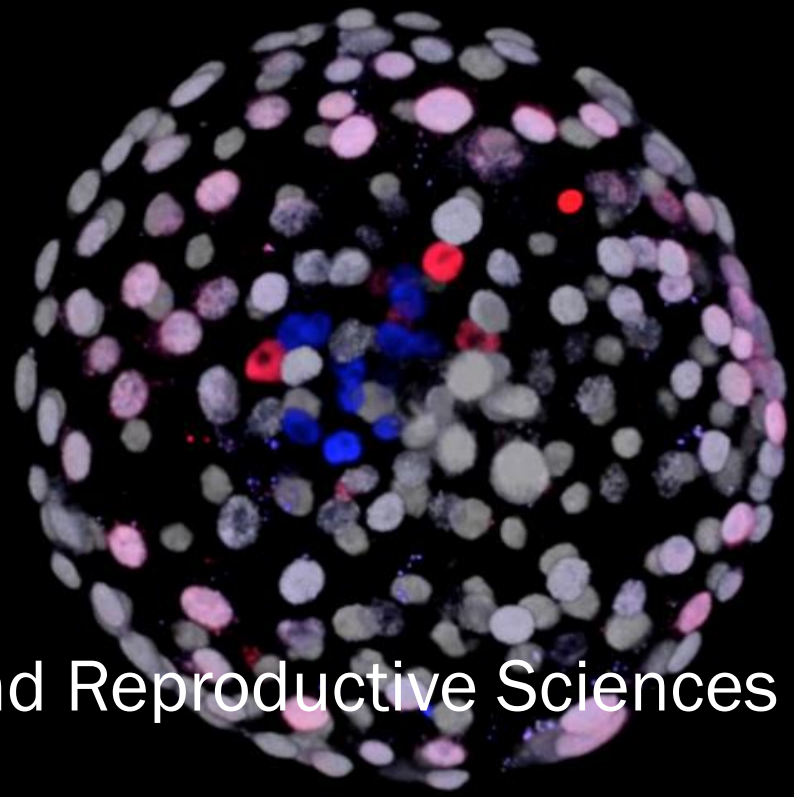
PREIMPLANTATION HUMAN EMBRYO DEVELOPMENT: A CLINICAL PERSPECTIVE



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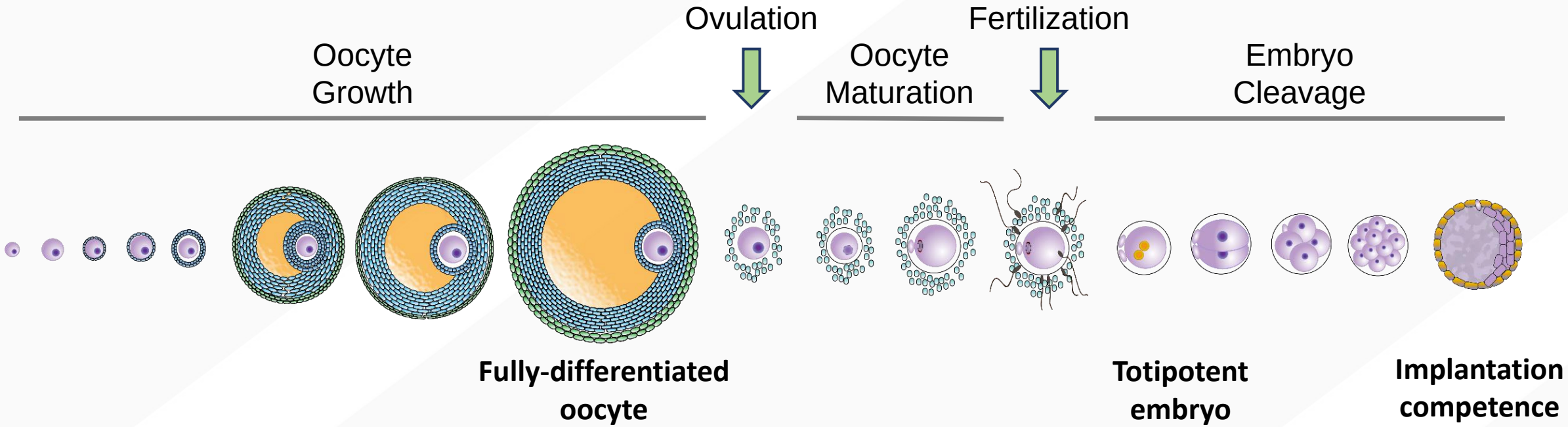
WHAT IS THE MOLECULAR BASIS OF EMBRYO QUALITY?



- What is the importance of studying human embryos in the context of infertility and reproductive technologies?
- What developmental benchmarks are important to reproduce in model systems?

HUMAN REPRODUCTION IS INEFFICIENT

Cyclic fecundity rates:

Mouse

85%

Silver et al., 1995

Non-human primate

70%

Stevens et al., 1995

Human

20-30%

Schwartz, 1983; Edwards et al., 1995

Understanding the molecular defects in embryo development that lead to these inefficiencies is critical to improve the diagnosis and treatment of infertility

OBSERVATIONS FROM IN VITRO FERTILIZATION AND EMBRYO CULTURE IN THE IVF CLINIC PROVIDE CRITICAL INSIGHTS

The first IVF baby turns 42 years old this year

Robert Edwards
Nobel Prize, 2010

Louise Brown

Letters to the Editor

BIRTH AFTER THE REIMPLANTATION OF A HUMAN EMBRYO

SIR,—We wish to report that one of our patients, a 30-year-old nulliparous married woman, was safely delivered by cæsarean section on July 25, 1978, of a normal healthy infant girl weighing 2700 g. The patient had been referred to one of us (P.C.S.) in 1976 with a history of 9 years' infertility, tubal occlusions, and unsuccessful salpingostomies done in 1970 with excision of the ampullæ of both oviducts followed by persistent tubal blockages. Laparoscopy in February, 1977, revealed grossly distorted tubal remnants with occlusion and peritubal and ovarian adhesions. Laparotomy in August, 1977, was done with excision of the remains of both tubes, adhesolysis, and suspension of the ovaries in good position for oocyte recovery.

Pregnancy was established after laparoscopic recovery of an oocyte on Nov. 10, 1977, in-vitro fertilisation and normal cleavage in culture media, and the reimplantation of the 8-cell embryo into the uterus 2½ days later. Amniocentesis at 16 weeks' pregnancy revealed normal α-fetoprotein levels, with no chromosome abnormalities in a 46 XX fetus. On the day of delivery the mother was 38 weeks and 5 days by dates from her last menstrual period, and she had pre-eclamptic toxæmia. Blood-pressure was fluctuating around 140/95, œdema involved both legs up to knee level together with the abdomen, back, hands, and face; the blood-uric-acid was 390 μmol/l, and albumin 0·5 g/l of urine. Ultrasonic scanning and radiographic appearances showed that the fetus had grown slowly for several weeks from week 30. Blood-œstriols and human placental lactogen levels also dropped below the normal levels during this period. However, the fetus grew considerably during the last 10 days before delivery while placental function improved greatly. On the day of delivery the biparietal diameter had reached 9·6 cm, and 5 ml of amniotic fluid was removed safely under sonic control. The lecithin: sphingomyelin ratio was 3·9:1, indicative of maturity and a low risk of the respiratory-distress syndrome.

We hope to publish further medical and scientific details in your columns at a later date.

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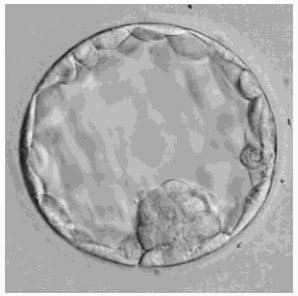
R. G. EDWARDS

Steptoe and Edwards, Lancet, 1978

POTENTIAL LIMITATIONS OF IN VITRO CULTURE AND IVF-DERIVED HUMAN EMBRYOS AS A MODEL SYSTEM

LOGISTICAL CONSIDERATIONS

- Stages available are limited
- Numbers available typically low
- Quality/morphology typically inferior
- Ploidy often abnormal or unknown
- Low numbers and high variability between patients and clinics pose challenges for analyses



THEORETICAL CONSIDERATIONS

- Contribution of *in vitro* stimulation and culture
- Contribution of underlying infertility
- Many of the same inefficiencies are observed in spontaneous pregnancies and in patients without underlying infertility.
- Addressing the inefficiencies observed *in vitro* is important to advance infertility treatment.

WHAT CAN IVF TEACH US ABOUT WHERE THE INEFFICIENCIES IN HUMAN REPRODUCTION MIGHT LIE?

These are important benchmarks to study in human embryos and to reproduce in model embryo systems

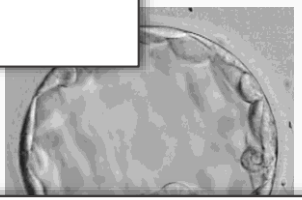
Oocyte Retrieval
Fertilization

Assess for
Fertilization

Evalu
Morph

Developmental arrest
40 - 50%

ification
Transfer

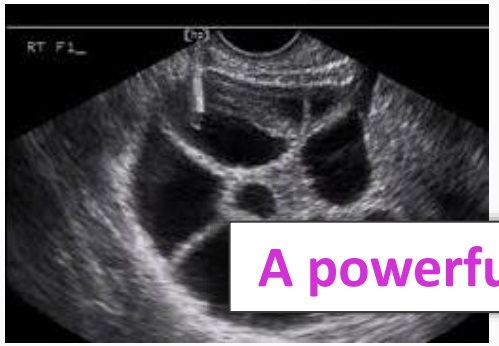


Aneuploidy
<40 yo: 25 - 60%
>40 yo: up to 90%

0 1 2 3 4 5/6

Assess for
Implantation

Ovarian Stimulation

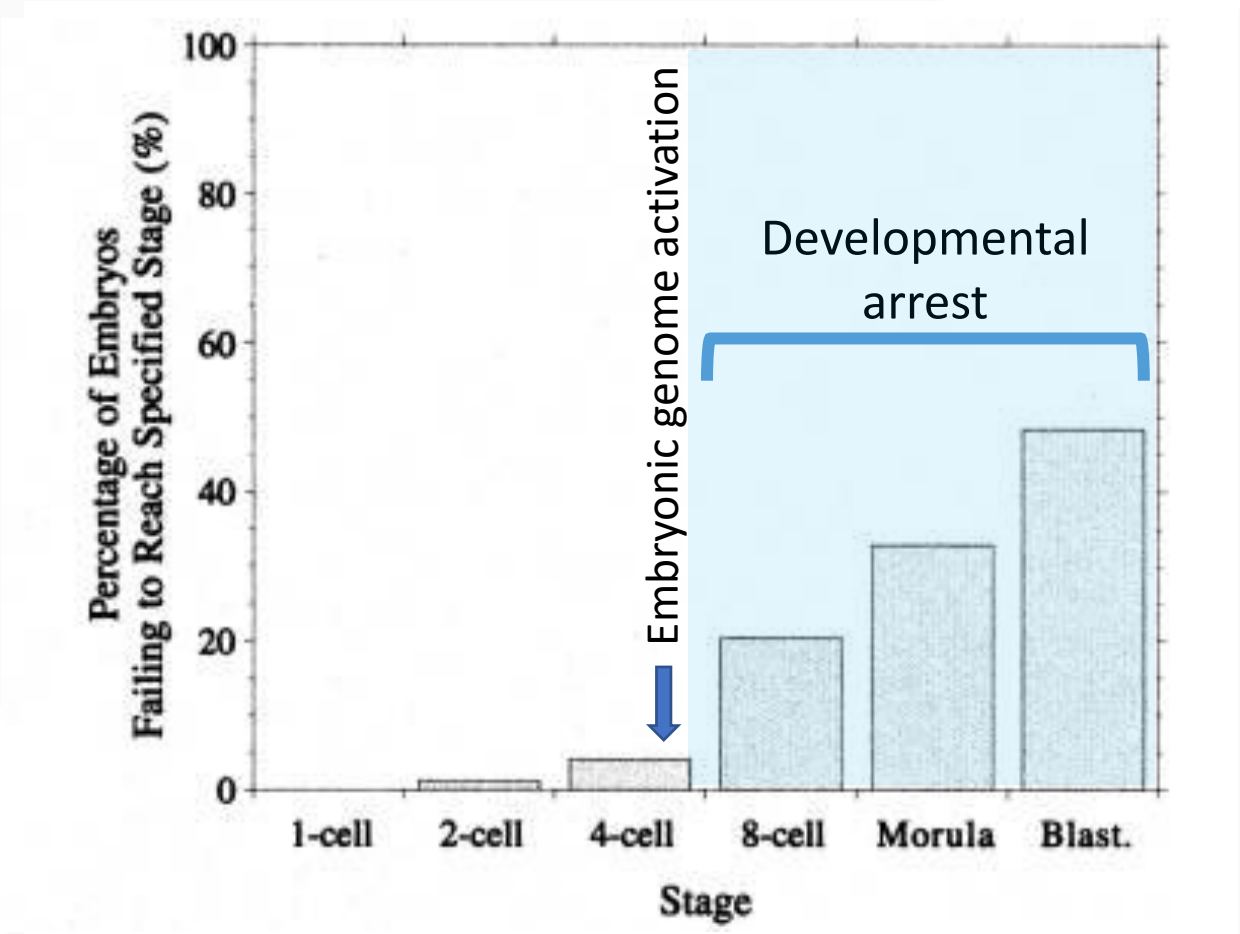


Days Post-
Fertilization

Implantation failure

A powerful opportunity to observe the earliest stages of human development

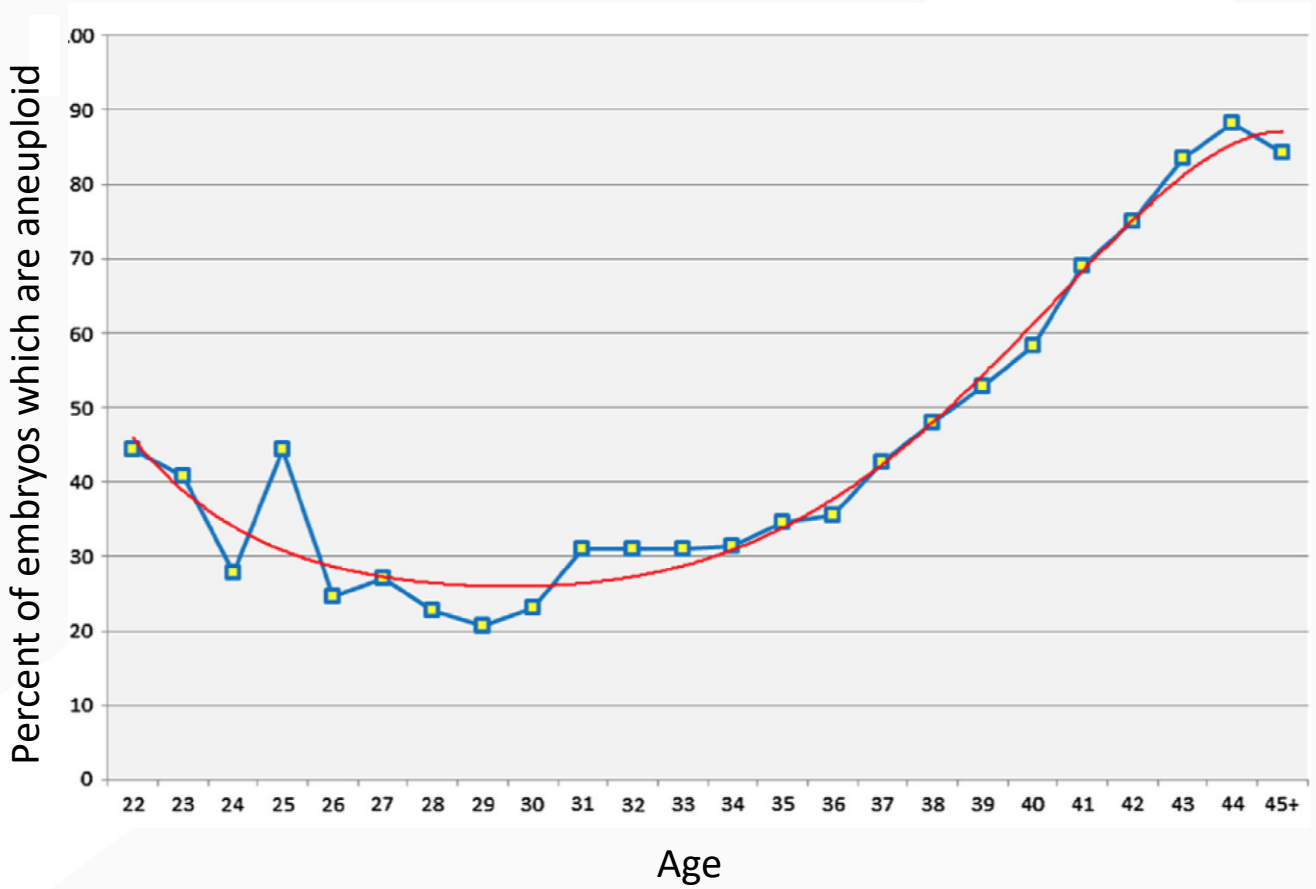
DEVELOPMENTAL ARREST – CURRENT CHALLENGES AND IMPORTANT QUESTIONS



- 40-50% of human embryos arrest between cleavage (D3) and blastocyst stage (Hardy et al., 2001)
- >30% of arrested embryos were euploid for all chromosomes tested (Maurer et al., 2015; Munne et al., 1994)
- Does arrest represent a failure to fully initiate embryonic genome activation?
- Or perhaps an even earlier defect in oocyte growth/quality?

Hardy et al., 2001

ANEUPLOIDY – CURRENT CHALLENGES AND IMPORTANT QUESTIONS



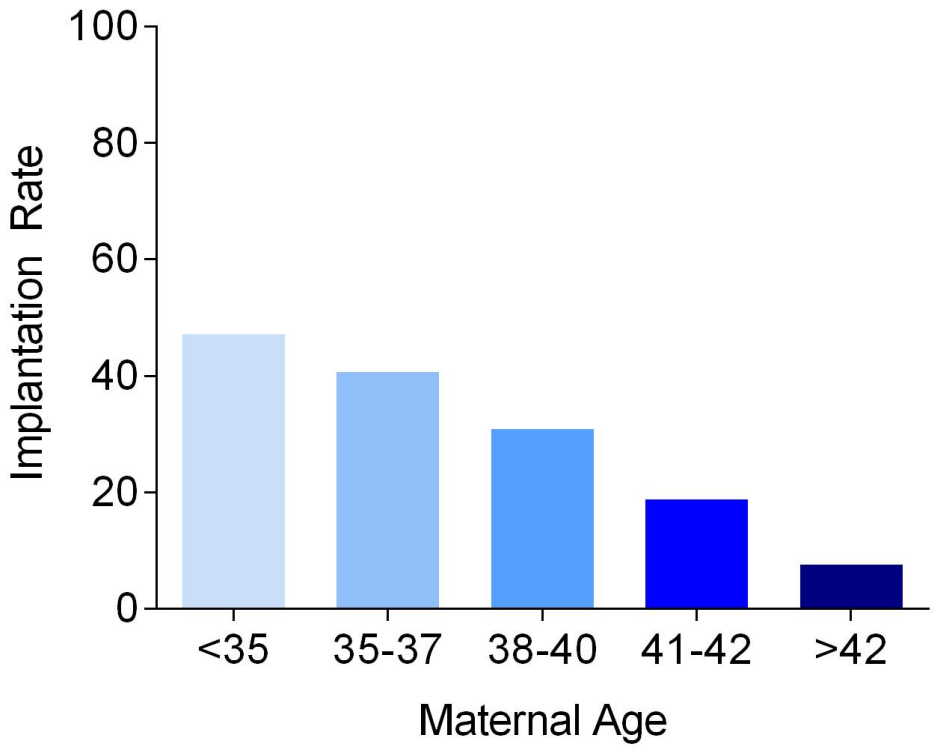
- Age 30 ~25% are aneuploid
- Age 35 35%
- Age 40 60%
- Age >42 80-90%

- What are the mechanisms by which aneuploidy occurs in the embryo?
- By what mechanisms can aneuploidy be corrected during embryo growth?
- To what degree does mosaicism affect implantation and fetal health?
- Can aneuploidy/mosaicism rates be decreased by improvements in IVF stimulation and/or culture protocols?

Franasiak et al., Fertility & Sterility, 2014

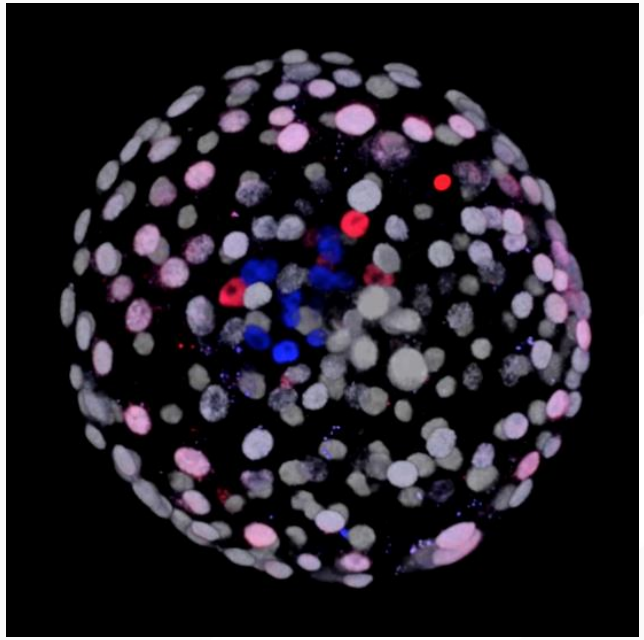
IMPLANTATION FAILURE – CURRENT CHALLENGES AND IMPORTANT QUESTIONS

Society for Reproductive Technologies (SART), 2017 data from US infertility clinics



- Early implantation failure has been estimated to account for >70% of lost pregnancies (Wilcox et al, 1988).
- In IVF cycles, overall rates of implantation failure for blastocysts average >50% in the US even in women <35 yo (SART National Report, 2017).
- Even euploid blastocysts with good morphology fail to to implant in >30% of transfers (Irani et al., 2017).
- Euploid blastocysts with delayed growth or suboptimal morphology fail to implant in ≥65% of transfers (Irani et al., 2017; Irani et al., 2018).
- What is required at the molecular level for successful implantation?
- How to best select the single embryo with the greatest implantation potential for transfer?

SUMMARY



- Human reproduction is inefficient with high rates of molecular or genetic defects in human embryos considered as major contributors.
- Studies in human embryos are necessary to identify and characterize reproductive efficiencies in human reproduction, infertility and ART.
- Genetically manipulatable animal embryo models remain vital for the discovery of mechanisms driving development and implantation. Stem cell-based models are a powerful addition to the model systems available and are providing exciting new insights.
- Important benchmarks to reproduce in embryo models to improve ART include preimplantation developmental progression, aneuploidy and implantation.

THANK YOU.

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