

STIMULATION AND OVULATION TRIGGERING

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DISCLOSURE

Nothing to disclose

Learning Objectives

At the conclusion of this presentation, the participant should be able to:

- Assess the role of GnRH analogs**
- Describe mild ovarian stimulation**
- Assess the role of GnRH agonists for triggering ovulation**
- Discuss the use of LH supplementation**
- Discuss the role of AMH in ovarian stimulation**

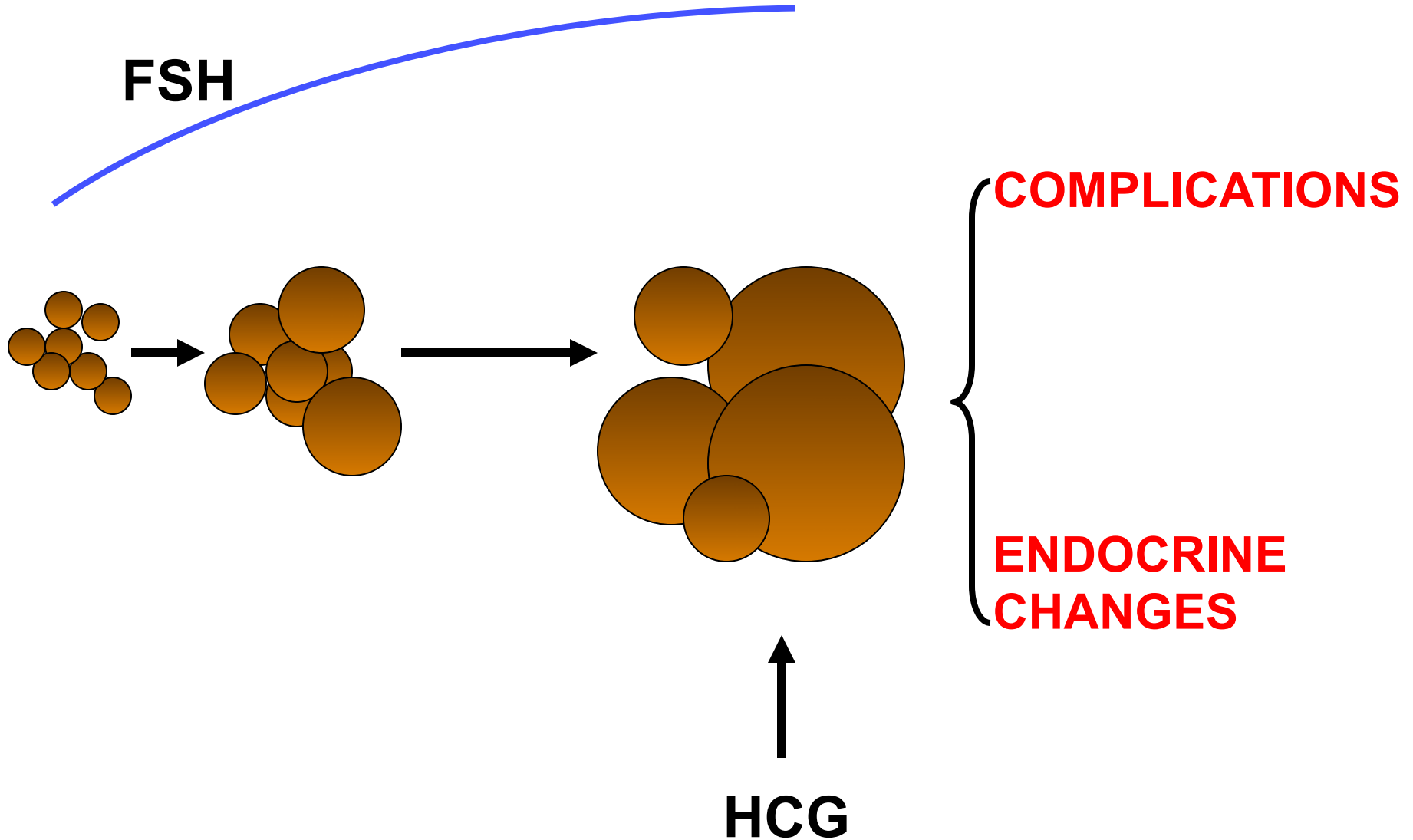
OUTLINE

- **GnRH analogues**
- **Mild protocol**
- **GnRH agonist triggering**
- **Exogenous LH**
- **Role of AMH**

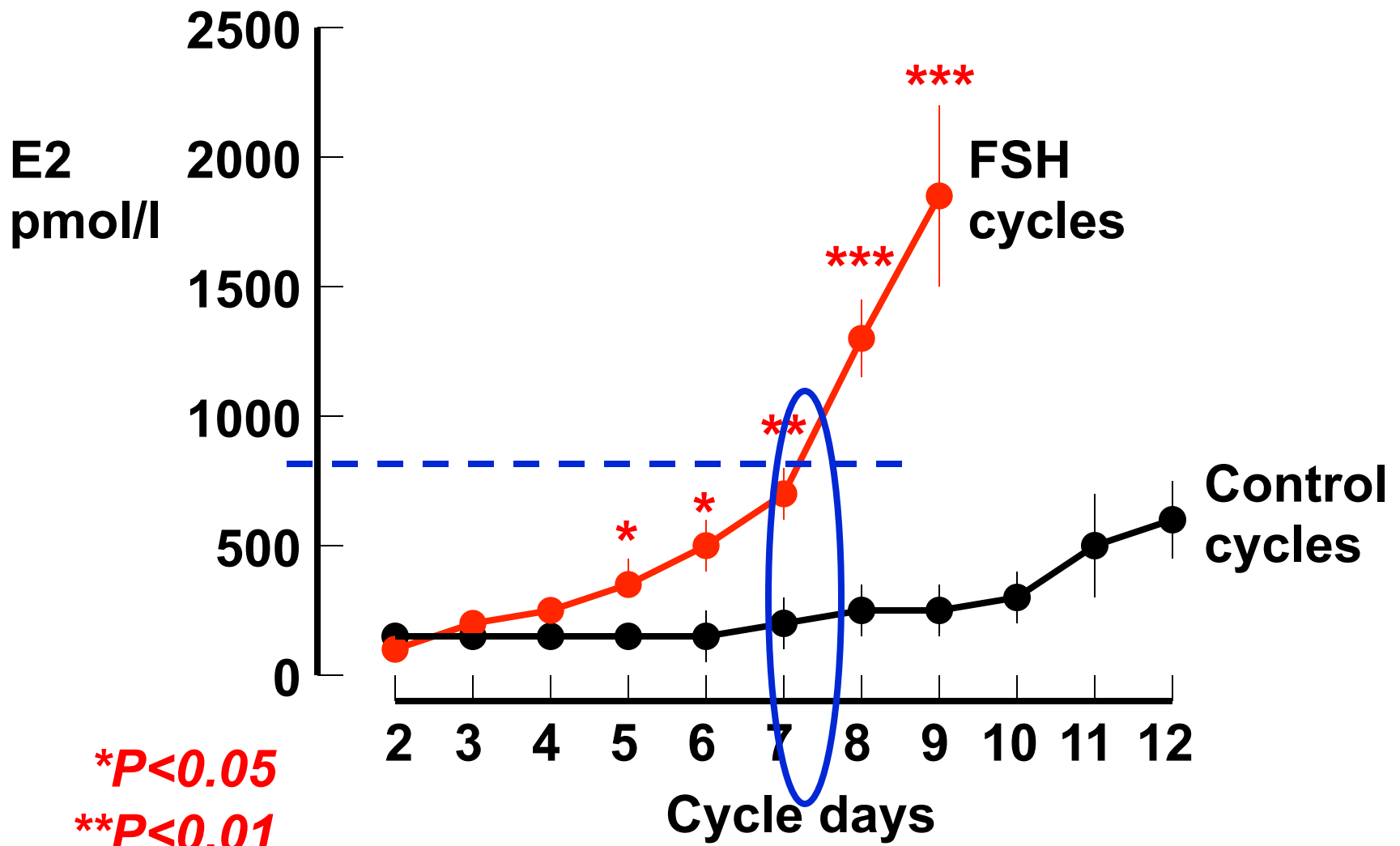
OUTLINE

- **GnRH analogues**
- Mild protocol
- GnRH agonist triggering
- Exogenous LH
- Role of AMH

MULTIPLE FOLLICLES



SUPEROVULATION INDUCTION



***P<0.05**
****P<0.01**
*****P<0.001**

Messinis & Templeton, 1986
Clin. Endocrinol. 25, 633-40

Gonadotrophin-releasing hormone agonist protocols for pituitary suppression in assisted reproduction.

Maheshwari A, Gibreel A, Siristatidis CS, Bhattacharya S.

Cochrane Database Syst Rev. 2011 Aug 10; (8):CD006919. Review.

PREMATURE LH PEAKS (>10 IU/L) AND LUTEINIZATION (>1 ng/ml)

Orgalutran and Cetrorelix studies:
up to 8%

CC/FSH/Cetrorelix:
up to 28%

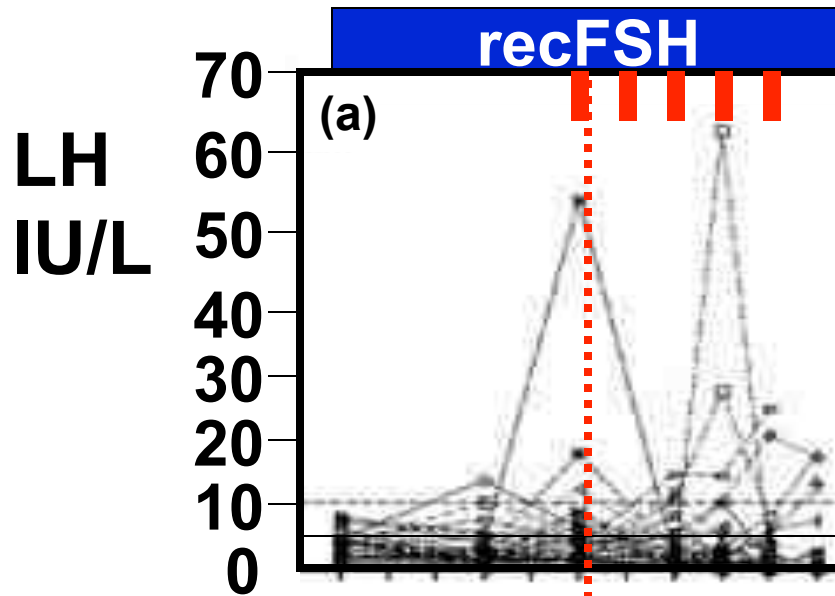
Borm & Mannaerts 2000

Felberbaum et al., 2000

Albano et al., 2000

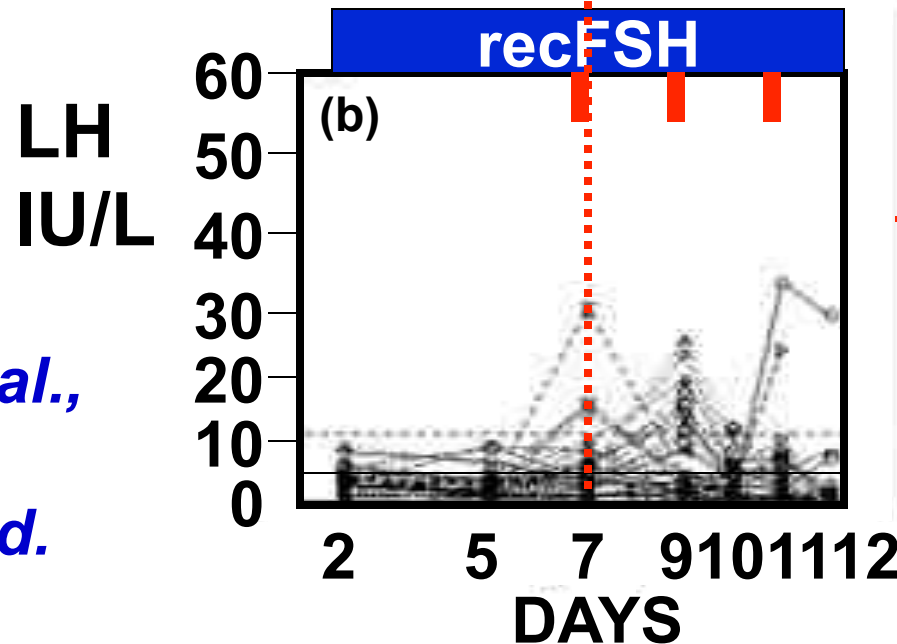
Engel et al., 2002

PREMATURE LH PEAKS



**GANIRELIX 0.25 mg
every day**

13/37 (35.1%)

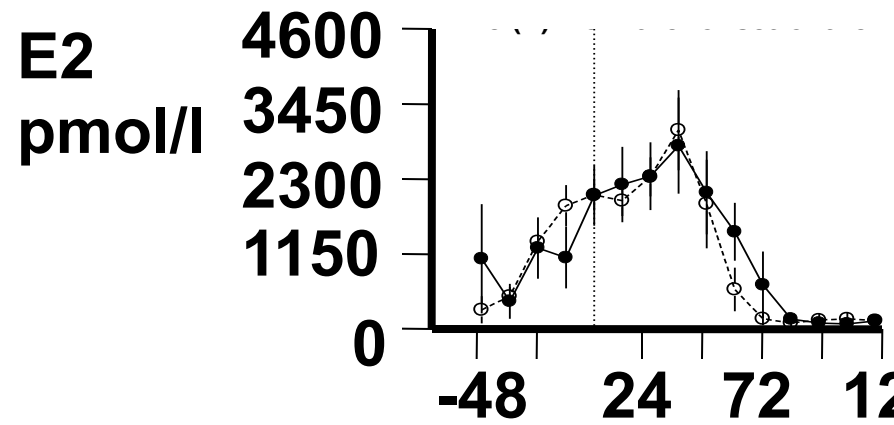
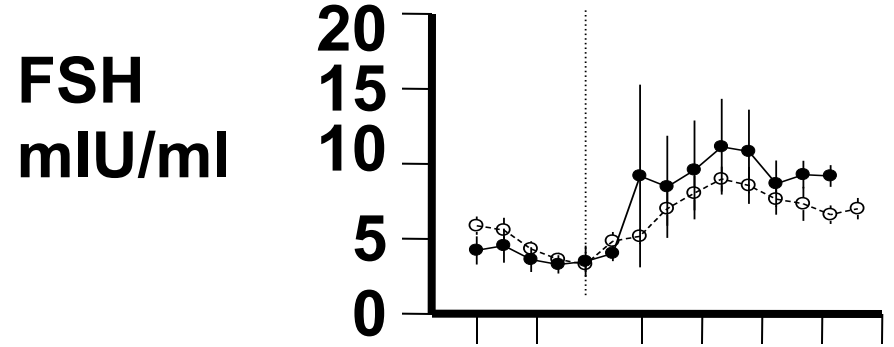
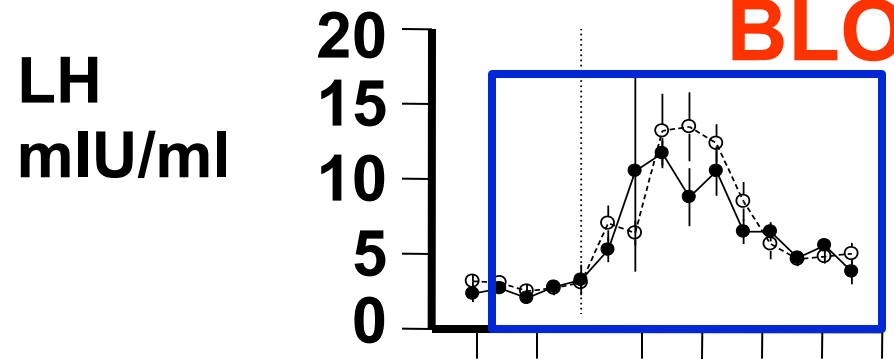


**GANIRELIX 0.25 mg
every other day**

14/36 (38.8%)

*Messinis et al.,
2005
Hum. Reprod.
20, 3192-97*

GANIRELIX DOES NOT BLOCK THE POSITIVE FEEDBACK EFFECT OF E2



- E2 (control)
- E2+ganirelix
0.25 mg/dX5 days

*Messinis et al., 2010
Fertil. Steril. 94, 1554-6*

Time (h) from LH surge onset

GnRH AGONISTS* vs ANTAGONISTS IN IVF/ICSI

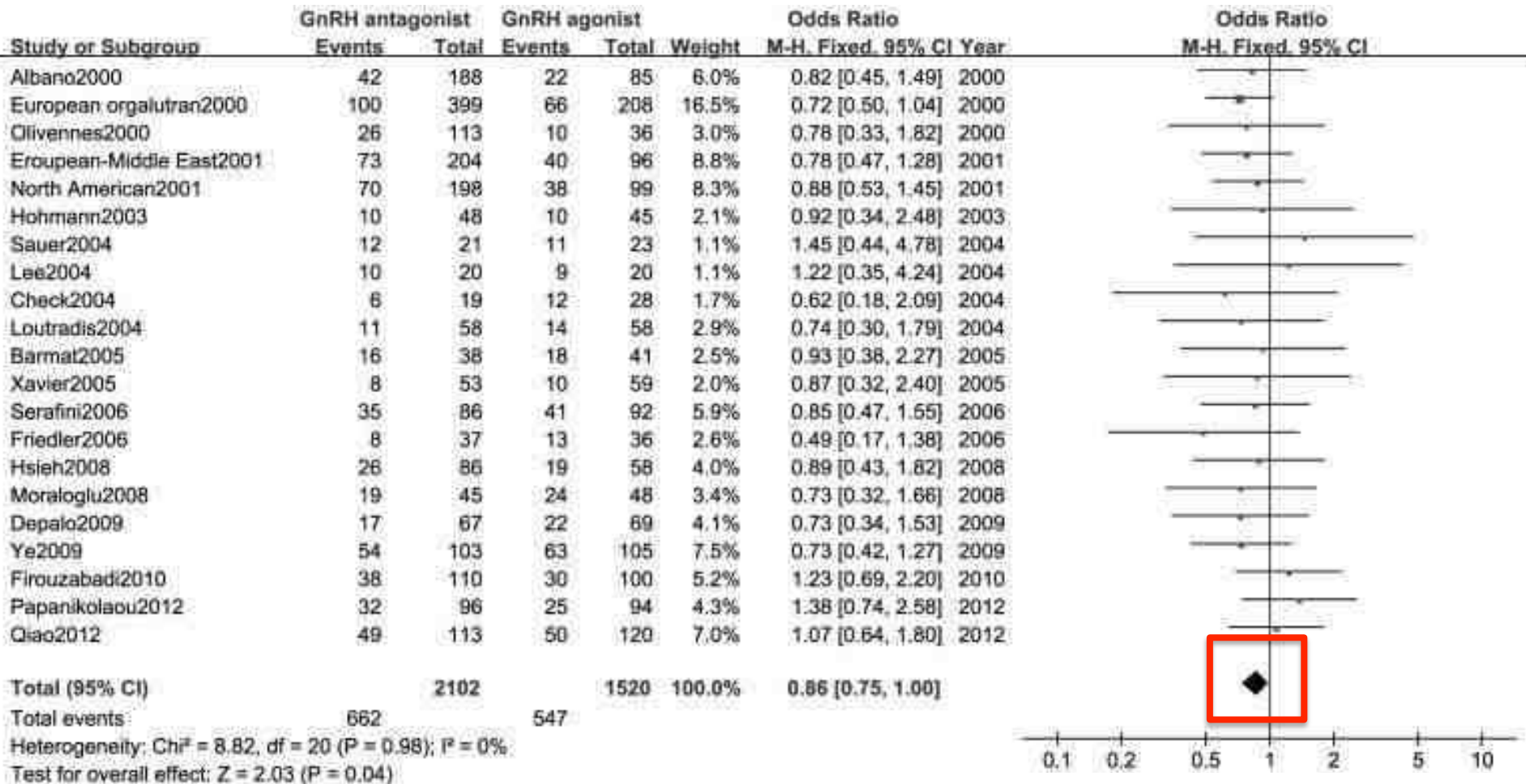
- Ongoing pregnancy (28 RCTs) OR:0.87, 95% CI 0.77 to 1.00
- Live birth (9 RCTs) OR: 0.86, 95% CI 0.69 to 1.08
- OHSS (29 RCTs) OR: 0.43, 95% CI 0.33 to 0.57

*Long protocol

Al-Inany et al., 2011

Cochrane Database Syst. Rev. May 11, (5): CD001750

GnRH ant. vs GnRH ag. IN NORMAL RESPONDERS



Clinical
Pregnancy
rate

Favours agonist antagonist

Xiao et al., 2014
PLoS One 9(9): e106854.

GnRH ant. vs GnRH ag. IN NORMAL RESPONDERS

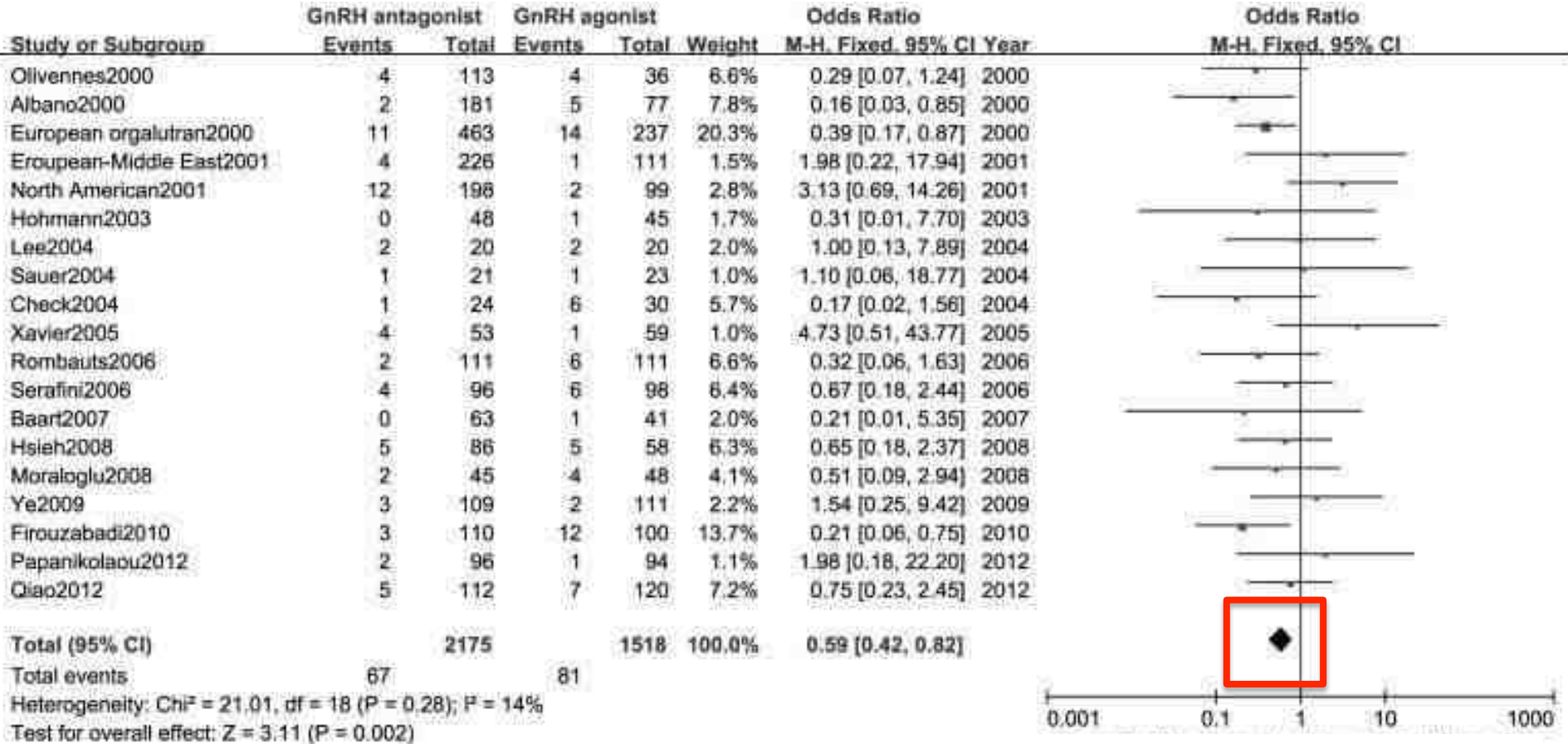


Favours agonist antagonist

Xiao et al., 2014
PLoS One 9(9): e106854.

Live birth rate

GnRH ant. vs GnRH ag. IN NORMAL RESPONDERS



Favours antagonist agonist

OHSS

*Xiao et al., 2014
PLoS One 9(9): e106854.*

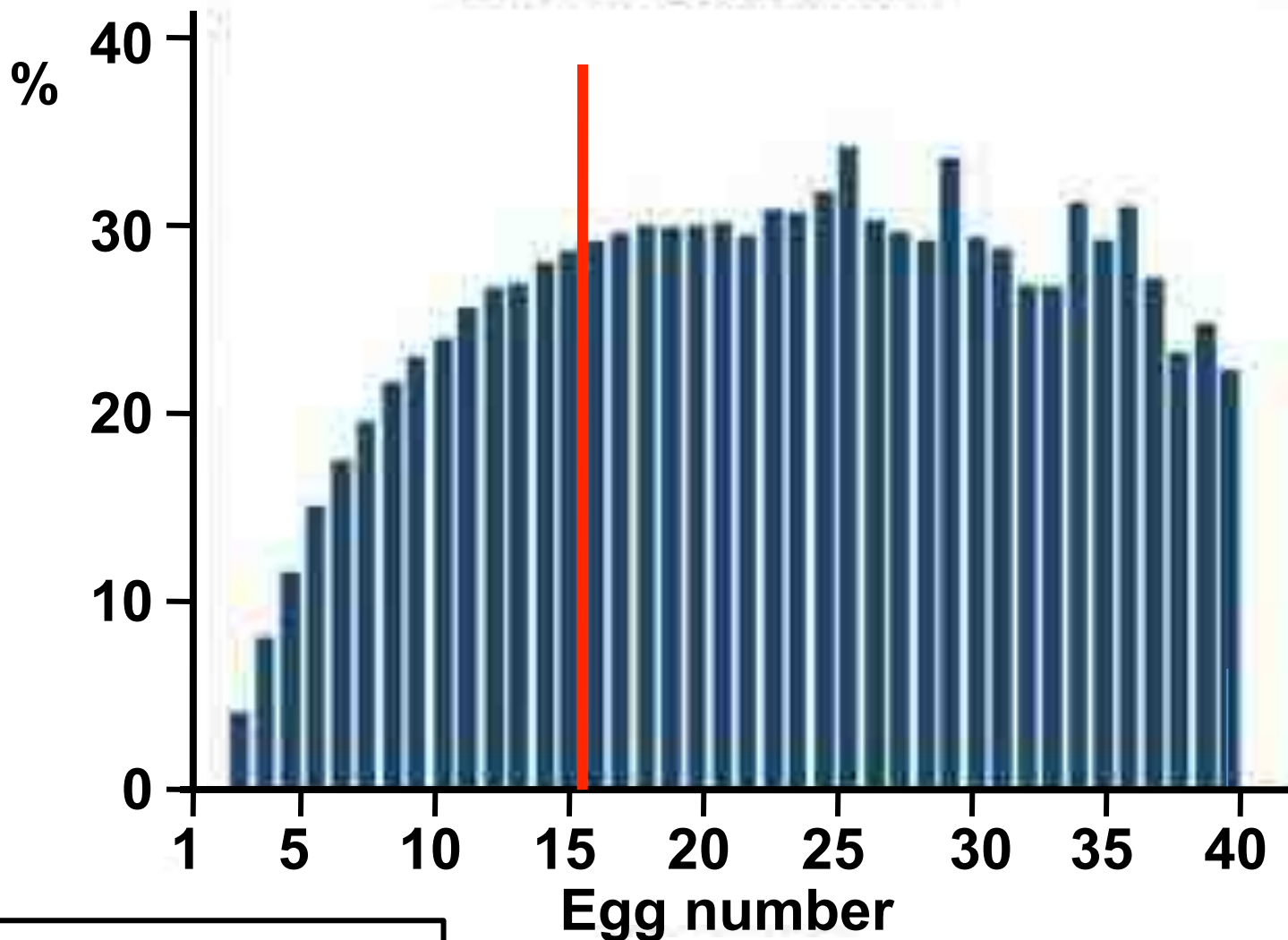
GnRH antagonists

- ***Good clinical outcome***
- ***Reduced OHSS rate***
- ***Friendly protocols***
- ***Agonist triggering***
- ***Cost-benefit analysis***

OUTLINE

- GnRH analogues
- **Mild protocol**
- Exogenous LH
- GnRH agonist triggering
- Role of AMH

LIVE BIRTH RATE IN RELATION TO THE NUMBER OF OOCYTES

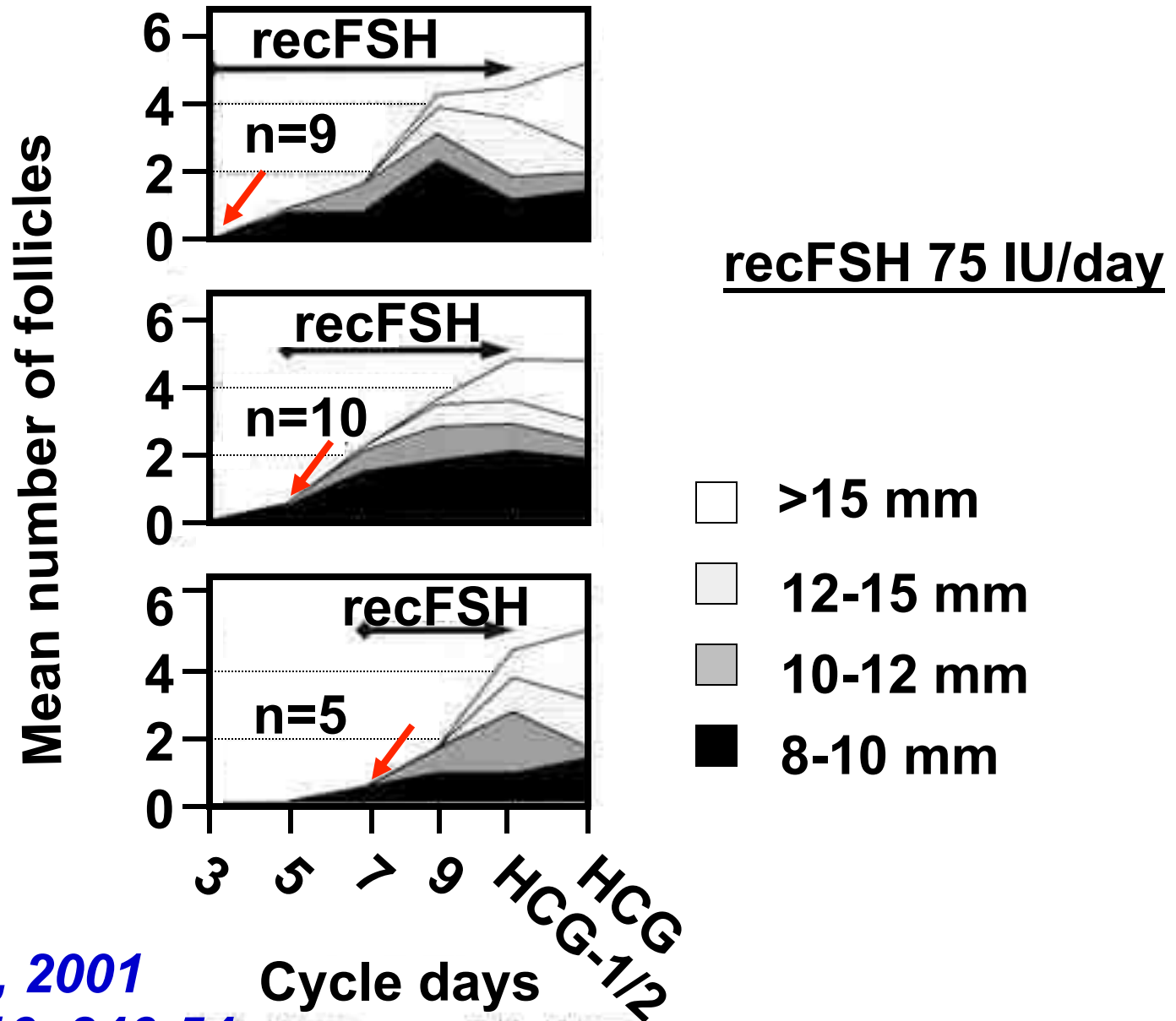


n=400135
Cycles (1991-2008)

Sunkara et al., 2011

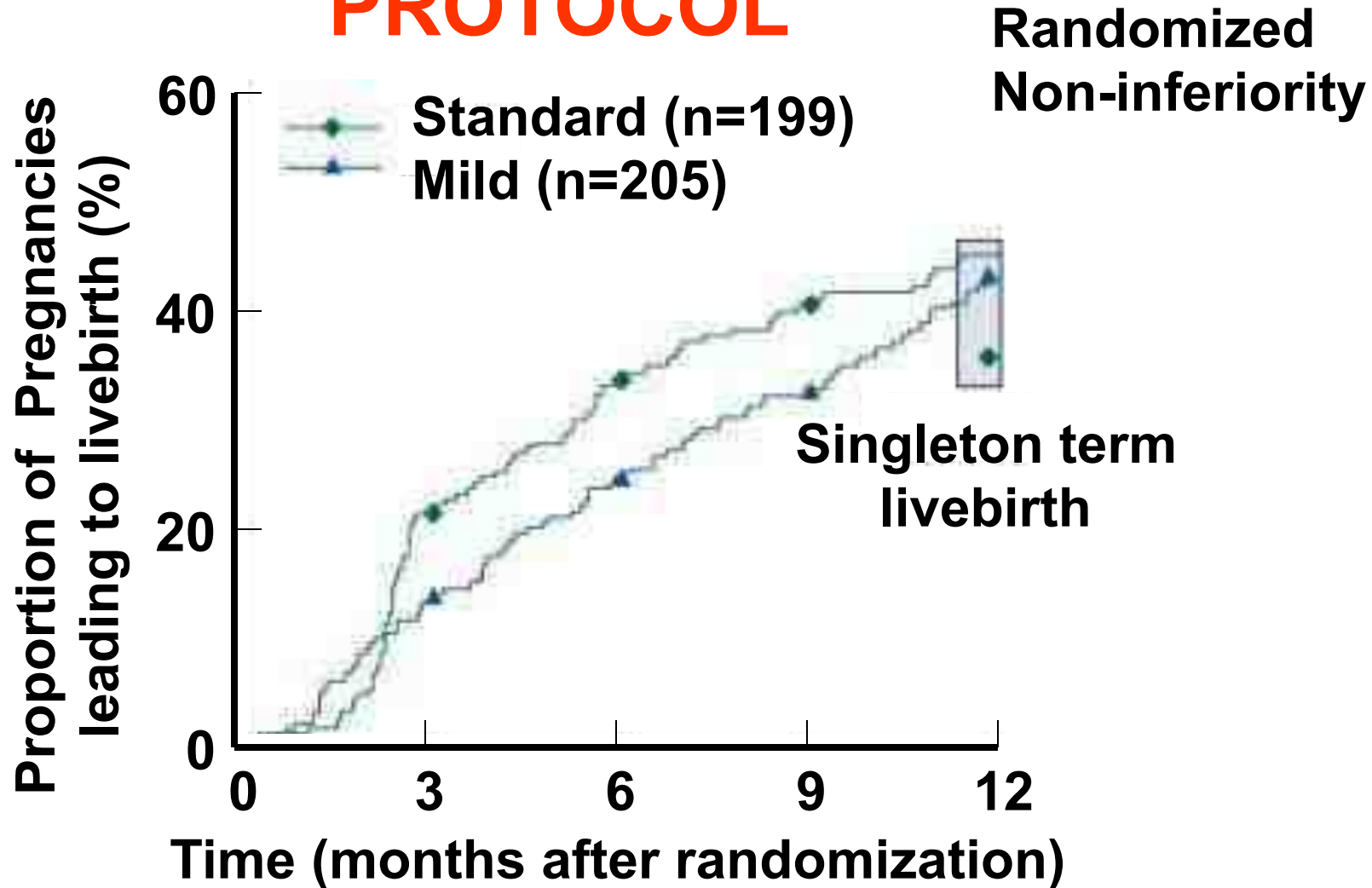
Hum. Reprod. doi: 10.1093/humrep/der106

WIDENING FSH WINDOW



Hohmann et al., 2001
Hum. Reprod. 16, 846-54

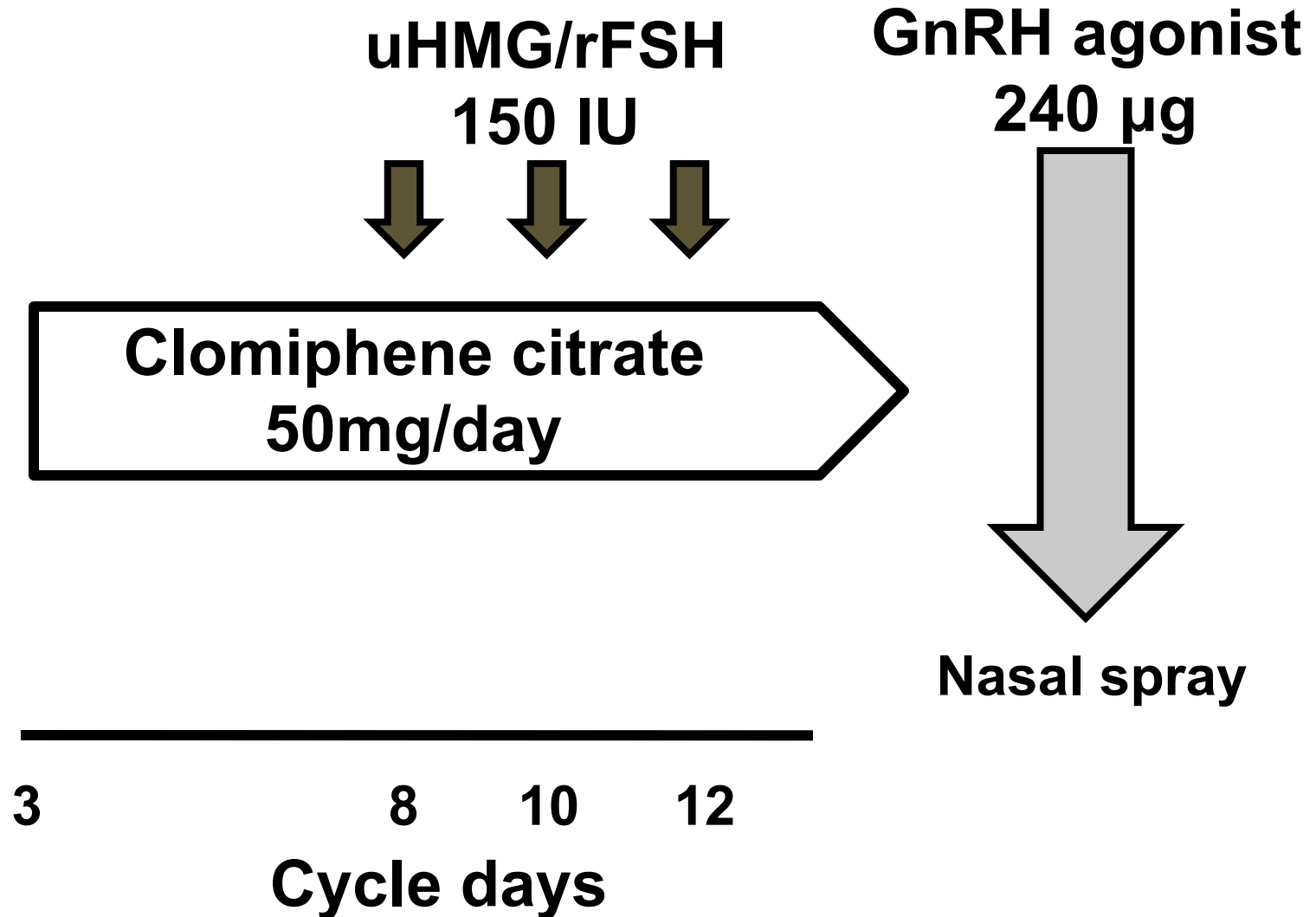
MILD OVARIAN STIMULATION PROTOCOL



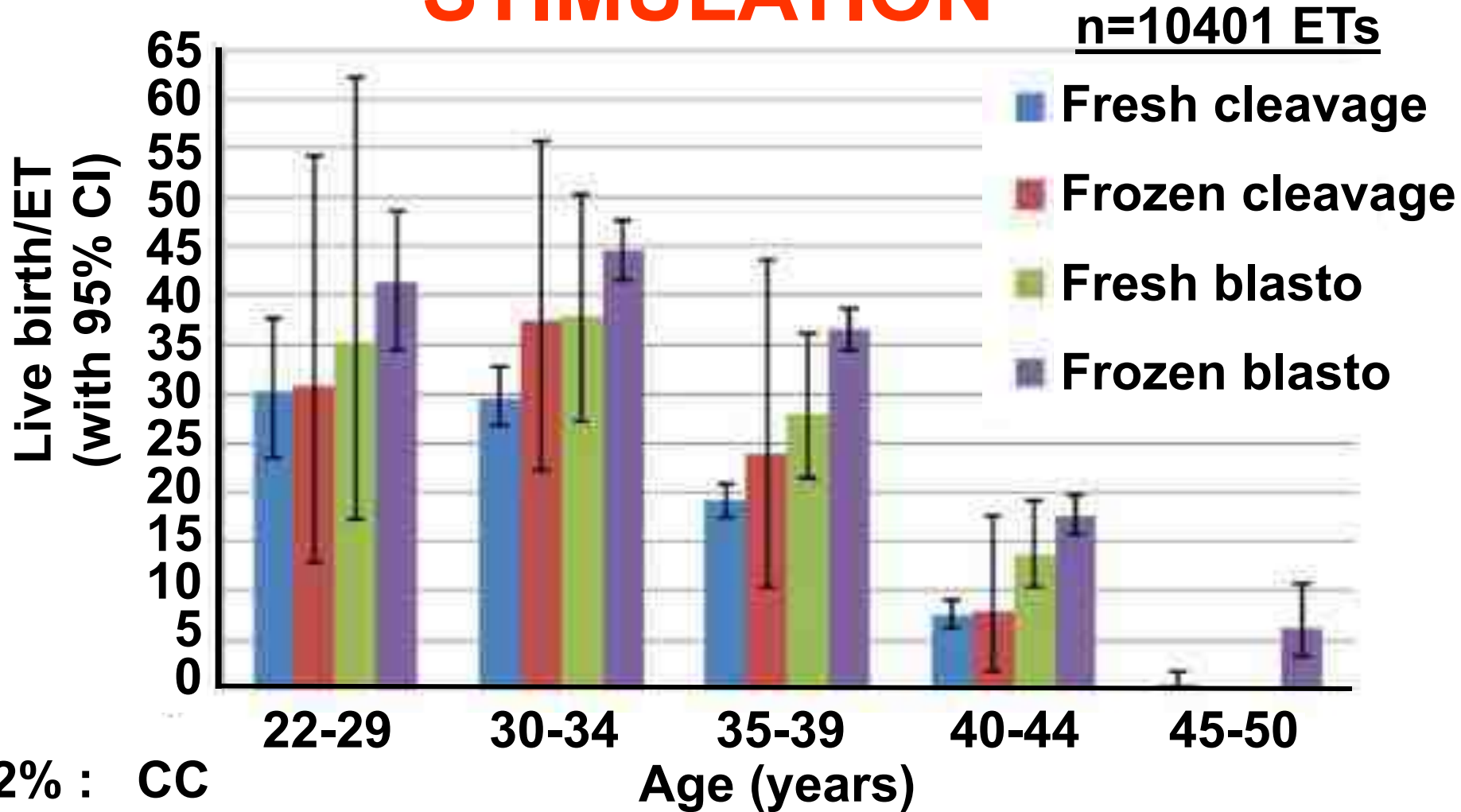
Mild: 150 IU/d (from day 5 + GnRH-ant)
Standard: 112-150 IU/d + GnRH-a

*Heijnen et al., 2007
Lancet 369, 743-749*

MILD – MIMIMAL OVARIAN STIMULATION PROTOCOL



MINIMAL OVARIAN STIMULATION



82% : CC

16.2%: natural cycle

1.8%: letrozole

Kato et al., 2012

Reprod. Biol. Endocrinol. 10, 35

Mild ovarian stimulation

- ***Women who want to avoid high FSH dosages***
- ***Women who do not need a high number of oocytes (usually if they have more than two children)***
- ***Poor responders (?)***

OUTLINE

- GnRH analogues
- Mild protocol
- **GnRH agonist triggering**
- Exogenous LH
- Role of AMH

GnRH AGONISTS vs HCG FOR TRIGGERING IN IVF/ICSI

Reduced

- OHSS (5 RCTs) OR: 0.10, 95% CI 0.01 to 0.82

Antagonist cycles

Youssef et al., 2011

Cochrane Database Syst. Rev. Jan 19

GnRH AGONISTS vs HCG FOR TRIGGERING IN IVF/ICSI

Reduced

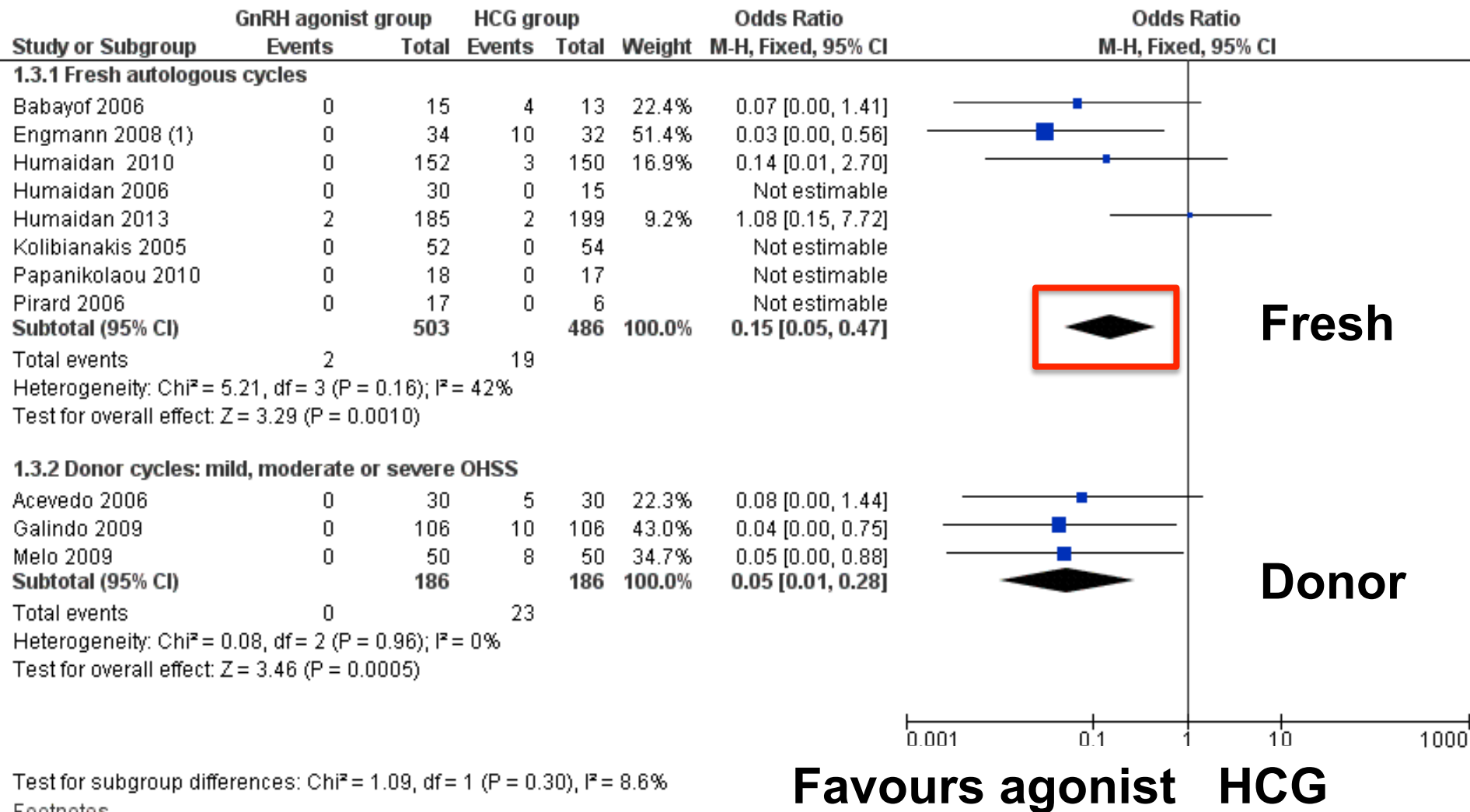
- Ongoing pregnancy (8 RCTs) OR:0.45, 95% CI 0.31 to 0.65
- Live birth (4 RCTs) OR: 0.44, 95% CI 0.29 to 0.68

Antagonist cycles

Youssef et al., 2011

Cochrane Database Syst. Rev. Jan 19

GnRH AGONIST TRIGGERING (OHSS)



Favours agonist HCG

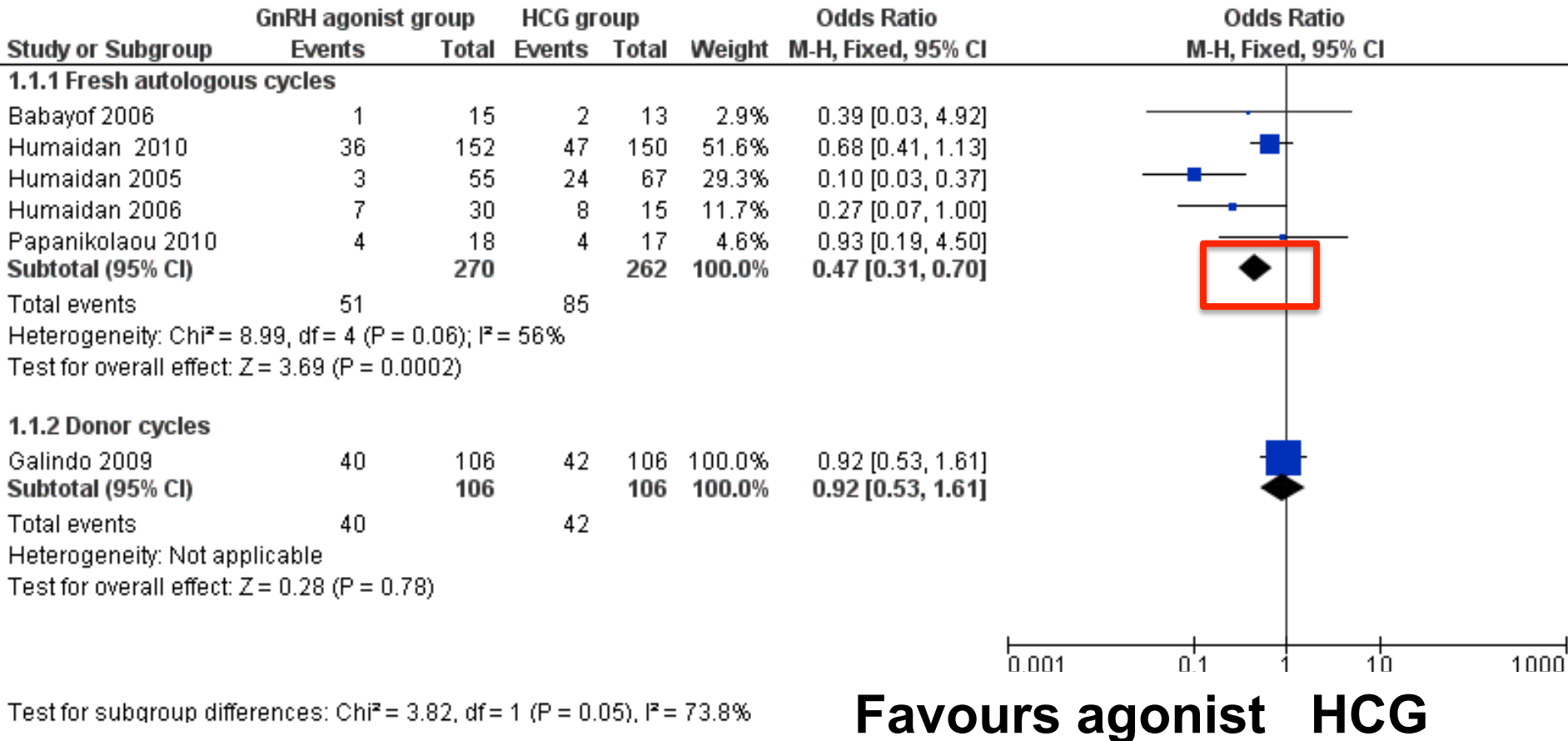
Footnotes

(1) A sensitivity analysis without Engman 2008 (as has high number of events) results in pooled OR (95% CI) 0.28 [0.08, 1.02]

Youssef et al. 2014

Cochrane Database Syst. Rev. Oct 31

GnRH AGONIST TRIGGERING (LBR)



Youssef et al. 2014

Cochrane Database Syst. Rev. Oct 31

GnRH agonist triggering

- **Intensive luteal phase supplementation-dual trigger (GnRH agonist + HCG)**
 - **GnRHa trigger + 1500 IU HCG (OPU)**
 - **GnRHa trigger + 1500 IU HCG (OPU+3)**
 - **Multiple doses of HCG**
- **“Freeze all” technique**

GnRH AGONIST vs HCG TRIGGERING

Pregnancy outcome in GnRH_a vs. hCG-group.

Variable	GnRH _a	hCG	OR (95% CI)	P Value
Patients, n	152	150		
Rate of transfer, n (%)	130/152 (86)	138/150 (92)	0.5 (0.4–0.7)	.054
Embryos transferred, median (range)	2 (1–2)	2 (1–2)		
Positive hCG per ET, n (%)	63/130 (48)	66/138 (48)	1.0 (0.9–1.2)	.36
Clinical pregnancy per patient, n (%)	50/152 (33)	55/150 (37)	0.8 (0.7–0.9)	.29
Ongoing pregnancy per patient, n (%)	40/152 (26)	49/150 (33)	0.7 (0.6–0.8)	.69
Delivery rate per patient, n (%)	36/152 (24)	47/150 (31)	0.7 (0.6–0.8)	.16
Early pregnancy loss, n (% of positive hCG)	13/63 (21)	11/66 (17)	1.3 (0.7–1.9)	.36

OHSS

0

3 (2%)

**RCT (n=302)
LPS (E2+P)**

**0.5 mg Buserelin plus
1500 IU HCG (OPU) - Dual
vs
HCG 10000 IU**

***Humaidan et al. 2010
Fertil Steril 93, 847-54***

OHSS IS NOT ELIMINATED

- 6/23 women (26%) severe OHSS (5 early)
 - GnRH agonist plus 1500 IU HCG
Seyhan et al, 2013
Hum Reprod 28, 2522-8
- OHSS: 0.72% (2 severe cases)
 - GnRH agonist plus 1500 IU HCG (OPU)
Iliodromiti et al., 2013
Hum. Reprod. 28, 2529-36
- Two severe cases of early OHSS
 - GnRH agonist without HCG
Fatemi et al., 2014
Fertil. Steril. 101, 1008-11

GnRH agonist triggering

- ***Women who choose to avoid fresh ET (for any reason)***
- ***Oocyte donors***
- ***Fertility preservation***

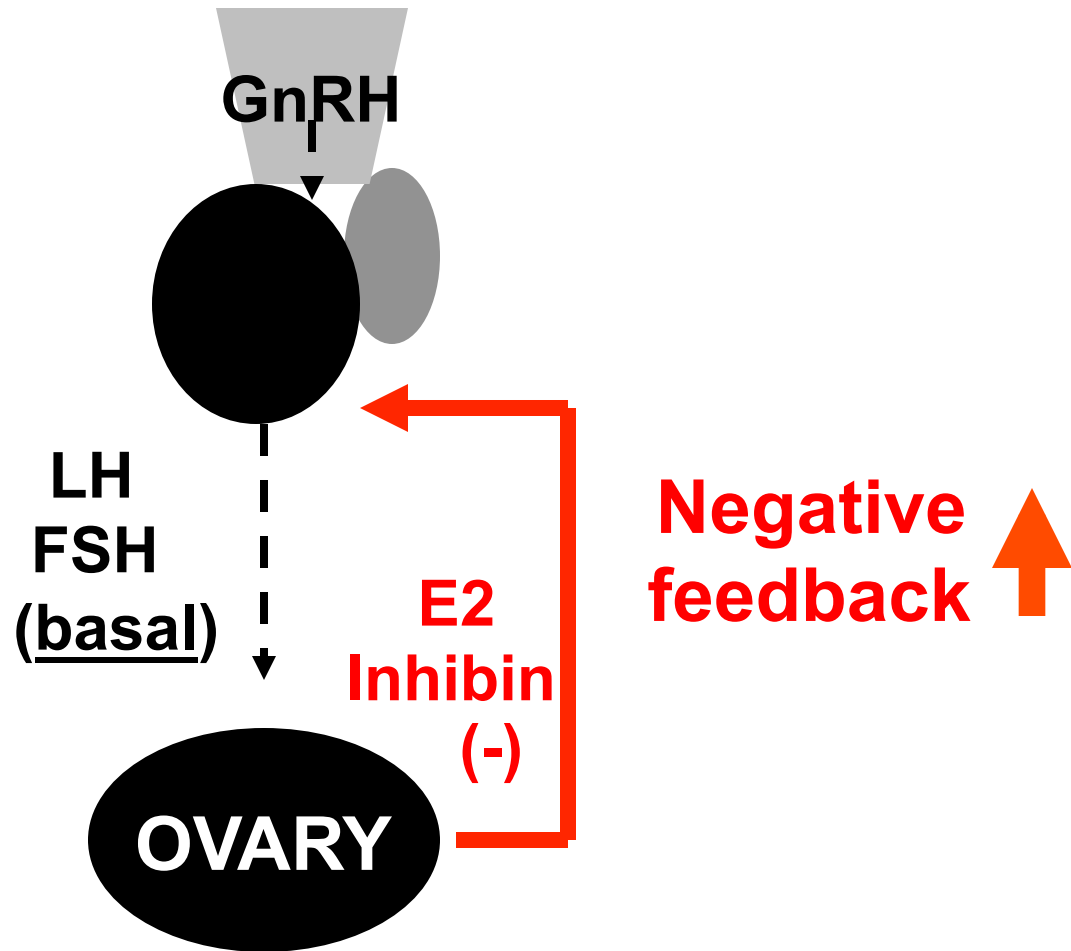
Youssef et al. 2014

Cochrane Database Syst. Rev. Oct 31

OUTLINE

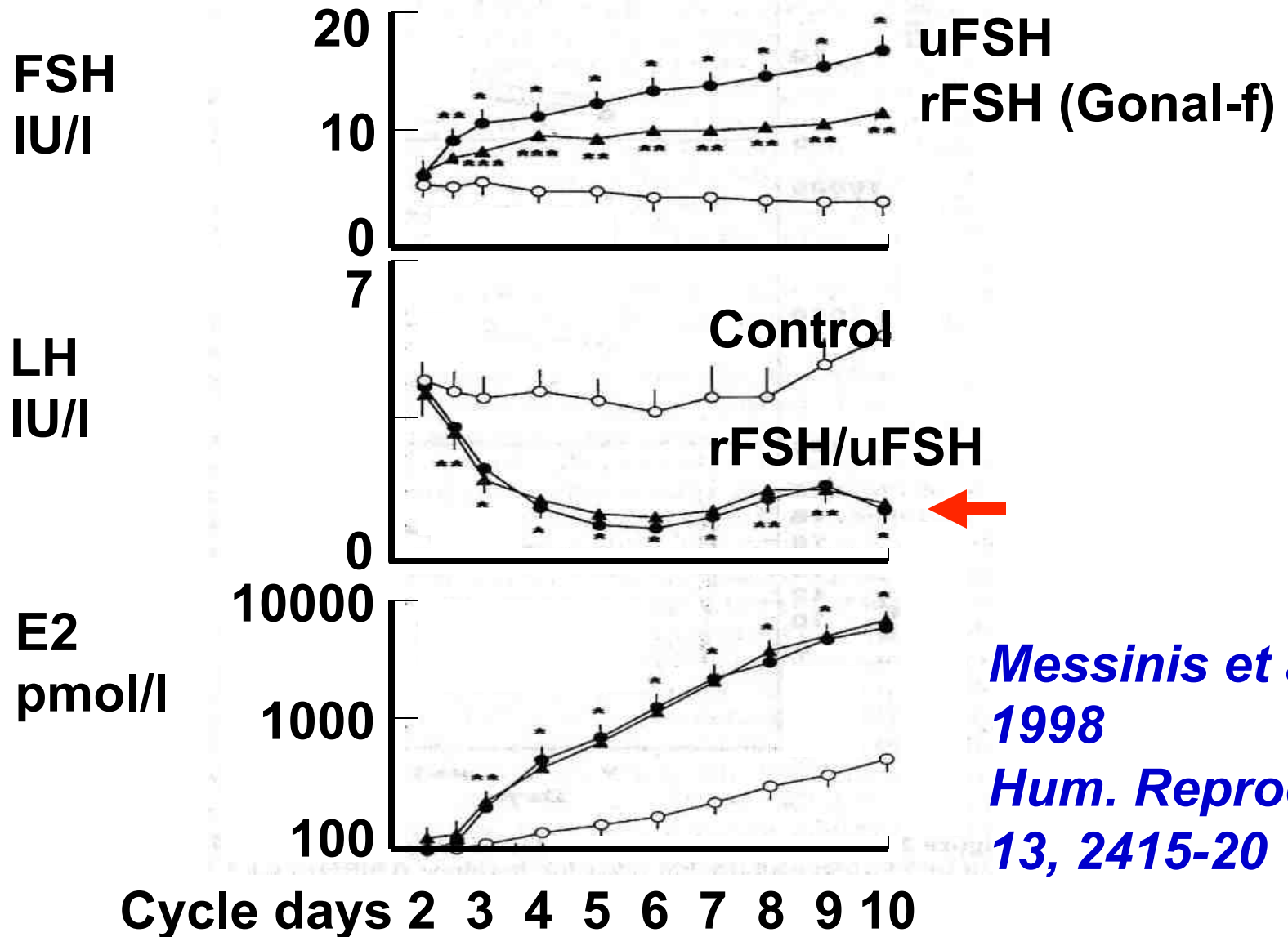
- GnRH analogues
- Mild protocol
- GnRH agonist triggering
- **Exogenous LH**
- Role of AMH

MULTIPLE FOLLICULAR DEVELOPMENT



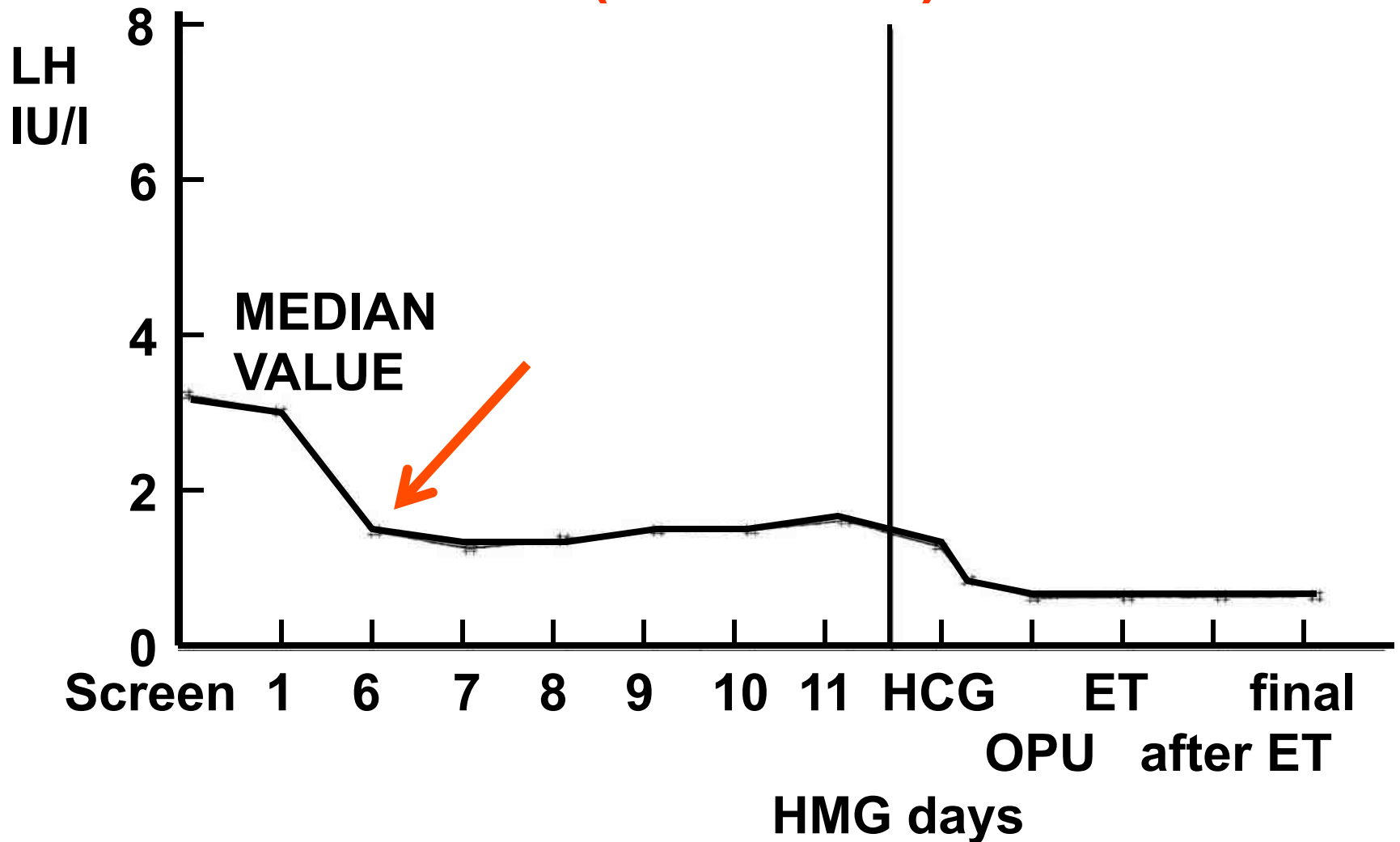
Messinis, 2006
Hum. Reprod. Update 12, 557-571

LH IS SUPPRESSED



*Messinis et al.,
1998
Hum. Reprod.
13, 2415-20*

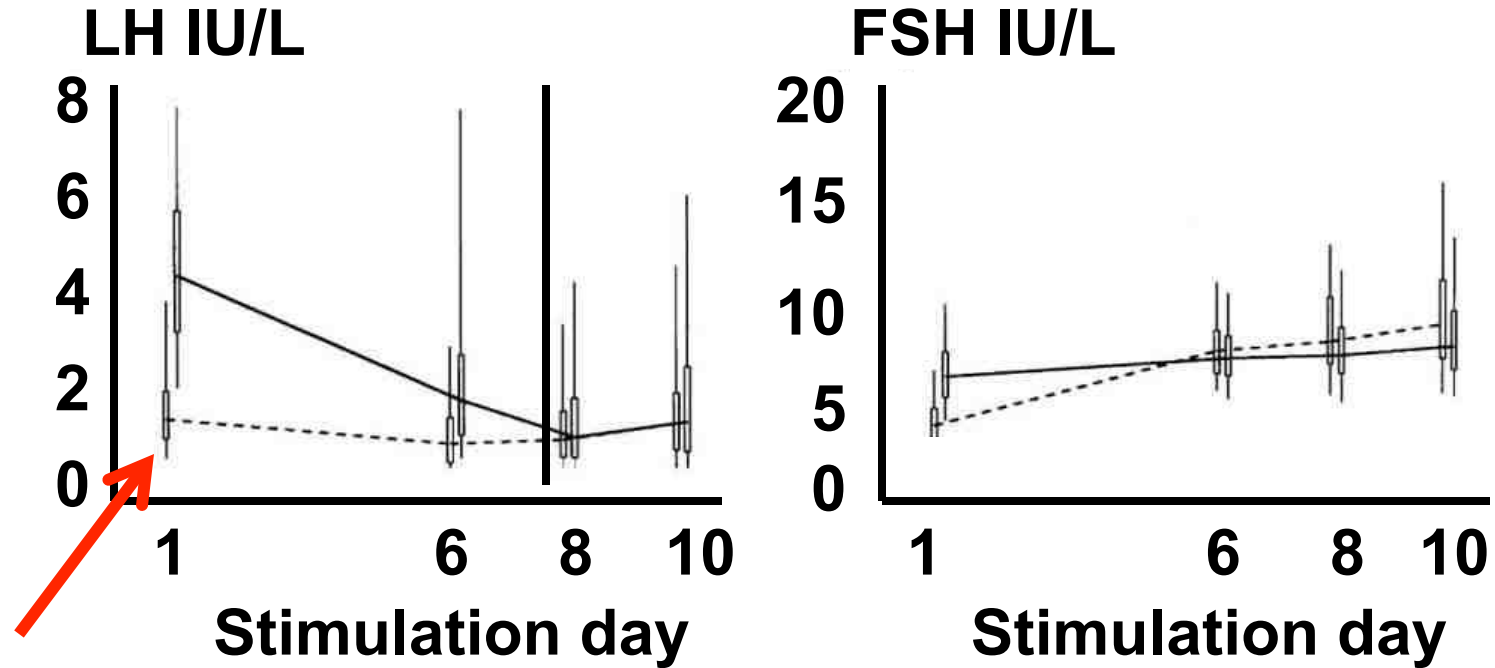
FSH PLUS A GnRH ANTAGONIST (cetrotorelix)



n=228 278 302 291 291 225 161 103 298 253 235 222 55

Felberbaum et al., 2000; Hum. Reprod. 15, 1015-1020

FSH PLUS A GnRH AGONIST (LONG)



— Ganirelix
..... Buserelin (LONG)

*Borm & Mannaerts, 2000
Hum. Reprod. 15, 1490-1498*

rFSH vs rFSH+rLH

(MID-FOLLICULAR rLH SUPPLEMENTATION)

	<u>r-FSH</u>	<u>r-FSH + rLH</u>	<u>P-value</u>
All patients	28.7% (n=261)	27.2% (n=265)	0.699
Patients ≤35 y	27.6% (n=210)	29.6% (n=216)	0.699
Patients >35 y	33.3% (n=51)	16.3% (n=49)	0.065

GnRH-ag long (IVF/ICSI)

***(ongoing live gestation
10-12 weeks)***

***NyboeAndersen et al., 2008
Hum. Reprod. 23, 427-34***

FSH vs FSH+rLH

Study	FSH+LH n/N	FSH n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI
Agonist					
Sills <i>et al.</i> (1999)	3/13	10/17		10.00	0.21 [0.04, 1.05]
Balash <i>et al.</i> (2001)	0/16	1/14		2.32	0.27 [0.01, 7.25]
Humaidan <i>et al.</i> (2004)	39/116	31/115		31.00	1.37 [0.78, 2.41]
Fabregues <i>et al.</i> (2006)	24/60	25/60		22.50	0.93 [0.45, 1.93]
Tarlatzis <i>et al.</i> (2006)	6/55	10/59		12.90	0.60 [0.20, 1.78]
Subtotal (95% CI)	72/260	77/265		78.72	0.94 [0.64, 1.39]
Antagonist					
Sauer <i>et al.</i> (2004)	9/25	10/24		9.80	0.79 [0.25, 2.49]
Griesinger <i>et al.</i> (2005)	8/62	9/65		11.48	0.92 [0.33, 2.56]
Subtotal (95% CI)	17/87	19/89		21.28	0.86 [0.40, 1.85]
Total (95% CI)	89/347	96/354		100.00	0.92 [0.65, 1.31]

Live birth rate

Favours FSH Favours FSH+LH

Kolibianakis et al., Hum Reprod Update. 2007, 13, 445-52

rFSH vs URINARY (HMG, P-FSH, HP-FSH) LIVE BIRTH RATE (IVF/ICSI)

NO DIFFERENCE

28 trials, 7339 couples:

- **Odds ratio 0.97, 95% CI 0.87 to 1.08**

*For 25% LBR using urinary gonadotrophins
the rate would be between 22.5% and 26.5%
in the rFSH group*

Van Wely et al., 2011

Cochrane Database Syst. Rev. Feb 16;(2):CD005354.

ADDITION OF HCG TO rFSH

	Dose 0 (n=16)	Dose 50 (n=20)	Dose 100 (n=16)	Dose 150 (n=15)
<i>Treat. days.</i>	10.3±1.4	9.3±1.4	9.9±1.3	10.4±1.1
<i>FSH dose...</i>	1538±209	1385±232	1475±195	1562±163
<i>Oocytes retrieved....</i>	9.3±6.3	8.5±4.4	9.2±4.2	11.3±5.7
<i>Top quality embr/pat....</i>	0.8±1.2	0.5±0.7*	1.2±1.7	1.5±1.7*
<i>Cl. Preg./ cycle.....</i>	25%	27%	38%	31%
<i>Live birth rate.....</i>	25%	27%	25%	31%

Prospective RCT
HCG in IU from day 1

*P=0.04

Thuesen et al. 2012
Hum. Reprod. 27, 3074-84

rLH IN POOR RESPONDERS

- Meta-analysis of 3 RCTs:

Higher pregnancy rate in favour of co-administering rLH

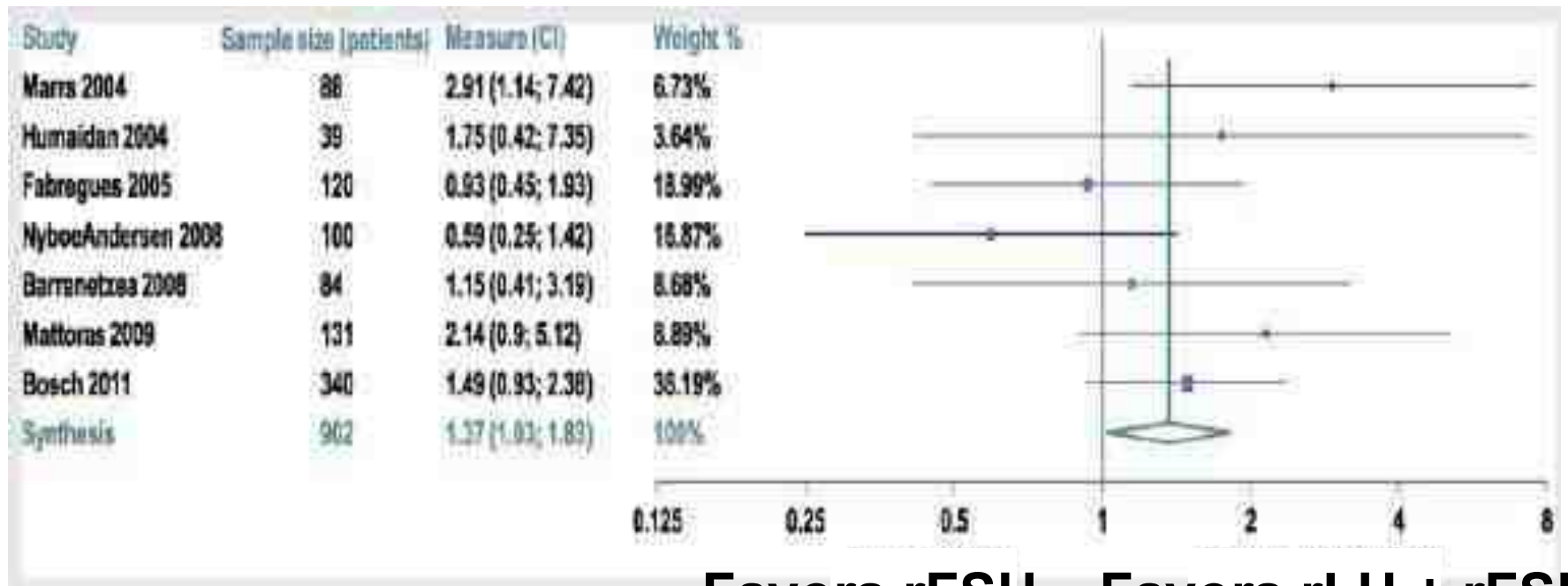
OR 1.85 (95% CI 1.10-3.11)

(Pooled pregnancy estimates)

rFSH+rLH vs rFSH

Meta-analysis

Clinical pregnancy rate



Favors rFSH Favors rLH + rFSH

Women \geq 35 years

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

POOR RESPONDERS

(Syst. Review and Meta-analysis)

rFSH+rLH vs rFSH

No of oocytes

0.75 (95% CI 0.14-1.36) ITT (n=12 studies)

0.75 (95% CI 0.13-1.36) PP

Clinical Pregnancy rate

1.30 (95% CI 1.01-1.67) ITT (n=14 studies)

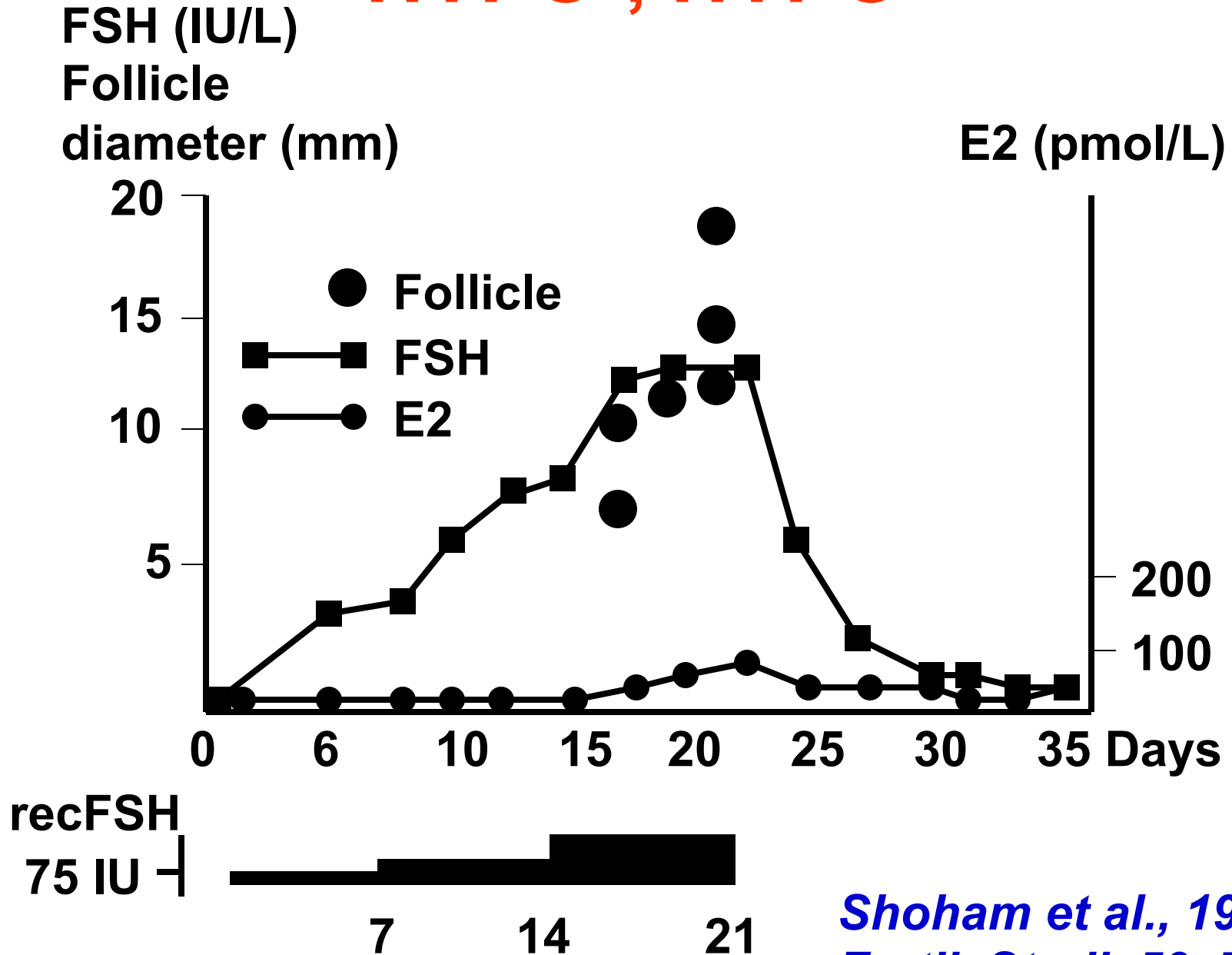
Ongoing pregnancy rate

1.36 (95% CI 1.04-1.79) ITT (n=11 studies)

Live birth rate: NS

*Lehert et al., 2014
Reprod. Biol. Endocrinol. 12, 17*

HYPO-, HYPO-



*Shoham et al., 1993
Fertil. Steril. 59, 738-42*

HYPOGONADOTROPHIC HYPOGONADISM (Usage of rFSH plus rLH)

	FSH IU	LH IU	E2 (pmol/l)
Couzinet et al., 1988	225 (HMG)	225 (HMG)	2753
Kousta et al., 1996	150	225	780
El-Shawarby et al., 2004	50-75	75	3155

Based on a review by:

Messinis, 2005

Hum. Reprod. 20, 2688-97

LH Supplementation

- ***Not necessary in unselected population***
- ***Possibly beneficial in poor responders***
- ***Absolutely necessary in hypogonadotropic hypogonadism***

Youssef et al. 2014

Cochrane Database Syst. Rev. Oct 31

OUTLINE

- GnRH analogues
- Mild protocol
- GnRH agonist triggering
- Exogenous LH
- **Role of AMH**

AMH IN DESIGNING PROTOCOLS

AMH < 2.2 pmol/l. Exclude, counsel,
Offer alternative ART

AMH 2.2-15.6 pmol/l. 300 IU hMG+GnRH
antagonist from day 6 of stimulation

AMH 15.7-28.6 pmol/l. 200 IU rFSH or
225 IU hMG in Long down regulation
protocol + GnRH agonist

AMH > 28.6 pmol/l. 150 IU hMG+GnRH
Antagonist from day 6 of stimulation

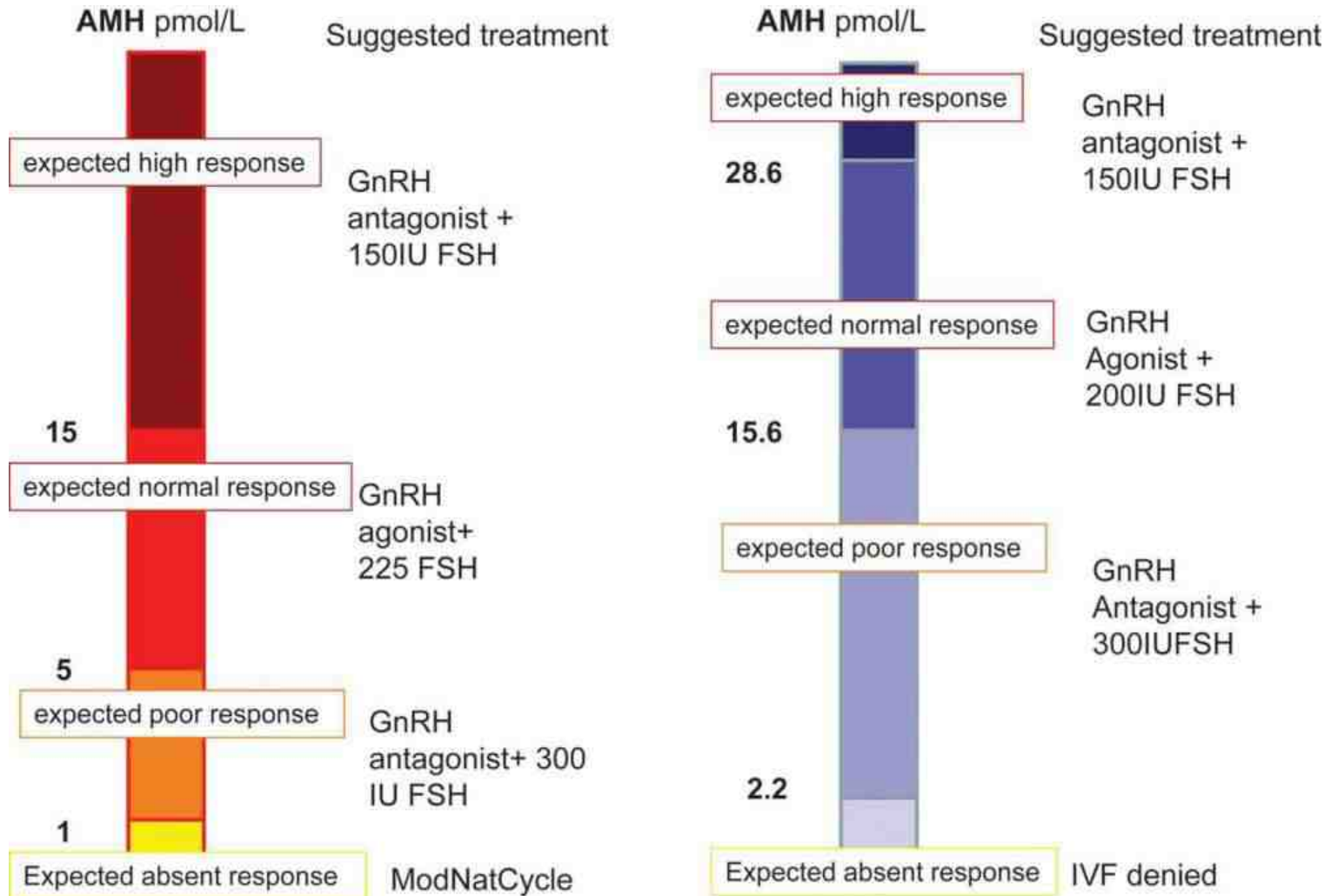
Retrospective

Pregn. rate ↑
Live birth rate ↑
OHSS ↓

AMH: 423 women
Conventional: 346 women

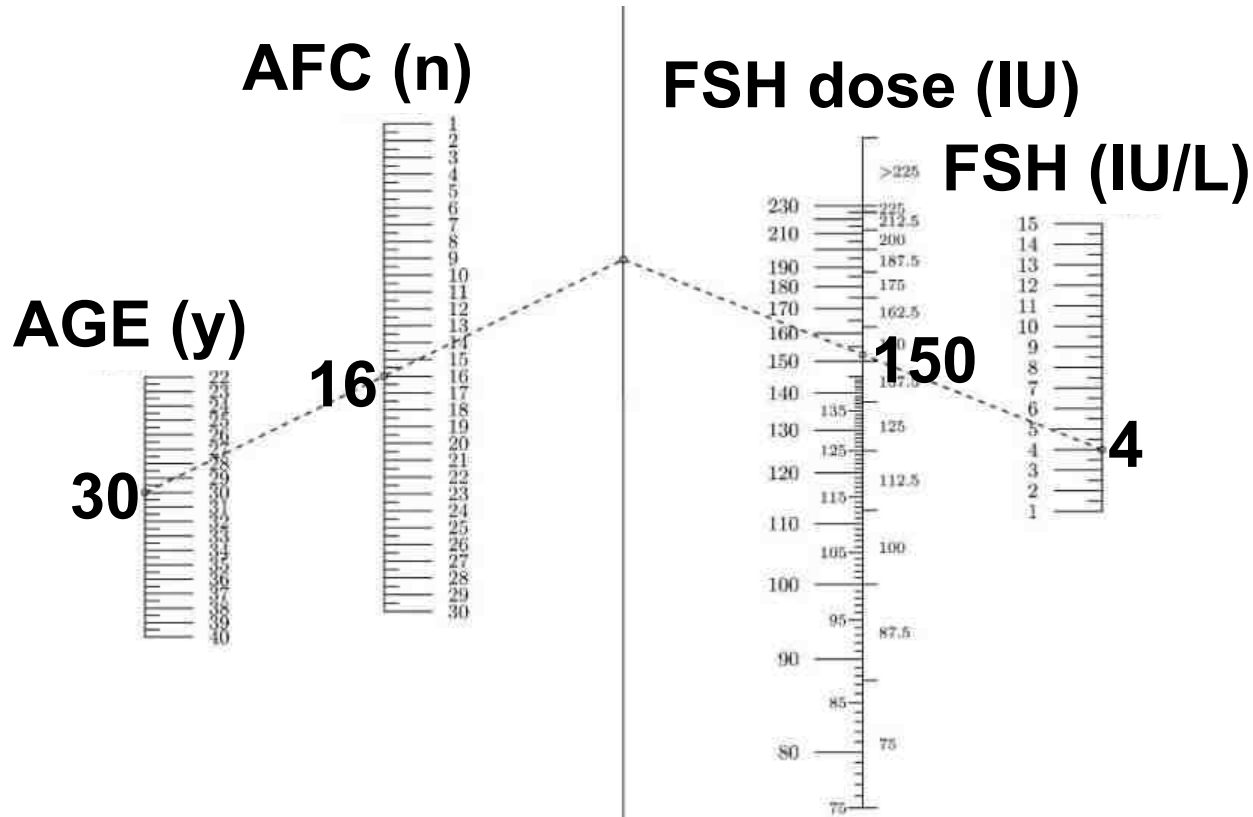
Yates et al., 2011
Hum. Reprod. 26, 2353-62

Strategic modelling of controlled ovarian stimulation on the basis of ovarian reserve



***La Marca & Sunkara, 2014
Hum. Reprod. Update 20, 124-40***

NOMOGRAM FOR CALCULATION OF FSH STARTING DOSE



*La Marca & Sunkara, 2014
Hum. Reprod. Update 20, 124-40*

TAKE HOME MESSAGES (1)

- **There are several debatable issues in ovarian stimulation**
- **Multiple follicular development disrupts the endocrinology of the normal cycle**
- **GnRH antagonists are equally efficacious with agonists but less effective in preventing the LH surge**
- **Mild ovarian stimulation protocols are clinically effective**

TAKE HOME MESSAGES (2)

- **Triggering final oocyte maturation with a GnRH agonist reduces markedly OHSS**
- **Supplementation of FSH with rLH is not justified in unselected population**
- **The use of AMH or AFC may help in designing patient's friendly protocols**



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