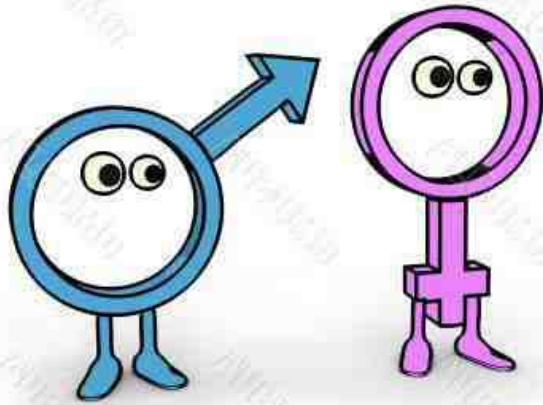


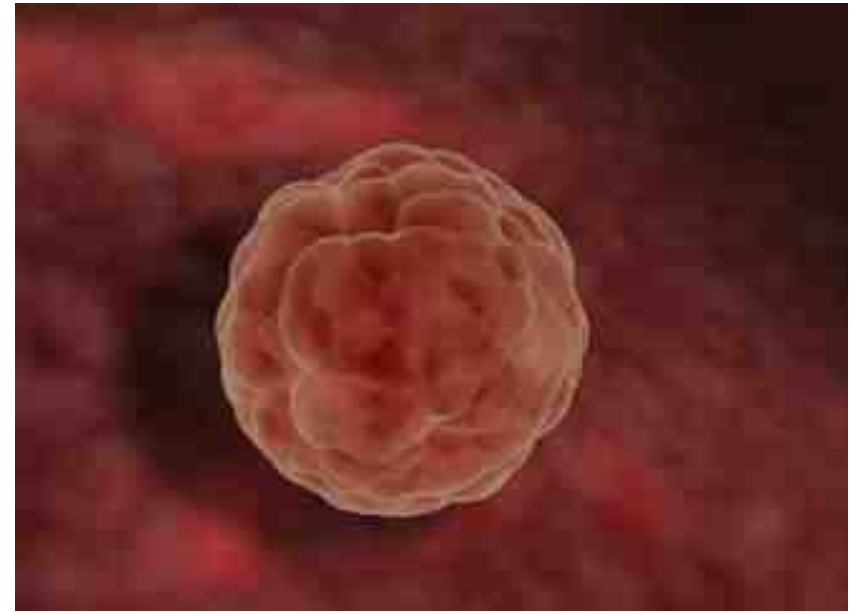
# Embryo transfer

## - How to select and when to transfer

*Kersti Lundin*  
*Reproductive Medicine*  
*Sahlgrenska University Hospital*  
*Göteborg, Sweden*



The implantation process  
- interaction embryo  
and endometrium



“Successful implantation at the very least, requires the presence of a healthy embryo, a receptive endometrium, a **synchronized and successful molecular dialogue between the two** and immune protection from the host”

*(Mahajan et al 2015)*

# When to transfer; endometrial receptivity and/or embryo selection

- Window of implantation (WOI) = receptive phenotype
- "Window of natural embryo selection"
- *Influenced by; hormonal stimulation (endogenous, exogenous)*

**and/or**

- Selection by embryo quality/potential
  - *(extended culture)*

# Early cleavage or blastocyst stage

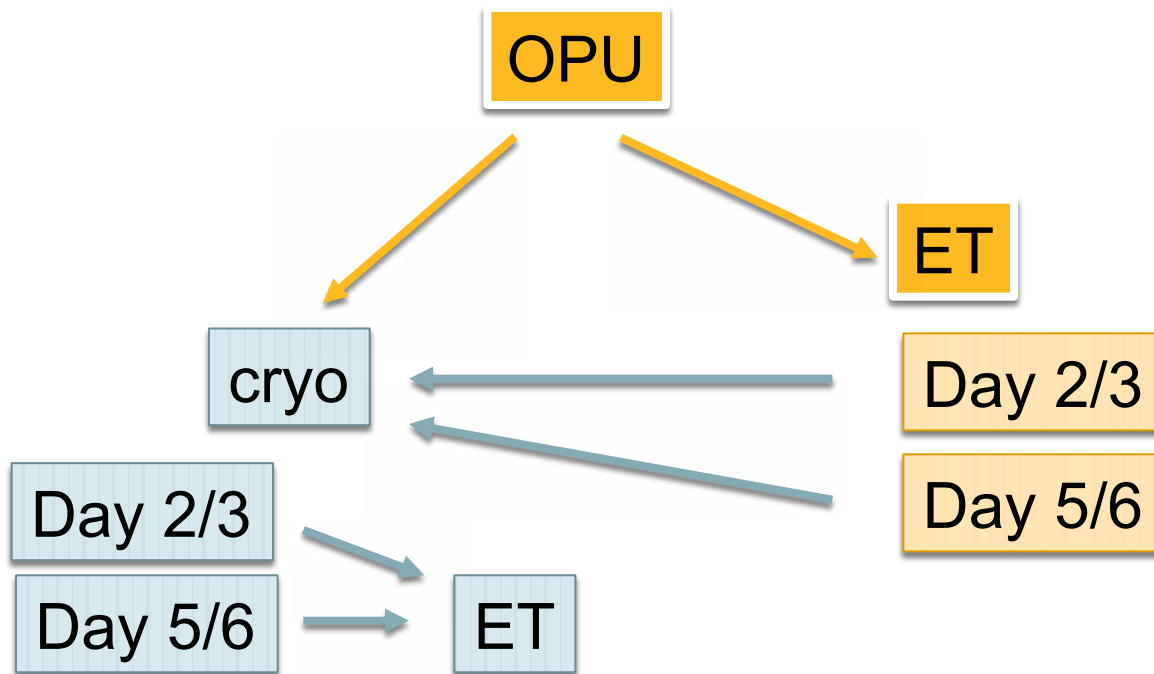
- LBR, analysed **per OPU** or per ET? (*= different patient populations, patient preselection*)
- Marginal difference in cumulative **LBR per OPU** (*cost-effective? Cost for extra culture vs. costs for more transfers*) *Cryo results – methods*
- Loss of viable embryos (pregnancies)? **But gain of others?**

!

Blastocyst culture will not increase  
embryo quality

Time to pregnancy.....

# Different strategies for when to transfer



Cumulative live births rates....

# Number of transfers

- Day 2/3 ET → Day 2/3 cryo → many transfers
- Day 2/3 ET → Day 5 cryo → fewer transfers
- Day 5/6 ET → Day 5 cryo → even fewer transfers...

Cost vs. Time to pregnancy....

# Day of vitrification and day of transfer

Patient selection..... ??

## *Day 2, 3, 5, or 6??*

- 6019 embryos in 3150 warming cycles
- Survival rates; 94.9% for day 2, 94.2% for day 3, 95.7% for day 5, and 97.6% for day 6
- LBR per cycle; 35.3% for day 2, 39.2% for day 3, 40.6% for day 5, and 32.5% for day 6



# Day of vitrification and transfer day

*Patients with good surplus embryos after day 3 transfer, and no pregnancy in fresh cycle (1190 patients, prospective observational study)*

- 625 in blastocyst culture group, 565 in day 3 cryo group
- 461 had blastocyst cryopreserved (74%) vs 100% day 3
- Thawing/warming on day of transfer
- Clinical pregnancy rate per **initiated** cycle; 43.2 vs. 34.9%
- Clinical pregnancy rate per **transfer** cycle; 59.5 vs. 35.4%

# Per number of surplus embryo

**Table 3** Clinical outcomes of warming cycles according to the number of surplus embryos available.

	<u>1–3 surplus embryos</u>		<u>4–6 surplus embryos</u>		<u>7–9 surplus embryos</u>		<u>≥10 surplus embryos</u>	
	<i>Blastocyst group</i> (n = 165)	<i>Control group</i> (n = 128)	<i>Blastocyst group</i> (n = 202)	<i>Control group</i> (n = 192)	<i>Blastocyst group</i> (n = 144)	<i>Control group</i> (n = 136)	<i>Blastocyst group</i> (n = 114)	<i>Control group</i> (n = 109)
Cryopreservation cycles (n)	77	128	150	192	124	136	110	109
Clinical pregnancy per initiated cycle	31/165 (18.8)	25/128 (19.5)	84/202 (41.6)	66/192 (34.4)	77/144 (53.5) <sup>a</sup>	56/136 (41.2)	78/114 (68.4) <sup>a</sup>	50/109 (45.9)
Cumulative pregnancy	31/165 (18.8)	25/128 (19.5)	86/202 (42.6)	79/192 (41.1)	87/144 (60.4)	81/136 (59.6)	89/114 (78.1)	78/109 (71.6)
Warming cycles (mean ± SD)	1.0 ± 0.1	1.0 ± 0.0	1.0 ± 0.2 <sup>a</sup>	1.4 ± 0.5	1.2 ± 0.4 <sup>a</sup>	1.6 ± 0.6	1.2 ± 0.5 <sup>a</sup>	1.9 ± 0.9

Values are n/total (%) unless otherwise stated. Blastocyst group: surplus embryos were cultured to the blastocyst stage and cryopreserved on day 5 or 6. Control group: surplus embryos were cryopreserved on day 3.

<sup>a</sup>P < 0.05 compared with the control group.

- No difference in clinical pregnancy rate if less than 4 surplus embryos
- No difference in **cumulative** pregnancy rate

# Day of blastocyst transfer

PMC Alt PDF

Day 5 expanded blastocysts transferred on same day have comparable outcome to those left for more extended culture and transferred on day 6  
J Assist Reprod Genet



Day 5 expanded blastocysts transferred on same day have comparable outcome to those left for more extended culture and transferred on day 6

Eman Elgindy and Mervat Sheikh-El-Arab Elseddek

Additional article information

Abstract

Objective

To study the outcome of blastocysts showing expansion on day 5 and



Fertility and Sterility

Volume 88, Supplement 1, September 2007, Pages S110



Poster presentations

Comparison of the pregnancy rate between day 6 blastocyst transfer and cryopreserved day 6 blastocysts transferred on day 5

H. Motoyama, A. Yanaihara, S. Monzen, T. Yorimitsu, H. Watanabe, T. Kawamura

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doi:10.1016/j.fertnstert.2007.07.357

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Fertility and Sterility

Volume 104, Issue 3, Supplement, September 2015, Pages e337

Scientific Program Supplement: Oral and Poster Session Abstracts

71st Annual Meeting of the American Society for Reproductive Medicine



Clinical outcomes after day 5 blastocyst transfer as compared to day 6 blastocyst transfer

F. Zhang, Y. Guo, Y. Sun, H. Jin

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doi:10.1016/j.fertnstert.2015.07.1048

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# Starting up blastocyst vitrification

## Single embryo transfer

Group	No of pat with cryo	% pat with cryo	Warmed	ET	Survival	Pregn %	CPR %
No GQE	105	35	48	43	89,6	51,2	41,5
> 11 GQE	27	100	34	30	88,2	44,4	33,3
>3 GQE	78	83	54	51	94,4	40,4	27,7
Year			Warmed	ET	Survival	Pregn %	CPR %
2014			69	57	82,6	35,8	26,4
2015			160	144	90,0	44,7	34,0

# Should we delay (all) transfers?

- Several **observational** studies showing improved pregnancy and live birth rates
- 3 RCTS on **good prognosis** patients showing improved pregnancy rates

# ”Freeze all” strategy

- + (Almost) no OHSS (*GnRH agonist triggering*)
- + Improved and synchronised endometrium
- + Higher birth rates? (*patient selection?*)
- + Possible to perform trophoctoderm biopsy
- +/- Obstetrical and neonatal outcomes
  - Birth weight - pros and cons
- +/- Cost effective?
- Loss of embryos during cryopreservation (ca. 10%)
- Longer time to pregnancy

”...and how to select ....”

Or, why...???

## .....impact on.....

- Time to pregnancy
- Survival after cryopreservation ?
- Cost for couples
- Endurance of couples



# Selection by the embryologist



- Morphology
- Development
- Aneuploidy (invasive)
- (*Aneuploidy / Metabolism; non-invasive?*)

# Embryo morphology – early cleavage stage



Early first cleavage

Number of cells at a certain time

Percentage of fragmentation

Relative cell size

Number of nuclei

# Embryo morphology - blastocyst

- Expansion
- Trophectoderm
- Inner cell mass



- Based on day 2, day 3 etc. morphology....?

# BUT.... embryo morphology assessment is:

- Subjective
- Very much relying on experience
- Correlates only partly to chromosomal status and success rates
- Independent predictors, but rather low predictive value

# Non-invasive, objective, embryo selection – in the pipeline ???

- Blastocoel analysis

- DNA

- miRNA

- Analysis of the culture

- Amino acid concentrations

- hCG

- Glucose

- Oxygen consumption (embryo respiration)

- The "omics"

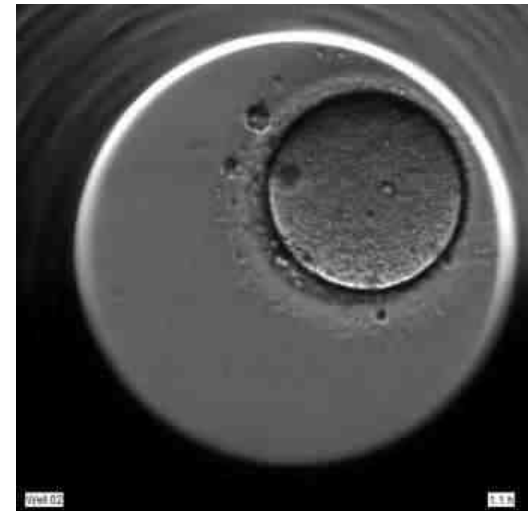
No clinically applicable results yet.....!

# Time-lapse

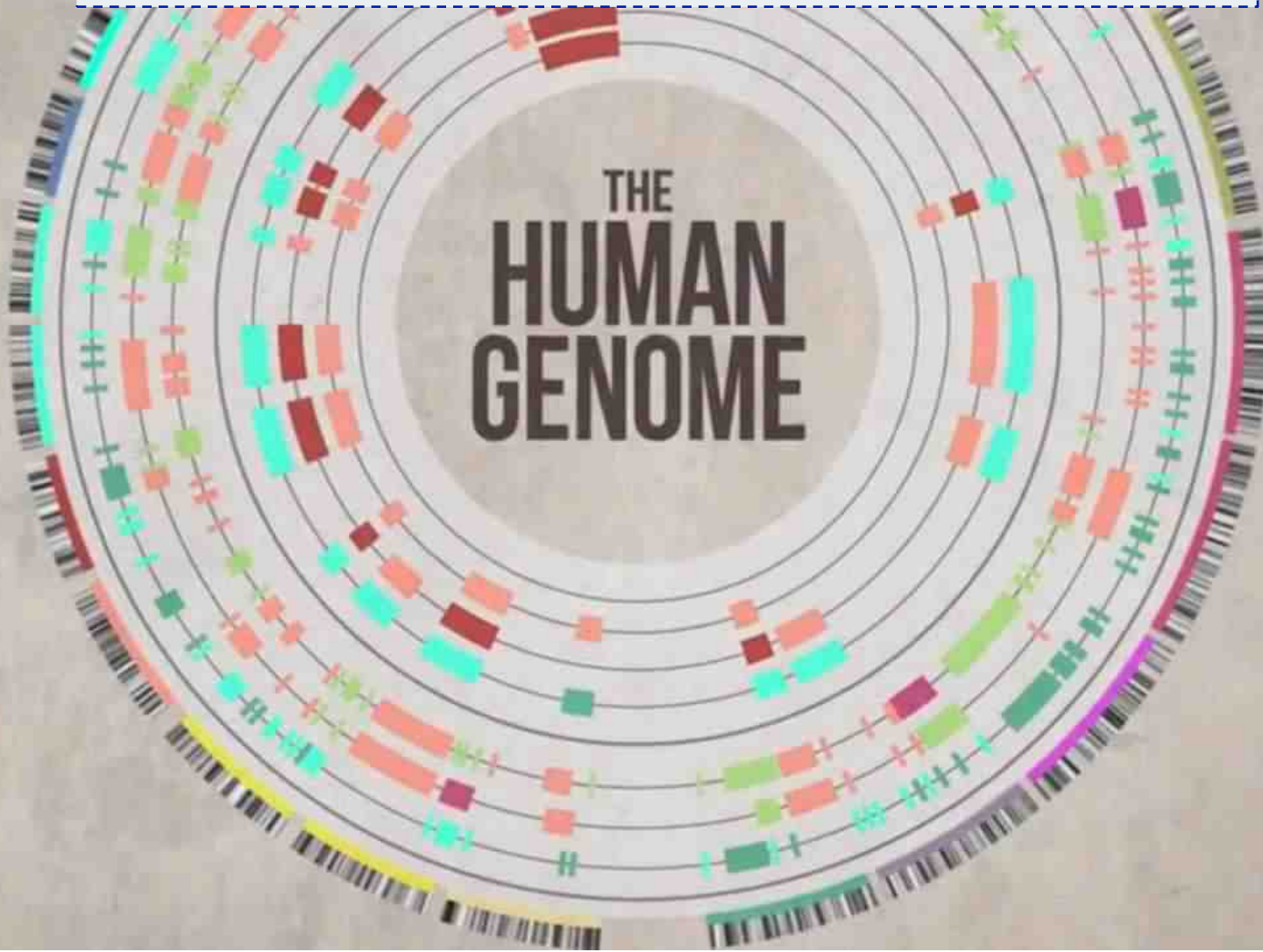


- Exact timing and “timing windows” instead of snapshots

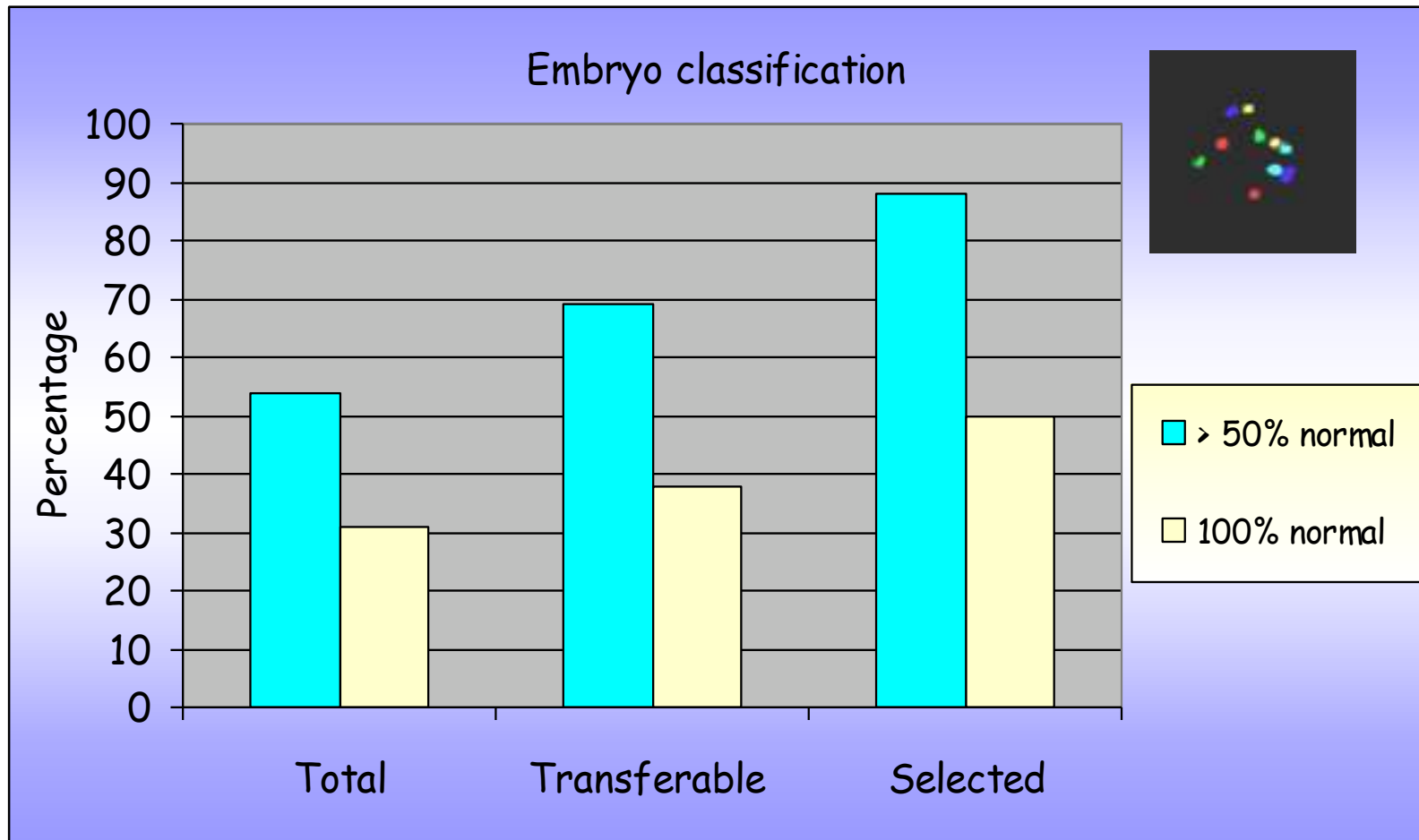
- Algorithms – generalisation?
- Adverse behaviour... **deselection**
- (logistics)



Genetically normal?

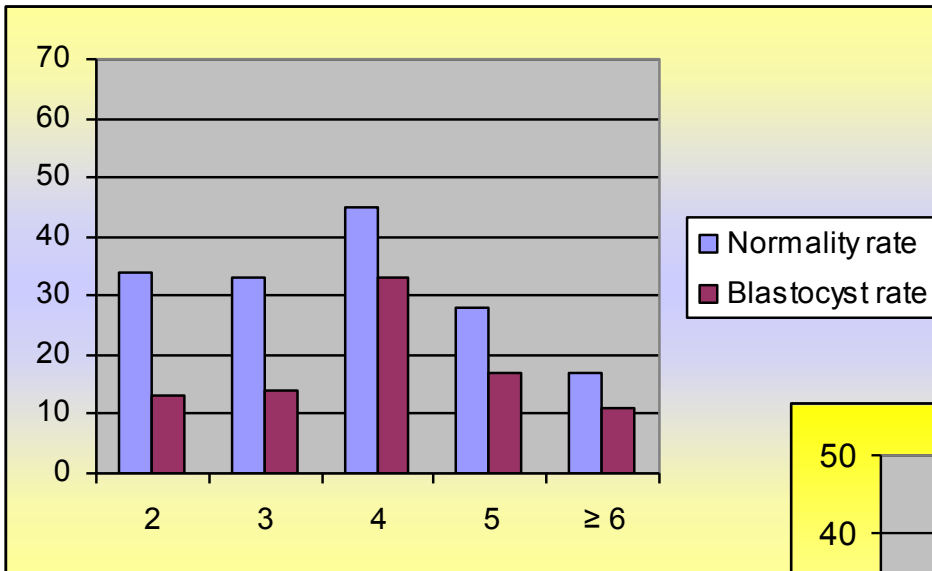


# Aneuploidy and embryo morphology

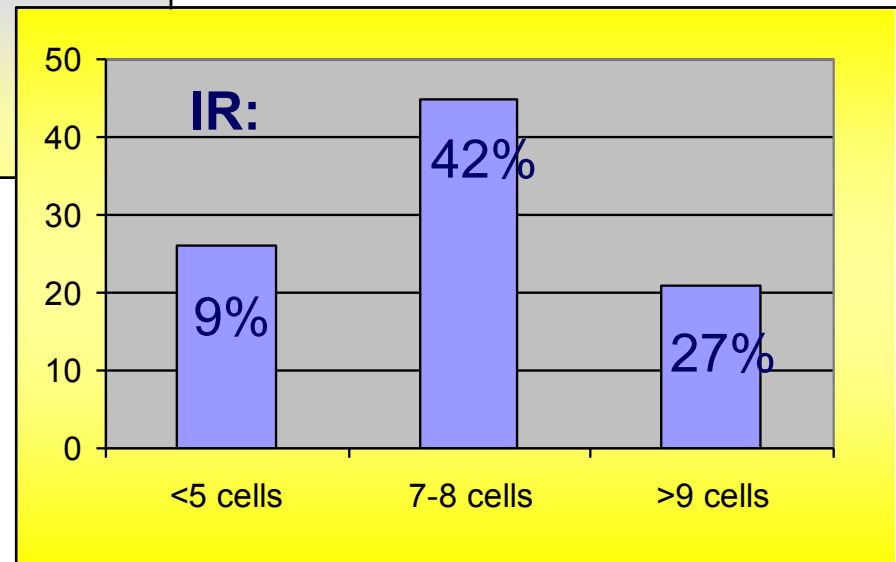




# Aneuploidy and cleavage rates day 2 and 3



De los Santos et al ESHRE 2006



Magli et al 2001, van Royen et al 2002, Kroener et al 2015

# Genetic status of the embryo

## "PGS 2.0" .... ?

- Blastocyst biopsy
- Comprehensive chromosomal screening
- 3 RCTs showing improved CPR
- Patient populations?



- **Euploidy – all or nothing? – What is "normal"?**

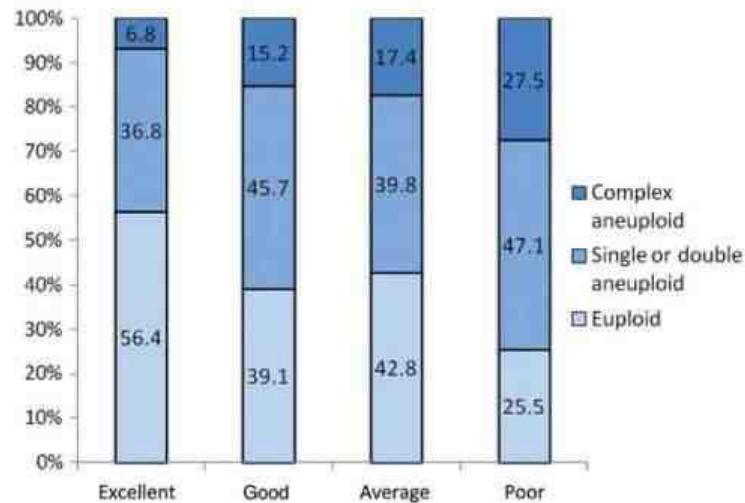
## Chromosomal normality and blastocyst morphology – **within patients**

Significantly higher rates of aneuploidy for day 6 blastocysts compared to day 5 blastocysts **on a per patients basis** (55.0 vs. 45.4) n= 421 and 413 blastocyst

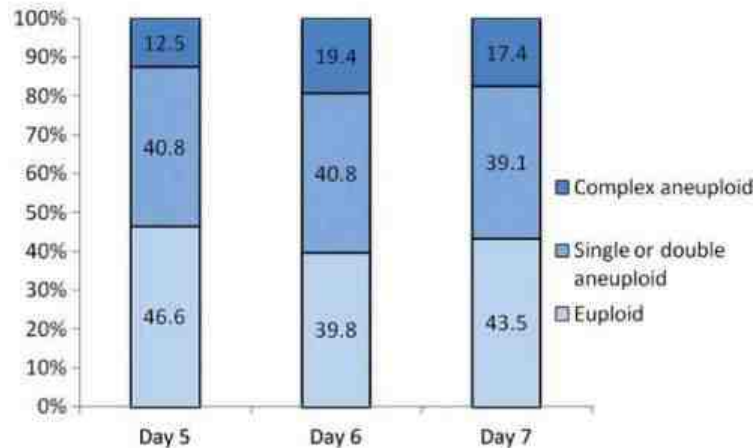
No significant difference was found in **IR or CPR** when only day 5 euploid blastocysts were transferred (38/65; 58.5%) compared with day 6 euploid blastocysts (26/48; 54.2%)

# Comprehensive chromosome screening data for 956 blastocysts according to morphology (A) and developmental rate (B).

**A** Aneuploidy screening data according to blastocysts morphology



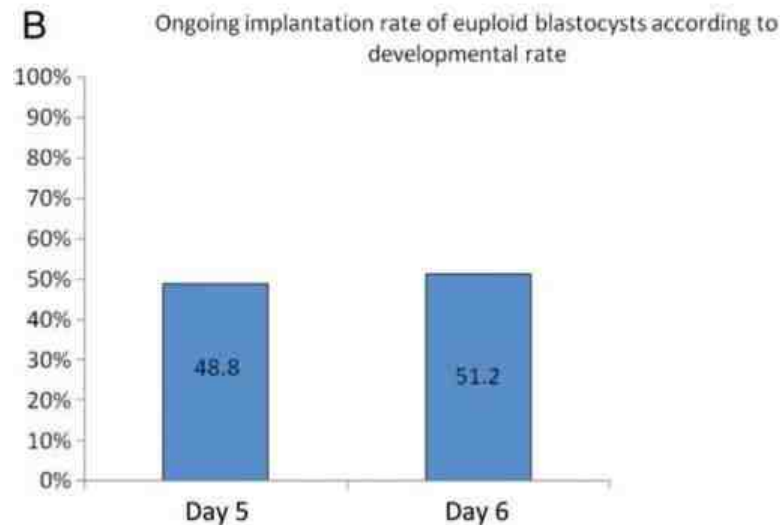
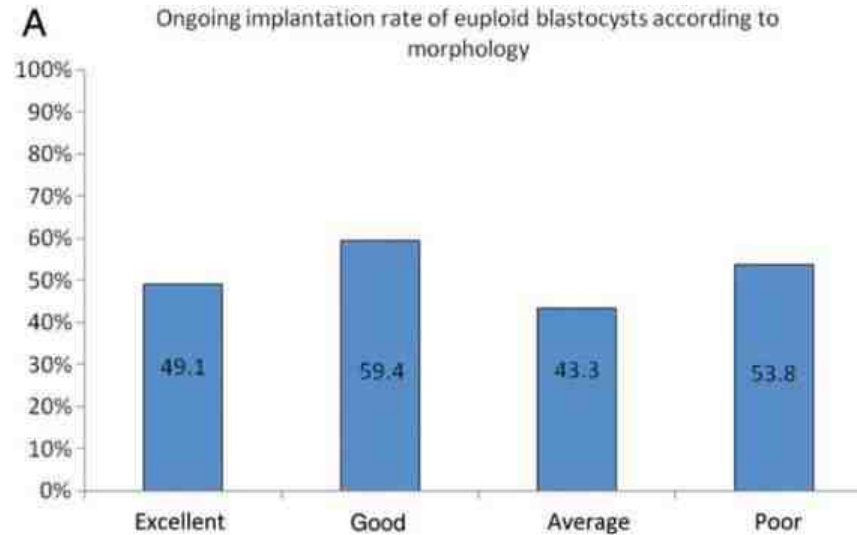
**B** Aneuploidy screening data according to blastocysts developmental rate



Antonio Capalbo et al. Hum. Reprod. 2014;29:1173-1181

human  
reproduction

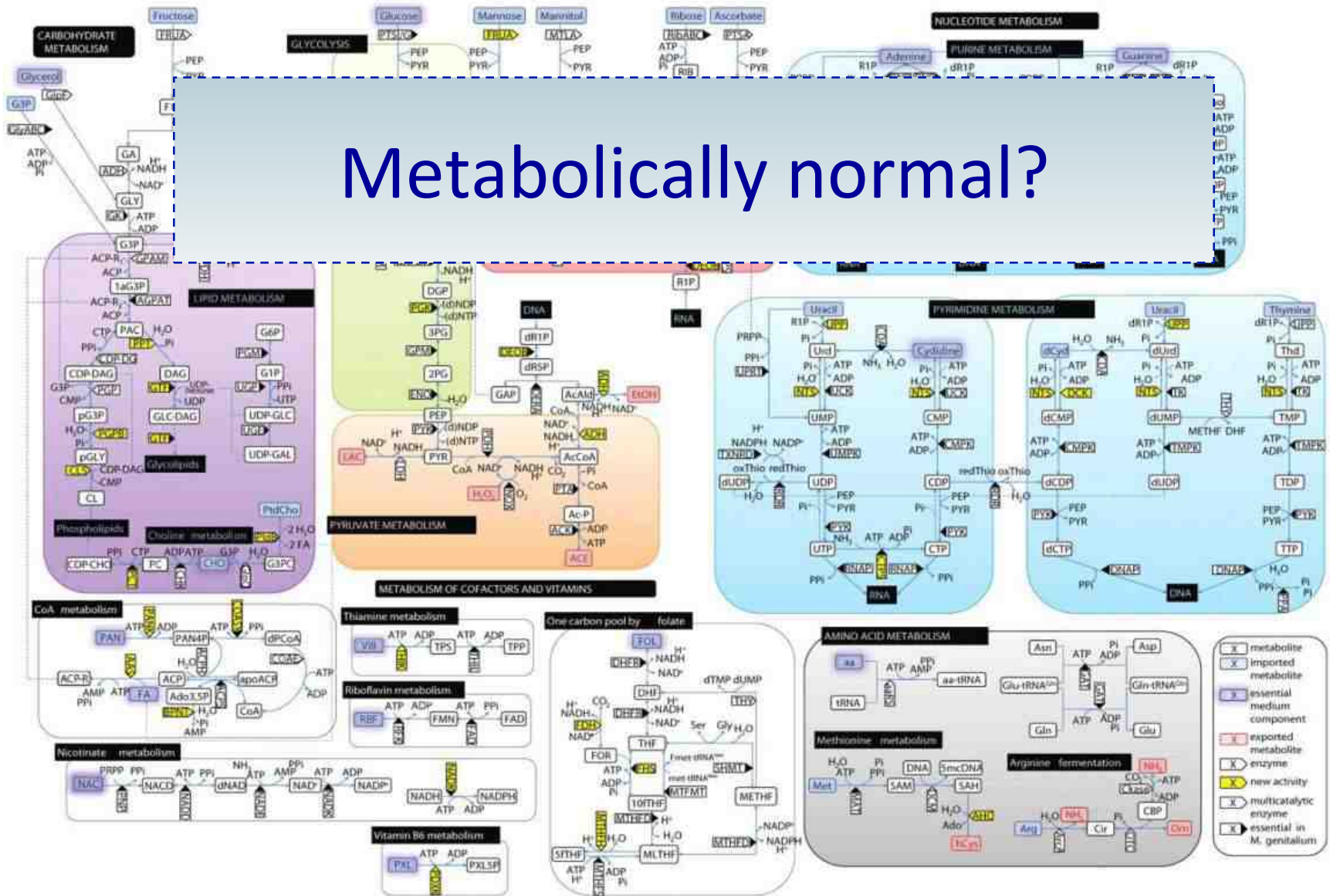
## Ongoing implantation rate of 215 euploid blastocysts according to morphology (A) and developmental rate (B).



Antonio Capalbo et al. *Hum. Reprod.* 2014;29:1173-1181

human  
reproduction

# Metabolically normal?



# Summary & how to do?

**Everything** for blastocyst culture (*those that don't make it are not good enough (?)*)

Blastocyst culture for **good prognosis patients** (*2PN?, GQE?*)

- Fresh transfer + cryo, or "freeze all"
- *Day of fresh transfer ≈ equal cLBR*
- *Day of vitrification ≈ equal cLBR*
- Add-on genetic analysis (*ranking or throwing away?*)

## ..... – our way....

- ET day 2/3 = *immediate satisfaction with high possibility of transfer and good LBR*
- culture all excess embryos for cryopreservation (also non-GQE!) = *high probability of having blastocysts cryopreserved*
- FET with blastocysts, = *"new strategy", very good results*
- Cumulative rates of LBR; → *70-80% per cohort*





Still fumbling in  
the dark.....?

Thank you for listening!