Pergoveris® – uloga LH u stimulaciji ovulacije

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RAZOTKRIVANJE

Predavač prezentira u ime tvrtke Merck koja je sponzor ovog predavanja. Prikazane informacije u skladu su sa svim primjenjivim zakonima.
Samo za zdravstvene radnike.

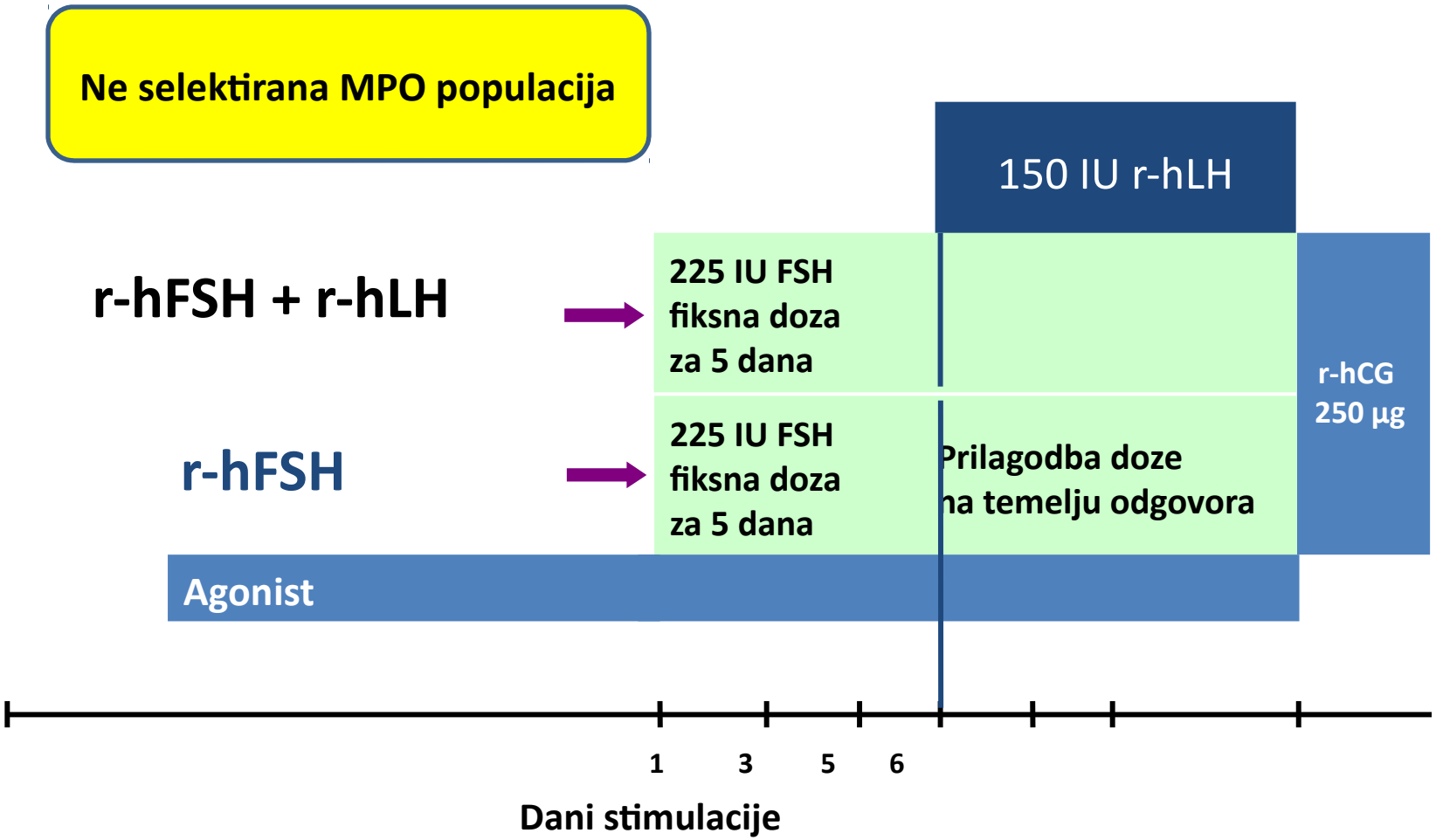
- Stimulacija ovulacije
- Primjena r-hLH
- Fiksna kombinacija r-hFSH + r-hLH
- Rezultati studija

PRIMJER 1

- Dokazi za korištenje r-hLH u:

  Ne selektiranoj MPO populaciji

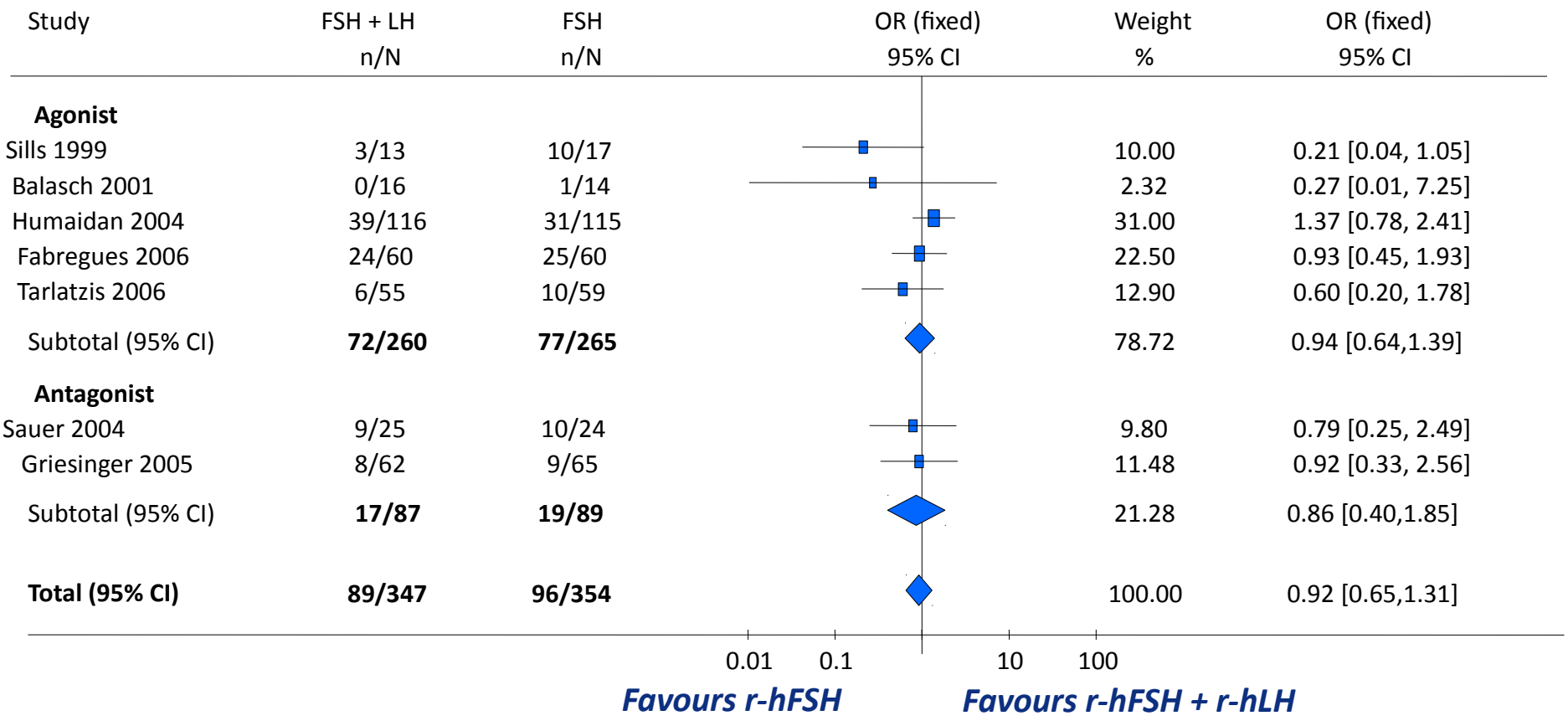
Komparativne MPO studije



adapted from Buhler et al. Recombinant human LH supplementation versus supplementation with urinary hCG-based LH activity during controlled ovarian stimulation in the long GnRH-agonist protocol. *Gynec Endocr,* 2012; 28(5): 345–350

Ne selekcionirana MPO populacija – Stopa živorođenih

r-hFSH vs r-hFSH + r-hLH (Kolibianakis EM, Hum Reprod Update, 2007)



Marginalno u korist r-hFSH, bez vjerodostojne razlike

Sažetak

- Dodavanje LH nije pokazalo korist u neselektiranih MPO pacijentica

- Određene podgrupe pacijentica mogu imati korist od dodavanja LH

Primjer 2

- Dokazi za upotrebu r-hLH u skladu:

Ovarijski odgovor

Stopa trudnoća vs r-hLH i bazalni FSH

	STOPA TRUDNOĆA	
	Bazalni FSH <10 IU/L	**Bazalni FSH ≥10 IU/L**
Samo FSH	22% (n=180)	0% (n=26)
37.5ij rLH	20% (n=69)	31% (n=26)
75ij rLH	34% (n= 47)	26% (n=23)

P<0.05

Lisi et al 2005 Fertil Steril 83, 310-315

Supplementation with r-hLH for Women showing hypo-responsiveness to FSH under GnRH agonist down-regulation

(Ferrareti et al 2004 SISMER Reproductive Unit, Italy)

Hyporesponsiveness

- Normal initial follicular recruitment
- (10 antral follicles >8 mm in diameter and E2 >100 pg/mL)

Between day 7 and day 10 of the cycle

- plateau of follicular growth
- no increase in the E2 level nor follicular size
- while continuing the same FSH dosage.

Ferraretti et al 2004 Fertil Steril 82, 1521-1526.

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- Of ***1,009 patients 130 patients were identified*** as Hyporesponsive to FSH and randomised to:
  - Group A (n = 54) increased dosage of FSH
  - Group B (n = 54) recombinant LH and increased dose of FSH
  - Group C (n = 22) given additional FSH and LH using hMG
  - Group D (n = 54) age-matched control normal responders

Hyporesponsiveness to FSH

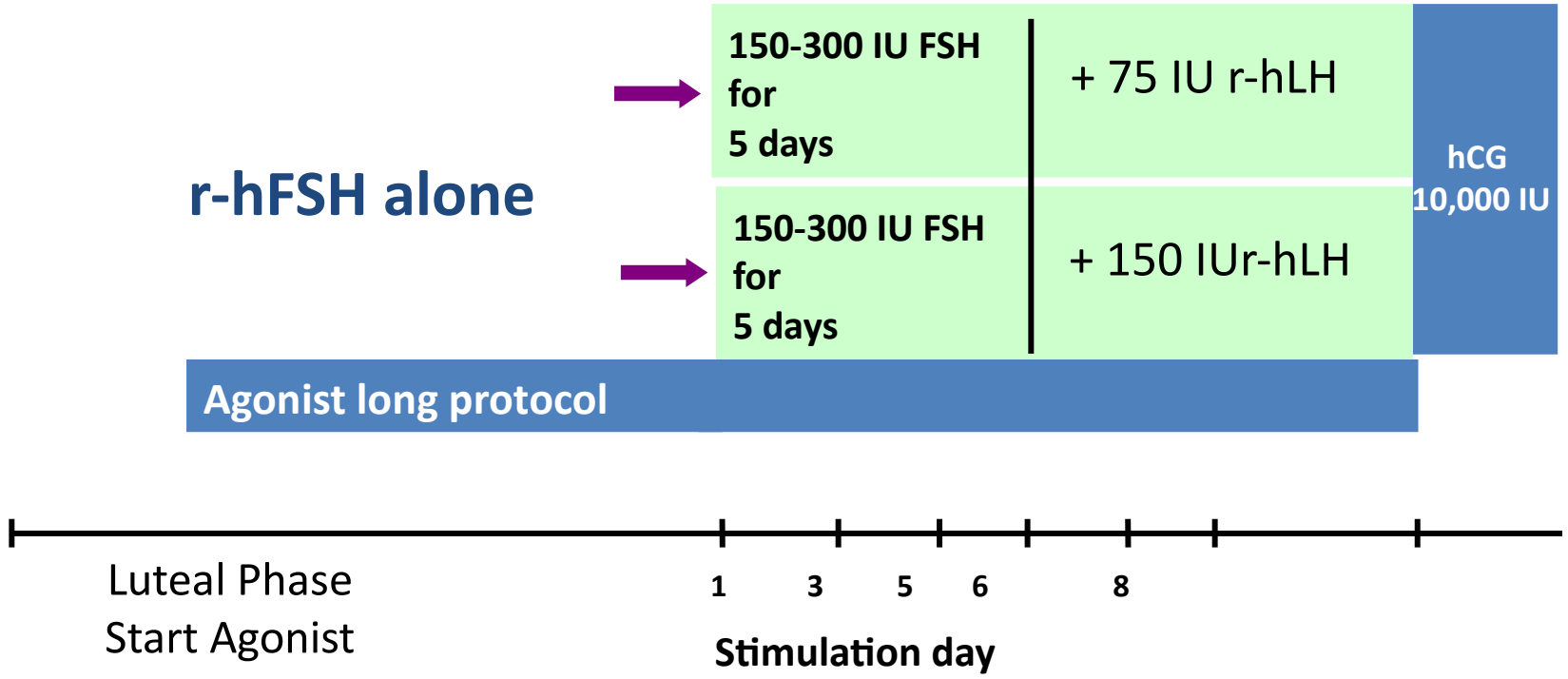
(Ferraretti et al 2004 Fertil Steril 82, 1521-1526)

	A. Increase r-hFSH	B. r-hLH & r-hFSH	C. HMG & r-hFSH	D. Control
N patients	50	54	22	54
Mean age	31.7	31.5	32.0	31.8
E2 level day hCG (pg/ml)	1020 *	1731	1539	1691
N oocytes	8.2 *	11.1 *	10.9	9.8
Preg rate / ET	24.4%*	54.0% *	11.0%	41.0%
IR	14.1%	36.8%	7.4%	35.4%
LH level on Day 7	0.99 ± 0.7	1.02 ± 1.3	1.3 ± 1	0.93 ± 0.6

* ***p< 0.05***

Poor responders to stimulation (E2<180 pg/ml, no follicle >10 mm) randomized (day 8) to 75 IU r-hLH vs 150 IU r-hLH

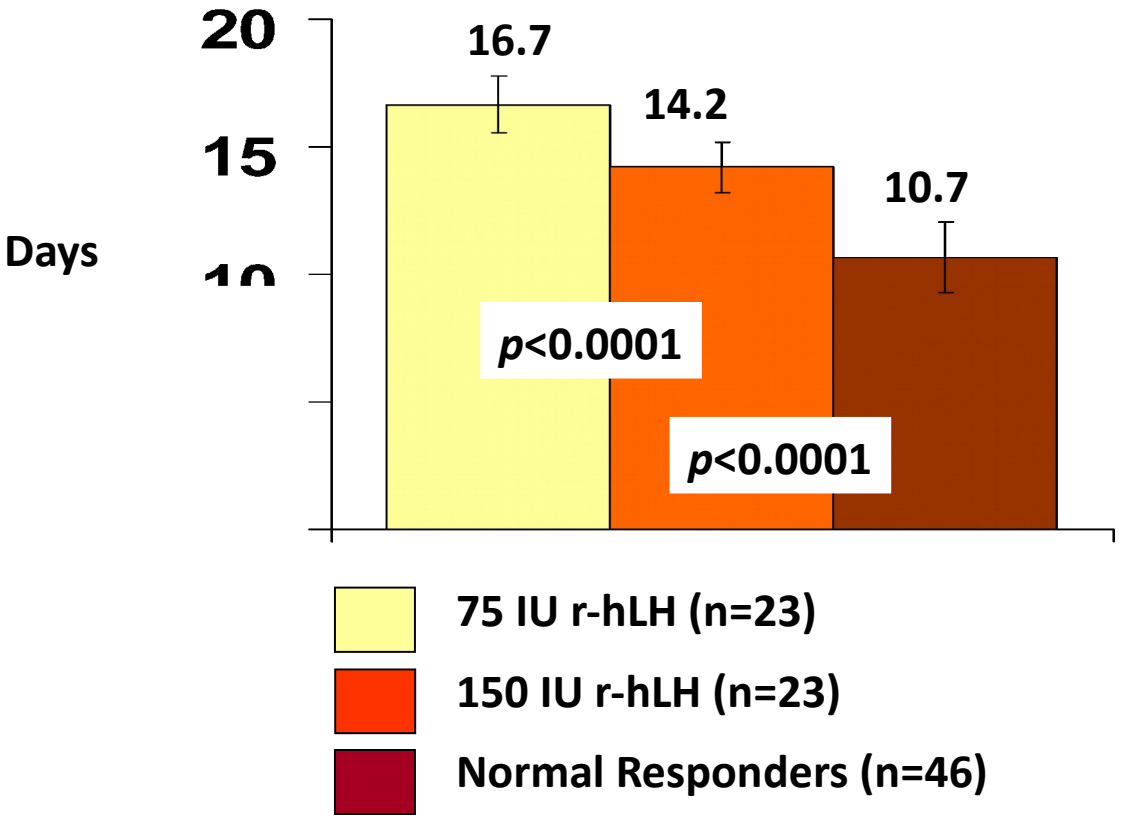
Control: normal responders hence no need for r-hLH



De Placido et al. 2004 Clinical Endocrinology 60, 637–643

75 IU r-hLH vs 150 IU r-hLH

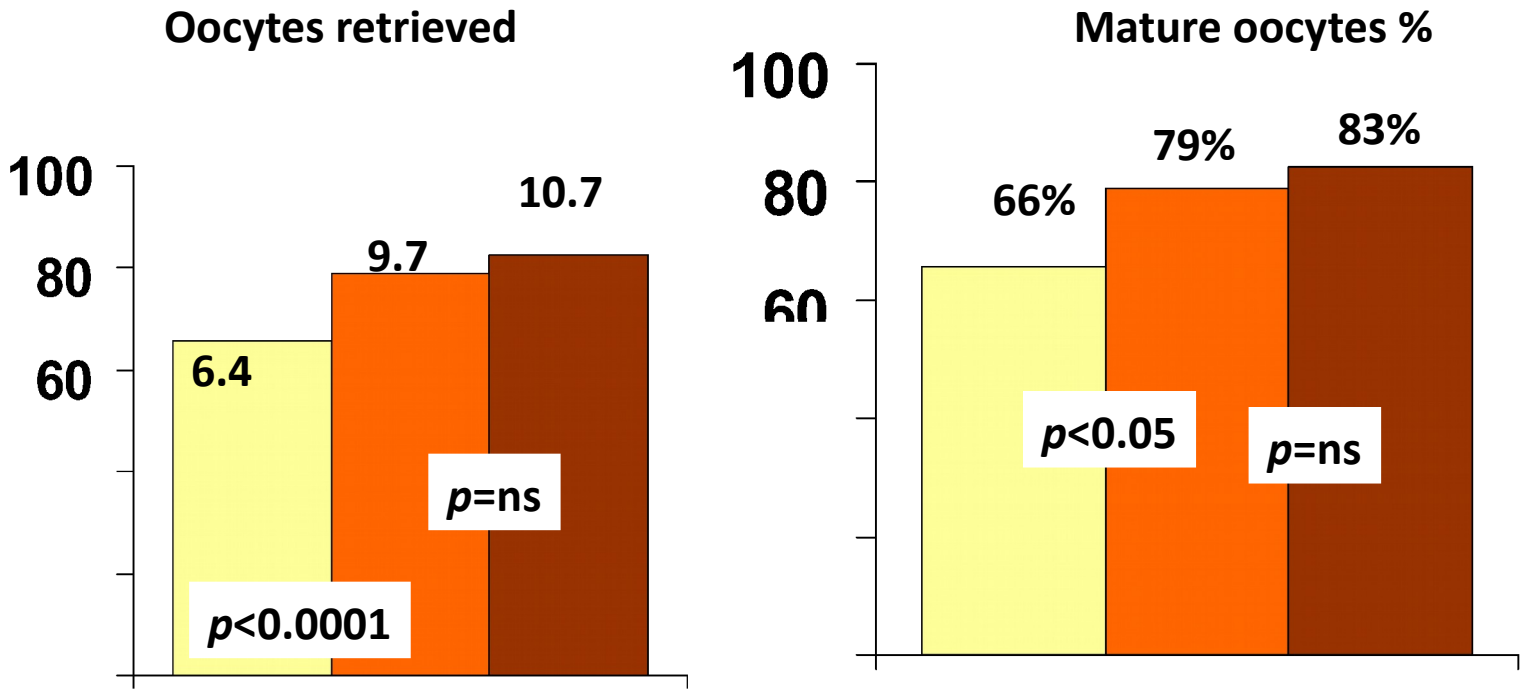
ART Results: days of ovarian stimulation



De Placido et al, 2004

75 IU r-hLH vs 150 IU r-hLH

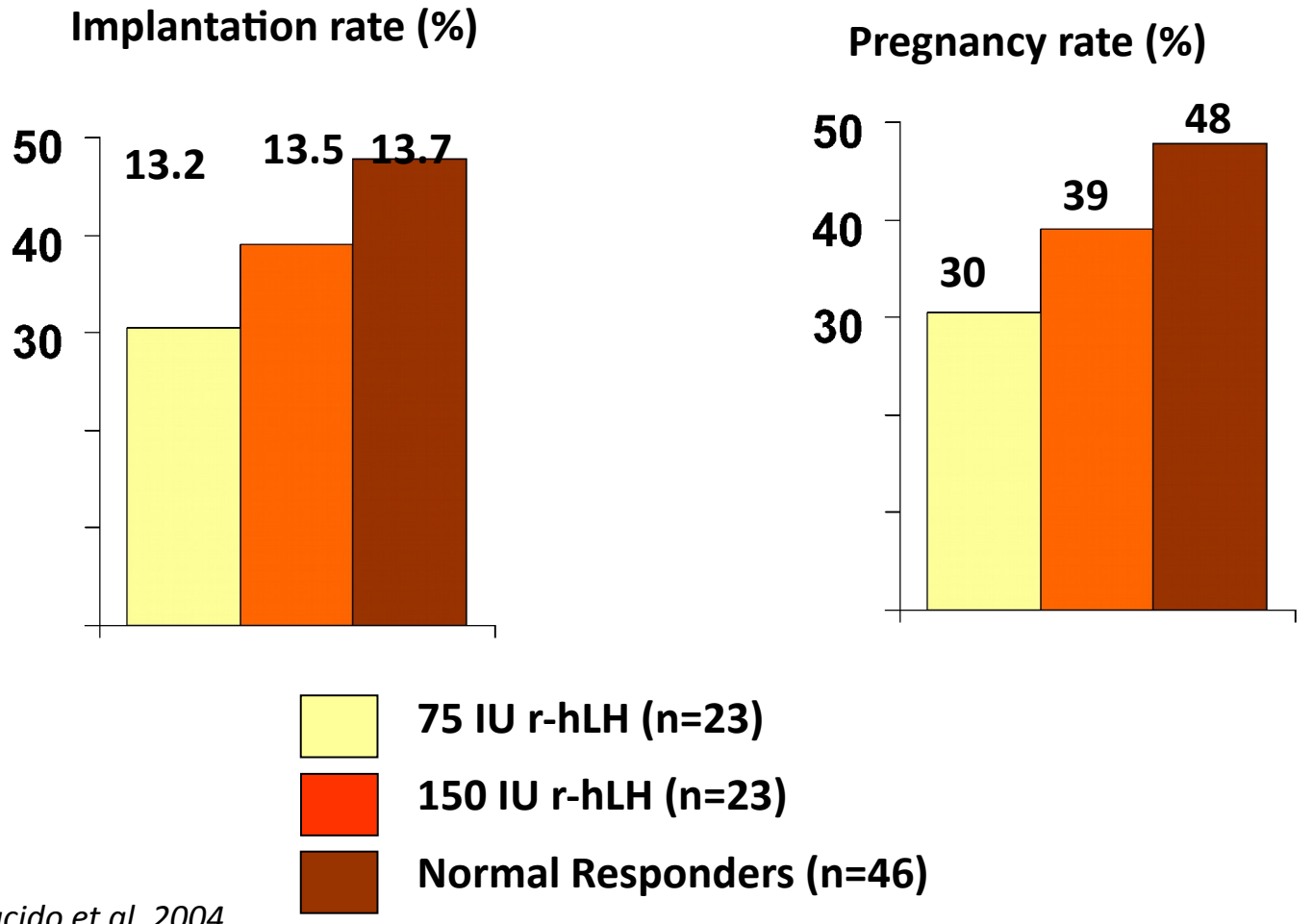
ART Results: oocytes



De Placido et al, 2004

75 IU r-hLH vs 150 IU r-hLH

ART Results: IVF/ICSI outcome



De Placido et al, 2004

De Placido et al. 2004

- Optimalna doza r-hLH za MPO je 75ij r-hLH dnevno.
- Rezultati studije sugeriraju višu dozu 150ij r-hLH dnevno.
- To je u suprotnosti s preporučenom dozom od 75ij r-hLH dnevno u hipogonadalnih hipogonadotropnih pacijentica.

Italian Collaborative Group on Recombinant Human Luteinizing Hormone

(De Placido et al. 2005 Human Reprod 20, 390–396)

- 225 IU FSH daily following depot GnRH agonist

“Steady response”:

Day 8 stimulation

- Patients with serum E2 levels <80 pg/ml
- Ultrasound evidence of at least six follicles ranging between 6 and 10 mm,
- No follicle with a mean diameter >10mm (‘steady response’) from day 5 to day 8.

Italian Collaborative Group on Recombinant Human Luteinizing Hormone

(De Placido et al. 2005 Human Reprod 20, 390–396)

- Of **1,389 patients, 130 patients were identified as "Steady response"** and randomised to:
  - Group A (n = 65) received 150 IU of r-hLH daily while maintaining same daily dose of r-hFSH
  - Group B (n = 65) had an increase of 150 IU in the daily dose of r-hFSH (step-up protocol).
  - Group C (n=130) normally responding control women

“Steady response” to FSH

(De Placido et al. 2005 Human Reprod 20, 390–396)

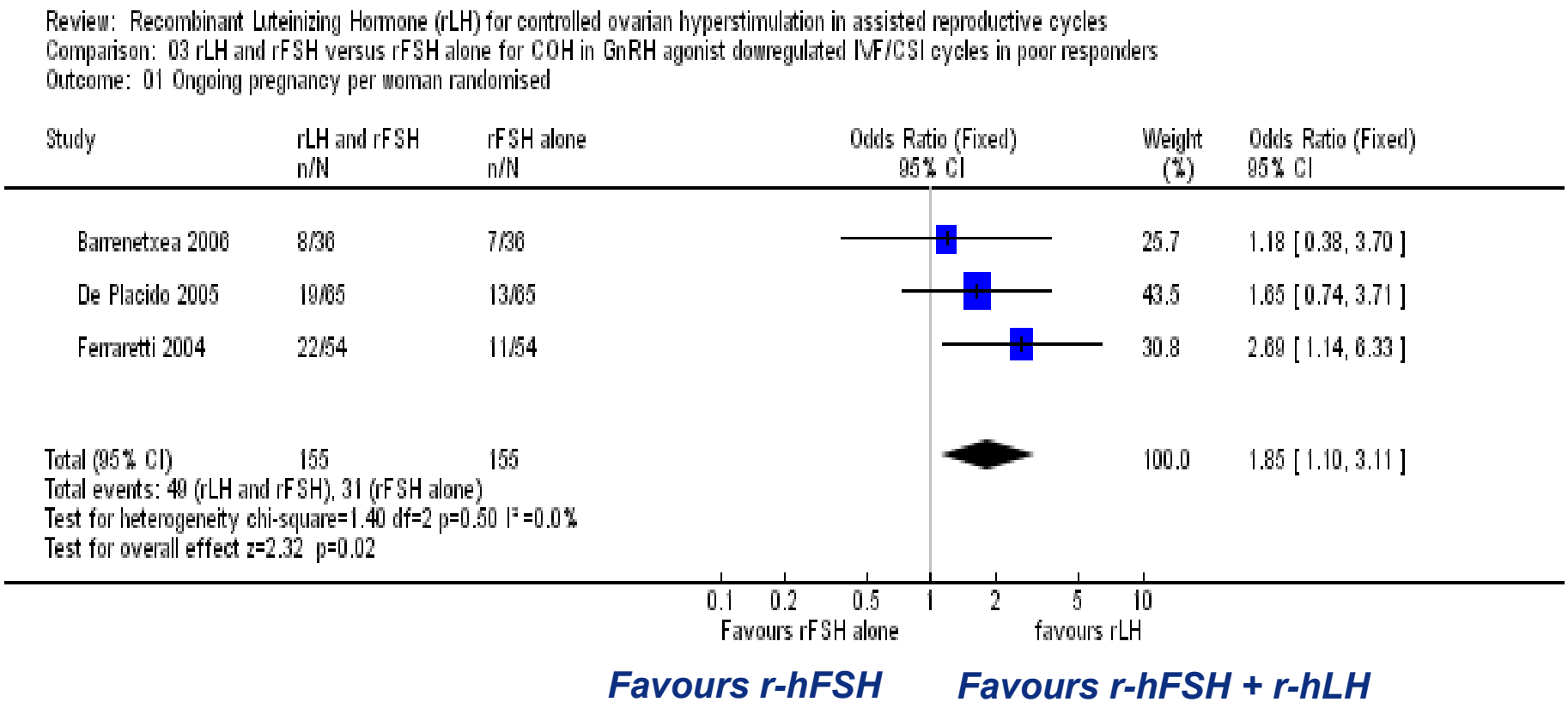
	A r-hLH 150IU & r-hFSH	B Increased r-hFSH 150IU	C Control
	N=59	N=58	N=112
Mean age	31.5	30.4	30.4
E2 level day hCG (pg/ml)	1779**	1248 **	2377
N oocytes	9.0 *	6.1 *	10.5
Ongoing Preg rate /cycle	32.5%	22.0%	40.2%
Implantation Rate	14.2%	10.5%	18.1%
Serum LH level	1.2	1.2	1.5

** **p< 0.001**

* **p< 0.01**

Poor responders r-hFSH alone vs r-hLH + r-hFSH

(Mochtar MH, Cochrane Database, 2007 issue 2)



Favours r-hFSH ***Favours r-hFSH + r-hLH***

Sažetak

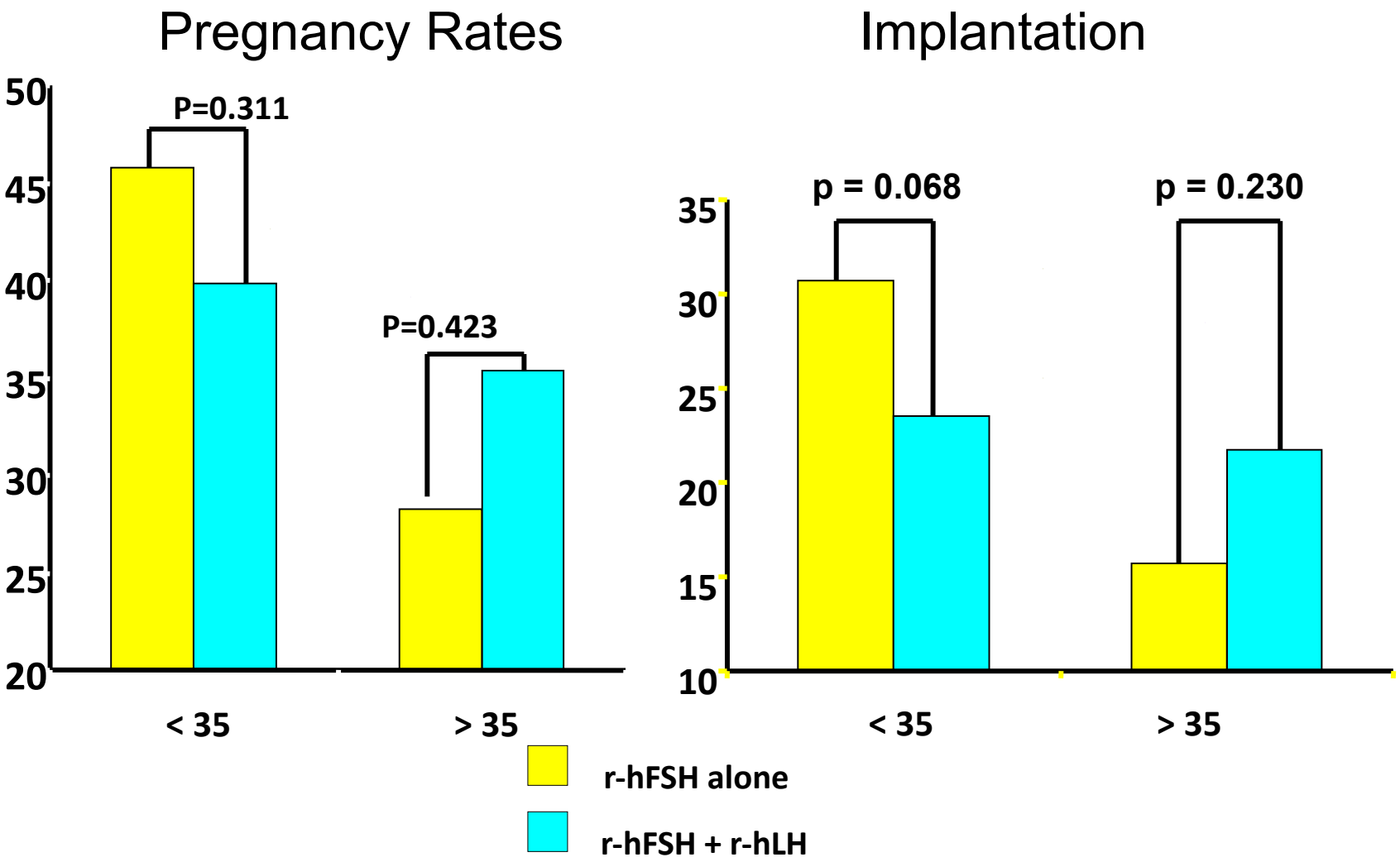
- Žene s umanjenim odgovorom na FSH mogu imati koristi od egzogenog r-hLH.
  - r-hLH može poboljšati razvoj oocite, implantaciju i stopu trudnoća u hiporespondersa na FSH.
- Cirkulirajuće razine LH nisu prediktivne kakav će biti odgovor

Primjer 3

- Dokazi za upotrebu r-hLH u skladu:

Dob pacijentice

Marrs et al, 2004

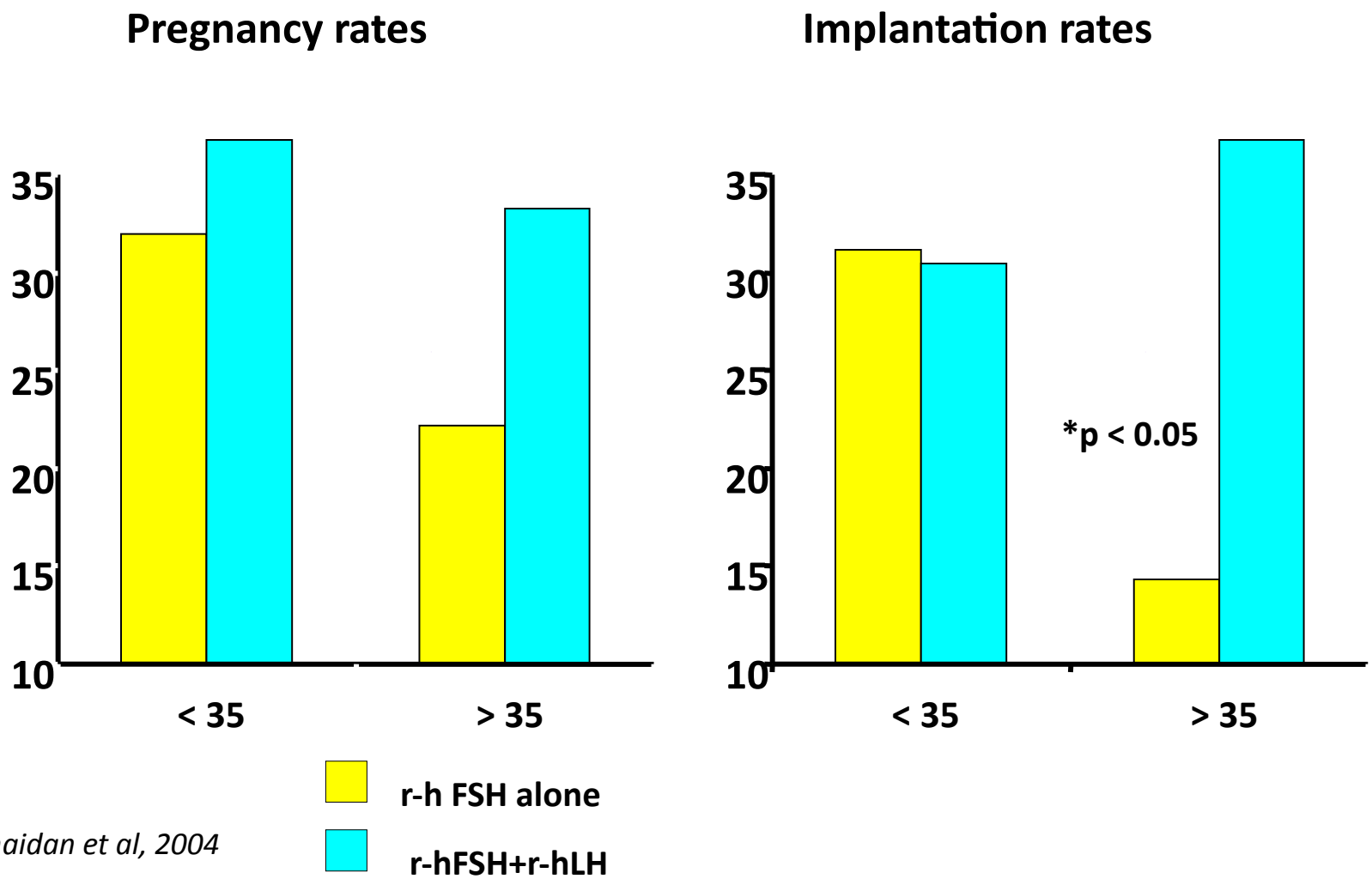


Humaidan et al., 2004

	< 35 years		> 35 years	
	With r-hLH	Without r-hLH	With r-hLH	Without r-hLH
Cycles (no)	95	97	21	18
Age (years)	29.4	29.3	37.0	37.2
Total dose of FSH (IU) (mean)	1961	1835	2225	2797 *
Duration (days)	11.2	11.2	10.6	11.0

*** p < 0.001 compared to 1835**
*** p < 0.05 compared to 2225**

Pregnancy and Implantation Rates

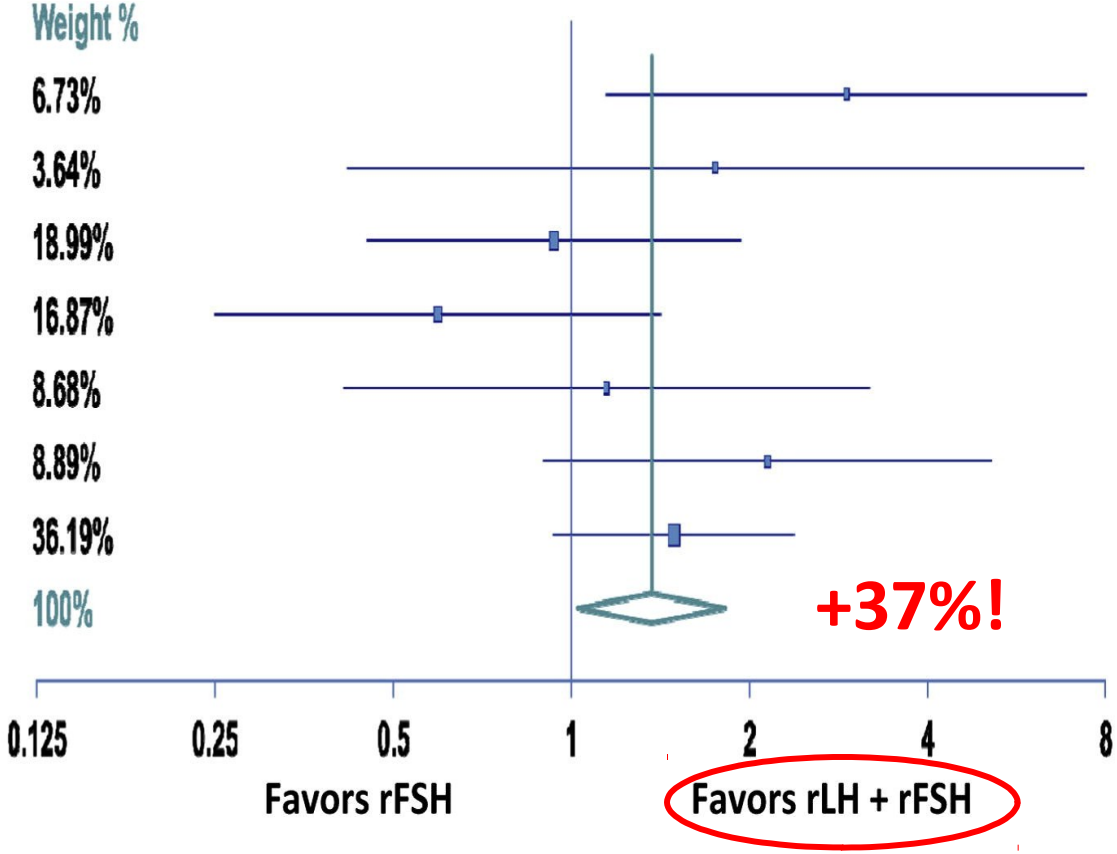


Humaidan et al, 2004

Upotreba r-LH u MPO u starijih žena

stopa kliničkih trudnoća

Study	Sample size (patients)	Measure (CI)	Weight %
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%
NyboeAndersen 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%



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

Sažetak

- U žena < 35 godina dodatak r-hLH ne donosi dobitak uz r-FSH
- U žena ≥ 35 godina dodatak r-hLH povezan je s nižom potrebnom dozom r-FSH, većom stopom implantacije i trudnoća.
- Dodatak LH možda može nadoknaditi smanjenje plodnosti zbog dobi, no potrebno je to potvrditi budućim studijama

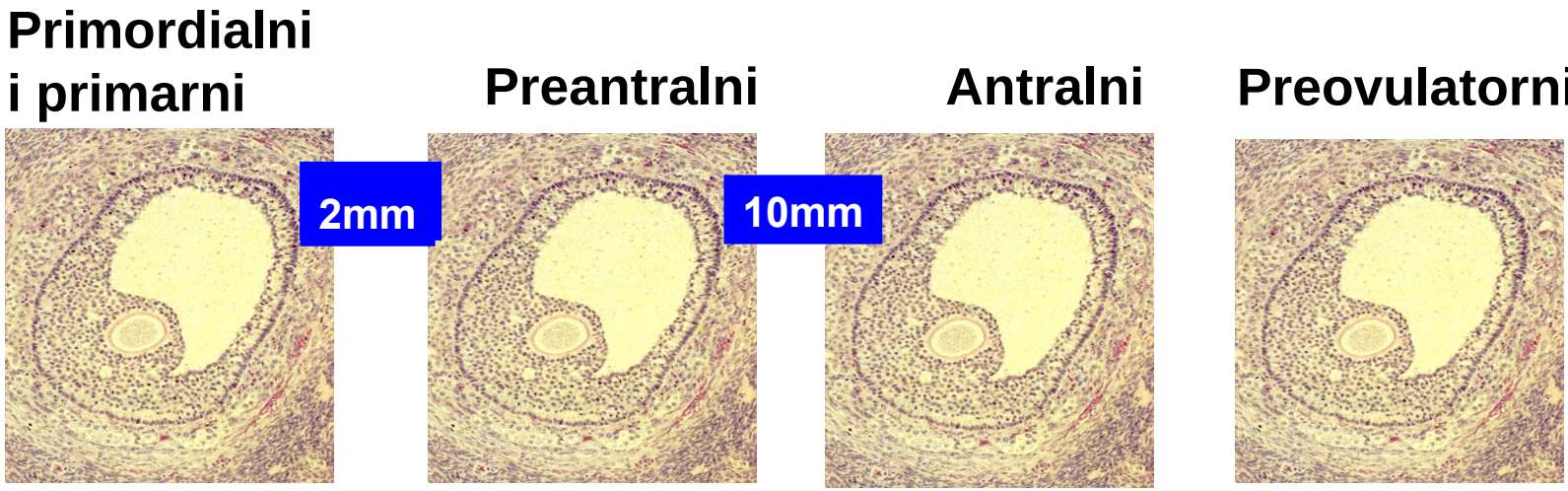
Pergoveris® kod pacijentica s teškim nedostatkom FSH i LH

Pergoveris® za pacijentice s teškim nedostatkom FSH i LH

- Dvostanična dvogonadotropinska hipoteza
- Uloga FSH i LH u menstruacijskom ciklusu
- Europska studija o dozi r-LH
- Iskustvo korištenja r-hLH za indukciju ovulacije kod pacijentica s teškim nedostatkom FSH i LH
- Pergoveris bioekvivalencija

SPC Pergoveris

Dvo stanična – dvo gonadotropinska hipoteza



Granuloza stanice	**FSH**	**FSH and LH**
Theca stanice	**LH**	**LH**

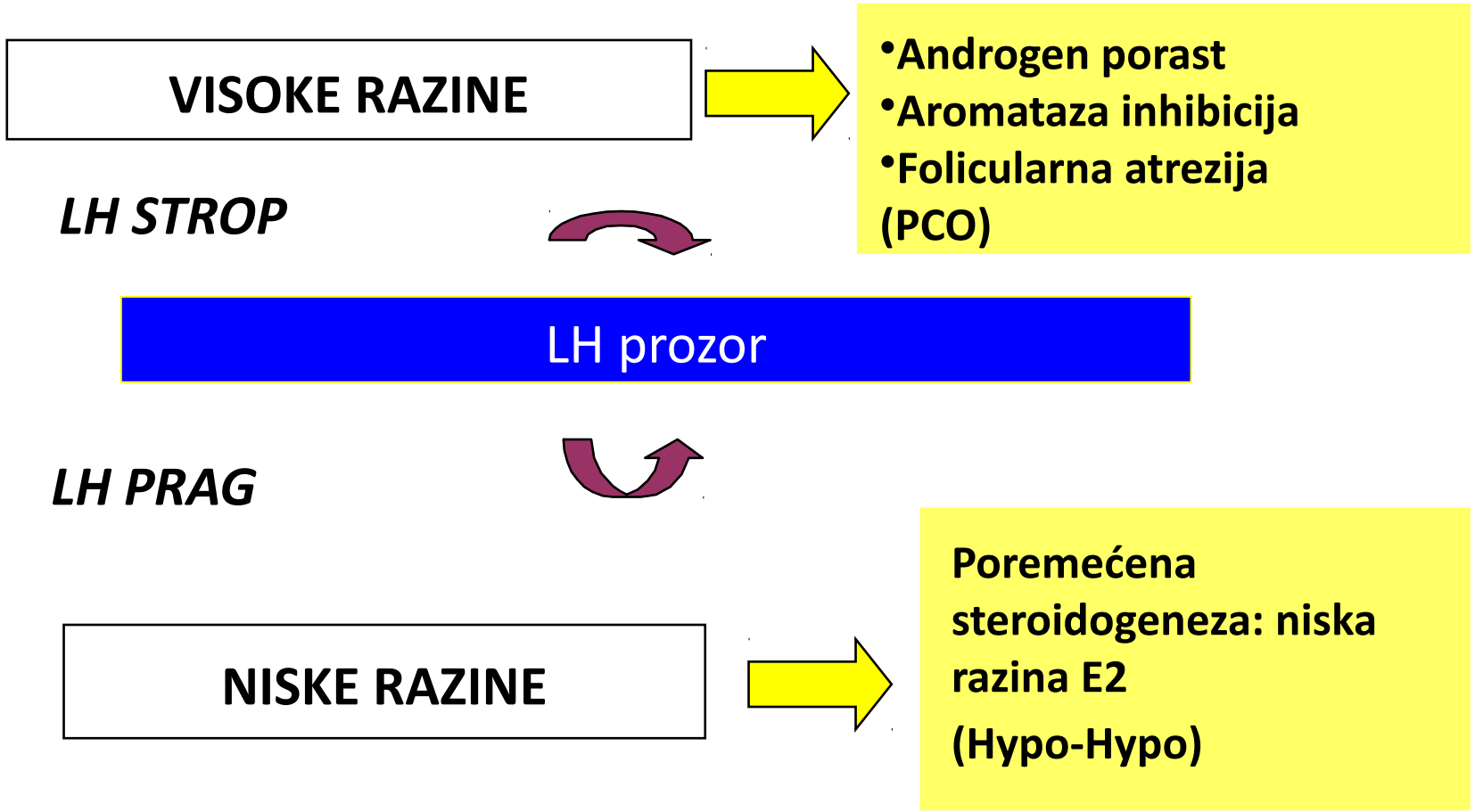
Uloga FSH u menstruacijskom ciklusu (temelj za dominanciju i selekciju)

1. Potiče razvoj folikula
2. Inducira aromataznu aktivnost u granuloza stanicama
3. Inducira sekreciju estradiola
4. Inducira LH receptore na granuloza stanicama
5. Negative povratna sprega za vlastitu sekreciju: temelj za dominantnost

Uloga LH u menstruacijskom ciklusu

Folikulinska faza	Sredina ciklusa	Luteinska faza
Potiče androgenu sekreciju u teka st. Sinergijsko djelovanje s FSH u stvaranju estrogena Podrška dominaciji kad se razina FSH smanji	Nastavak mejoze u oociti Sazrijevanje cumulus oophorus s oocitom Ruptura folikula Luteinizacija granuloze	Održavanje žutog tijela i sekrecija progesterona

LH učinak je ovisan o dozi

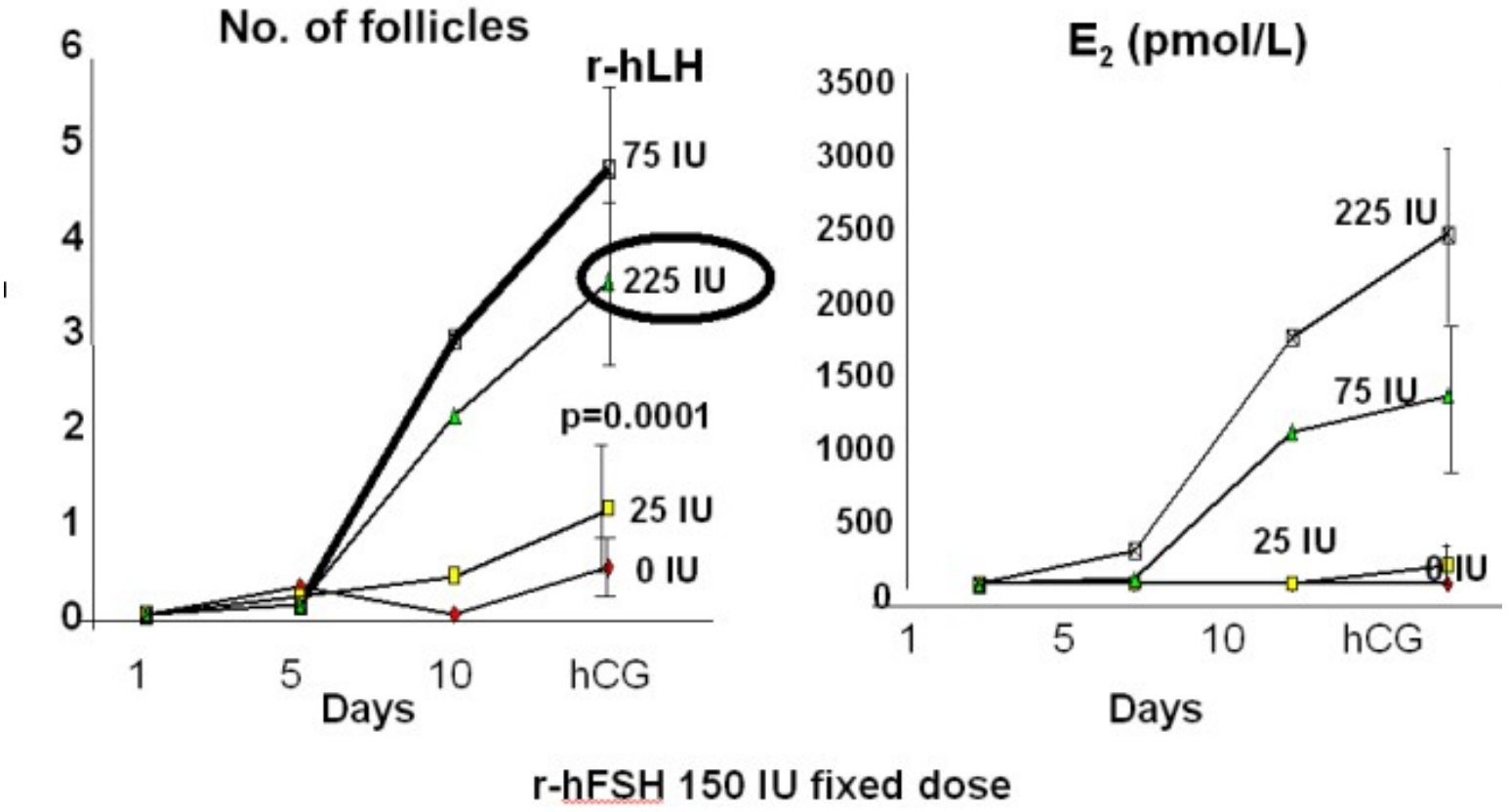


Hillier SG, Hum Reprod. 1994, 9:188-191

Sažetak

- FSH koncept praga (threshold concept)”: regrutacija i rast folikula je ovisan o pragu FSH. Ispod praga je folikularni rast zaustavljen ***(Brown, 1978)***
  - Inicijalni folikularni rast je neovisan o LH.
  - LH prag je potreban za adekvatnu steroidogenezu
- LH koncept stropa (ceiling concept)”: rastući folikuli trebaju ograničenu količinu LH. Iznad te razine progresija je zaustavljena. ***(Hillier, 1994)***
  - Visoka razina r-LH može zaustaviti rast folikula

LH study group – LH dose finding study



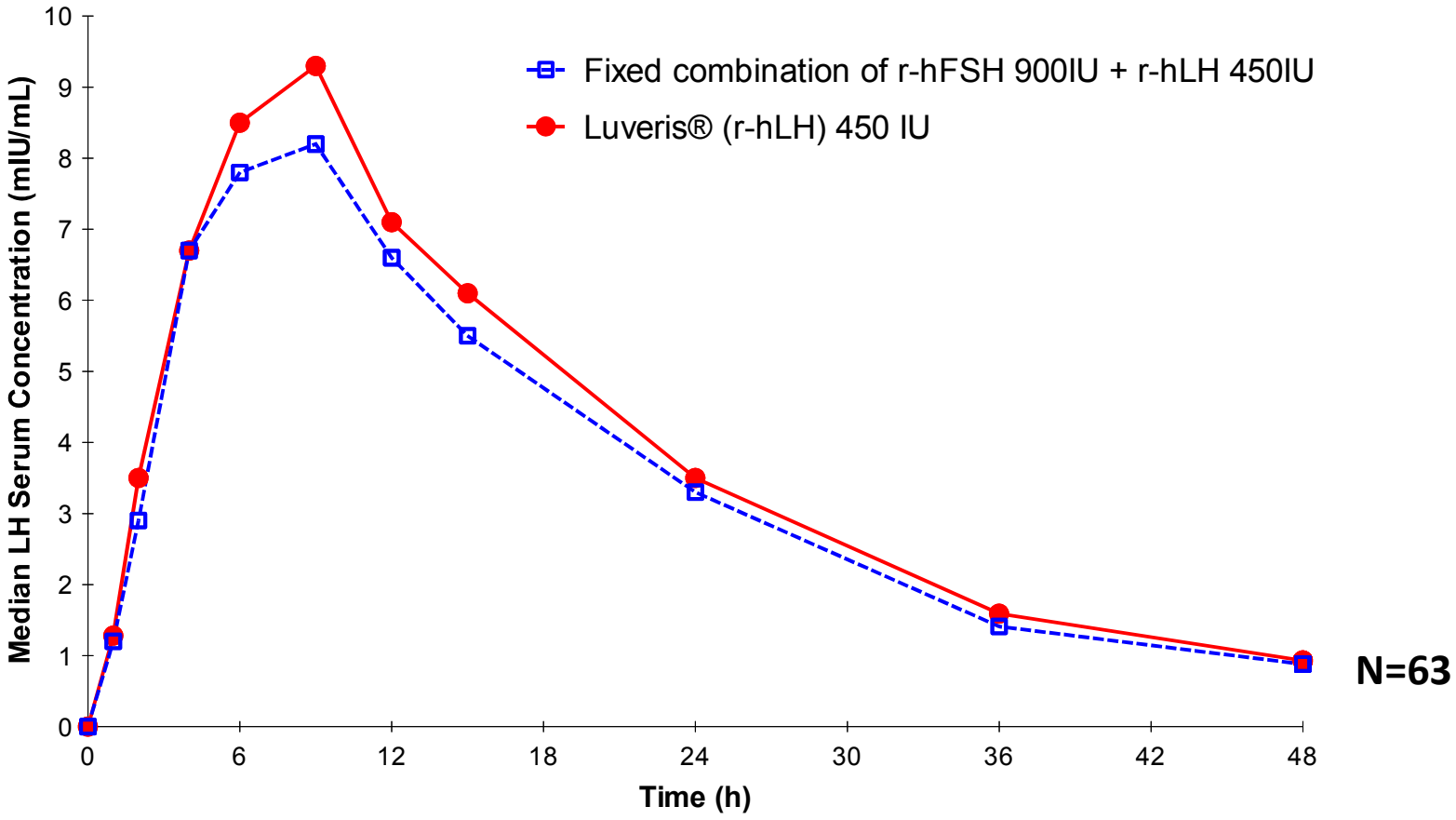
The European Recombinant Human LH Study Group, *JCEM* 1998; 83:1507

LH study group – Stope trudnoća

Groups	n	hCG cycle (%)	Clinical pregnancy rate per initiated hCG (%)	Clinical pregnancy rate per
0 IU	8	2 (25%)	0/8 (0%)	0/2 (0%)
25 IU	10	5 (50%)	0/10 (0%)	0/5 (0%)
75 IU	12	7 (58%)	2/12 (17%)	2/7 (29%)
225 IU	9	5 (56%)	1/9 (11%)	1/5 (20%)
75 + 225 IU	21	12 (57%)	3/21 (14%)	3/12(25%)

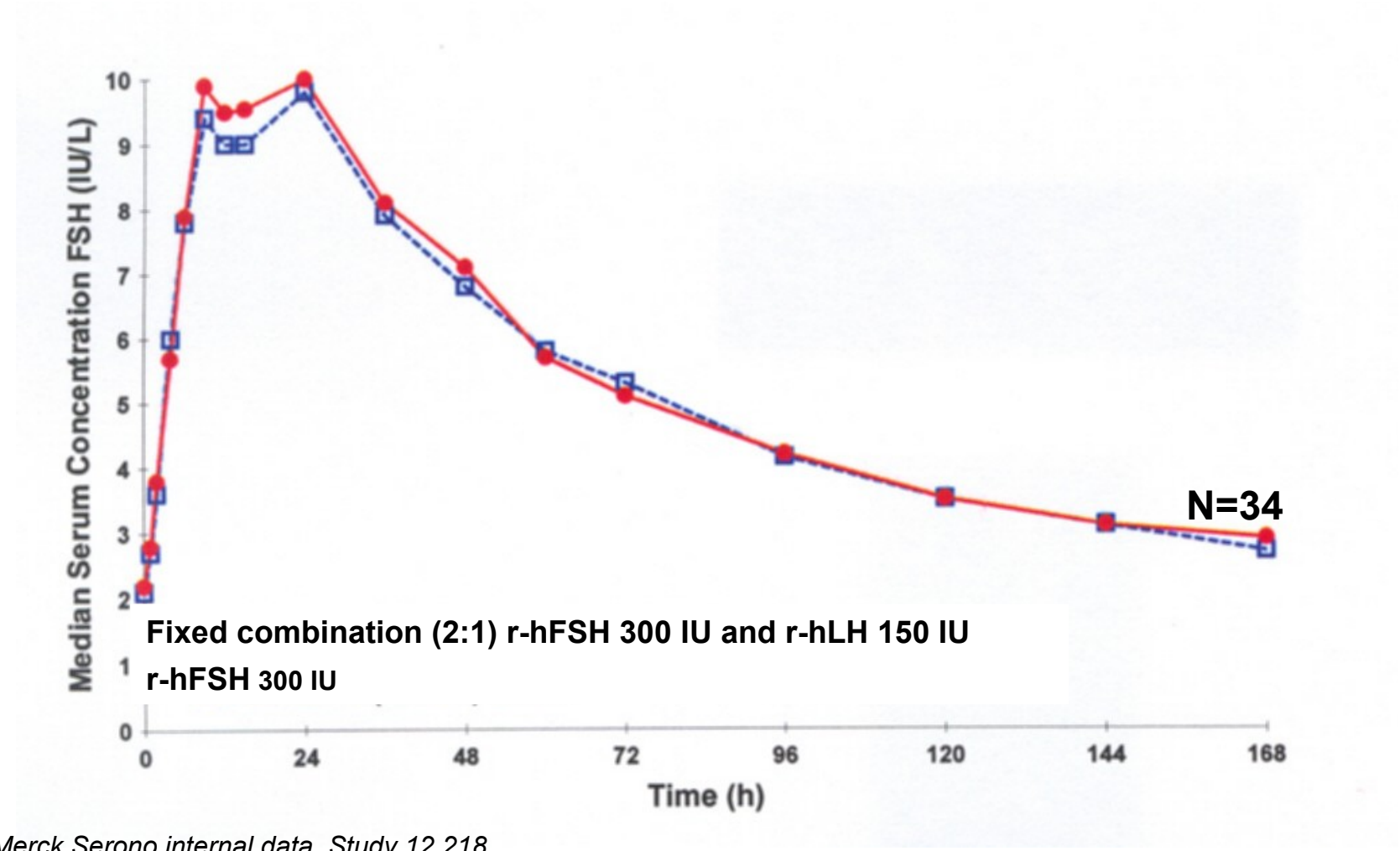
The European Recombinant Human LH Study Group, JCEM 1998; 83:1507

Srednja vrijednost LH u serumu nakon sc primjene 450 i.j. r-hLH vs. r-hLH u fiksnoj kombinaciji s 900 i.j.r-hFSH



Merck Serono internal data, Study 12,219

Srednja vrijednost LH u serumu nakon sc primjene 150 i.j. r-hLH vs. r-hLH u fiksnoj kombinaciji s 300 i.j.r-hFSH



Merck Serono internal data, Study 12,218

Zaključak

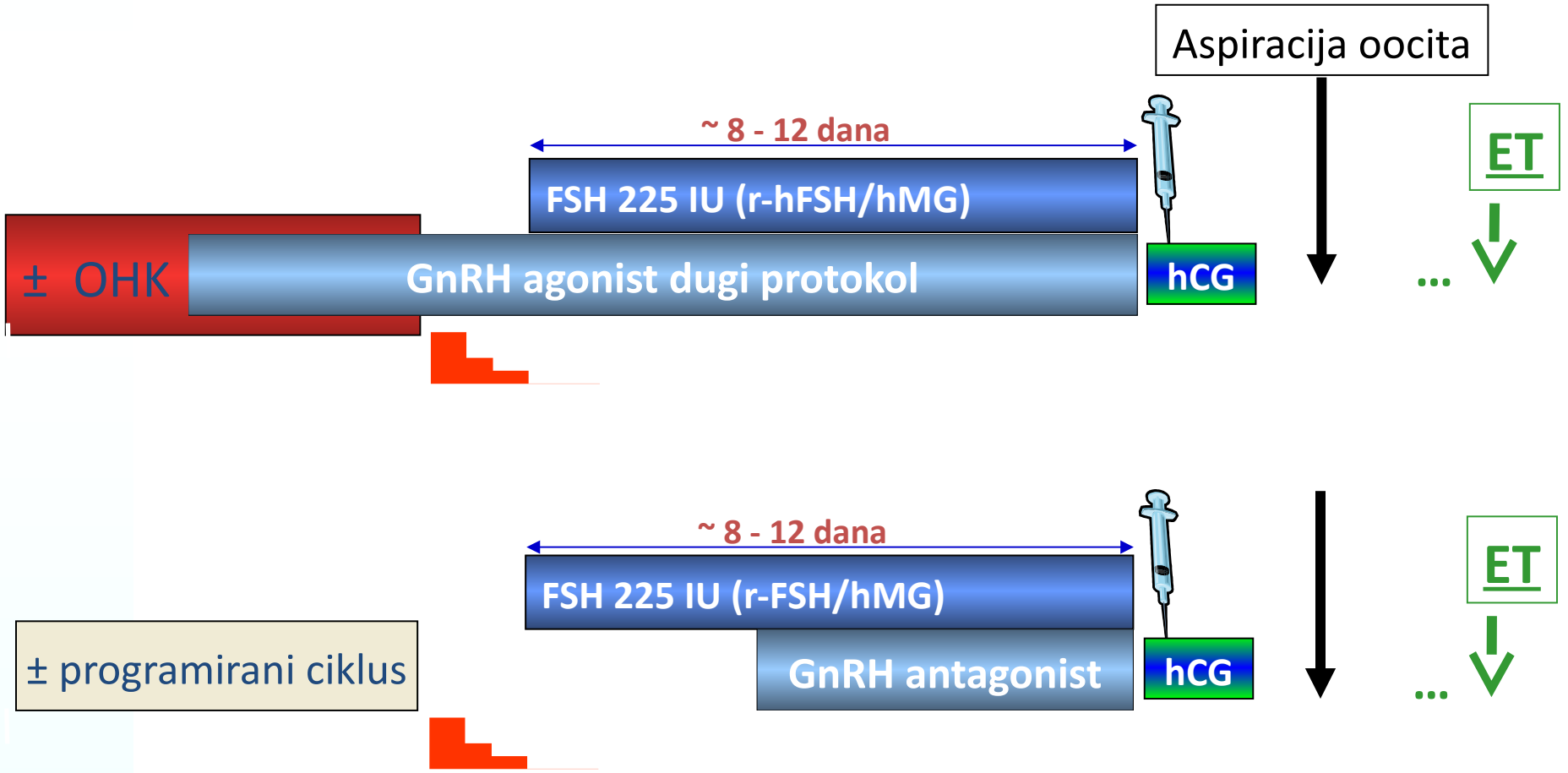
- Minimalna doza LH potrebna za indukciju ovulacije u pacijentica s teškim oblikom nedostatka LH je 75ij/dan.
- Optimalni odnos FSH i LH za indukciju ovulacije u navedenih pacijentica je odnos 2:1.

- Terapijske indikacije:
  - PERGOVERIS je indiciran za stimulaciju razvoja folikula u pacijentica s teškim nedostatkom FSH i LH.
  - U kliničkim studijama kriterij za odabir pacijentica je razina endogenog serumskog LH < 1,2 ij/L.

SPC Pergoveris

OVARIJSKA STIMULACIJA za IVF/ICSI

20. stoljeće **Fiksni protokol**



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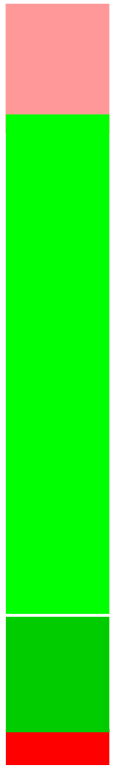
OVARIJSKA STIMULACIJA za IVF/ICSI

2016.: INDIVIDUALIZACIJA

INDIVIDUALIZACIJA

KRITERIJI:

- **dob**
- **BMI**
- **Očekivani ovarijski odgovor na AMH, AFC, ...**



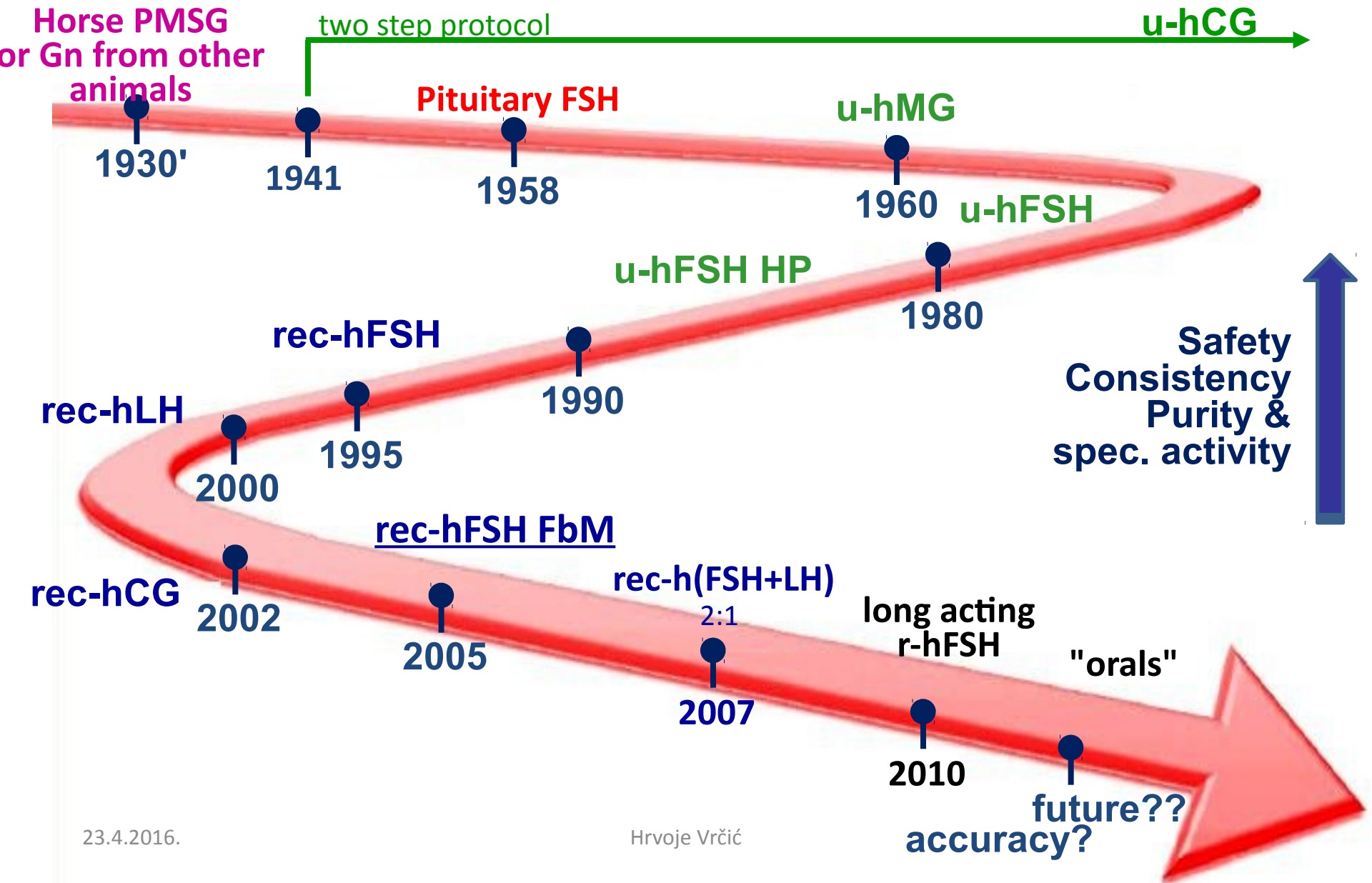
Snažni odgovor
Rizik OHSS

Normalni odgovor

Reducirani odgovor

Zanemariv odgovor

PREKRETNICE razvitak fertilitetnih lijekova



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- Normal initial follicular recruitment
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Between day 7 and day 10 of the cycle

- plateau of follicular growth
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Smanjeni odgovor na FSH

(Ferraretti et al 2004 Fertil Steril 82, 1521-1526)

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Mean age	31.7	31.5	32.0	31.8
E2 level day hCG (pg/ml)	1020 *	1731	1539	1691
N oocytes	8.2 *	11.1 *	10.9	9.8
Preg rate / ET	24.4%*	54.0% *	11.0%	41.0%
Implantation rate	14.1%	**36,8%**	7.4%	35.4%
Life birth rate /cycle	22,0%	**40,7%**	18%	37%
LH level on Day 7	0.99 ± 0.7	1.02 ± 1.3	1.3 ± 1	0.93 ± 0.6

* ***p< 0.05***

Zaključak

Smanjena osjetljivost na FSH može biti povezana uz nedostatak LH što sve zajedno može utjecati na kompetentnost oocite

Hipoteza ovog istraživanja da je potrebno povećati dozu FSH je pojedinačni biološki indeks (neizravni, ali vrlo specifičan) nedostatka LH, koji se ne može identificirati određivanjem razine LH u krvi.

Smanjena kompetentnost oocite ne može se povećati porastom doze FSH (grupa A). Može se povećati primjenom r-hLH (grupa B). Stopa trudnoća i implantacijska stopa su vjerodostojno veće u odnosu na grupu B i kontrolu.

Dodavanje male količine rekombinantnog LH može sačuvati kompetentnost oocite za stvaranje kvalitetnog zametka.

Ferraretti et al 2004 Fertil Steril 82, 1521-1526

Zašto su takve razlike LH aktivnost između

rec-hLH i u-hMG?

The more steps of purification applied, the higher the amount of real LH lost and the hCG spiked

Products	LH IU /vial	hCG IU /vial
Pergonal	**11-18** MetaClone **(n=3)**	**4.7-6.1** MetaClone **(n=3)**
Menogon (EU)	2.3-5.0 MetaClone (n=3)	11-18 MetaClone (n=3)
Repronex (US) similar to Menogon	n.a.	n.a
Menopur (Giudice 2001)	0.85 Delta	11.3 Delta
Menogon-HP	0.61 (n=7)	11.7 (n=7)
Menopur organon paper (EM)	**3 (n=6)**	**10 (n=6)**
Menopur current pubblication	**0.47 (n=6)** Delta	**11.3 (n=6) = 77 IU LH activity**

Approximately 95% of LH bioactivity in Menopur is due to presence of hCG

Claudio Wolfenson et al. , RBM Online 10, 4: 2006 van de Weijer et al. Reprod Biomed Online 2003;7:547–557; Giudice et al. Giudice et al J Clin Res 2001;4:27–33

Publications

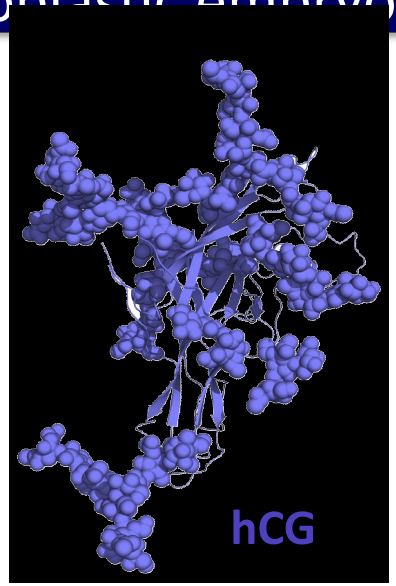
n de Weijer *et al.* RBM Online 2003;7:547–557;
olfenson C. et al., RBM Online2005:4:442-454
udice *et al.* J Clin Res 2001;4:27–33
sset et al.. RBM Online 2009

Ako više pacijentica treba LH suplementaciju kod kontrolirane ovarijske stimulacije ...

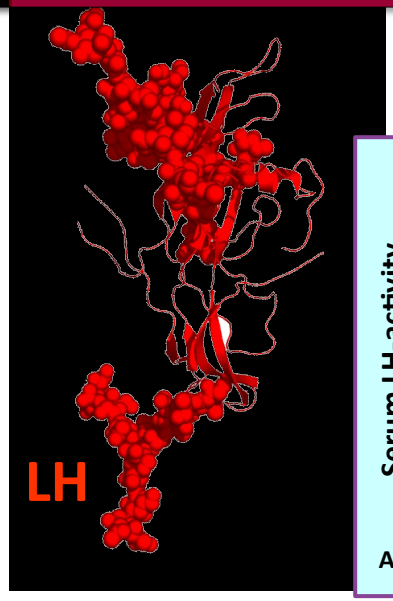
- Koji tip LH ili LH slična aktivnost bi trebali dati i kojoj pacijentici?
- Jesu li različiti tipovi LH aktivnosti ekvivalentni?

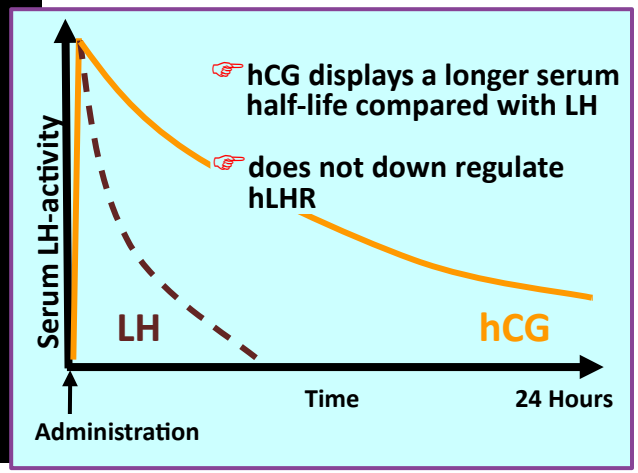
Jesu li LH i hCG isti?

- hCG - α 92 aa - β 145 aa
  Glycosylation sites - 37 kDa
- Trophoblastic embryonic cells



- LH - α 92 aa - β 121 aa
  Glycosylation sites – 28kDa
- Anterior Pituitary Gland





Molecule and Dose	rLH 150 IU	rhCG 250mcg
Initial or Distribution Half-life (hrs)	1.0 ± 0.2	4.7 ± 0.8
Terminal Half-life (hrs) IV route	11 ± 8	28 ± 3
Terminal Half-life (hrs) SC route	21-24	72-96

Cotonnec, et al. FS 1998;69:201-9; Trinchard, et al. RBMonline 2002;4:106-15

LH i hCG su različiti!

1. Različit izvor nastanka
2. Različita molekularna težina
3. Različit broj aminokiselina u beta lancu
4. Različit broj glikoziliranih mjesta
5. Različit poluvijek života
6. Različit učinak na receptorske puteve/jezgru
7. Različit učinak na gensku ekspresiju

Ezcurra and Humaidan A review of luteinising hormone and human chorionic gonadotropin when used in assisted reproductive technologyReproductive Biology and Endocrinology 2014, 12:95

OVARIJSKA STIMULACIJA
Treba li r-hLH u MPO?

Korisni učinci LH suplementacije u različitih populacija pacijentica

Dob	Humaidan 2004, Marrs 2004, Barrenetxea 2008, Bosch 2011, Patterson 2012, Hill 2012
Folikularna stagnacija	Ferraretti 2004
Povišen bazalni FSH	Lisi 2005
Inicijalni loš odgovor	Placido 2004, Ruvolo 2007, Lehert 2014
Visoki endogeni LH nakon GnRHa down-regulacije	Humaidan et al. 2004
v-ßLH-mutation	Alviggi et al. 2006

LH predtretman u POR

LH pretretman: 4d / 150 IU
Prije početka FSH 400IU/d

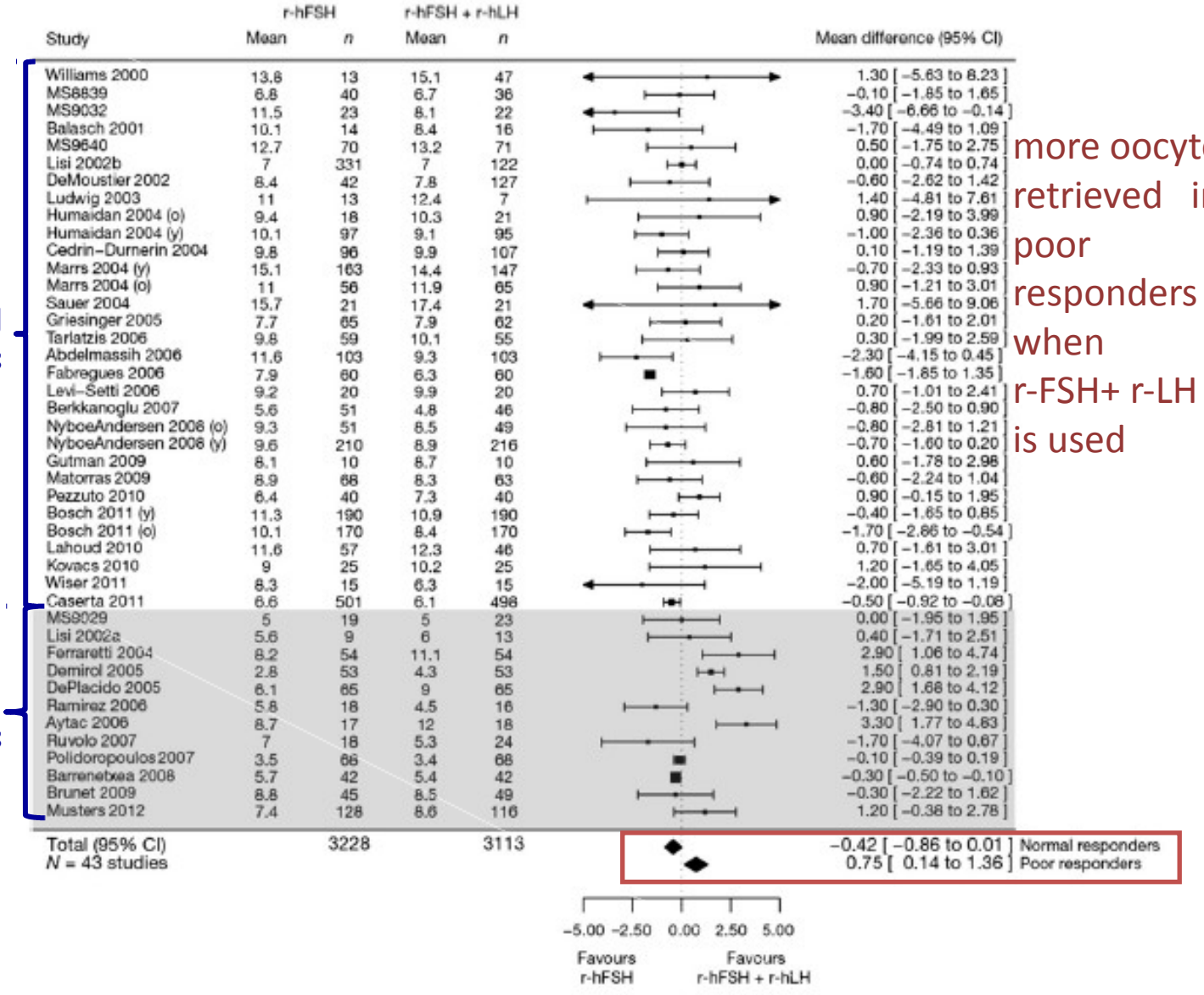
	LH pretreatment	Previous cycles	
Cycles	79	154	
Cancellation rate	22% (17)	51% (79)	p<0.001
Number of collected oocytes	3.5 ± 1.9	2.5 ± 1.2	p<0.05
Fertilization rate	80% (141/176)	83% (135/163)	
Cleavage rate	92% (130/141)	62% (84/135)	
Transferred cycles (mean embryos/ET)	54 (1.7 ± 0.5)	58 (1.5 ± 0.5)	
Implantation rate	22.3% (23/103)	4% (4/89)	p<0.001
Clinical pregnancy rate/ET	37% (20/54)	7% (4/58)	
Early miscarriages	1	4	
Live birth rate/started cycle	24%	0%	
Live birth rate/patient	29%	0%	

Ferraretti AP, et al. Biomed Res Int,201:4926172,Epub 2014Aug

rec-h(LH+FSH) vs r-FSH: meta-analysis of 6443 patients

Lehert, et al. Meta-Analysis on clinical relevance of r-hLH supplementation in ART.
Reproductive Biology and Endocrinology 2014, 12:17

Oocyte retrieved

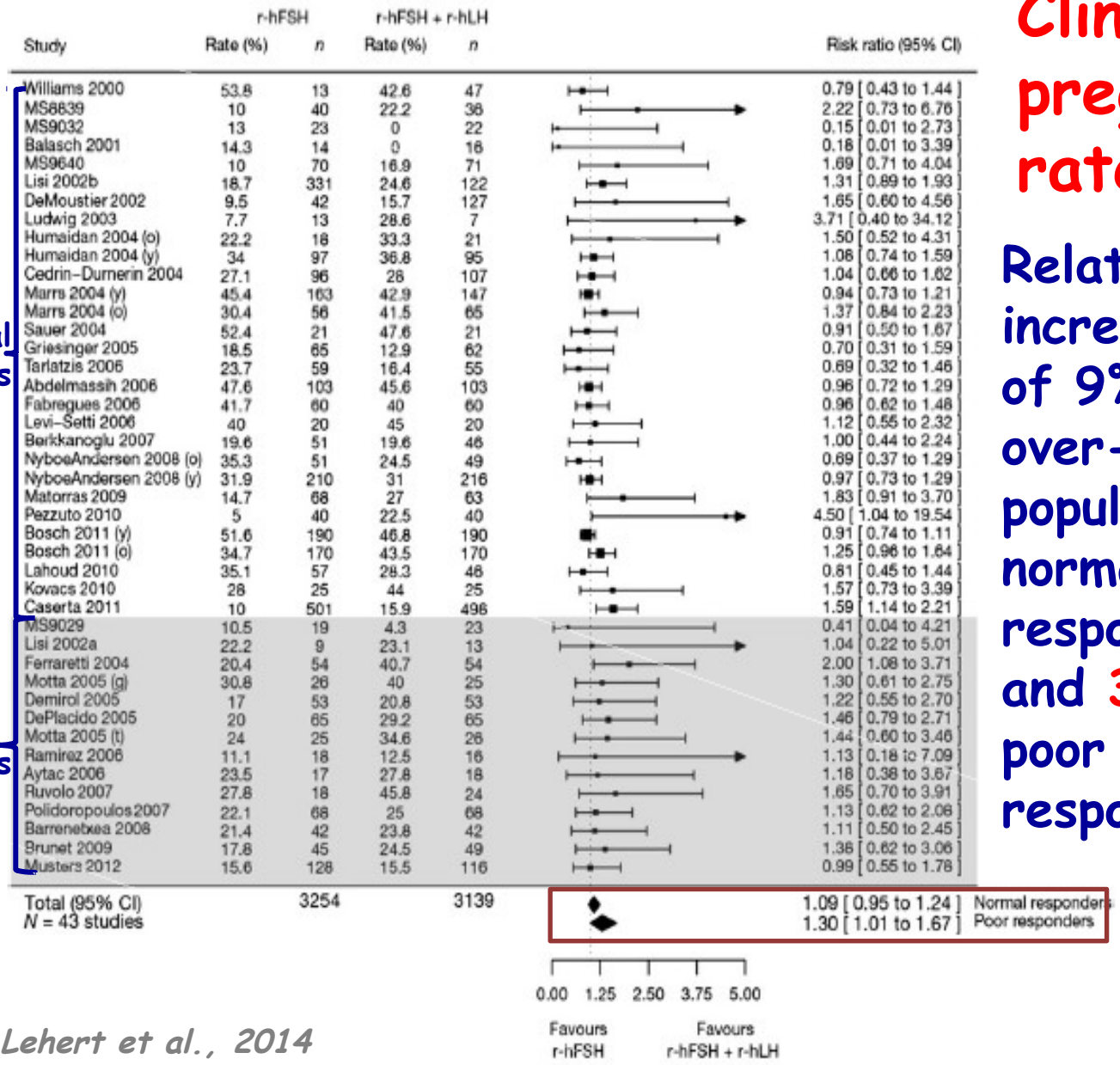


Normal responders

Poor responders

more oocyte retrieved in poor responders when r-FSH+ r-LH is used

rec-h(LH+FSH) vs r-FSH: meta-analysis of 6443 patients



Lehert et al., 2014

Clinical pregnancy rate

Relative increase of 9% in the over-all population of normal responders and 30% in poor responders

ZAKLJUČAK

- iOS treba egzaktne, pouzdane i sigurne gonadotropine
- rekombinantni humani gonadotropini pružaju konzistentniji i predvidiv klinički ishod
- recombinantni gonadotropini posjeduju najvišu dostupnu čistoću
- U normo respondera suplementacija LH aktivnosti nije neophodna kao niti u protokolima s GnRHa GnRHant
- Neke pacijentice imaju potrebu za suplementaciju LH aktivnosti. U njih r-hLH pruža bolje rezultate