A.G.E.O.
Corso di aggiornamento in Ginecologia ed Ostetricia
Bologna 29-30 Settembre 2017

PMA : attualità e prospettive

40 anni dopo la nascita di Louise Brown

Anna Pia Ferraretti

Luca Gianaroli

Maria Cristina Magli

PMA

Tecniche

Fase clinica

Fase extra-corporea

Pabmed :
> 60.000 publications and
3231 reviews and meta-analysis

Basic science items (i.e. early embryonic development)
> 40.000 publications

della maggior parte delle forme di infertilità di coppia

Efficacia
Rischi

Standardizzazione termini e definizioni

The International Glossary on Infertility and Fertility Care, 2017

Hum Reprod 2017

Fertil Steril 2017

Terza revisione dal 2002

PMA

- ***Aspetti etico-culturali***

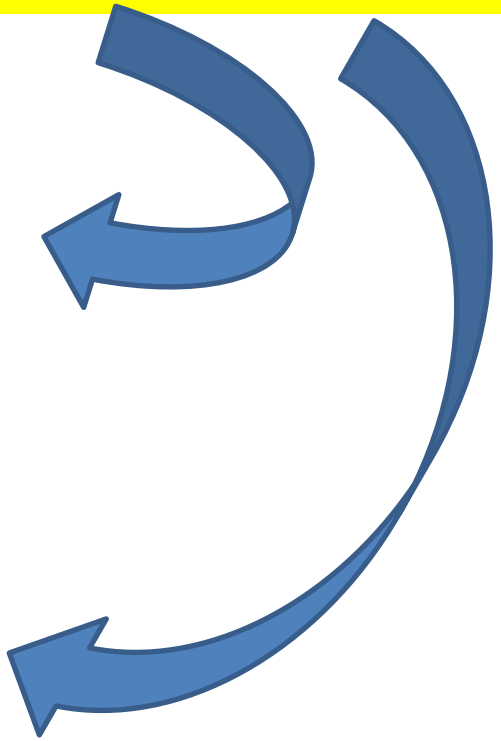
- ***Aspetti socio- economici***

Legislazioni e politiche sanitarie

- ***Disponibilità/accessibilità***

- ***Aspetti clinici***
- ***Aspetti tecnici***
- ***Aspetti scientifici***

-***Efficacia-rischi***



ART Surveillance

IFFS - Global Reproductive Health 2016

Settima Edizione

“To provide a better understanding of the complexity of the issues surrounding ART provision”

PMA in Italia

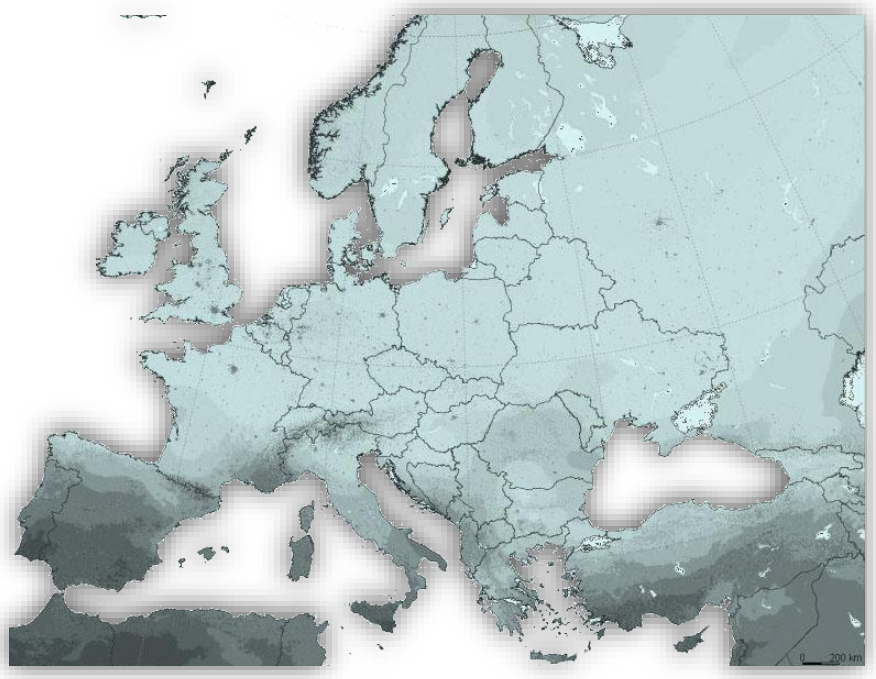
- **Divieti della Legge 40 dl 2004**

- *Inseminazione di un max di 3 ovociti*
- *Divieto della crioconservazione di embrioni*
- *Divieto alla analisi degli embrioni (PGD e PGS)*
- *Divieto della donazione di gameti (eterologa)*

Donazione di gameti

Lecito un rimborso "appropriato"

Per donazione di ovociti varia da 200 euro (Finlandia) a 1500 euro (in Belgio)
Maggior parte di Paesi : 500-1000 euro



In Italia è vietata ogni forma di rimborso

CONFERENZA DELLE REGIONI E DELLE PROVINCE AUTONOME
14/109/CR02/C7SAN

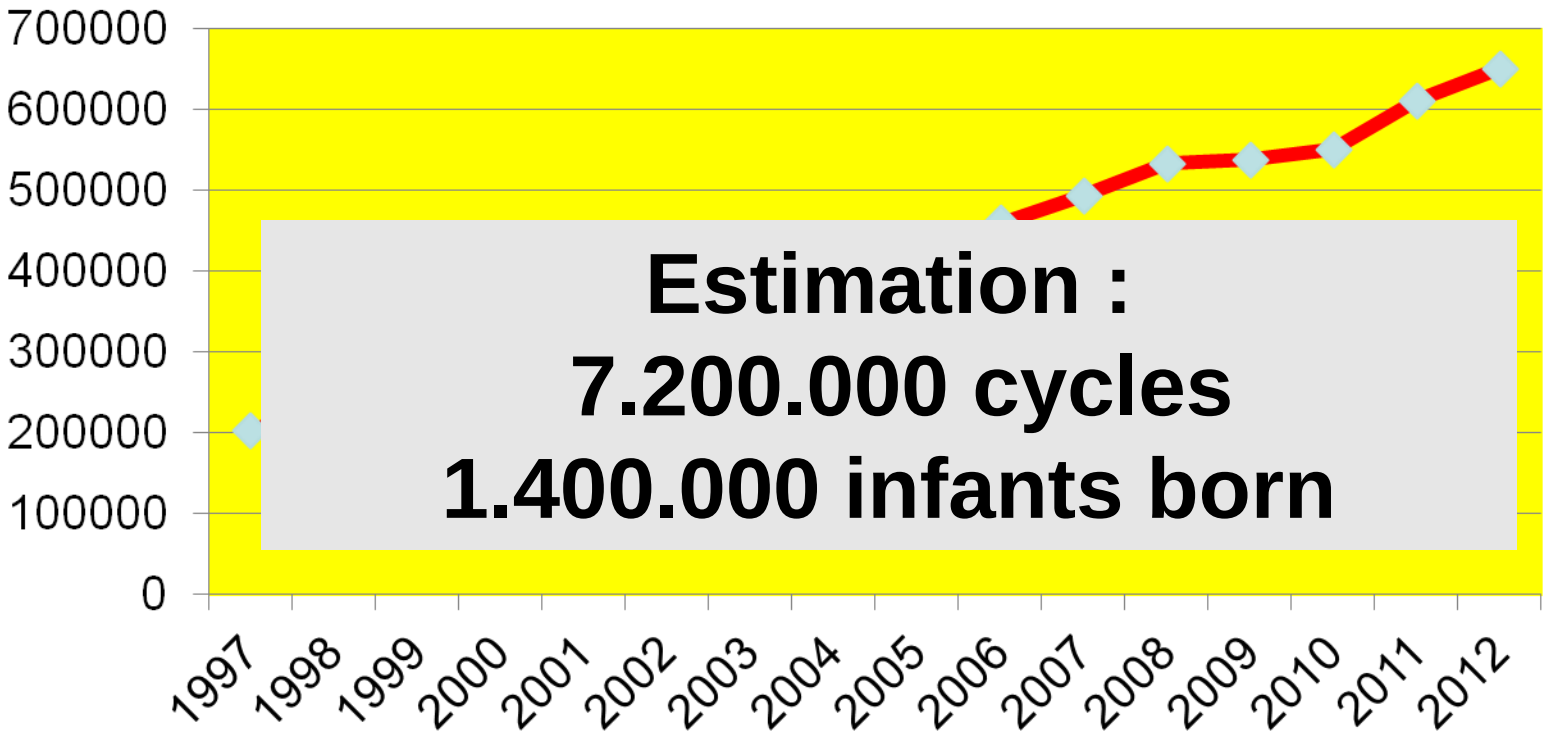
DOCUMENTO SULLE PROBLEMATICHE RELATIVE ALLA FECONDAZIONE ETEROLOGA A SEGUITO DELLA SENTENZA DELLA CORTE COSTITUZIONALE NR. 162/2014

L'importazione ed esportazione di gameti sono consentite solo da e verso istituti autorizzati ai sensi della normativa europea vigente in materia (Decreto Min Salute del 10-10-2012 attuativo del DLgs 191/07)

ART monitoring
Registri PMA nel Mondo

- ***Europa* : vari *Registri Nazionali obbligatori o volontari fin dal 1982. In Italia dal 2005.***
- ***Raccolta Europea* dal 1997**
- ***USA* dal 1988**
- ***Australia e Nuova Zelanda* dal 1992**
- ***America Latina* dal 1995**
- ***Medio Oriente* dal 1999**
- ***India* dal 2008**
- ***Africa* : in via di organizzazione**
- **Nessun dato nazionale dalla *Cina***

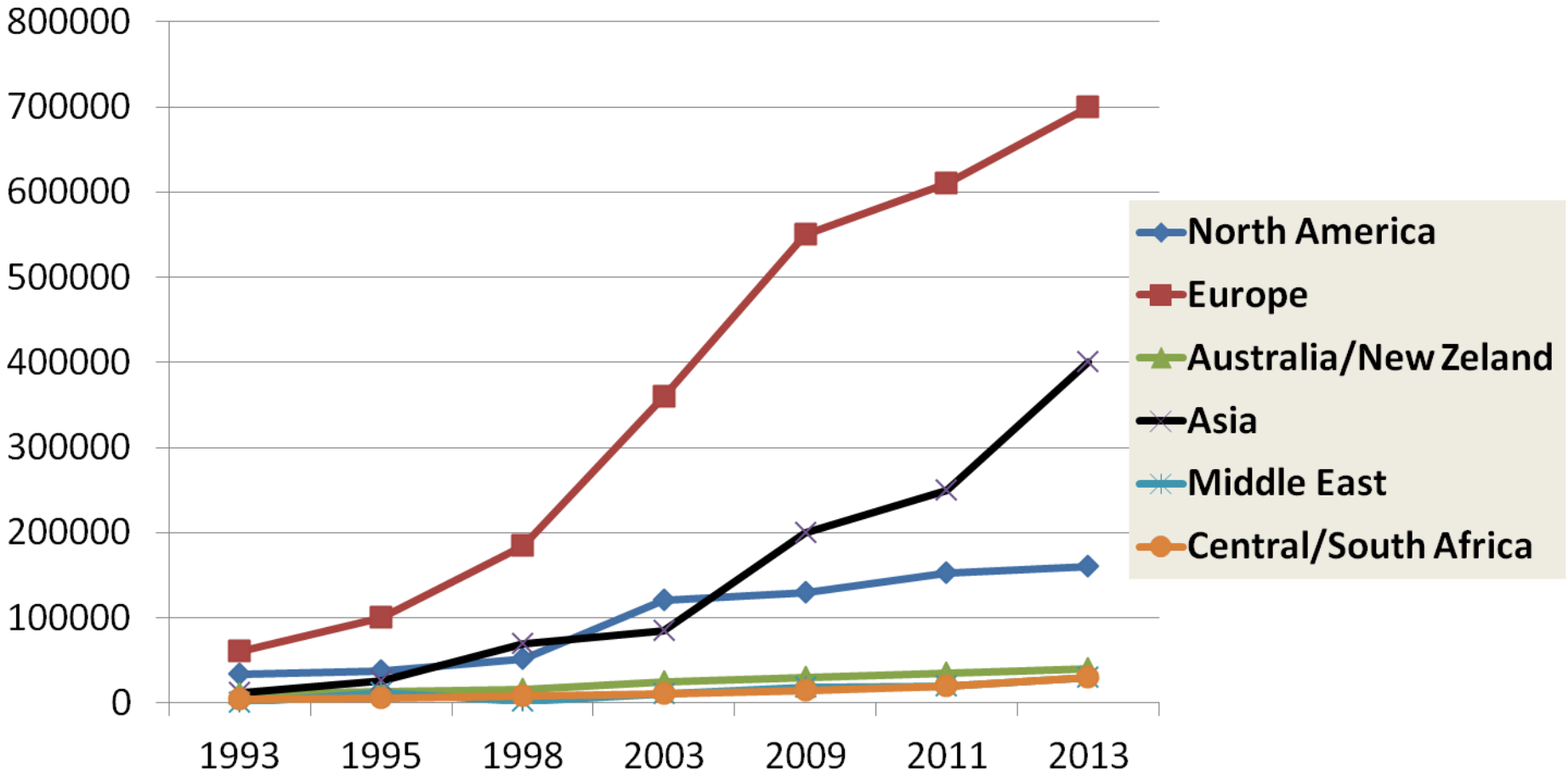
Europe EIM-Total cycles reported per year



Trends over 15 years in ART in Europe
Ferraretti et al , Human Reproduction Open 2017

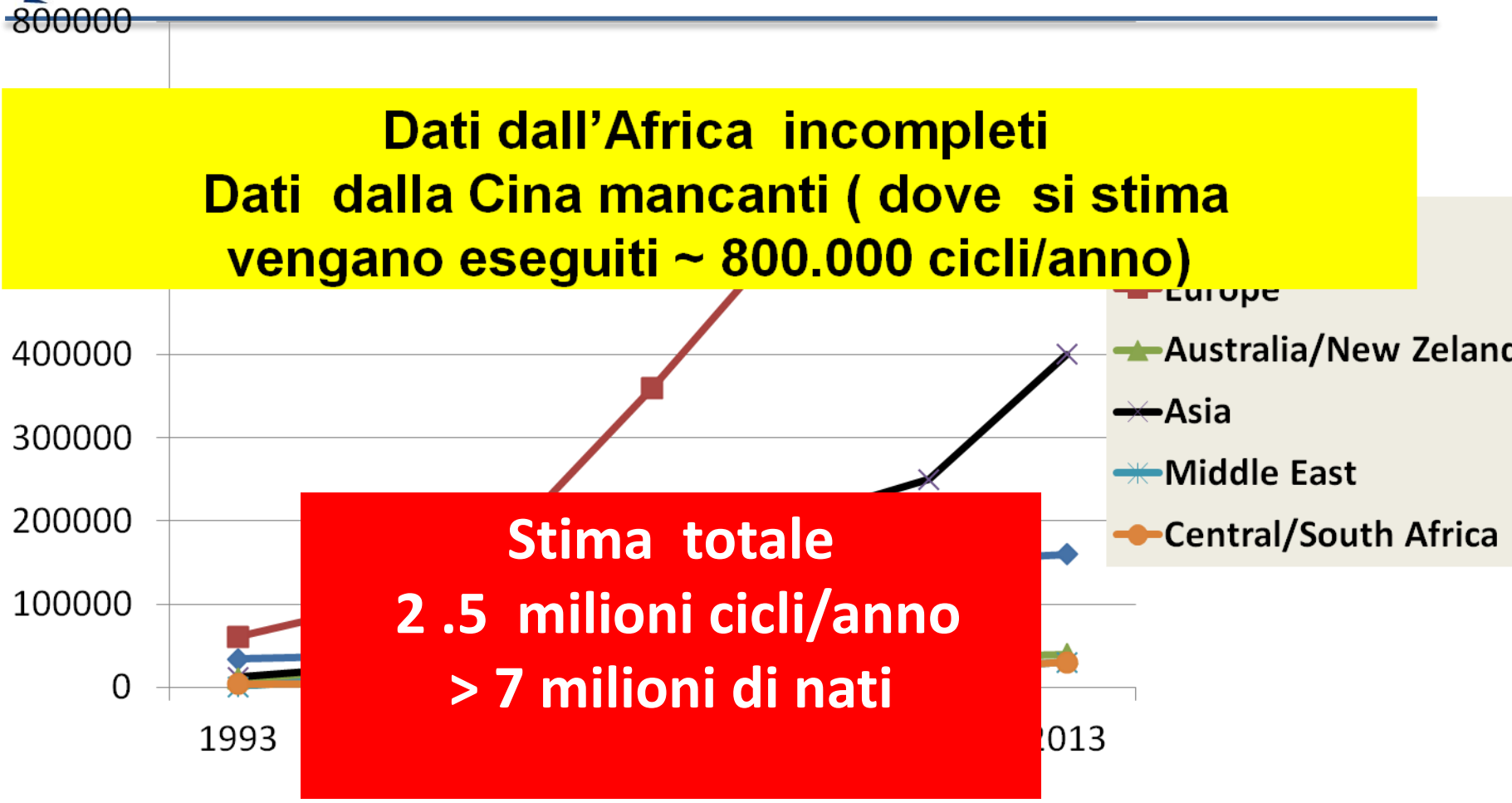
eshre
SCIENCE MOVING PEOPLE MOVING SCIENCE

ICMART- World ART Reports
Number of cycles



ICMART- World ART Reports

Dati dall'Africa incompleti
Dati dalla Cina mancanti (dove si stima vengano eseguiti ~ 800.000 cicli/anno)



Stima totale
2 .5 milioni cicli/anno
> 7 milioni di nati

Availability

(cycles/million inhabitants/year)

Availability of infertility services is a **complex** product of public and private health policies and economic, political and social/cultural forces that determine the allocation of facilities, personnel and equipment.

The global need for ART is estimated to be *al least* 1.500 cycles/million population per year *(Collins et al, Hum Reprod Update, 2002)*

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Availability in the world
(number of cycles/ million inhabitants)

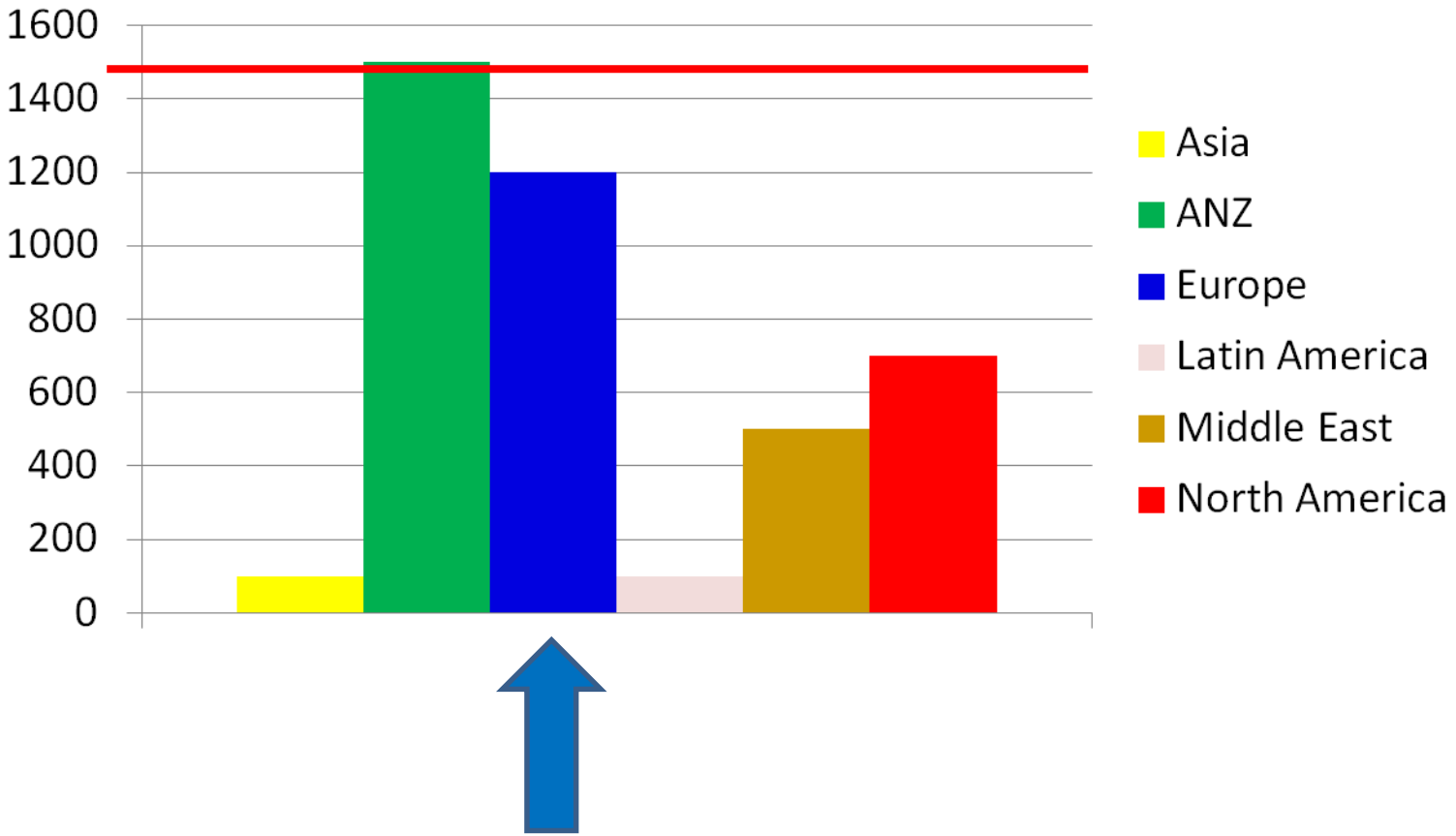
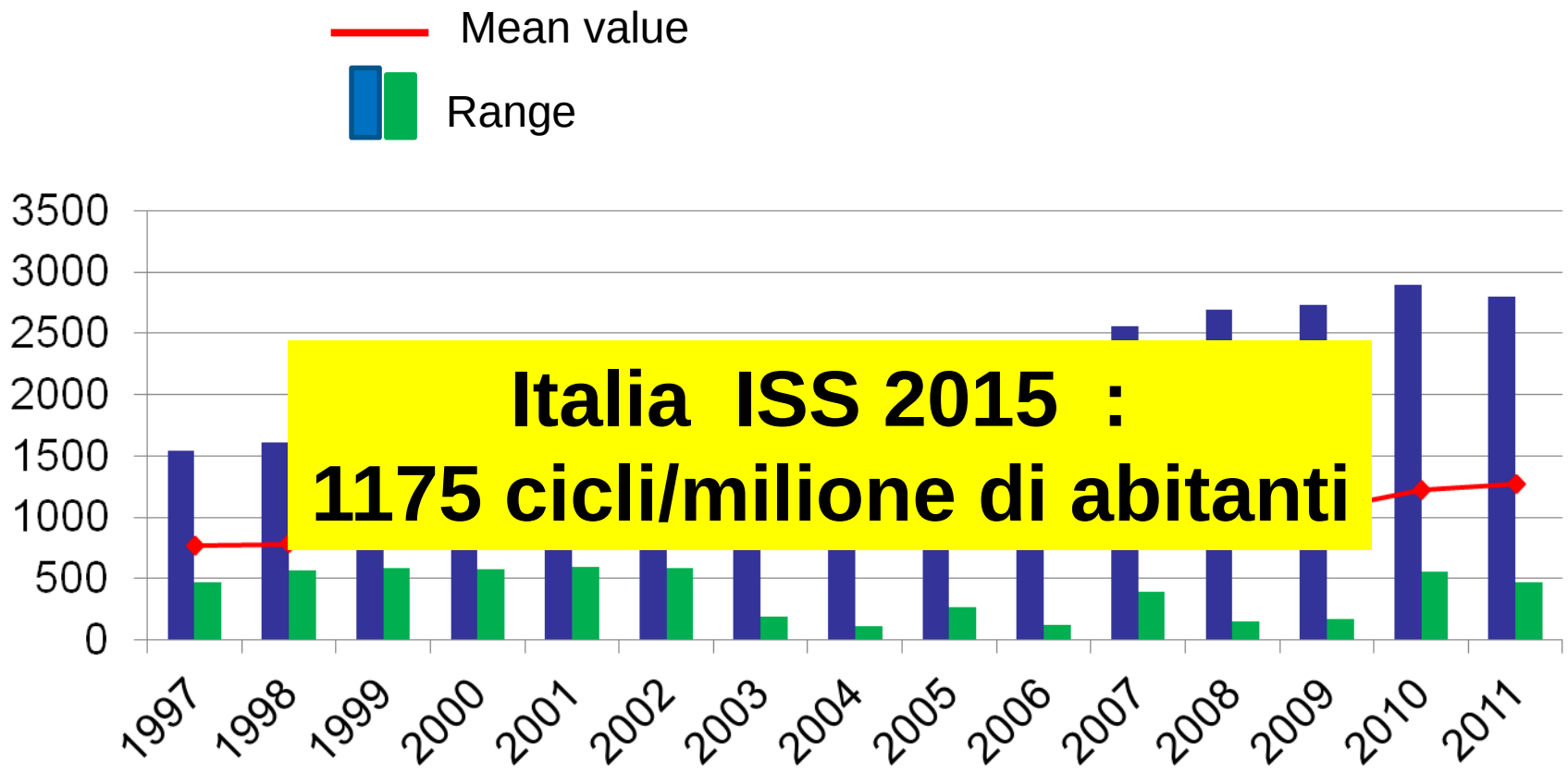


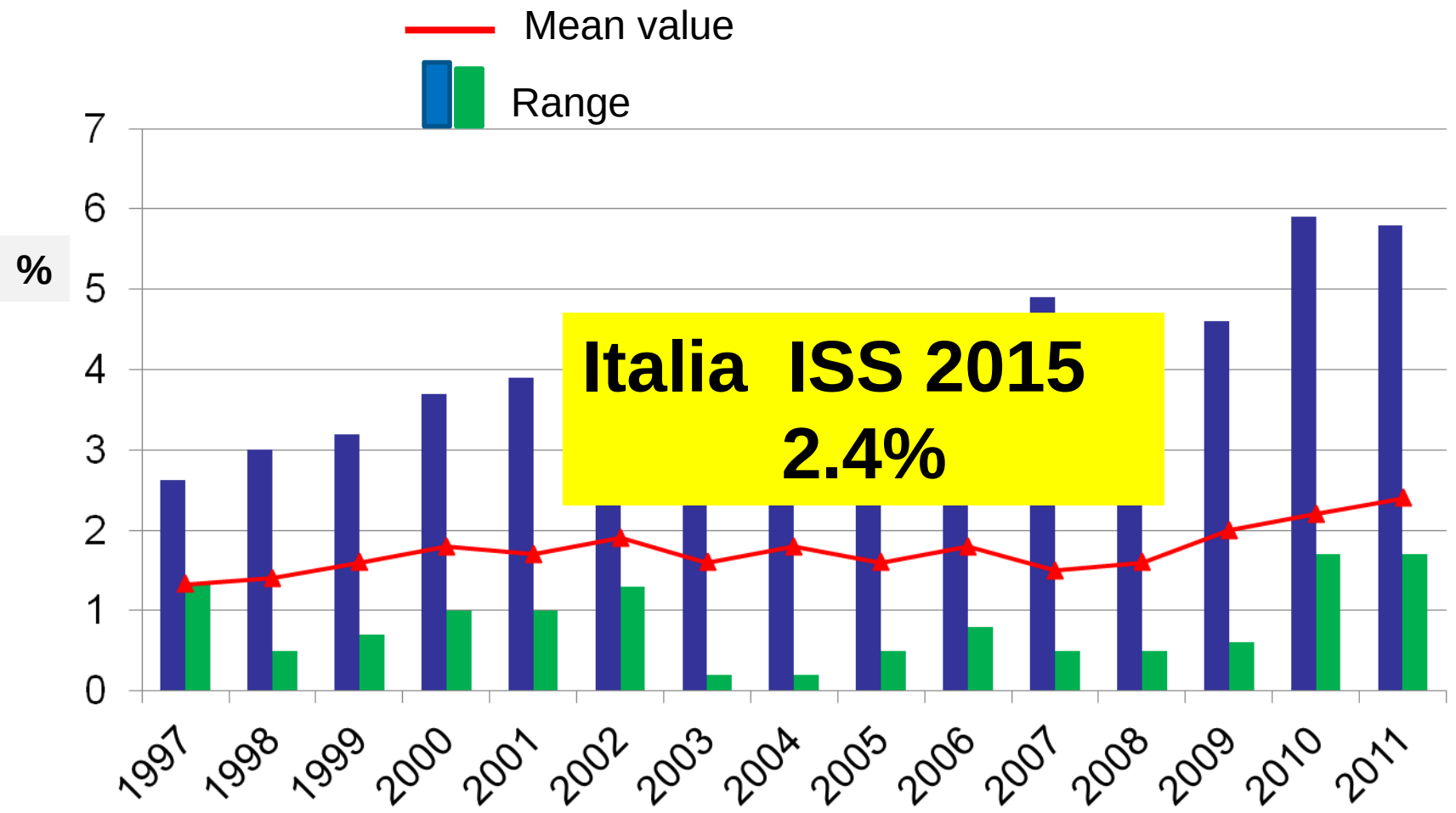
Figure 2- Number of cycles / million inhabitants in the countries where data coverage was 100%



Trends over 15 years in ART in Europe
Ferraretti et al , Human Reproduction Open 2017

SCIENCE MOVING
PEOPLE
MOVING SCIENCE

Figure 3- Percent of ART babies on the total infants born in the Countries with a 100% coverage



Trends over 15 years in ART in Europe
Ferraretti et al , Human Reproduction Open 2017

PMA

Tecniche

-IVF
-ICSI
-Donazione Gameti
-PGT (PGS-PGD)
-Crioconservazione ovociti/embrioni
-IVM

Fasi cliniche

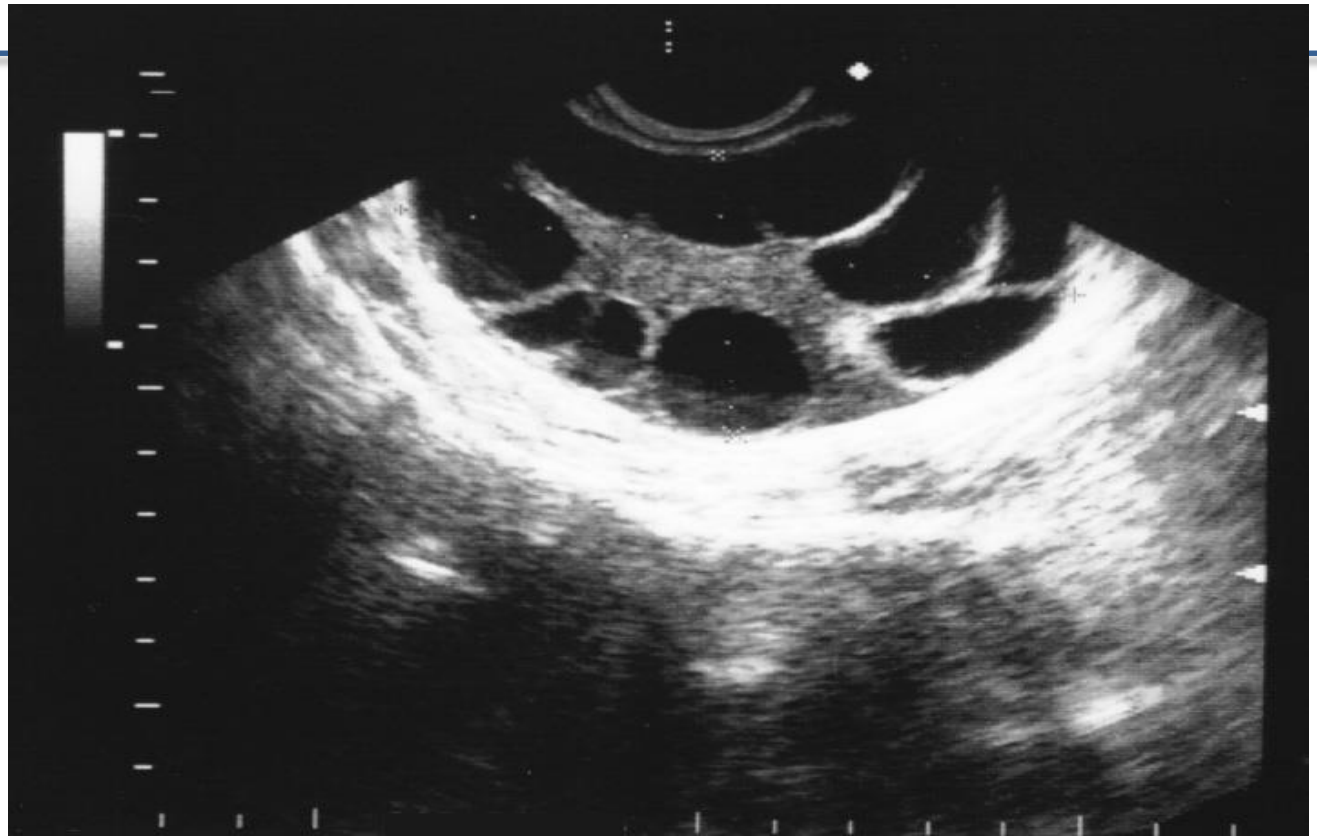
-Stimolazione ovarica
- Prelievo di ovociti
-Trasferimento embrioni

Fase extra-corporea

-Inseminazione
- Coltura
- Valutazione qualità
-Selezione
-Crioconservazione

Efficacia
Rischi

Superovulation for ART



COH is used > 95% of the cycles performed in the world

ART Complications- European data

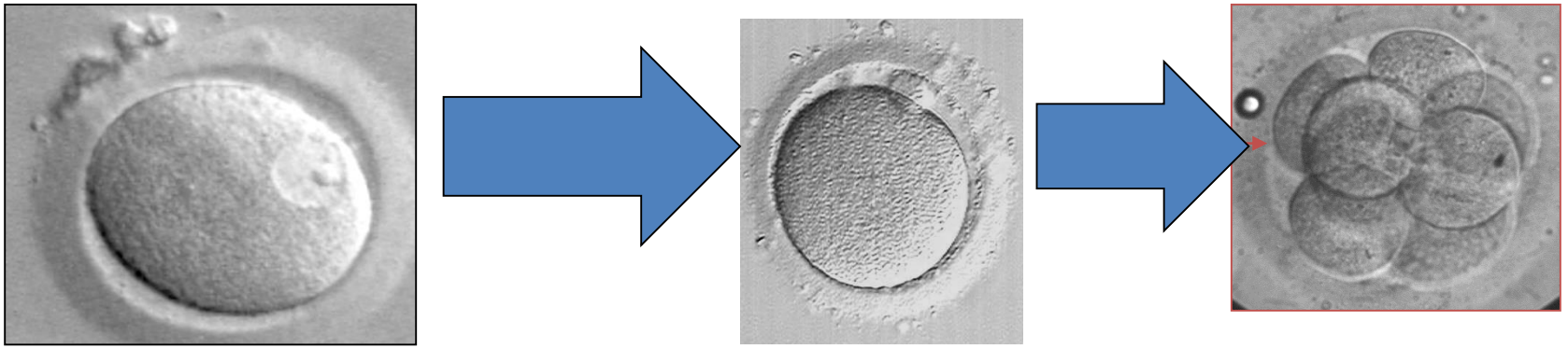
Year	OHSS	(%)	bleeding	infections	Maternal deaths
1999	1083	0.9	84	30	1
2000	1586	1.1	388	36	0
2001	1851	0.9	294	24	1
2002	2148	1.0	622	227	2
2003	2646	1.0	799	135	2
2004	2858	1.2	520	362	4
2005	3347	1.2	523	207	0
2006	2753	0.8	544	42	2
2007	2470	0.8	574	64	3
2008	2947	1.0	652	49	1
2009	2137	0,8	570	61	1
2010	1500	0,3	641	53	2
2011	1705	0,6	711	59	1
tot	29.031		6922	1349	20

Ferraretti et al , Human Reproduction Open 2017

re
MOVING
PEOPLE
MOVING SCIENCE

IVM
In Vitro Maturation



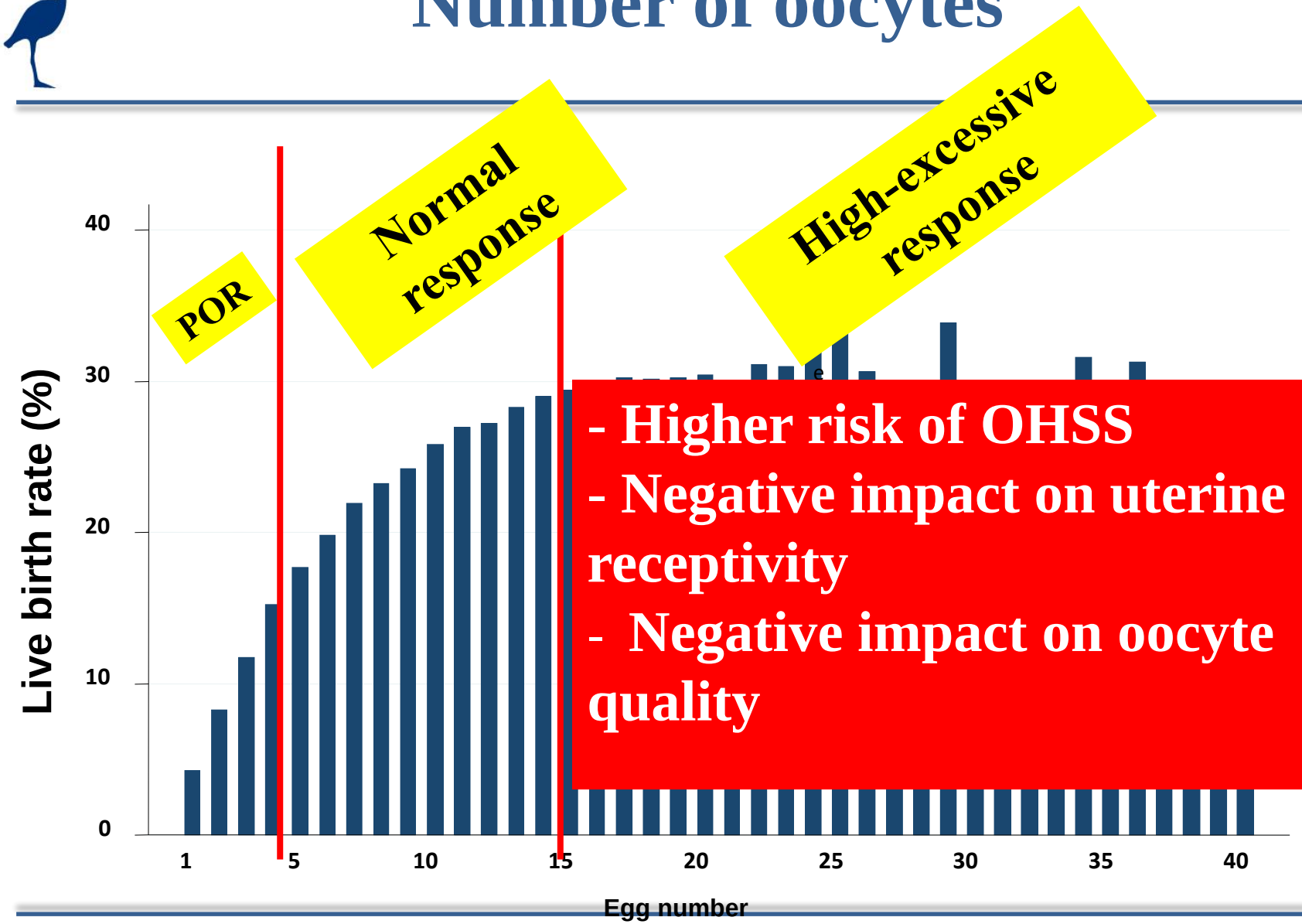


MORE OOCYTES, MORE PREGNANCIES

A wide-ranging programme of studies with Organon's recombinant FSH has demonstrated almost 100 per cent purity and better batch-to-batch consistency. Puregon provides clinically relevant benefits in the routine treatment of infertility

ORGYN, Puregon special issue,1996

Number of oocytes



Sunkara et al., Hum Reprod 2011

Prediction of the ovarian response to personalize the stimulation

The past

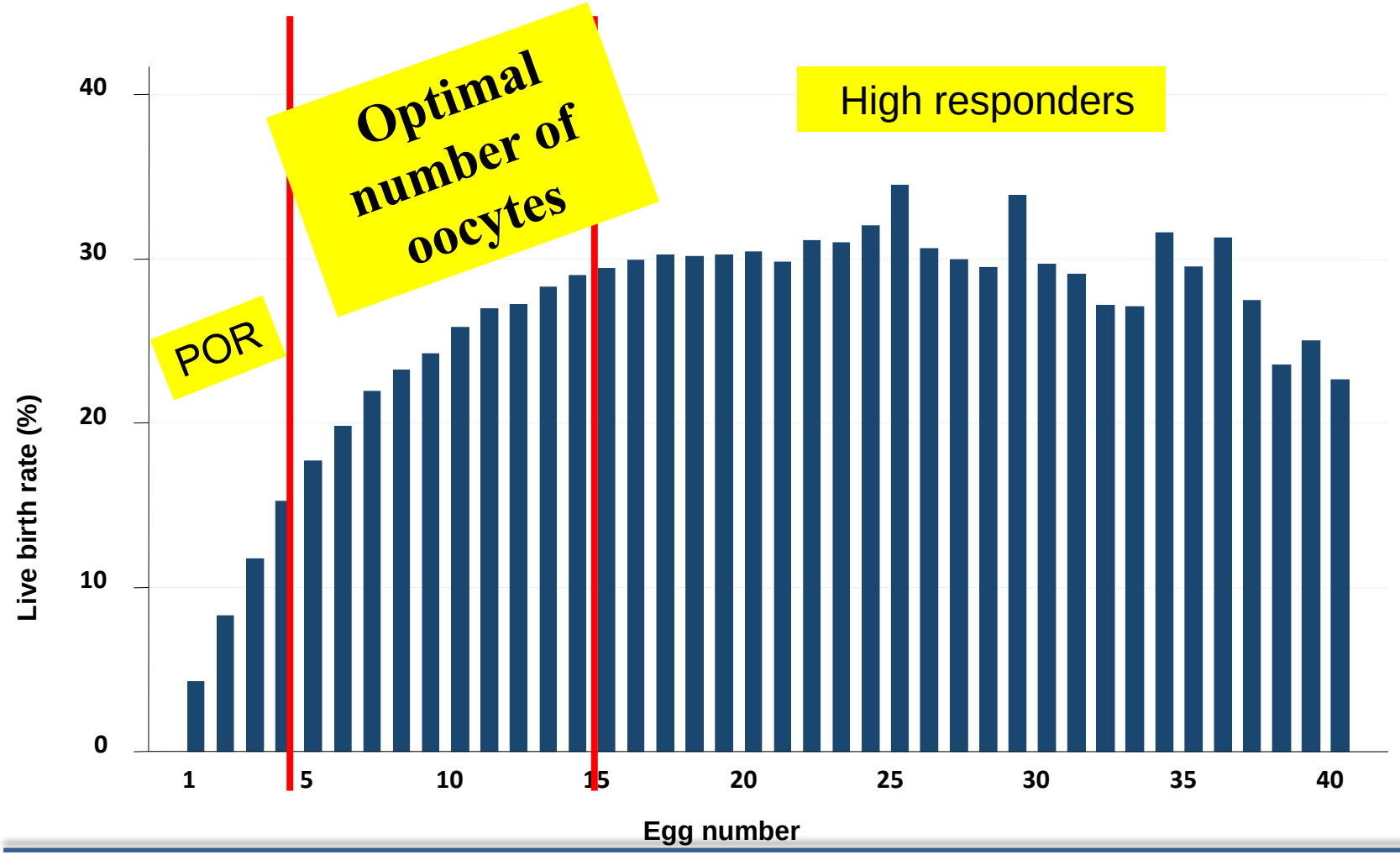
- *Age*
- *BMI*
- *Basal FSH*
- *PCOS*
- *Previous cycles*

The present

New ovarian reserve tests

- **AMH**
- **AFC**

Personalization

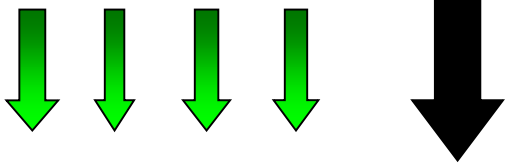


Sunkara et al., Hum Reprod 2011

Unexpected High responders Treatment strategy

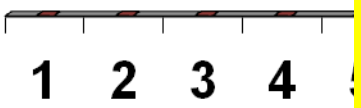
GnRH antagonist

GnRH agonist



FSH/HMG basso dosaggio





Crioconservazione di embrioni per impatto negativo su recettività endometriale

Human Reproduction, Vol.26, No.10 pp. 2593–2597, 2011
Advanced Access publication on August 9, 2011 doi:10.1093/humrep/der251

human reproduction OPINION

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)*

PMA

Tecniche
-IVF
-ICSI
-Donazione Gameti
-PGT (PGS-PGD)
-Crioconservazione ovociti/embrioni
-IVM

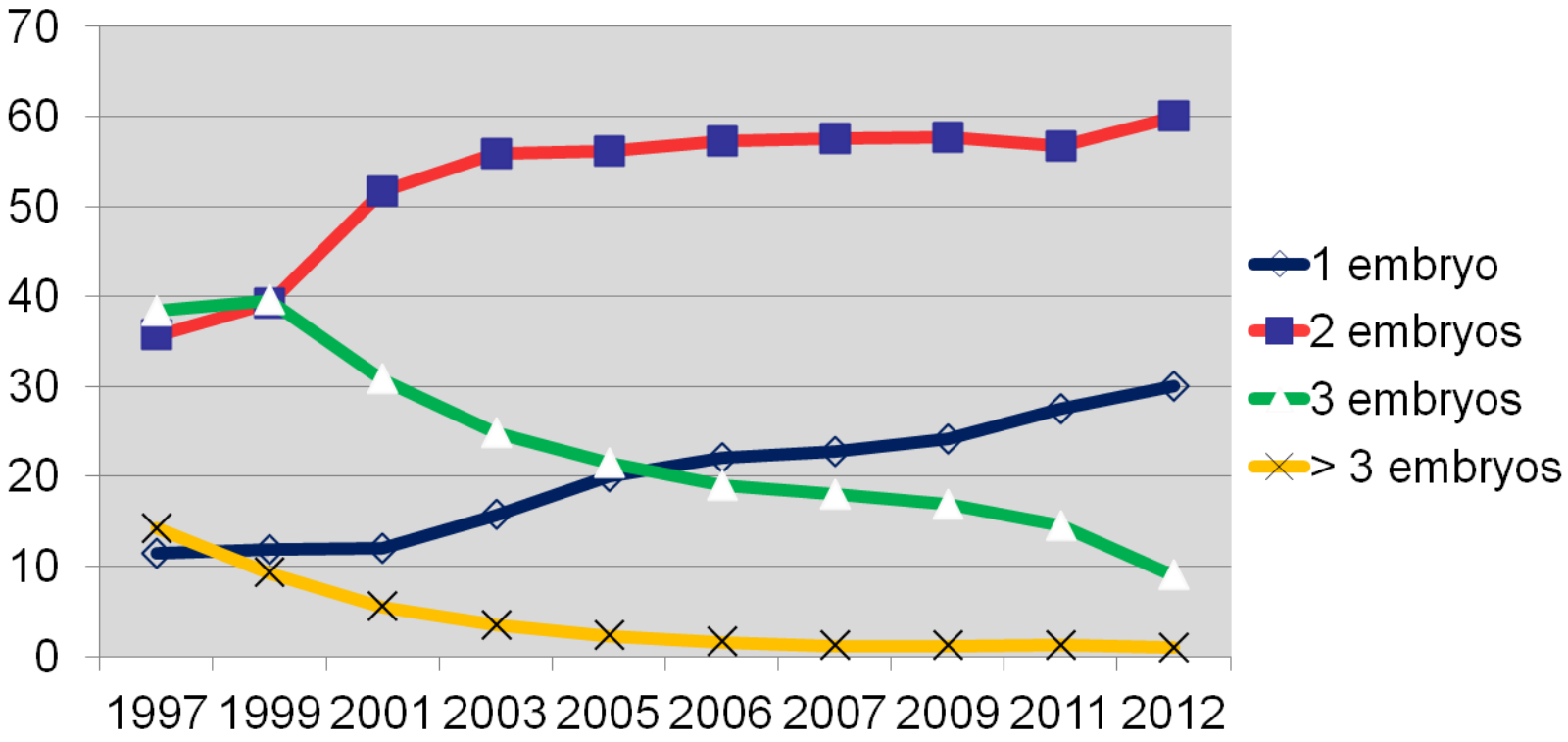
Fasi cliniche
-Stimolazione ovarica
- Prelievo di ovociti
-Trasferimento embrioni

Fase extra-corporea
-Inseminazione
- Coltura
- Valutazione qualità
-Selezione
-Crioconservazione

Efficacia
Rischi

Europe- Number of embryos transferred

% of transfers

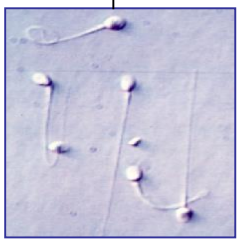


Trends over 15 years in ART in Europe
Ferraretti et al , Human Reproduction Open 2017

SCIENCE MOVING
PEOPLE
MOVING SCIENCE

ART System



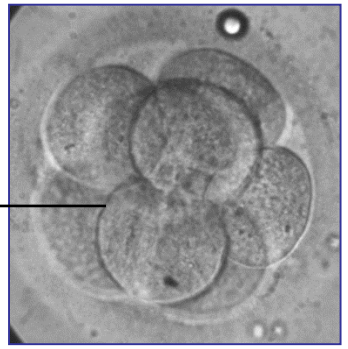


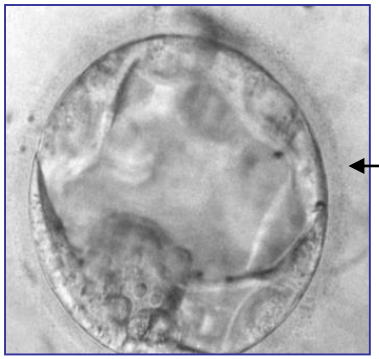


2PN









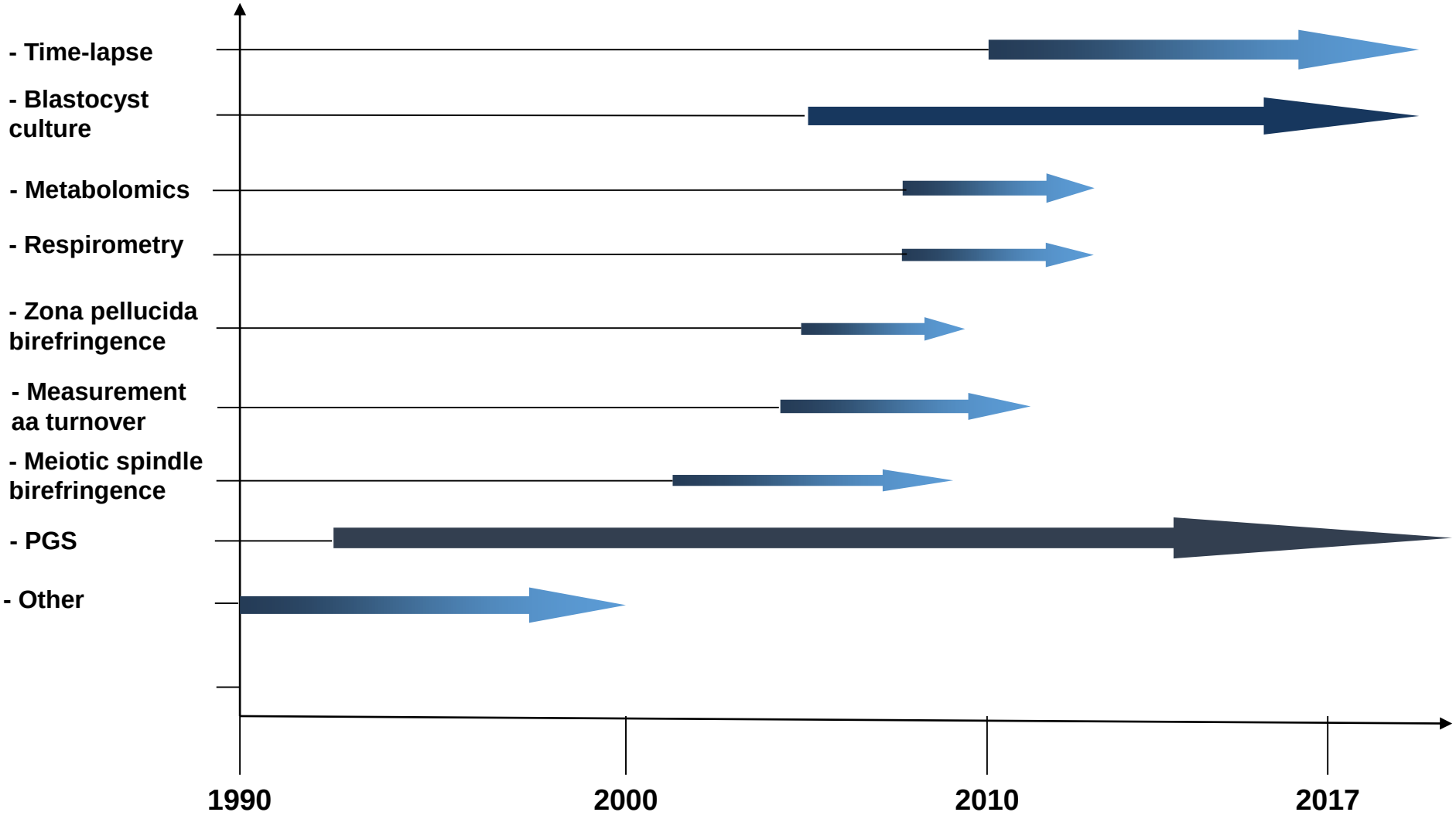
Cryopreservation of surplus embryos

Vitrification

Transfer of 1-2 embryos

Embryo's selection

Embryo selection



PGT: SOURCE OF DNA for Chromosomal analysis

Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6

Polar Body Biopsy



Cleavage stage biopsy

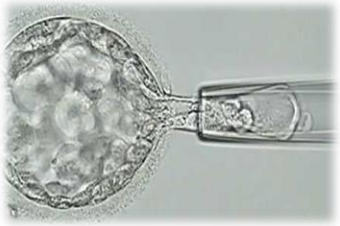


Morula stage biopsy



Blastocyst biopsy

Trophectoderm



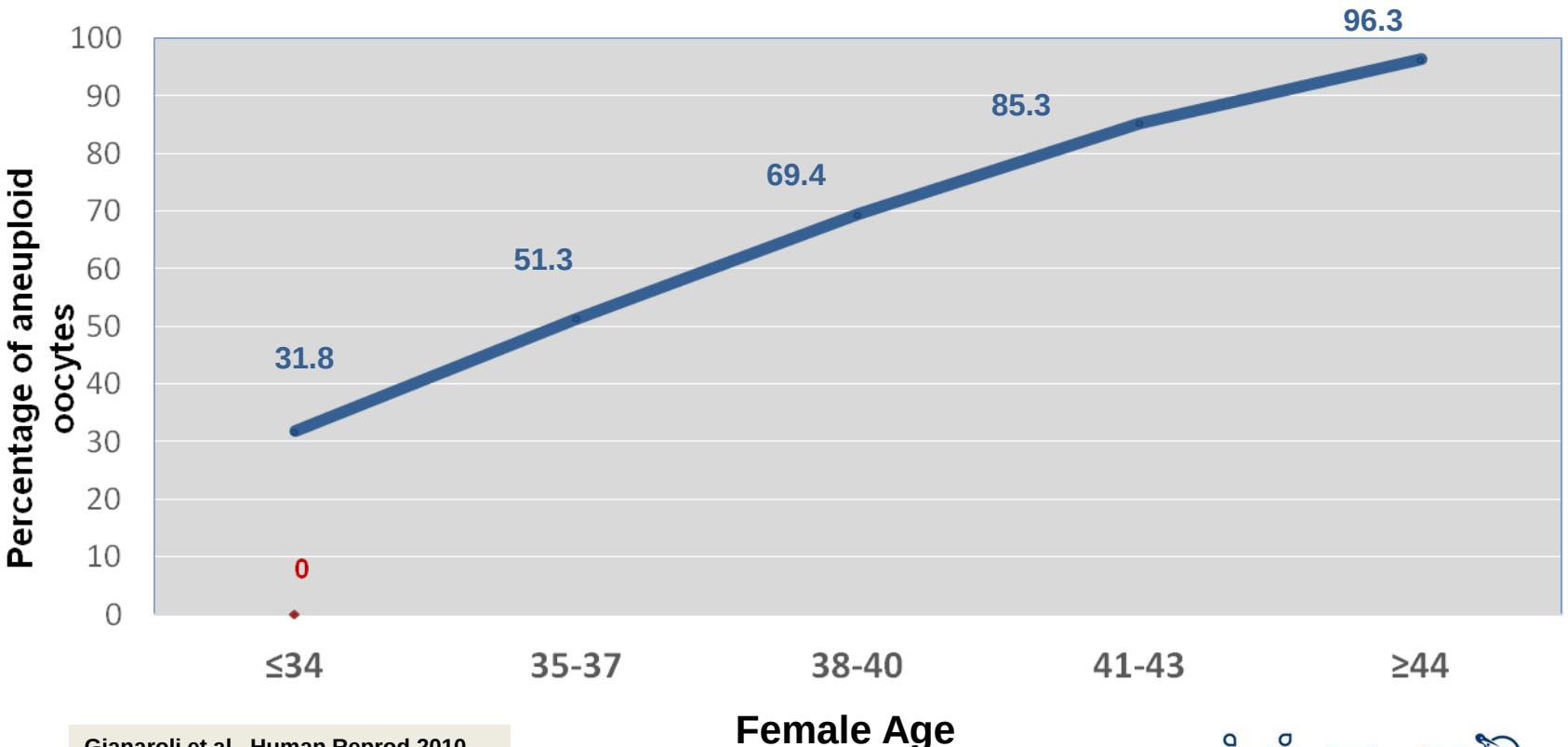
Aim : to select euploid embryos

**(women of advanced maternal age, repeated IVF failure ,
repeated miscarriages,severe male factor)**

POLAR BODY BIOPSY:
Frequency of meiotic errors

n=735 oocytes (CGH on Pb1 and Pb2)

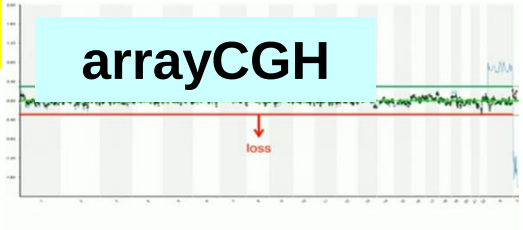
The proportion of aneuploid oocytes increases with female age



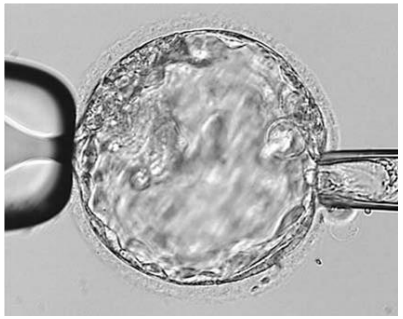
Gianaroli et al., Human Reprod 2010,

PGS new generations

The present



TROPHECTODERM BIOPSY



More DNA: less no results

Less mosaicism

Reduced (no) impact on embryo implantation

Characteristics of included randomized and observational studies.

Study	Design	Indication	Embryo biopsy	Genetic platform	Main outcomes
Randomized studies					
Yang et al., 2012 (24)	Pilot RCT	Good-prognosis patients, 1st IVF cycle	Blastocyst	aCGH	Clinical PR, ongoing PR (>20 wk)
Forman et al. 2013 (22)	Noninferiority trial (RCT)	Normal ovarian reserve, ≤1 previous IVF failure	Blastocyst	qPCR	Ongoing PR (>24 wk), multiple PR
Scott et al., 2013 (75)	RCT	Normal ovarian reserve, ≤1 previous IVF failure	Blastocyst	qPCR	Sustained IR, delivery rate
Observational studies					
Sher et al., 2009 (58)	PCS	AMA + RIF + RPL	Cleavage	mCGH	IR, Live birth rate
Schoolcraft et al., 2010 (55)	PCS	Previous IVF failure	Blastocyst	aCGH	IR
Fishel et al., 2011 (79)	PCS	RIF	Polar Body	aCGH	IR
Forman et al., 2012 (23)	RCS	1st SET cycle	Blastocyst	qPCR	Ongoing PR (>12 wk)
Keltz et al., 2013 (76)	RCC	AMA + RIF + RPL	Cleavage	aCGH	IR
Greco et al., 2014 (43)	PCS	RIF	Blastocyst	aCGH	IR
Lee et al., 2015 (77)	RCS	AMA	Blastocyst	aCGH	IR, Live birth rate
Feichtinger et al., 2015 (78)	RCS	RIF + AMA	Polar Body	aCGH	Live birth rate

Note: aCGH = array comparative genomic hybridization; AMA = advanced maternal age; IR = implantation rate; mCGH = metaphase comparative genomic hybridization; qPCR = quantitative polymerase chain reaction; PCS = prospective cohort study; PR = pregnancy rate; RCC = retrospective case-control; RCS = retrospective cohort study; RCT = randomized controlled trial; RIF = repeated implantation failure; RPL = recurrent pregnancy loss; SET = single-embryo transfer.

Conclusions:

- PGT with the use of CCH technology increases clinical and sustained IRs, thus improving embryo selection, particularly in patients with normal ovarian reserve.

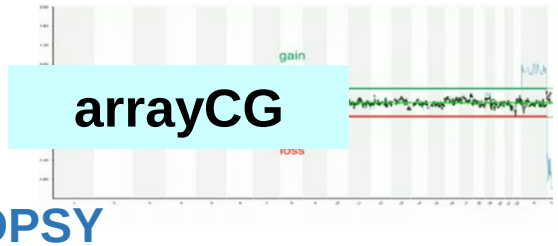
- Results from ongoing RCTs conducted on different patient populations (e.g., decreased ovarian reserve) and different embryo stage biopsy (e.g., PB, day-3) may further clarify the role of this technology.

Dahdouh et al., *Fertil Steril* 2015

PGS new generations

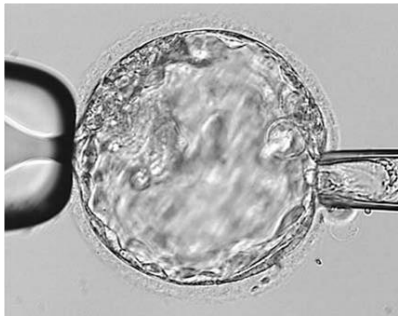
The present

The future

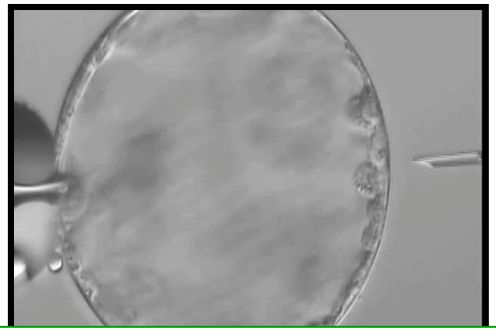


arrayCG

TROPHECTODERM BIOPSY



Blastocentesis



More DNA: less no results

Less mosaicism

Reduced (no) impact on embryo implantation

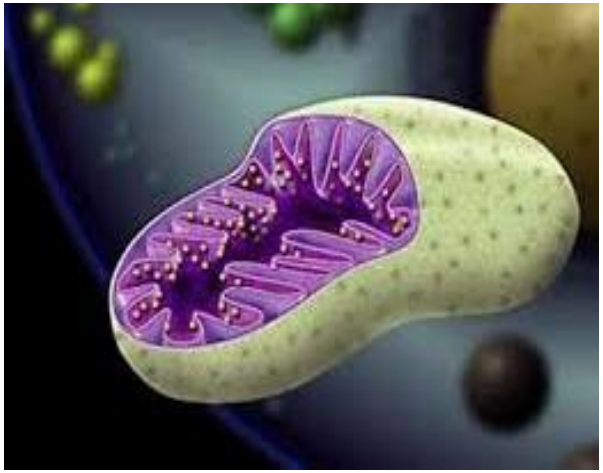
Blastocentesis: a source of DNA for preimplantation genetic testing. Results from a pilot study

Luca Gianaroli, M.D., M. Cristina Magli, M.Sc., Alessandra Pomante, Ph.D., Anna M. Crivello, B.Sc., Giulia Cafueri, B.Sc., Marzia Valerio, B.Sc., and Anna P. Ferraretti, M.D.

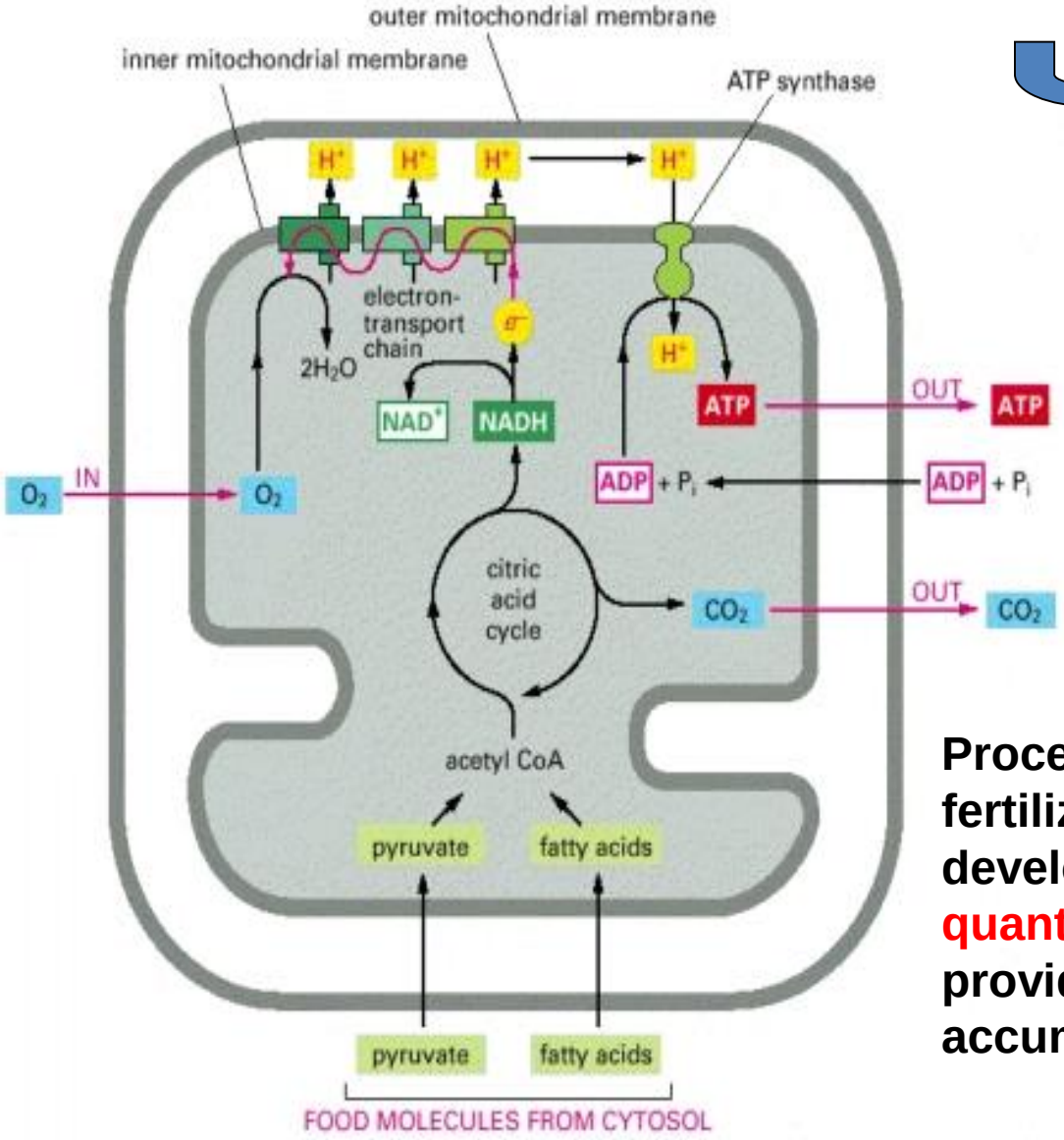
Reproductive Medicine Unit, Sodetà Italiana Studi di Medicina della Riproduzione, Bologna, Italy

NOVELTY IN PGT

MITOCHONDRIAL DNA ANALYSIS



MITOCHONDRIA

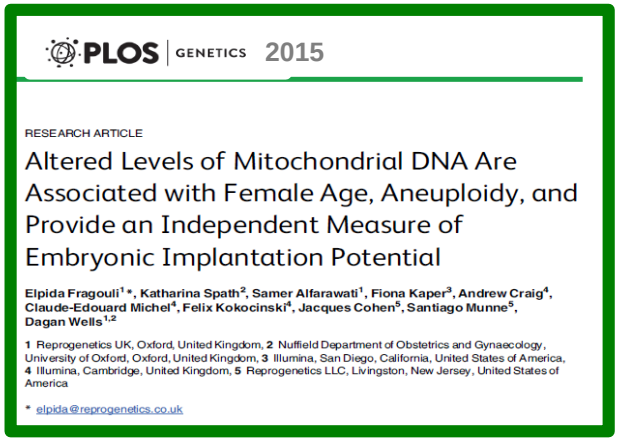


Primary function is the production of energy thorough the synthesis of ATP (adenosine triphosphate).

Processes like oocyte maturation, fertilization and embryo development require great quantity of energy which is provided by the mitochondria accumulated during oogenesis.

http://www.madsci.org/posts/archives/2007-01/1168019185.Cb.r.h

mtDNA levels and EMBRYO VIABILITY


PLOS | GENETICS 2015

RESEARCH ARTICLE

Altered Levels of Mitochondrial DNA Are Associated with Female Age, Aneuploidy, and Provide an Independent Measure of Embryonic Implantation Potential

Elpida Fragouli[1]*, Katharina Spath[2], Samer Alfarawati[1], Fiona Kaper[3], Andrew Craig[4], Claude-Edouard Michel[4], Felix Kokocinski[4], Jacques Cohen[5], Santiago Munne[5], Dagan Wells[1,2]

1 Reprogenetics UK, Oxford, United Kingdom, 2 Nuffield Department of Obstetrics and Gynaecology, University of Oxford, Oxford, United Kingdom, 3 Illumina, San Diego, California, United States of America, 4 Illumina, Cambridge, United Kingdom, 5 Reprogenetics LLC, Livingston, New Jersey, United States of America

* elpida@reprogenetics.co.uk

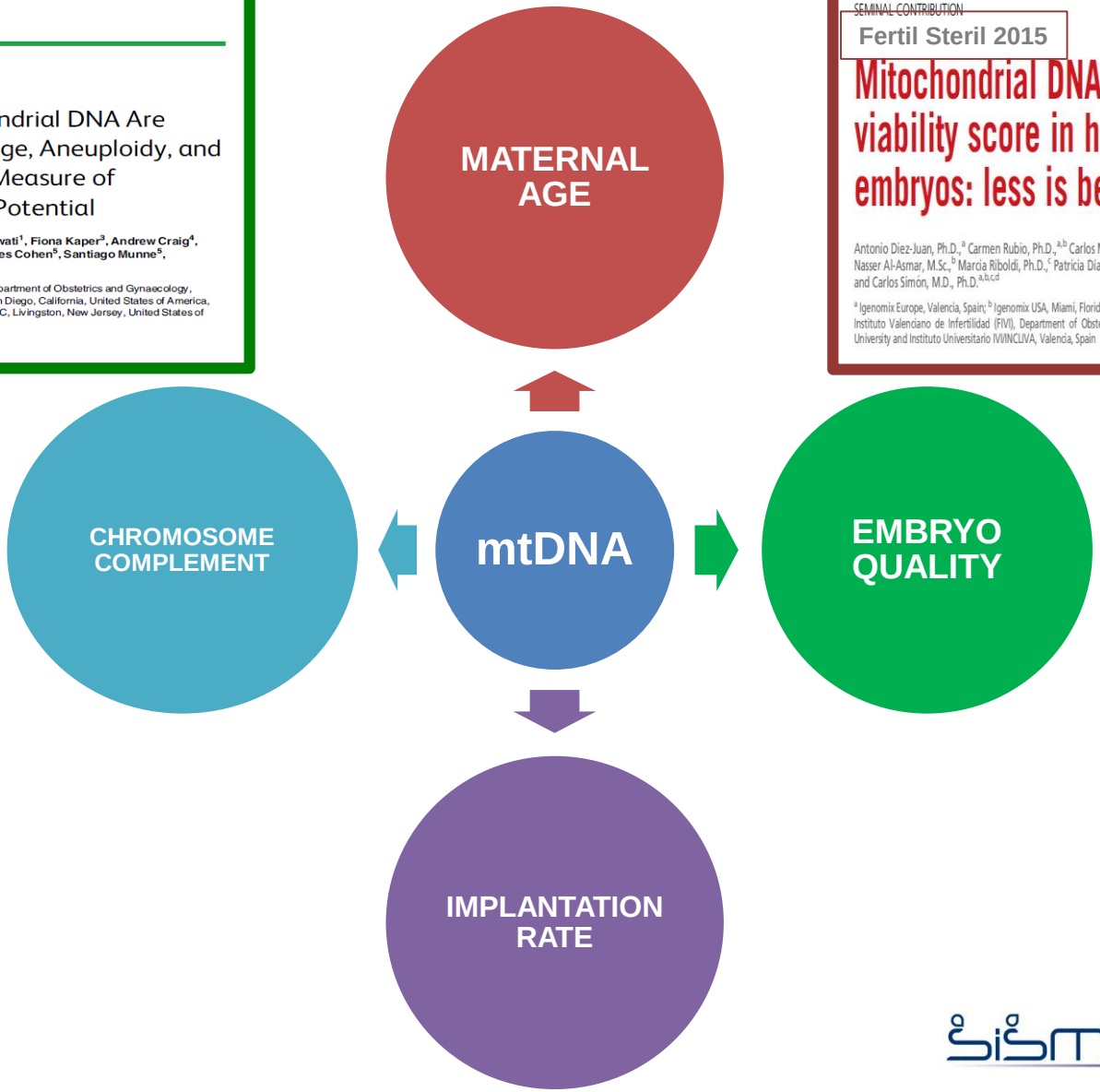

SEMINAL CONTRIBUTION

Fertil Steril 2015

Mitochondrial DNA content as a viability score in human euploid embryos: less is better

Antonio Diez-Juan, Ph.D.,[a] Carmen Rubio, Ph.D.,[a,b] Carlos Marin, B.Sc.,[a] Sebastian Martinez, B.Sc.,[a] Nasser Al-Asmar, M.Sc.,[b] Marcia Riboldi, Ph.D.,[c] Patricia Diaz-Gimeno, Ph.D.,[d] Diana Valbuena, M.D., Ph.D.,[a] and Carlos Simón, M.D., Ph.D.[a,b,c,d]

[a] Igenomix Europe, Valencia, Spain; [b] Igenomix USA, Miami, Florida; [c] Igenomix Brasil, São Paulo, Brazil; and [d] Fundación Instituto Valenciano de Infertilidad (FIVI), Department of Obstetrics and Gynecology, School of Medicine, Valencia University and Instituto Universitario IVIVINCLIVA, Valencia, Spain



PMA

Tecniche
-IVF
-ICSI
-Donazione Gameti
-PGT (PGS-PGD)
-Crioconservazione ovociti/embrioni
-IVM

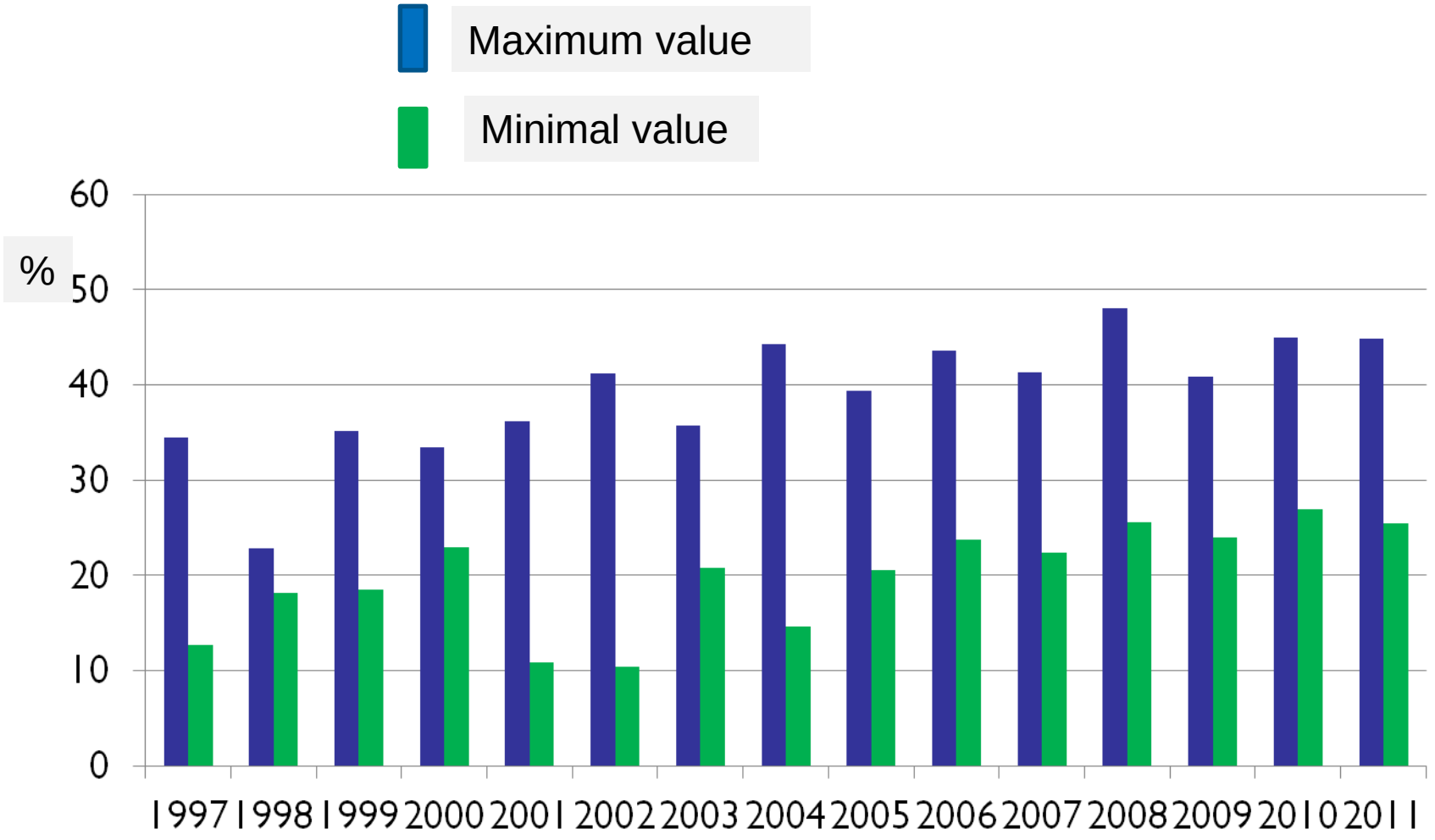
Fasi cliniche
-Stimolazione ovarica
- Prelievo di ovociti
-Trasferimento embrioni

Fase extra-corporea
-Inseminazione
- Coltura
- Valutazione qualità
-Selezione
-Crioconservazione

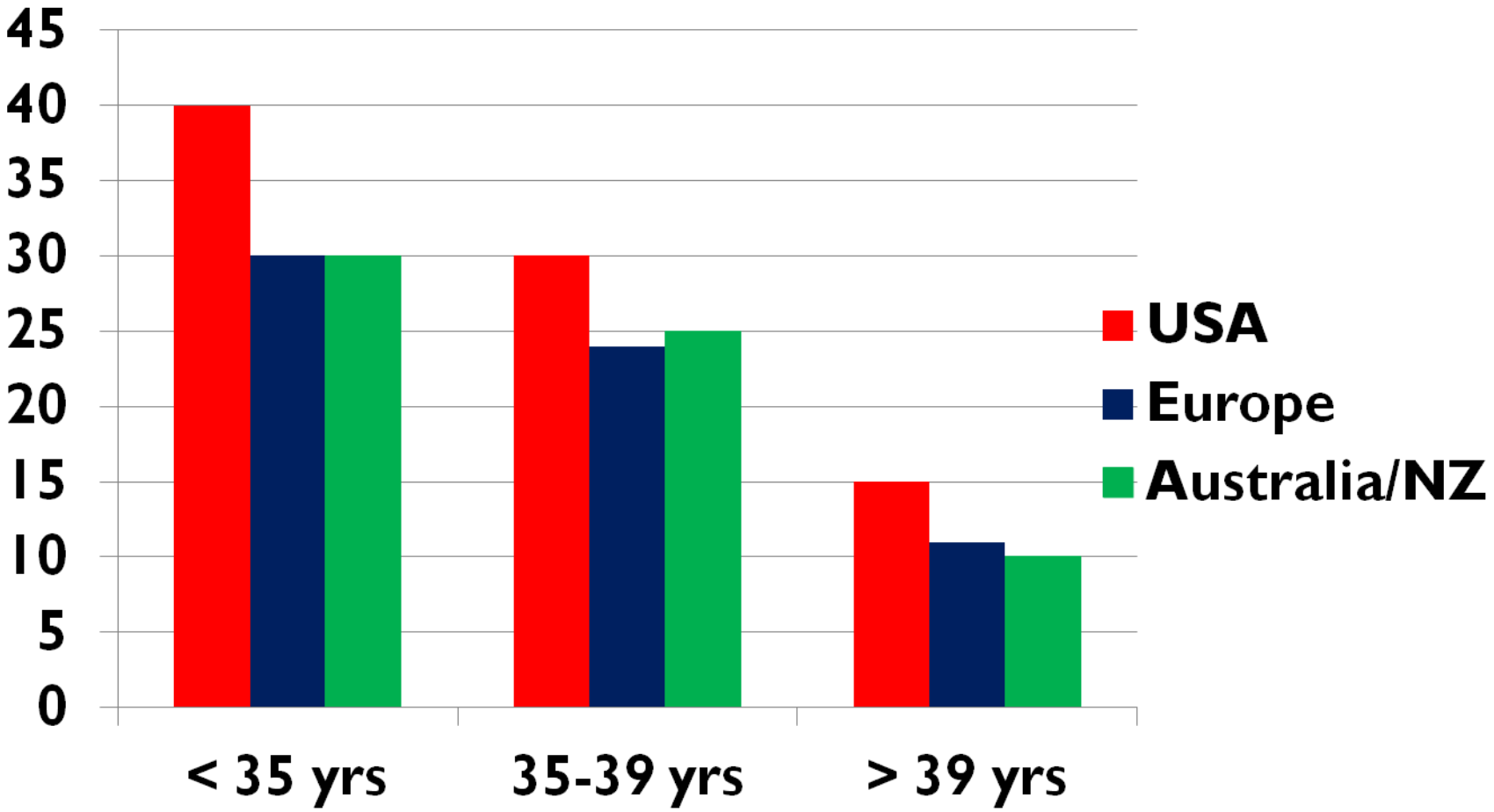
Efficacia

La efficacia dipende da età e da riserva ovarica

Range of the pregnancy rate per embryo tranfers (ICSI plus IVF cycles) in Europe

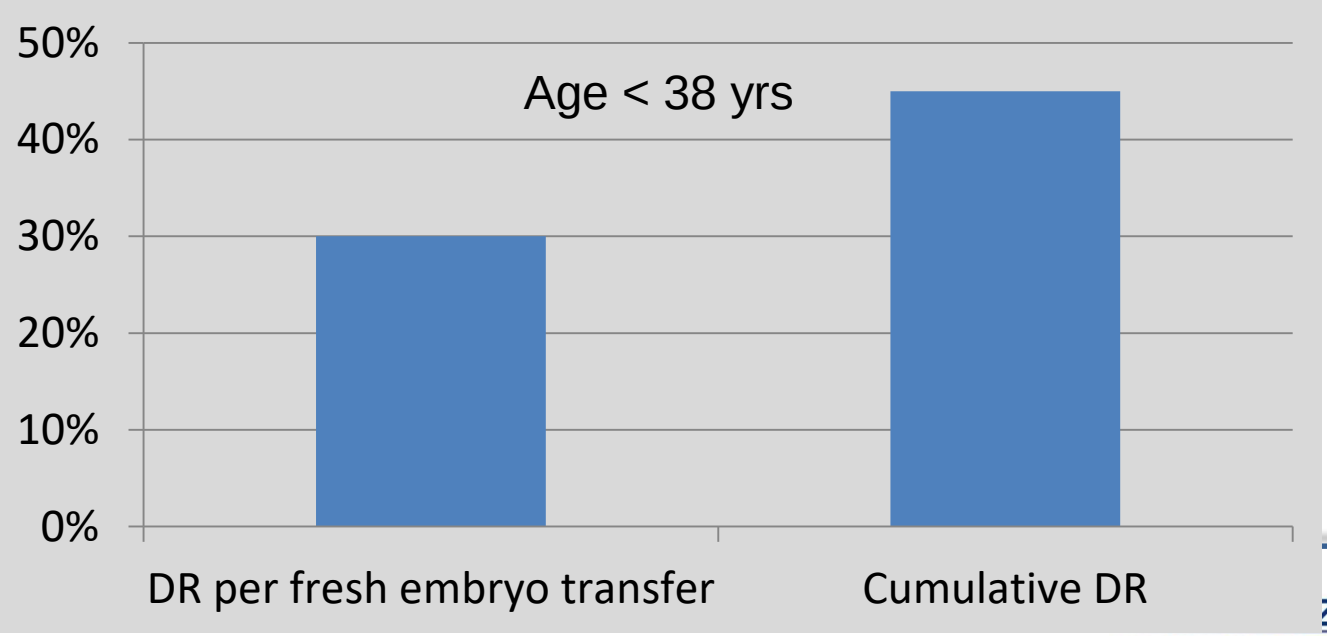


DR in base ad età



PMA-Come misurare la efficacia ?

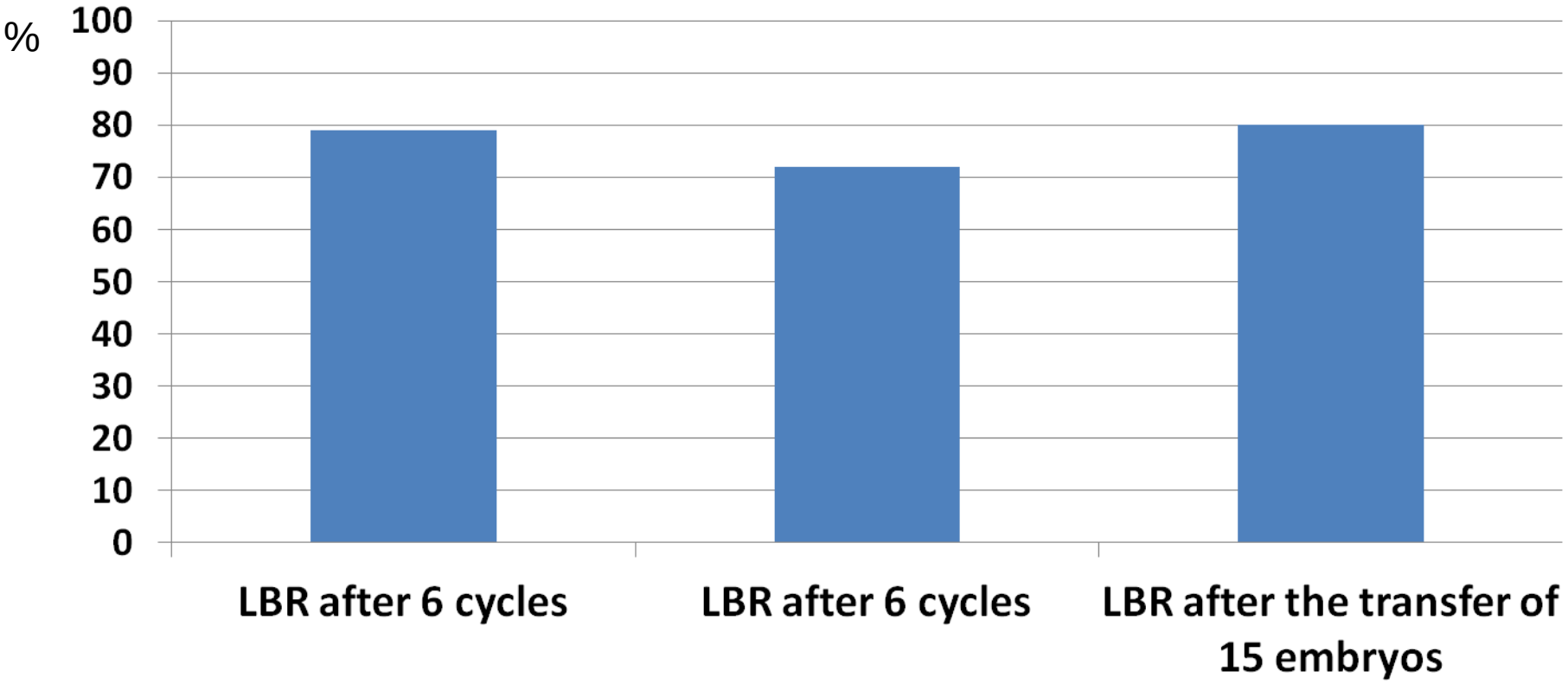
- Clinical pregnancy rate and delivery rate per single transfer
- Cumulative delivery rate per aspiration (including fresh and frozen embryo transfers)



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 after fertility treatment per patient (after a specific time and following all IVF treatments)

Cumulative live delivery after the exposure to multiple cycles of IVF (more than the usual 2 or 3 !) in patients < 40 years



Stewart et al, Fertil Steril, 95- 2011

Gnoth et al Hum Reprod 26,2012

Garrido et al, Fertil Steril, 96,2011

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

Drop-out

> 30% di coppie

abbandonano il percorso

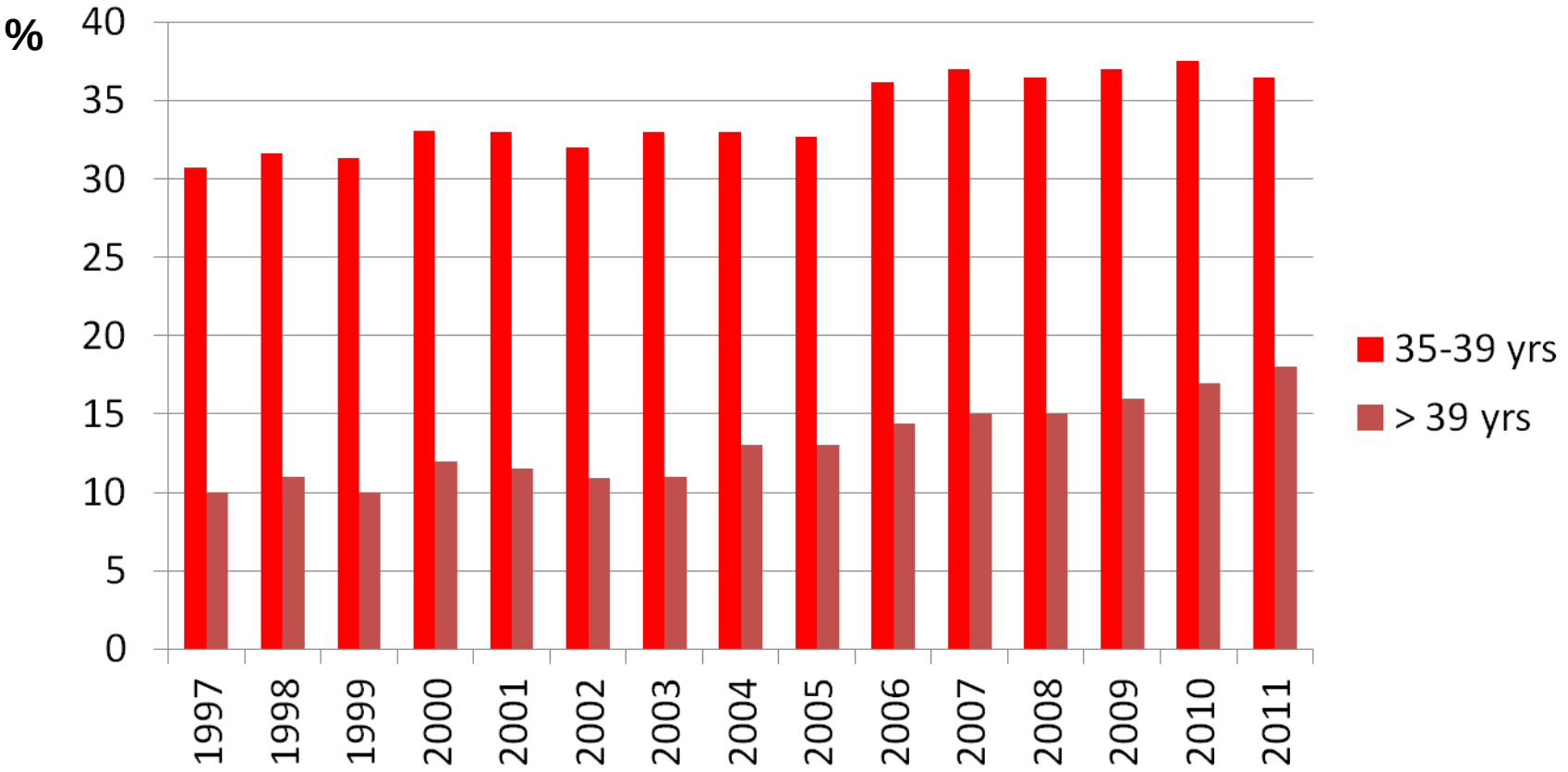
"Acceptable costs for the patient and society"

Chambers et al, Fertil Steril 2013,100.319

"Under some circumstances, ART represents good values of money from a social perspective : the monetary values of providing ART treatments can be far covered by the revenue of ART children"

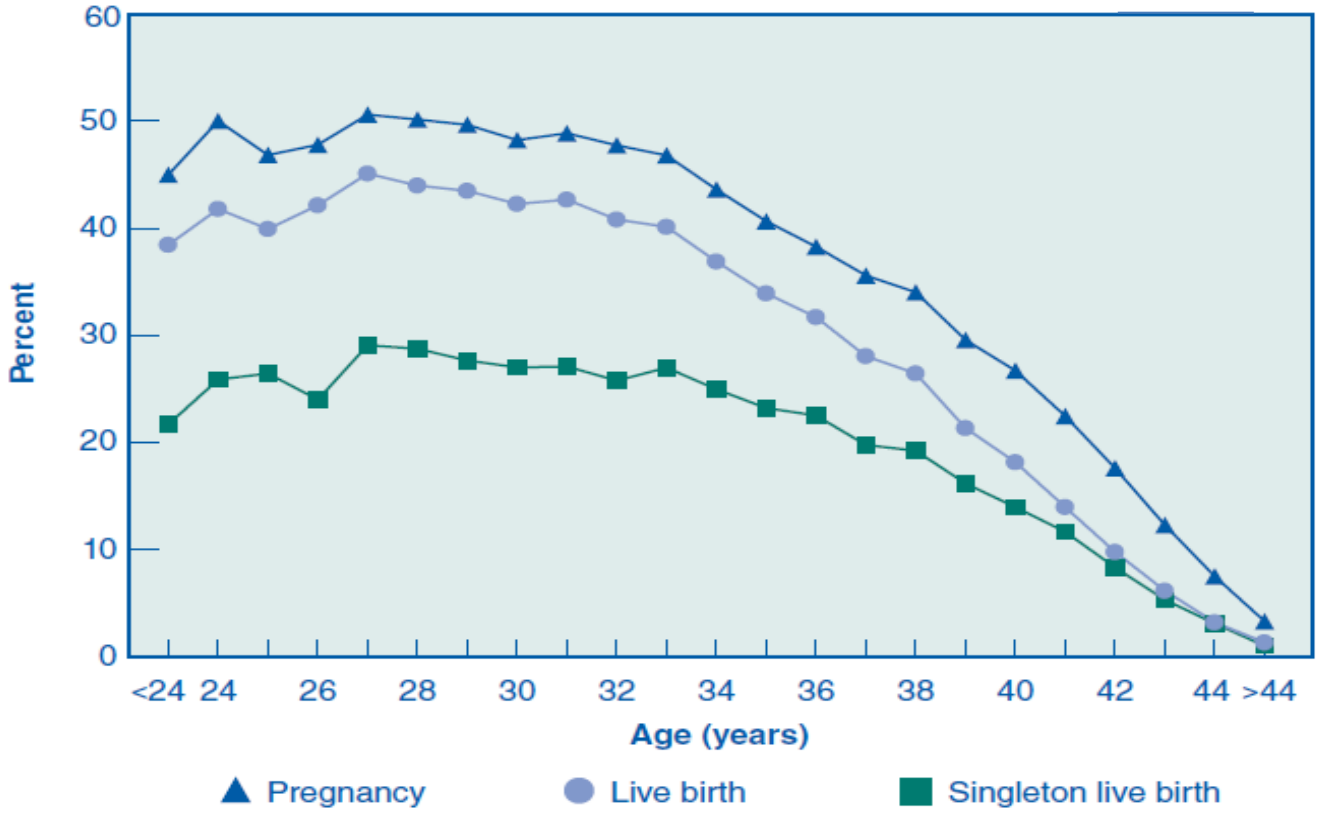
"These clinical circumstances are if babies born as singleton"

Female age (% of advanced aged patients)

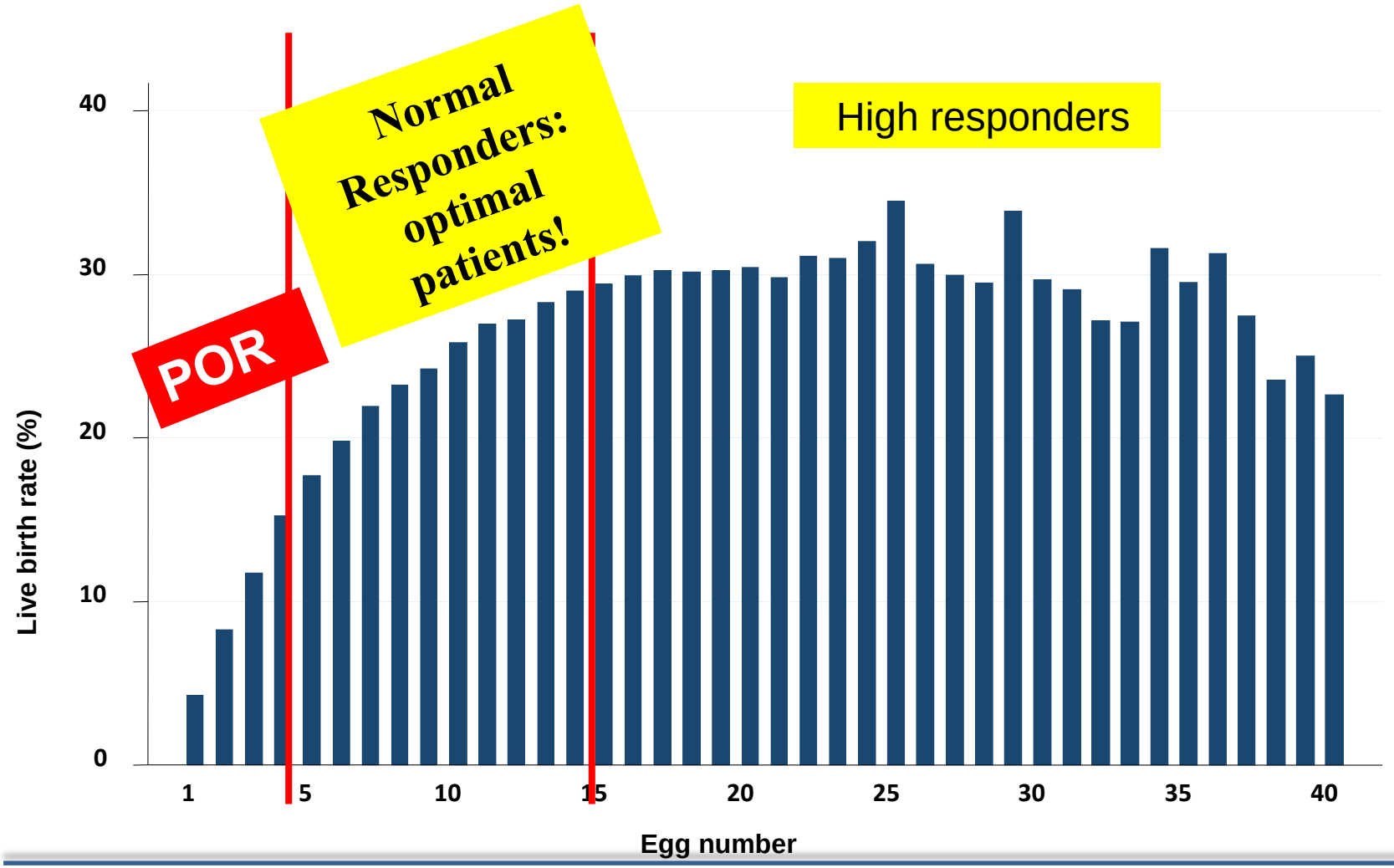


Possibilità di gravidanza con la PMA in relazione ad età

Percentages of ART Cycles Using Fresh Nondonor Eggs or Embryos That Resulted in Pregnancies, Live Births, and Singleton Live Births, by Age of Woman,* 2008

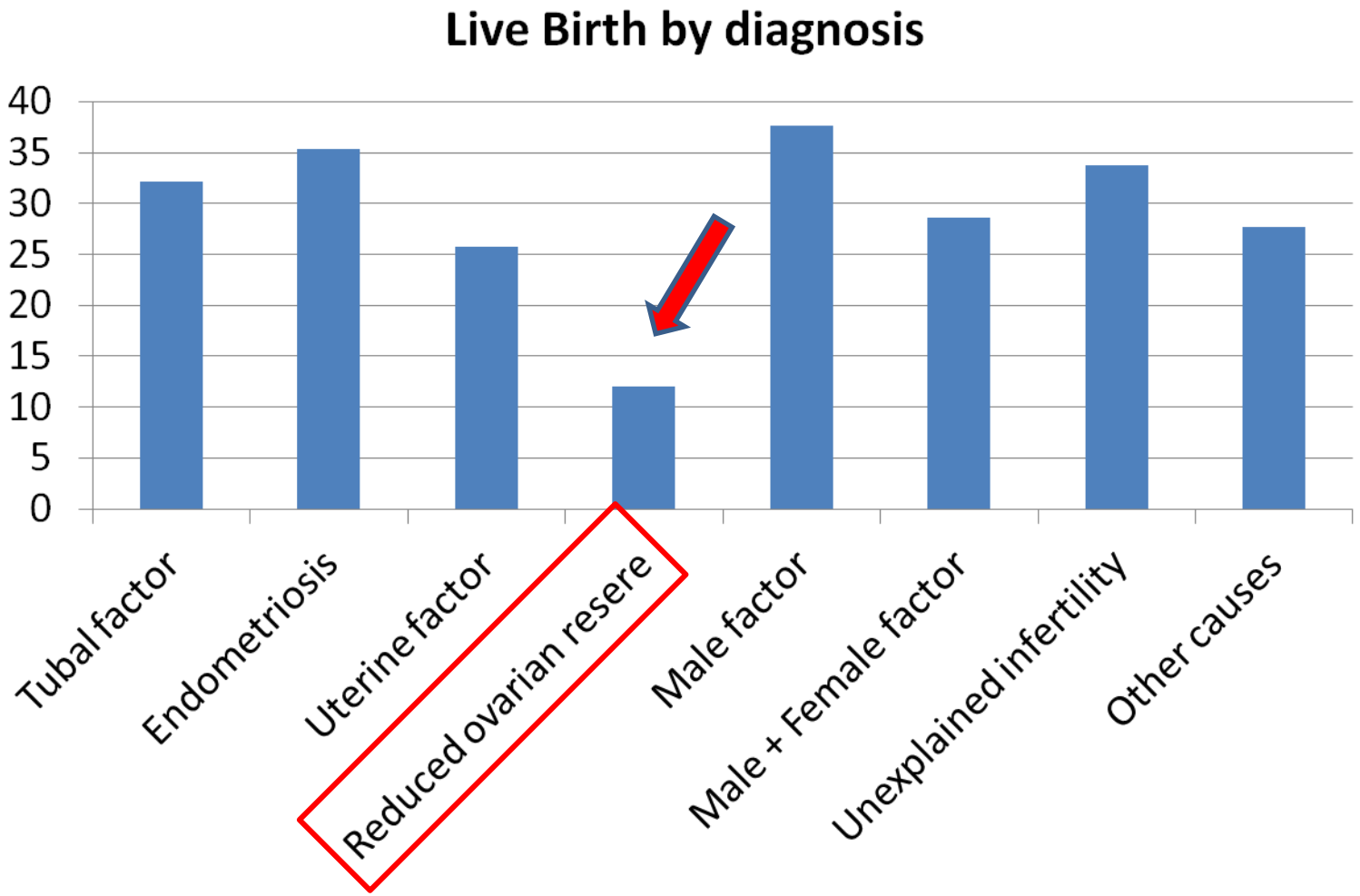


Ovarian response

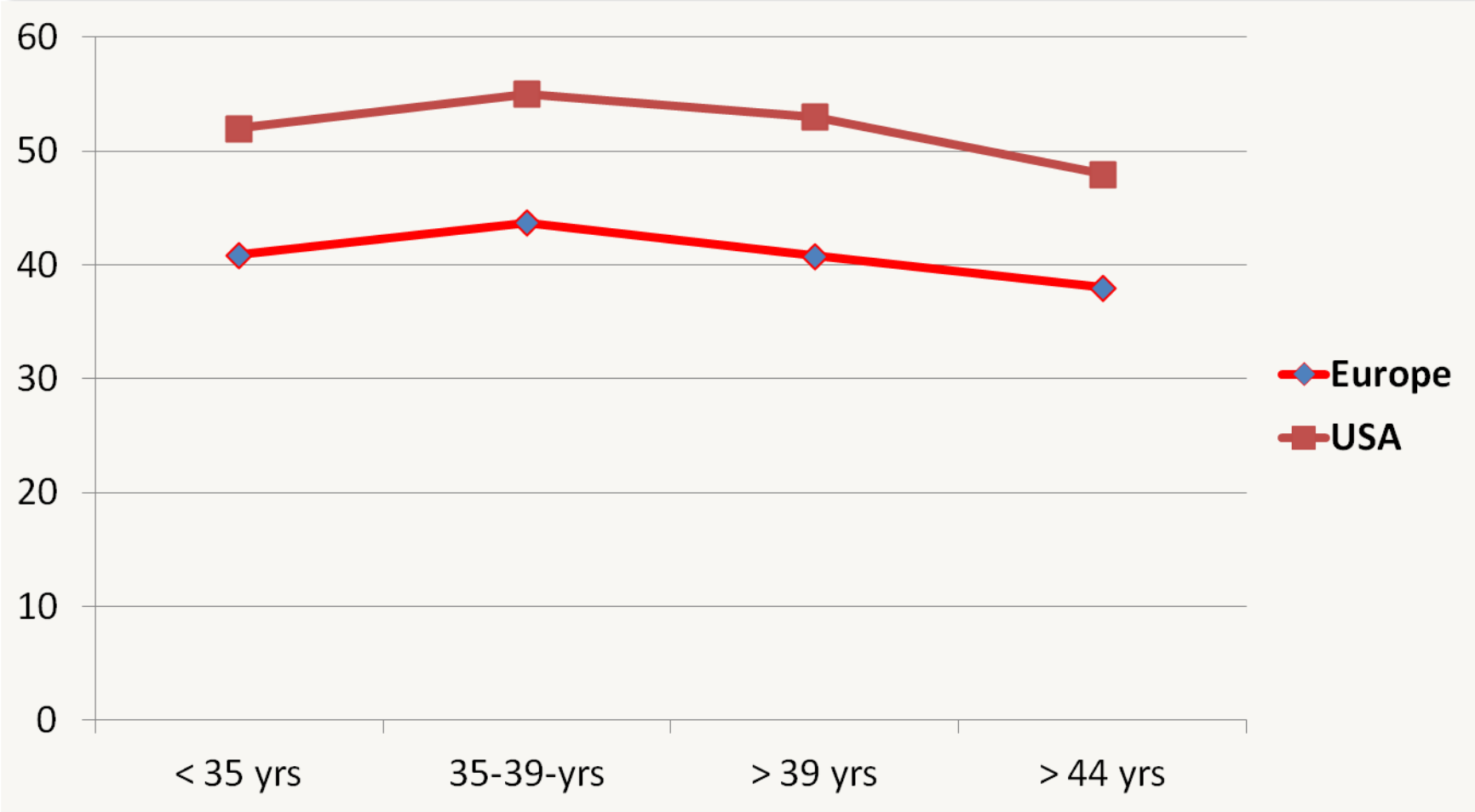


Sunkara et al., Hum Reprod 2011

Data from USA Register 2013



Oocytes donation (DR/ET)



Human Reproduction, 2012

Oocyte cryopreservation for age-related fertility loss

ESHRE Task Force on Ethics and Law, *including, W. Dondorp1,*,*

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P. Barri6, and K. Diedrich7

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