

Are RCT's the best way to demonstrate benefits of PGT-A or any PGT?

Joe Leigh Simpson, MD

***Florida International University
Miami, FL, USA***

***Reproductive Genetic Innovations
Chicago, IL, USA***

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Human Reproduction Debates in 2008 following Mastenbroek et al. 2007 (NEJM)

- Joe Leigh Simpson, Human Reproduction 10:2179, 2008

What next for preimplantation genetic screening?

Randomized clinical trial and assessing PGS; necessary but not sufficient

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Randomized Clinical Trials (JLS, 2008)

- “The randomized clinical trial (RCT) is a powerful experimental design that when properly executed produces generalizable results.
- When comparing a new drug to conventional therapy or absence thereof, few pitfalls should arise. No special diagnosis or technical processes is necessary”

Types of RCTs

Straight Forward

- Comparison of two drugs.
- Comparison standard drug vs no drug.

Complex

- Invasive diagnostic procedure versus no procedure. Need criteria for selection of operator.
- Accepted (standard) invasive diagnostic procedure vs. novel diagnostic procedure. Experience of operators pivotal.

- **JLS (2008): Complex RCT: “Conducting a RCT becomes more complex when technical skills are required. RCTs assessing the value of preimplantation genetic screening and euploidy testing require three general prerequisites-**
 - proper study design
 - skilled operators (embryo biopsy)
 - skilled laboratory cytogeneticists (diagnosis).

Lacking either of the latter two, even an elegantly designed RCT is not necessarily valid.”

Randomized Clinical Trials Show Benefit of PGT-A

<u>IMPLANTATION RATES</u>	<u>CONTROL</u>	<u>PGT</u>
Yang et al. 2012 (aCGH)	46%	69%
Scott et al. 2013 (qPCR)	63%	80%
Forman et al. 2013 (qPCR)	40%	58%
Dahdouh et al. Meta Analysis	53%	73%
	p<0.001	

Predictive Value Analysis can Replace RCT.

What is the Predictive Value of Transferring a Euploid vs an Aneuploid Embryo?

Experimental Design

1. Biopsy embryo
2. Transfer embryo without knowledge of chromosomal results
3. Compare pregnancy outcomes of euploid transfer vs aneuploid transfer

2021: Non-selective Predictive Value based on Next Generation Sequencing (NGS)

- 648 Couples 2014-2019
- 2110 Blastocysts (2.8% no-call rate)
 - 60.2% euploid
 - 24.6% aneuploid
- Transfer based only on morphology; trophectoderm biopsy PGT-A results learned 13 weeks later.

	<u>Implanted</u>	<u>Clinical Preg</u>	<u>Delivery</u>
• Euploid	82.1%	73.1%	64.7%
• Aneuploid	40.2%	23.5%	0%

Failure to Achieve Pregnancy is Low after Successive Single Euploid Transfers

How often is recurrent miscarriage not aneuploid?

Study Design

- 4429 women underwent up to 3 successive PGT-A euploid transfers
- Mean age 35.5 years

	<u>Sustained Implantation</u>	<u>Delivery</u>
1 st Transfer	69.9%	64.8%
2 nd Transfer	59.8%	54.5%
3 rd Transfer	60.3%	54%
Total	92.2%	

Why did Euploid Embryos not always result in Sustained Pregnancy?

1. Euploid mutation could exist (e.g. endometrial receptor defect)
2. If persisting, maternal mutation should have precluded successful transfer of euploid embryo in subsequent cycles
3. If later cycles with euploid transfer successful, stochastic explanation (bad luck) most likely

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Conclusion

1. RCTs ideally suited for straight forward questions that need not take into account surgical or laboratory qualifications
2. RCTs less suited for comparisons that need to take into account surgical or laboratory qualifications.
3. Predictive Value analysis involving non-selection of transferred embryos. Assessed by retrospective analysis avoids potential biases.

Thank you !

Joe Leigh Simpson, MD, FACOG, FACMG
simpsonj@fiu.edu

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NIH RCT: Chorionic Villus Sampling (CVS) vs. Amniocentesis

Experimental Design: RCT comparing outcomes in two cohorts
Operators (obstetricians) had performed CVS at academic centers and experienced.

Results: No increase in procedure- related pregnancy loss rates with CVS.

- Rhodes et al. 1989, NEJM
- Jackson et al. 1992, NEJM
- Mujezinovic and Alfirevic, Obstet Gynecol, Systematic Review. 2007

Conclusion: CVS a viable first trimester option

MRC RCT: Medical Research Counsel

Study Design:

RCT: CVS versus. Amniocentesis.

Outcome: Completed Pregnancies

Operators (Obstetricians) complete 30 “practice” CVS procedures

Results:

- 4.4 % fewer pregnancies in CVS cohort
- Medical Research Counsel European Trials of Chorionic Villus Sampling. Lancet 1999

Conclusion:

- Introduction of CVS delayed in Europe