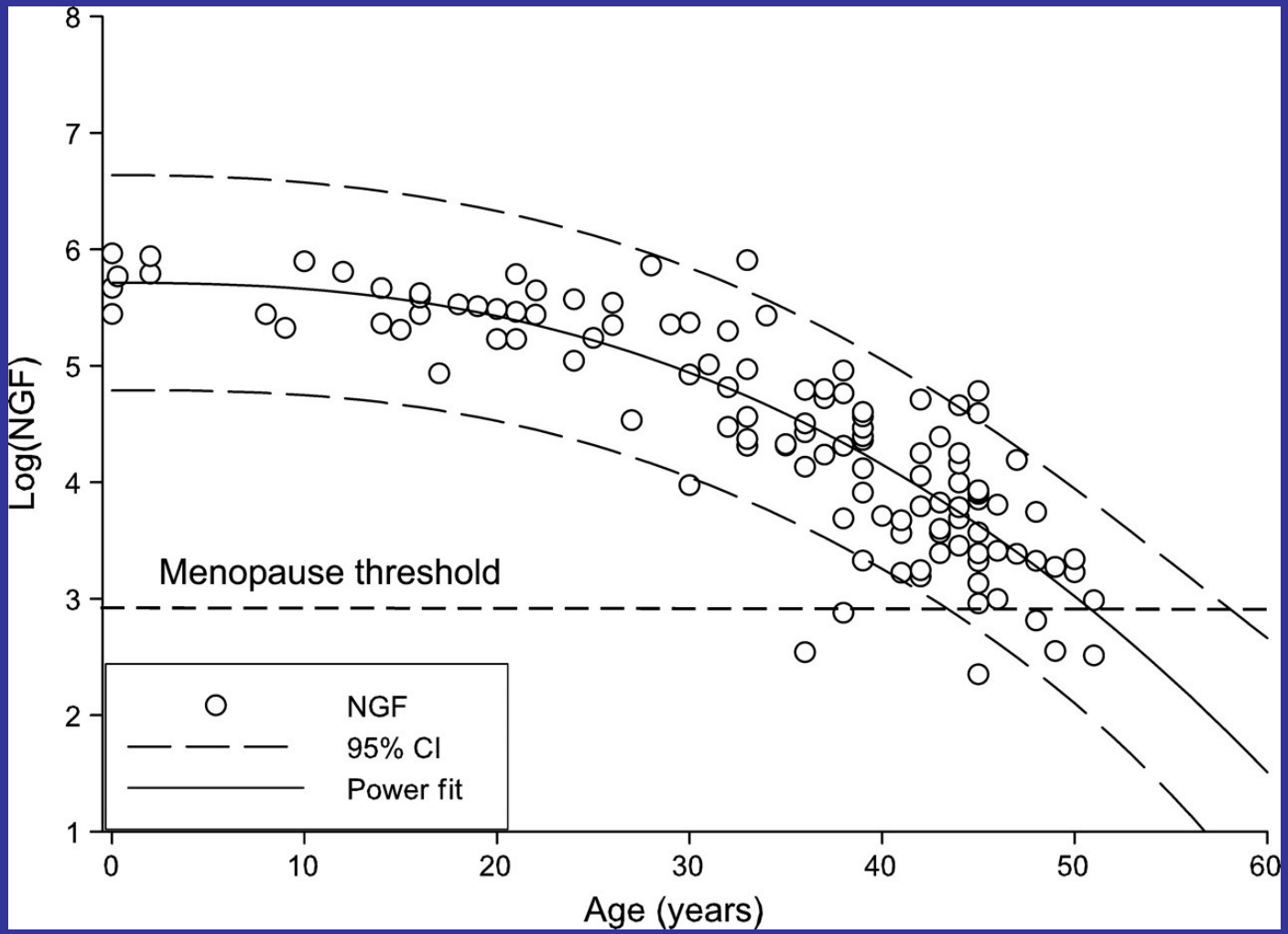
Dynamics between gonadotropins and follicles in the ageing ovary

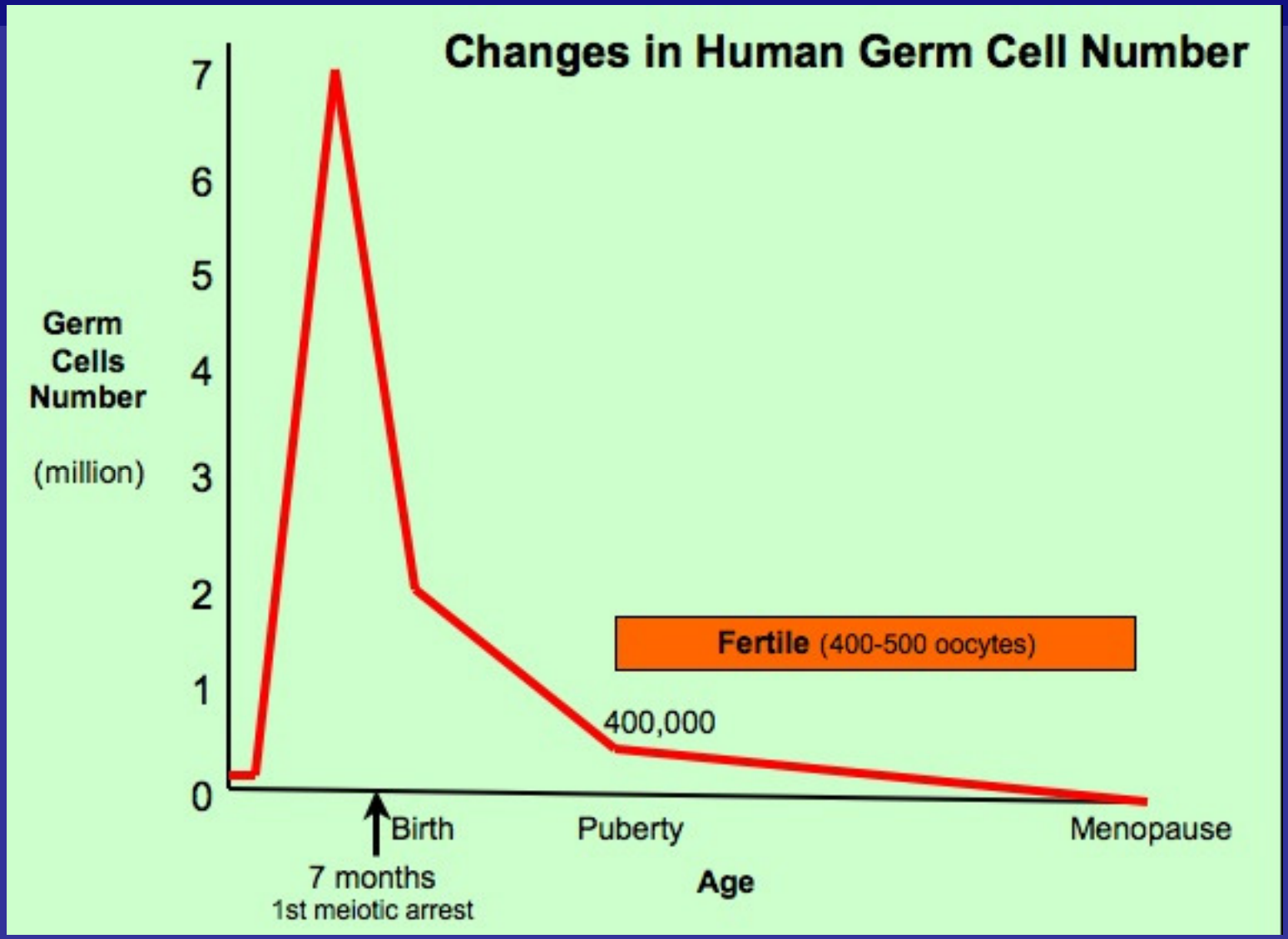
C.B. Lambalk

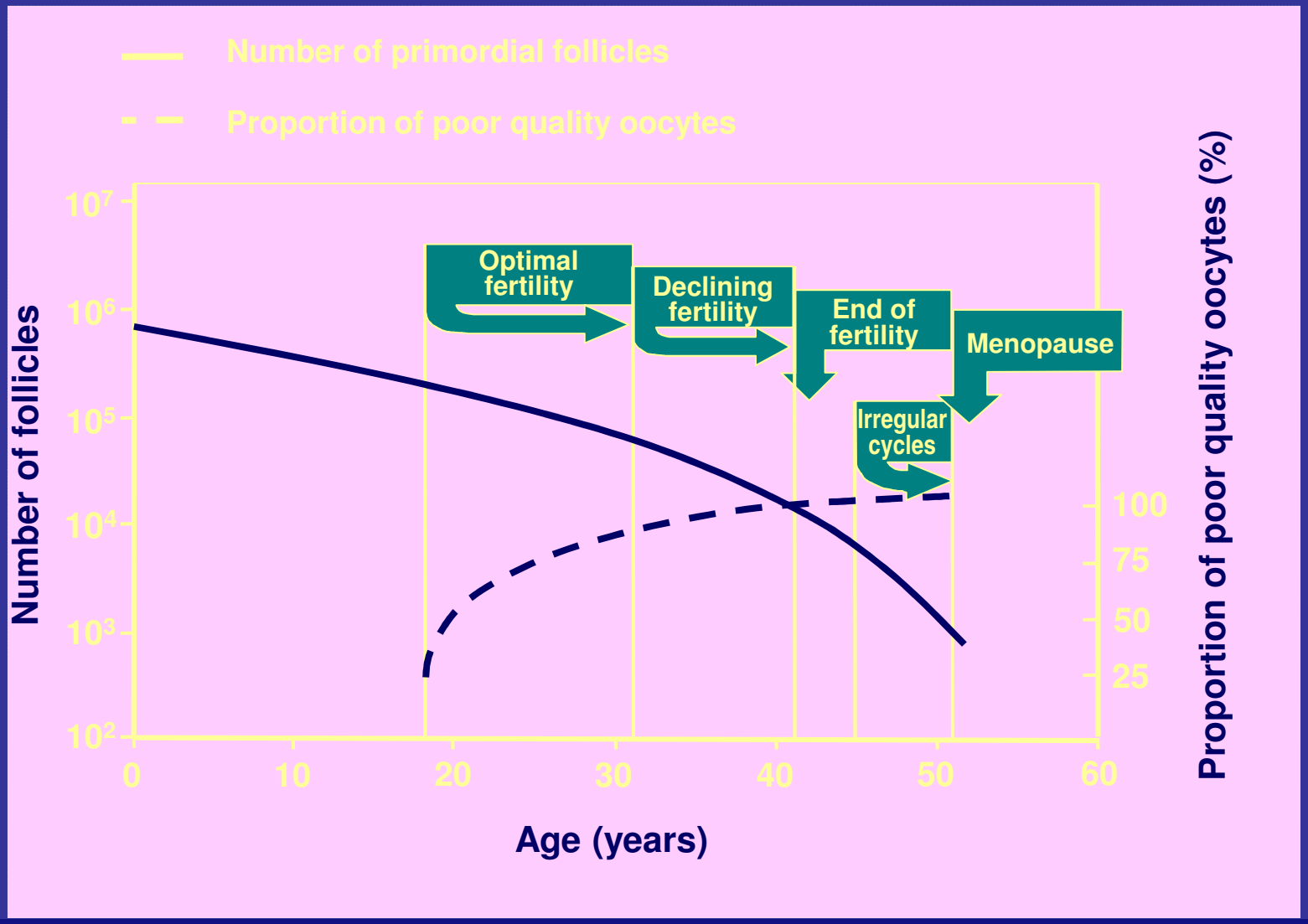
(in honour of Lars Westergaard)

Power-model of ovarian Non Growing Follicle decay



Hansen, K. R. et al. Hum. Reprod. 20088

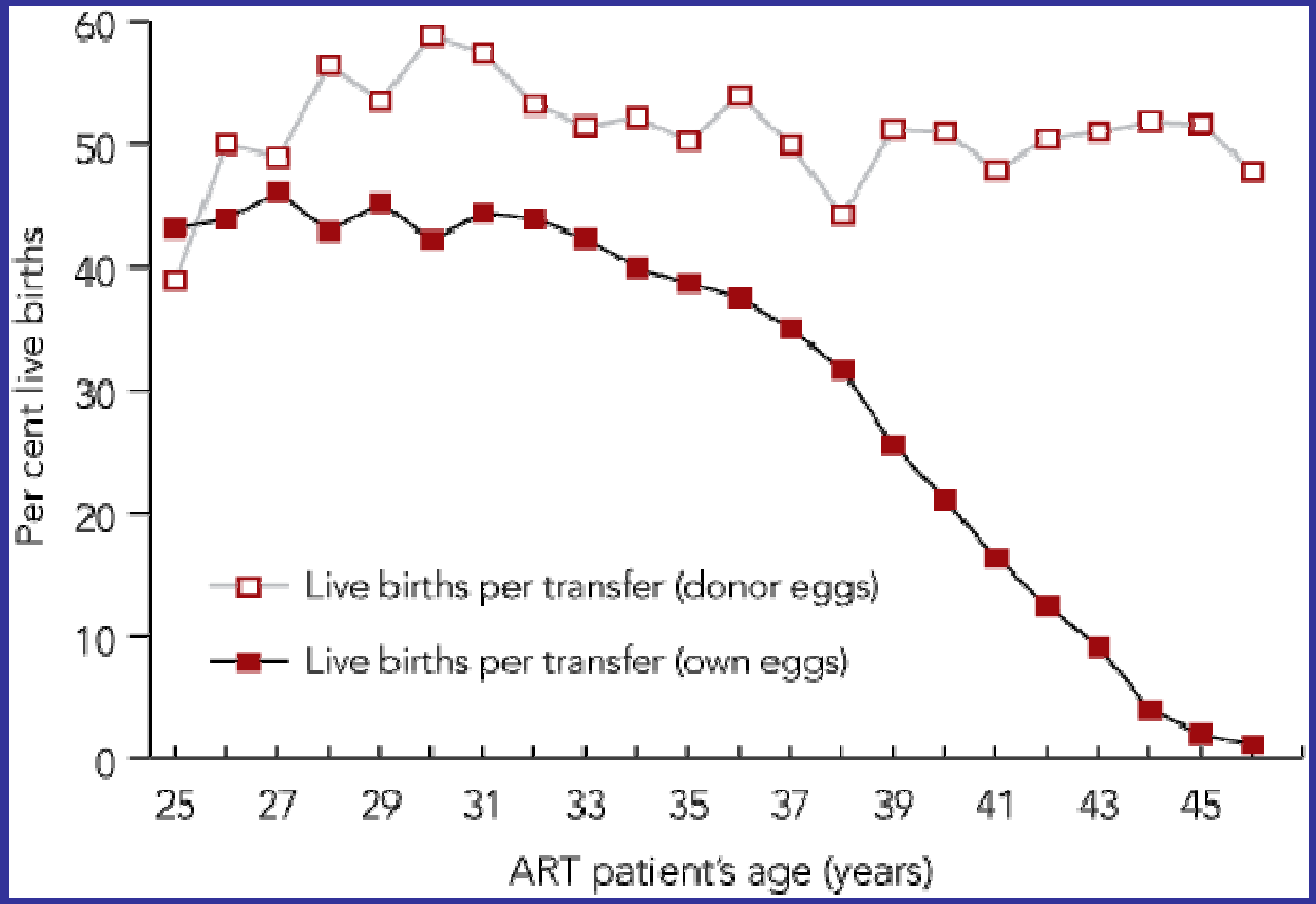

Changes in Human Germ Cell Number
Germ Cells Number
(million)
7
6
5
4
3
2
1
0
Fertile (400-500 oocytes)
400,000
Birth
7 months
1st meiotic arrest
Puberty
Menopause
Age



Broekmans et al , Endocrine Reviews 2009

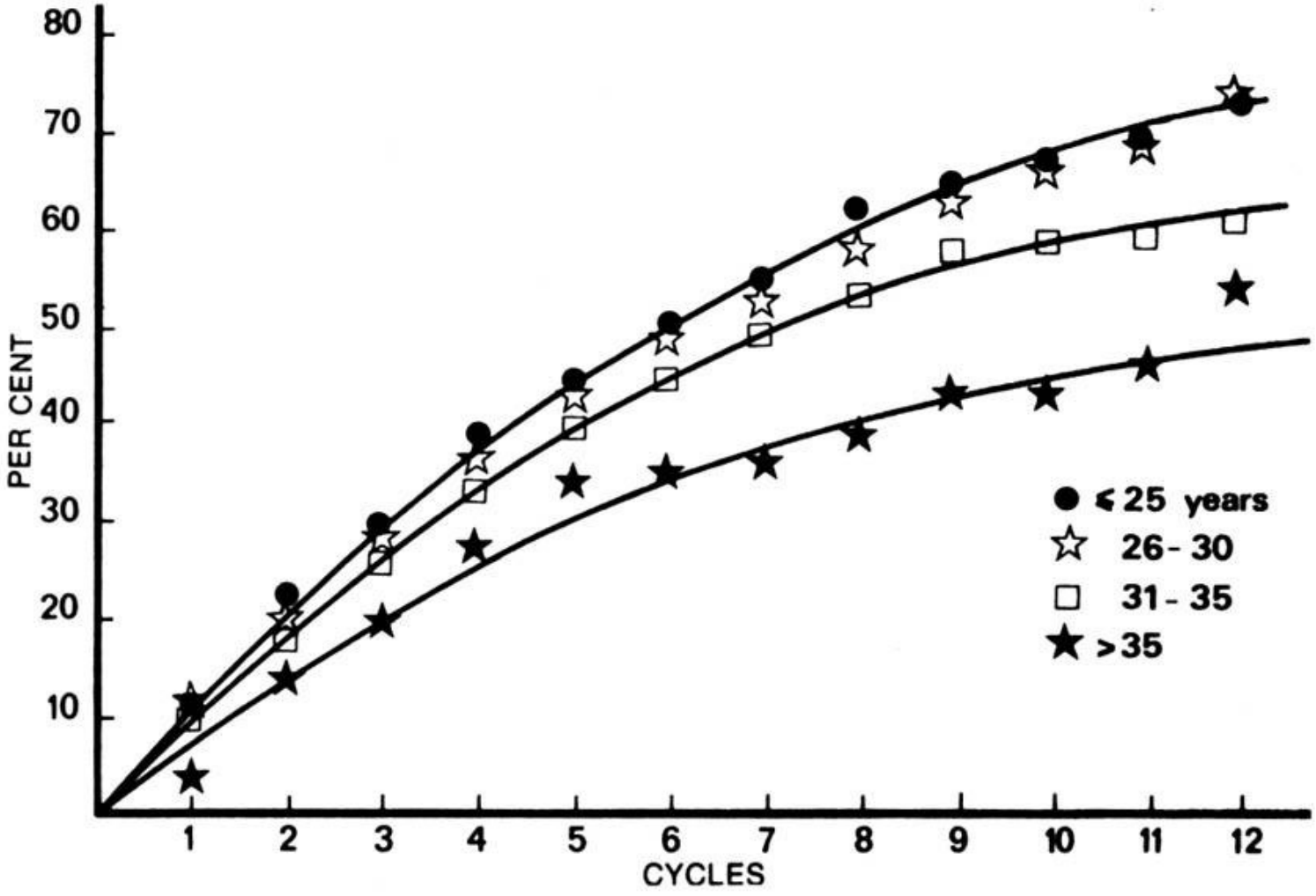
VU university medical center

Age dependent oocyte quality decay



Bachrach Med J Aust 2006

Age dependent fertility loss



Schwartz and Mayaux New Engl J Med 1982

Contents

- Introduction
- Cycle characteristics with ageing
- Changing pituitary responsiveness
- Changing ovarian responsiveness
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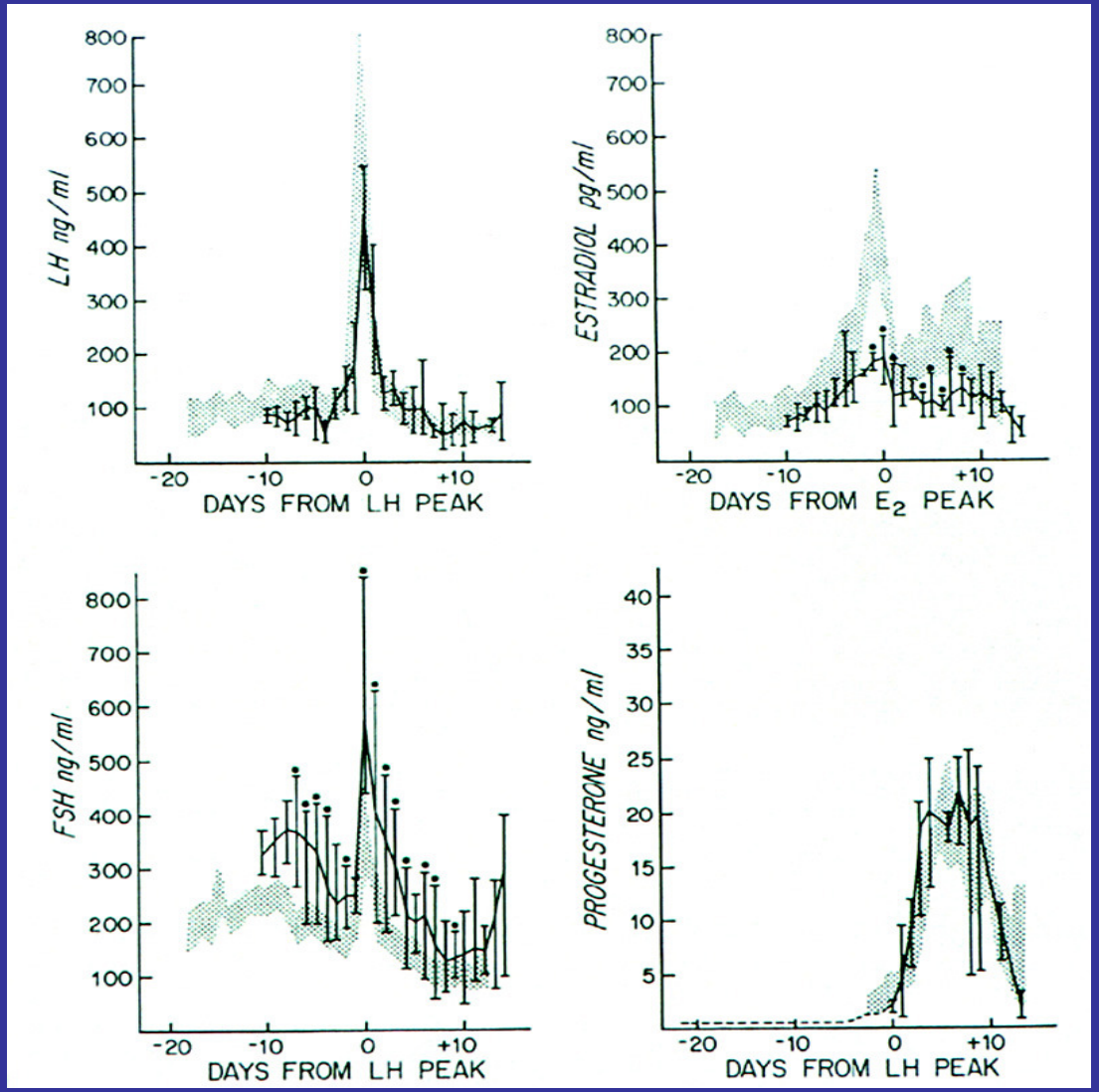
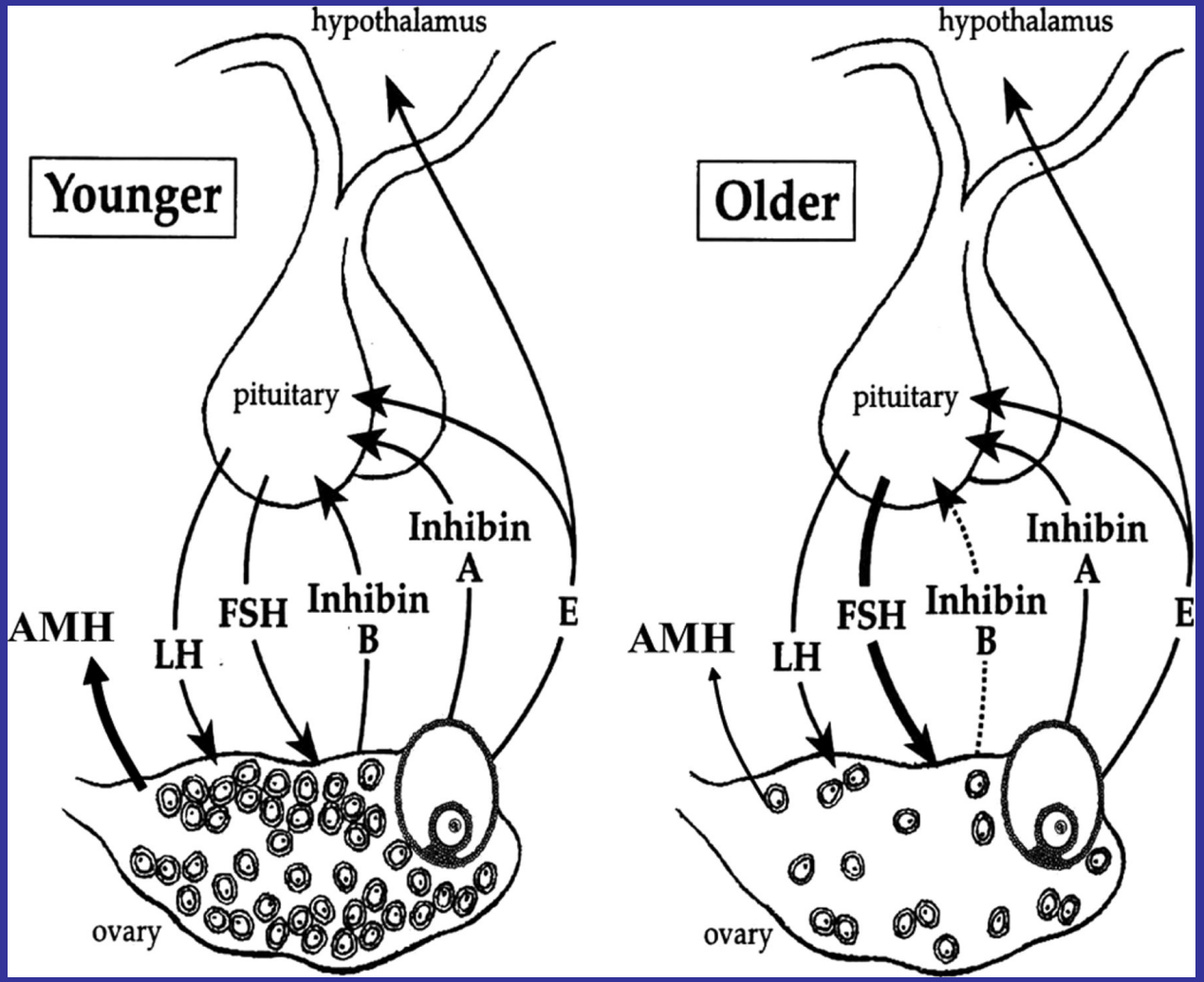
- Clinical consequences
- Conclusions

Hormones/cycle length change with ageing



Sherman and Korenman J Clin Invest 1975

Ovarian pituitary interaction with ageing



Broekmans et al Endocrine Reviews 2009

Details cycle with elevated FSH

Daily measurements FSH, LH, E_2, Prog, InhA, InhB

De Koning et al Hum Reprod, 2008

Details cycle with elevated FSH

	High, High	High, Low	Control	*P*
n				
Age				
Day 3 FSH				

De Koning et al Hum Reprod, 2008

Details cycle with elevated FSH

	High, High	High, Low	Control	*P*
n				
AMH (ug/L)				
FSH (IU/L)				
LH (IU/L)				
E2(pmol/L)				
InhA(ng/L)				
InhB(ng/L)				

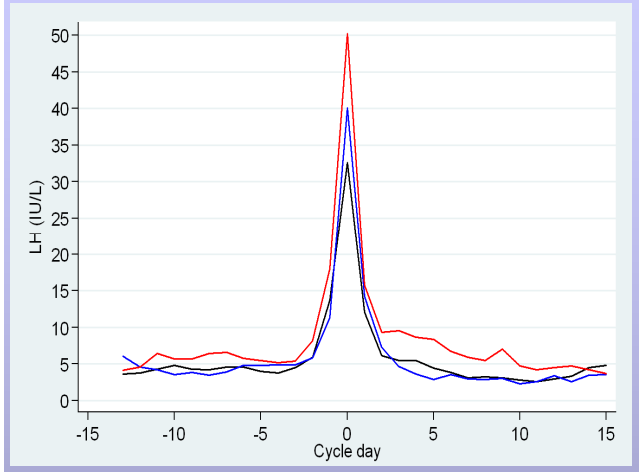
De Koning et al Hum Reprod, 2008

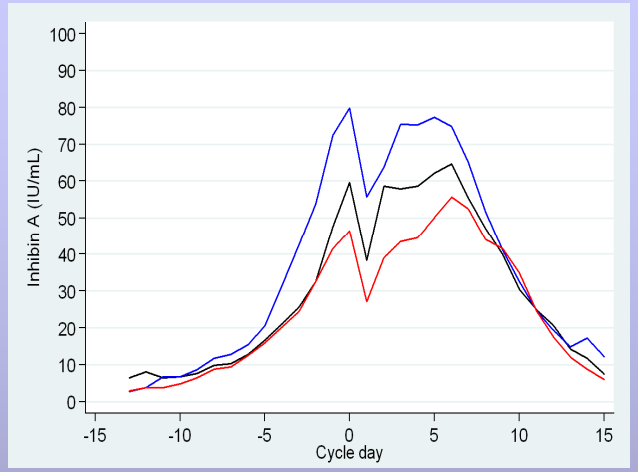
Cycle length

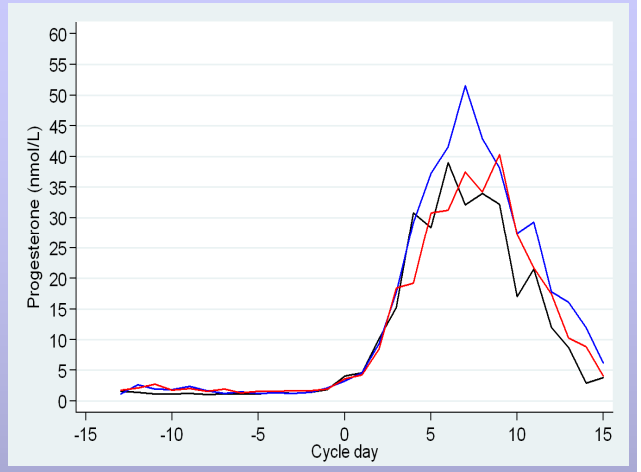
	High,High group (n=11)	High,Low group (n=11)	Controls (n=16)
Cycle length			
Follicular phase length			
Luteal phase length			

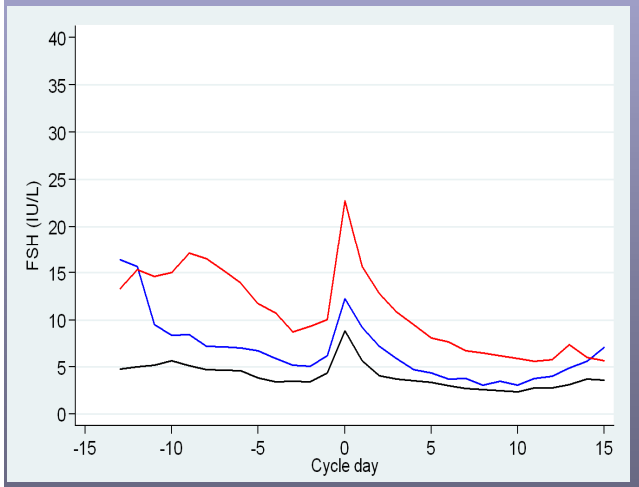
De Koning et al Hum Reprod, 2008

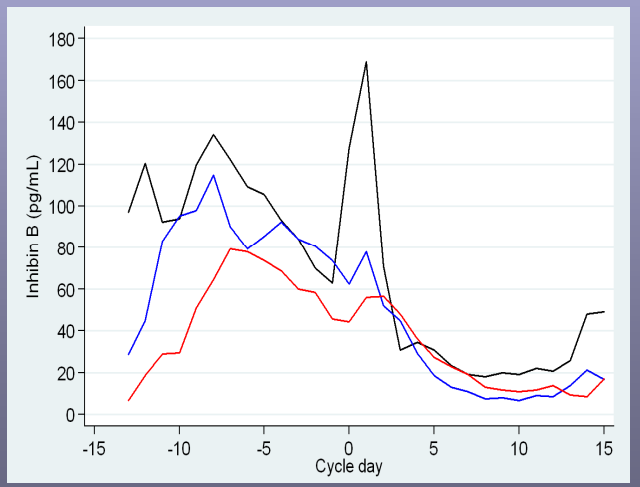
Temporary normalization of elevated basal FSH

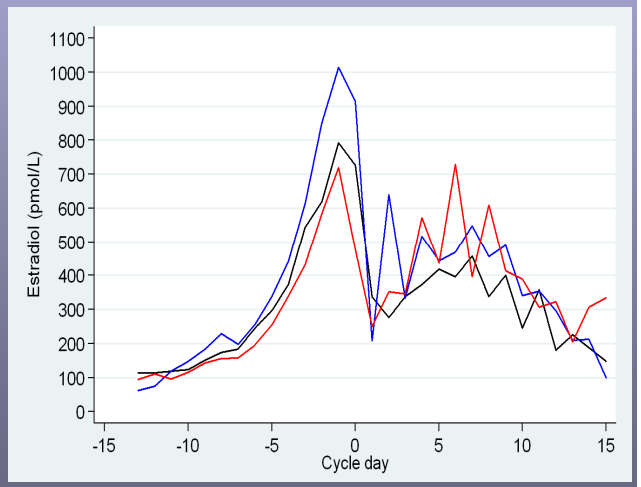












HH HL LL

De Koning et al Hum Reprod, 2008

Follicle growth

	High, High group (n=11)	High, Low group (n=11)	Controls (n=16)
Growth velocity (mm/d)			
Maximal diameter (mm)			
Muliple follicles			

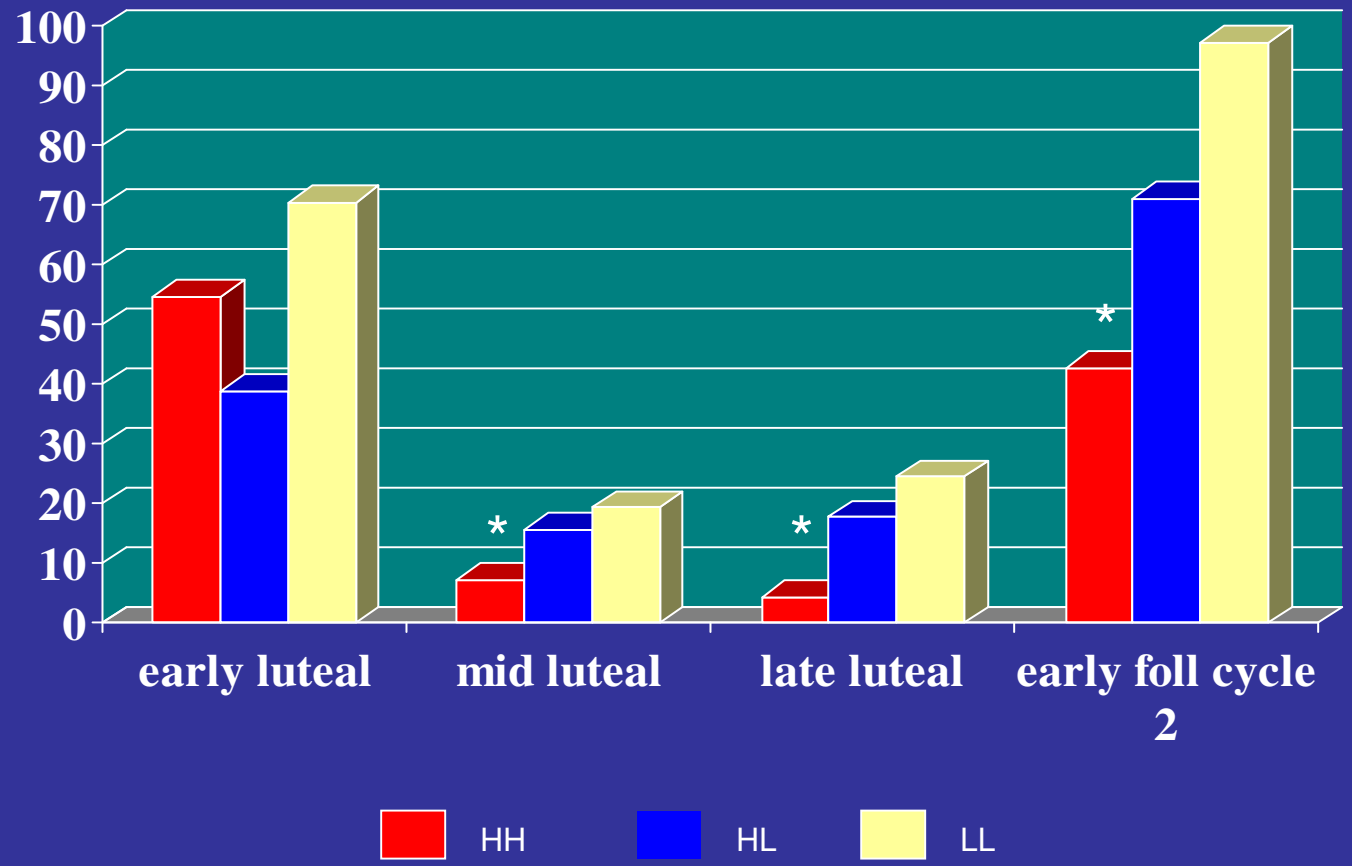
De Koning et al Hum Reprod, 2008

Details cycle with elevated FSH

Daily measurements FSH, LH, E_2, Prog, InhA, InhB

De Koning et al Hum Reprod, 2008

Inh B in luteal phase preceding cycle



De Koning et al Hum Reprod, 2008

Contents

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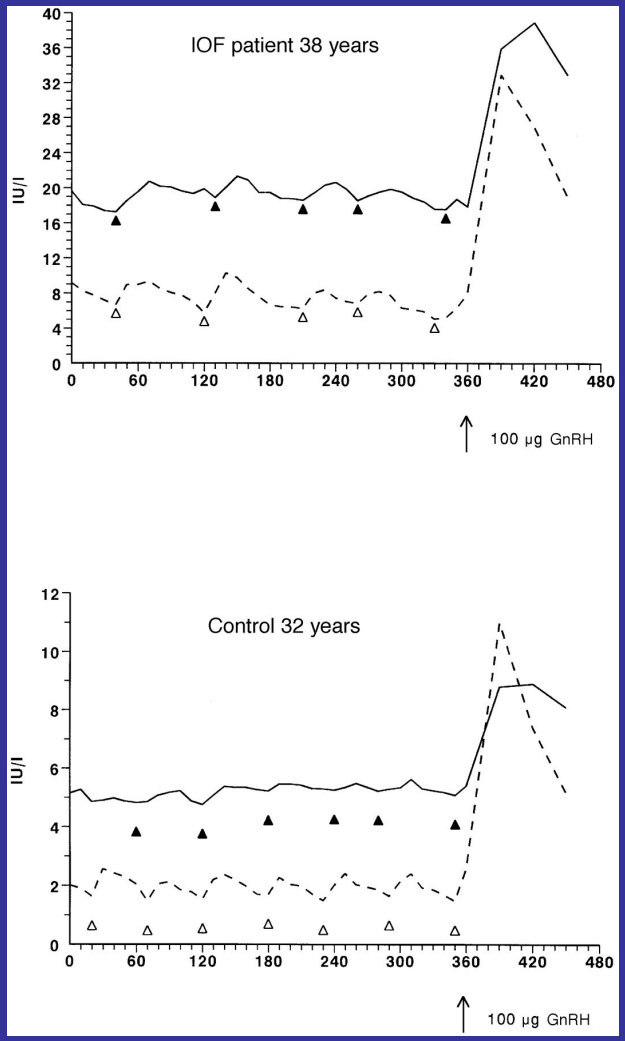
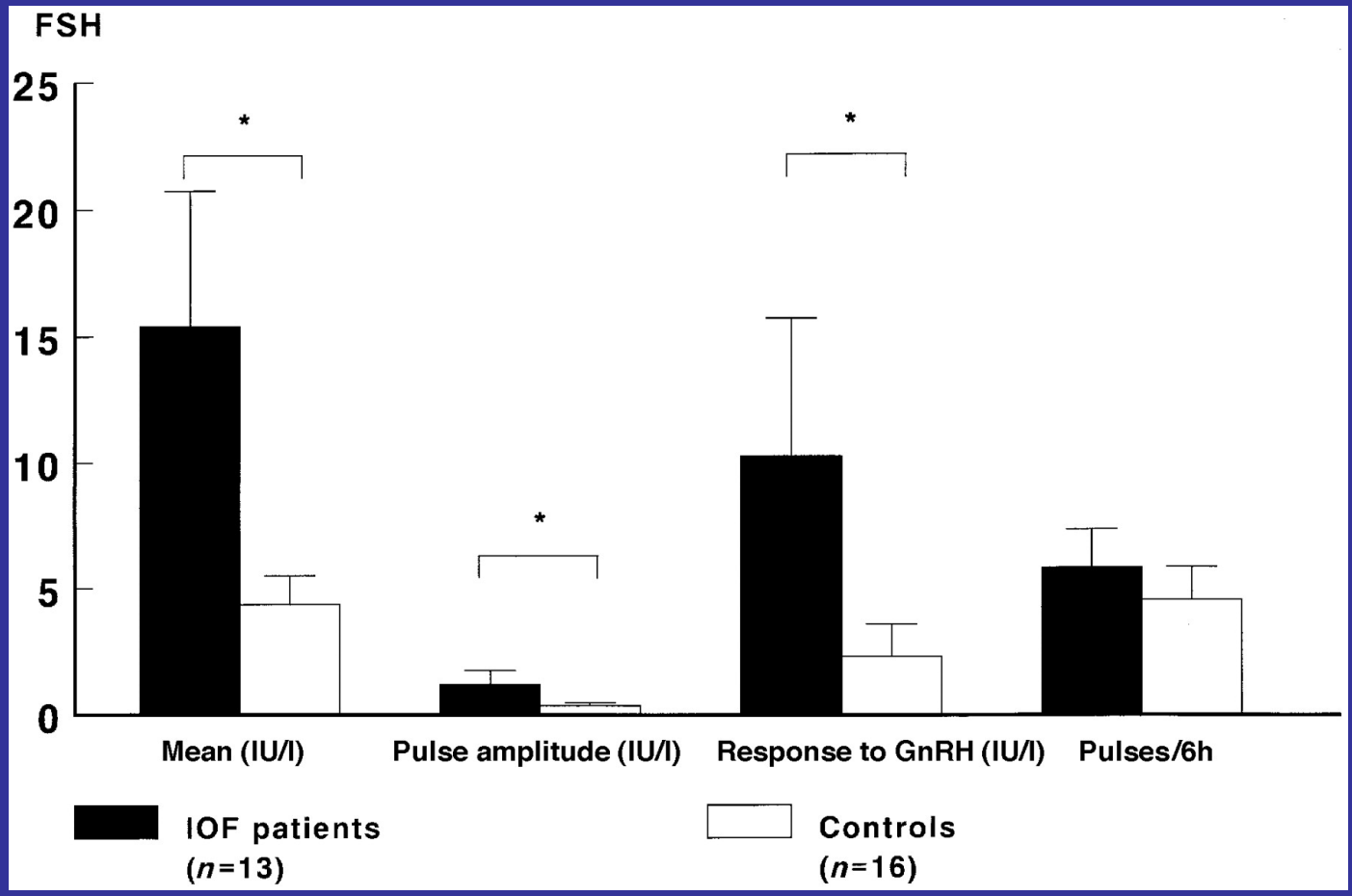
- Changing ovarian responsiveness
- Physiological consequences
- Clinical consequences
- Conclusions

Episodic LH and FSH and pituitary response



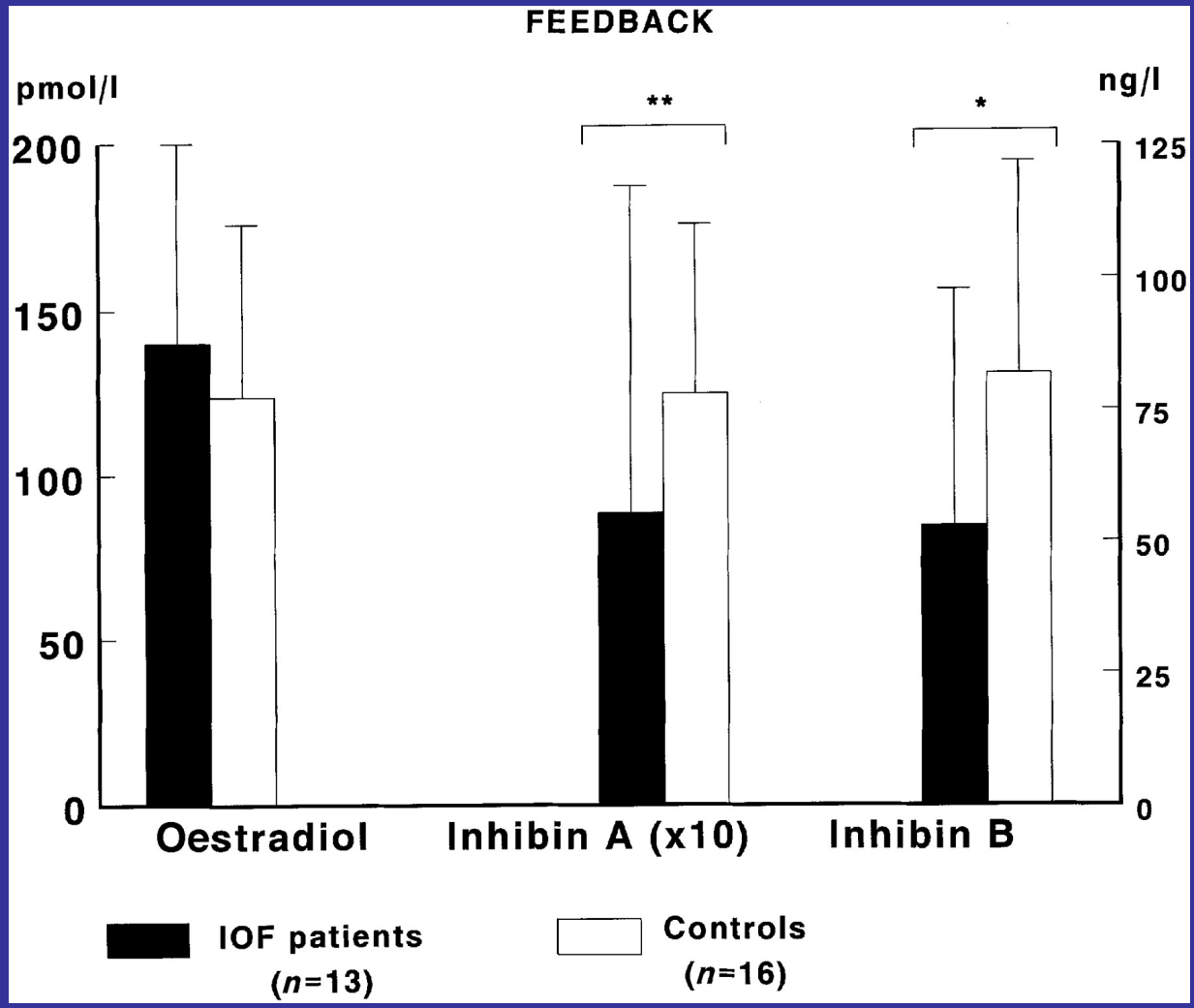
De Koning et al Hum Reprod, 2000

Episodic FSH and pituitary response to GnRH



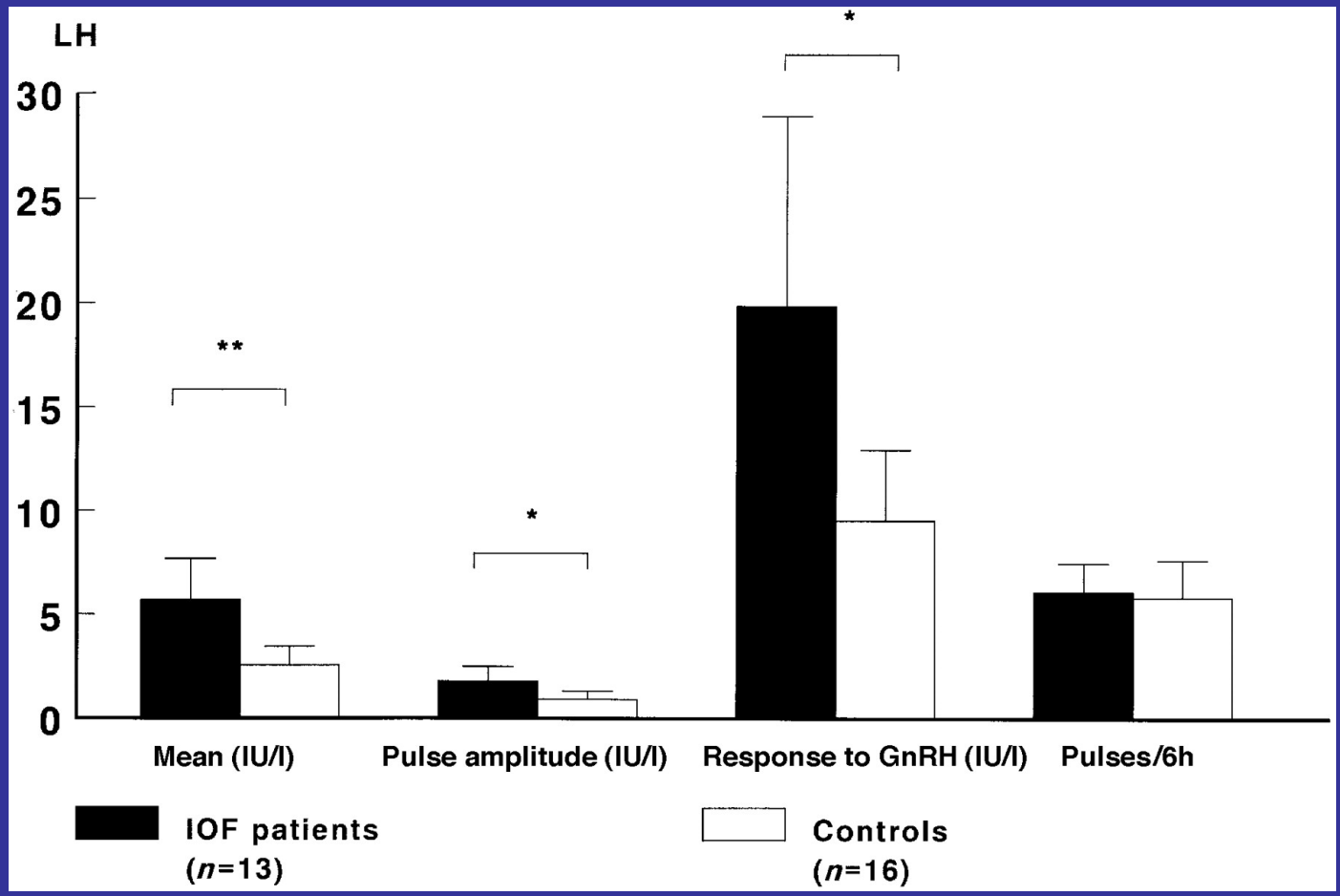
De Koning et al Hum Reprod, 2000

Ovarian feedback



De Koning et al Hum Reprod, 2000

Episodic LH and pituitary response to GnRH



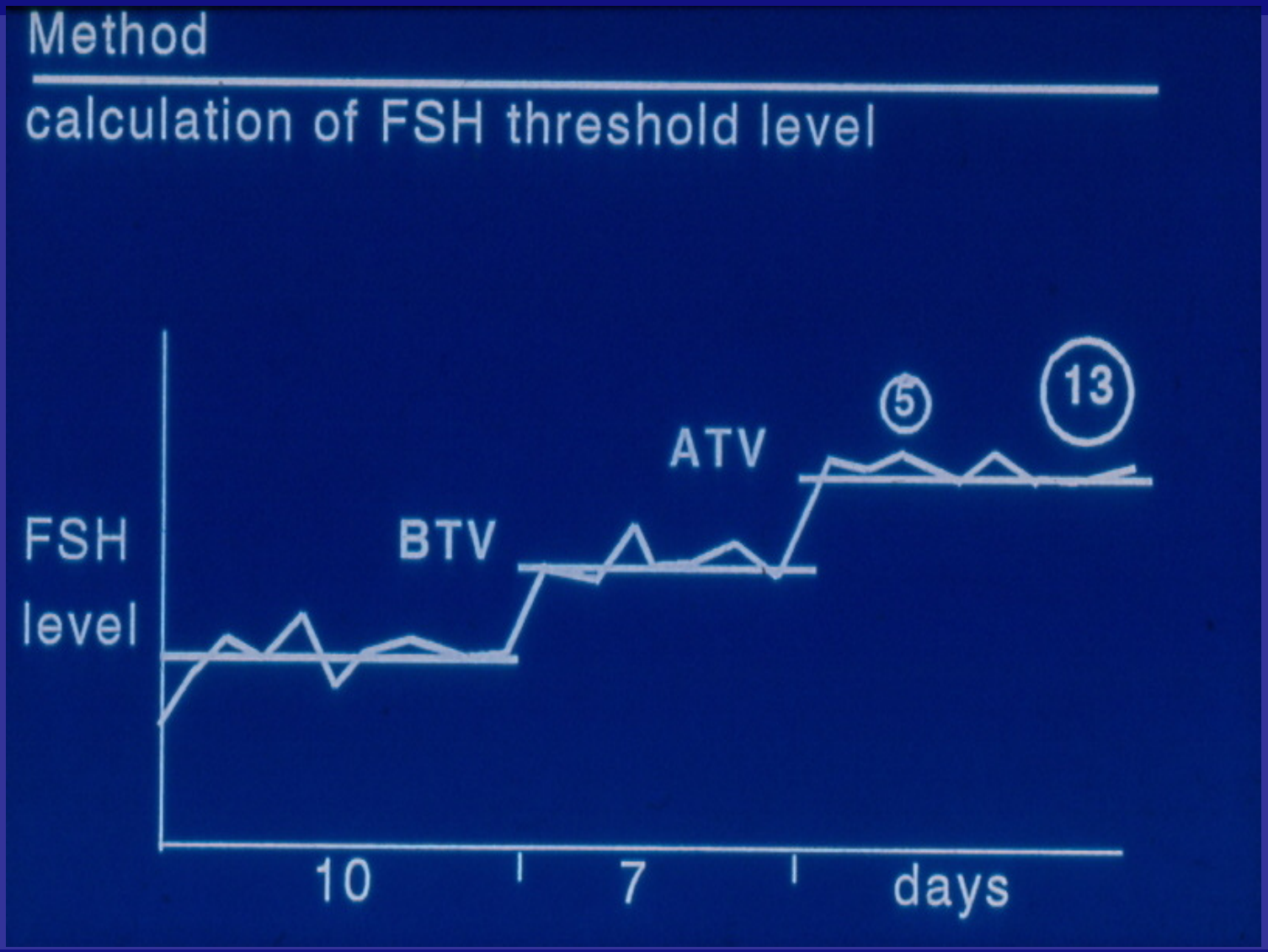
De Koning et al Hum Reprod, 2000

Contents

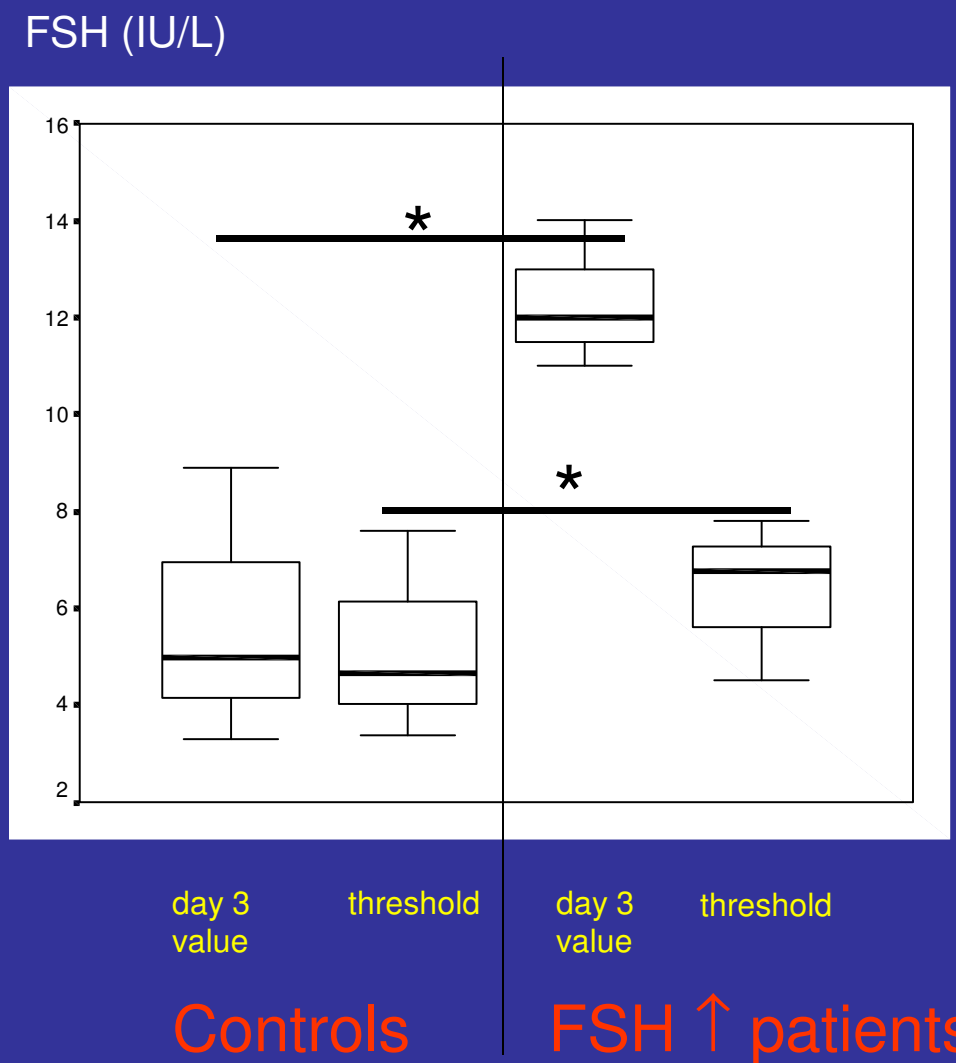
- Introduction
- Cycle characteristics with ageing
- Changing pituitary responsiveness
- Changing ovarian responsiveness
- Physiological consequences
- Clinical consequences
- Conclusions

Method

calculation of FSH threshold level



Day 3 FSH and FSH threshold

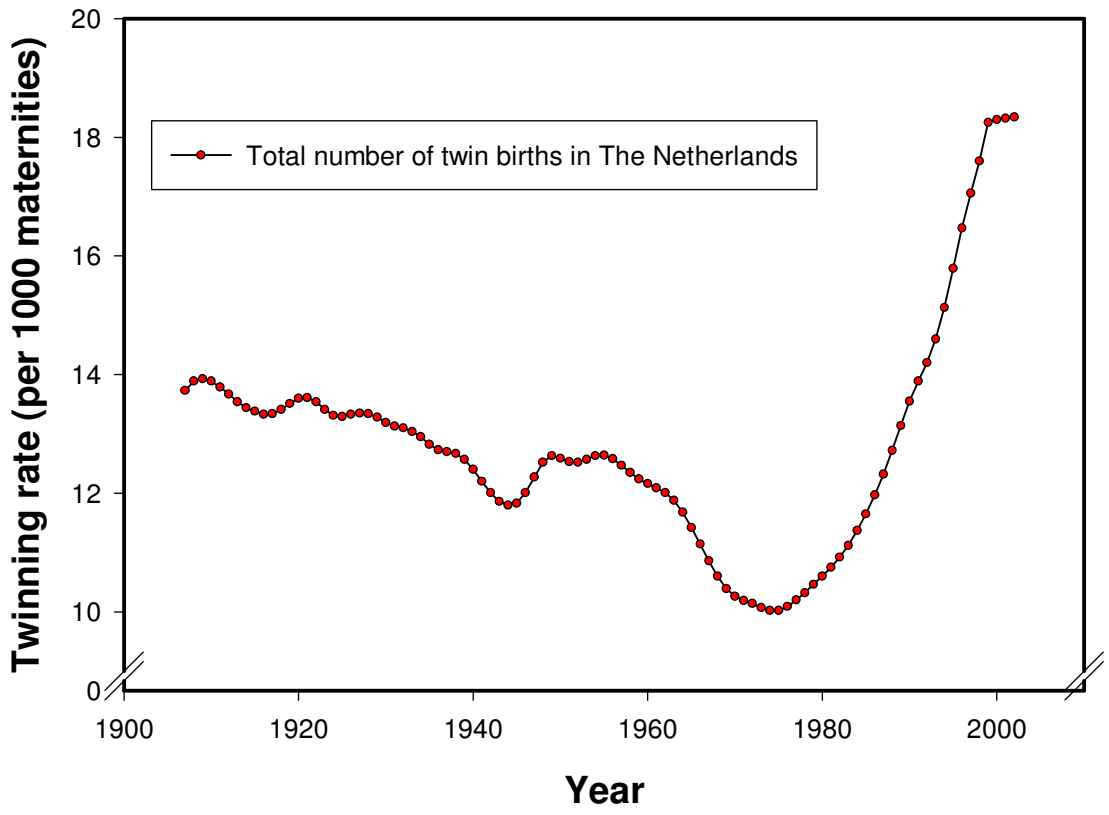


De Koning et al Fertil Steril, Sept 2004

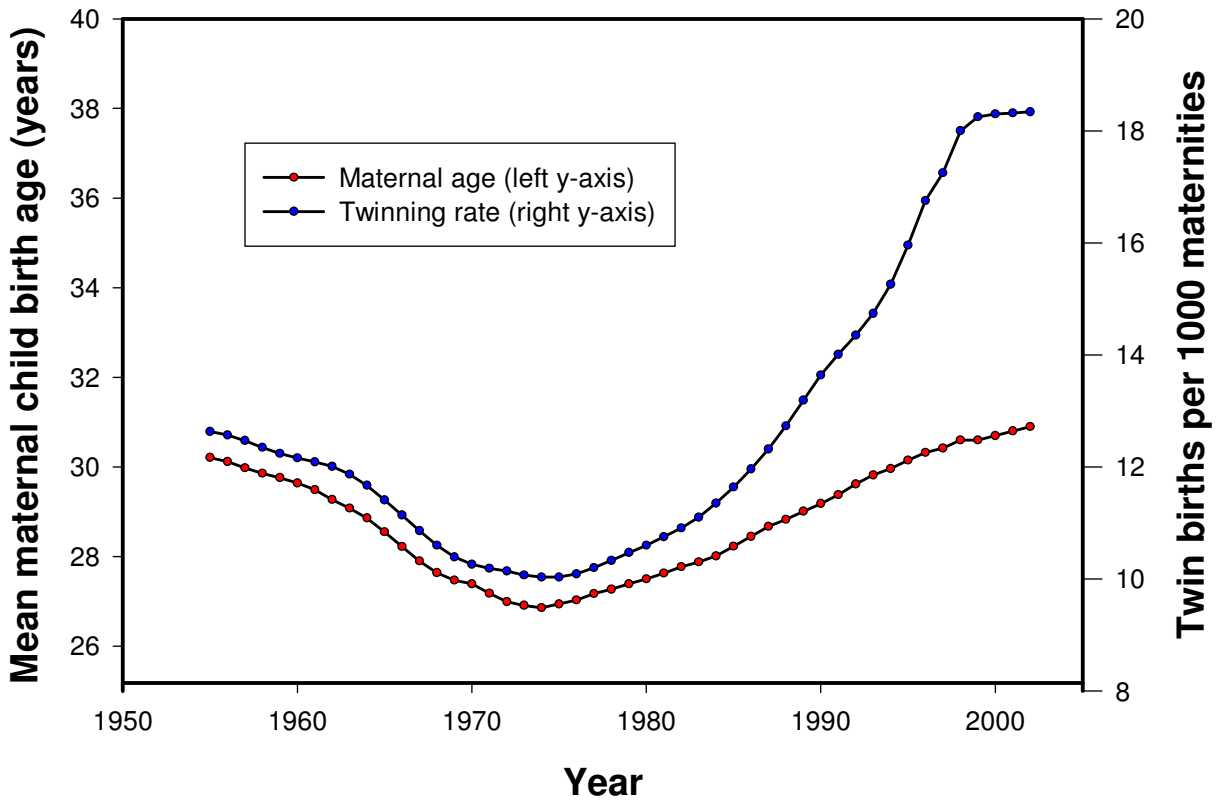
Contents

- Introduction
- Cycle characteristics with ageing
- Changing pituitary responsiveness
- Changing ovarian responsiveness
- Physiological consequences
- Clinical consequences
- Conclusions

Twinning rate In The Netherlands



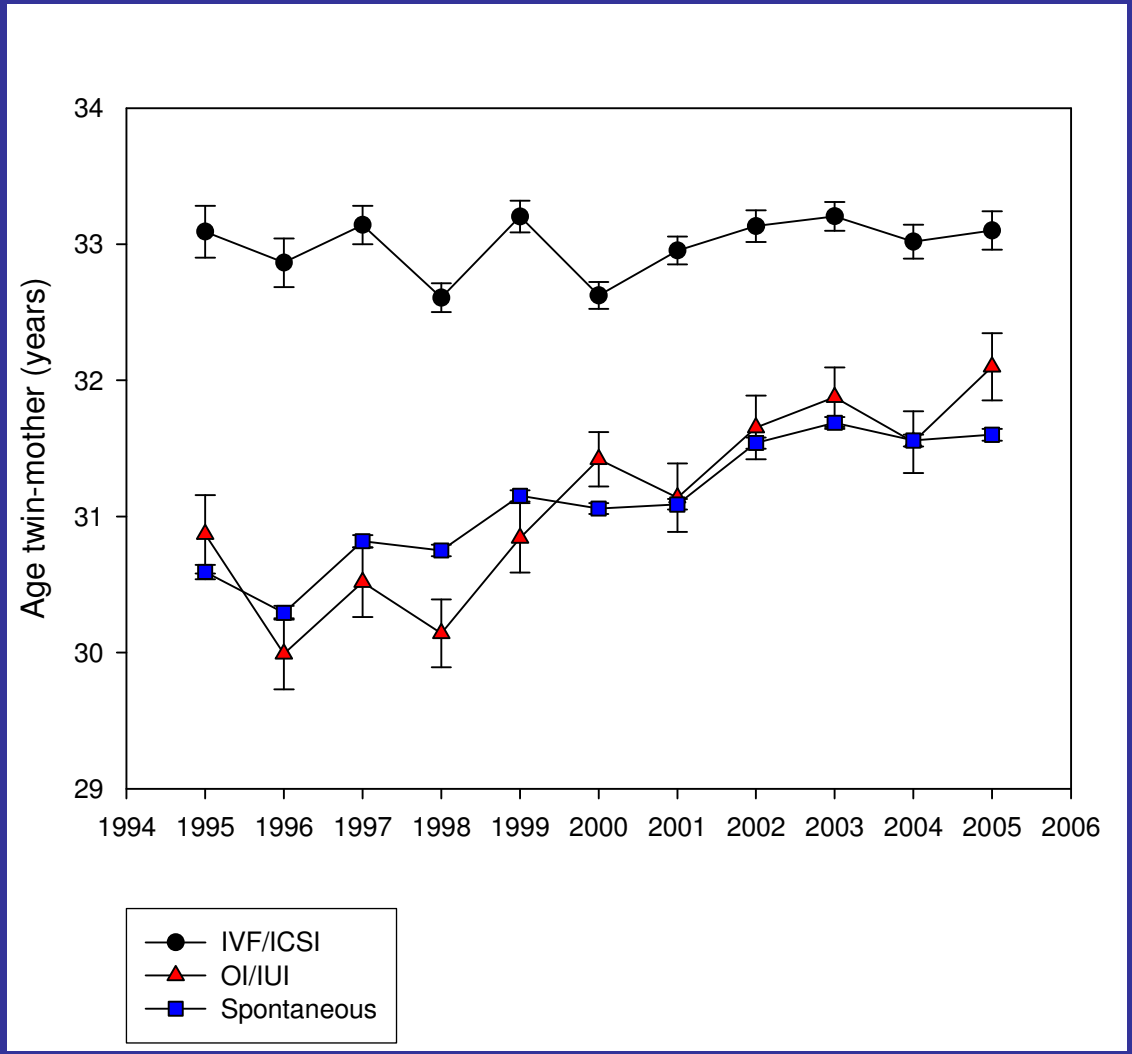
Twinning and maternal age in The Netherlands



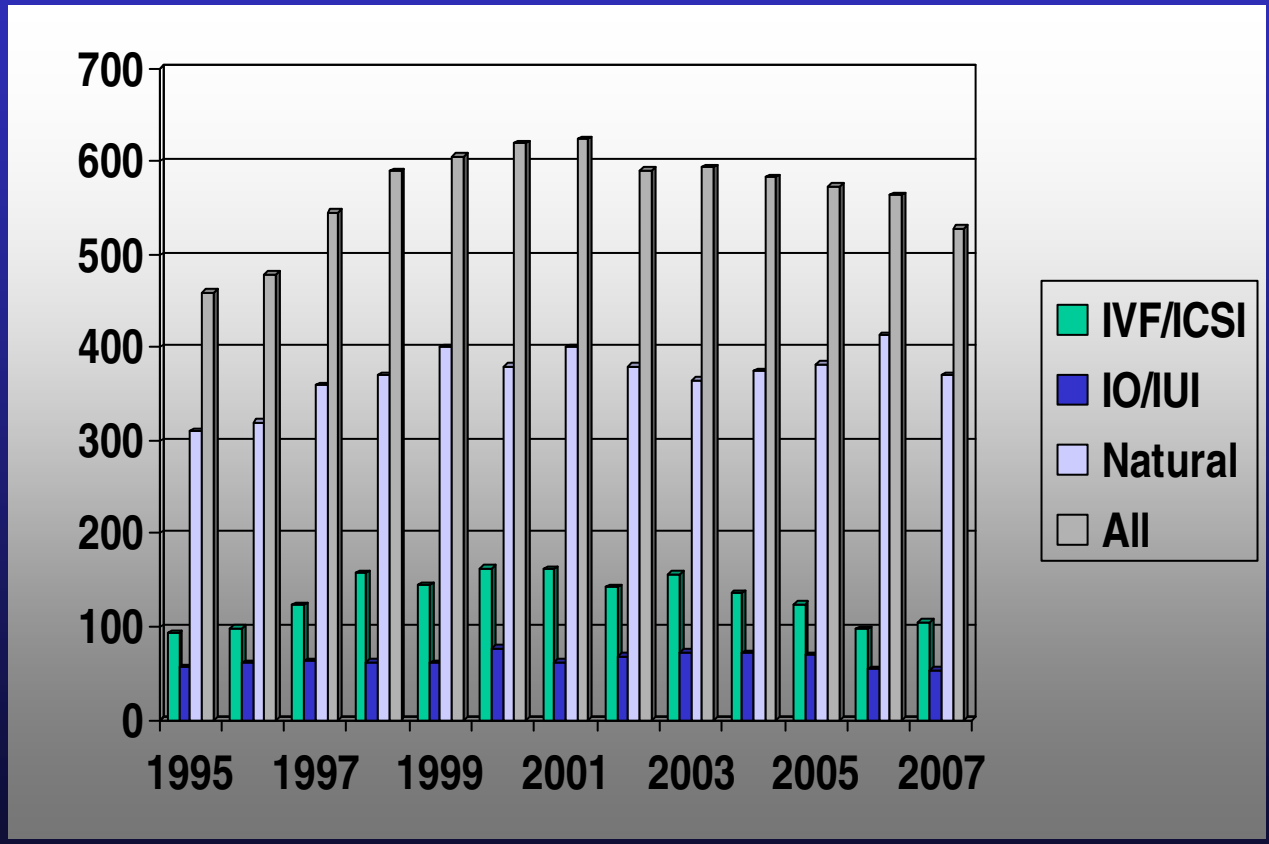
Increase of Boy/girl twins 1995-2001

	1995	2001	Increase	Contribution to increase
Natural conception	578	803	225(39%)	58%
OI/IUI	107	124	17(16%)	4%
IVF/ICSI	174	323	149(86%)	38%
All	859	1250	391(46%)	

Age of twin mothers The Netherlands



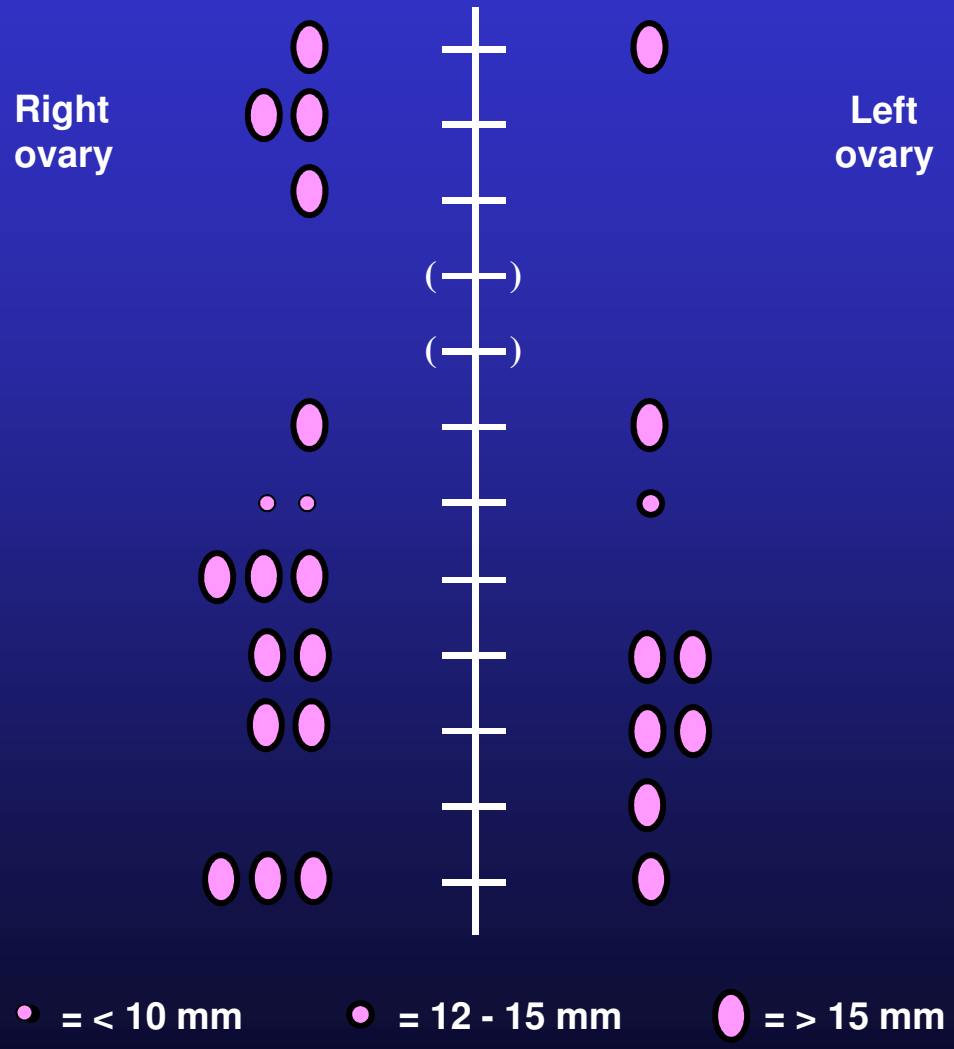
Numbers of boy/girl twins/100.000 deliveries according to conception type born in The Netherlands(1995-2007)



Number of Boy/girl twins 2001-2007

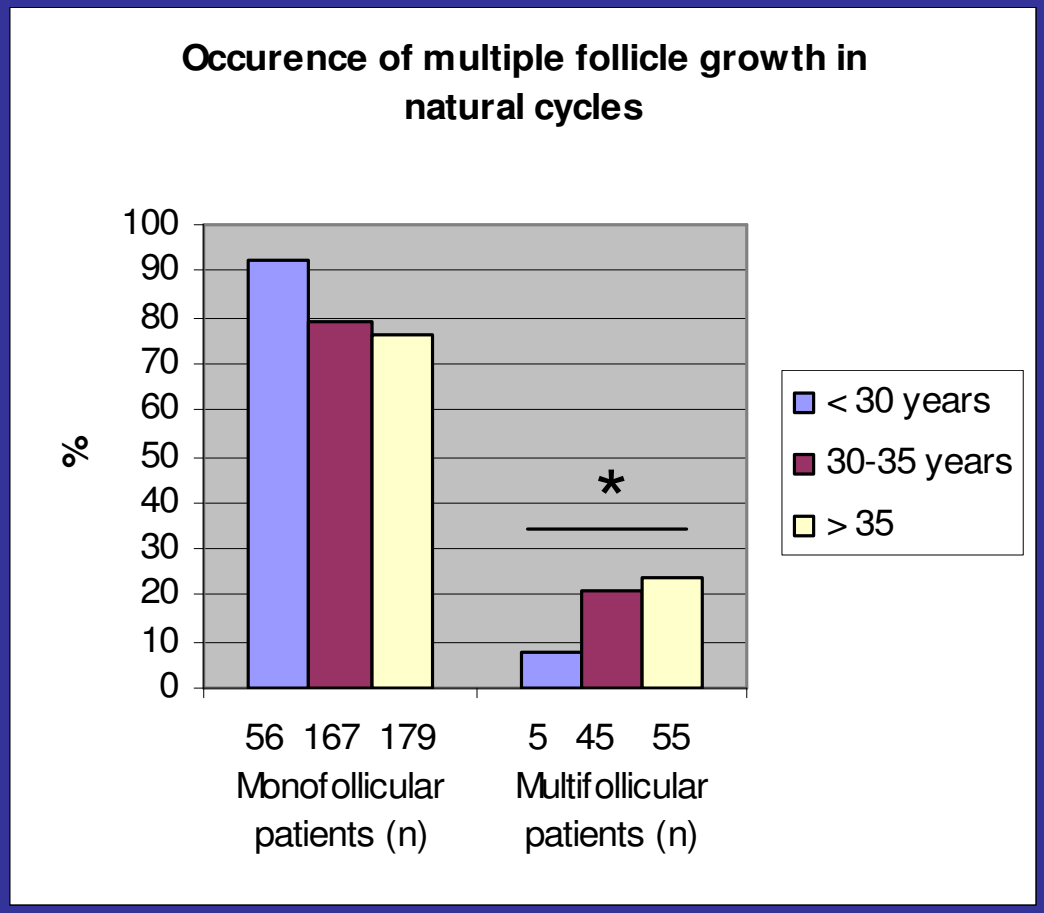
	2001	2007	Change	Contribution to change
Natural conception	803	660	- 143(19 %)	31 %
OI/IUI	124	88	- 36(29 %)	27 %
IVF/ICSI	323	188	- 135(42 %)	42 %
All	1250	926	- 324(26 %)	

Extreme follicle development monitored by ultrasound on cycle day 12 in mother of familial DZ twin



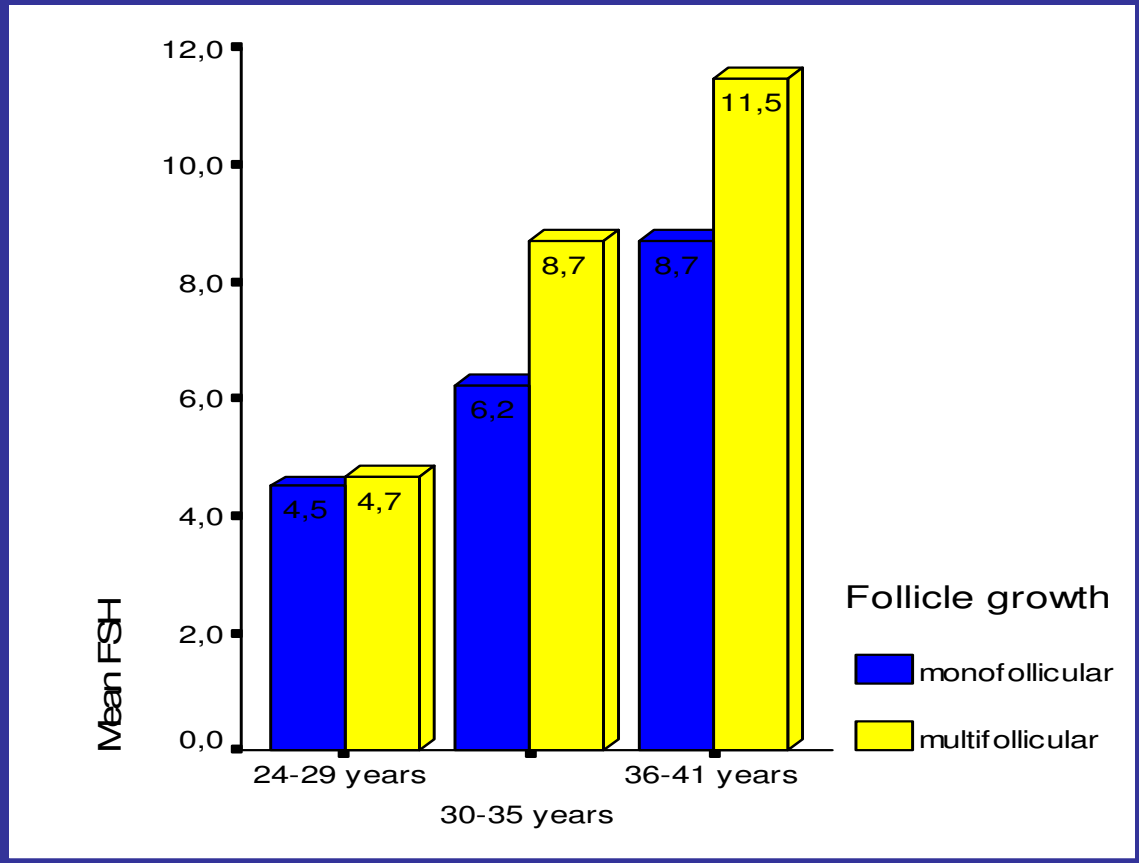
Martin et al Acta Genet Med Gemellol 1991

Natural multi follicular development and age



Beemsterboer et al Hum Reprod 2006

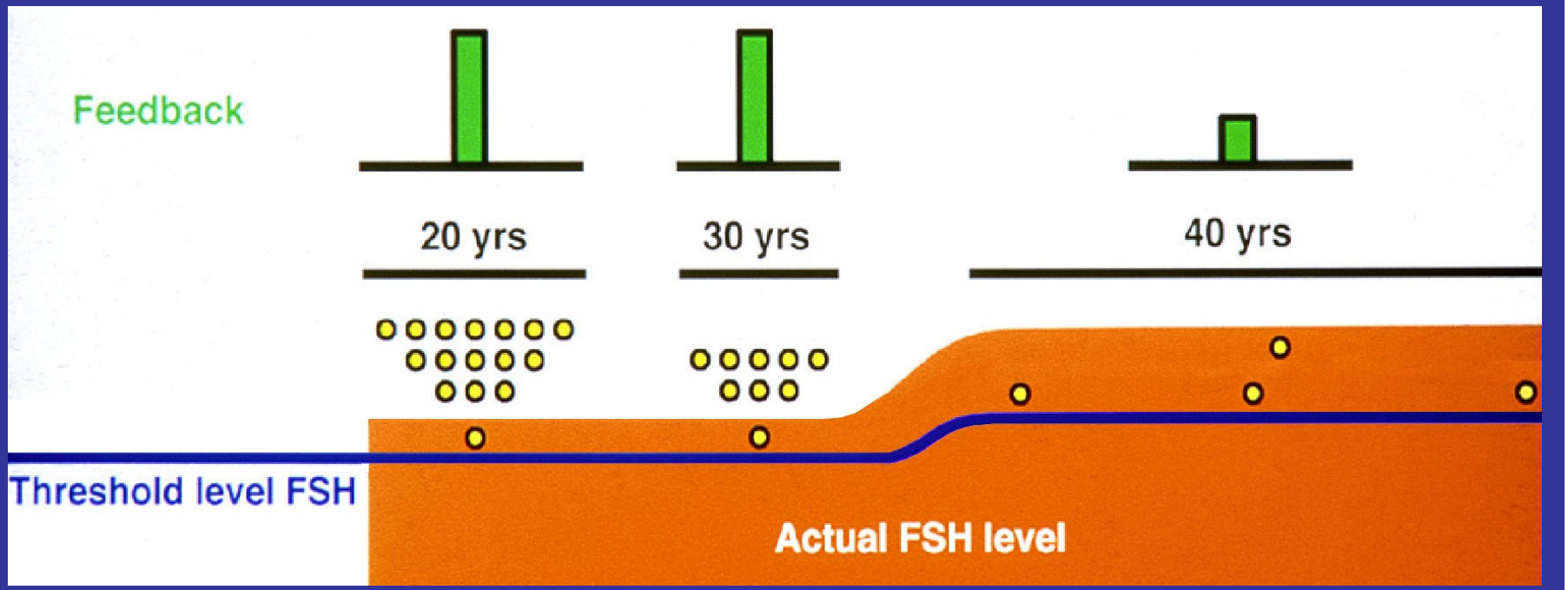
FSH with monofollicular or multifollicular growth per age



P<0.02

Beemsterboer et al Hum Reprod 2006

Model for DZ twinning with ageing

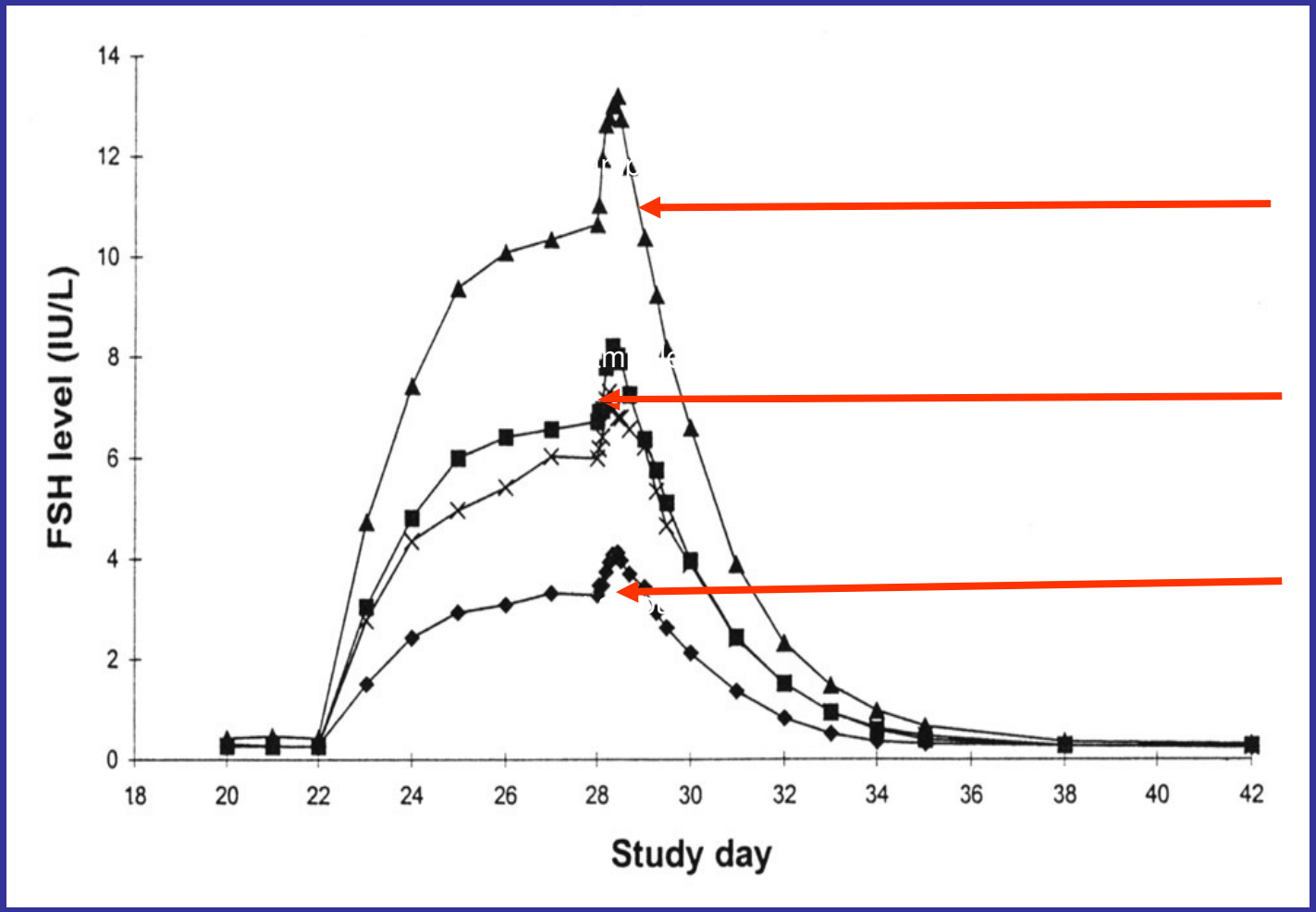


Lambalk Lancet 2001

Contents

- Introduction
- Cycle characteristics with ageing
- Changing pituitary responsiveness
- Changing ovarian responsiveness
- Physiological consequences
- Clinical consequences
- Conclusions

FSH dose versus serum levels



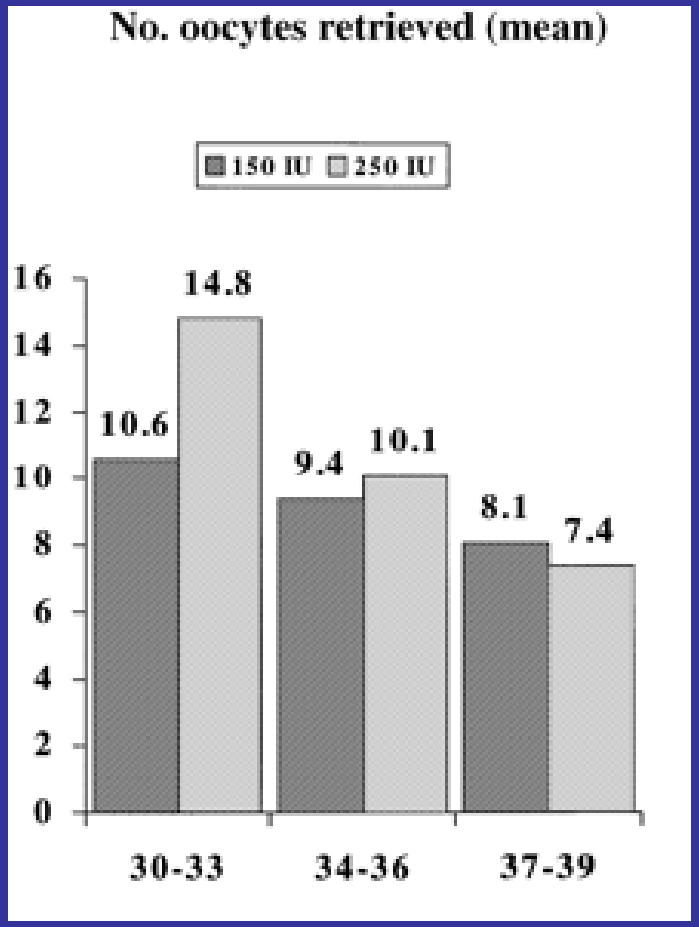
225 IU

150 IU

75 IU

Voortman et al Fertil Steril 2000

FSH dose ovarian response versus age



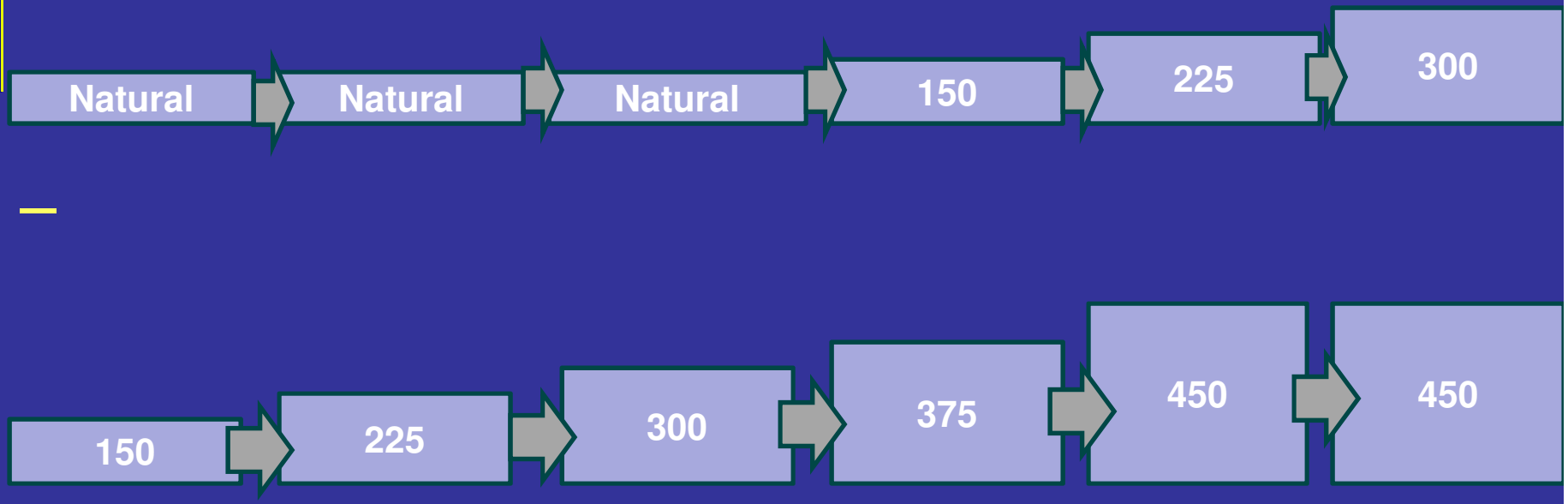
Age yrs

Out et al Hum Reprod 2000

Intra-Uterine Insemination

- Rationale of FSH treatment: to obtain multiple follicle growth
- Increased chance of pregnancy
- With endogenously elevated FSH no additional multiple follicle growth with administration of exogenous FSH?

RCT FSH in IUI patients with elevated FSH



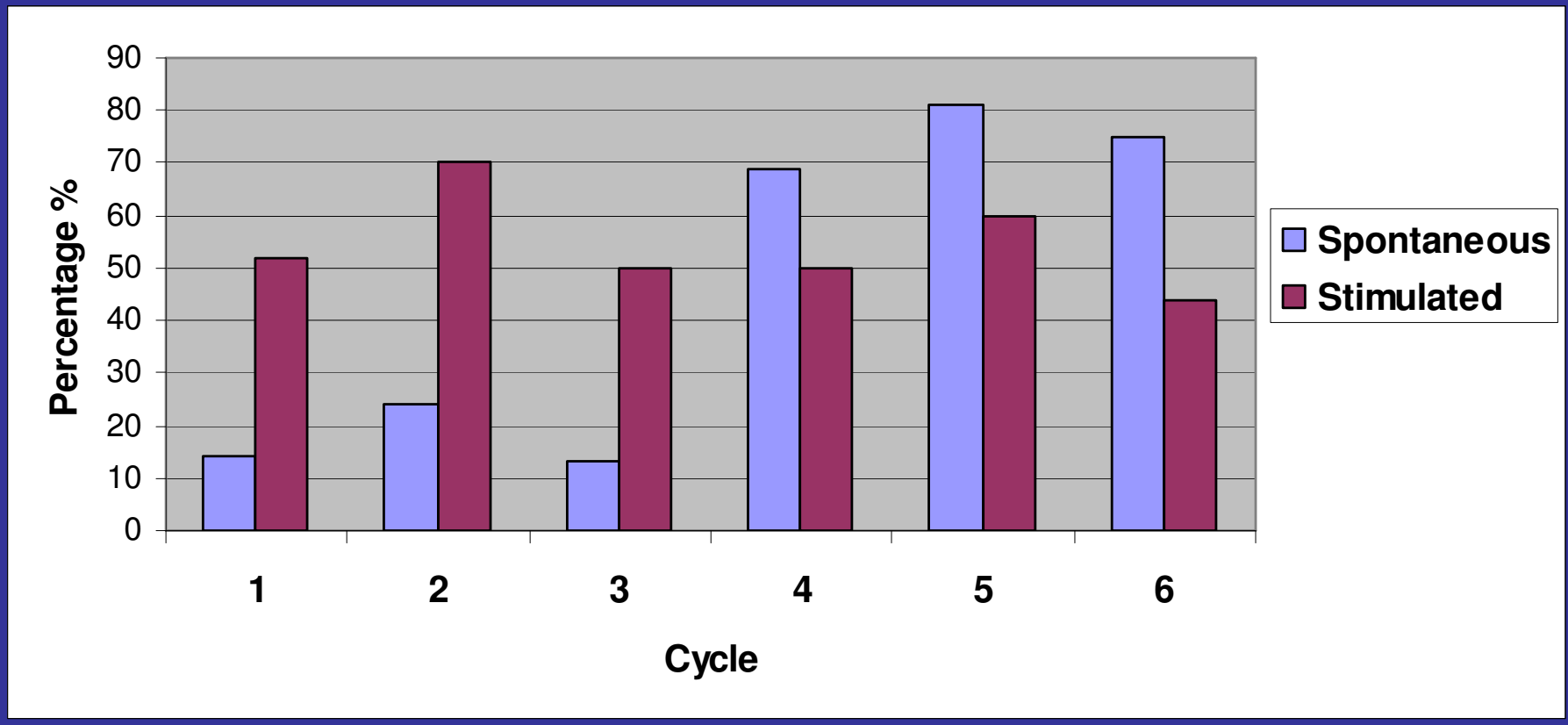
Inclusion

- FSH >10 IU/L op CD 2-4
- Between 18 and 41 yrs
- Regular ovulatory menstrual cycle (25 - 35 days)
- IUI indication
- Tubal patency
- Post wash semen: > 2 million progressive motiles

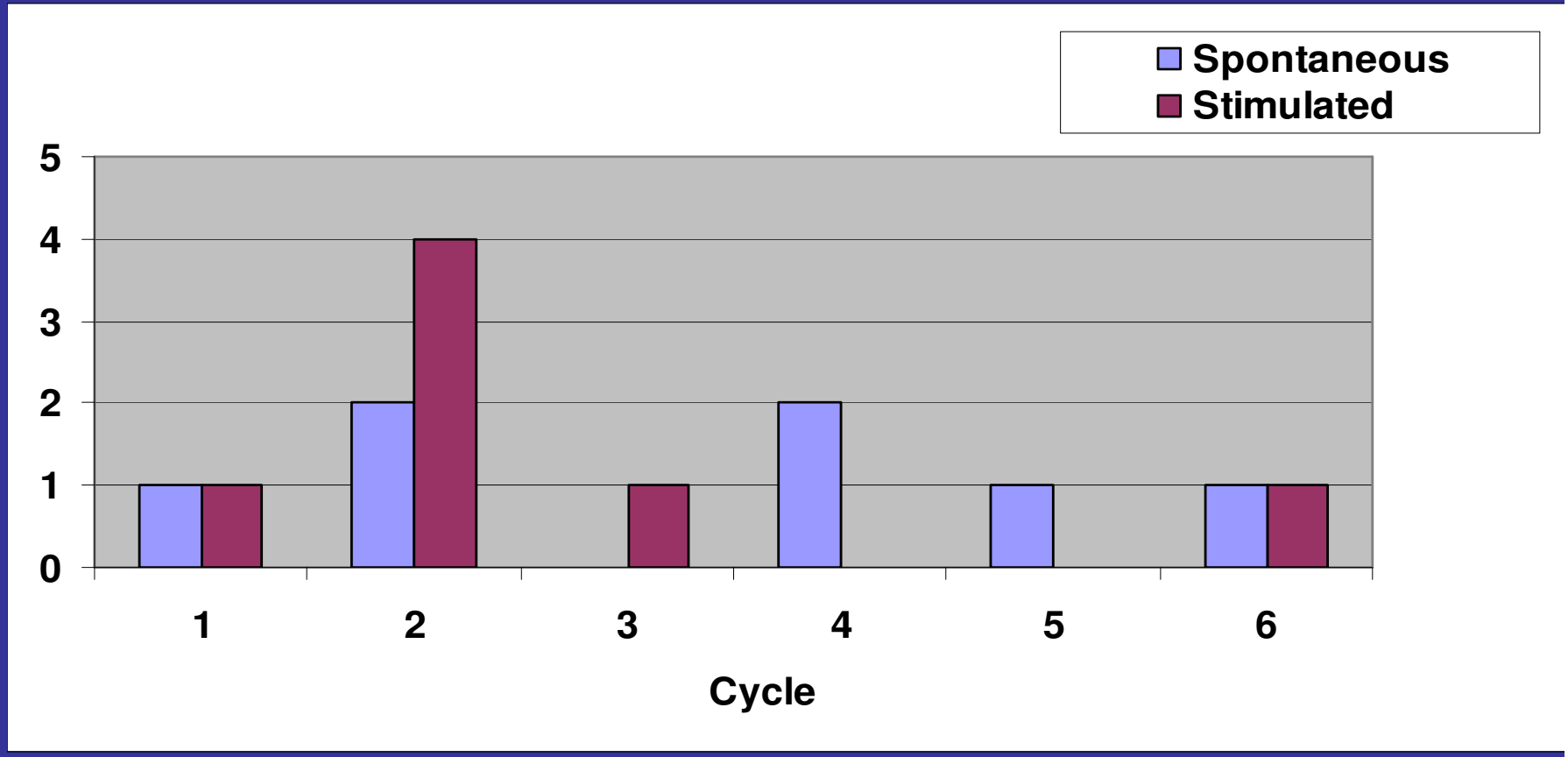
Baseline

	Natural N=23	Stimulated N=25
Age	36,52	36,16
BMI	24,44	22,79
Duration of infertility (months)	29,05	29,57
FSH day 3	16,04	17,25
AFC day 3 (L+R)	6,17	5,70
AMH	0,70	0,45
FSH receptor		
NN	8	6 (14)
NS	7	13 (20)
SS	6	5 (11)

Multifolliculair growth



Ongoing pregnancy per cycle



Predictors for multifollicular growth

Natural cycles

- Length infertility
- Low AMH

Stimulated cycles

- Low FSH at begin stimulation
- FSH receptor genotype
  - NS/NN variant

Predictors for ongoing pregnancy

- Low baseline FSH
- Higher baseline AFC
- Higher AMH
- Lower actual FSH at begin of treatment cycle
- Multifollicular development

Too low LH levels

Human Reproduction vol.15 no.5 pp.1003–1008, 2000

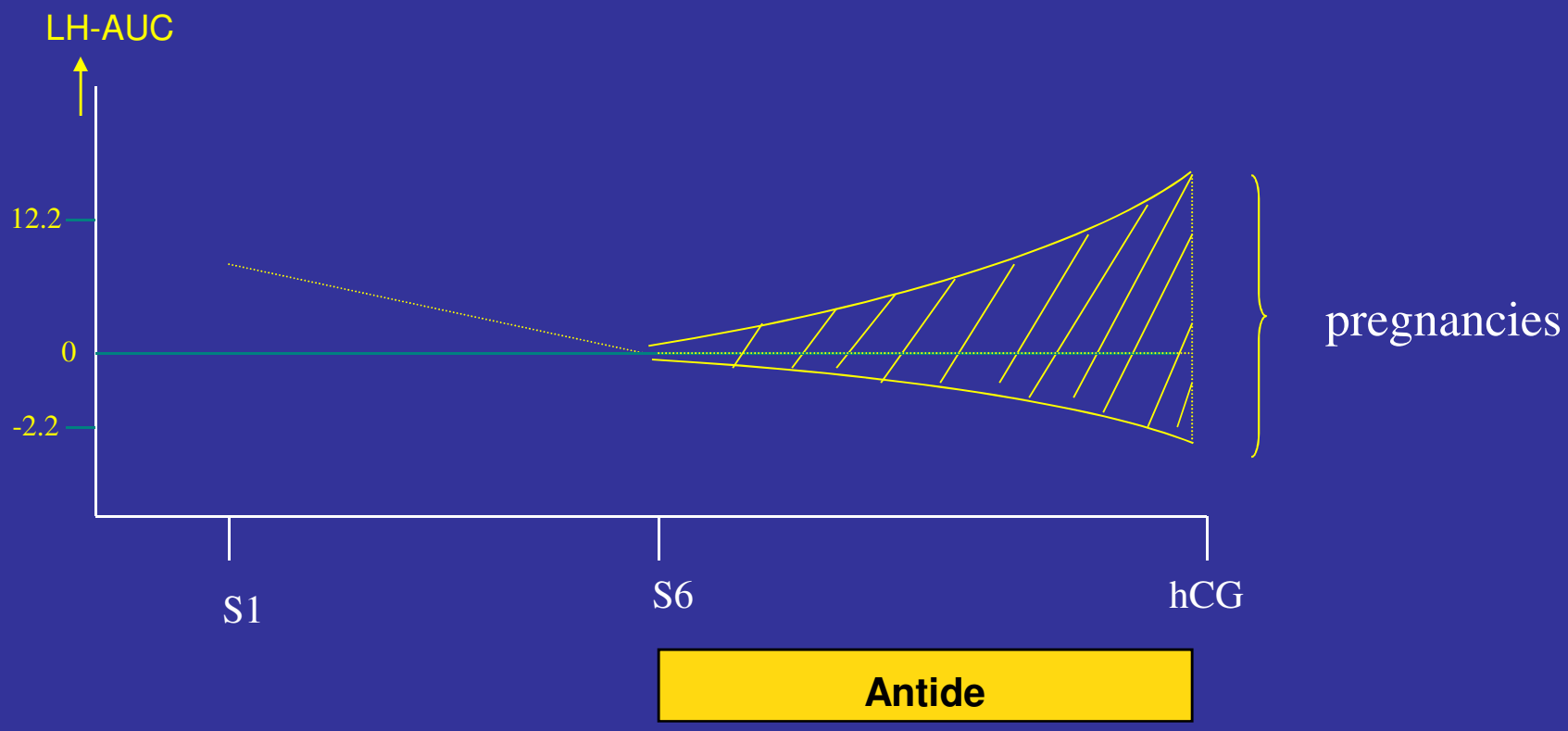
Increased risk of early pregnancy loss by profound suppression of luteinizing hormone during ovarian stimulation in normogonadotrophic women undergoing assisted reproduction

Lars G.Westergaard[1,3], Steen B.Laursen[1] and Claus Yding Andersen[2]

[1]Fertility Clinic, Odense University Hospital, Odense and [2]Laboratory of Reproductive Biology, Rigshospitalet, Copenhagen, Denmark

- Pregnancy loss 9% if LH > 0.5 U/L
- Pregnancy loss 45 % if LH < 0.5 U/L

Optimal changes of LH levels



Huirne et al Hum Reprod 2005

?

‘Elderly’ women

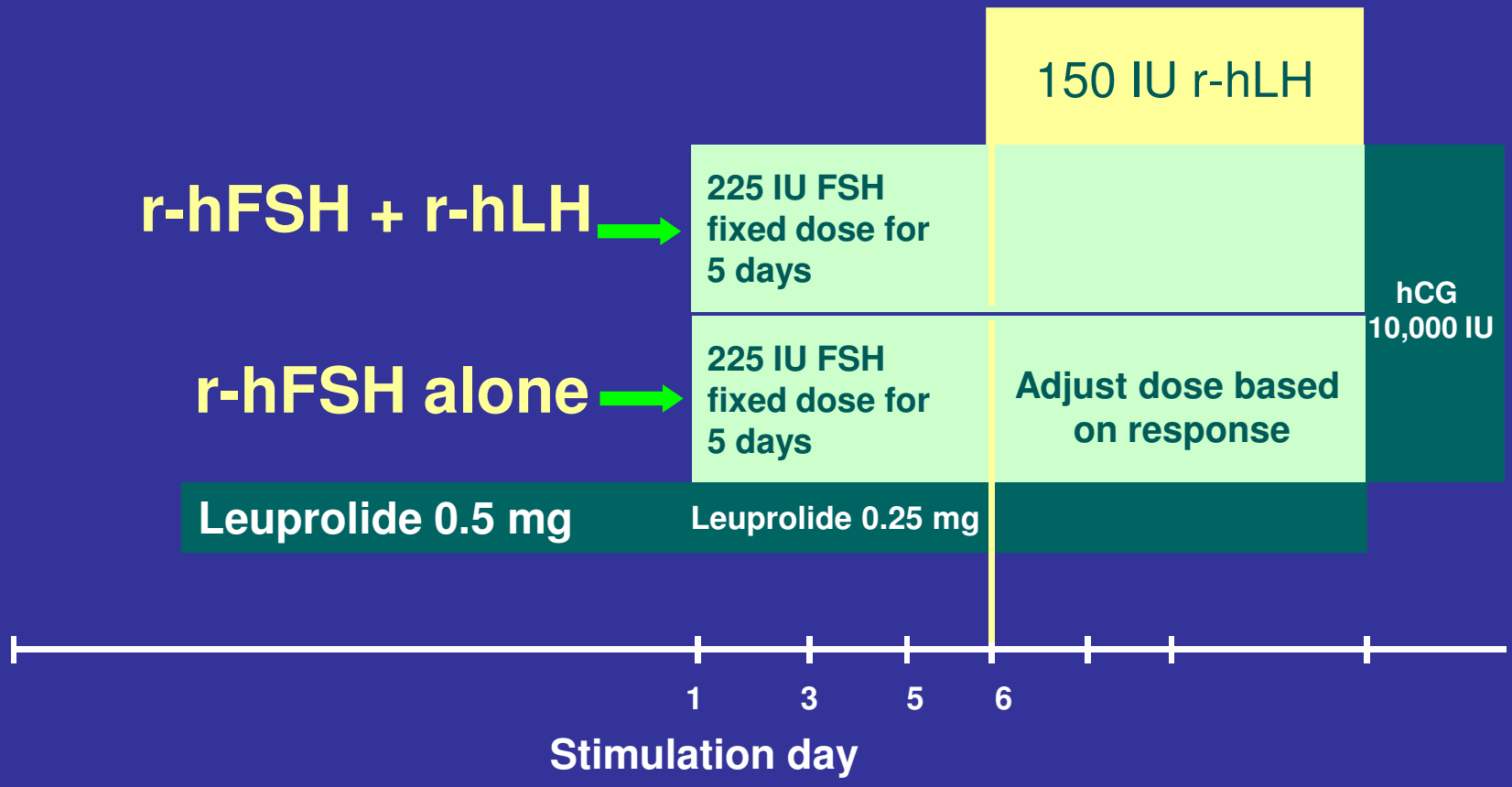
+

Pituitary over suppression

=

Bad news

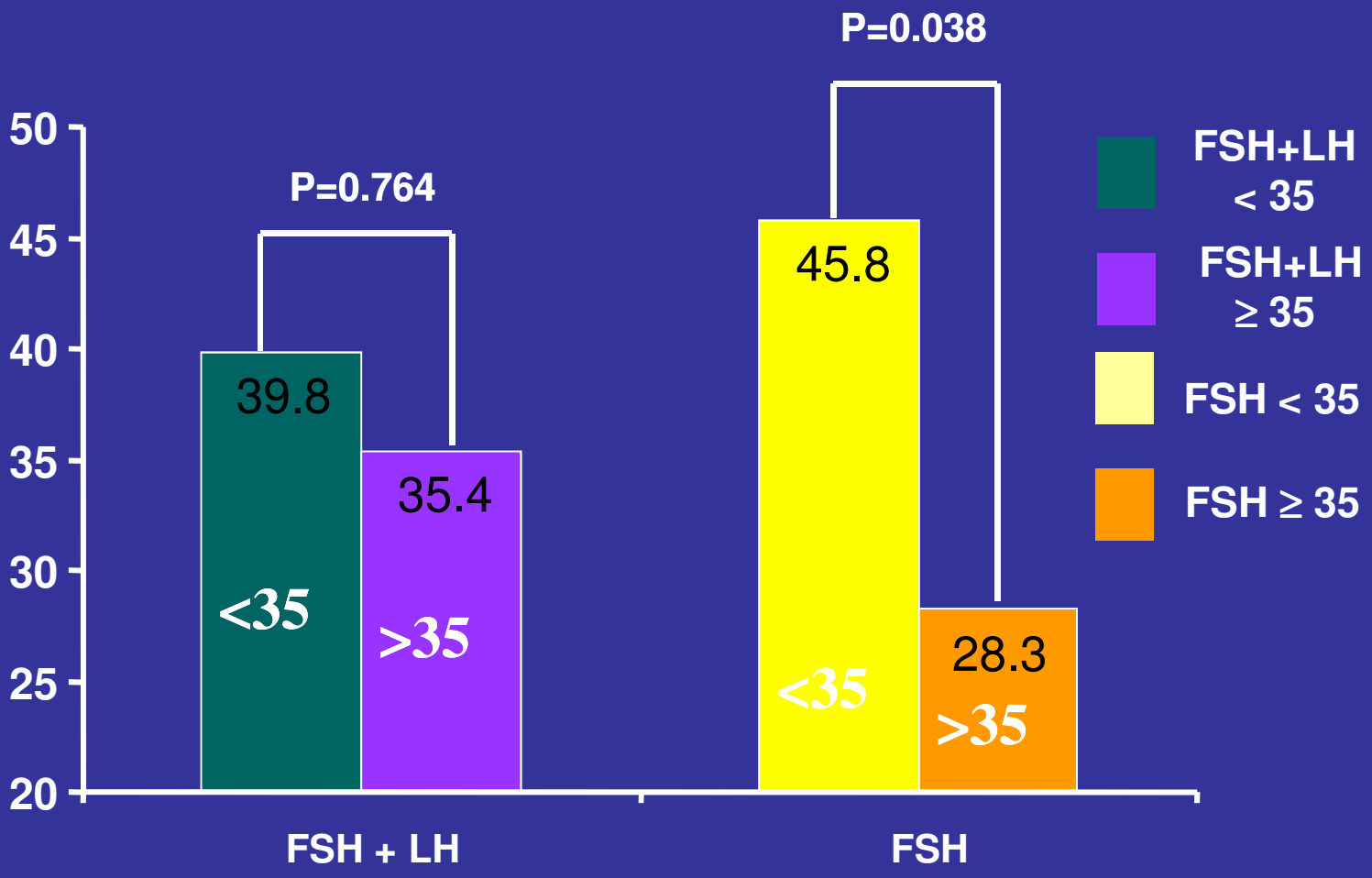
Stimulation Protocol



Marrs et al RBM Online, 2004

VU university medical center

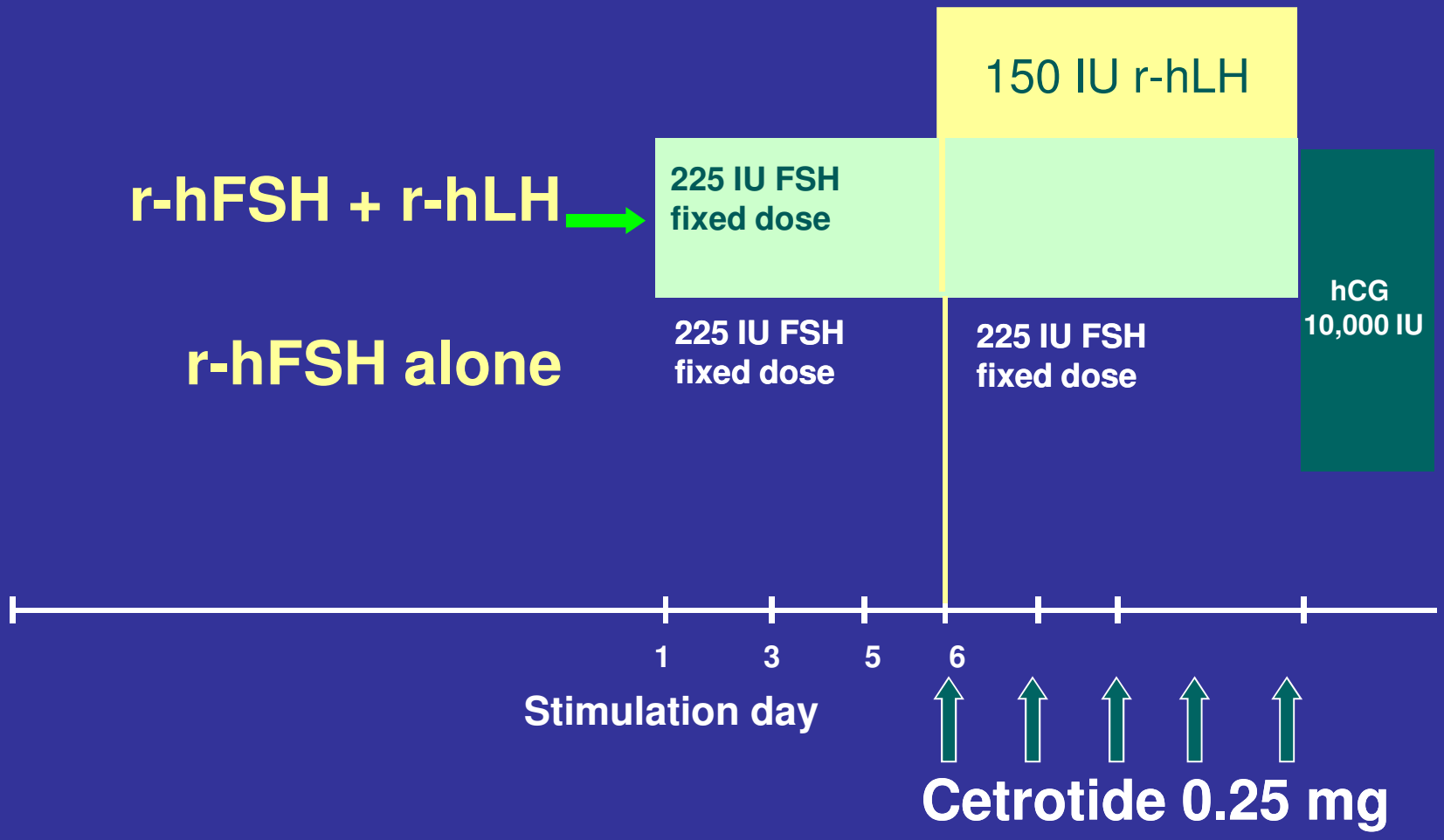
Pregnancy Rate/Cycle; FSH+LH or FSH



Marrs et al RBM Online, 2004

VU university medical center

Stimulation Protocol; IVF/ICSI; >35 yrs



Pilot data

	Implantation rate	Clinical pregnancies	Miscarriages	Ongoing pregnancies
LH added	23%	9/22 41%	2/9	7
Controls	25%	8/22 36%	3/8	5

Pilot data

	Implantation rate	Clinical pregnancies	Miscarriages	Ongoing pregnancies
LH added	19.9 %	24/67 35.8 %	6/24	18
Controls	18.3 %	18/67 26.9 %	3/18	15

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Conclusions

- Rise of FSH
  - Late marker of derailment of HPO-axis interaction with ageing
  - A consequence of increased pituitary sensitivity
  - Only slightly increased ovarian threshold
  - Subject to strong inter-cyclic variation
  - Depending on acute ovarian feedback conditions
  - Could be potential functional marker for the quality in addition to quantity of an actually available cohort

Conclusions

- Clinical consequences
  - Natural multiple follicle growth with more natural twinning
  - Improved ovarian response to exogenous FSH but in particular immediately in case of an instantaneous drop of endogenous FSH
  - A possible role for LH co-treatment