Cumulative birth rates

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Outline

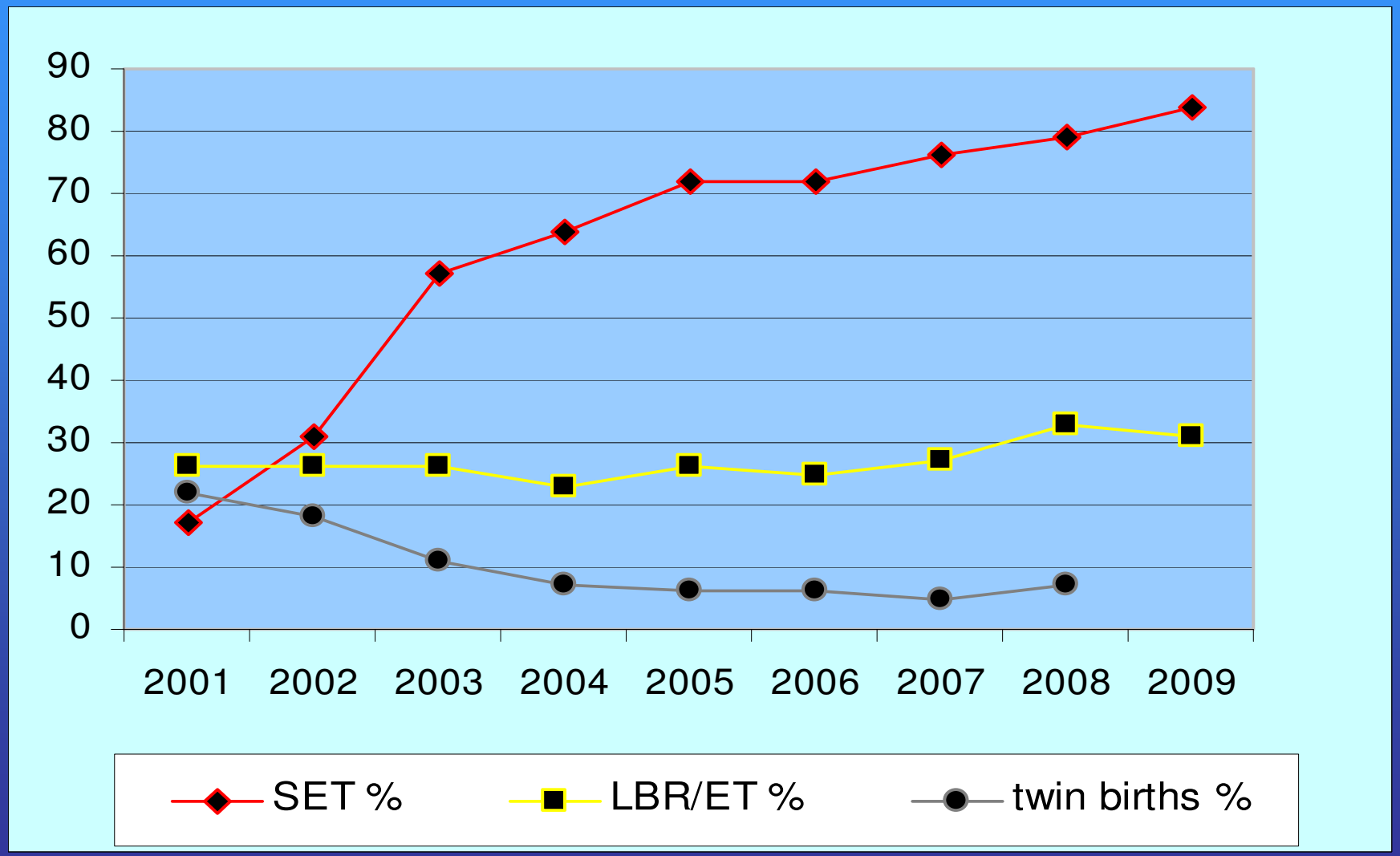
- Single embryo transfer
- Fresh transfers
- Frozen-thawed transfers
- Cumulative results
- Blastocyst transfers

Aim: MBR↓ Birth rates ↑→

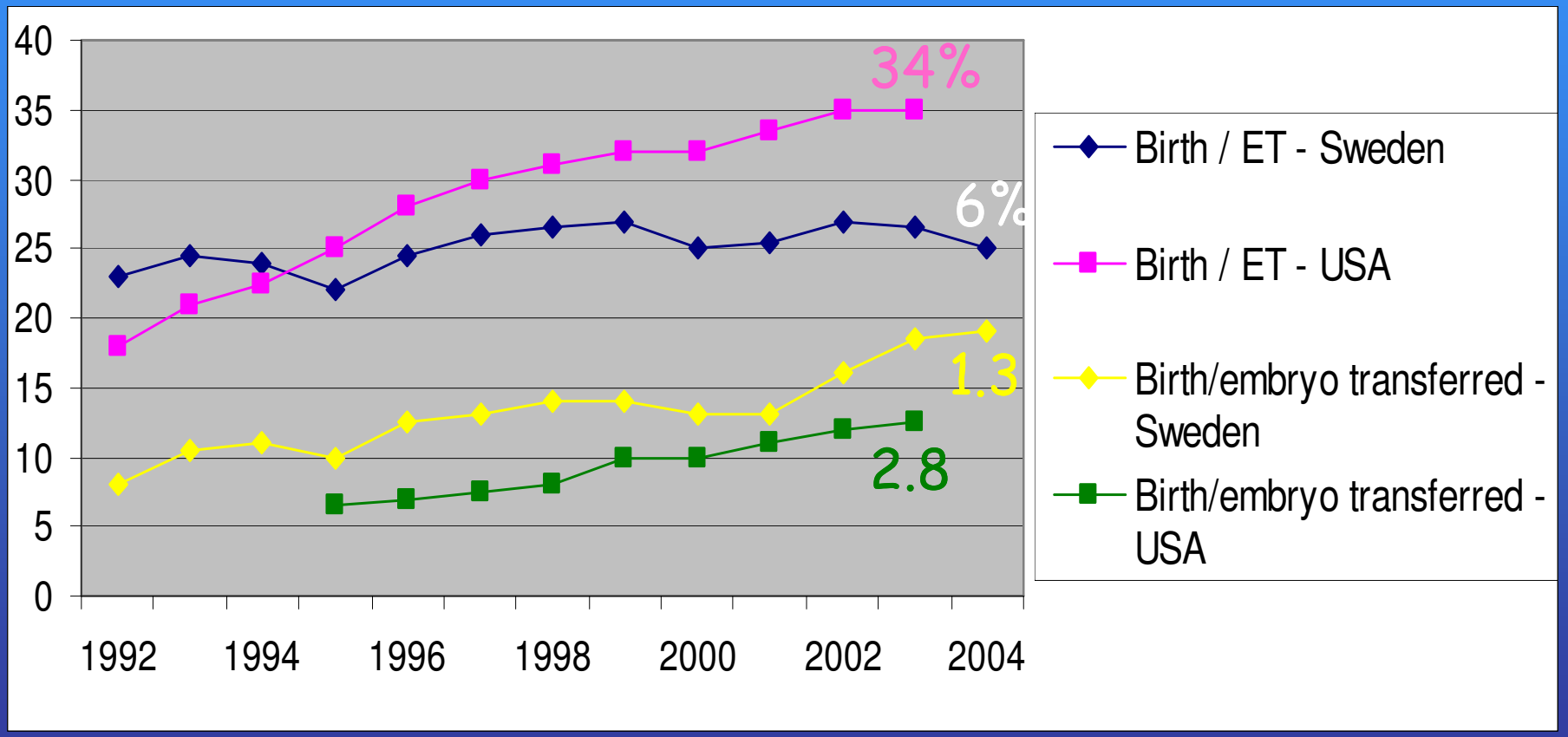
MPR SET: ~ 1 %

MPR DET: 30 - 50%

Sweden / Sahlgrenska

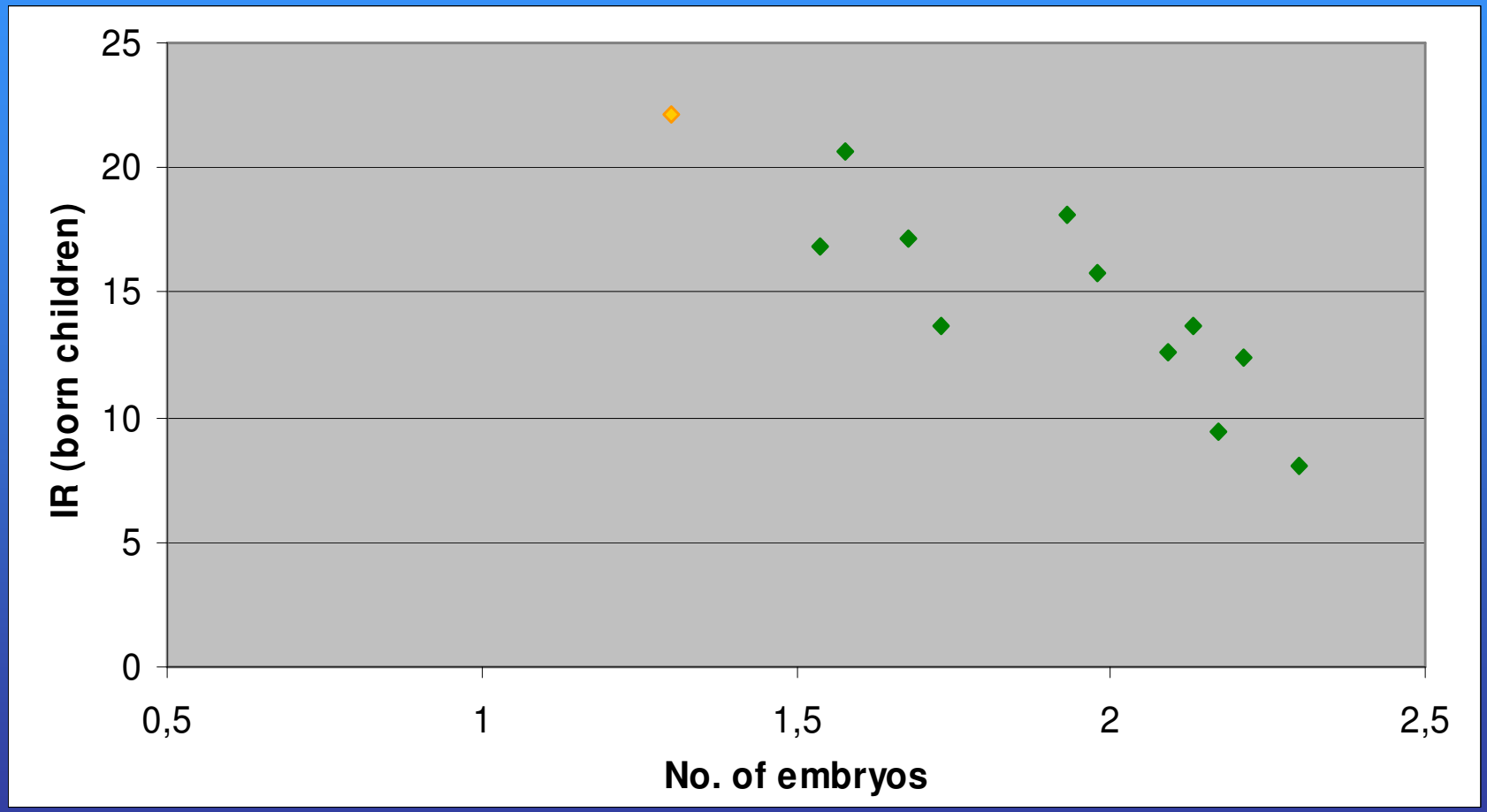


Births / transfer – two different strategies



From Karlström and Bergh, 2007

Born children per number of transferred embryos - data from 2006



Countries with > 4000 transfers; Belgium, Denmark, Finland, France, Germany, Greece, Italy, Norway, Russia, Spain, **Sweden**, UK

(NL and Turkey no data)

ESHRE data, Hum Rep 2010

”Fresh” transfers

Embryo ”quality”

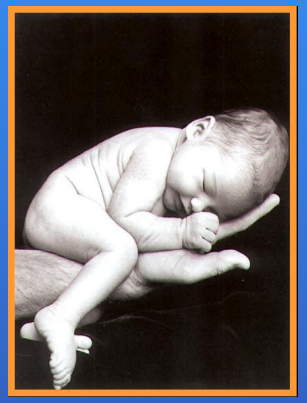
Single embryo culture
Single embryo transfer

Embryo scoring

Things to look at….

- Day 1
  - (PN score)
  - Early cleavage
- Day 2/3
  - Number of cells
  - Fragmentation
  - Cell size
  - Number of nuclei
- Day 5/6
  - ICM
  - Trophectoderm
  - Expansion

* Cytoplasmic maturity
* Embryo cleavage (time-lapse)
* Chromosomal normality
* Metabolism



Fresh transfers;

Independent embryonic predictive factors for implantation/ birth

Logistic regression analyses

- Lundin et al 2001
  - Early cleavage ICSI (10 798 scored embryos, 306 transfers)

- Saldeen and Sundström 2005
  - Mononucleate cells (861 SET with 4-cells)

- Thurin et al 2005
  - 4 cells (520 transfers with 0% or 100% implantation)

- Ziebe et al 2007 (Multicenter trial)
  - Early cleavage (for top quality embryos)

- Holte 2007 – Construction of an evidence-based integrated morphology cleavage embryo score for implantation potential of embryos scored and transferred on day 2 after oocyte retrieval (2266 DET cycles)
  - 4 cells, even sized, mononuclear

Fragmentation etc. ??

Frozen-thawed transfers;

Independent embryonic predictive factors

Logistic regression

- 822 double embryo transfers
- 420 single embryo transfers
- Delivery rate 18.7 vs. 14.3%

- Predictive factors:
  - Embryo quality (≥ 4 cells, intact after thawing)

Salumets et al 2006

- 410 transfers
- 1-3 embryos
- 10.4% IR

Five parameters predictive for implantation:

- Four or more cells at freezing day 2
- (Resumption of meiosis – only if ≥ 2 cells cleaved)
- More than six cells at transfer day 3
- Assisted hatching
- Child in previous fresh cycle

Gabrielsen et al 2006

- 622 single embryo transfer cycles
- 16% live birth
- Independent predictive factors (embryonic):
  - Blastomere survival rate

Olivius et al 2008

Cumulative data

Cumulative rates

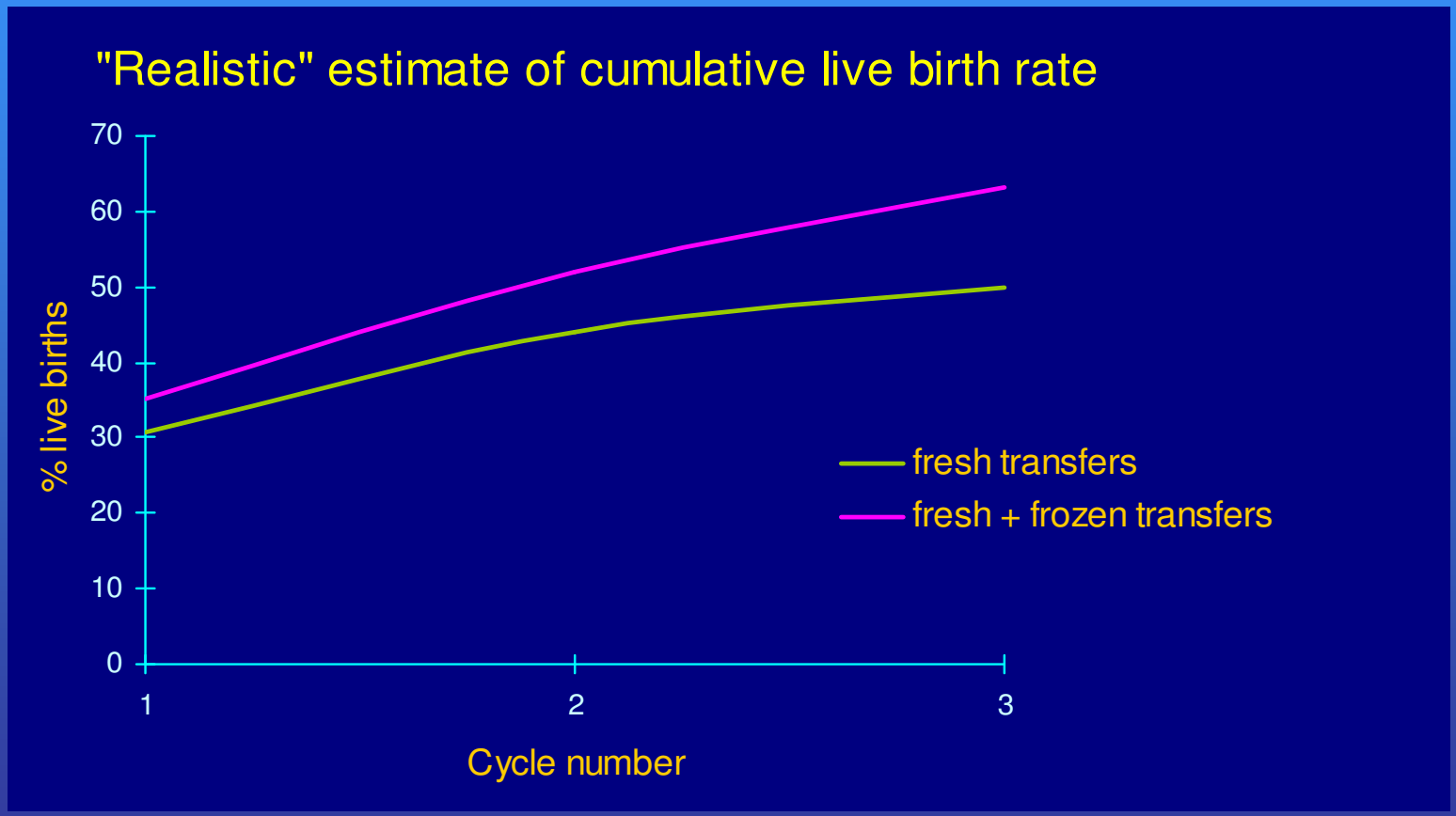
- Cumulative rates per OPU (all pregnancies/births from one OPU)
- A full treatment program (a number of fresh cycles)
- A full treatment program including frozen-thawed transfers

SET + frozen (SET or DET)
Early cleavage stage transfer

- Martikainen et al 2001, 144 randomised couples

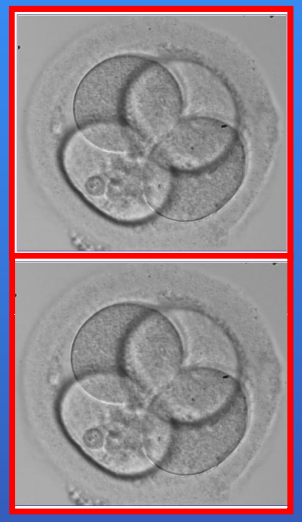
CPR; SET	32.4%
CPR; DET	47.1%
CUM live birth; SET	47.3%
CUM live birth; DET	58.6%
MPR; SET	6%
MPR; DET	28%

Addition in live births from freezing-thawing transfers in a DET programme



Olivius et al 2002

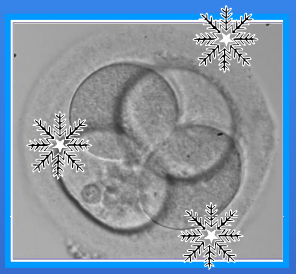
1+1 = 2 ??
(randomised multicenter study, 661 patients)



≈

27.6%

+



16.4%

Live birth rate
= 42.9% (142/331)
Multiple birth rate
= 33.1%

Live birth rate
= 38.5% (127/330)
Multiple birth rate
= 0.8%

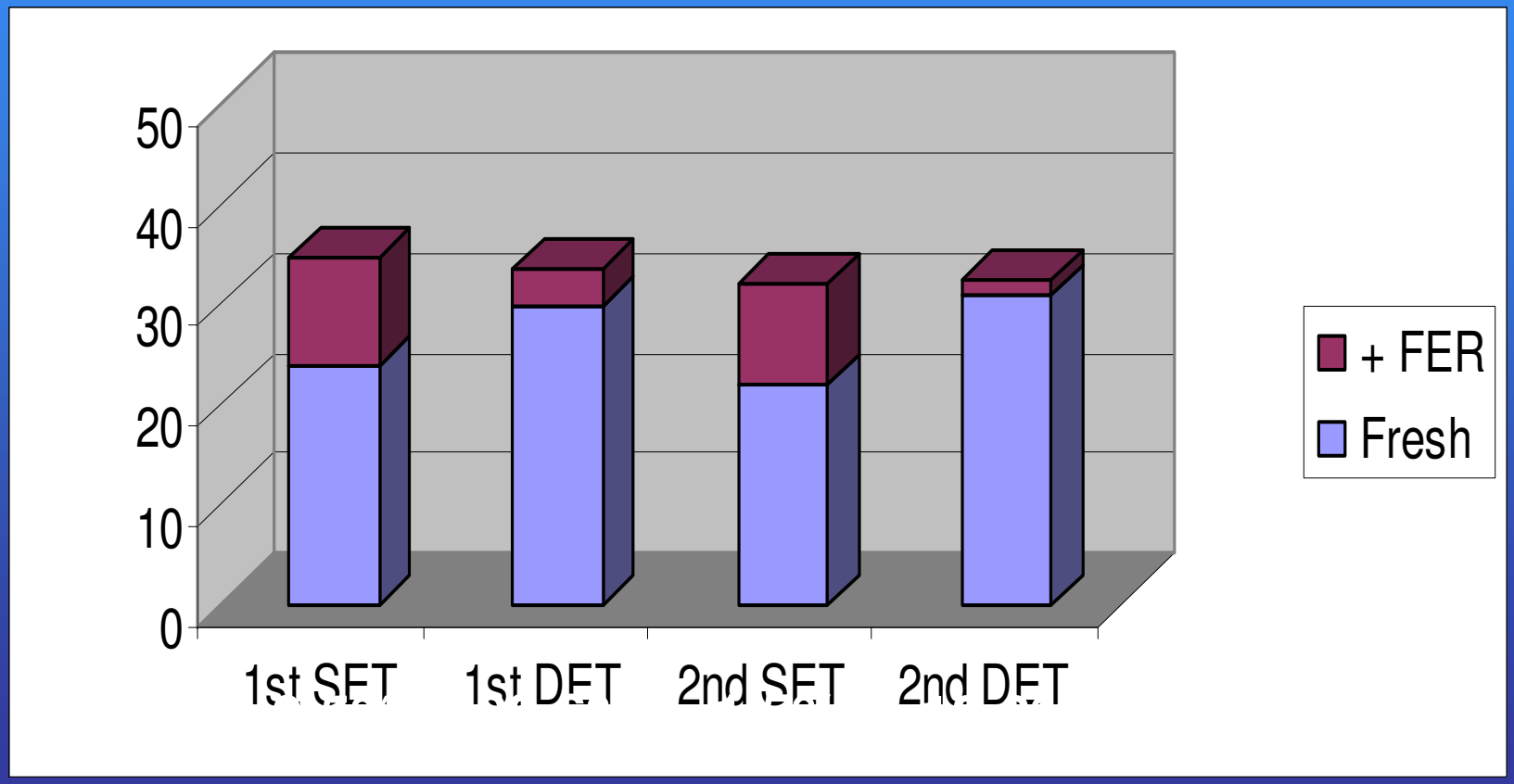
Thurin et al 2004

SET + frozen (SET or DET)
Early cleavage stage transfer

- Hyden-Granskog et al. 2005 42.8%
- Le Lannou et al. 2006 43.0%
- De Neubourg et al 2010 55.0%

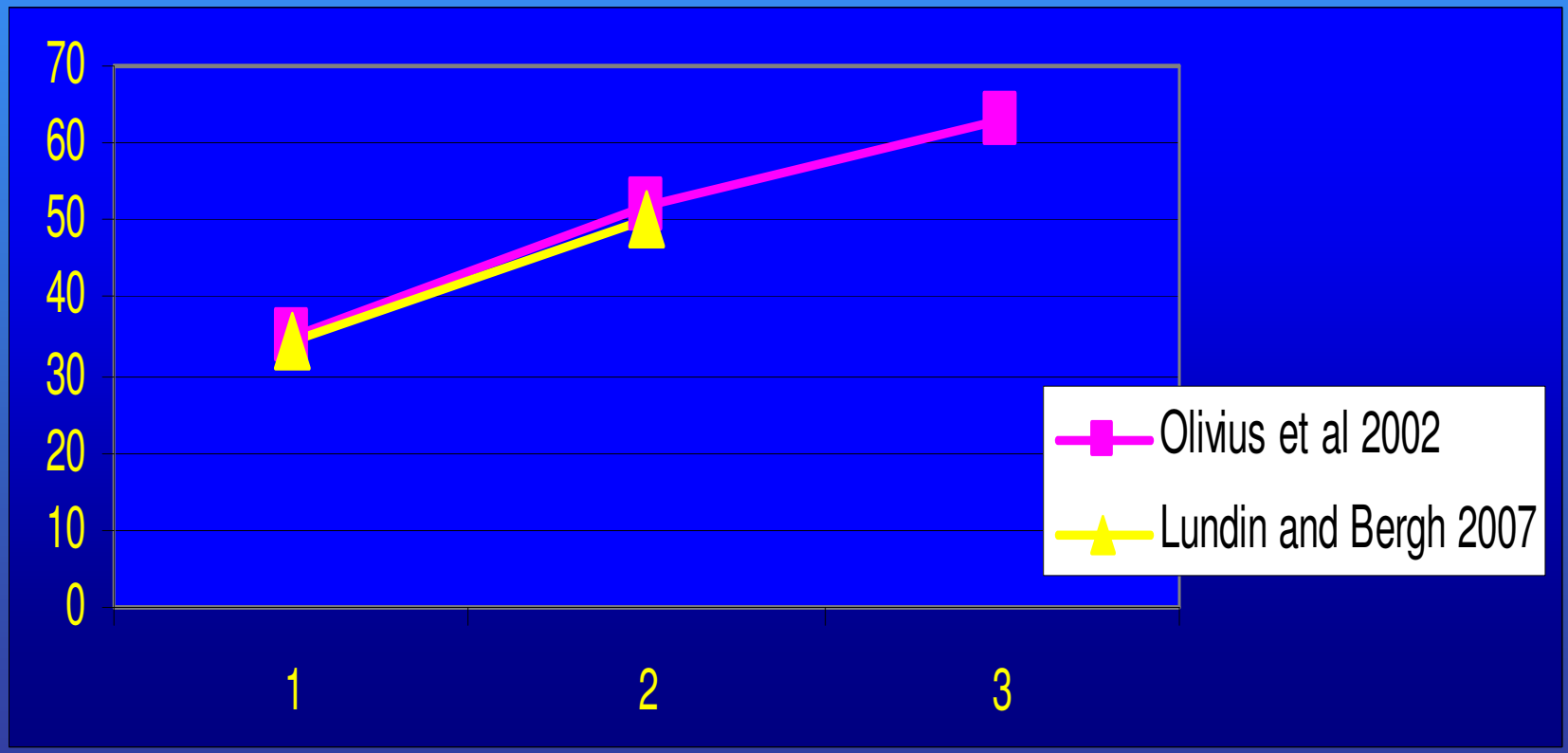
MPR 0-7%

Cumulative birth rates - Addition in live births from freezing-thawing transfer (689 couples)



Lundin and Bergh 2007

Total cumulative rate live birth Fresh + frozen



Independent predictors for cumulative birth rate – Logistic regression

Cycle 1:

- No. of good quality embryos +
  p<0.0001, OR =1.381 95% CI =1.28-1.50

Cycle 2:

- No. of good quality embryos +
  p<0.0001, OR = 1.20, 95% CI =1.10-1.31

Lundin and Bergh 2007

- *Cumulative* (fresh + frozen) live birth rate was not correlated to transfer of one or two embryos in the fresh cycle
- However, more FER were needed in the SET group to achieve the same success rate (*1st cycle x1.5, 2nd cycle x1.3*)

Lundin and Bergh 2007

Blastocyst transfers – cumulative data

Cumulative pregnancy rates; A randomised prospective study of SET vs. SBT

404 couples, female <36 years, >5 oocytes, > 3 TQE day 2

- Day 2

52 ET

IR (fresh) 46.2%

51 FET

IR (frozen) 8.7%

CPRcum 51.9%

- Day 5/6

55 ET

IR (fresh) 41.8%

42 FET

IR (frozen) 20.0%

CPRcum 49.1%

Brugnon et al 2010, ESHRE

Cumulative pregnancy rates; A prospective, non-randomised study of SET vs. SBT

478 couples

- Day 2

243 ET (100%)

Del./ET 29.6%

127 FET

Del. /FET 17.3%

CPRcum 34.2%*

- Day 5/6

235 ET (93%)

Del./ET 36.7%

61 FET

Del./FET 14.8%

CPRcum 37.9%

*higher number of transfers/couple (x1.25)

Guerif et al 2009, Hum Rep

Blastocyst vitrification

- ”Between January 2004 and February 2009, 8449 blastocysts from 2453 patients were vitrified. After 1398 vitrified embryo transfers (VET) of both day-5 and day-6 blastocysts with a mean patient age of 34.6 +/- 5.0 years, the study centre (Illionois) has seen a survival rate of 96.3% (2730/2835), with an implantation rate of 29.4% ”

Liebermann 2009, RBM

Cumulative blastocyst transfer with vitrification

So…..

- DET has higher delivery rates than SET
- Blastocyst transfer has higher delivery rates than cleavage stage transfer

But…..

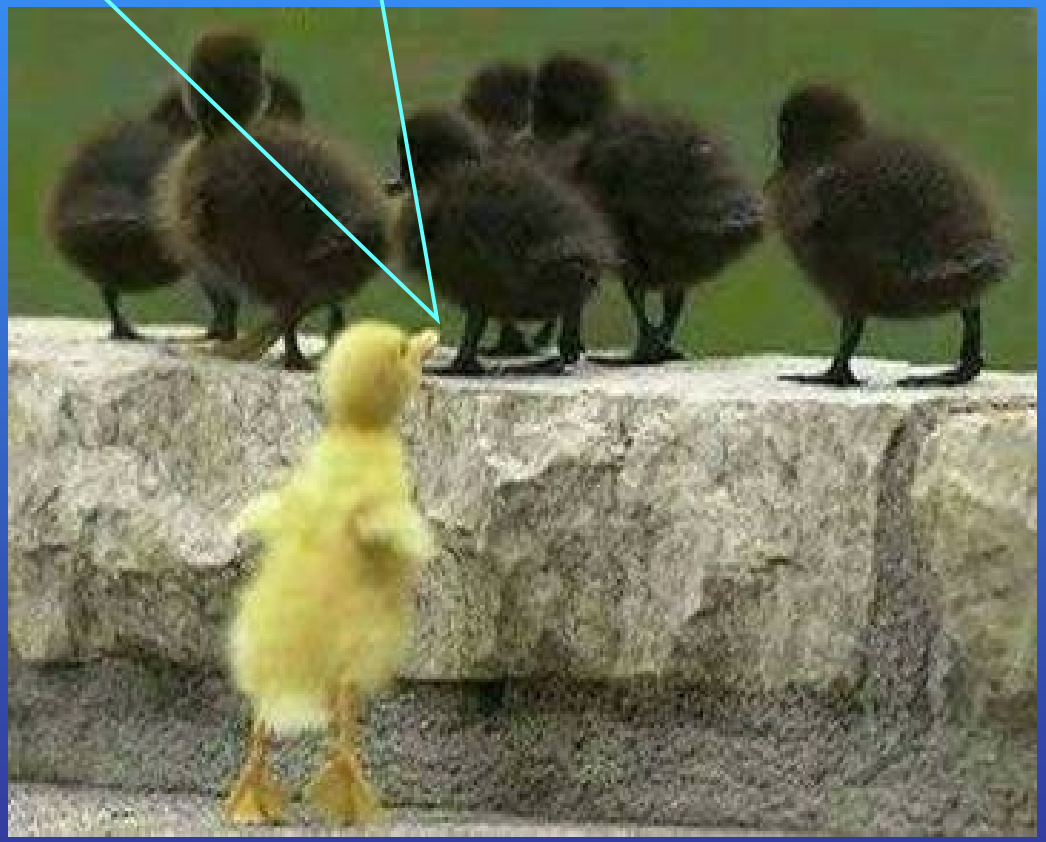
- Increased numbers of transfers (fresh and/or frozen) results in similar (cumulative) results for DET and SET

- I.e. the same delivery results with much less multiples can be acheived by performing more cryo-transfers (*~25-50%)*

And…..

- RCTs indicate higher survival rate with vitrification as compared with slow freezing
- ……but similar pregnancy rates
- Prospective trials needed to confirm
- Small number of births and few controlled studies

Thanks for listening !



Predictors of blastocyst development

- Number of oocytes retrieved/fertilised
- PN size symmetry
- Early cleavage
- Number of 4/8-cell embryos on day 2/3

Only about 40-50% of blastocysts were preselected on day 3

E.g. Neuber et al 2003, Ebner et al 2003, Fenwick et al. 2002, Guerif et al 2007

Predictors of development to a good morphology blastocyst – 4042 embryos

- Early cleavage
- Being a 4 cell embryo on day 2

and implantation ?

- If a good morphology blastocyst was transferred, there was no further impact of early stage morphology

Guerif et al 2007

SET in frozen-thawed cycles

872 DET and 775 SET frozen embryo transfers

– 25.7 vs. 19.% live birth rate (28.6% for eSET)

– 21.9% vs. 2.0% twin rate

Hydén-Granskog et al 2005

Blastocyst vs. Cleavage stage (selected patients….)

- eSET day 2 (top quality embryo) – 50% IR
  (all embryos) - 36% IR
  (Salumets et al 2003)

- eSET day 3 (top quality embryo) – 47% IR
  (all embryos) - 37% IR
  (Gerris et al 1999)

- eSET day 5 41 – 60% IR
  (Gardner et al 2004, Papanikolaou et al 2006, Zech et al 2007)

Single vs. double embryo transfer of blastocysts

Observational:

- Criniti et al 2005 (n=107)
  - DET: 66% IR, 79% PR, 62% twins
  - SET: 76% IR and PR, 3% twins
- Henman et al 2005 (n=406)
  - DET: 64% LBR, 34% twins
  - SET: 65% LBR, 7% twins
- *Randomised:*
- Gardner et al 2004 (n=48)
  - DET: 56% IR, 76% PR, 47% twins
  - SET: 60% IR and PR, 0% twins

Thank you for your attention!