Fertility preservation in women with endometriosis: patient profile and technique indication

Prof. Juan A Garcia-Velasco

IVI-Madrid

Spain

FERTILITY PRESERVATION

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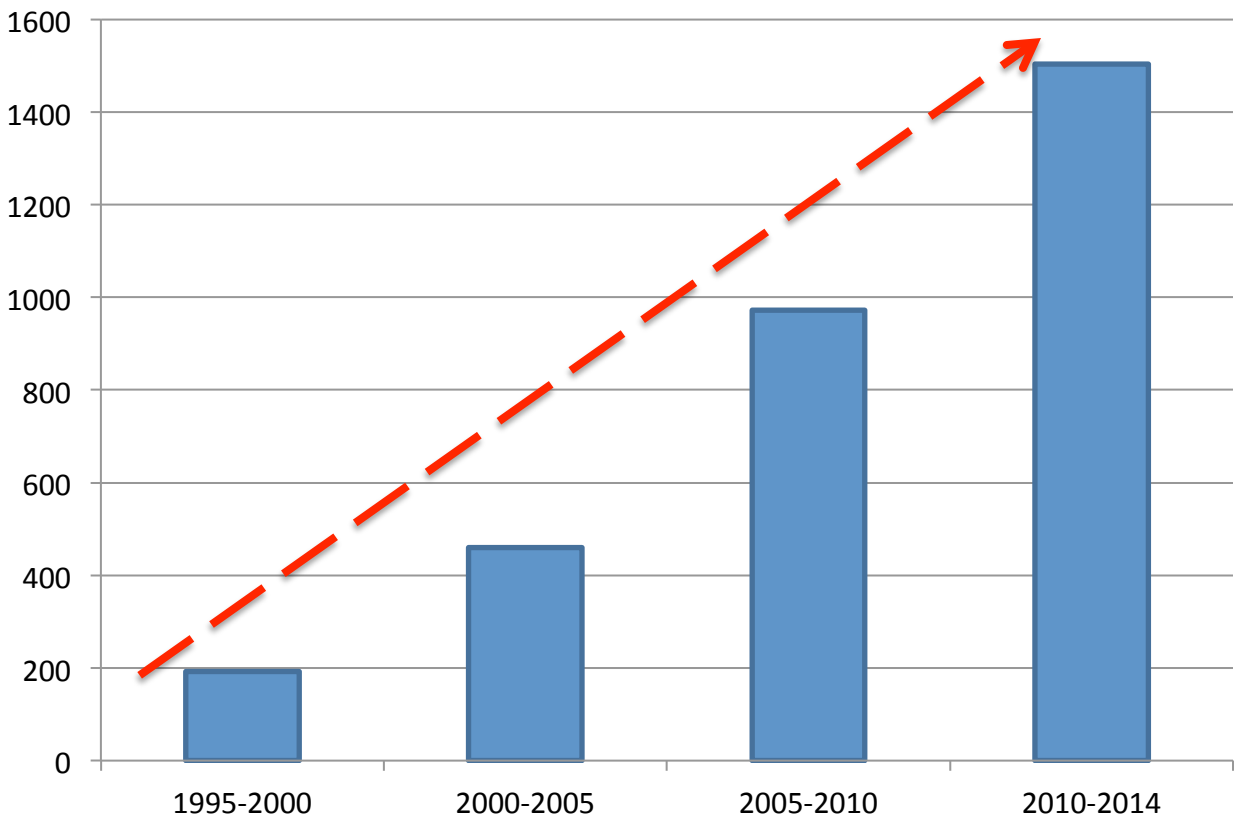


Endometriosis: reproductive outcomes

- Poor oocyte quality
- Impaired folliculogenesis
- Altered embryogenesis
- Decreased fertilisation rates
- Decreased pregnancy rates

Hamdam et al. Obstet Gynecol 2015

TREATMENT. Main objectives:

- Reduce pain
- Delay recurrence for as long as possible
- Preserve and improve fertility

Donnez J et al. Front Biosci 2012

human reproduction ORIGINAL ARTICLE ESHRE pages

ESHRE guideline: management of women with endometriosis†

Grade of recommendation

In infertile women with endometriosis, clinicians should not prescribe hormonal treatment for suppression of ovarian function to improve fertility (Hughes et al., 2008)

A

Dunselman GA et al. Hum Reprod. 2014

human reproduction ORIGINAL ARTICLE ESHRE pages

ESHRE guideline: management of women with endometriosis†

Grade of recommendation

A

In infertile women with endometrioma undergoing surgery, clinicians should perform excision of the endometrioma capsule, instead of drainage and electrocoagulation of the endometrioma wall, to increase spontaneous pregnancy rates (Hart et al., 2008)

Dunselman GA et al. Hum Reprod. 2014

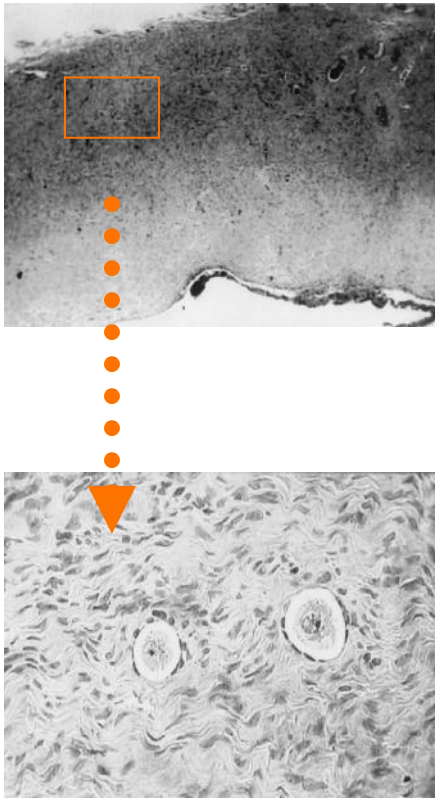
SURGERY-MEDIATED DAMAGE:

SURGERY-MEDIATED DAMAGE:

- Accidental removal of a consistent amount of ovarian tissue during cystectomy

- Surgery-related local inflammation or vascular compromise following electrosurgical coagulation

- Impaired ovarian vascularization



Muzii et al 2002

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

TABLE 3. Serum AMH values before and after surgery for all studies included in the meta-analysis

Author	Number of excisions	Baseline (preoperatively)	1 wk postoperatively	1 month postoperatively	3 months postoperatively	6 months postoperatively	9 months postoperatively
Biacchiardi *et al.* (28)[a]	43	3.0 ± 0.4			1.4 ± p.2		1.3 ± 0.3
Ercan *et al.* (34) (2010)	47	1.62 ± 1.09		1.39 ± 1.16			
Ercan *et al.* (27) (2011)	36	2.03 ± 0.41			1.95 ± 0.62		
Hirokawa *et al.* (35)[a]	38	3.9 ± 2.5		2.1 ± 1.6			
Hwu *et al.* (29)	31	3.95 ± 2.34			2.01 ± 1.17		
Kitajima *et al.* (25)[a]	19	4.27 ± 3.0			3.024 ± 2.48		
Lee *et al.* (36)[a]	13	4.69 ± 2.5	2.77 ± 1.56	2.77 ± 1.46	3.29 ± 2.11		
Tsolakidis *et al.* (24)	10	3.9 ± 1.26				2.9 ± 0.63	

Significant damage to ovarian reserve – up to 40% fall in serum AMH after cystectomy (endo)

Raffi F et al. J Clin Endocrinol Metab. 2012

ENDOMETRIOSIS. SURGICAL TREAMENT

STUDY GROUP

28 women
IVF/ICSI cycle
Endometrioma > 2 cm

CONTROL GROUP

28 egg donors

	AMH levels	p
Ovary (endometrioma)	4.1 ± 2.7 ng/ml	*
Contralateral ovary	4.9 ± 2.6 ng/ml	*
Control group	6.2 ± 3.0 ng/ml	-

García-Velasco JA et al. J Endometr 2009

Reduced Antral Follicle Count

	Operated ov	Non - operated
AFC	4.5	7.4 *

Almog et al. Fertil Steril 2010

RISKS OF SURGICAL REMOVAL:

- Risk of postsurgical ovarian failure
- Experience of the laparoscopist
- Risk of disease recurrence
- Impaired ovarian vascularization
- Costs
- No improvement of reproductive outcomes

Tsoumpou I et al. Fertil Steril. 2009

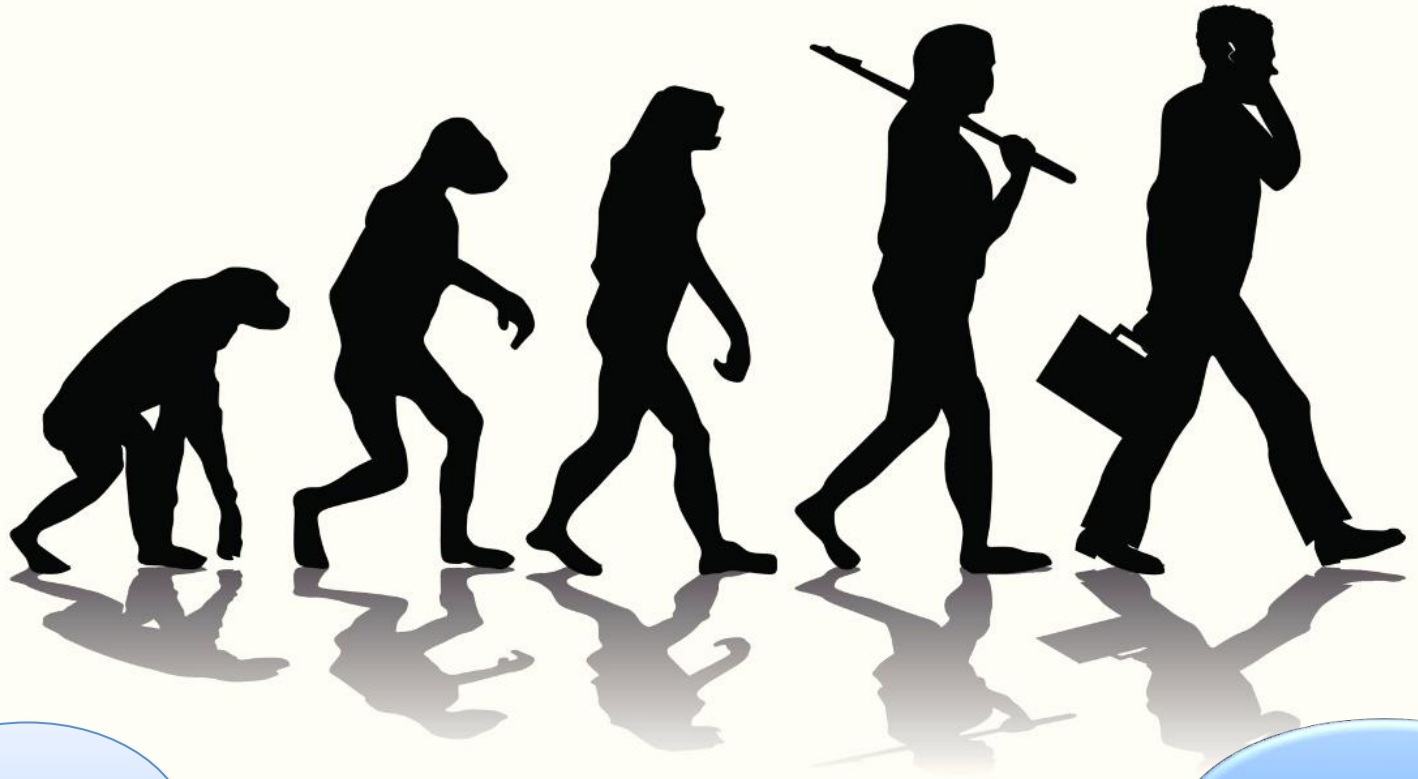
Management of endometriomas in women requiring IVF: to touch or not to touch

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	≥ I
Ovarian reserve[a]	Intact	Damaged
Pain symptoms	Present	Absent
Bilaterality	Monolateral disease	Bilateral disease
Sonographic feature of malignancy[b]	Present	Absent
Growth	Rapid growth	Stable

García-Velasco JA et al. Hum Reprod. 2009

MANAGEMENT OF OVARIAN ENDOMETRIOMAS



Surgical approach

Conservative approach

human reproduction ORIGINAL ARTICLE ESHRE pages

2014

ESHRE guideline: management of women with endometriosis†

	Grade of recommendation
In infertile women with endometrioma larger than 3 cm there is no evidence that cystectomy prior to treatment with ART improves pregnancy rates (Donnez et al., 2001; Hart et al., 2008; Benschop et al., 2010).	A
In women with endometrioma larger than 3 cm, the GDG recommends clinicians only to consider cystectomy prior to ART to improve endometriosis-associated pain or the accessibility of follicles.	GPP

Dunselman GA et al. Hum Reprod. 2014

HOWEVER…

Management of endometrioma prior to IVF: ESHRE-sponsored survey

Table 2 Current practice in the management of endometrioma (>3 cm) prior to IVF in women without previous ovarian surgery (results stratified by hospital setting).

Hospital setting	*Expectant*	*Medical*	*Surgical*	*Medical followed by surgical*	*Surgical followed by medical*	*Total*
District general hospital	3 (10.7)	2 (7.1)	14 (50.0)	1 (3.6)	8 (28.6)	28 (100)
University teaching hospital with IVF set-up	10 (14.3)	3 (4.3)	38 (54.3)	5 (7.1)	14 (20.0)	70 (100)
University teaching hospital with no IVF set-up	1 (11.1)	0	7 (77.8)	0	1 (11.1)	9 (100)
Total	14 (13.1)	5 (4.7)	59 (55.1)	6 (5.6)	23 (21.5)	107 (100)

Values are number (%).

Surgical treatment: 82.2%

Gelbaya TA et al. Reprod Biomed Online. 2010

human reproduction ORIGINAL ARTICLE ESHRE pages

ESHRE guideline: management of women with endometriosis†

	Grade of recommendation
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 considered carefully if the women has had previous ovarian surgery	GPP

Dunselman GA et al. Hum Reprod. 2014

Who?

- Before surgery, in reproductive-age women at risk of developing POF

- Patients <38 years old with endometriosis who want to delay childbearing

Somigliana et al. Hum Reprod Update 2015

FERTILITY PRESERVATION OPTIONS

- ✓ Embryo cryopreservation
- Oocyte cryopreservation
- Ovarian cortex cryopreservation

EMBRYO CRYOPRESERVATION

ETHICAL AND LEGAL LIMITATIONS:

- Immediate reproductive use
- Single women: donor sperm sample ?
- Couples: embryo disposition upon divorce ?
- Objections for religious/moral reasons

Today it should not be a 1st option


OOCYTE
VITRIFICATION
EMBRYO
VITRIFICATION

FERTILITY PRESERVATION OPTIONS

- ✓ o Embryo cryopreservation
- ✓ o Oocyte cryopreservation
- o Ovarian cortex cryopreservation

OOCYTE VITRIFICATION

- ✓ Safety
- Efficacy
- Cost-effective
- Ethically acceptable

Safety for the patient

- Current protocols
  - rFSHr / Antag/ GnRHa

Complications	0.41% (17)
Intraabdominal bleeding	0.34% (14)
Severe pain	0.05% (2)
Ovarian torsion	0.02% (1)

Bodri et al. 2008

- No risk of OHSS
  - No hCG
  - No embryo transfer

Safety for the patient

Table III Influence of IVF on endometriosis-related symptoms.

Symptoms	Pre-IVF	Post-IVF	P
Dysmenorrhea			
BB-scale			0.21
0	25 (39%)	21 (33%)	
1	22 (34%)	29 (45%)	
2–3	17 (27%)	14 (22%)	
VRS-scale	3.7 ± 3.3	3.8 ± 3.3	0.78
Dyspareunia			
BB-scale			0.08
0	44 (69%)	44 (69%)	
1	11 (17%)	16 (25%)	
Other symptoms	15 (23%)	13 (20%)	0.69

Ovarian stimulation for IVF does not have an impact on endometriosis associated symptoms

Benaglia L et al., Hum Reprod. 2011

Safety for the baby

- Similar chromosomal abnormalites by FISH

Cobo et al. Fertil Steril. 2001

- 1027 newborns, similar to infertile patients

Cobo et al. Fertil Steril 2014

- 200 newborns, similar to infertile patients

Chian RC et al. Reprod Biomed Online. 2008

ASRM PAGES

Mature oocyte cryopreservation: a guideline

The Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology

Society for Reproductive Medicine and Society for Assisted Reproductive Technology, Birmingham, Alabama

There is good evidence that fertilization and pregnancy rates are similar to IVF/ICSI with fresh oocytes when vitrified/warmed oocytes are used as part of IVF/ICSI for young women. Although data are limited, no increase in chromosomal abnormalities, birth defects, and developmental deficits has been reported in the offspring born from cryopreserved oocytes when compared to pregnancies from conventional IVF/ICSI and the general population. Evidence indicates that oocyte vitrification and warming should no longer be considered experimental. This document replaces the document last published in 2008 titled, "Ovarian Tissue and Oocyte Cryopreservation," Fertil Steril 2008;90:S241-6. (Fertil Steril® 2012;■:■–■.

Use your smartphone

OOCYTE VITRIFICATION

- ✓ Safety
- ✓ Efficacy
- Cost-effective
- Ethically acceptable

Efficacy

o Survival	90-97%
o Fertilization	71-79%
o Implantation	17-41%
o Pregnancy rate	36-61%
o Pregnancy/ thawed oocyte	4.5-12%

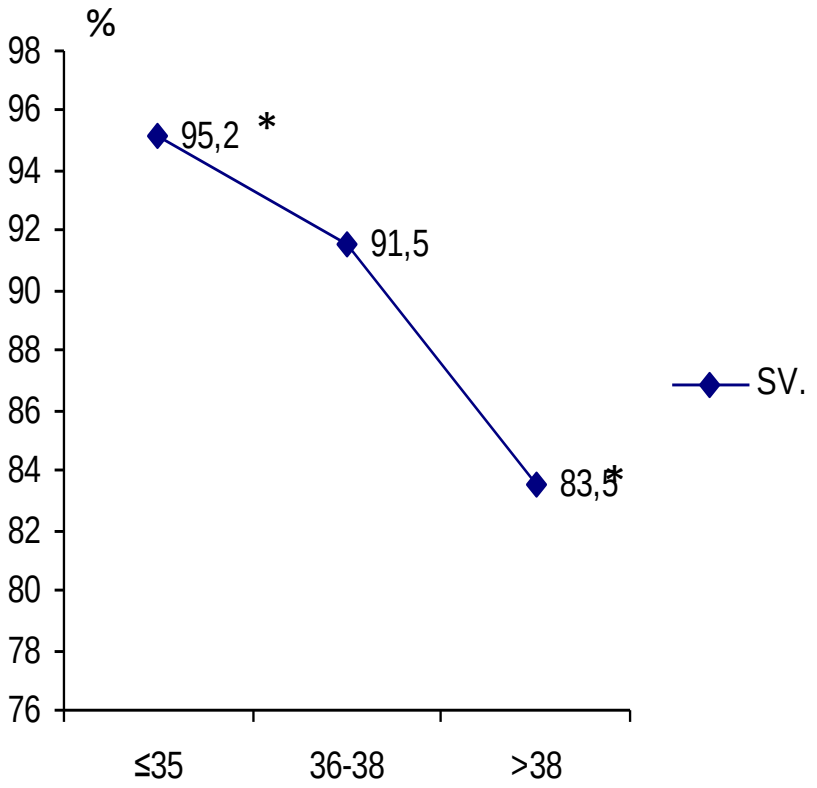
Mainly in women <35 years

ASRM Practice Committee 2012

Survival / age

Group	n	MII oocytes (mean±SD)
≤35	50	605 (12.5±1.8)[a]
36-38	33	428 (9.1 ± 3.0)[b]
>38	47	252 (3.7±3.9)[c]

a≠b≠c (p<0,05)



*** p=0,016**

Efficacy

Table III Clinical outcome according to the type of oocytes received

	Egg-bank	Fresh
Number of embryos transferred	267 (90.5)	259 (89.6)
Mean number of embryos replaced	513 (1.74 ± 0.7)	498 (1.72 ± 0.7)
Number of cycles with embryo 're-vitrification'/cryopreservation	196 (66.7)	216 (74.7)*
Mean number of re-vitrified or cryopreserved embryos	592 (2.0 ± 2.1)	743 (2.5 ± 2.3)*
Implantation rate	205 (39.9)	204 (40.9)
Positive hCG test/cycle	165 (55.9)	159 (55.0)
Clinical pregnancy rate/cycle	148 (50.2)	144 (49.8)
Positive hCG test/transfer	165 (61.8)	159 (61.4)
Clinical pregnancy rate/transfer	148 (55.4)	144 (55.6)
Twin pregnancy rate	48 (32.4)	54 (37.5)

Unless otherwise indicated values are mean ± SD or *n* (%).
*$P < 0.05$.

Cobo et al Hum Reprod, 2010

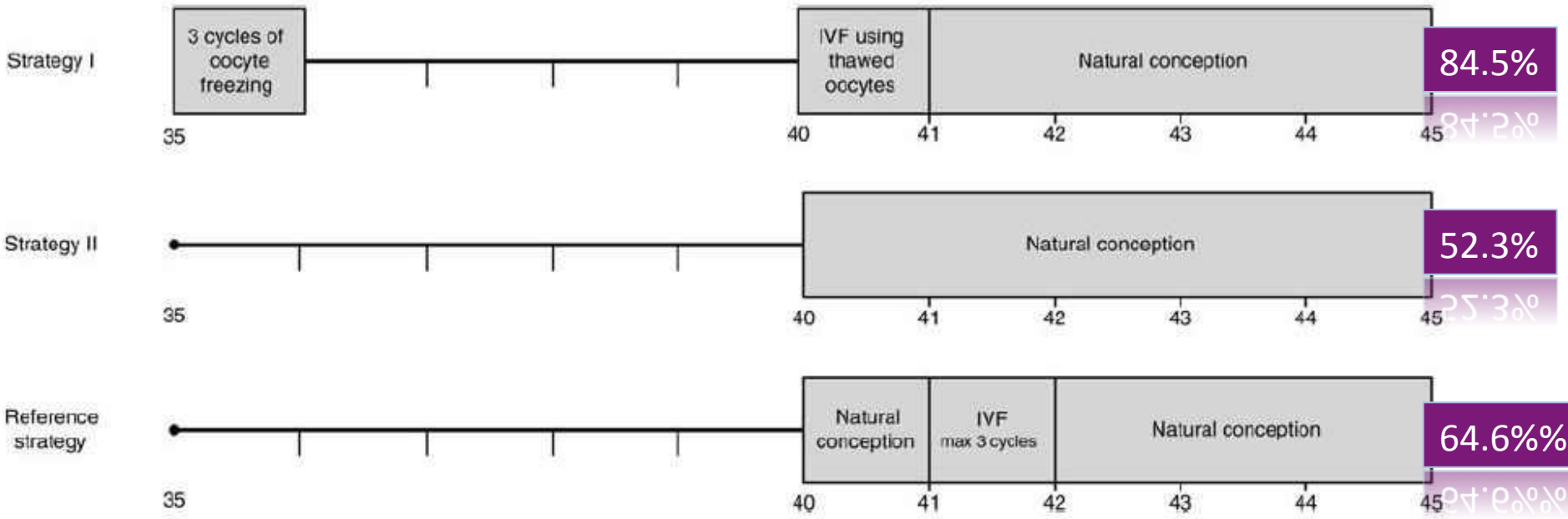
OOCYTE VITRIFICATION

- ✓ Safety
- ✓ Efficacy
- ✓ Cost-effective
- Ethically acceptable

Cost-effective

- Egg freezing is more cost-effective than IVF
- 35 years who wants to wait till 40

Cumulative live Birth rate (%)



Van Loendersloot et al. Hum Reprod. 2011

OOCYTE VITRIFICATION

- ✓ o Safety
- ✓ o Efficacy
- ✓ o Cost-effective
- ✓ o Ethically acceptable

Ethically acceptable

- Reduces the need for donor eggs
- Children with their own gametes at AMA
- Reduces the number of poor prognosis cycles we do today
- Provides women reproductive autonomy

Gorthi 2001, Loockwood 2011, Pennings 2011

Oocyte vitrification—Women's emancipation set in stone

Fertility and Sterility® Vol. 91, No. 4, Supplement, April 2009

Roy Homburg, F.R.C.O.G.[a,b]
Fulco van der Veen, M.D.[c]
Sherman J. Silber, M.D.[d]

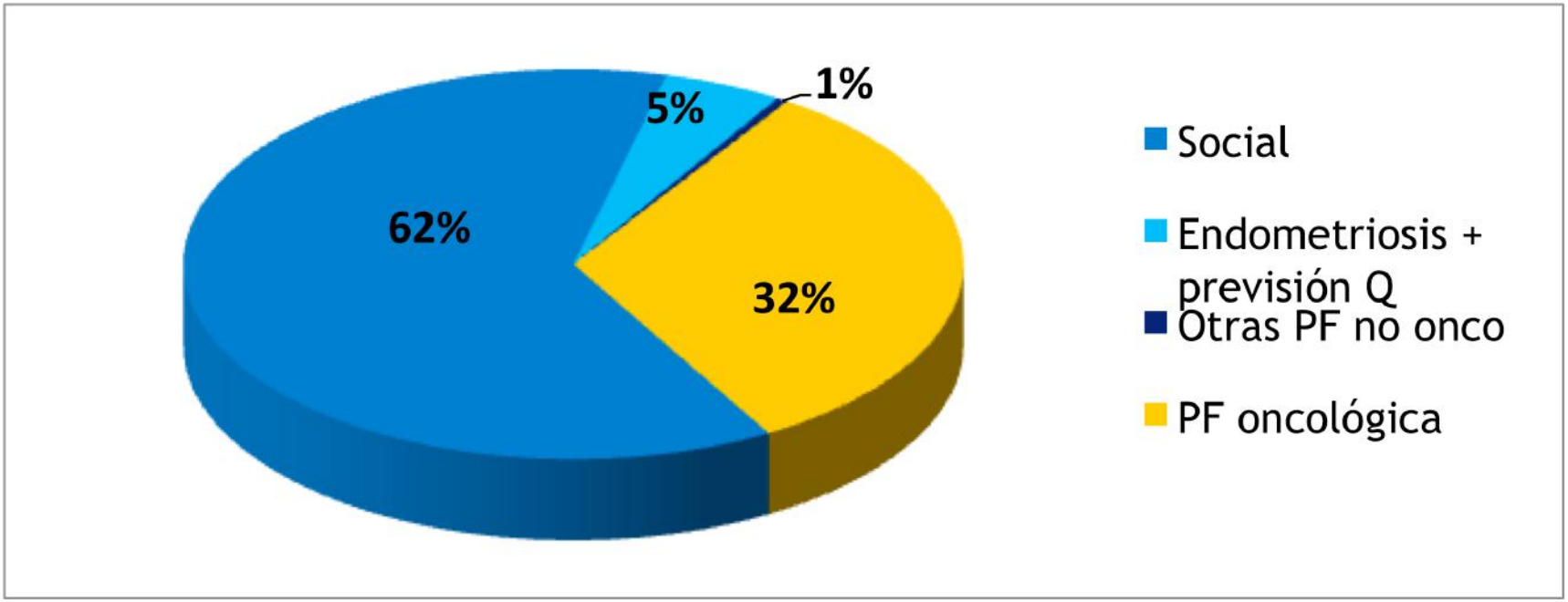
sex
vs
reproduction

1960's

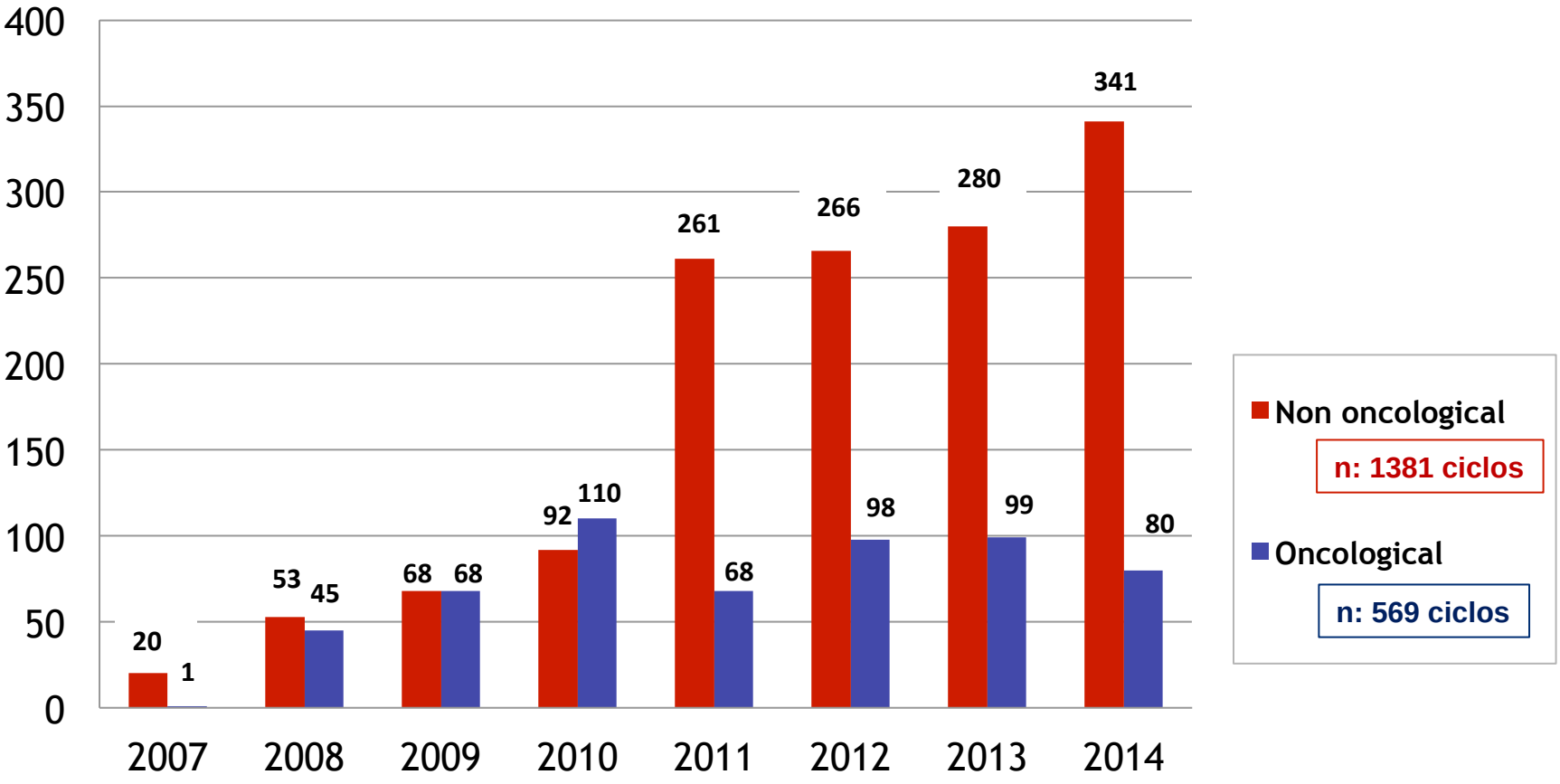
reproduction
vs
age

21st century

FP Programme at IVI



Evolution of the number of stimulated cycles for fertility preservation due to oncological and non-oncological reasons through the years.



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

Juan A. Garcia-Velasco, M.D.,[a,d] Javier Domingo, M.D.,[b] Ana Cobo, Ph.D.,[c] Maria Martinez, M.D.,[a] Luis Carmona, M.D.,[b] and Antonio Pellicer, M.D.[c] VOL. 99 NO. 7 / JUNE 2013 Fertility and Sterility®

32 babies.

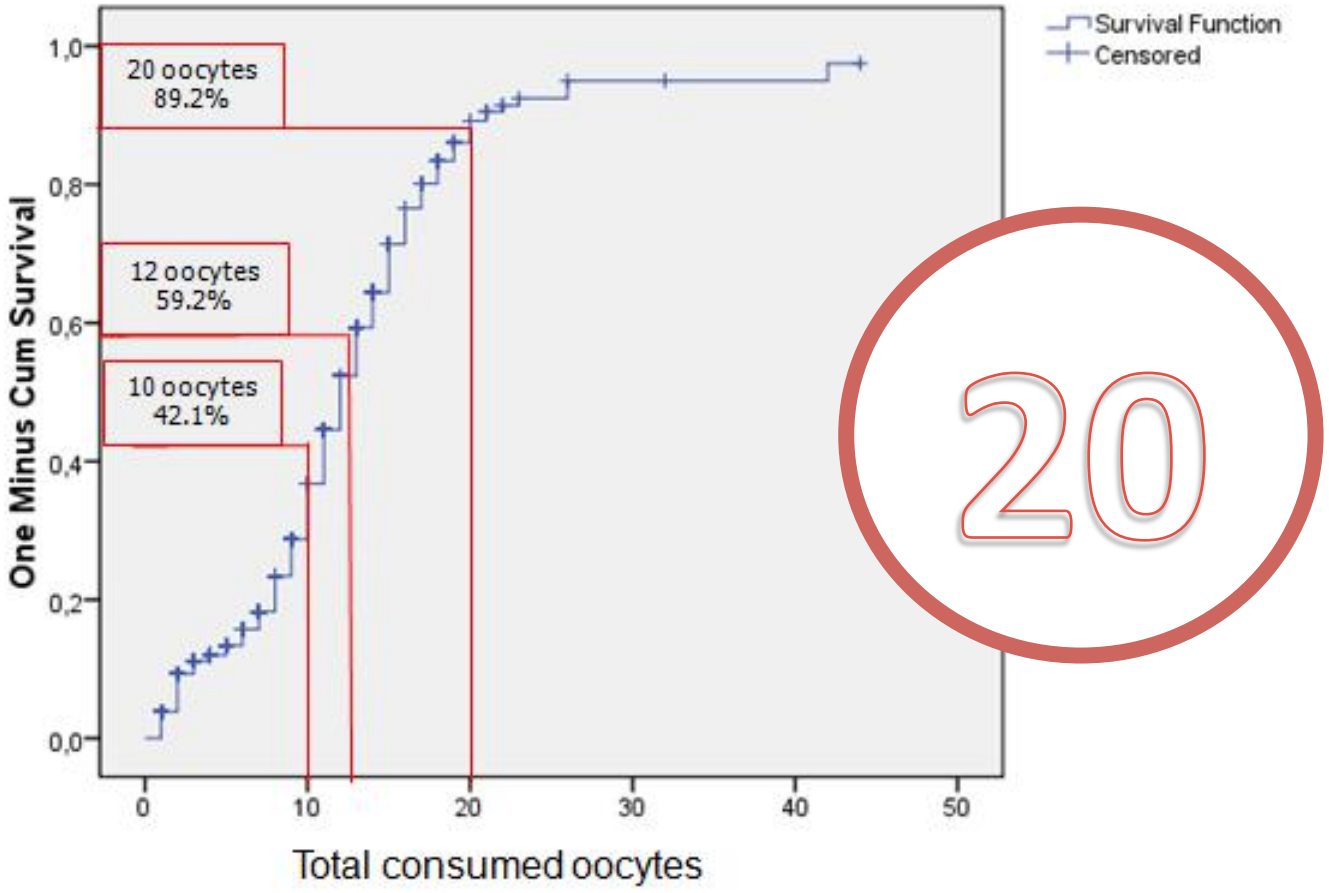
	Non oncological	Oncological
Nº Cycles FP	1633	569
Nº Patients FP	1217	386
Nº Patients using their vit. oocytes	85	16
Mean age at vitrification	31.5± 8.8	31.4 ± 6.4
Mean age at warming	39.2±3.7	36.1 ± 3.5
Nº oocytes vitrified/patient	9.188 (9.2±5.1)	4837 (8.5±1.7)
Nº oocytes warmed	729 (5.2±3.4)	106 (6.6 ± 0.7)
Survival rate	639 (87.7)	90 (84.9)
Nº embryos transferred	1.56 ±0.9	2 ± 0.7
Nº patients with surplus embryos	19(18.1)	6 (37.5)
CPR/patient	37 (44.0)	7 (43.8)
OPR/patient	36 (35.2)	5 (31.2)
Live birth	22	4*

**1 still ongoing*

Updated 5-years experience of applying oocyte vitrification for Fertility Preservation at IVI.

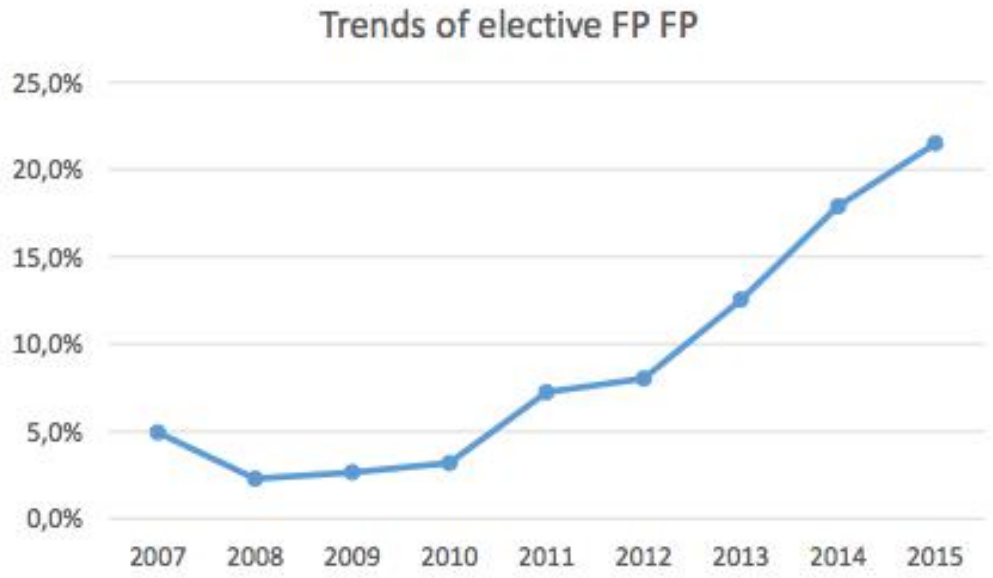
PR per # vitrified oocytes

NNF –number needed to freeze?



Cobo et al. Fertil Steril 2016

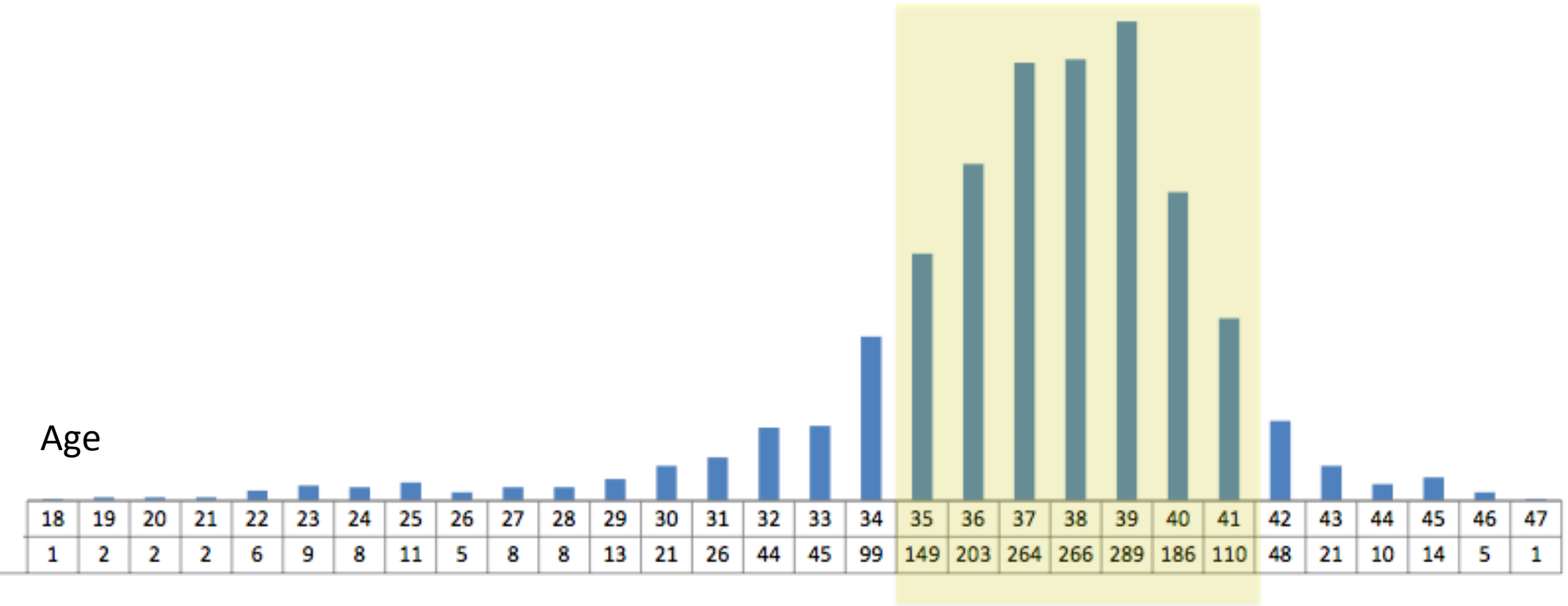
IVI – updated 2016



Year	Total vit. Cycles*	Total elective FP	% elective FP**
2007	568	28	4.9
2008	2018	46	2.2
2009	2682	71	2.6
2010	3110	99	3.2
2011	3368	244	7.2
2012	3241	260	8.0
2013	2951	370	12.5
2014	2951	528	17.9
2015	1084	233	21.5
Total	**21973**	**1879**	**8.8**

IVI – updated 2015

Patients still come too late



Outcome after thawing – social FP

Clinical outcome according to different groups of age

Age	Nº patients	Nº warming cycles	Survival rate %	CPR/cycle (%)	OPR/cycle (%)	Nº Live Births
≤26	4	7	87.8	4/7 (57.1)[a]	4/7 (57.1)[a]	6
30-34	16	19	90.9	11/19 (57.8)[a]	10/19 (52.6)[a]	6
35-39	78	121	79.8	53/121 (43.8)[a]	31/121 (25.6)[b]	20
40-44	24	28	85.3	6/28 (21.4)[b]	4/28 (14.3)[c]	0

Different superscripts in the same column indicate statistical differences (P<0.05)

FERTILITY PRESERVATION OPTIONS

- ✓ o Embryo cryopreservation
- ✓ o Oocyte cryopreservation
- ✓ o Ovarian cortex cryopreservation

OVARIAN CORTEX CRYOPRESERVATION

ASRM PAGES

Ovarian tissue cryopreservation: a committee opinion

The Practice Committee of the American Society for Reproductive M ine
American Society for Reproductive Medicine, Birmingham, Alabama

"Ovarian tissue cryopreservation should not be offered to women who wish to delay childbearing or to women with benign conditions such as ovarian cysts that are best managed with fertility-sparing surgery"

Practice Committee of the ASRM. Fertil Steril. 2014

Conclusions

- We should inform women who are willing to undergo endo cystectomy about the impact of surgery on the ovarian reserve
- Embryo freezing or ovarian cortex freezing should not be an option today for FP in women with endometriosis
- Oocyte vitrification is a safe and efficient technique for FP in women with endometriosis
- We freeze gametes – not fertility

Thank you!

juan.garcia.velasco@ivi.es