Assisterad reproduktion 40+ år efter Louise Brown

- var står vi idag och vart är vi på väg?

Kersti Lundin

Reproduktionsmedicin

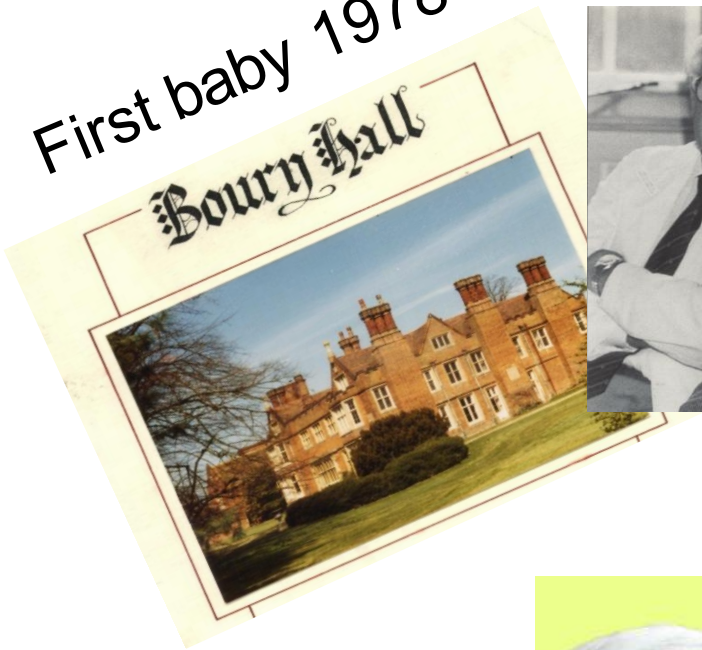
Sahlgrenska

Conflicts of interest

I have no conflicts of interest that may influence this presentation.

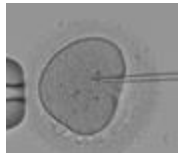
Assisted reproduction

First baby 1978



First baby in Scandinavia; Gothenburg, Sept 1982

Nobel Price in Medicine 2010



Changing scenarios – some milestones

- Oocyte aspiration (laparoscopic → transvaginal US)
- Hormonal stimulation (agonists – antagonists, urinary – rec)
- In vitro fertilisation (IVF, ”good” sperm) →
  → Microinjection (poor IVF result or ”poor” sperm, ICSI)
- Cryopreservation (slow freeze → vitrification)
- Own gametes → donated gametes (embryos)
- Short → long (blastocyst) culture
- ”Snapshot” embryo assessment → closed culture
  → continuous assessment (timelapse) → AI
- Preimplantation genetic diagnosis (screening)

Where are we now

- >10 million children
world-wide (est. >>10 mill. frozen embryos….)

- 1-6 (9)% of all children in industrial countries

- >70 000 children in Sweden

- Safe (not causing harm)…. so far
- → use ….

Changing perspectives

Sex = reproduction

↓

Sex without reproduction (contraceptives)

↓

Reproduction without sex (IVF)

↓

Delayed/planned reproduction (cryopreservation)

↓

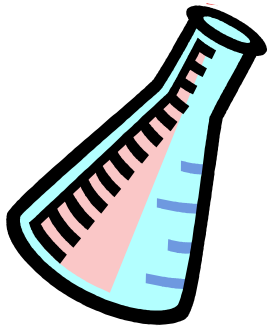
Reproduction without (own) gametes

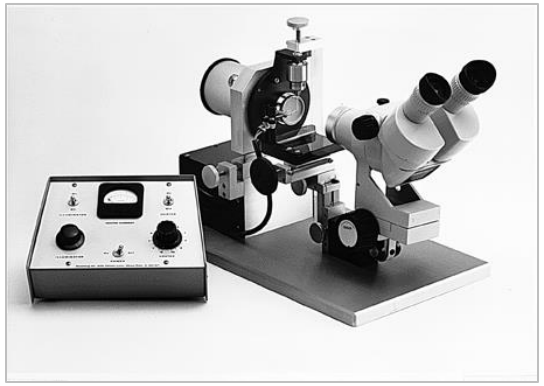
↓

Reproduction without (own) partner

From handmade and ”homemade”…

- Buffered salt solution
- Patient/staff serum
- Pipettes
- PVP
- Washing and sterilisation





…to machine-made and ”Ready to use”

…. Time-saving……quality and batch controlled…. **but costly**!

Improvements – pros and cons….

- Increased use of IVF
- Increased success rates
- Increased multiple rates

→Child outcome studies / registries

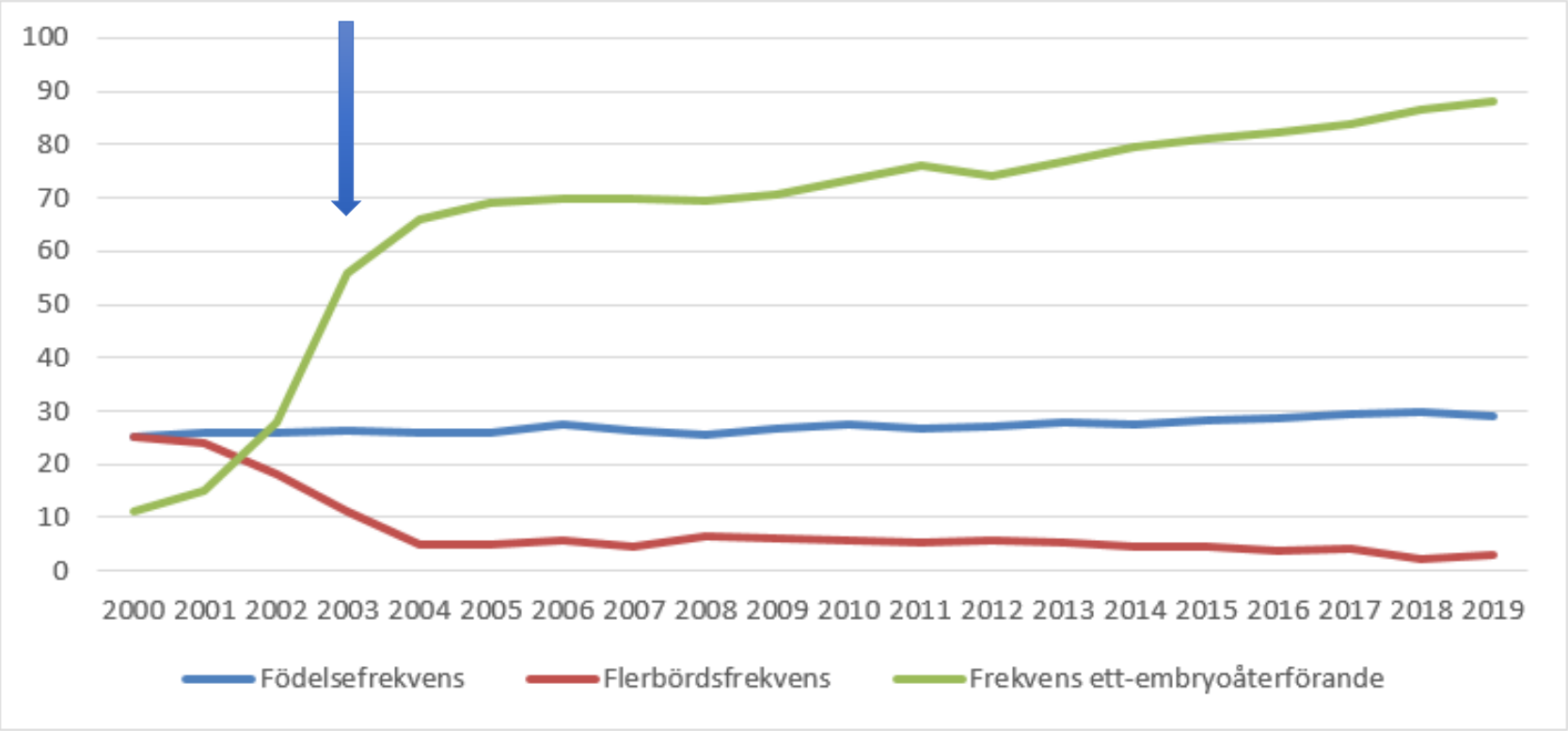
OHSS

Multiple births

ESHRE data - - SART data

Sweden; rates of single embryo transfer, births and multiple births

Figur 19 *Andel förlossning per embryotransfer- flerbörd samt SET-frekvens per år.*



Q-IVF

Improved results for offspring

- One healthy child at a time….
- > 92 000 ART children

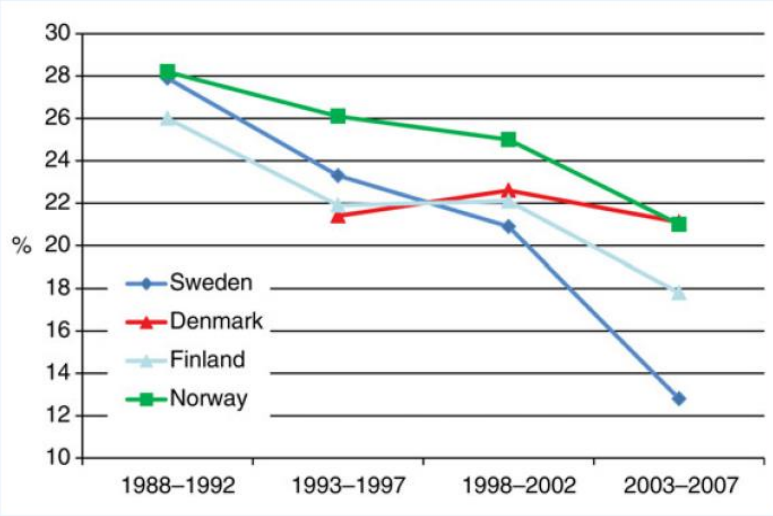


Figure 3 Preterm births among children conceived by ART in four Nordic countries (singletons + twins).

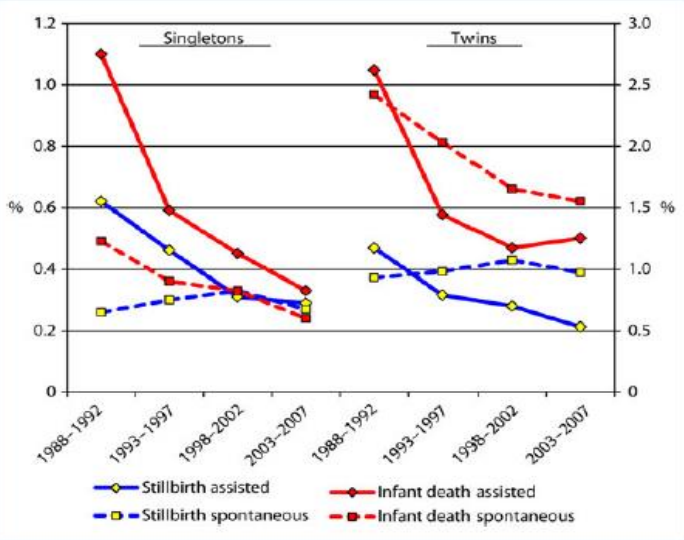


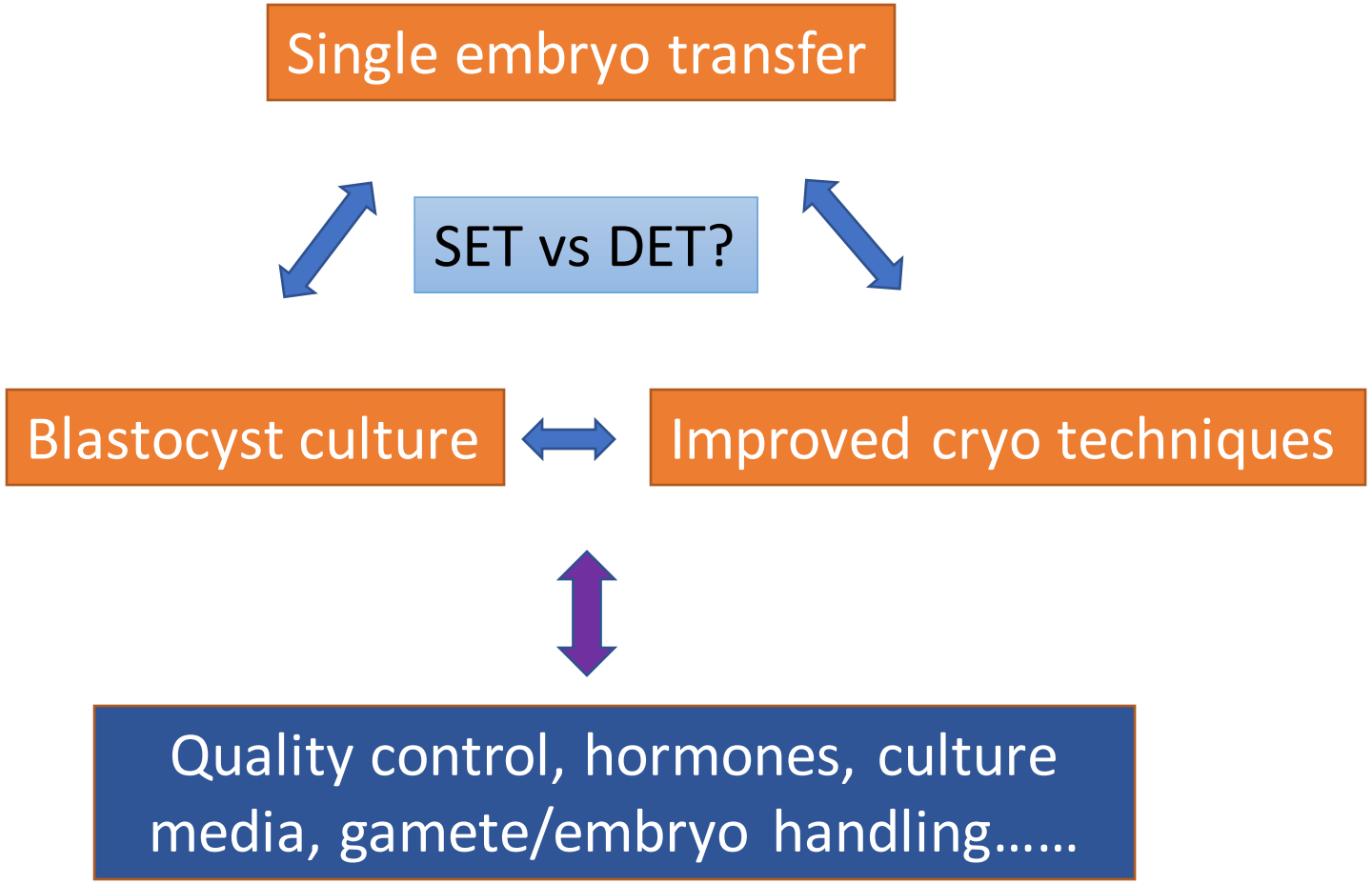
Figure 6 Rates of stillbirth and infant death in singletons and twins after assisted versus spontaneous conception.

ConArtas group, Henningsen et al 2015

Improvements – pros and cons….

- Increased use of IVF
- Increased success rates
- Increased multiple rates

→**Child outcome studies**



Why blastocysts?
… and when to go for it

- Selection method, **not improvement of embryo quality**
- Higher pregnancy and LBR from (**each**) blastocyst

- B**ased on what** could we extend the culture
  - Number of (mature) oocytes/zygotes (MII, 2 PN)?
  - Number of cleaved embryos (GQE / GQE + non-GQE)?
  - Previous cycles?

- Risk of no (fresh) transfer day 5 (or day 6 cryo)?

Cumulative live birth rates

”Cumulative live birth rates after Day 3 and 5 transfers were similar in young patients when the vitrified embryo transfers were also taken into account”.

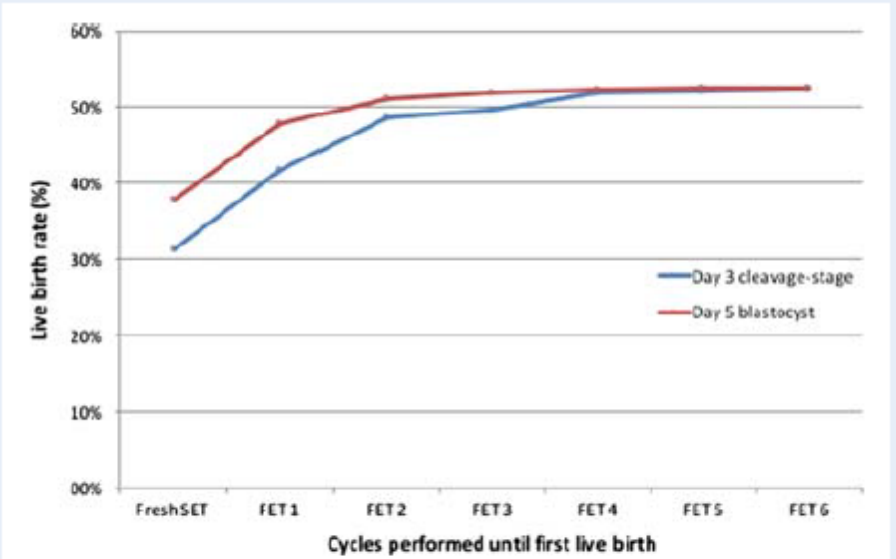


Figure 1 Cumulative live birth rates in relation to transfer day. SET, single embryo transfer; FET, frozen embryo transfer.

It is ”only” a matter of time…

De Vos et al 2016

Single embryo transfer and blastocysts
Swedish data (Q-IVF)

Year of treatment	2007	2011	2017
Oocyte aspirations, n	**9782**	**11 467**	**11 931**
SET, fresh	70%	74%	84%
SET, cryo	74%	89%	98%
Blastocyst transfer rate, fresh	5%	11%	31%
Blastocyst transfer rate, cryo	6%	30%	88%

Zaket et al 2021

Cryopreservation in ART

- To preserve fertility (medical, non-medical)
- Gamete donation (egg- and sperm banks)
- To increase (cumulative) success rates

↕

- To decrease multiple birth rates without increasing number of oocyte pick-ups

Slow freezing vs. vitrification

Vitrification;

Snap-freeze in high concentrations

No (less) intracellular ice formation

High survival rates, **esp. oocytes and blastocysts**

Development of good quality blastocysts

1028 IVF/ICSI cycles Sahlgrenska (2016-2020)

- Good Quality Embryo on day 2 (n= 3206) → 59% GQB
- Non-Good Quality Embryo on day 2 (n=2760) → 24% GQB

Ahlström & Lundin

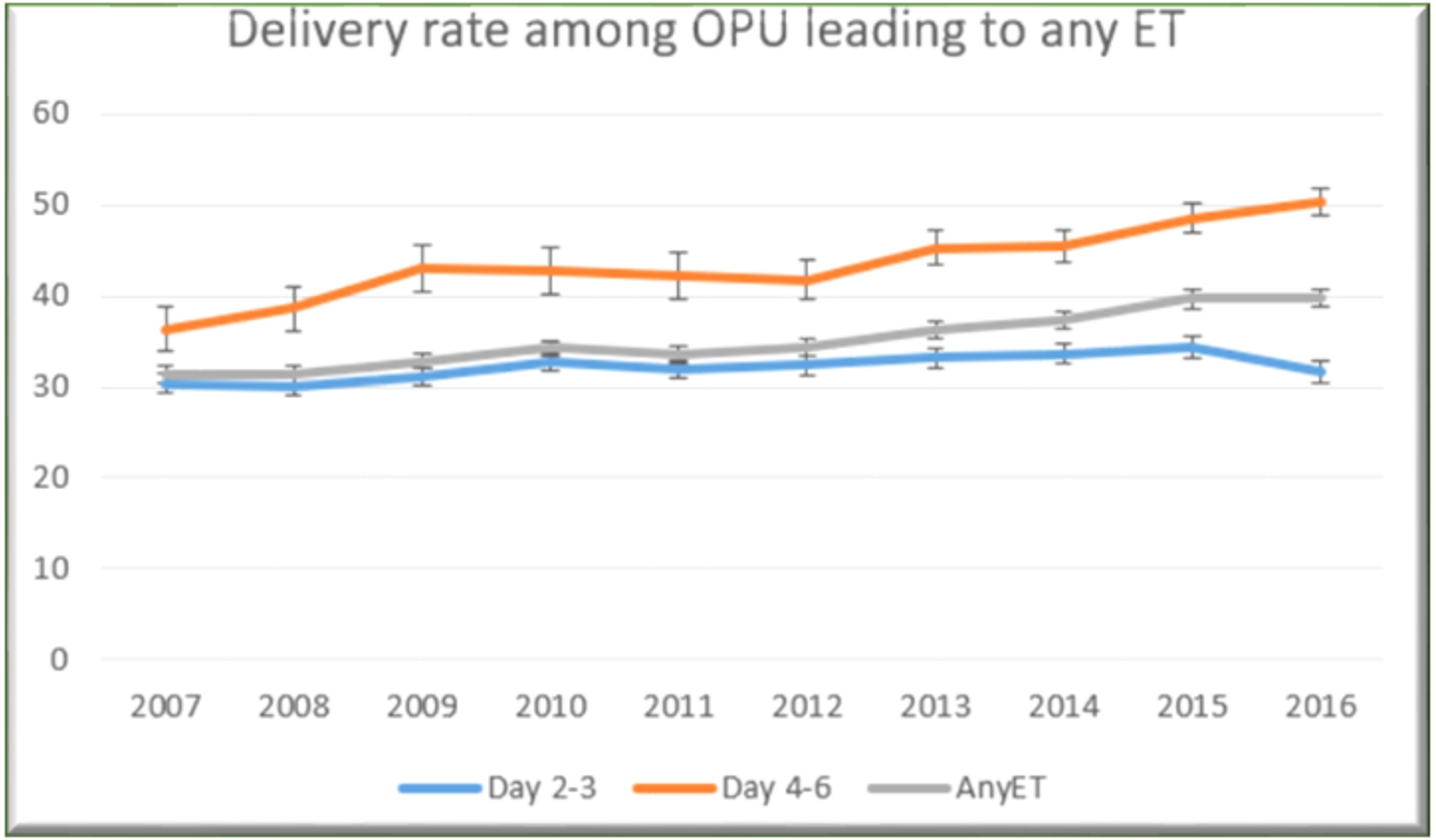
Cryopreservation of blastocysts and quality

2336 blast FET, 750 patients, Sahlgrenska

- **GQE day 2** (n=788), 262 births → 37% births
- **NGQE day 2** (n=400), 129 births → 36% births

Ahlström & Lundin

Swedish results - live birth from one transfer (*fresh or cryo*)



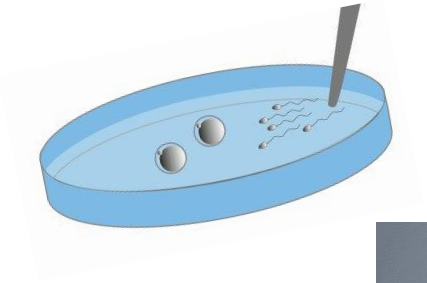
Q-IVF

doing pretty good so far….

….can we do better?

Working towards improvement in;

- Safety
  - Treatments
  - Patients and offspring



- Outcomes
  - Fertilisation, embryo/blastocyst rates and quality, cryosurvival, live birth rates

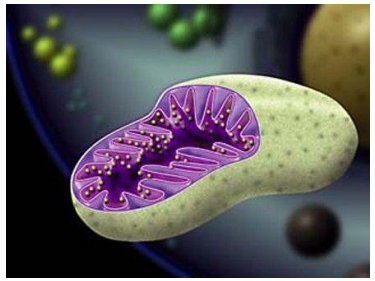
More patient friendly

- Fewer injections, fewer blood samples, fewer ultrasounds
- Shorter protocols
- Milder stimulation
- Less visits to the clinic
- …… increasing success rates ☺ (Blastocysts – cryo)
- Less OHSS
- Less multiples = more healthy babies –and mothers !

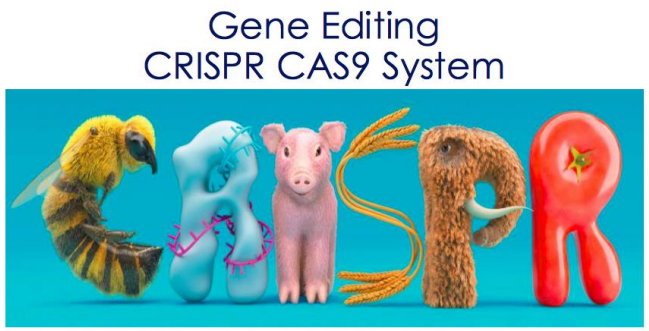
…but also more invasive – for the oocyte / embryo

- Cell biopsies (PGD/PGS, ”omics”)
- Oocyte activation
- Mitochondrial injections

  (donor egg --- own precursor cells?)



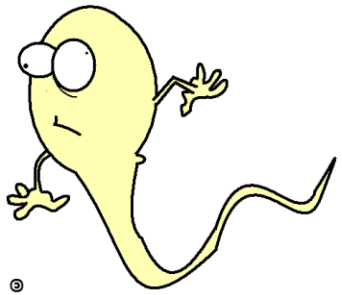
- Nuclear transfer
- Germ line editing…

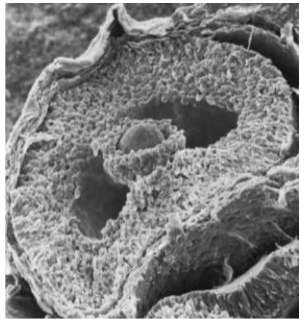


Germline Gene Editing - ESHRE Campus
Amsterdam IX.2016

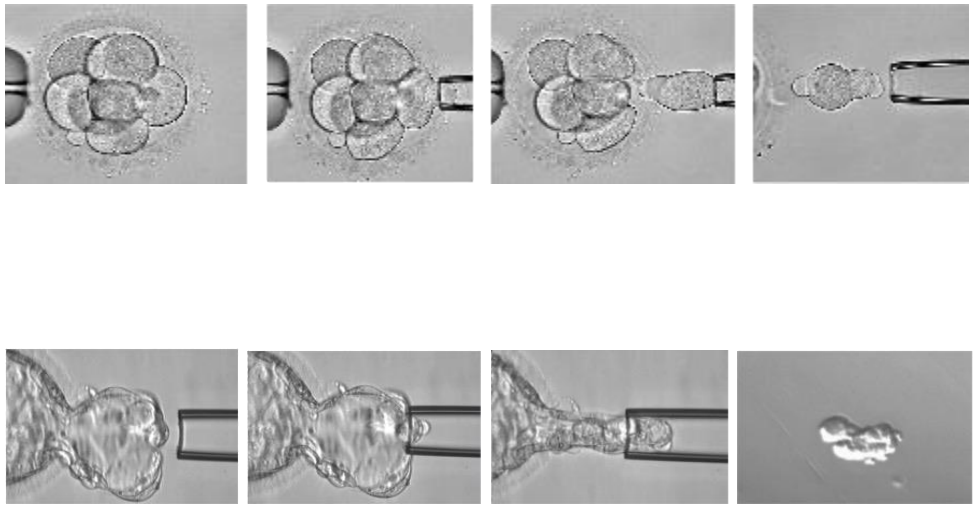
…and for the patient…

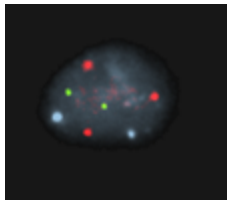
- Testis biopsies
- Ovarian biopsies (fertility preservation, maturation in vitro, precursor cells, follicle activation)
- Endometrial biopsies
- Endometrial scratching
- Ovarian manipulation (transfer of precursor cells, gene correction of precursor cells)

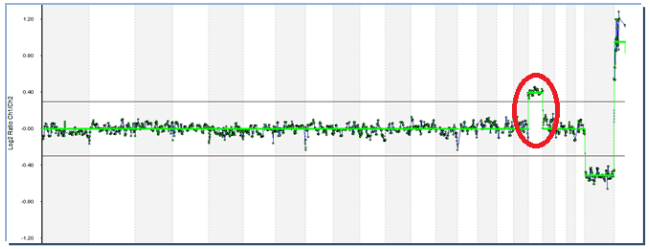




Genetics; PGT-M, PGT-SR, PGT-AS…….





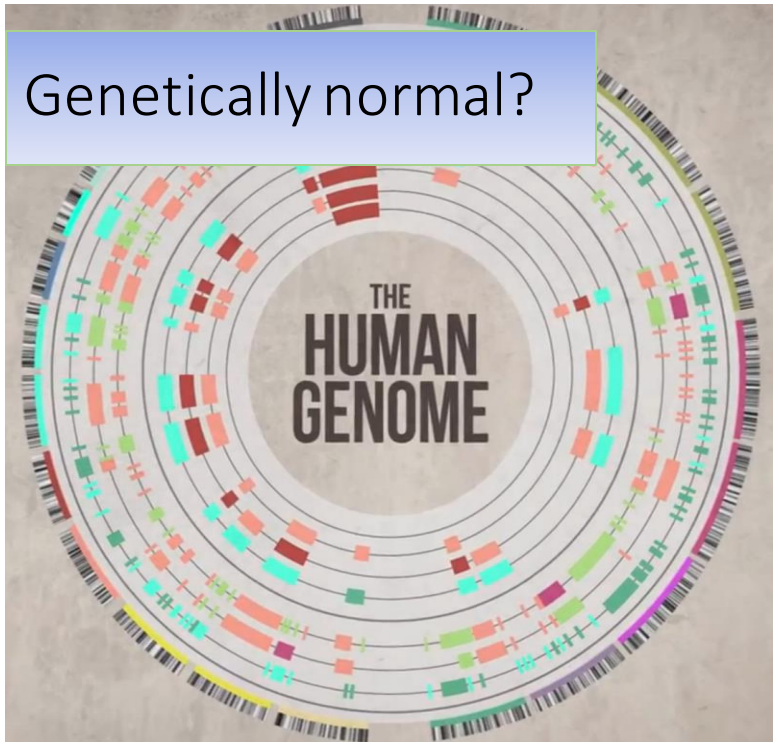


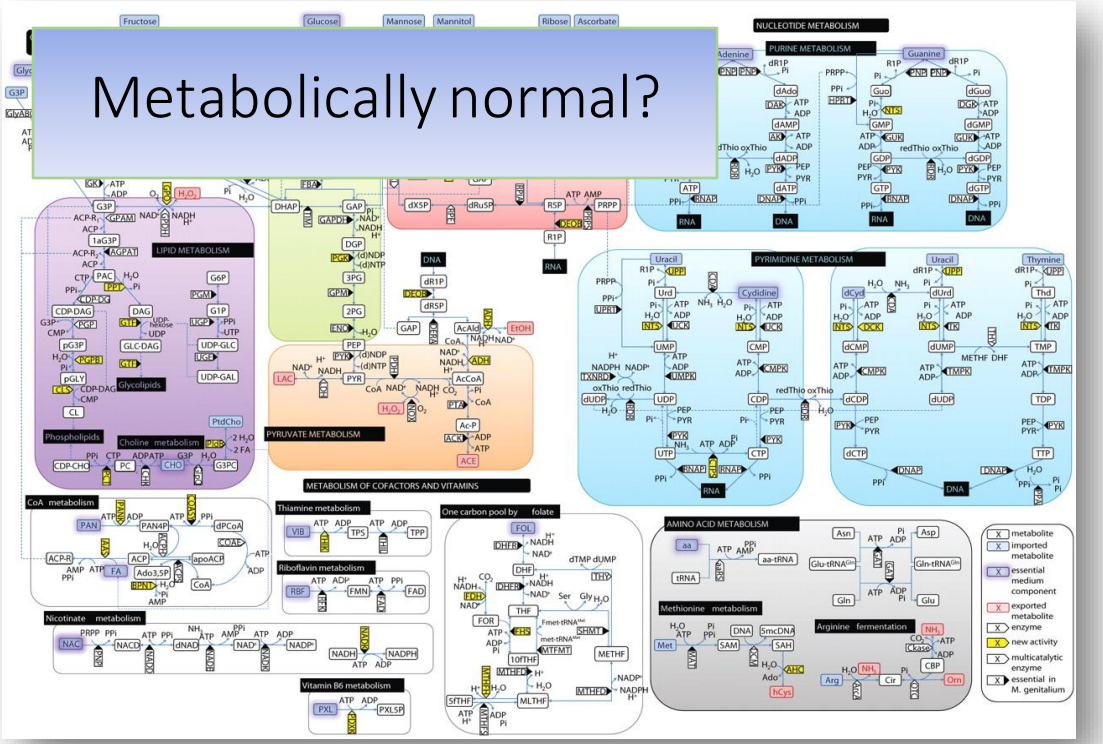
- Cell biopsies – 1-2 cells (day 3) or 5-10 cells (day 5/6) aspirated for genetic analysis
- **Diagnosis** for hereditary disease
- **Screening** for embryo chromosomal status

PGT status….

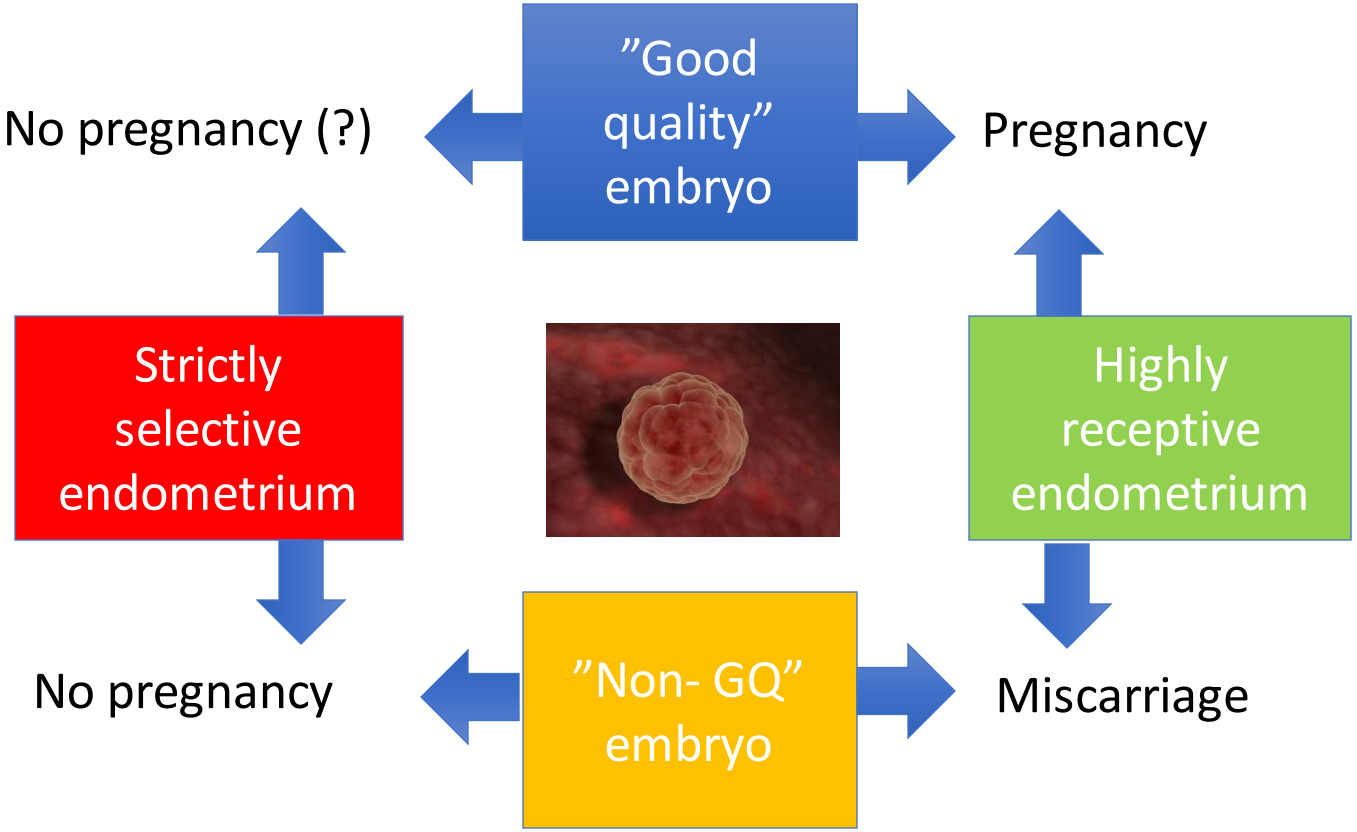
- Does not result in more good quality embryos (you have what you have)!
- Similar cumulative birth rates, with/without PGS
- Patients > 37 years may have a shorter time to pregnancy/birth, if many GQE embryos
- PGS should be used mainly to rank embryos, not to discard
- →(mosaicism rate acceptabel for transfer?)
- Patient information (?!)

and, what is "Normal"??
....and what about mosaicism?



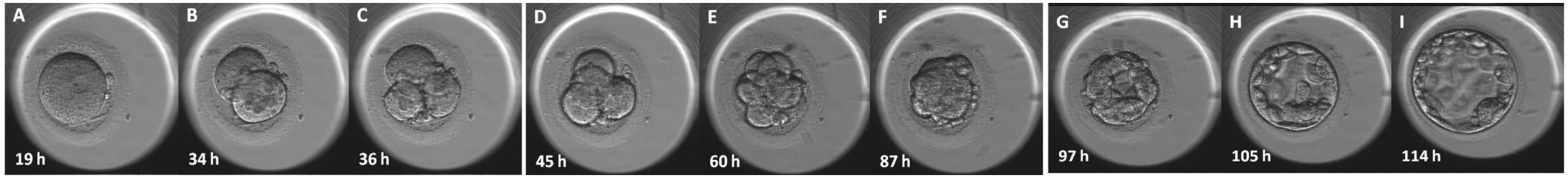


Still so much that we do not know……



(S. Quenby)

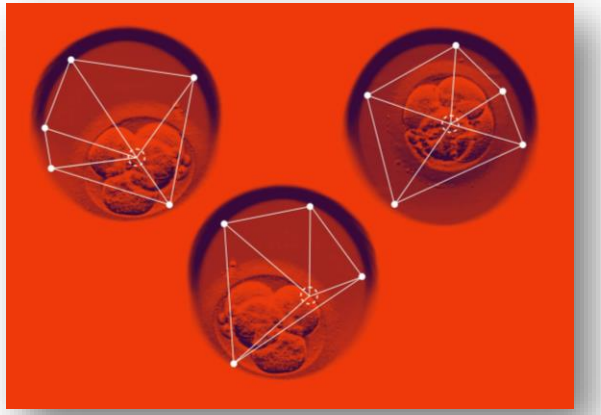
Coming up….Continous embryo assessments **Timelapse** – ”tool or toy”?



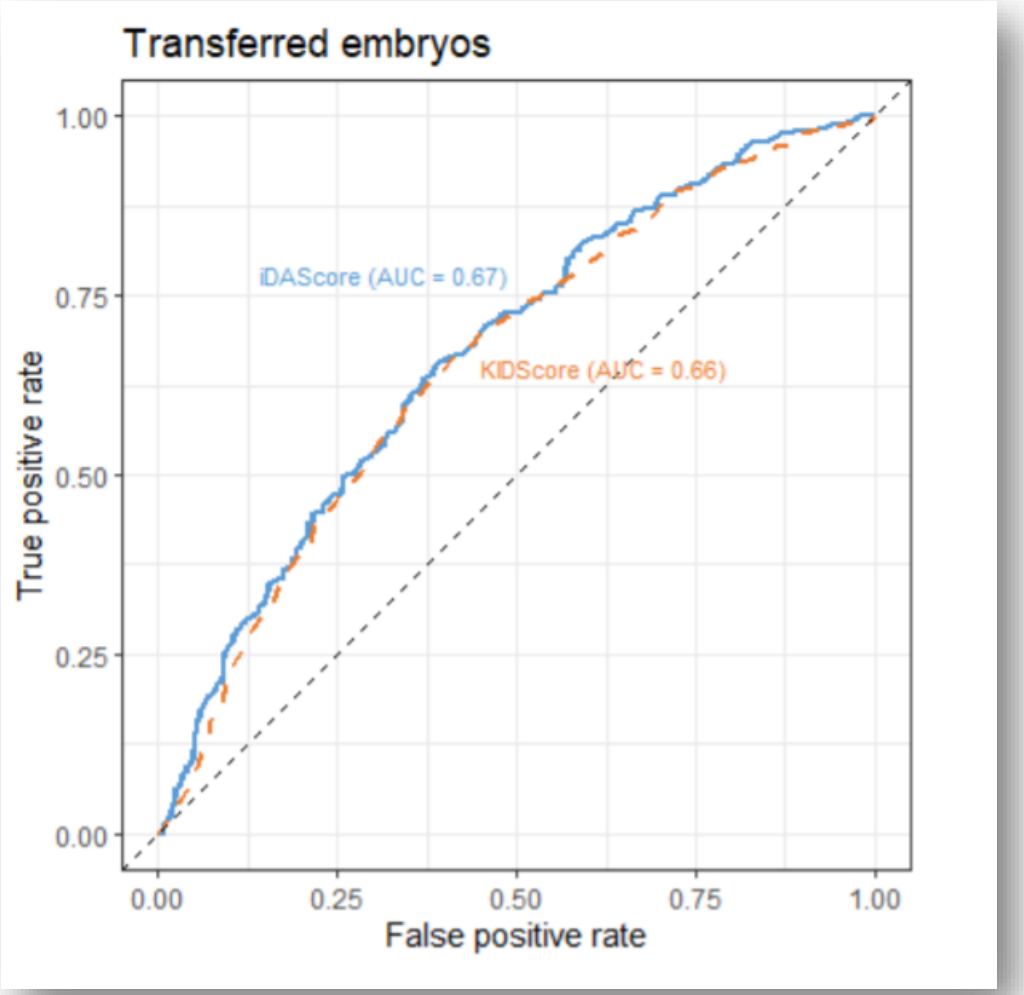
- (morphokinetic algorithms??) → machine learning?
- (time-saving?)….
- Logistics in the lab
- More stable environment
- Training, validation
- Learning about embryo development behaviour
- ”…its here to stay!”

Machine learning (AI) for embryo selection

- Using **ALL** time-lapse data (focal planes, times, patterns)
- Compare unconditionally to outcome (pregnancy, birth)
- Thousands of runs until correlations no longer increase



Embryo selection via machine learning (n=7932) vs. traditional scoring (n=1094)

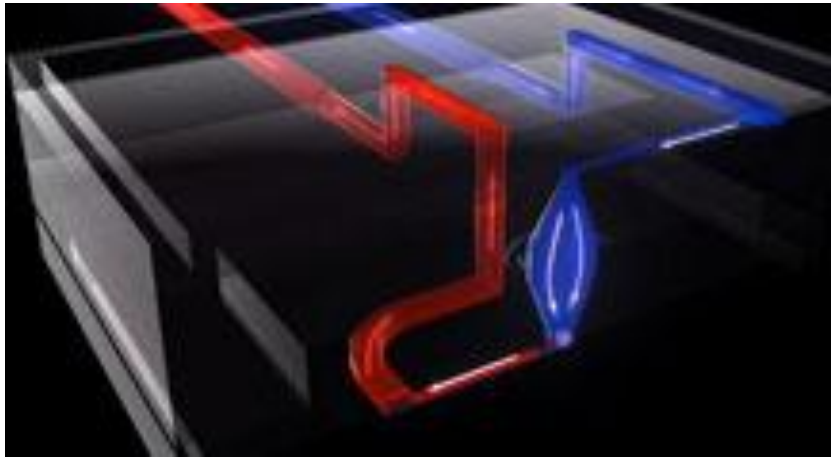


- AUC similar
- I.e. no improvement shown for machine learning, but possibly less subjective and less time consuming (no learning curve?)
- Transferrable through clinics?

Berntsen et al 2021

The future IVF lab - Automatic embryo culture

"Lab on a chip"



- Microfluidic chambers/channels for sperm and oocytes
- Automatic insemination / ICSI
- Automatic time-lapse imaging and scoring – machine learning?
- Sampling for genetic and metabolic markers?
- **Ranking** of embryos

The future clinic….

"Lab on a chip"

1. More technology driven; *automized laboratory*

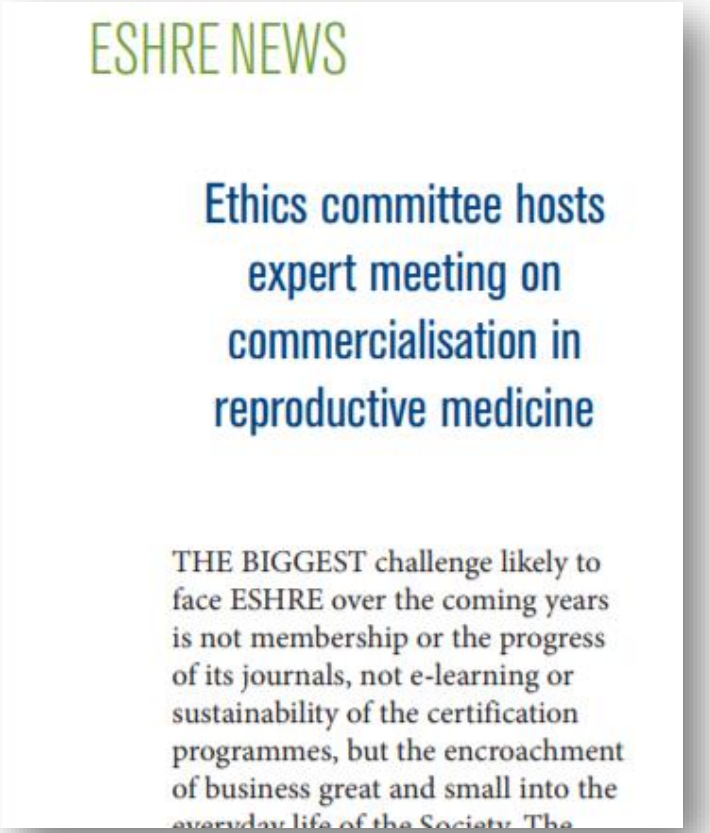
2. More patient control and demands of their reproductive rights; *when, where and how…(egg banking, surrogate motherhood, "all" options for treatment, free flow, accessability, treatment options…..)*

The future embryologist….

The future clinician….

Infertility and Assisted reproduction in the society

- Defined by WHO as a “disease of the reproductive system”
- However, in many countries there is a lack of financing and reimbursement
- → ART is to a large extent performed in the private sector (industrial scale…)
- More subjected to competitiveness (results <=> economic), with a need to be in the forefront and to supply “on demand” to their patients
- ART mainly involves individuals/couples who are relatively young and healthy, i.e they have a strong voice and are often willing to try (and pay for) almost anything



ESHRE NEWS

Ethics committee hosts expert meeting on commercialisation in reproductive medicine

THE BIGGEST challenge likely to face ESHRE over the coming years is not membership or the progress of its journals, not e-learning or sustainability of the certification programmes, but the encroachment of business great and small into the

Focus on Reproduction, 2016:

"With the ART 'business' now posting an annual growth of around 7%, former ESHRE Chairman Arne Sunde forecast an **$11 billion** industry by 2021, 'a safe investment with a relatively high return' for those scanning the commercial horizon."

'The weak link in all this is us,' said Sunde. 'We accept these developments with little question and minimum evidence. Clinics (*and media and patients*) are easily seduced by these new technologies.'

ART = a fast developing field
→ “Add-ons” and Commercialization

- Driven by the industry (pharmaceutical / lab /…)
- Driven by the clinics

- Increasing mixture of clinics and industry…..

- Results vs ”risk” vs economical gain

IVF add-ons - BBC Panorama 2016

thebmj Research Education News & Views Campaigns Archive

financial burden on patients, especially as 59% of procedures are not NHS funded.[3] On top of this UK fertility treatment centres offer a range of additional investigations and treatments,[4] costing from £50 for a single screening blood test to as much as £8000 for egg freezing packages (box 1).

Box 1: Example of costs for interventions additional to standard IVF

- Individual screening blood tests—start at £50
- Embryoglue—up to £160
- Intralipid infusions—up to £250
- Percutaneous epididymal sperm aspiration
- Preimplantation genetic screening—£3500
- Egg freezing packages—up to £8000

Health

'No solid evidence' for IVF add-on success

By Deborah Cohen
BBC Panorama

28 November 2016 | Health

Share

...ts offered by UK fertility clinics to increase
...are not supported by high-quality evidence
...s revealed.

...commissioned by BBC Panorama and
...e for Evidence-Based Medicine, world

...the use of almost 30 'unproven' add-on treatments was not to improve outcomes for patients, but to increase the profitability of the clinics offering them....

?

Patient oriented information; Traffic lights system (HFEA)

TABLE 1 HUMAN FERTILITY AND EMBRYOLOGY AUTHORITY TRAFFIC LIGHT RATING SYSTEM FOR IVF 'ADD-ONS'

Sign	Explanation	Add-ons
Red	No evidence that this add-on is effective and safe	• Assisted hatching; • PGS; • IMSI; • PICSI; • Intrauterine culture; • Reproductive immunology tests and treatment
Amber	There is a conflicting body of evidence for this add-on, further research is required	• Artificial egg activation calcium ionophore; • Elective freeze all cycles; • Embryo glue; • Endometrial scratching; • PGS; • Time-lapse imaging
Green	RCTs prove that the add-on is effective and safe	None

RCT = randomized controlled trial.

Adapted from www.hfea.gov.uk/treatments/explore-all-treatments/treatment-add-ons.

Macklon 2019

”Add-ons”:
Adding (selling) diagnostic or therapeutic treatments that have not been shown to have any effect

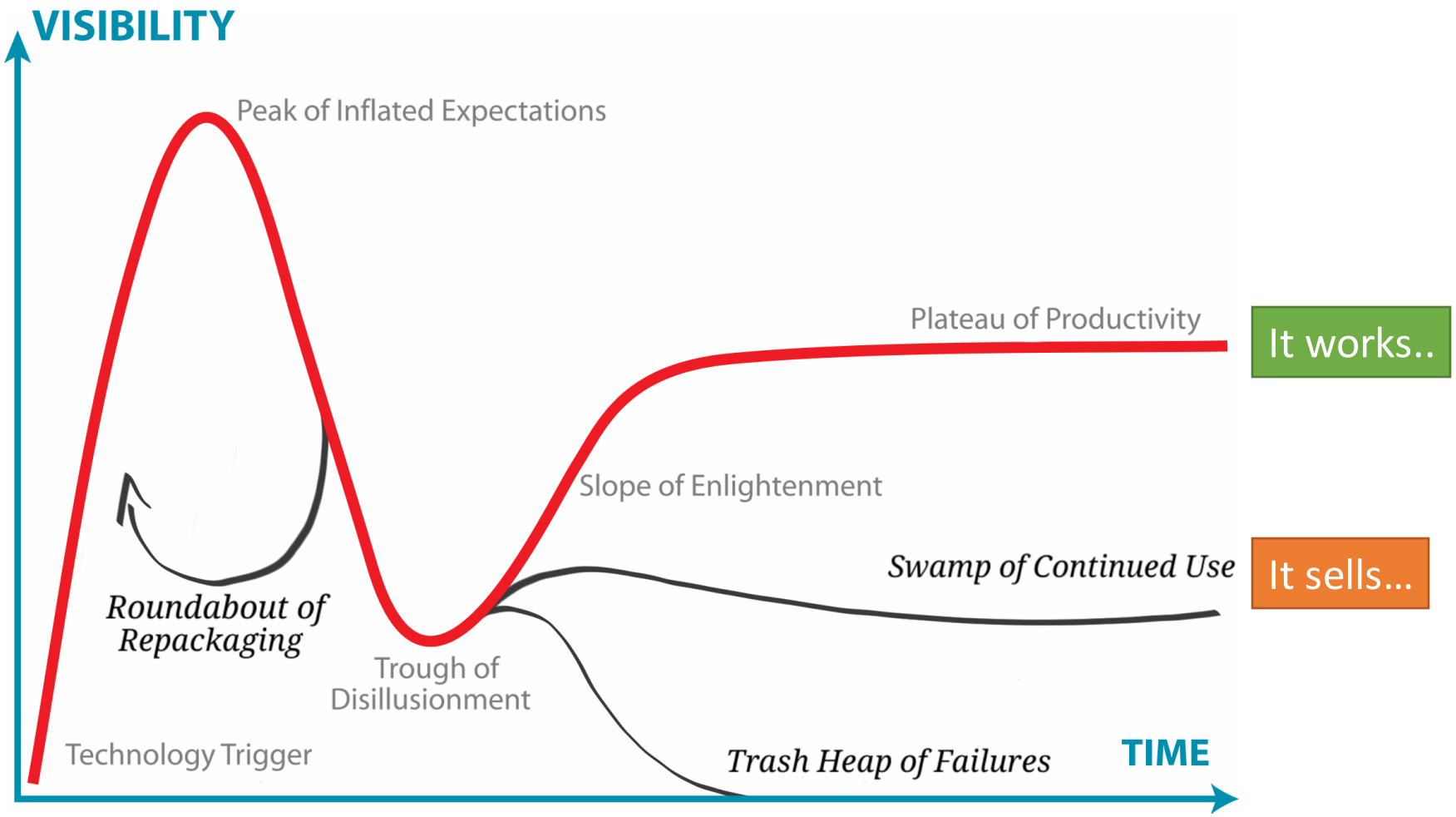
- Safe but overused – *ICSI for all……, ”Freeze all” for all…., PGS for all….*
- Overtreatment - *Treatments initiated too early…*
- Safe but results not shown to be improved - *Time-lapse*

- Not safe? – *mitochondrial treaments, oocyte boosting….*

→Providing unrealistic expectations and often extra costs

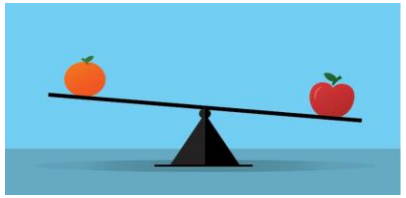
? When does an add-on become clinical practice?

So many hopes we have had…..

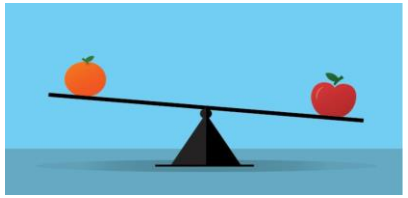


Modified from Gartner's Hype Cycle for Emerging Technologies (Fenn and LeHong, 2011)

- In ART safety and efficiency involves both the patient, the embryo (development) → **the future child**



In summary



Improvements in

- Overall results
- OHSS
- Multiple rates
- Offspring outcome
- Quality control, follow up, registries, guidelines etc…..

Threats?

- Invasiveness
  - ……
- Commercialisation
  - clinics
  - industries
- Add-ons
  - Effective
  - Safe
  - Cost?

Thank you
for listening