Infertility Meeting, Misurata, 26th October 2007

New Developments in Reproductive Medicine

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Number of infertile couples in Germany:

approx. 15 - 20% of all couples

(1.2 – 1.6 Millions)

Once upon a time…

Birth after reimplantation of a human embryo
Steptoe P.C. / Edwards R.G.
Lancet 2 (1978): 366

07/78 Louise Brown was born

Milestones in reproductive medicine

- 1960 - ovarian stimulation with clomifene and gonadotrophins
  - radioimmunoassay
- 1970 - secretion, synthesis, mechanism of GnRH a. gonadotrophins
  - in vitro fertilisation
- 1980 - GnRH-agonists and gonadotrophins
  - cryopreservation
- 1990 - recombinant gonadotrophins
  - preimplantation genetic diagnosis
  - intracytoplasmatic sperm injection (ICSI)
  - GnRH-antagonists
- 2000 - in vitro maturation of oocytes
  - embryonic stemcells
  - SET (single embryo transfer)
  - vitrification

Probability of successfull infertility treatment

after: Dor et al., 1996

cause of infertility	pregnancy rate
ovarian	57.7%
tubal	63.3%
male	71.4%

Children after ART until 2004 *worldwide*

- **1.9 Millions after ivF**
- **800 000 after ICSI**
- **Germany (1982-2004): 108 000**

<u>birthrate per cycle</u>:

- **after ivF 21% (DIR, 2004)**
- **after in vivo fertilisation 24%**

C. Nygren, 2004

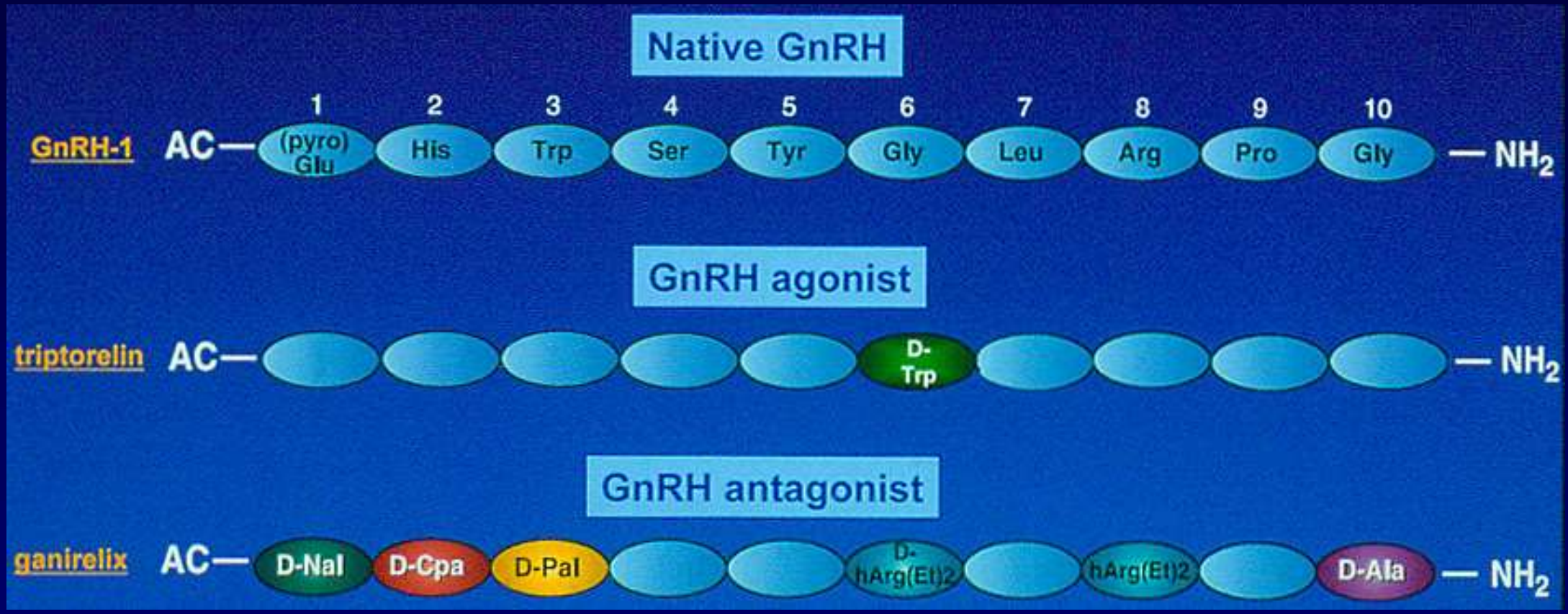
New Developments in Reproductive Medicine

- Ovarian stimulation: GnRH-antagonists
- Elective single embryotransfer (eSET)
- Blastocyst transfer
- In-vitro-maturation
- Cryopreservation and vitrification
- Preimplantation genetic diagnosis and screening

History of ovarian stimulation

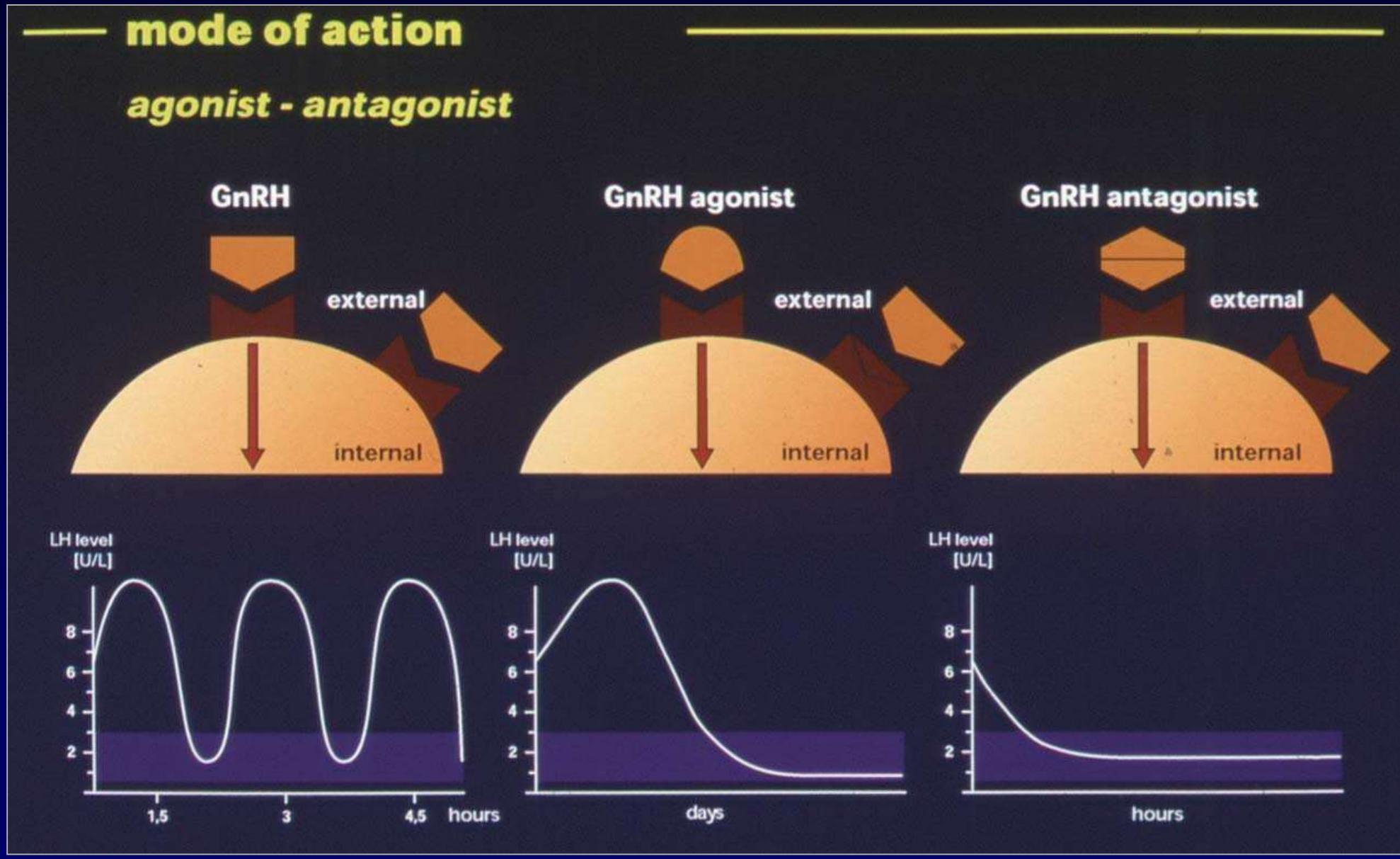
- 1970 Clomifen
  hMG
- 1980 GnRH-agonist / hMG
- 1990 recFSH
  GnRH-antagonist / hMG or recFSH
- 2000 long acting FSH

Structure of GnRH and analogues



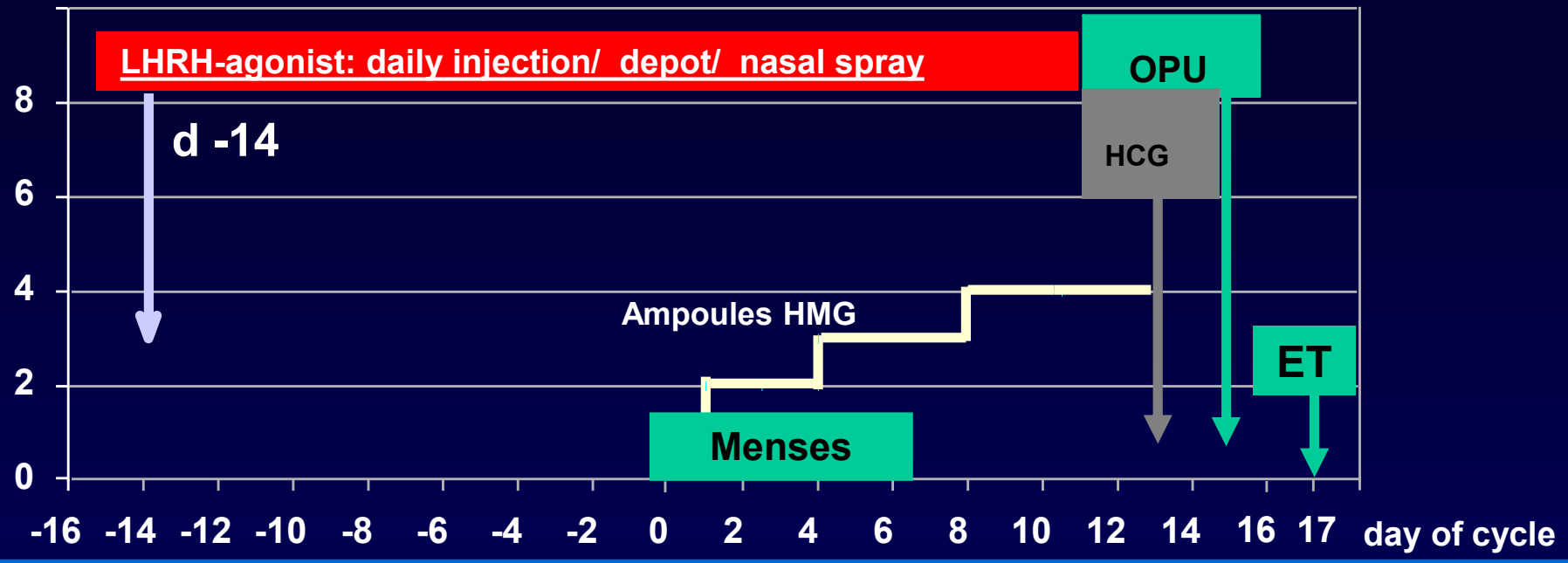
mode of action

agonist - antagonist

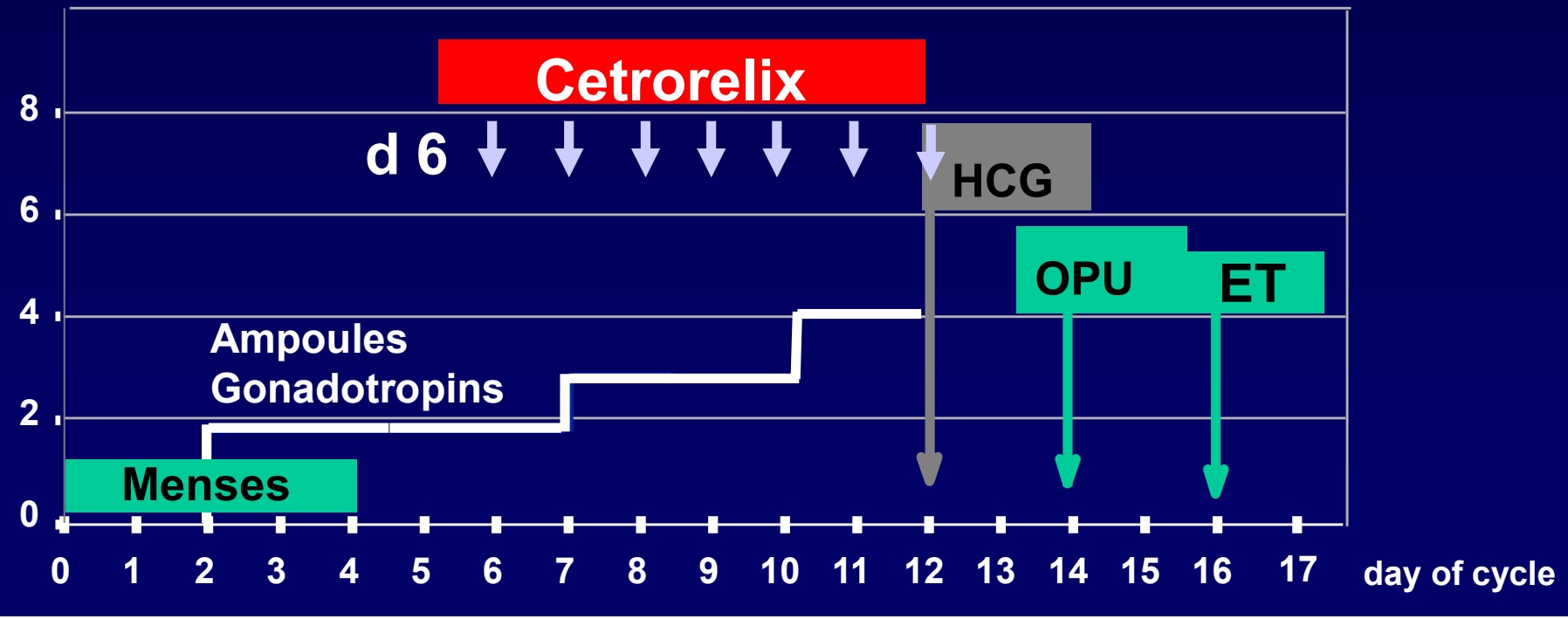


GnRH-agonist and antagonist protocol

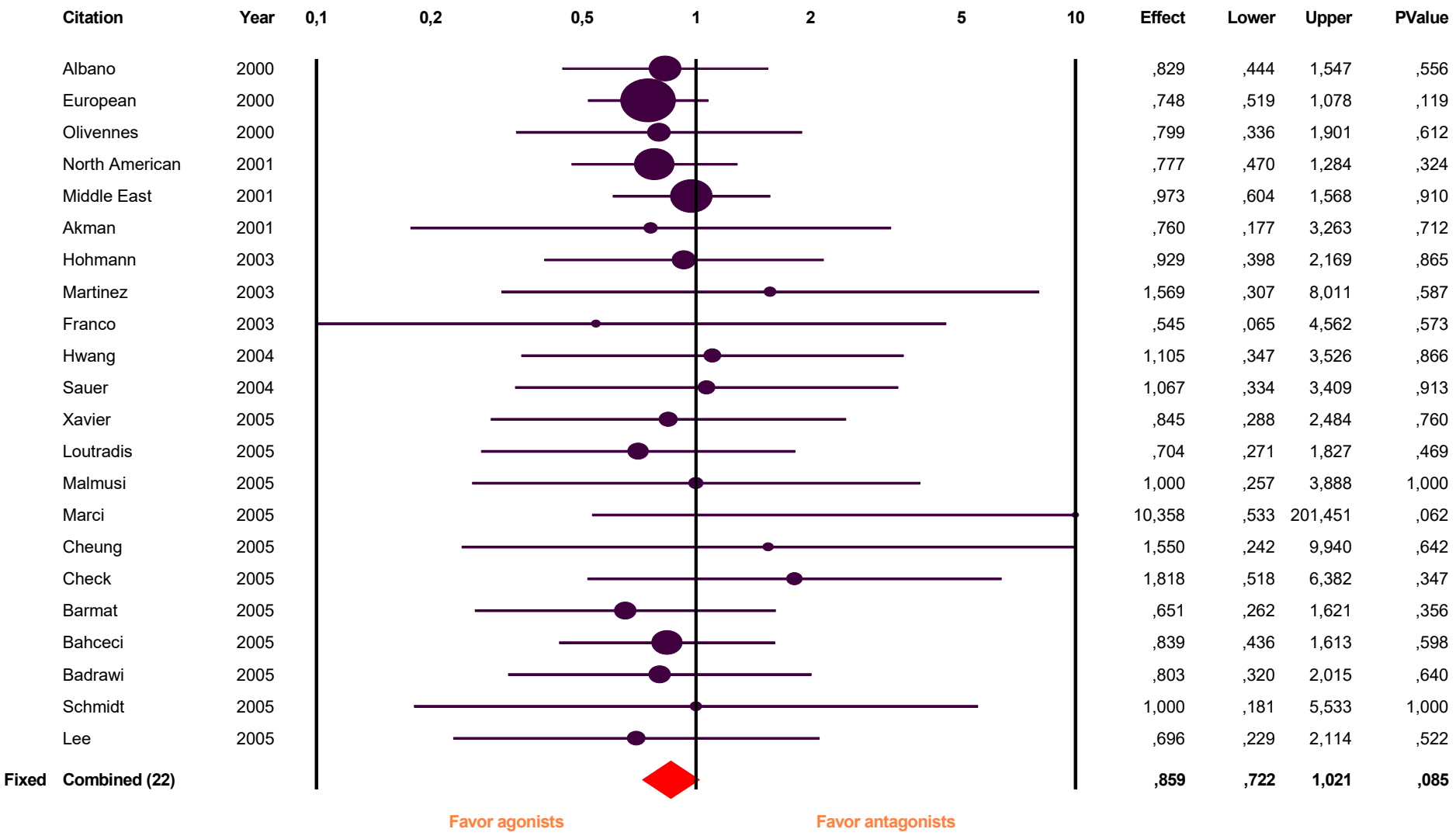
„long protocol“



„Lübeck protocol“



LIVE BIRTH



Odds ratio:0.859

p=0.085

Griesinger et al., 2006

Rate difference

2.7%

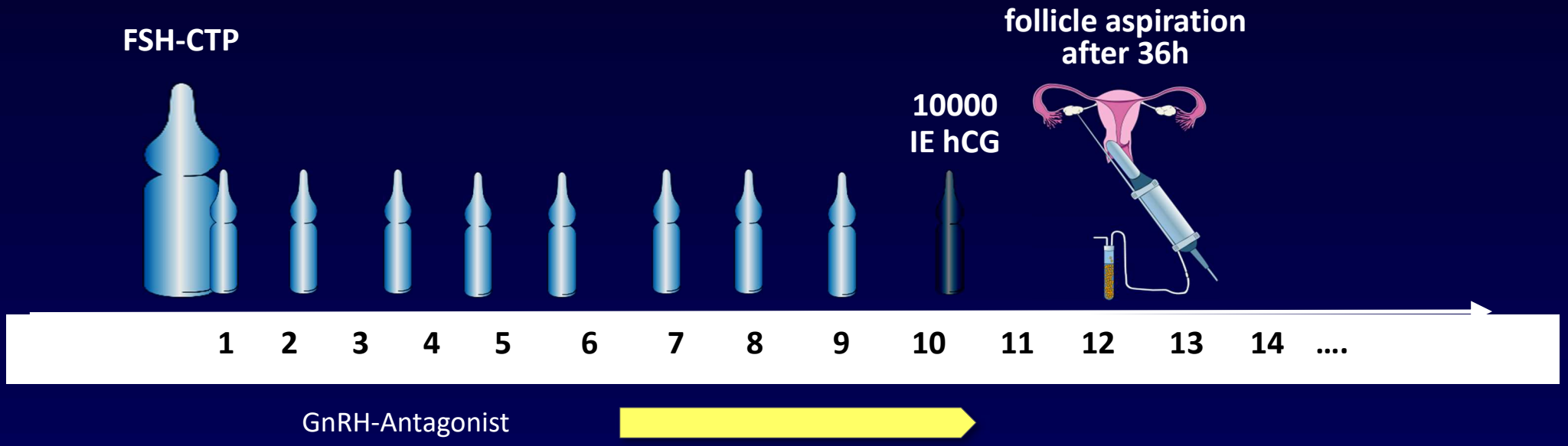
Advantages of GnRH-antagonists

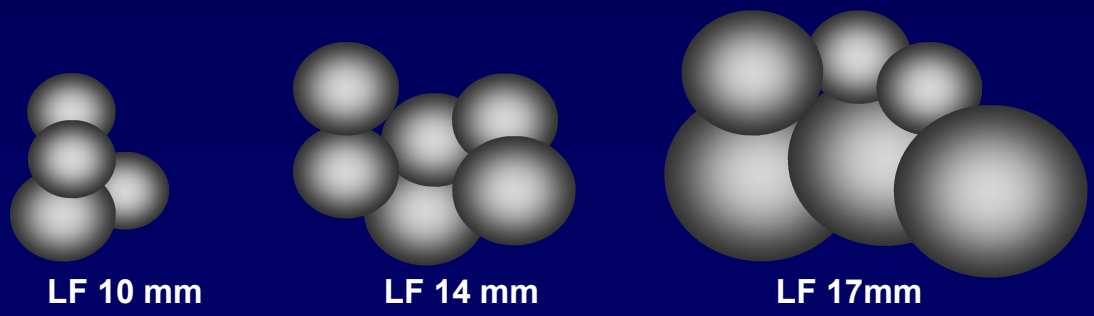
- simple stimulation
- fixed initiation of GnRH-antagonist on day 6
- no LH supplementation
- no increase of gonadotrophin dose at GnRH-antagonist initiation
- ovulation induction for ART by dominant follicle of $\geq$ 17mm
- luteal phase supplementation is mandatory

Advantages of GnRH-antagonists

- fits into the normal cycle („the patients like it“)
- less side effects in comparison to the long protocol:
  1. Ø cysts
  2. Ø hormonal withdrawl
  3. less OHSS
- **no significant difference in the probability of live birth between GnRH-agonists and antagonists**

long acting FSH





Children after ART: 1997-2002

	IVF	ICSI	Total	%
Singleton	11455	12096	23551	59.83
Twin	6782	6553	13335	33.87
Triplet	1228	1221	2449	6.22
Quadruplet	23	8	31	0.08
Total	19488	19878	39366	100

DIR 2001

Donald and Louis Keith – the founders of the Center for Study of Multiple Birth – pictured at the age of 3½, Chicago, photographer unknown.

Problems of multiple pregnancies

- pregnancy related diseases
- prematurity
- increase of neonatal morbidity and mortality
- costs

Aims

1. To avoid multiple pregnancies
2. Improve the pregnancy and life birth rate

Solution: Transfer of one selected embryo

Embryo selection

> 30% **< 5%**

Implantation

Pregnancy rate after elective single embryo transfer (eSET) and elective double embryo transfer (eDET)

eSET = 40.3% pregnancy rate

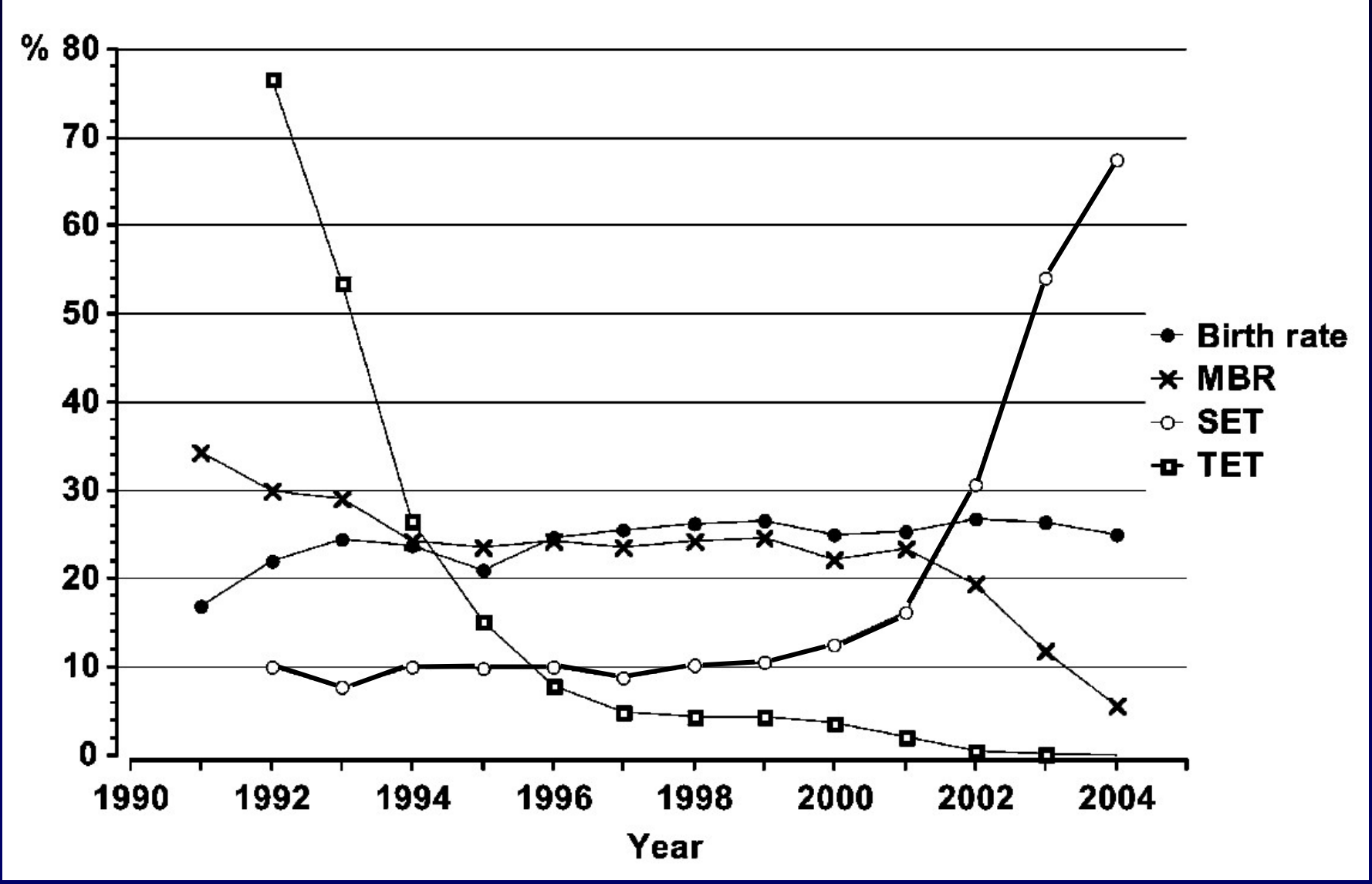
1% gemini

eDET = 44% pregnancy rate

32% gemini

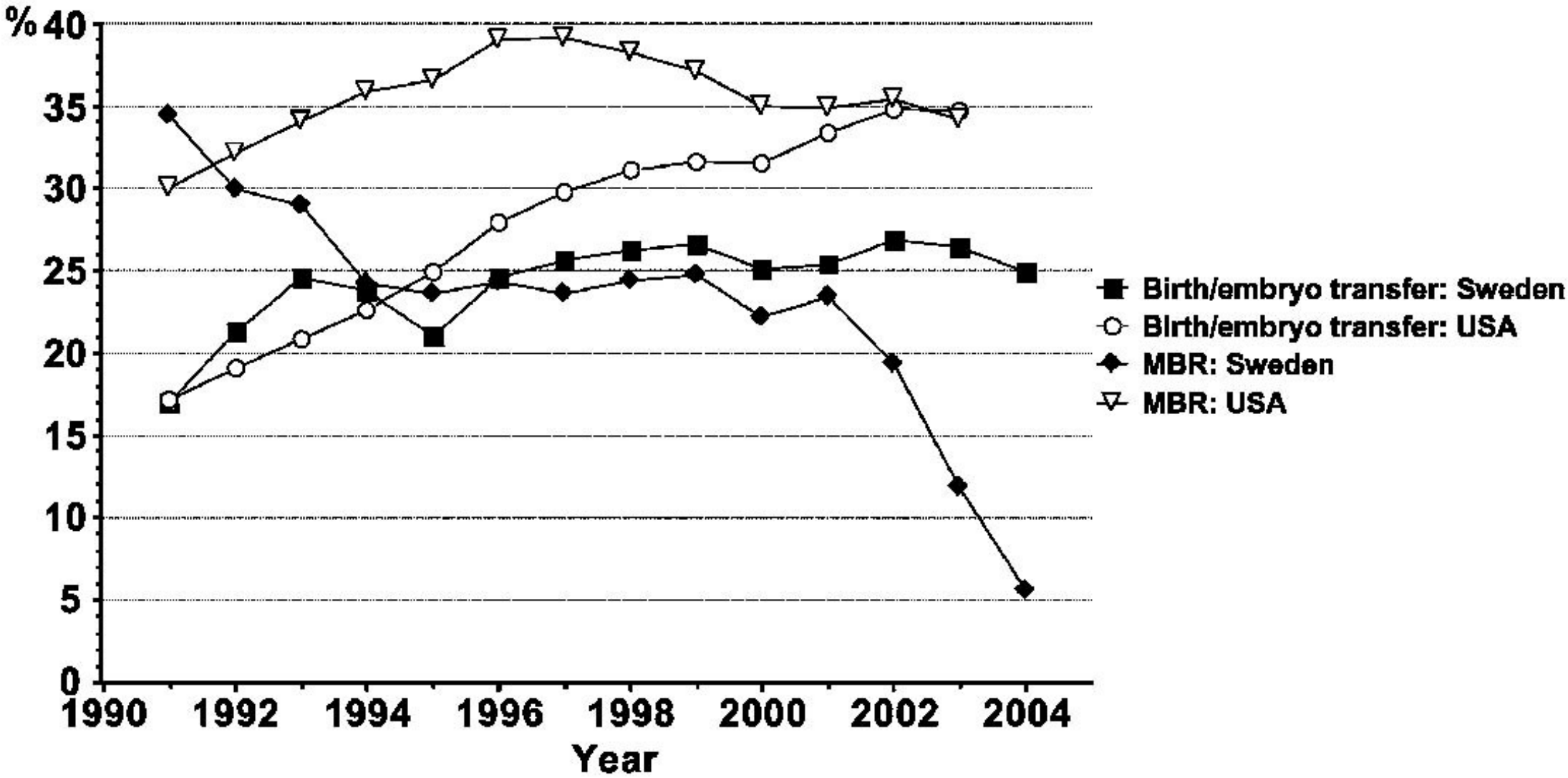
Gerris, 2005
ESHRE

Birth rate and MBR in relation to the percentage of SET and triple embryo transfer (TET) in Sweden 1991–2004

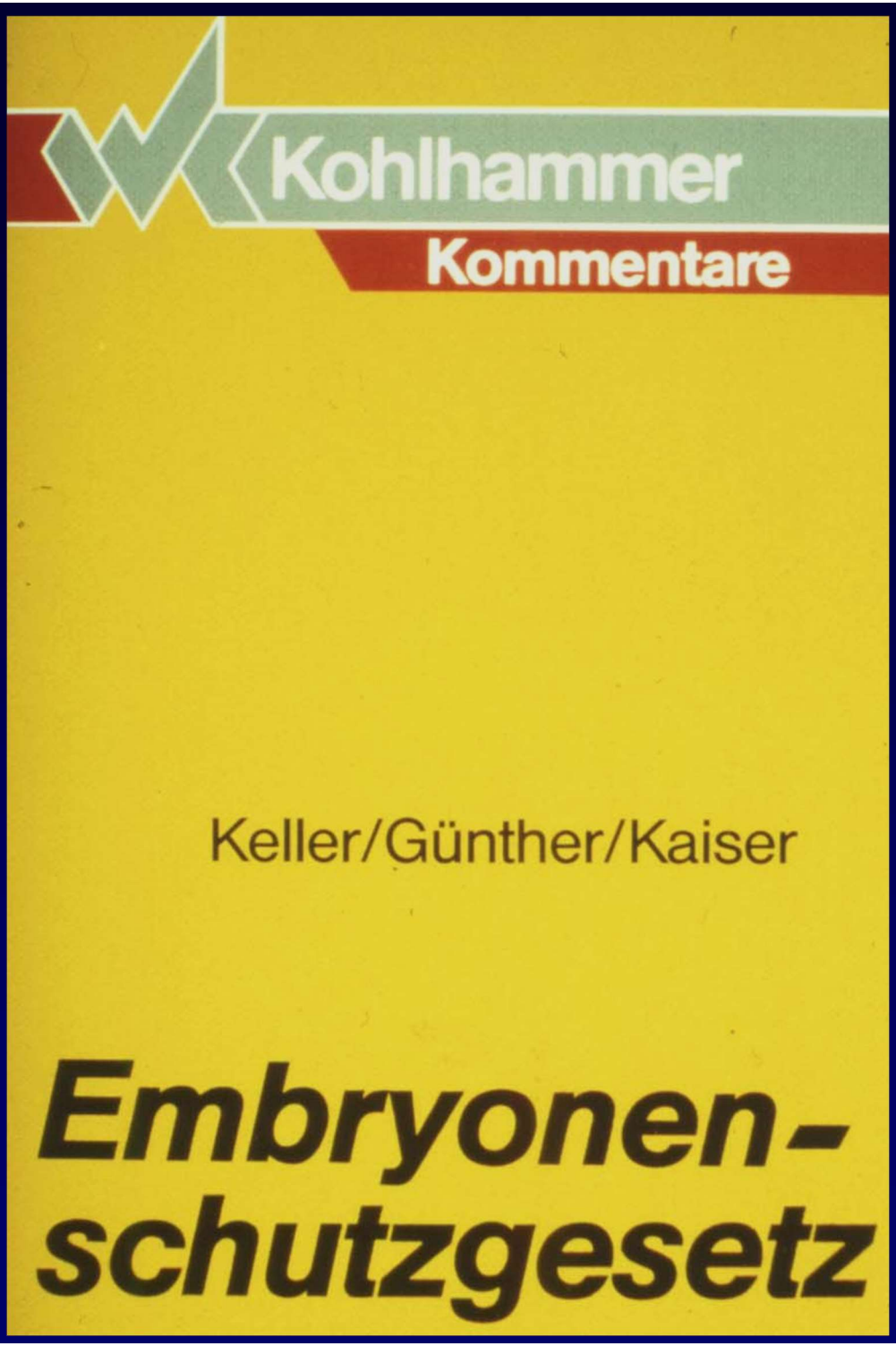


Karlström u. Bergh, HumRep 22: 2007

Birth per embryo transfer (%) and MBR in Sweden and USA



Karlström u. Bergh, HumRep 22: 2007



Prison sentence up to three years or financial penalty for

§ 1, Abs. 1, Nr. 3

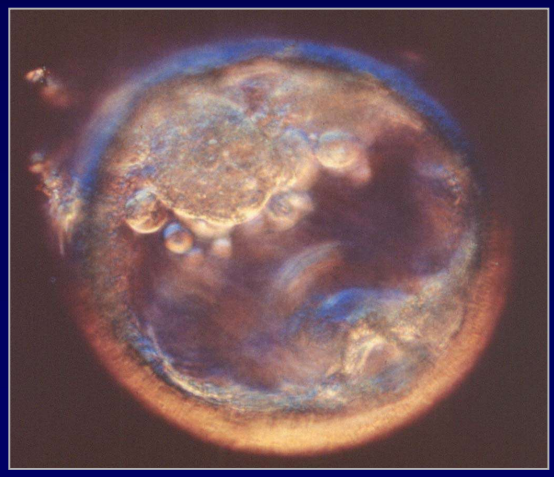
„a person transfering more than 3 embryos to the womb in the course of one treatment cycle“

§ 1, Abs. 1, Nr. 5

„a person fertilizing more oocytes than he or she intends to tranfer in the course of one treatment cycle“

Metaanalysis of blastocyst transfer: day 2/3 versus day 5/6 of embryo transfer

- no significant difference (OR=0,91; 95% CI 0,71-1,17)
- disadvantage of long-term cultivation



Blake et al. 2004

Preimplantation genetic screening (PGS)
University of Brussels

Inclusion criteria:

- 37 yrs and older
- prospective randomized controlled study
- examined chromosomes: X, Y, 13, 18, 21

Results PG-Screening

University of Brussels

Preimplantation genetic screening (PGS)		control
Patients	86	82
Embryo transfer	48 (55%)	70 (85%)
Abnormal embryos	20	
Pregnancies per embryo transfer	10 (20.9%)	18 (26.5%)
No of embryos per ET	2.1 (100)	3.1 (210)
Implantation rate per embryo	10%	8%

Devroey, 2006

Conclusion of the Brussels study:

A positive effect of PGS on implantation and abortion rate of this study and others is not clearly documented.

Methods of cryopreservation

slow cooling

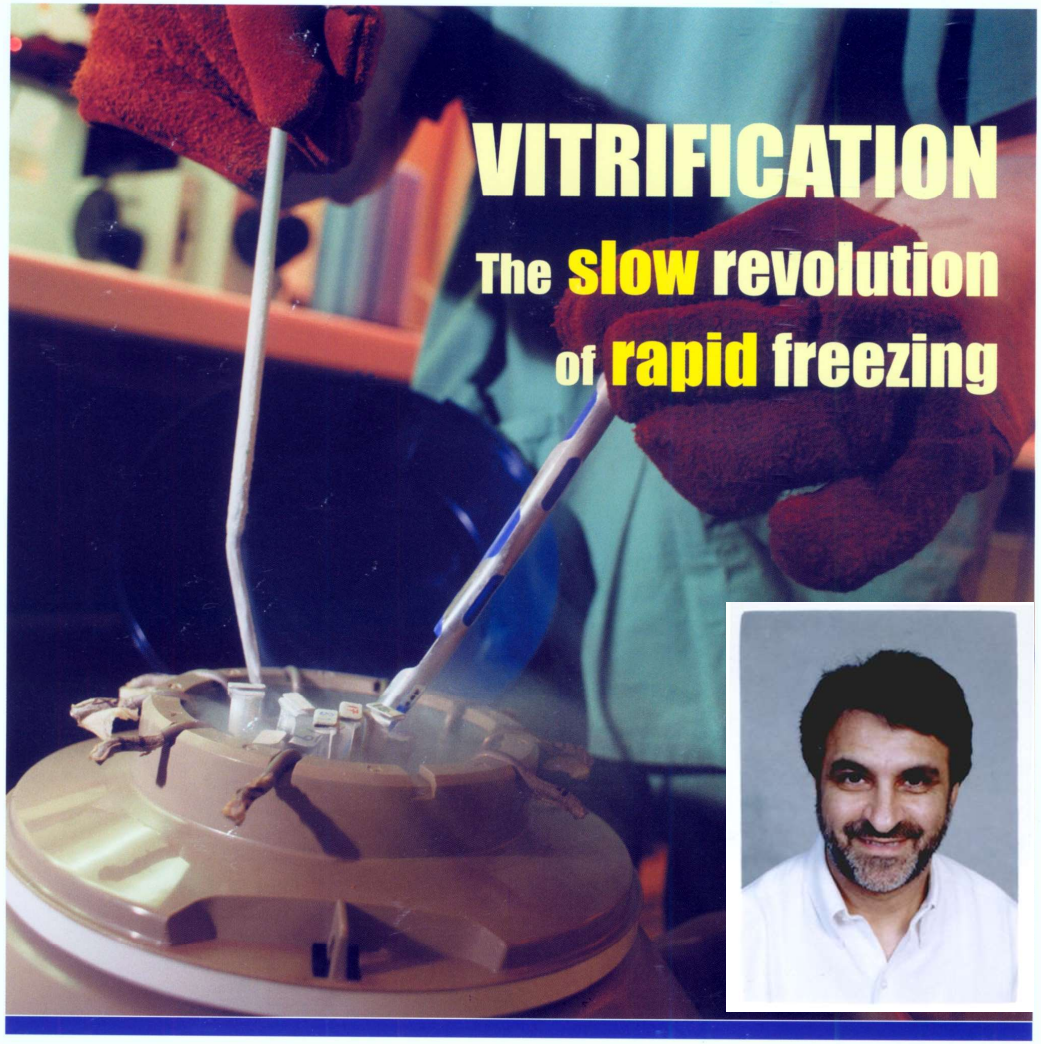
vitrification

Clin. pregnancies / ET after cryo transfer (1996-2004)

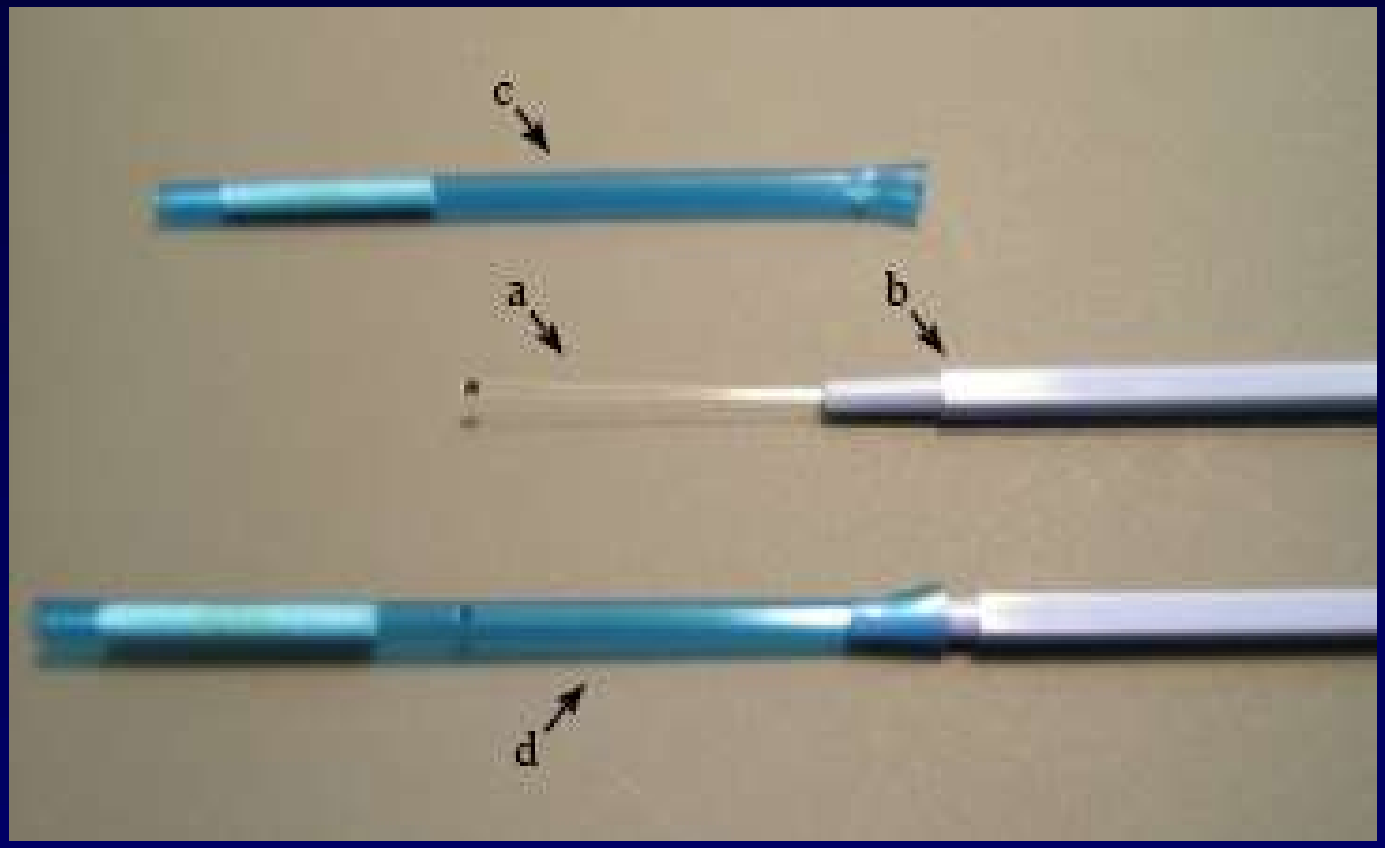
Cryo transfer	67,257
Clin. pregnancy / ET	15.5 %
Abortion rate after cryo transfer	21.64 %

German IVF Index 2004

FOCUS ON
Reproduction
EUROPEAN SOCIETY OF HUMAN REPRODUCTION AND EMBRYOLOGY



Cryotop for vitrification

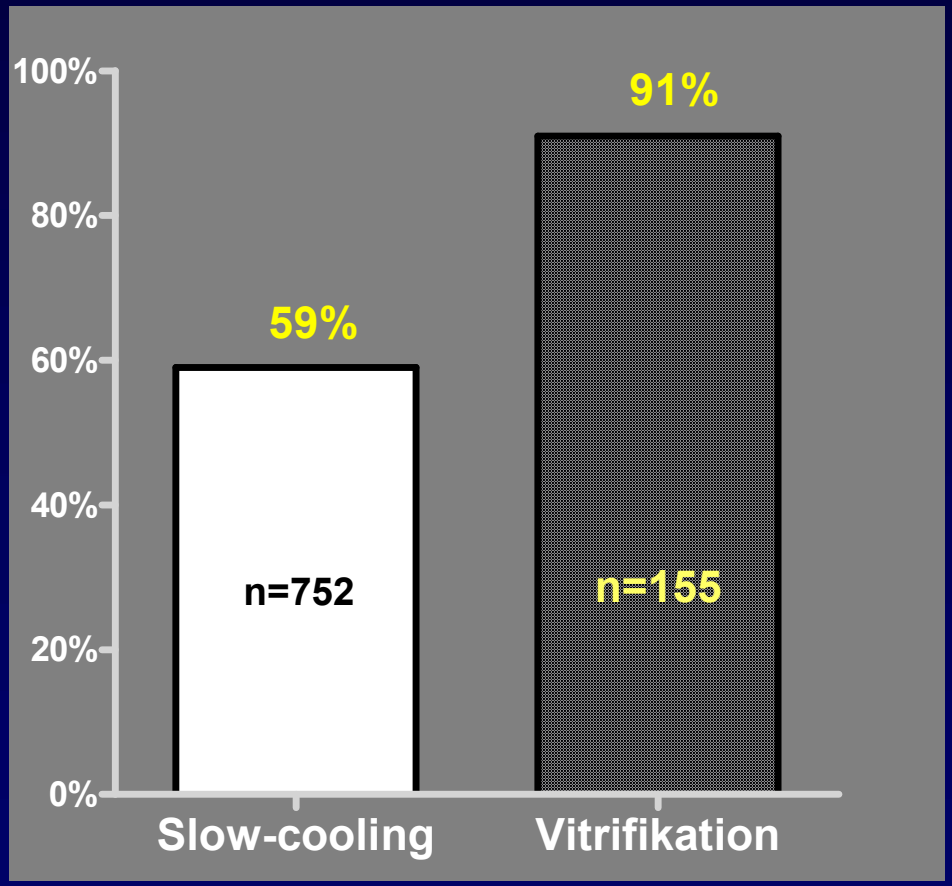


a. Polypropylen strip
b. Hartplastik-Griffstück
c. Hartplastik-Schutzhülle
d. Schutz für LN_2 Lagerung

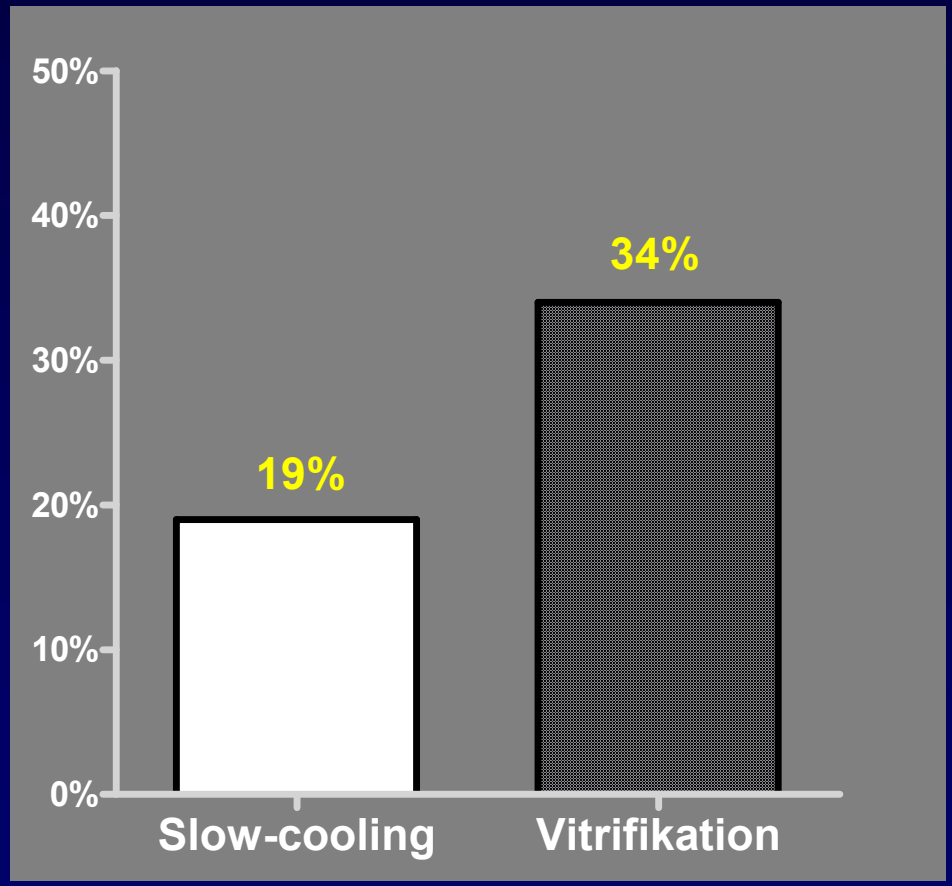
after Kuwayama, RBM-online 2005, pp.300-308

Lübeck Results
(till 01/2007)

survival rate



pregnancy rate



First oocyte maturation in vitro

The Lancet 1965

„Oocytes from antral follicles can finalize their meiotic maturation in vitro in 24 – 48 hours“

R.G. Edwards et al.

Edwards RG et al. 1965

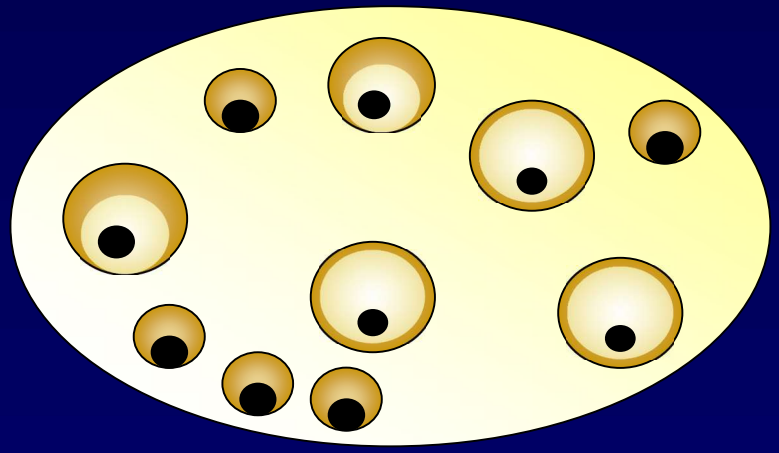
Development of IVM

1983	***Veeck***	**First birth after IVM**
1991	***Cha***	**IVM on immature oocyte extracted by using ovarian biopsy during a cesarean section resulted in healthy twins**
2000	***Cha***	**birth of 20 healthy children afte IVM**
2003	***Mikkelsen***	**birth of 33 healthy children after IVM**
today		**>300 children after IVM**

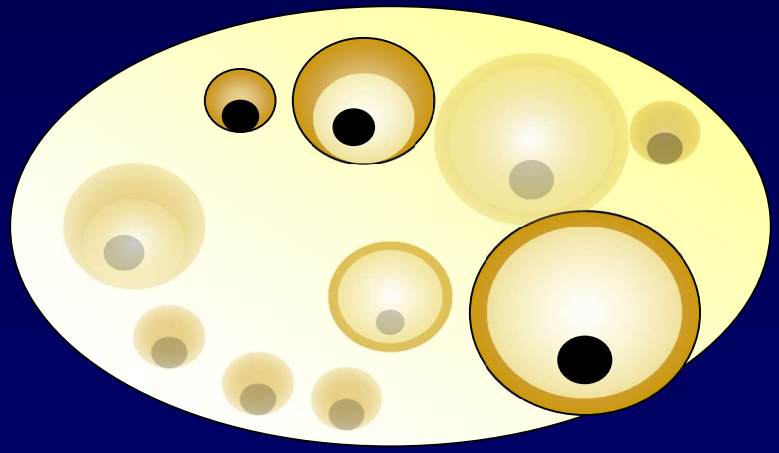
Physiological basics of IVM

Early oocyte retrieval from antral follicles before selection and atresia . . .

day 3



day 8 - 12



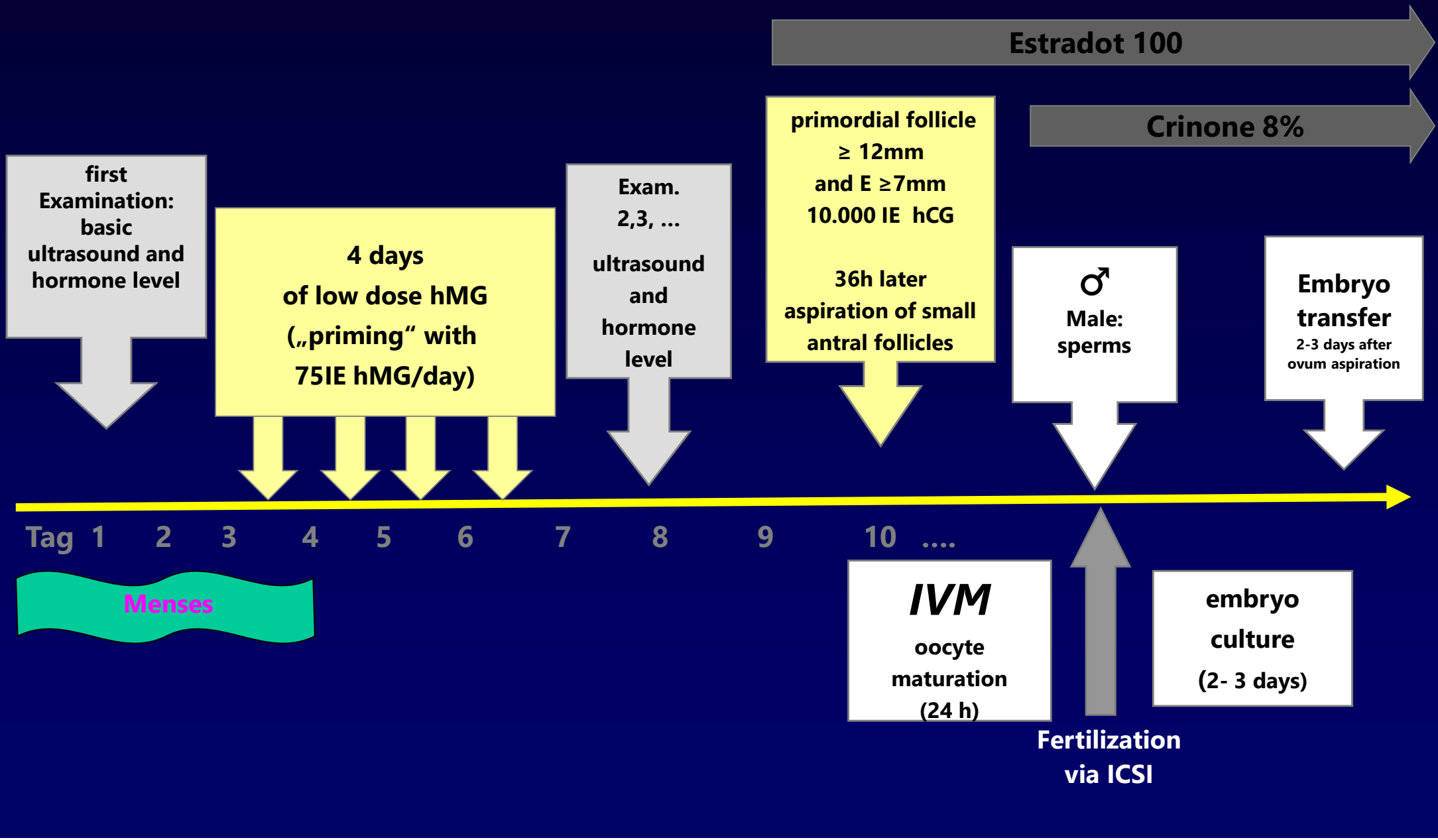
d>10mm

Therapeutic indications for IVM

- PCOS
- high responder with a risk for OHSS
- normo-cyclic patients
- cryopreservation of oocytes (oncology)
- low responder
- implantation failure

Mikkelsen et al. 2003, Smitz 2005, von Otte 2005

Treatment protocol



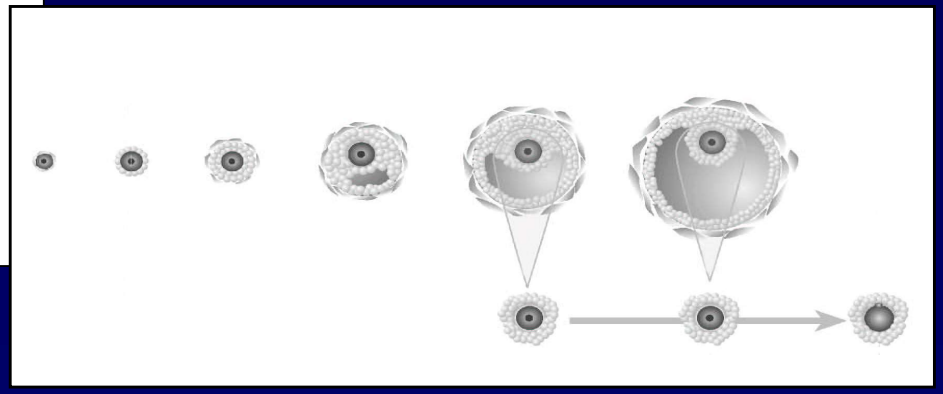
Fertilization and outcome

N= 100 cycles	total	%	Mean ± SD
Mature oocytes/ ovum aspiration	310		4.2 ± 3.4
Pronuclei/ ovum aspiration	138	44	1.77 ± 1.44
Cycles with embryo transfers	55/85	67%	
Embryos/ transfer	122		2.2
Pregnancies/ transfer	13	13%	
Cryopreservation	4	5.9%	

in the future:
„TESE“ for the woman?

- ovarian biopsy and cryopreservation

- in vitro Growth („IVG“) followed by In vitro Maturation („IVM“)



Oktay et al. 2004

Future of Reproductive Medicine

- new embryo protection law (european?)
- improvement of pregnancy rate by the elective single embryo transfer (morphological criteria)
- avoid multiple pregnancies
- vitrification
- in vitro maturation
- aim of infertility treatment: simple, safe, comfortable, successful and cheap