle	77/182 (42.3) <sup>a</sup>	32/72 (44.4)	22/48 (45.8)	18/41 (43.9)	5/21 (23.8)
Clinical pregnancy rate per ET	77/172 (44.8) <sup>b</sup>	32/66 (48.5)	22/46 (47.8)	18/40 (45.0)	5/20 (25.0)
Implantation rate	101/435 (23.2) <sup>c</sup>	46/153 (30.0)	29/116 (25.0) <sup>f</sup>	21/112 (18.7)	5/54 (9.2)
Abortion rate	9/77 (11.7)	3/32 (9.4)	2/22 (9.0)	3/18 (16.7)	1/5 (20.0)
Ongoing pregnancy rate per fresh cycle	68/182 (37.4) <sup>d</sup>	29/72 (40.3)	20/48 (41.7) <sup>g</sup>	15/41 (36.6)	4/21 (19.0)
Ongoing implantation rate	90/435 (20.7) <sup>e</sup>	42/153 (27.4)	26/116 (22.4) <sup>h</sup>	18/112 (16.1)	4/54 (7.4)
Warmed cycles: clinical outcomes					
No. of cycles	115	37	30	30	18
No. of ET	111 (96.5)	35/37 (94.6)	29/30 (96.7)	30/30 (100)	17/18 (94.4)
Clinical pregnancy rate per cycle	35/115 (30.4) <sup>a</sup>	17/37 (45.9)	7/30 (23.3)	7/30 (23.3)	4/18 (22.2)
Clinical pregnancy rate per ET	35/111 (31.5) <sup>b</sup>	17/35 (48.6)	7/29 (24.1)	7/30 (23.3)	4/18 (22.2)
Implantation rate	43/266 (16.1) <sup>c</sup>	21/77 (27.3)	8/73 (10.9) <sup>f</sup>	9/75 (12.0)	5/41 (12.2)
Abortion rate	6/35 (17.1)	1/17 (5.9)	3/7 (42.8)	1/7 (14.3)	1/4 (25.0)
Ongoing pregnancy rate per warmed cycle	29/115 (25.2) <sup>d</sup>	16/37 (43.2)	4/30 (13.3) <sup>g</sup>	6/30 (20.0)	3/18 (16.6)
Ongoing implantation rate	35/266 (13.2) <sup>e</sup>	19/77 (24.7)	5/73 (6.8) <sup>h</sup>	8/75 (10.7)	3/41 (7.3)

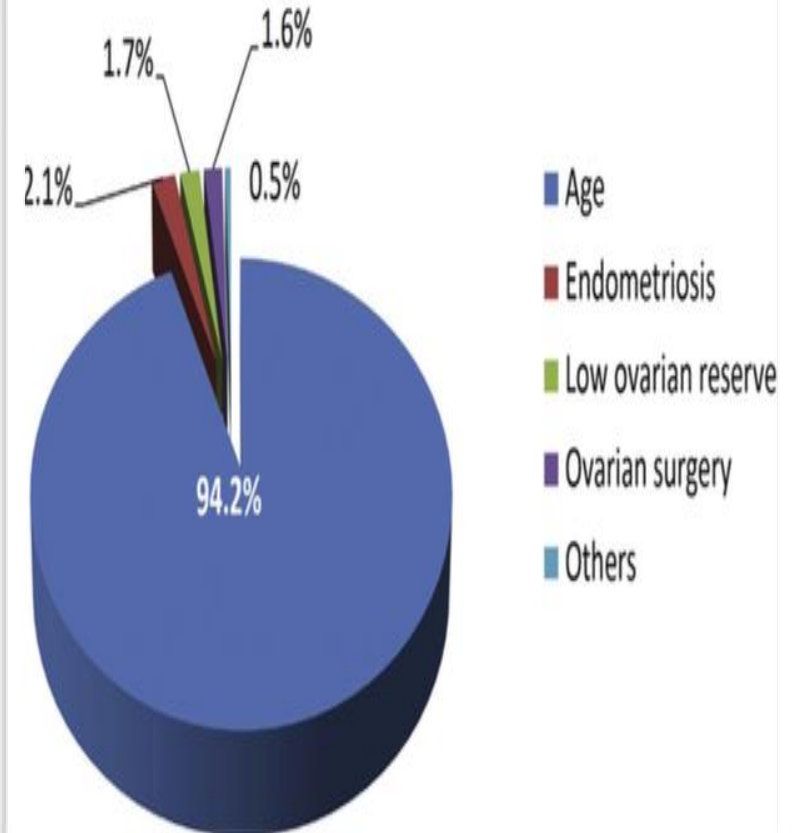
Data are expressed as absolute and percentage frequency. ET, embryo transfer.  
<sup>a,c,e,g,h</sup>p < 0.05.

# Elective Fertility Preservation

Trends of elective FP

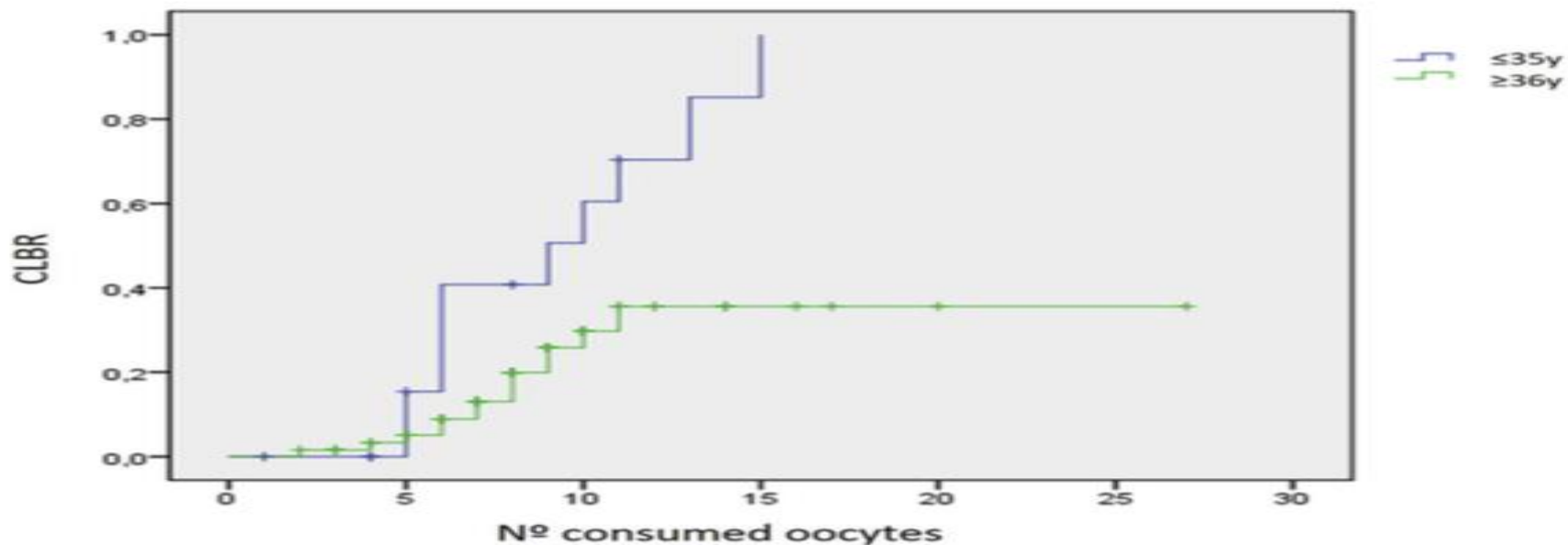


Distribution of Elective FP cycles



# Elective fertility preservation

CLBR according to age ( $\leq 35$  vs  $\geq 36$ ) and N° oocytes consumed



$\leq 35$ years old		$\geq 36$ years old	
N°oocytes	CLBR (IC95%)	N°oocytes	CLBR (95% CI)
5	15,4 (-4.2-35.0)	5	5,1 (-0.6-10.7)
8	40.8 (13.2-68.4)	8	19,9 (8.7-31.1)
9	50,6 (31.6-79.6)	9	25.8 (12.7-38.9)
10	60,5 (34.5-89.5)	10	29,7 (15.2-34.2)
15	85,2 (60.5-100)	11	35,6 (18.4-52.8)

**Table III Primary and secondary outcomes measures: fertilization, pronuclear morphology, embryo development and embryo morphology of fresh and vitrified sibling oocytes**

	Fresh ICSI	Vitrified/Warmed ICSI (%)	Absolute difference (%) (95% CI)	OR (95% CI)	P
Fertilization (2PN) per sibling oocyte	100/120 (83.3) <sup>b</sup>	95/124 (76.6) <sup>a</sup>	-6.73 (-16.6 to 3.39)	0.65 (0.33 to 1.29)	0.20
Fertilization (2PN) per injected oocyte	100/120 (83.3) <sup>b</sup>	95/120 (79.2) <sup>b</sup>	-4.17 (-14.0 to 5.7)	0.76 (0.37 to 1.53)	0.50
Normal 2PN morphology	96/100 (96.0) <sup>c</sup>	86/95 (90.5) <sup>c</sup>	-5.47 (-13.4 to 1.84)	0.39 (0.08 to 1.49)	0.16
1PN oocytes	3/120 (2.5) <sup>b</sup>	6/120 (5.0) <sup>b</sup>	2.5 (-2.82 to 8.22)	2.05 (0.42 to 12.9)	0.50
3PN	1/120 (0.83) <sup>b</sup>	2/120 (1.66) <sup>b</sup>	0.83 (-3.09 to 5.1)	2.01 (0.10 to 119.9)	1
Degenerated oocytes post-ICSI	1/120 (0.83) <sup>b</sup>	4/120 (3.34) <sup>b</sup>	2.51 (-1.75 to 7.47)	4.08 (0.39 to 203.5)	0.37
Day 2 embryo development	100/100 (100) <sup>c</sup>	82/95 (87.0) <sup>c</sup>	-17.9 (-23.2 to -12.6)	0.0 (0.00 to 0.22)	0.24
Excellent quality embryos	52/100 (52.0) <sup>d</sup>	49/95 (51.6) <sup>d</sup>	-0.43 (-14.2 to 13.3)	0.98 (0.53 to 1.79)	0.90
Good quality embryos	38/100 (38.0) <sup>d</sup>	41/95 (43.2) <sup>d</sup>	5.16 (-8.49 to 18.6)	1.24 (0.67 to 2.28)	0.47
Fair/poor quality embryos	10/100 (10.0) <sup>d</sup>	3/95 (3.16) <sup>d</sup>	-6.84 (-14.6 to 0.42)	0.29 (0.05 to 1.19)	0.10

<sup>a</sup>Percentages, expressed per warmed oocyte.

<sup>b</sup>Percentages, expressed per inseminated oocyte.

<sup>c</sup>Percentages, expressed per 2PN fertilized oocyte.

<sup>d</sup>Percentages, expressed per cleaved oocyte.

**Table III Cumulative ongoing pregnancy rate after the fresh cycle, first warming cycle and second warming cycle according to female age.**

	Overall	<34 years	35-37 years	38-40 years	41-43 years
Fresh cycle	68/182 (37.4%)	29/72 (40.3%)	20/48 (41.7%)	15/41 (36.6%)	4/21 (19.0%)
(95% CI)	(31.2-45.1)	(29.7-51.9)	(28.8-55.8)	(23.6-52.0)	(7.8-40.3)
I warming cycle	94/182 (51.6%)	45/72 (62.5%)	23/48 (47.9%)	20/41 (48.8%)	6/21 (28.6%)
(95% CI)	(44.4-58.8)	(50.9-72.8)	(34.4-61.7)	(34.2-63.6)	(13.9-50.2)
II warming cycle	97/182 (53.3%)	45/72 (62.5%) <sup>a</sup>	24/48 (50.0%)	21/41 (51.2%)	7/21 (33.3%) <sup>a</sup>
(95% CI)	(40.0-60.0)	(50.9-72.8)	(36.3-63.6)	(36.4-65.8)	(17.2-54.9)

Data are expressed as absolute, percentage frequency and 95% CI.

<sup>a</sup>P = 0.006.

# Ongoing and cumulative pregnancy rate after cleavage-stage versus blastocyst-stage embryo transfer using vitrification for cryopreservation: Impact of age on the results

	D3 group (n=46)	D5 group (n=58)	Statistical significance
Patients with no ongoing pregnancy in fresh IVF with vitrified embryos	65.7 % (23/35)	54.4 % (18/33)	<i>p</i> =0.347
Patients going through VET	87 % (20/23)	88.8 % (16/18)	<i>p</i> =0.369
No. VET transfers/patient	1.1±0.6 (22/20)	1.5±0.9 (24/16)	<i>p</i> =0.236
No. Embryos transferred/cycle	1.7±0.47	1.33±0.48	<i>p</i> =0.02
Embryo survival rate	78.8 % (37/47)	82.1 % (32/39)	<i>p</i> =0.7
Clinical pregnancy rate/ VET cycle	50 % (11/22)	41.6 % (10/24)	<i>p</i> =0.571
Implantation rate	43.2 % (16/37)	34.4 % (11/32)	<i>p</i> =0.452
Miscarriage rate	18.1 % (2/11)	20 % (2/10)	<i>p</i> =0.916
Multiple pregnancy rate	45.4 % (5/11)	10 % (1/10)	<i>p</i> =0.072
Ongoing pregnancy rate/patient in VET	45 % (9/20)	50 % (8/16)	<i>p</i> =1.000
Cumulative ongoing pregnancy rate/ patient (fresh + VET)	43.4 % (20/46)	56.8 % (33/58)	<i>p</i> =0.174

Table 5 Pregnancy outcome depending on age

	< 35 years old		≥35 years old	
	Day 3 (n=15)	Day 5 (n=27)	Day 3 (n=31)	Day 5 (n=31)
Clinical pregnancy rate/ fresh IVF cycle	46.6 % (7/15)	51.8 % (14/27)	29 % (9/31)	54.8 % (17/31) a
Ongoing pregnancy rate/ fresh IVF cycle	33.3 % (5/15)	37 % (10/27)	19.3 % (6/31)	48.4 % (15/31) b
Cumulative ongoing pregnancy rate / patient (fresh + VET)	80 % (12/15)	55.5 % (15/27)	25.8 % (8/31)	58 % (18/31) c

a *p*=0.039

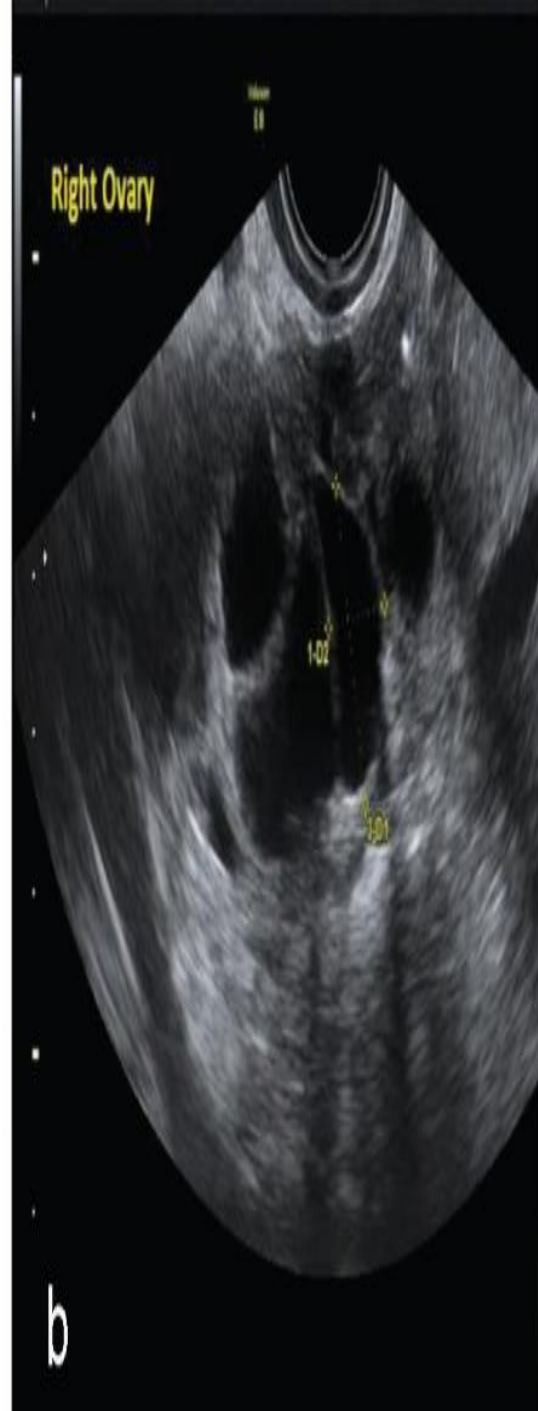
b *p*=0.016

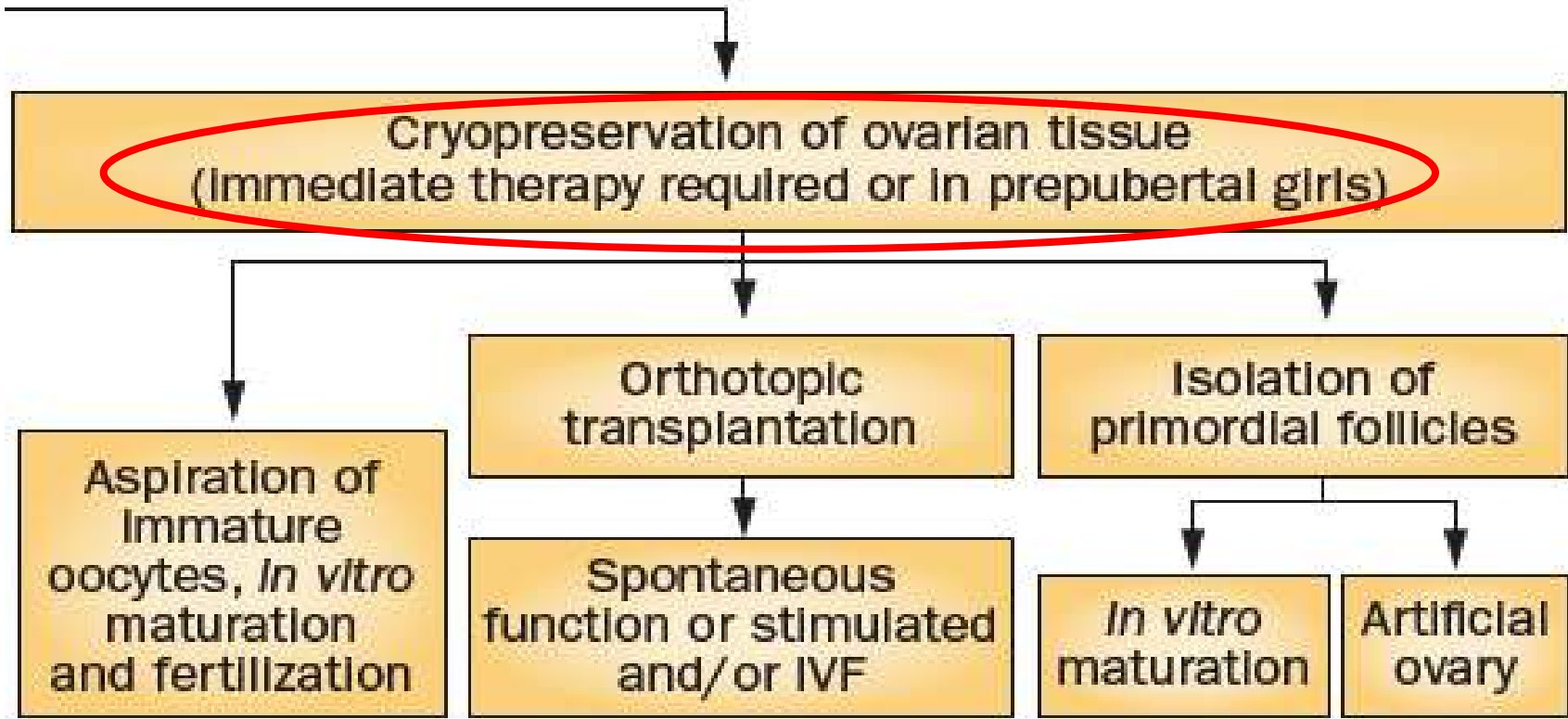
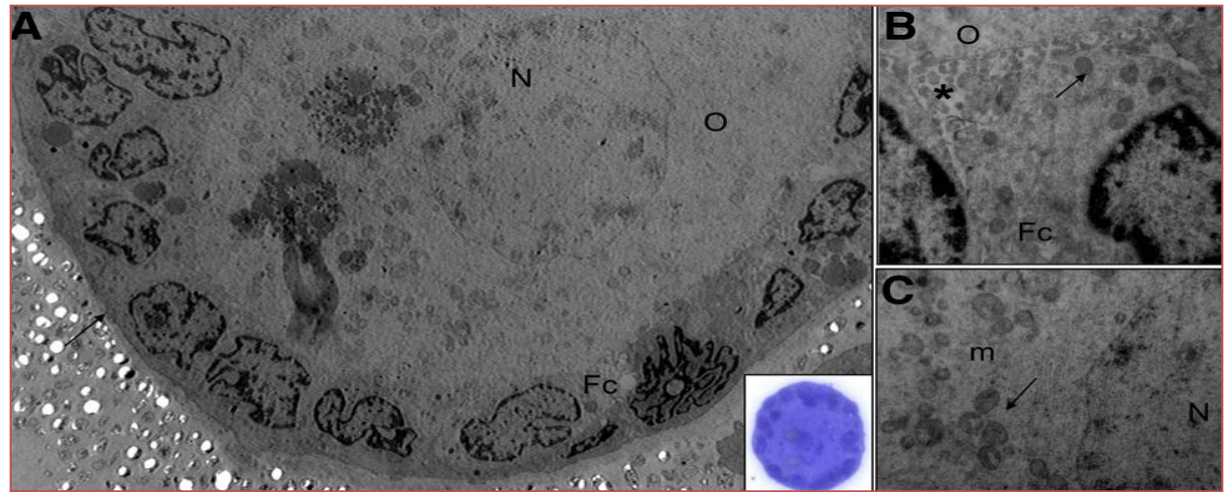
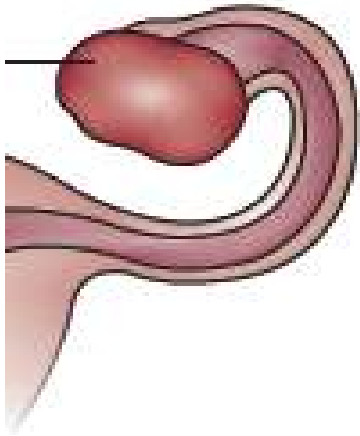
c *p*=0.01

# Single-embryo transfer of vitrified-warmed blastocysts yields equivalent live-birth rates and improved neonatal outcomes compared with fresh transfers

Singleton neonatal outcomes for fresh and vitrified-warmed blastocyst transfers.

	Fresh	Vitrified	P value
Maternal age <sup>d</sup>	34.8 ± 3.6	34.8 ± 4.0	
Median (IQR)	35.1 (32.1–37.8)	35.0 (32.1–37.8)	.858
Gestational age <sup>a</sup> (wk)	39.0 ± 2.2	39.3 ± 2.0	
Median (IQR)	39.4 (38.4–40.3)	39.4 (38.8–40.6)	.047
Preterm birth rate	44/507 (8.7%)	13/229 (5.7%)	.158
Live-birth weight <sup>a</sup> (g)	3,296 ± 563	3,441 ± 554	
Median (IQR)	3,300 (3,000–3,660)	3,465 (3,173–3,778)	<.001
Low-birth-weight rate	28/507 (5.5%)	10/229 (4.4%)	.512
Neonatal death rate	1/507 (0.2%)	1/229 (0.4%)	1







## Live birth after allografting of ovarian cortex between genetically non-identical sisters

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Dominique Demylle<sup>1</sup>, Anne Delbaere<sup>2</sup>, Laetitia Armenio<sup>2</sup>,  
Yvon Englert<sup>2</sup>, Anne-Céline Cheron<sup>3</sup>, Pascale Jadoul<sup>1</sup>,  
and Marie-Madeleine Dolmans<sup>1</sup>

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**ABSTRACT:** Aggressive chemotherapy generally results in the loss of both endocrine and reproductive functions. If the patient has not undergone previous oocyte, embryo or ovarian tissue cryopreservation, orthotopic allotransplantation of fresh ovarian tissue from a genetically non-identical sister may be considered. Here, we describe a case report. The patient, aged 15 years and presenting with homozygous sickle cell anemia, underwent chemotherapy (busulfan, cyclophosphamide) and total body irradiation before bone marrow transplantation, the donor being her HLA-compatible sister. HLA group analysis later revealed complete chimerism. When the patient was 32 years old, ovarian allografting was performed, with the ovarian tissue donor being the same sister who had already donated bone marrow. The goal was to restore ovarian activity and natural fertility. No immunosuppressive therapy was administered. No sign of rejection was observed. Restoration of ovarian function was achieved 3.5 months after transplantation, as proved by the first estradiol peak and follicular development detected by ultrasound. After 9 months of regular ovulatory cycles, IVF was attempted because proximal tubal stenosis (unknown at the time of grafting) could not be repaired by tubal reanastomosis. After stimulation, three oocytes were retrieved. Two embryos were obtained. One embryo was frozen and the other was transferred, resulting in an ongoing pregnancy. The patient delivered a healthy baby girl weighing 3.150 g at 37 2/7 weeks of gestation.

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FERTILITY PRESERVATION

### Ovarian cortex transplantation: 60 reported live births brings the success and worldwide expansion of the technique towards routine clinical practice

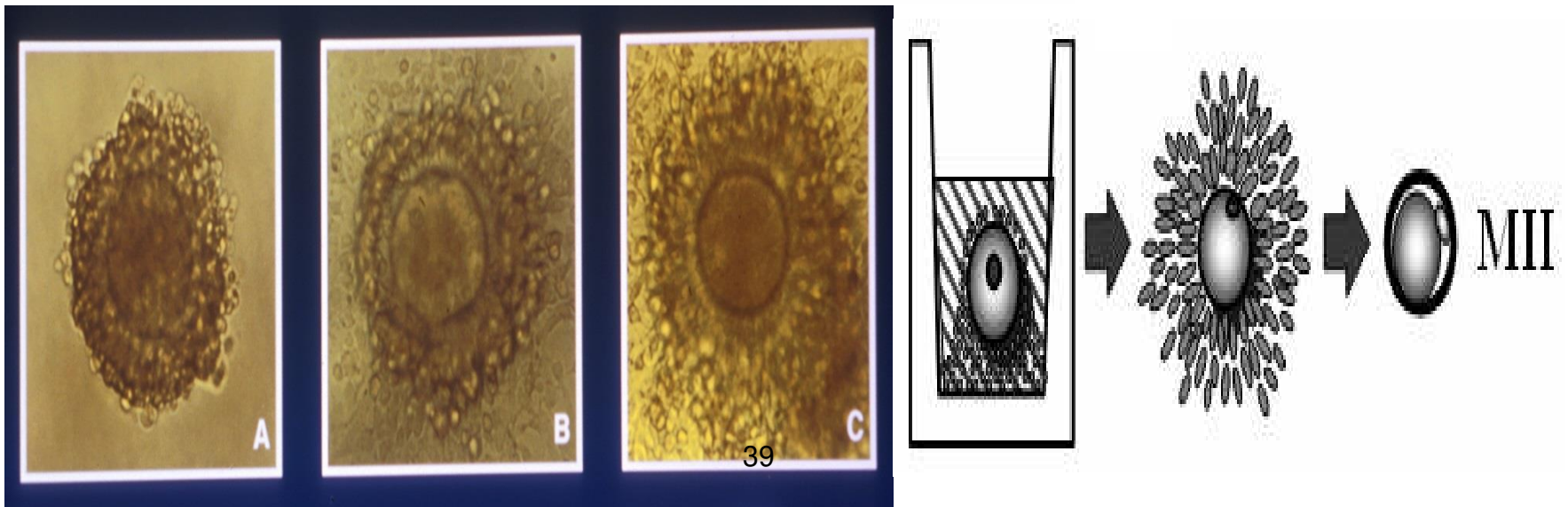
Jacques Donnez<sup>1</sup> · Marie-Madeleine Dolmans<sup>2</sup>

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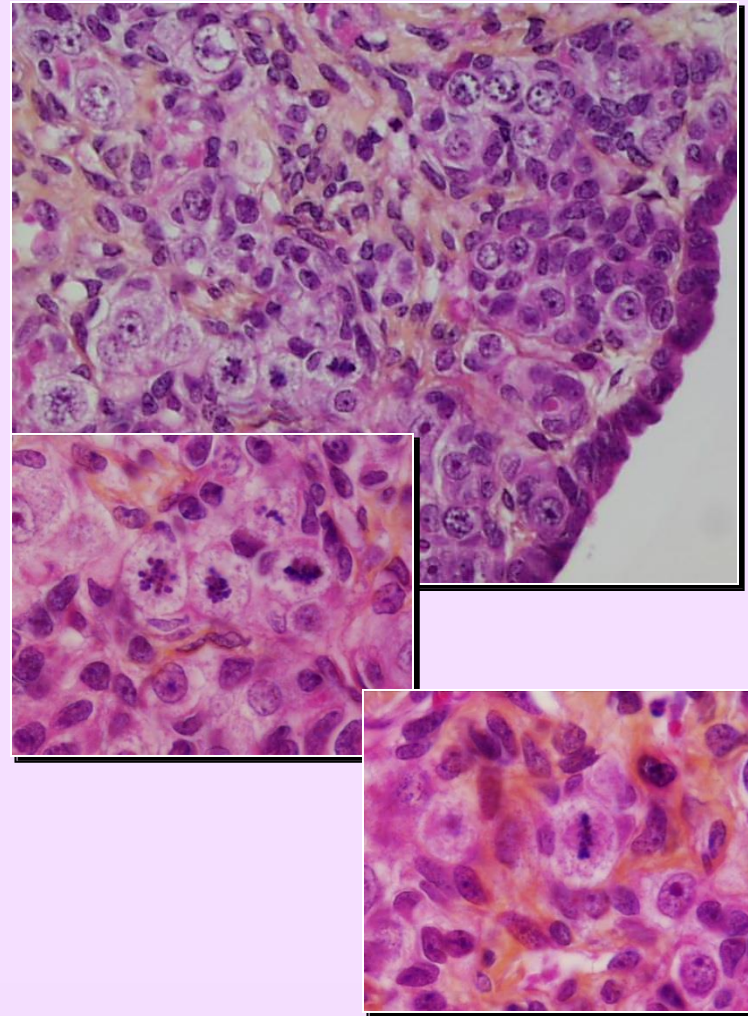
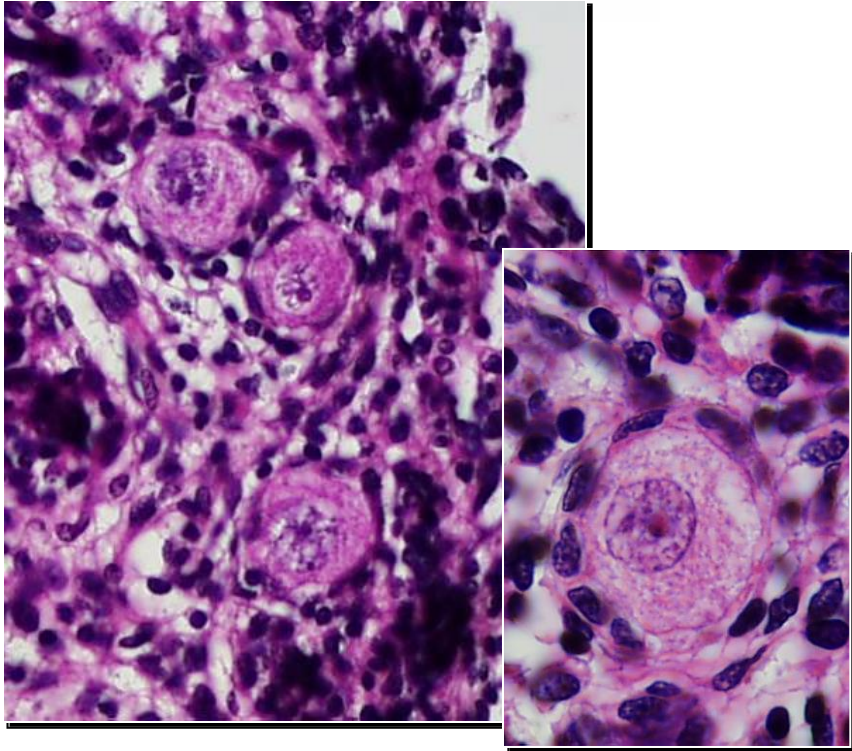
# IVM Oocytes

## *Cumulus Cell Expansion*

Retrieval of oocytes from non-or minimally- stimulated ovaries followed by IVM / ICSI / Embryo Transfer



## F - T foetal tissue



**2 weeks oogonia culture  
pairing process = normal**

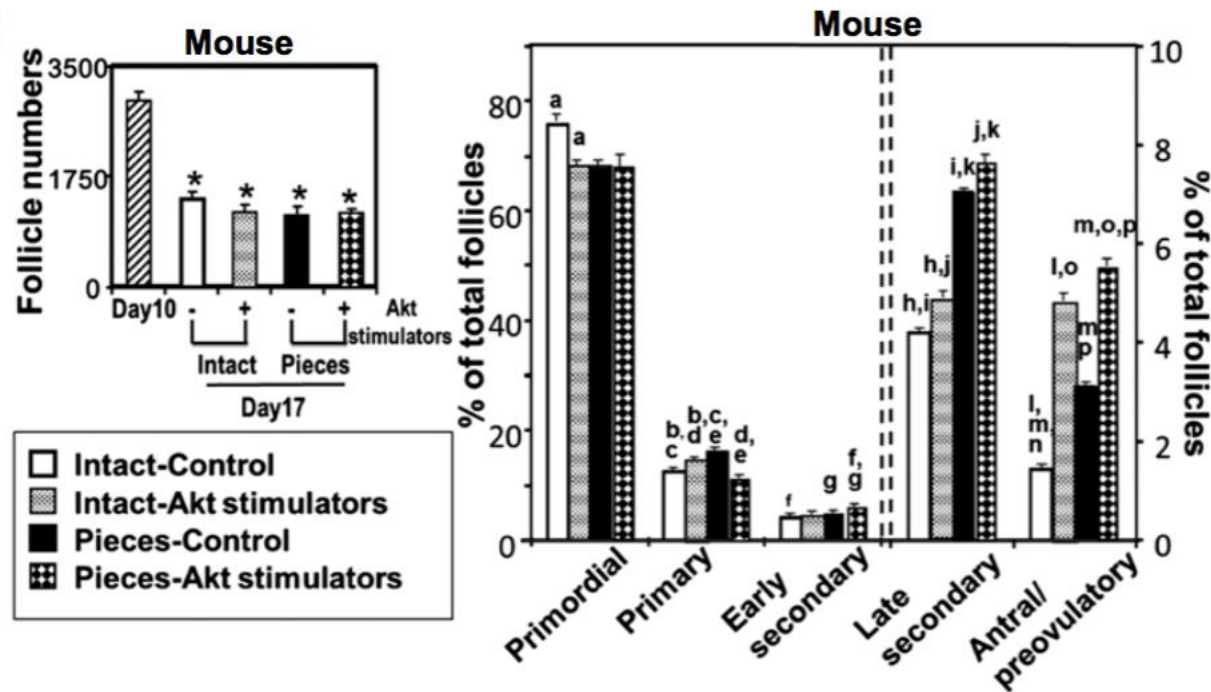
*Ignaci Roig, 2005* Z-VUB

# Hippo signaling disruption and Akt stimulation of ovarian follicles for infertility treatment

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Edited by John J. Eppig, The Jackson Laboratory, Bar Harbor, ME, and approved August 21, 2013 (received for review July 8, 2013)

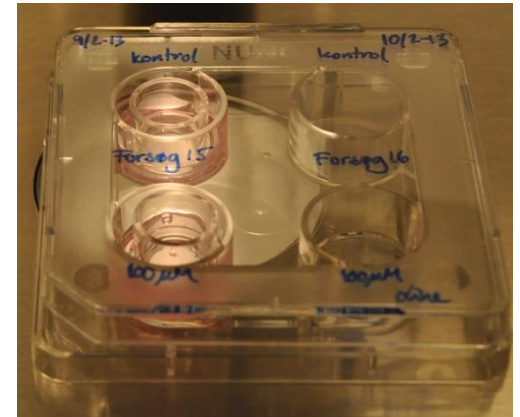


# Activation of follicle growth *in vitro*

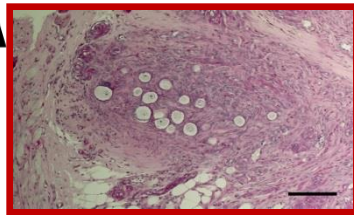
Ovarian cortical



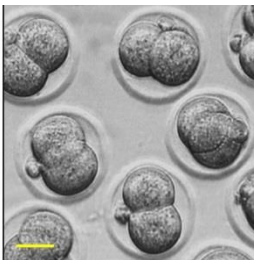
*In vitro* activation of follicles



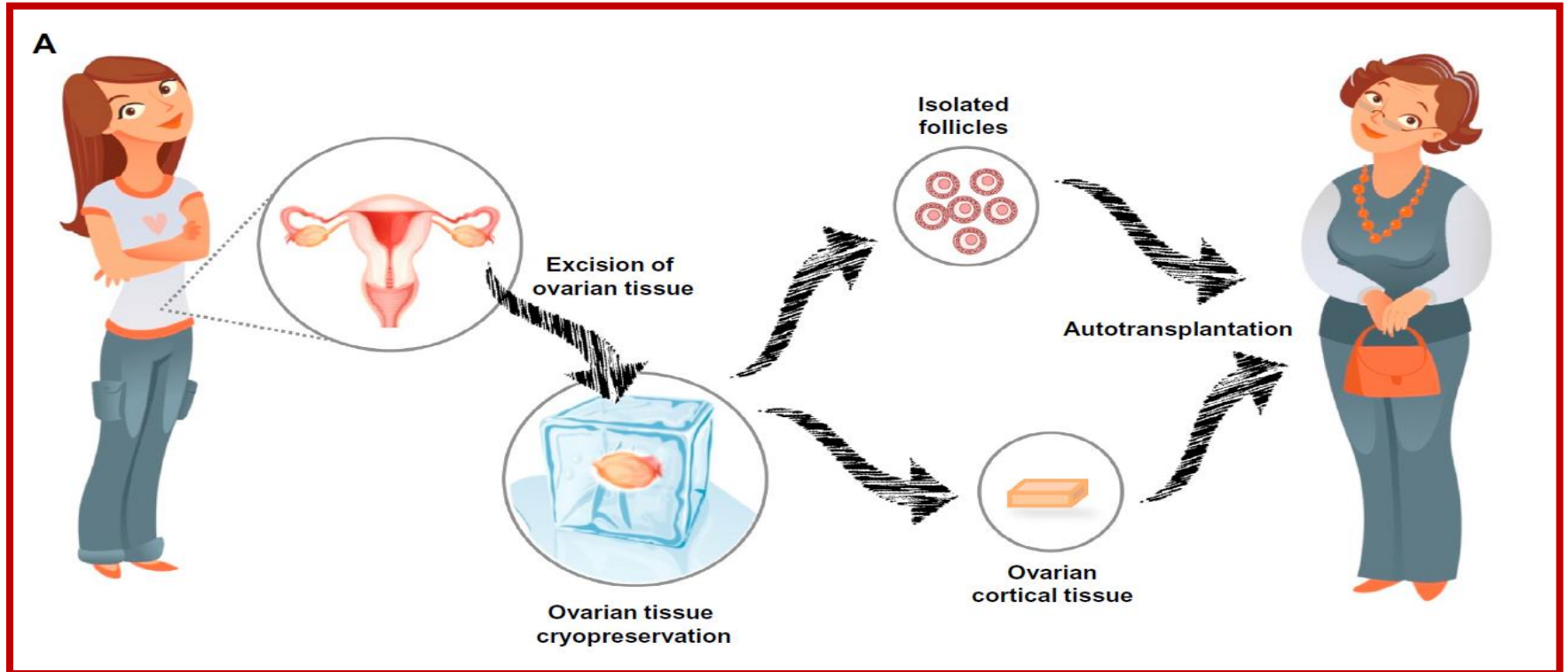
Autotransplantation



IVF



Not only to be able to produce babies when needed  
but also to potentially postpone menopause  
and avoid the sequelae of loss of endogenous hormones  
either autologous or allogenic



# Impaired receptivity and Implantation in women with endometriosis, adenomyosis

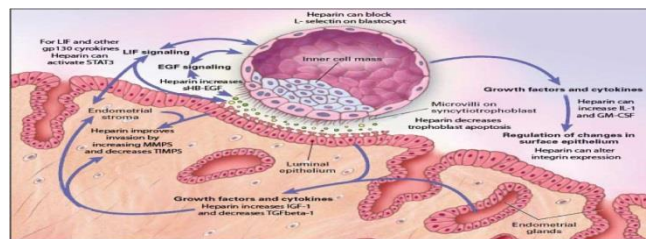
- Abnormally expression of endometrial receptivity biomarkers

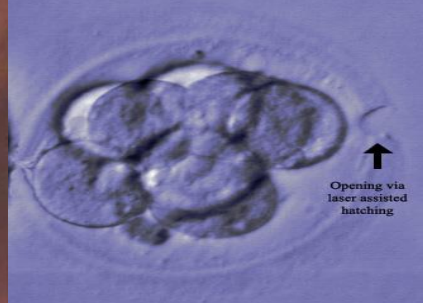
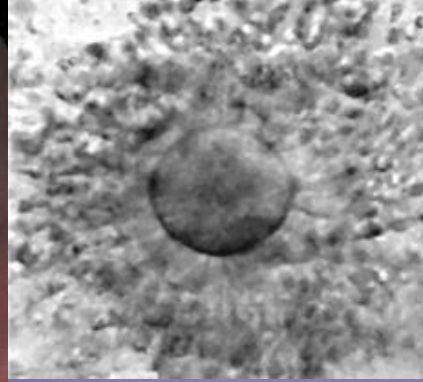
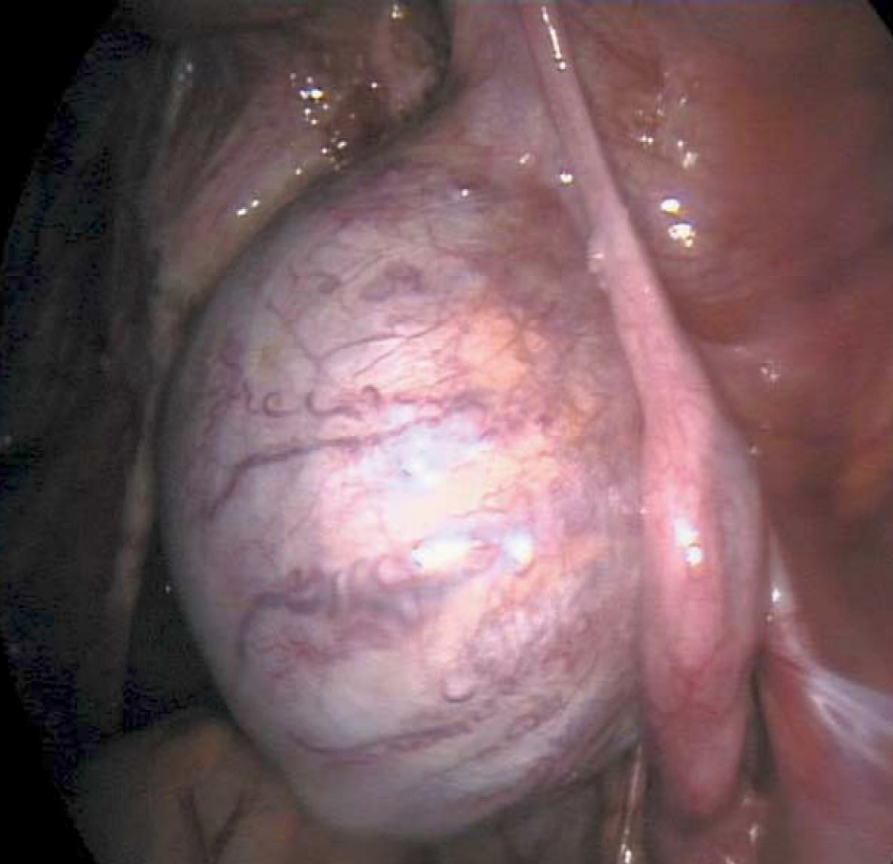
**Table 1** Implantation factors with altered concentrations in adenomyosis-associated infertility.

<i>Publications</i>	<i>Factors affected</i>	<i>Effect</i>
Goteri et al. (2009)	Hypoxia-inducible factor-1 $\alpha$ (HIF-1 $\alpha$ )	Increased
Yang et al. (2006)	Interleukin-6	Increased
Ulukus et al. (2006)	Interleukin-8 receptor CXCR1–CXCR2	Increased
Wang et al. (2009)	Interleukin-10	Increased
Li et al. (2006), Tokyol et al. (2009)	Matrix metalloproteinases (MMP2 and MMP9)	Increased
Li et al. (2006), Goteri et al. (2009)	Vascular endothelial growth factor	Increased
Li et al. (2006)	Microvessel density (MVD)	Increased
Yen et al. (2006), Xiao et al. (2010)	Leukaemia inhibitory factor (LIF)	Decreased
Yen et al. (2006)	Interleukin-11	Decreased
Yen et al. (2006)	LIF-receptor $\alpha$	Decreased
Fischer et al. (2011)	<i>HOXA10</i>	Decreased
Wicherek (2009)	RCAS1	Decreased
Lessey et al. (2006)	Cytochrome P450	Increased
Ota et al. (1999)	Nitrogen oxide synthase, xanthine oxidase, superoxide dismutase	Increased
Igarashi et al. (2002)	Catalase	Increased

# Novel Therapies

- Endometrial injury
- Periferal blood monocytes culture
- Cumulus cell culture
- Intrauterine G-CSF (Granulocyte Macrophage Colony Stimulatin Factor) Perfusion
- Embryogen (G-CSF cointaining culture media)/Cumulus Cell Co-Culture
- Embryogen/intrauterine GM-CSF perfusion





# **Endometriomas and IVF/ICSI**

**Individualized** treatment plan can be developed, executed and modified as necessary based on :

- **Bilaterality**
- **Number of endometriomas**
- **Size of the endometrioma**
- **Surgical technic**
- **Previous ovarian surgery**
- **Ovarian reserve**
- **Other factor(s) which contribute(s) to infertility**
- **Age**
- **Social,psychocological and financial issues**

#### 2.4.4 Surgery for treatment of pain associated with ovarian endometrioma

##### Clinical evidence

and co-workers reviewed two RCTs comparing laparoscopic excision of (3 cm or larger) to drainage and coagulation by bipolar diathermy (a, et al., 1998, Hart, et al., 2008). Both studies demonstrated lower a and dyspareunia after cystectomy compared to drainage and fewer cyst recurrences with the excisional approach. Need for further i-menstrual pain were less likely after cystectomy.

not included in the Cochrane review compared cystectomy with CO<sub>2</sub> d that recurrence of cysts was more common at 12 months, but not at rization, and that the time to recurrence was shorter, compared to cystectomy (Carmona, et al., 2011).

Another recent RCT looked at direct stripping of endometrioma at the original adhesion site compared to circular excision at the initial adhesion site followed by stripping (Mossa, et al., 2010). This trial showed that initial circular excision followed by stripping was quicker, had shorter haemostasis times and had higher complete excision rates. However, the recurrence rates were not different. The average cyst size was bigger in the direct stripping group and blinding was unclear, hence the results should be interpreted with caution. Risk of ovarian failure after bilateral ovarian endometrioma removal is reported to be 2.4% (Busacca, et al., 2006).

##### Conclusion and considerations

Cystectomy is superior to drainage and coagulation in women with ovarian endometrioma (≥ 3cm) with regard to the recurrence of endometriosis-associated pain and the recurrence of endometrioma. Cystectomy is probably more effective than CO<sub>2</sub> laser vaporization in women with ovarian endometrioma (≥3cm) with regard to recurrence of endometrioma.

Although the three RCTs on which the recommendations of this section are based (Alborzi, et al., 2004, Beretta, et al., 1998, Carmona, et al., 2011) included patients with endometriomas of 3cm or larger, surgical treatment of smaller endometriomas is also recommended for the treatment of pain, based on the studies included in section 2.4a (Jacobson, et al., 2009). Whilst superiority of excision over drainage and coagulation/ablation can be expected, possible difficulties in removal of very small endometriomas should be kept in mind due to lack of a clear surgical plane.

##### Recommendations

When performing surgery in women with ovarian endometrioma, clinicians should perform cystectomy instead of drainage and coagulation, as cystectomy reduces endometriosis-associated pain (Hart, et al., 2008).	A
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Clinicians can consider performing cystectomy rather than CO <sub>2</sub> laser vaporization in women with ovarian endometrioma, because of a lower recurrence rate of the endometrioma (Carmona, et al., 2011).	B
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#### 4.3.2 Surgery prior to treatment with ART in women with ovarian endometrioma

##### Clinical evidence

With regard to the surgical therapy for cysts, a Cochrane review based on four randomized trials involving 312 women, concluded that laparoscopic aspiration or cystectomy of endometrioma prior to ART does not show evidence of benefit over expectant management with regard to the clinical pregnancy rate (Benschop, et al., 2010).

A systematic review confirms these results, but states that excision is more favourable than drainage with regard to recurrence of the endometrioma and of pain, and with regard to spontaneous pregnancy (Hart, et al., 2008). Other smaller cohort studies show partly contradictory results. In one cohort study the conclusion was drawn that cyst wall vaporisation does not impair IVF outcome (Donnez, et al., 2001). There is a need for more randomized controlled trials in order to answer the question as to whether small ovarian endometriotic cysts should be removed prior to ART.

##### Conclusion and considerations

Laparoscopic ovarian cystectomy in women with unilateral endometriomas before ART may not be useful in improving cycle outcome. This conclusion is drawn from several studies but is weak because of limited consistency in the interpretation of the results. Based on no difference in pregnancy rate, some authors advise cystectomy, whereas others advise caution with surgery because of the possible harmful effect on ovarian reserve.

Clinical evidence and recommendations on surgery for pain in women with ovarian endometrioma are discussed in section 2.4d.

##### Recommendations

In infertile women with endometrioma larger than 3 cm there is no evidence that cystectomy prior to treatment with assisted reproductive technologies improves pregnancy rates. (Benschop, et al., 2010, Donnez, et al., 2001, Hart, et al., 2008).	A
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In women with endometrioma larger than 3 cm, the GDG recommends clinicians only to consider cystectomy prior to assisted reproductive technologies to improve endometriosis-associated pain or the accessibility of follicles.	GPP
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The GDG recommends that clinicians counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery.	GPP
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