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# Poor Ovarian Response Review of definitions

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# Poor ovarian response

- Definition ???
- Pathogenesis and prognosis ??
- Prediction ???
- Incidence ?
- Stimulation protocol ???
- Oocyte quality ??



# Who are the poor ovarian responders ?

- Patients with an *intrinsic* aptitude to recruit few follicles and produce few eggs (for **their age**) under conventional COH



# Terminology of ovarian stimulation in ART (ISMAAR Consensus Group)

## Conventional COH :

- *down regulation with GnRH agonist*
- *GnRH antagonist*
- *flare-up*

*and conventional starting doses of FSH or HMG ( 100-400 IU/day) according to age*

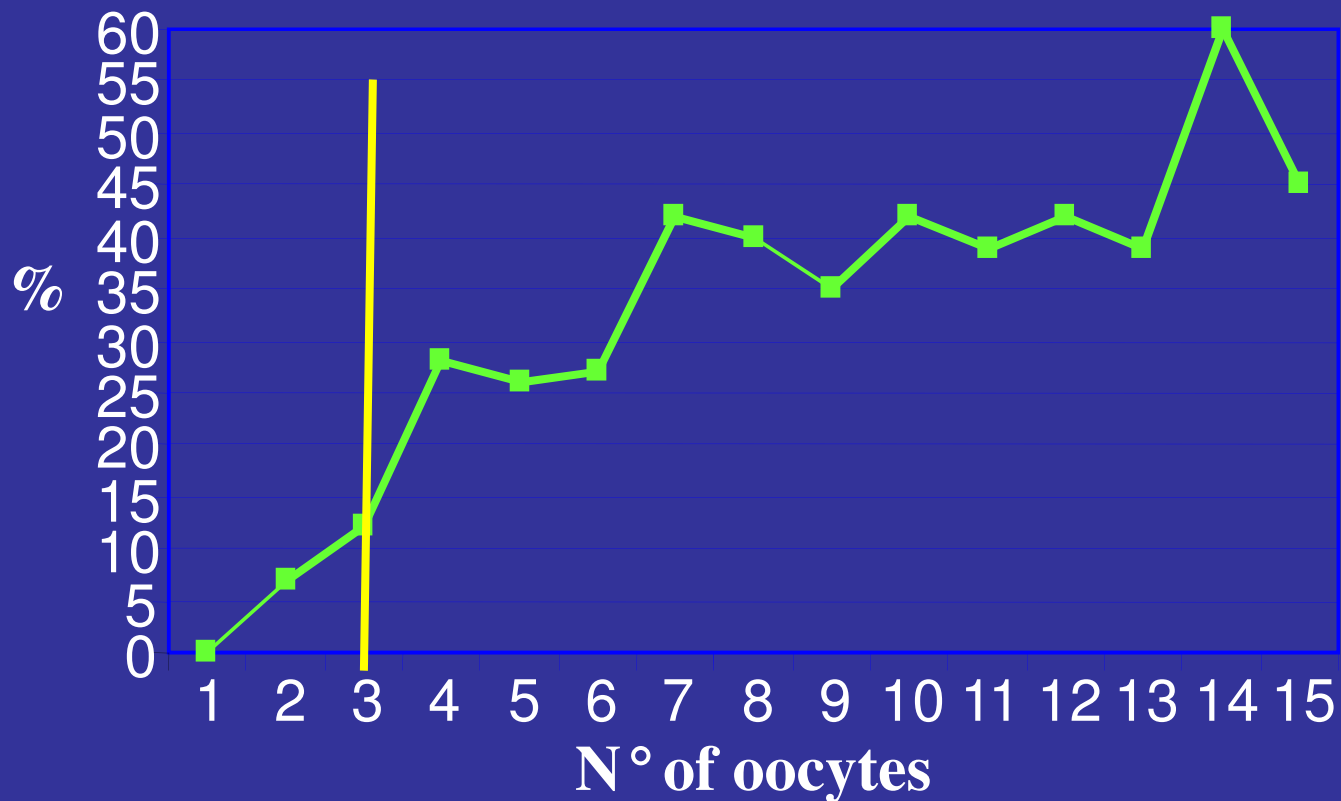
**Mild IVF** : *fixed low doses of FSH or HMG ±CC ( and antagonist )*

# Who are the poor ovarian responders ?

- Patients with an intrinsic capability to recruit **few** follicles and to produce **few** eggs for their age under (conventional) COH
- The number is **“low”** when patient is exposed to a significantly lower PR compared to women from whom **“more”** oocytes are retrieved



# Pregnancy rate/egg retrieval in relation to the number of collected oocytes (SISMER 2000 consecutive cycles)

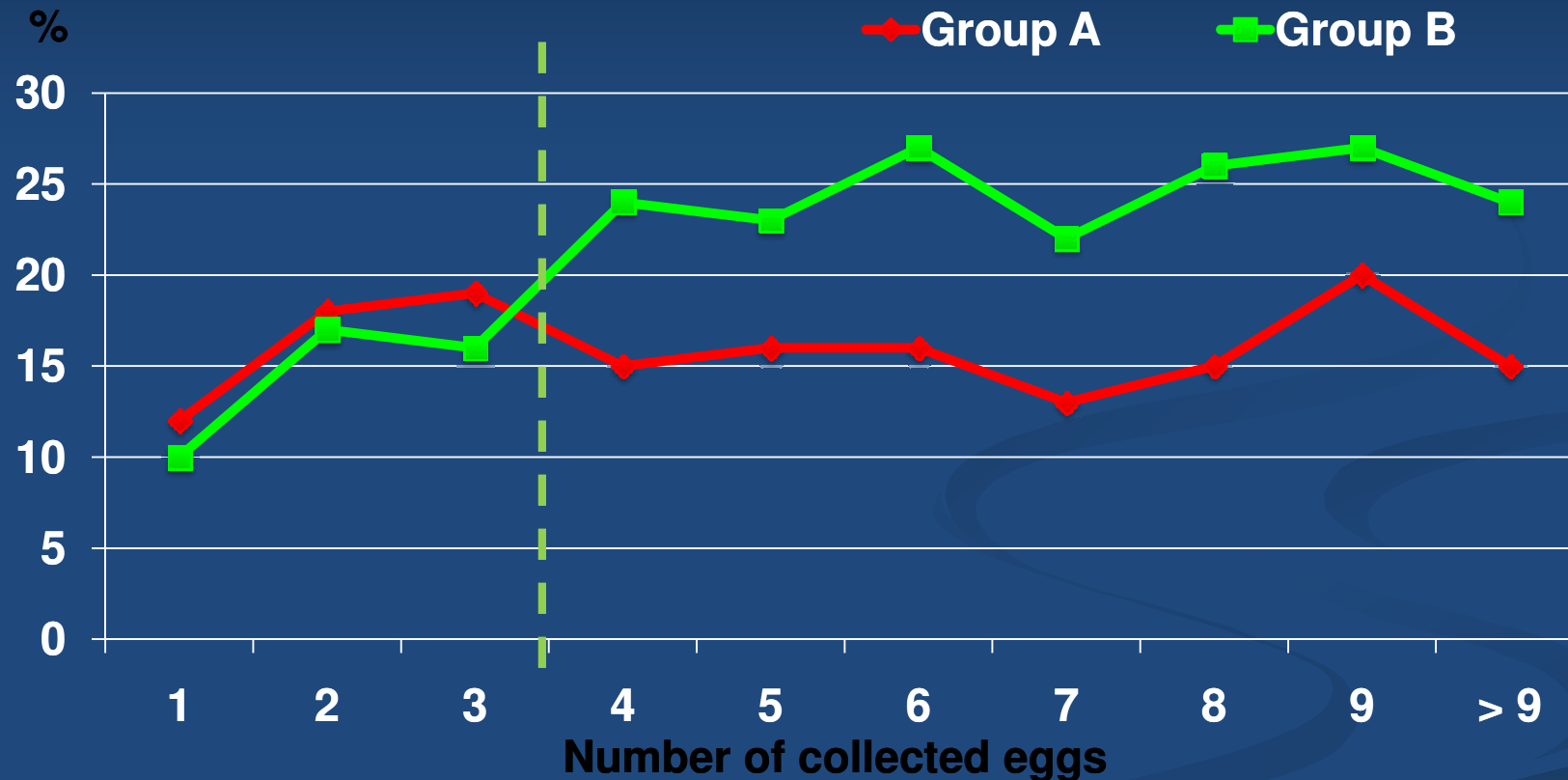


— Cut-off point of statistically significant difference



# Results depending on the number of collected oocytes

## Implantation Rate

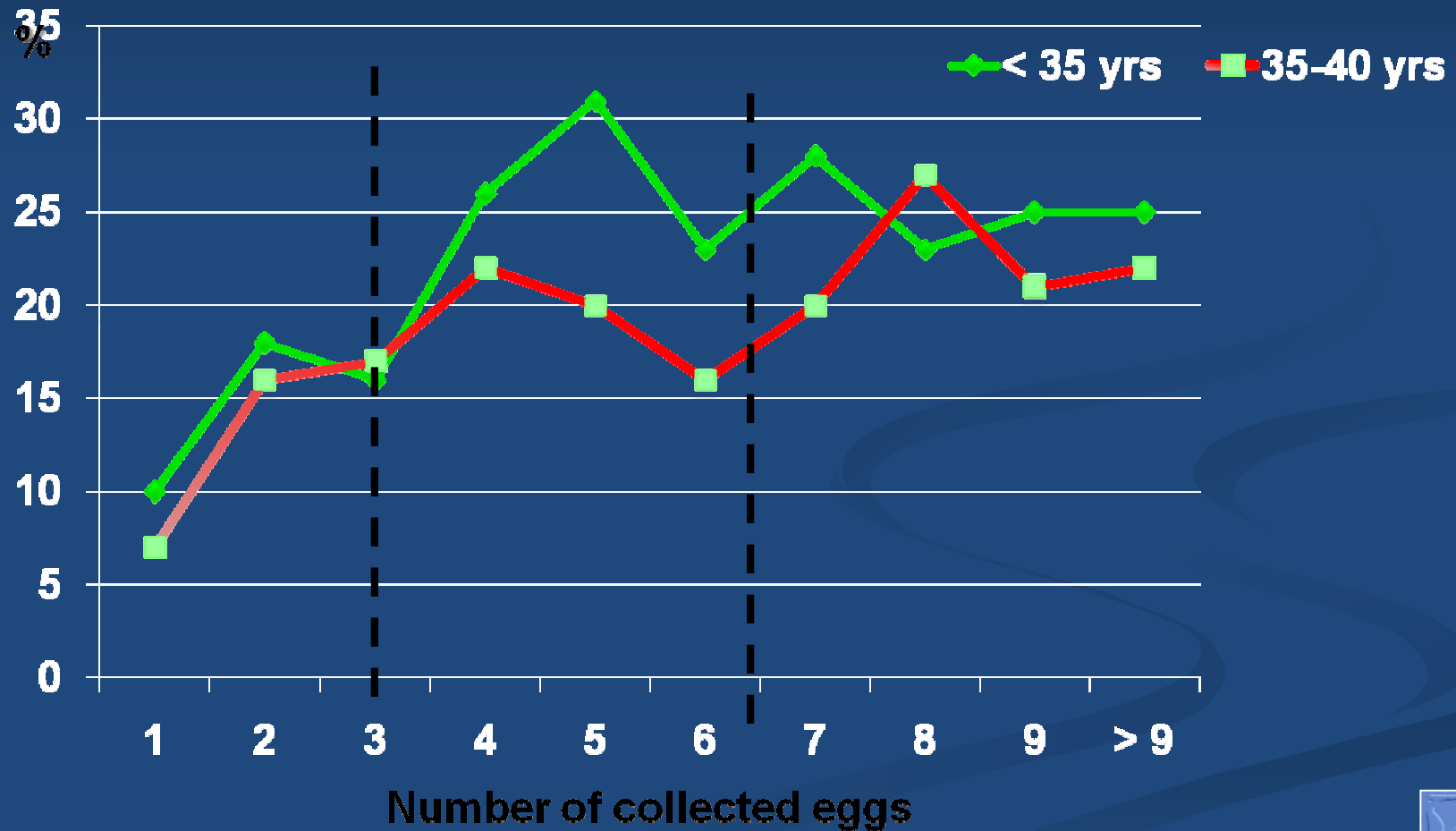


**Group A** : insemination of a maximum of 3 eggs in all cycles (according to the Law approved in 2004)

**Group B** : insemination of all eggs ( pre-law period)



# Implantation rate



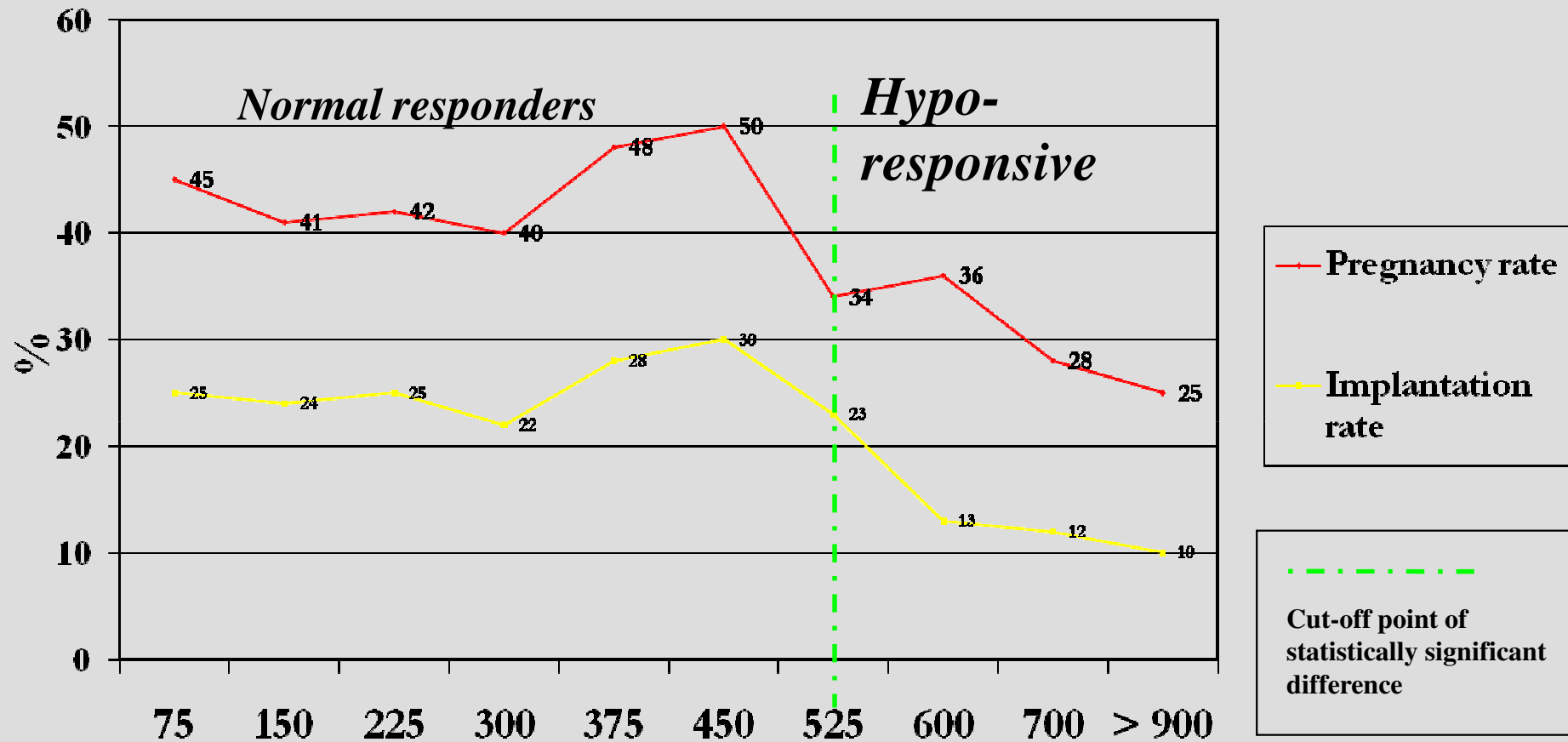


# Who are the poor ovarian responders ?

- Patients with an intrinsic capability to recruit few follicles and produce few eggs under COH
- The number is “low” when it expose the woman to a significantly lower PR compared to similar aged women with “more” oocytes
- **Are not :**  
**hypo-responders to FSH**



## GnRH agonist down regulated cycles ≥ 6 collected oocytes



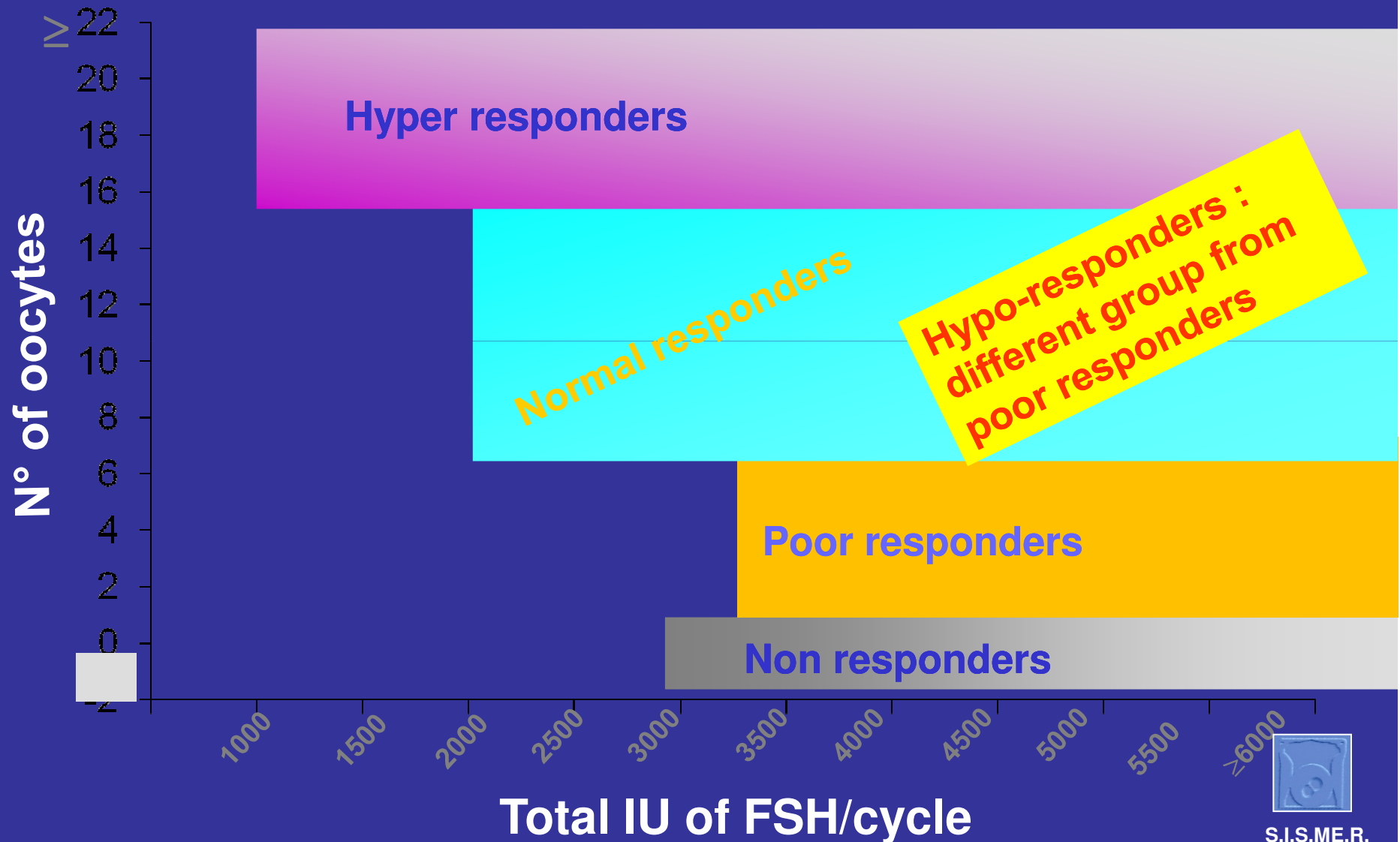
**FSH IU for each collected oocytes**

*Ferraretti et al. Hum Reprod, 119-20, 2002*



S.I.S.M.E.R.  
VISION 2000

# Ovarian response to COH



# Hypo-responsiveness to Gn

- **Patient's dependent ?** Gene-regulated :
  - lower sensitivity to exogenous FSH
  - lower sensitivity to endogenous LH

- **Protocol's dependent ?**

Profound suppression of bioactive LH  
by agonist protocols



# Poor ovarian response

- **Nomenclature ?**
- Definition ???



# Which term to choose to define this population of women ?

- **Poor ovarian response**
- **Low ovarian response**
- **Bad ovarian response**
- **Non-responders**
- .....



# Nomenclature ?

- **Poor** ovarian response (*D.Kyrou, ... and B.C. Tarlatzis, Review Fertil Steril 2009*)
- **Low** ovarian response (*B.C.Tarlatzis Review Hum Reprod 2003*)
- Bad ovarian response
- Non -responders
- .....



# Nomenclature

- **Poor ovarian response**

**Acronym : POR**

- Low ovarian response
- Bad ovarian response
- Non -responders
- .....





# Poor ovarian response

- Nomenclature
- **Definition** : *which criteria to use to identify POR ???*



# E.S. Surrey et al, *Fertil Steril* 23,2000

Criteria used to define "poor responders."	
Criteria	Reference
No. of mature follicles	
<2	2, 3
<3	4, 5, 6, 7
≤4	1, 10
<5	8, 9
Early follicular phase levels (mIU/mL)	
>6.5	17
>9	12
>12	11
>15	3, 13, 14, 15
↑ FSH:LH ratio	17
Maximal E <sub>2</sub> level (pg/mL)	
<100 on day 5	10
<300	7
<400	14, 18
<500	3, 6, 21
<660	27
"Efficacy index"	19
Age >40 y	11
Mean daily gonadotropin dose	
>300 IU	2, 12, 22, 23
Total gonadotropin dose	
>25 ampules	11
>44 ampules	41
Days of gonadotropin therapy	2, 11, 13
No. of mature oocytes retrieved	
≤3	6
≤4	24
<6	25
Single dominant follicle	6
Spontaneous LH surge	7
Failed "Lupron screening test"	55, 86
Failed conception	27
Undefined	49, 51



**E.S. Surrey et al, *Fertil Steril* 23,2000**

## **Conclusions**

- *Lack of a uniform definition is the most basic factor that makes impossible to compare studies and very difficult to develop or assess any protocol to improve the outcome*
- *A standard definition is urgently needed*



## **In the last 10 years, the review of :**

- **A. Demirol et al. Fertil Steril 2009; 92,481**
- **K. Kahraman et al. Fertil Steril 2009; 91, 2437**
- **L.G. Nardo et al. Fertil Steril 2009; 92,1586**
- **K. Jayaprakasan et al. Fertil Steril 2009; 92,1862**
- **W. Schoolcraft et al. Fertil Steril 2008; 89,151**
- **C. Kailasam et al. Hum Reprod 2004; 19,1544**
- **V.N. Weitzman et al. Fertil Steril 2009; 92,266**
- **G. Barrenetxea et al. Fertil Steril 2008; 89,546**
- **F. Fabregues et al. Hum Repord 2008; 24,349**
- **T. Brodin et al. Fertil Steril 2008; 90,1656**
- **H. Yarali et al. Fertil Steril 2009; 92,231**
- **J.L. Frattarelli et al. Fertil Steril 2008; 89,1118**
- **J.L. Frattarelli et al. Fertil Steril 2008; 89, 1113**
- **N. Massin et al. Hum Repord 2006; 21,1211**
- **L. Detti et al. Fertil Steril 2005; 84,1401**
- **L.P. Cheung et al. Hum Reprod 2005; 20,616**



- **J.Yen-Ping et al. Fertil Steril 2005; 83,883J**
- **.A. Garcia-Velasco et al. Fertil Steril 2005; 84,82**
- **E.Kolibianakis et al. Hum Reprod 2004; 19,2549**
- **S.K. Goswami et al. Hum reprod 2004; 19,2031**
- **A.Weissman et al. Fertil Steril 2003; 79,886**
- **F. Martinez et al. Hum Reprod 2002; 17,634**
- **M.M.Biljan et al. Hum rRprod 2001; 15,2140**
- **M.A. Akman et al. Hum Reprod 2001; 16,868**
- **J.A. Garcia-velasco et al. Hum Repord 2001; 15,2292**
- **M.Dirnfeld et al, Fertil Steril 2001; 72,406**
- **G. De Placido et al. Hum Reprod 2001; 15,17**



# **In the last 10 years, compared to the Surrey review ,**

- **Few criteria no more used :**
  - dynamic tests : with Clomiphene Citrate (CCCT)  
FSH ( EFORT ) or GnRH agonist (GAST)
  - total gonadotropins dose and days of therapy



# **In the last 10 years, compared to the Surrey review**

- **.... and new criteria added to the list:**
  - **US ovary evaluation**  
(AFC, volume, blood flow )
  - **new bio-markers of ovarian reserve**  
( Inhibin B, AMH)
  - **menstrual cycle length**  
( Brodin et al, Fertil Steril 2008)
  - **IU of gonadotropins used for each oocyte recovered**



# Agreement (2010)

- A standard definition is **“still”** urgently needed





# Uniform definition of poor ovarian response

Way is important ?

- *for clinical practice*
- *to estimate the incidence*
- *to select homogeneous population of patients for clinical trials*
- *to assess the proposed strategies to improve the outcome*



**“Exogeneous LH in COH for ART “ : a  
prospective randomized study**

*A.P.Ferraretti et al Fertil Steril,82, 2004*

**Material and Methods :**

*...patients showing **hypo-responsiveness** to  
FSH...*



**Addition of rLH to rFSH for controlled ovarian  
hyperstimulation in assisted reproductive cycles**

**( Cochrane Review 2009- 14 trials )**

**Mochtar MH, Van der Veen F, Ziech M, van Wely M**

*..... one study included only **poor**  
**responders ( Ferraretti 2004) .....***

**How to improve the probability of pregnancy in poor responders : a systematic review and meta-analysis  
(D. Kyrou et al , Fertil Steril 2009 )**

*“ Available evidence originates from both retrospective and prospective studies that used variable definition of POR.*

*A systematic appraisal of the available evidence aiming to draw reliable conclusions is currently lacking “*



# Identification criteria to select POR in the literature

## Based on

**Predictive criteria**  
( expected or potential  
POR)

**Previuos**  
**ovarian cycle(s)**  
( past POR )



# Predictive criteria for POR ( potential POR)

## Biological criteria

- *Advanced reproductive age ( > 38 or > 40 ? )*
- *Basal FSH ( > 10 or > 12 mIU/ml ? )*
- *AFC  $\leq 6$*
- *(AMH- Inhibin B )*

## Clinical criteria

- *Shortening of menstrual cycles*
- *(Repeated ) pelvic surgery*
- *Previous chemio-radioteraphy*
- *(Familiar early menopause)*



# A systematic review of tests predicting ovarian reserve (ORT)

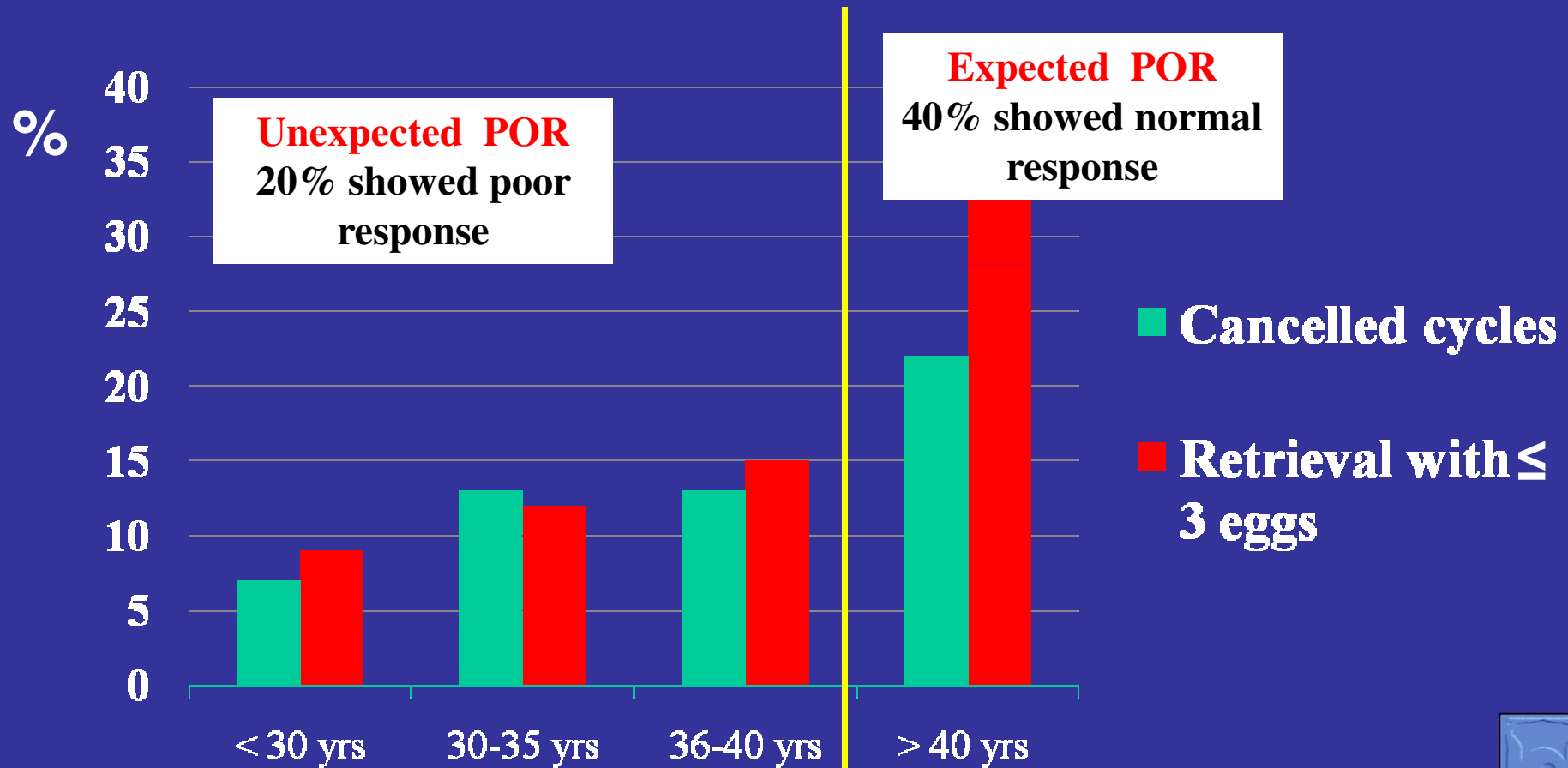
Broekmans et al , Human Reprod Update 2006

- *Accuracy of testing for POR to COH appears to be **modest** ( unless very high thresholds are used)*



# Poor ovarian response according to age

( SISMER - 3847 patients entering the 1° cycle )





# Identification criteria to select POR in the literature

## Based on

Predictive criteria  
( expected or potential  
POR)

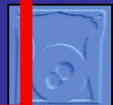
Usefull for assessing the Gn starting dose , but  
~40-50 % of “potential” POR will show a  
normal response



# A systematic review of tests predicting ovarian reserve (ORT)

Broekmans et al , Human Reprod Update 2006

- *Accuracy of testing for POR to COH appears to be modest ( unless very high thresholds are used)*
- *An abnormal test necessitates confirmation by another test. This other test may be a first IVF attempt*
- *Entering the first cycle without any prior testing seems to be the preferable strategy*



# Identification criteria to select POR in the literature

Based on

**Predictive criteria**  
( expected or potential  
POR)

**Previuos**  
**ovarian cycle(s)**  
( past POR )



# POR identification ( under treatment )

- Cycle cancelled because  $\leq 3$  dominant follicles ?
- $< 4$  (5) collected oocytes ?
- Estradiol  $< 500$  pg/ml
- Correlation between FSH dosage and n.of oocytes recovered ( $\leq 3 - 5$  oocytes and  $> 3000$  IU of Gn ) ?



# Identification criteria to select POR in the literature

## Based on

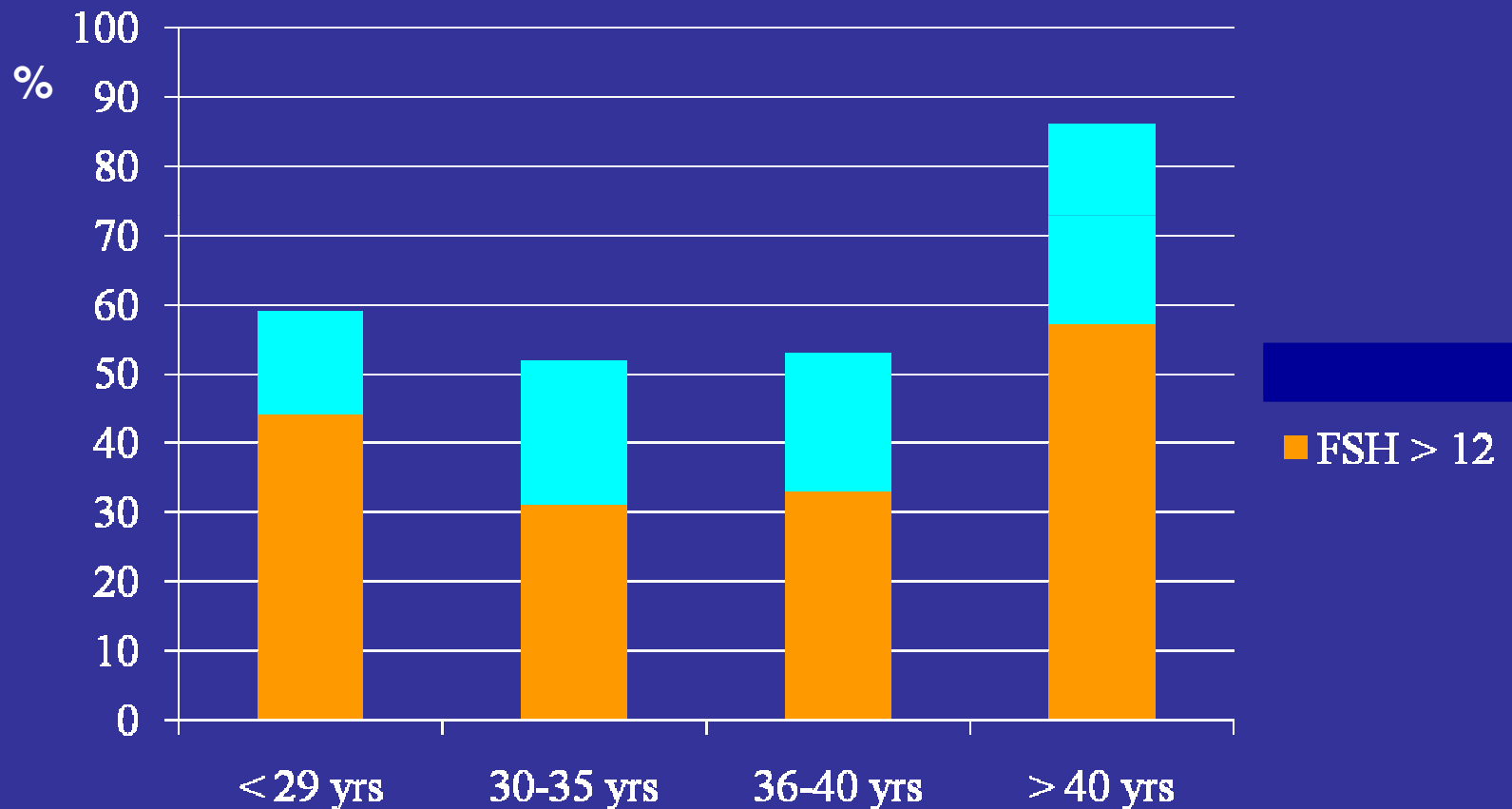
Previous ovarian cycle(s)  
( past POR )

Most Authors select patients as POR for  
further studies after one cycle

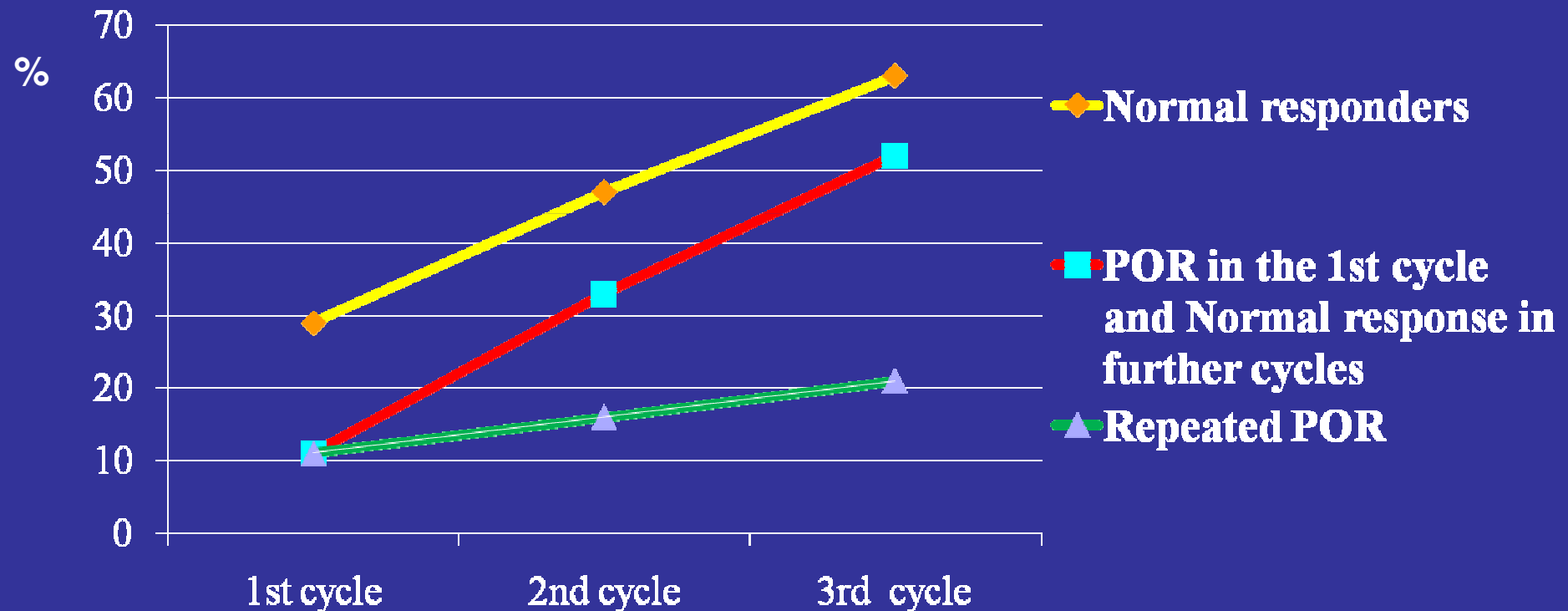


# Second cycle in previous POR ( different analogue protocol and higher doses of Gn)

**% of patients who showed a repeated POR**



# Life table ( age $\leq$ 40 yrs ) (Ongoing pregnancy rate)



# A systematic review of tests predicting ovarian reserve

Broekmans et al , Human Reprod Update  
2006

- Entering the first cycle without any prior testing seems to be the preferable strategy
- Once a POR is obtained, the question arises whether this finding is based on depleted ovaries or other causes
- **A repeat cycle** with adequate maximal stimulation (or *post hoc*- performed ORT ) may **correctly classify** POR



# Identification criteria to select POR in the literature

Based on

Predictive criteria  
( **potential POR** )

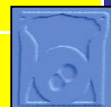
Previous ovarian cycle(s)  
( **past POR** )

Both populations



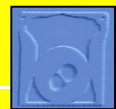
## Prospective randomized studies to improve outcome in POR : results depending on definition

Author	Definition	N. of patients	Oocytes collected in the study (proposed protocol vs control)
Schoolcraft 2008	Past and Potential	534	12.6 vs 13.5
Weitzman 2009	Past and Potential	121	9.1 vs 8.9
Frattarelli 2008	Past and Potential	60	11.8 vs 9.5
Detti 2005	Past and Potential	61	10.8 vs 7.8
Frattarelli 2008	Past and Potential	1230	9.1 vs 9.0
Yarali 2009	Past and Potential	1382	6.7 vs 5.1
Cheung 2005	Past and Potential	66	5.8 vs 5.6
Massin 2006	Past and Potential	53	3.5 vs 3.2



## Prospective randomized studies to improve outcome in POR : results depending on definition

Author	Definition	N. of patients	Oocytes collected in the study
Barrenetxea 2008	Potential ( age > 40)	84	5.4 vs 5.7
Fabregues 2009	One previous cycle	62	5.1 vs 4.3
Dirnfeld 2000	One previous cycle	63	6.5 vs 7.7
Velasco 2005	One previous cycle	147	6.1 vs 4.3
Velasco 2000	One previous cycle	70	8.7 vs 6.2
Kahraman 2009	One previous cycle	42	5.8 vs 5.6
Weissman 2002	One or more previous cycles	60	4.4 vs 3.1
Goswami 2004	One or more previous cycles	38	1.6 vs 2.1
Akman 2002	Two previous cycles	48	5.5 vs 4.5



# POR definition

To select homogeneous populations of patients for clinical studies

- One previous POR and altered ORT
- At least 2 previous POR ( $\pm$  altered ORT)

POR : cycle cancelled or  $\leq 3$  (?) oocytes



**Once identified real POR,  
to divide young POR and old POR  
because different strategies may be  
applied**

- **Age > 40 yrs** : egg donation ?
- **Age < 40 yrs** : to set up new strategies to improve the outcome ( focus on oocyte **competence** since the number may be not increased )





**Thank you !**

