Individualized treatment based on ovarian reserve markers

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Prediction

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Ovarian reserve markers

➢ Reflect the number of non-growing follicles in the female ovary

➢ Can predict the level of ovarian response after ovarian stimulation

Which is the ideal ovarian reserve marker?

❑ Can predict excessive and poor response to stimulation
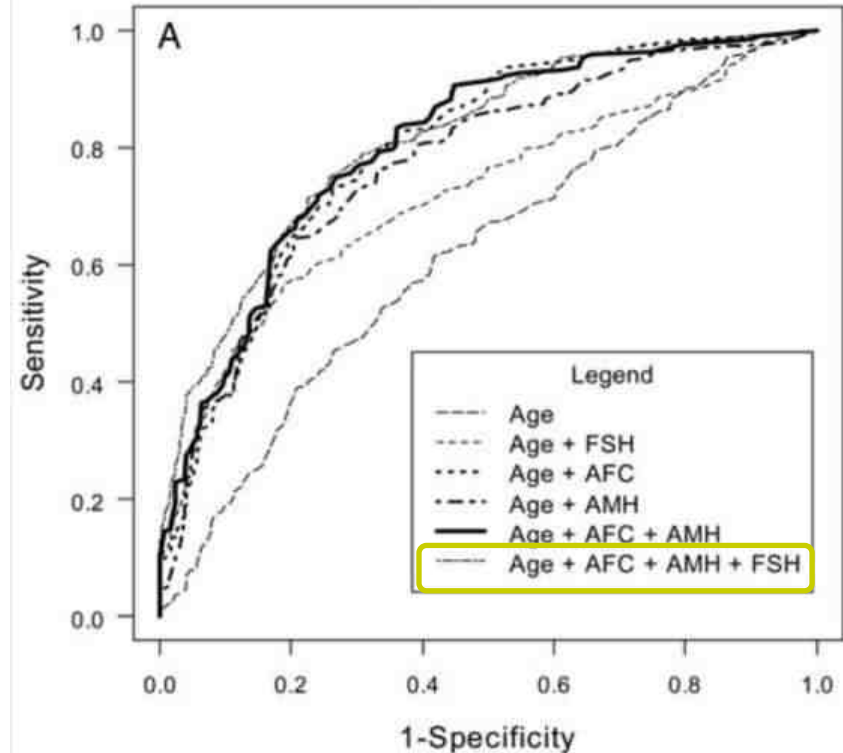
❑ Reliable

❑ Stable (can be measured anytime we want)

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Ovarian reserve tests and response prediction

Excessive response
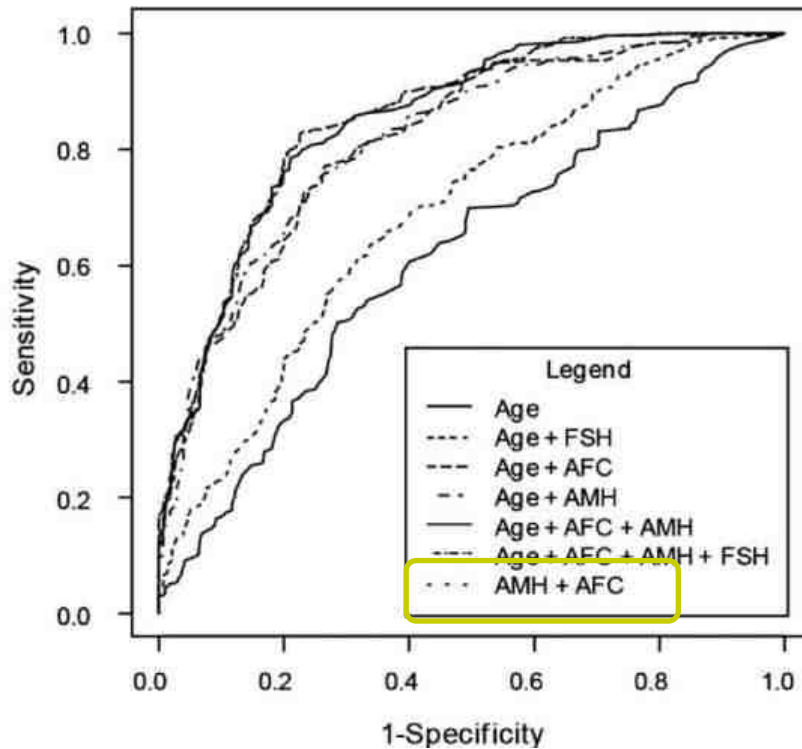
Broer et al. Fertil Steril 2013

Low response

Broer et al. Hum. Reprod. Update 2013
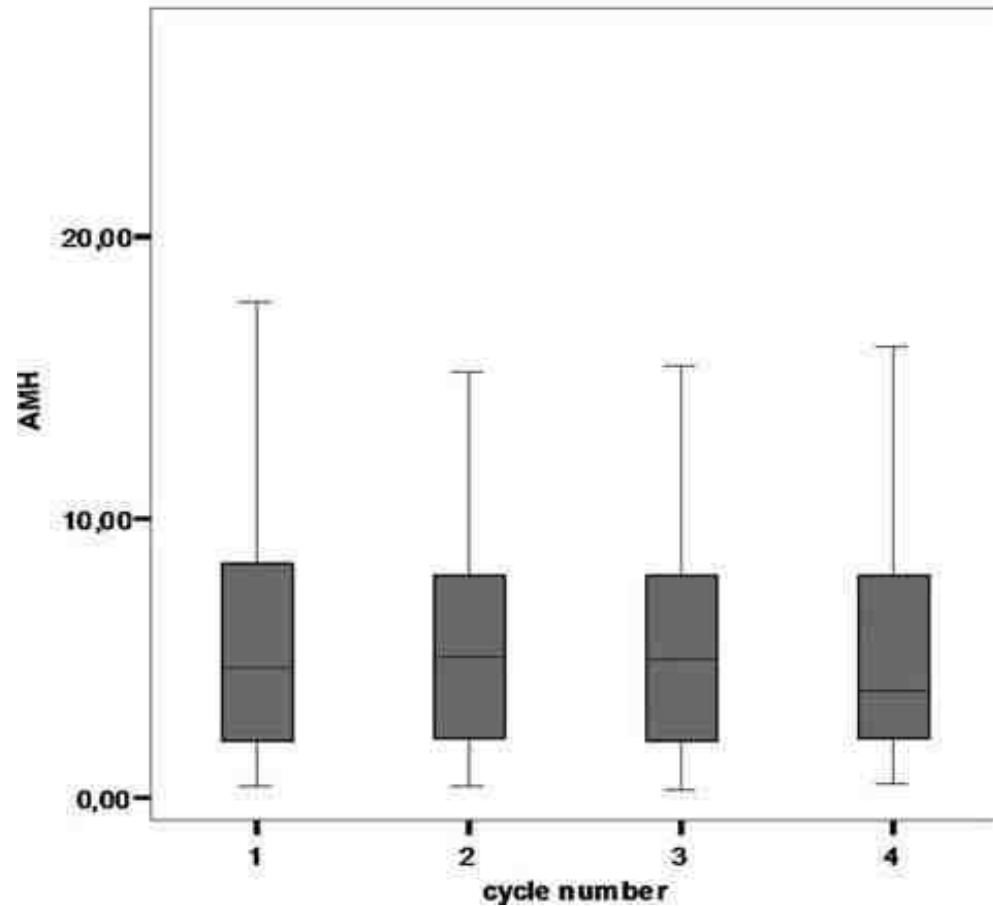
Antral follicle count (AFC)

LIMITATIONS

- AFC may have variability when different or inexperienced sonographers perform the scan

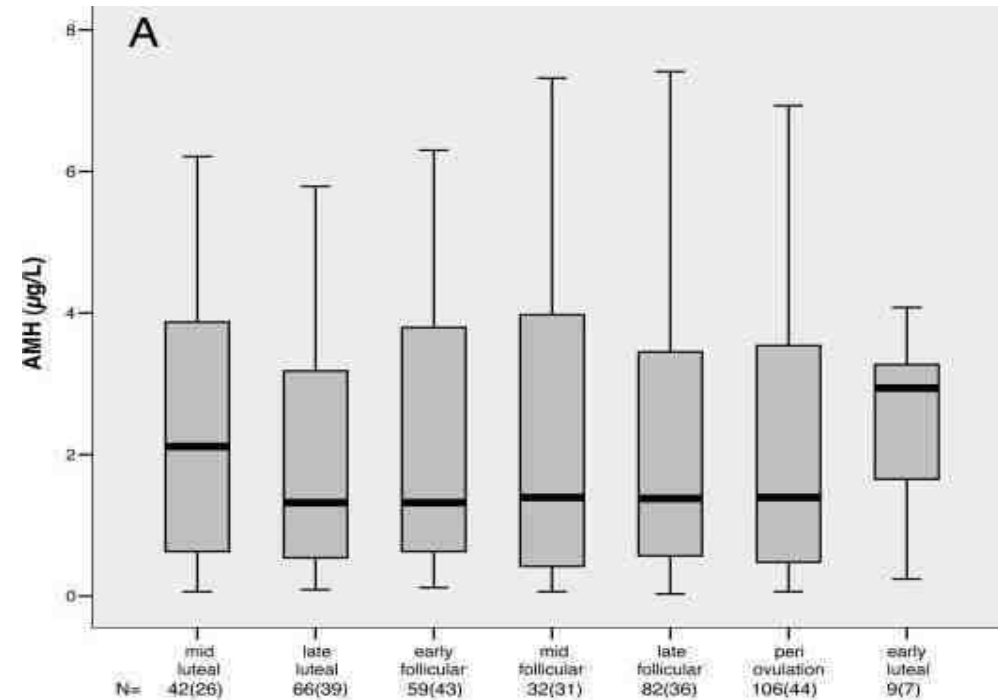- It is better to be measured on day 2-3 of the menstrual cycle

Stability
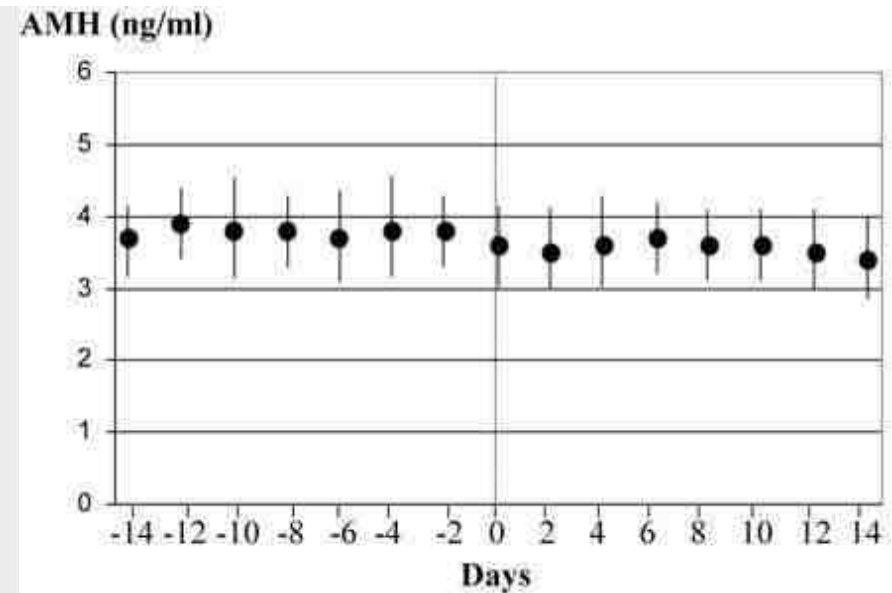
AMH is a stable marker across 4 consecutive cycles

Stability is higher compared to AFC

van Disseldorp Hum Reprod 2010

Stability

Hehenkamp JCEM 2006

La Marca Hum Reprod 2006

AMH can be measured any day of the menstrual cycle

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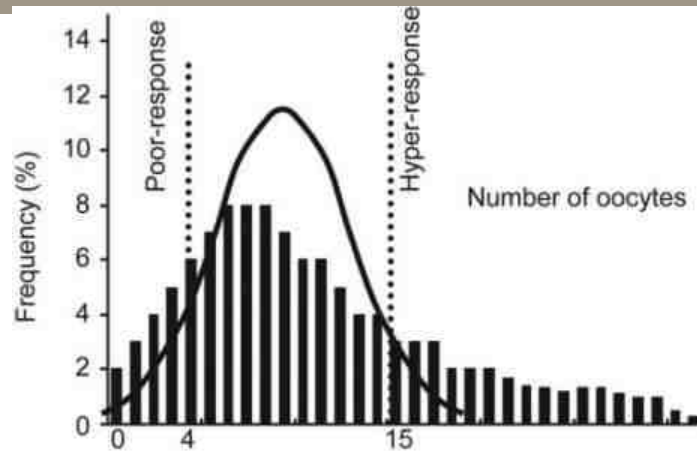# Can ovarian reserve markers predict pregnancy ?
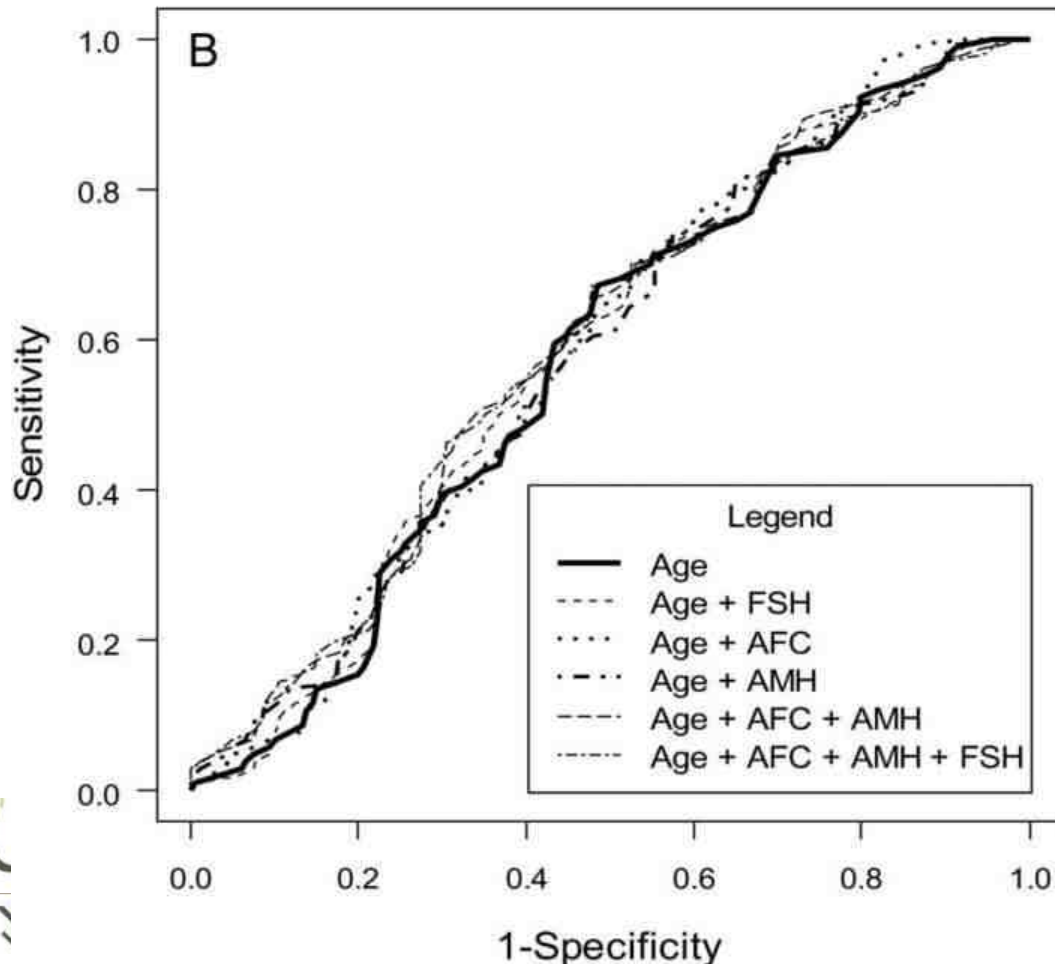
Broer et al. Hum. Reprod. Update 2013

Why do we need to individualize treatment if we can't predict pregnancy?

Importance of personalized treatment

Sunkara et al., Hum Reprod 2011
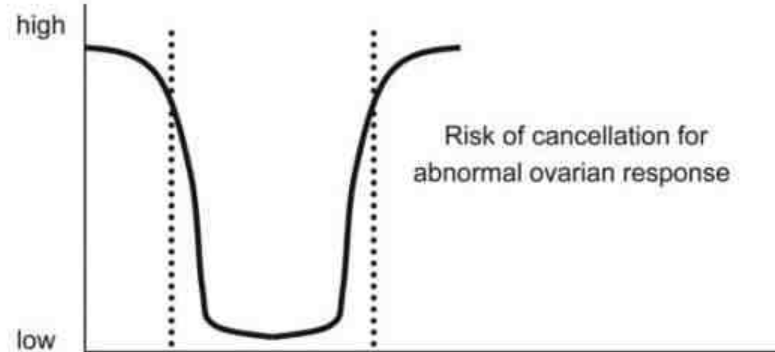
La Marca &Sunkara Hum Reprod 2013

iCOS (individualized controlled ovarian stimulation)

One size does not fit all

Based on ovarian reserve markers we can select the

1. Type of analogue
2. The dose of gonadotropins

Ovarian stimulation can be

- Patient friendly
- Safe
- Effective
- Cost-effective

Is this really true?

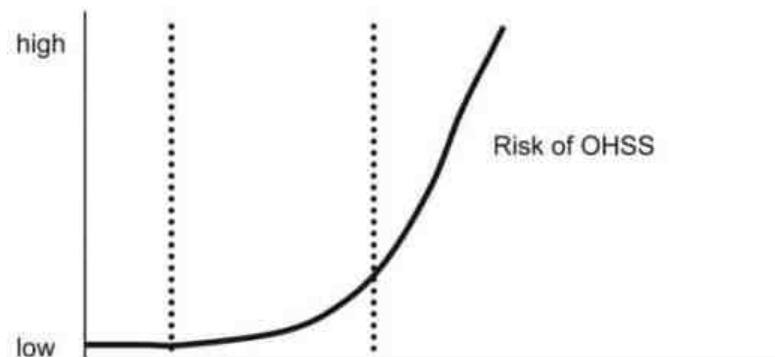# AMH –guided ovarian stimulation (1)

AMH group (pmol/l)	Centre 1	Centre 2
<1.0	Antagonist-375IU	Modified natural cycle
1.0 to <5	Agonist-375IU	Antagonist-300IU
5.0 to <15	Agonist-225IU	Agonist-225IU
≥15.0	Agonist-150IU	Antagonist-150IU

Nelson et al., Hum Reprod 2009

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AMH –guided ovarian stimulation (2)

Protocol	Centre 1 *Antagonist* *+ 150 IU*	Centre 2 *Agonist* *+ 150 IU*	Pvalue
Number of oocytes collected	10 (8.5–13.5)	14 (10–19)	<0.001
Freeze all n (%)	0 (0%)	27 (18.2%)	0.003
Hospitalized for OHSS	0 (0%)	20 (13.9%)	0.021
Cancelled cycle n (%)	1 (2.9%)	4 (2.7%)	1.0
Clinical pregnancy per cycle n (%)	21 (61.7%)	47 (31.8%)	0.002

SAFE

EFFECTIVE

High (AMH>15pmol/I)

Nelson et al., Hum Reprod 2009

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SAFE

EFFECTIVE

COST-EFFECTIVE

Yates et al., Hum Reprod 2011
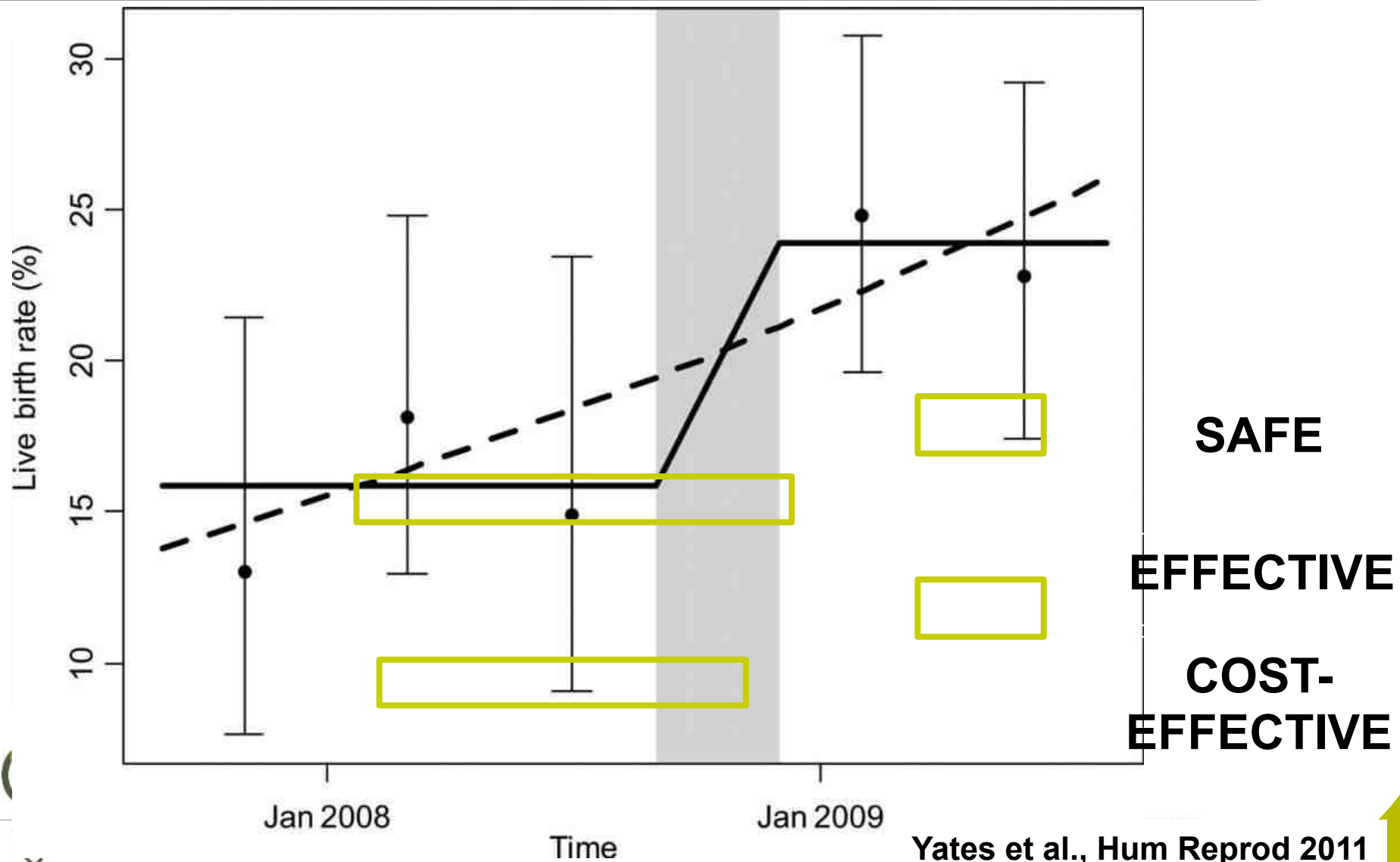
AMH-guided stimulation

The ESTHER trial

Evidence-based Stimulation Trial With Human rFSH in Europe and Rest of World

~1400 women are randomized

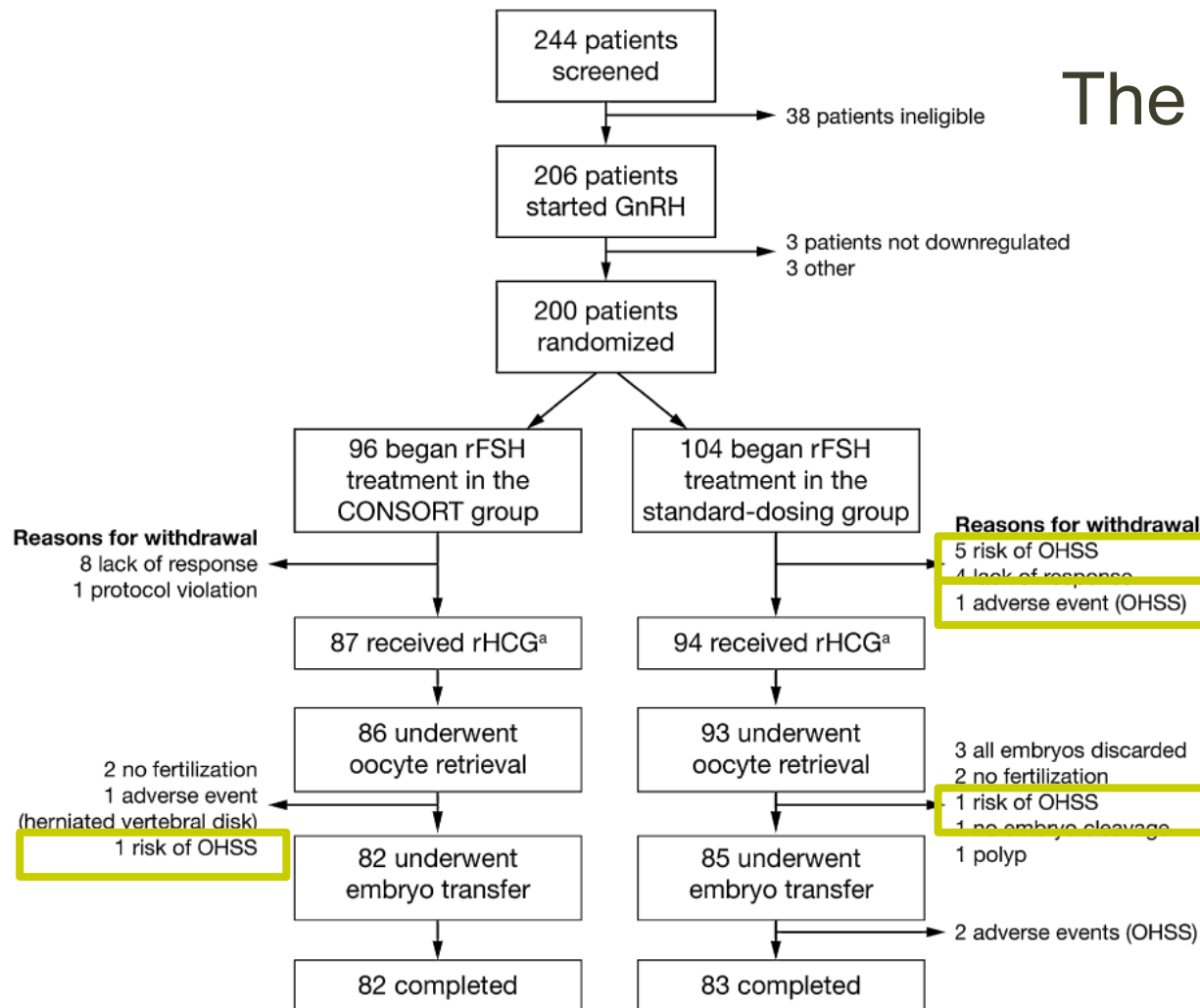New human rFSH with individualized dosing based on AMH values

VS

Fixed dose 150IU Follitropin beta

The CONSORT trial

Olivennes RBMonline 2015

AFC-guided stimulation

The OPTIMIST trial

Figure 1 Study procedure.
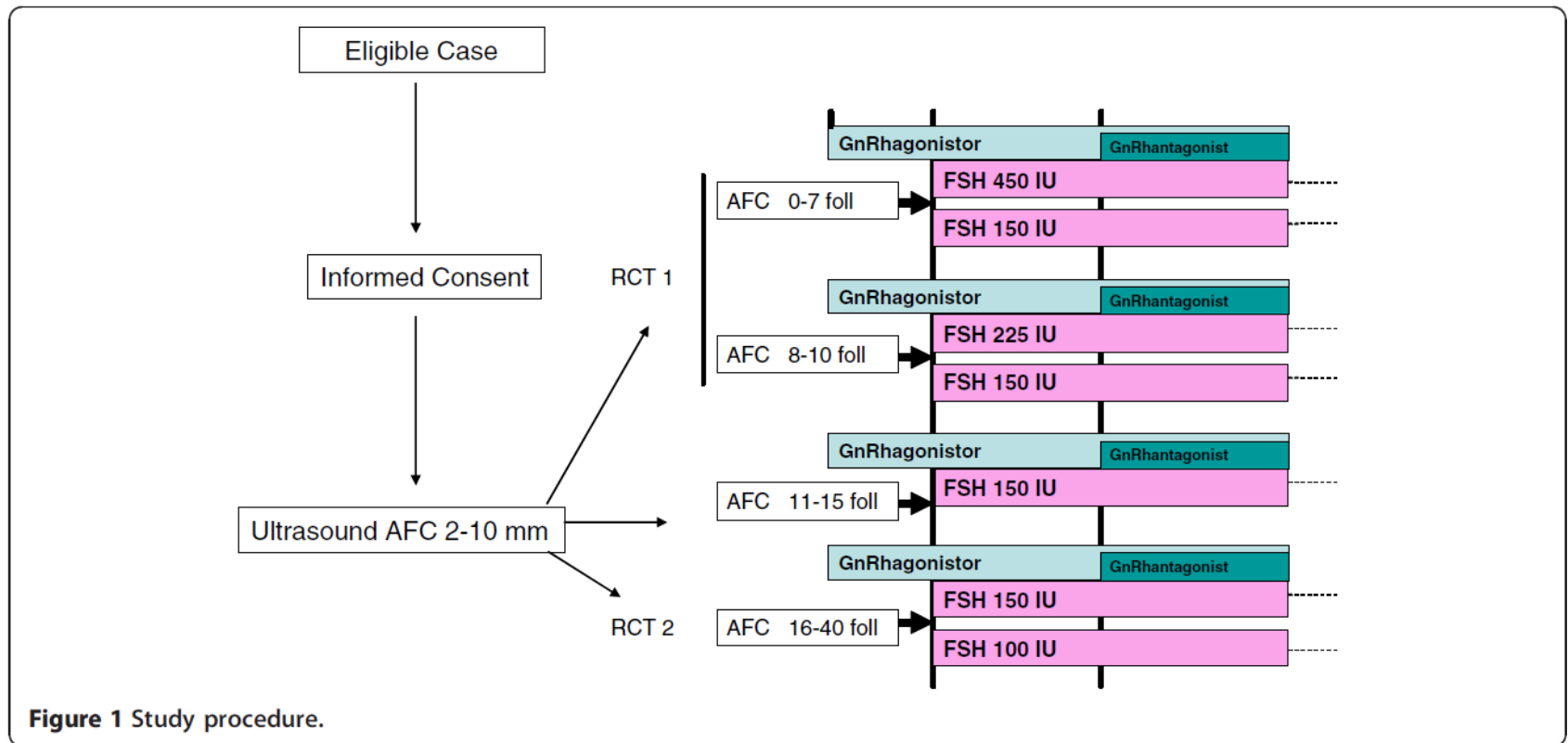
AFC **AMH**

Comparison of AMH and AFC personalized treatment

AMH values (ng/ml)	AFC values	FSH starting dose
<0.7	<6	375
0.7-2.1	6-15	225
>2.1	>15	150

Lan et al., RBMonline 2013

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Comparison of AMH and AFC personalized treatment

	AMH	AFC	P-value
Hyper-response	15 (8.7)	30 (17.4)	**0.02**
Cycles cancelled	4 (2.3)	3 (1.7)	NS
Duration of stimulation	11.8 ± 1.6	11.6 ± 1.3	NS
FSH dose			
Total (IU)	2694 ± 1053	2872 ± 1188	NS
Daily (IU/day)	224 ± 71	243 ± 84	**0.03**
Oocytes retrieved	10.8 ± 6.3	13.6 ± 7.3	**<0.01**
Embryos	6.3 ± 4.1	8.1 ± 4.7	**<0.01**
Frozen embryos	1.7 ± 2.5	2.7 ± 3.3	**<0.01**
Beta-HCG positive/ET	72 (45.6)	80 (55.2)	**NS**
Clinical pregnancy/ET	60 (38.0)	68 (46.9)	**NS**

Lan et al., RBMonline 2013

How should we individualize treatment?

Agonist

Long

Short flare up
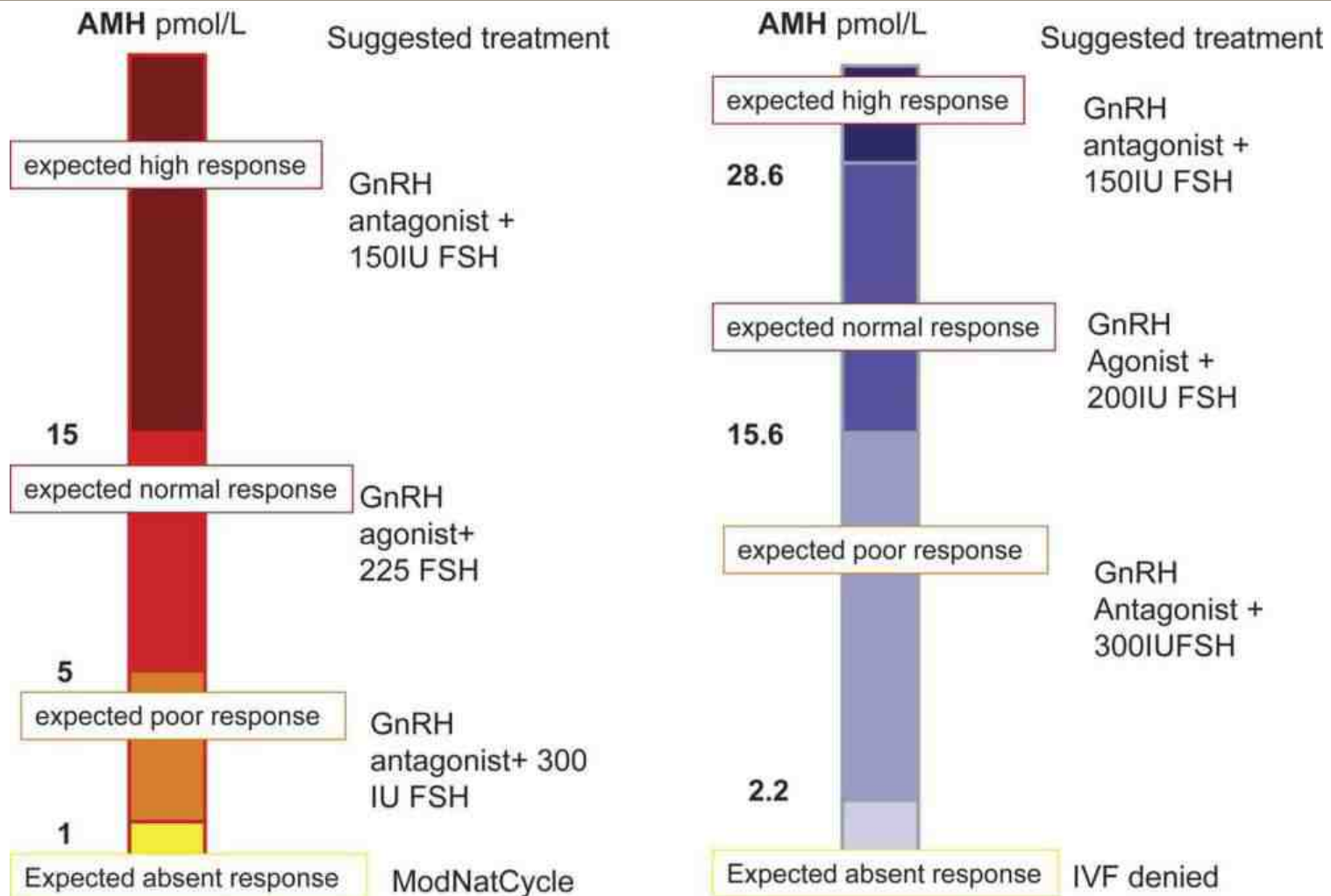
Antagonist

rFSH

rLH

hpHMG

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**La Marca &Sunkara Hum Reprod 2013
(modified from Nelson 2009 and Yates 2011)**

La Marca &Sunkara Hum Reprod 2013
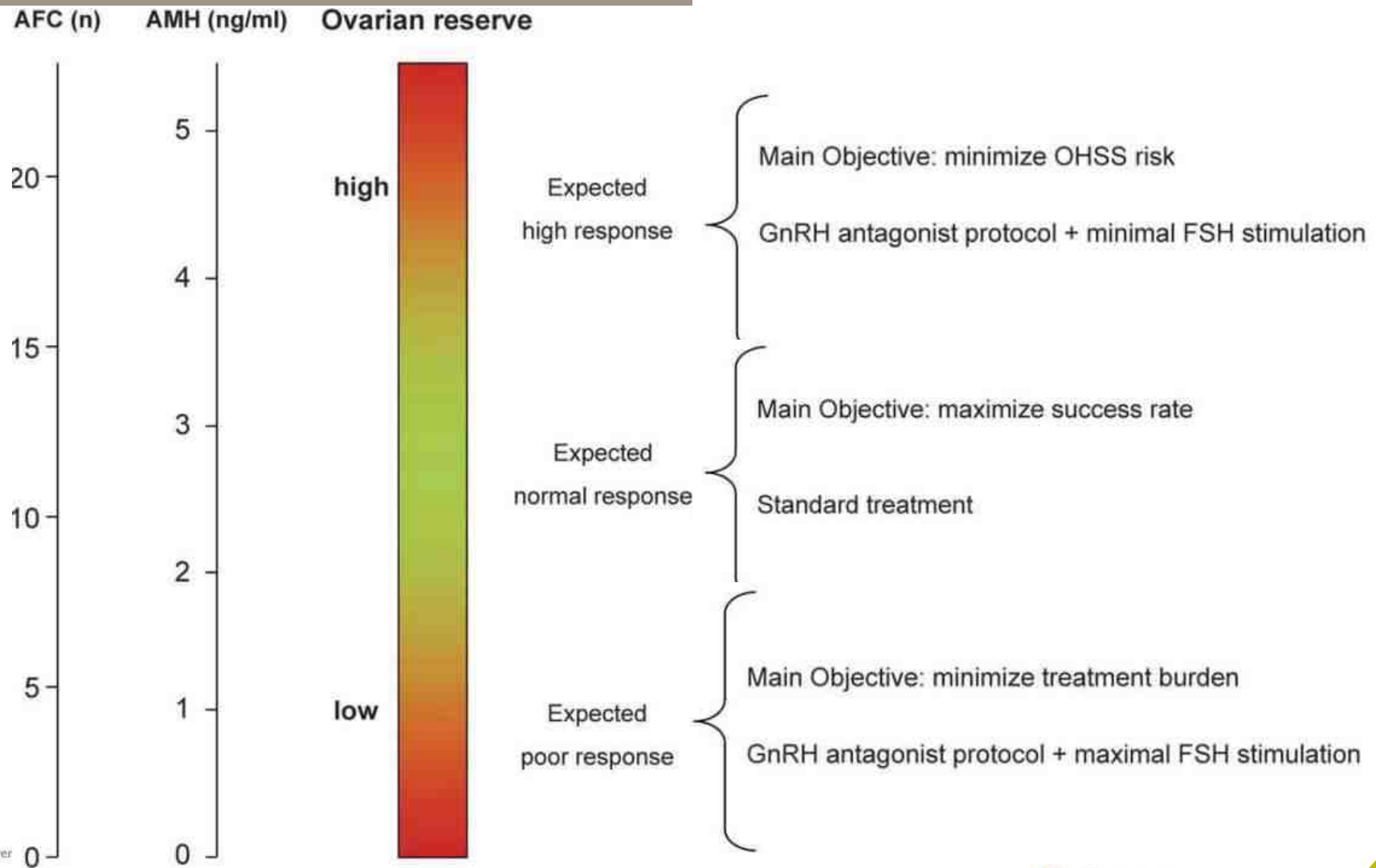
Previous failed attempt

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Poor responders	How normal is the normal responder?	High responders
↓	↓	↓
<4 oocytes	4-15 oocytes	>15 oocytes

Is it the same to obtain 4, 5, 6 oocytes with retrieving 12,13 or 14 oocytes
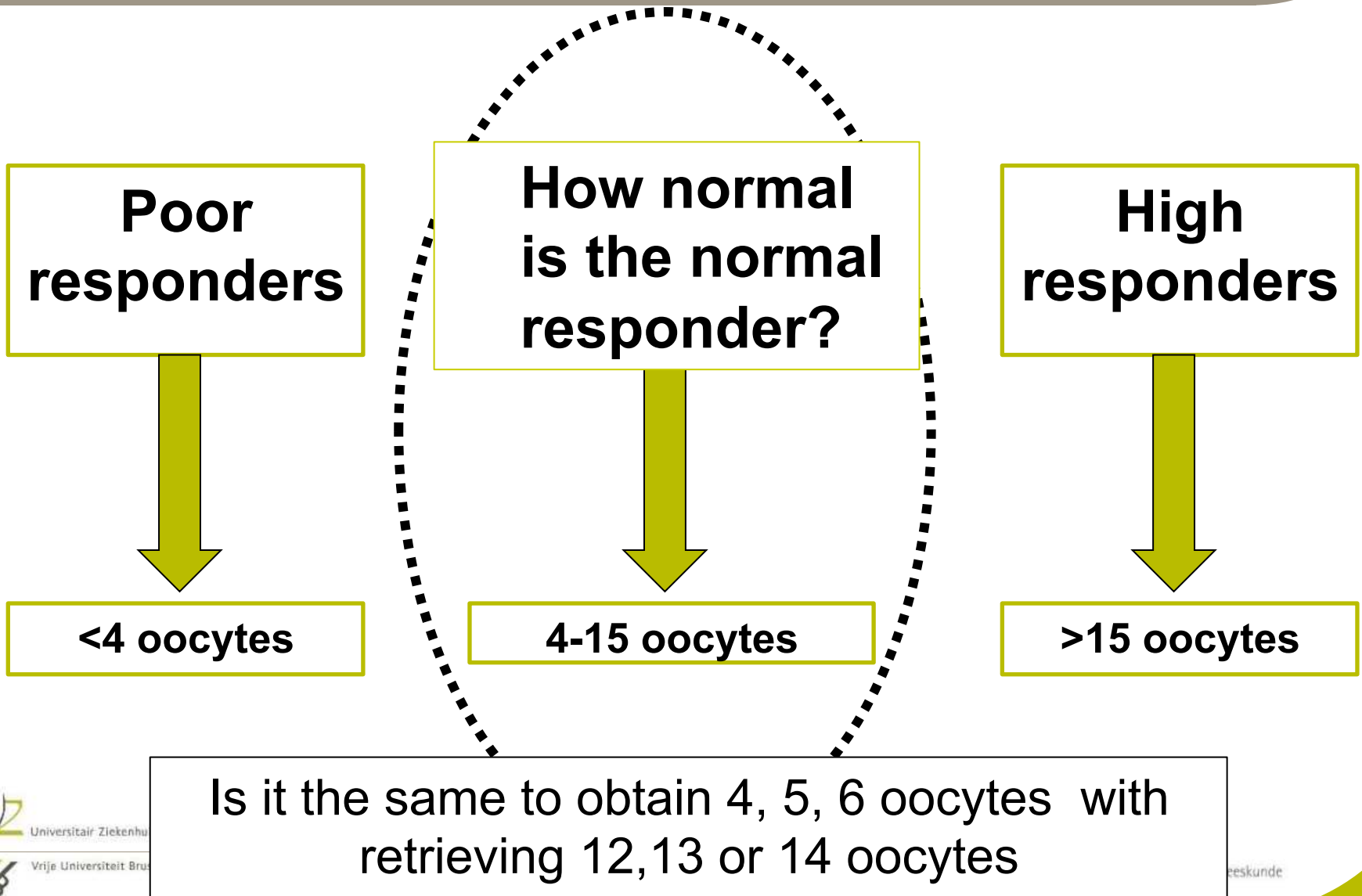
Definition

> 4-9 oocytes retrieved after conventional stimulation

Who are these patients?

> Reduced sensitivity to gonadotropins
> (e.g. FSH or LH receptor mutations)

Why do they not respond according to their ovarian reserve?

> Ovarian reserve markers predict the number of follicles and <u>NOT</u> their sensitivity to gonadotropins

Aim in this group

> Increase number of oocytes retrieved to 10-15 oocytes

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Polyzos & Sunkara Hum Reprod 2015

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The suboptimal responders: Why should they be identified ?

They are a lot!

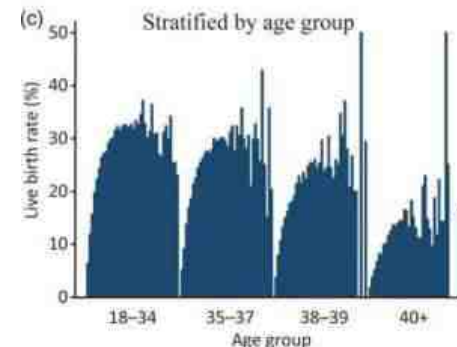43.3% of all IVF cycles (174.000/ 402.000 IVF cycles UK – HFEA)

It may be easy to improve the outcome

By using different more potent gonadotropins or higher doses

An increase in oocyte yield can substantially improve pregnancy rates

Increase ~20-30% in the pregnancy rates in fresh IVF cycles

Sunkara et al. Hum Reprod.
2011 Jul;26(7):1768-74.

Increase in cumulative pregnancy rates from fresh and frozen embryos

Cumulative live birth rates according to ovarian response

❑ 1099 women undergoing their 1st stimulation for IVF/ICSI

❑ 150-225IU rFSH and eSET

	Ovarian response groups				
	1-3 oocytes n=83	4-9 oocytes n=471	10-15 oocytes n=327	>15oocytes n=218	P- value
Age	32.8 (3.9)	31.6(4.1)	30.5(3.8)	30.3(3.5)	<0.001[a]
Moderate-severe OHSS	0	0	2 (0.6%)	9 (4.1%)	<0.001[c]
Live birth in the fresh cycle [a*]	14 (16.87%)	140 (29.72%)	111 (33.94 %)	70 (32.11%)	0.02[b]
Cumulative live birth [a*]	18 (21.69%)	187 (39.70%)	165 (50.46 %)	134 (61.47%)	<0.001[b]

Conclusions

❑ Ovarian reserve markers are ideal for predicting oocyte quantity but not quality

❑ Individualized treatment based on AMH and AFC may result in a safer and more effective ovarian stimulation

❌ However ovarian reserve markers cannot predict pregnancy outcome

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Conclusions

❑ Ovarian response in a previous IVF cycle can guide management for future attempts

❑ Ovarian response categories may need to be revisited

❑ Suboptimal responders may be a new response category which we need to focus in the future