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The Selective Endometrium

A new paradigm for understanding implantation

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complete™ FERTILITY CENTRE SOUTHAMPTON

Southampton NHS
University Hospitals NHS Trust

Implantation after IVF

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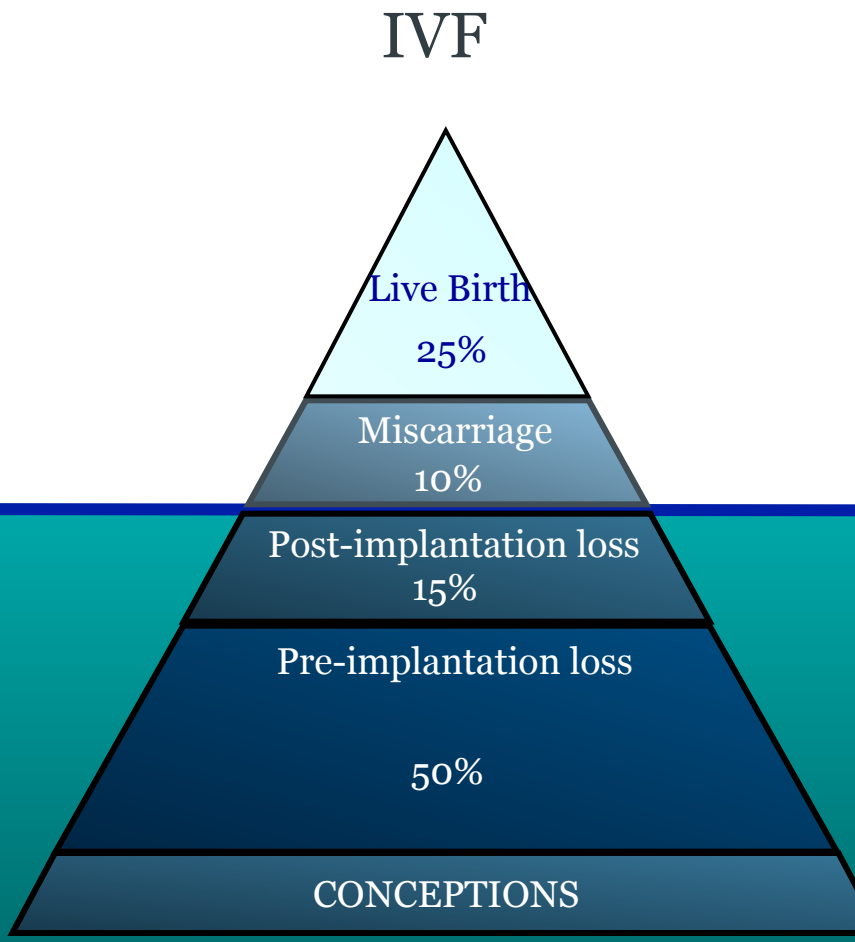

(Boomsma et al,
Hum Reprod , 2009)

The Bigger Picture

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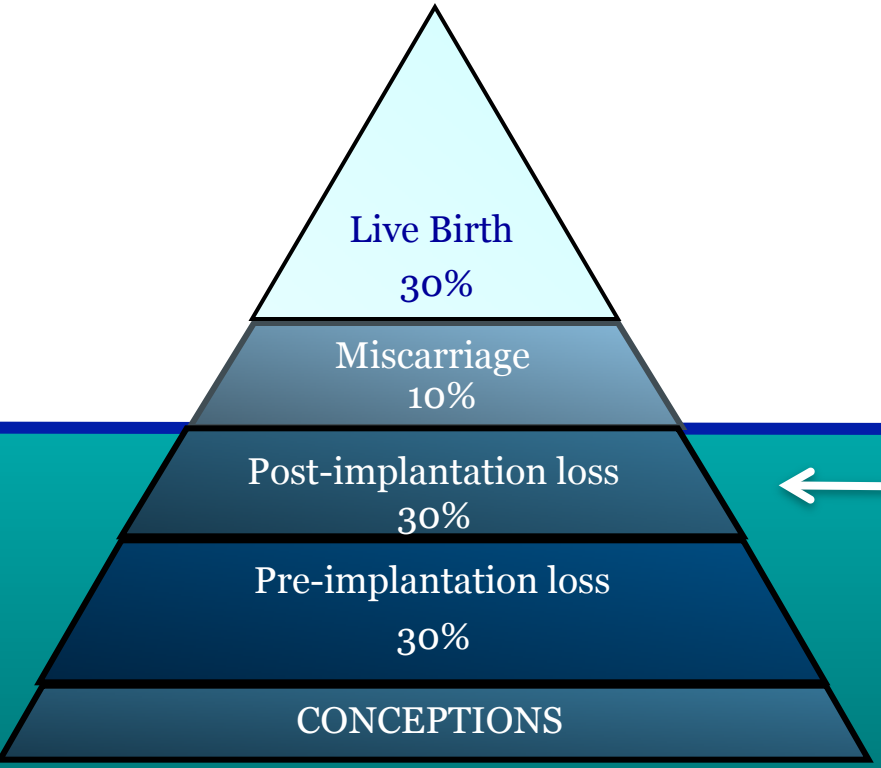
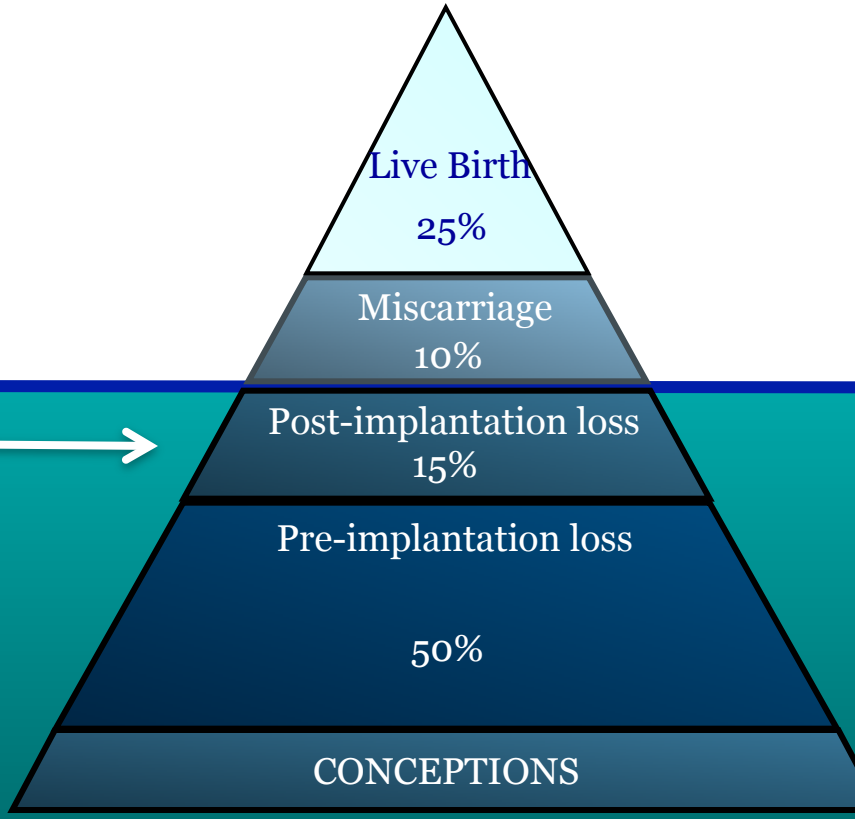
Spontaneous



(Macklon et al,
Hum Reprod Update, 2002)

IVF



(Boomsma et al,
Hum Reprod , 2009)

Why such a high rate of attrition?

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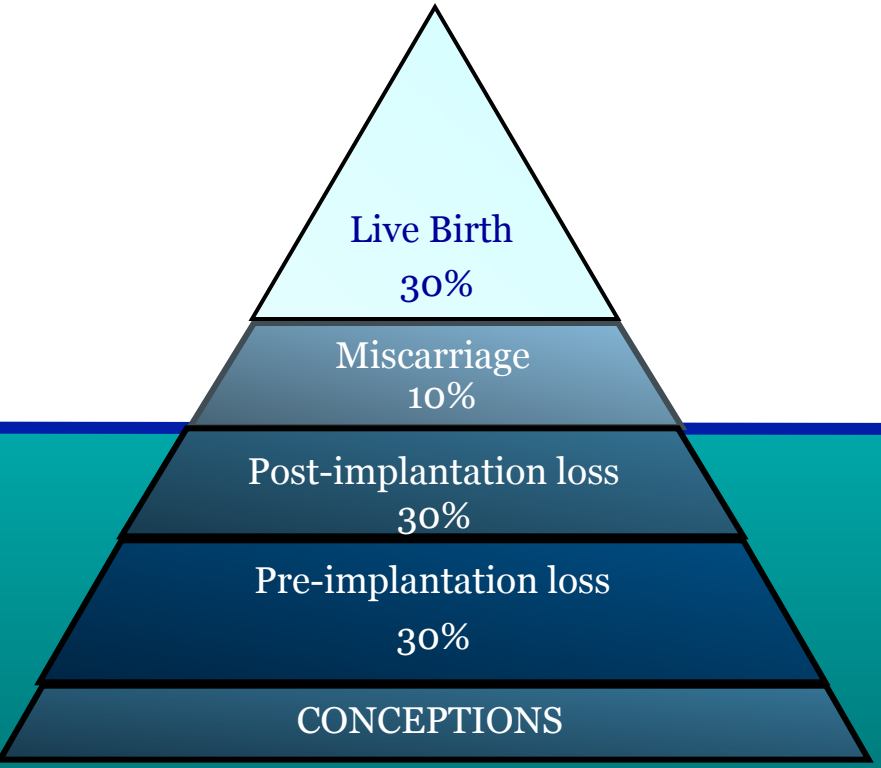
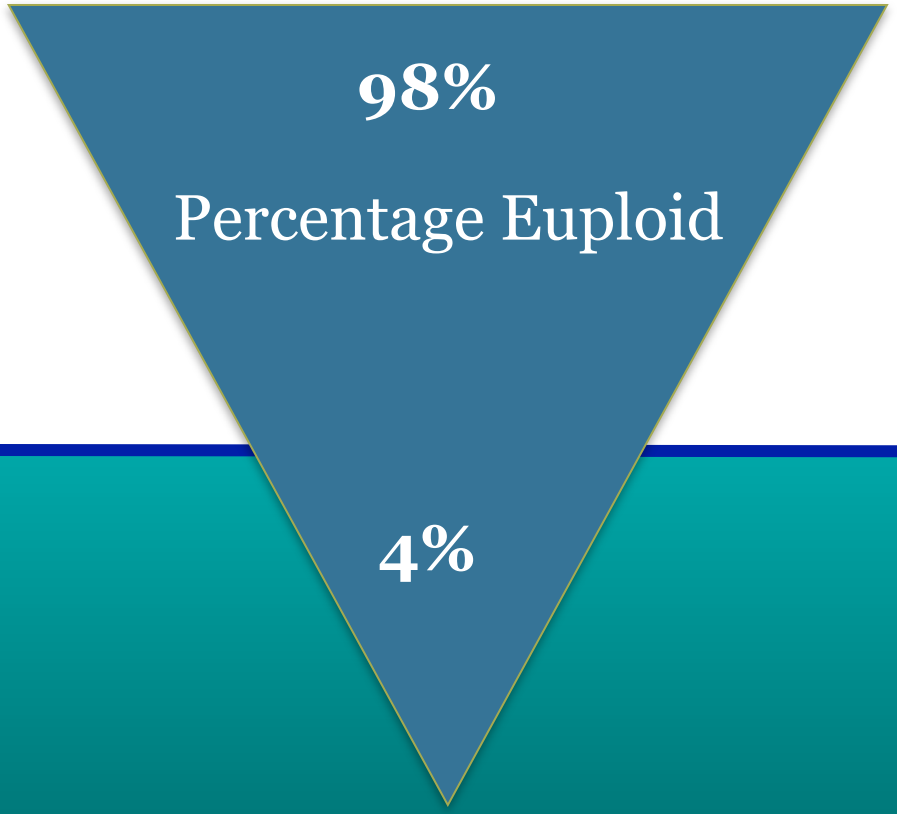


(Macklon et al, Hum Reprod Update, 2002)



(Vanneste et al, Nat Med, 2009)

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

Emerging concepts in the science of implantation

Decidualised stromal cells recognize the incompetent embryo

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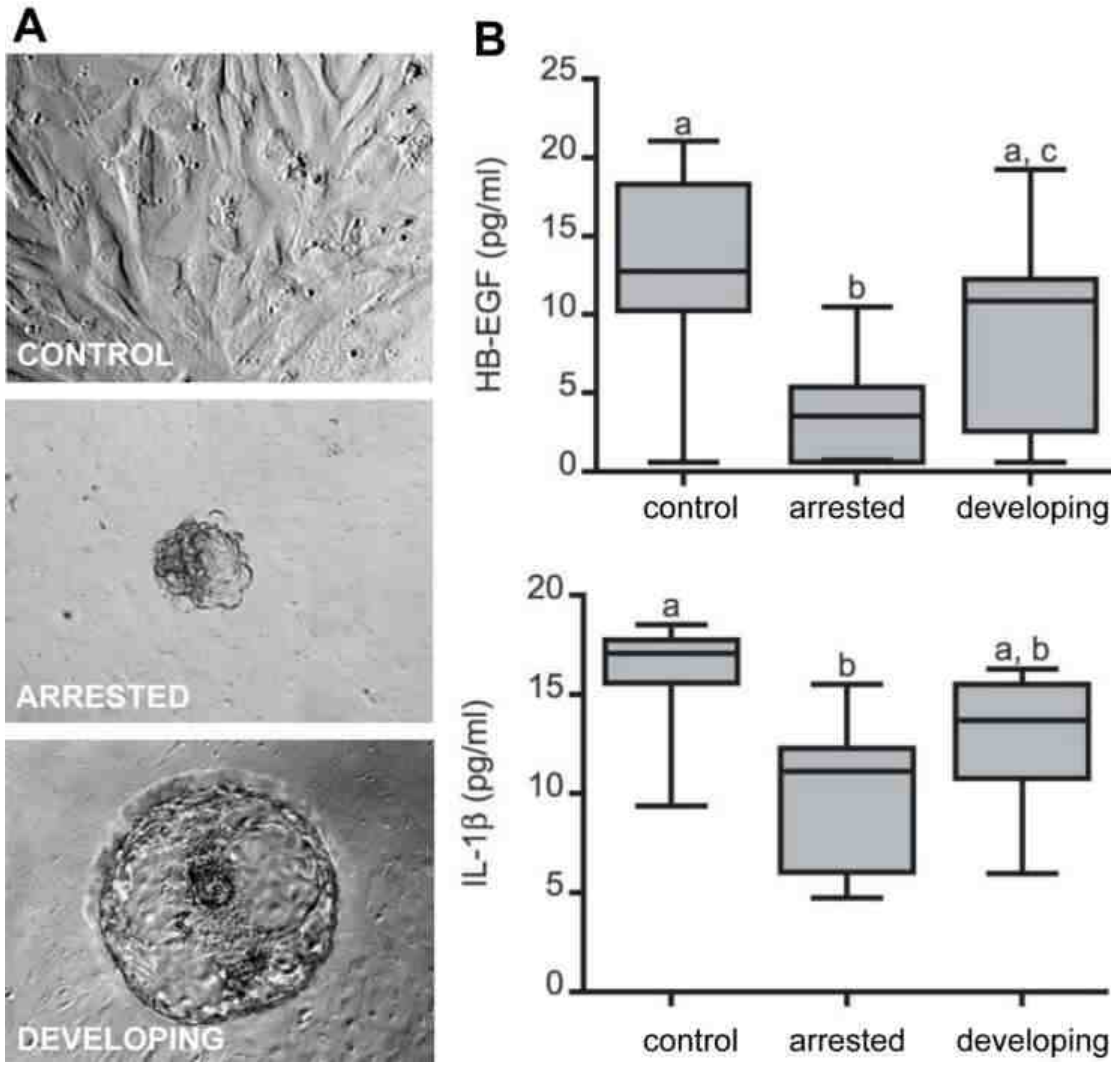
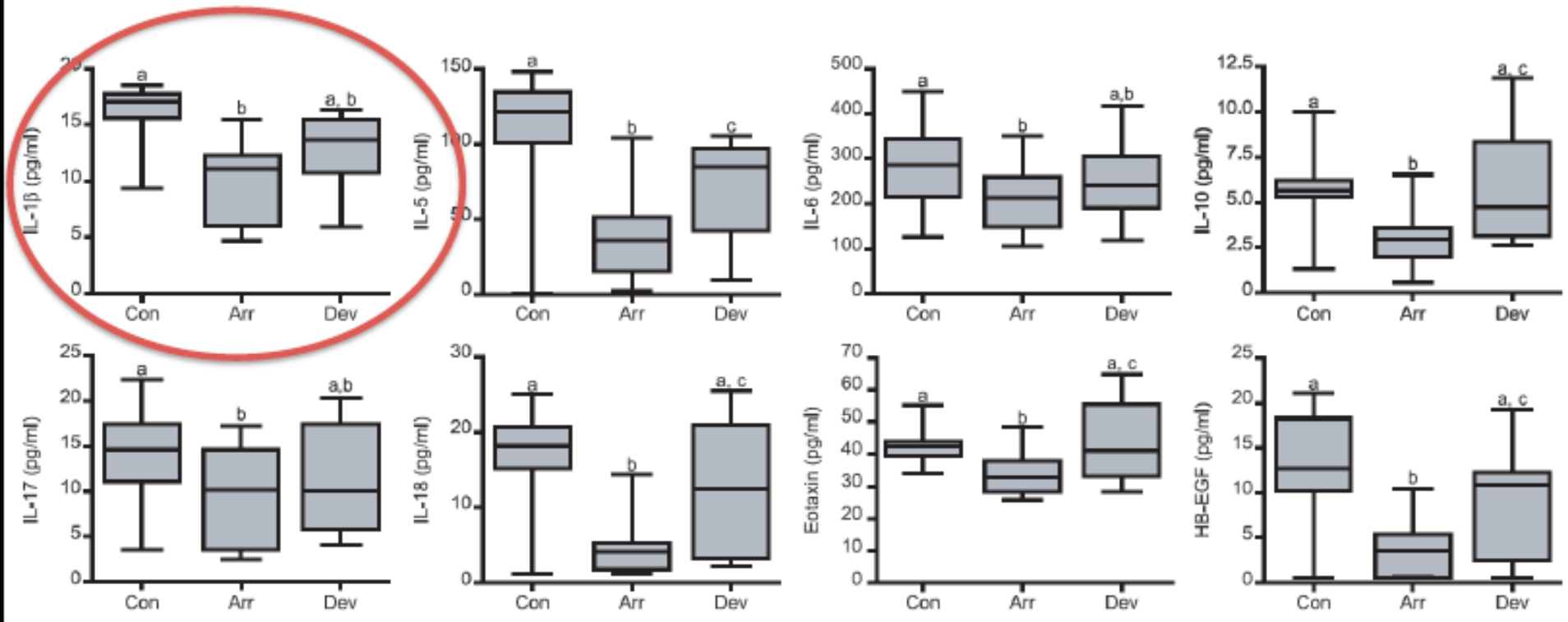


Teklenburg et al, 2010

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 endometrium:no biosensor response.

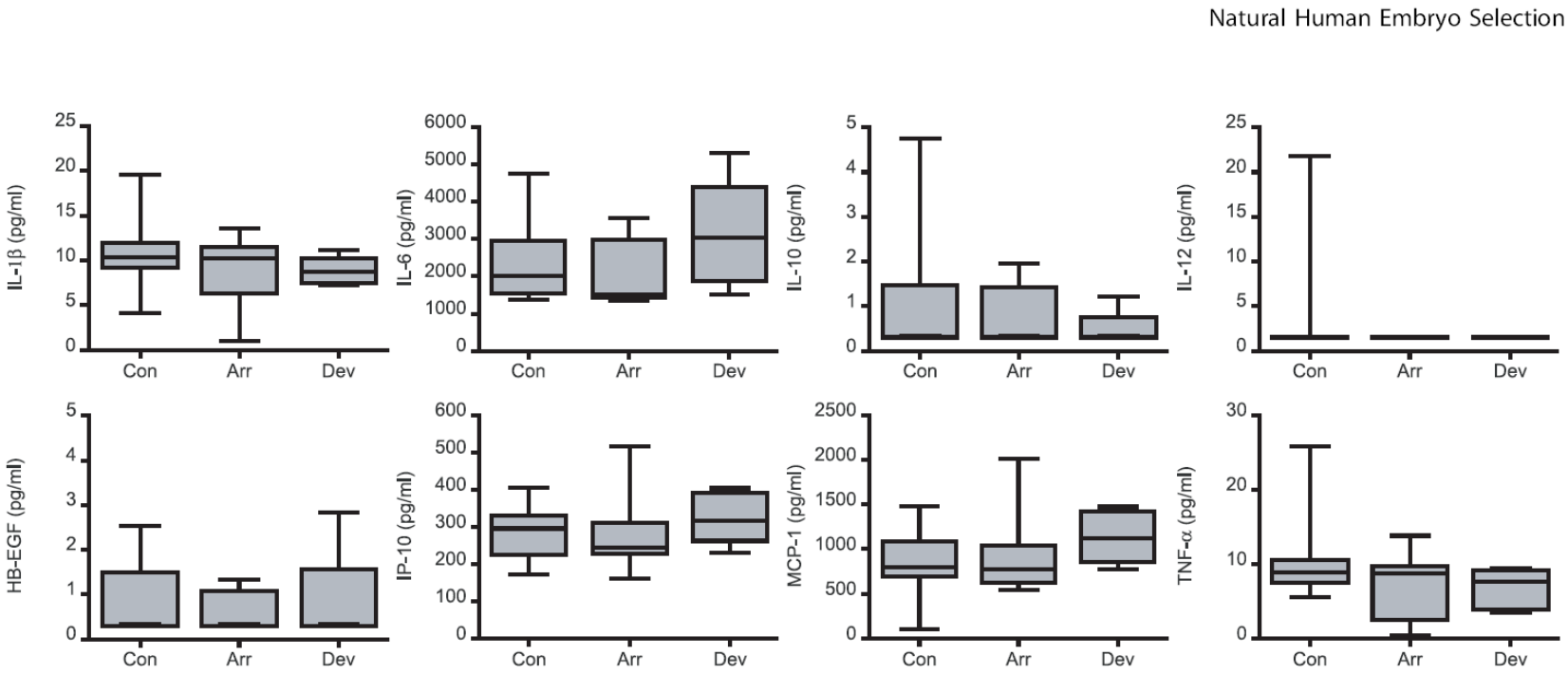

Figure 4. The human embryo does not elicit a secretory response in undifferentiated endometrium. Undifferentiated primary ESCs were co-cultured with embryos or not (control cultures, Con). Over the 72-hour co-culture period, 15 embryos arrested (Arr) whereas 6 continued to develop normally (Dev). Co-culture 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

How does the endometrium recognize the incompetent embryo?

SCIENTIFIC REPORTS

OPEN

SUBJECT AREAS:
REPRODUCTIVE BIOLOGY
EMBRYOLOGY

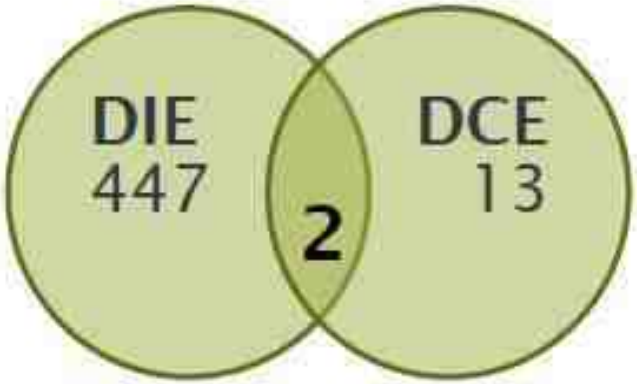
Received
2 October 2013

Uterine Selection of Human Embryos at Implantation

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]

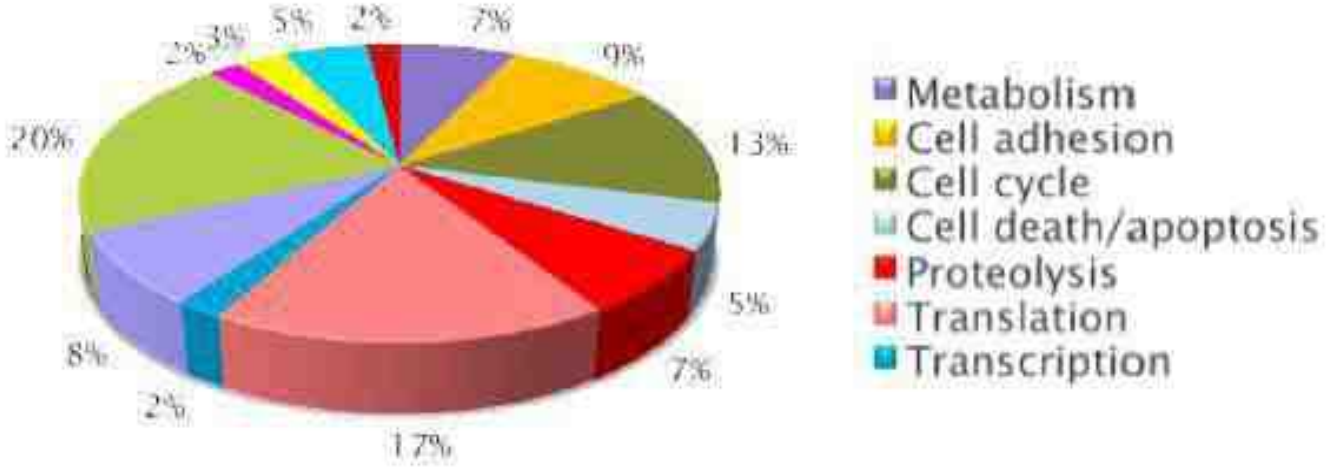
DIEs trigger far greater transcriptional response than DCEs

Developmentally impaired embryos



Developmentally competent embryos

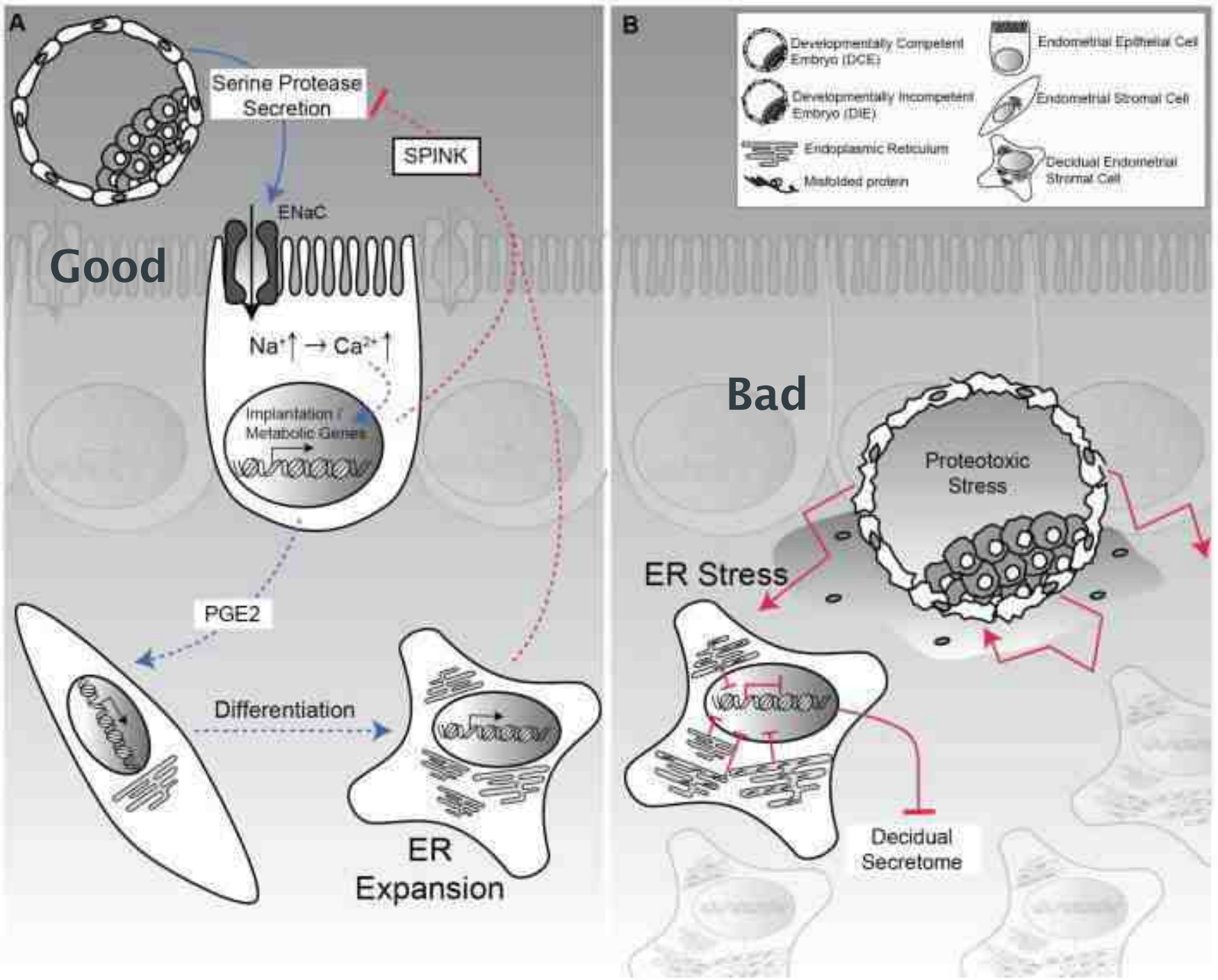
DIE

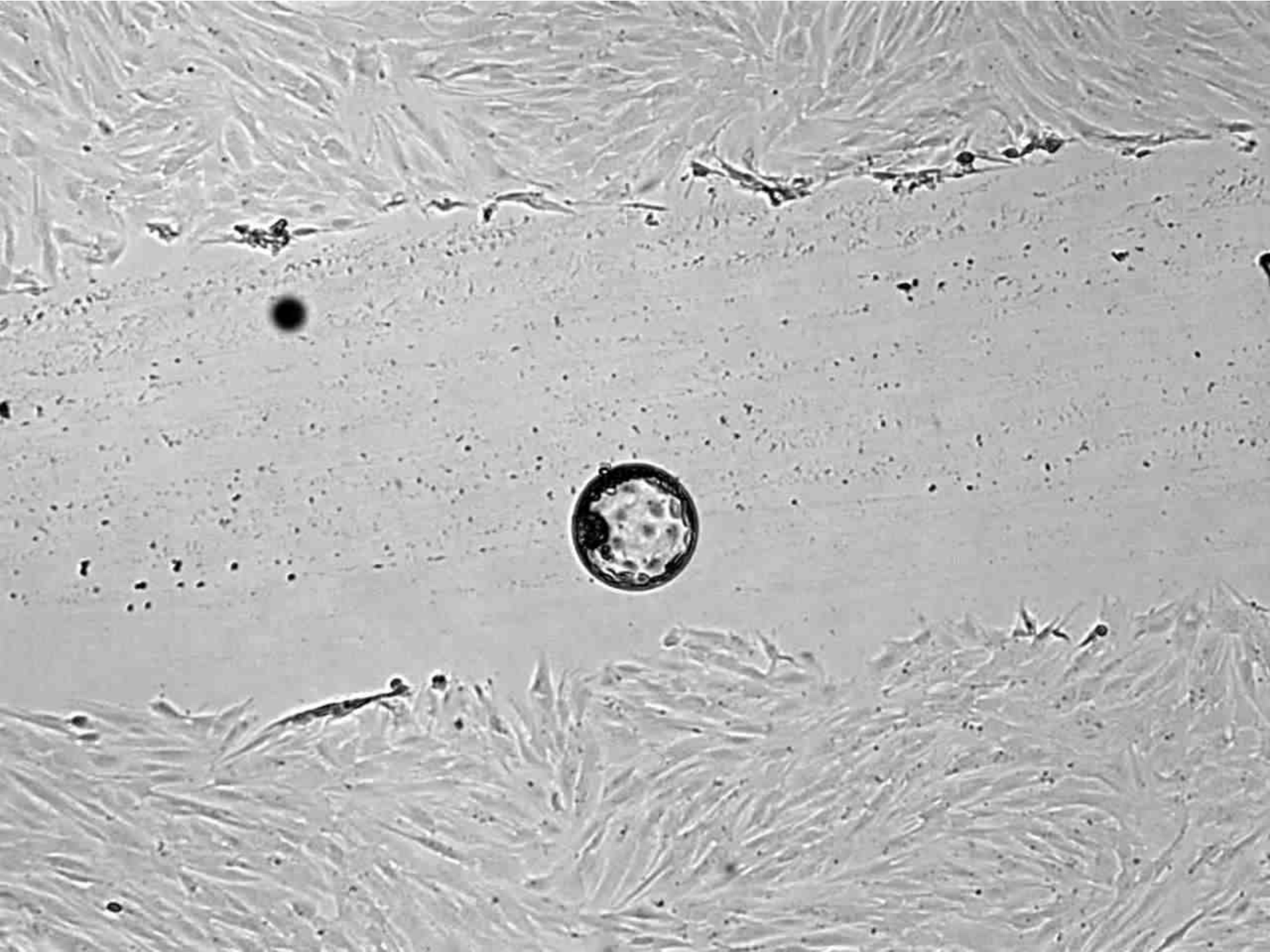


Most dysregulated gene: HSP8- induces stress response

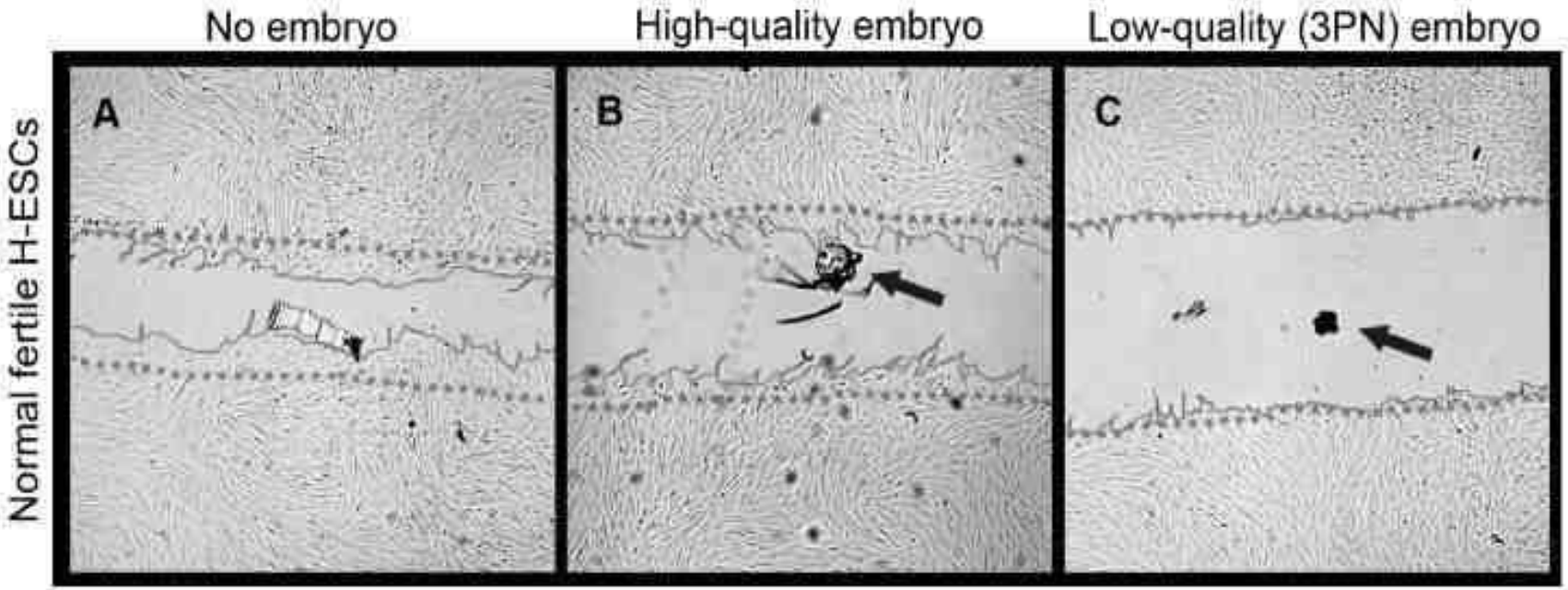
PCR, polymerase chain reaction

Brosens et al 2014 SCIENCE Report


A
Serine Protease Secretion
SPINK
ENaC
Good
Na+↑ → Ca2+↑
Implantation / Metabolic Genes
PGE2
Differentiation
ER Expansion
B
Developmentally Competent Embryo (DCE)
Developmentally Incompetent Embryo (DIE)
Endoplasmic Reticulum
Misfolded protein
Endometrial Epithelial Cell
Endometrial Stromal Cell
Decidual Endometrial Stromal Cell
Bad
Proteotoxic Stress
ER Stress
Decidual Secretome



Stromal cells don't migrate to low quality embryos



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

What if mother does not respond to these signals?

What if she is not choosy enough?

The less choosy mother will experience more miscarriages.

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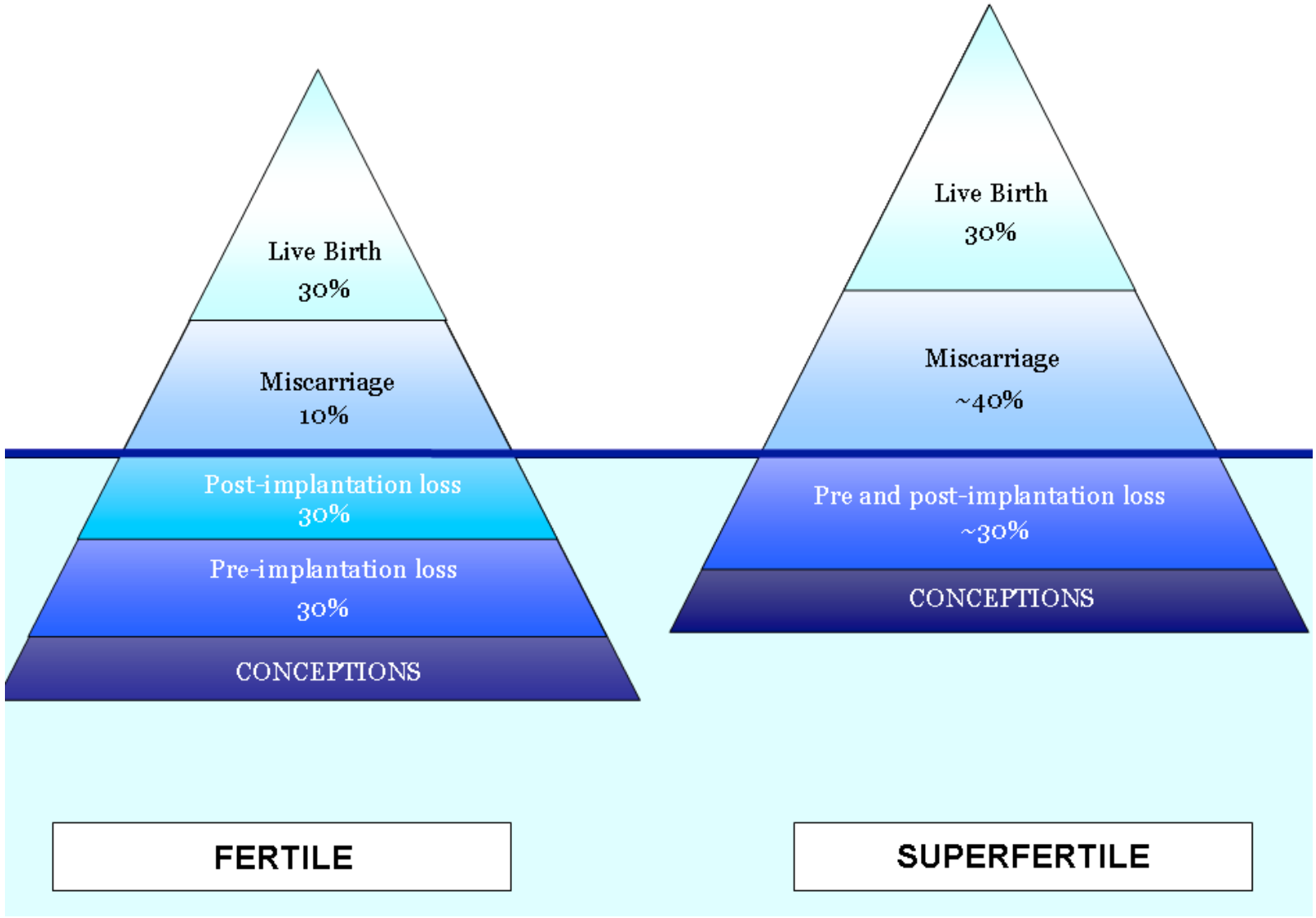


Is Superfertility Associated with Recurrent Pregnancy Loss?

Orlando J, Coulam C. Is superfertility associated with recurrent pregnancy loss? Am J Reprod Immunol 2014

3% controls superfertile

32% RPL superfertile

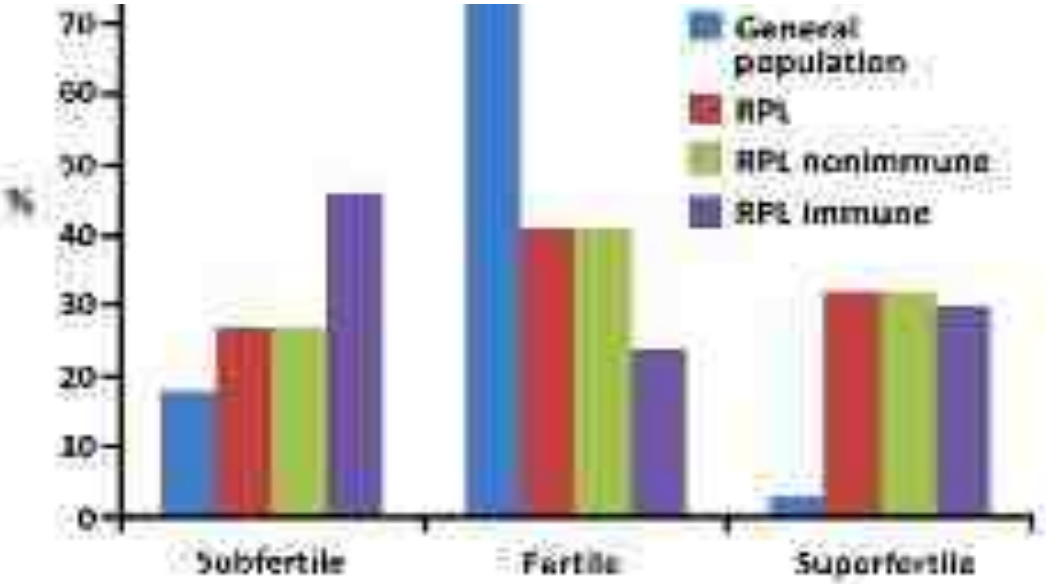
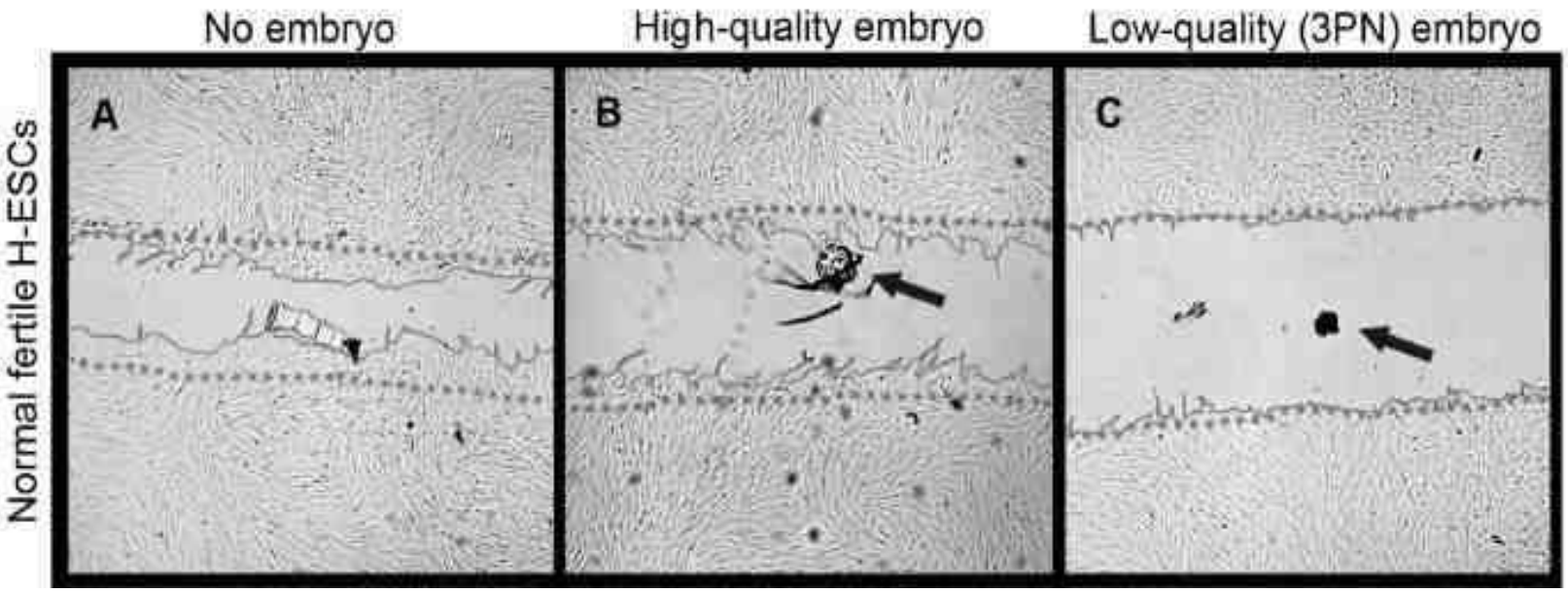


Fig. 1 Prevalence of subfertile, fertile, and superfertile women experiencing recurrent pregnancy loss compared with the model of Tietze[7] for the general population.

Conclusion

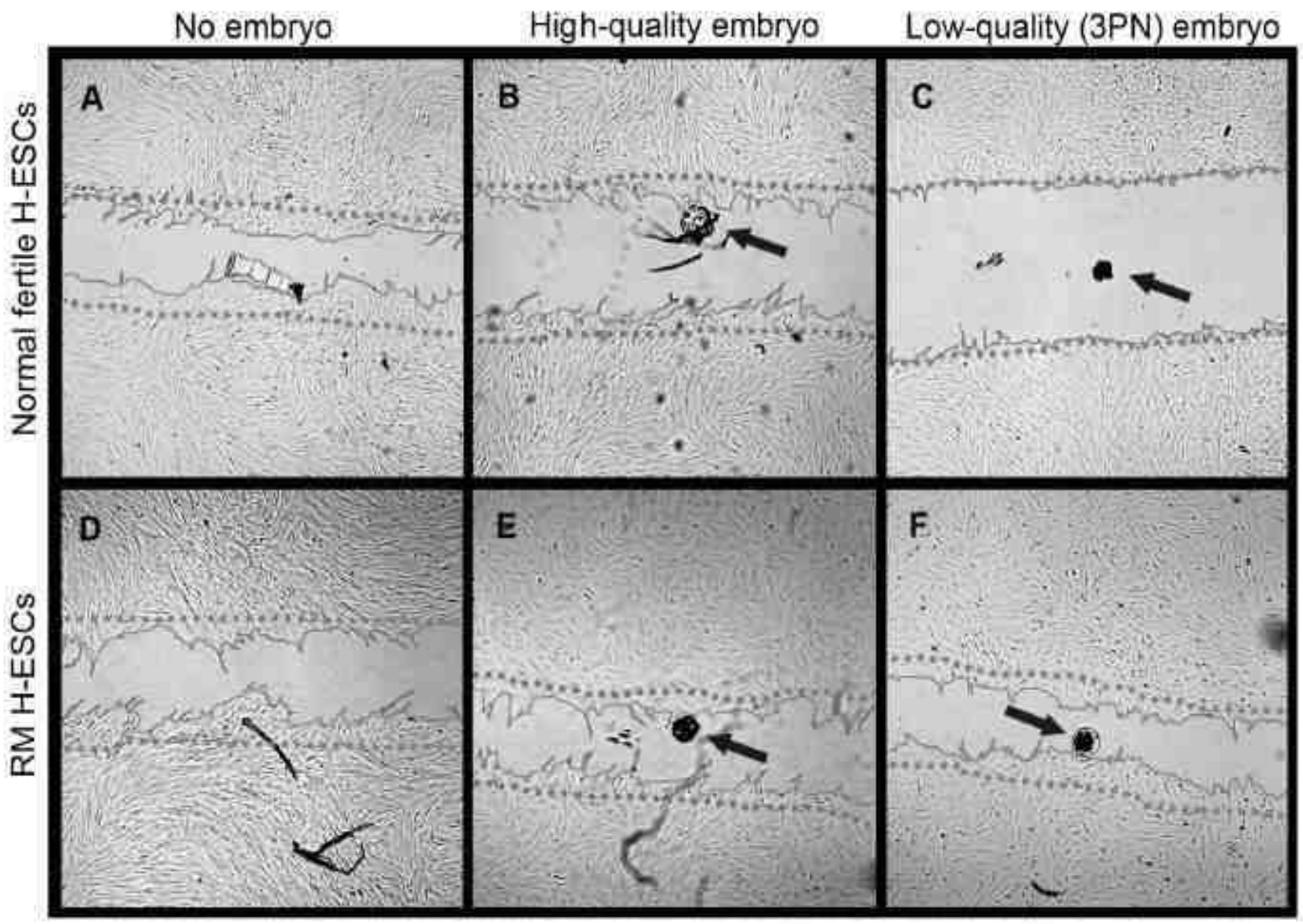
Recurrent pregnancy loss is associated with superfertility in 32%, immunologic risk factors in 30% and a 20% frequency of chromosomally abnormal pregnancy losses. Thus, implantation failure can result from too much or too little implantation.

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

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Could Recurrent Implantation Failure represent the opposite problem?

Mother is too choosy?

Implantation failure arises from excessive selectivity?

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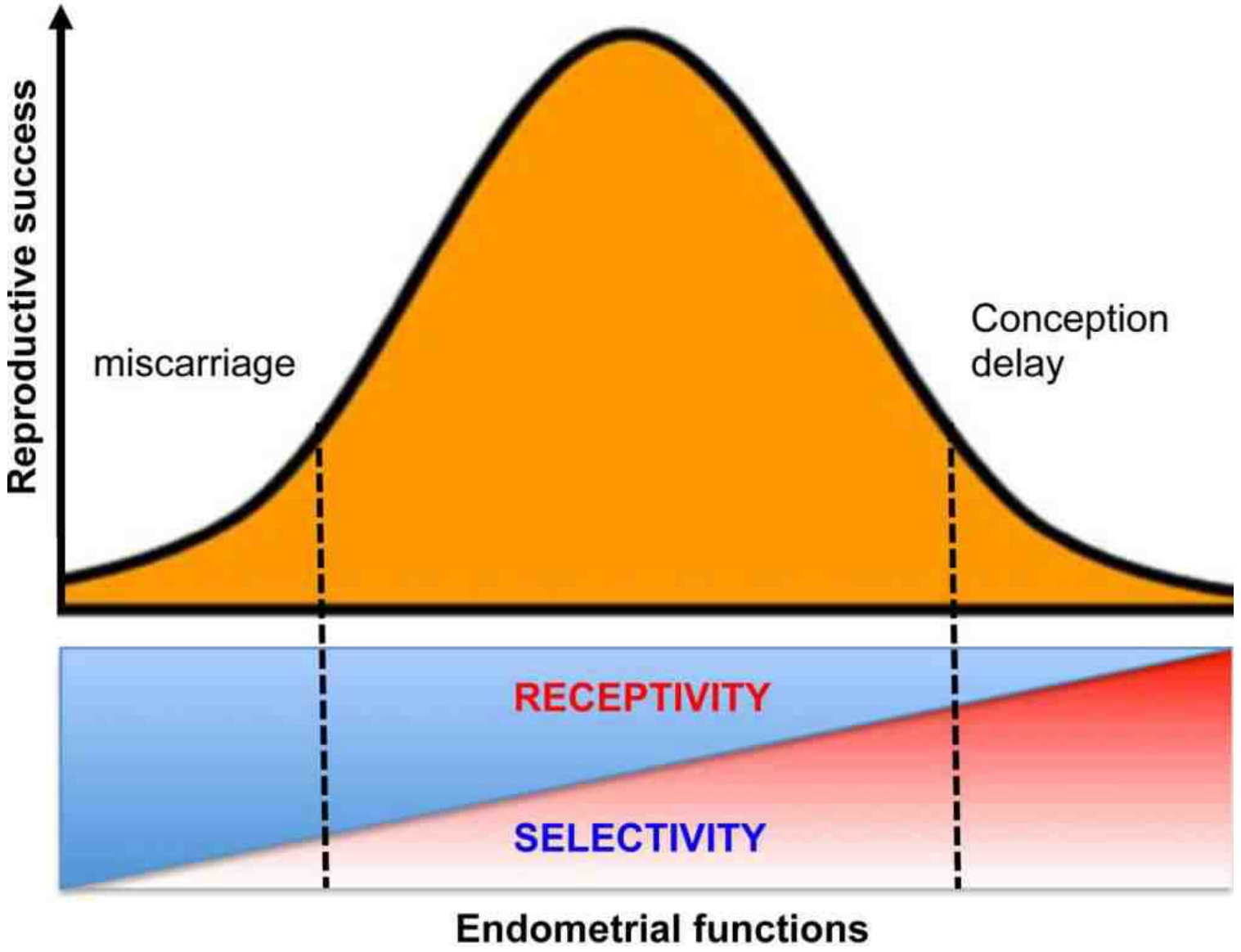

Macklon and Brosens, Biol Reprod 2014

If a good embryo tries to implant, it wont matter if the woman is not selective enough, or too selective.

Eventually, a good one should get there.

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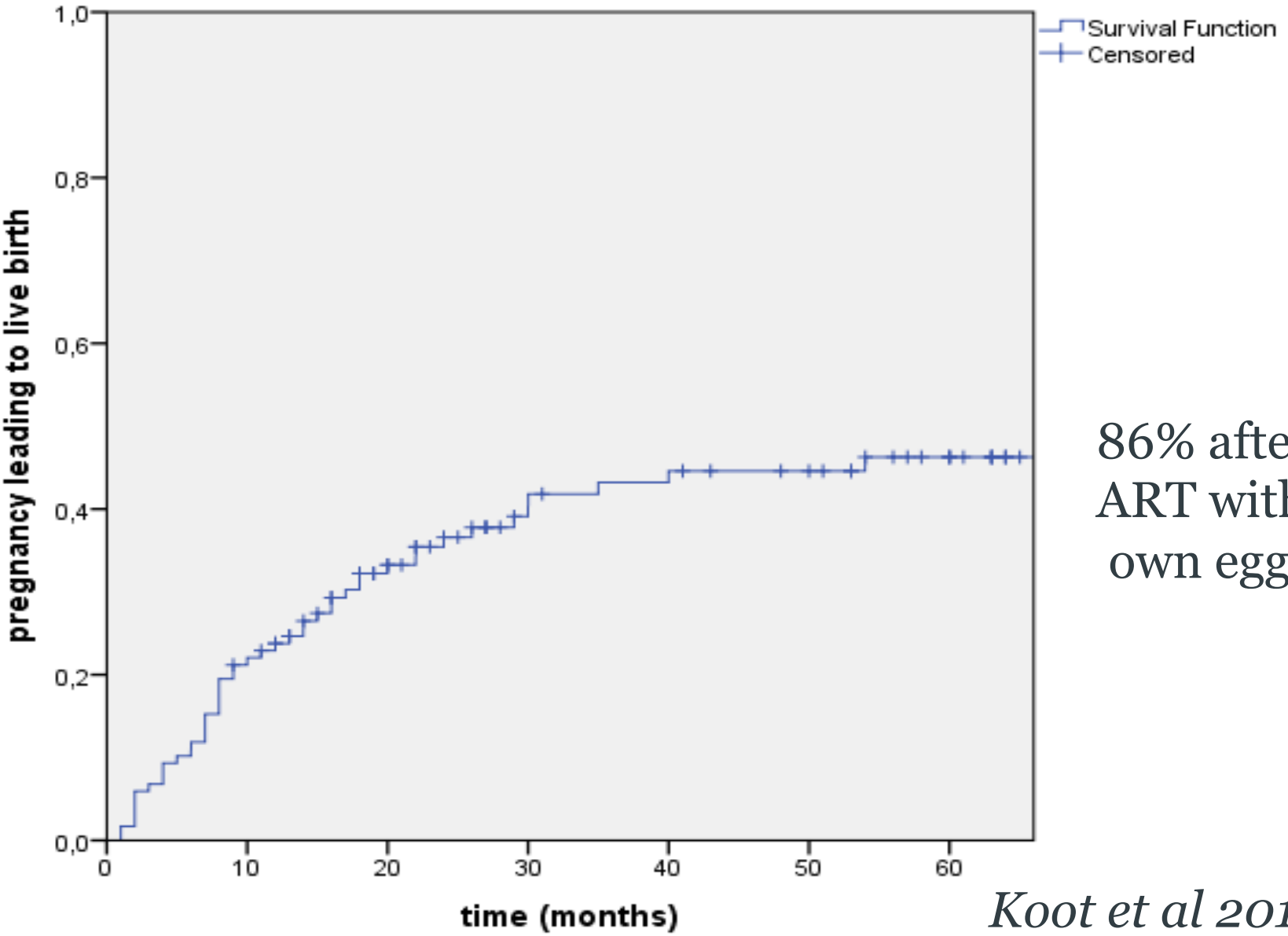
Prognosis for next pregnancy after recurrent miscarriage

AGE	2	3	4	5
20	92	90	88	85
30	84	80	76	71
40	69	64	58	52
45	60	54	48	42

Dutch Assocation for Obsetrics and Gynaecology, 2007

Cumulative pregnancy rates after RIF



86% after ART with own eggs

Koot et al 2015

Conclusions

- Previous paradigms of receptivity have not led to effective interventions.
- Evidence is emerging for a biosensor function of the decidualized endometrium.
- Recurrent miscarriage may arise from failure of embryo selection.
- Recurrent implantation failure may represent an ‘over selective’ endometrium.
- Interventions should focus on quality of decidualization,as well as ‘quantity’ of endometrium thickness.

Further reading?

BIOLOGY OF REPRODUCTION (2014) 91(4):93, 1–8
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Minireview

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

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[3]Division of Reproductive Health, Warwick Medical School, Clinical Sciences Research Laboratories, University Hospital, Coventry, United Kingdom

ABSTRACT

Human reproduction is characterized by a high degree of embryo wastage, which is largely ascribed to a high prevalence of embryo aneuploidy. It is proposed that maternal strategies have evolved that prevent inappropriate investment in invasive, but poorly viable embryos. Key to this is the emerging concept of the endometrium as biosensor, first identified in human in vitro embryo/decidualized stromal cell coculture systems and recently confirmed in an in vivo mouse model. In this review, the growing supporting experimental evidence for the biosensor component of decidualized endometrium is outlined, and recent insights into the nature of the embryo-derived signal detected by the endometrium and the biological processes by which this signal is thought to be converted into a go or no-go endometrial response are described. Finally, the clinical implications of this new paradigm of the choosy uterus are addressed.

decidualization, embryo, endometrium, implantation, selection

INTRODUCTION

Compared with other mammalian species, human reproductive efficiency is not impressive. The probability of achieving a pregnancy within one menstrual cycle, defined as the monthly fecundity rate (MFR), is 20%–30%. In contrast, the MFR may be as high as 80% in baboons and 90% in rabbits [1–3]. Those concerned about the impact of the rising population on the Earth's resources may find some reassurance in this observation, but for couples suffering from the distress of reproductive failure and their clinicians it is an enervating source of frustration. Progress in assisted reproductive techniques has led to the majority of couples undergoing in vitro fertilization (IVF) treatment obtaining embryos for transfer, but only around half implant, and up to half of these are lost soon after [4]. However, this high rate of peri-implantation loss is not solely a feature of assisted conception treatment. The first indications of the high peri-implantation attrition that characterizes human reproduction were revealed by Hertig and colleagues 1950s exploration of 210 postovulation hysterectomy specimens where only 34 yielded fertilized ova, good, bad, and indifferent [5]. The development of sensitive urinary human chorionic gonadotropin (hCG) assays led to the landmark study of Wilcox et al. [6] in which serial urinary samples collected over 6 mo or until a positive pregnancy test were collected from 221 women trying to conceive. Urinary hCG measurements revealed that implantation occurred in 19% of cycles, but more than a third were then lost, a majority before any clinical sign of conception had presented. When considered in conjunction with subsequent studies, it has been estimated that around 50% of human conceptions fail to progress to an ongoing pregnancy [7]. A greater understanding of the etiology and teleology of peri-implantation loss is key to improving reproductive outcomes, but human studies are stained by ethical and technical challenges. However, a combination of informative animal models and novel in vitro systems is beginning to throw new light on what has previously been considered the implantation "black box".

THE NEED TO BE DISCERNING

The exceptional rate of early pregnancy loss that characterizes human reproduction is now thought to derive from two key features of human embryos: their intrinsic invasiveness and their high prevalence of chromosomal abnormalities. Genome-wide screening of individual blastomeres taken from high-quality cleavage-stage embryos IVF has shown that around 70% have complex chromosomal abnormalities, mostly arising from mitotic rather than meiotic nondisjunction [8–10]. This rate of aneuploidy, estimated to be at least 10 times greater than that observed in other mammalian species, appears to decrease during development to the blastocyst stage. Fluorescent in situ hybridization analysis of 10 chromosomes in individual blastocysts from viable human IVF embryos has shown that the prevalence of aneuploidy decreases from 83% on Day 4 of development to 42% on Day 5 [11]. Consistent with these findings, microarray comparative genomic hybridization analysis of 5 to 10 trophectoderm cells from 1046 blastocysts identified a total of 1113 distinct aneuploidies in 808 (58%) embryos [10], emphasizing that peri-implantation human embryos are intrinsically chromosomally diverse and predominantly mosaic.

[1]S.S.M. was supported by the NIHR BRC in Nutrition, Southampton, UK, and by Zon Mw, The Netherlands. J.J.B. was supported by the Biomedical Research Unit in Reproductive Health, a joint initiative between the University Hospitals Coventry and Warwickshire NHS Trust and Warwick Medical School.
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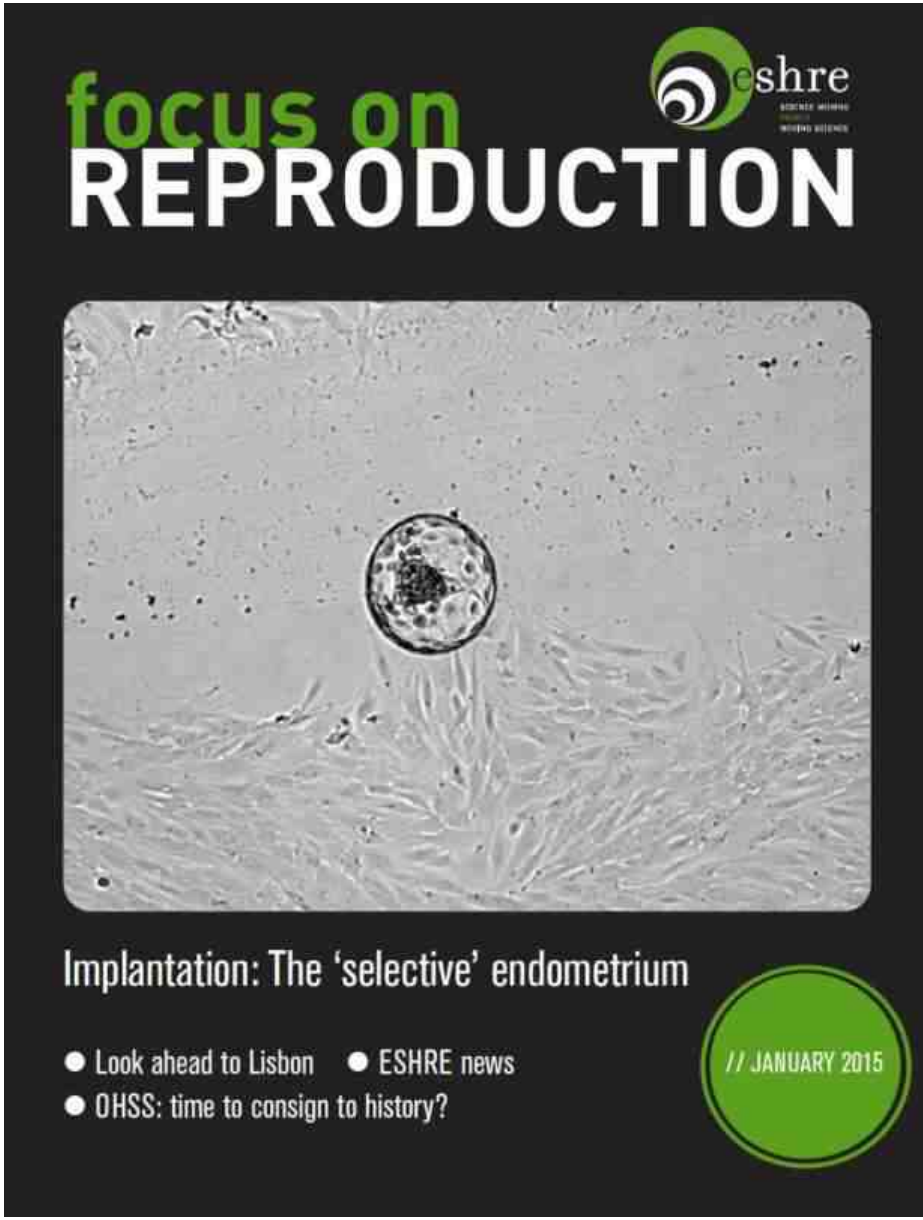

Monday Morning

Friday evening

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Cobi Heijnen

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Jan Brosens

and..