eshre
SCIENCE MOVING
PEOPLE
MOVING SCIENCE

The challenges of embryo transfer

Paramedical Group

1

3 July 2011
Stockholm, Sweden

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Organised by
The ESHRE Paramedical Group

Contents

Course coordinators

Jolieneke Schoonenberg-Pomper (The Netherlands) and Heidi Van Ranst (Belgium)

Course description

This course is particularly suitable for laboratory, nursing and related staff who wish to have the opportunity to comprehend the challenges of embryo transfer. By the end of the day the delegates will have an understanding of how colleagues work which will enhance working relationships and benefit patient care.

Target audience

Nurses, midwifes, lab technicians, counsellors, psychologists and ESHRE certified clinical embryologists.

Scientific programme

Chair: Jolieneke Schoonenberg-Pomper (The Netherlands) / Co-chair: Heidi Van Ranst (Belgium)

09.00 – 09.10	Introduction - **Jolieneke Schoonenberg-Pomper (The Netherlands)**
09.10 – 09.30	Nurses role at an IVF-clinic - **Charlotte Wrangel (Sweden)**
09.30 – 10.00	Development of the embryo - **Lynette Scott (USA)**
10.00 – 10.30	How to select the best embryo for transfer - **Kersti Lundin (Sweden)**
10.30 – 11.00	Coffee break
11.00 – 11.30	Nurses performing embryo transfer - **Helen Kendrew (United Kingdom)**
11.30 – 12.00	The myths of embryo transfer - **Rebecca Goulding (United Kingdom)**
12.00 – 12.30	What to do with non selected embryos? - **Claus Yding Andersen (Denmark)**
12.30 – 13.30	Lunch

Hands-on sessions – coordination: Liz Corrigan (United Kingdom)
group 1: max 40 participants
group 2: max 40 participants

13:30 – 15.00	group 1	Time-lapse assessment of embryos – **Helle Bendtsen (Denmark) & Helle Andersen (Denmark)**
	group 2	Performing embryo transfer - **Helen Kendrew (United Kingdom) & Bea Lintsen (The Netherlands)**
15.00 – 15.30	Coffee break	
15.30 – 17.00	group 2	Time-lapse assessment of embryos - **Helle Bendtsen (Denmark) & Helle Andersen (Denmark)**
	group 1	Performing embryo transfer transfer - **Helen Kendrew (United Kingdom) & Bea Lintsen (The Netherlands)**

ESHRE – European Society of Human Reproduction and Embryology

What is ESHRE?

ESHRE was founded in 1985 and its **Mission Statement** is to:

- promote interest in, and understanding of, reproductive science and medicine.
- facilitate research and dissemination of research findings in human reproduction and embryology to the general public, scientists, clinicians and patient associations.
- inform politicians and policy makers in Europe
- promote improvements in clinical practice through educational activities
- develop and maintain data registries
- implement methods to improve safety and quality assurance

The Paramedical Group (1/3)

The ESHRE Paramedical Group was established to assemble nurses, laboratory technicians and other support personnel active in the field of reproductive medicine and science.

The group serves as a platform for paramedics and organises specific sessions during the Annual Meeting and workshops.

ESHRE is one of the only organisations with a forum for paramedicals, who are represented in the Executive Board by Jolieneke Schoonenberg-Pomper.

The Paramedical Group (2/3)

- Established in 1987
- Meets 3 times a year
- Board Members:
  Jolieneke Schoonenberg-Pomper (chair)
  Heidi Van Ranst (past chair)
  Patricia Baetens
  Helle Bendtsen
  Inge Rose Jorgensen
  Helen J. Kendrew
  Eline Dancet
  Cecilia Westin

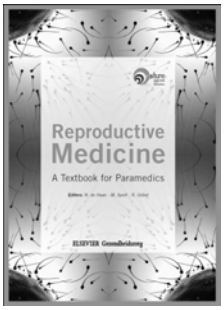
Paramedical Group (3/3)

- Nurses/Midwives
- Laboratory technicians
- Counsellors/Psychologists
- ESHRE certified clinical embryologists (Bsc level)

ESHRE Book for Paramedicals

ESHRE Book for Paramedicals

- First English textbook in Europe
- Free copy for every paramedical member
- Order it now - ask a member of staff



www.eshre.eu

ESHRE Campus and Data Collection

Campus / Workshops

- Meetings are organised across Europe by Special Interest Groups and Task Forces
- Visit www.eshre.eu under CALENDAR

Data collection and monitoring

- European IVF Monitoring Group data collection
- PGD Consortium data collection

ESHRE Journals

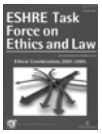
Human Reproduction with impact factor 3.859

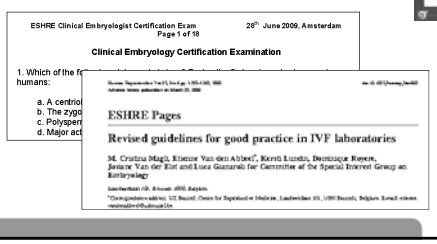
Human Reproduction Update with impact factor 7.042

Molecular Human Reproduction with impact factor 3.005

ESHRE Activities

- Embryology Certification
- Guidelines
- Position papers




ESHRE Clinical Embryologist Certification Exam 28th June 2009, Amsterdam
Page 1 of 18

Clinical Embryology Certification Examination

ESHRE Pages

Revised guidelines for good practice in IVF laboratories

ESHRE Community

RSS feeds for news in reproductive medicine

Since launch 12/2009: **1,360 Fans**

Since launch 12/2009: **190 followers** (journalists, scientific organisations, patient societies, governmental bodies)

Retweets to MHR

Find a member

Special Interest Groups (SIGs)

The SIGs reflect the scientific interests of the Society's membership and bring together members of the Society in sub-fields of common interest

- Andrology
- Early Pregnancy
- Embryology
- Endometriosis / Endometrium
- Ethics & Law
- Safety & Quality in ART
- Psychology & Counselling
- Reproductive Genetics
- Reproductive Surgery
- Stem Cells
- Reproductive Endocrinology

ESHRE Membership

4,017	Europe
476	Asia
372	North America
332	Middle East
221	Africa
142	Oceania
99	South America

TOTAL MEMBERSHIP*: 5 659 members

* as of July 2010

Paramedical Membership (1/3)

	ESHRE Members	Paramedical Members	%
2009	5.541	545	9,8
2010	5.659	596	10,5

Paramedical Membership (2/3)

	1 yr	3 yrs
Paramedical Member	€ 30	€ 90

1) Reduced registration fees* for all ESHRE activities:

Annual Meeting	€ 240	(€ 360)
General Workshops	€ 150	(€ 250)
Paramedical Workshops	€ 100	(€ 150)

2) Reduced subscription fees to ESHRE journals – e.g. for Human Reproduction €191 (instead of € 573)

* fees may vary

*fees may vary

ESHRE Membership – Benefits (3/3)

3) ESHRE Book for Paramedicals
- First English textbook in Europe
- Free copy for every paramedical member

4) ESHRE monthly e-newsletter

5) News Magazine 'Focus on Reproduction'

6) Paramedical Website 'Members only' access

7) Active participation in the Society's policy-making

Paramedical Group – Future Activities

Basic training course for paramedics working in reproductive health
3 - 4 March 2011
Berlin, Germany

Preconception care in a fertility clinic
12 May 2011,
Winchester, United Kingdom

Pre-Congress Course - The Challenges of Embryo Transfer
3 July 2011
Stockholm, Sweden

The management of infertility- training workshop for junior doctors, paramedicals and embryologist
7 and 8 September,
St Petersburg, Russia

Research course
8 and 9 March 2012, Amsterdam , The Netherlands

Basic training course for paramedics working in reproductive health.
24 an 25 May 2012, Copenhagen, Denmark.

ESHRE 2011, Stockholm, Sweden

When: **3 - 6 July 2011**
Where: **Stockholmsmässan,**
Mässvägen 1, Älvsjö, Sweden
www.stockholmsmassan.se

Chair of conference: **Kersti Lundin**

Hotel and Travel:
MCI - Stockholm Office
Phone: +46 (0)8 54651500
E-mail: eshre@mci-group.com

For updates visit www.eshre.eu

Annual Meeting – Paramedical Programme

Monday 4 July

Nursing Session:

- US nurses exchange lecture
- Paper free clinic, future or fiction?

AGM Annual General assembly Meeting (13:00-14:00)
for al paramedical members

Tuesday 5 July

Session: Quality assurance and safety in human cryopreservation laboratories

- Risk of contamination of germ plasm during cryopreservation and cryobanking in IVF units
- Managing risks associated with cryopreservation

Annual Meeting – Paramedical Programme

Tuesday 5 July

Session: Emerging technologies in human IVF laboratories

- Comparative genomic hybridisation: a powerful tool to investigate the chromosomal normality in human embryos
- Microfluidics in human IVF laboratories

Wednesday 6 July

Interactive Debate: "Should we pay donors?"

- Pro: *Herman Tournaye (Belgium)*
- Contra: *Laura Witjens (United Kingdom)*

Certificate of attendance

1/ Please fill out the evaluation form during the campus

2/ After the campus you can retrieve your certificate of attendance at www.eshre.eu

3/ You need to enter the results of the evaluation form online

4/ Once the results are entered, you can print the certificate of attendance from the ESHRE website

5/ After the campus you will receive an email from ESHRE with the instructions

6/ You will have TWO WEEKS to print your certificate of attendance

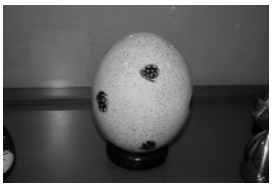
Contact

ESHRE Central Office
Tel: +32 (0)2 269 09 69
info@eshre.eu / www.eshre.eu

Paramedical Board

- Vacancy for a laboratory technician/ESHRE certified clinical embryologist (Bsc level)

Nurses role at an IVF-clinic in Sweden



Charlotte Wrangel

Reg. nurse

About 1000 IVF treatments a year

About 5000 consultations

References: H. Holter Infertility and first IVF-treatment Göteorgs Universitet 2007
A.Kjellberg Litteraturstudie Instution för vårdvetenskap och hälsa, Göteborgs Universitet 2008
H. Volgsten Mood Disorders, Personality and Grief in Women and Men undergoing IVF, Uppsala Universitet 2009

Nursing theoretician

Jean Watson

Stresses existential phenomenological factors in care.

The nurse sees herself in existential contexts

Joyce Travelbee

Communication is the basis of good patient contact

The nurse's role is to care

Nursing theory Katie Ericksson
Professor in caring science

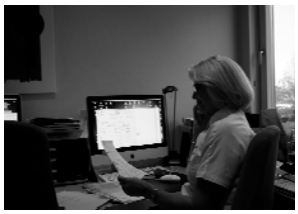
Comprehensive view

Reflection and production

The nurse's responsibility in care, what does it look like?

Support – Good availability
Two incoming phonelines
Phone-hours

E-mails
Rian Oy 2007,2008, 2009



The meeting with the couple

- Listening
- Asking questions
- Understanding
- Offer hope
- Engagement
- Support

Daily meeting

- 

Information

OPU
OHSS
Advice
Follow-up

What does the future look like?

Network
Meetings
Updating
Education
Supervision
Network between nurses

Survey at The IVF Clinic Öresund 2011

Rian Oy 2011

50 couples participated.

The woman and the man answered the ”four question survey” separately

Criteria

At least one IVF treatment at the IVF Clinic Öresund

All answers were given at the visit to the clinic.

Result

Results are not yet summarized.
Will be presented in 4-6 slides.

Anna and Per

First visit at our clinic in 2006

First IVF in October 2006

A total of nine IVF treatments

After the fourth IVF Anna got pregnant but had to terminate the pregnancy due to trisomy 18 in week 13.

Prior to their fifth IVF these figures were made

My (involuntary) friends

This is **Uncertainty**

He is big and always present.
Can't get rid of him.
I have to accept him in my life, but hate when he tries to kill Hope**.**

My (involuntary) friends

This is **Hope**

She is actually the leading actress, even though she is small and is often badly treated by her fellows

My (involuntary) friends

This is **Moody**

He is the capricious director who can choose a new leading actor as often as every 7th second. Totally unpredictable and unreliable.
I don't like him. He is very hard to tame.

My (involuntary) friends

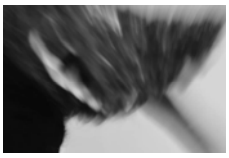
This is **Some** and **Others**

These guys are often referred to. Some and Others are also full of good ideas; which they like to share.
One idea they often propose is that I should relax and not think so much. Well…..

My (involuntary) friends

This is **Odds** and **Statistics**

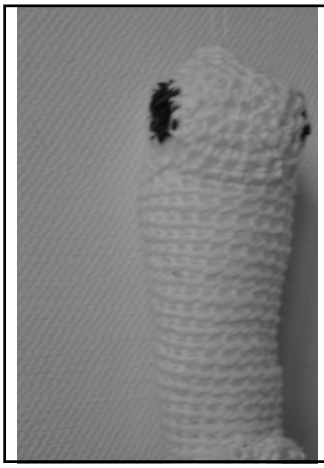
This couple is also often referred to.
Because they are rhetorically skilled they may seem reliable. Once I believed in them and put my trust in them. Today I am not that sure anymore.
Some love them. Others hate them.



My (involuntary) friends

This is **Horror**

He can grow fast and strike me with his terror. He goes from tame to a bloody beast in a second. Needs to be kept locked in.



My (involuntary) friends

This is **Sorrow**

She is also always present, but most often she takes a back seat. In periods of time she has had the leading role.
I accept her and she is not all bad.

My (involuntary) friends

There is a pair of Sisters I have deliberately chosen to keep out of my album. They have tried many times, but I have refused their admission. One is Injustice. She is a fake. She does not exist and neither does her sister Justice.

Foto saknas

My (involuntary) friends

This is Me.
It seems I have lost my arms.
But who cares? As long as I have my Tubes and Uterus.

People will forget what you said

People will forget what you did

But people will never forget how you made them feel

-Maya Angelou

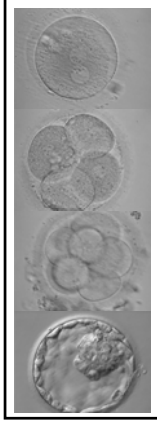
Thank you

Eshre Post Grad Course

The Challenges of Embryo Transfer

Development of the Embryo

Lynette Scott, PhD, HCLD
MA, USA



Learning Objectives

1: Understand the sequential development of embryos
2: Become familiar with the time course of development and developmental clocks
2: Learn how to identify features that are abnormal
3: Understand the origin and consequences of these abnormalities

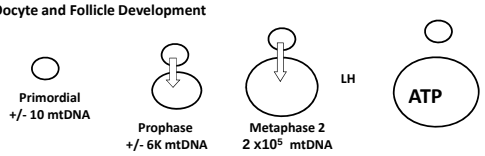
At the end of the course the participant should be able to identify all features in a sequential scoring system which indicate a normal vs. abnormal embryo development

In the beginning….

- 2 Gametes form the embryo
- Fundamentally flawed gametes can not make a normal embryo
- The oocyte is the most powerful cell in the body, carrying all mitochondrial DNA, the ability to start life and she also has mechanisms to repair a certain amount of sperm DNA damage
- The sperm contributes half of the DNA and the spindle organizing apparatus, the centromere

Mitochondrial Load in Oocytes
ATP Source

Oocyte and Follicle Development



Mitochondrial Load is Fixed

ATP

Glycolysis provides small amounts

Cumulus cells = Glycolysis provides small amounts initially

In Developing follicle OxPOs provide the bulk of ATP so the follicle needs to be well supplied with oxygen

Oocyte MT are activated after final maturation initiation = all ATP supply

Polarity vs. Asymmetry

- Invertebrate and vertebrate oocytes have dramatic asymmetry in organelle distribution
- Often this asymmetry is a manifestation of structural and molecular polarity
- But asymmetrical distribution does not impose or indicate polarity
- Only when asymmetry is invariable, non-interchangeable, irreplaceable is it considered polarity

Animal Oocyte and Embryo Polarity

- Well established in lower order animals
  - in insects, worms, reptiles, avians
- For years it was disputed in mammals
- Suggested that polarity only occurred at the first phase of differentiation, i.e. "inside-outside" with compaction and then blastocyst formation

Origin of Centrioles

- **In humans (and all other mammals) they come from the sperm**
- **Rodents: Centrioles are formed in the oocyte**
- **This may be a difference in patterning and polarity between mouse and human oocytes and embryos**

Oocyte and Embryo Time-Clocks

- Oocytes and early embryos are on strict time clocks
- There are 2 types of clocks
  - Those involving cyclic or sequential systems
  - Those that need threshold levels of some factors or the hour glass timers
- Zygotic clocks are initiated at fertilization and are involved in X inactivation
- Zygotic or Embryo Gene Activation which fully occurs at the 4-8 cell in the human is regulated by iRNAs

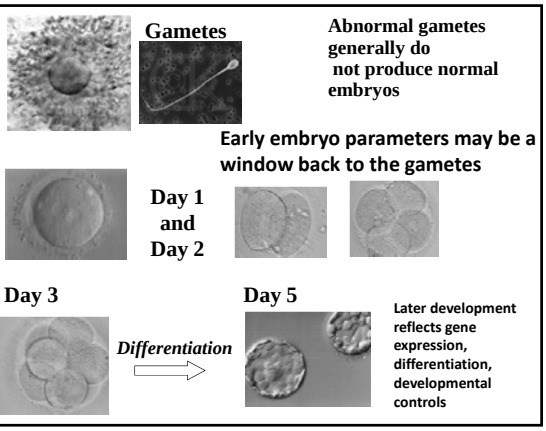
Time

The 4th Dimension of Embryo Development

- All timing in embryo development is controlled by temporal clocks
- The main switch is the LH surge (hCG injection)
- Gene activation and deactivation is dynamic temporal and developmentally regulated
- Some genes are only function for a very short period in the whole life of the embryo and resulting off spring

Embryo Selection

- Abnormal oocytes generally do not produce a normal embryo
- Early embryo parameters are a window back onto the gametes (sperm and oocytes)
- Later developmental parameters reflect gene expression, developmental controls
- These are likely connected to gamete quality and should therefore also be connected to early selection criteria



Timing in Embryos

- The embryo is on a "clock" which starts with the LH surge/hCG injection
- Development is dynamic, cell-division timing is dictated by the LH surge/hCG injection, and is controlled by check point genes and developmentally specific gene expression
- Embryos that deviate too far from the median (either slow or fast) will be developmentally compromised, having too few/many cells and likely abnormal gene expression of certain developmental regulating genes
- For non-time lapse observation the *median* time for each observation should be elucidated

Alpha/Eshre Consensus Meeting Istanbul 2010

Timing by consensus for each of the scoring points was reached and related to post-insemination (PI)

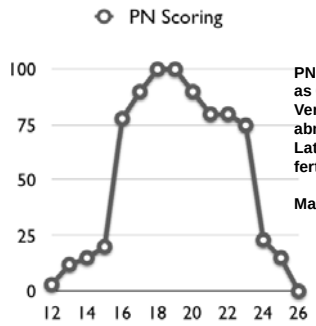
- **2pn 16-18 hrs PI**
- **EC 24 h +/- 1 hour PI**
- **Day 2 check 44 h +/- 1 hour PI**
- **Day 3 check 68 h +/- 1 hour PI**
- **Day 4 check 92 h +/- 2 hours PI**
- **Day 5 check 116 +/- 2 hours PI**

SCORING TIME POINTS

Time Point	hCG	ER	Insem.	D 1 Fert./EC	D 2 2-4 cell	D 3 6-8 cell	D5 Blast
Hours/ hCG	0	36-37	40	58-59 64-65	83-84	105-106	152-154
Hours/ Insem.	0	0	0	17-18 23-24	42-43	64-65	112-114

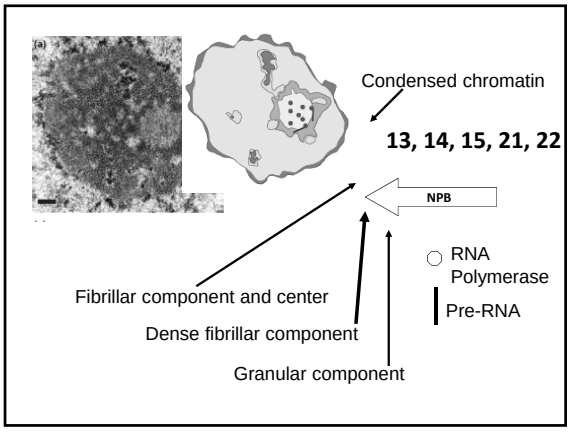
Most ER are 36-37 hours post hCG.
Maximum mature (M11) occurs 40-41 h post hCG
Time of maturation is important (Montag, 2008)
Strip for ICSI at 38 h, separate M11, M1, GV
Stabilized PN's are from 16-18 hours post insem.
EC will start at 20 h post insem, max 25-26

PRONUCLEAR FORMATION



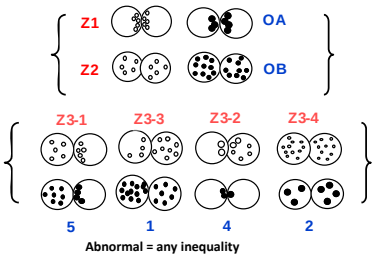
PN formation can start as early as 6 hr post insemination
Very early PN formation is abnormal, too fast
Late PN formation is delayed fertilization= abnormal

Max 16-19



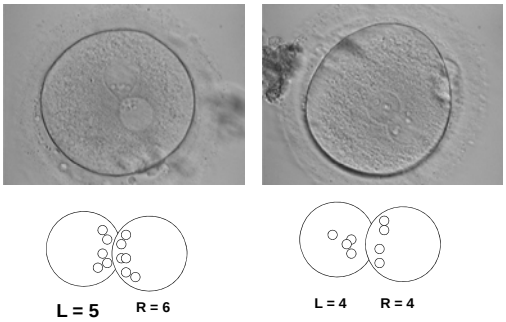
Nucleolar Precursor Body (NPB) Pattern

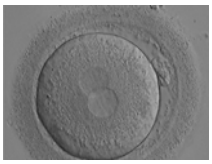
Normal = equality between nuclei



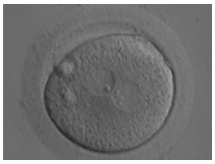
Abnormal = any inequality

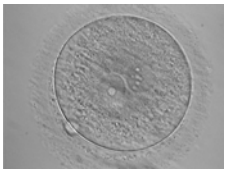
NPB RATIO





Evidence for epigenetic/ imprinting errors in these oocytes
Sperm or oocyte?
NPBs associated with imprinting errors, heterochromatin

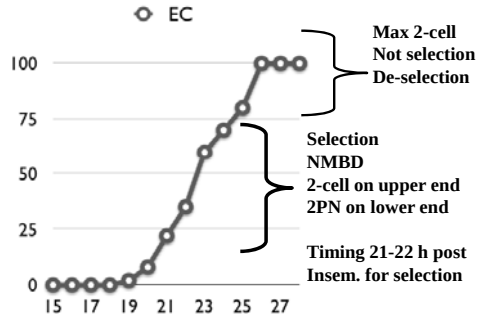




Lessons from NT

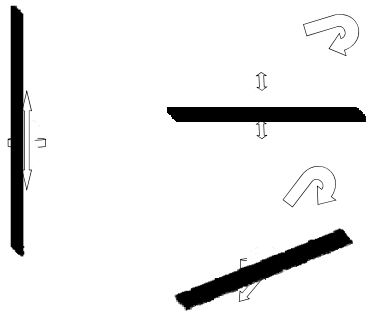
- **Evidence of delayed embryonic genome activation in NT embryos**
- **The delay is due to the late onset of functional NPB and nuclioli formation**
- **NPBs and nucleoli play an important role in Embryonic Gene Activation and cell cycle**
  - ***Savarcova et al. 2009***

EARLY CLEAVAGE



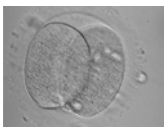
Fertilized Oocyte Polarity

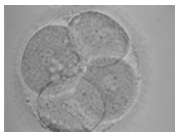
- What happens at the 2PN stage? Where is the first cleavage and does it matter?
- Mouse 3 theories
  - Through the polar axis defined by the PB
  - Through the sperm entry site which is always defined
  - Through the pronuclear axis



Day 2 Development

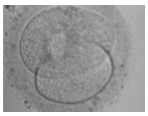
- Timing is important for scoring
- 42-43 h post-insem
- Cell number
- Blastomere relative size
- Status of nucleation
- Fragmentation

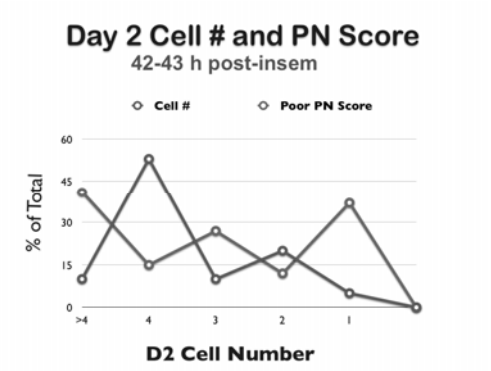




Empiric observations

- **Uneven cleavage at the first mitotic division is not compatible with delivery**
- **Muti-nucleation in blastomeres at the 2-4 cell stage is not compatible with delivery**
- **Off-Center Nuclei at the 1 cell stage is not compatible with delivery**
  - ***Scott et al 2007***



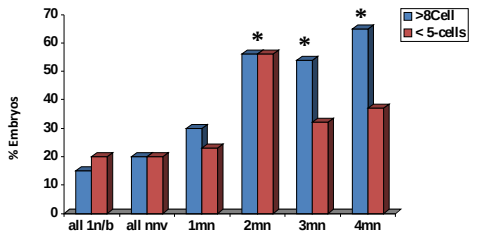



Embryo Development and MN

- **Embryo development is compromised by MN**
- **Increased numbers of embryos presenting with more than 8 cells on D3 (64h post insemination, 104 post hCG) or developmental arrest (≤5 cells at 64 h post insemination)**
- **9462 embryos grown to Day 3**
- **971 embryos (7.9%) were > 8-cell**
- **649 (67%) had at least 1 cell MN on D2**

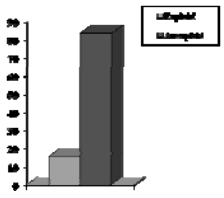
Fast and arrested development vs. MN

971 >8-cell (8%); 649 MN (67%)
1959 ≤5 cell (28%); 1690 MN (49%)



MN and Ploidy

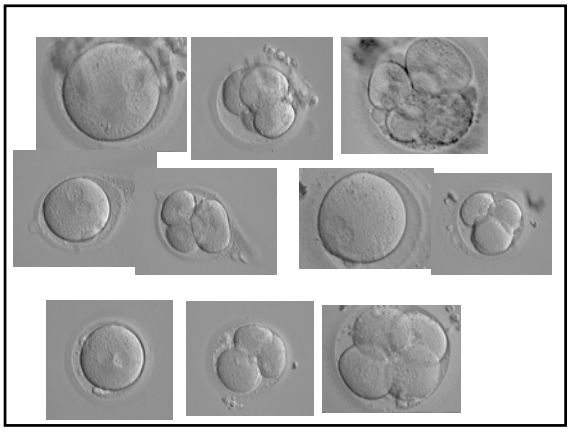
- **MN is associated with Aneuploidy.**
- **2034 embryos biopsied**
- **317 (15%) were MN**
- **50 of these euploid (16%)**
- **267 aneuploid (84%)**

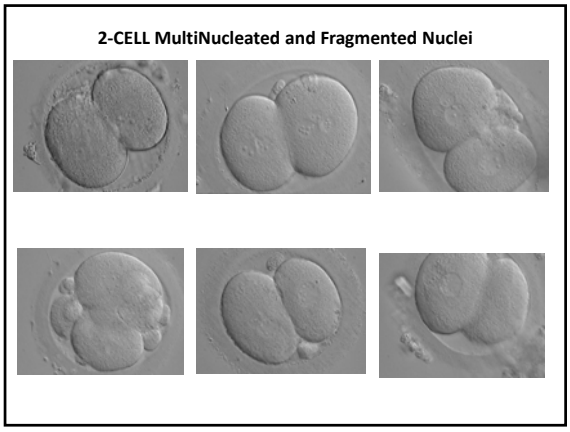


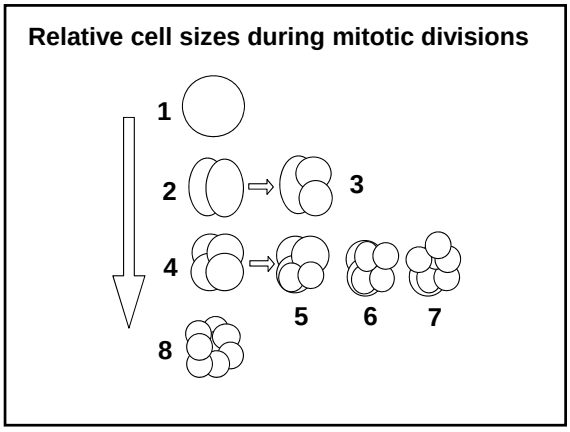
Finn et al, 2010; Kligman et al, 1996

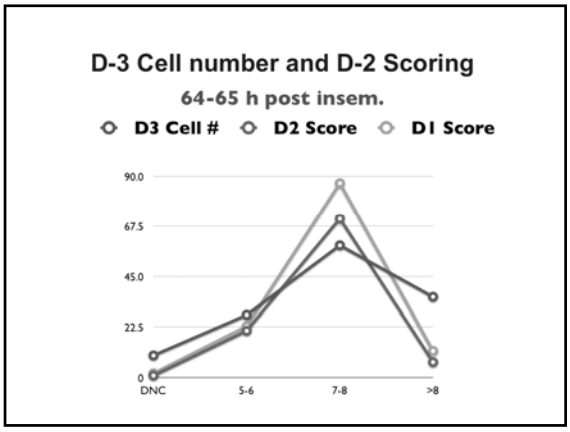
MN and Developmental Stage

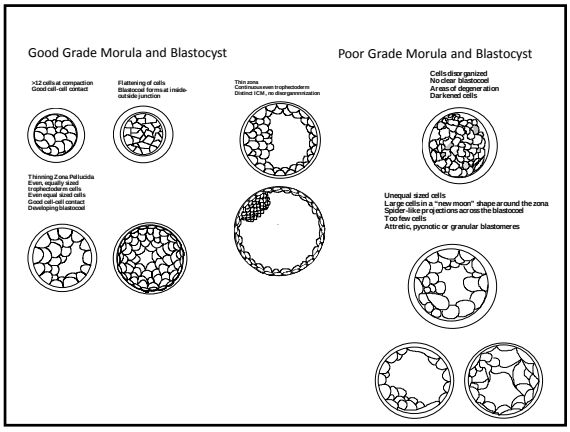
- **MN is associated with either arrested development or increased cell number that is not consistent with normal development.**
- **The increased cell number results from 1 blastomere dividing into 3 or 4 cells in 1 mitotic division (exploding)**
- **Day 2 MN check is a simple method of *De-Selecting* embryos**

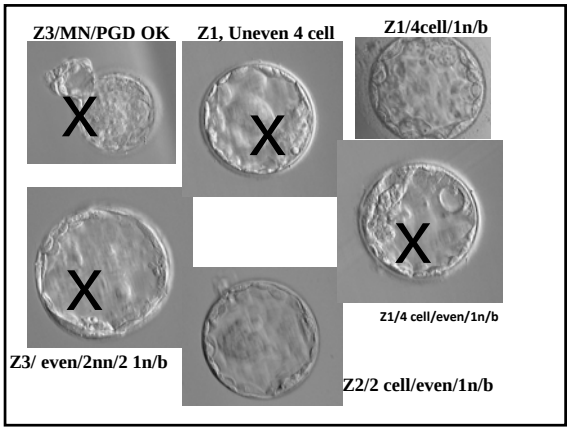



2-CELL MultiNucleated and Fragmented Nuclei

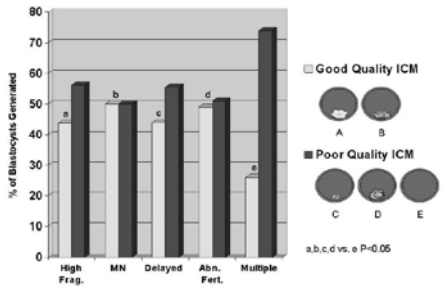

Relative cell sizes during mitotic divisions
1
2
3
4
5
6
7
8


D-3 Cell number and D-2 Scoring
64-65 h post insem.
D3 Cell #
D2 Score
D1 Score
90.0
67.5
45.0
22.5
0
DNC
5-6
7-8
>8


Good Grade Morula and Blastocyst
Poor Grade Morula and Blastocyst
>12 cells at compaction
Good cell-cell contact
Flattening of cells
Blastocoel forms at inside-outside junction
Thin zona
Continuous even trophectoderm
Distinct ICM, no disorganization
Thinning Zona Pellucida
Even, equally sized trophectoderm cells
Even equal sized cells
Good cell-cell contact
Developing blastocoel
Cells disorganized
No clear blastocoel
Areas of degeneration
Darkened cells
Unequal sized cells
Large cells in a "new moon" shape around the zona
Spider-like projections across the blastocoel
Too few cells
Attretic, pycnotic or granular blastomeres


Z3/MN/PGD OK
Z1, Uneven 4 cell
Z1/4cell/1n/b
Z1/4 cell/even/1n/b
Z3/ even/2nn/2 1n/b
Z2/2 cell/even/1n/b

Blastocyst, ICM and Poor Quality Embryos



From T. O' Leary et al, 2010

Poor Quality Trait	Embryos Cultured	Blastocysts Plated and Attached	hESC Lines (% of attached blastocysts)	hESC Lines (% of embryos cultured)
High Fragmentation	309	47	8 (17.0)[a]	8 (2.6)[a]
Multinucleated Blastomeres	129	19	2 (10.5)	2 (1.5)
Delayed Development	185	21	3 (14.3)	3 (1.6)[a]
Abnormal Fertilization	174	20	3 (15.0)	3 (1.7)[a]
All single traits combined	797	107	16 (14.9)[b]	16 (2.0)[a]
≥2 Poor Traits	424	25	0[c]	0[b]
Total	1221	132	16 (12.1)	16 (1.3)

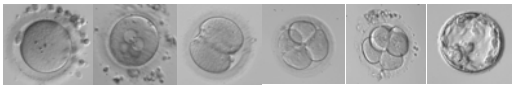
From T. O' Leary et al, 2010

Published Literature

- ***Gardner 1996 and Edwards 1997*** **suggested that it does exist in oocytes and it dictates all further polarity and axes**
- **An animal-vegetal pole exists dictated by the polar body**
- **Contrarily, *Zernika-Goetz* stated "there are no essential components that are localized uniquely to the animal or the vegetal pole *1998***
- **That the axis is set up by Sperm Entry site = first axis of development *Zernika-Goetz, 2002***
- **Alternately, it is the plane separating the 2 pronuclei as they move to the center of the oocyte which sets up the first axis *Hiiragi and Solter, 2004, 2005***

How to select the best embryo for transfer

Kersti Lundin
Reproductive Medicine
Sahlgrenska University Hospital
Gothenburg
Sweden



What is "embryo quality"?

How do we define "the best embryo"?

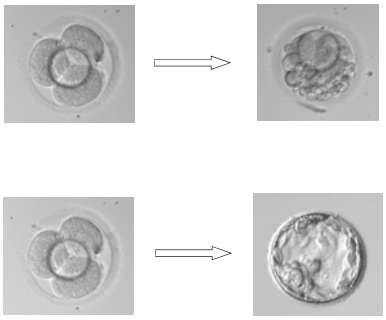
Does embryo quality correlate to embryo scoring?

"Embryo quality" (IVF)

An embryo that has the potential to implant in the uterus and give rise to the birth of a healthy baby

"Success rate" for human embryos

- Morphology day 2/3: ~ 45-60% GQE
- Chromosomal normality ~ 25-30%
- Implantation rates: ⟹ 40-50%
- Births (SET): ⟹ 30-35 %



Embryo development variables
Implantation
Live birth

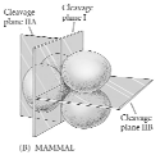
Polarity / symmetry ⇕ Timing / Synchronisation

Nuclear status / cytoplasmic status / metabolic status / environment / chromosomal status

The first cleavages

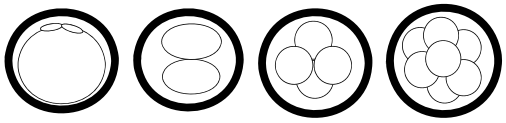
Mammals

- Holoblastic cleavage
- Rotational cleavage



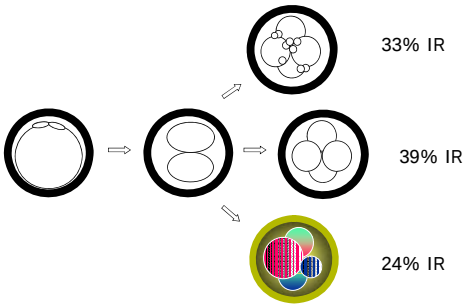
Embryo (a)symmetry

- Each cleavage results in daughter cells with uneven content of transcription factors



- Leptin, STAT3, Bcl-X, TGFb2,...

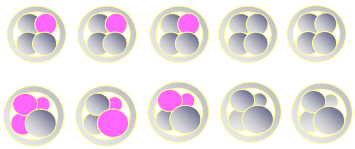
Antzak and Van Blerkom, Human Reprod, 14, 429-447, 1999



Hardarson et al 2001

And the chromosomal status…?

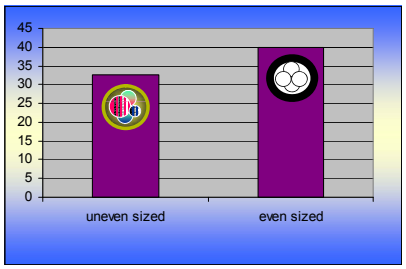
Chromosomes 13, 18, 21, X and Y	Even cleavage	Uneven cleavage	P
Embryo aneuploidy	4/13 (31%)	6/11 (55%)	0.24
Blastomere aneuploidy	4/47 (9%)	10/34 (29%)	0.014



Only GQE

Hardarson et al 2001

Chromosomal normality and blastomere size



Munné et al 2004, 2006

Cell size and multinucleation

Cell size ($\mu m^3 \times 10^6$)	2 cell	4 cell
Mononucleated	0.210	0.118
Multinucleated	0.314	0.203

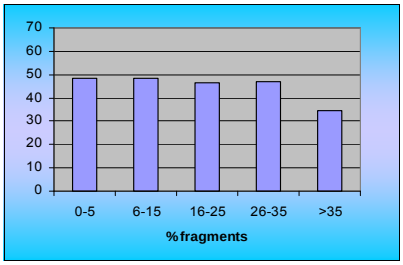
p=<0.001

Hnida et al 2004

Summary; blastomere size

Unequal sized blastomeres (2-, 4-, 8- cells) correlates to aneuploidy, to multinucleation and to lower implantation rates

Chromosomal normality and fragmentation



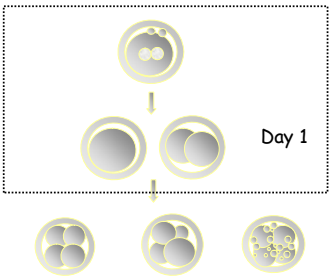
Munné et al 2004, 2006

Summary; embryo fragmentation

- No studies (multivariate) show an independent predictive influence of fragmentation (up to 20 (-30)%) for implantation

Van Royen et al 2001, Munné et al 2004, 2006, Holte 2007

First mitotic cleavage
("early cleavage")



Scoring time
! Medium
Temperature

Early first cleavage and embryo development

	Early	Late
Numbers (%)	3 046 (26.9)	6 749 (73.1)
GQE (%)	1 903 (62.5)	2 593 (33.4)
Numbers (%)	85 (14.7)	494 (85.3)
Blastocysts (%)	19/59 (32.2)	61/367 (16.6)

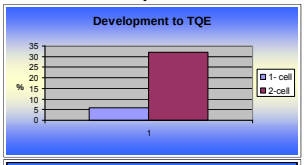
Lundin et al 2001; Fenwick et al 2002

Early first cleavage and ICSI
(25 – 27 h, n =450 cycles)

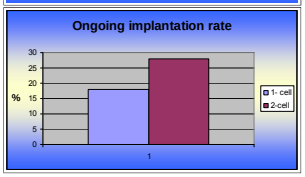
	Pregnancy	Birth
No. GQE	p <0.0001	p <0.0001
Early cleavage	NS	p =0.015

Lundin et al 2001

Early cleavage, embryo development and implantation rates



N= 5648
p=<0.001



N= 448
p=<0.05

Lundin et al, ASRM 2005

More about early (first) cleavage….

- Logistic regression analysis showed that EC is an independent predictor for both pregnancy and blastocyst development in addition to cell morphology and cell number

  Van Montfoort et al 2004
- EEC (even early cleavage) strongly correlated to GQE

  Terriou et al 2007
- EC a putative marker of embryo quality but weak input on clinical pregnancy rate

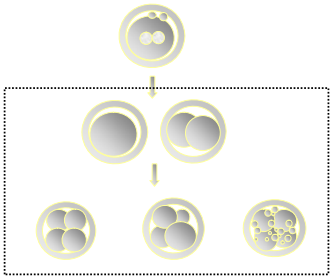
  Rehman et al 2007

Early cleavage and chromosomal errors

- No correlation between time of first cleavage and chromosomal status was found

Ziebe et al 2003

Second mitotic cleavage (time-lapse)



Second mitotic cleavage

(Lemmen et al 2008, time-lapse)

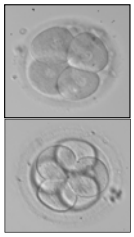
- Synchrony in appearance of nuclei after the first cleavage and second cleavage was significantly associated with pregnancy success ($P < 0.05$).
- IVF embryos more **synchronised** than ICSI?

Summary; early cleavage

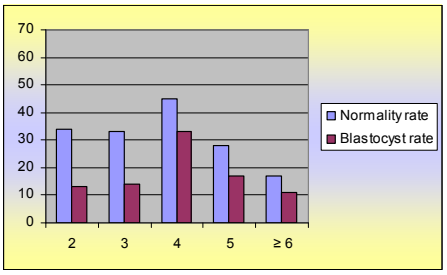
- Correlates to embryo development
  - Good quality embryo
  - Blastocyst development
- Correlates to implantation, pregnancy and birth rates (ICSI)
- Does not correlate to aneuploidy rates

Cleavage rate - number of cells

- van Royen et al, 2002 – day 3
  4 - 8/9 cells: 42% IR
  ≠ 4 – 8/9 cells: <33% IR
- Thurin et al 2005, (SET) – day 2, multicenter study (661 cycles)
  4 cells: 28% IR
  ≠ 4 cells: 16% IR
  (p=0.013)

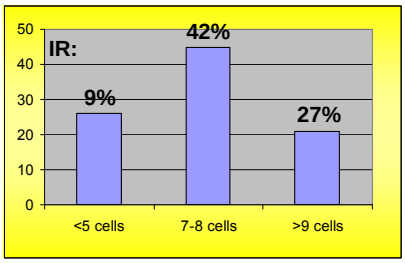


Chromosomal normality and cleavage rate day 2



De los Santos et al ESHRE 2006, 447

Chromosomal normality and cleavage rate day 3

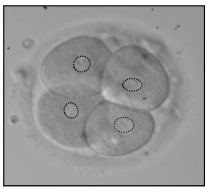


Magli et al 2001, van Royen et al 2002

Summary; number of cells

- Number of cells day 2 and day 3
  - Correlates to blastocyst rates
  - Correlates to pregnancy/implantation rates
  - Correlates to aneuploidy rates

Visible nuclei

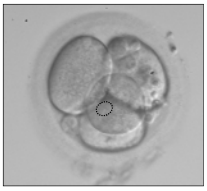


744 embryos
Overall IR 15.5%
Nuclei IR 26.1%
Top embryos with no visible nuclei IR 6.3%

Moriwaki et al 2004

Visible nuclei

4 / 4

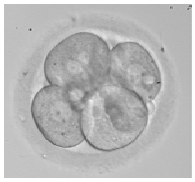


1 (0) / 4

IR 42% IR 22% Saldeen et al 2005
predictive factor (multivariate) Holte et al 2007

Multinucleation

- Associated with lowered pregnancy and implantation rates
- Occurs in ~ 25-50% of embryos on day 2/3
- Decreased incidence in good quality embryos ~ 15%

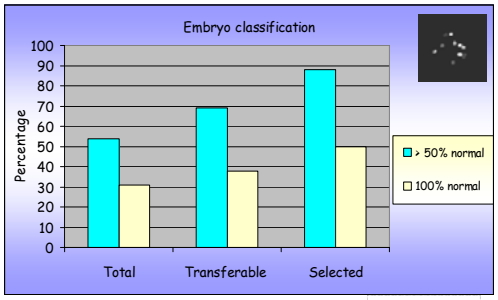


Palmstierna et al 1997, Kligman et al 1996, Jackson et al 1998, van Royen et al 2001, 2003, Hardarson, 2001, Hnida et al 2004

Visible nuclei

- Number of visible single nuclei correlates to implantation rate
- Multinucleation correlates to lowered implantation rates

Chromosomal normality and embryo selection (n=144 embryos)



Ziebe et al 2003,

Can we predict PR/IR/BR from embryo scoring day 2/3?

Multivariate analyses

Independent embryo predictors

- Randomized trial (n=661)
- ”Good prognosis women (<37 years, ≥ 2 GQE)
- Identification of specific maternal and/or embryo variables independently correlated with ongoing implantation in IVF/ICSI
- **Number of cells** independent predictors of ongoing implantation

Thurin et al 2005

Independent embryo predictors

- Retrospective analysis
- 861 SET transfers with a four-cell embryo
- Analysis of multinucleated blastomeres, equal-sized blastomeres and fragmentation
- **Number of mononucleate cells** independent predictors of ongoing implantation
- Blastomere size and fragmentation not predictive

Saldeen and Sundström 2005

An integrated evidence-based model for prediction of implantation

- 2266 double embryo transfers
- Only 100% or 0% implantations assessed
- Numbers of blastomeres, blastomere size and mononuclearity in the blastomeres independent predictors
- Fragmentation no predictor
- Early cleavage not analysed

Holte et al 2007

Thus,

Morphologically ”good quality” embryos are on average genetically more normal than ”poor” quality embryos

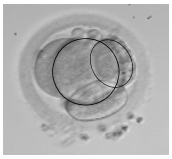
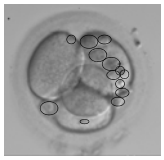
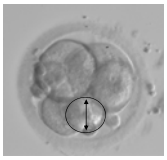
Selection of an day 2/ day 3 embryo with good potential can be performed - to a large extent - according to a number of well defined morphological variables

BUT…..

….. embryo morphology is:

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

Are we scoring the same things?

Uneven size

Grade of fragmentation

Blastomere/fragment

What other variables could we use for selection?

- Blastocyst culture?
- Genetic/chromosomal ”normality”?
- Improved morphology scoring (time-lapse)
- Metabolic ”normality”?
- All or nothing? – or degrees?

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

PGS - FISH

- 11 randomised control trials (embryos) so far (age, poor/good prognosis patients)
- Show no improvement in delivery rates

- Limited number of analysed chromosomes
- High rates of embryo mosaicism
- Poor correlation between results and implantation (*M. Hughes*)
- Invasive

”Metabolic” assessments of the embryo or the surrounding, e.g.:

- Amino acid turnover (non-invasive)
- The ”omics” (invasive / non-invasive)

Take home message

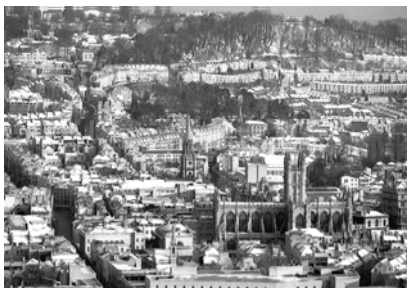
- Embryo selection on day 2 / day 3 should include assessment of:
  - Early cleavage
  - Number of cells (4 / 8)
  - Equality of blastomere size
  - Nuclei
  - Fragmentation

Synchrony!!

Nurses performing embryo transfers in the United Kingdom

Helen Kendrew
Matron/Fertility Services Manager

Bath



Learning objectives

- To understand the embryo transfer procedure
- To assess training needs and competence of staff
- To be able to undertake training
- To become a competent practitioner
- Audit practice
- Maintain a quality service

Bath Fertility Centre

- 2 Consultants
- 2 full time specialist nurses
- 3 part time specialist nurses
- 1 part time support nurse
- 4 embryologists
- 1 trainee
- 1 lab technician
- 4 administrators
- 2 counsellors

Bath Fertility Centre

Treatments

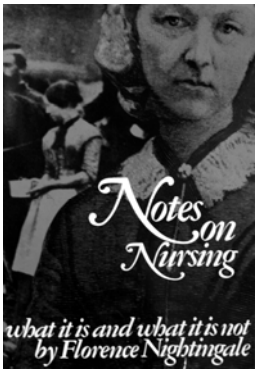
- IVF
- ICSI
- Frozen embryo transfers
- Intra uterine insemination
- Donor insemination
- Egg donation
- Surrogacy

Bath Fertility Centre

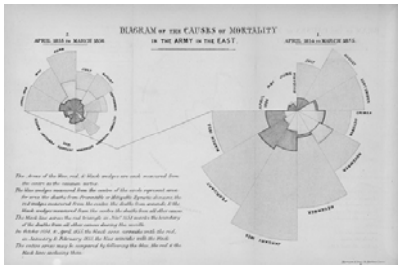
Nurse roles

- Consultations
- Ultrasound scanning – baseline, follicle tracking, pregnancy
- Manage and monitor cycles – timing of HCG
- Oocyte retrieval
- Surgical sperm retrieval
- IUI
- Embryo transfer
- Patient advocacy and support

Bath Fertility Centre



Bath Fertility Centre



Bath Fertility Centre

Professional/personal development

- Mandatory training
- Appraisal
- Personal training plans
- Training and support for new techniques
- Competence
- Nursing and Midwifery council
- Royal college of Nursing
- British Fertility Society

Bath Fertility Centre

Practical Training

- Identify individual need
- Attend a recognised training course
- Study day
- Supervisor/ mentor - observation and support
- Log book
- Laboratory practice
- IUI
- 50 embryo transfers
- Audit of pregnancy rates

Bath Fertility Centre

Relationships

- Clinic staff
- Patients
- Support services
- Directorate
- Director of Nursing
- Chief Executive

Bath Fertility Centre

External relationships

- HFEA
- Care Quality Commission
- Primary Care Trusts
- Department of Health
- Professional Societies – RCN, BFS
- Patient support groups
- General Practitioners
- Media
- NICE

Bath Fertility Centre

Challenges

- Patients expectations
- Doctors roles
- Maintaining standards
- Difficult embryo transfers
- Single embryo transfer
- Vitrification
- Internet

Bath Fertility Centre

Positive outcomes

- Patient pathway
- Clinic activity, appointments
- No delays for patients and staff
- Maintenance of pregnancy rates
- High level of satisfaction for patients and practitioners

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Maintaining standards

- Individual portfolios for all professional development
- Embryo transfer logs - maintain skills 50 ET
- Key performance indicators - 40% pregnancy rate
- Regular audit of practice – Senior team and individual performance

Bath Fertility Centre

Dealing with poor performance

- Audit
- Analysis
- Observation of practice against the Standard Operating Procedure
- Observing each other
- Laboratory training
- Retraining

Bath Fertility Centre

May 2009 – May 2010

All ETs			Pts <38, excl day 2 ETs		
No. ET	No. pos	% pos	No. ET	No. pos	% pos
103	52	50.5%	59	35	59.3%
32	13	40.6%	11	6	54.5%
97	36	37.1%	47	25	53.2%
95	36	37.9%	50	20	40.0%
97	30	30.9%	51	22	43.1%
12	4	33.3%	6	2	33.3%
12	4	33.3%	5	3	60.0%

Bath Fertility Centre

Business planning

- Activity
- Income generation
- New services
- Impact on workforce
- Redefining of roles

Bath Fertility Centre

Bath Fertility Centre

Bath Fertility Centre

Chelsea and Westminster Hospital NHS
NHS Foundation Trust

The Myths of Embryo Transfer

Rebecca Goulding RGN BA Hons
Senior Fertility Sister

Chelsea Westminster Hospital NHS Foundation Trust
London United Kingdom

Introduction

- ~ 85% embryos fail to implant *(Edwards, 1995)*
- ET technique
- Factors affecting success of ET:
  - Blood
  - Mucus
  - Bacterial contamination of ET catheter
  - Excessive uterine contractions
  - Ultrasound guidance
  - Use of soft vs. hard ET catheter

Learning Objectives

- Ultrasound Guidance
- Position of the catheter tip
- Acupuncture
- Bed rest post embryo transfer

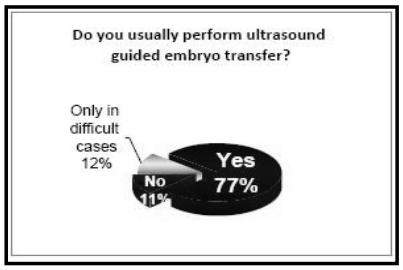
Ultrasound Guidance

- Ultrasound vs. clinical touch
- Clinical touch = unreliable *(Woolcott, 1997)*
- Ultrasound = increased PR *(Buckett, 2003)*

•"Women undergoing in vitro fertilisation treatment should be offered ultrasound guided embryo transfer as it can help to improve pregnancy rates"

National Institute for Clinical Excellence (2004) Assessment and treatment for people with fertility problems. London: NICE.

Ultrasound Guided Embryo Transfer I



www.ivf-worldwide.com

Advantages of Ultrasound Guided Embryo Transfer II

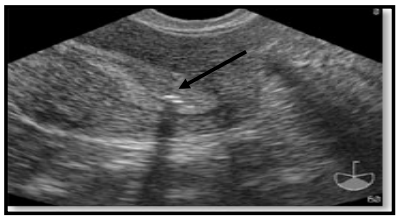
- Identification of complications – OHSS
- Excess fluid in the endometrial cavity
- Embryo retention in catheter *(Awonuga, 1998)*
- Check endometrial thickness (>5mm lower PR) *(Bassil, 2001)*

Advantages of Ultrasound Guided Embryo Transfer III

- Length of cervical canal
- Orientation/straightening of the uterus - full bladder (Bassil, 2001)
- Optimum positioning of the catheter (Mansour, 2002)
- Patient reassurance

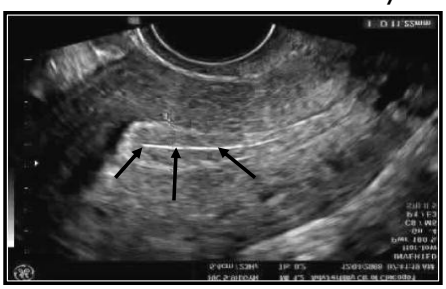
Advantages of Ultrasound Guided Embryo Transfer IV

- Ultrasound image showing the echogenic flash post ET



Position of the Catheter Tip I

Location in the endometrial cavity:



Position of the Catheter Tip II Study One

- Retrospective analysis - 699 ET
- Post ET - Cavity length - CL
- Depth of Catheter insertion – DCI
- The distance from the fundus – TDF
- TDF = CL – DCI
- Distance ≤ 0mm from fundus reduced PR and increased ectopic

Pope et al, 2004

Position of the Catheter Tip II Study One- Results

- Optimal distance of >1mm within the upper cavity
- No comparison between upper vs. lower
- Increased pregnancy rates if the TDF was >5mm

Pope et al, 2004

Position of Catheter Tip III Study Two

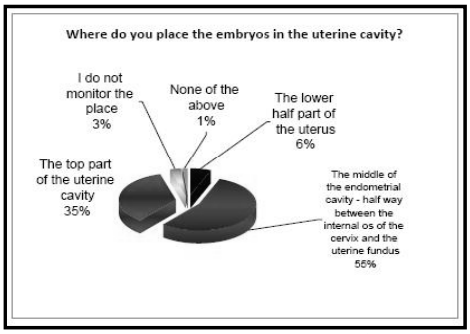
- PR in ET between upper and lower part of uterine cavity
- Prospective Randomised controlled trial
- 400 embryo transfers
- No statistical difference between the two groups

Franco et al, 2004

Position of the Catheter Tip Summary of Two Studies

- Optimum transfer position 1mm – 20mm from the fundus
- Reduce ectopic pregnancies

Position of the Catheter VI



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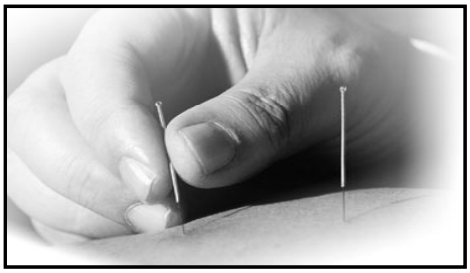
Acupuncture I



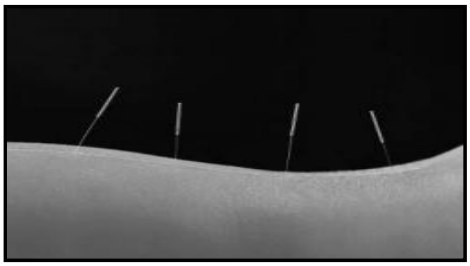
Acupuncture II

- Systematic review and meta-analysis of acupuncture in IVF
- 13 trials, 2500 women
- Acupuncture vs. Control group
- CPR and LBR

(El-Toukhy, 2008)

Acupuncture III

Insufficient evidence



Bed Rest Post Embryo Transfer I

www.Life.com

Bed Rest Post ET II

•Prospective Study

• Ultrasound to detect movement of embryo associated air bubble post ET

•101 ET's reviewed

• No movement occurred in 94.1% cases

• Movement > 1-5 cm in 6% of cases

Woolcot et al, 1998

Bed Rest Post ET III

• Prospective randomised trial

• 180 ET's allocated to two groups:

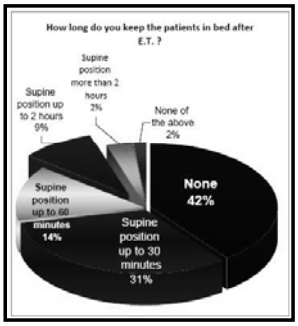
➢Groupone 24 hour bed rest

➢ Group two 20 minute bed rest

• No statistical difference in PR, IR or miscarriage rates between the two groups

Botta et al, 1997

Bed Rest Post ET VI



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Bed Rest Post ET V

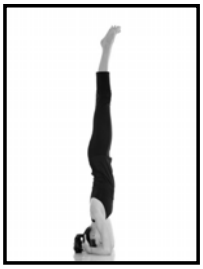
Bed Rest Post ET VI

•Reduce anxiety

•Reduce stress

• Psychosocial support

• Evidence



Summary

• Ultrasound guidance is advisable

• Optimum transfer position 1mm – 20mm from the fundus

• ET catheter should not touch the fundus

Summary

- Insufficient evidence acupuncture improves IVF CPR and LBR
- No evidence to support bed rest post embryo transfer improves PR

Chelsea and Westminster Hospital NHS
NHS Foundation Trust

Thank you

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Woolcott, R, Stranger, J (1998) Ultrasound tracking of the movement of embryo associated air bubbles on standing after transfer. Human reproduction 13 (8) 2107-2109

Woolcott, R, Stranger, J (1997) Potentially important variables identified by transvaginal ultrasound-guided embryo transfer. Human Reproduction 12 (5) 963-966

What to do with non selected embryos?

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Faculty of Health Science, University of Copenhagen,
Copenhagen, Denmark

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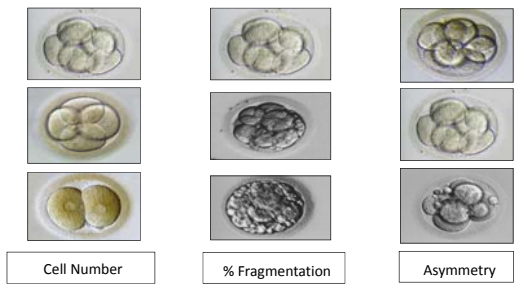
27th Annual Meeting – ESHRE 2011 – Stockholm, Sweden, 3-6 July 2011
Paramedical Group – Pre-congress course 3 July 2011

Content

- Selection of embryos for transfer and discarding embryos
- Developmental potential of discarded embryos
- Use of discarded embryos for deriving human embryonic stem cells
- Characteristics of human embryonic stem cells
- Regenerative medicine and its perspectives

Traditional Morphological Evaluation



Cell Number | % Fragmentation | Asymmetry

Why do some embryos not get selected?

- They are not considered fit!
- Poor morphology
- Asymetric blastomer size
- Is not likely to survive cryopreservation
- Multinucleated

No uniformly accepted selection criteria has been developed

Selection of embryos for transfer

- Lucinda Veeck, Cornell, New York, USA

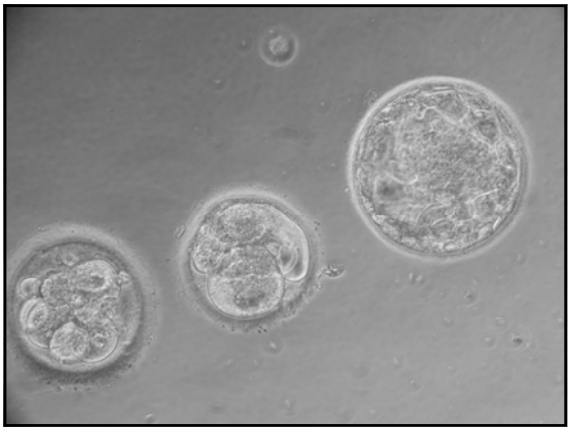
"Although embryo grading systems may furnish clues which enhance our proficiency at choosing the best pre-embryos for transfer, these systems are severely limited in their ability to provide undisputable evidence for subsequent normal development.
Thus, selection during very early preembryonic development remains, at least for the time being, a somewhat random exercise "

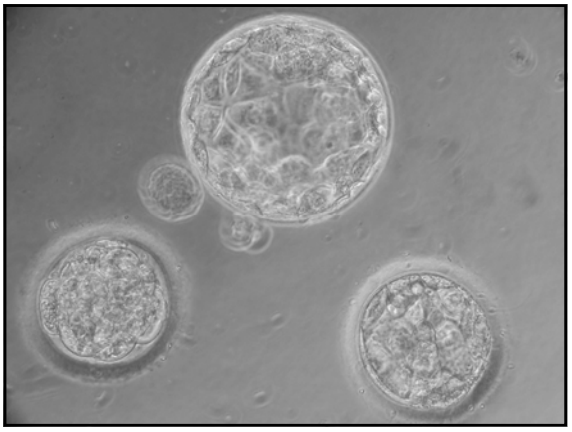
- David Gardner,

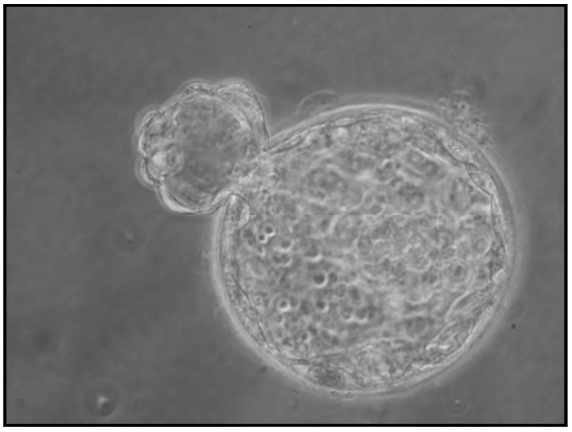
"It is true to say that more than 20 years of research on human embryo development has failed to provide a reliable, cost-effective and efficient predictive test of embryo viability"

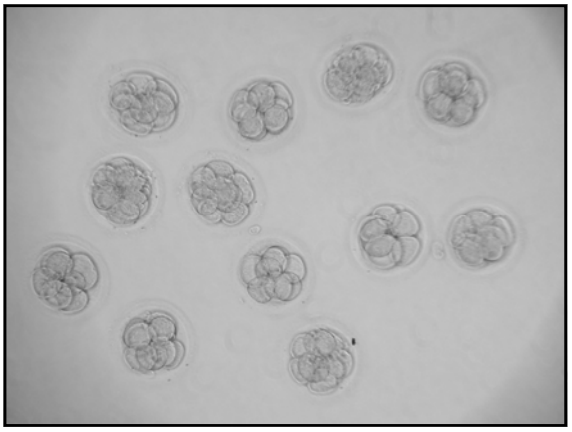
Does this lead to mistakes and discarding of good embryos

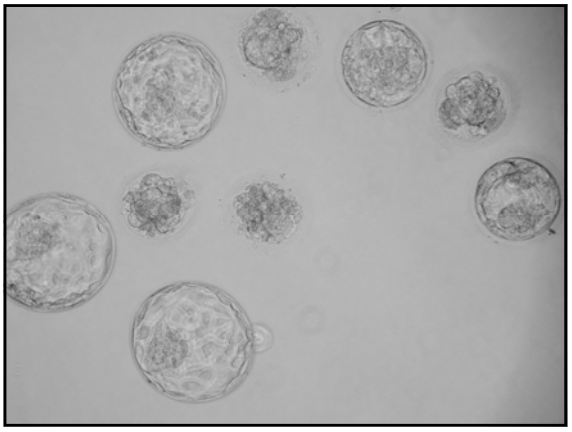
- Yes, it does – indeed
- Of course this is good for the researcher
- But if I were a patient, I would ask the laboratory to culture my embryos to the blastocyst stage and cryopreserve those with a nice innercell mass

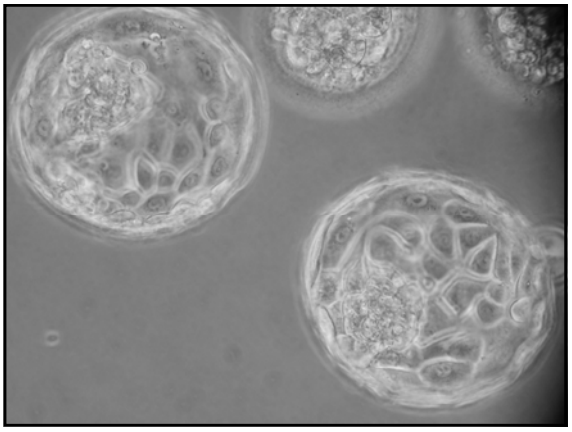


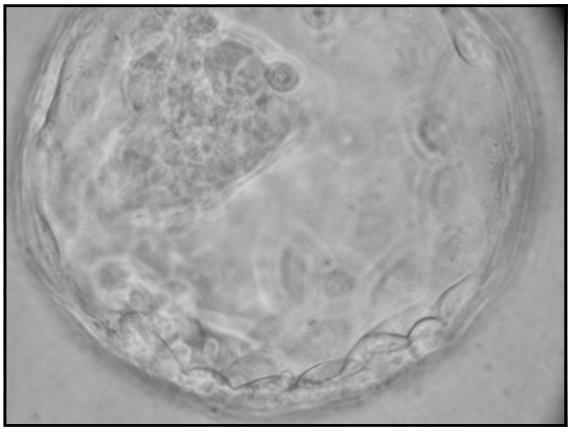




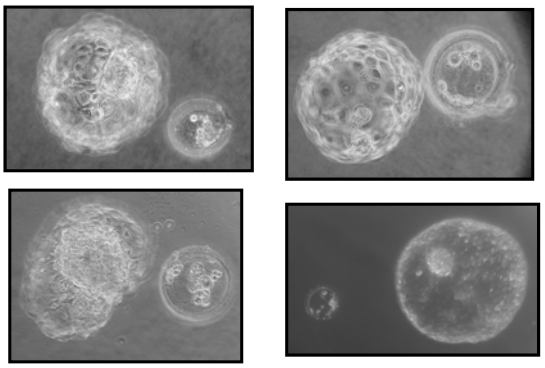






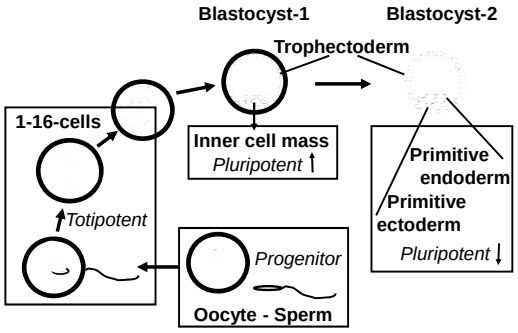


Hatched human blastocysts

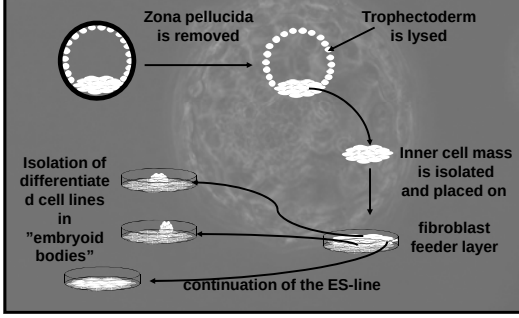


Derivation of human embryonic stem cells from surplus embryos obtianed from IVF patients

Embryonic stem cell lines,"ES"- cell



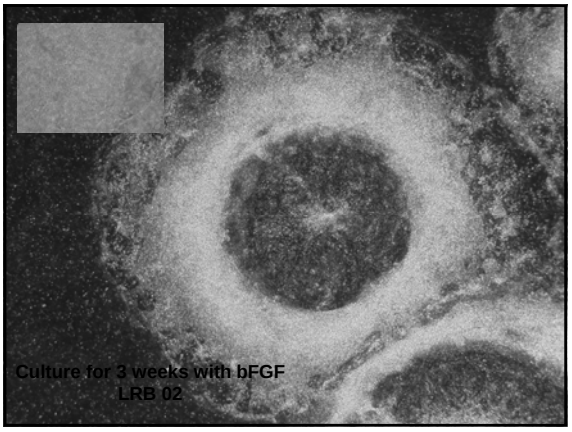
Establishment of "ES" cell lines, *in vitro*



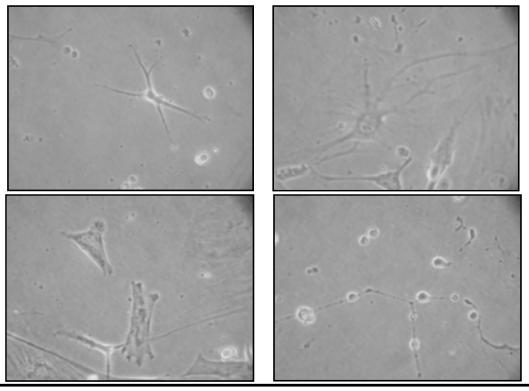
Human Embryonic Stem Cell Line established at Rigshospitalet February 2005

The first human embryonic stem cell line established at Rigshospitalet February 2005

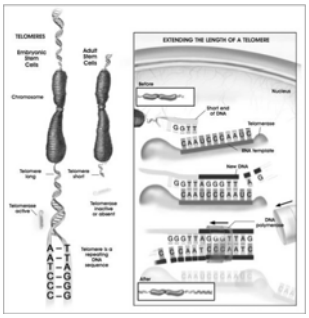
- Currently 11 different hESC lines have been created at LRB
- In Denmark a total of 21 hESC lines
- Around 400 hESC lines globally



Spontaneous differentiation of hES cell during culture

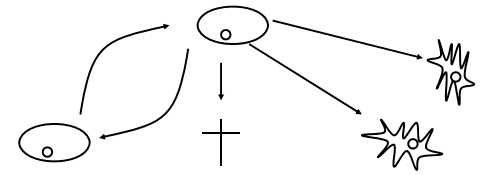


Why ES cells doesn't grow old - Telomerase



Stem cells - definitions

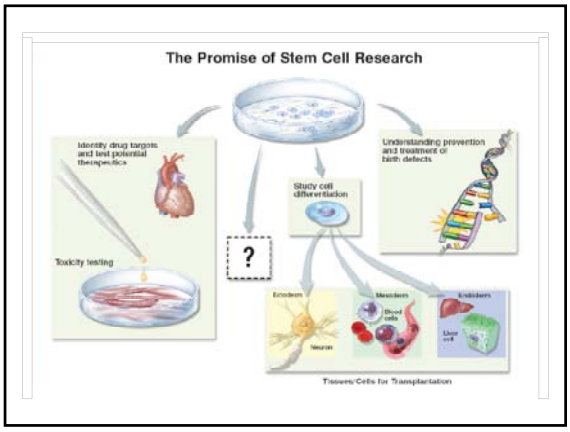
- **Unspecialised cells**
- **They can remain in the undifferentiated for a long time**
- **They can turn into specialised celltypes**



Self-renewal Apoptosis Differentiation

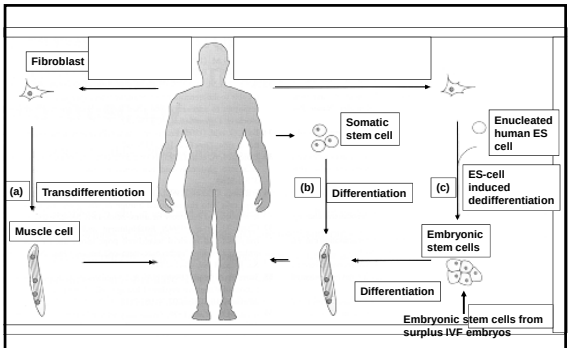
Stem cells – different types

- **Embryonic:**
  Cells isolated from an embryo (a blastocyst)
- **Adult or mesenchymal:**
  Bone marrow, peripheral blood or umbilical cord blood
- **Germ cell:**
  From the early stages of a fetus



Characteristics of pluripotent hESC

- Expression of surface markers and transcription factors associated with an undifferentiated state
- Their capacity to differentiate
- Extended proliferative capacity
- Normal karyotype (also over time)



Strategies for stem cell based treatments

Possible therapeutical areas

NIH suggested areas of use:

Neurological disorders (Parkinson, Alzheimer, Spinal cord injury, multipel sclerose)

Diabetes

Coronary heart infact

Liver diseases

Kidney diseases

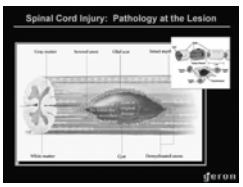
Diseases of the blood

Visual function

and several more rare diseases

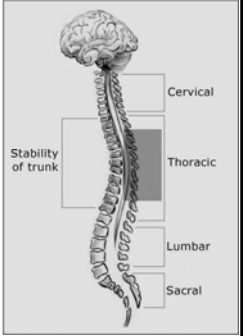
VIDEO OF RAT WITH SPINAL CORD INJURY

Data from Geron a US based biotech company



GRNOPC1 Phase 1 Multi-Center Spinal Cord Injury Trial

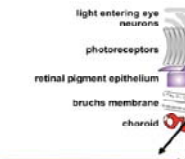
- **Open Label Trial**
- **Subacute, Functionally Complete Spinal Cord Injury with a Neurological Level of T3 to T10**
- **$2x10^6$ Cells**
- **Transplant 7-14 Days Post Injury**
- **Temporary Immunosuppression with Low Dose Tacrolimus**
- **Primary Endpoint: Safety**
  - *Neurological*
  - *Overall*
- **Secondary Endpoint: Efficacy**
  - *ASIA Sensory Score*
  - *Lower Extremity Motor Score*



RPE Cell Function

RPE

Layer Deteriorates in Patients with AMD and other Retinal Degenerative Diseases



hES derived RPE cells

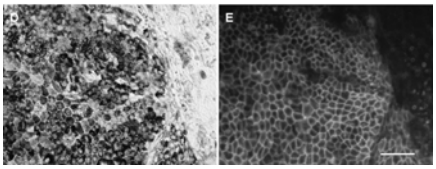
- Pigmented cells
- Allow for direct selection
- Adhere to Bruchs membrane
- Phagocytose shed photoreceptor segments
- Produce trophic factors

14

ADVANCED CELL TECHNOLOGY

Human Embryonic Stem Cell–Derived Cells Rescue Visual Function in Dystrophic RCS Rats

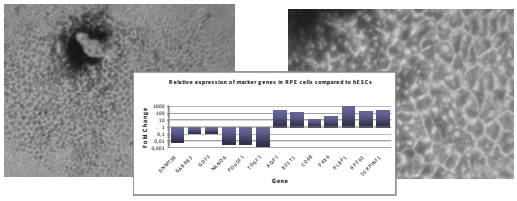
Retinal pigment epithelium

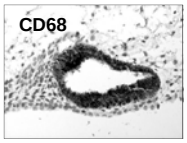


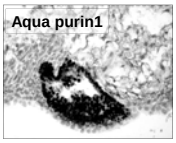
- **Reproducible regeneration for more than 67 passages**
- **Rats with photoreceptor loss improved visual function in 100 % of the cases**
- **Without evidence of ontoward pathology**
- **RPE dysfunction affects more than 30 millions worldwide and is the leading course of blindness in people over the age of 60 in the US**
- **Approximately 15% of people over 75 years of age have the condition**
- **A $28 billion dollar market**

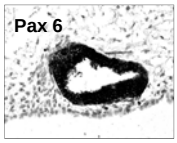
Lund RD; *Cloning and stem cells*, 2006,8,16

Retinal pigment epithelium at Laboratory of Reproductive Biology





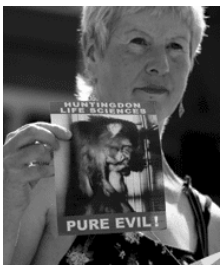




Other potentail applications

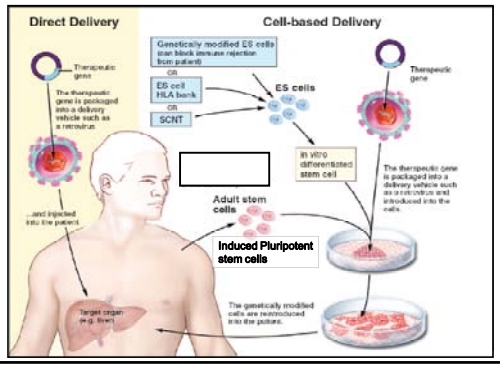
- Unlimited production of Red Blood Cells and other types of blood cells
- Insulin producing cells
- Cardiomyocytes

Human ESC may be toxicology's new best friends



- Avoids the use of animals
- Existing toxicity testing using human or animal cell lines often poorly reflect human physiology.
- Animal-rights protests have motivated toxicology research with hES cells
- EU is considering toxicity testing of some 30.000 existing chemicals

Targeted genetherapy – a future option



Comment in an American newspaper to the current financial crisis

- **A number of surplus embryos have a developmental potential**
- **They can be used for research purposes**
- **Development of human embryonic stem cells**
- **That has immense potential for regenerative medicine**

Performing Embryo Transfer

Dr. Bea Lintsen, Fertility-physician
Radboud University Nijmegen Medical Centre
The Netherlands

Inserting a catheter atraumatic and standardized

Steps, Tips and Tricks

IVF in the Netherlands

13 IVF centres
70 IVF transport clinics

Radboud UMCNijmegen
1500 OPU / year
2000 ET / year (+ cryo-ET)
3 fertility physicians
3 fertility gynaecologists (weekends)

IVF in the Netherlands

Success rates, lifestyle, psychological factors and costs

A.M.E. Lintsen

Thesis on prognostic factors in IVF treatment (2010)

Performing Embryo Transfer **Material**

- Three people: P1,2,3
- Vaginal speculum
- Gauzes, steril water
- Abdominal ultrasound
- Catheter, obturator

- P1. vaginal speculum (doctor?)
- P2. abdominal ultrasound (nurse?)
- P3. standardize the amount of fluid in the catheter and press syringe (labspecialist)

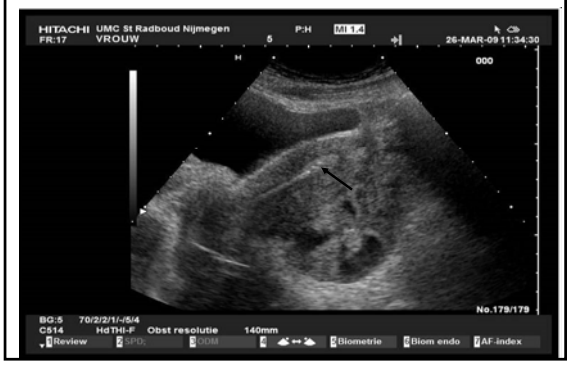
Performing Embryo Transfer **Conditions**

- Full bladder
- Keep the embryo warm
- Get acquainted with one transfer catheter
- Use the stiffer outer catheter when necessary
- Minimize the amount of fluid in the catheter

Performing Embryo Transfer
Steps

- Insert speculum
- Swipe away the progesteronwaste/mucus
- Position uterus: anteversion or retro flexion
- Insert loaded catheter
- Feel the outer catheter goes just through internal ostium.
- Watch the monitor (confirm the touch)
- End of the catheter in the middle of the endometrial plate
- Press syringe (labspecialist)

The embryo lies between two airbubles in middle of the endometrial plate



Performing Embryo Transfer
Tips and Tricks

- When you feel resistance at the internal ostium
- Use a stiffer outer catheter without the embryo (obturator), bend the end (metal stylet)
- Insert obturator until just through internal ostium, take stylet out.
- Inner catheter (with embryo) can follow through
- Watch the monitor (confirm)
- End of catheter in the middle of the endometrial plate
- Press syringe

Performing Embryo Transfer
Tips and Tricks:

- When obturator does not go through the internal ostium.
- Change the curve of the tip
- Change the position of the speculum
- Change the position of the patient
- Distract the patient
- Be patient
- Reassure you, or somebody else will succeed

Mark your calendar for the upcoming ESHRE campus workshops!

- Early pregnancy disorders: integrating clinical, immunological and epidemiological aspects
  23-26 August 2011 - Copenhagen, Denmark
- The management of infertility – training workshop for junior doctors, paramedicals and embryologists
  7-8 September 2011 - St. Petersburg, Russia
- Basic genetics for ART practitioners
  9 September 2011 - Bucharest, Romania
- The whole man
  22-23 September 2011 - Sevilla, Spain
- Accreditation of a Preimplantation Genetic Diagnosis Laboratory
  3-4 October 2011 - Athens, Greece
- Human reproductive tissues, gametes and embryos: Innovations by science-driven culture and preservation systems
  9 October 2011 - Cairns, Australia
- Comprehensive preimplantation screening: dynamics and ethics
  13-14 October 2011 - Maastricht, The Netherlands
- Endometriosis and IVF
  28-29 October 2011 - Rome, Italy
- Endoscopy in reproductive medicine
  23-25 November 2011 - Leuven, Belgium
- What you always wanted to know about polycystic ovary syndrome
  8-10 December 2011 - Sofia, Bulgaria

www.eshre.eu
(see "Calendar")

Contact us at info@eshre.eu

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