Recent Developments in the Transmission of Human Life

19-21 January 2023

Berlin, Germany

Welcome to all Participants

SCIENTIFIC SEMINARS
INTERNATIONAL FOUNDATION

What is the balance of implantation failure due to embryo competence versus endometrial receptivity?

Result of extrapolation analysis

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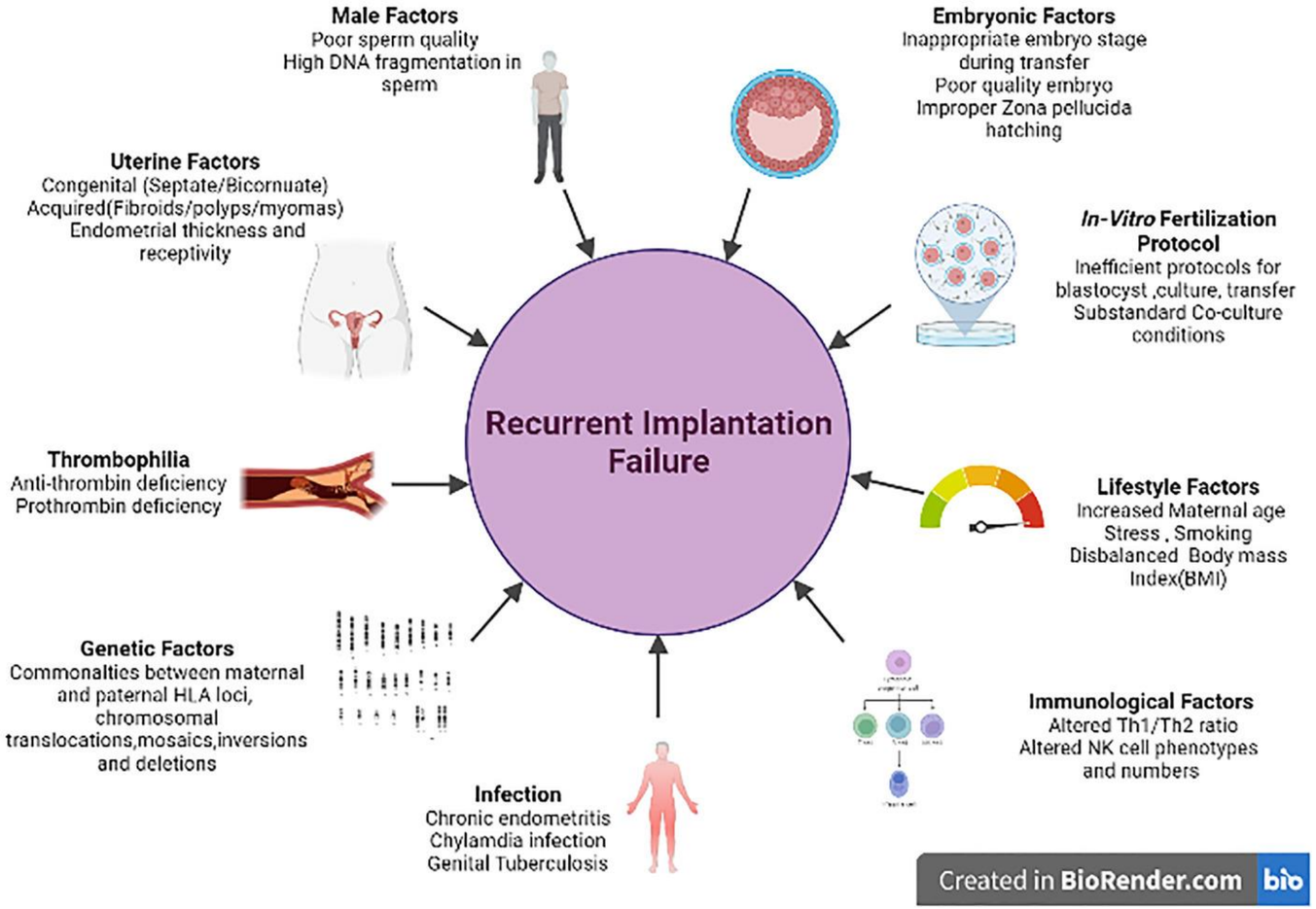
Faculty Disclosure

I have no potential conflict of interest to declare

What needs to be done to validate the diagnosis of RIF? What evidence is needed to be compelling ?

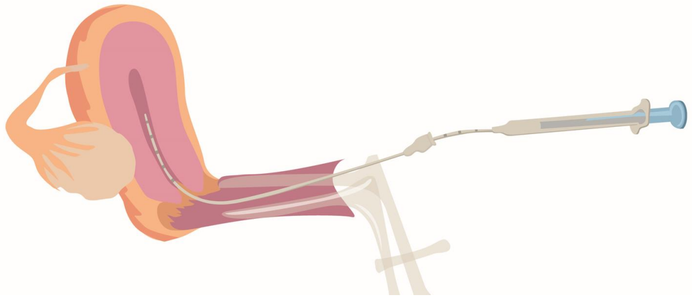


Many studies saying what causes RIF
Few studies defining what it is!…

RIF = Recurrent Implantation Failure

76 different definitions (*Polanski et al 2014)*

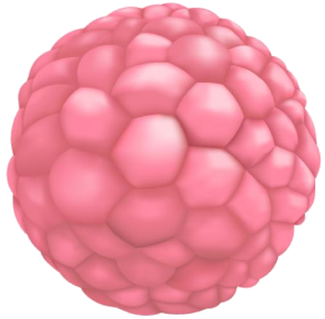
General consensus



X 3

3 or more embryo transfers

OR



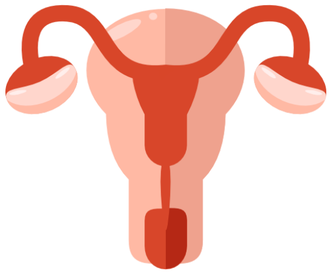
X 4

4 blastocysts transfered

Margaiot et al 2006; Simon and Laufer 2012; Polanski et al 2014;Coughlan C. et al 2014

DEFINITION - *Potential causes*

1. Chromosomal abnormality



2. Endometrial factors

- Receptivity *Li et al, 2019; Paria et al, 2001*
- Endometriosis *Lessey et al, 2017; Moreno et al, 2018*
- Immunological *Gaynor et al, 2017; Di Pietro et al, 2018*

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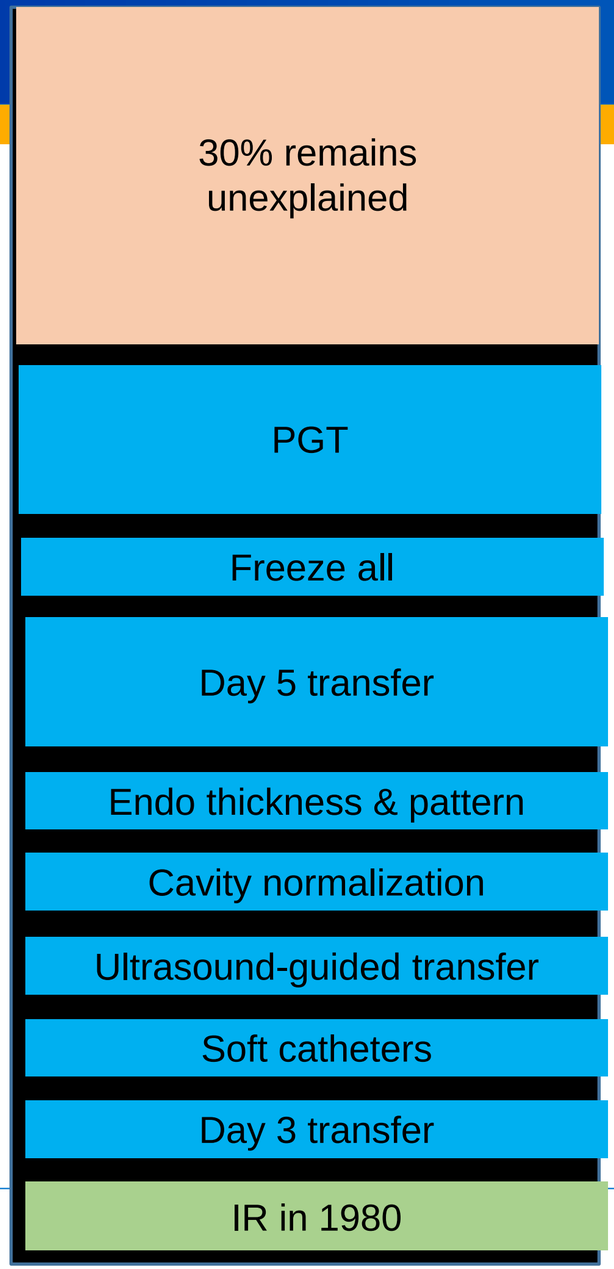
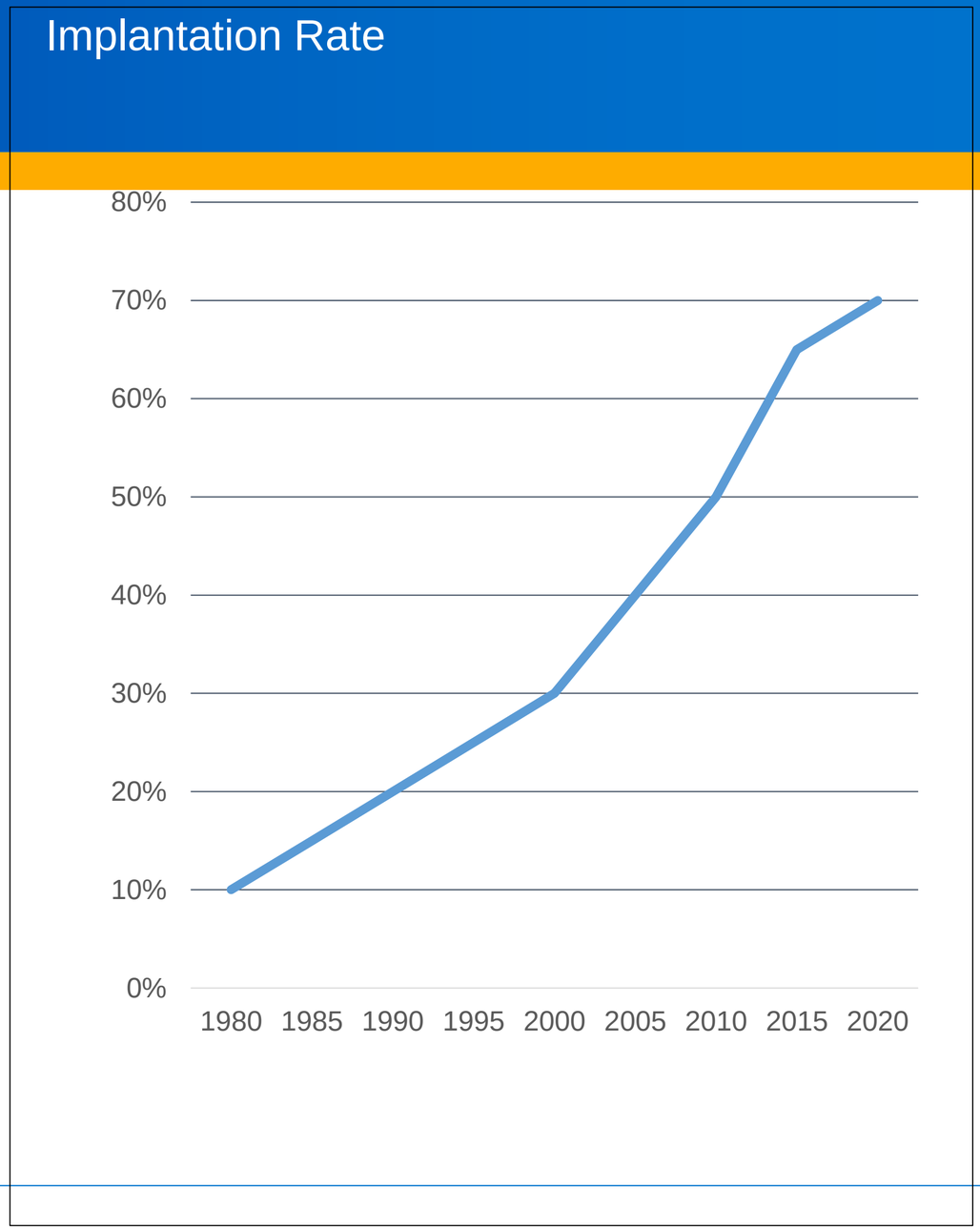


Implantation Rate



What we know / What we don't know ?

Live birth rates = 43 - 77%

With frozen euploid embryos

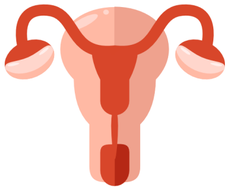
Scott et al, 2013; Forman et al, 2013; Capalbo et al, 2014; Dahdouh et al, 2015

↓

Not all euploid embryos implant

↓

RIF / implantation failure causes ?



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Persistent endometrial factors ?

OBJECTIVE

> To determine the true prevalence of RIF in women undergoing 3 successive frozen euploid single embryo transfers (FE-SET).

SEMINAL CONTRIBUTION

Rate of true recurrent implantation failure is low: results of three successive frozen euploid single embryo transfers

Paul Pirtea, M.D.,[a,b] Dominique De Ziegler, M.D.,[b] Xin Tao, Ph.D.,[c] Li Sun, Ph.D.,[c] Yiping Zhan, Ph.D.,[c] Jean Marc Ayoubi, M.D.,[b] Emre Seli, M.D.,[a,d] Jason M. Franasiak, M.D., H.C.L.D.,[a] and Richard T. Scott Jr., M.D., H.C.L.D.[a]

[a] IVIRMA New Jersey, Basking Ridge, New Jersey; [b] Hospital Foch, Paris, France; [c] Foundation for Embryonic Competence, Basking Ridge, New Jersey; and [d] Yale School of Medicine, New Haven, Connecticut

MATERIAL & METHODS - *Study Population*

Retrospective cohort study
Jan. 2006 to Jul. 2018

RMANJ
Reproductive Medecine Associates
Basking Ridge, New Jersey

PGT-A
qPCR and NGS based

Frozen Euploid Single Embryo Transfer (FE-SET)

MATERIAL & METHODS - *Inclusion criteria*

Included

- 4429 patients
- 19-46 years
- 14< BMI <51 kg/m2
- Aneuploidy screening
- Frozen Euploid Single Embryo Transfer FE-SET
- Morphologic Normal Uterus

Excluded

- Egg donation cycles
- Gestational carrier
- Indication for monogenic disease
- Endometrial thickness < 7 mm

n = 4429

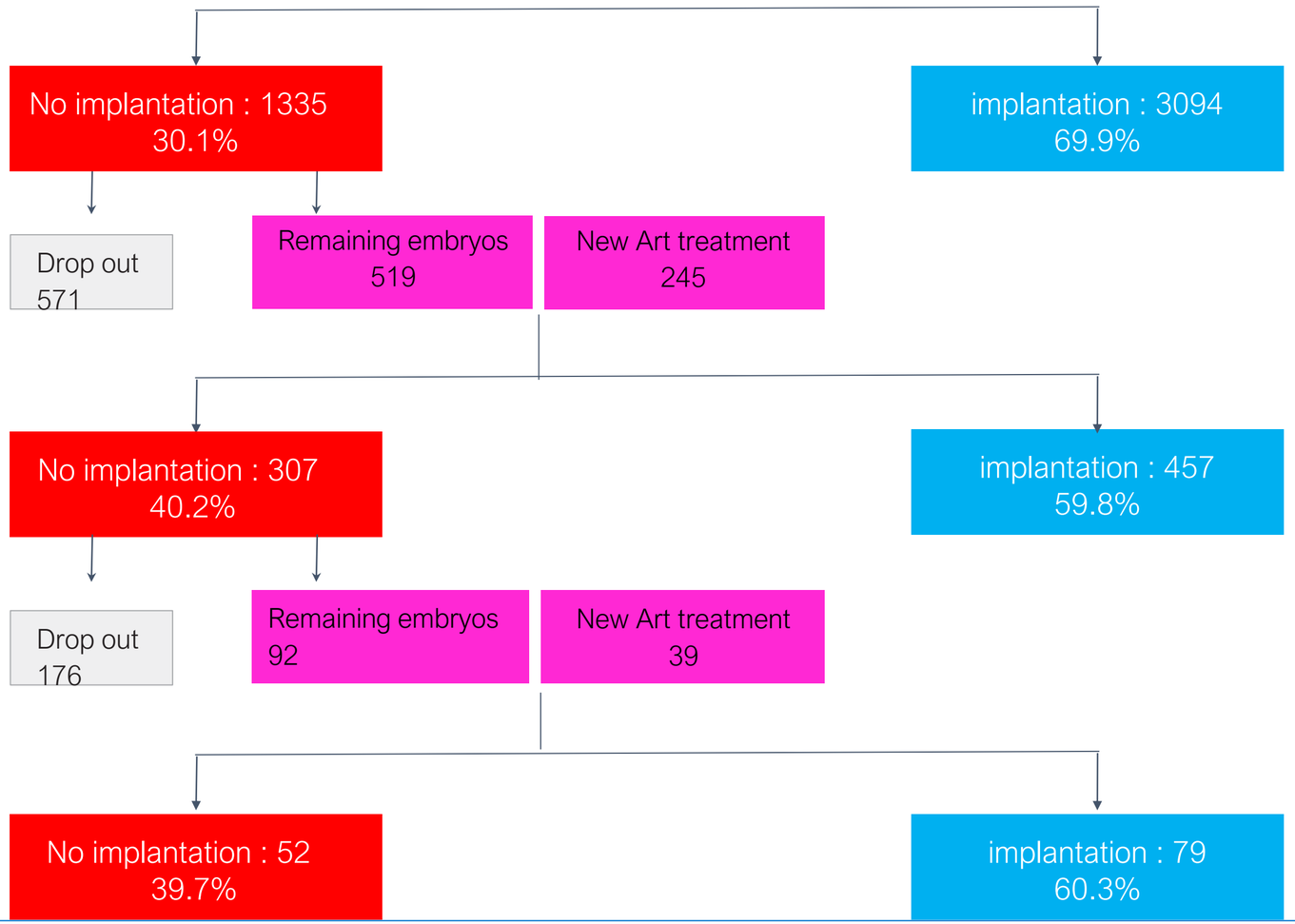
MATERIAL & METHODS - *Statistics*

- Descriptive statistics
- Linear regression models*
- Survival analysis

* Adjusted for :

- Age

RESULTS - *Implantation Rates*

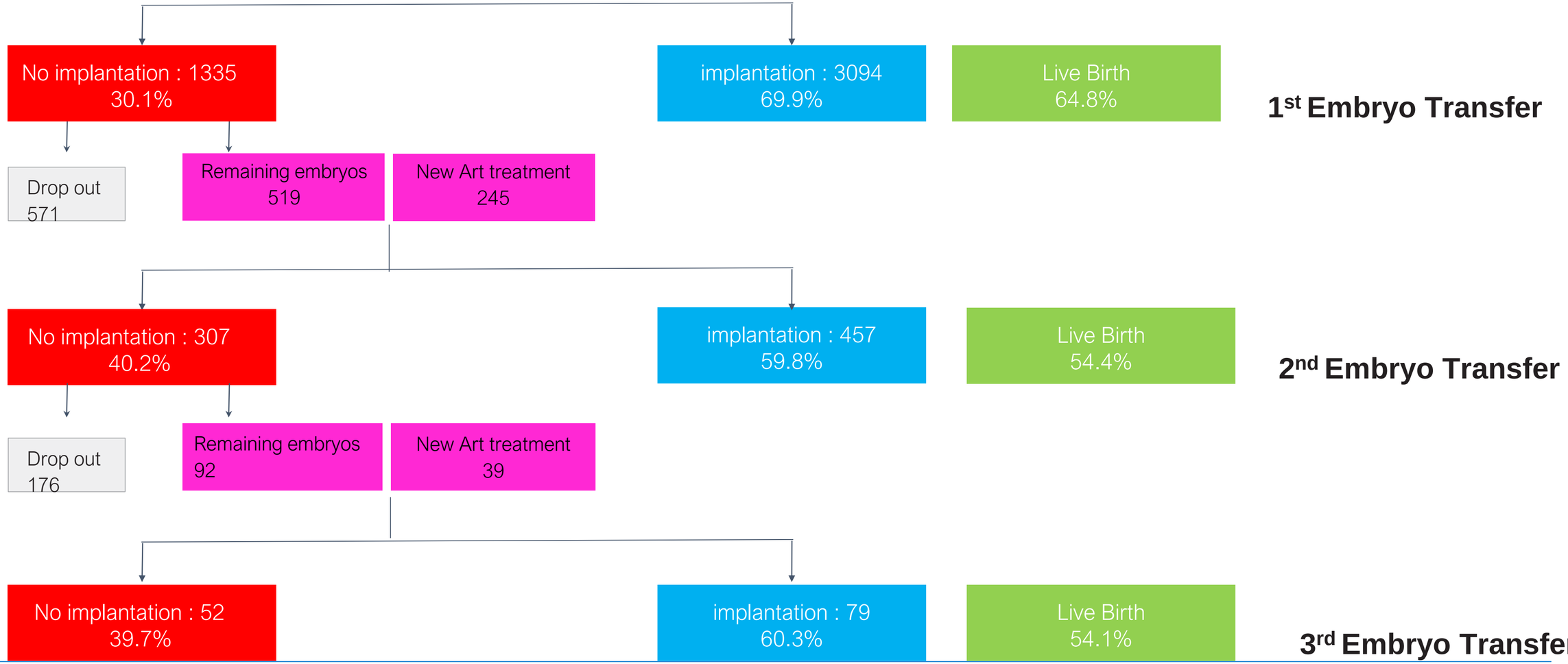


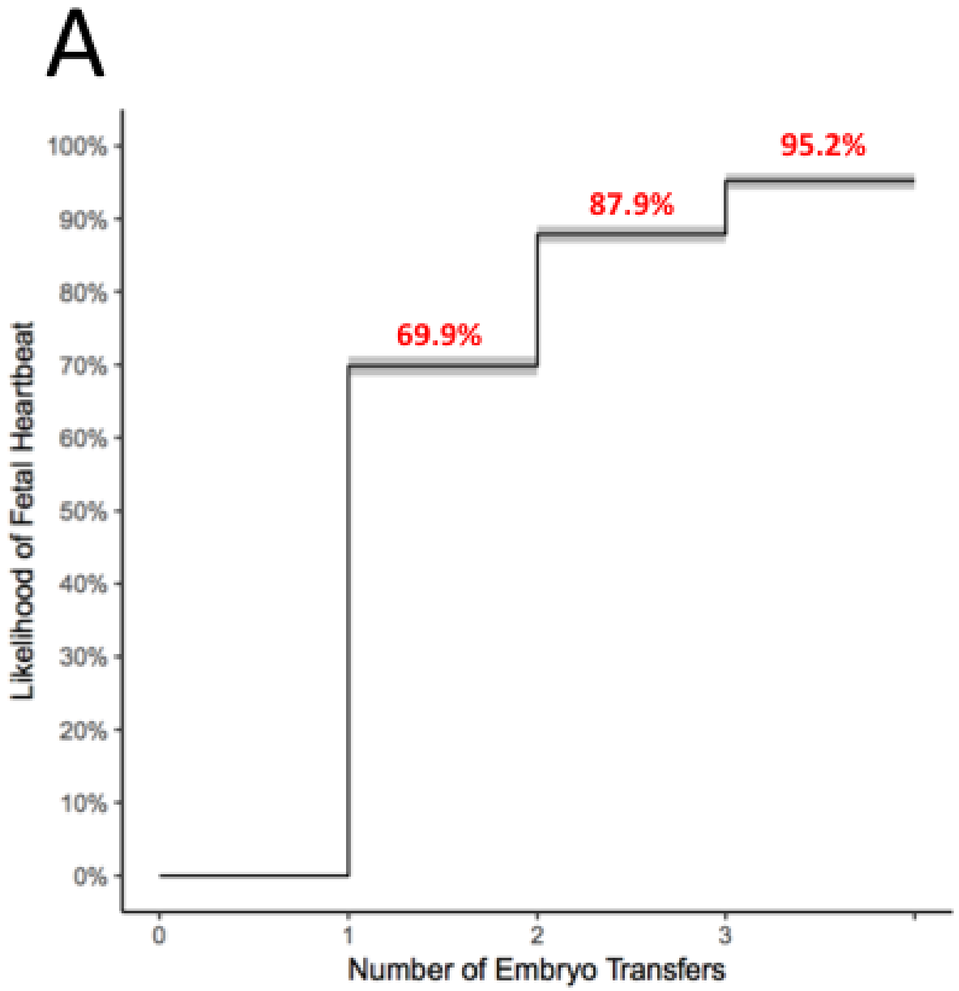
1st Embryo Transfer

2nd Embryo Transfer

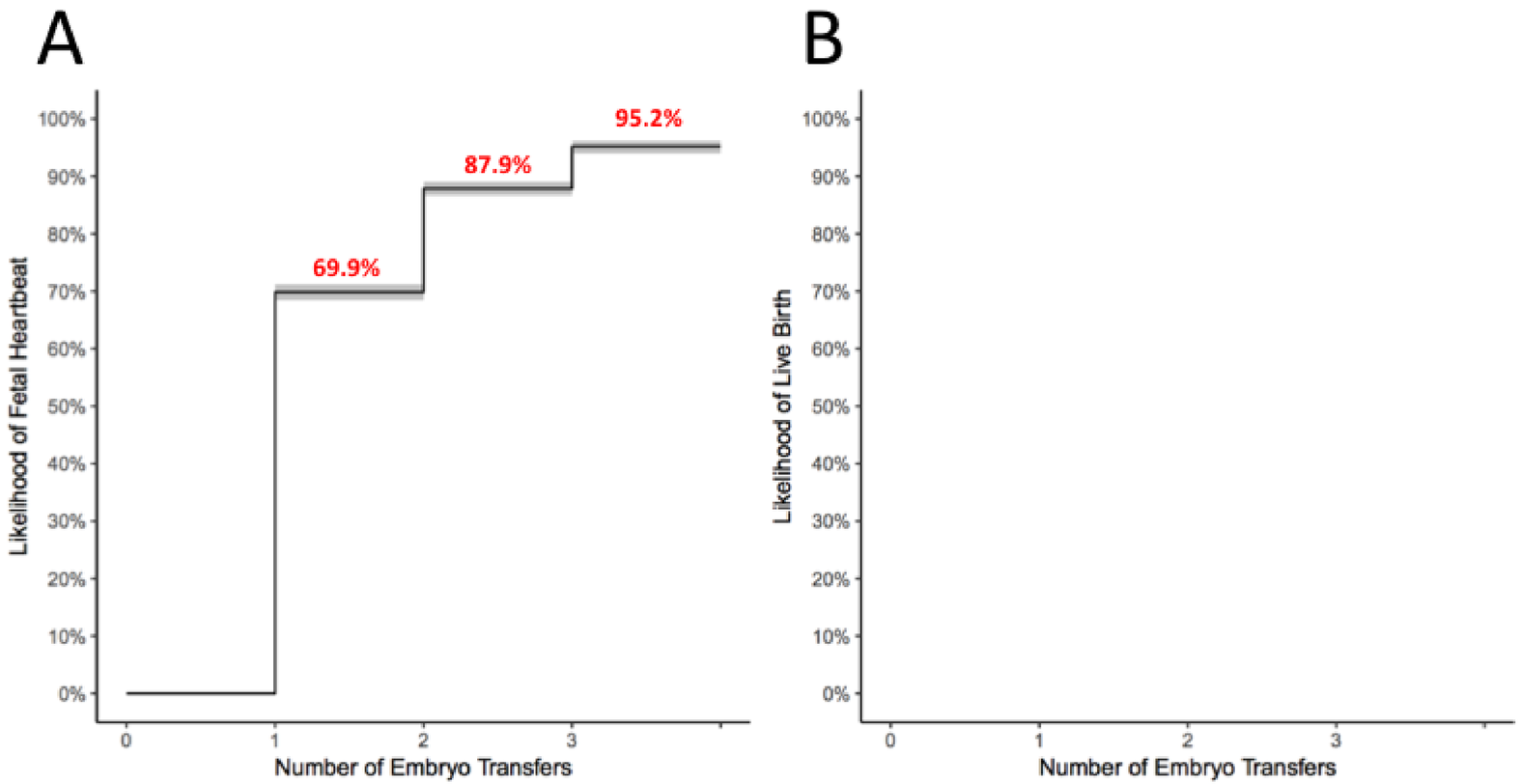
3rd Embryo Transfer

RESULTS - *Implantation Rates and Live Birth*

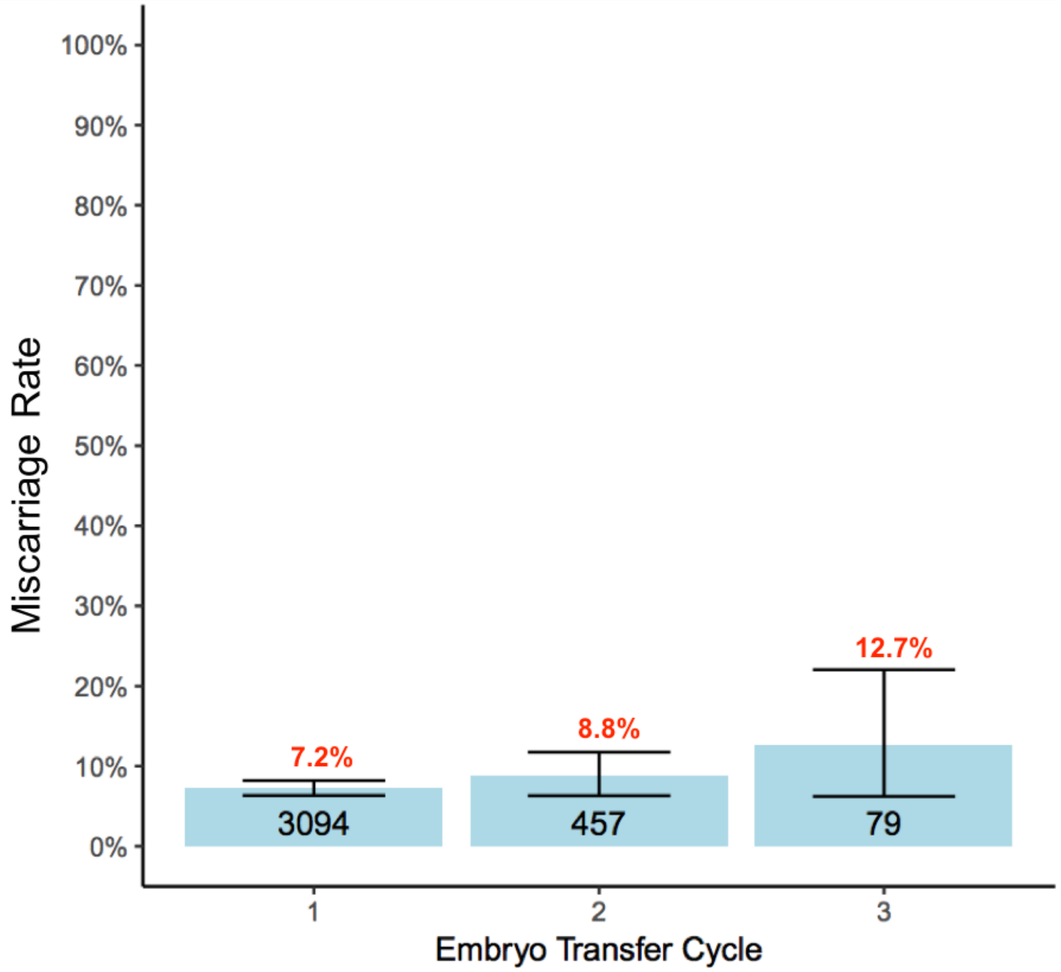



A
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Likelihood of Fetal Heartbeat
69.9%
87.9%
95.2%
0
1
2
3
Number of Embryo Transfers

RESULTS – *cumulative IR (panel A) and cumulative LBR (panel B)*



RESULTS - *Miscarriage Rate*



P=0.143

NS when ajusted for age

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At most a 5% decline per transfer
(but likely due in part to embryo quality)

Rate of true recurrent implantation failure is low: results of three successive frozen euploid single embryo transfers

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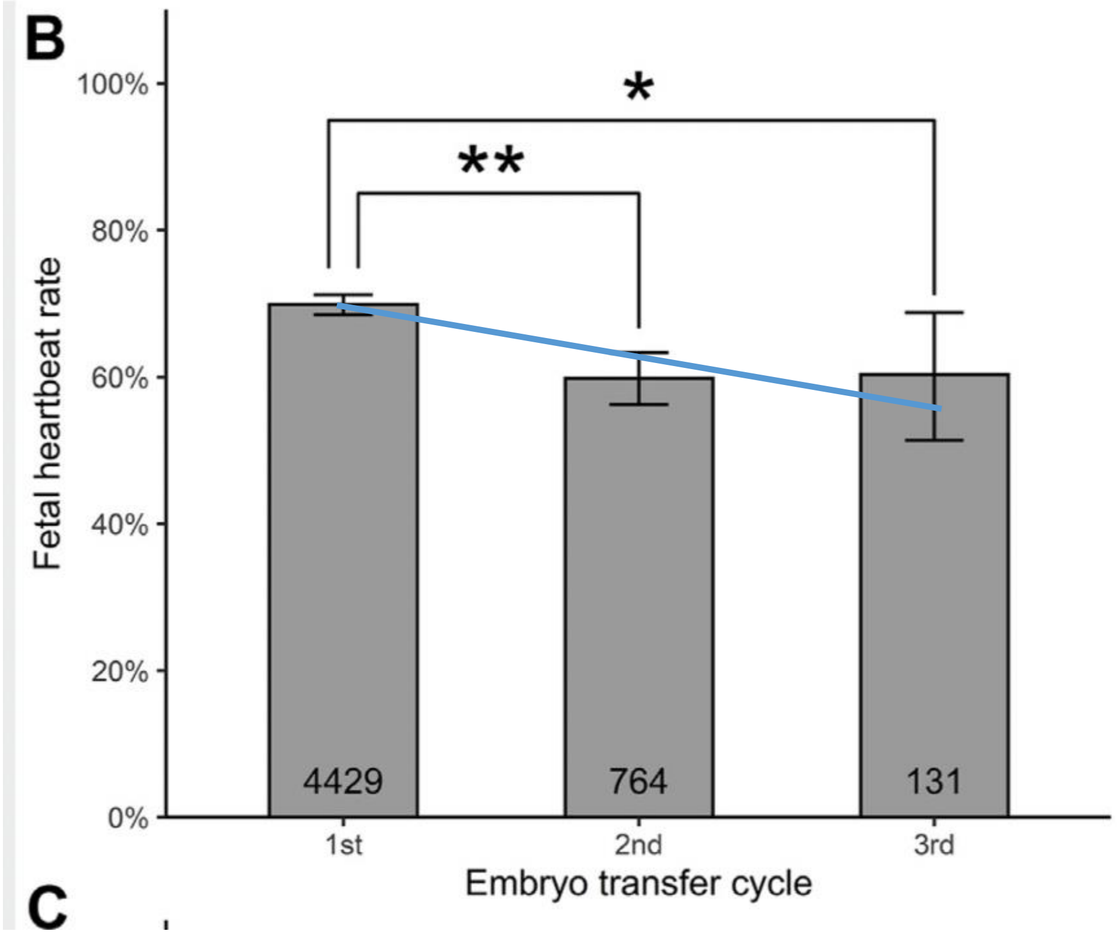
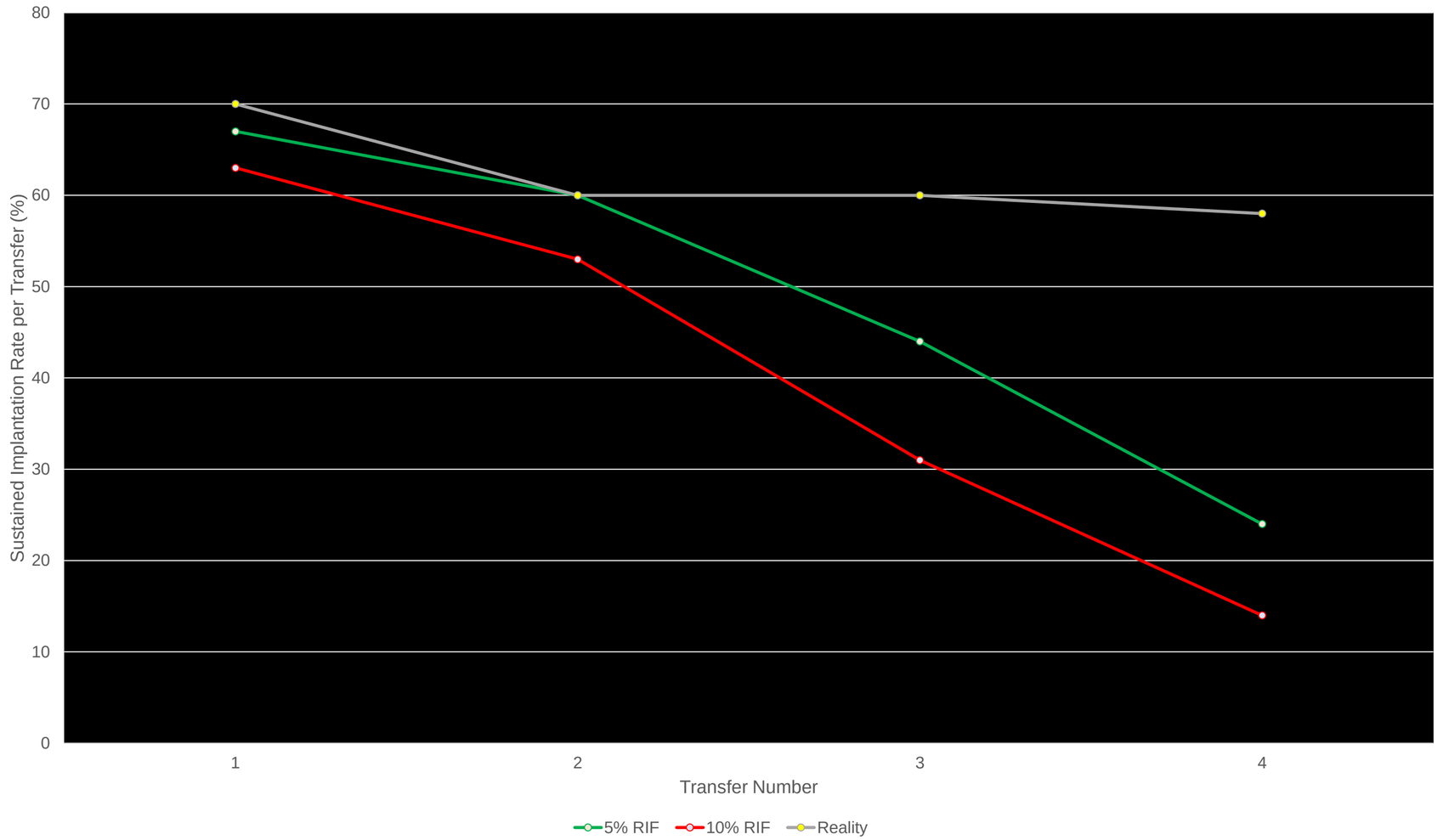


Cumulative Live Birth: **70%** **88%** **95%**

Predicted Sustained Implantation Rate (SIR)

- General Population
- Prevalence of RIF
  - 5%
  - 10%
- Assumes constant SIR of 70% amongst the NON-RIF patients
- Decreasing implantation rates reflects fixed number of RIF pts



"Reality" Data from Pirtea et al Fertil Steril 2020

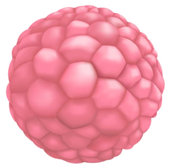
Estimation of the number of unscreened good quality embryos needed to be equivalent to 3 euploid ET

Age	Observed aneuploidy rate	Number of untested blastocysts
< 35	20%	5
35-37	30%	6
38-40	50%	9
41-42	70%	16
43+	85%	34

DISCUSSION

Women who failed to implant following a course of FE-SET do not have a marked increase incidence of failing again to implant in subsequent 2nd and 3rd FE-SET.

RIF rates following 3 successive FE-SET has an incidence of <5%.



Our data suggest that implantation failures of uterine origin are rare when euploid embryos are transferred in women with a morphologically normal uterus.

LIMITATIONS & STRENGHTS

Retrospective nature

Large size of the cohort and its extensive nature

Some successive FE-SETs came from different ART cycles

IR of the 2 subgroups after the 2nd FE-SET we noticed similar results

All FE-SET over seven years

Our series is the largest reported of sequential FE-SET
→ Reliably call into question the role of uterine factors in RIF

CONCLUSIONS

Our findings suggest that true endometrial RIF is rare when euploid embryos are transfered .

In patients who have euploid blastocysts, 95.2% achieve clinical pregnancy after 3 frozen euploid single embryo transfers.

Implantation rates decline minimally with increasing transfers.

Additional euploid embryo transfers offer hope of a good outcome.

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THE LUGANO CONSENSUS

RECURRENT IMPLANTATION FAILURE (RIF): REALITY OR STATISTICAL MIRAGE?

Excerpts from the July 1, 2022 Lugano Workshop on repeated implantation failures (RIF)

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RMA
Reproductive Medicine Associates of New Jersey

Take-home messages

- **Considering that euploid blastocysts have a chance to implant of between 45% and 65% regardless of age**
- **The unsuccessful transfer of 3–4 euploid blastocysts is required to diagnose RIF (as then the expected cumulative probability exceeds 95%) (1)**
- **Support for different thresholds for research vs. clinical investigation of RIF**

1. **Somigliana et al. RBMO 2022.**
2. **ASRM Practice Committee 2012.**

THANK YOU

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