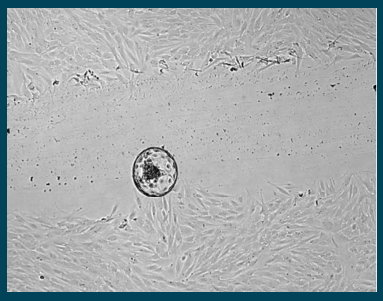

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Aneuploidies: the uterus' point of view

Nick Macklon
Professor of Obstetrics and Gynaecology, University of Copenhagen (Roskilde) and University of Southampton, UK.

complete FERTILITY CENTRE SOUTHAMPTON · University of Southampton · Region Sjælland – vi er til for dig · University of Copenhagen

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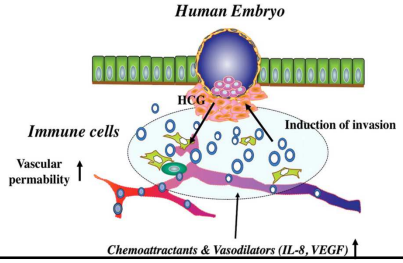
'Receptive' endometrium: implying a passive role in implantation

- *Allows* the embryo to *adhere*, before it

breaches the epithilium and *invades* the stroma.....



Mother has a problem...

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The frequency of meiotic errors is high in the human

Yeast	< 1%
C. elegans	< 1%
Drosophila	< 1%
Mouse	2%
Human	**10 - 50%**

...and she is dealing with it.

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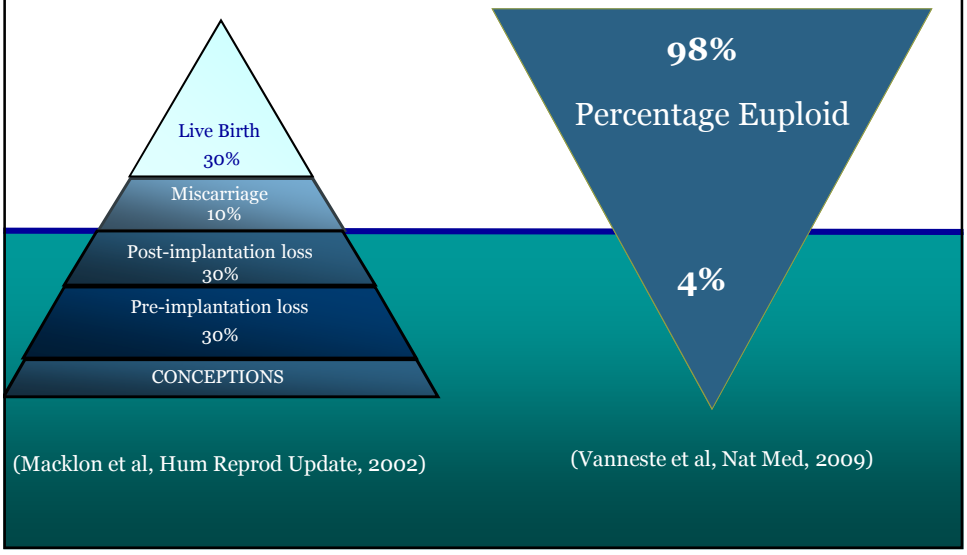

(Macklon et al, Hum Reprod Update, 2002)

(Vanneste et al, Nat Med, 2009)

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How is mother dealing with the challenge of aneuploid but invasive embryos?

The endometrium as a biosensor

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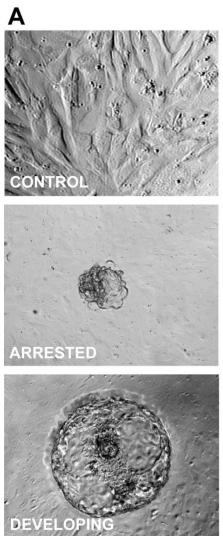
Decidualised stromal cells recognize the incompetent embryo



Teklenburg et al, 2010

Decidualised stromal cells recognize the incompetent embryo

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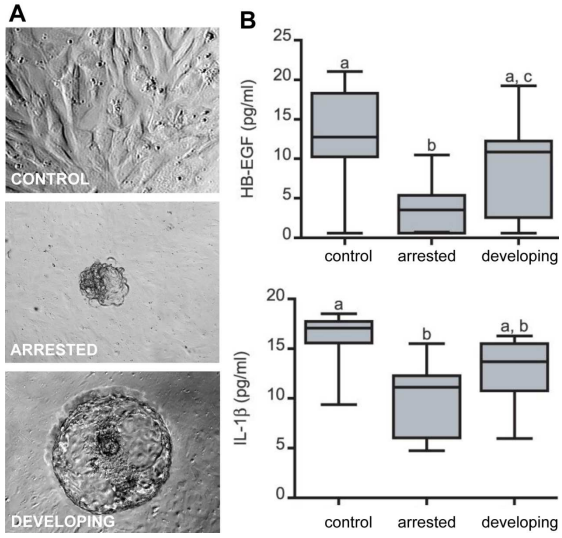
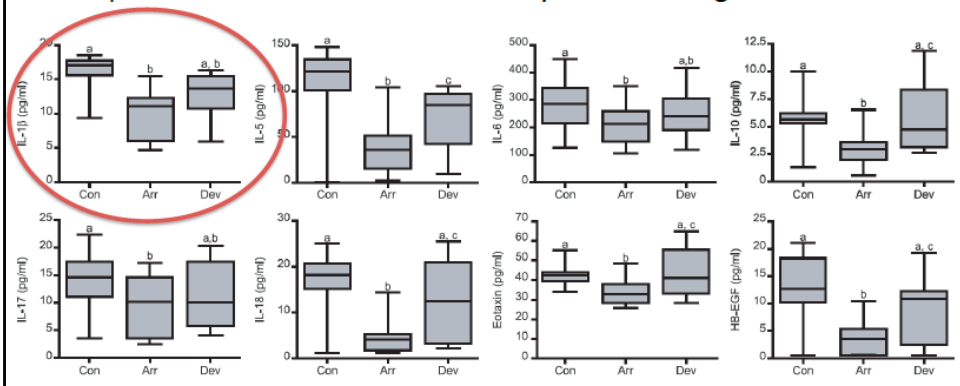


Teklenburg et al, 2010

Decidual cell response to arresting vs. developing embryos

Developmentally impaired embryos (DIE) inhibit selective implantation modulator secretion by decidualising ESCs



Teklenburg G et al. PLoS ONE: April 2010; e10258

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The non-decidualised endomterium:no response

Natural Human Embryo Selection

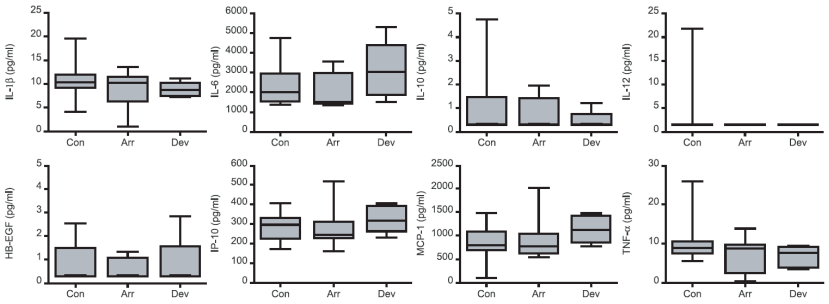

Figure 4. The human embryo does not elicit a secretory response in undifferentiated endometrium. Undifferentiated primary ESCs were co-cultured with embryos or not (control cultures, Con). Over the 72-hour co-culture period, 15 embryos arrested (Arr) whereas 6 continued to develop normally (Dev). Co-culture with either an arrested or developing embryo had no impact on the secreted levels of the indicated factors ($P>0.05$). The concentrations of IL-5, -12, -15, -17, -18, and eotaxin in culture supernatants of undifferentiated ESCs were below the level of detection.
doi:10.1371/journal.pone.0010258.g004

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Is mother listening out for a distress signal?

The incompetent embryo is noisy.

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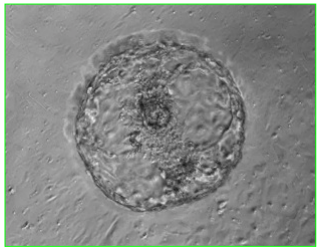
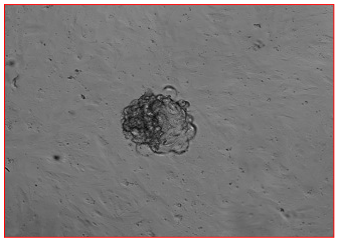


The viable embryo:
Metabolically QUIET

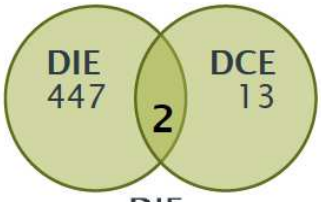


Less viable embryo:
Metabolically NOISY

Competent embryos contain **less** mitochondrial DNA
Fragouli et al PLoS Genetics 2015
Diaz et al Fertility Sterility 2015

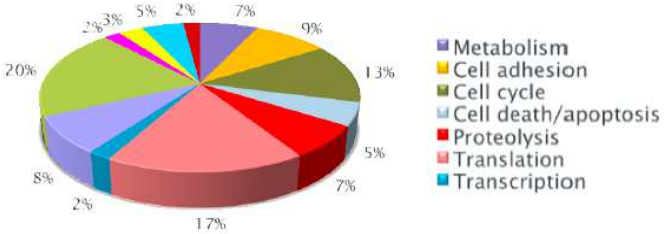
DIEs trigger far greater transcriptional response than DCEs

Developmentally impaired embryos



Developmentally competent embryos

DIE



PCR, polymerase chain reaction

Brosens et al 2014 SCIENCE Report

How does the endometrium recognize the incompetent embryo?

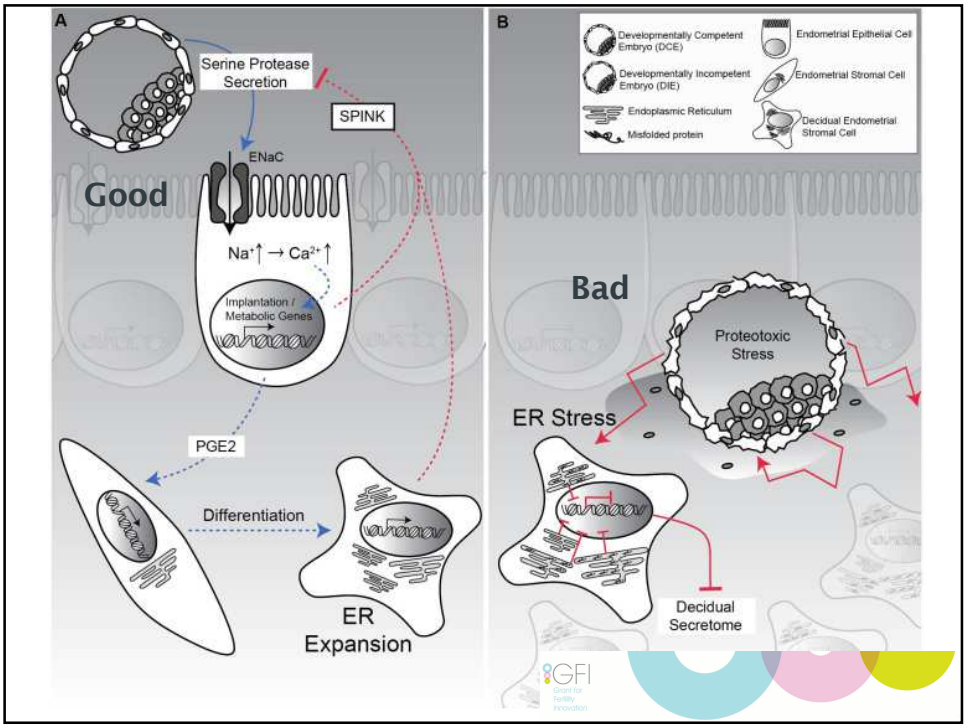
OPEN

Uterine Selection of Human Embryos at Implantation

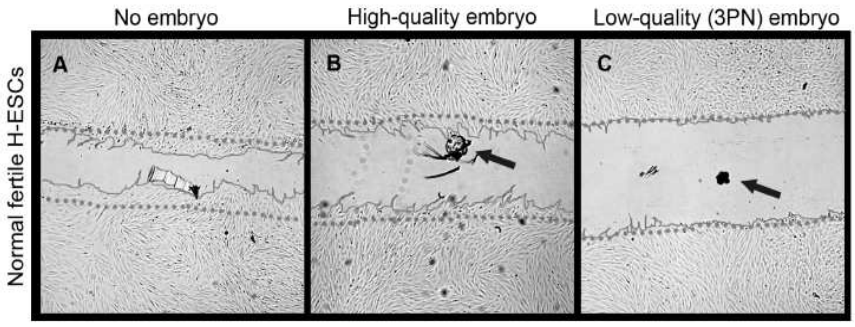
SUBJECT AREAS:
REPRODUCTIVE BIOLOGY
EMBRYOLOGY

Received
2 October 2013

Jan J. Brosens[1], Madhuri S. Salker[1,2], Gijs Teklenburg[3], Jaya Nautiyal[2], Scarlett Salter[1], Emma S. Lucas[1], Jennifer H. Steel[2], Mark Christian[1], Yi-Wah Chan[4], Carolien M. Boomsma[3], Jonathan D. Moore[4], Geraldine M. Hartshorne[1], Sandra Šućurović[5], Biserka Mulac-Jericevic[5], Cobi J. Heijnen[3], Siobhan Quenby[1], Marian J. Groot Koerkamp[6], Frank C. P. Holstege[6], Anatoly Shmygol[1] & Nick S. Macklon[3,7]



Stromal cells don't migrate to low quality embryos



Weimar C et al. PLoS ONE: July 2012; e41424

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What if mother does not respond to these signals?

What if she is not choosy enough?

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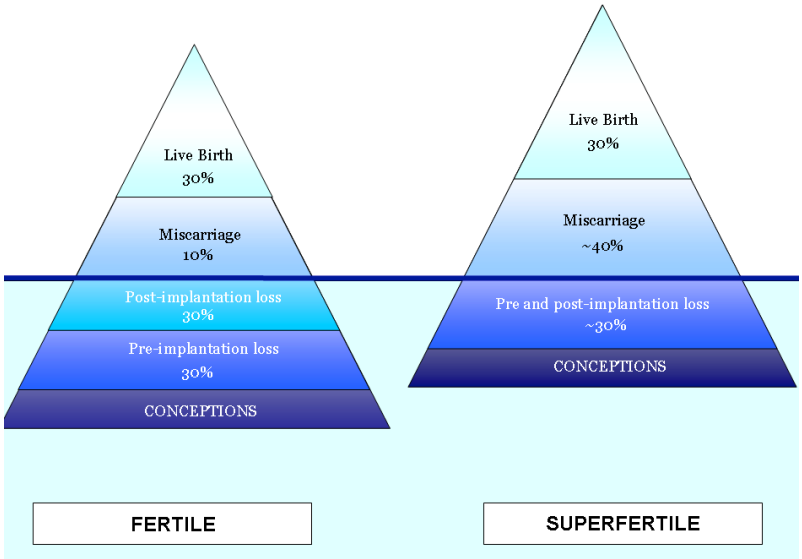
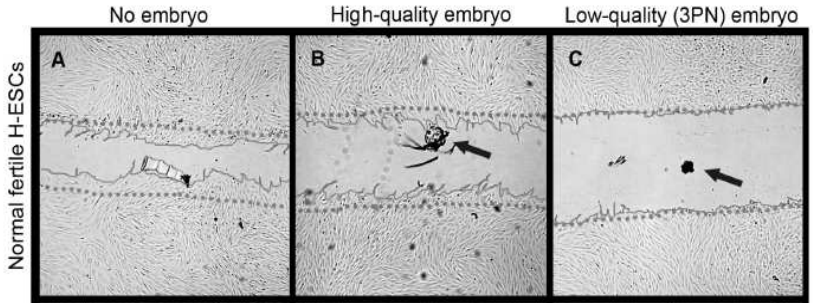
The less choosy mother will experience more miscarriages.

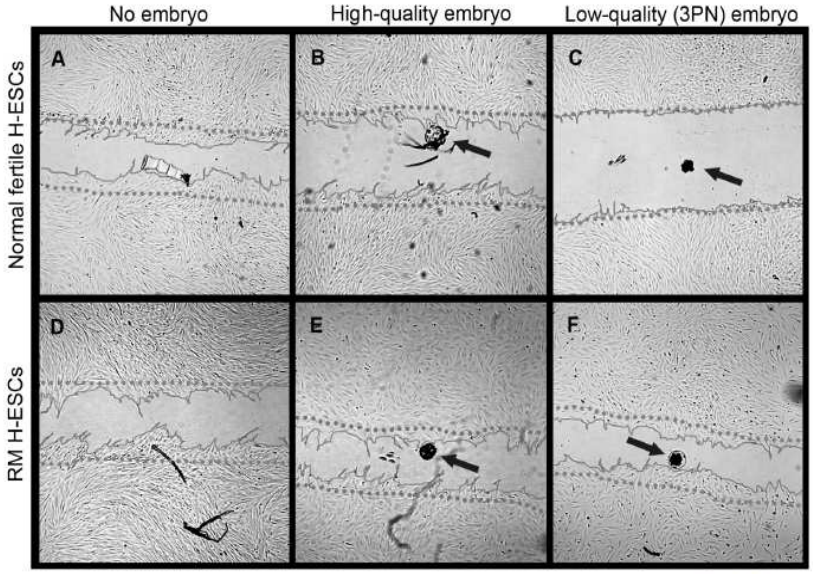


Endometrial stromal cells of women with RPL *do* migrate to low quality embryos



Weimar C et al. PLoS ONE: July 2012; e41424

Endometrial stromal cells of women with RPL *do* migrate to low quality embryos



Weimar C et al. PLoS ONE: July 2012; e41424

Implantation failure arises from excessive selectivity?

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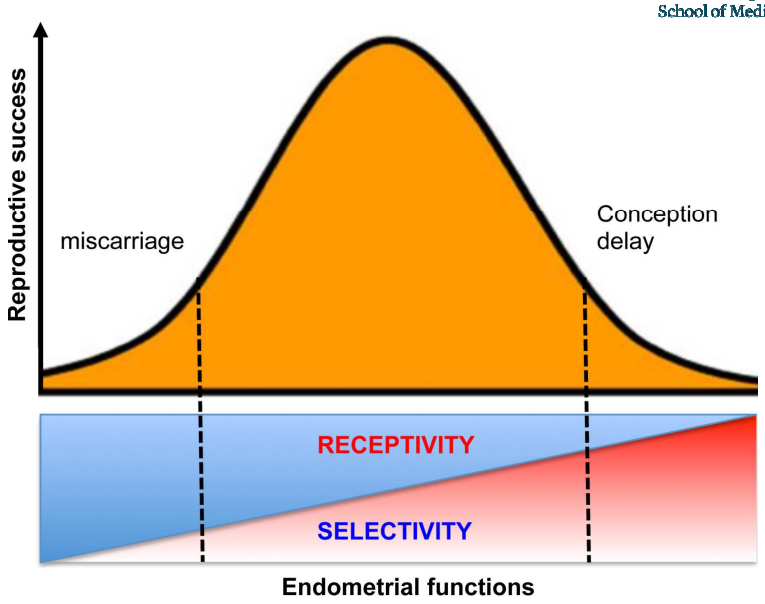

Macklon and Brosens, Biol Reprod 2014

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BIOLOGY OF REPRODUCTION (2014) **91**(4):98, 1–8
Published online before print 3 September 2014.
DOI 10.1095/biolreprod.114.122846

Minireview

The Human Endometrium as a Sensor of Embryo Quality[1]

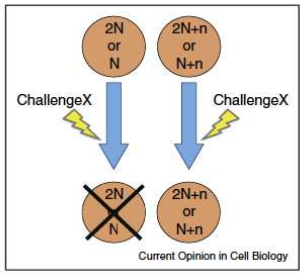
Nick S. Macklon[2,3] and Jan J. Brosens[4]

Why are human embryos so often aneuploid?

Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Cell Biology

Consequences of aneuploidy in sickness and in health

Samuel D Rutledge and Daniela Cimini



- Can confer a selective advantage under stressful environmental conditions
- Overexpression of specific genes may allow for rapid evolution of advantageous phenotypic traits (eg: hepatocytes)
- May confer invasiveness

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Were you euploid?

nature COMMUNICATIONS

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ARTICLE

Received 10 Jun 2015 | Accepted 26 Feb 2016 | Published 29 Mar 2016

DOI: 10.1038/ncomms11165 OPEN

Mouse model of chromosome mosaicism reveals lineage-specific depletion of aneuploid cells and normal developmental potential

Helen Bolton[1], Sarah J.L. Graham[1], Niels Van der Aa[2], Parveen Kumar[2], Koen Theunis[2], Elia Fernandez Gallardo[2], Thierry Voet[2,3] & Magdalena Zernicka-Goetz[1]

Professor Magdalena Zernicka-Goetz underwent a standard test that showed 25 per cent of the cells in her developing embryo could be abnormal

Are tests for Down's syndrome needlessly alarming women into abortions? Cambridge University don warns tests can mislead after she had a healthy boy at 44

- Abnormalities detected in early embryos are not a sure sign a baby will be born with a birth defect, University of Cambridge scientists suggest
- New research shows abnormal cells can be eliminated and replaced by healthy cells, repairing and fixing the embryo in many cases
- Each cell in human embryo should contain 23 pairs of chromosomes
- Some will carry multiple copies of chromosomes, which cause defects
- For example, multiple copies of chromosome 21 leads to Down's syndrome
- Even when half cells in an embryo are 'abnormal' in early stages, the embryo has an 'amazing' ability to correct itself

By COLIN FERNANDEZ FOR THE DAILY MAIL and LIZZIE PARRY FOR DAILYMAIL.COM

Conclusions

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- The mother has a problem: aneuploid but invasive embryos
- She is dealing with it: evidence is emerging for a biosensor function of the decidualized endometrium.
- When the biosensor fails, implantation failure or miscarriage may arise.
- Greater understanding of active endometrial participation in determining successful implantation can lead to novel therapies.
- PGS might help. A bit.

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The uterine point of view:
Find me a nice partner.
They dont have to be perfect..

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Bart Fauser

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Jan Brosens

Xiao Shilong
Hywel Morgan
Ying Cheong

Morten Petersen
Soeren Ziebe
Sven Skouby
Thomas Hvidd