



**AGEO**

**3° corso di AGGIORNAMENTO  
in Ginecologia e Ostetricia  
Bologna, 22-23 Novembre 2019**

**PMA :**

**Approccio unico o personalizzato?**

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# Medicina di precisione



# Algoritmi in Medicina



**Analisi di varie migliaia di immagini e informazioni da intelligenza artificiale**

***Diagnosi precoce e precisa***

***Maggiore aderenza terapeutica***

***Miglioramento della prognosi***

# Convegno Nazionale Sezione di Radiologia Informatica

## Intelligenza artificiale in Diagnostica per Immagini

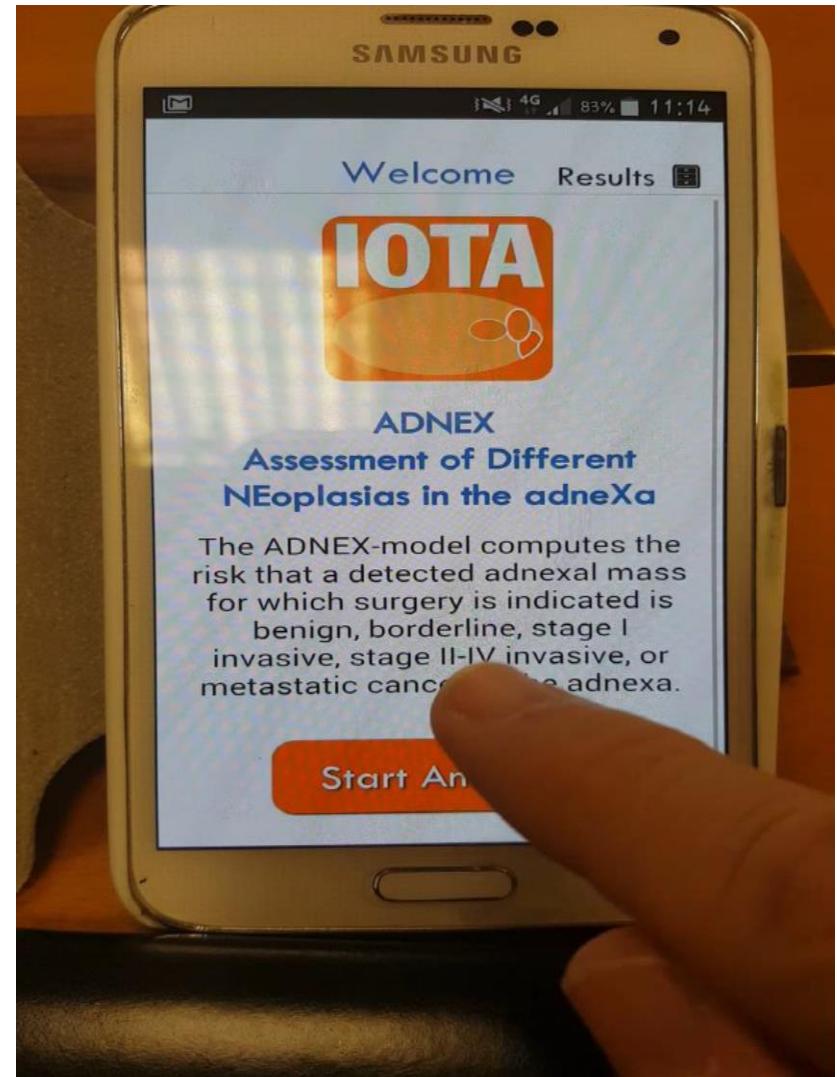


Bologna 24 maggio 2019  
Palazzo dell'Archiginnasio

# In Ecografia ?

**Reliability of IOTA  
(International Ovarian  
Tumor Analysis) score and  
ADNEX model**

**ADNEX (Assessment of  
Different Neoplasias in the  
adnexa) model to predict  
the risk that an ovarian  
mass is benign,  
borderline or malignant.**

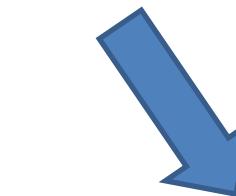




# Approccio personalizzato della fase terapeutica



**Prognosi**



**Trattamento**

**Aumentare la aderenza  
al trattamento**

**Evitare trattamenti inutili**

**Ottimizzare efficacia**

**Ridurre effetti collaterali**

**Ottimizzare rapporto costi-benefici**

## Coppie

## Tecniche

### Inferti

- *Età*
- *Riserva ovarica (AMH-AFC)*
- *Fattore/i di infertilità*
- *Storia riproduttiva*

**Età come causa unica di infertilità**

### Ferti/potenzialmente fertili

- *A rischio di trasmissione di malattie genetiche*
- *Singles*
- *Coppie omosessuali*

- **FIVET**
- **ICSI** *con seme eiaculato*
- **ICSI** *con seme prelevato chirurgicamente*
- **Donazione di gameti**
- **PGT** (*per aneuploidie, traslocazioni, malattie genetiche*)

# PMA trattamento

## Fase clinica

- Stimolazione ovarica*
- *Prelievo di ovociti*

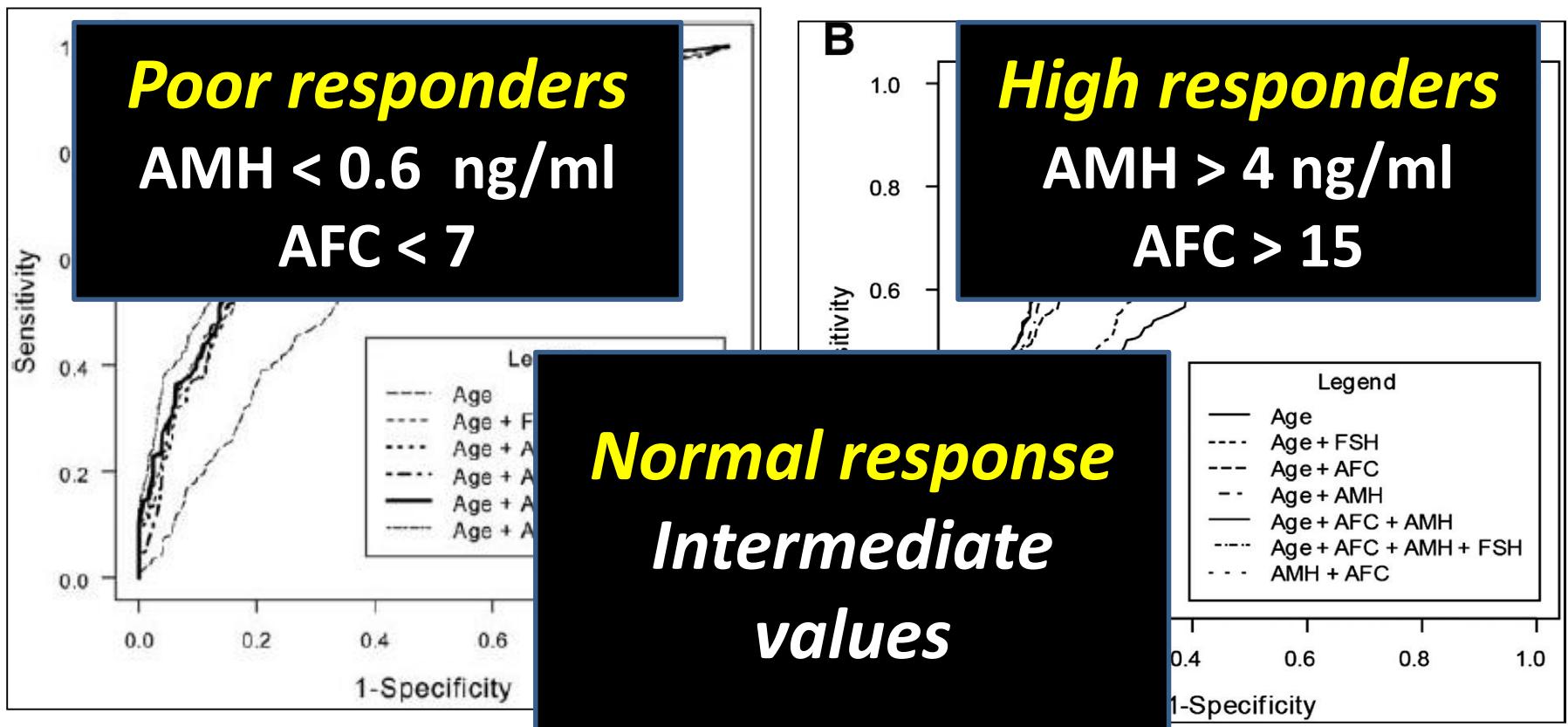
## Fase extra-corporea

- *Inseminazione ovociti*
- *Coltura degli embrioni*
- *Valutazione qualità*
- *Selezione embrioni per il trasferimento*
- *Crioconservazione*

Trasferimento embrioni



# Ovarian stimulation: individualized protocol based on ovarian reserve tests ( and age)



## An OHSS-Free Clinic by segmentation of IVF treatment

Paul Devroey\*, Nikolaos P. Polyzos, and Christophe Blockeel

- *Identification of the risk population*
  - *Low dose Gn in antagonist protocol*
  - *GnRHa triggering*
- 
- *Elective cryopreservation ( vitrification) of all embryos and embryo replacement in a receptive, non-stimulated endometrium (natural cycle or with artificial endometrial preparation)*

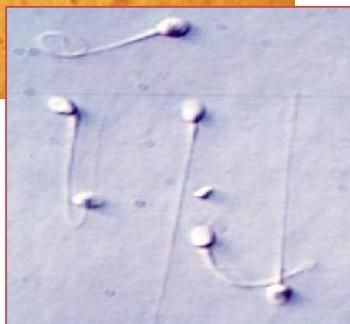
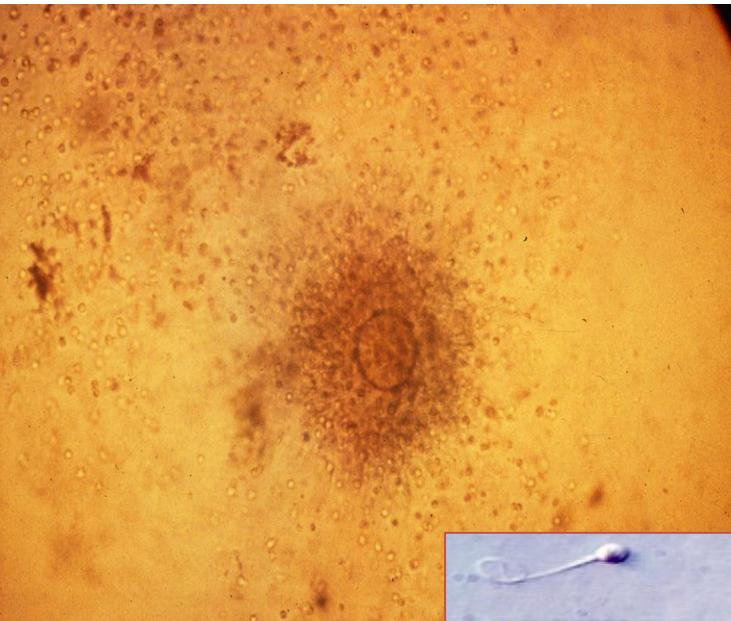


## Table 3 – OHSS in Europe

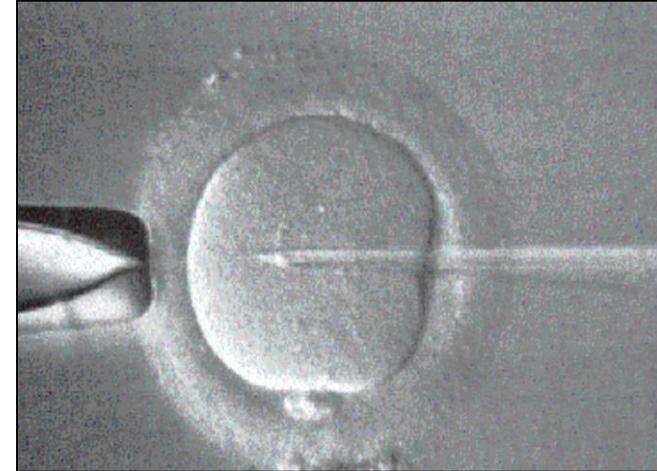
Year	OHSS	(%)
2000	1586	1.1
2002	2148	1.0
2003	2646	1.0
2005	3347	1.2
2007	2470	0.8
2009	2137	0,8
2010	1500	0,6
2011	1705	0,3
2013	850	0.2
2015		0.2

# Tecnica di inseminazione

**FIVET :**  
**normospermia**

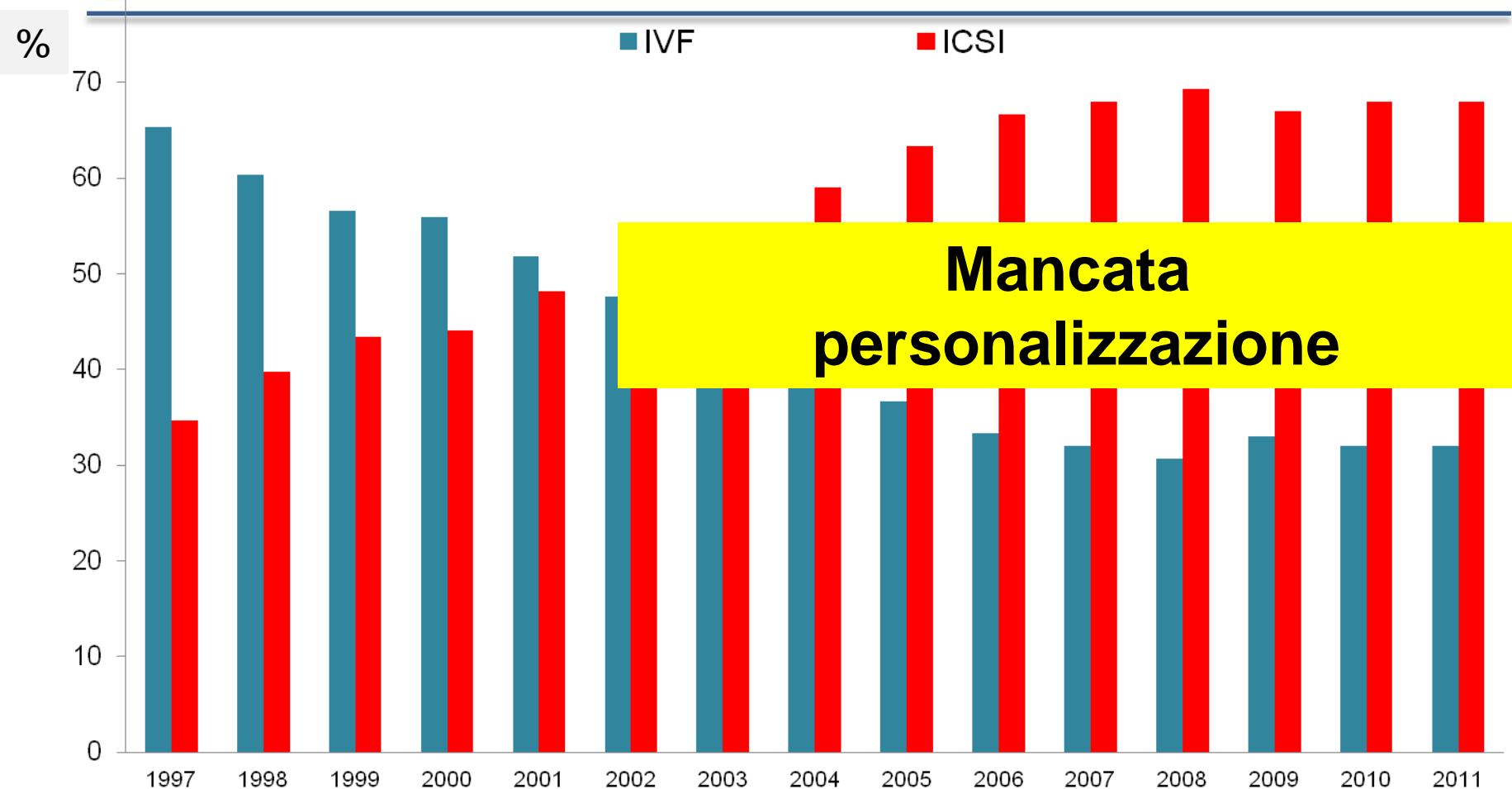


**ICSI :**  
**fattore maschile**





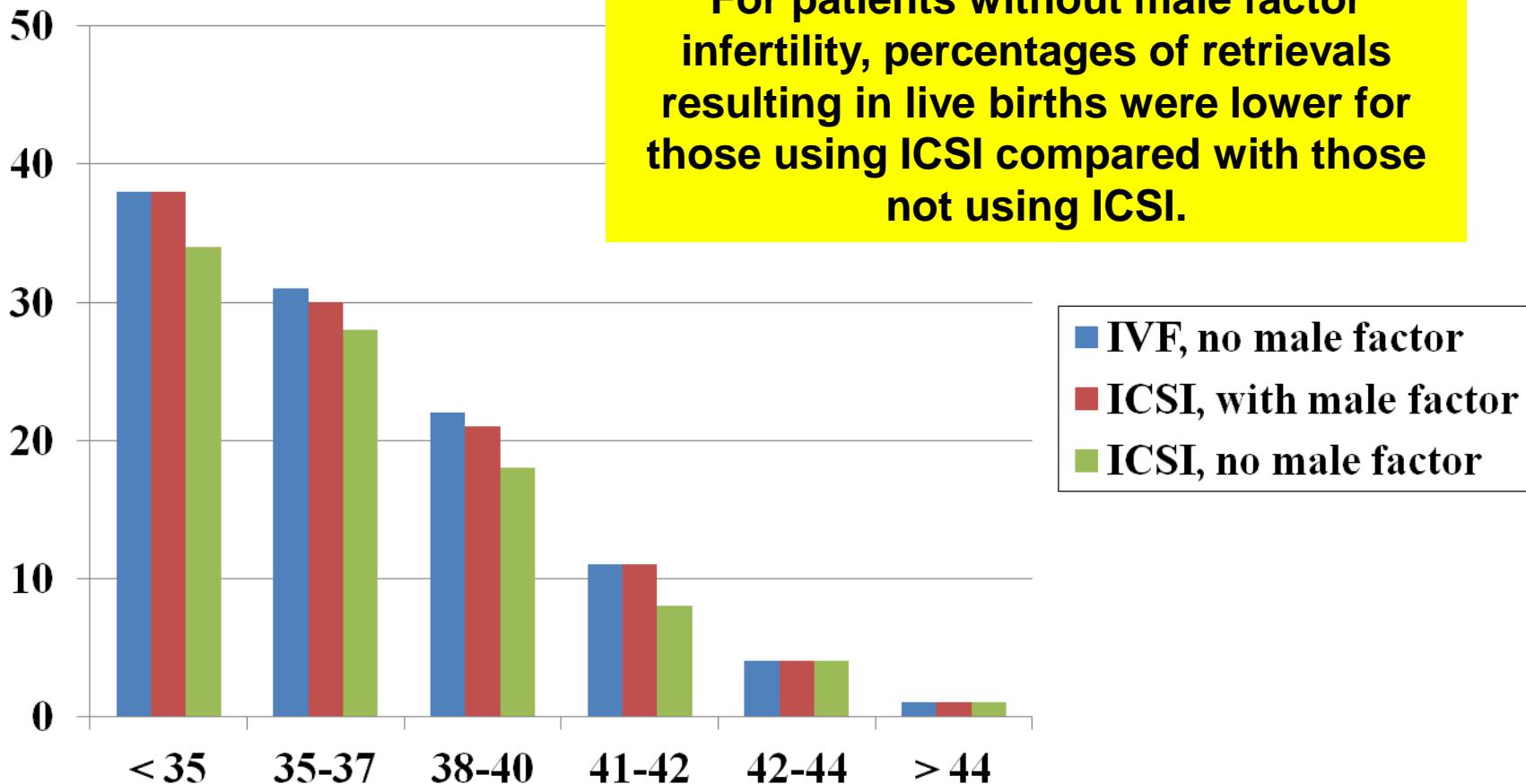
## Figure 5 - Trends in Techniques ( IVF vs ICSI)



# US Register 2015

## LBR

%





# Approccio personalizzato

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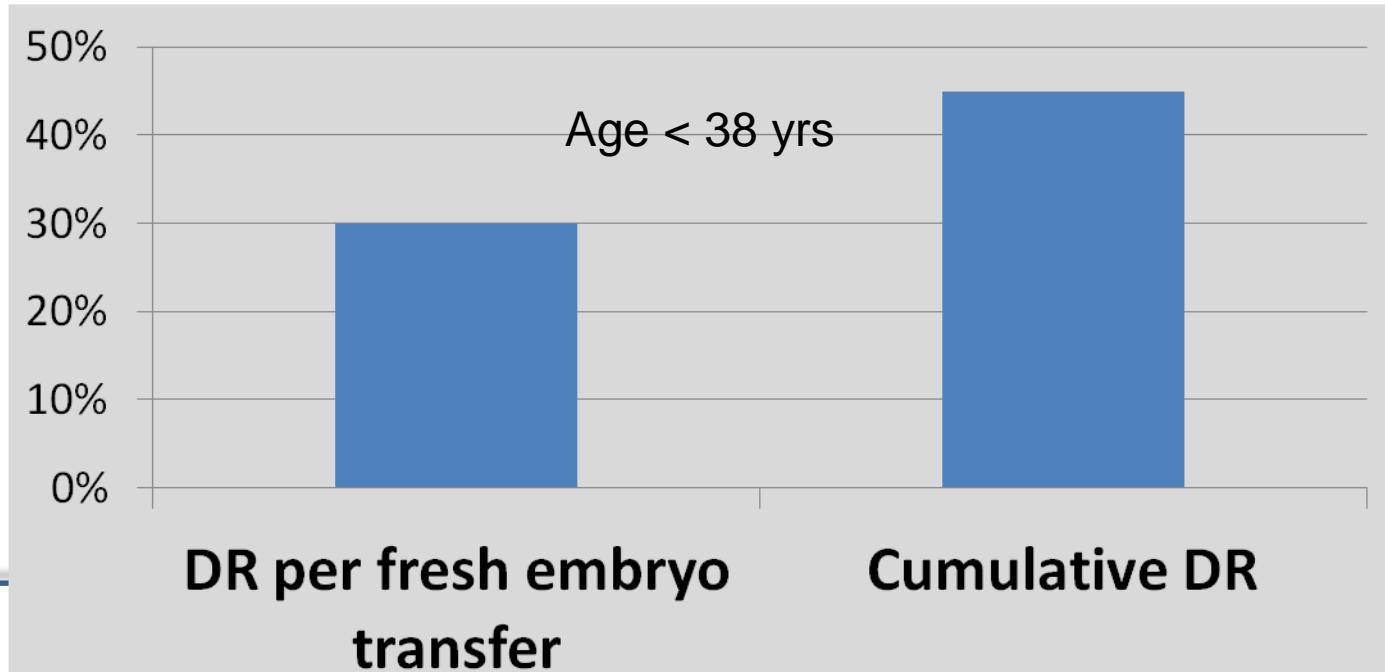
**Prognosi :**  
*probabilità di una gravidanza a termine*

**Goal : single healthy baby**



# PMA-Come misurare la efficacia ?

- Clinical pregnancy rate and delivery rate per single transfer
- Cumulative delivery rate per aspiration (including fresh and frozen embryo transfers)





# PMA-Come misurare la efficacia ?

- Clinical pregnancy rate and delivery rate per single transfer
- Cumulative delivery rate per aspiration (including fresh and frozen embryo transfers)
- Delivery rate per patient (after repeated IVF treatments)



# Prognosis of pregnancy

Individualized decision-making in IVF: calculating the chances of pregnancy : a prediction model

van Loendersloot LL<sup>1</sup>, et all Hum Repord 2013

Accurate Probability of an ongoing pregnancy .

**Range : from 0.00 to 0.72**

## Couples characteristics

*Female age*

*Duration of infertility*

*Type of infertility*

*Ovarian reserve*

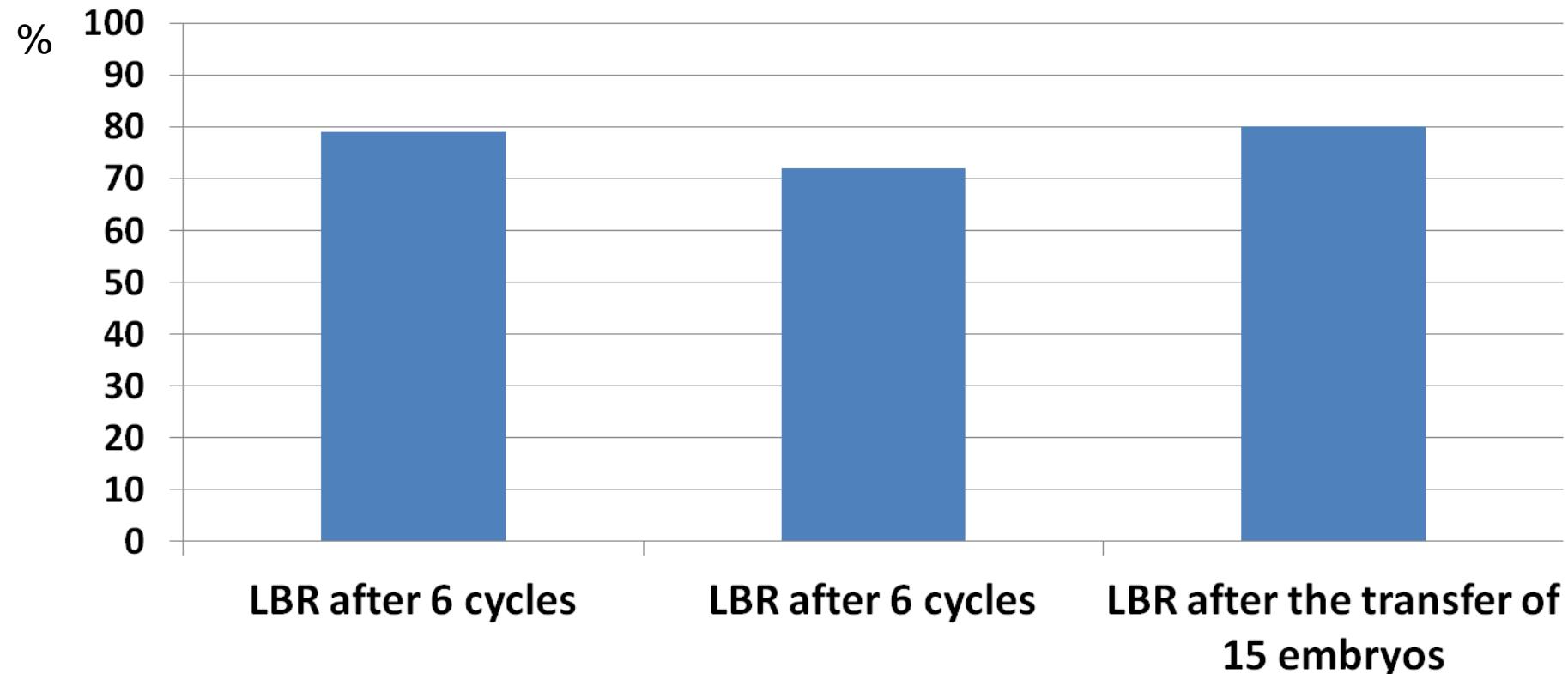


# Personalizzazione della Prognosi (e tempo alla gravidanza)

- Età < 38 anni ( ottimanle < 35 anni)
- Normale riserva ovarica
- Non fattore maschile severo
- Non patologie uterine
- Cariotipo normale



## Cumulative live delivery after the exposure to multiple cycles of IVF in patients $\leq 38$ years



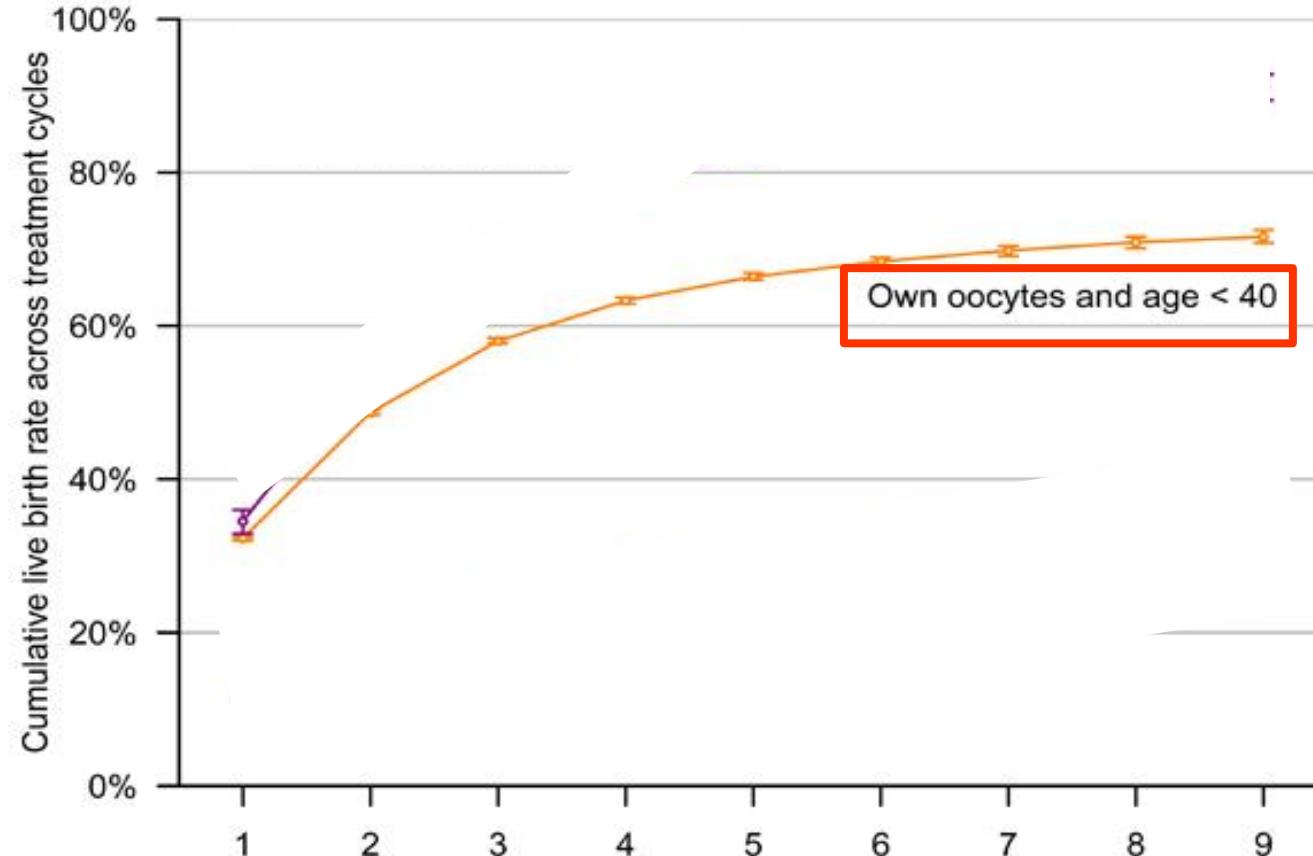
*Stewart et al,*  
*Fertil Steril, 95- 2011*

*Gnoth et al*  
*Hum Reprod 26,2012*

*Garrido et al,*  
*Fertil Steril, 96,2011*

LBR with repeat IVF  
Smith et al  
JAMA ,2015

156,947 women  
257,398 cycles



The live-birth rate for women < 40 yrs **conceiving naturally**, who had been trying for 12 menstrual cycles, varied between **58%** and **74%** depending on the woman's age and frequency of intercourse .



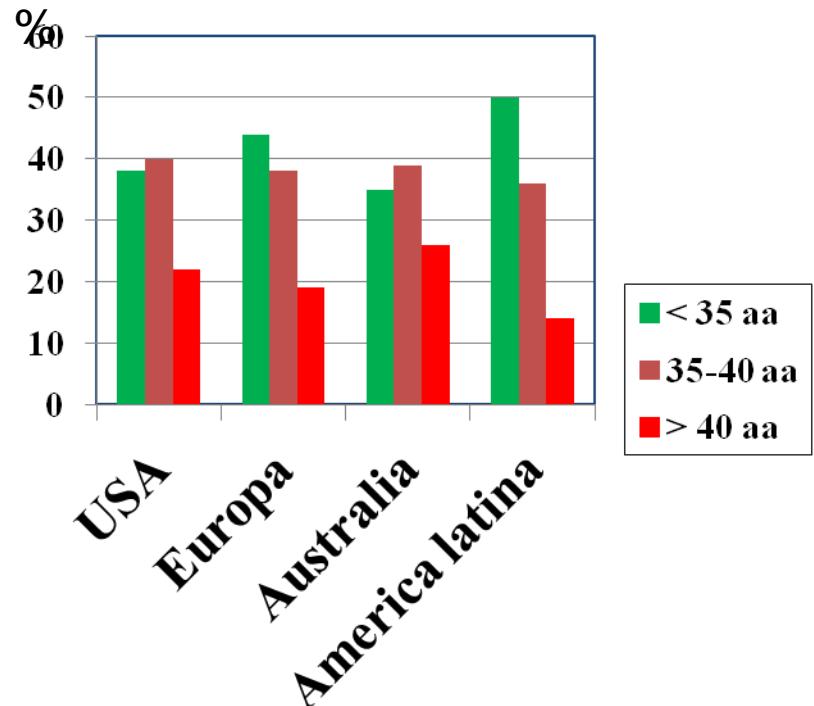
# Prognosi (e tempo alla gravidanza)

- Età < 38 anni ( ottimanle < 35 anni)**
- Normale riserva ovarica**
- Non fattore maschile severo**
- Non patologie uterine**
- Cariotipo normale**

**Pazienti ottimali < 50%**

# PMA - Età femminile

## Data from Registers (2014)



Ferraretti et al.  
*Hum Reprod* 2011

Età	Ridotta riserva ovarica
< 30	2%
30-35	5%
35-40	10%
41-43	35%
> 43	60%

Boivin et al (2012). Tackling burden in ART: an integrated approach for medical staff. Hum Reprod 27, 941-50

## Drop-out

> 40% di coppie

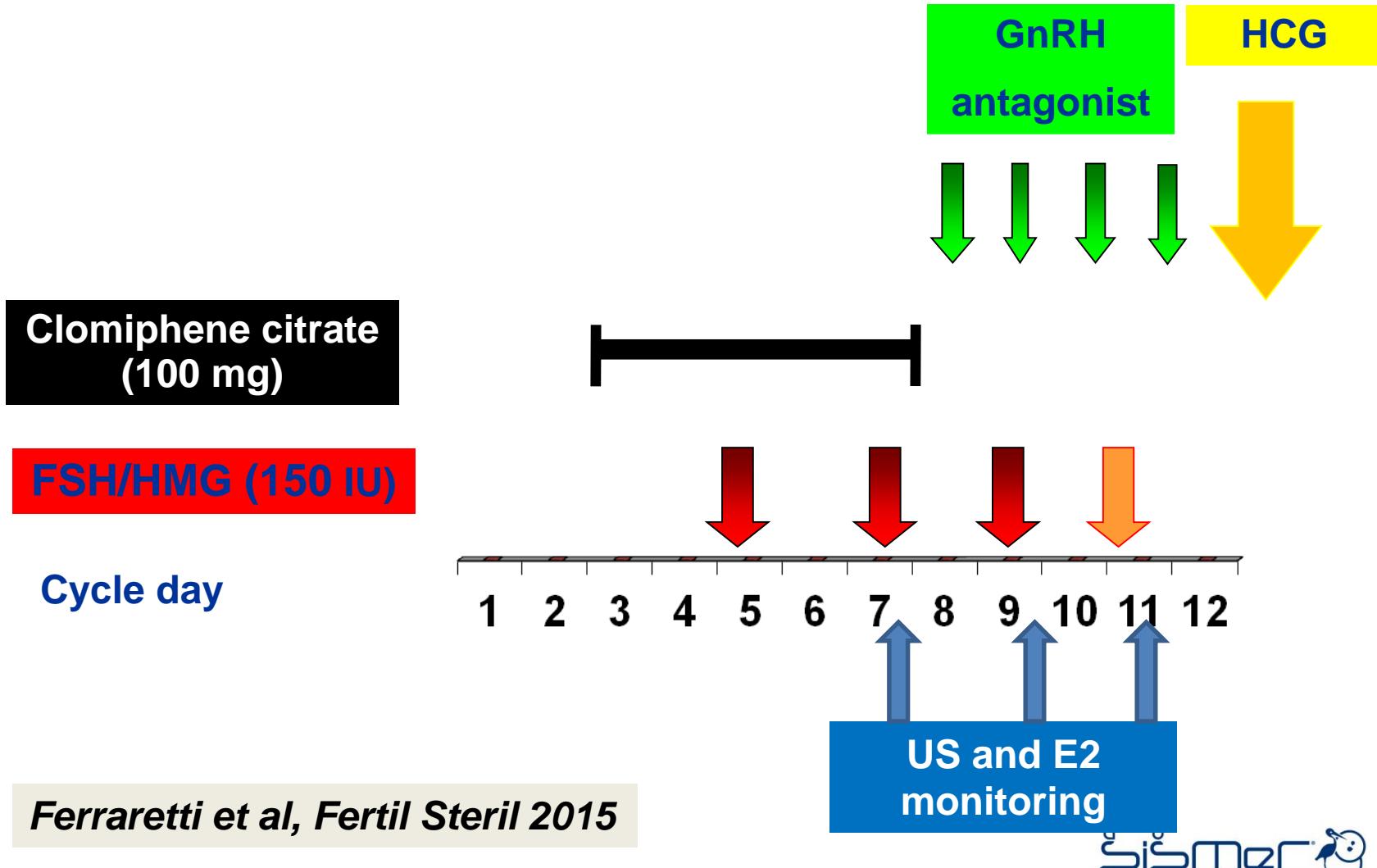
abbandonano il percorso dopo 2-3 cicli



Riduzione della potenzialità del trattamento

# Lite IVF in expected normal responders

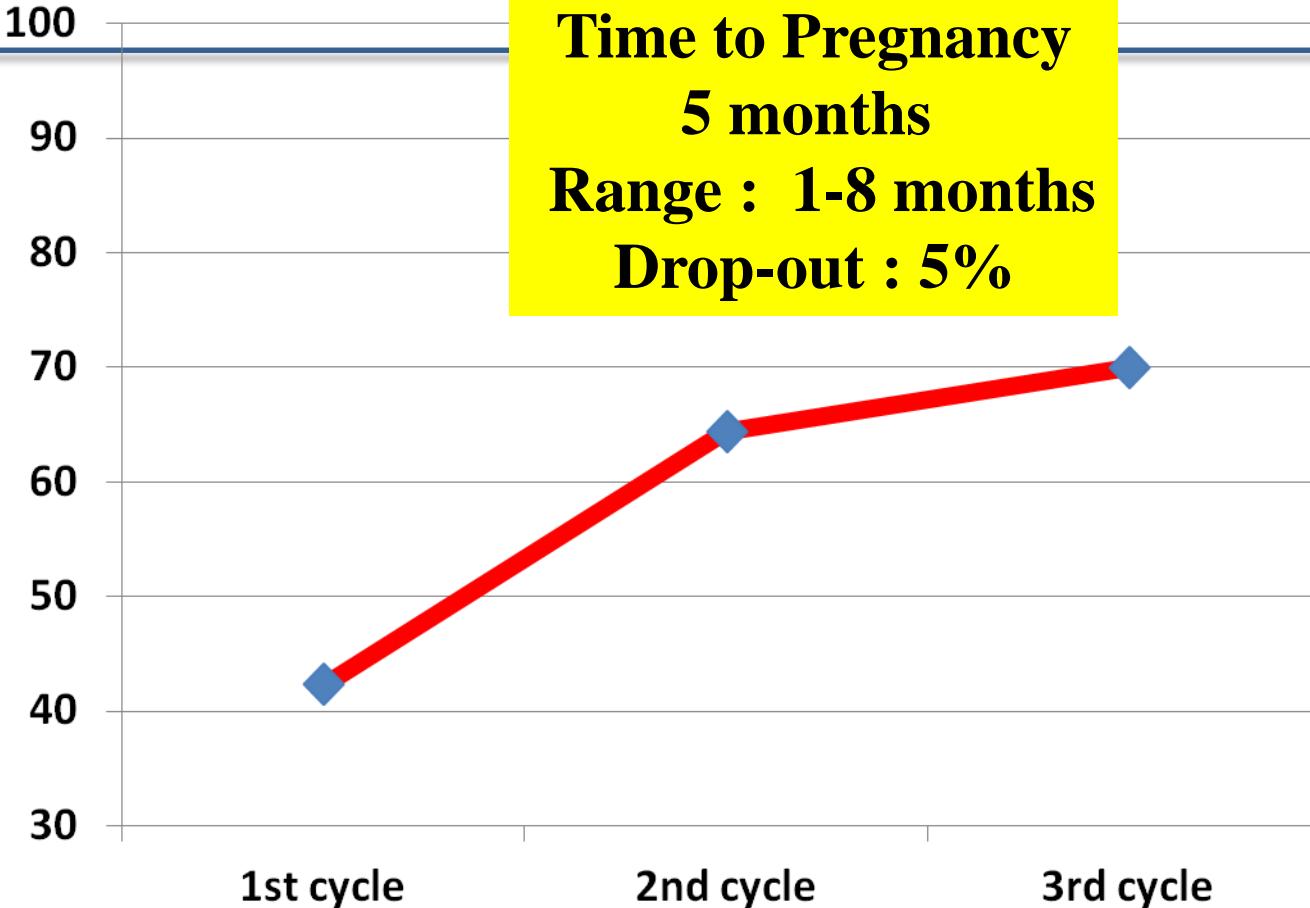
$\leq 38$  yrs –normal ovarian reserve



Ferraretti et al, Fertil Steril 2015



# Cumulative Delivery Rate

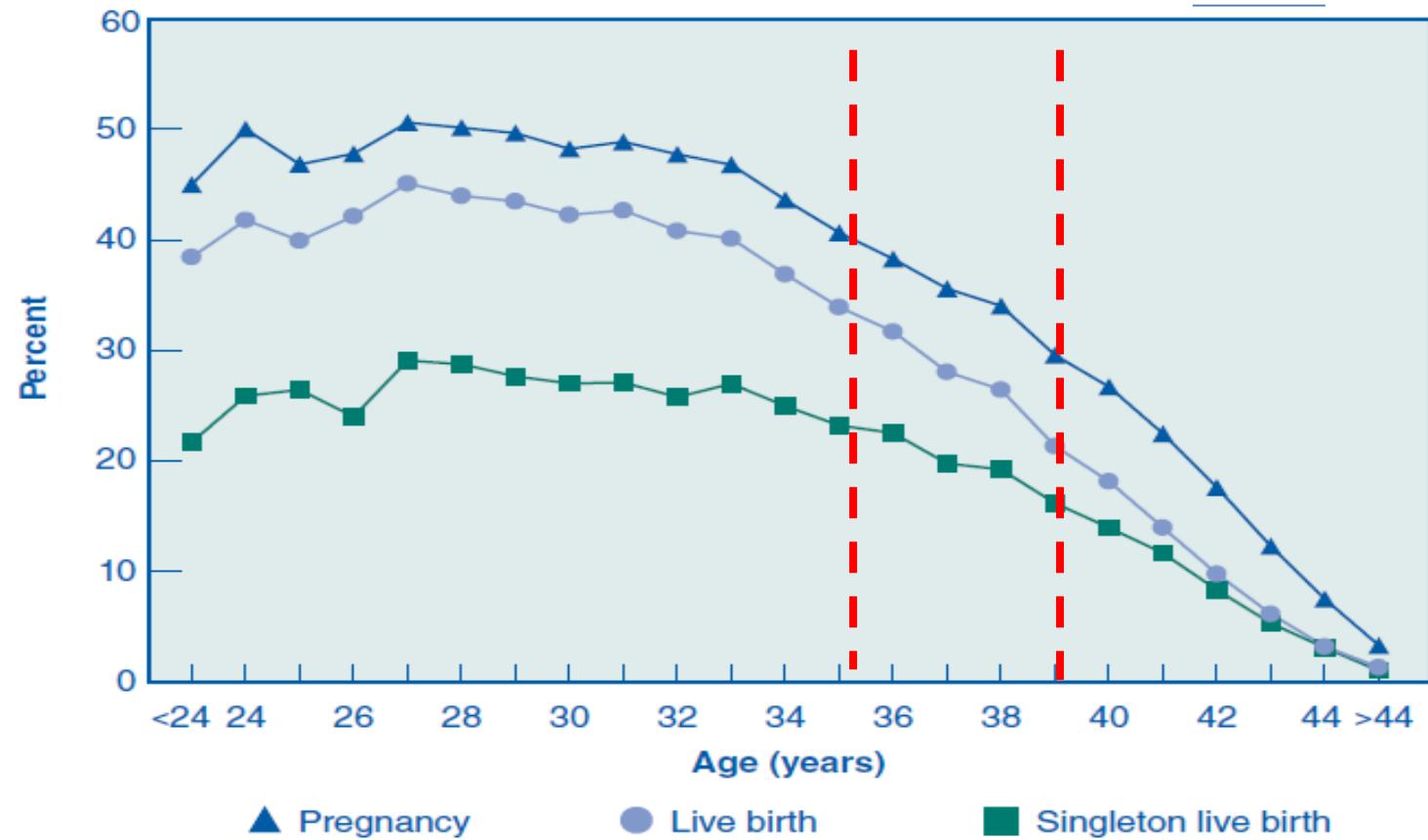




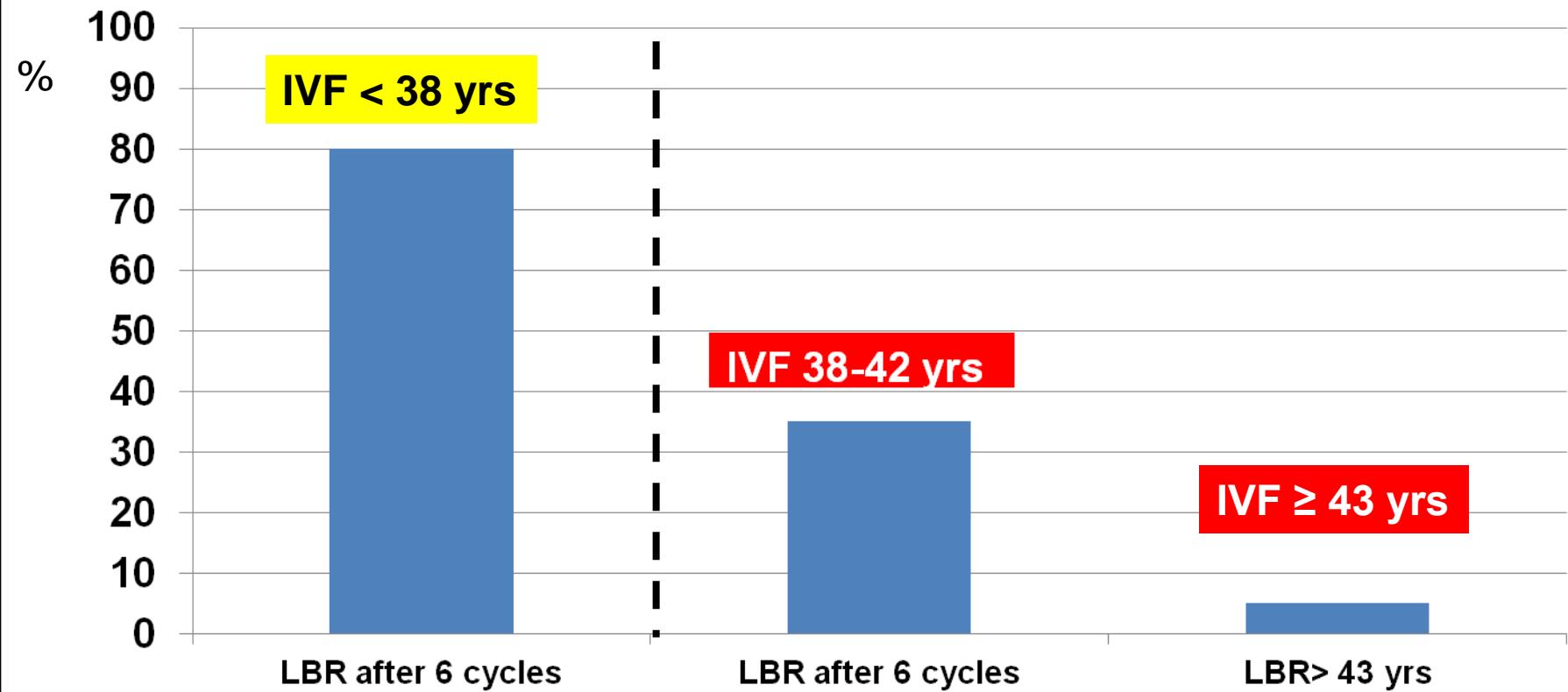
# Personalizzazione della Prognosi

- Età > 38 (>40) anni**
- Normale riserva ovarica (in relazione ad età)**
- Non fattore maschile severo**
- Non patologie uterine**
- Cariotipo normale**

# Possibilità di gravidanza a termine **in un ciclo** di PMA in relazione ad età Dati del Registro USA



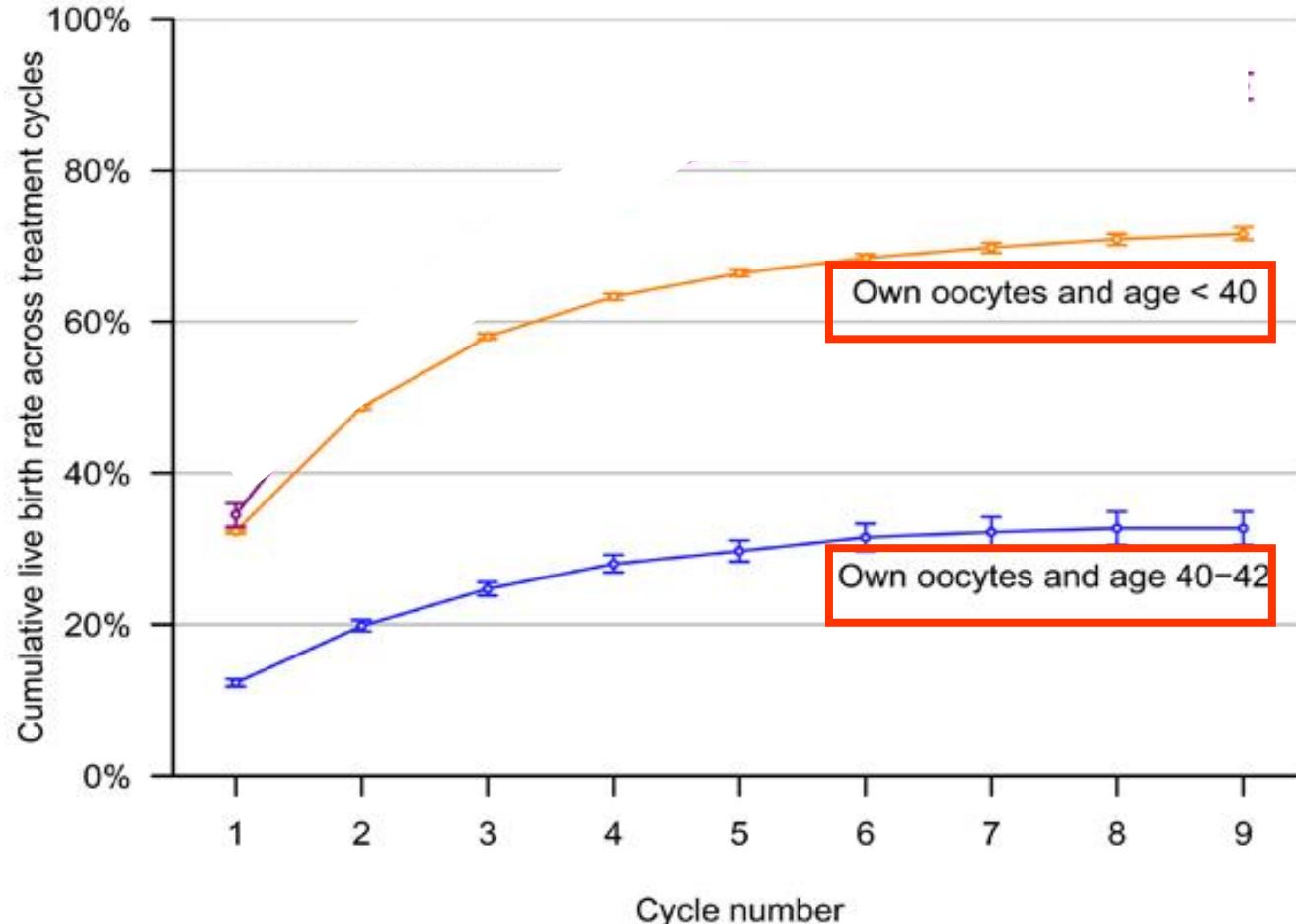
# Cumulative live delivery after the exposure to multiple cycles



*Stewart et al, Fertil Steril, 95- 2011  
Gnoth et al Hum Reprod 26,2012*

LBR with repeat IVF  
Smith et al,  
JAMA ,2015

156,947 women  
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#### Number of women

Own oocytes and age < 40	133,379	53,568	19,719	6,641	2,357	882	335	131	51
Own oocytes and age 40-42	15,561	6,671	2,579	884	301	130	60	36	20
Own oocytes and age > 42	4,420	1,578	509	160	67	24	10	5	4
Donor oocytes, all ages	3,587	1,636	939	554	287	126	53	27	8

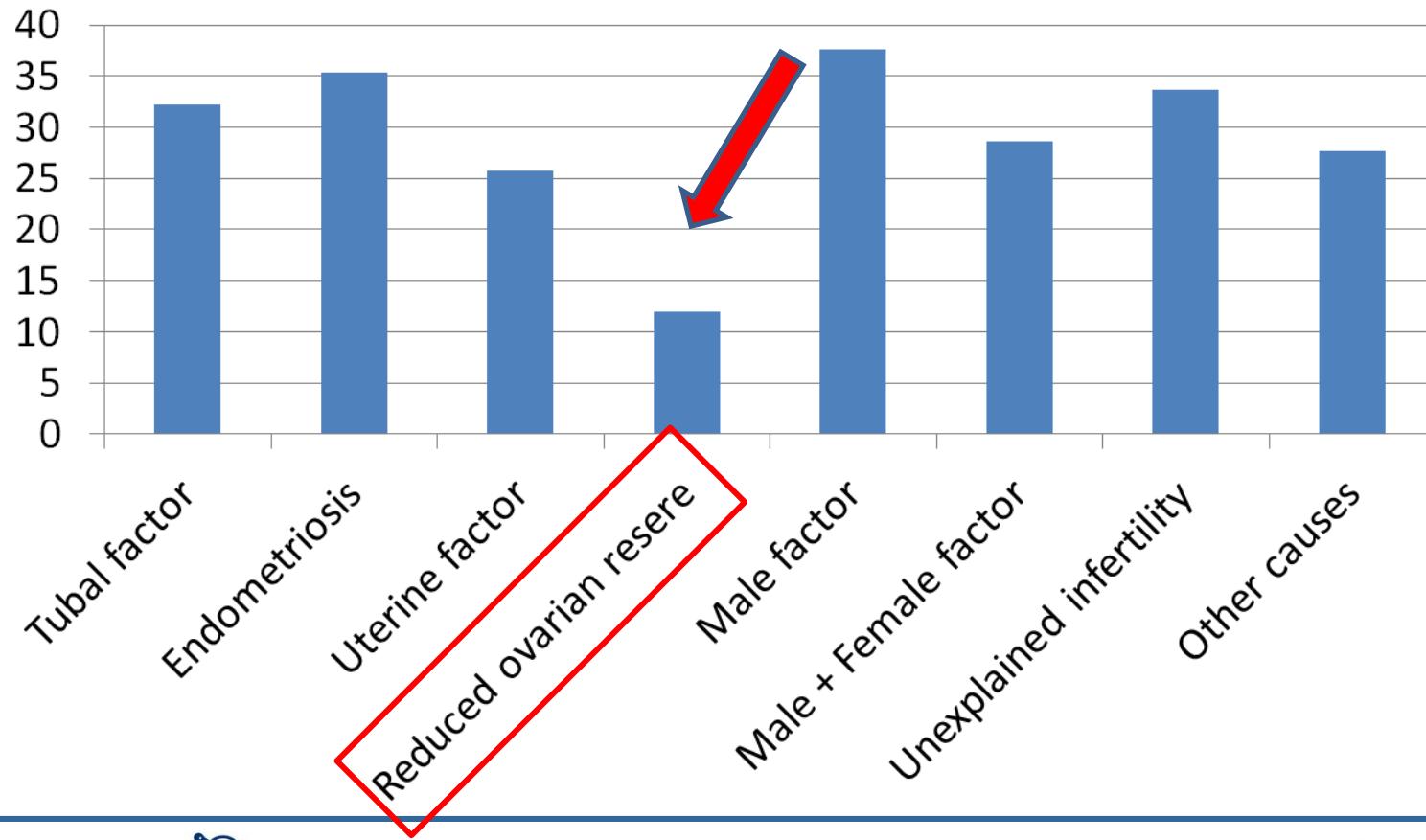


# Personalizzazione della Prognosi

- Tutte le età
- Ridotta riserva ovarica
- Non fattore maschile severo
- Non patologie uterine
- Cariotipo normale

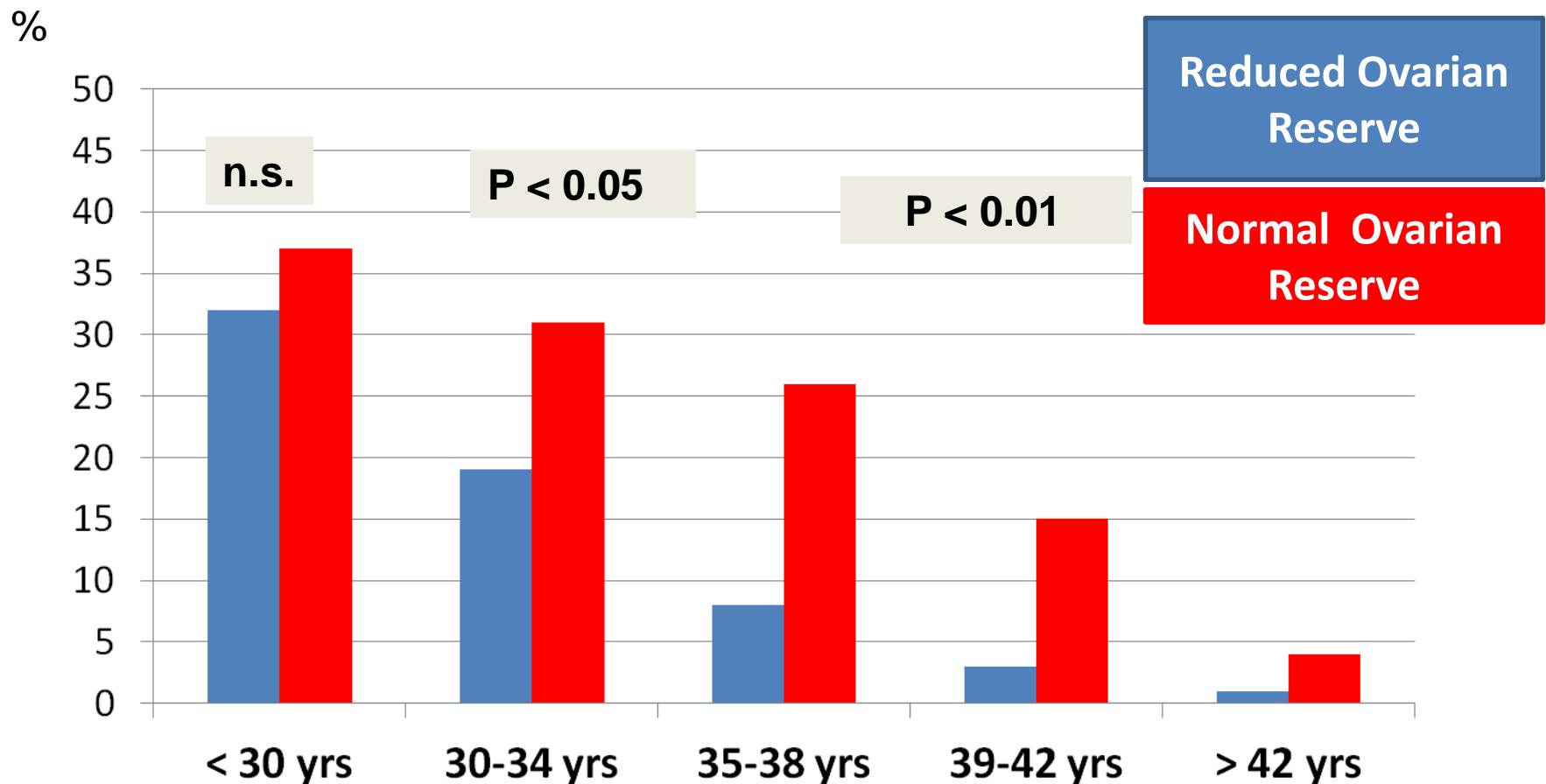
# Data from USA Register 2015 (All age groups)

## Live Birth per cycle by diagnosis

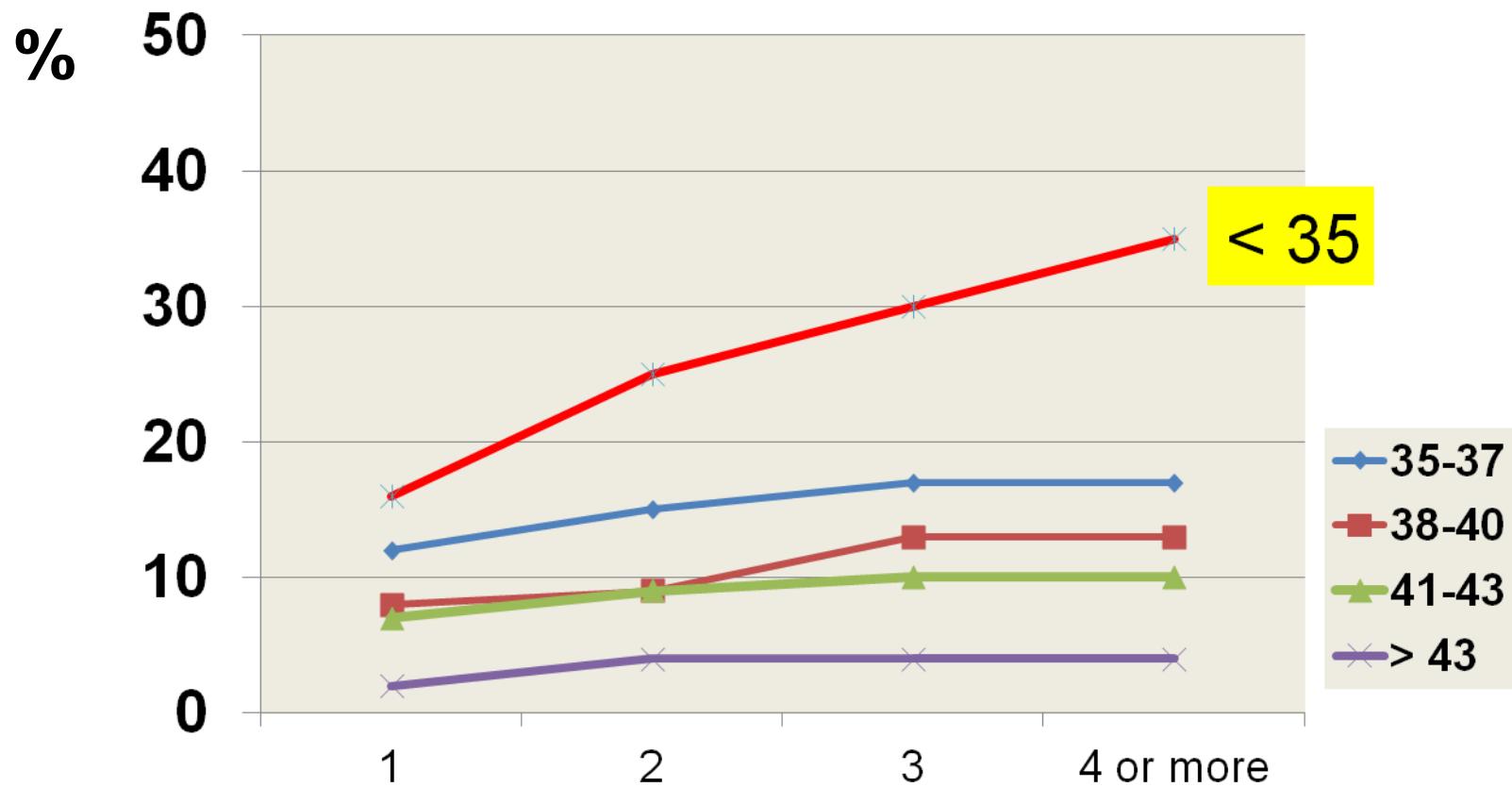


# The age factor in the reduced ovarian reserve

## The LBR per transfer ( S.I.S.Me.R 2780 cycles)



**LBR in 3000 women age  $\geq 35$  yrs with reduced ovarian reserve**  
**A 15 yrs survey of final outcome (Xu et al, FS I 2018)**





# Personalizzazione della Prognosi

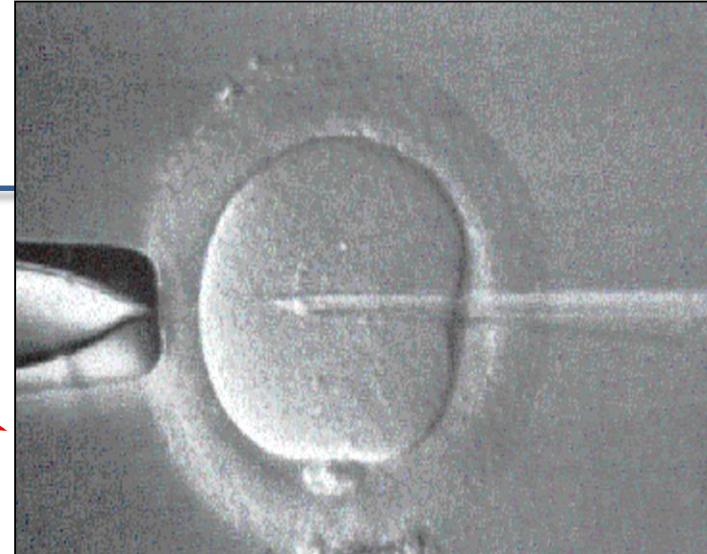
- Età
- Riserva ovarica
- Fattore maschile
- Non patologie uterine
- Cariotipo normale



# Fattore maschile di infertilità

- 1) OAT lieve/moderata
- 2) OAT severa
- 3) Azospermia ostruttiva ( OA): *recupero di spermatozoi da epididimo*
- 4) Azospermia non ostruttiva( NOA): *recupero di spermatozoi da testicolo*

# ICSI



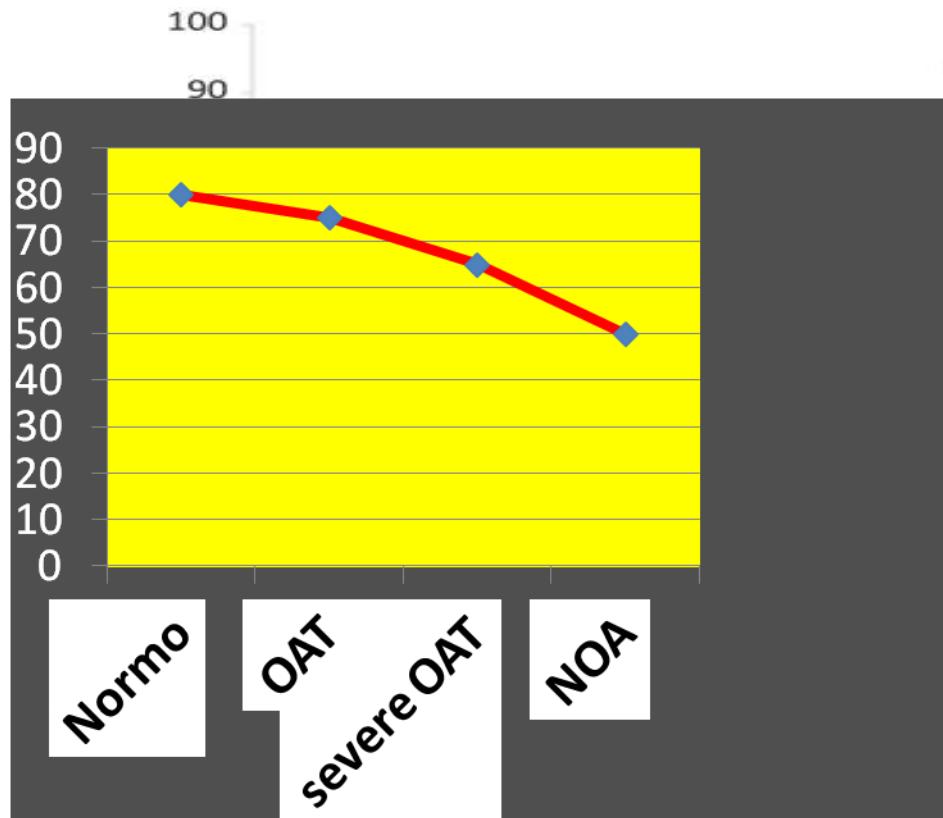
No barrier to fertilization

No selection against  
DNA damaged sperm

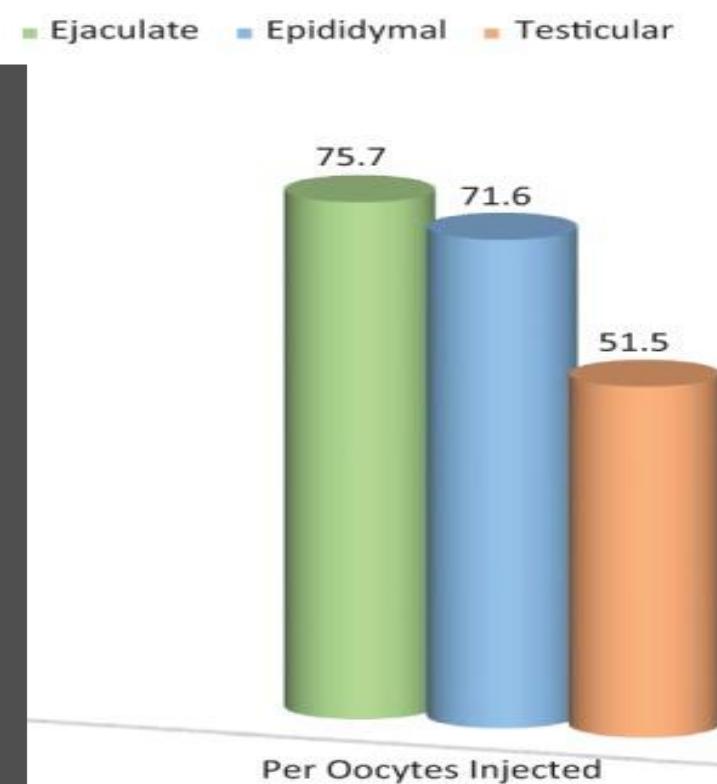


# Fertilization rate

SISMER  
2010-2017

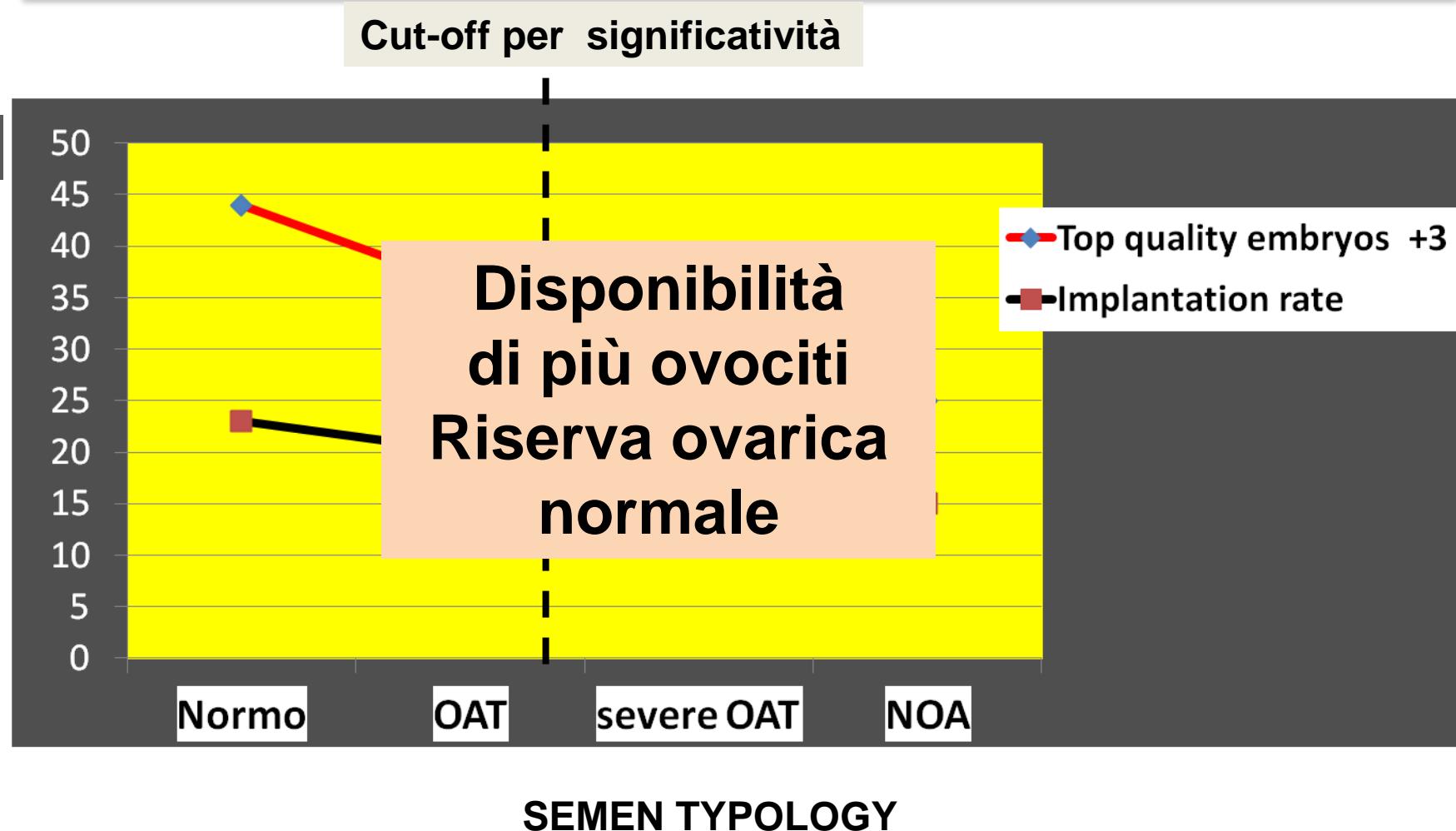


Palermo GD et al,  
Reporoduction, 2017

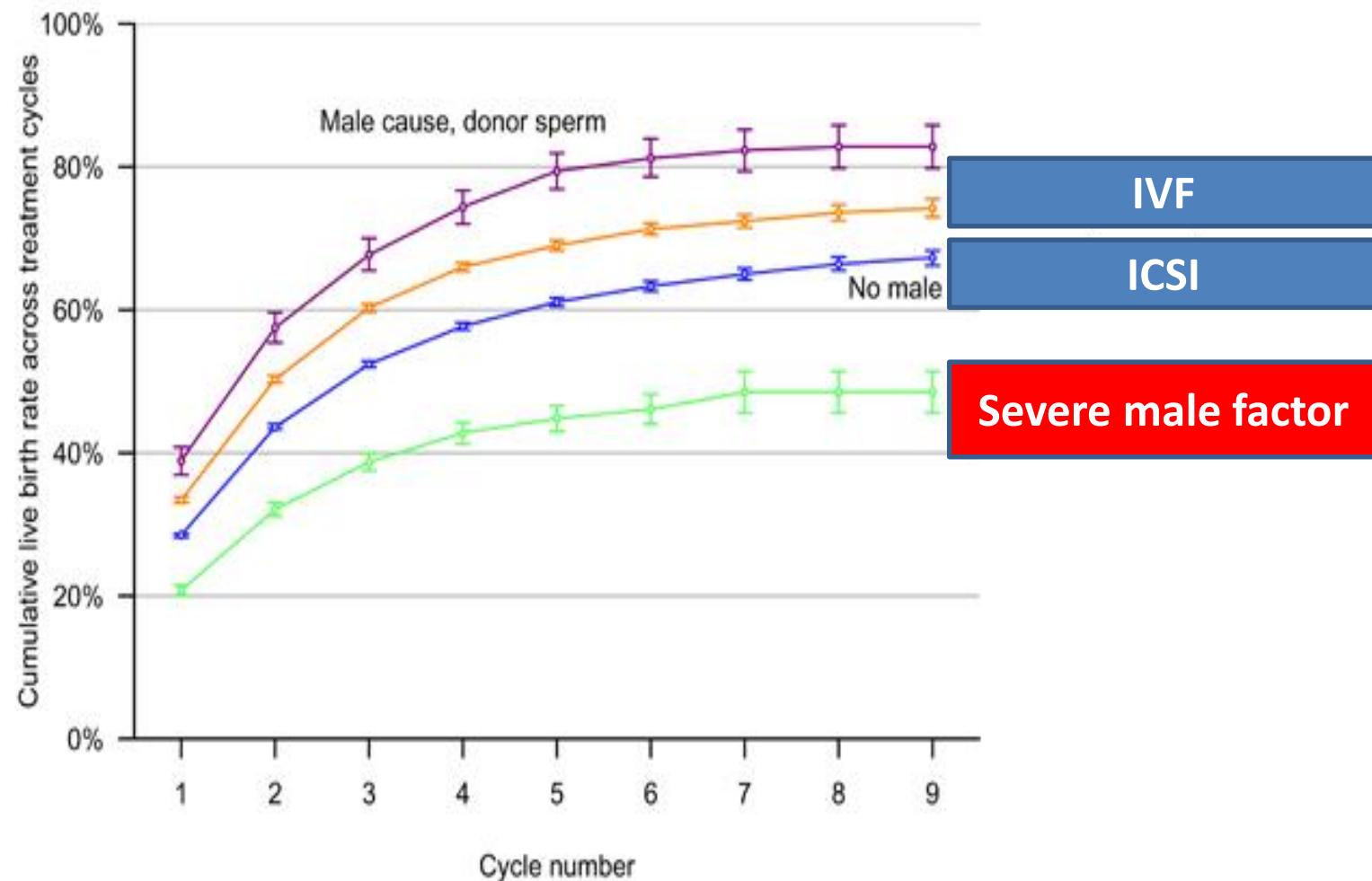




# Sperm parameters and *in vitro* performance



# Fattore maschile ed età femminile < 40 anni



LBR with repeat cycles *Smith et al, JAMA ,2015*



# Prognosi

- Età > 40 anni
- Ridotta riserva ovarica
- Fattore maschile severo

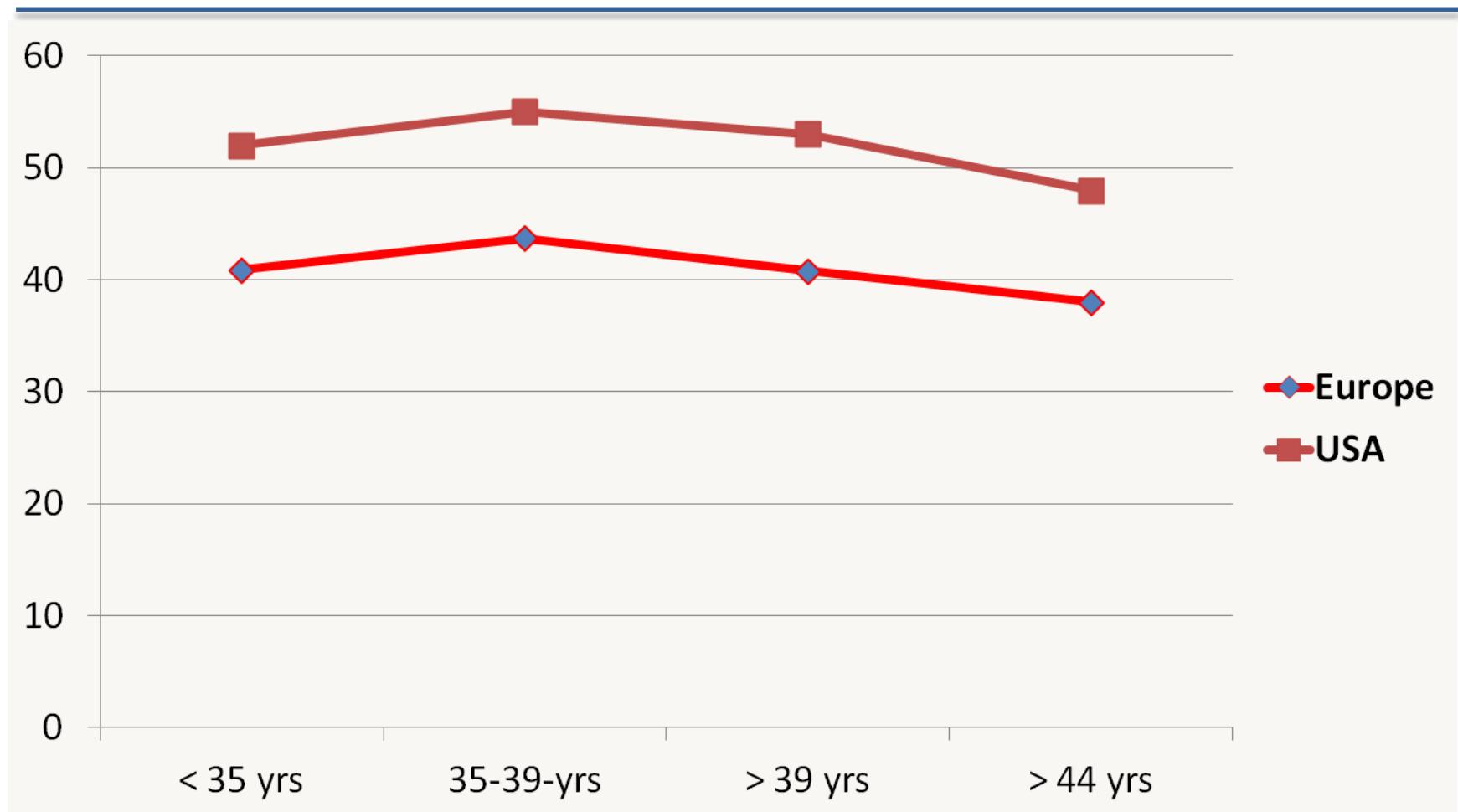
- Età > 43 anni

**Personalizzazione del trattamento PMA ?**

**Eterologa**



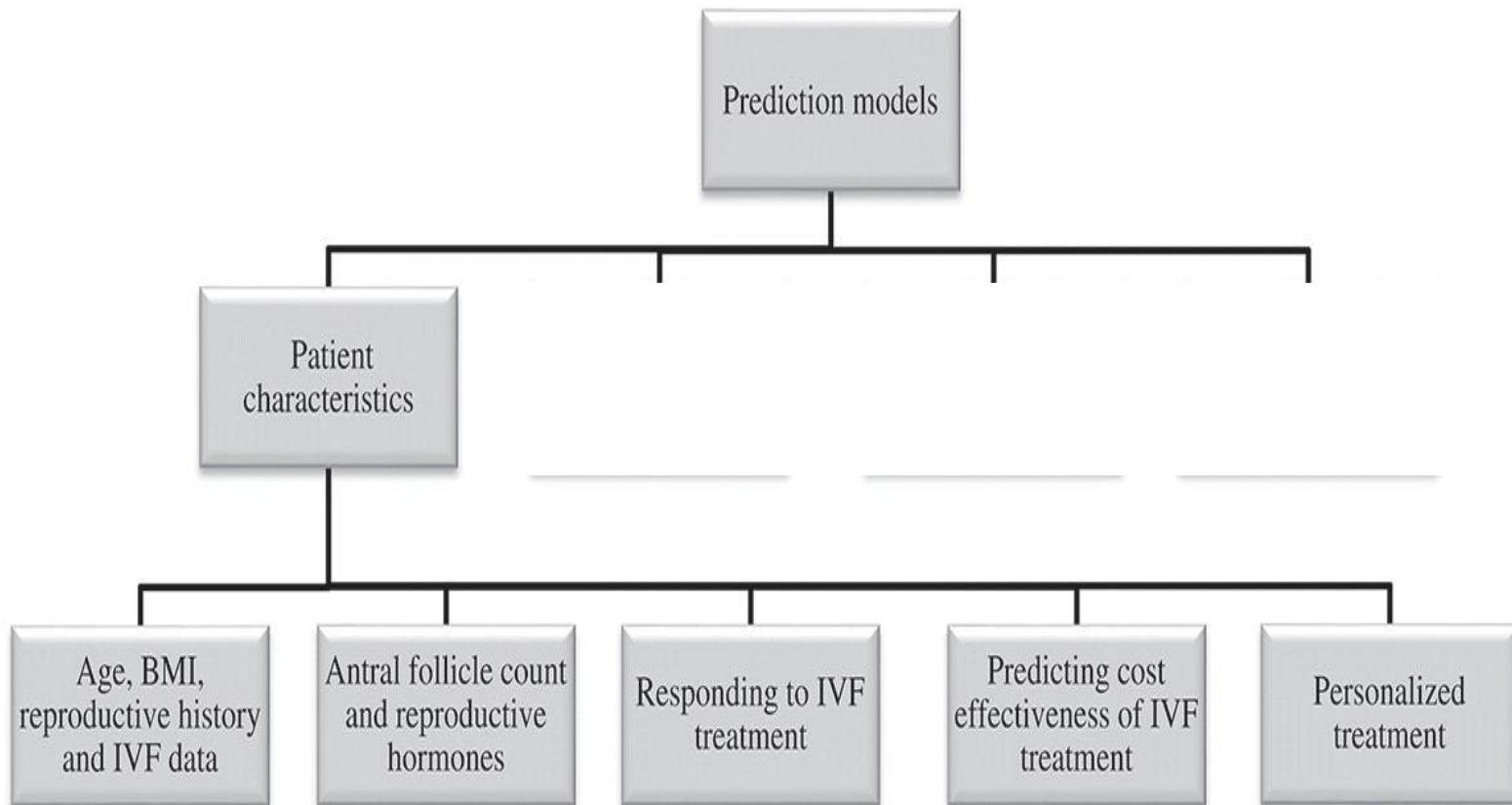
# Oocytes donation (DR/ET)



# Making IVF more effective through the evolution of prediction models:

## is prognosis the missing piece of the puzzle

M. SimopoulouJ. of Systems in Reproductive Medicine  
2018



# **Personalized prediction of live birth prior to the first in vitro fertilization treatment: a machine learning method**

*Jiahui Qiu et al, Journal of Translational Medicine, 2018*

## **Live birth prediction before the first IVF treatment**

\*A complete IVF cycle refers to the fresh cycle and all the following frozen thawed cycles from one round of ovarian stimulation.

### **Predicting IVF Outcome: A Proposed Web-based System Using Artificial Intelligence:**

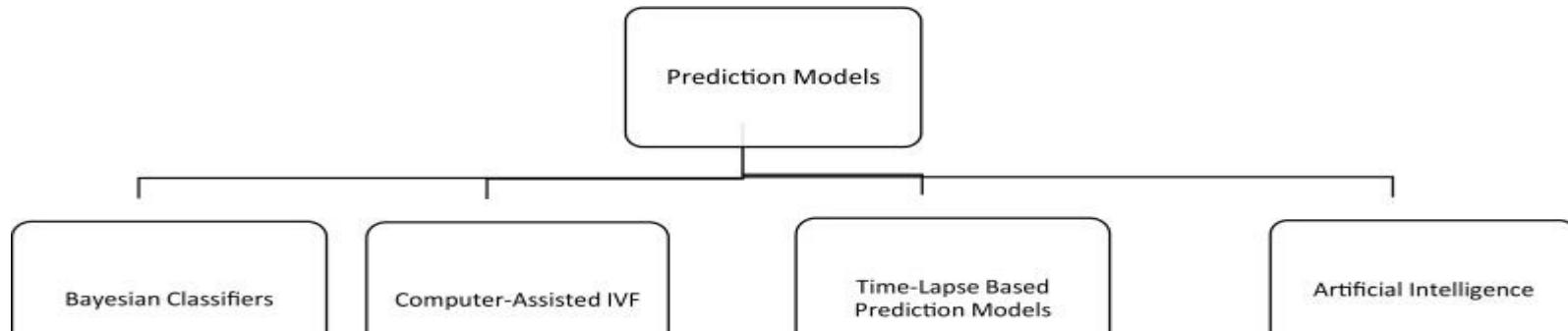
**A system able to recalling and evaluating  
the vast amount of information to provide  
an objective indication on the outcome of  
IVF**

[\*Siristatidis et al, In Vivo, 2019\*](#)

**Submit**

# Are computational applications the “crystal ball” in the IVF laboratory? The evolution from mathematics to artificial intelligence

M.Simopoulou, J.Assist Reprod Genet

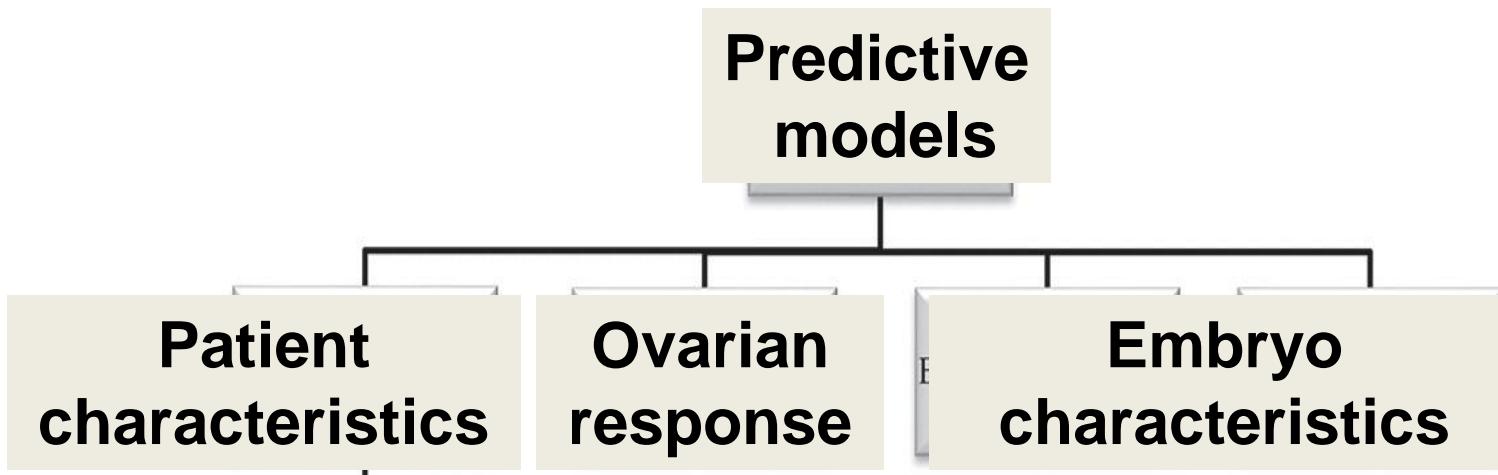


**Analysis of mathematical models , device and software employed in the IVF laboratory by the artificial intelligence to ascertain efficient embryo selection and to secure optimal pregnancy rate**

euploidy

potential

# **The evolution from basic mathematics to bioinformatics of the predictive models....**



**.... may be the means to foretell a promising future  
for the IVF clinical practice**

# Can Computers Be Made to Respect the Art of Medicine?

**Neil J. Nusbaum, JD, MD, 2017**

One of the common criticisms of the application of **automated medical decision** pathways is that although they may yield the **correct answer** in the case of straightforward clinical presentations, **they fail** to capture the nuances (*sfumature*) of more complex scenarios in which **human** clinical judgment and the **art of medicine** become more important