THE RELATIVITY THEORY OF OVARIAN AGING

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Ology Medical Education | Event Planet

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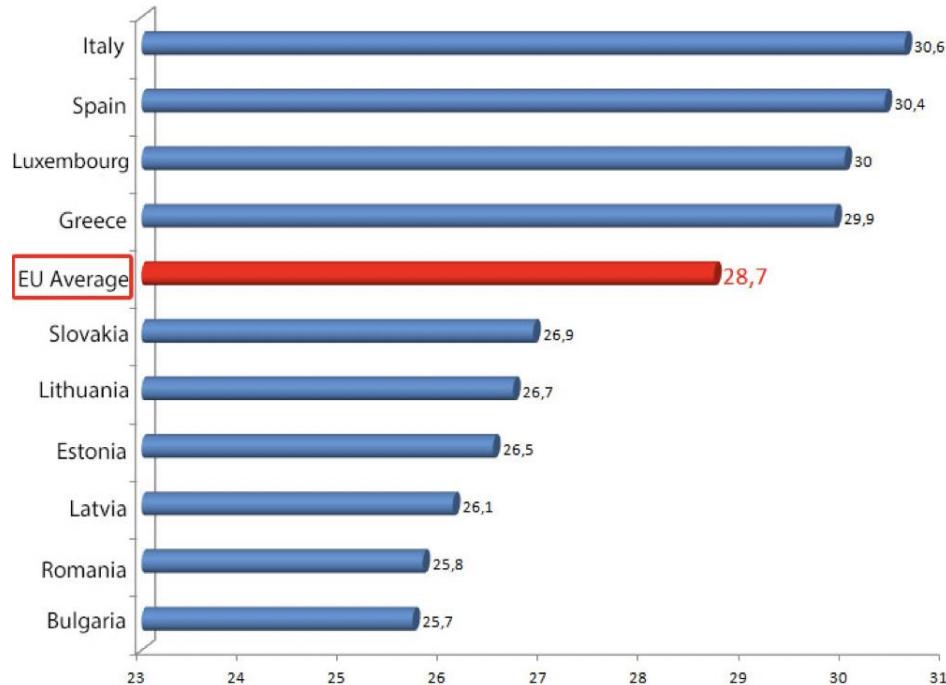
Disclosures

- Speakers bureau and honoraria: Ferring Pharmaceuticals, Merck Serono, MSD

- Advisory board: MSD, Finox, Roche Diagnostics

- Grants: Finox

Educational objectives
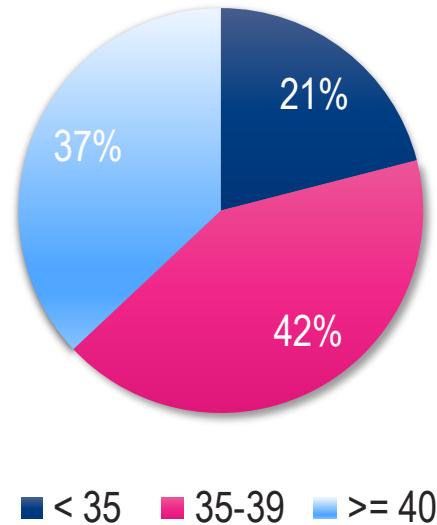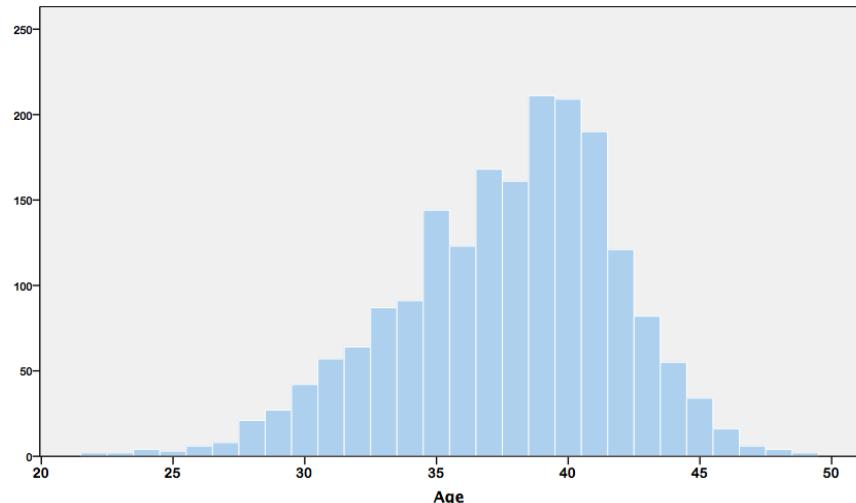
- Identify the age-related decline in fertility and discuss the impact on both the embryo and oocyte quality

- Recognize ovarian aging as a possible cause of LH and androgen deficiency

- Review novel therapeutical strategies in women of advanced age

Age of motherhood in EU (2015)

Source: Eurostat

Age for IVF (IVI Valencia 2018)

IVI Valencia in house data.

Late reproduction stage
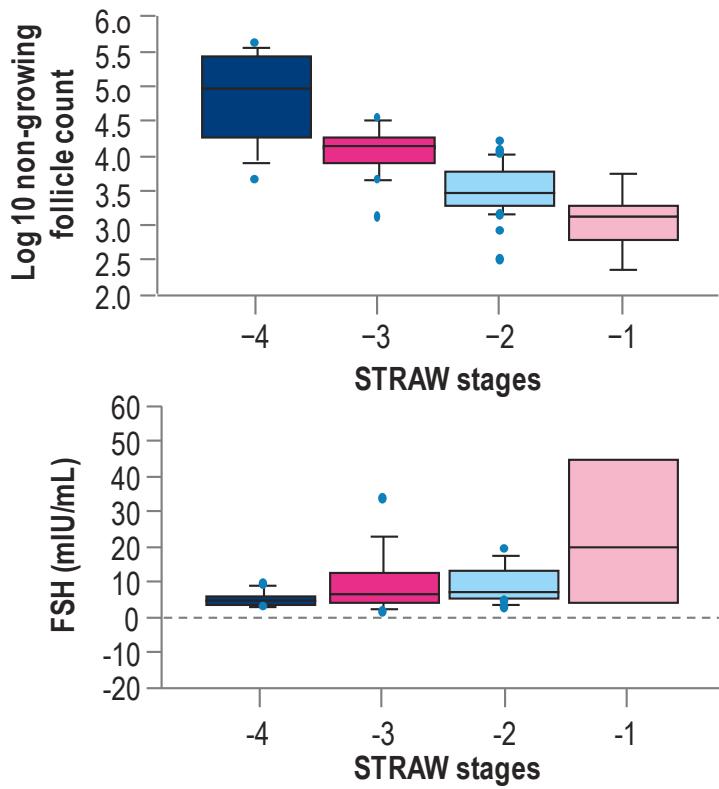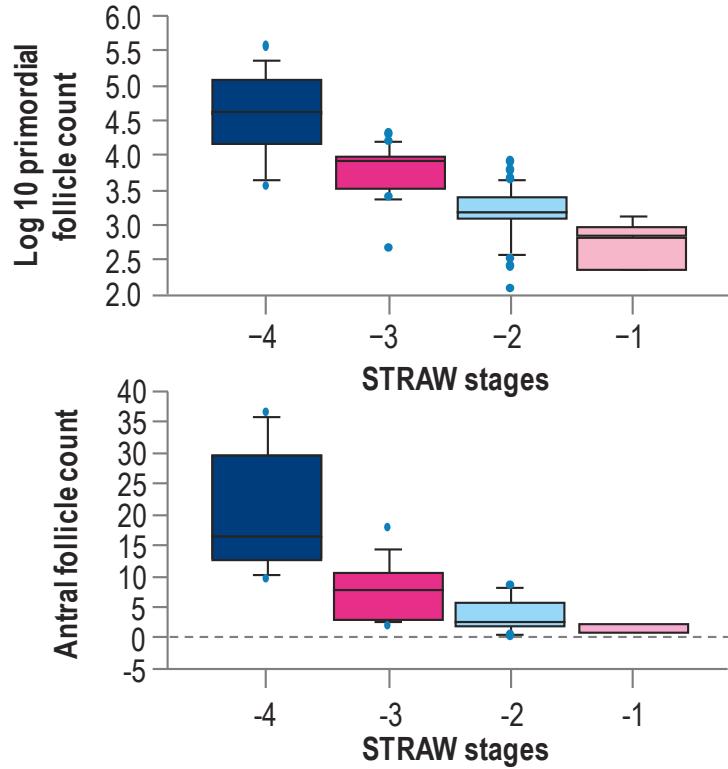
Stage	-5	-4	-3b	-3a	-2	-1	+1 a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1-3 years	2 years (1+1)	3-6 years		*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length* Persistent ≥7- day difference in length of consecutive cycles	Interval of amenorrhea of >=60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Low Low Low	Variable* Low Low	↑ Variable* Low Low	↑ >25 IU/L** Low Low	↑ Variable Low Low	Stabilizes Very Low Very Low		
Antral Follicle Count			Low	Low	Low	Low	Very Low	Very Low		
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing symptoms of urogenital atrophy*

* Blood draw on cycle days 2-5 ↑ = elevated
**Approximate expected level based on assays using current international pituitary standard[67-69]
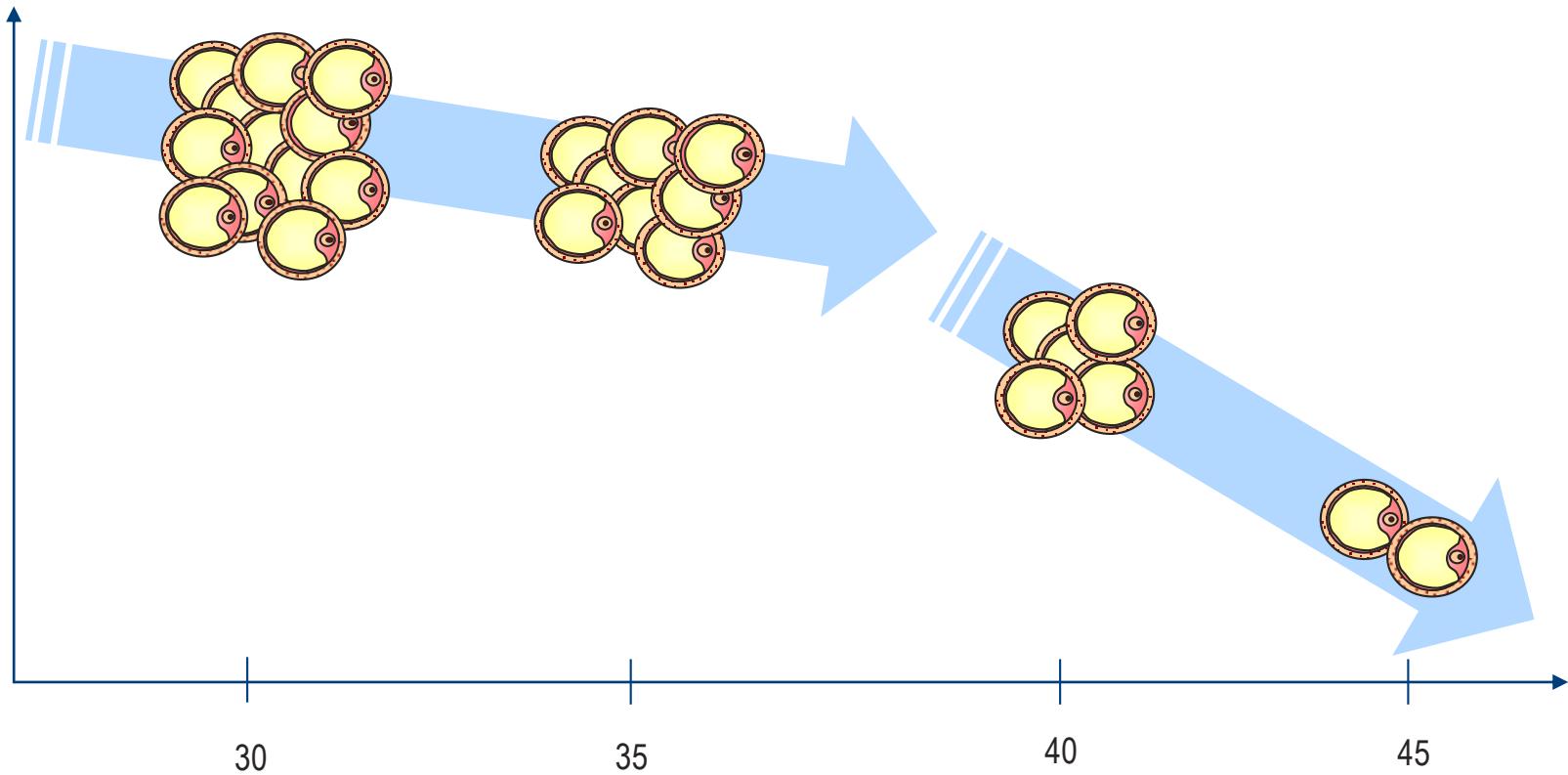
Fig. 1. The 2011 Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women.

Hale GE, et al. J Steroid Biochem Mol Biol. 2014;142:121-31.
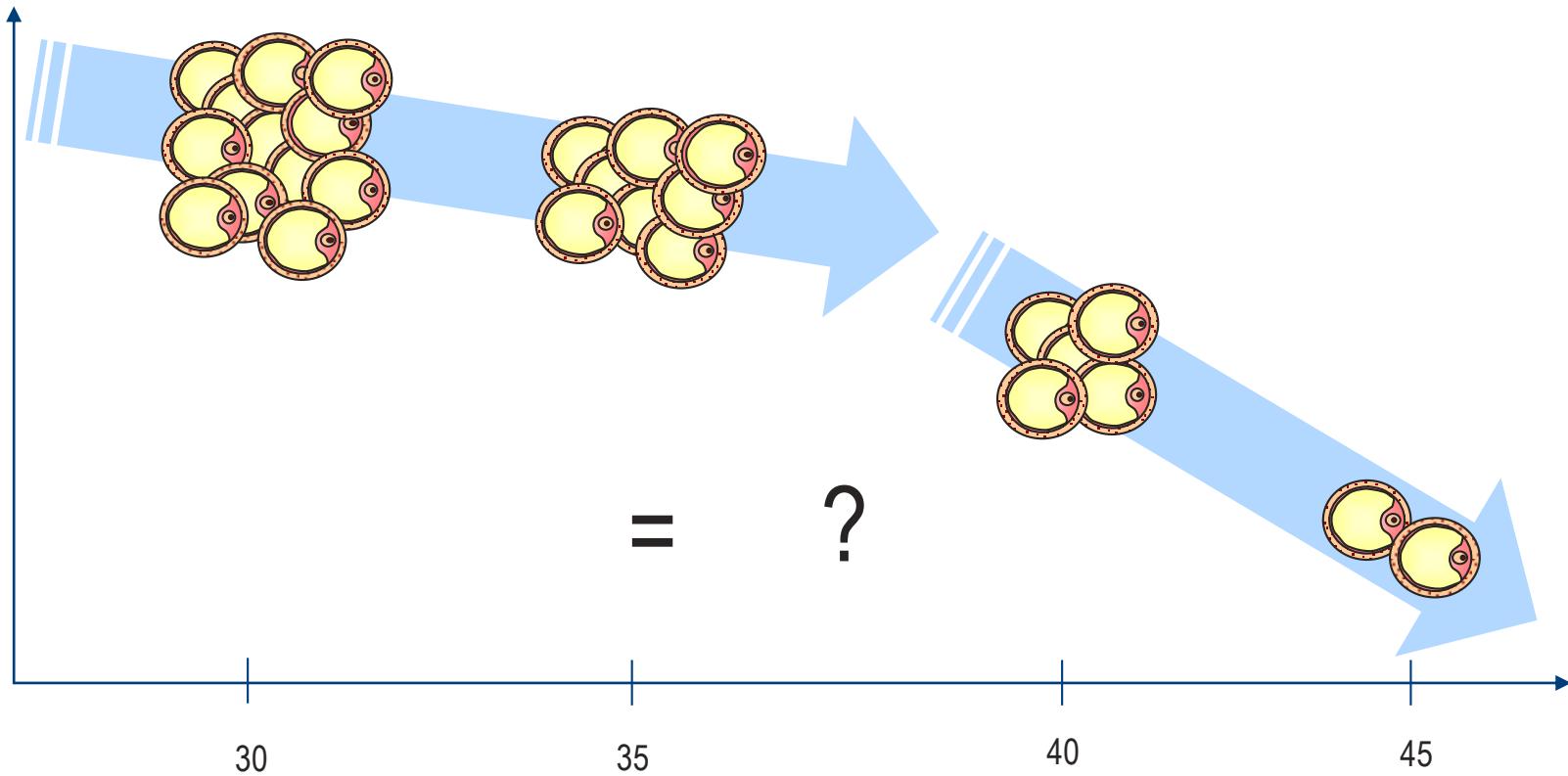
Ovarian aging: follicle count

Hale GE, et al. J Steroid Biochem Mol Biol. 2014;142:121-31.
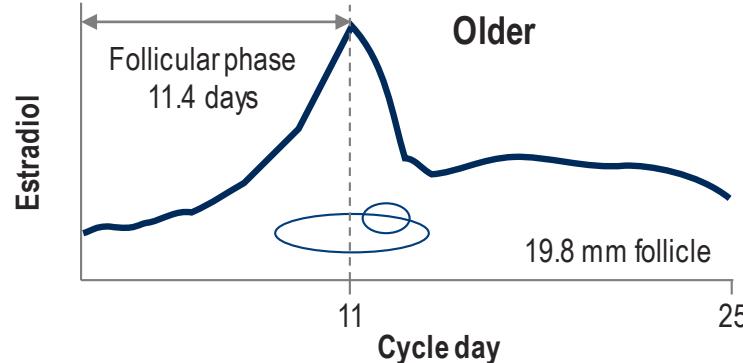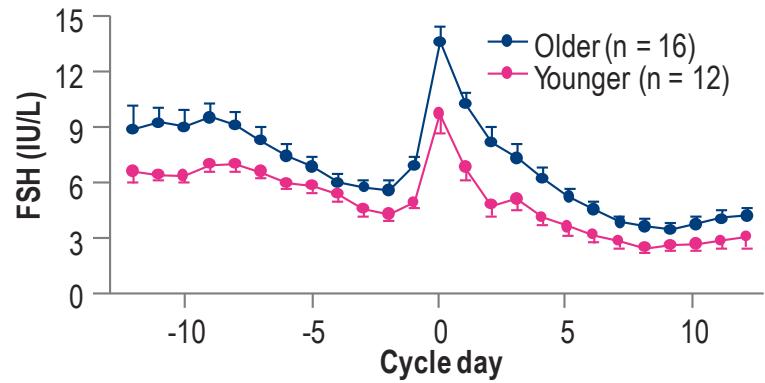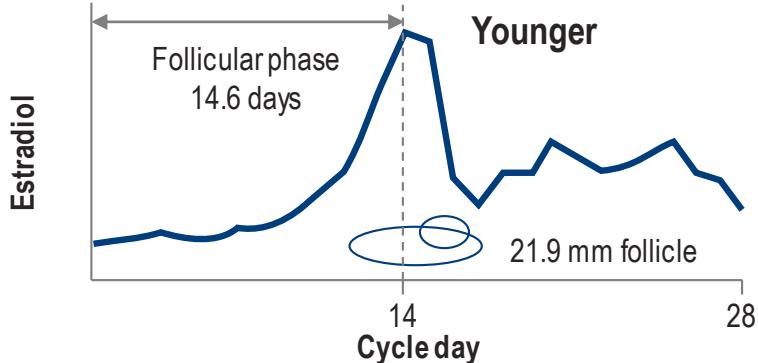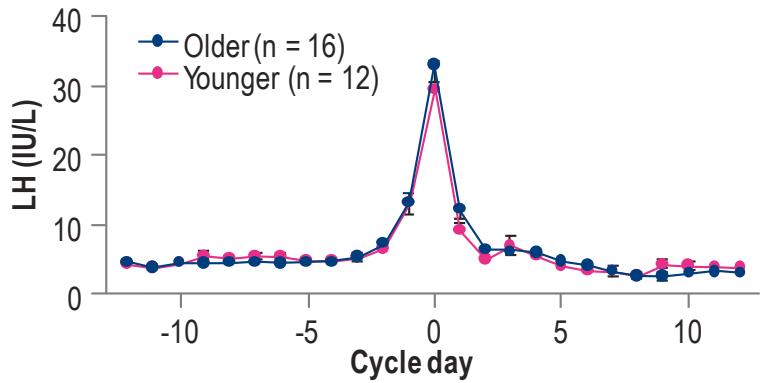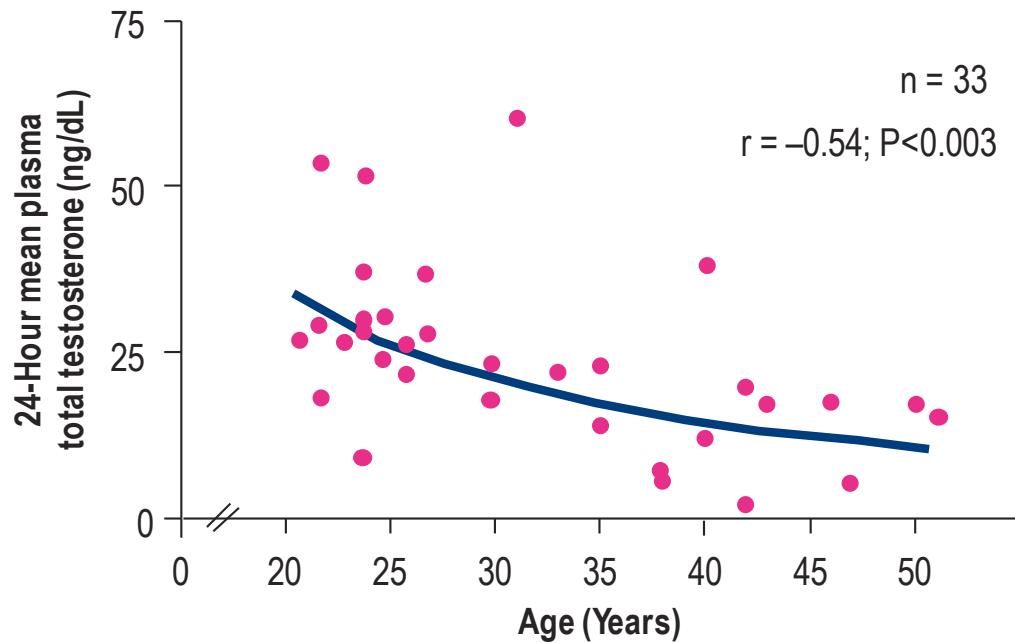
Ovarian aging

Ovarian aging

= ?

30   35   40   45

Ovarian aging

Klein NA, et al. J Clin Endocrinol Metab. 1996;81:1038-45.
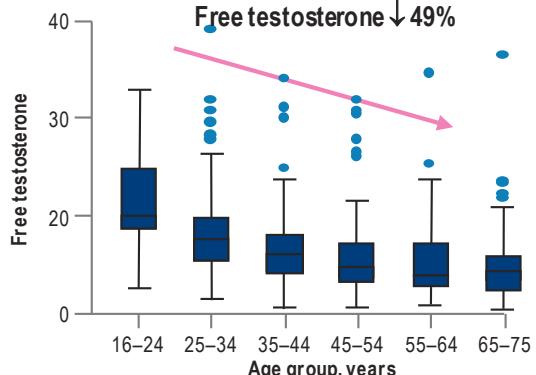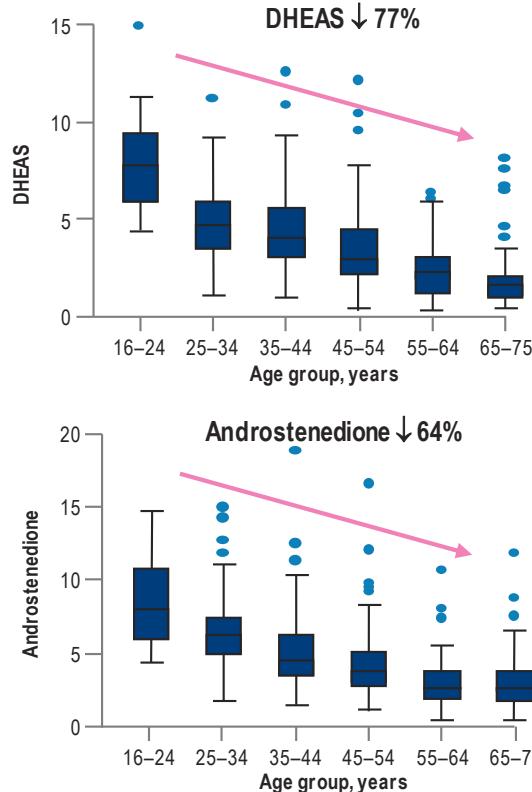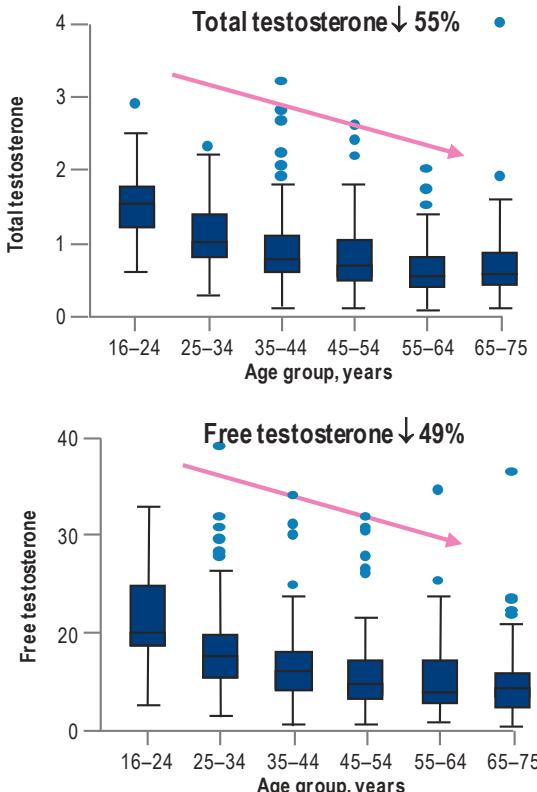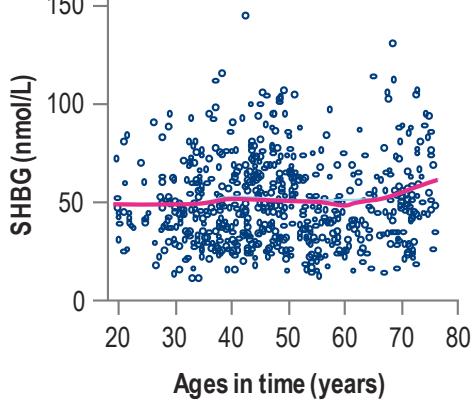
Ovarian aging: testosterone

n = 33

r = –0.54; P<0.003
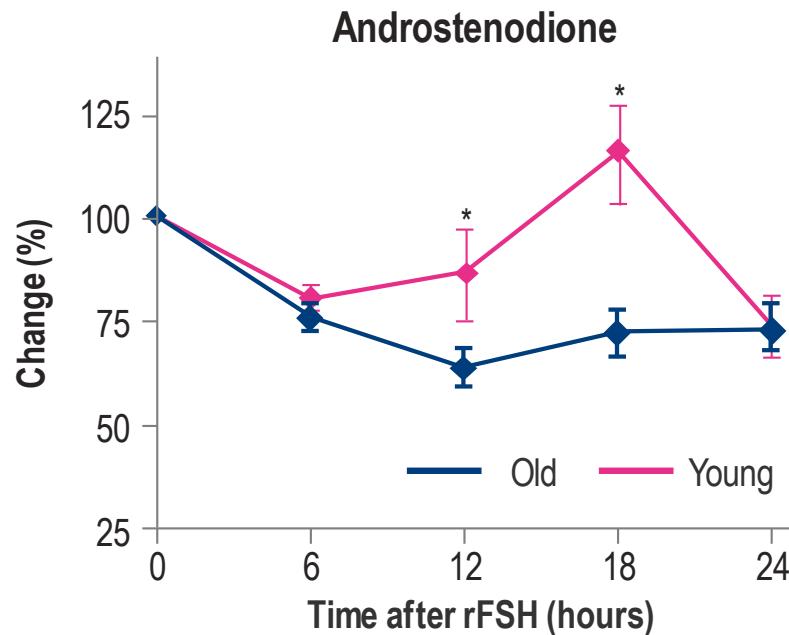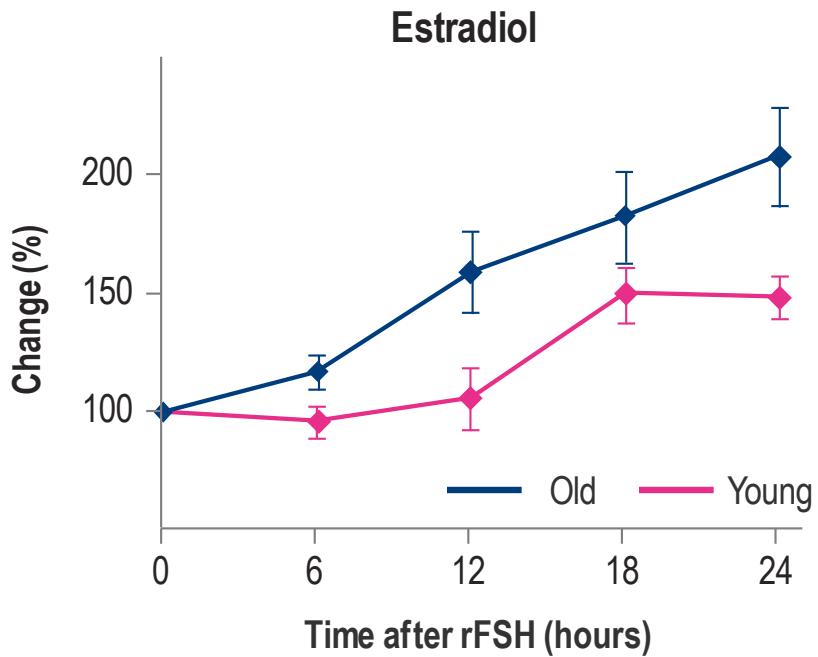
Total testosterone levels in women decrease with age

Zumoff B, et al. J Clin Endocrinol Metab. 1995;80:1429-30.

Ovarian aging

n = 1423

SHBG (nmol/L) vs Ages in time (years)

Regression line
Lowess curve

Total testosterone ↓ 55%

Free testosterone ↓ 49%

DHEAS ↓ 77%

Androstenedione ↓ 64%

Davison SL, etal. J Clin Endocrinol Metab. 2005;90:3847-53.
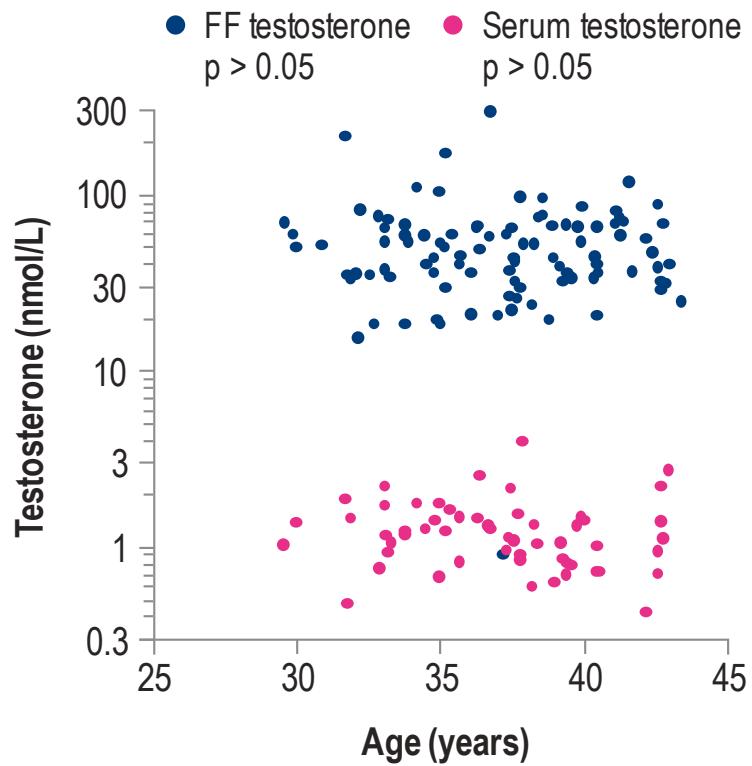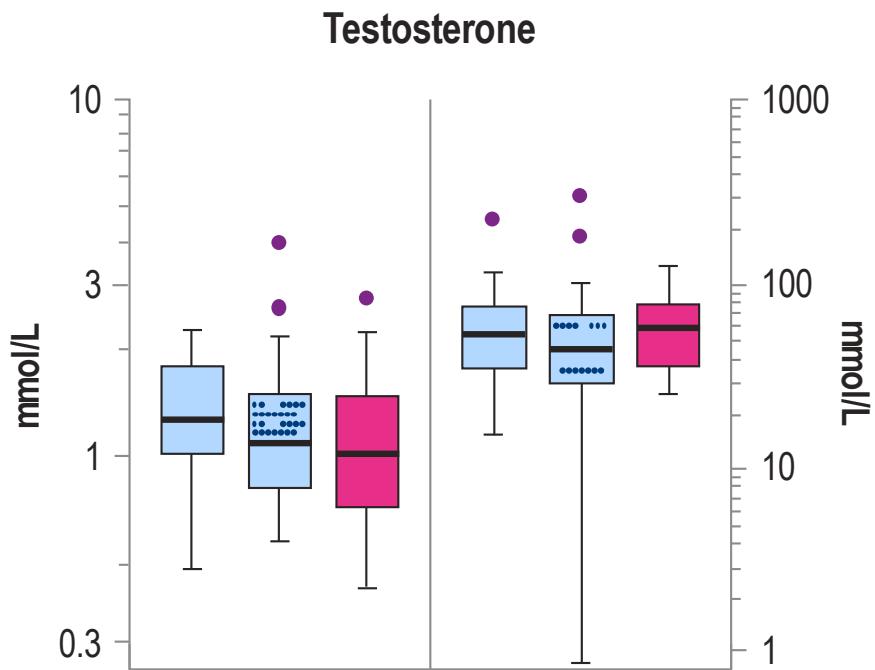
Ovarian aging: estradiol and androstenodione

Ovarian aging: follicular fluid

Klein NA, et al. J Clin Endocrinol Metab. 1996;81:1946-51.

Ovarian aging: follicular fluid

Testosterone

Von Wolff M, et al Reprod Biomed Online. 2017;35:616-23.
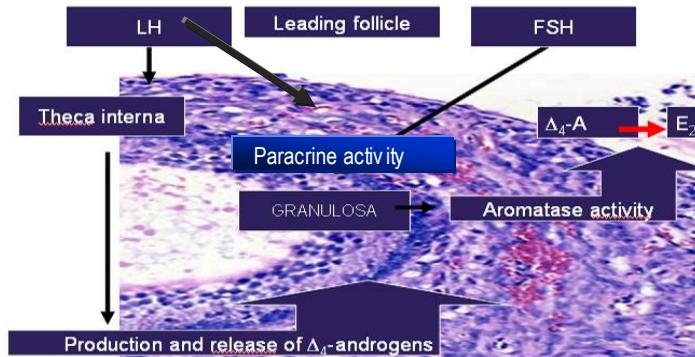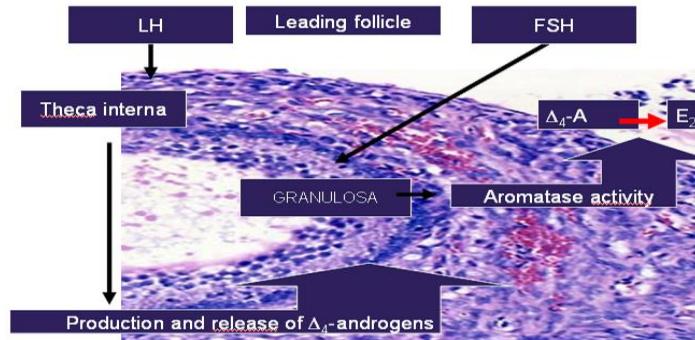
LH during folliculogenesis in the natural cycle

Early follicular phase
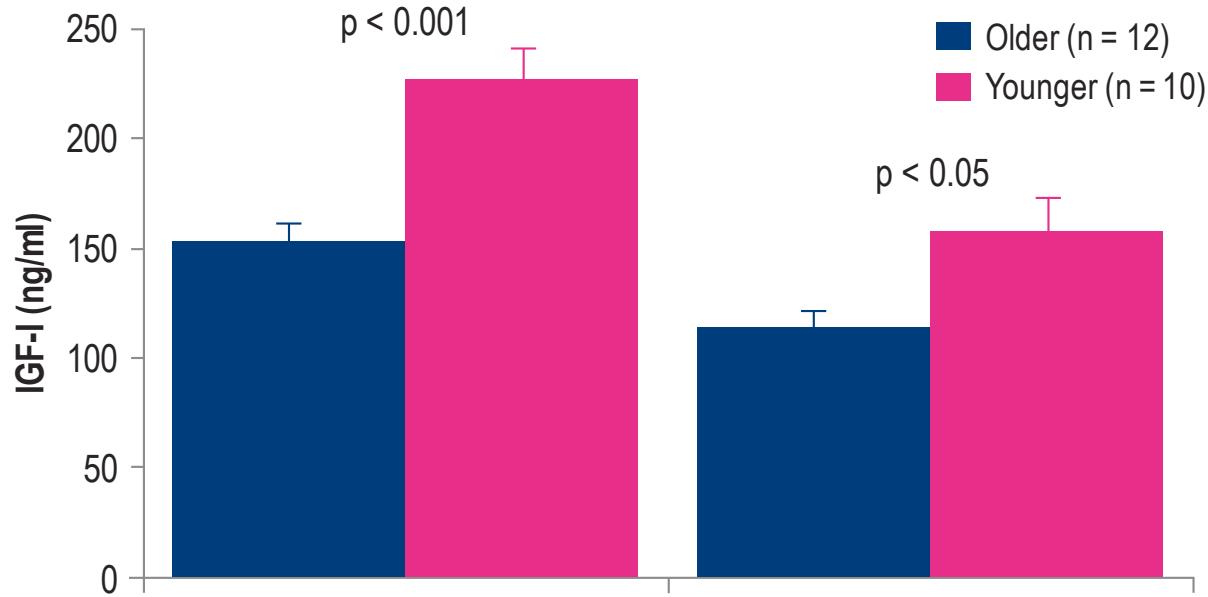
- Induction of androgens production in the theca cells

- Increase in follicular recruitment

From intermediate follicular phase
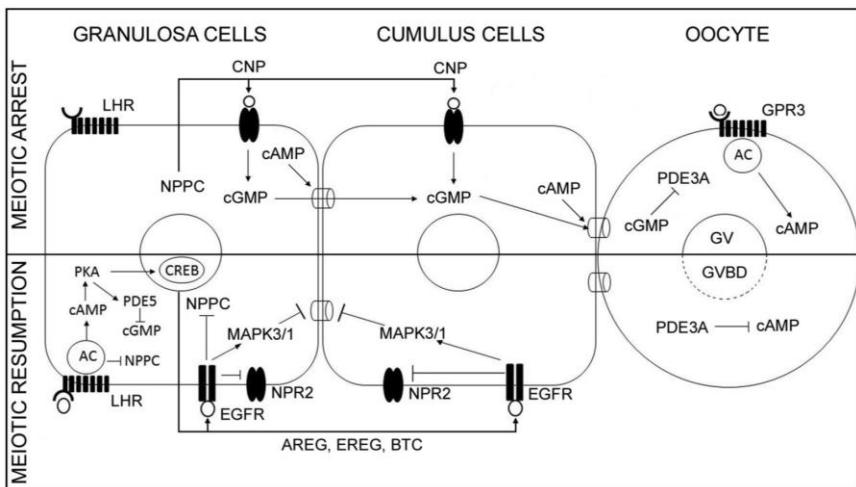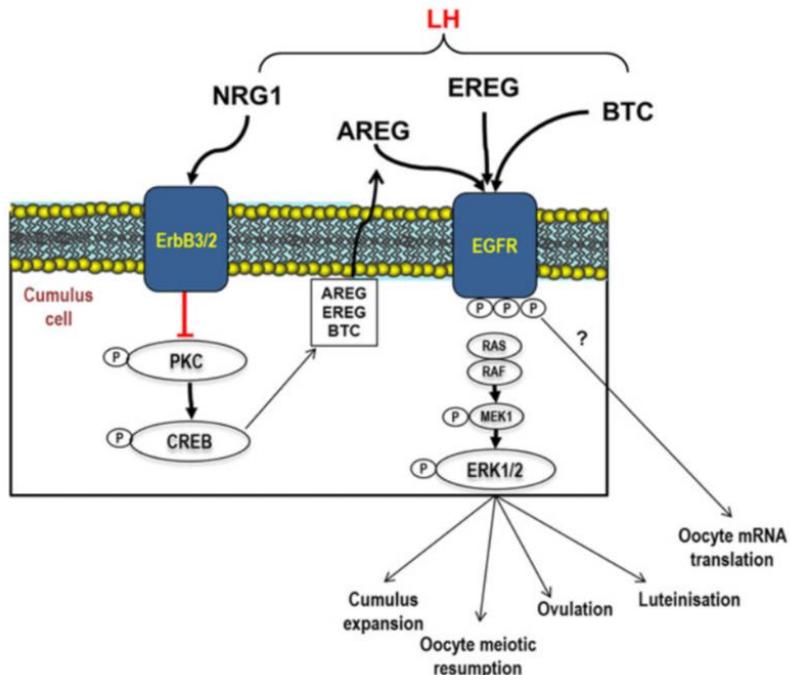
Expression of LH receptors in the granulosa

- Optimization of steroidogenesis

- Sustained FSH-dependent granulosa activities, including aromatase induction and growth factors release (IGF-1, EGF etc…)

Jeppesen JV, et al. J Clin Endocrinol Metab. 2012;97:E1524-31.

Oocyte competence LH regulation (IGF)

Klein NA, et al. J Clin Endocrinol Metab. 1996;81:1946-51.

Oocyte competence LH regulation (EGF)

Prochazka R, etal, Biol Reprod. 2017;97:537-49.
Richani D, Gilchrist RB. Hum Reprod Update. 2018;24:1-14.
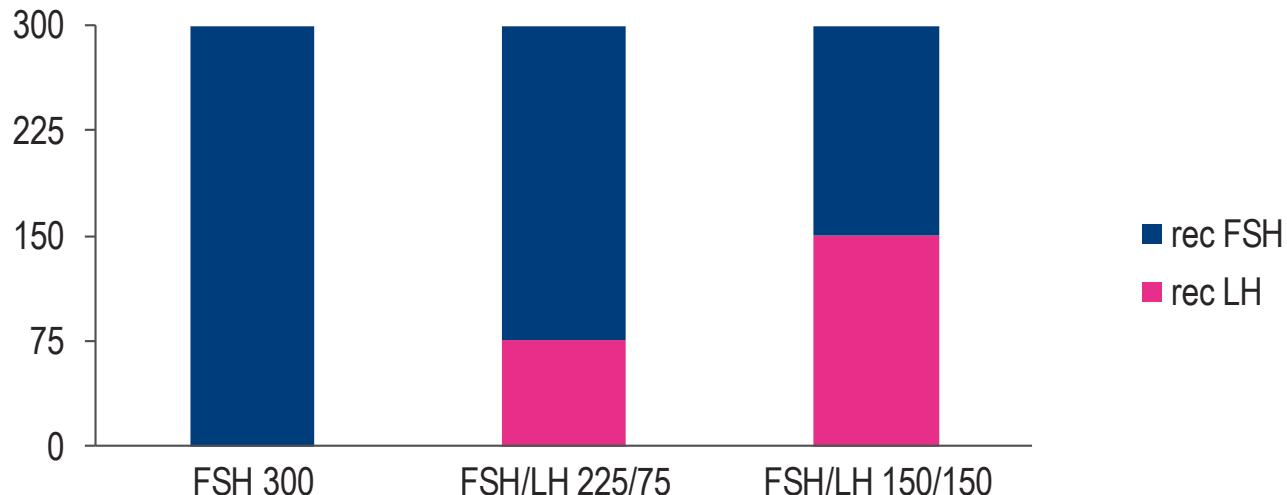
Impact of LH administration in COS for IVF

- 30 oocyte donors (< 35 years, normogonadotrophic)
- Long protocol: GnRH agonist + intranasal nafarelin

Bosch E, et al. Fertil Steril. 2006;86:Suppl.2:S425.
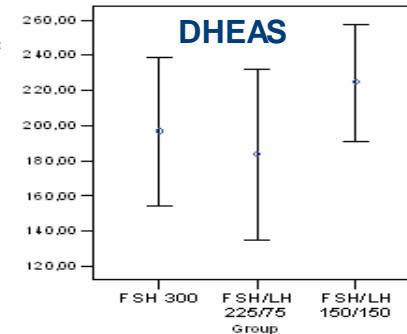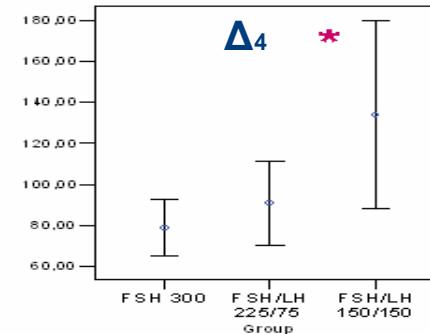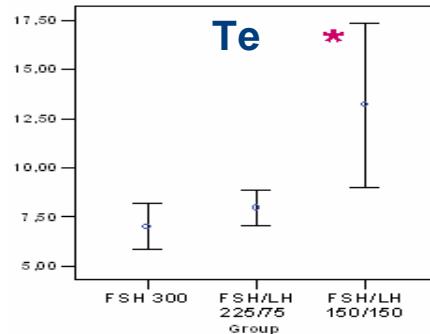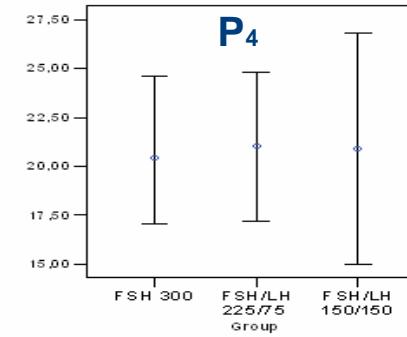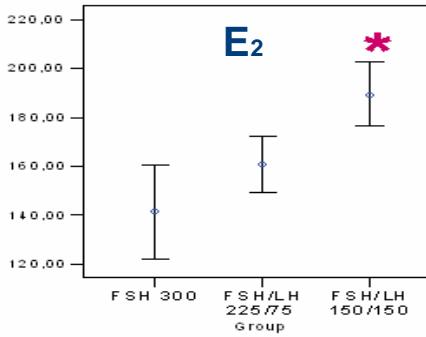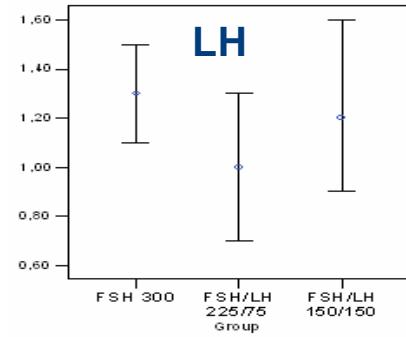
Impact of LH administration in COS for IVF

Serum hormone determinations on day of hCG

	FSH 300 IU	FSH/LH 225/75 IU	FSH/LH 150/150 IU	p
E2 (pg/mL)	2662	2208	2700	NS
P4 (ng/mL)	1.1	0.6	0.6	NS
FSH (mIU/mL)	13.4[a]	8.6[b]	7.5[b]	0.009 (a > b)
LH (mIU/mL)	2.0	1.6	2.2	NS
Te (ng/mL)	0.6	0.5	0.8	NS
Δ4 (ng/mL)	2.7	2.4	2.9	NS
DHEAS (µg/dL)	206	190	192	NS

Bosch E, et al. Fertil Steril. 2006;86:Suppl.2:S425.

Impact of LH administration in COS for IVF

Follicular fluid hormone determinations

Bosch E, et al. Fertil Steril. 2006;86:Suppl.2:S425.
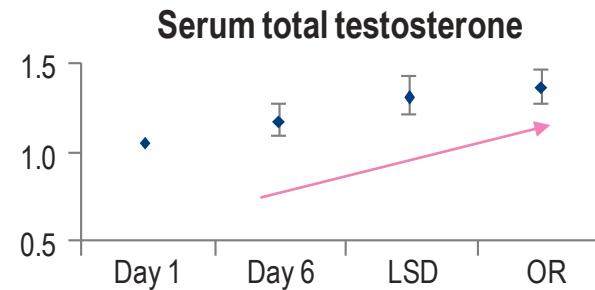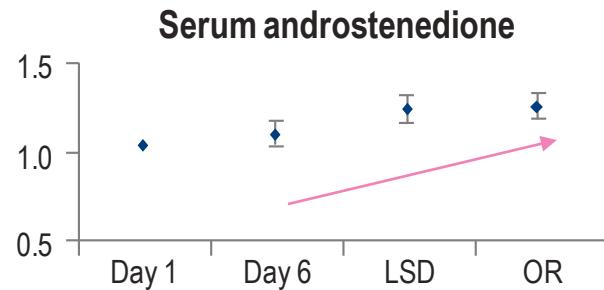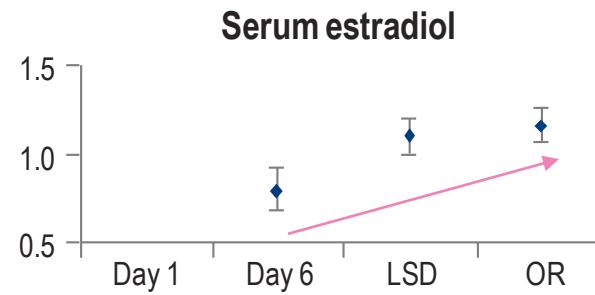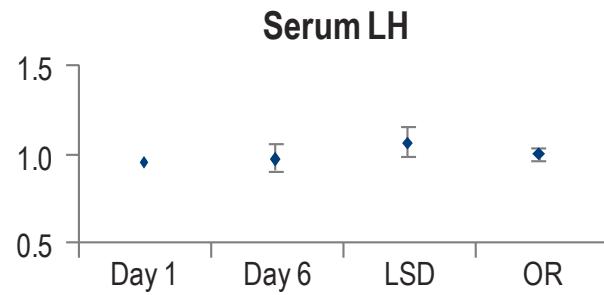
Impact of LH administration in COS for IVF

Relationship between follicular steroids levels and oocyte maturation
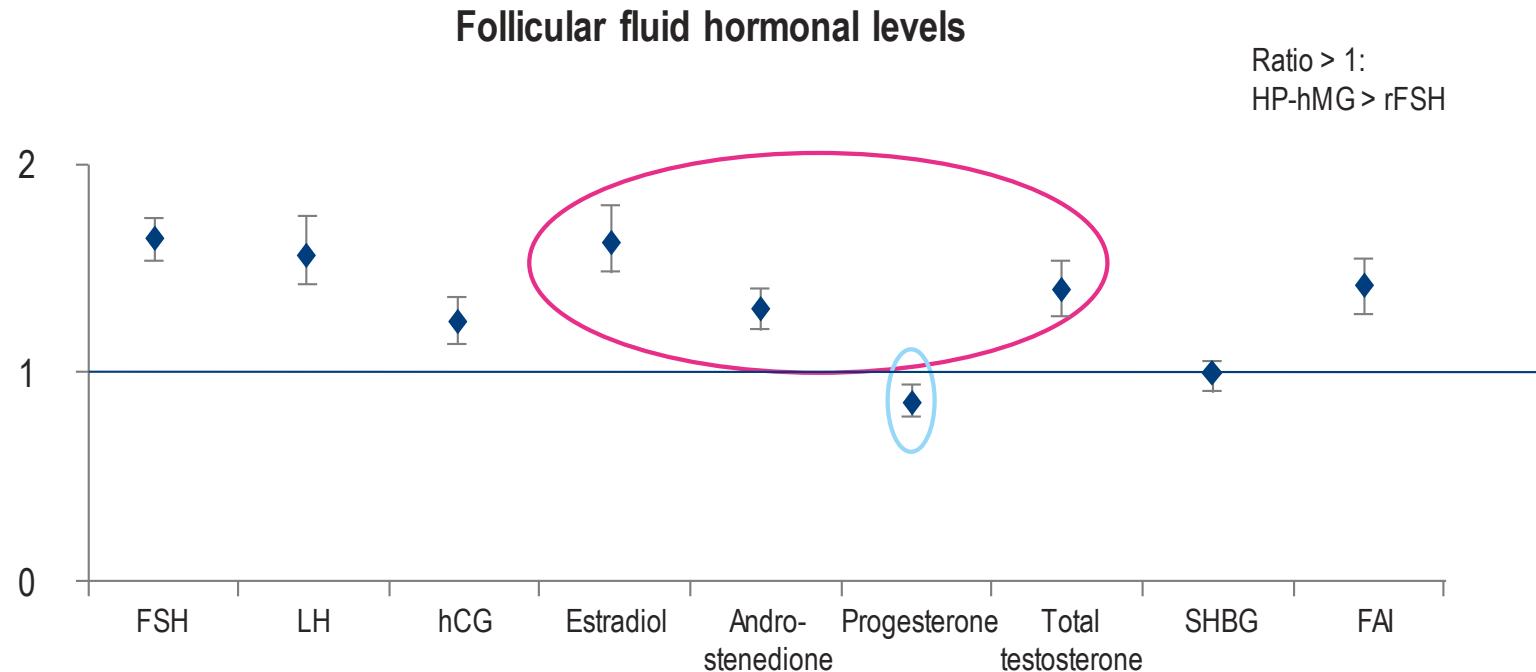
	Metaphase II	Metaphase I	GV	p
E2 (pg/mL)	165[a]	91	175[a]	0.04 (a > b)
P4 (ng/mL)	17.5	15.0	23.7	NS
LH (mIU/mL)	1.4	1.1	1.3	NS
Te (ng/mL)	7.8[b]	21.6	12.4	0.007 (a > b)
A (ng/mL)	94.1[b]	302	161	< 0.001 (a > b)
DHEAS (µg/dL)	219	270	228	NS

Bosch E, et al. Fertil Steril. 2006;86:Suppl.2:S425.

Impact of LH activity administration in COS for IVF

Serum hormonal profile during stimulation

Serum LH

Serum estradiol

Serum androstenedione

Serum total testosterone

Smitz J, et al. Hum Reprod. 2007;22:676-87.

Impact of LH activity administration in COS for IVF

Follicular fluid hormonal levels

Ratio > 1:
HP-hMG > rFSH

Smitz J, et al. Hum Reprod. 2007;22:676-87.
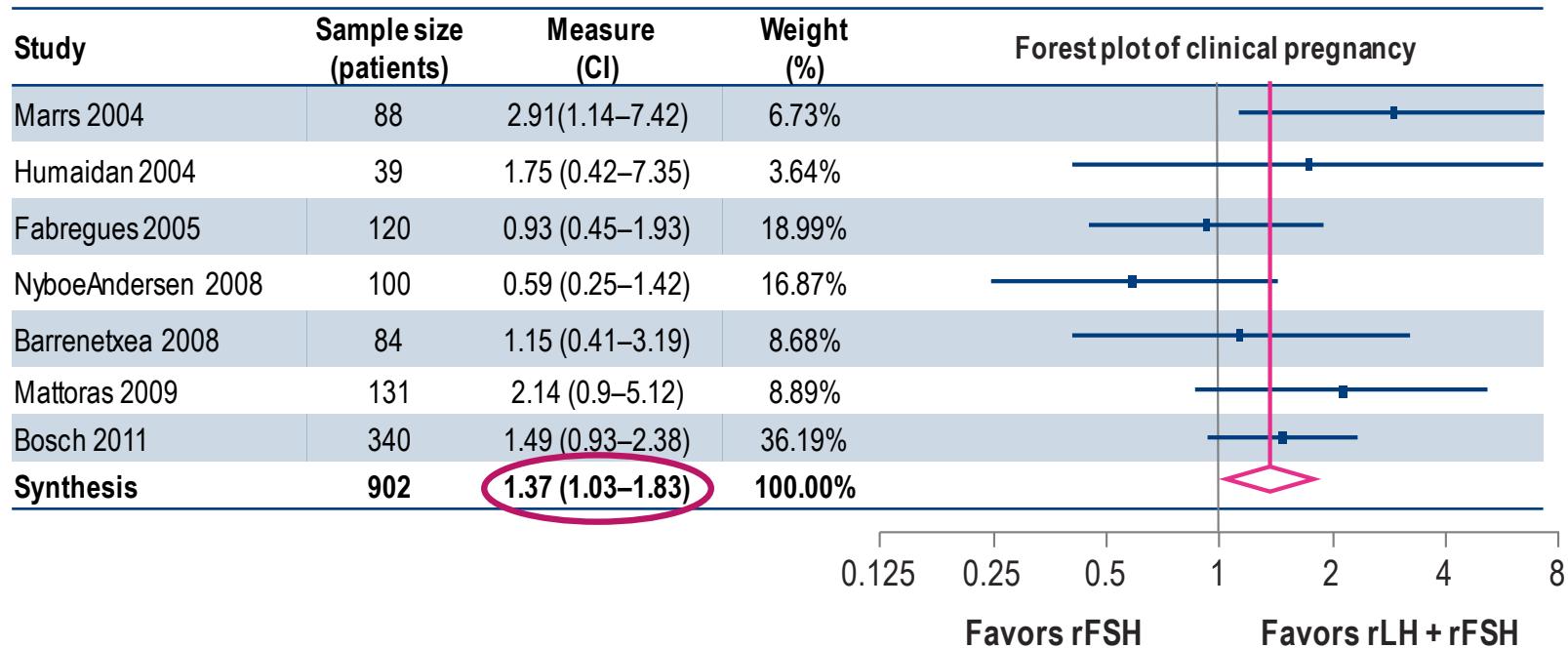
Impact of LH activity administration in COS for IVF

Ongoing pregnancy rate per started cycle transfer according to androgen levels

	FSH	FSH+LH	RR (95% CI)	p
Te ≤ 0.45 ng/mL	33.1	44.4	1.34 (0.98-1.85)	**0.06**
Te > 0.45 ng/mL	50.0	40.0	0.80 (0.53-1.20)	0.28
DHEAS ≤ 156 mcg/L	32.4	38.2	1.18 (0.82-1.69)	0.37
DHEAS > 156 mcg/L	47.3	43.4	0.92 (0.65-1.30)	0.63
Δ_4 ≤ 1.90 ng/mL	39.1	46.0	1.18 (0.87-1.60)	0.30
Δ_4 > 1.90 ng/mL	40.3	47.9	1.19 (0.82-1.72)	0.35

LH administration in the elderly patient

Study	Sample size (patients)	Measure (CI)	Weight (%)	Forest plot of clinical pregnancy
Marrs 2004	88	2.91 (1.14–7.42)	6.73%	
Humaidan 2004	39	1.75 (0.42–7.35)	3.64%	
Fabregues 2005	120	0.93 (0.45–1.93)	18.99%	
Nyboe Andersen 2008	100	0.59 (0.25–1.42)	16.87%	
Barrenetxea 2008	84	1.15 (0.41–3.19)	8.68%	
Mattoras 2009	131	2.14 (0.9–5.12)	8.89%	
Bosch 2011	340	1.49 (0.93–2.38)	36.19%	
Synthesis	**902**	**1.37 (1.03–1.83)**	**100.00%**	

0.125 0.25 0.5 1 2 4 8

Favors rFSH   **Favors rLH + rFSH**

Hill MJ, et al. Fertil Steril. 2012;97:1108-14.

LH administration in the elderly patient
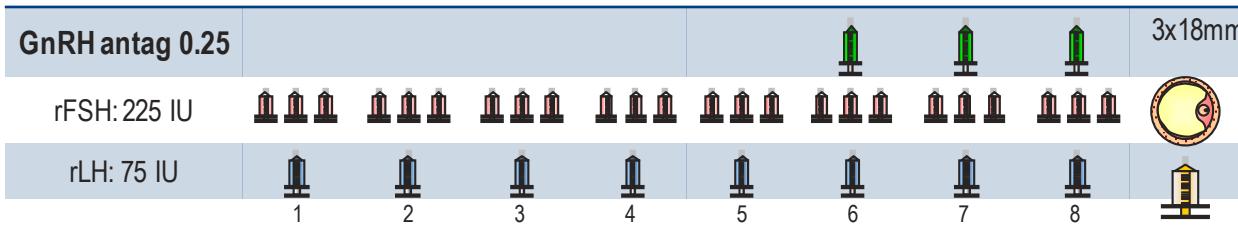
Study	Age	Protocol	LH administration
Marrs 2004	≥ 35	GnRH agonist long	150 UI from day 6
Humaidan 2004	≥ 35	GnRH agonist long	Ratio 2:1 from day 8
Fábregues 2006	≥ 35	GnRH agonist long	150 UI from day 6
NyboeAndersen 2008	≥ 35	GnRH agonist long	75 UI from day 6
Barrenechea 2008	≥ 40 or POR	Flare up	150 UI from day 7
Matorras 2009	35-39	GnRH agonist long	150 UI from day 6
Bosch 2011	36-39	Antagonist	75 UI from day 1

Hill MJ, et al. Fertil Steril. 2012;97:1108-14.

Impact of LH administration on GnRH-releasing hormone antagonist cycles: an age-adjusted analysis
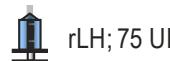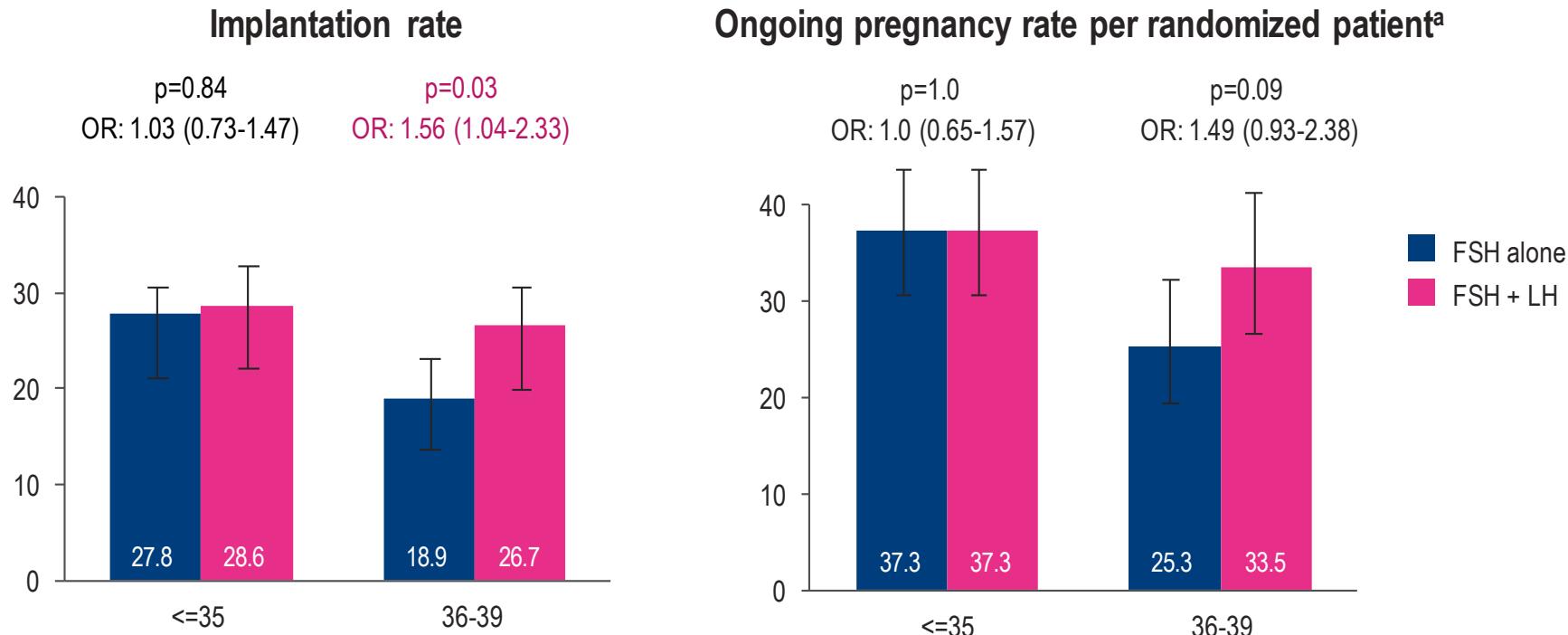
Previous cycle: OC (0.030 mg of etinyl-estradiol + 3.0 mg of drospirenone)

Bosch E, et al. Fertil Steril. 2011;95:1031-6.

Impact of LH administration on GnRH-releasing hormone antagonist cycles: an age-adjusted analysis

≤ 35	FSH (n=172)	FSH + LH (n=161)	P
E2 on day of hCG (pg/ml)	1.542	1.625	0.436
P on day of hCG (ng/ml)	0.85	0.69	**0.002**
No. of oocytes	11.3	10.9	0.180
No. of MII (ICSI)	7.8	7.3	0.255
Fertilization rate	67.4	67.4	0.998
No. of transferred embryos	1.9	1.9	0.488
OHSS	5.3	7.0	0.493
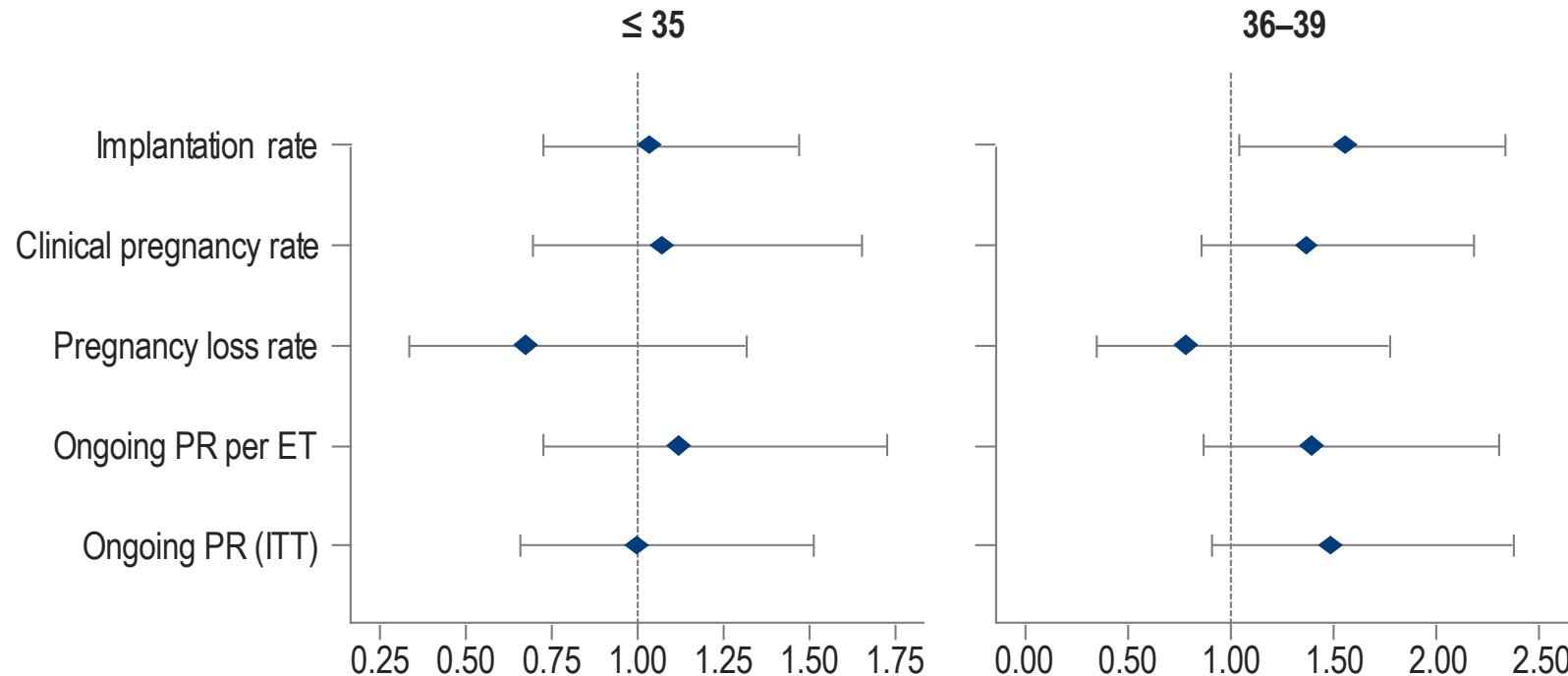
36-39	FSH (n=142)	FSH + LH (n=150)	P
E2 on day of hCG (pg/ml)	1.388	1.560	0.064
P on day of hCG (ng/ml)	0.89	0.67	**< 0.01**
No. of oocytes	10.1	8.4	**0.008**
No. of MII (ICSI)	7.0	6.6	0.303
Fertilization rate	61.2	68.0	**0.027**
No. transferred embryos	1.7	1.9	0.109
OHSS	5.0	3.0	0.360

Bosch E, et al. Fertil Steril. 2011;95:1031-6.

Impact of LH administration on GnRH-releasing hormone antagonist cycles: an age-adjusted analysis

Implantation rate

p=0.84
OR: 1.03 (0.73-1.47)

p=0.03
OR: 1.56 (1.04-2.33)

Ongoing pregnancy rate per randomized patient[a]

p=1.0
OR: 1.0 (0.65-1.57)

p=0.09
OR: 1.49 (0.93-2.38)

FSH alone
FSH + LH

[a] ITT analysis.

Bosch E, et al. Fertil Steril. 2011;95:1031-6.

Impact of LH administration on GnRH-releasing hormone antagonist cycles: an age-adjusted analysis

Bosch E, et al. Fertil Steril. 2011;95:1031-6.
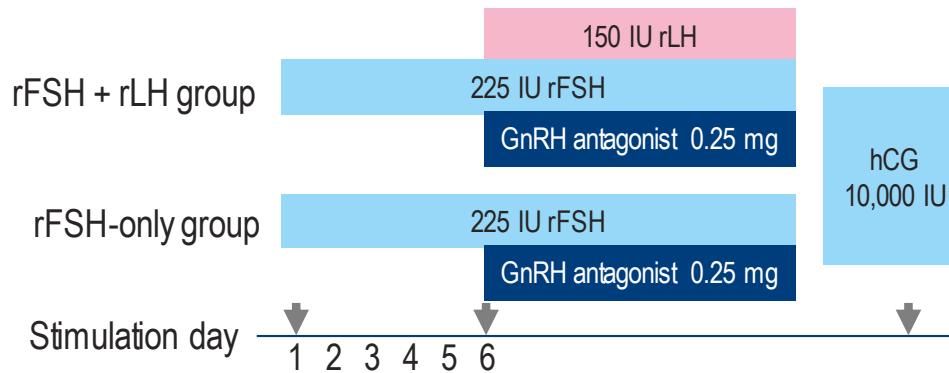
LH administration in Bologna patients

Observed (unadjusted) live birth rates according to BSC and treatment group

BSC	Patients with a previous ART cycle	Patients with no previous ART cycle	r-hFSH/r-hLH (N = 462)		r-hFSH (N = 477)	
			n (%)	Live birth rate, n (%)	n (%)	Live birth rate, n (%)
0 (mild)	< 40 years old **AND** previous ART cycle with ≥ 2 oocytes retrieved	< 40 years old **AND** AMH > 0.5 ng/ml	170 (36.8)	18 (10.6)	156 (32.7)	34 (21.8)
1 (moderate)	≥ 40 years old **OR** previous ART cycle with < 2 oocytes retrieved	≥ 40 years old **OR** AMH ≤ 0.5 ng/ml	209 (45.2)	23 (11.0)	254 (53.3)	19 (7.5)
2 (severe)	≥ 40 years old **AND** previous ART cycle with < 2 oocytes retrieved	≥ 40 years old **AND** AMH ≤ 0.5 ng/ml	83 (18.0)	8 (9.6)	67 (14.0)	3 (4.5)
Overall			462 (100.0)	49 (10.6)	477 (100.0)	56 (11.7)

BSC, baseline severity score.

Humaidan P, et al. Hum Reprod. 2017;32:544-55.

Different findings when LH is started on Day 6

	rFSH (n = 128)	rFSH + rLH (n = 125)	p value
Oocyte retrieval	123	120	
Total oocytes	10.9	10.2	0.38
Fertilization rate (%)	58.1	58.2	0.97
Total embryos	6.6	5.6	0.11
No. of patients per protocol	113	116	
Clinical pregnancies	38 (33.6)	35 (30.2)	0.78
Ongoing pregnancies	28 (24.8)	25 (21.6)	0.76
Implantation rate (%)	23.5	20.3	0.84

König TE, et al. Hum Reprod. 2013;28:2804-12.

Different findings when LH is started on Day 6

	rFSH n or n/N	(n=120) Value	rFSH/rLH n or n/N	(n = 120) Value	Between-group difference (95% CI)	p value
Ovarian stimulation						
Oocytes, n	102	8 (5, 11)	109	7 (4,11)	1 (−1−3)	0.516
Embryos, n	102	4 (3, 6)	109	3 (2, 6)	1 (−1−2)	0.321
Good embryos	101	1 (1, 2)	107	1 (0, 2.5)	0 (−1−1)	0.519
Embryos cryopreserved	96	0 (0, 2)	106	0 (0, 2)	0 (0−0)	0.866
Embryo transfer						
No. transferred	93	2 (2, 3)	100	2 (1, 3)	0 (−1.0−1.0)	0.272
Clinical pregnancy rate	27/120	22.5%	27/120	22.5%	0.0 (−10.6−10.6)	1.0
Implantation rate	93	11.13	100	12.47	−1.34 (−9.48−6.81)	0.746
Miscarriage rate	6/120	5.0%	7/120	5.8%	−1.8 (−8.0−4.7)	0.554
Ovarian hyperstimulation	0/120	0.0%	0/120	0.0%	0.0 (0.0−0.0)	−
Live birth rate	21/120	17.5%	20/120	16.7%	0.8 (−9.5−11.2)	0.864

Different findings when LH is started on Day 6

Reply: Comment on 'Recombinant LH supplementation to a standard GnRH antagonist protocol in women of 35 years or older undergoing IVF/ICSI: a randomized controlled multicentre study'

LH supplementation from stimulation Day 6 onwards does not seem to be beneficial. However, we agree that there might be a potential beneficial effect of LH supplementation from stimulation Day I in an antagonist cycle especially with pretreatment of oral contraceptives in this specific group of older women. Further studies are indeed necessary to address this issue.

Bosch E. Hum Reprod. 2014;29:636-7.

Take-home messages

- Women in their late reproductive stage are the most frequent group of patients undergoing IVF

- The aging ovary shows a different endocrine basal situation, but also a different follicular environment and a different response to rFSH, suggesting a thecal insufficiency

- LH administration enhances follicular steroidogenesis, increasing the synthesis of androgens for their later aromatization to estrogens

- This function seems to be beneficial for women > 35 undergoing COS for IVF
  - To achieve this improvement, LH should be administered from the first day of stimulation