Gonadotropin role & administration strategies in 2009: bases & new trends

Salvador, Brazil – May 8-9, 2009

LH administration for low responders

Jean-Noel Hugues

Fertility Merck Serono Meeting

Individualized Treatment

MERCK SERONO FERTILIDADE

LH administration for low responders

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Gonadotroin role & administration strategies in 2009
Bases & new trends

Salvador , Brazil. May 8 - 9, 2009

Low - Poor responders to COH

No consensus on definition

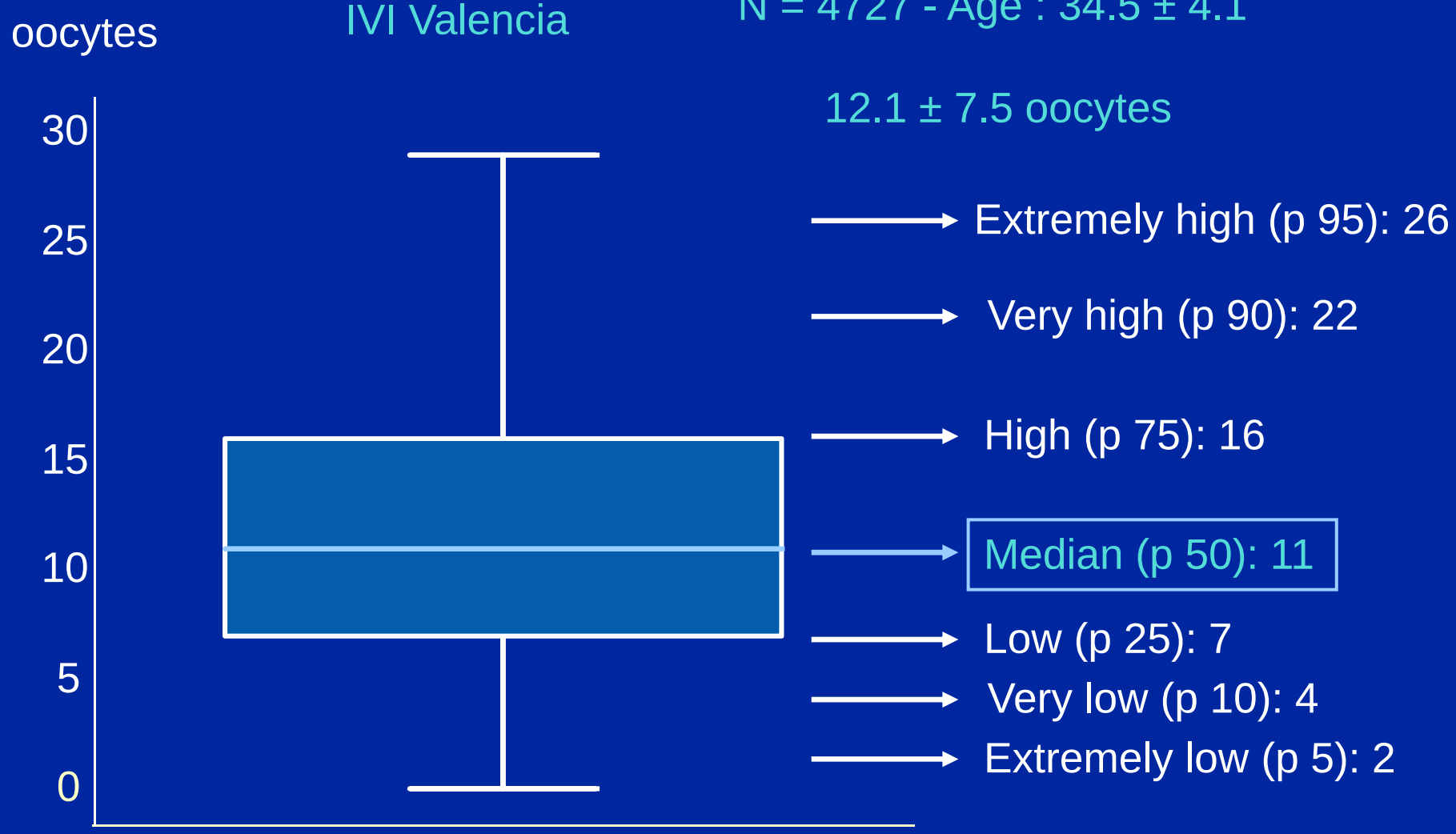
- Plasma E2 levels
  - < 700 pg/mL
  - < 300 pg/mL
  - < 100 pg/mL
- Follicle - Oocyte numbers
  - < 3
  - < 4
  - < 5
- Cycle cancellation

Inadequate response : Quantitative concept

IVI Valencia

N = 4727 - Age : 34.5 ± 4.1

12.1 ± 7.5 oocytes



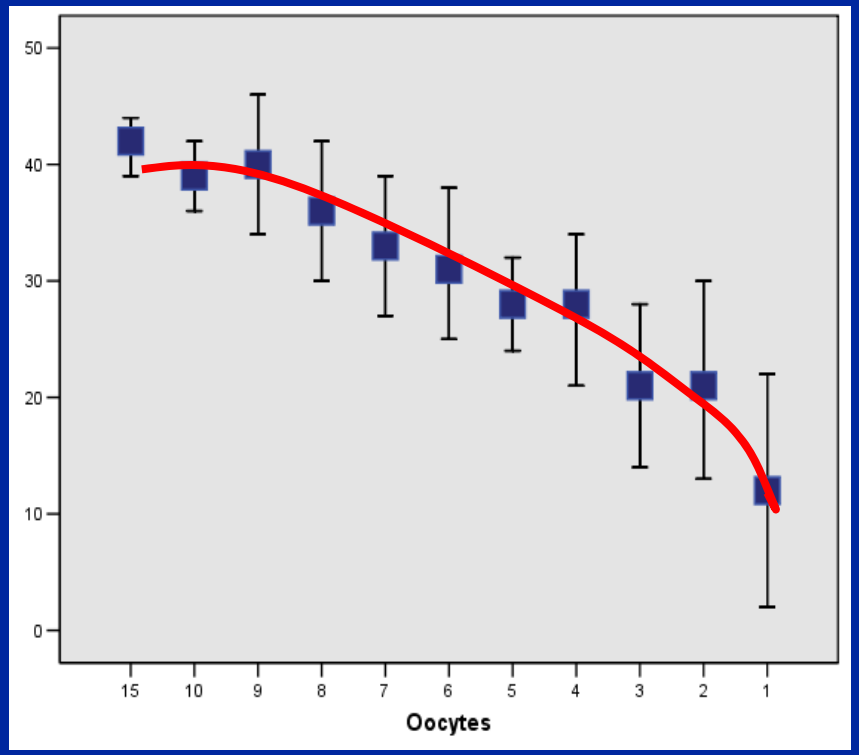
Low responders : < 7 oocytes

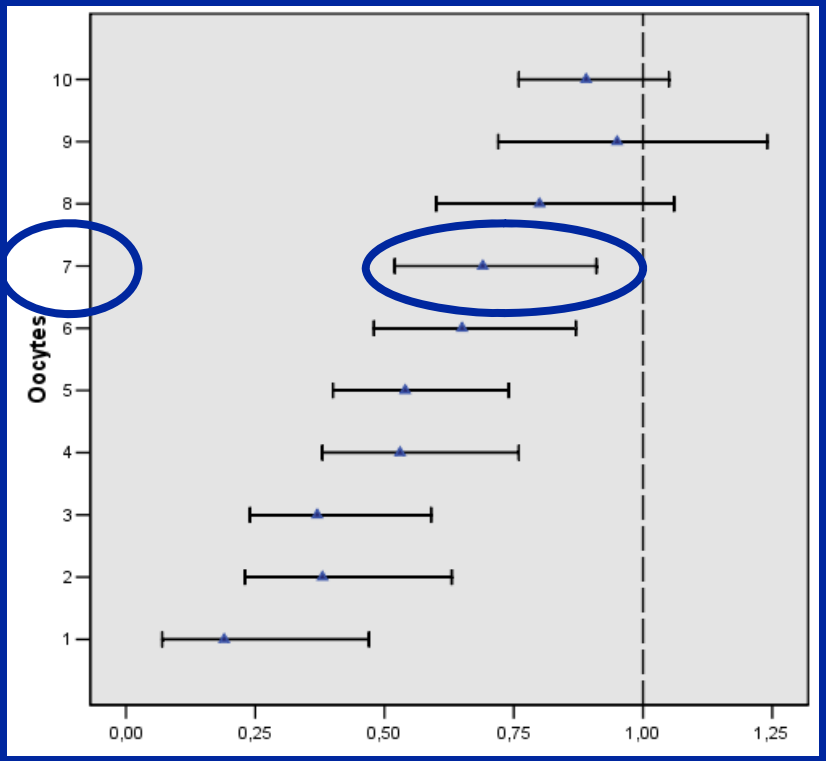
Inadequate response : Quantitative concept

Ongoing PR

* M-H test for trend

*p < 0.000001



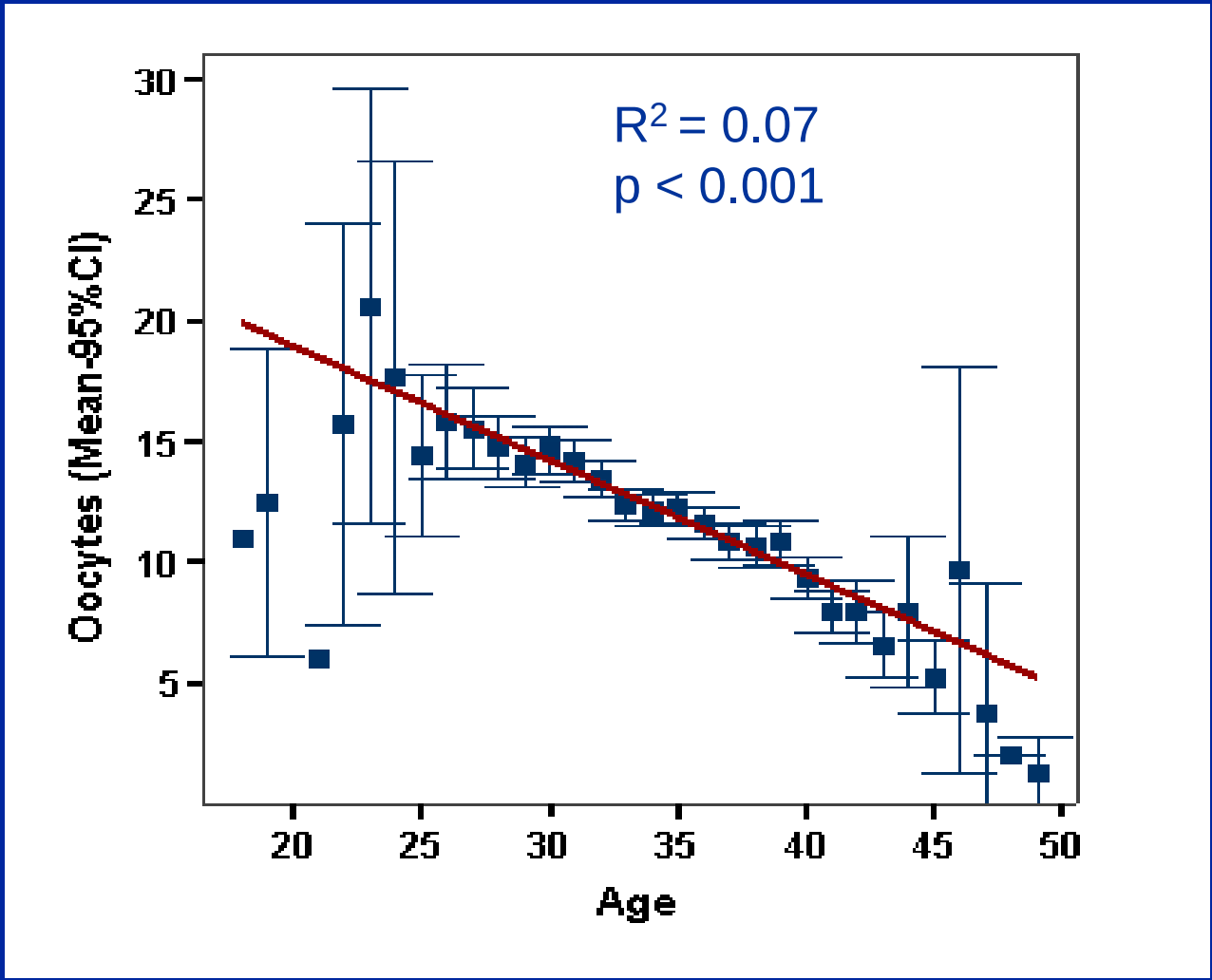


OR (CI 95%)
0.90 (0.76-1.05)
0.95 (0.72-1.24)
0.80 (0.60-1.06)
0.69 (0.520.91)*
0.65 (0.48-0.87)*
0.54 (0.40-0.74)*
0.54 (0.38-0.76)*
0.38 (0.24-0.59)*
0.38 (0.23-0.63)*
0.19 (0.07-0.47)*

Clear relationship between nb of oocytes and pregnancy rate

Relative comparison : below 7 oocytes significant reduction in pregnancy rate

Age related inadequate response



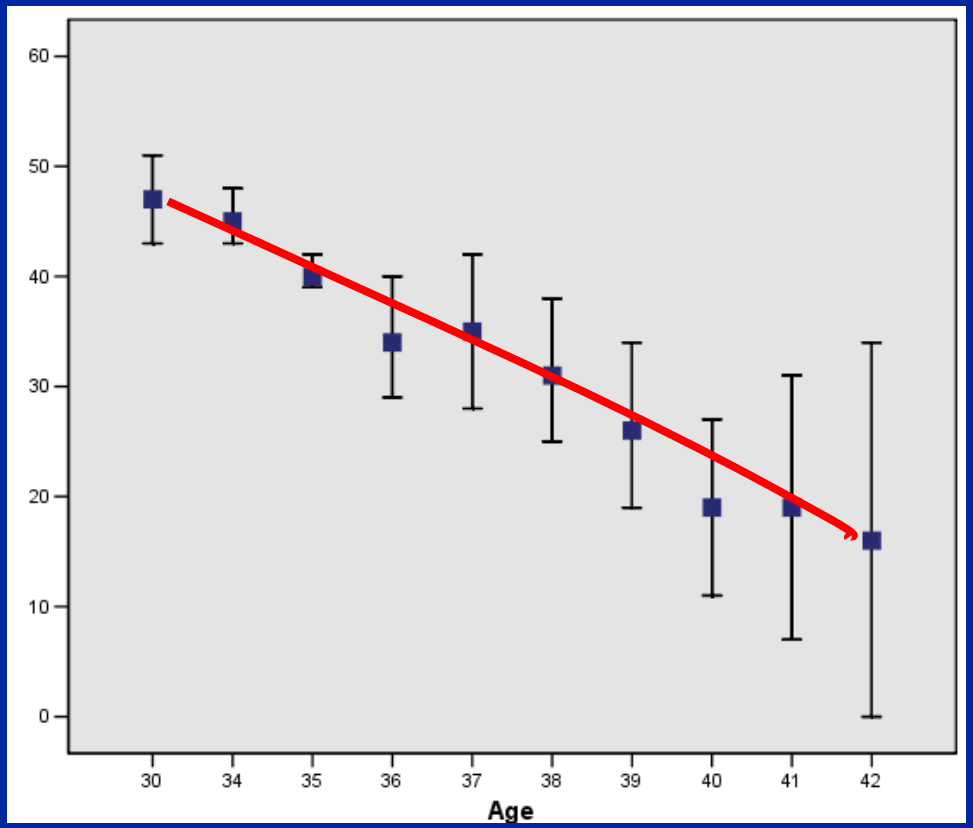
Significant correlation between number of oocytes and age

Inadequate response: Qualitative concept

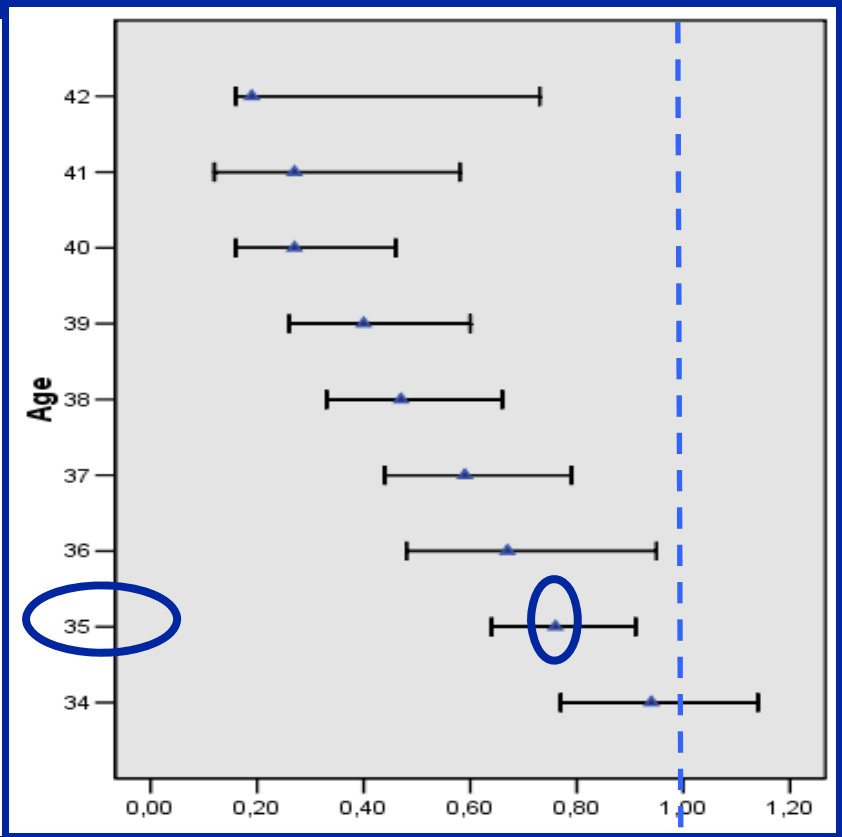
Ongoing pregnancy rate when oocytes ≥ 8

* M-H test for trend

*p < 0.000001



Significant correlation between age and pregnancy rate

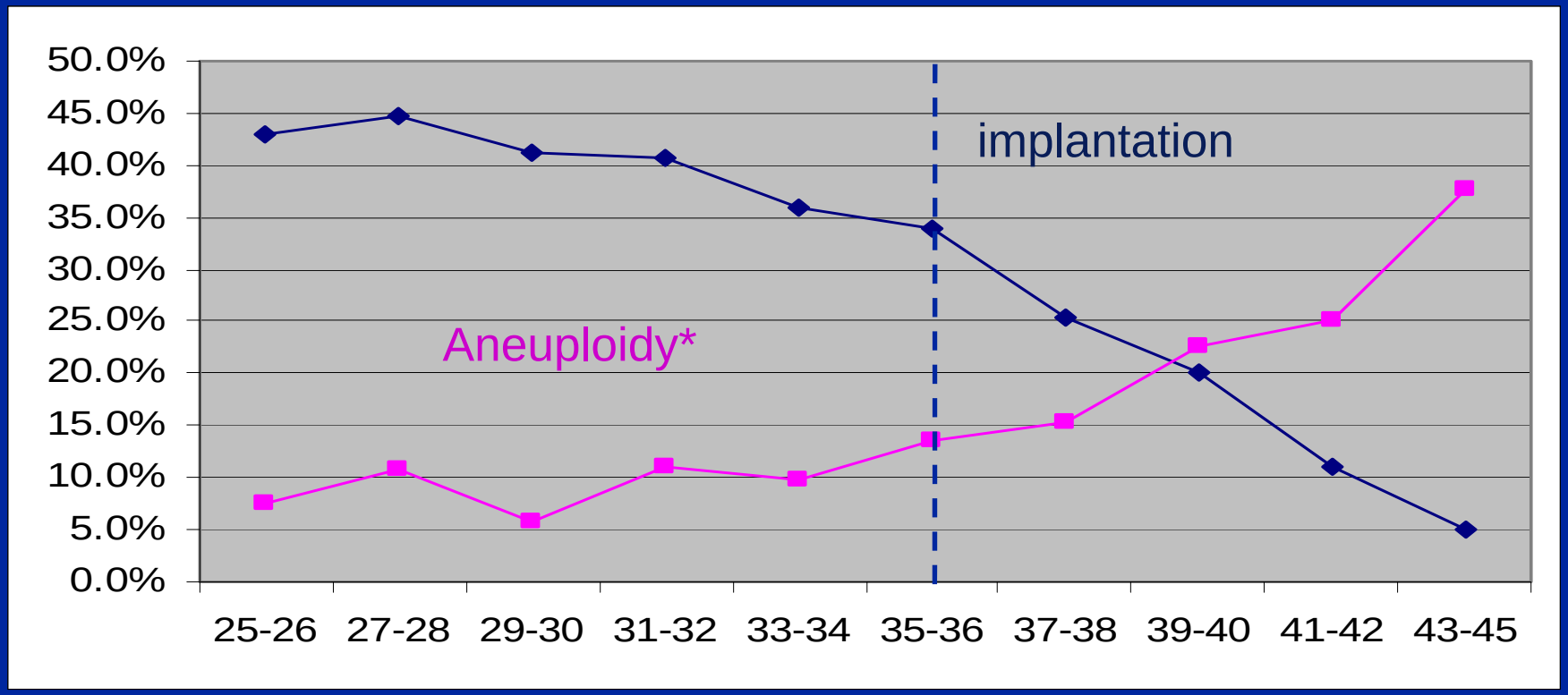


OR (CI 95%)
0.21 (0.06-0.73)*
0.27 (0.12-1.59)*
0.27 (0.16-0.46)*
0.40 (0.26-0.61)*
0.47 (0.33-0.66)*
0.59 (0.44-0.79)*
0.67 (0.48-0.95)*
0.76 (0.64-0.91)*
0.94 (0.77-1.14)

Pregnancy rate is significantly reduced in women aged ≥ 35 yrs

Ovarian Ageing is associated with

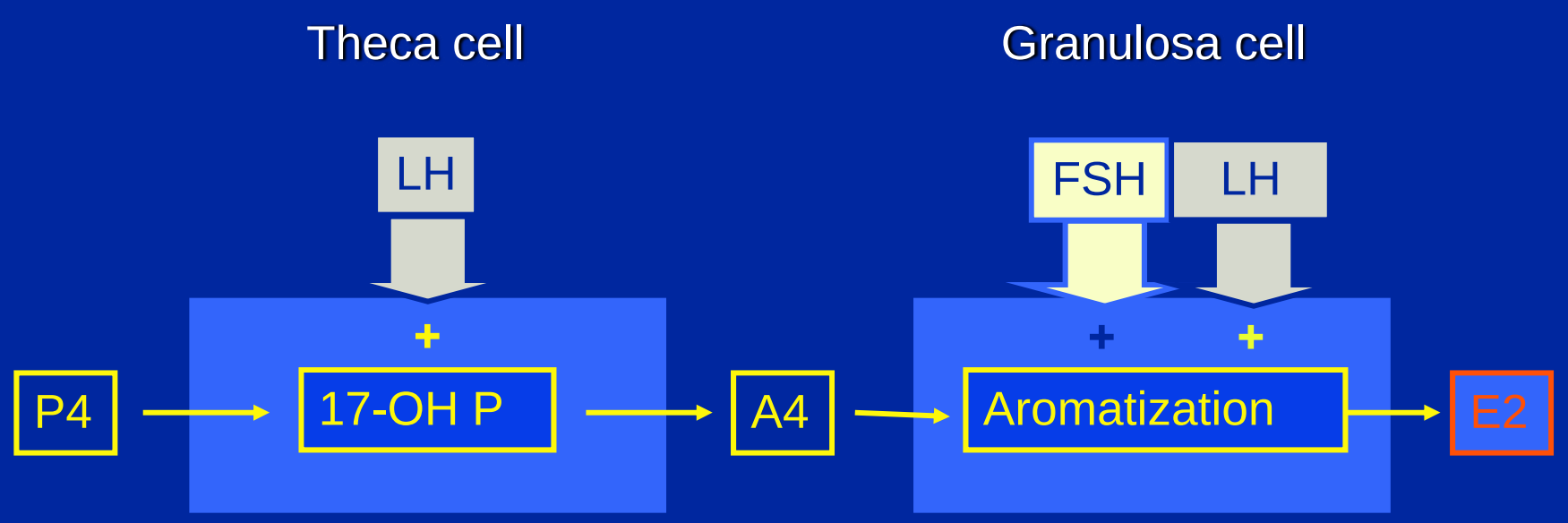
1. Reduced no. harvested oocytes with high FSH dose
2. Reduced quality of oocytes with age
   - Increase in aneuploidy (Munne et al 1995)



Rationale to use LH supplementation

- Effects of LH on ovarian function
- Concept of LH window
- Thecal cell function according to the age

Differential effects of LH activity according to the stage of folliculogenesis



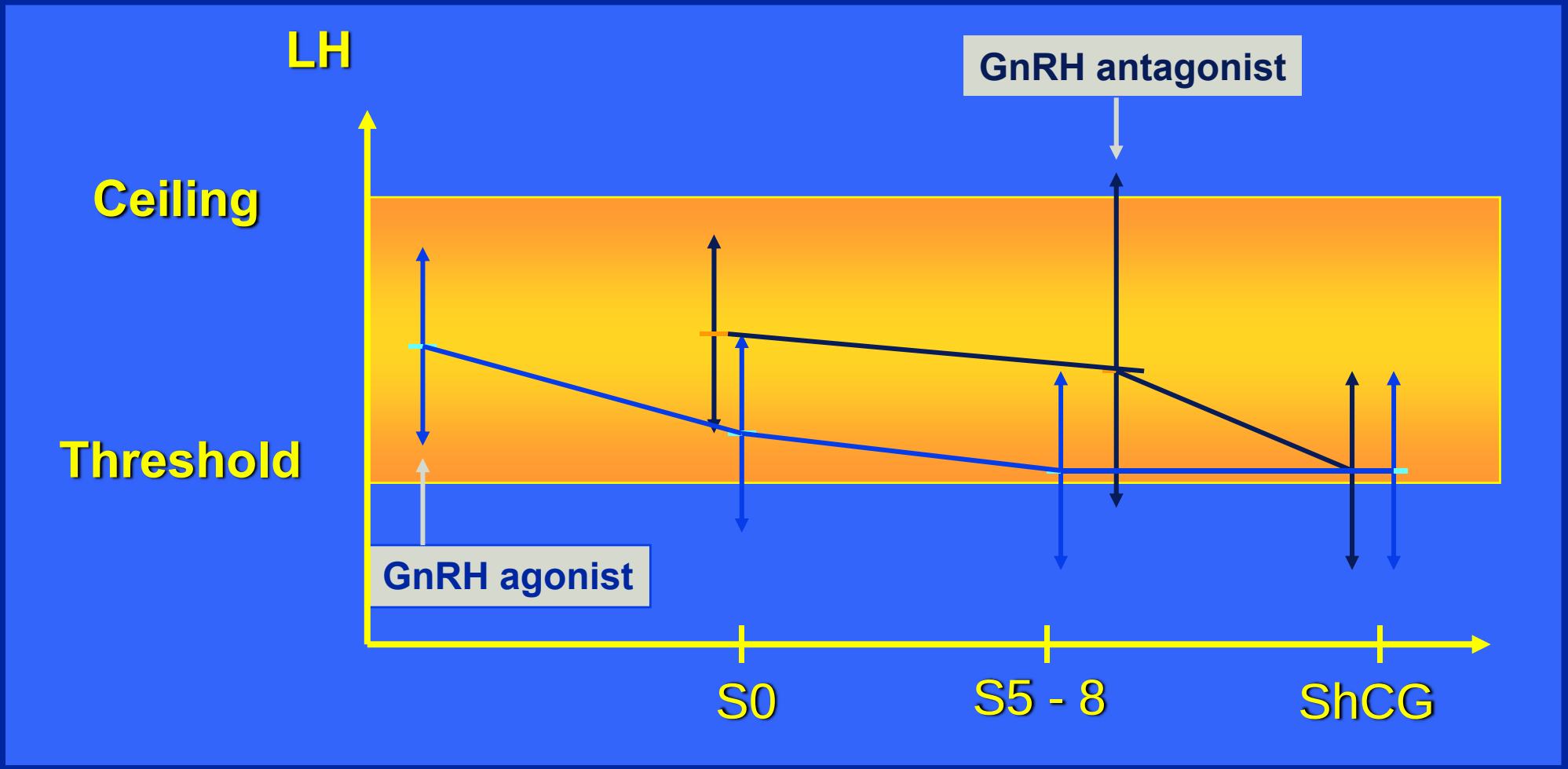
Early foll. phase

Late foll. Phase (Foll > 12 mm)

LH supplementation
- increases androgen synthesis
- stimulates follicular recruitment

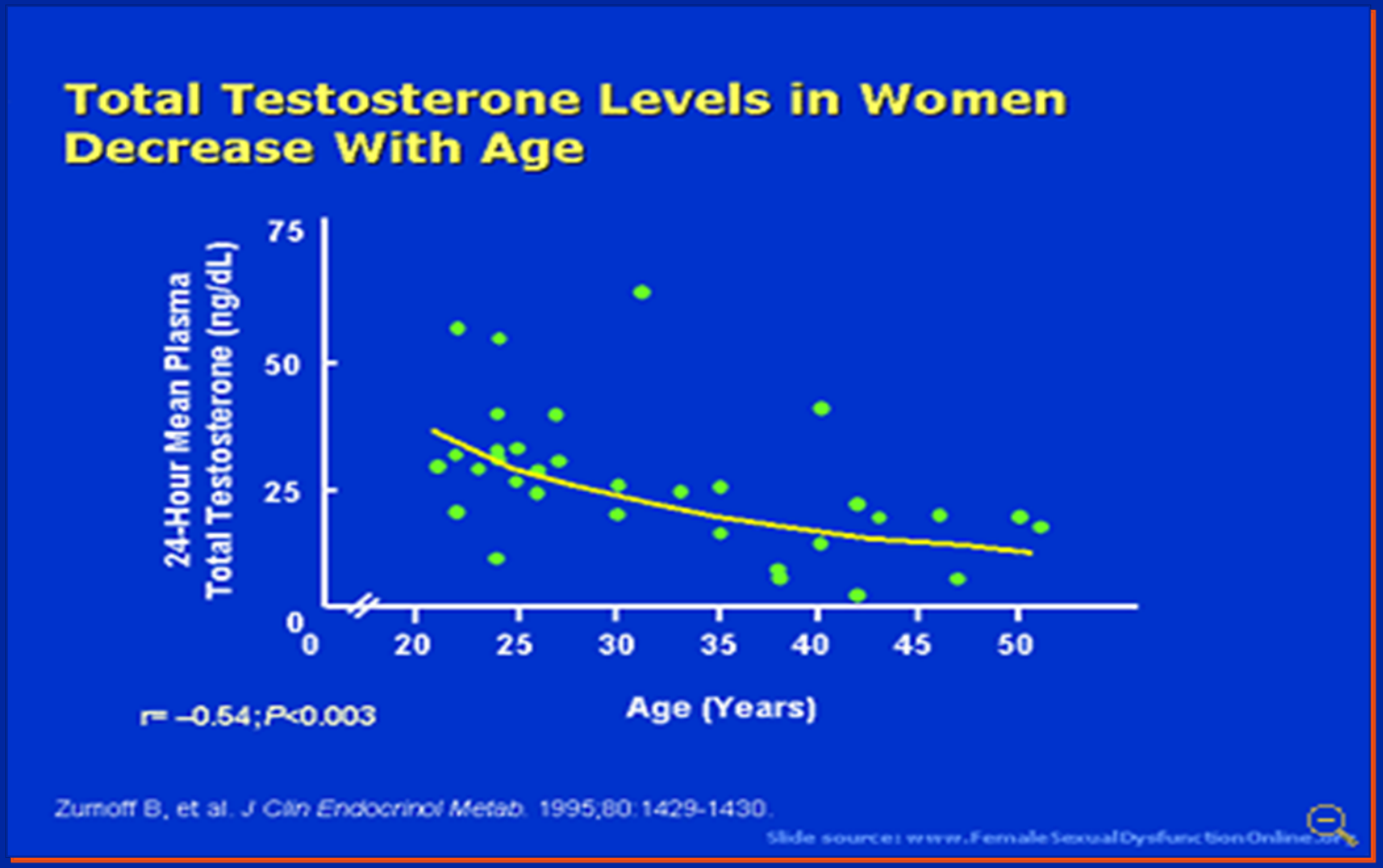
LH supplementation
- increases oestrogen synthesis
- controls follicular growth

Follicular phase LH window



Need for an optimal LH supply to ensure adequate folliculogenesis

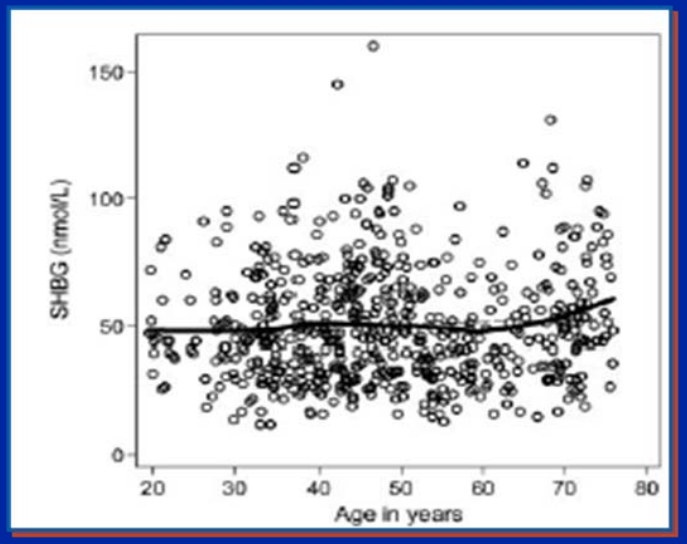
The ageing ovary: endocrinological changes



Zumoff et al JCEM 1995;80:1429

The ageing ovary: endocrinological changes

n = 1423

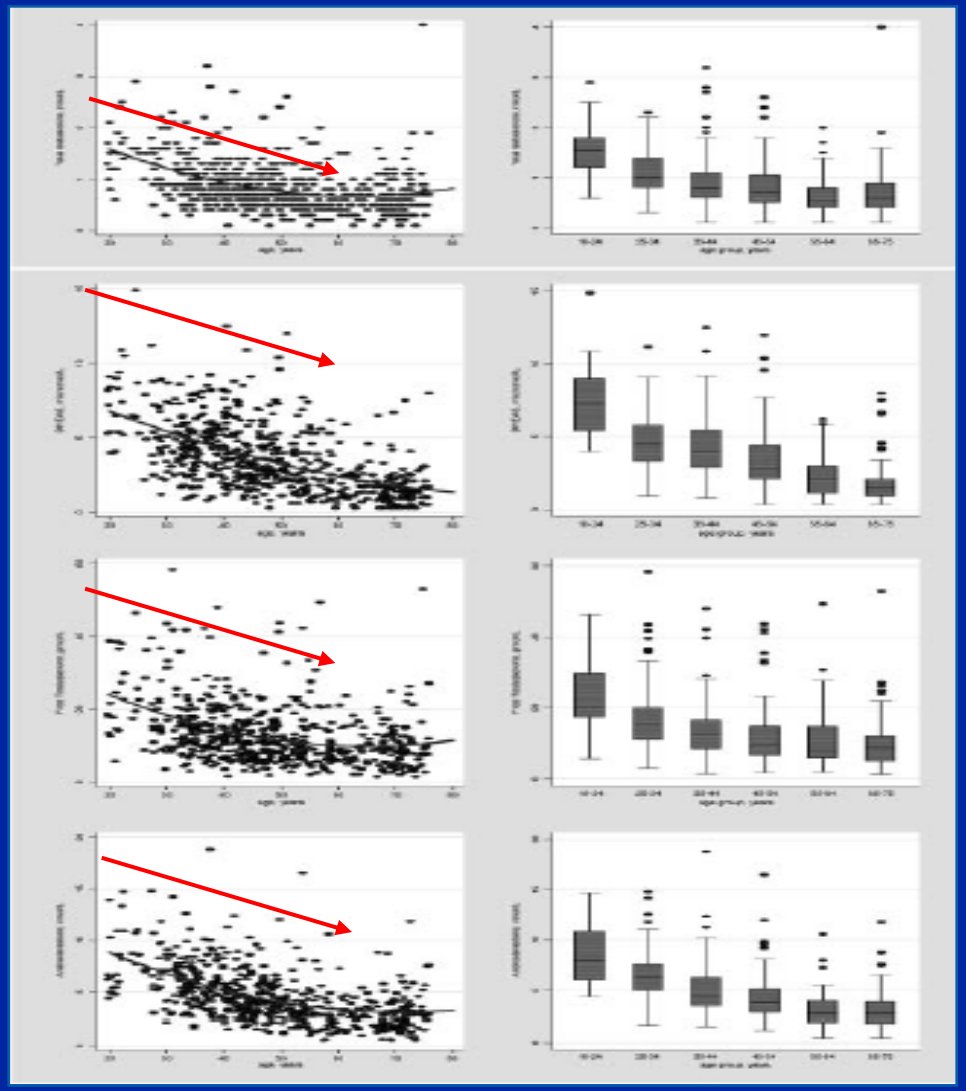


Total Testosterone ↓ 55%

DHEAS ↓ 77%

Free Testosterone ↓ 49%

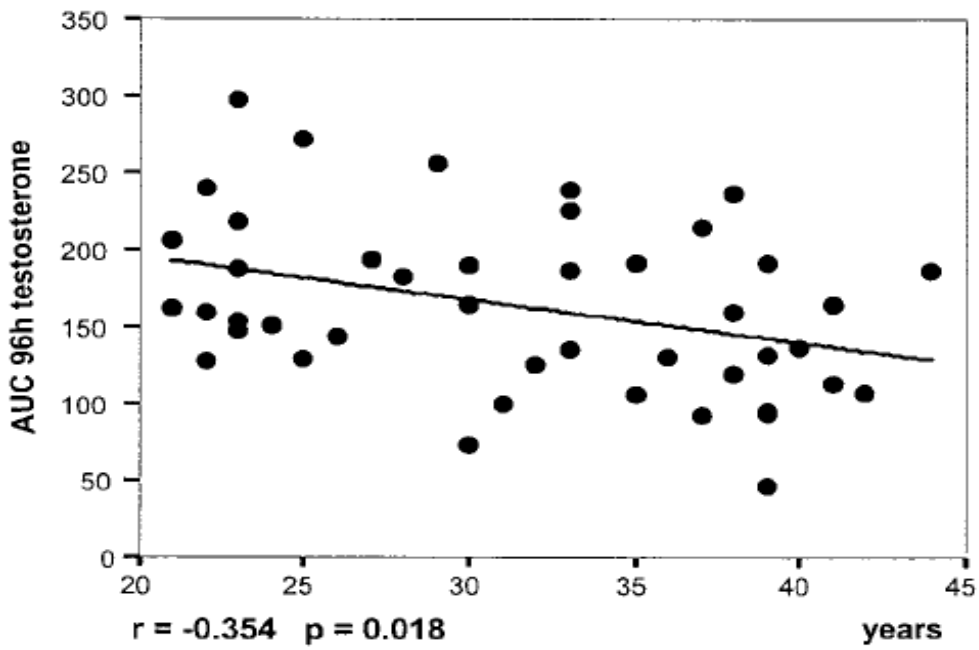
Androstenedione ↓ 64%



Davison et al JCEM 2005

Ovarian Age-Related Responsiveness to Human Chorionic Gonadotropin

TERHI PILTONEN, RIITTA KOIVUNEN, AIMO RUOKONEN, AND JUHA S. TAPANAINEN



- To study age-related changes in androgen secretion and ovarian capacity to synthesize/release androgens in response to hCG test (5000 IU) in women aged 20–44 yr.
- The responses of 17-OHP, A, and T to hCG, *i.e.* areas under the curves (AUC; 96 h), correlated negatively with age (17-OHP: r 0.427;*P* 0.004; A: r 0.266; *P* 0.081; T: r 0.354; *P* 0.018

JCEM 2003

LH supplementation for IVF/ICSI-ET

Which improvement can be expected?

Ovarian effect

- better follicular recruitment
- higher number of

total oocytes - fertilized oocytes - high quality embryos

Endometrial effect

improved implantation rate

LH supplementation for IVF/ICSI-ET

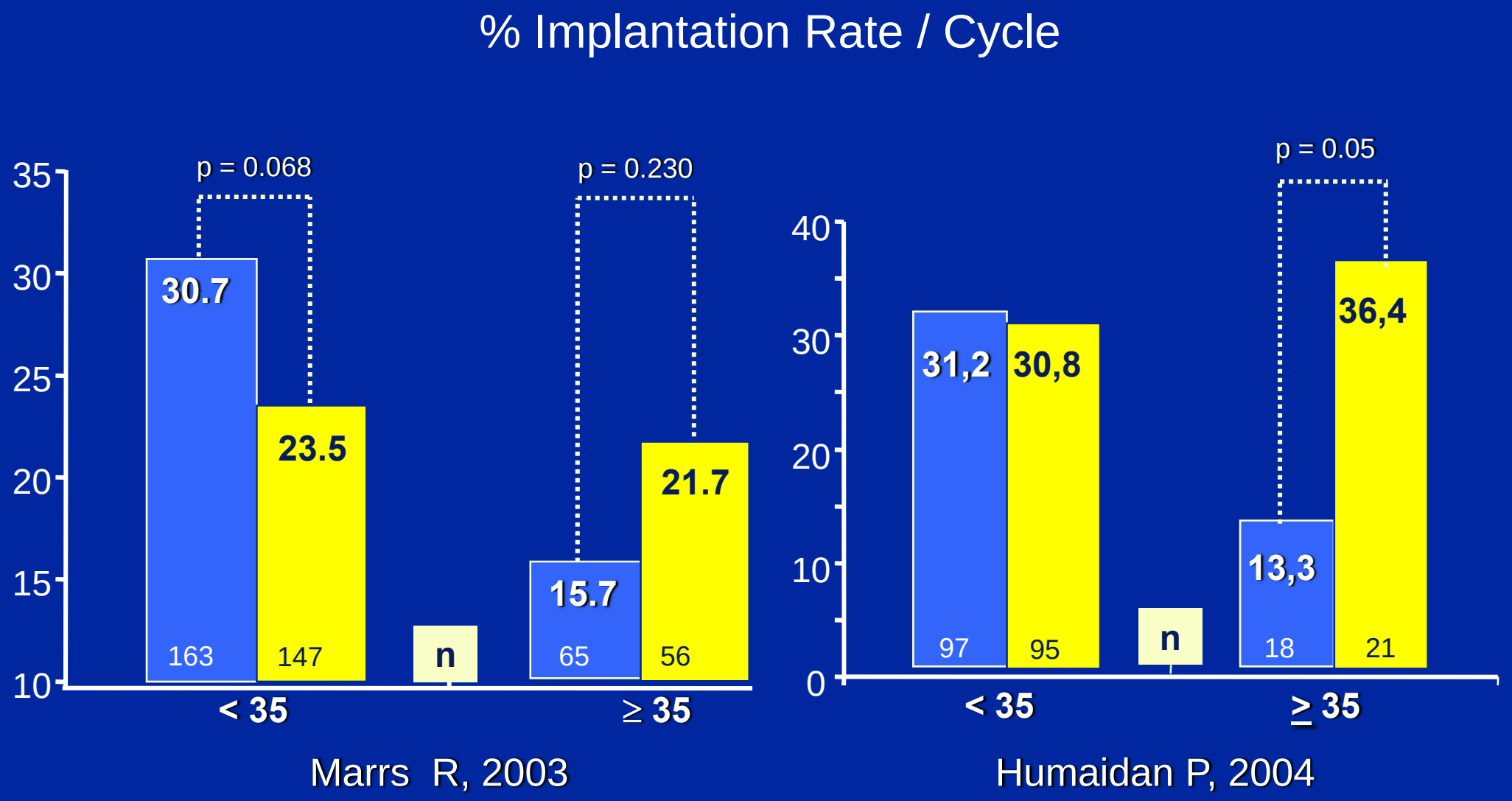
- Controverted topic
- Confusing evidences
- Lack of consensus
  - No benefit in unselected population
  - Potential benefit in low / poor response
  - Profound LH suppression in GnRH agonist long protocol
  - Better outcome in patients > 35 years old ?

Mochtar et al, 2007 Cochrane Database Syst Rev.18: 2

Effects of LH supplementation

in women over the age of 35

LH supplementation (from S8) according to the age



Nordic LH Study Group Treatment protocol

- Down-regulation from day 21 with nafarelin 200 μg IN x 3 for 2 weeks, followed by 200 μg x 2 during stimulation

- Randomisation on stimulation day 1 to :
  - rFSH + rLH from day 6 of stimulation (n = 261)
  - rFSH alone from day 6 of stimulation (n = 265)

Patients	≤ 35 years	> 35 years
R FSH	150 IU /d	225 IU /d
R LH	75 IU / d	150 IU /d

Nordic LH Study Group

Ongoing pregnancy according to women 's age

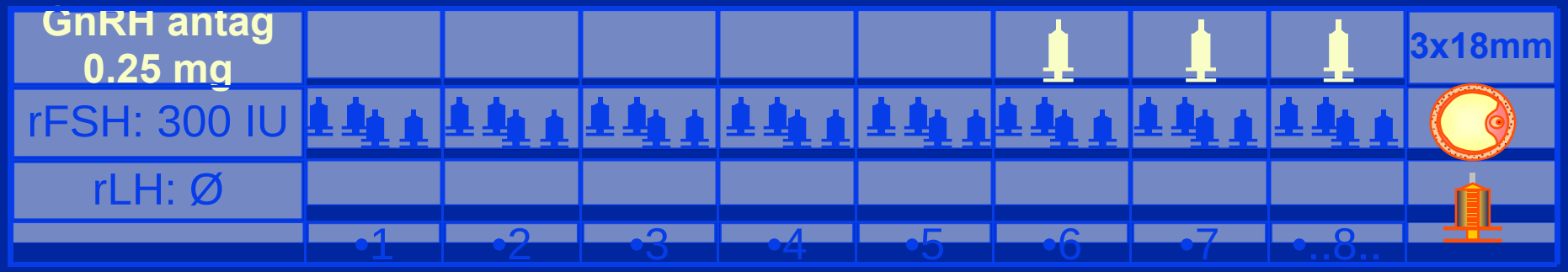
	(≤ 35 years)		(> 35 years)	
	rFSH	rFSH + rLH	rFSH	rFSH + rLH
	(n = 210)	(n = 216)	(n = 51)	(n = 49)
Clinical pregnancy	70 (33.3%)	69 (31.9%)	18 (35.3%)	14 (28.6%)
Live pregnancy	67 (31.9%)	67 (31.0%)	18 (35.3%)	12 (24.5%)
Ongoing pregnancy	58 (27.6%)	64 (29.6%)	17 (33.3%)	8 (16.3%)
	p = 0.67		p = 0.065	

Protocol GnRH antagonist in 36-39 yr old women

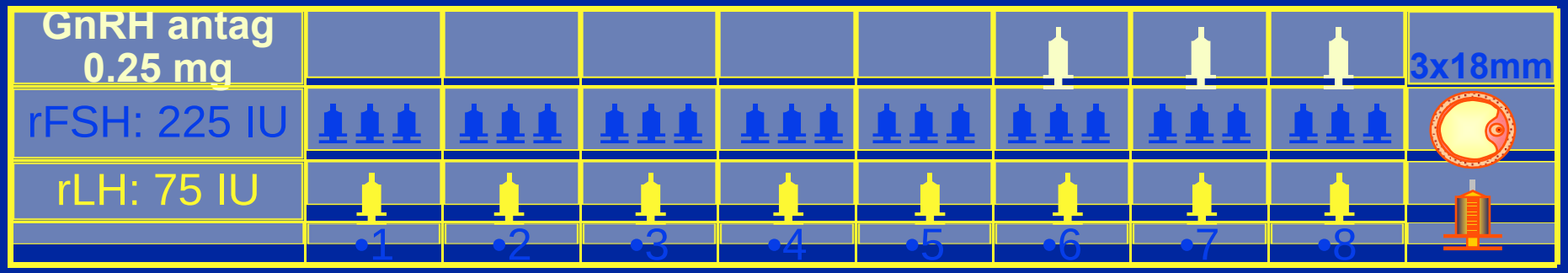
Previous cycle: OC (0.030 mg of etinyl-estradiol + 3.0 mg of drospirenone)

Bosch et al., ASRM 2008

FSH alone



FSH + LH



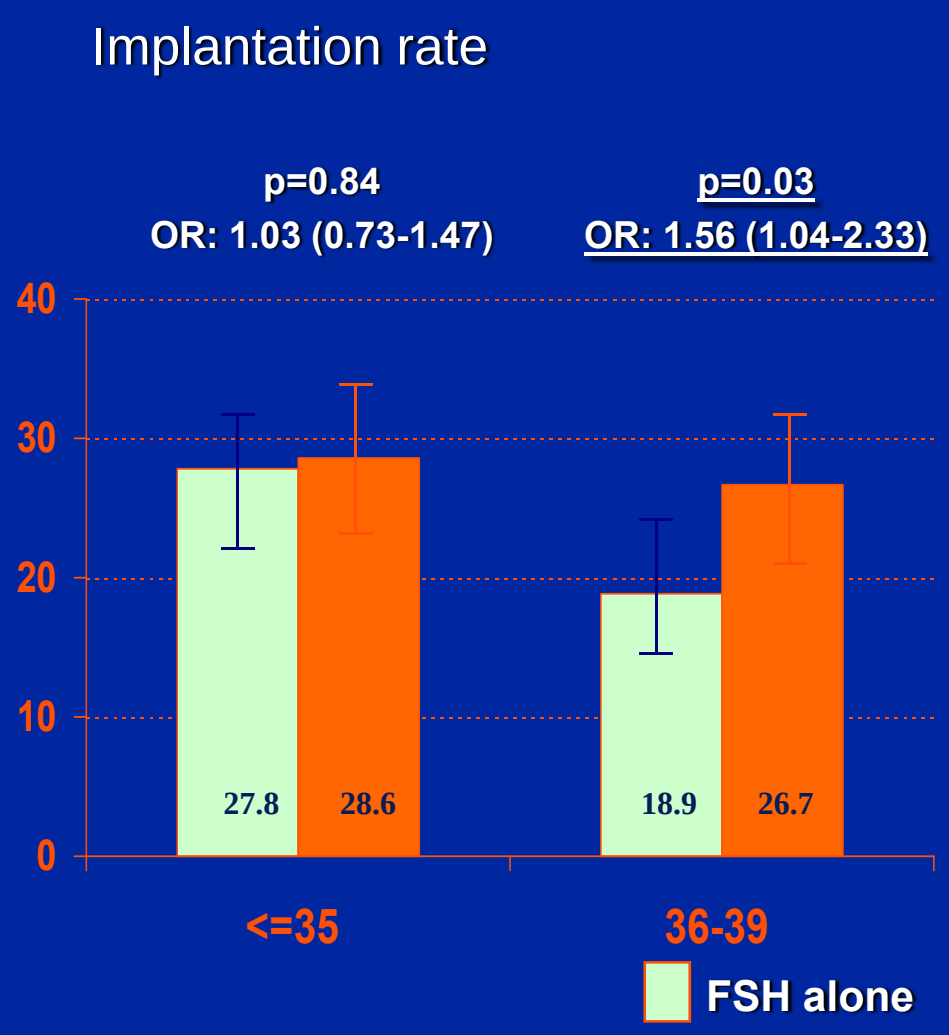
rFSH: 75 UI **rLH: 75 UI** **Cetrorelix: 0.25 mg** **rCG: 6500 UI**

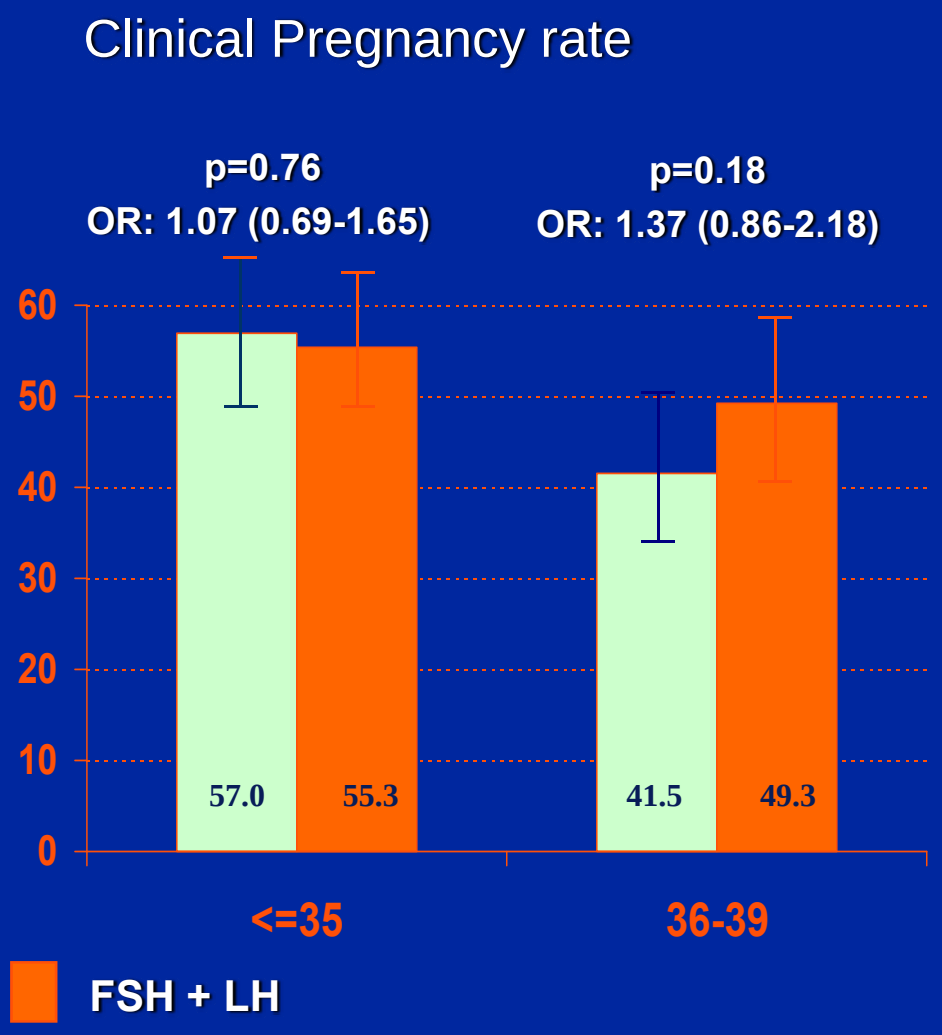
Ovarian stimulation outcome (36-39)

•	FSH (n=142)		FSH + LH (n=150)		*P*-value
• Total Gn dose (IU)	2562	724	3355	998	< 0.001
• Days of stimulation	10.3	1.9	10.6	1.89	0.088
• E_2 on day of hCG (pg/ml)	1388	721	1560	806	0.064
• P on day of hCG (ng/ml)	0.89	0.44	0.67	0.38	< 0.001
• Nº of oocytes	10.1	6.3	8.4	4.5	0.008
• Nº of Metaphase II (ICSI)	7.0	4.3	6.6	3.1	0.303
• Fertilization rate	61.2	27.3	68.0	25.0	0.027
• Nº Transferred embryos	1.7	0.7	1.9	0.8	0.109
• Nº Cryopres. embryos	1.2	2.1	0.7	1.3	0.008
•Ovarian Hyperstimulation	5.0 (2.1-9.6)		3.0 (1.0-6.8)		0.360

Bosch et al., ASRM 2008

Reproductive outcome





FSH alone

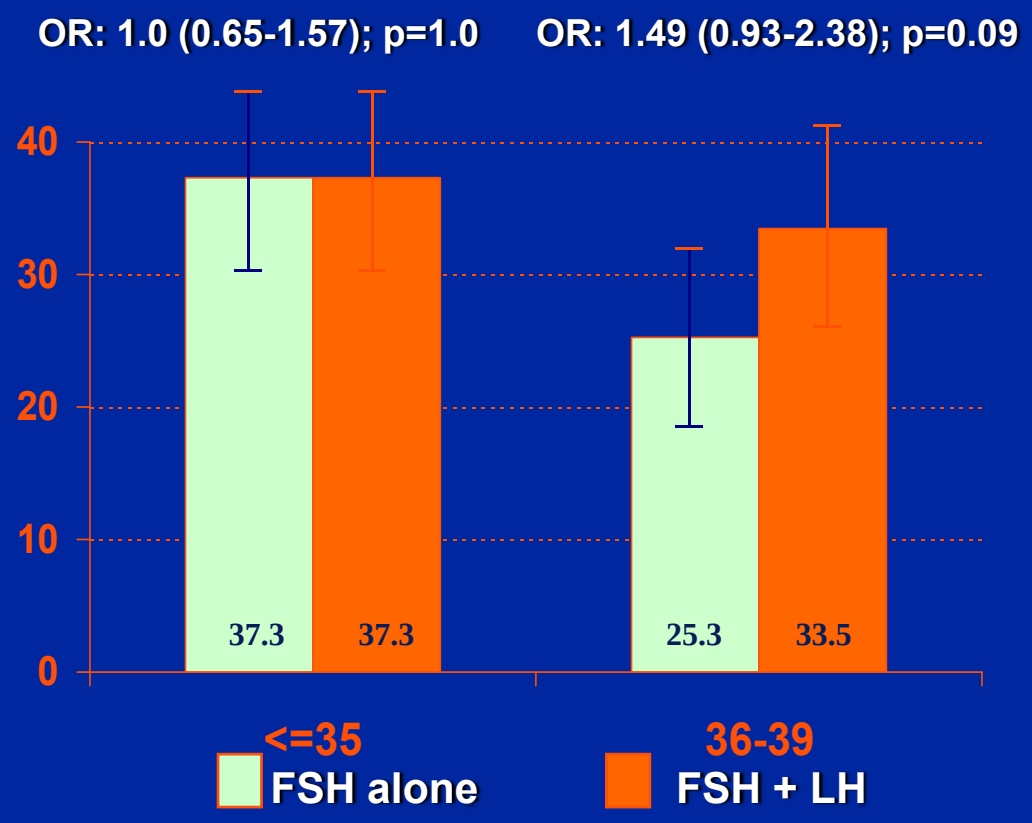
FSH + LH

Barrs represent mean and whiskers the 95% CI

Bosch et al., ASRM 2008

Reproductive outcome

Ongoing Pregnancy rate per Randomized patient (ITT analysis)



Bosch et al., ASRM 2008

Barrs represent mean and whiskers the 95% CI

Effects of LH supplementation over the age of 35

No evidence for improvement in ovarian parameters

LH supplementation from the S1 ?

Implantation rate : improved in some studies

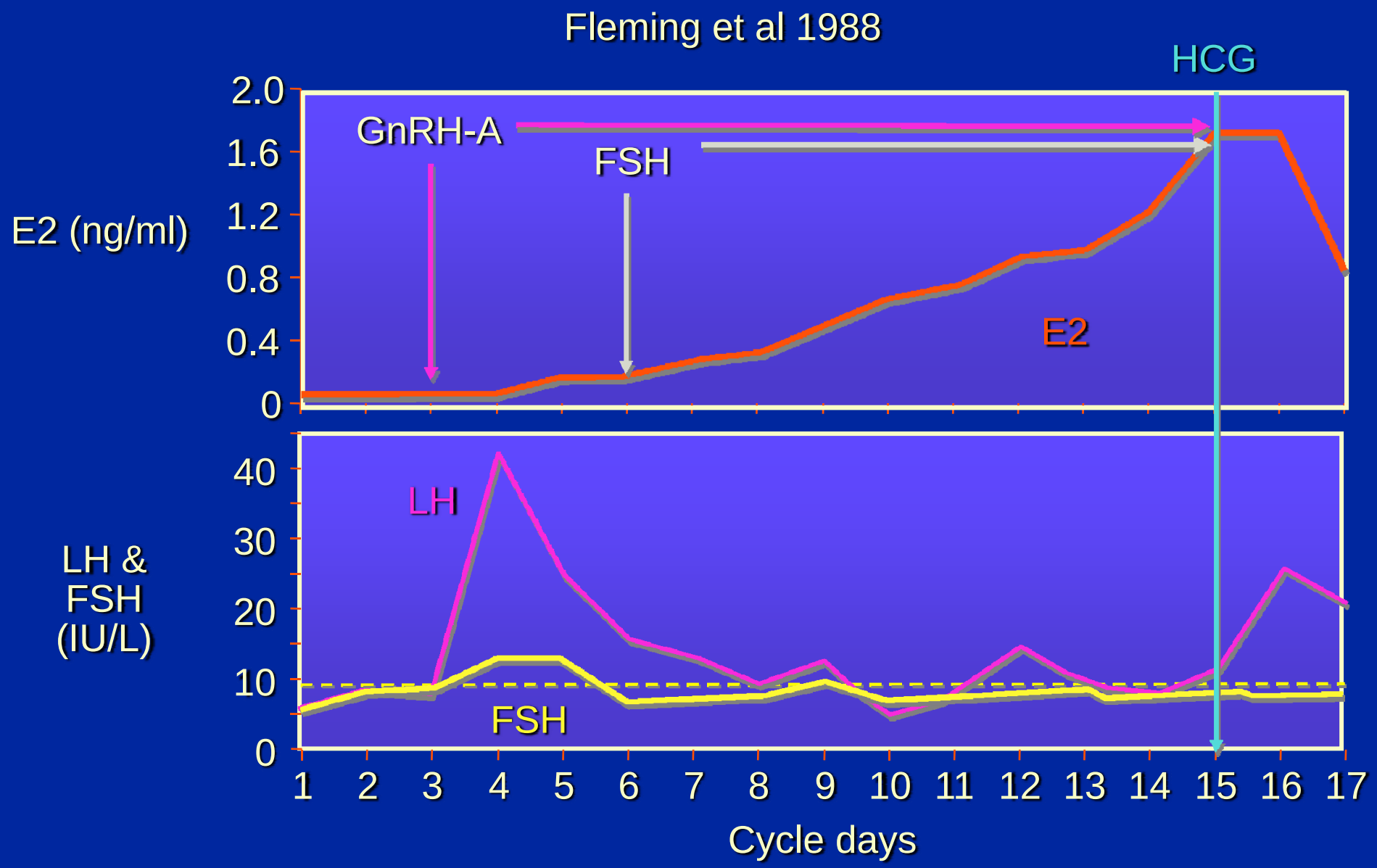
Better results in women treated with GnRH antagonist protocols

Further investigation required: thecal cells assessment

Effects of LH supplementation

in women with a low response to FSH

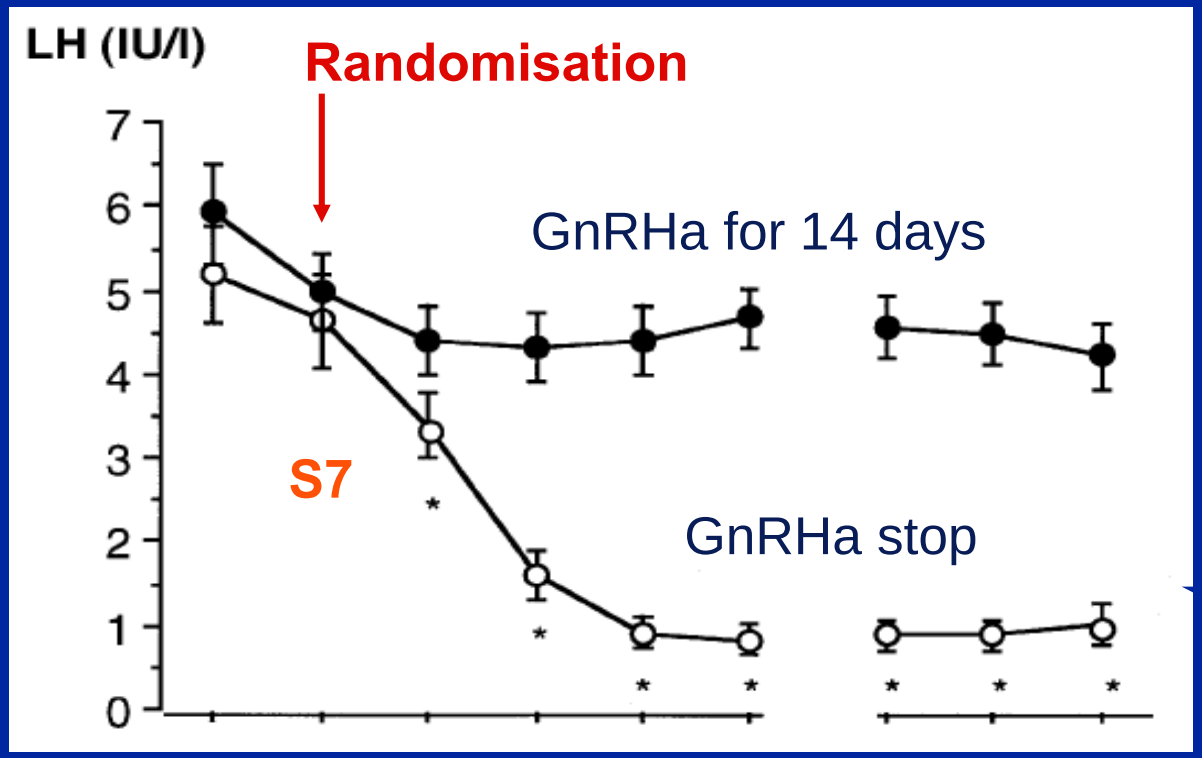
Short GnRH Agonist protocol and FSH



What happens to LH levels if GnRH agonist (Flare up protocol) is stopped during FSH stimulation?

Cedrin - Durnerin et al 2000

LH Goes up, stays same level or goes down ??



LH Levels fall

+

Requirement of higher doses of FSH

Maintain GnRH agonist administration up to hCG

LH in women needing high doses of gonadotrophin

	r-FSH alone (n = 17)	r-FSH + r-LH* (n = 12)	*p*
No. MII per cycle	3.76 ± 1.60	4.17 ± 1.70	NS
Fertilization (%)	60.9	86.0	0.006
No. embryos transferred	1.76	2.75	NS
Clinical pregnancies	1 (5.9%)	6 (50.0%)	0.011

*** 75 IU added to r-FSH from stimulation day 7**

Lisi et al RBM Online 2001;3:1904

Lower apoptosis rate in human cumulus cells after administration of r.LH

Ruvolo, Fertil Steril, 2007

42 women - Poor responders in previous cycle - FSH nl
GnRH agonist (Bus) cycles - r.FSH 225 IU / d
Randomisation on day 8 : r.LH 150 IU / d (n = 24 vs 18 control)

In favor of r.LH Pregnancy rate : 45.4 vs 25 % ($p<0.01$)
Implantation rate : 15.6 vs 12.5 ($p<0.01$)

Study Group	Cells (n)	TUNEL Assay (%)	Anti – 3 Caspase (%)
Control	568 ± 72	18.2	17.0
LH	612 ± 77	12.1	11

Increase in PR correlated with the reduction in apoptosis

Effects of LH supplementation

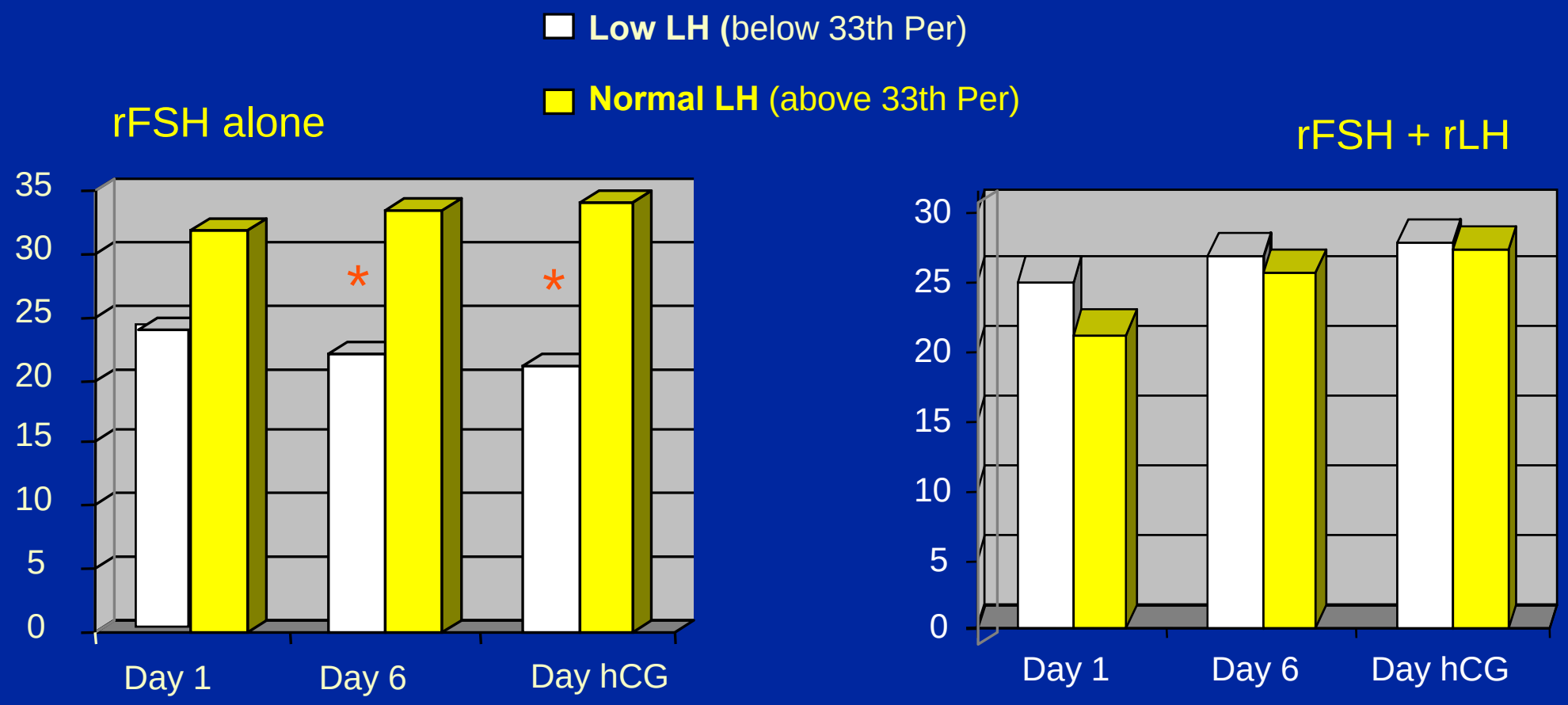
in women with a suboptimal response to FSH

Low endogenous LH levels

Steady ovarian response to r.FSH

Nordic LH Study Group

% Ongoing pregnancy according to serum LH



Low serum LH values : significant lower PR with FSH alone
Difference eliminated by supplementation with rLH

Different Agonists have varying Potencies

GnRH

Triptorelin

Leuprolide

Buserelin

Nafarelin

INCREASING POTENCY OF AGONIST

Fabregues, 2006; 0.1/0.05mg sc

Marrs, 2004; 0.5/0.25mg sc

Humaidan, 2004; 0.5/0.2 mg sc

Nyboe, 2008; 0.6/0.4 mg nasal

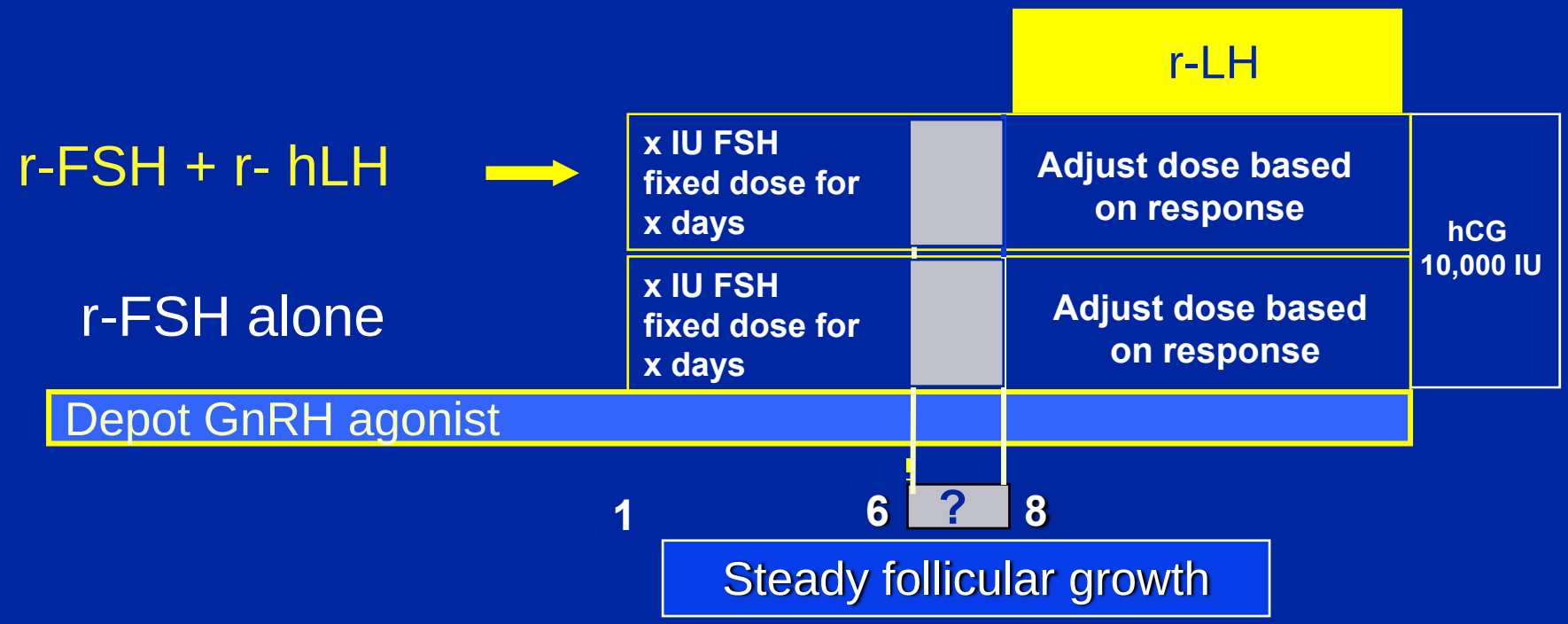
Intra-nasal

Daily Subcut

Depot

r- hLH & GnRH agonist long protocols

steady ovarian response to r.FSH



Authors	Agonist	r-FSH dose	r-LH start	r-LH dose
Ferrarreti AP,2004	Depot agonist	150-225	S10 n = 54	75-150
De Placido G, 2004	Triptorelin 3.75 mg	150-300	S8 n = 46	75-150
De Placido G,2005	Triptorelin 3.75 mg	225	S8 n = 59	150

Addition of r.LH improves ovarian response to FSH and implantation rate

LH in women hyporesponsive to FSH

Normal initial follicular recruitment (> 10 AF) with standard FSH dose

Plateau of follicular growth (E2 level) from day 8-10

Clinical outcomes.	↑ r-FSH	Add r-LH *	Add HMG	Control
	Group A (n = 50)	Group B (n = 54)	Group C (n = 22)	Group D (n = 54)
No. of fresh ETs	45	41	18	41
No. of embryos/ET (mean)	1.93	1.85	1.63	1.92
No. of pregnancies/ET (pregnancy rate/ET)	11 (24.4%)	22 (54%)[a]	2 (11%)	17 (41%)
Implantation rate (%)	14.1 (12/85)	36.8 (24/65)	7.4 (2/27)	35.4 (29/79)
No. of pregnancies after 2PN thawing	1	2	2	5
Total no. of abortions	1	2	0	2
Live birth rate/started cycle (n)	22% (11)	40.7% (22)	18% (4)	37% (20)

[a] Group B vs. groups A and C; $P < .05$.

*** 75–150 IU**

Ferraretti et al Fertil Steril 2004;82:1521

LH in women hyporesponsive to FSH

Table II. Cycle outcomes	+ 150 IU r-LH		+ 150 IU r-FSH
	Group A ($n = 59$)	P value (A versus B)	Group B ($n = 58$)
Suppressed LH[a]	1.2 (0.2–4.1)		1.2 (0.5–4.6)
Duration of stimulation (days)[b]	14.5 ± 1.3		15.0 ± 1.1
No. of rFSH ampoules[b]	41.9 ± 7.1	< 0.001	56.7 ± 8.0
No. of rLH ampoules	12.9 ± 2.9		
Total no. of ampoules of rLH + rFSH[b]	54.2 ± 7.4	0.077	56.7 ± 8.0
Day 5 E_2 concentration (pg/ml)[b]	48.3 ± 16.5		52.2 ± 17.7
Day 8 LH concentration (IU/l)[a]	0.7 (0.1–3.6)		0.7 (0.1–4.0)
Day 8 E_2 concentration (pg/ml)[b]	116.8 ± 43.6		122.0 ± 42.4
E_2 at hCG day (pg/ml)[b]	1778.9 ± 778.6	< 0.001	1248.0 ± 472.4
No. of COC retrieved[b]	9.0 ± 4.3	< 0.01	6.1 ± 2.6
No. of mature oocytes (MII)[b,c]	7.8 ± 4.3	< 0.01	4.7 ± 1.6
Fertilization rate (%)[d]	71.8		69.2
No. of transferred embryos[a]	3.5 (0–4)		3 (0–4)
Cumulative implantation rate (%)[d]	14.2		10.5
Cumulative pregnancy rate (%)[d]	37.2		29.3
Cumulative abortion rate (%)[d]	17.0		22.0
Cumulative ongoing pregnancy rate (%)[d]	32.5		22.0

De Plácido et al Hum Reprod 2005;20:3906

Cochrane Review 2007
"Slow" responders

r-hFSH alone vs r-hLH + r-hFSH

Review: Recombinant Luteinizing Hormone (rLH) for controlled ovarian hyperstimulation in assisted reproductive cycles
Comparison: 03 rLH and rFSH versus rFSH alone for COH in GnRH agonist dowregulated IVF/CSI cycles in poor responders
Outcome: 01 Ongoing pregnancy per woman randomised

Study	rLH and rFSH n/N	rFSH alone n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Barrenetxea 2006	8/36	7/36		25.7	1.18 [0.38, 3.70]
De Placido 2005	19/65	13/65		43.5	1.65 [0.74, 3.71]
Ferraretti 2004	22/54	11/54		30.8	2.69 [1.14, 6.33]
Total (95% CI)	155	155		100.0	1.85 [1.10, 3.11]

Total events: 49 (rLH and rFSH), 31 (rFSH alone)
Test for heterogeneity chi-square=1.40 df=2 p=0.50 I^2=0.0%
Test for overall effect z=2.32 p=0.02

0.1 0.2 0.5 1 2 5 10

Favours r-hFSH

Favours r-hFSH + r-hLH

Conclusions : use of r-LH supplementation in potential low responders

r.hLH beneficial in some subgroups of patients

- in patients > 35 yrs

some advantages in terms of implantation rate

but the exact mechanism is unknown

- In women with a low or a poor ovarian reponse to FSH

but no consensus on the definition

- In patients with low serum LH after down regulation

but no consensus on LH assays and LH threshold values

Conclusions : use of r-LH supplementation in ART

Unanswered questions

- Optimal FSH / LH ratio ?

R-LH : 1/2 or less

- What LH-like activity ?

Use of of rLH or hCG

- Ideal timing for r-LH supplementation ?

Beginning, middle or end of FSH stimulation

Before FSH stimulation « LH Priming »

Thank you for your attention

Thank you for your attention

Intra-ovarian ageing

- Androgen secretory capacity reduced
  (Piltonen et al., 2003; Barbieri et al., 2005)

- Decreasing numbers of functional LH receptors
  (Vihko et al., 1996)

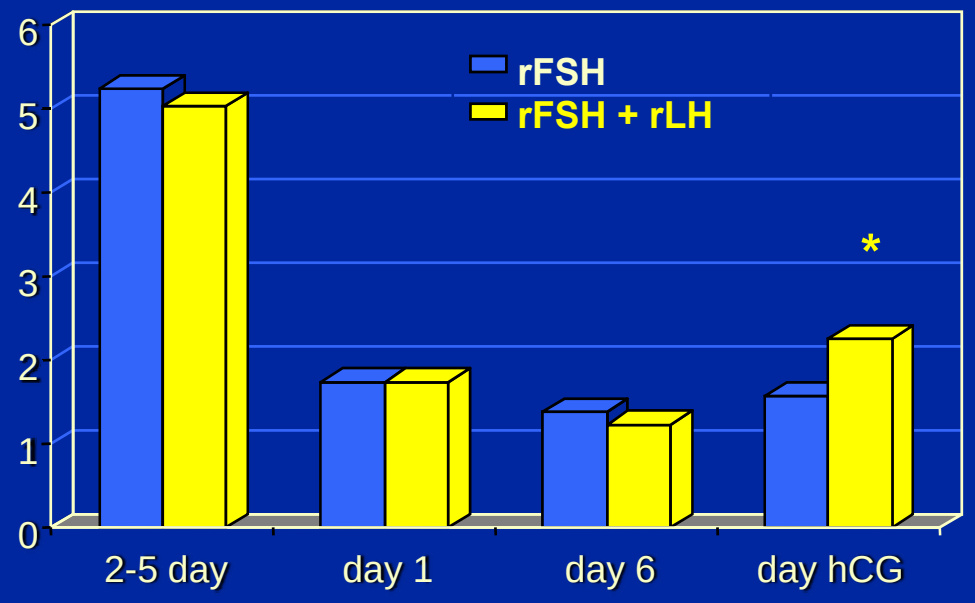
- GnRHa down-regulation per se causes a marked decrease in LH receptors (Ranta et al., 1984)

- Bioactivity of LH reduced while immunoreactivity unchanged
  (Mitchell et al., 1995; Marama et al., 1984)

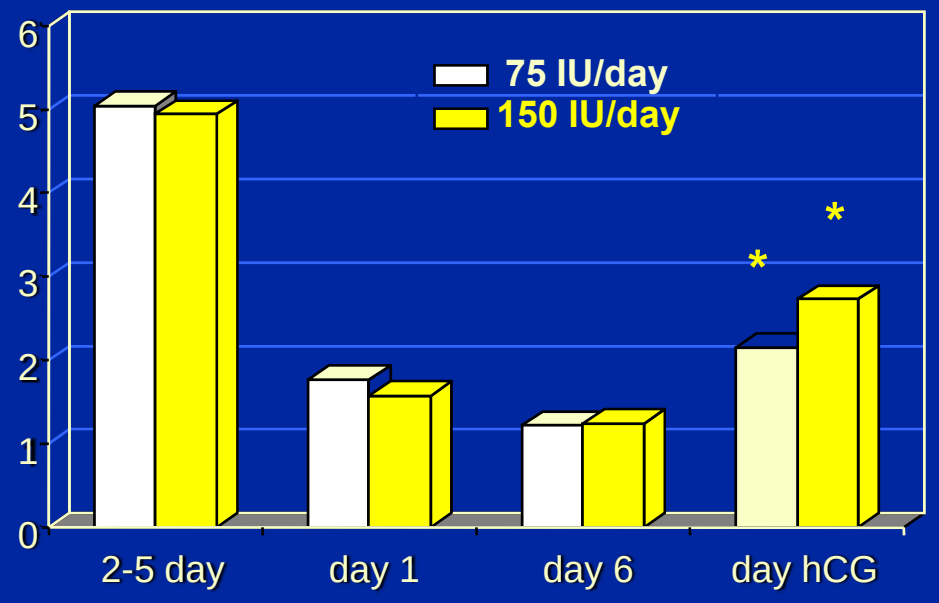
- Ovarian paracrine activity decreases with age
  LH activity is enhanced locally by paracrine activities
  (Hurwitz and Santoro, 2004)

Nordic LH Study Group

Serum LH before and during LH supplementation



* P < 0.001

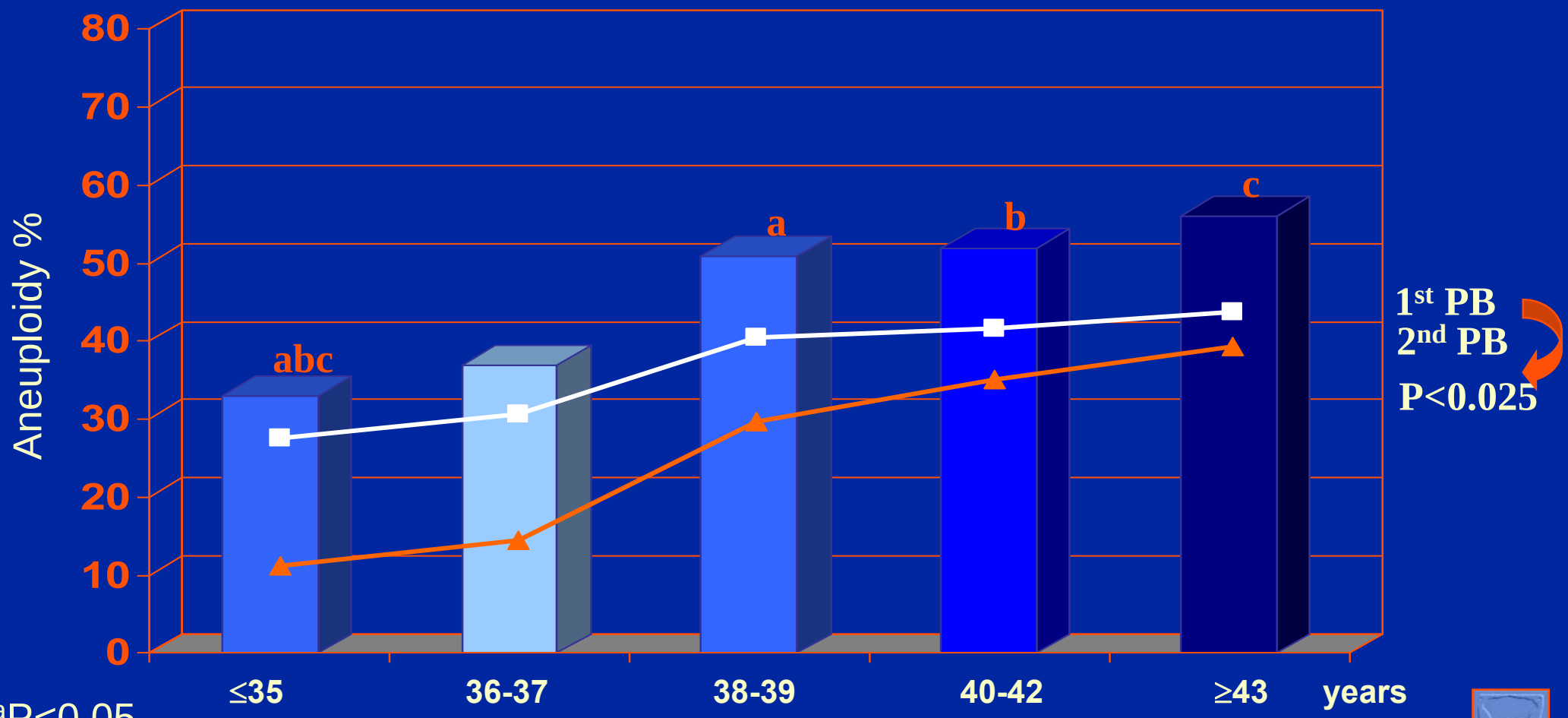


* P <0.001 between 75 and 150
* P < 0.001 compared to day 6

FIRST AND SECOND POLAR BODY ANALYSIS

INCIDENCE OF ANEUPLOIDY ACCORDING TO AGE

n=357



[a]P<0.05
[b]P<0.01
[c]P<0.005

Use of LH Supplementation in patients at risk of a low response to FSH

- Age

  Marrs et al. 2004
  Humaidan et al. 2004
  Fabregues et al. 2006
  Nyboe Andersen et al. 2008
  Bosch et al. 2008

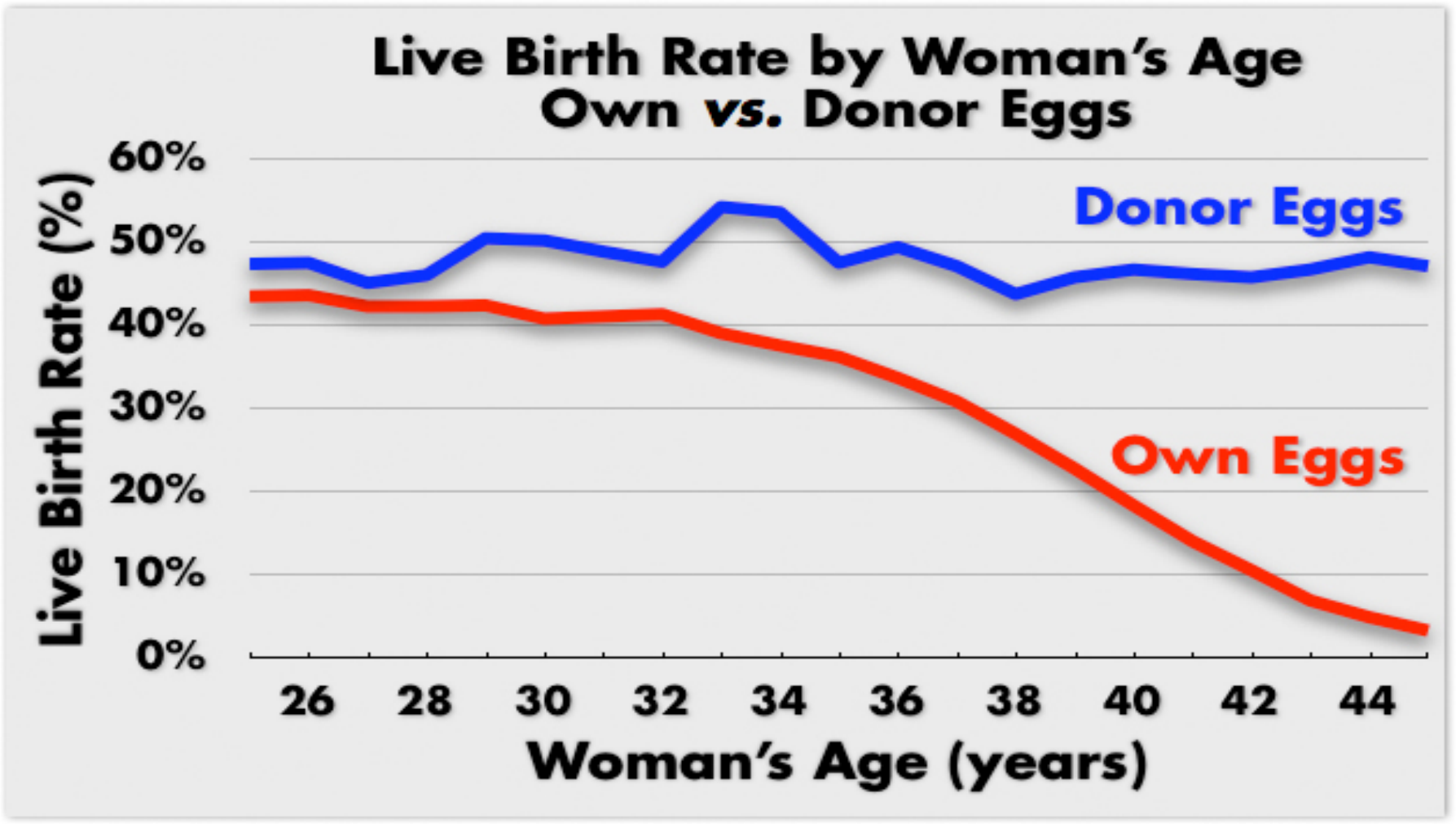
- Low response to FSH : “ initial low response”

  Lisi et al. 2001
  Ruvolo et al. 2007

- Suboptimal response to FSH : « Follicular stagnation »

  Barrenatexea 2000
  Placido et al. 2004
  Ferraretti et al. 2004

The ageing ovary



Comparative studies rFSH vs rFSH + rLH according to age

		< 35 years old	> 35 years old
GnRH agonist	Marrs et al, 2004 Humaidan et al, 2004 NyboeAndersen et al, 2008 Fábregues et al, 2006	FSH = FSH + LH (n=310) FSH = FSH + LH (n= 192) FSH = FSH + LH (n=426)	FSH + LH > FSH (n=88) FSH + LH > FSH (n=38) FSH + LH = FSH (n=100) FSH + LH = FSH (n=120)
GnRH antagonist	Sauer et al , 2004 Griesinger et al, 2005 Levi-Setti et al, 2006	FSH = FSH + LH (n=49) FSH = FSH + LH (n=126) FSH = FSH + LH (n=40)	?

Cycle outcome: Relative comparison FSH+LH vs FSH alone