Hastaya Göre KOH Protokolleri
Individualized COH (iCOH)

Gürkan Bozdağ

Department of OBGYN

School of Medicine, Hacettepe University

Ankara-TÜRKİYE

One size fits all !

- Appropriate for everyone!
  - Single type COH
  - Single type gonadotropin
  - Single dose of gonadotropin

  - Individualized COH (iCOH)

What should be the measure of success in an IVF cycle?

Individualized COH (iCOH)

1. **Maximum live birth rate**
2. **“Enough” ovarian response !**
3. **Minimum side effects and complications** (OHSS, multiple pregnancy)
4. **Patient friendly strategies** (least injection and infrequent monitorization)

“Enough” ovarian response !

Sunkara SK et al, HR, 2011 (n= 400 135 cycles)

- **Nonlinear relation between no. of oocyte and LBR !**

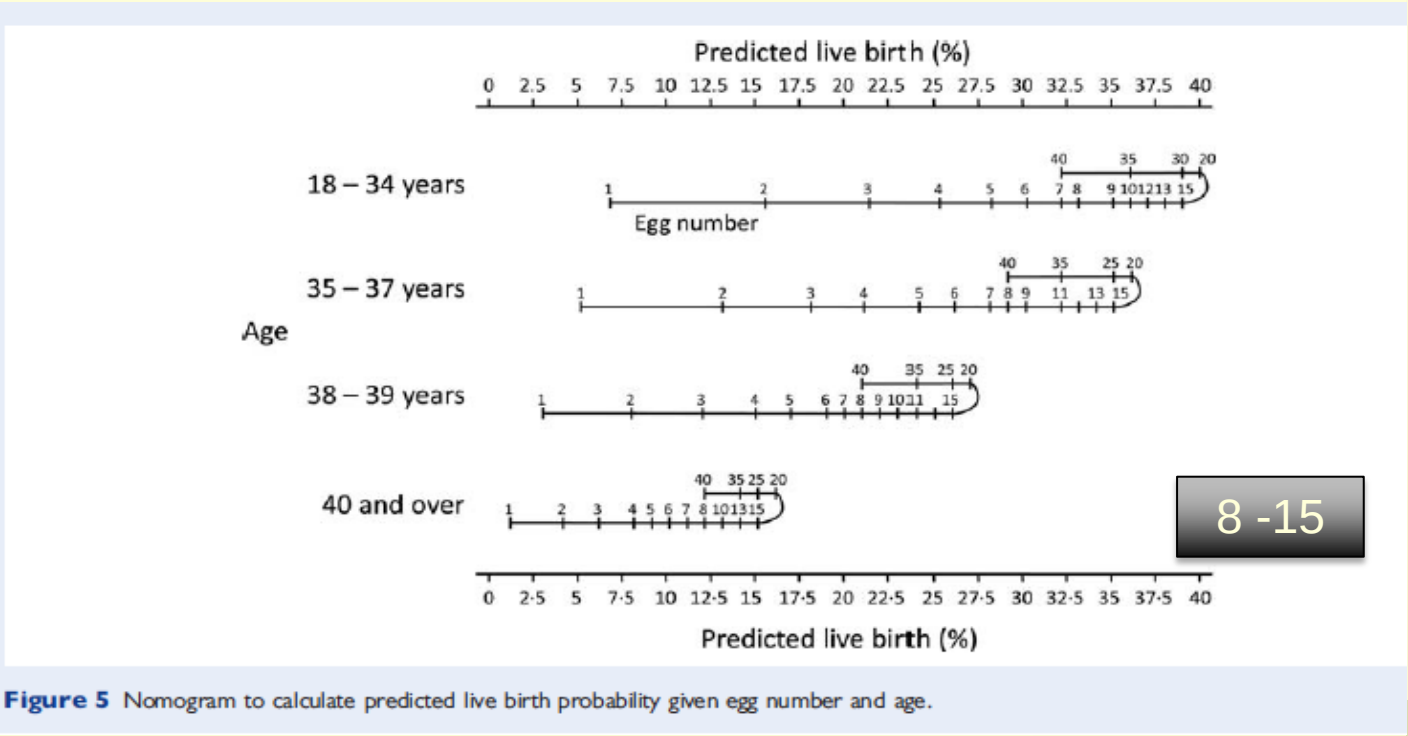


Figure 5 Nomogram to calculate predicted live birth probability given egg number and age.

Ovarian response
Prediction !

- **Ovarian reserve**
  - **Female age**
  - **AFC**
  - **AMH**
  - **FSH**

Ovarian reserve tests

Poor ovarian response (FSH, AFC, AMH)

	Three-test study group				Total study group			
	AUC	95% CI	*P*-value	*n*	AUC	95% CI	*P*-value	*n*
Poor response prediction								
Univariable models								
Age	0.61	0.54–0.68	NA	617	0.60	0.57–0.64	NA	4034
FSH	0.68	0.61–0.74	0.051	617	0.66	0.62–0.69	0.004	3652
AFC	0.76	0.70–0.82	<0.001	617	0.73	0.69–0.77	<0.001	2118
AMH	0.78	0.72–0.84	<0.001	617	0.81	0.77–0.84	<0.001	1274
Multivariable models								
Age and FSH	0.71	0.65–0.78	<0.001	617	0.69	0.66–0.72	<0.001	3652
Age and AFC	0.79	0.73–0.85	<0.001	617	0.76	0.72–0.80	<0.001	2118
Age and AMH	0.77	0.70–0.83	<0.001	617	0.80	0.76–0.84	<0.001	1274
Age and AMH and AFC	0.80	0.74–0.86	<0.001	617	0.80	0.74–0.86	<0.001	618
Age and AMH and AFC and FSH	0.81	0.75–0.86	<0.001	617	0.81	0.75–0.86	<0.001	617

Ovarian reserve tests

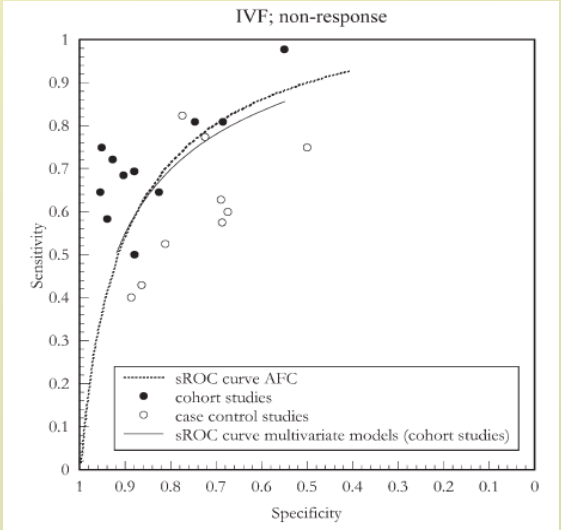
Multivariate models

- **Verhagen ve ark, HRU, 2008**
  - 11 trials
  - Models in the of prediction of POR değil

Table II. Prediction variables used in different models to predict ovarian reserve in IVF patients.

Author	Prediction variables	Poor response (n)	Normal response (n)	Total (%)	Sensitivity (%)	Specificity
Balasch *et al.* (1996)	Age+FSH	40	80	120	53	81
	Age+inhibin B	40	80	120	59	67
	Inhibin B+FSH	40	80	120	57	69
	Age+FSH+inhibin B	40	80	120	39	89
Ranieri *et al.* (1998)	FSH+GAST	48	129	177	97	55
Creus *et al.* (2000)	Age+FSH	40	80	120	83	77
	Age+inhibin B	40	80	120	74	50
	FSH+inhibin B	40	80	120	77	73
	Age+FSH+inhibin B	40	80	120	83	77
Fábregues *et al.* (2000)	FSH+inhibin B	28	52	80	42	86
Bancsi *et al.* (2002)	AFC+inhibin B+FSH	36	84	120	75	95
	AFC+FSH	36	84	120	72	93
	AFC+inhibin B	36	84	120	69	88
	FSH+inhibin B	36	84	120	58	94
Van Rooij *et al.* (2002)	AMH+inhibin B+FSH	35	84	119	68.6	90.5
Durmusoglu *et al.* (2004)	Age+AFC	24	67	91	52	88
Erdem *et al.* (2004)	Abnormal CCCT+age	16	16	32	81	69
	Abnormal CCCT+age+OV+AFC	16	16	32	81	75
Muttukrishna *et al.* (2004)	FSH+inhibin B+AMH[§]	17	52	69	62.5	83.3
Hendriks *et al.* (2005a)	FSH+AFC	17	46	63	65	96
Penarrubia *et al.* (2005)	Age+FSH	129	129	258	63.1	68.8

CCCT, clomiphene citrate challenge test; OV, ovarian volume; AFC, antral follicle count; FSH, follicle stimulating hormone; GAST, gonadotrophin agonist stimulation test; AMH, anti-Mullerian hormone.
[§]Threshold values: FSH>10 mIU/ml, inhibin B>80 pg/ml and AMH>0,1 ng/ml.

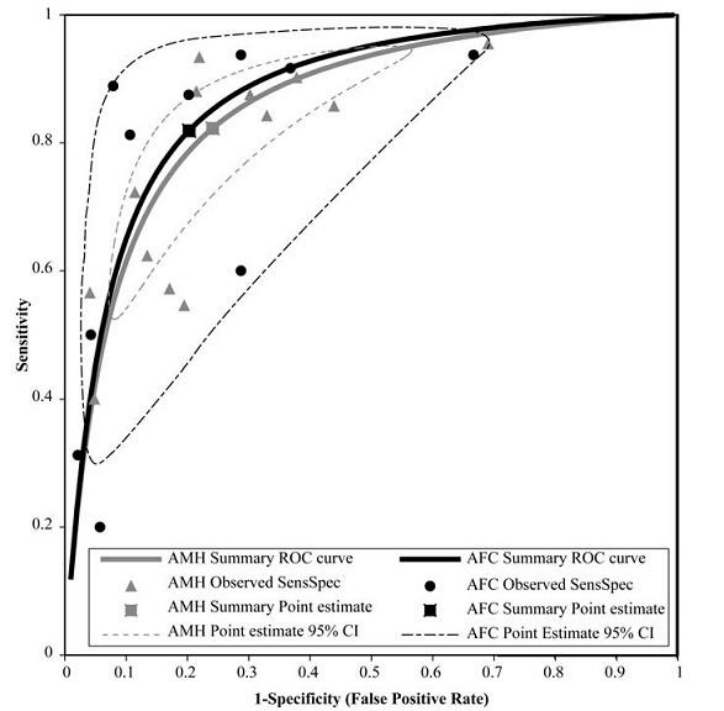


- **Multivariate models and AFC have similar performance.**

Ovarian reserve tests

Excessive ovarian response (AFC, AMH)

- **Broer SL et al, HRU, 2011.**
  - **AMH (n=9) and AFC (n=5)**



AMH: sensitivity %82, specificty %76
AFC : sensitivity %82, specificity %80

Ovarian reserve tests

Ongoing pregnancy (FSH, AFC, AMH)

	Three-test study group				Total study group			
	AUC	95% CI	*P*-value	*n*	AUC	95% CI	*P*-value	*n*
Ongoing pregnancy prediction								
Univariable models								
Age	0.57	0.47–0.66	NA	420	0.56	0.54–0.59	NA	5207
FSH	0.53	0.43–0.62	0.348	420	0.54	0.51–0.58	0.084	3521
AFC	0.50	0.40–0.59	0.100	420	0.52	0.48–0.57	0.612	1977
AMH	0.55	0.45–0.64	0.630	420	0.58	0.51–0.64	0.495	1008
Multivariable models								
Age and FSH	0.58	0.48–0.67	0.195	420	0.60	0.57–0.64	0.116	3521
Age and AFC	0.58	0.48–0.67	0.247	420	0.57	0.52–0.61	0.709	1977
Age and AMH	0.57	0.48–0.67	0.753	420	0.59	0.53–0.65	0.415	1008
Age and AMH and AFC	0.59	0.49–0.68	0.371	420	0.59	0.49–0.68	0.341	421
Age and AMH and AFC and FSH	0.58	0.49–0.68	0.414	420	0.58	0.49–0.68	0.414	420

Ovarian reserve tests

Live birth rate (AMH)

- **La Marca et al, RBM Online, 2011**
  - 2005-2008, IVF database(n=381)
  - Logistic regression (for LBR)
    - Only female age and AMH level

Table 5 Probability (95% CI) of live birth after IVF according to age and AMH.

Age (years)	*AMH (ng/ml)*		
	<0.4	*0.4–<2.8*	*≥2.8*
<31	0.13 (0.04–0.36)	0.38 (0.26–0.51)	0.52 (0.38–0.67)
31–37	0.09 (0.02–0.24)	0.27 (0.21–0.35)	0.40 (0.28–0.54)
>37	0.05 (0.01–0.16)	0.18 (0.12–0.26)	0.29 (0.17–0.44)

Probability of live birth was obtained by using the parameters estimated from the logistic model:

$$P(\text{live birth}) = \frac{\exp(-2.88 + 1.38 * \ln AMH_{1-2} + 1.96 * \ln AMH_{3} + 1.01 * age_{<31} + 0.52 * age_{31-36})}{1 + \exp(-2.88 + 1.38 * \ln AMH_{1-2} + 1.96 * \ln AMH_{3} + 1.01 * age_{<31} + 0.52 * age_{31-36})}$$

For LBR, sensitivity % 79.2 and <u>spesificity 44.2%</u>

Ovarian reserve tests

Clinical use (AFC, AMH)

Marker	Poor response	Excessive response
AMH (ng / ml)	0.7 – 1.3 (IBC and DSL)	3.5 – 3.9 (Gen II)
AFC (2 – 10 mm)	5 – 7	16

CHANGES OF AFC IN YEARS

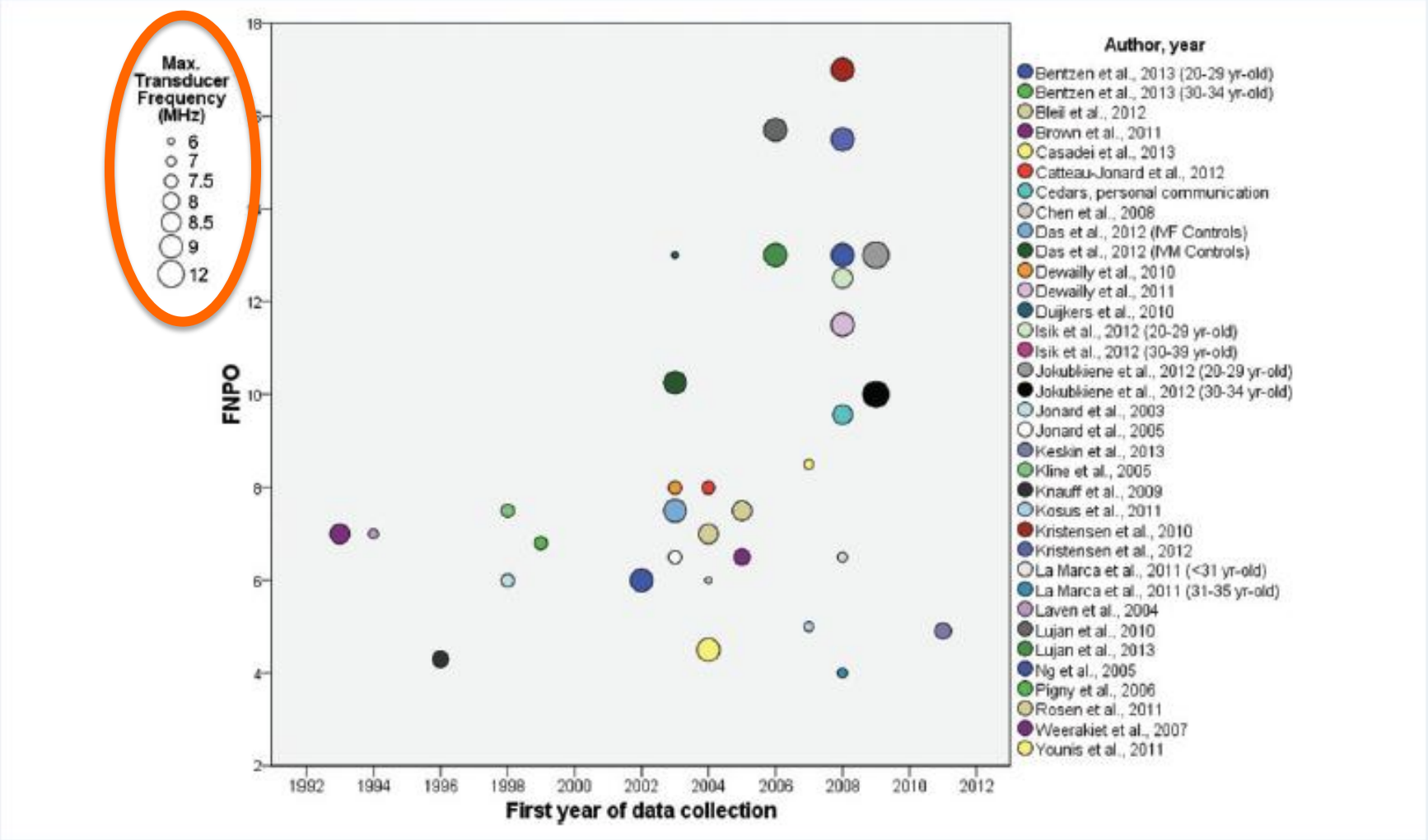


Figure 2 Changes in reported values for the mean or the median (depending on available data) of follicle number per ovary (FNPO) in healthy women

AMH INSTABILITY

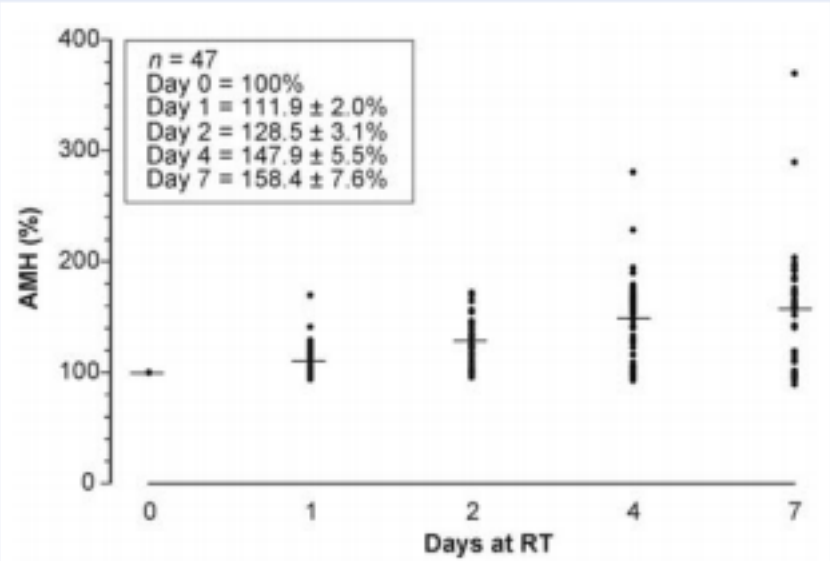


Figure 2 Stability of AMH in serum at RT. Results at each time interval are expressed as a percentage of the patient's AMH concentration at Day 0. Means ± SEM are indicated.

Table V Stability of AMH in serum on storage for 5 days.

Sample no.	AMH (pmol/l)		
	Fresh	−20°C, PS	−80°C, PP
1	12.41	15.51	13.12
2	42.17	75.42	45.08
3	11.93	17.12	12.39
4	10.42	12.82	12.28
5	9.56	9.05	8.79
6	19.02	26.01	18.84
7	24.02	20.16	23.62
8	1.45	1.37	1.32

PS, polystyrene LP4 tube; PP, polypropylene 2 ml tube.

Interval result

- **Broer SL et al, HRU, 2013.**
  - **Since ovarian reserve tests predict cycle cancellation but do not predict no-pregnancy, women should not be refrained from an IVF cycle based on abnormal reserve tests.**
  - **Unfortunately, OR tests are the most frequently used tools to tailor COH, among the available variables.**

Based on ovarian reserve

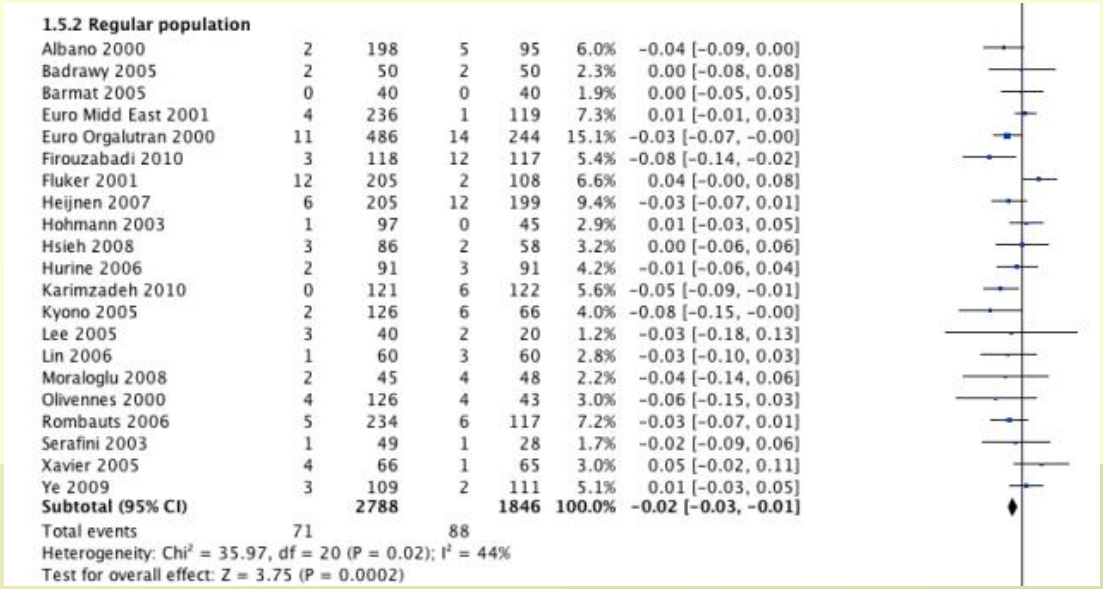
- Expected poor ovarian responders
- Expected hyper ovarian responders
- **Expected normal ovarian responders**

Expected normal ovarian responders

- **Best protocol?**
- **Optimal type of gonadotropin ?**
- **Optimal dose of gonadotropin ?**

Best protocol !
GnRH agonist vs antagonist

- **Al-Inany, Cochrane, 2011 (45 RCTs)**
  - **vs long agonist protocol**
  - **LBR: -0.86; (95%CI: 0.76 to 1.04), 9 RCTs**
    - Similar for fixed and flexible protocols in subgroup analysis
  - **OHSS, 21 RCTs, regular population**



1.5.2 Regular population						
Albano 2000	2	198	5	95	6.0%	-0.04 [-0.09, 0.00]
Badrawy 2005	2	50	2	50	2.3%	0.00 [-0.08, 0.08]
Barmat 2005	0	40	0	40	1.9%	0.00 [-0.05, 0.05]
Euro Midd East 2001	4	236	1	119	7.3%	0.01 [-0.01, 0.03]
Euro Orgalutran 2000	11	486	14	244	15.1%	-0.03 [-0.07, -0.00]
Firouzabadi 2010	3	118	12	117	5.4%	-0.08 [-0.14, -0.02]
Fluker 2001	12	205	2	108	6.6%	0.04 [-0.00, 0.08]
Heijnen 2007	6	205	12	199	9.4%	-0.03 [-0.07, 0.01]
Hohmann 2003	1	97	0	45	2.9%	0.01 [-0.03, 0.05]
Hsieh 2008	3	86	2	58	3.2%	0.00 [-0.06, 0.06]
Hurine 2006	2	91	3	91	4.2%	-0.01 [-0.06, 0.04]
Karimzadeh 2010	0	121	6	122	5.6%	-0.05 [-0.09, -0.01]
Kyono 2005	2	126	6	66	4.0%	-0.08 [-0.15, -0.00]
Lee 2005	3	40	2	20	1.2%	-0.03 [-0.18, 0.13]
Lin 2006	1	60	3	60	2.8%	-0.03 [-0.10, 0.03]
Moraloglu 2008	2	45	4	48	2.2%	-0.04 [-0.14, 0.06]
Olivennes 2000	4	126	4	43	3.0%	-0.06 [-0.15, 0.03]
Rombauts 2006	5	234	6	117	7.2%	-0.03 [-0.07, 0.01]
Serafini 2003	1	49	1	28	1.7%	-0.02 [-0.09, 0.06]
Xavier 2005	4	66	1	65	3.0%	0.05 [-0.02, 0.11]
Ye 2009	3	109	2	111	5.1%	0.01 [-0.03, 0.05]
Subtotal (95% CI)		**2788**		**1846**	**100.0%**	**-0.02 [-0.03, -0.01]**
Total events	71		88			
Heterogeneity: $Chi^2 = 35.97$, df = 20 (P = 0.02); $I^2 = 44\%$						
Test for overall effect: Z = 3.75 (P = 0.0002)						

Expected normal ovarian responders
GnRH antagonist (Devroey P, 2009)

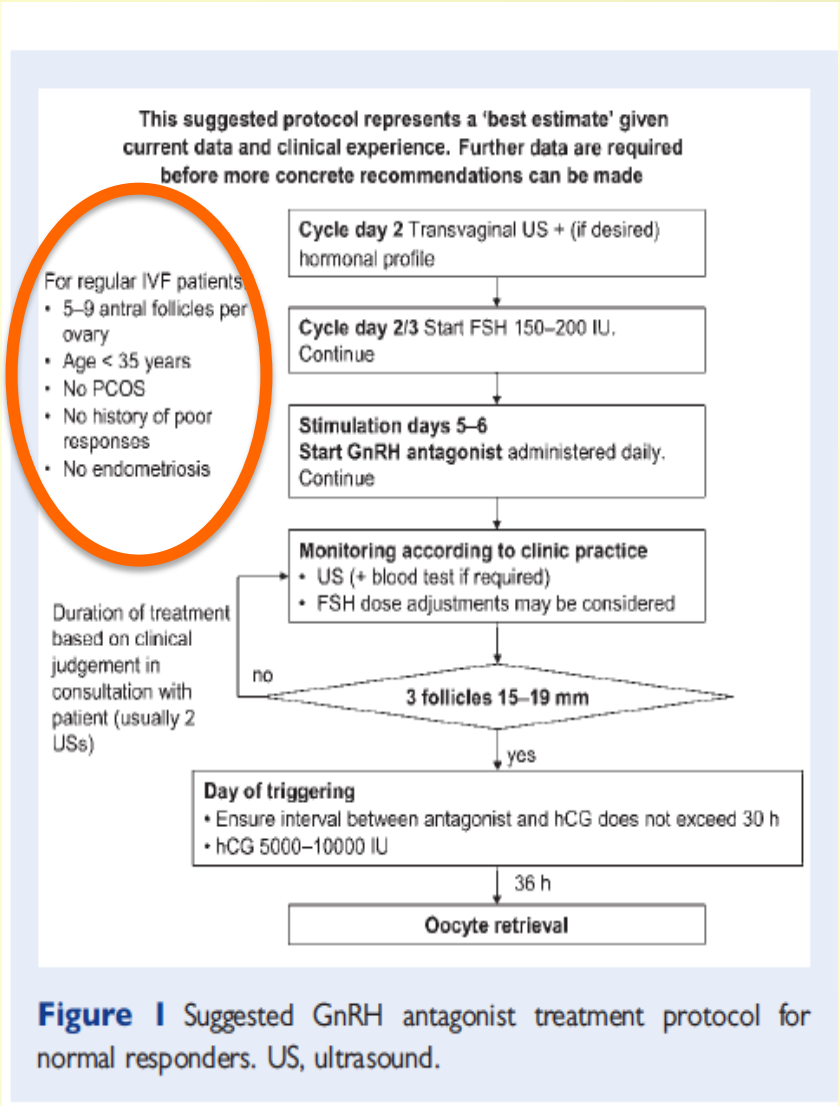


Figure 1 Suggested GnRH antagonist treatment protocol for normal responders. US, ultrasound.

Expected normal ovarian responders
Mild stimulation (ISMAAR)

- **2- 7 oocyte, low dose FSH/hMG, GnRH antagonist cycle (± anti-estrogen)**
- **Verberg, HRU, 2009 (3 RCTs)**
  - vs long agonist protokol
  - Median oocyte is 6 vs 9 (p< 0.001)

		Started treatment cycles (all first cycles)	Retrieval procedures	Embryo transfers	Ongoing pregnancy rate*	Live birth rate
Hohmann *et al.* (2003)	Mild	49	32	28	16%	n.a.
	Conventional	45	38	26	18%	n.a.
Heijnen *et al.* (2007)	Mild	201	147	124	13%	13%
	Conventional	193	176	160	33%	31%
Baart *et al.* (2007)	Mild	63	56	41	21%	n.a.
	Conventional	41	40	33	18%	n.a.
Total	Mild	313	235	193	15%	n.a.
	Conventional	279	254	219	29%	n.a.

Types of Gonadotropins

	FSH content	LH activity content	Brand name
HUMAN DERIVED			
HP hFSH	75 IU	< 0.1 IU	*Fostimon, Bravelle*
hMG	75 IU	75 IU	*Pergonal, Humegon, Menogon*
HP hMG	75 IU	75 IU	*Merional, Menopur*
hCG	absent	250-5,000 IU	*Gonasi, Choriomon, Pregnyl*
RECOMBINANT			
rFSHα	75-1,050 IU	absent	*Gonal F*
rFSHβ	50-900 IU	absent	*Puregon, Follistim*
rLH	absent	75 IU	*Luveris*
rCG	absent	250 μg	*Ovidrel*
rFSHα + rLH	150 IU	75 IU	*Pergoveris*

Expected normal ovarian responders
Optimal type of gonadotropin !

- **Van Wely, HRU, 2012**
- **Rec FSH vs urinary** (HMG, highly purified HMG, purified urinary FSH and highly purified urinary FSH)
  - **28 RCTs, 7339 patients**
  - **Similar LBR (OR 0.97, 95% CI 0.87–1.08)**
- **Rec FSH vs hMG**
  - **11 RCTs, 3197 patients**
  - **Higher LBR in favor of hMG (OR 0.84, 95% CI 0.72–0.99)**[2]

Expected normal ovarian responders
Long acting gonadotropin

- **Pouwer AW, Cochrane, 2012**
  - **4 RCTs (23.335 women)**
  - **Daily vs long acting FSH**
  - **Similar LBR and OHSS**
  - **Low dose long acting (60 – 120 mcg) vs daily FSH**
    - Lower LBR (OR: 0.60; 95% CI 0.40 to 0.91)

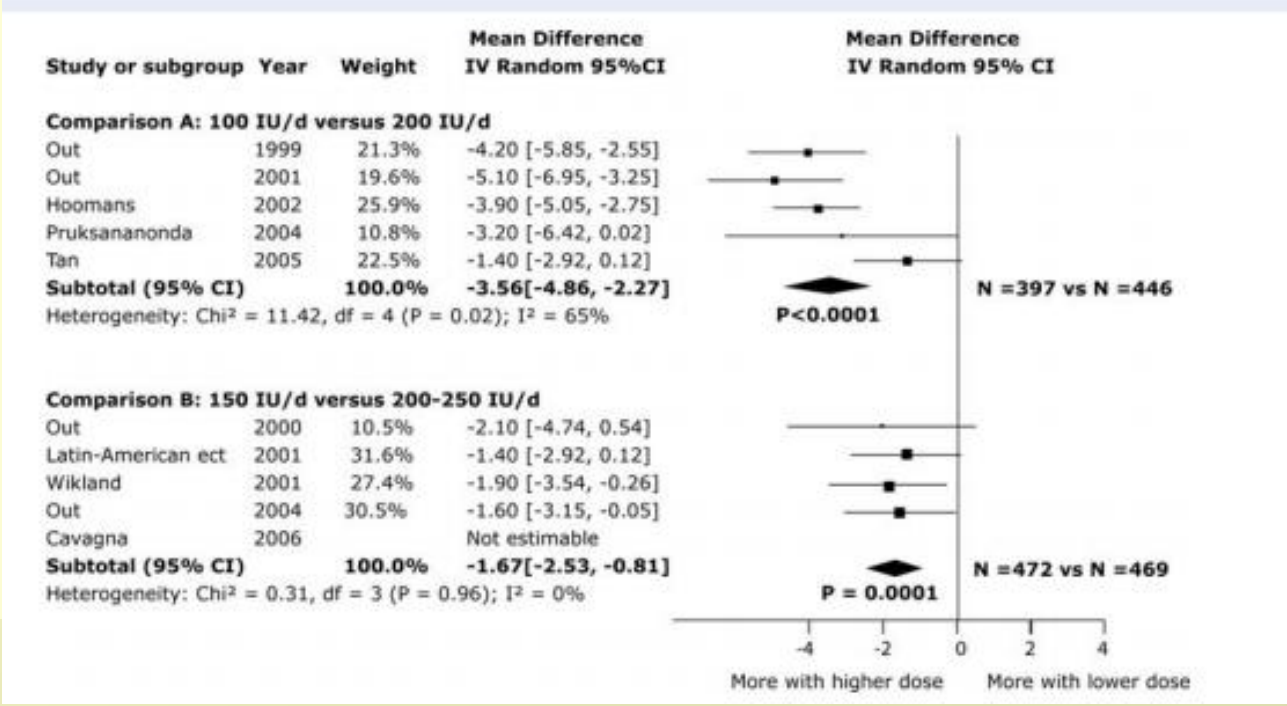
Expected normal ovarian responders
Optimal dose !

- **The prediction of “optimum” starting gonadotropin dosing is a challenge and is currently based on physician preference rather than evidence based.**

- **To avoid hypo- and hyper-ovarian response.**

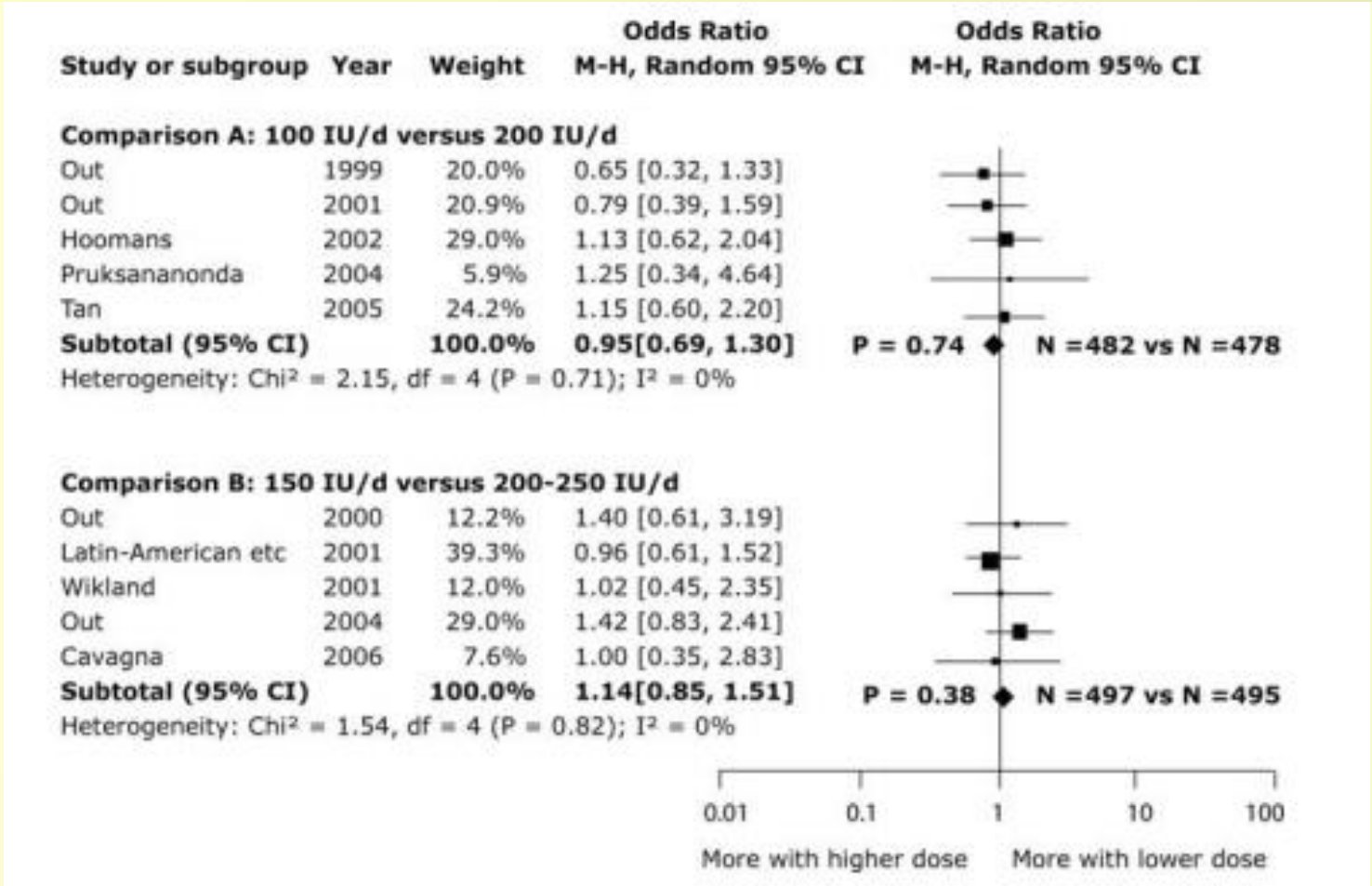
Expected normal ovarian responders
Optimal dose – no. of oocytes

- **Sterrenburg et al, HRU, 2011 (10 RCTs)**
  - **Incremental dose is related with higher no. of oocytes.**



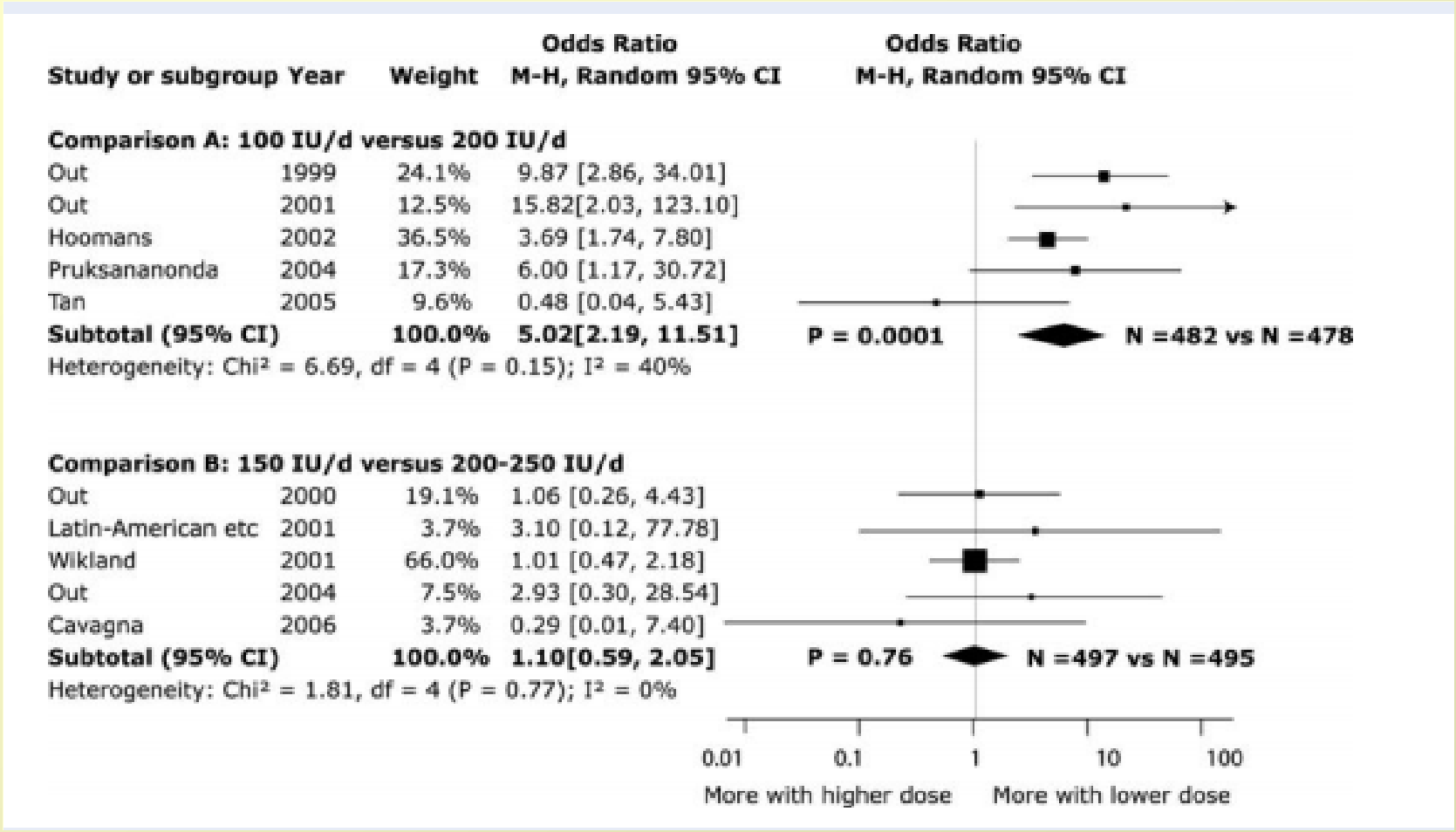
Expected normal ovarian responders

Optimal dose – CPR



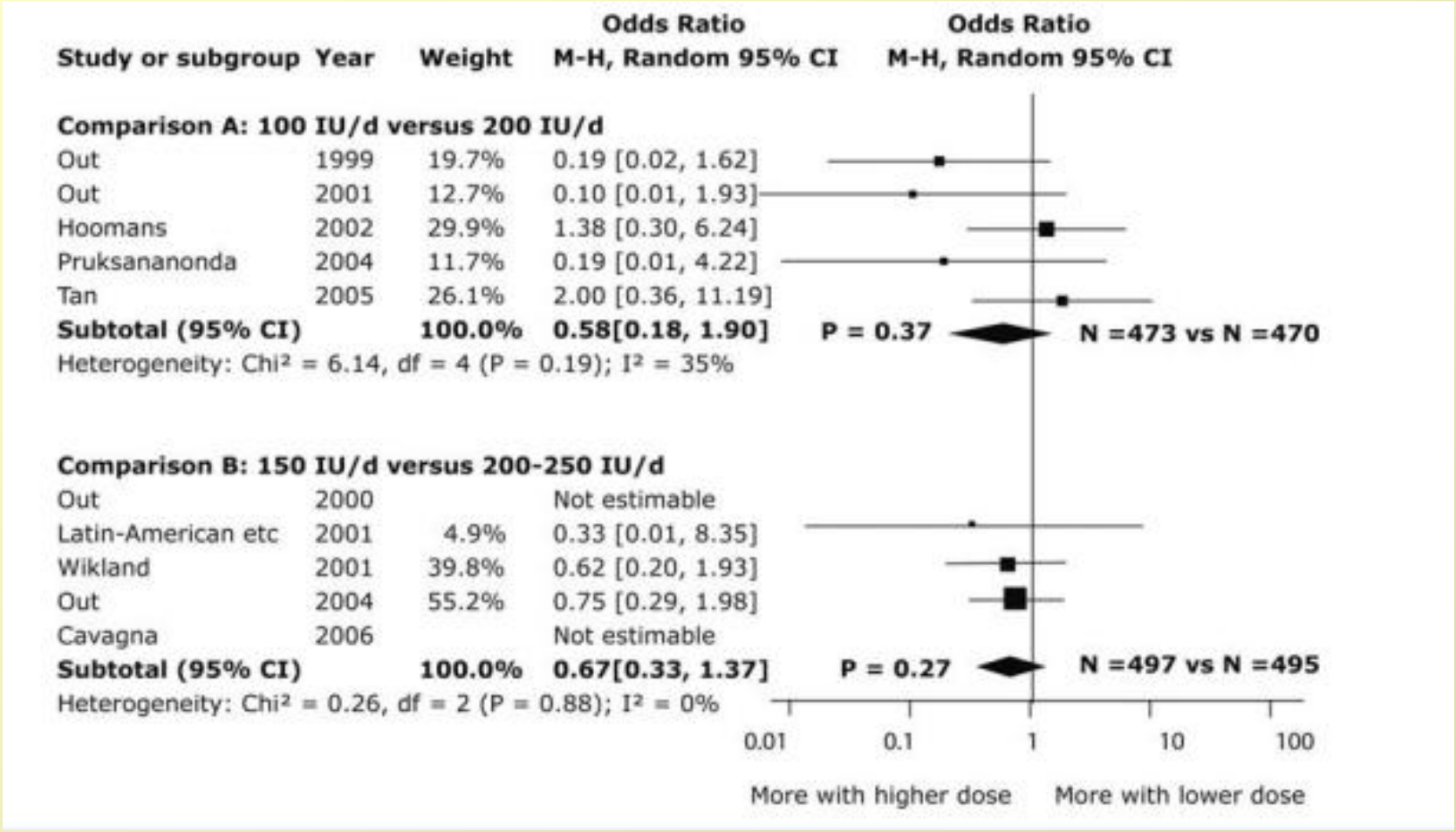
Expected normal ovarian responders

Optimal dose – unexpected POR



Expected normal ovarian responders

Optimal dose – excessive response



Expected normal ovarian responders
Optimal dose – CPR

- **Sterrenburg et al, HRU, 2011 (10 RCTs)**
- **Expected normal responders**
  - **Female age** : 18 – 39
  - **Menstrual pattern** : Düzenli
  - **BMI** : < 30
  - **GnRH agonist or antagonist**

- **Ideal dose is around 150 / day.**
- **Similar for agonist and antagonist**

Interval result

Expected normal responders

- **Best protocol**
  - **Agonist = antagonist (secondary adv.)**
- **Best dose of Gn**
  - **Around 150 IU/day**
- **Best type of Gn**
  - **Conflict of interest in the available literature.**
  - **Final decision is not given, and probably will not…**

- **Tailoring the COH (Protocol ± Gn ± Dose)**

  - **Predictive models for the whole population !**
    - **Univariate**
    - **Multivariate**

iCOH-univariate models (AMH)

Optimal protocol and dose of gonatropin

Table I Deployment of GnRH analogues and doses of follicle stimulating hormone in the groups categorized by anti-Müllerian hormone in the two centres

AMH group (pmol/l)	Centre 1		Centre 2	
	FSH daily dose	GnRH analogue	FSH daily dose	GnRH analogue
<1.0	375	Antagonist	(Modified natural cycle)	(Antagonist)
1.0 to <5	375	Agonist	300	Antagonist
5.0 to <15	225	Agonist	225	Agonist
≥15.0	150	Agonist	150	Antagonist

AMH, anti-Müllerian hormone; FSH, follicle stimulating hormone.

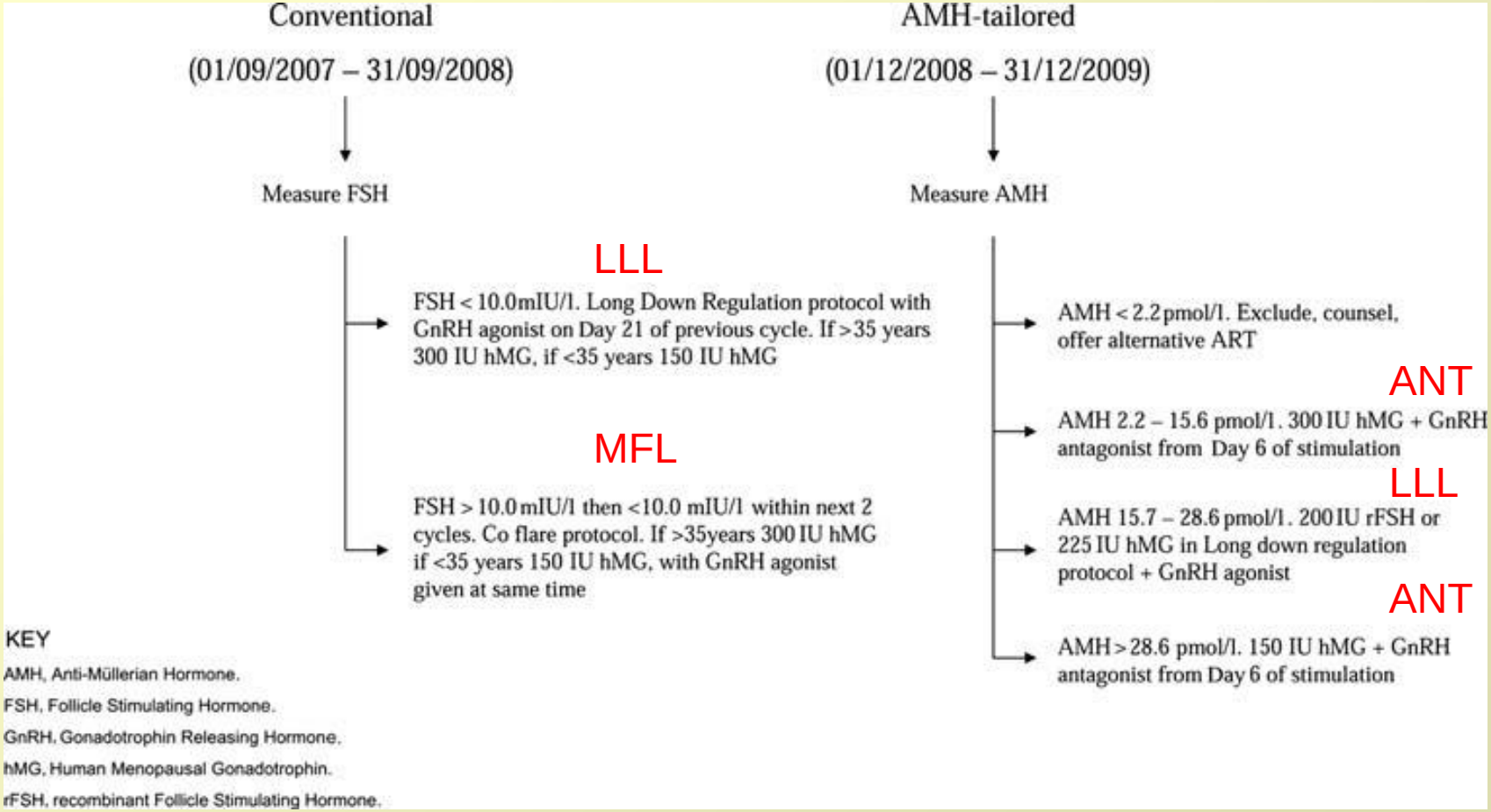
Nelson, HR, 2009 (n=538)

≥ 15 pmol/l : Higher CPR with GnRH antagonist = OR 4.40 (95%CI 1.95 –9.93)

: Risk of hospitalisation due to OHSS= 0% vs 14%.

iCOH-univariate models (AMH)

Optimal protocol and dose of gonatropin



Yates AP, HR, 2011 (n=769)

% 79 vs % 87, p = 0.002)

Increase in LBR (% 15.9 vs % 23.9, p = 0.007)

iCOH-multivariate models

Prediction of the optimal dose of gonadotropin

Human Reproduction Vol.18, No.4 pp. 781–787, 2003 DOI: 10.1093/humrep/deg181

A prospective study of predictive factors of ovarian response in 'standard' IVF/ICSI patients treated with recombinant FSH. A suggestion for a recombinant FSH dosage normogram

B.Popovic-Todorovic[1,3], A.Loft[1], A.Lindhard[1], S.Bangsbøll[1], A.M.Andersson[2] and A.Nyboe Andersen[1]

Table VII. rFSH dosage normogram

Total number of antral follicles <10 mm day 2–5	FSH score IU/day	rFSH starting dose
<15	90	
15–25	60	
>25	50	
Total ovarian volume day 2–5		Score
<9 ml	90	
9–13 ml	60	
>13 ml	50	
Total Doppler score day 2–5		Score
2–3	30	
4	20	
5	10	
6	0	
Age (years)		Score
>35	20	
>30 – ≤ 35	10	
≤ 30	0	
Smoking habits cigarettes/day		Score
>10	20	
≤10	10	
Non smoker	0	
Total FSH score (sum of scores) same as dose IU/day		

131 women are randomized

- **1. arm** iCOH
- **2. arm** 150 IU, fixed
- **Definition of optimal response: 5-14 oocytes,**
  - Optimal response 77.1% vs 65.6%; p<0.05)
  - OPR 36.6% vs 24.4% (p<0.01).
- **Clinical use !**

iCOH-multivariate models

Prediction of the optimal dose of gonadotropin

Individualizing FSH dose for assisted reproduction using a novel algorithm: the CONSORT study

Francois Olivennes attended medical school in Paris and then studied for his PhD in Biology of Reproduction at the University Pierre et Marie Curie in Paris. Following a fellowship under Pr Zev Rosenwaks in Cornell Medical College in New York, he returned to work in France. He was successively medical director of the french ART units in A. Beclere Hospital in Clamart with Rene Frydman and in Cochin Hospital in Paris. He is now coordinator of the private IVF centre of Eylau La Muette in Paris. He was a member of the ESHRE executive comittee from 2003 to 2007. His research interests include obstetric and peadiatric outcome of IVF, development of ovarian stimulation protocols and prevention of IVF complications.

Dr François Olivennes

$$Y\ (\text{oocytes retrieved}) = \alpha + \beta_1 AGE + \beta_2 AGE^2 + \beta_3 BMI + \beta_4 FSH + \beta_5 FOLL\_LT11 + \beta_6 DOSE$$

Therefore

$$DOSE = (Y - (\alpha + \beta_1 AGE + \beta_2 AGE^2 + \beta_3 BMI + \beta_4 FSH + \beta_5 FOLL\_LT11))/\ \beta_6$$

- **A prospective, <u>uncontrolled</u> (18-centre)**
- **Basal FSH, BMI, age and AFC (LLL) based doses**
  - Howles CM, Current Medical Research and Opinion, 2006
- **Normo-ovulatory women aged 18–34 years**
- **Overall, a median of 9.0 oocytes were retrieved.**

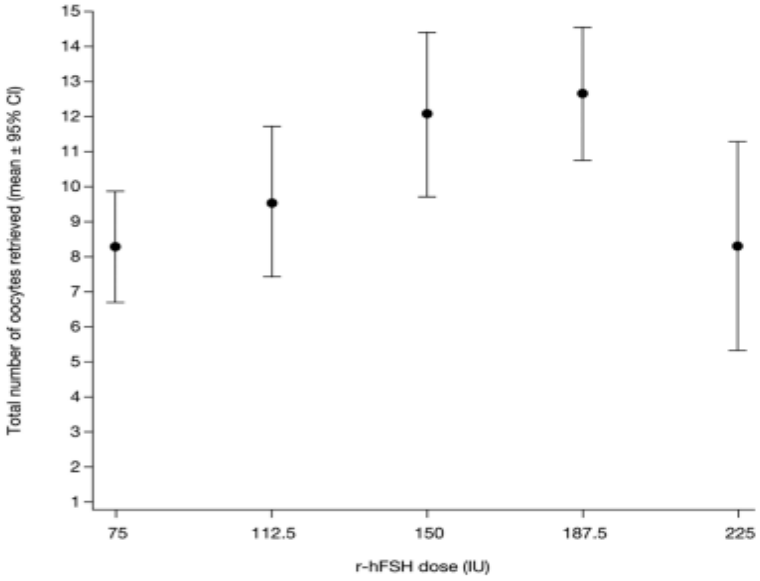
iCOH-multivariate models

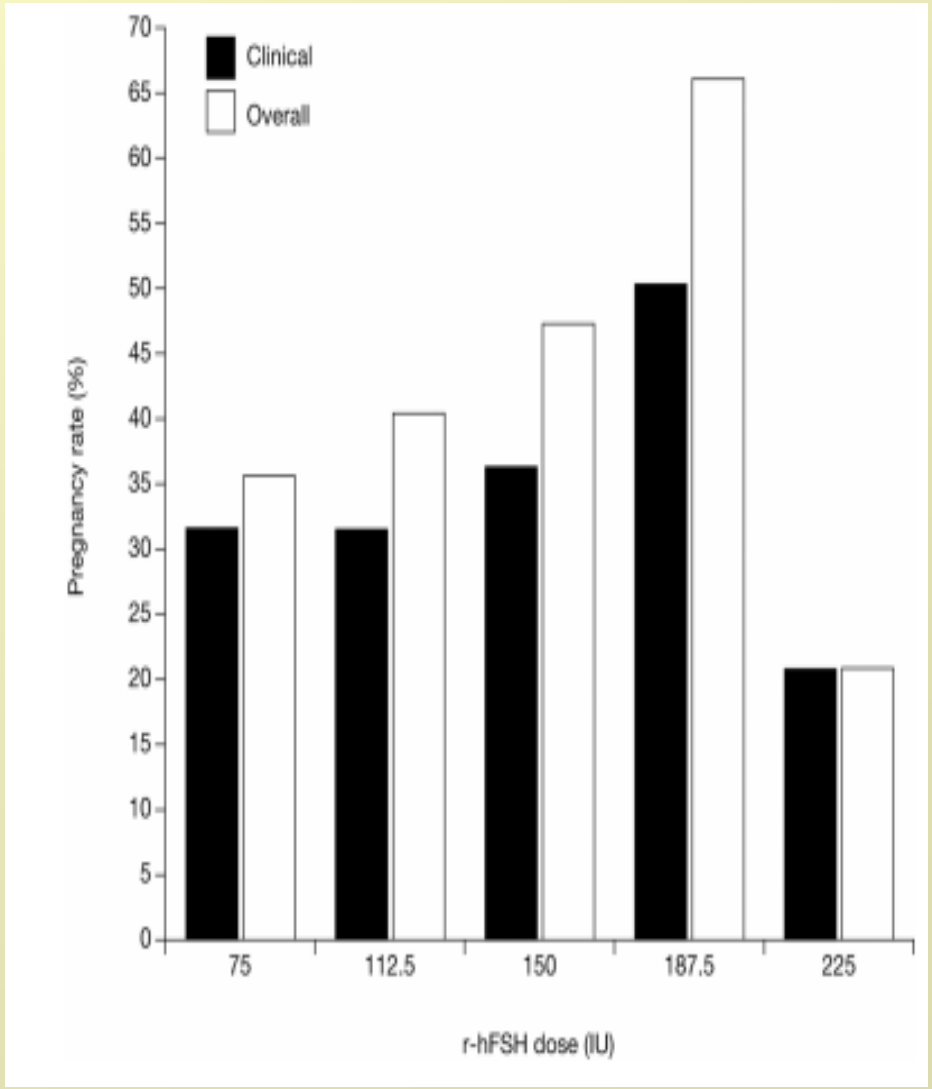
Prediction of the optimal dose of gonadotropin

Individualizing FSH dose for assisted reproduction using a novel algorithm: the CONSORT study

Francois Olivennes attended medical school in Paris and then studied for his PhD in Biology of Reproduction at the University Pierre et Marie Curie in Paris. Following a fellowship under Pr Zev Rosenwaks in Cornell Medical College in New York, he returned to work in France. He was successively medical director of the french ART units in A. Beclere Hospital in Clamart with Rene Frydman and in Cochin Hospital in Paris. He is now coordinator of the private IVF centre of Eylau La Muette in Paris. He was a member of the ESHRE executive comittee from 2003 to 2007. His research interests include obstetric and peadiatric outcome of IVF, development of ovarian stimulation protocols and prevention of IVF complications.

Dr François Olivennes





iCOH-multivariate models

Prediction of the optimal dose of gonadotropin

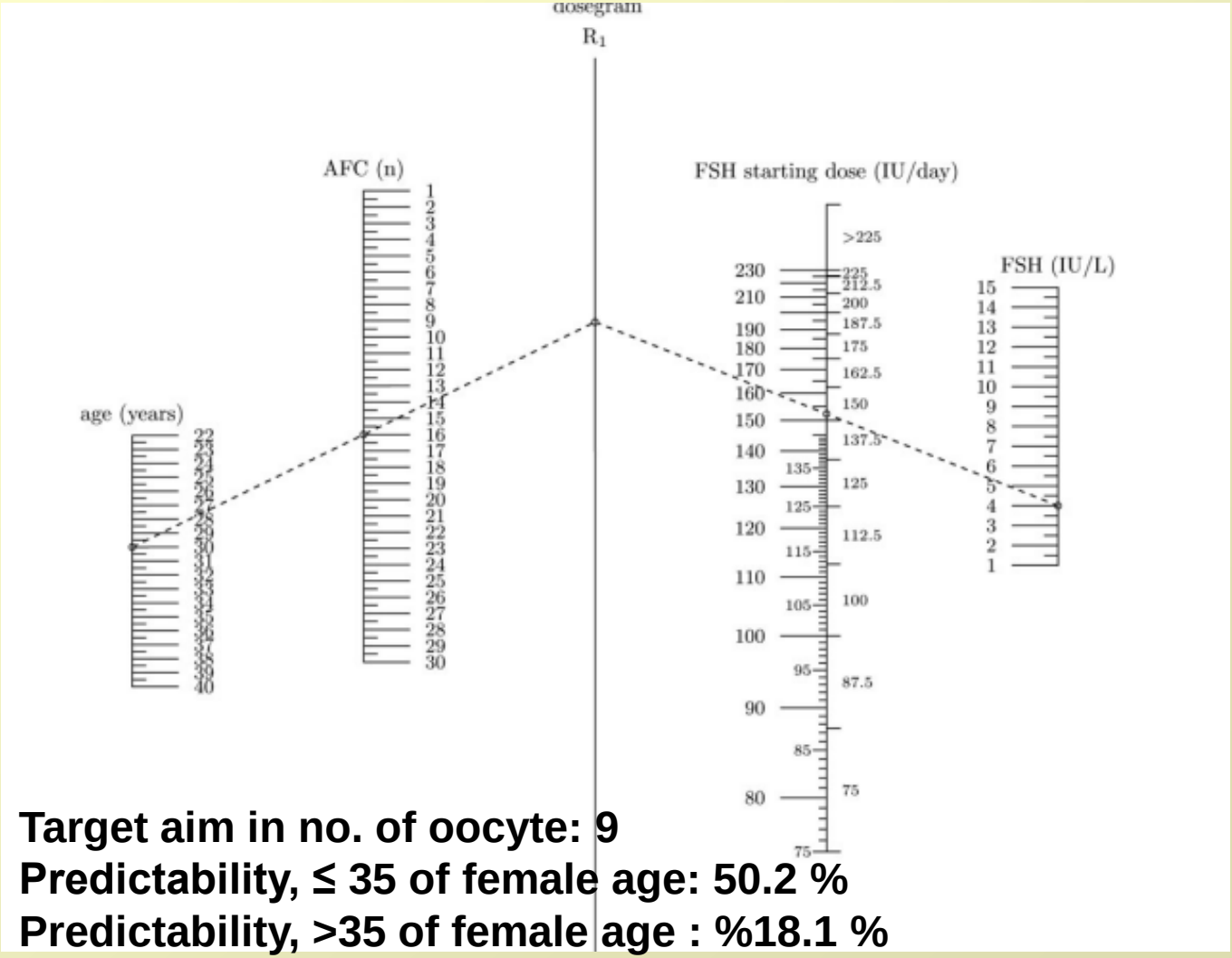
La Marca, BJOG 2012 - La Marca, J Ovarian Res 2013

Table 2 Predictors of number of retrieved oocytes in univariate and multivariate backward regression analysis

Variable	Univariate			Multivariate		
	Regresssion coefficient	Standard Error	p	Regresssion coefficient	Standard Error	p
Age	−0,28116	0,05076	<0.0001	−0,08732	0,05046	0.02
FSH	−0,32630	0,06085	<0.0001	−0,22924	0,05726	0.0001
AFC	0,41664	0,03041	<0.0001	0,35517	0,03538	<0.0001
BMI	−0,002	0,00005	0.01	−0,001	0,00005	ns
Height	−0,01227	0,00358	ns	−0,01	0,003	ns
Weight	0,04202	0,02488	0.09	0,03	0,02	ns
Basal estradiol	−0,00664	0,00503	ns	−0,004	0,005	ns
Smoking status	−0.00051	0.00008	0.01	−0.0005	0.00003	ns

iCOH-multivariate models

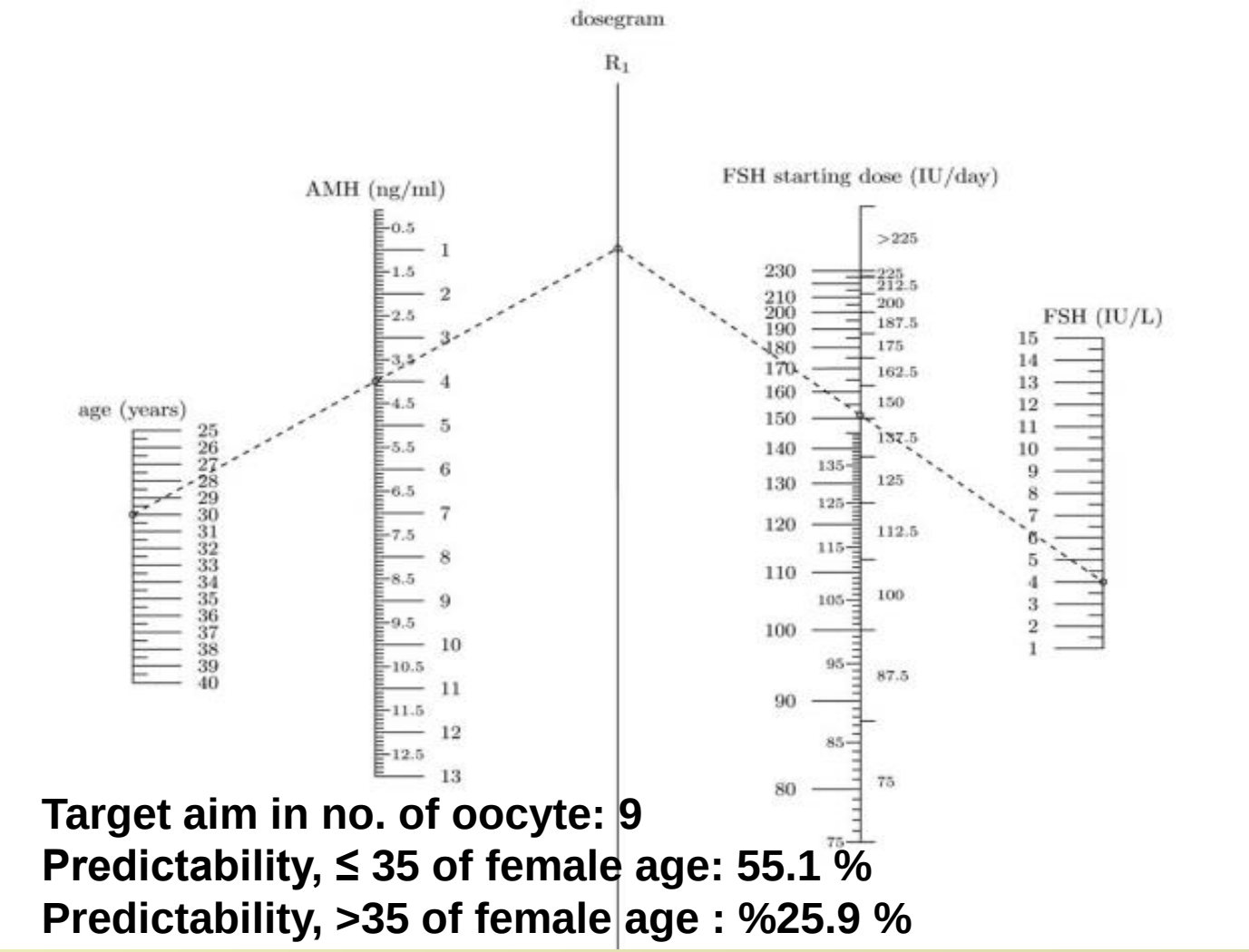
Prediction of the optimal dose of gonadotropin



Target aim in no. of oocyte: 9
Predictability, ≤ 35 of female age: 50.2 %
Predictability, >35 of female age : %18.1 %

iCOH-multivariate models

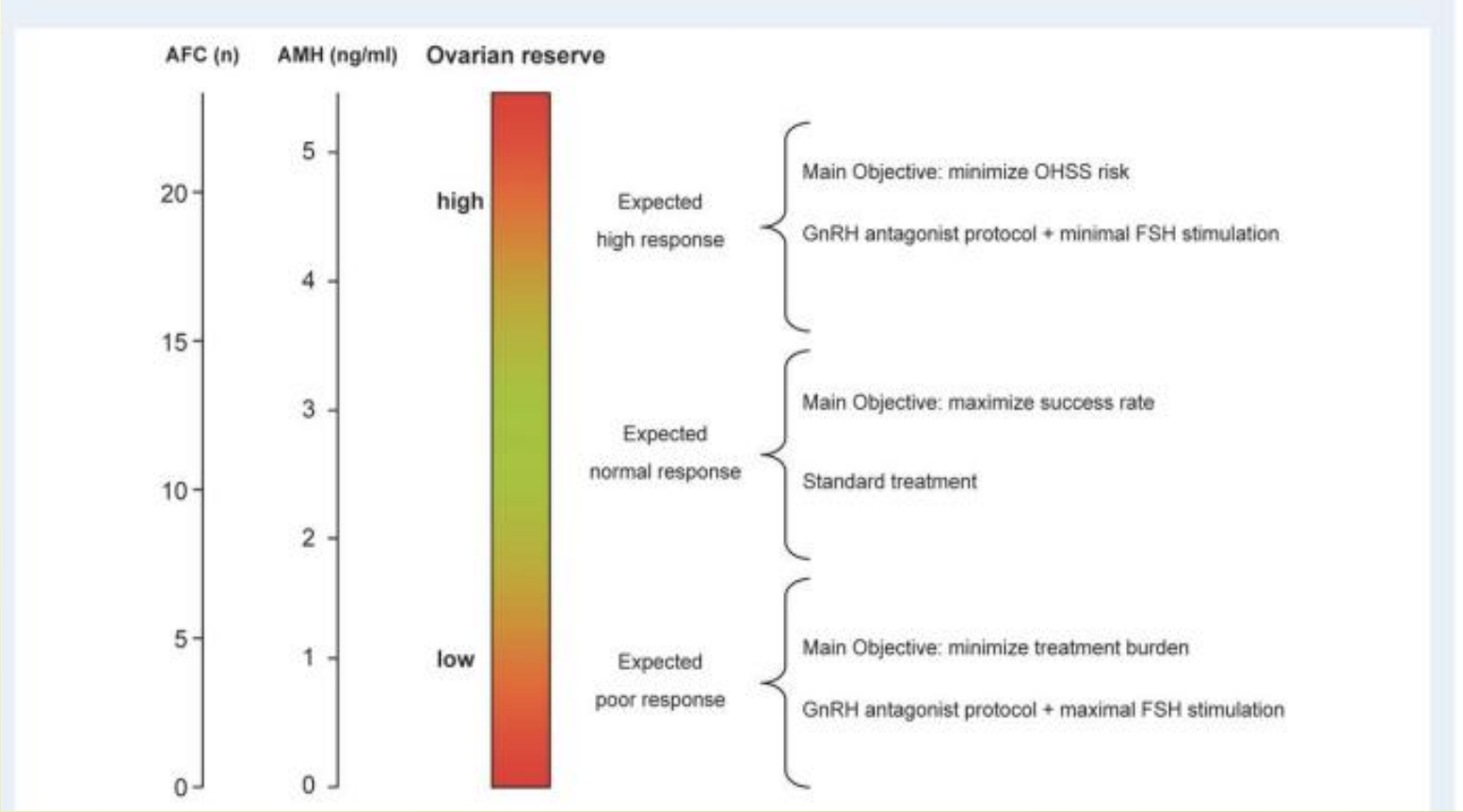
Prediction of the optimal dose of gonadotropin



Target aim in no. of oocyte: 9
Predictability, ≤ 35 of female age: 55.1 %
Predictability, >35 of female age : %25.9 %

iCOH (current status)

La Marca and Sunkara, HRU, 2013



iCOH (future)

- **iCOH is feasible**
  - **But questionable with the available tools**
- **Multivariate > univariate models**
- **Proper tools ?**
  - **Genetic biomarkers** (Gonadotropin response assay)