

Protocoles en vue de FIV - ICSI

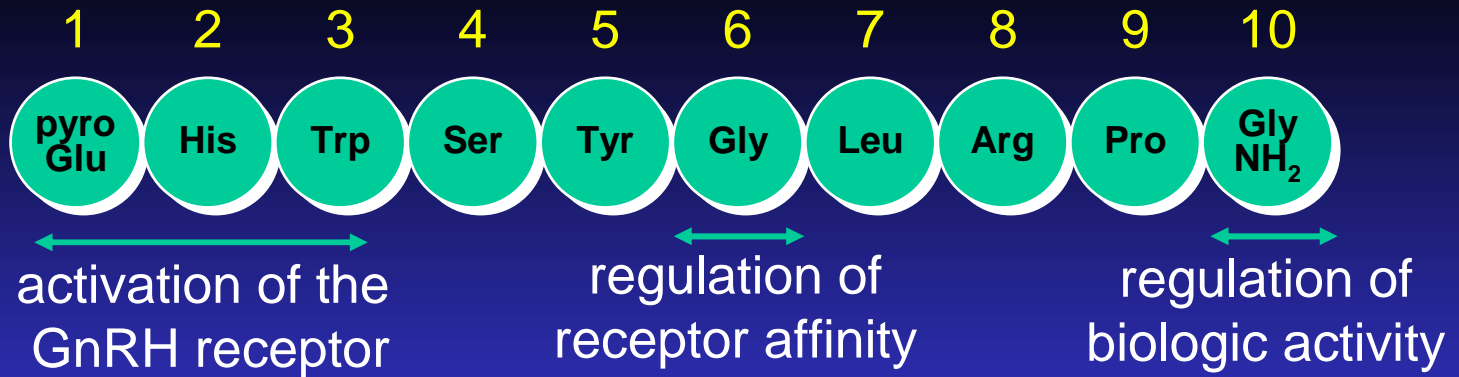
JN Hugues M.D, Ph.D

Service de Médecine de la Reproduction

Hôpital Jean Verdier

Université Paris XIII, France

Native GnRH



Karten MJ & Rivier JE, 1986

GnRH Agonists

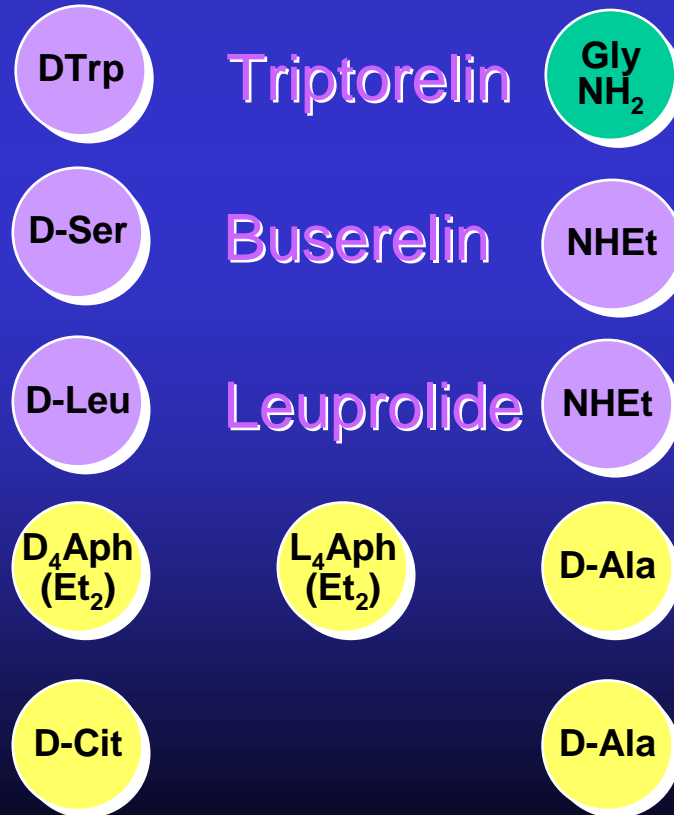
GnRH Antagonists

Third-Generation

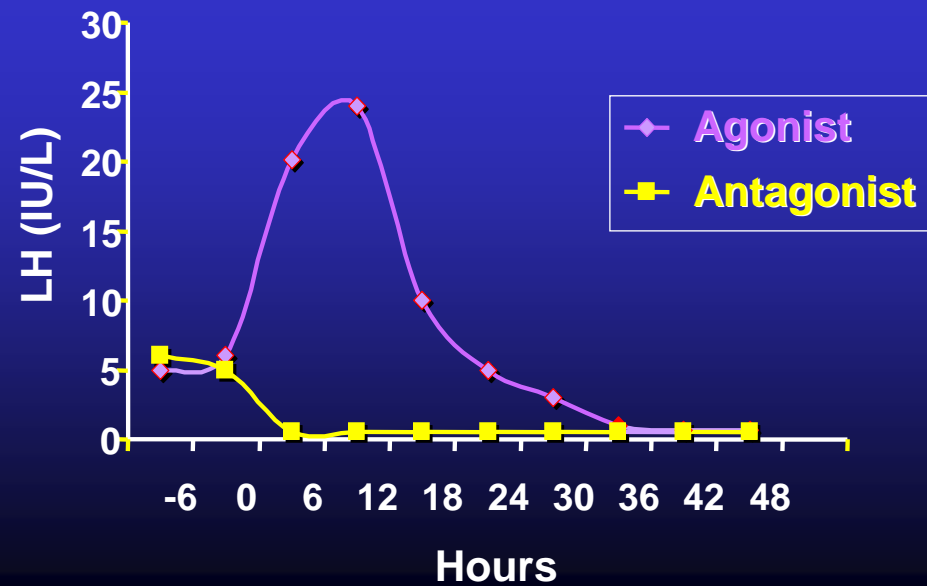
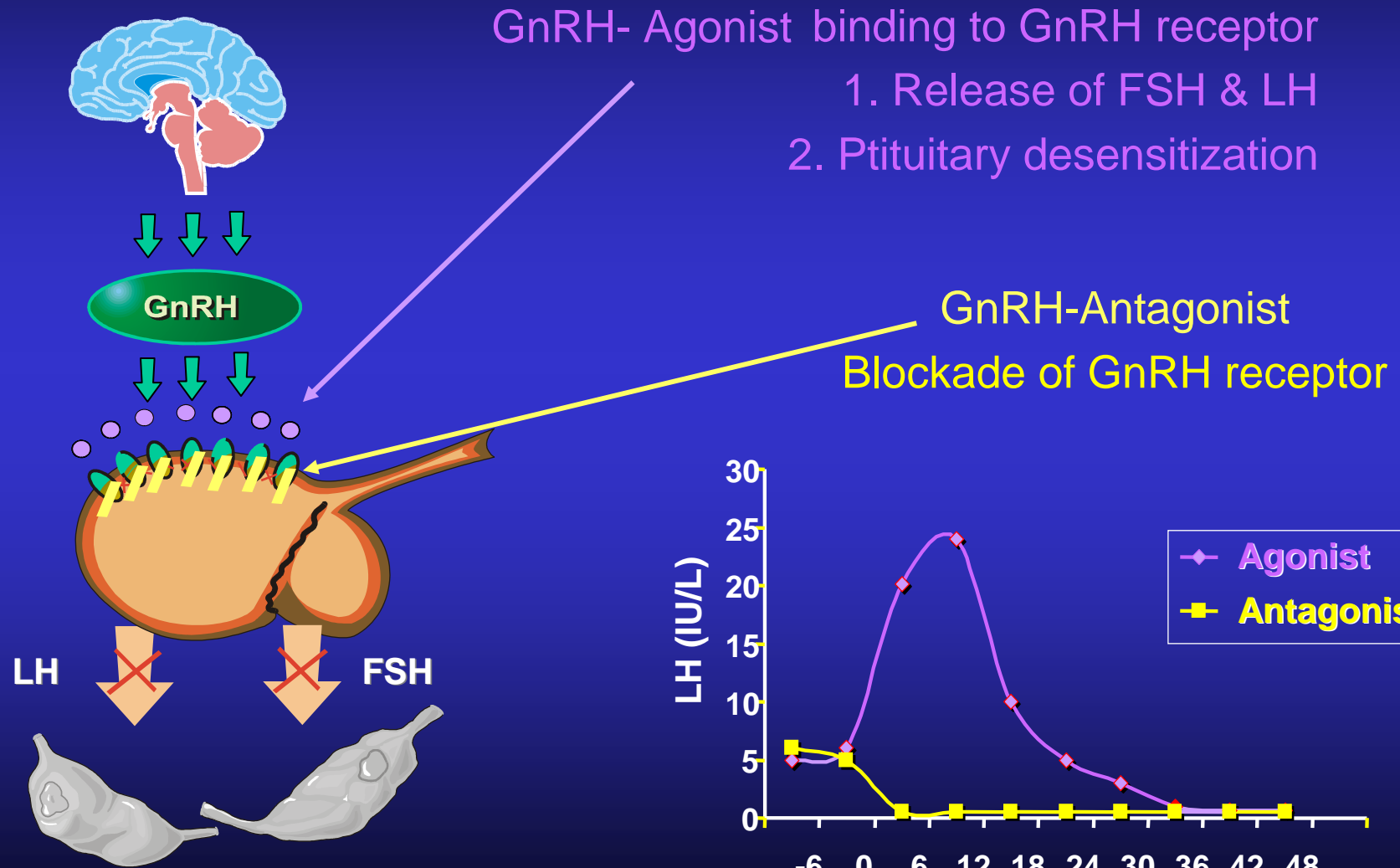
Ganirelix



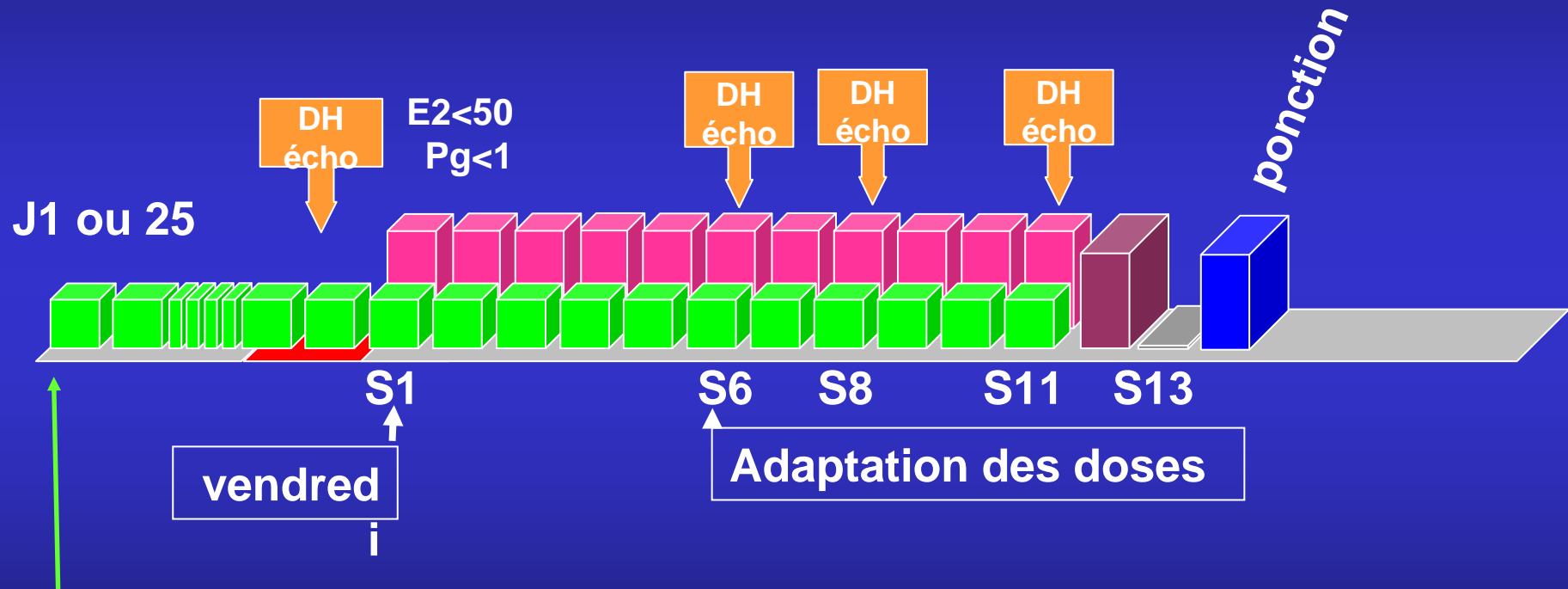
Cetrotide



How do GnRH analogs work ?

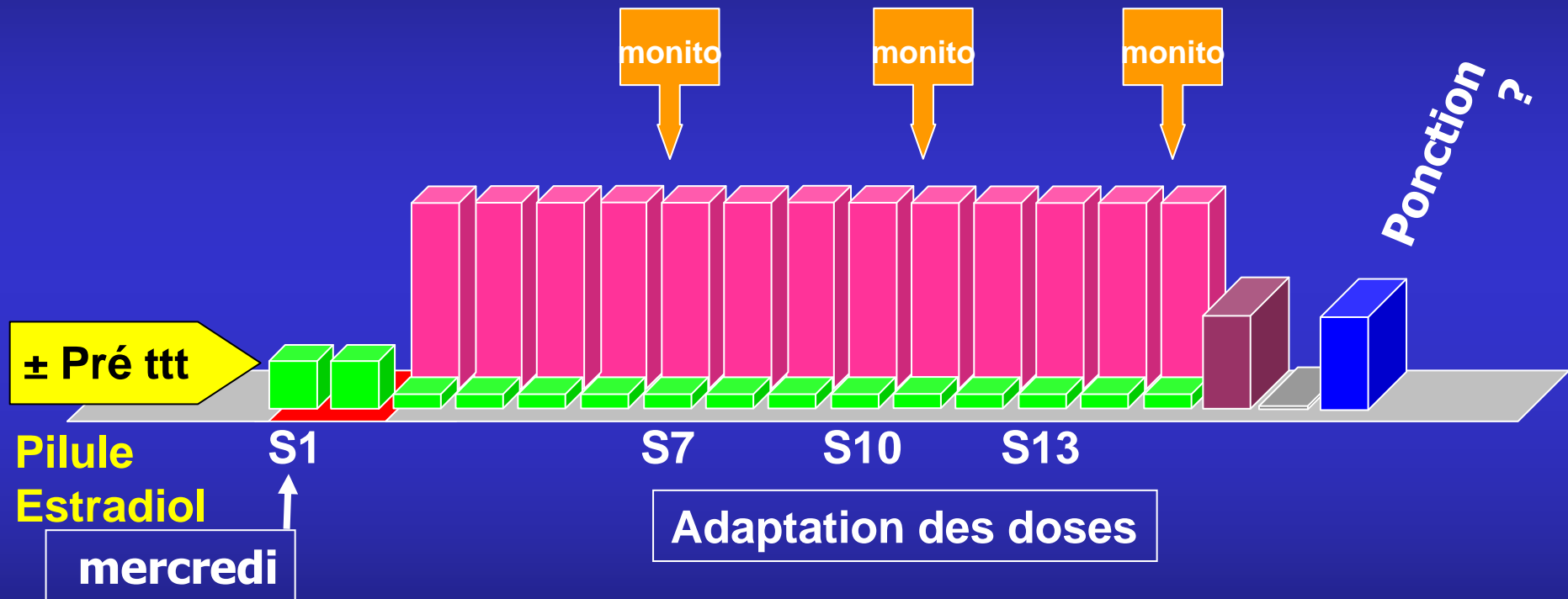


Protocole Long Agoniste du GnRH



Agoniste du GnRH
Formulation quotidienne
ou long acting (30 – 40 J)

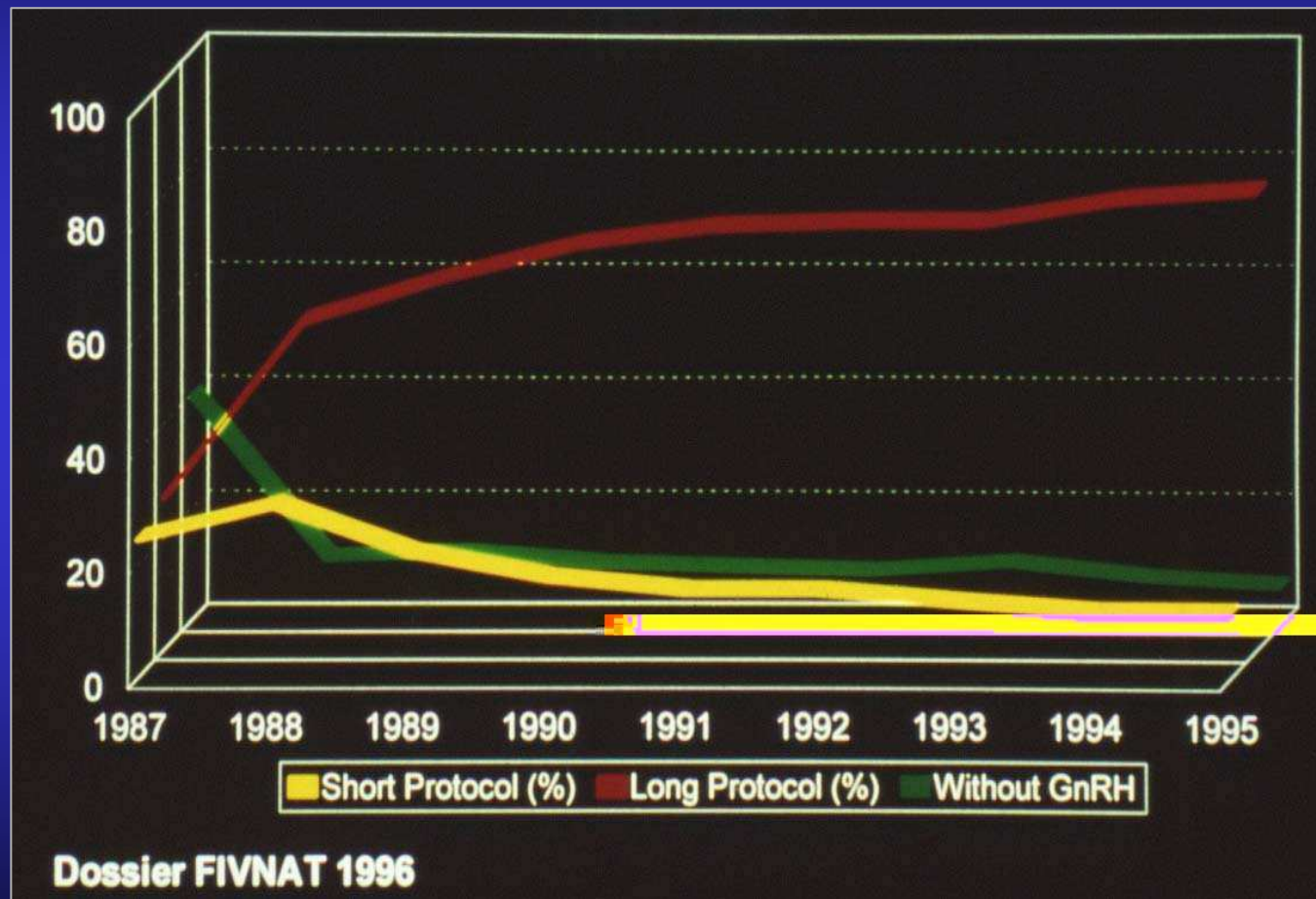
Protocole Court Agoniste du GnRH



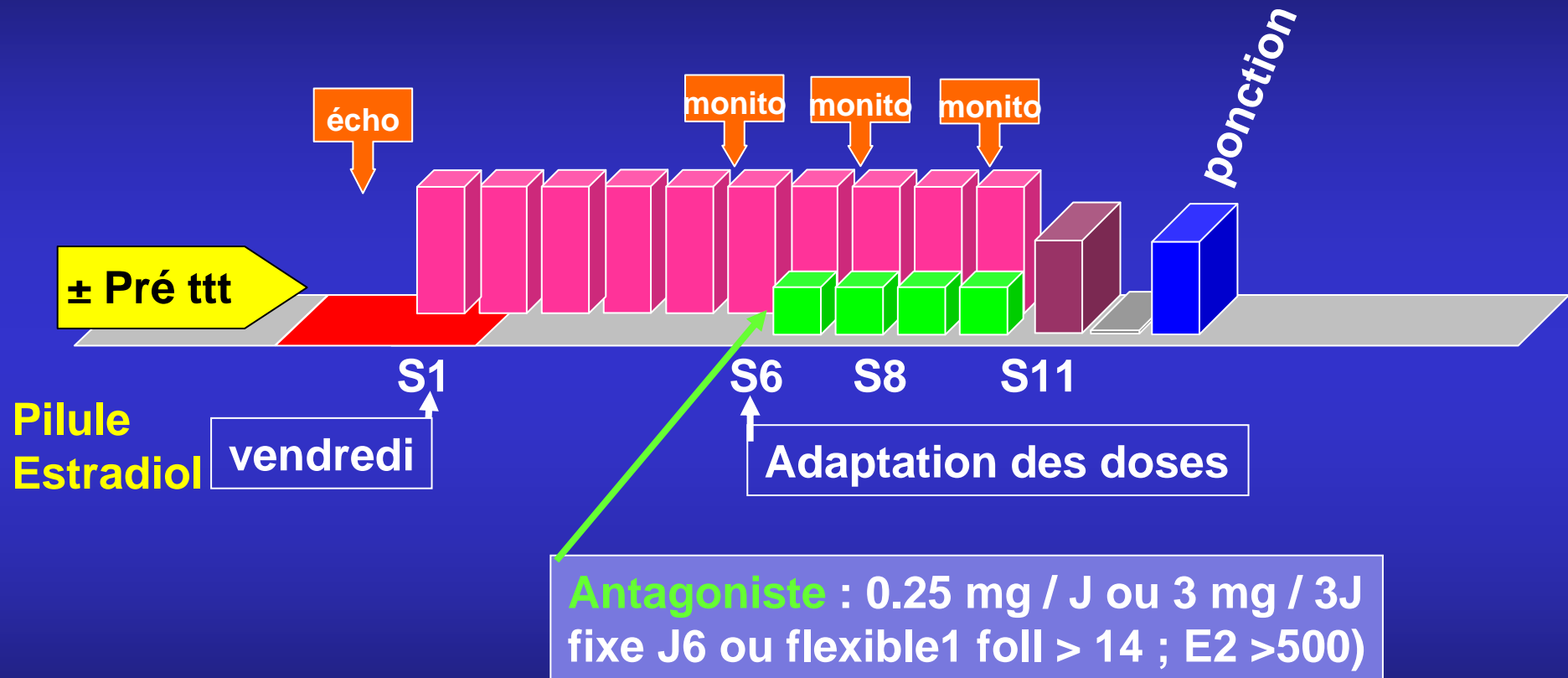
-  Agoniste quotidien 1/2 ou 1/4 de dose
-  FSH 225-450 UI
-  HCG

A éviter si cycles courts

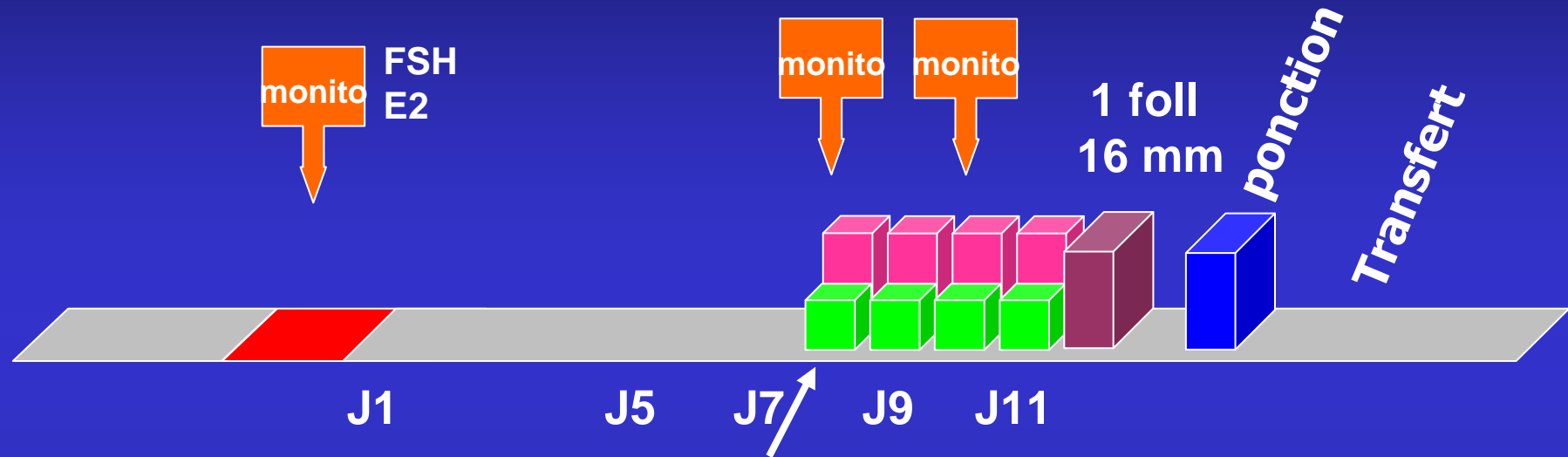
Controlled ovarian hyperstimulation (COH) for IVF/ICSI in France : 1987-1995



Protocole antagoniste du GnRH



Protocole « semi naturel »



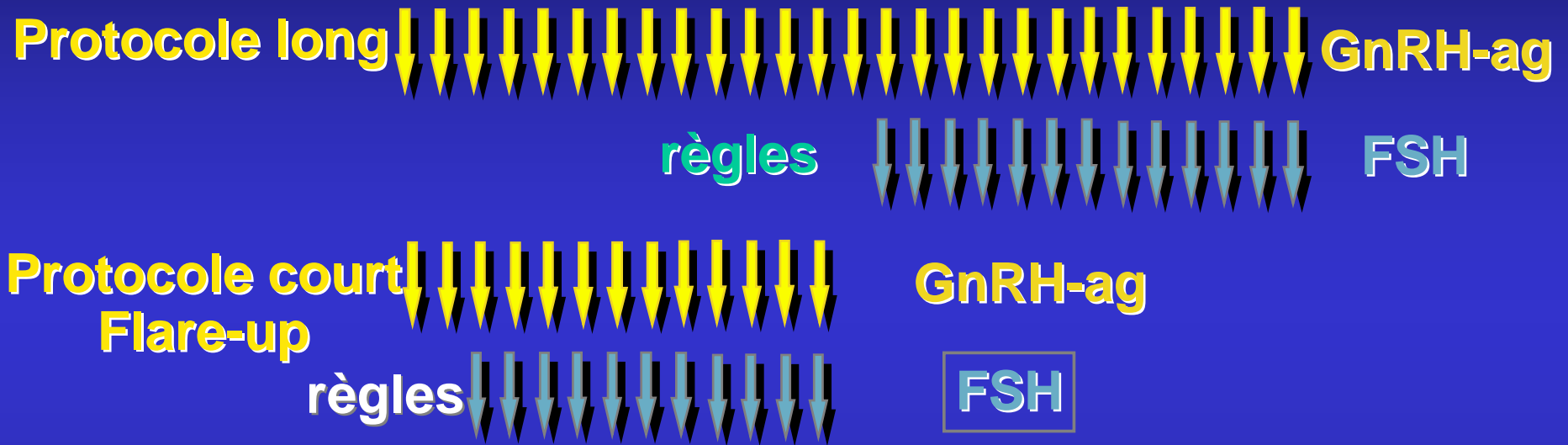
Début quand au - 1 foll
évolutif avec E2
correspond

 Antagoniste
 150 UI
 HCG

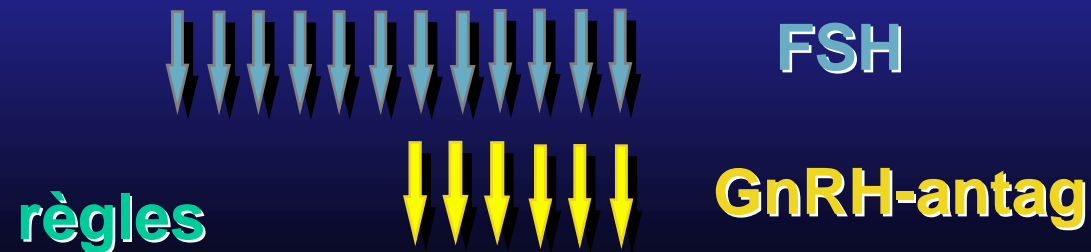
- Objectif 1 ou 2 ovos
- 50% chance avoir ovo
 - 30% de transfert
- Taux de G fonction de l'âge +++ < 35 ans

LA STIMULATION POUR FIV

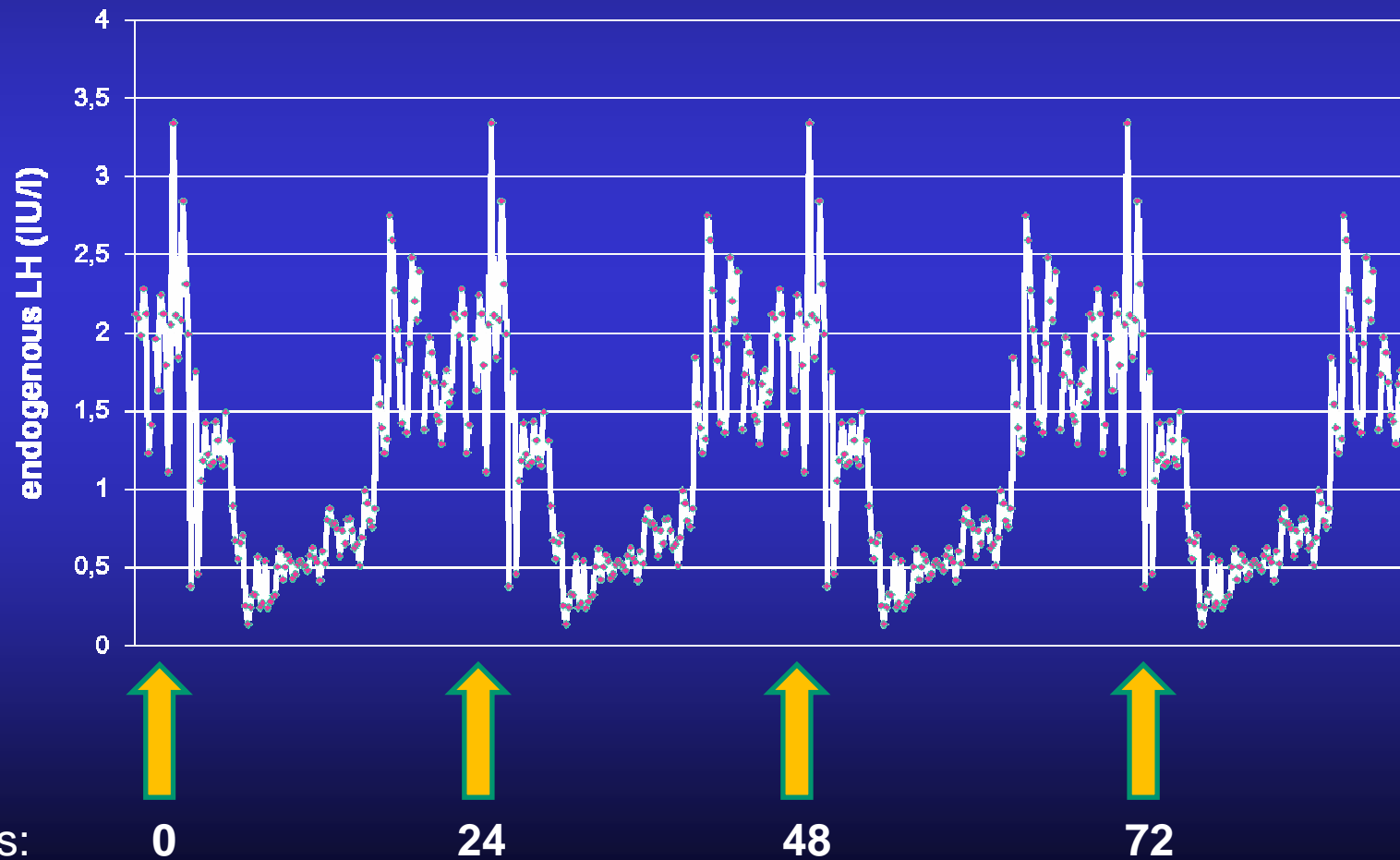
Blocage par agoniste de la GnRH

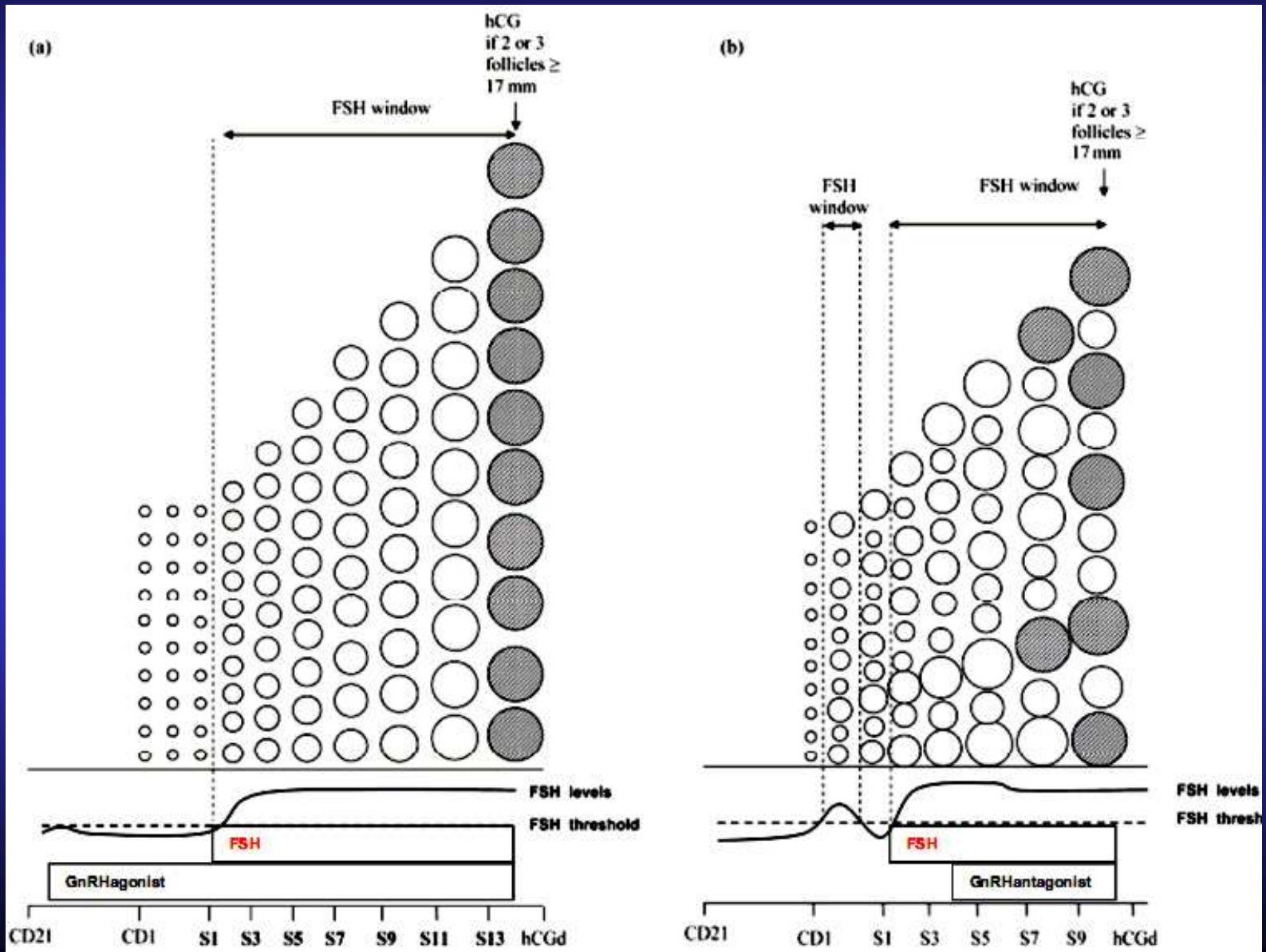


Blocage par antagoniste de la GnRH



LH pulsatility profile with GnRH antagonist





Evidence based comparison

Pharmalogical mechanisms of GnRH agonists and antagonists

Agonists

Hypophyseal Desensitization

- Initial **stimulatory** effect (flare-up)
 - then **suppression** of Gn synthesis (within days)

Long term effect

After stopping administration
Recovery period (5-7 days)

Antagonists

Competitive blockage of the receptor

- Immediate **suppressive** effect
 - Decrease of Gn secretion (within hours)

Short term effect

After stopping administration
Immediately reversible

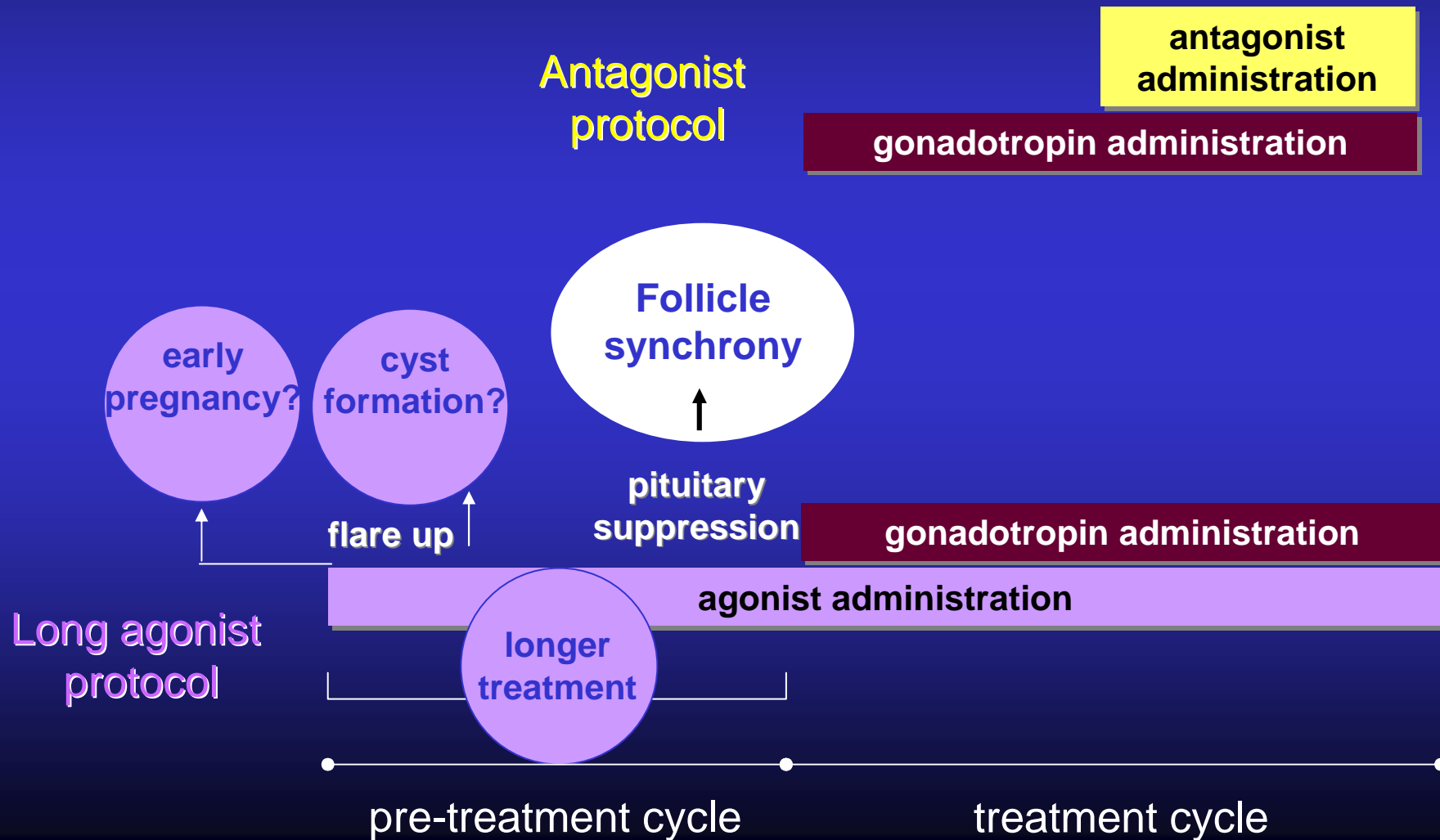
Evidence based comparison

Pharmacological characteristics and principles of action

	GnRH agonist	GnRH antagonist
Duration of action		
* <u>Short-acting formulation</u>	24 hours	24 hours
* <u>Long-acting formulation</u>	30 days	3 days
Dose response curve	Not done	0.25 mg
Start of administration	Prior or concomittantly	Mid stimulation
Protocols	Long - Short	Fixed - Flexible

Evidence based comparison

Mostly used protocols in normo-responders



Evidence based comparison

Synchronisation of the follicular cohort

	GnRH agonist	GnRH antagonist
Synchrony	Long protocol	
No Synchrony	Short protocol	Fixed & Flexible
Pre-treatment	OCP	OCP
		Estrogens
	Progestins	Progestins
		GnRH antagonist

For synchronisation: short-term agonist and antagonist protocols require steroid pre-treatment

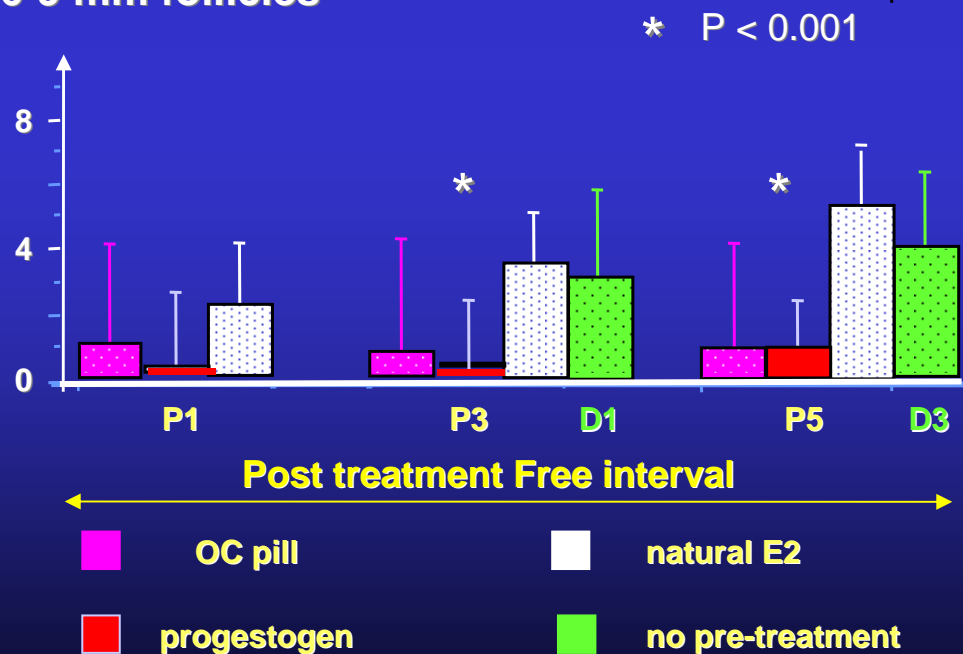
Evidence based comparison

Impact of pre-treatment to homogenise the follicular cohort

Cedrin-Durnerin et al., 2007

OCP and Progestogens effective

6-9 mm follicles



Meta-analysis
Griesinger et al., 2007

Four RCT

Nb of retrieved oocytes

Increased : + 1.63
p = 0.11

Pregnancy rate:
Similar

No evidence that steroid pre-treatment actually improves cycle outcome

Evidence based comparison

Gonadotrophin administration

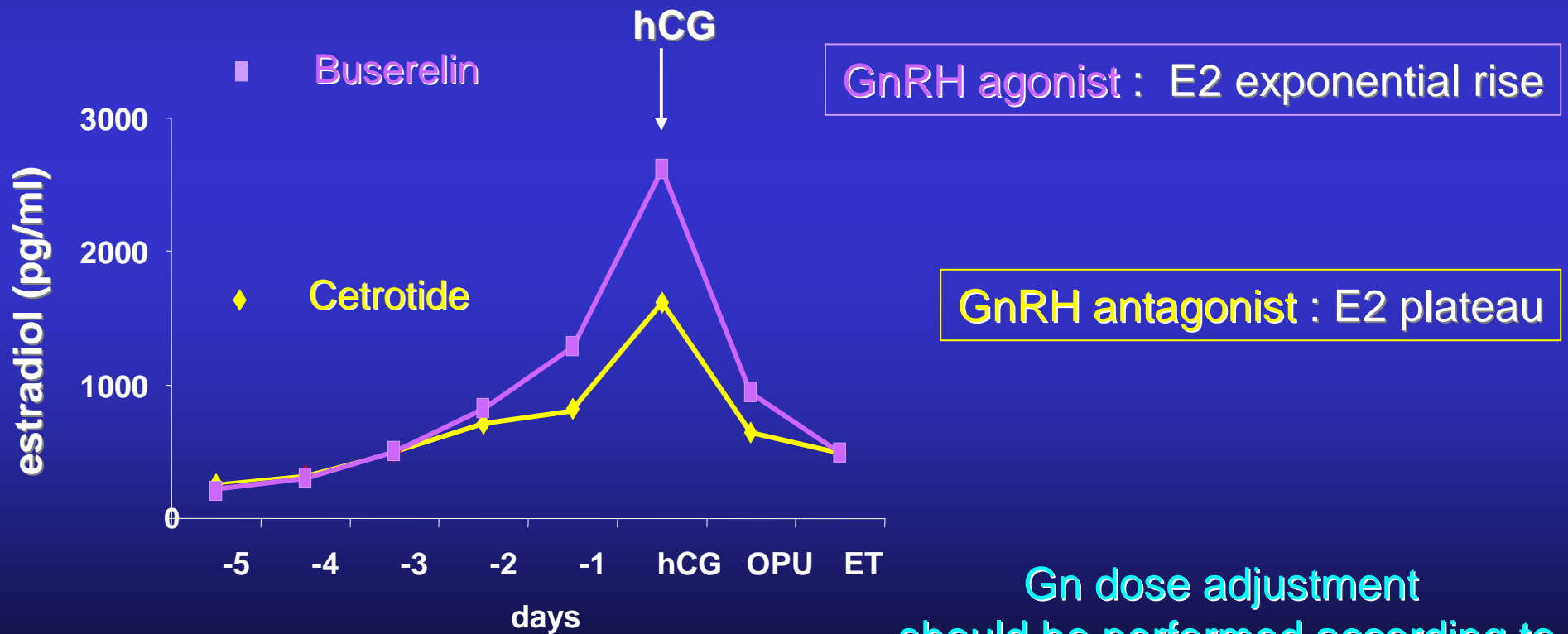
* Kolibianakis et al, 2006 : Meta-analysis of 22 RCT

	GnRH agonist	GnRH antagonist	
Starting dose	150 IU	150 IU	
Type	NS	NA	
Duration		Shorter -1.13 d (-1.83 ; -0.44)	P < 0.05
Total dose		Reduced -3.04 amp (- 6.27 ; + 0.19)	NS

Antagonist protocol : a friendly approach

Evidence based comparison

Estradiol pattern in GnRH agonist and antagonist protocols

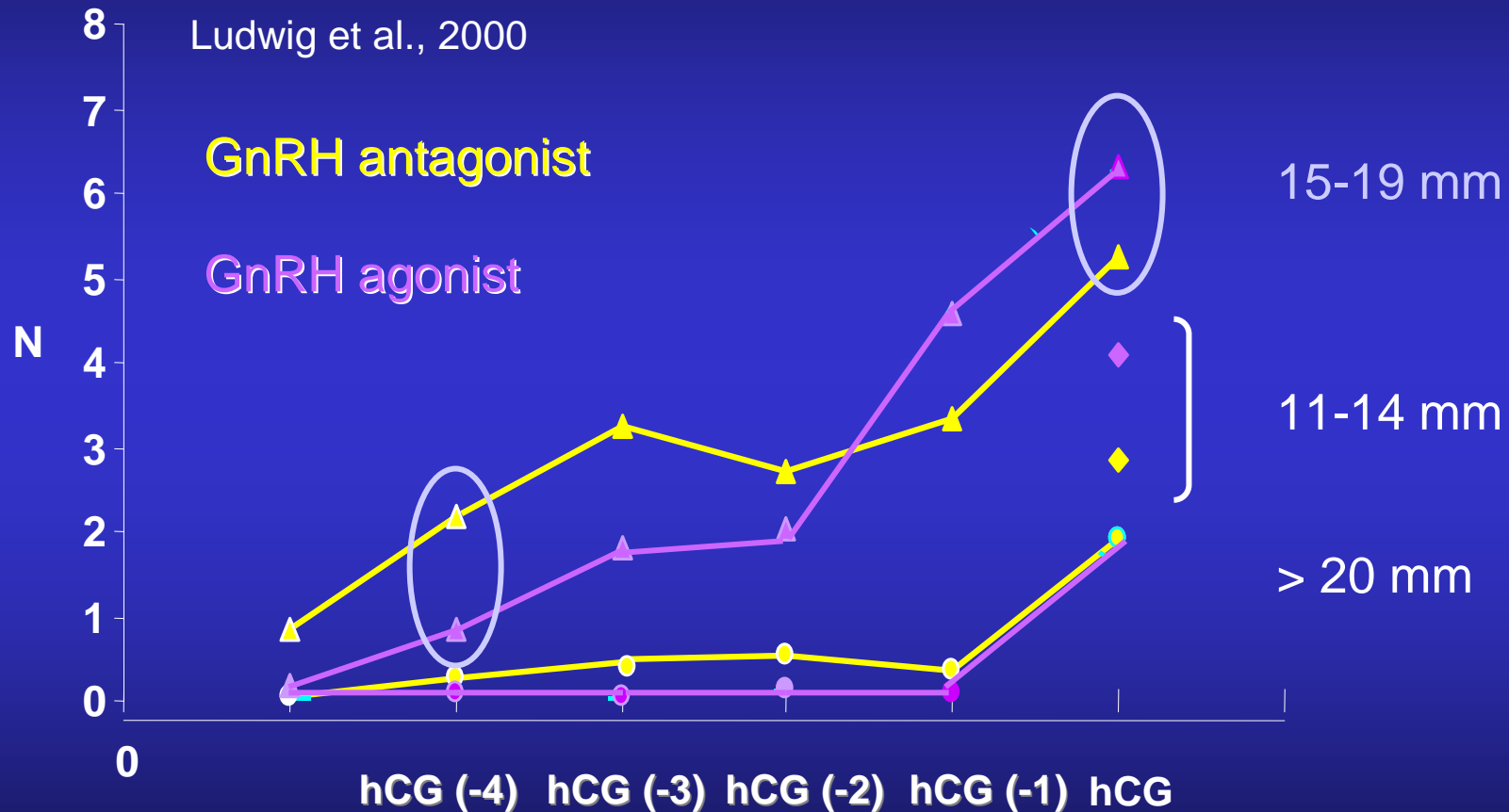


Ludwig et al., 2000

Gn dose adjustment should be performed according to the type of GnRH analog used

Evidence based comparison

Follicular growth in GnRH agonist and antagonist protocols



GnRH antagonist
faster initial follicular growth

GnRH agonist
higher number of 11 - 19 mm follicles

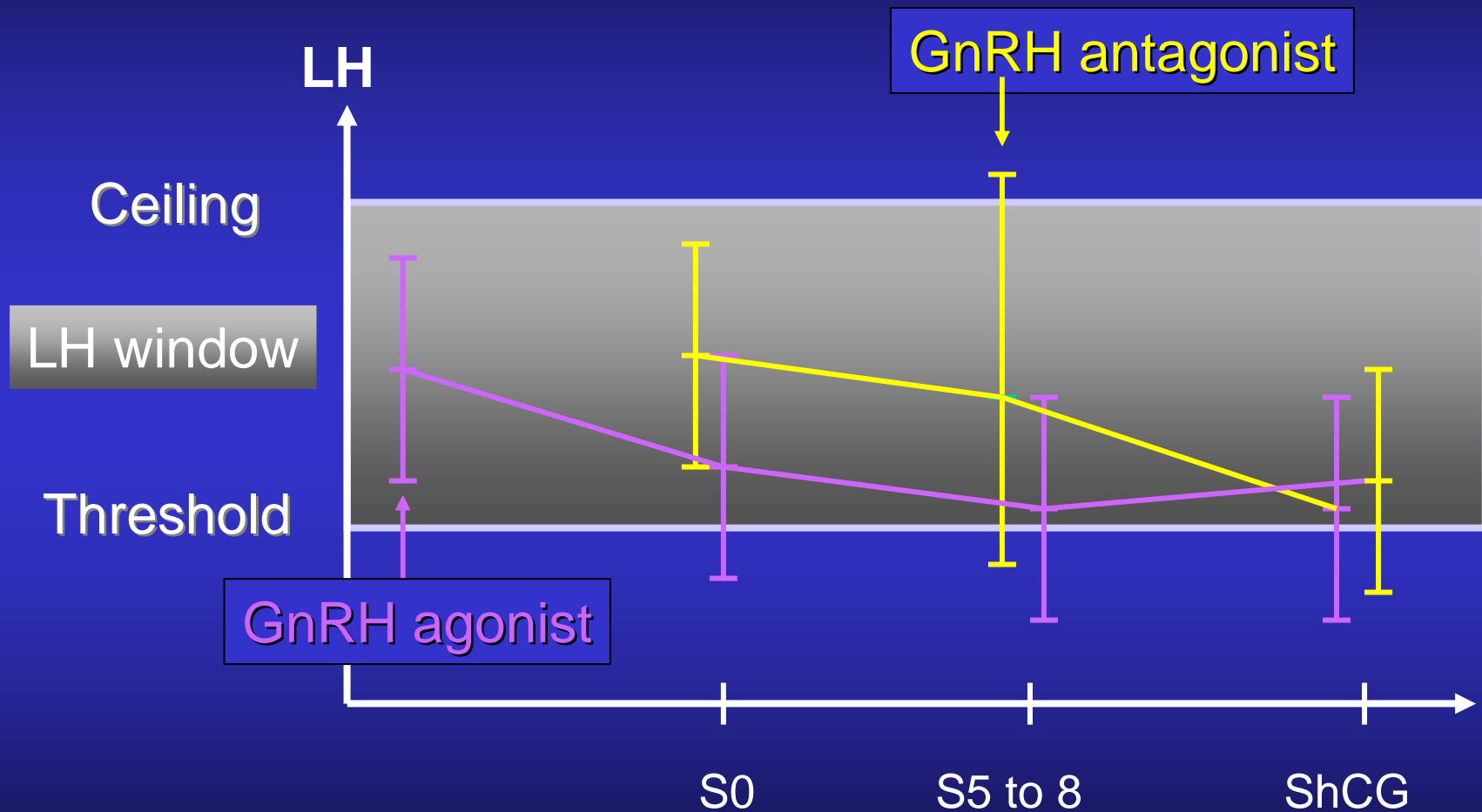
Evidence based comparison

E2 - follicular growth patterns

	GnRH agonist	GnRH antagonist
FSH S1 – S6	low	high
E2 production	exponential	Early rise & plateau
Follicular growth	homogenous	heterogenous
Correlation E2 - Follicle	good	weak

Serum FSH, E2 patterns and correlation E2 - follicular growth are not similar

Evidence based comparison



The risk of serum LH values below the LH threshold is much higher with the use of GnRH agonist

Evidence based comparison

Predictive value of serum LH during stimulation

GnRH agonist

Negative impact (50% patients)

- Fleming 96,98, 00 0.7
- Westergaard 00,01 0.5
- Esposito 2001 3
- Humaidan 2002 0.5
- Tesarik 2002 1

No negative impact (10% patients)

- Loumaye 1997 0.5
- Balasch 2001 0.5-1
- Penarrubia 2003 ROC
- Cabrera 2005 ROC

No definite LH threshold

GnRH antagonist

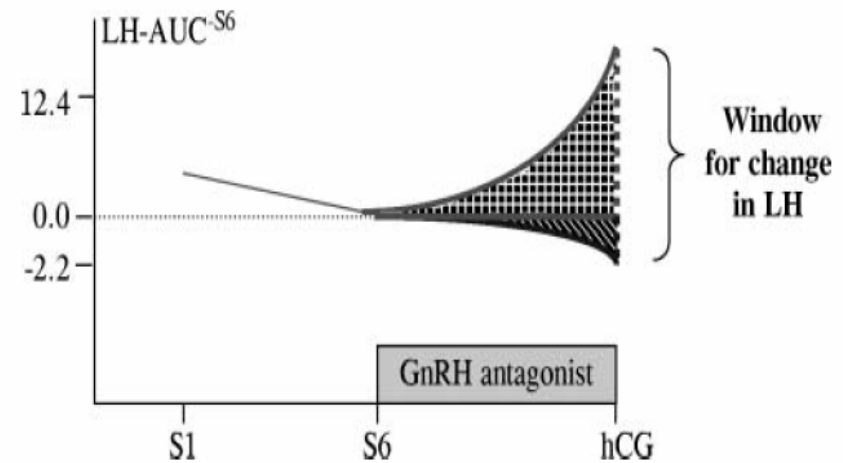


Figure 6. The interpretation of change in LH levels (LH-AUC^{S6}) in relation to clinical pregnancy. S1 = stimulation day 1; S6 = stimulation day 6.

Huirne et al. 2005

Optimal LH window (AUC)

quite large with the use of antagonist

Evidence based comparison

Should we add LH in analog cycles ?



No evidence for any benefit of LH addition

Evidence based comparison

Ovarian parameters

Kolibianakis et al. 2006

With GnRH agonists

- COC : 1.2 more
- Cryopreserved embryos : 0.23 more

With GnRH antagonists

OHSS : 2 times (RR : 0.47) less

GnRH antagonist protocol : a less aggressive approach

Evidence based comparison

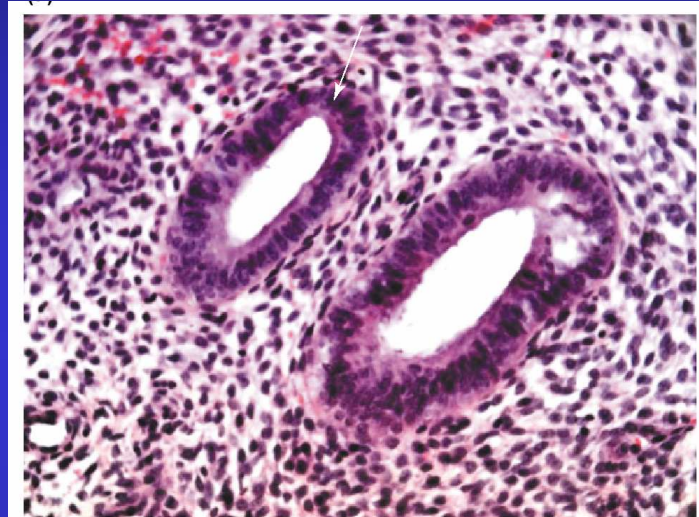
Effects of ovarian stimulation on endometrium

Endometrial biopsy (Noyes criteria)

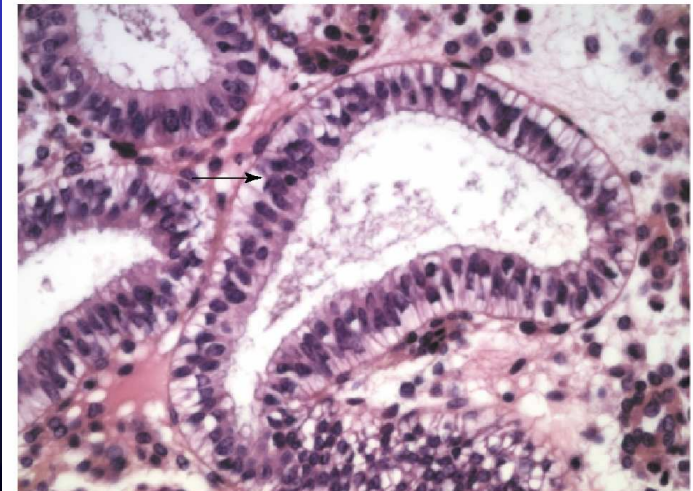
at oocyte pick - up

Kolibianakis et al. 2002

- Endometrial advancement in all stimulated cycles
- No pregnancy when endometrial advancement > 3 days



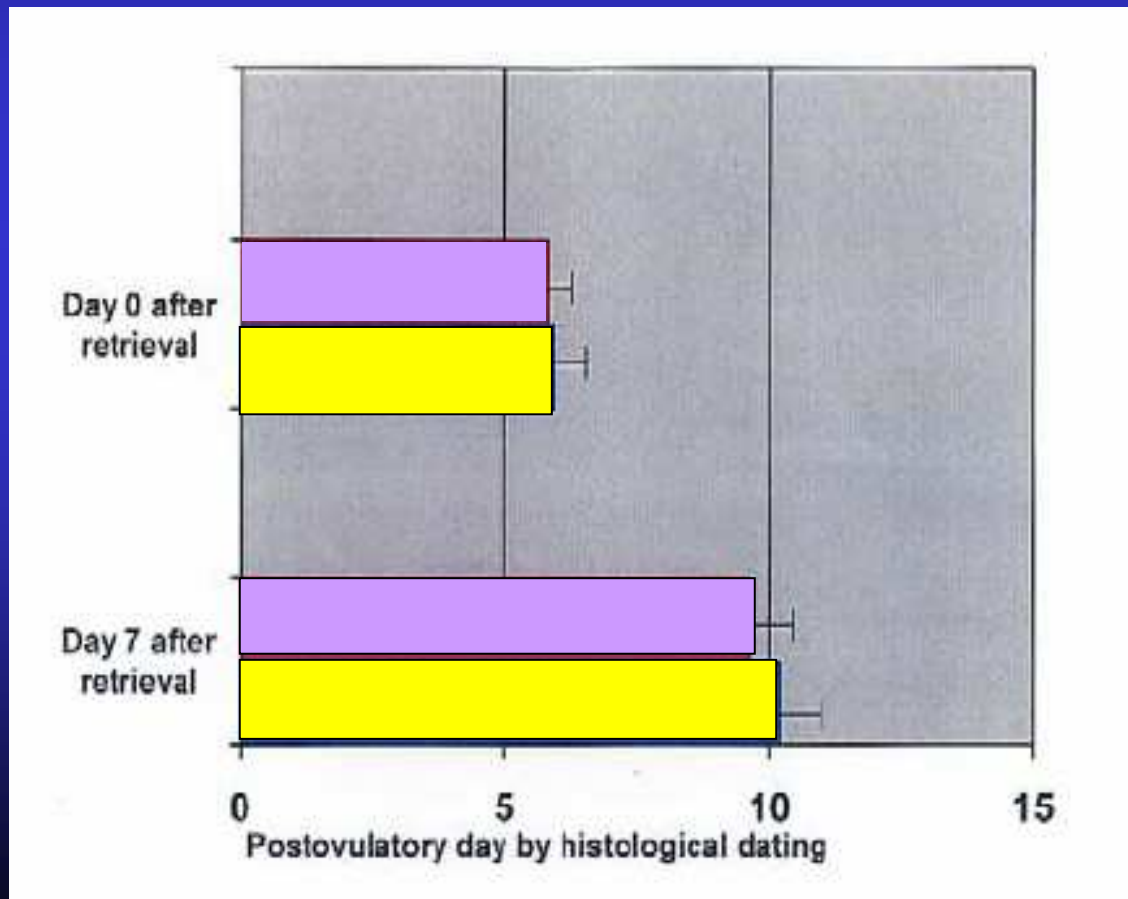
(b)



Evidence based comparison

Endometrial histo-morphology

■ Agonist (5) ■ Antagonist (10)



Oocyte donors

Saadat et al. 2004

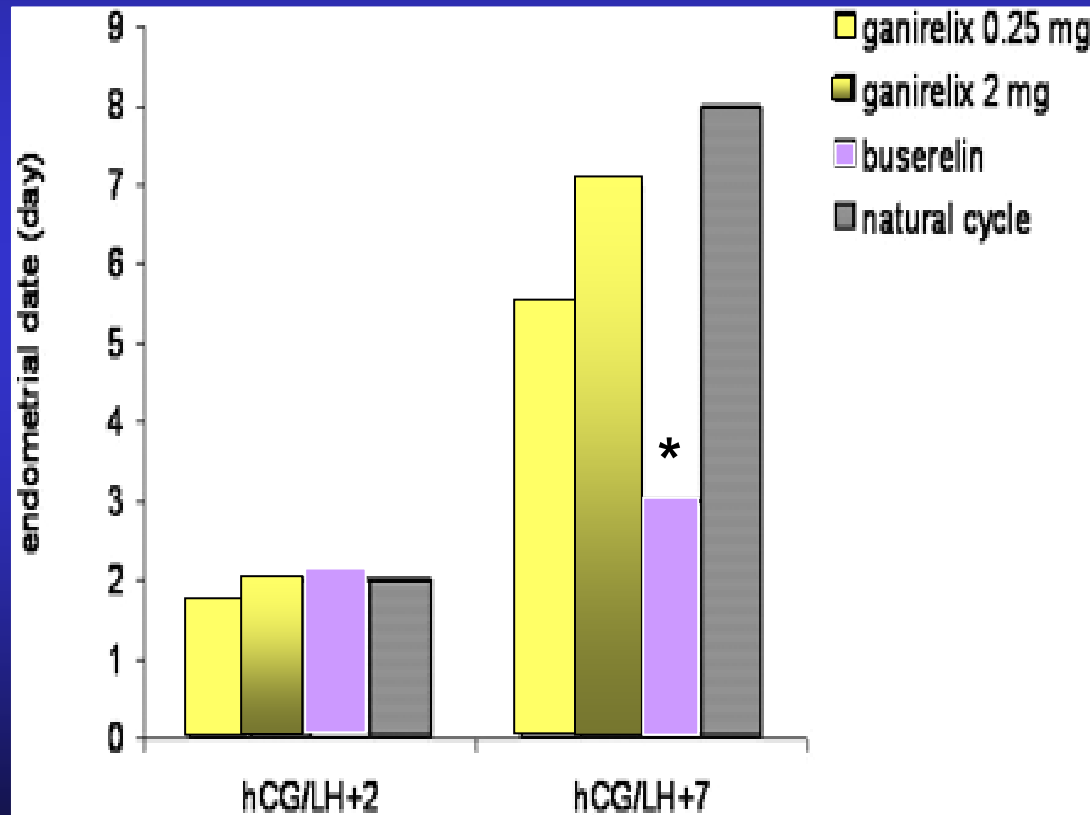
Similar advancement in
endometrial dating
at day 0 and 7

Similar endometrial aspects
between GnRH analogs

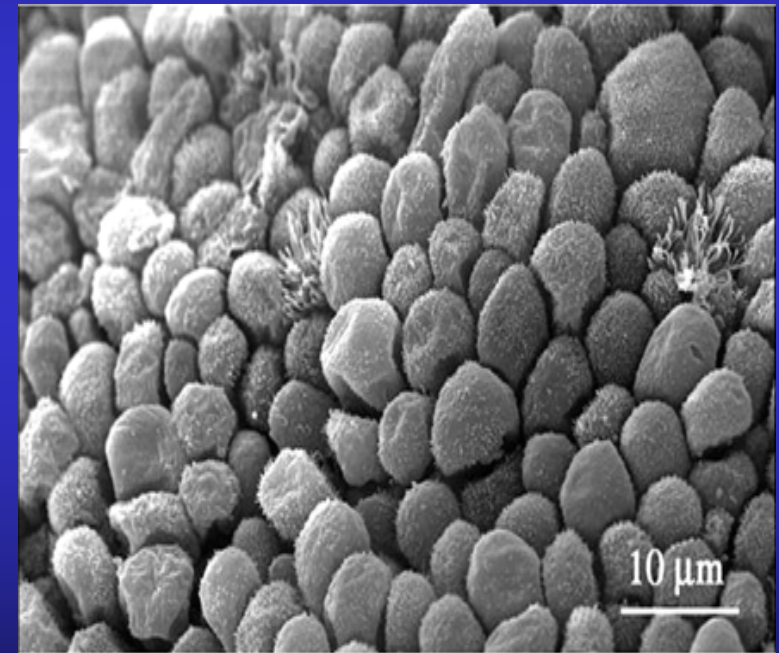
Evidence based comparison

Endometrial development in luteal phase

Simon et al. 2005



Oocyte donors



Pinopode expression

In GnRH antagonist cycles, endometrial biopsy is close to natural cycle

Evidence based comparison

Luteal support

Absolutely required for both
GnRH agonists and antagonist protocols

(Becker et al., 2003)

- Progesterone (IM or vaginal)
 - HCG optional
- Estrogen supplementation : not effective

Cycle outcome

Pregnancy rate

Arch Gynecol Obstet (2001) 265:175–182

© Springer-Verlag 2001

ORIGINAL ARTICLE

M. Ludwig · A. Katalinic · K. Diedrich

**Use of GnRH antagonists in ovarian stimulation for assisted reproductive technologies compared to the long protocol
Meta-analysis**

No difference
in **PR**

Human Reproduction, Vol. 17, No. 4, 874-885, April 2002

© 2002 [European Society of Human Reproduction and Embryology](#)

COCHRANE REVIEWS

**GnRH antagonist in assisted reproduction:
a Cochrane review**

Hesham **Al-Inany**¹ and Mohamed Aboulghar

5% lower PR with
antagonists

7th International Symposium on GnRH Analogues in Cancer and Human Reproduction

Abstracts

**A COMPARISON OF CLINICAL PREGNANCY RATES IN THE EFFICACY
EVALUATION OF GnRH AGONIST VERSUS ANTAGONIST USE FOR ASSISTED
REPRODUCTION – A META-ANALYSIS USING AN INTENTION-TO-TREAT
APPROACH**

S. Daya

McMaster University, Hamilton, Ontario, Canada

No difference
in **PR**

Cycle outcome

Live birth rate

Gonadotrophin-releasing hormone antagonists for assisted conception (Review)

Al-Inany HG, Abou-Setta AM, Aboulghar M

This record should be cited as:

Al-Inany HG, Abou-Setta AM, Aboulghar M. Gonadotrophin-releasing hormone antagonists for assisted conception. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No.: CD001750. DOI: 10.1002/14651858.CD001750.pub2.

This version first published online: 19 July 2006 in Issue 3, 2006.

Date of most recent substantive amendment: 19 May 2006

3.7% lower
ongoing/live birth
rate with
antagonists

Human Reproduction Update, Vol.12, No.6 pp. 651–671, 2006
Advance Access publication August 18, 2006

doi:10.1093/humupd/dml038

Among patients treated for IVF with gonadotrophins and GnRH analogues, is the probability of live birth dependent on the type of analogue used? A systematic review and meta-analysis

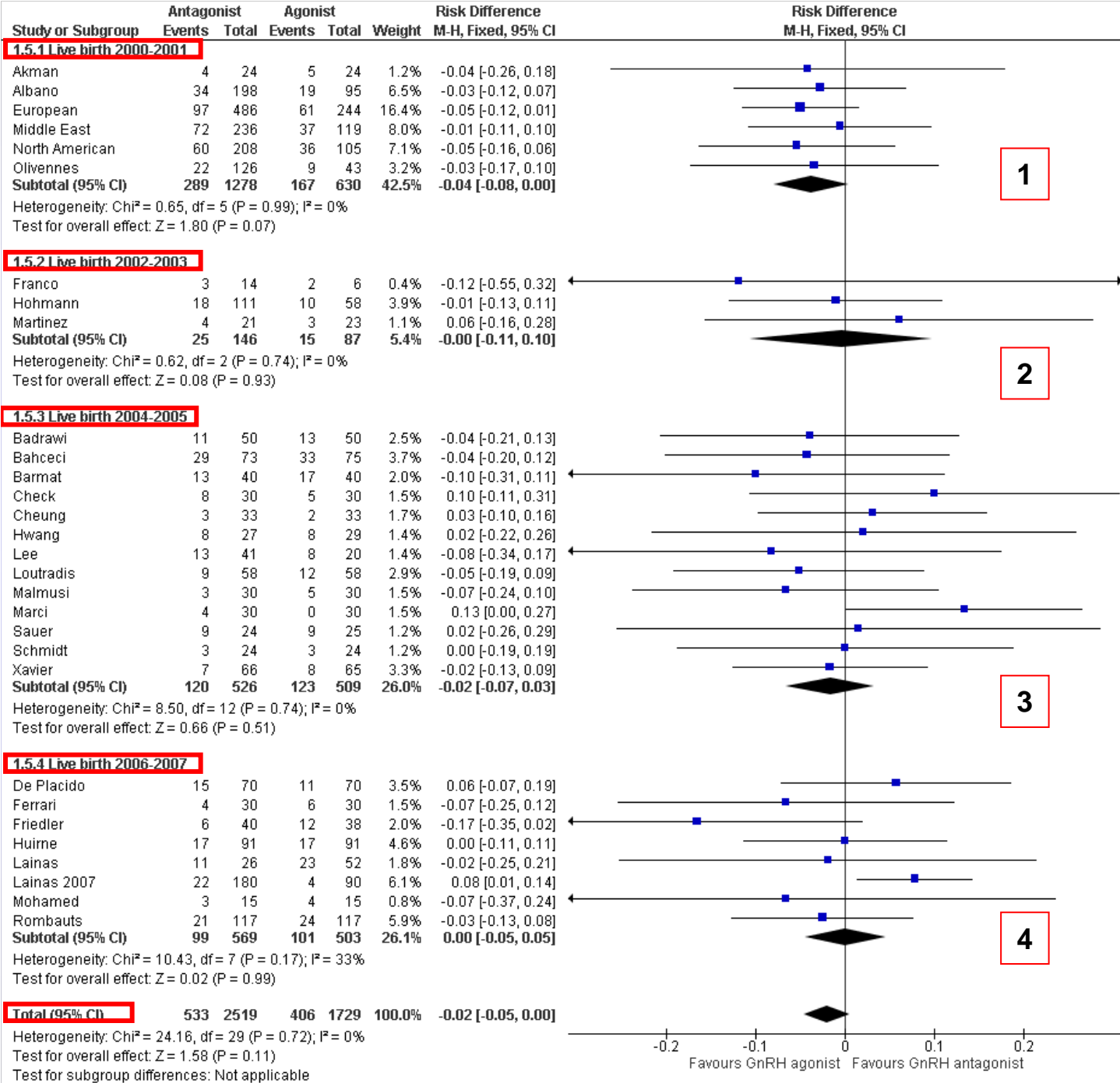
No difference in
live birth rate

E.M.Kolibianakis^{1,5}, J.Collins², B.C.Tarlatzis¹, P.Devroey³, K.Diedrich⁴ and G.Griesinger⁴

Learning curve

Live birth rate depending on year of publication

Kolibianakis and Griesinger unpublished



GnRH antagonists in ovarian stimulation: a treatment regimen of clinicians' second choice? Data from the German national IVF registry

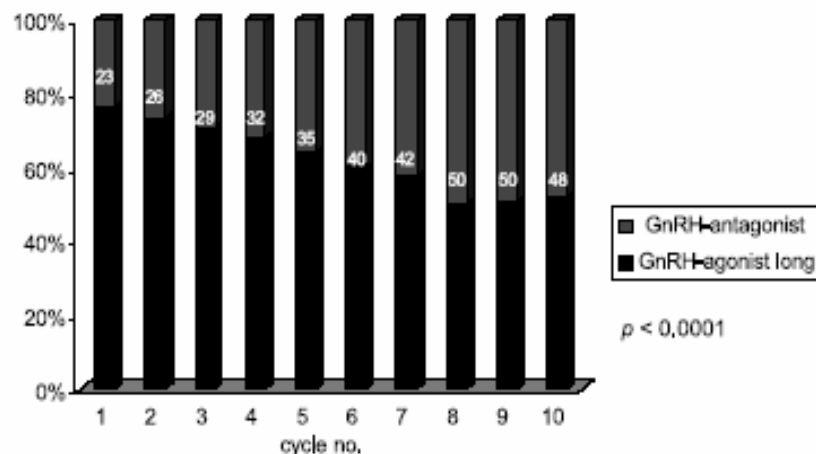
Georg Griesinger^{1,3}, Ricardo Felberbaum² and Klaus Diedrich¹

Table I. Proportion of patients in different age categories being treated in either GnRH agonist long or GnRH antagonist protocols from 2000 to 2003 (χ^2 -test for linear trend)

Age categories (years)	GnRH agonist (%)	GnRH antagonist (%)	<i>P</i>
18–30	28.5	25.4	<0.0001
31–35	41.1	36.6	
36–40	26.3	30.1	
41–55	3.8	7.9	

GnRH ant protocol used more in older patients and following initial treatment failure

BUT: in young patients with tubal infertility



women with tubal infertility, first treatment cycles, and age < 35 years, where the pregnancy rate was 37.83 and 36.07% for the GnRH agonist long protocol and GnRH antagonist protocol respectively.

Evidence based comparison

Live birth rate

In 2008

is quite similar between patients treated with either a GnRH antagonist or a GnRH agonist protocol.

Reasons

- More thorough understanding of how COH can be refined
 - Higher experience of clinical teams
- Use as a first line therapy in « standard » patients

Evidence based comparison

Advantages of GnRH antagonist over agonist protocols

- Easier prevention of premature LH increase
- Lower requirement for exogenous gonadotrophins
 - Shorter duration of ovarian stimulation
 - Less patient discomfort

« Friendly approach »

Disadvantages of GnRH antagonist over agonist protocols

- Novel approach. Room for optimization
- Less flexibility ? Interest of pre-treatment still in progress
 - Minor reduction in pregnancy rate : still true ?

Indications of GnRH antagonist protocol

In « standard » patients

In patients at risk of hyper - response

OCP
programmation

5 Days

Menses



FSH Low dose

FSH

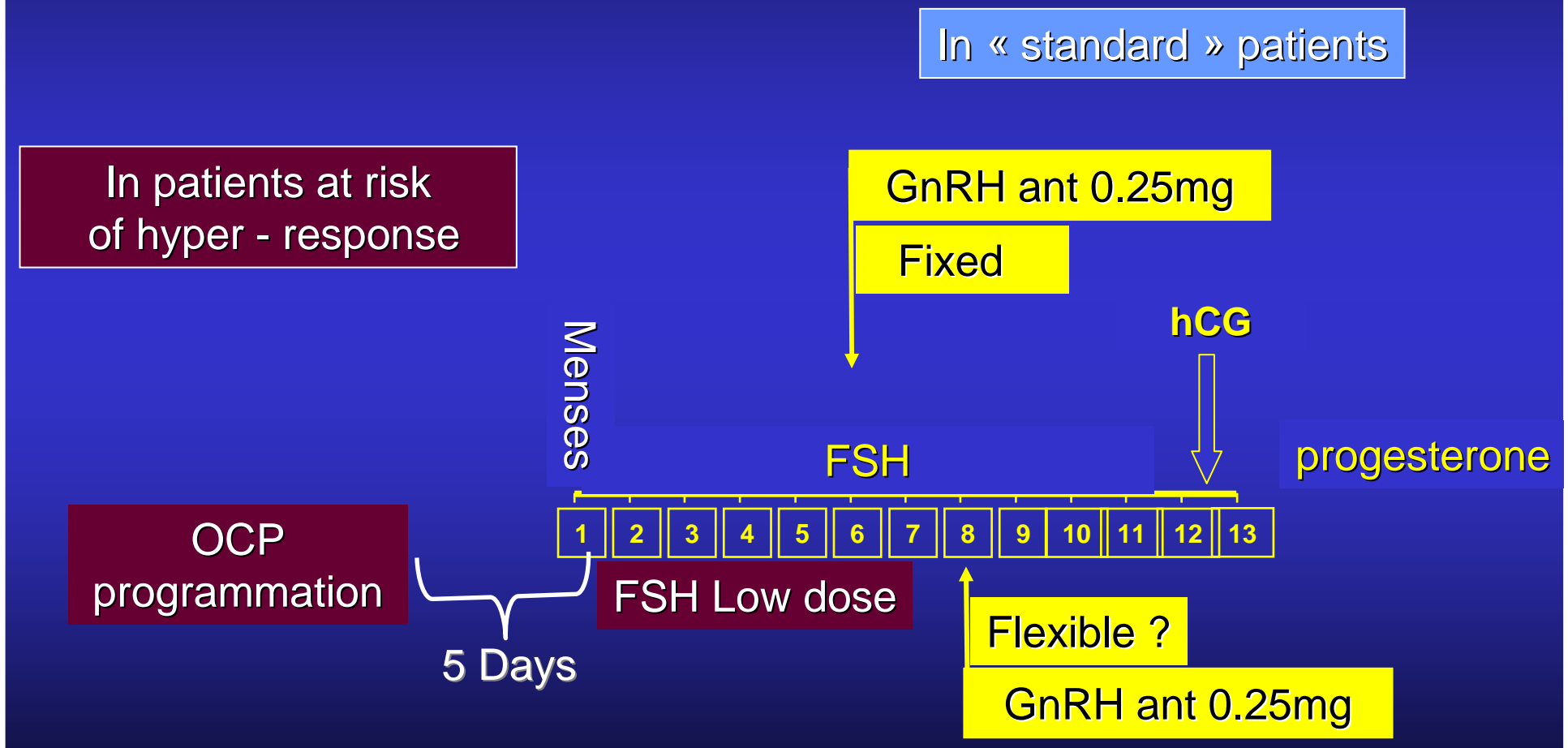
GnRH ant 0.25mg
Fixed

hCG

progesterone

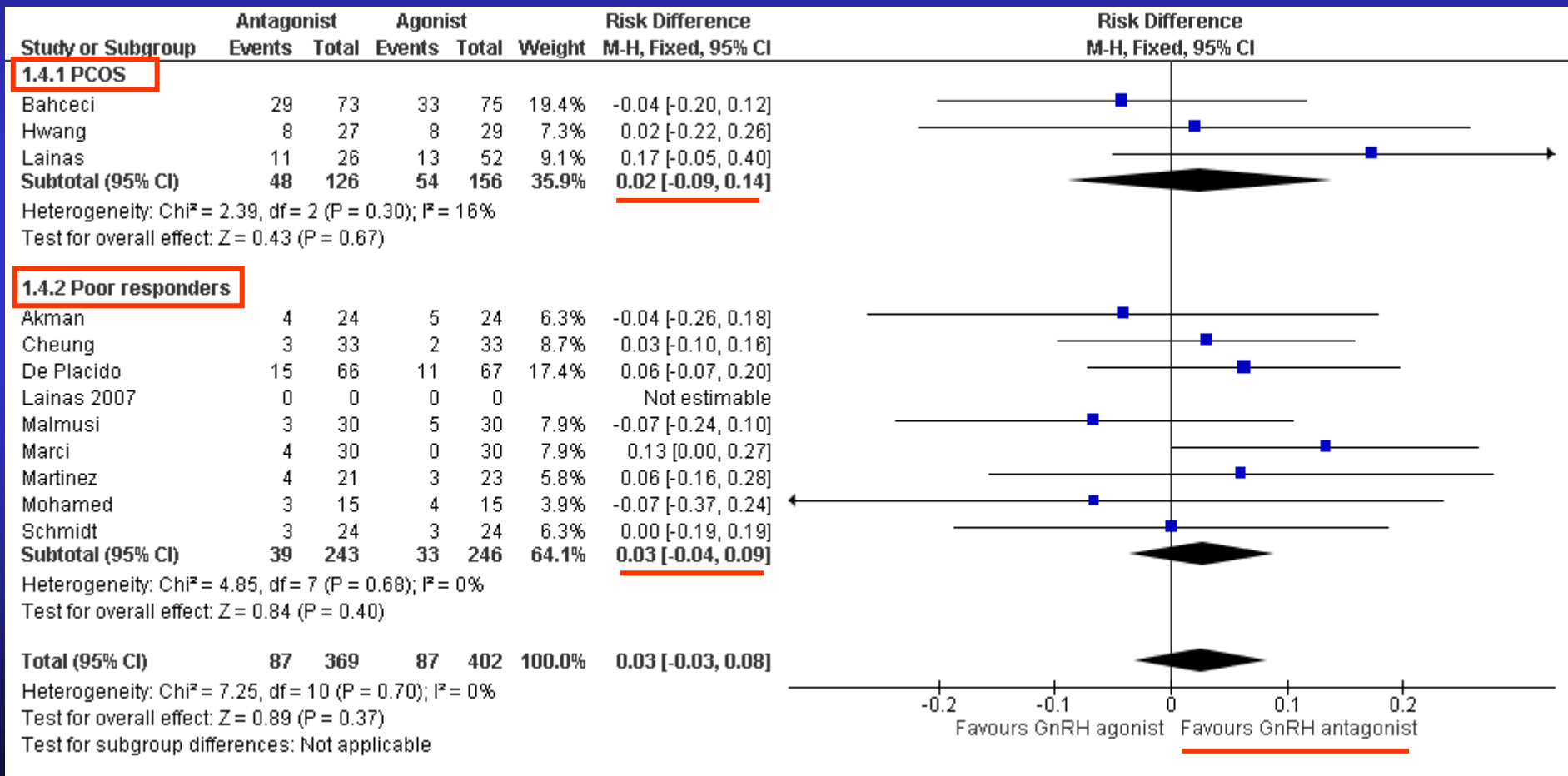
Flexible ?

GnRH ant 0.25mg



Live birth in PCOS patients and poor responders

Kolibianakis and Griesinger unpublished

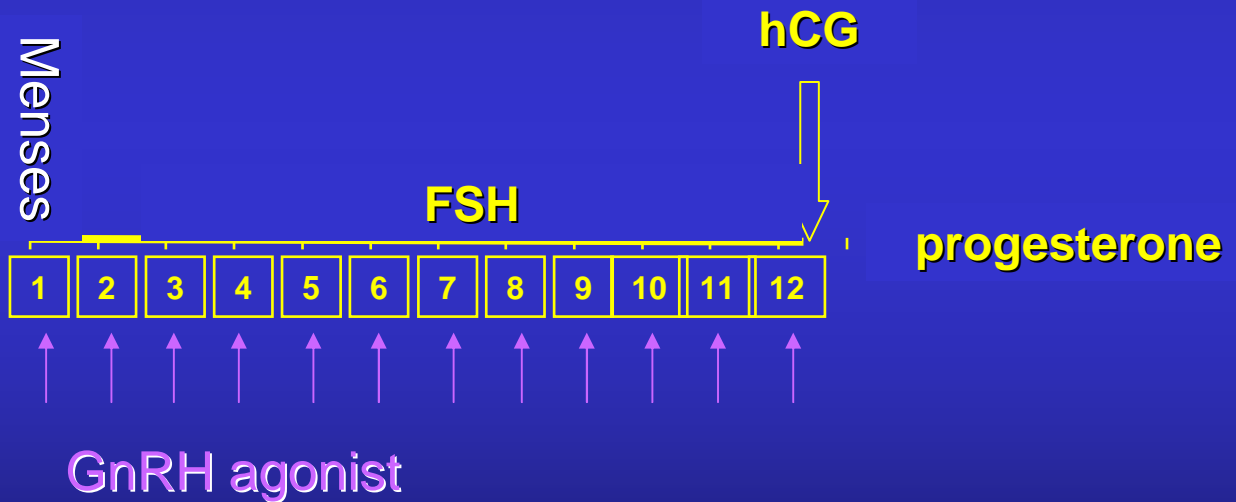


Protocols for poor responders

2 options

Micro - dose flare - up protocol

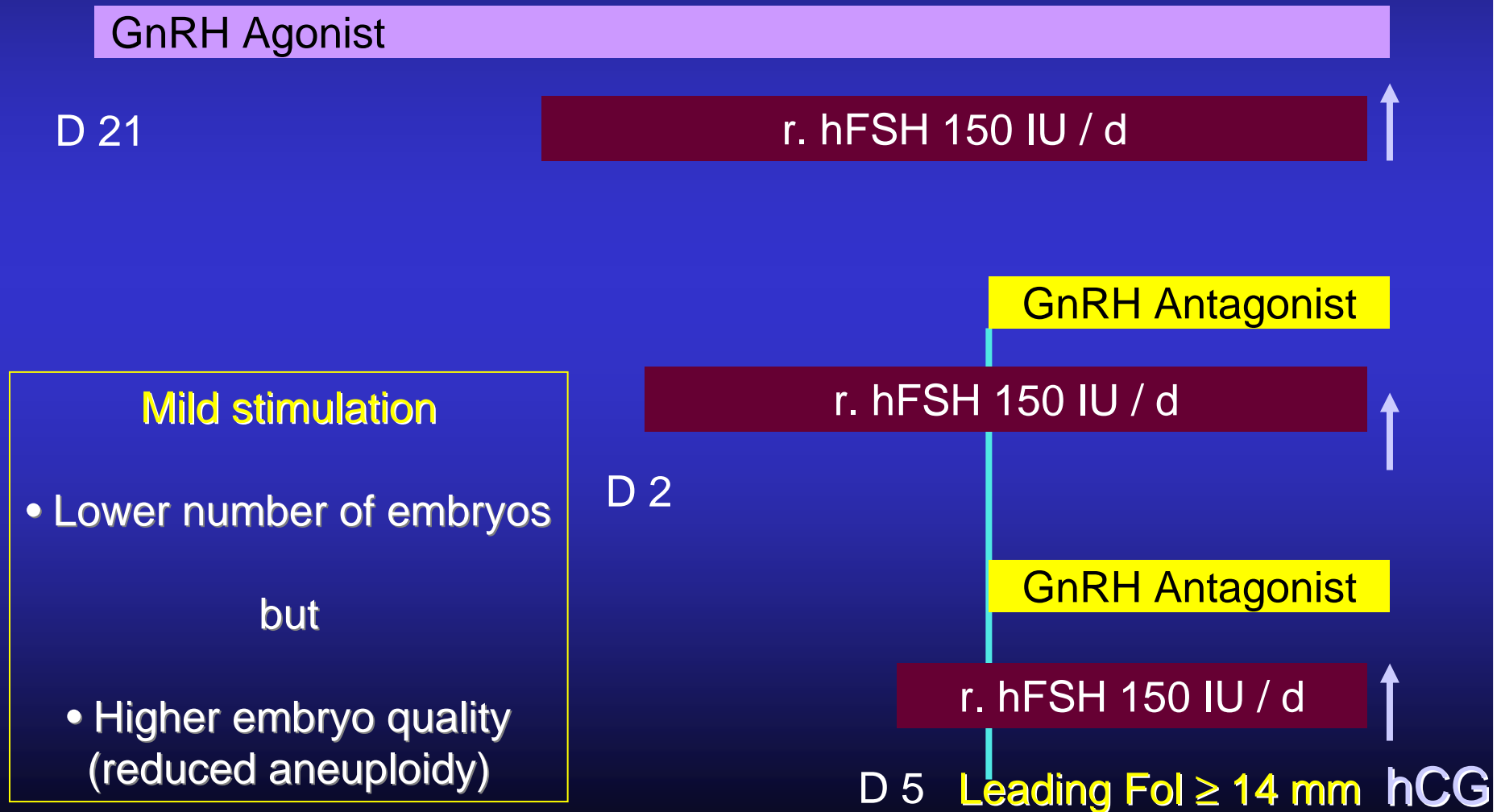
OCP



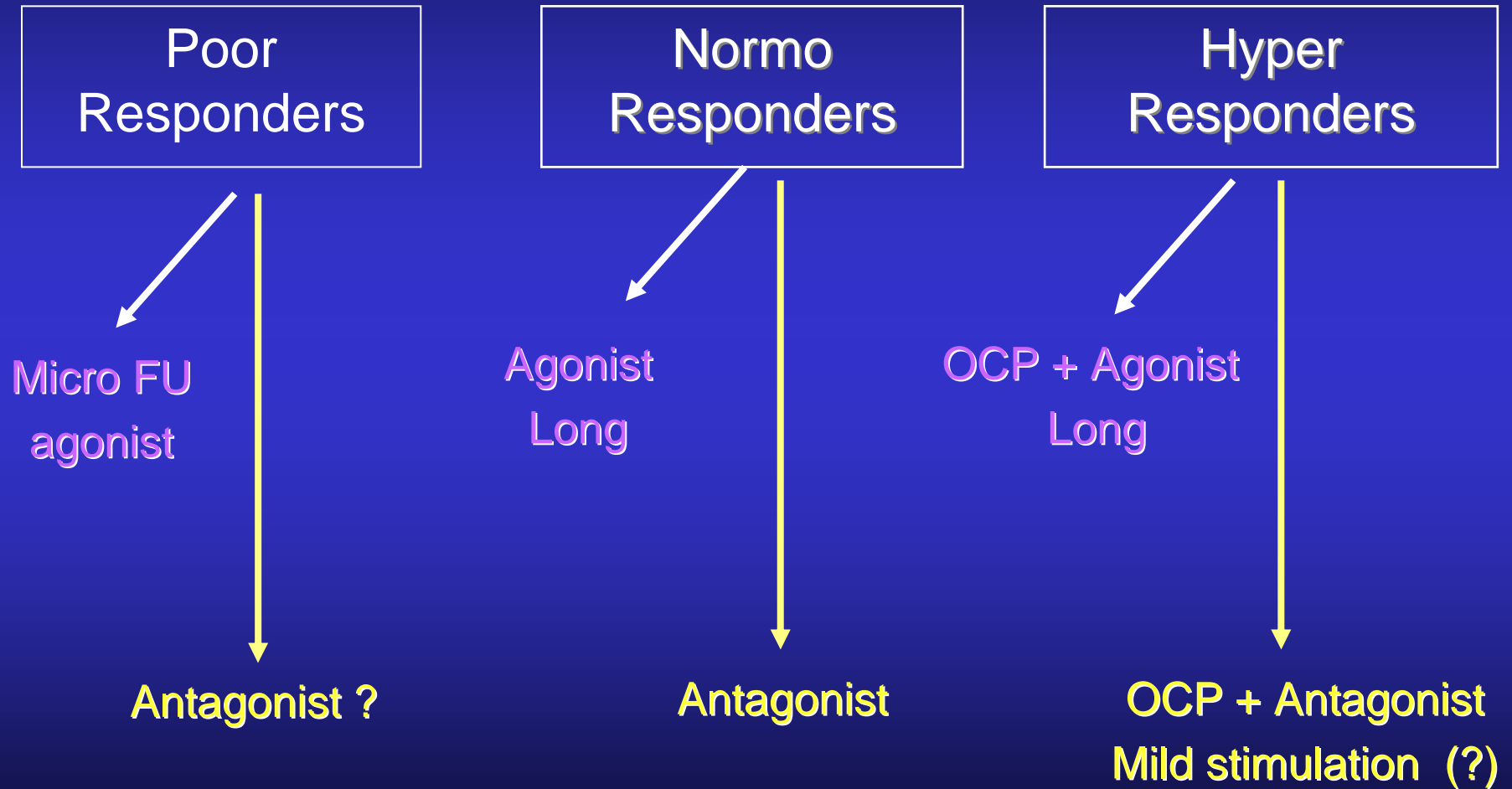
Or GnRH antagonist protocol

Mild Stimulation Protocol

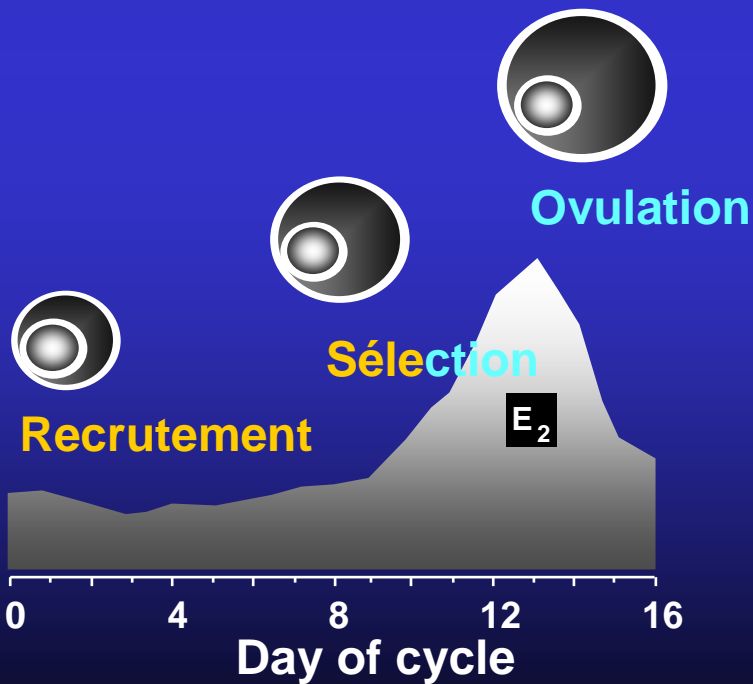
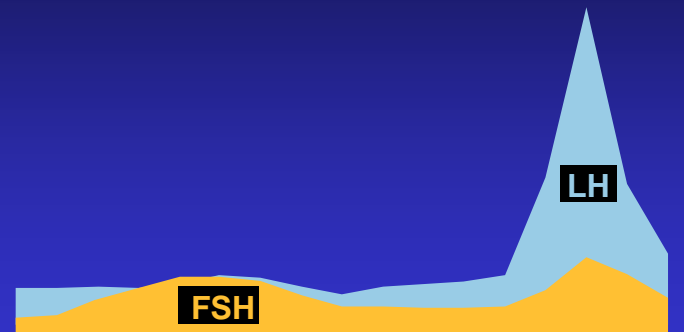
Hohmann et al., 2003 - Baart et al., 2005



Strategy for IVF - ICSI procedure

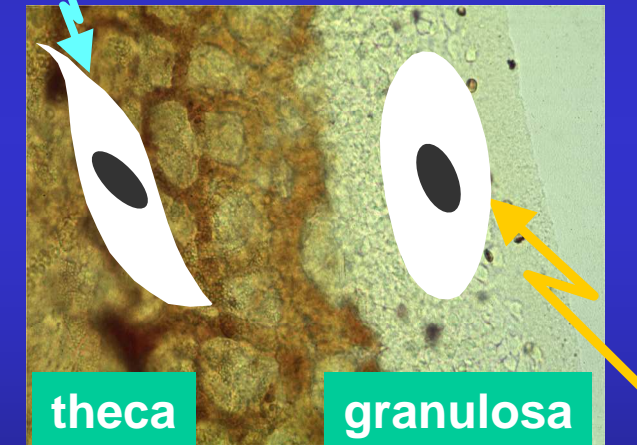


Gonadotrophines et folliculogénèse



Phase folliculaire précoce

Effet « constitutif »
dès le stade pré-antral

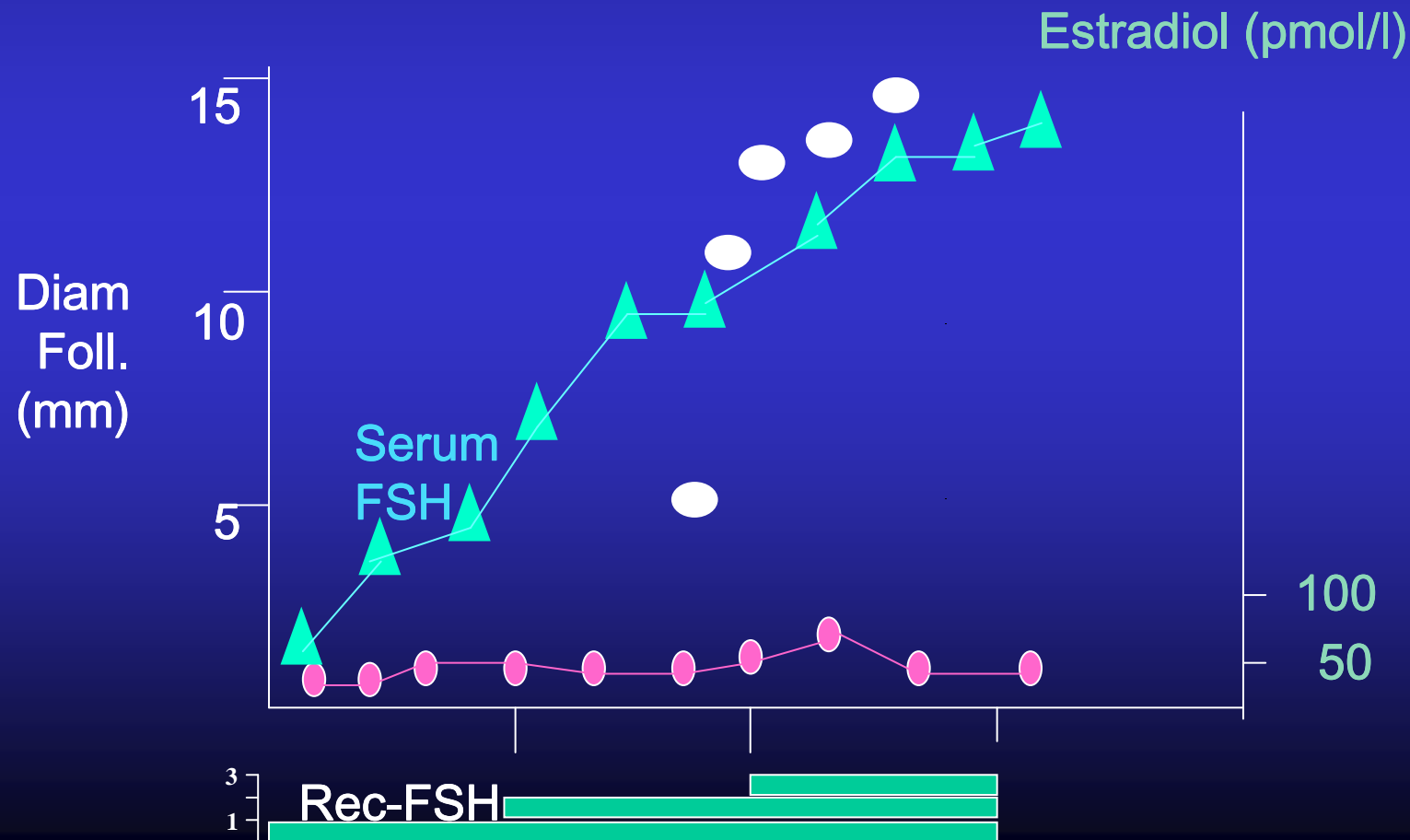


FSH

Théorie bi-cellulaire

Modèle: Hypogonadisme Hypogonadotrope

1. La LH est indispensable à la production d'oestradiol



European LH Study (1998)

Hypogonadisme hypogonadotrope (rFSH 150 IU/d ± r.hLH)

rLH Treatment	Cycles in patients wishing to conceive	Cycles in patients wishing to conceive and who received hCG	Number of clinical pregnancies	Clinical pregnancy rate per initiated cycle (%)	Clinical pregnancy rate per cycle with hCG (%)
0 IU	8	2 (25%)	0	0/8 (0%)	0/2 (0%)
25 IU	10	5 (50%)	0	0/10 (0%)	0/5 (0%)
0 + 25 IU	-	-	0	0/18 (0%)	0/7 (0%)
75 IU	12	7 (58%)	2	2/12 (17%)	2/7 (29%)
225 IU	9	5 (56%)	1	1/9 (11%)	1/5 (20%)
75 + 225 IU	-	-	3	3/21 (14%)	3/12(25%)

75 IU r. LH : dose minimale efficace

Modèle : Hypogonadisme Hypogonadotrope

2. LH : effet synergique avec FSH sur la folliculogénèse

TABLE 1. Ovarian response in the FSH and LH-FSH treatment cycles in eight patients studied

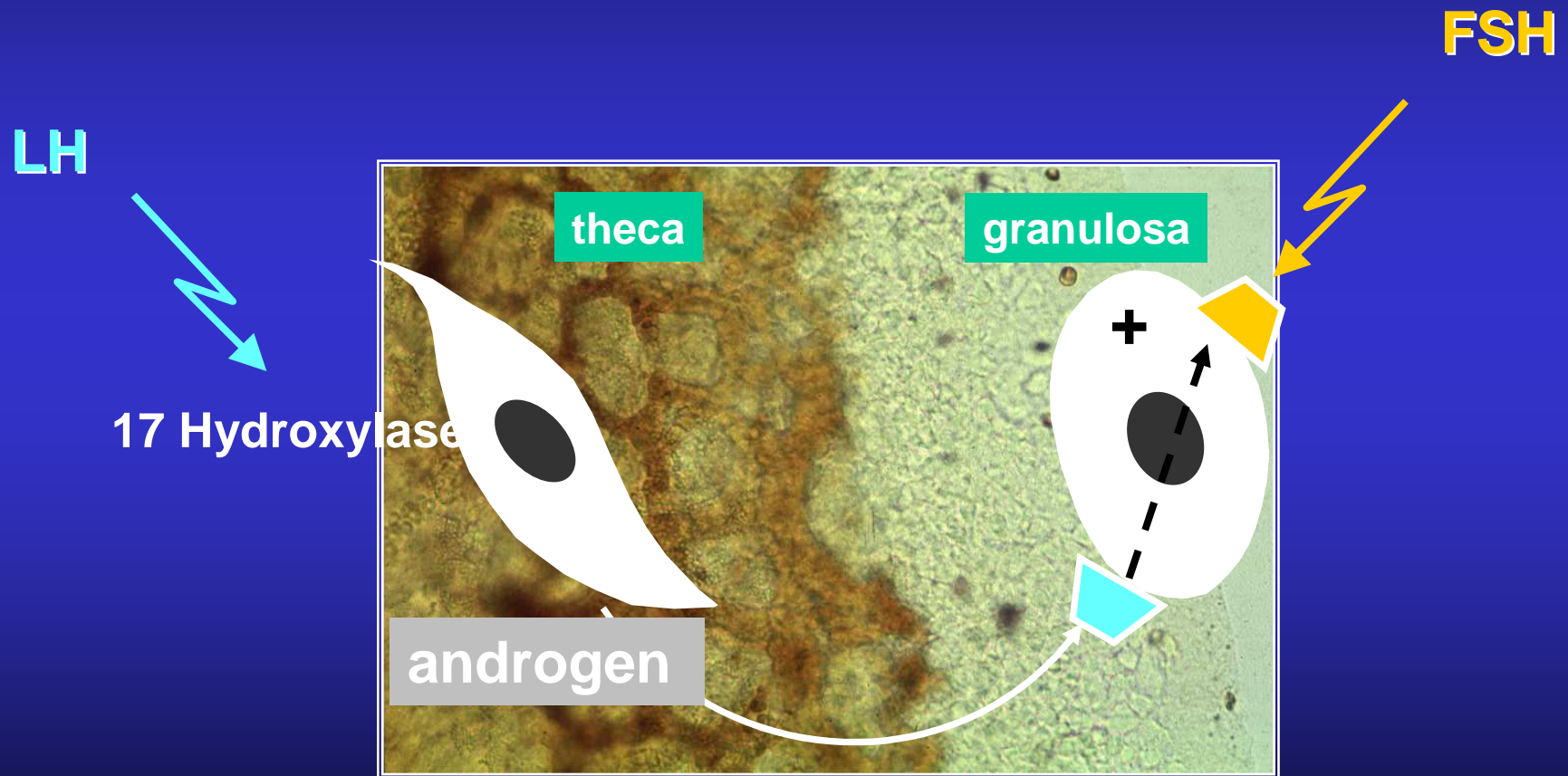
Parameter	FSH	LH-FSH	P
No. of treatment cycles	8	8	NS
Cancelled cycles (no response)	2	1	NS
Responsive cycles	6	7	NS
FSH required ^a			
Days of treatment	18 ± 2.59	18.2 ± 2.1	NS
IU	3175 ± 591	2250 ± 151	NS
Daily effective dose (IU)	225 ± 0.7	171.4 ± 21.4	0.03
Day of last assessment ^a			
No. of follicles 10 to <14 mm	2 ± 1.2	2 ± 0.7	NS
No. of follicles 14 to <17 mm	2.1 ± 1.3	1 ± 0.3	NS
No. of follicles >17 mm	1.6 ± 0.2	1.4 ± 0.3	NS
Serum estradiol (pg/ml)	80.3 ± 12.7	218.3 ± 37.9	0.02
Endometrial thickness (mm)	5.9 ± 0.5	8.0 ± 0.4	0.02

Effet « priming »

R. hLH : 300 IU pd 7 J
avant stimulation /
FSH

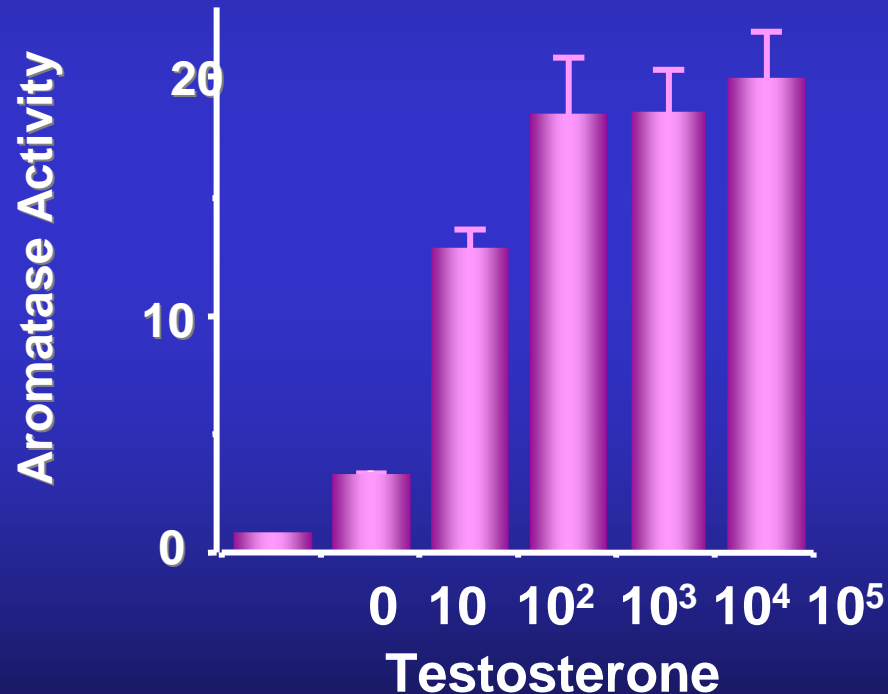
Diminution de la dose
efficace de FSH

Effets de la LH sur la granulosa : médiation par les androgènes

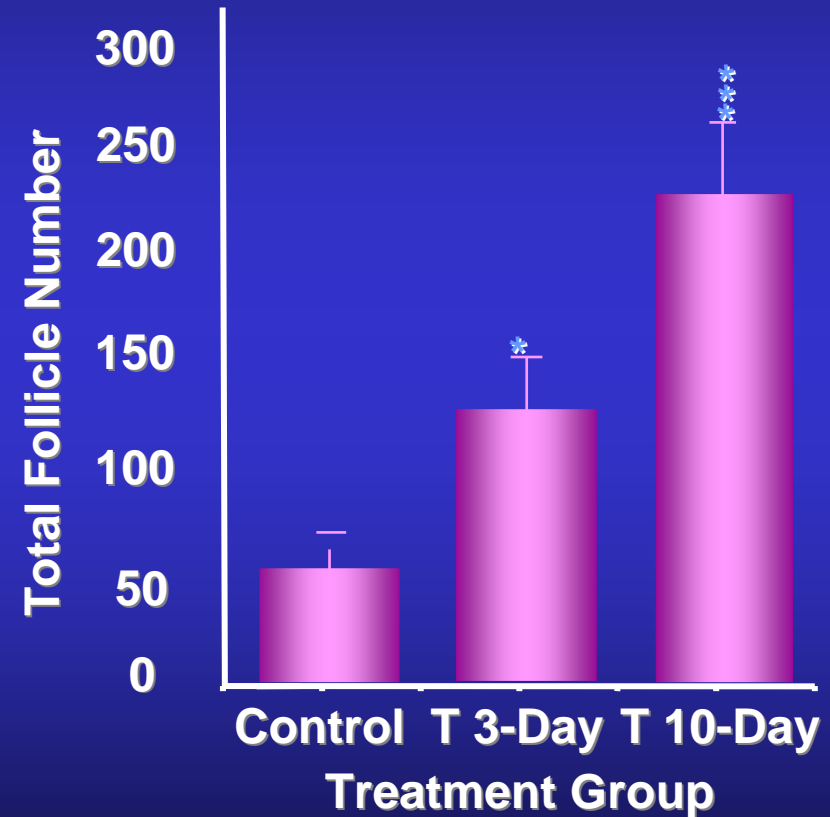


(Hillier 2001)

Effets de la LH sur l'expression des gènes des cellules de la granulosa

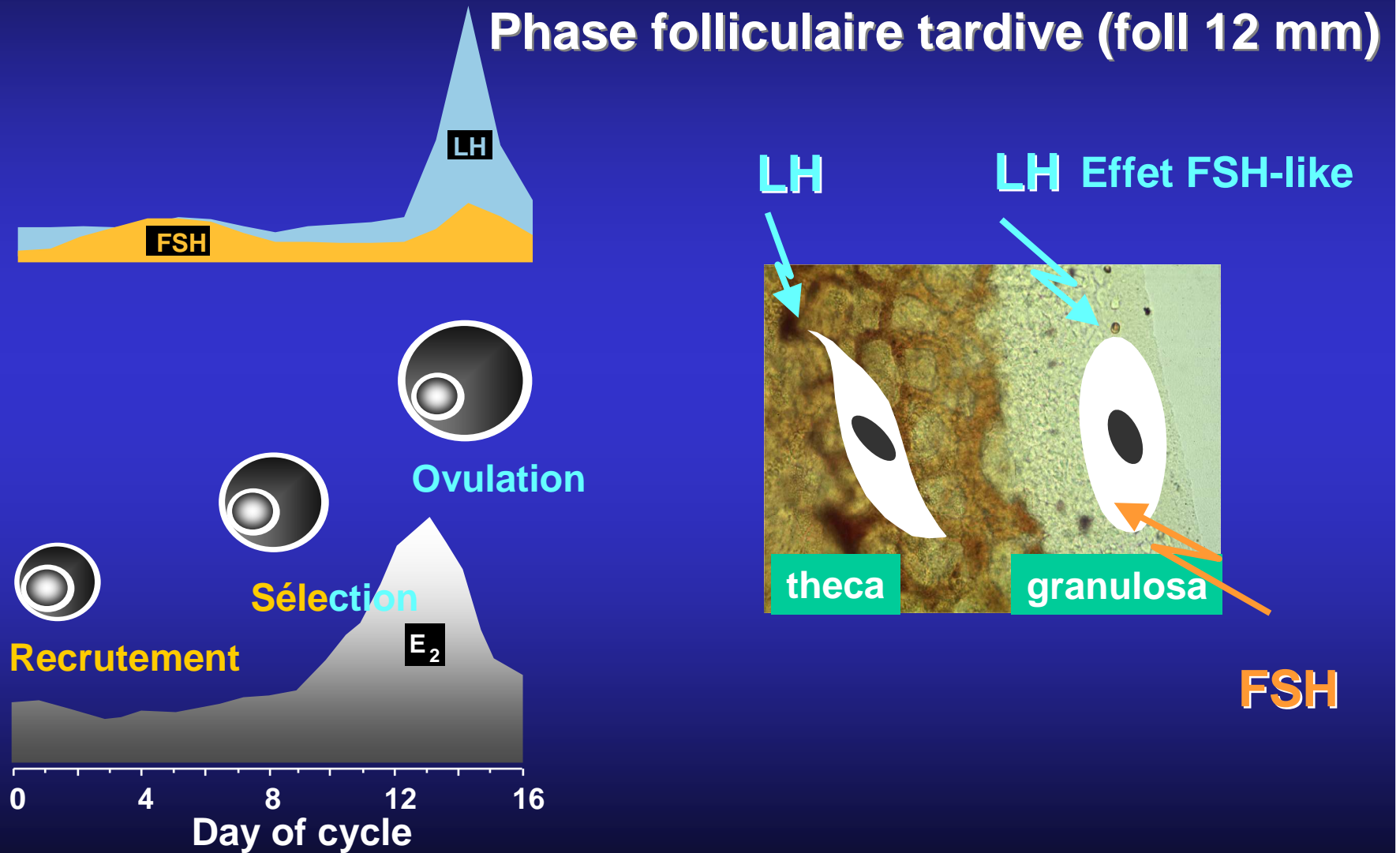


(Hillier et al. 1998)



(Vendola et al. 1998)

Gonadotrophines et folliculogénèse

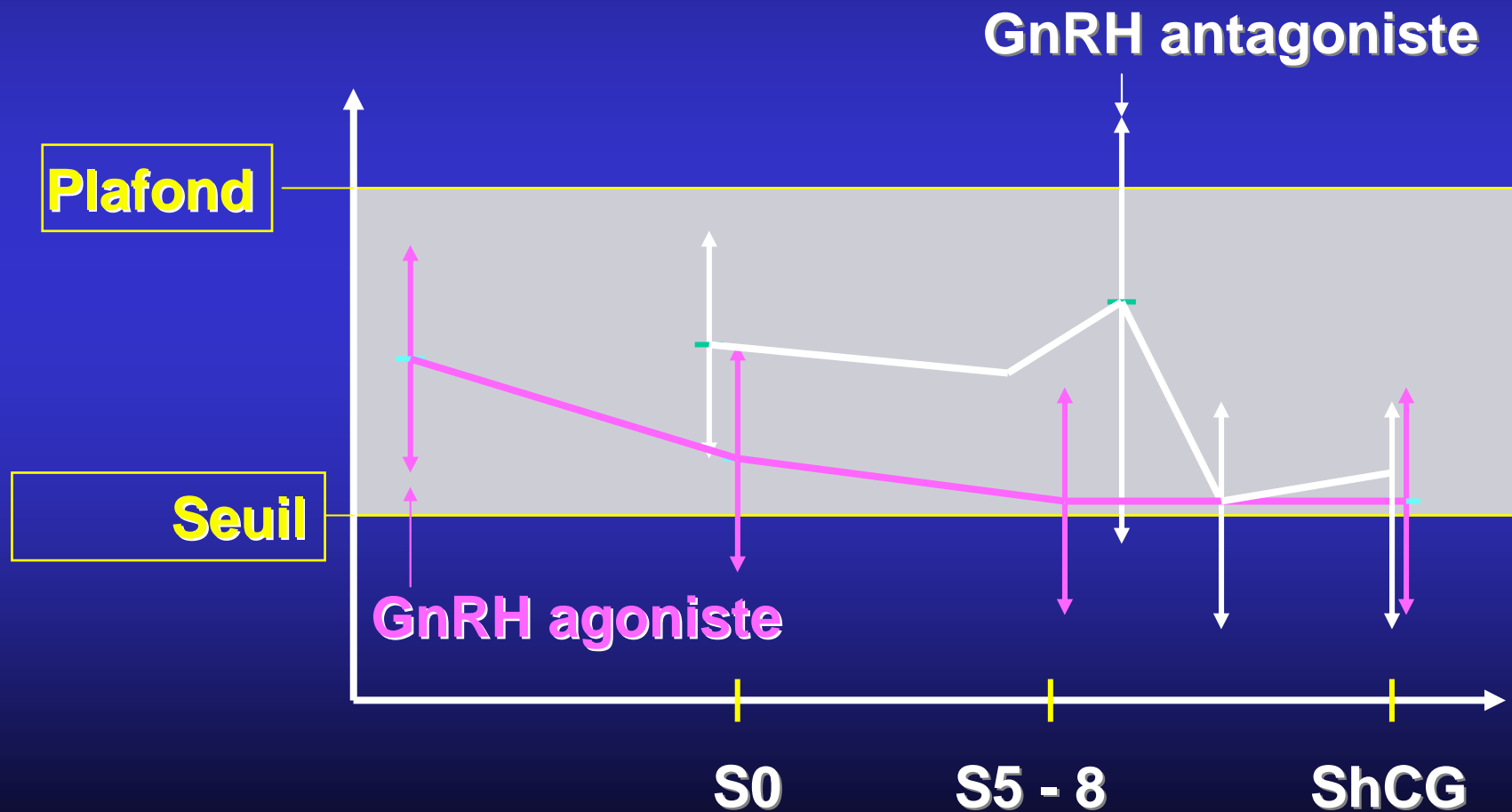


Dans le cycle Physiologique

- La LH (et non l'hCG) est sécrétée par l'hypophyse de manière pulsatile durant l'ensemble de la phase folliculaire, à un niveau inférieur à celle de la FSH.
- La LH agit de manière constitutive sur la thèque interne pour produire les androgènes,
& substrats de l'aromatase de la granulosa
(Production d'oestrogènes)
& stimulateurs de la folliculogénèse
- La LH en fin de phase folliculaire agit sur la granulosa (récepteurs spécifiques) avec un effet FSH-like sur la production d'oestrogènes

Hypogonadisme Hypogonadotrope induit par les analogues du GnRH

Serum LH



Evaluation de la sécrétion de LH endogène

La mesure de la LH sérique : peu informative

Sécrétion de LH : pulsatile

Différences entre les méthodes de dosage

LH immunologique # LH biologique

Dépend du type d'agonistes du GnRH utilisé :

Type & Dose & Voie



Triptoreline
Leuprolide
Busereline
Nafareline

Intra-nasale
Sous-cutanée
Quotidienne
Depot



GnRH agoniste - long protocole

Valeur prédictive des taux sériques de LH

Impact négatif

- Fleming 1996, 1998, 2000
- Westergaard 2000, 2001
- Esposito 2001
- Humaidan 2002
- Tesarik 2002

0.7
0.5
3
0.5
1

Agoniste puissant (busereline)
ou forme dépôt

Un seul point d'évaluation de LH

50 % patientes avec valeurs basses
de LH

Diminution du n° oocytes & FR
Plus d'ampoules FSH

Pas d'impact

- Loumaye 1997
- Balasch 2001
- Penarrubia 2003
- Cabrera 2005

0.5
0.5-1
ROC
ROC

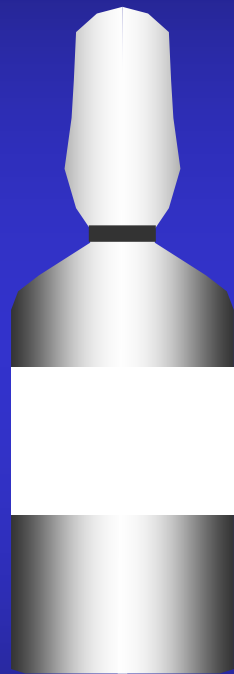
Agoniste moins puissant (leup or tript)
Séries de LH

10% de patientes avec valeurs basses
de LH

ROC analyse
Pas de différence

LH supplémentation

Quelle préparation ?



FSH	75	75	0	0
LH	75	0	75	0
hCG	0	10	0	50-200

Contenu en Gonadotrophines (IU) par ampoule

hMG vs FSH

Meta - analyses (Taux de grossesse)

Van Wely 2003 (6 RCT) & Al Inany 2003 (20 RCT)

NS des taux de grossesse ou de naissance par patiente

Al Inany 2007 (12 RCT)

Taux de naissance OR = 1.20 (1.01 - 1.42) en faveur hMG

HP-hMG (n=4) : OR = 1.18 (0.97 - 1.44) NS

Coomarasamy 2008 (7 RCT)

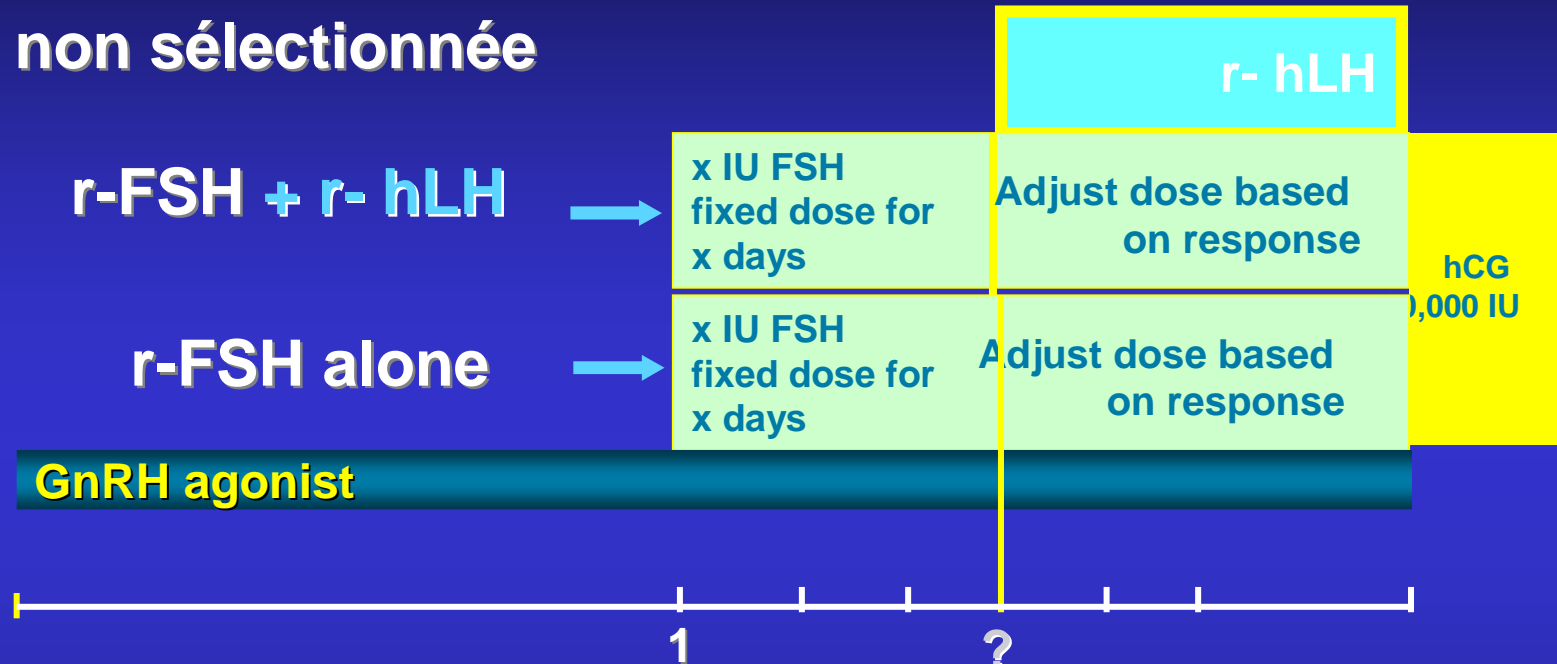
Taux de naissance OR = 1.18 (1.02-1.38) en faveur hMG

HP-hMG (n=3) : différence statistique non confirmée

Bénéfice clinique : pas actuellement démontré
plus lié à la LH qu' à l' hCG !

LH Recombinante

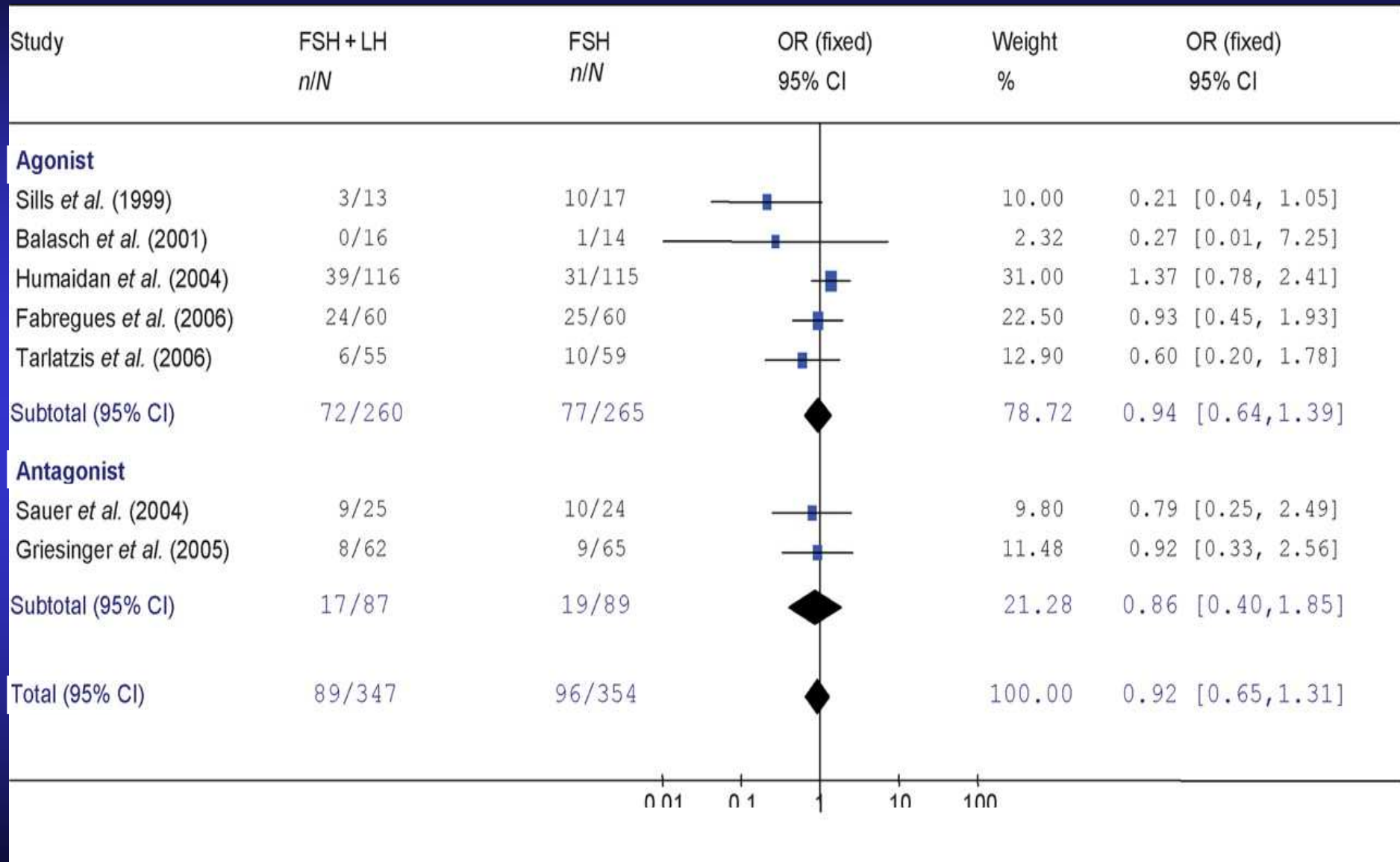
Population non sélectionnée



Authors	Agonist	r-FSH dose	r-LH start	r-LH dose
Lisi 2002	Triptorelin 0.1 mg	150	S7 n=122	75
Marrs 2003	Leuprolide 0.5/0.25 mg	225	S6 n= 206	150
Humaidan 2004	Buserelin 0.5/0.2 mg	112.5-375	S8 n=116	FSH / LH= 2/1
Lisi 2005	Triptorelin 0.1 mg	150	S7 n=188	37.5 / 75

Pas d'effet démontré en terme de grossesse

Supplementation avec R. LH : résultats globaux

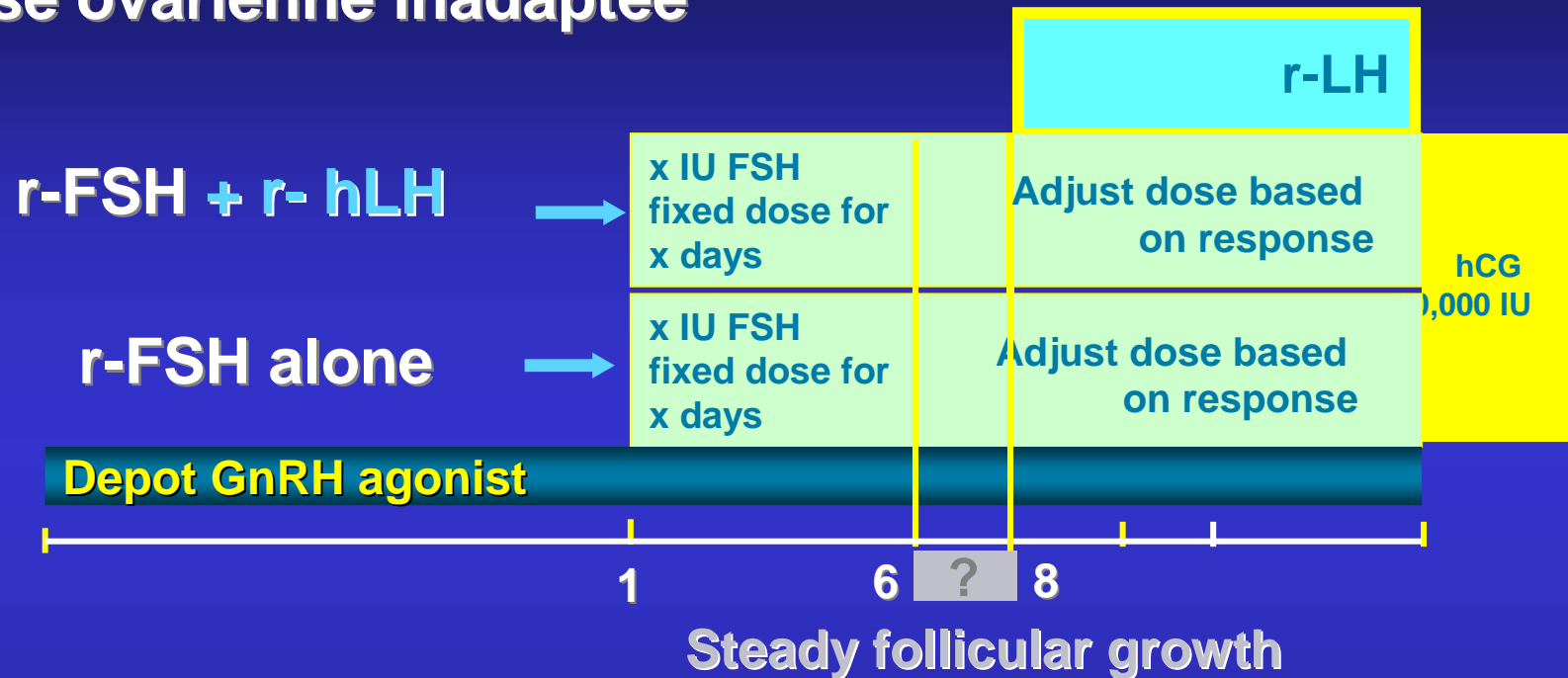


Quel sous-groupe de patientes susceptible de bénéficier de l'apport de LH recombinante ?

- 1. Hypogonadisme Hypogonadotrope induit par les formes Dépôt de GnRH**
- 2. Patientes nécessitant de fortes doses de FSH**
- 3. Patientes de plus de 35 ans**

1. Protocoles agoniste du GnRH (Dépôt)

Réponse ovarienne inadaptée

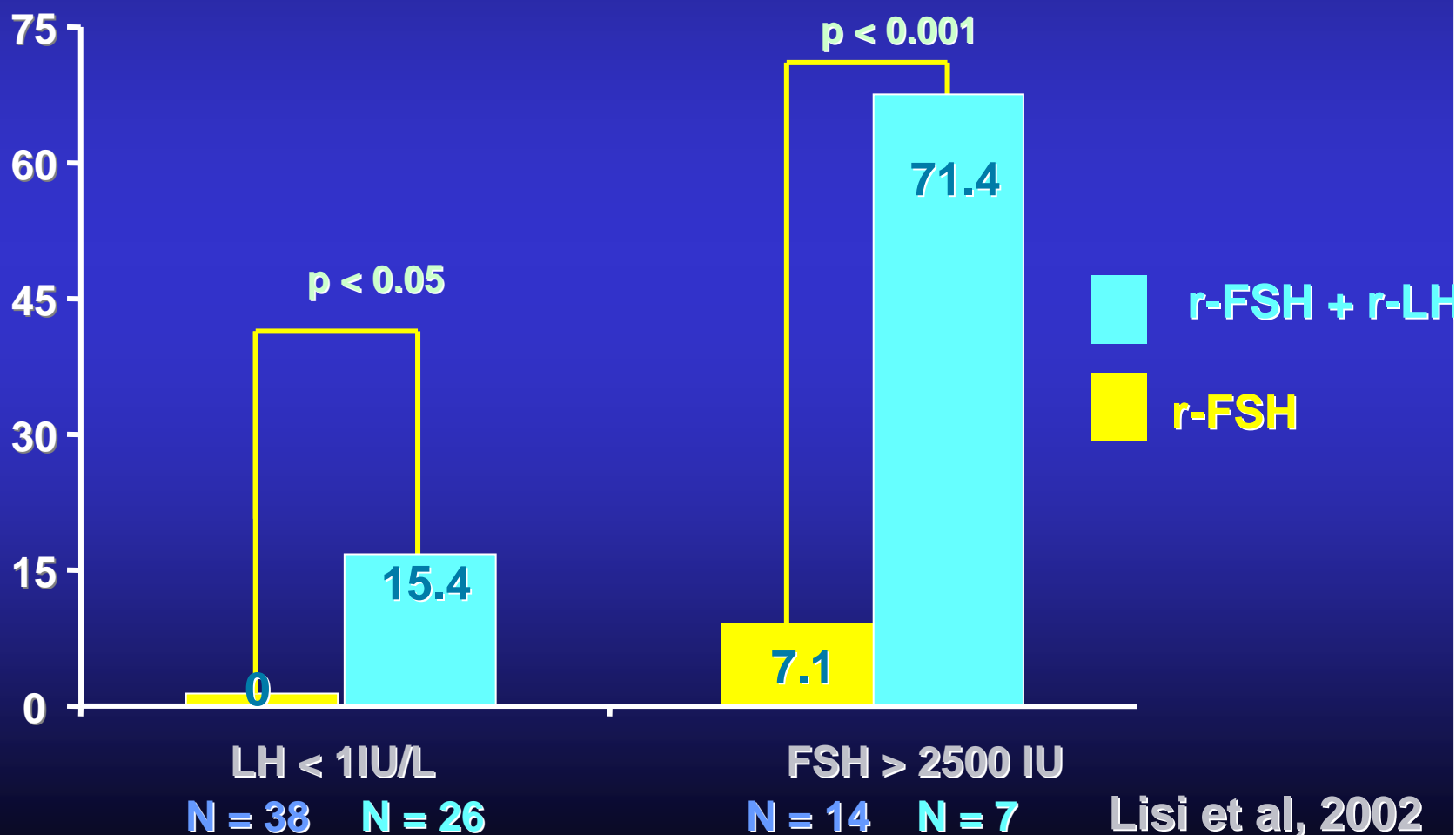


Authors	Agonist	r-FSH dose	r-LH start	r-LH dose
Ferrarreti 2004	Depot agonist	150-225	S10 n=54	75-150
De Placido 2004	Triptorelin 3.75 mg	150-300	S8 n=46	75-150
De Placido 2005	Triptorelin 3.75 mg	225	S8 n=59	150

Effet bénéfique de l'addition de LH (150 > 75 IU / d)

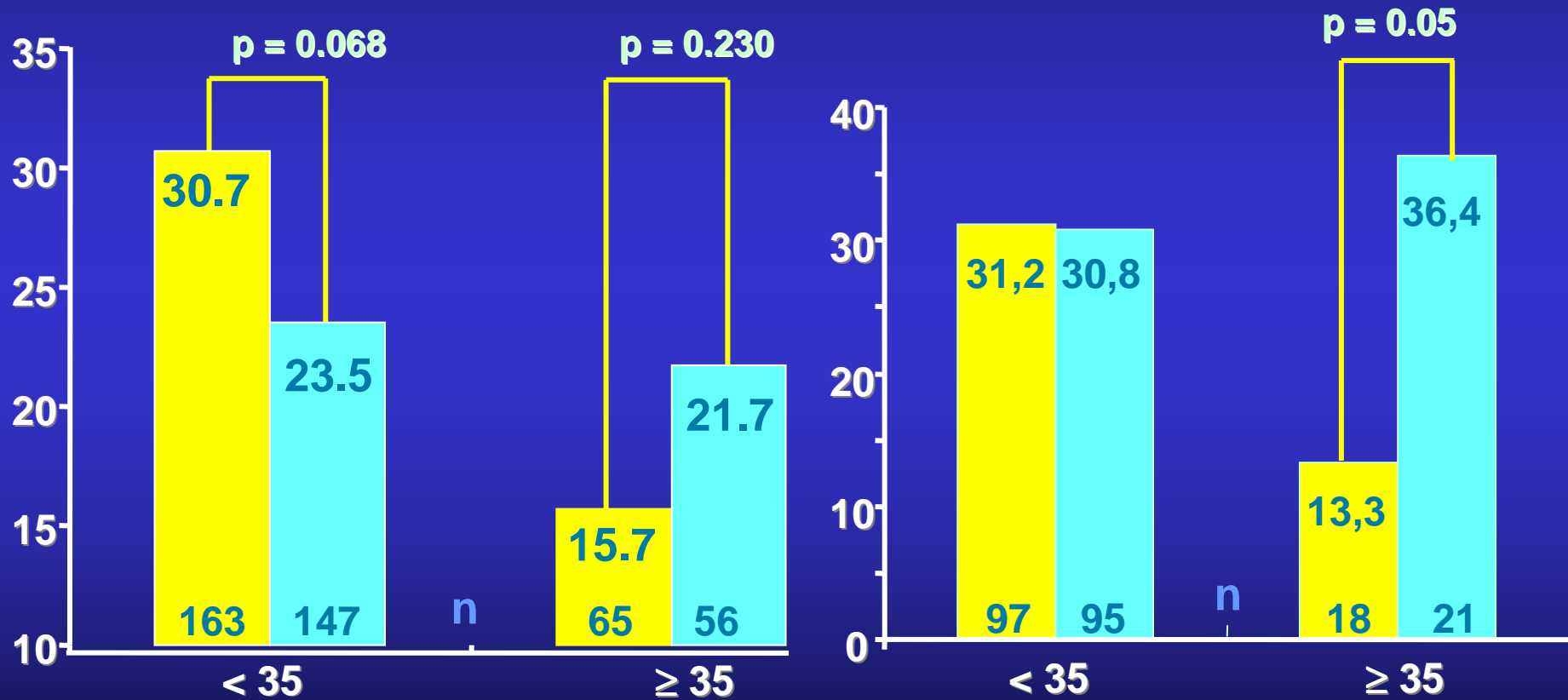
2. Analyse en fonction du taux de LH à la désensibilisation et de la dose de FSH

% Implantation par Cycle



3. Analyse selon l'âge

% Implantation / Cycle



Marrs R. et al. 2003

Humaidan et al. 2004

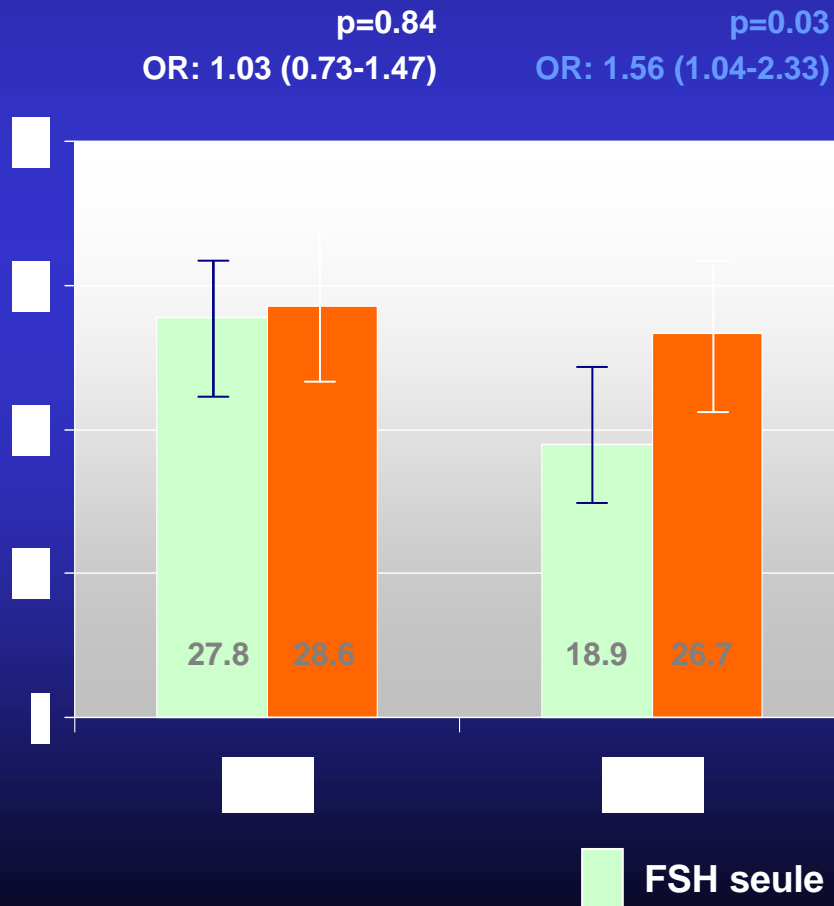
■ r-FSH ■ r-FSH + r-LH

LH Recombinante

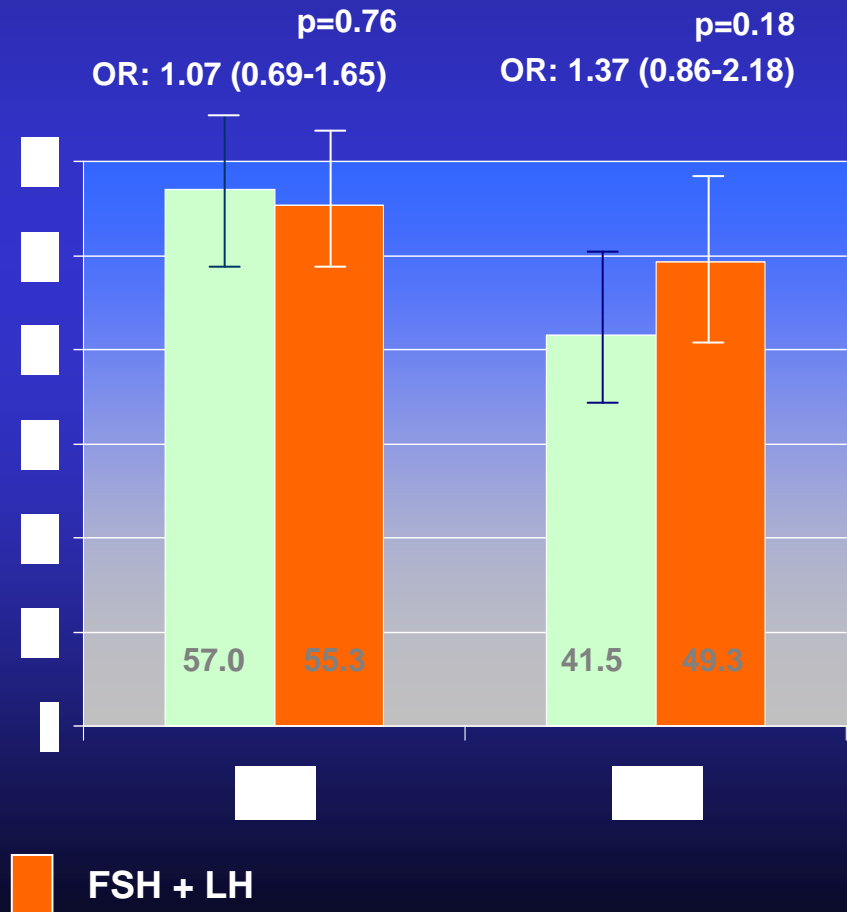
Protocole antagoniste du GnRH

Bosch E. ASRM 2008

Taux Implantation



Taux grossesse Clinique



Effets de l'âge sur la production thécale d'androgènes

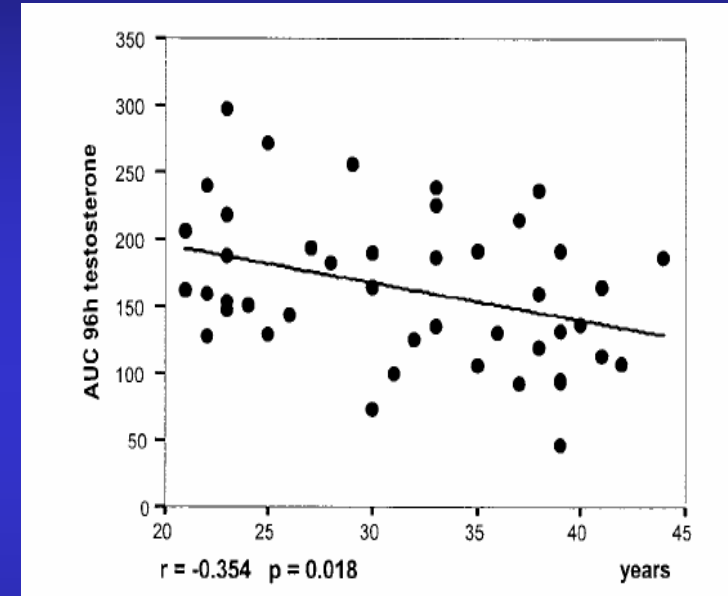
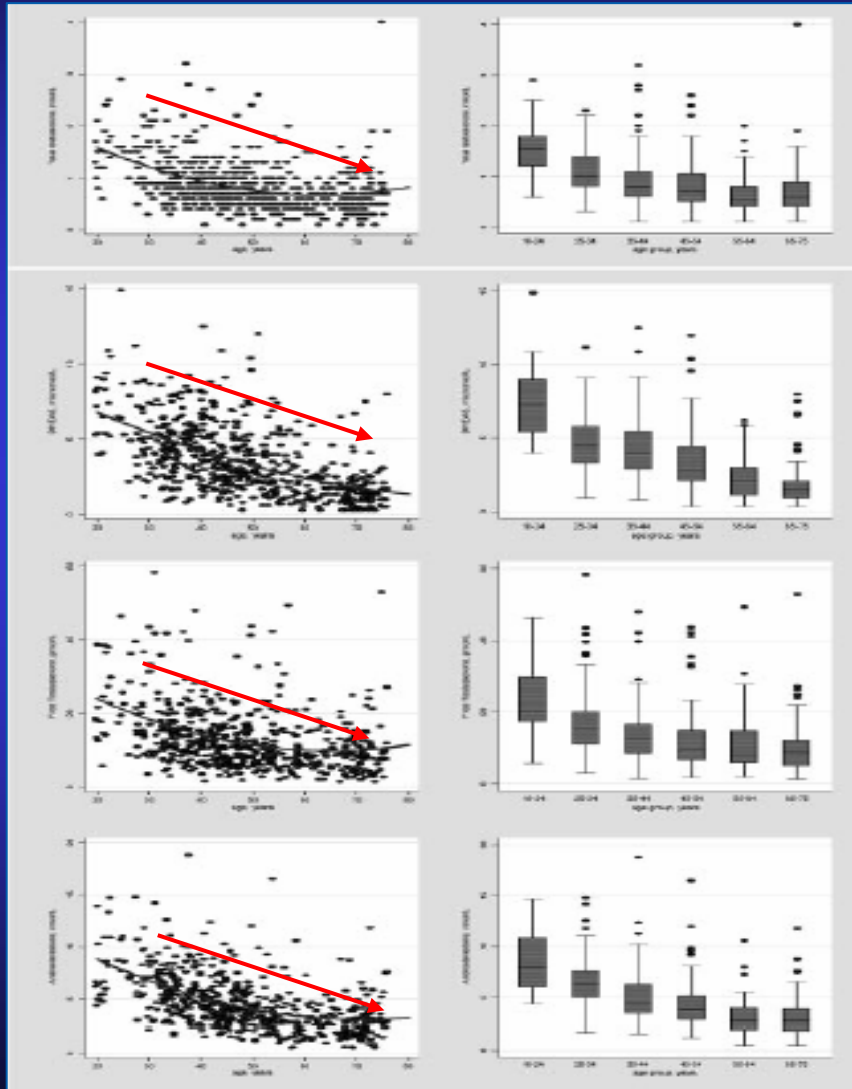
n = 1423

Total T
↓ 55%

DHEA S
↓ 77%

Free T
↓ 49%

Androst
↓ 64%



Réponse de 17-OHP, A et à hCG (AUC; 96 h) corrélée négativement à l'âge

Piltonen et al JCEM
2003

Davison et al JCEM 2005

Hormone Chorionique (hCG)

Substitution à FSH en fin de phase folliculaire

Meta-analyse (Kosmas IP et al., 2009)

9 Etudes (3 Abstracts - 6 Prospectives)

25 - 200 IU hCG vs r.FSH - hMG

Protocoles GnRH agoniste Long, Court & antagoniste

Etudes Prospectives : NS Grossesse / OHSS

Protocoles Agoniste & Antagoniste : NS Grossesse / OHSS

Blockeel C et al., 2009

**Protocole Antagonist - 200 IU hCG qd 6 foll > 12 mm & E2 > 600 pg/ml
NS Grossesse / OHSS**

Conclusions: supplémentation par “activité LH”

Population Générale

Pas de différence (grossesse – naissance)
quelque soit le protocole GnRH analogue

Quelques pistes pour la r. hLH

- Protocole long (Dépot) si réponse inadaptée à FSH seule
- Patientes nécessitant des doses fortes de FSH (> 2.500 UI)
 - Patientes de ≥ 35 ans

Questions à débattre

Quand débiter la supplémentation en LH ?

Très grande majorité : S6 – S8 :

Effet de type FSH sur les récepteurs de la granulosa

Quel est le ratio optimal FSH / LH ?

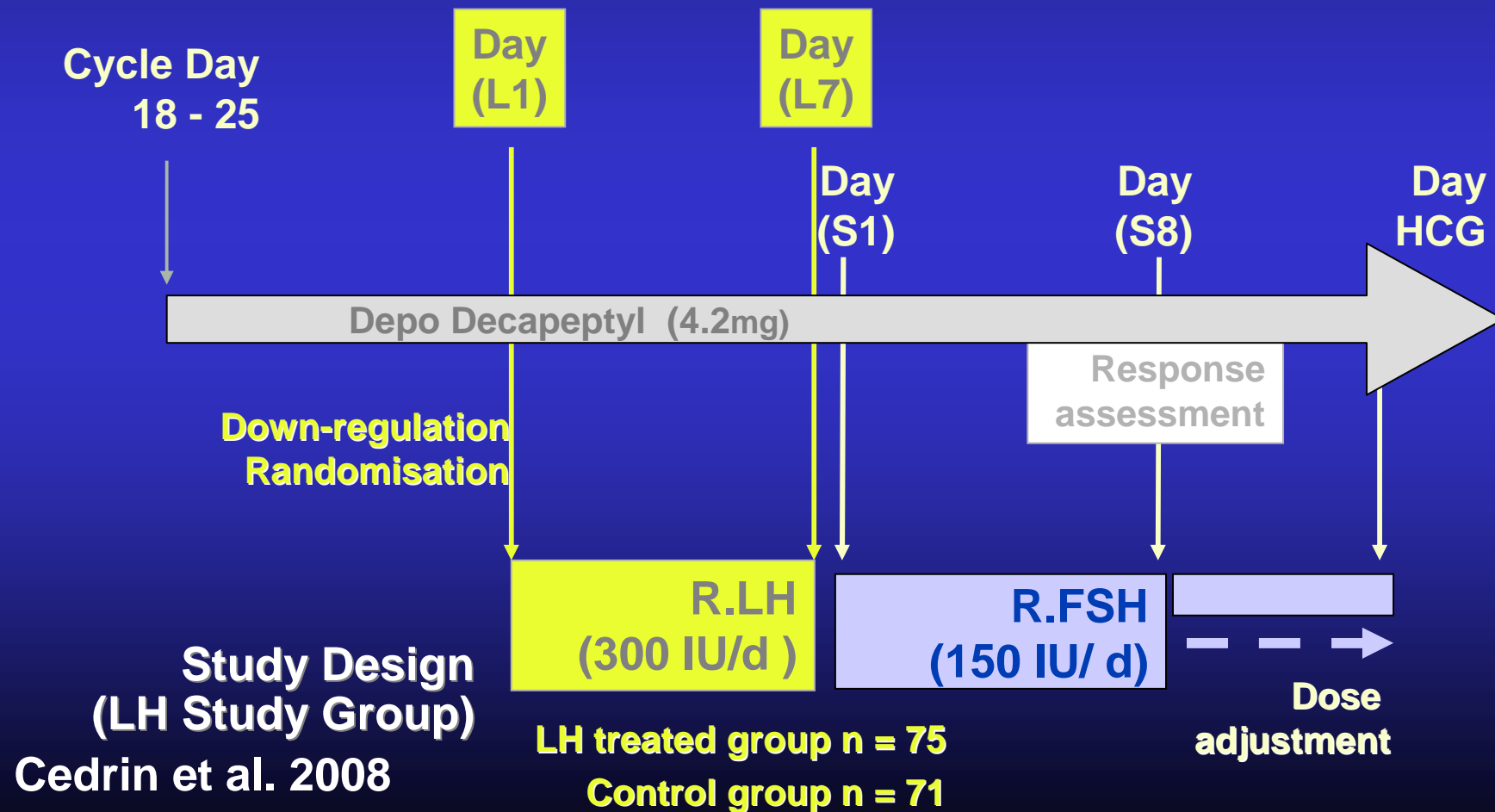
Physiologiquement : 2 / 1

Quelle type de préparation utiliser ?

R. hLH & hCG

“LH priming”

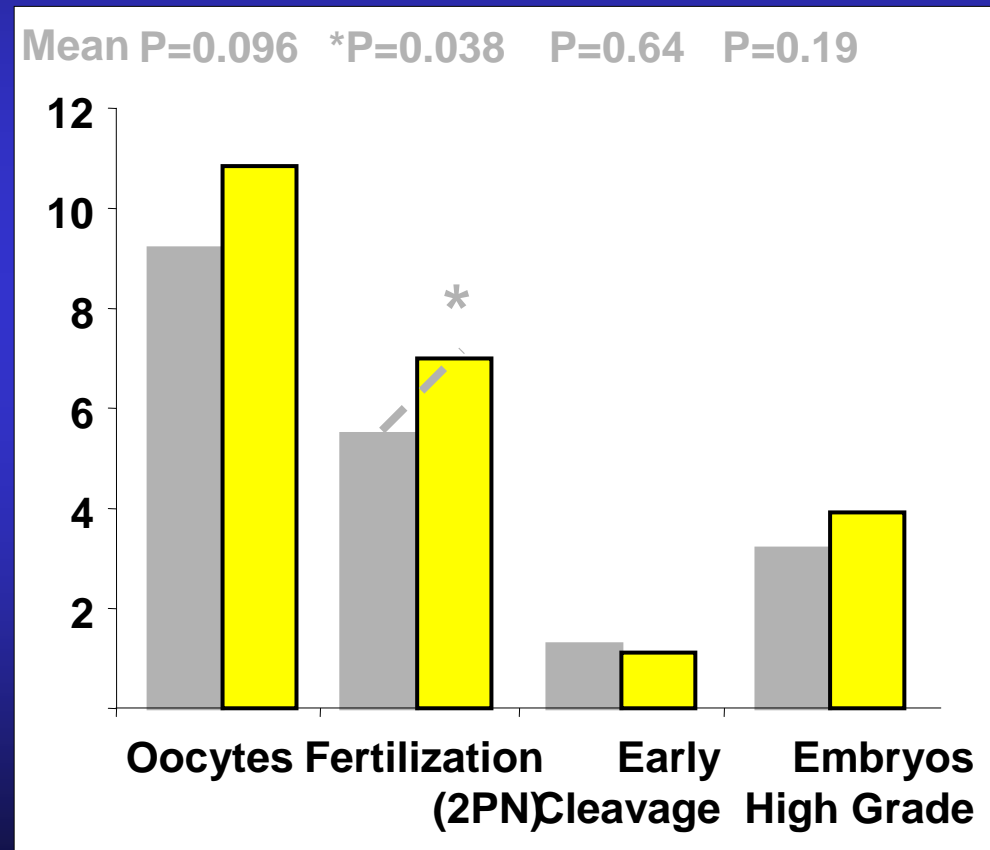
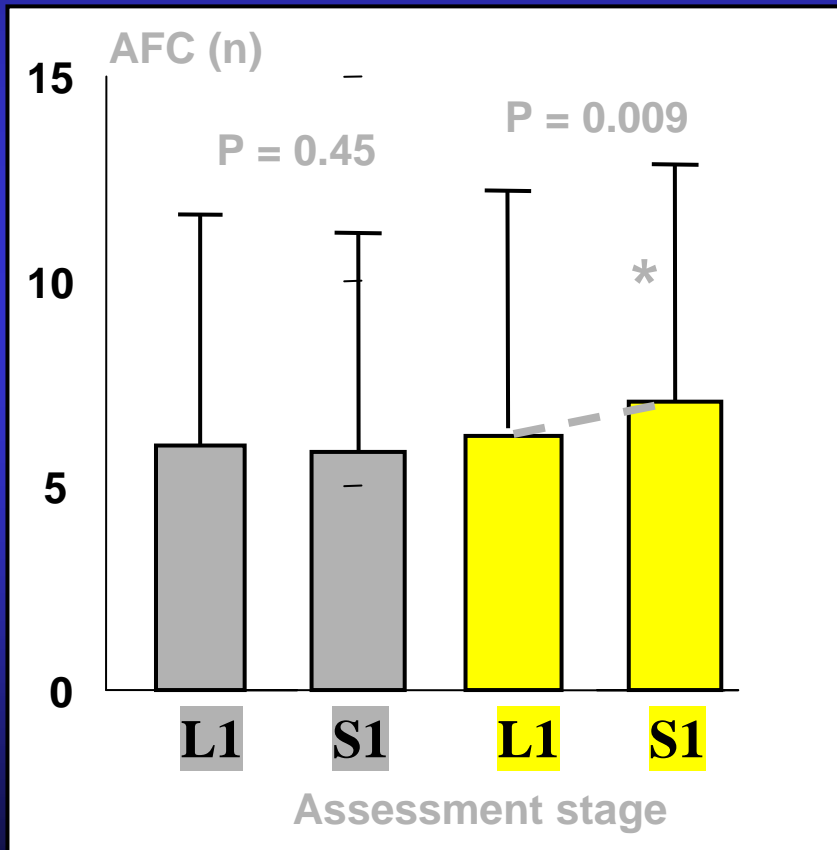
LH avant FSH : production d' androgènes ovariens ---
augmentation du nb de follicules et de la sensibilité à la FSH



LH Priming

LH seule avant FSH : Augmentation du nombre de follicules

Augmentation de la sensibilité à la FSH (nb d'ovocytes et d'embryons)



No Pre-treatment LH Pre-treatment

Cedrin et al., HR 2008

Quelle préparation utiliser ?

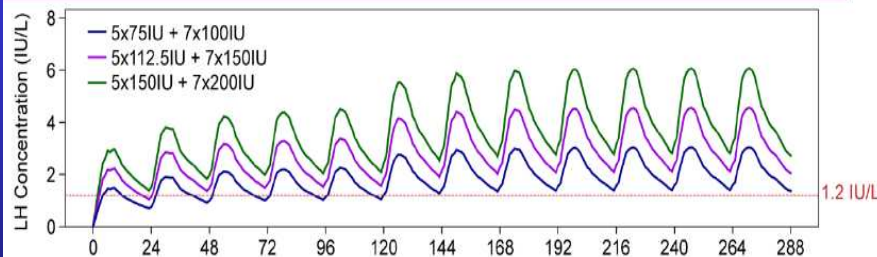
LH

physiologique – sécrétion pulsatile
demi vie brève (6-10h)
pas d'accumulation sérique

hCG

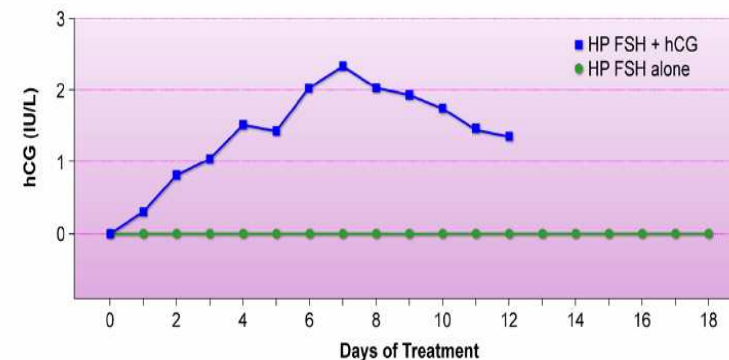
non physiologique en phase folliculaire
demi vie longue (48h)
accumulation sérique

Simulated Profiles (3 Dose Regimens from 158 Simulated Pharmacokinetic Profiles)



Dosing Regimen	Injection 5 (96-120h)			Injection 12 (264-288h)		
	C _{max} (IU/L)	C _{max} Ratio to 1.2	AUC _T (IU/L-h)	C _{max} (IU/L)	C _{max} Ratio to 1.2	AUC _T (IU/L-h)
5x75 + 7x100 IU	2.3	1.9	38.7	3.0	2.5	52.7
5x112.5 + 7x150 IU	3.4	2.8	58.0	4.5	3.8	79.1

hCG Accumulation in Serum



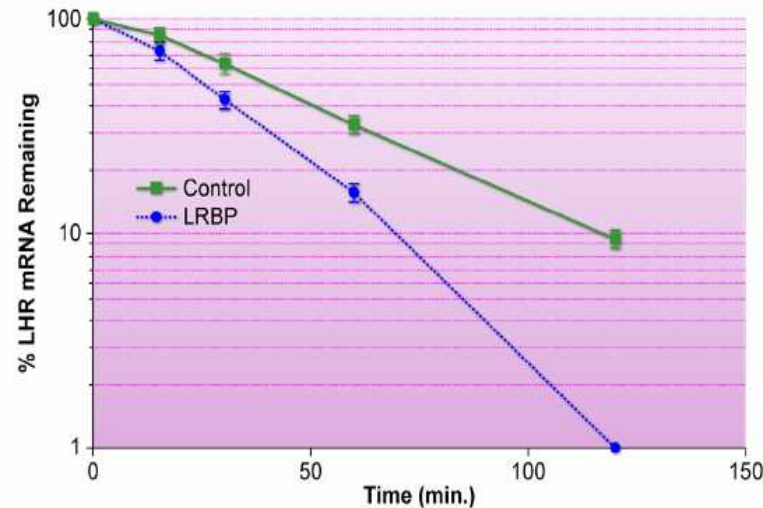
Following hCG administration AUC hCG IU/L/day = 3.8 ± 0.6

Différences R.LH & hCG

Importance du modèle pulsatile en Endocrinologie

Conséquences d'un message hormonal non intermittent
internalisation du récepteur et non réponse cellulaire
« Down régulation cellulaire » (Ex: agoniste du GnRH)

A Novel Post-Transcriptional Mechanism of Regulation of Luteinizing Hormone Receptor Expression by an RNA Binding Protein from the Ovary*



*Supported by NIH Grant HD-08856.
Menon KM, Nair AK, Wang L. *Mol Cell Endocrinol.* 2006 Feb 26;248(1-2):135-41.

Liaison de hCG au récepteur LH : réduction de son expression pd 48 h

Take home messages

LH (# l'hCG) : hormone physiologique de la phase folliculaire

Effet thécal : rôle essentiel des androgènes sur la stéroïdogénèse et la folliculogénèse

Quelles patients peuvent bénéficier de l'addition de LH ?

- Déplétion LH importante et faible réponse à la FSH
 - ≥ 35 ans

Quand débiter et quel ratio FSH / LH ?

Dès le début du cycle (Protocole agoniste long) - ratio : 2 / 1

Quelle préparation utiliser ?

LH plus adaptée si administration quotidienne

Conclusion : A little LH means a lot !

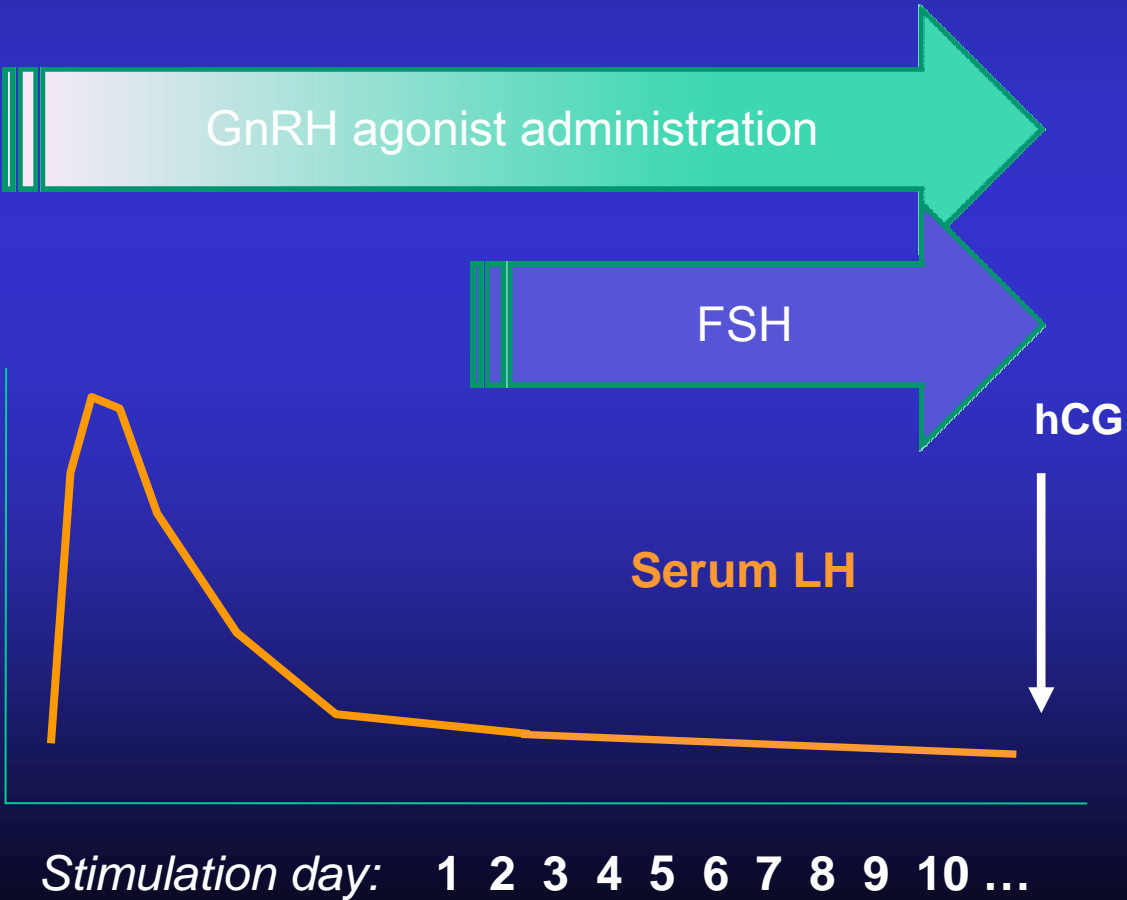
S Hillier





**Thank you
for your
attention !**

GnRH agonist long protocol



GnRH antagonist protocol

