XXXVIII
SABATO DELL'ANDROLOGIA

COLLOQUI IN PMA
TRA GINECOLOGI,
BIOLOGI E ANDROLOGI

17 FEBBRAIO 2018
PADERNO DUGNANO

L'induzione dell'ovulazione: personalizzazione o standarizzazione?

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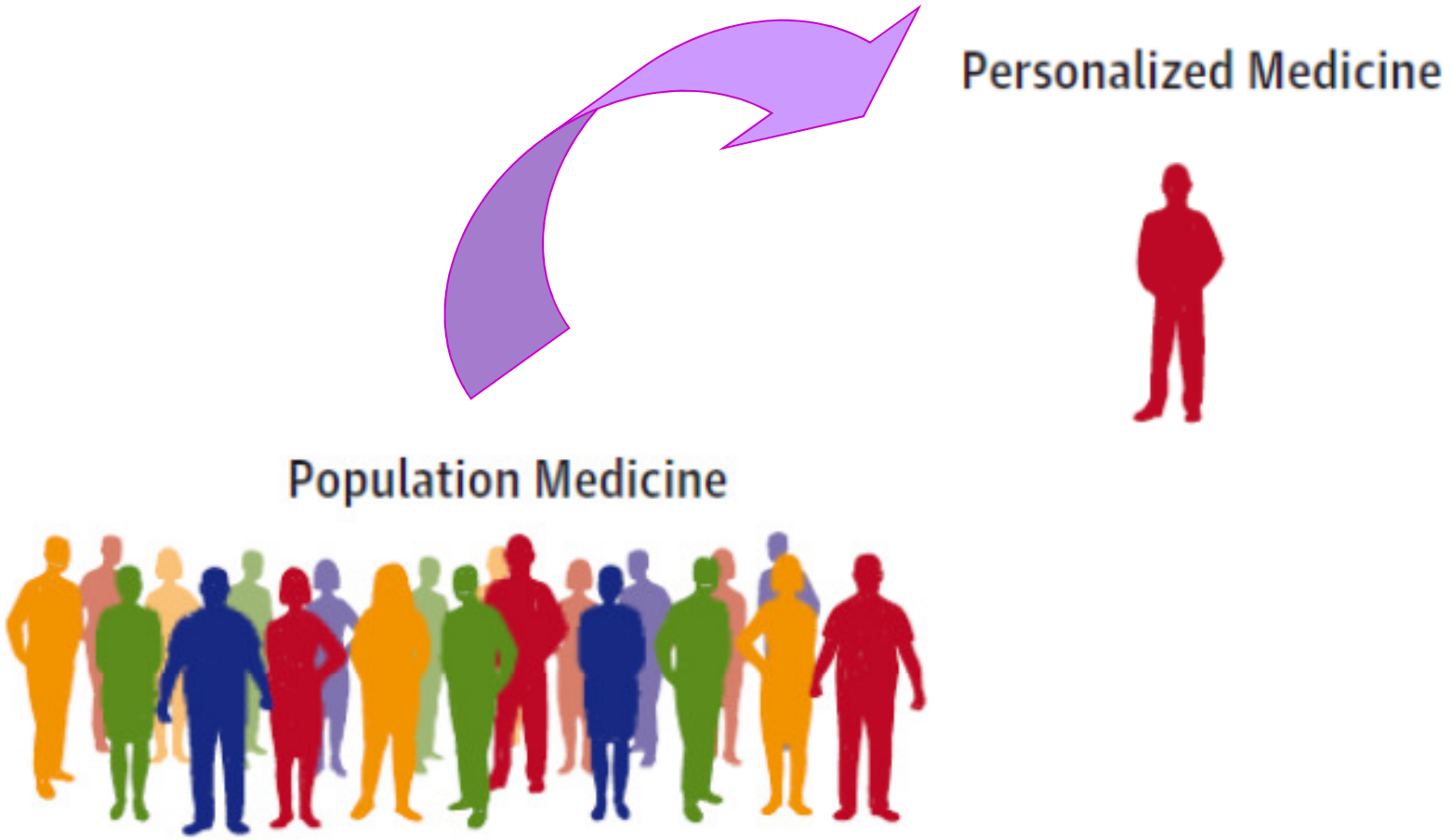


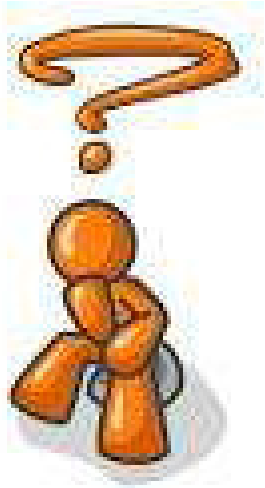
Hamburg, The path to personalized medicine. NEJM 2010; 363:301-4

Mega, Population and personalized medicine in the modern era. JAMA 2014; 312: 1969-70

Vantaggi auspicati della medicina personalizzata in PMA

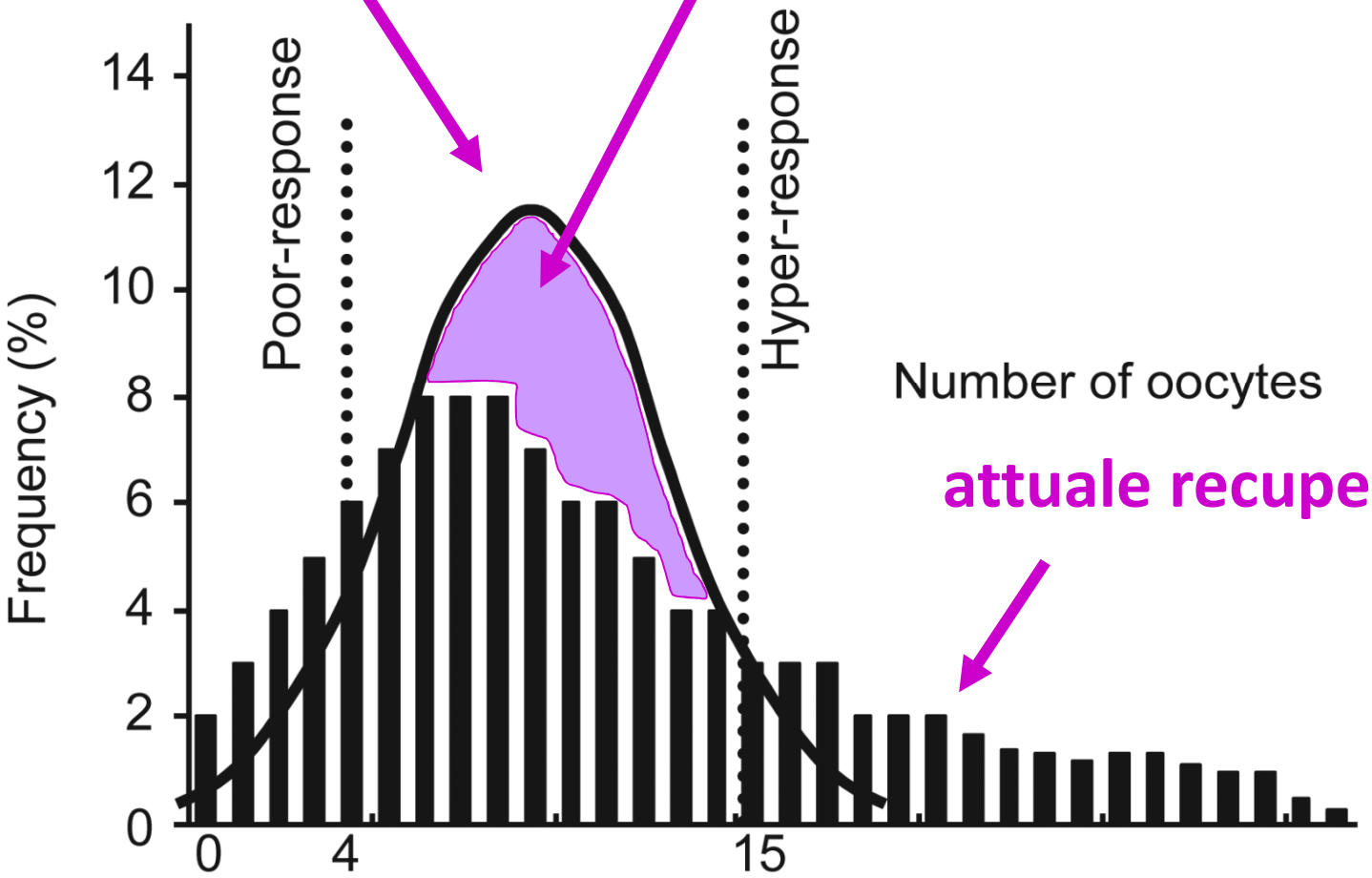
- risultati migliori: recupero oo, PR e TTP
- minor rischio di OHSS
- minor rischio di cancellazione del trattamento
- riduzione dei costi: < dose Gn totale

…ma è proprio così?!?



curva del recupero ideale

recupero inadeguato



attuale recupero ovocitario

Sunkara SK, 2011: 26:1768-1774

la scelta della starting dose e del protocollo

effettuata in base a:

- riserva ovarica
- età e BMI della donna
- precedenti stimolazioni

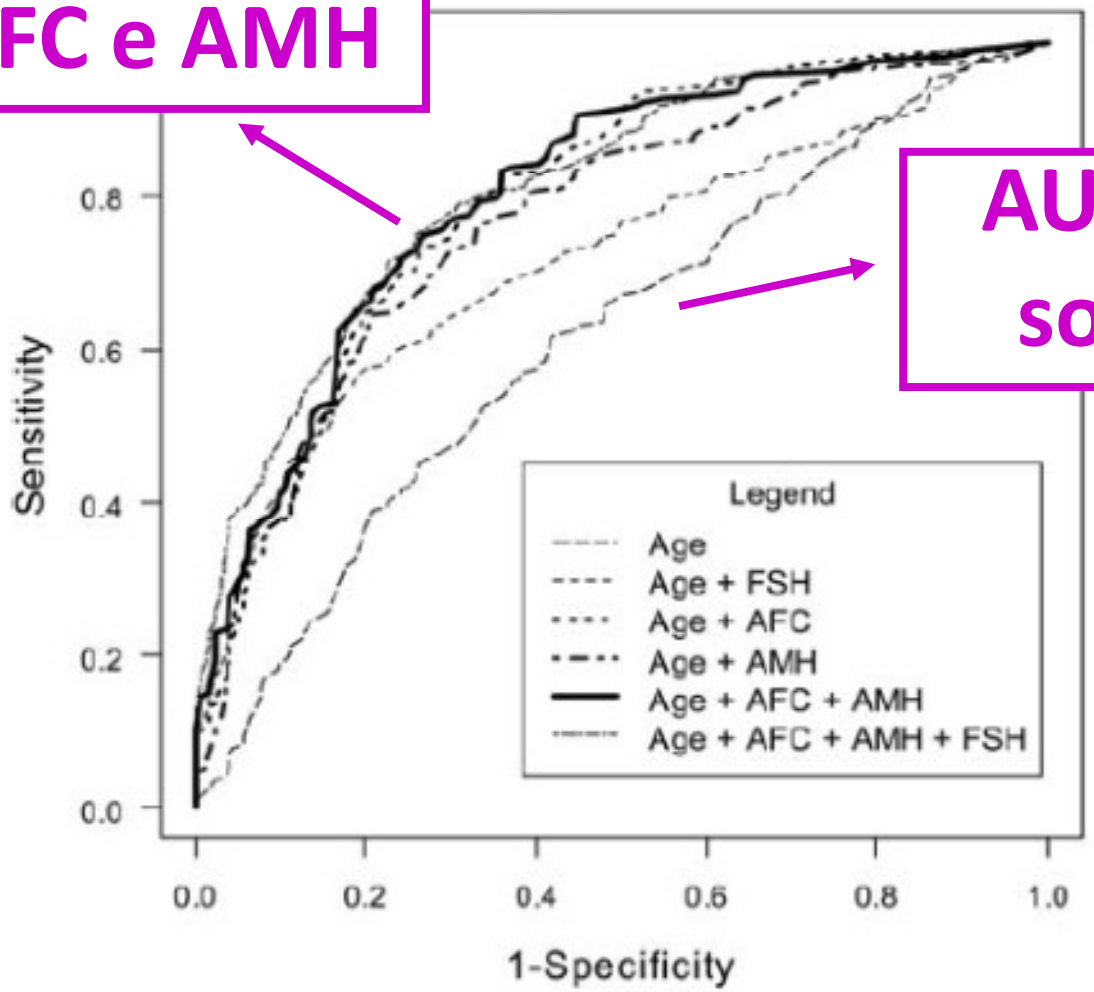
i test di riserva ovarica

Characteristics for a Good Marker	Age	AMH	FSH	AFC
Prediction of poor response	+	+++	++	+++
Prediction of hyper response	+	+++	+	+++
Low inter-cycle variability	+++	++	−	++
Low intra-cycle variability	+++	++	−	++
Applicable to all patients	+++	++	+	+
Economic	+++	−	−	−

La Marca et al. Hum Reprod Update. 2010;16:113-130

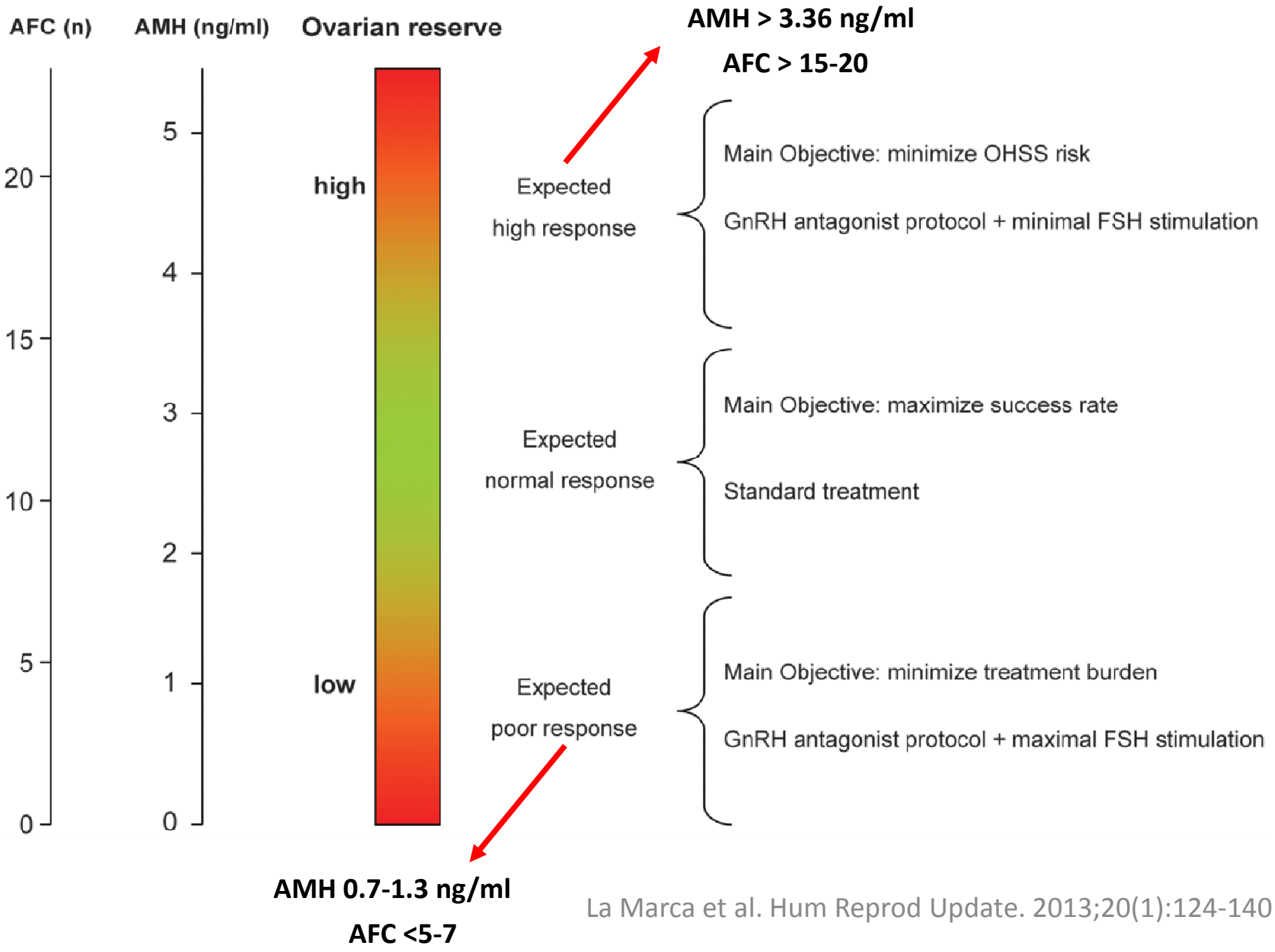
IMPORT study: predittività della risposta

AUC 0.80
età + AFC e AMH



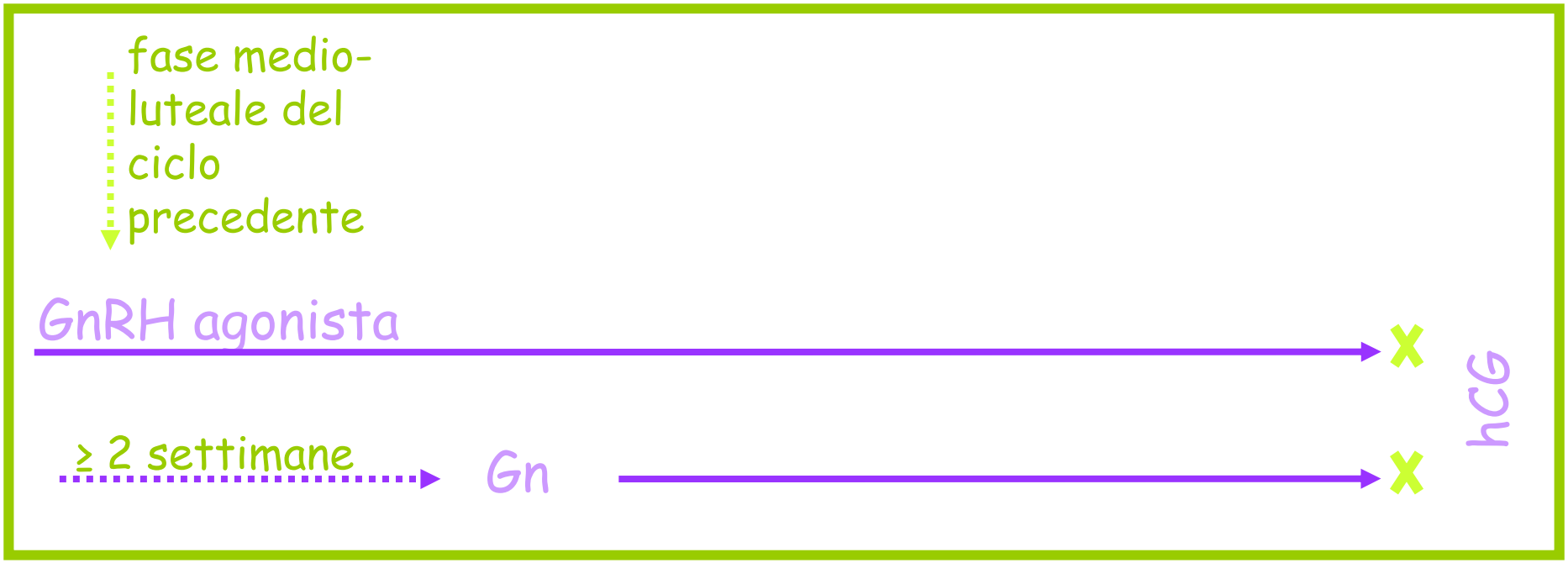
AUC 0.61
solo età

Broer et al. Hum Reprod Update. 2013;19:26-36

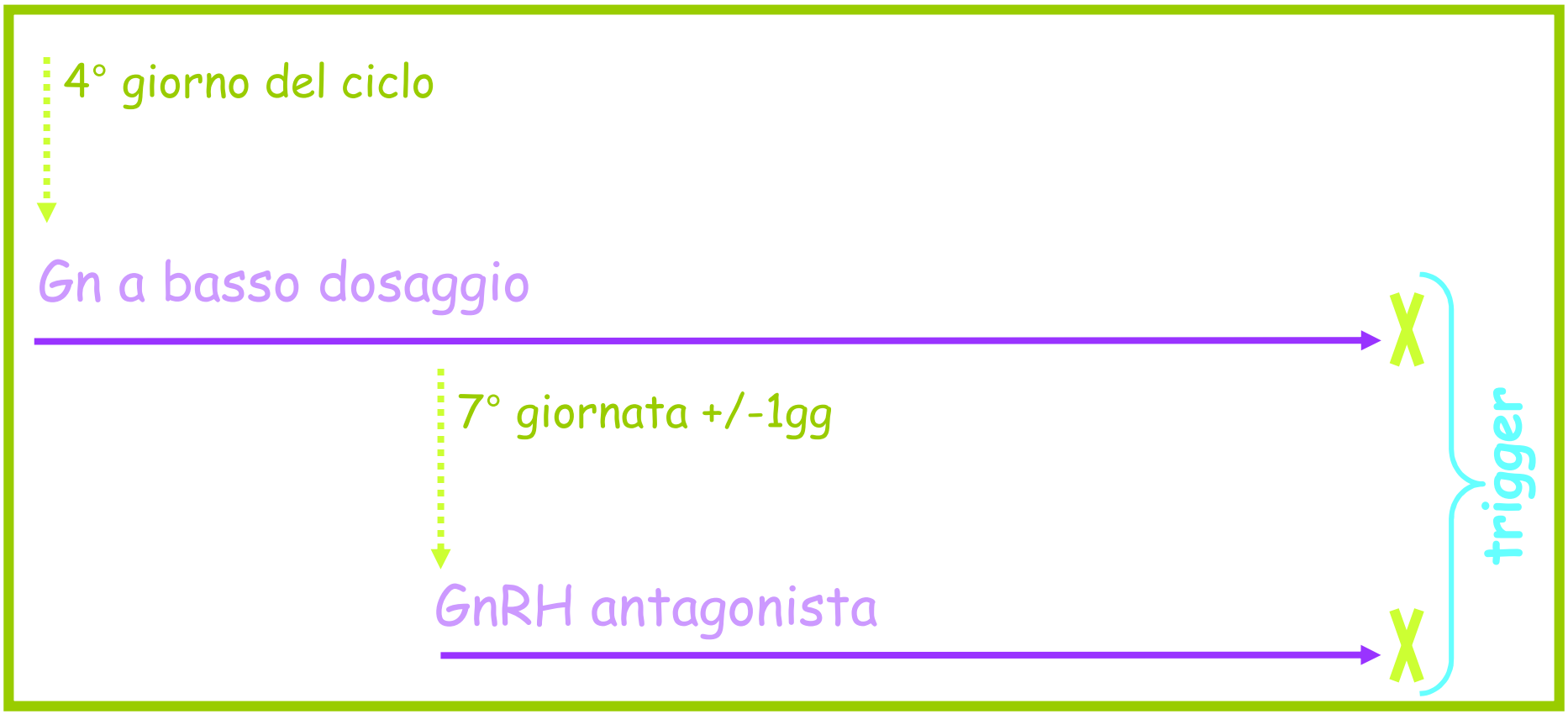


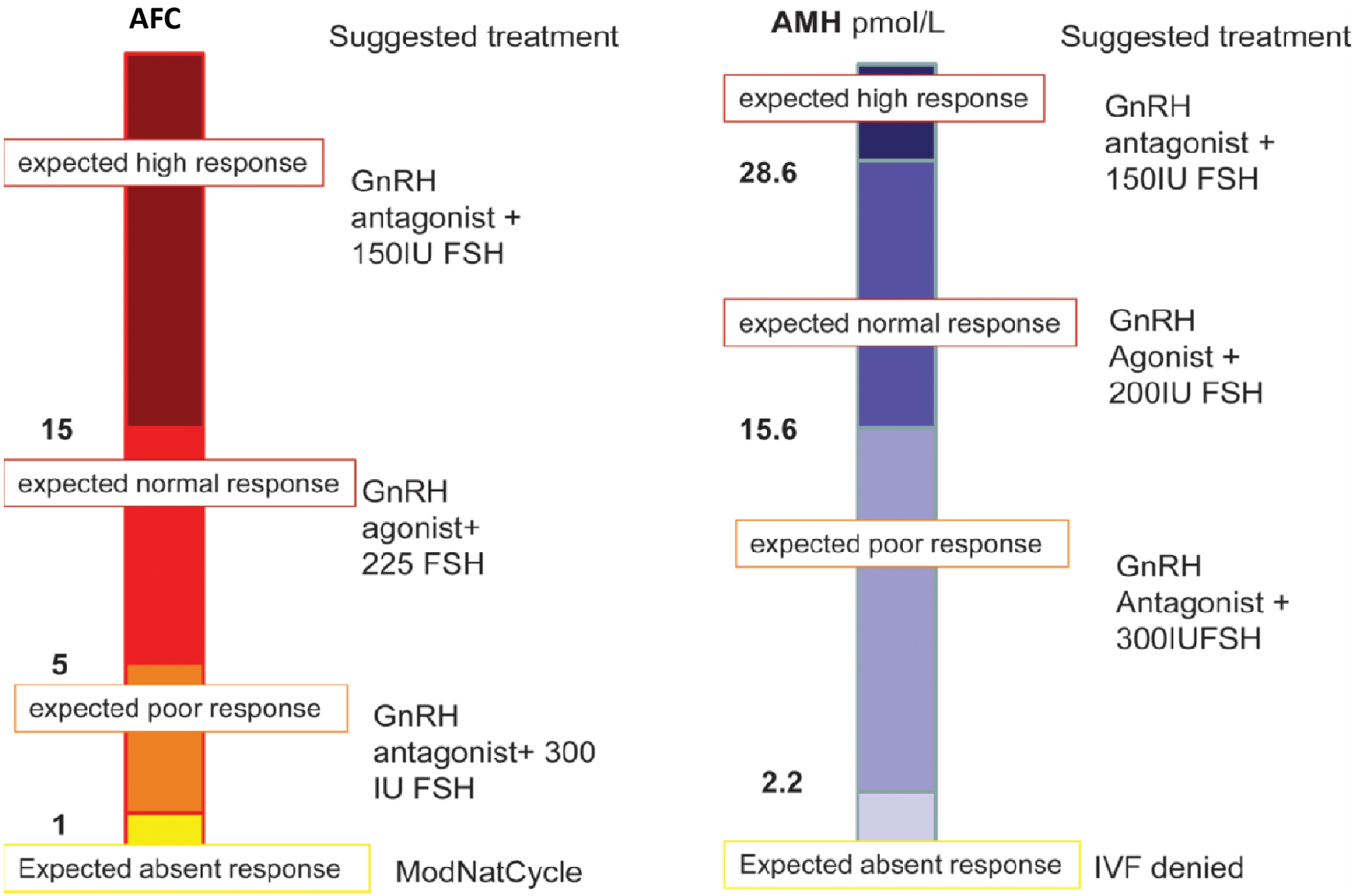
La Marca et al. Hum Reprod Update. 2013;20(1):124-140

stimolazione ovarica con GnRH-ago + FSH protocollo lungo



stimolazione ovarica con FSH + antago GnRH protocollo corto





La Marca et al. Hum Reprod Update. 2013;20(1):124-140

Human Reproduction Update, Vol.20, No.1 pp. 124–140, 2014
Advanced Access publication on September 29, 2013 doi:10.1093/humupd/dmt037

human reproduction update

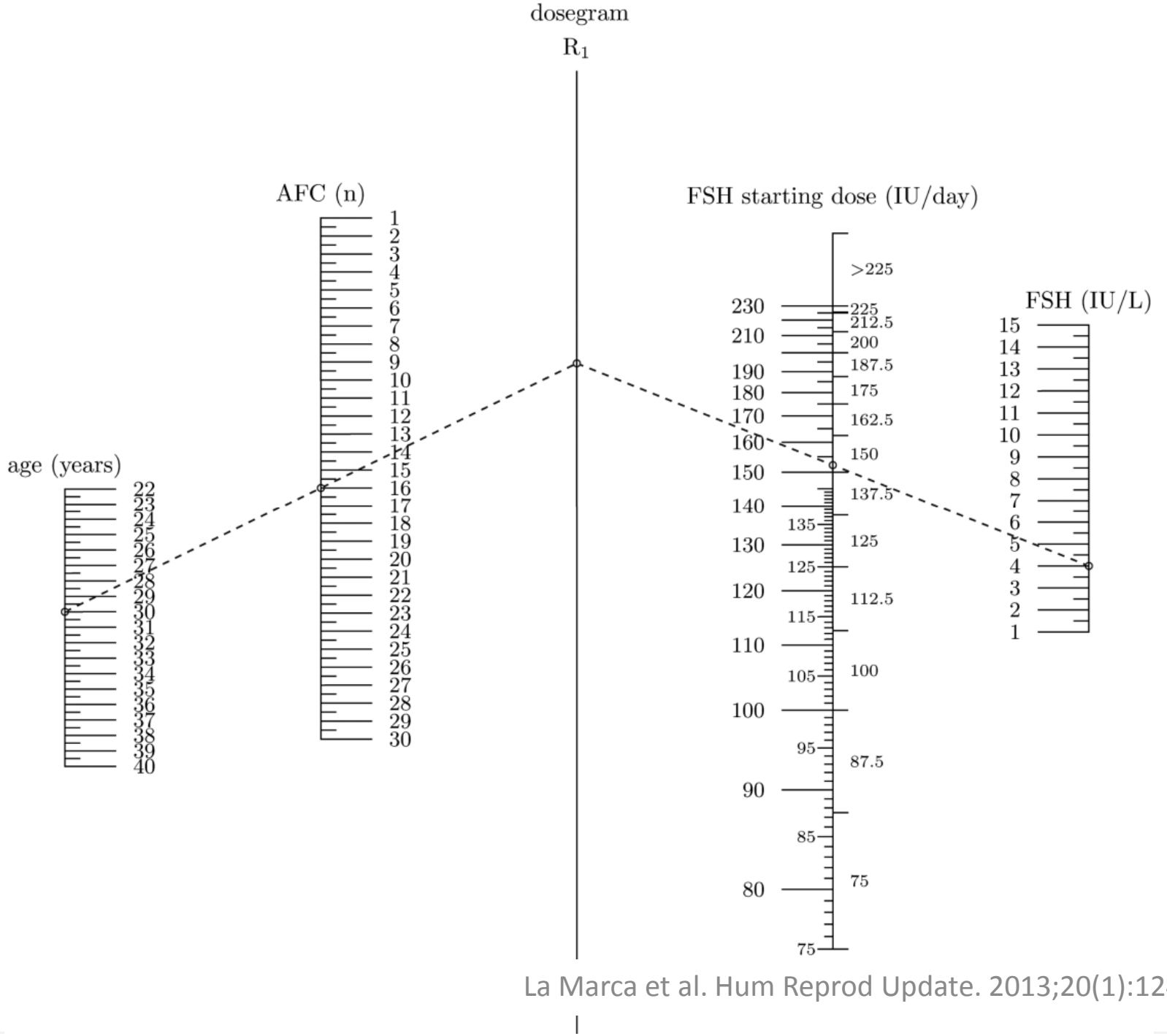
Individualization of controlled ovarian stimulation in IVF using ovarian reserve markers: from theory to practice

utilizzando 3 parametri di routine

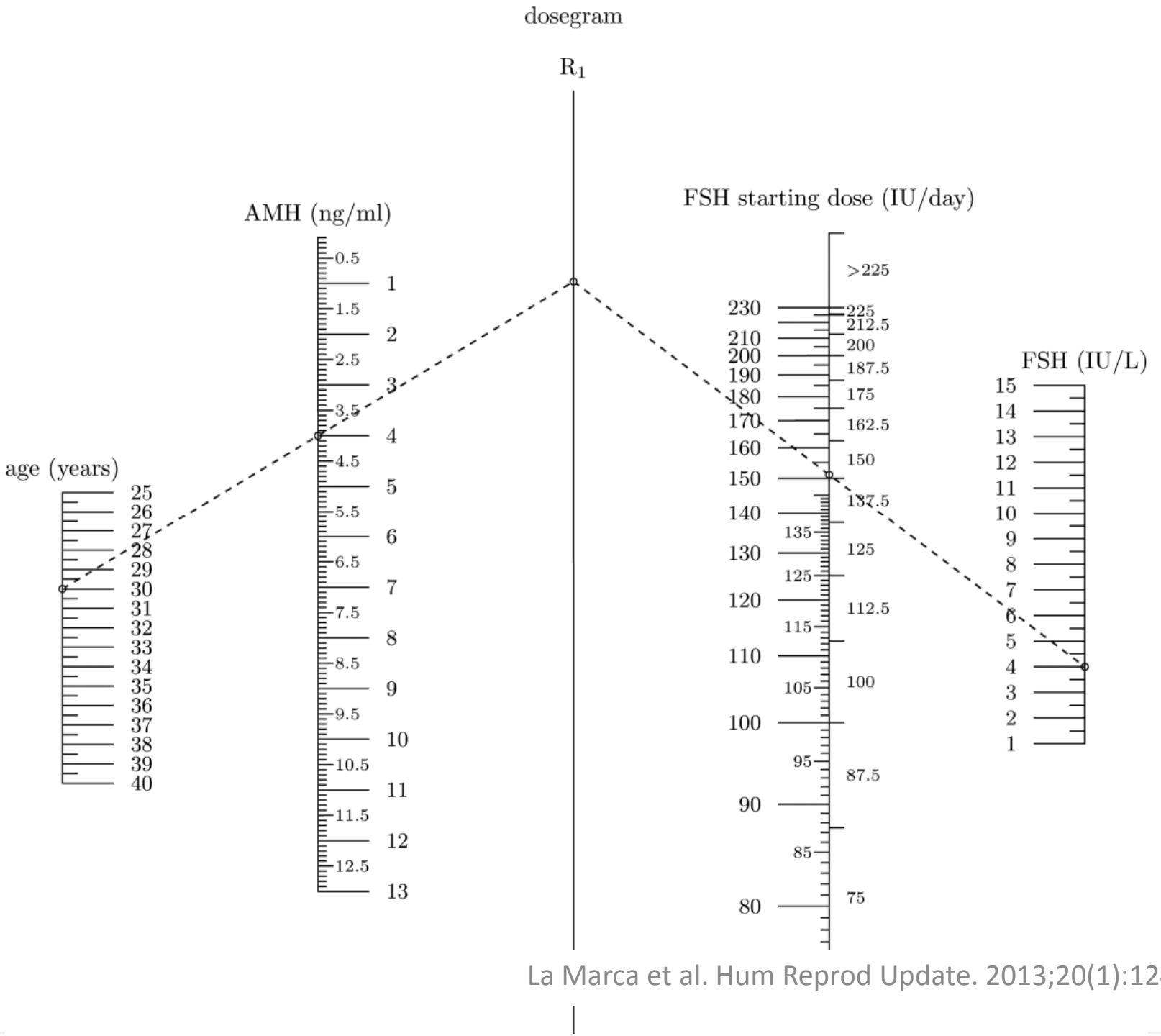
AFC o AMH + età + FSH

Ø 2-10mm

La Marca et al. Hum Reprod Update. 2013;20(1):124-140



La Marca et al. Hum Reprod Update. 2013;20(1):124-140



La Marca et al. Hum Reprod Update. 2013;20(1):124-140

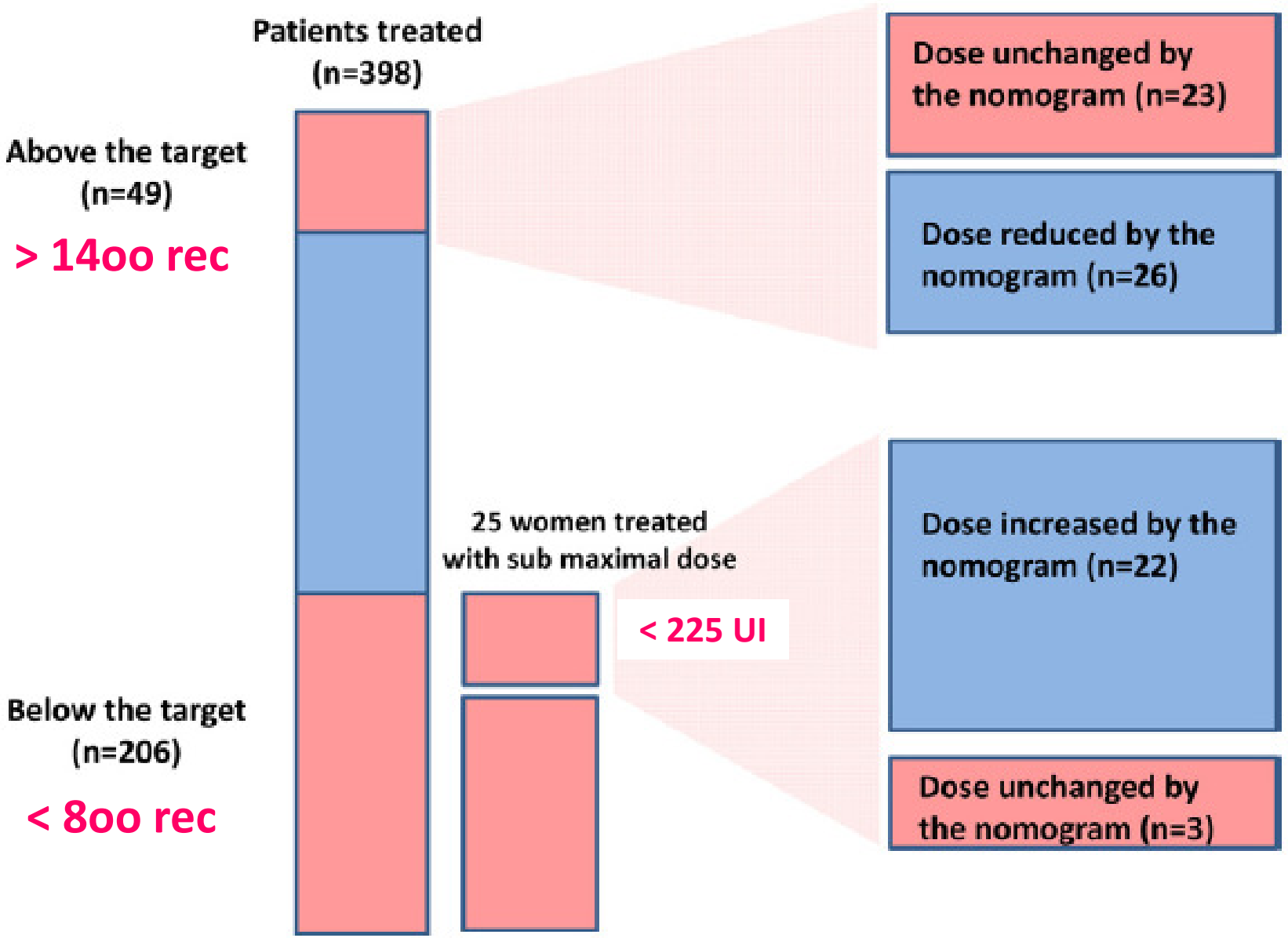
European Journal of Obstetrics & Gynecology and Reproductive Biology 207 (2016) 94–99

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Clinical application of a nomogram based on age, serum FSH and AMH to select the FSH starting dose in IVF/ICSI cycles: a retrospective two-centres study



Papaleo et al. 2016 Eur J Ob Reprod Biol 207:94-99

Reproductive BioMedicine Online (2015) 30, 248–257

www.sciencedirect.com
www.rbmonline.com

ARTICLE

Randomized, controlled, open-label, non-inferiority study of the CONSORT algorithm for individualized dosing of follitropin alfa

parametri utilizzati: età BMI AFC FSH
per donne <35aa, normoovulatorie
protocollo lungo con agonista

End-point, mean (SD)	*CONSORT dosing* n = *86*	*Standard dosing :150 UI* n = *93*
Ovarian stimulation characteristics		
Duration of stimulation (days)	10.6 (1.7)	10.7 (1.6)
Total dose of rFSH (IU)	1288.5 (301.0)*	1810.0 (546.9)
Daily dose of rFSH (IU)	121.5 (22.6)	167.4 (30.8)
Serum levels of		
Oestradiol (pmol/L[a])	7492.4 (4042.0)	9303.4 (4887.2)
Progesterone (nmol/L[b])	5.4 (7.6)	4.9 (2.2)
Elevated progesterone levels on day of rHCG, *n* (%)[c]	30 (38.0)	52 (59.1)

* ***Starting dose 112.5 UI rFSH per 83.7% delle donne***

Olivennes 2015 RBO 30 248-357

	CONSORT dosing n = *86*	*Standard dosing :150 UI* n = *93*
Primary end-point		
Number of oocytes retrieved, mean (SD)	10.0 (5.6)	11.8 (5.3)
Secondary end-points		
Implantation rate, mean[a]	31.1%	31.2%
Clinical pregnancy rate, % (*n*)	36.0% (31)	35.5% (33)
Multiple pregnancies, *n*[b]	6	9
Pregnancy outcomes, *n*		
Live outcome	24 (27.9%)	25 (26.9%)
Spontaneous / missed abortion	2	3
Unknown[c]	5	5

Olivennes 2015 RBO 30 248-357

CONSORT calculator

rischio OHSS

CONSORT = standard (2casi per braccio)

rischio cancellazione ciclo

CONSORT 9.4% vs standard 4.8% (9/96 vs 6/104)

…numeri piccoli!

Olivennes 2015 RBO 30 248-357

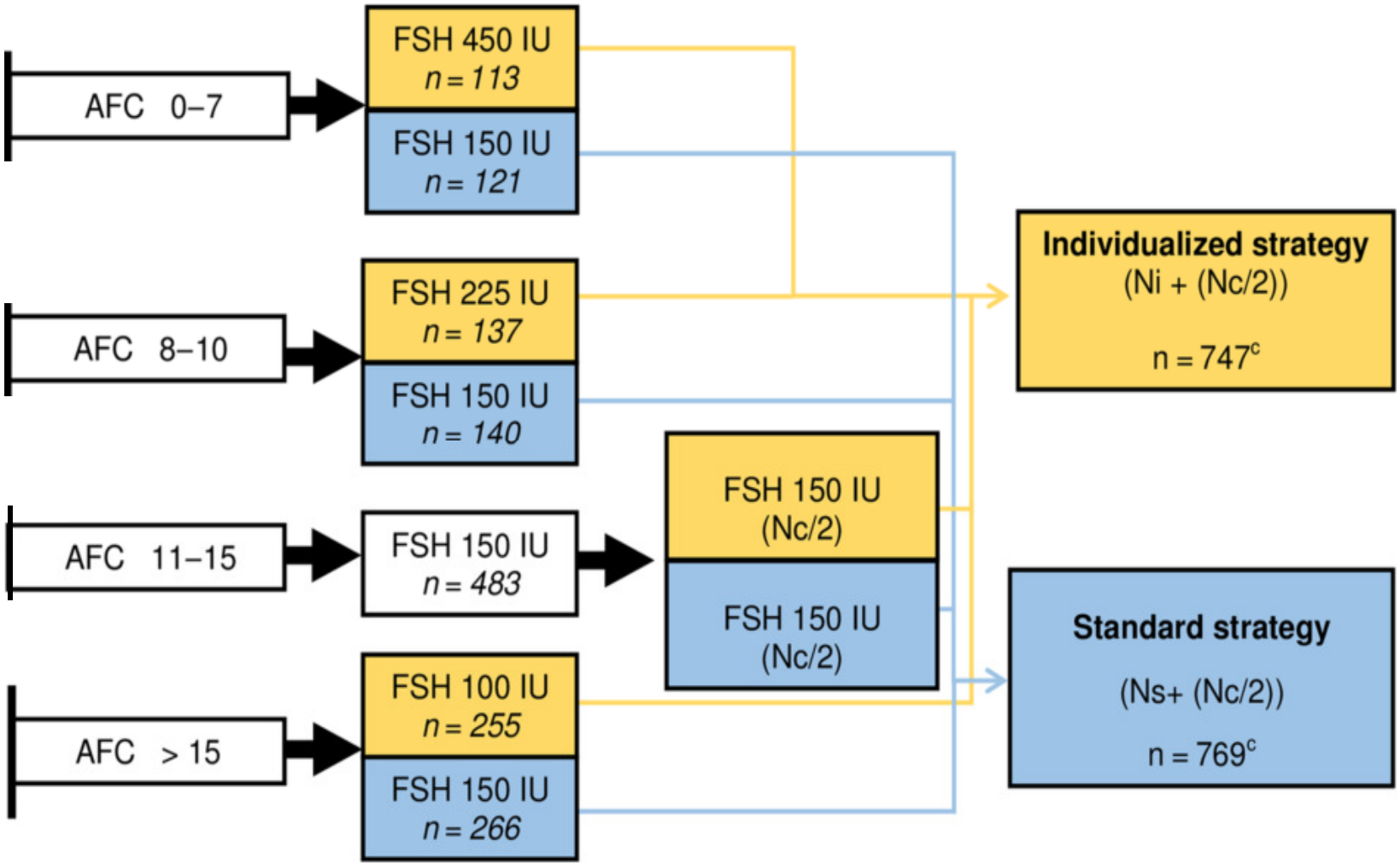
OPTIMIST study

Human Reproduction, Vol.32, No.12 pp. 2485–2495, 2017
Advanced Access publication on November 7, 2017 doi:10.1093/humrep/dex321

human reproduction

ORIGINAL ARTICLE *Reproductive endocrinology*

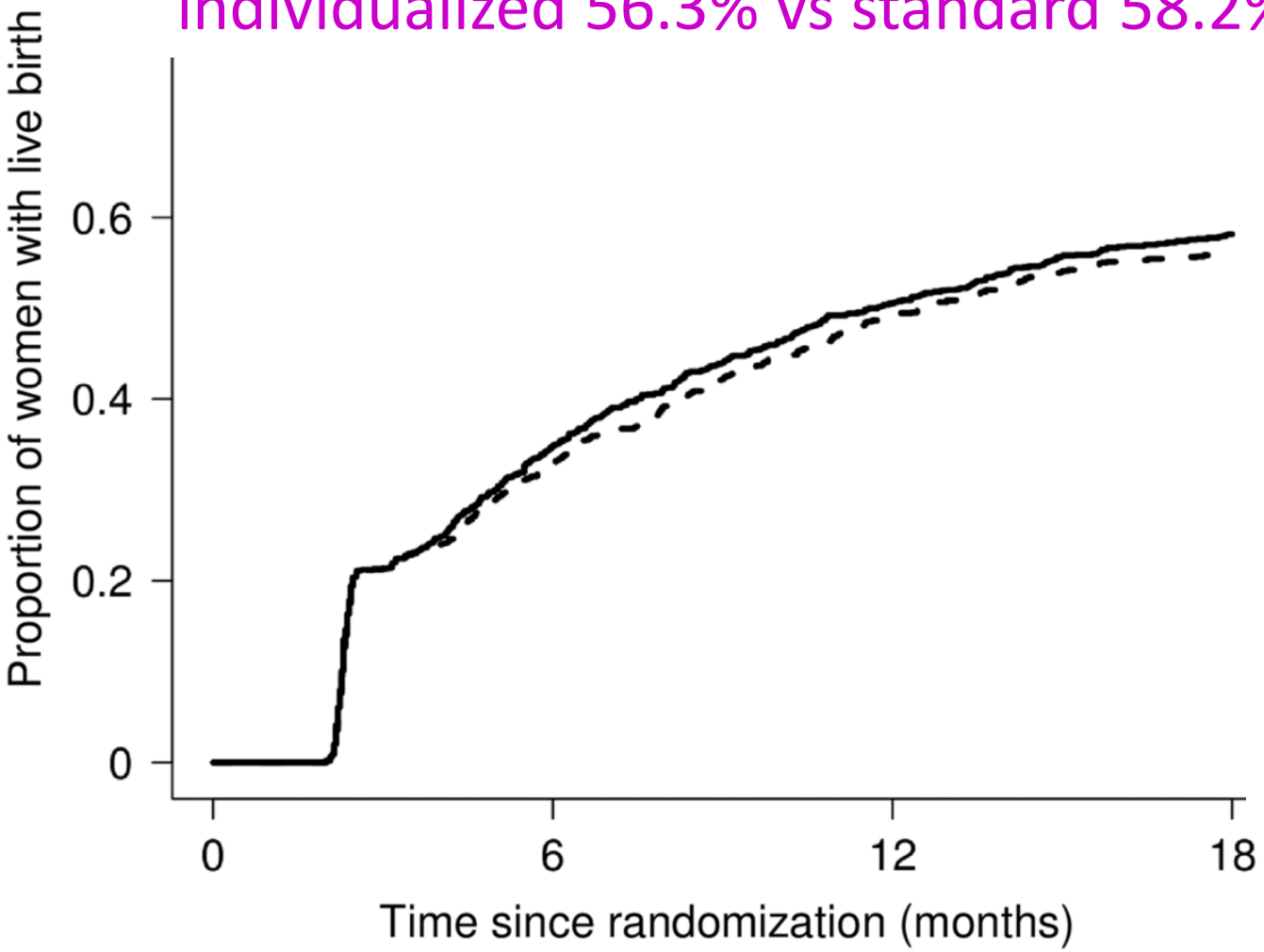
Individualized FSH dosing based on ovarian reserve testing in women starting IVF/ICSI: a multicentre trial and cost-effectiveness analysis



OPTIMIST study group Hum Reprod. 2017;32(12):2485-2495.

LBR 18mesi

individualized 56.3% vs standard 58.2% p0.38



OPTIMIST study group Hum Reprod. 2017;32(12):2485-2495.

First cycle results	Individualized ($n = 745$)	Standard ($n = 768$)	*P*-value
Total FSH used IU	2201 (1420)	1701 (451)	<0.001
Total duration stimulation days	11.5 (2.9)	11.3 (2.8)	0.14
Cancellations[a]	103 (13.8%)	117 (15.2%)	0.34
Number of oocytes[b]	8.8 (5.2)	10.0 (6.0)	<0.001
Poor response[c]	220 (29.6%)	197 (25.7%)	0.04
Hyper response[c]	93 (12.4%)	148 (19.2%)	<0.001
Number of fresh embryo transfers	570 (76.6%)	587 (76.5%)	0.94
Number of fresh embryos per transfer	1.1 (0.3)	1.1 (0.3)	0.51
OHSS classification[c]			0.005
No OHSS	707 (95.1%)	702 (91.5%)	0.001[d]
Mild OHSS	28 (3.7%)	49 (6.3%)	0.004[d]
Moderate OHSS	3 (0.4%)	11 (1.4%)	0.010[d]
Severe OHSS	6 (0.8%)	6 (0.8%)	0.86[d]
Number of cryo cycles with transfer/woman	0.5 (1.0)	0.5 (1.0)	0.21
Number of cryo embryos per transfer	1.1 (0.3)	1.1 (0.2)	0.44
Live birth (fresh only)[e]	163 (21.9%)	169 (22.0%)	0.94
Live birth (fresh and cryo)[e]	215 (28.9%)	236 (30.7%)	0.32

OPTIMIST study group Hum Reprod. 2017;32(12):2485-2495.

Cost item	Unit	Unit costs (€)	Individualized strategy (total costs €)	Standard strategy (total costs €)
Ovarian reserve test				
Antral follicle count	1	62.52[a]	46 500	0
Stimulation phase IVF/ICSI (medication)				
Gonadotrophins	1 IU	0.30[a]	966 500	813 800
GnRH agonist	0.1 mg	10.58[b]	303 500	319 600
GnRH antagonist	0.25 mg	37.81[b]	65 600	66 100
hCG	10 000 IU	11.57[b]	14 800	15 200
Stimulation phase IVF/ICSI (monitoring)	1	504.83[a]	695 900	722 700
Laboratory phase IVF/ICSI				
IVF (OPU, IVF, ET, cryopreservation)	1	869.20[a]	501 100	516 700
ICSI (OPU, IVF, ET, cryopreservation)	1	1204.49[a]	782 300	773 900
Escape IUI (including insemination)	1	218.84[a]	6300	9000
Luteal phase (progesteron)	600 mg*18 days	21.60[b]	23 900	24 100
Cryo treatment (including monitoring and medication)	1	554.60[a]	413 200	424 800
OHSS complication				
Mild/moderate OHSS	1	819.86[a]	39 800	67 600
Severe OHSS	1	2524.88[a]	20 200	20 200
Total costs per woman			5215	4940

a 18 mesi

OPTIMIST study group Hum Reprod. 2017;32(12):2485-2495.

ESTHER study

Individualized versus conventional ovarian stimulation for in vitro fertilization: a multicenter, randomized, controlled, assessor-blinded, phase 3 noninferiority trial

Individualized follitropin delta dosing regimen.

Serum AMH concentration (pmol/L)	Daily dose[a] (fixed throughout stimulation)
<15	12 μg
15–16	0.19 μg/kg
17	0.18 μg/kg
18	0.17 μg/kg
19–20	0.16 μg/kg
21–22	0.15 μg/kg
23–24	0.14 μg/kg
25–27	0.13 μg/kg
28–32	0.12 μg/kg
33–39	0.11 μg/kg
≥40	0.10 μg/kg

[a] Maximum daily dose is 12 μg.

parametri utilizzati: BMI e AMH

Nyboe Andersen Fertil Steril 2016 Individualized ovarian stimulation

Outcome per started cycle	Individualized follitropin delta (n = 665)	Conventional follitropin alfa (n = 661)	Difference (95% CI)[a]
Primary endpoints			
Ongoing pregnancy[b]	204 (30.7)	209 (31.6)	−0.9% (−5.9% to 4.1%)
Ongoing implantation[c]	206/585 (35.2)	209/584 (35.8)	−0.6% (−6.1% to 4.8%)
Secondary pregnancy endpoints			
Women with live birth[d]	198 (29.8)	203 (30.7)	−0.9% (−5.8% to 4.0%)
Women with live neonate(s) at 4 wk after birth[e]	198 (29.8)	201 (30.4)	−0.6% (−5.5% to 4.3%)
Birth weight (g)[f]	3,186 ± 601	3,168 ± 624	22.8 (−97.2 to 142.8)
Gestational age (d)[f]	272.3 ± 15.6	272.3 ± 16.9	0.1 (−3.1 to 3.3)
Positive hCG[g]	257 (38.6)	266 (40.2)	−1.5% (−6.8% to 3.7%)
Clinical pregnancy[h]	232 (34.9)	241 (36.5)	−1.5% (−6.6% to 3.6%)
Vital pregnancy[i]	211 (31.7)	221 (33.4)	−1.6% (−6.7% to 3.4%)
Implantation[j]	233/585 (39.8)	241/584 (41.3)	−1.4% (−7.0% to 4.2%)
Multiple pregnancy rate	4 (2.0)	8 (3.8)	−2.0% (−5.0% to 1.1%)

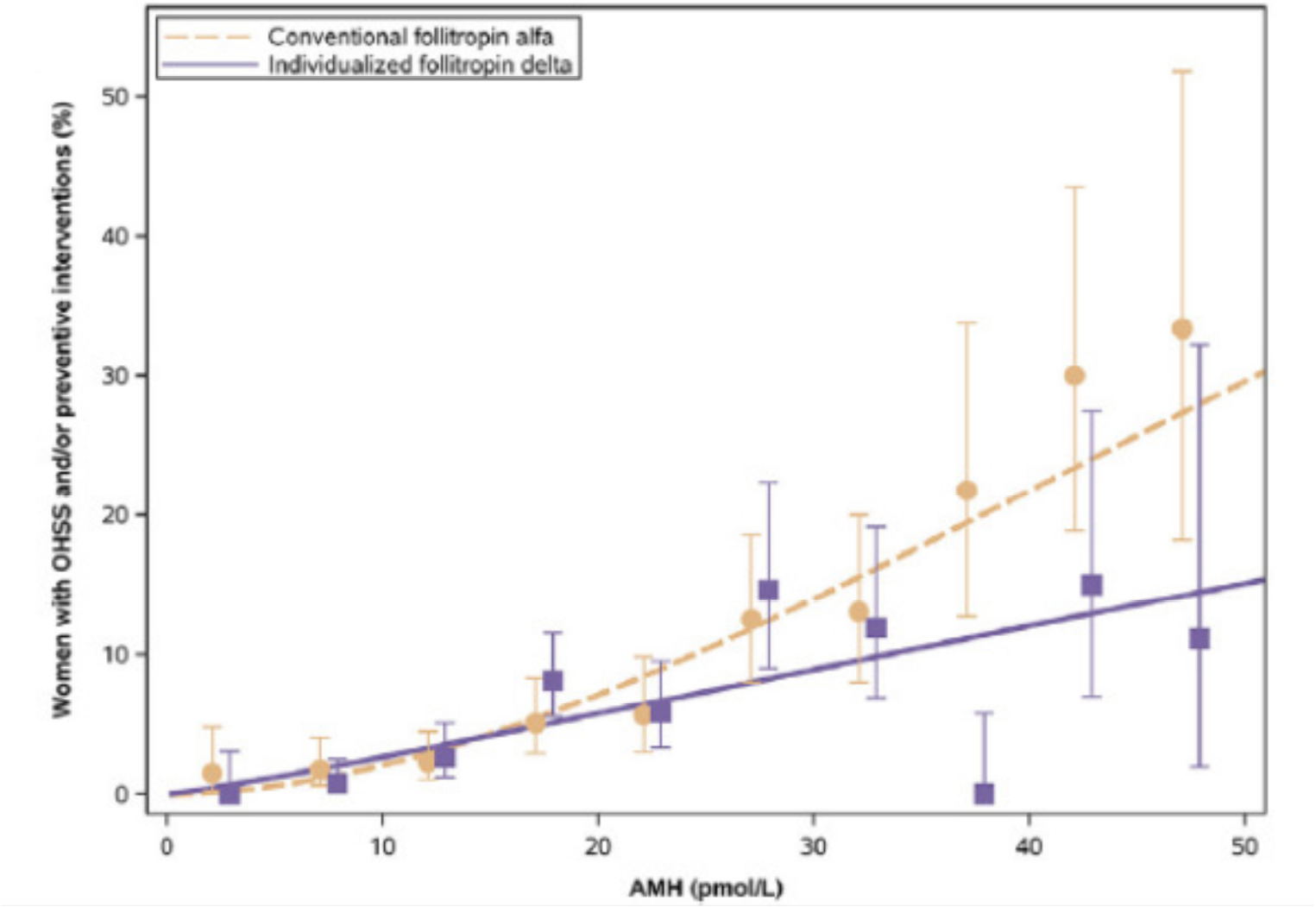
PR δ = α **follitropina**

ESTHER study group Fert & Ster 2017 107 (2): 387-396

Outcome variable	Individualized follitropin delta (n = 665)	Conventional follitropin alfa (n = 661)	*P* value
Ovarian response endpoints			
Duration of stimulation (d)	8.9 ± 1.9	8.6 ± 1.7	.062[a]
Total dose (μg)	90.0 ± 25.3	103.7 ± 33.6	< .001[a]
Women with investigator-requested gonadotropin dose adjustments[b]	221 (33.2)	243 (36.8)	.178[c]
Women with dose adjustments implemented	0 (0.0)	243 (36.8)	< .001[c]
Poor response leading to cycle cancellation[d]	25 (3.8)	18 (2.7)	.302[e]
Excessive response leading to triggering with GnRH agonist[f]	10 (1.5)	23 (3.5)	.019[e]
Oocytes retrieved[g] (n)	10.0 ± 5.6	10.4 ± 6.5	.692[a]
Target ovarian response[g] (8–14 oocytes retrieved)	275 (43.3)	247 (38.4)	.019[h]
Extreme ovarian response[g]			
<4 or ≥15 oocytes	169 (26.6)	201 (31.3)	.001[h]
<4 or ≥20 oocytes	92 (14.5)	118 (18.4)	.002[h]
Ovarian response stratified by AMH[g]			
Women with AMH <15 pmol/L (at risk of hypo-response) (n)	280	290	
Oocytes retrieved (n)	8.0 ± 4.3	7.0 ± 3.9	.004[i]
Poor responders (<4 oocytes)	33 (11.8)	52 (17.9)	.039[c]
Women with AMH ≥15 pmol/L (at risk of hyperresponse) (n)	355	353	
Oocytes retrieved (n)	11.6 ± 5.9	13.3 ± 6.9	.002[i]
Excessive responders (≥15 oocytes)	99 (27.9)	124 (35.1)	.038[c]
Excessive responders (≥20 oocytes)	36 (10.1)	55 (15.6)	.030[c]
Fertilized oocytes[j] (n)	5.5 ± 3.7	5.9 ± 4.4	.498[a]
Fertilization rate[j] (%)	56.0 ± 24.5	57.0 ± 23.8	.530[a]
Embryos, day 3[j]			
Total (n)	5.4 ± 3.7	5.7 ± 4.3	.590[a]
Good-quality[k] (n)	4.2 ± 3.3	4.5 ± 3.7	.414[a]
Blastocysts, day 5[j]			
Total (n)	3.3 ± 2.8	3.5 ± 3.2	.344[a]
Good-quality[l] (n)	2.0 ± 2.2	2.1 ± 2.4	.580[a]
Cryopreserved (n)	1.9 ± 2.4	2.2 ± 2.6	.262[a]
Women with blastocysts cryopreserved	402 (60.5)	402 (60.8)	.892[c]

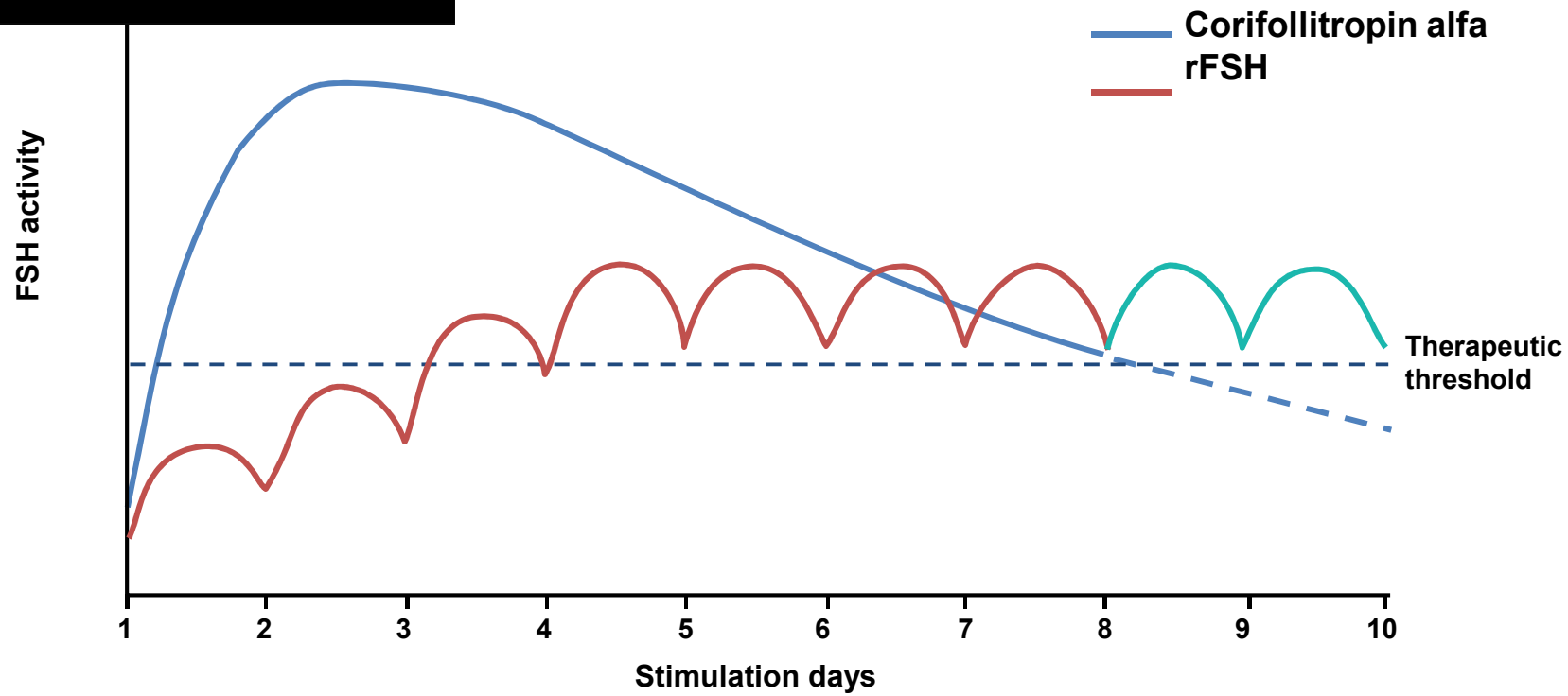
ESTHER study group Fert & Ster 2017 107 (2): 387-396

ESTHER study:
profilo di sicurezza δ vs α follitropina



ESTHER study group Fert & Ster 2017 107 (2): 387-396

corifollitropina vs rFSH: diversa cinetica



Devroey et al. J Clin Endocrinol Metab. 2004;89:2062; Duijkers et al. Hum Reprod. 2002;17:1987.

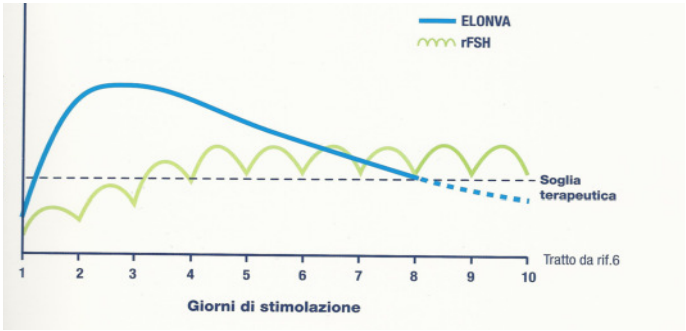
BMI ed età
per la posologia della corifollitropina

		Peso corporeo		
		< 50 kg	**50 – 60 kg**	**≥ 60 kg**
Età	**≤ 36 anni**	100 mcg	100 mcg	150 mcg
	> 36 anni	non studiato	150 mcg	150 mcg

stimolazione ovarica
GnRH-antago + FSH long acting
protocollo normal/poor

2°-3°giorno del ciclo

r-FSH long acting 100/150mcg



5°-6° giornata di stimolazione

GnRH antagonista → X

8° giornata

ev Gn a somministrazione quotidiana → X

hCG

	ENSURE (18-36 anni di età) (peso corporeo ≤ 60 kg)		ENGAGE (18-36 anni di età) (peso corporeo > 60 kg e ≤ 90 kg)		PURSUE (35-42 anni di età) (peso corporeo ≥ 50 kg)	
	cFSH 100 µg	recFSH 150 UI	**cFSH 150 µg**	recFSH 200 UI	**cFSH 150 µg**	recFSH 300 UI
	N=268	N=128	**N=756**	N=750	**N=694**	N=696
Numero medio di ovociti	**13,3**	10,6	**13,8**	12,6	**10,7**	10,3
Differenza [IC al 95%]	**2,5 [1,2; 3,9]**		**1,2 [0,5; 1,9]**		**0,5 [-0,2; 1,2]**	

ENSURE study Human Reproduction, Vol.24, No.12 pp. 3063–3072, 2009

ENGAGE study Reproductive BioMedicine Online (2010) 21, 66– 76

PURSUE study Fertility and Sterility® Vol. 104, No. 1, July 2015

Parametro	1) ENGAGE† (18-36 anni di età) (peso corporeo superiore a 60 kg e inferiore o uguale a 90 kg)			2) PURSUE‡ (35-42 anni di età) (peso corporeo superiore o uguale a 50 kg)		
	Elonva 150 µg	recFSH 200 UI	**Differenza (IC al 95%)**	**Elonva 150 µg**	recFSH 300 UI	**Differenza (IC al 95%)**
	N=756	N=750		**N=694**	N=696	
Tasso di gravidanze vitali	**39,9 %**	39,1 %	**1,1 [-3,8; 5,9]**	**23,9 %**	26,9 %	**-3,0 [-7,3; 1,4]**
Tasso di gravidanze in corso	**39,0 %**	38,1 %	**1,1 [-3,8; 5,9]**	**22,2 %**	24,0 %	**-1,9 [-6,1; 2,3]**
Tasso di nati vivi*	**35,6 %**	34,4 %	**1,3 [-3,5; 6,1]**	**21,3 %**	23,4 %	**-2,3 [-6,5; 1,9]**

ENGAGE study Reproductive BioMedicine Online (2010) 21, 66– 76

PURSUE study Fertility and Sterility® Vol. 104, No. 1, July 2015

In conclusione

i vantaggi auspicati della medicina personalizzata in PMA

- **risultati**

TTP a 18mesi e PR uguali

- **rischio di OHSS**

minore

- **rischio di cancellazione del trattamento**

minore

- **costi**

maggiori

grazie

Outcome variable	Individualized follitropin delta (n = 665)	Conventional follitropin alfa (n = 661)	*P* value
Safety outcomes			
Preventive interventions	15 (2.3)	30 (4.5)	.005[m]
Early OHSS[n]			
Any grade	17 (2.6)	20 (3.0)	.291[m]
Moderate/severe	9 (1.4)	9 (1.4)	.644[m]
Any grade and/or preventive intervention	31 (4.7)	41 (6.2)	.046[m]
Moderate/severe and/or preventive intervention	24 (3.6)	34 (5.1)	.019[m]
All OHSS			
Any grade	23 (3.5)	32 (4.8)	.238[m]
Moderate/severe	14 (2.1)	19 (2.9)	.514[m]
Any grade and/or preventive intervention	37 (5.6)	53 (8.0)	.037[m]
Moderate/severe and/or preventive intervention	29 (4.4)	44 (6.7)	.013[m]
Hospitalization due to OHSS	2 (0.30)	6 (0.90)	.108[o]
Mean duration of hospitalization[p] (d)	4.0	8.7	.276[i]
Total duration of hospitalization[p] (d)	8	52	N/A[q]

ESTHER study group Fert & Ster 2017 107 (2): 387-396

Demographic and baseline characteristics.

Characteristic	Individualized follitropin delta (n = 665)	Conventional follitropin alfa (n = 661)
Age (y)		
All women	33.4 ± 3.9	33.2 ± 3.9
<35	394 (59.2)	392 (59.3)
35–37	161 (24.2)	167 (25.3)
38–40	110 (16.5)	102 (15.4)
Race (%)		
American Indian or Alaska Native	0	0.2
Asian	3.8	4.4
Black or African American	1.1	1.8
Native Hawaiian or other Pacific Islander	0.5	0
White	94.7	93.6
Body weight (kg)	64.7 ± 10.7	63.4 ± 10.4
Body mass index (kg/m^2)	23.7 ± 3.4	23.3 ± 3.3
Infertility history		
Duration of infertility (mo)	35.3 ± 24.4	34.9 ± 21.7
Primary infertility (%)	70.7	71.3
Primary reason for infertility (%)		
Unexplained	42.3	41.3
Tubal	13.8	14.5
Male factor	40.3	39.3
Endometriosis I/II	3.3	4.4
Other	0.3	0.5
Endometrial thickness (mm)	4.1 ± 1.8	4.1 ± 1.7
Ovarian volume (mL)	6.2 ± 3.2	6.0 ± 3.3
AFC, 2–10 mm (n)	14.7 ± 6.9	14.4 ± 6.8
Endocrine profile		
AMH (pmol/L)	16.3 (9.0–24.8)	16.0 (9.1–25.5)
FSH (IU/L)	7.5 (6.2–9.2)	7.7 (6.5–9.4)
LH (IU/L)	4.5 (3.5–5.8)	4.4 (3.6–5.8)
E_2 (pmol/L)	158 (128–199)	162 (130–201)
P (nmol/L)	1.7 (0.8–2.4)	1.7 (0.8–2.3)
Inhibin A (pg/mL)	5.0 (5.0–5.0)	5.0 (5.0–5.0)
Inhibin B (pg/mL)	94 (68–125)	97 (72–121)
TSH (μIU/mL)	1.5 (1.0–2.0)	1.5 (1.1–2.0)
Prolactin (μg/mL)	10.3 (7.4–13.9)	9.8 (7.5–13.6)

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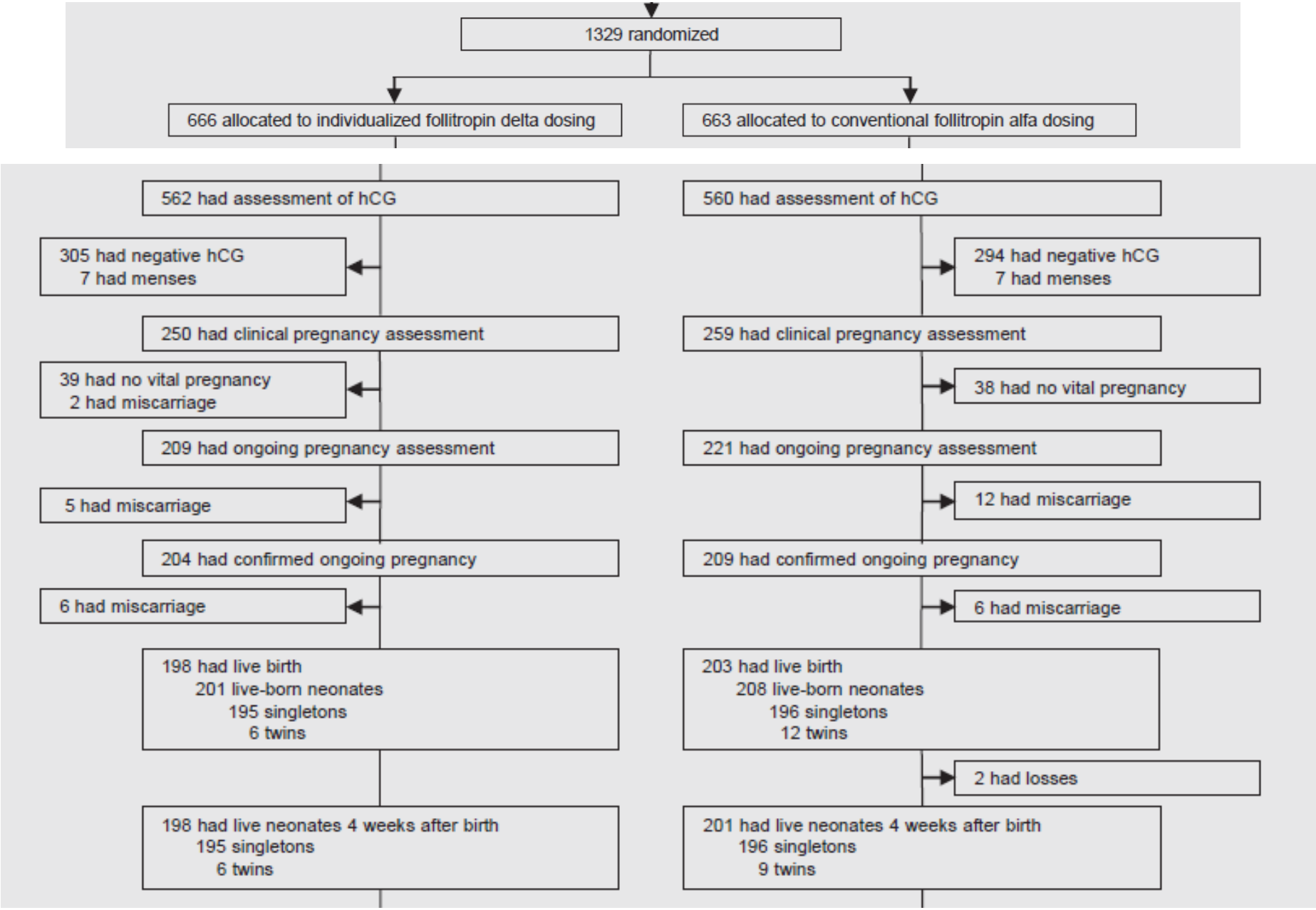

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poor responders: criteri di Bologna

età >40aa

o altro fattore di rischio

per scarsa riserva ovarica

genetico (S.Turner) o acquisito (endometriosi, pregr ch)

<3oo in precedente ciclo IVF

AFC <5-7 o AMH <0.5-1.1 ng/ml

almeno 2 dei 3

HR 2011 ESHRE consensus

Pregnancy data per woman[a]	Individualized ($n = 747$)	Standard ($n = 769$)	*P*-value
Ongoing pregnancy resulting in live birth within 18 months of FU	420 (56.3%)	447 (58.2%)	0.38
Multiple pregnancy[b]	16 (2.1%)	26 (3.3%)	0.07
Conception mode (% of live birth)			0.78
Spontaneous	35 (8.2%)	30 (6.6%)	
IVF/ICSI fresh[c]	298 (71.0%)	314 (70.2%)	
IVF/ICSI frozen	84 (19.9%)	95 (21.2%)	
Other[d]	4 (1.0%)	9 (2.0%)	
Time to ongoing pregnancy leading to live birth, days (mean)	188.0 (128.0)	187.1 (128.6)	0.89

OPTIMIST study group Hum Reprod. 2017;32(12):2485-2495.

Cumulative cycle results	Individualized ($n = 745$)	Standard ($n = 768$)	*P*-value
Number of fresh cycles started/woman	1.9 (0.9)	1.9 (1.0)	0.56
Cycle cancellation[a]	166 (11.7%)	213 (14.5%)	0.01
Number of oocytes[b]	8.7 (5.0)	9.2 (5.6)	0.003
Poor response[c]	393 (28.0%)	425 (29.0%)	0.47
Hyper response[c]	149 (10.6%)	220 (15.0%)	<0.001
Number of fresh embryo transfers[a]	1120 (79.4%)	1133 (77.2%)	0.08
Number of embryos per transfer	1.2 (0.44)	1.2 (0.43)	0.87
OHSS classification[d]			0.003
No OHSS	1343 (95.9%)	1371 (93.6%)	<0.001[e]
Mild OHSS	44 (3.1%)	68 (4.6%)	0.01[e]
Moderate OHSS	6 (0.4%)	18 (1.2%)	0.004[e]
Severe OHSS	8 (0.6%)	8 (0.5%)	0.89[e]
Number of cryo cycles with transfer/woman	0.8 (1.3)	0.8 (1.3)	0.72

OPTIMIST study group Hum Reprod. 2017;32(12):2485-2495.