THE RECOMBINANT FOLLICLE STIMULATING HORMONE : A NEW ALTERNATIVE IN INDUCTION OF OVULATION AND TREATMENT OF POLYCYSTIC OVARY SYNDROME

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INTRODUCTION

Induction ovulation is need for :

in-vitro fertilisation

treatment for polycystic ovary syndrome

Using controlled ovarian hyperstimulation :

getting more eggs

getting better eggs

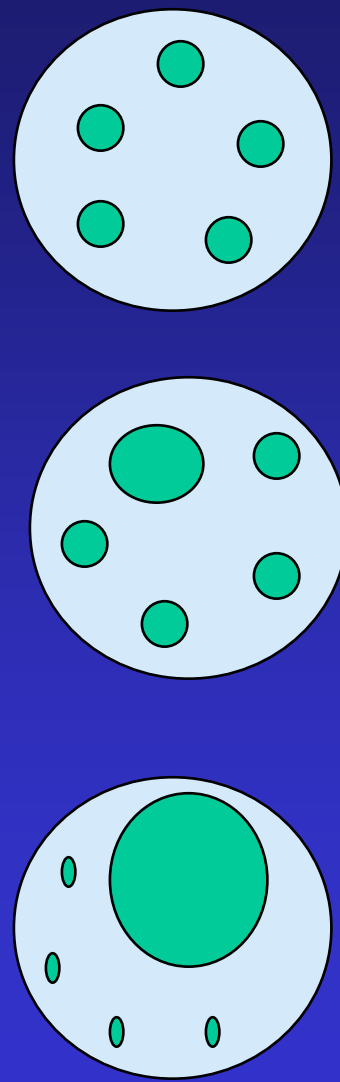
better pregnancy rate

FOLLICULAR GROWTH AND OVARIAN FUNCTION

- The ovaries functions :
  - a gamete
  - a sex hormone producer
- Hypothalamic-pituitary-ovaries axis mechanism

FOLLICULAR GROWTH AND OVARIAN FUNCTION

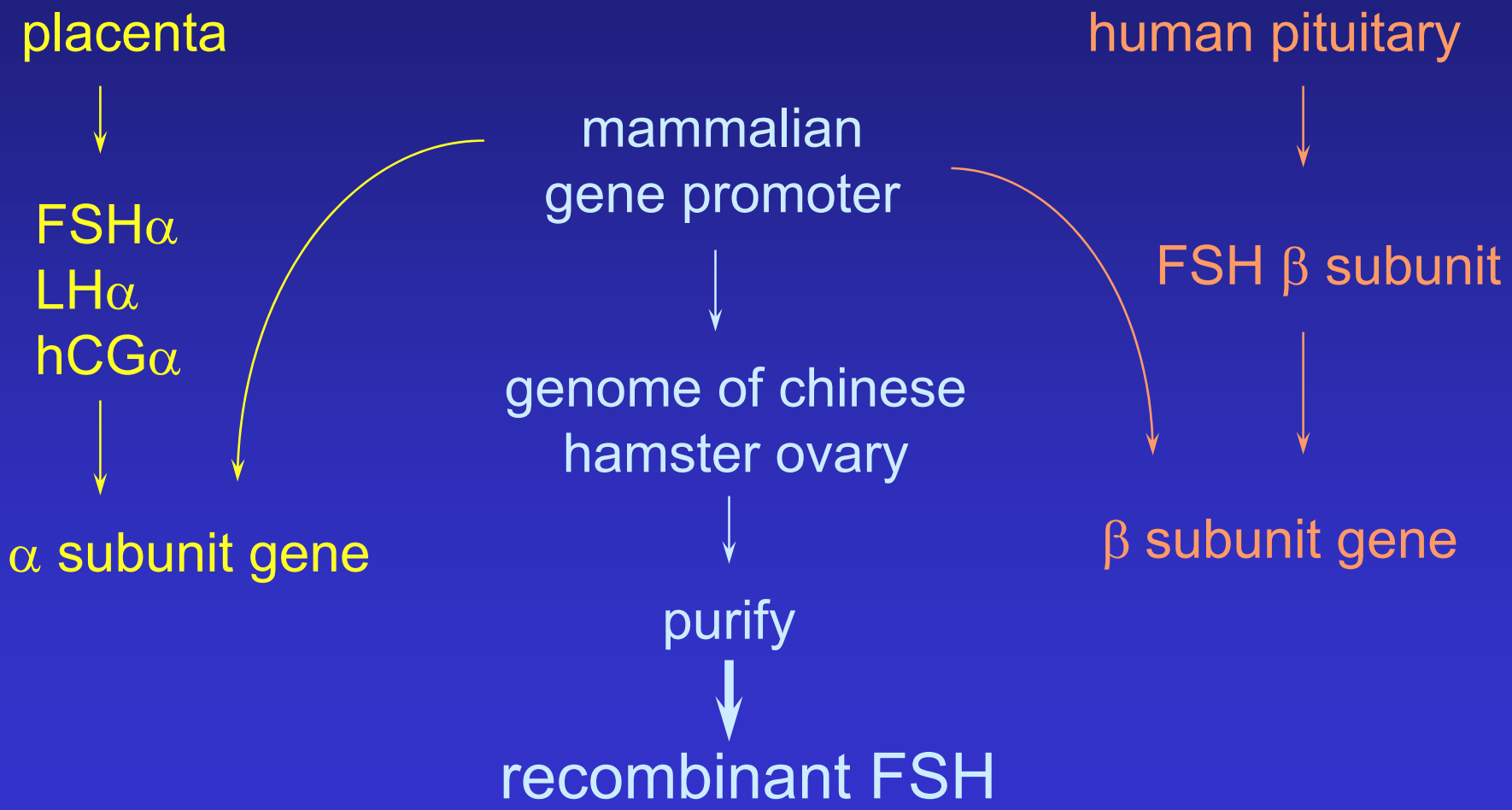
- Follicular recruitment
- Follicular selection
- Follicular dominance



RECOMBINANT DNA

- It can be used to identify, isolate, clone, produce specific protein
- Advantages : identifying mutation, diagnosing hereditable disease, etc
- Manufacture a large qualities of specific protein (hormone, vaccines)

RECOMBINANT FSH



PHARMACOKINETICS OF rFSH

- The pharmacokinetics characteristics of rFSH are similar to uFSH
- Terminal half life of FSH is approximately 1 day
- The pharmacokinetics of rFSH appear to be linear

PHARMACOKINETICS OF rFSH

	Recombinant FSH			
Route	IV	IM	SC	SC(7X)
Labeled dose (IU)	150	150	150	150
Immunoassay dose (IU)	160	160	160	160
Parameter*				
AUC_{o-oo} (IU.h/L)	309 ± 119	177 ± 53	235 ± 144	187 ± 61**
C_{max} (IU/L)	35 ± 15	3 ± 1	3 ± 1	9 ± 3 §
t_{max} (h)	---	25 ± 10	16 ± 10	8 ± 6 §
Total clearance (L/h)	0.6 ± 0.2	---	---	---
Renal clearance (L/h)	---	---	---	---
$t_{1/2}$ absorption (h)	---	8.3 ± 3.7	4.7 ± 4.4	7.2 ± 4.1
$t_{1/2}$ initial (h)	2.4 ± 1.1	---	---	---
$t_{1/2}$ terminal (h)	18 ± 6	37 ± 25	37 ± 28	24 ± 8
V_{ss} (L)	11 ± 5	---	---	---
MRT (h)	20 ± 5	---	---	---
Bioavaibility (%)	---	61 ± 18	75 ± 29	---

!Values are means ± SD

*AUCo-oo, area under the concentration-time curve from time = 0 to infinity;
Cmax, maximal concentration; t max, time of Cmax; t 1 2 absorption , absorption half life
t 1 2 initial; initial half life; t 1 2 terminal, terminal half life; V ss, volume distribution
at steady state; MRT, mean residence time.

**AUC steady state = AUC 144-168h for repeated administration

§ Value after the last dose (t = 144 h) for repeated SC administration

CONTROLLED OVARIAN HYPERSTIMULATION BY USING rFSH

- Germond et al reported a succesful in-vitro fertilisation and embryo transfer after treatment with rFSH

  4 oocytes were recovered

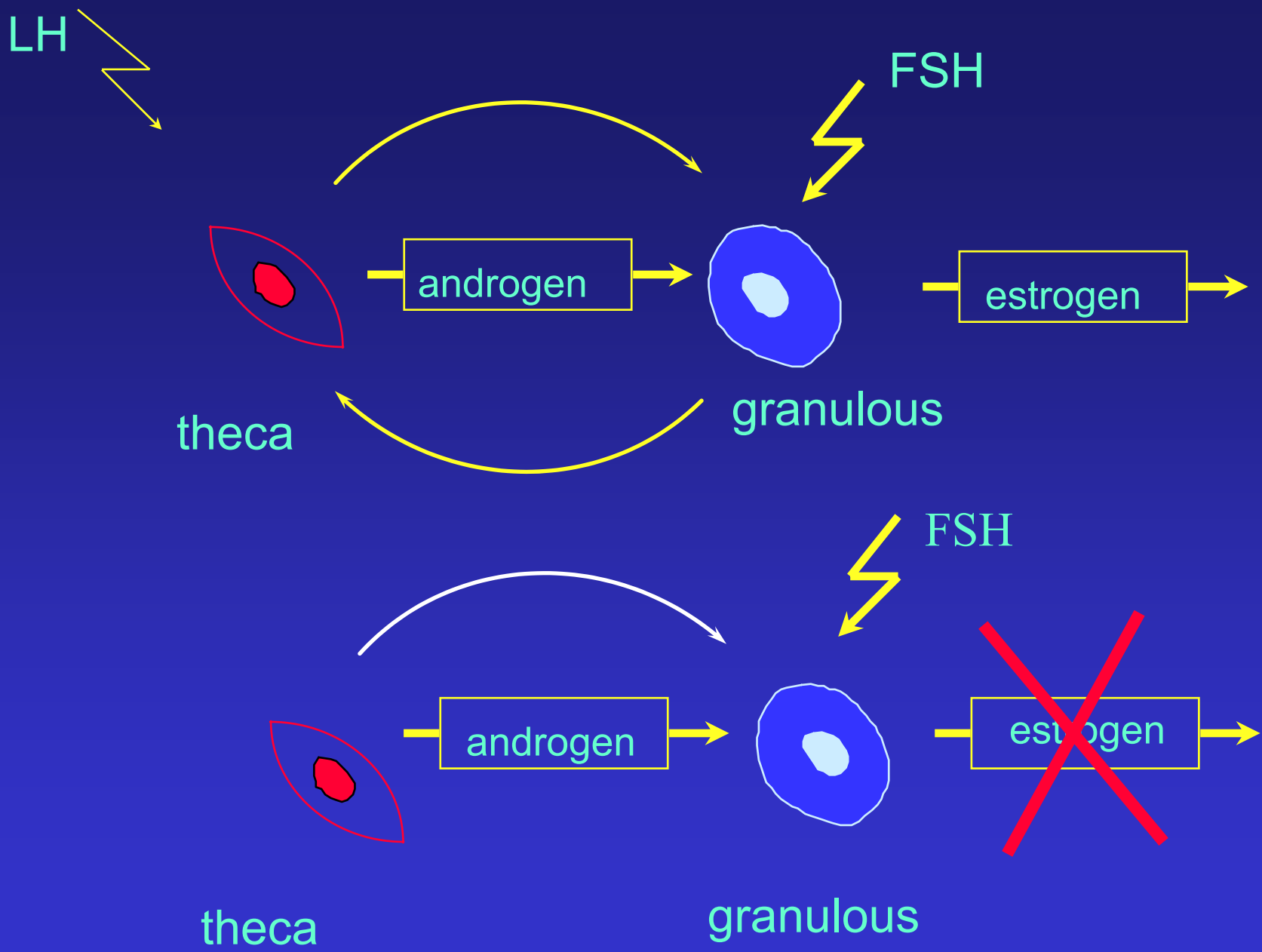
- Devroey et al reported a pregnancy and birth after stimulating ovarian using rFSH (IVF/ET)

  9 oocytes were recovered

CONTROLLED OVARIAN HYPERSTIMULATION BY USING rFSH

- Schoot et al can induce multiple follicles in a woman with isolated gonadotropin deficiency using rFSH

- Follicle development was coincided with increasing serum FSH, and no significant estrogen was produced.


LH
FSH
androgen
estrogen
theca
granulous
FSH
androgen
estrogen
theca
granulous

Recombinant human FSH study group compared the efficacy and the safety of rFSH with uFSH

No difference in :

- ° follicular development
- ° ovum pick-up (OPU)
- ° IVF result

Table 1. Follicular development, OPU, and IVF result

Variables	Recombinant hFSH	Urinary hFSH	*P*
No. of >10mm follicles on the day of hCG*	10.3 + 4.9 (60)	11.2 + 5.2 (63)	0.177!
No. of ≥14mm follicles on the day of hCG*	7.8 + 3.6 (60)	9.2 + 4.5 (63)	0.037!
No. of oocytes recovered per patient*	9.3 + 5.0 (55)	10.7 + 5.3 (59)	0.35!
No. of fertilised oocytes per patient*	5.6 + 3.8 (55)	6.5 + 4.3 (59)	0.43!
No. of patient with > 1 fertilised oocyte			
Yes	53 (96)	52 (88)	0.068#
No	2 (4)	7 (12)	0.12!
No. of cleaved embryos per patient*	5.0 + 3.8 (53)	6.1 + 3.4 (52)	
No. of patient for each no. of transferred embryos§			
1	0	4 (8)	
2	12 (24)	6 (11.5)	
3	34 (68)	35 (67)	0.77#
4	4 (8)	6 (11.5)	
5	0	1 (2)	

*Values are means + SD with number in parentheses

!ANOVA

#Cohcran-Mantel-Haenszel test

§Values in parentheses are percentages

Out JH et al studied ongoing preg-nancy rates (PR) in IVF after treatment with rFSH a compared with uFSH

- a meta-analyses study from 25 IVF center
- the ongoing PR was higher in rFSH compared to uFSH (22.9 % vs 17.9 %)
- if the cryoprogram was included, the treatment difference increased to 6.4 %

Strowitzki et al studied the ovarian stimulation using rFSH (Gonal-F)

- compare 225 IU with 300 IU
- 6.26 and 5.88 oocytes were collected
- transferred embryo was 2.4 and 2.2
- clinical pregnancy rate of 23.8 % per transfer

FOLLICLE STIMULATING HORMONE FOR POLYCYSTIC OVARIY SYNDROME

- the result after hMG treatment is not good enough
- uFSH appeared to be similiar to hMG in premature luteinisation, follicle development and pregnancy

Bennink et al reported a study which compared rFSH and uFSH in women with CC-resistant, normogonadotropic, and chronic anovulation (WHO group II)

→ *rFSH more efficient than uFSH*

Table 2. Result on rFSH and uFSH treatment

	rFSH	uFSH
cumulative pregnancy rate	27%	24 %
miscarriage rate	31%	32 %
No. of follicles of ≥ 12 mm	3.6 + 2.9	2.6 + 2.6
No. of follicles of ≥ 15 mm	2.0 + 1.7	1.7 + 1.7
No. of follicles of > 18 mm	1.1 + 1.1	0.9 + 0.9
ovulation	69.5 %	66.7 %
dose	750 IU	1,035 IU
duration of treatment	10 days	13 days

CONCLUSION

- Recombinant FSH is a new alternative in induction of ovulation
- As good as urinary FSH,moreover better, in follicular development
- May be better pregnancy rates

CONCLUSION

The advantages of recombinant FSH are :

- better isohormone profile
- better pharmacokinetics formulation
- no contaminating protein
- small differences in the oligosaccharide structure

CONCLUSION

- Suggested that recombinant FSH has also a better result in treating PCO syndrome
- It still needs more studies

Merci beaucoup