
OVA SCIENCE SM
TRANSFORMING FERTILITY

Autologous Mitochondria Injection to Improve Oocyte Function in Women Undergoing IVF

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and TRIO Fertility

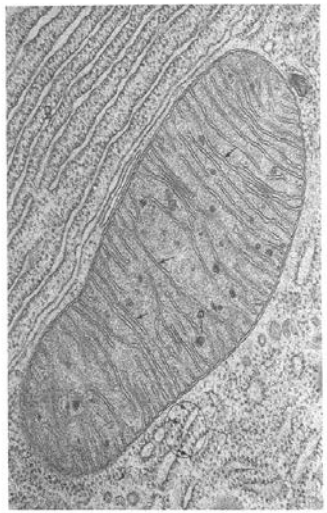
Disclosures

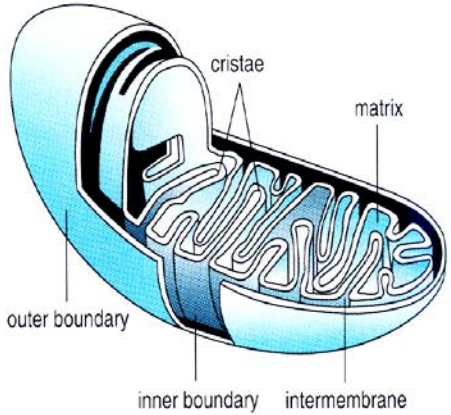
- Member of Scientific Advisory Board of OvaScience and Fertility Neutraceuticals
- Joint CIHR/OvaScience Research grant
- Discussion of commercial treatment

Global Demand for Fertility Treatments is Growing

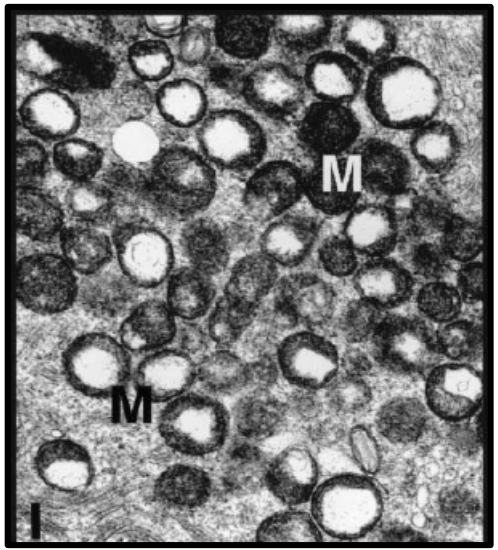
- Approximately 1.5 million *in vitro* fertilization (IVF) cycles reported per year worldwide
- IVF has been in clinical practice for 35+ years
- Despite significant gains in the live birth rate in good prognosis patients, there are few treatment options for repeated IVF failures

Somatic versus Human Oocyte Mitochondria





Somatic Cell Mitochondria

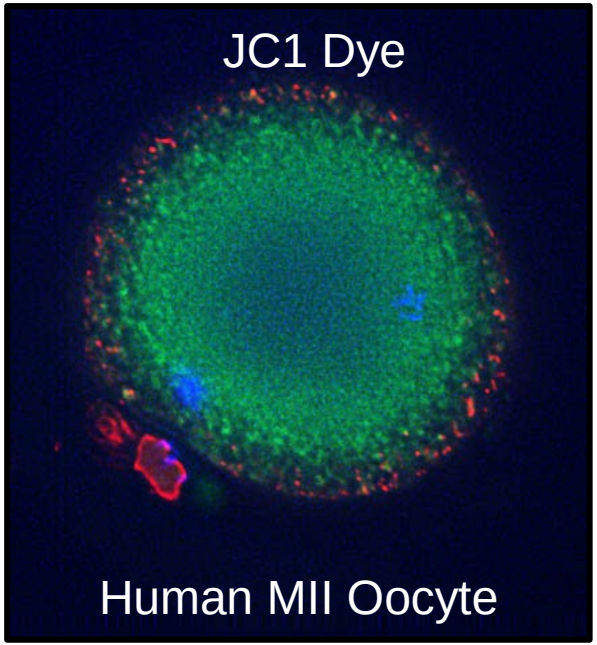


Human Oocyte Mitochondria

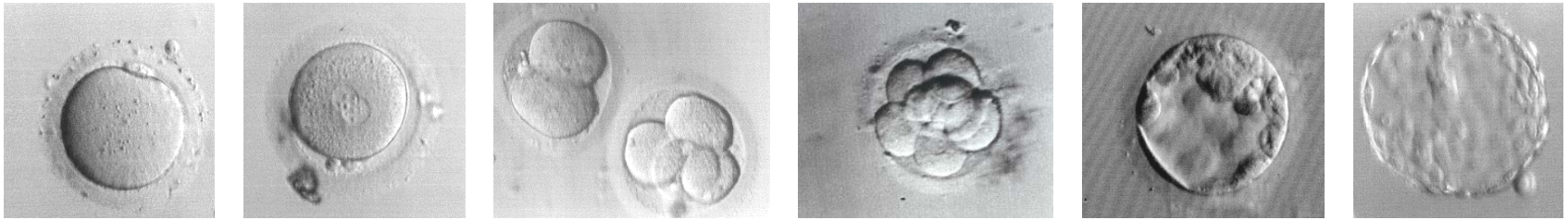
Van Blerkom et al, Hum Reprod 1998

Human Oocyte Mitochondria

- Between 200,000 and 500,000 mtDNA copies per oocyte
- At least 100 times more than most somatic cells



Mitochondrial Dilution During Embryo Development



Day 0 Day 1 Day 2 Day 3 Day 5 Day 6

Embryo Development

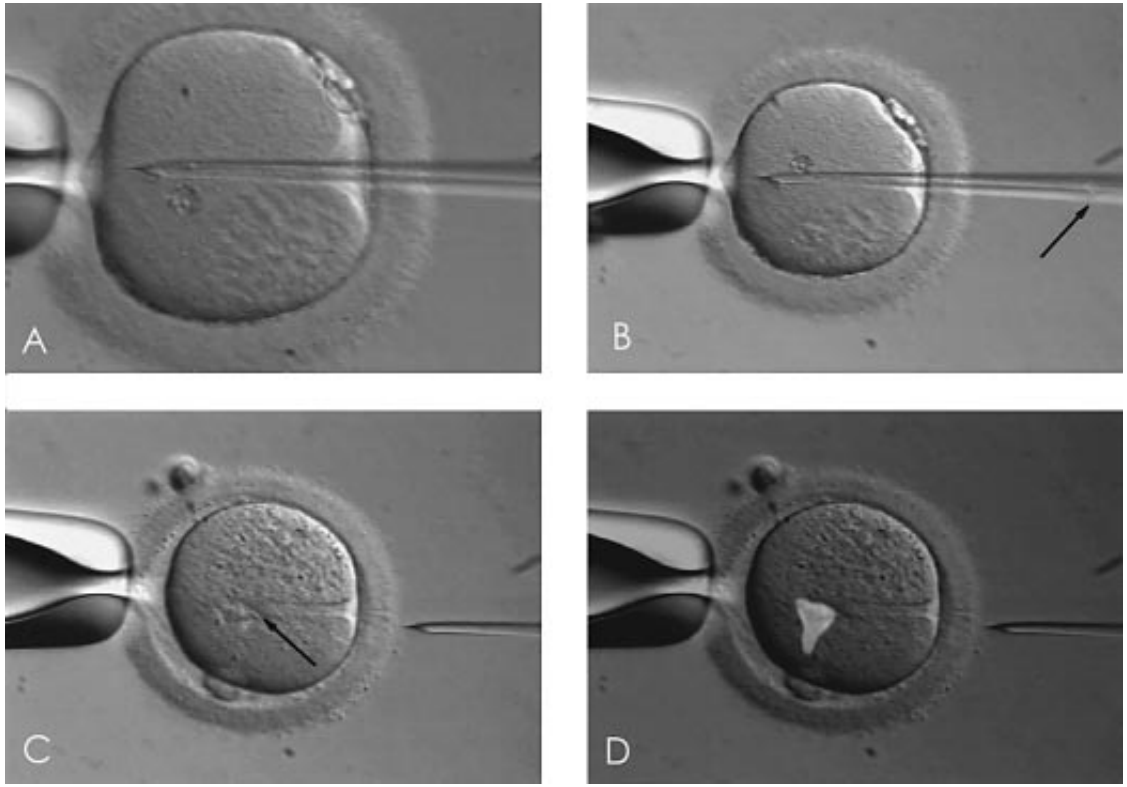
Human Ooplasmic Transfer

Ooplasmic Transfer

- Ooplasmic transfer from donor oocytes pioneered by Jacques Cohen, USA, 1997
- Beneficial effect seen on embryo development
- Several pregnancies obtained

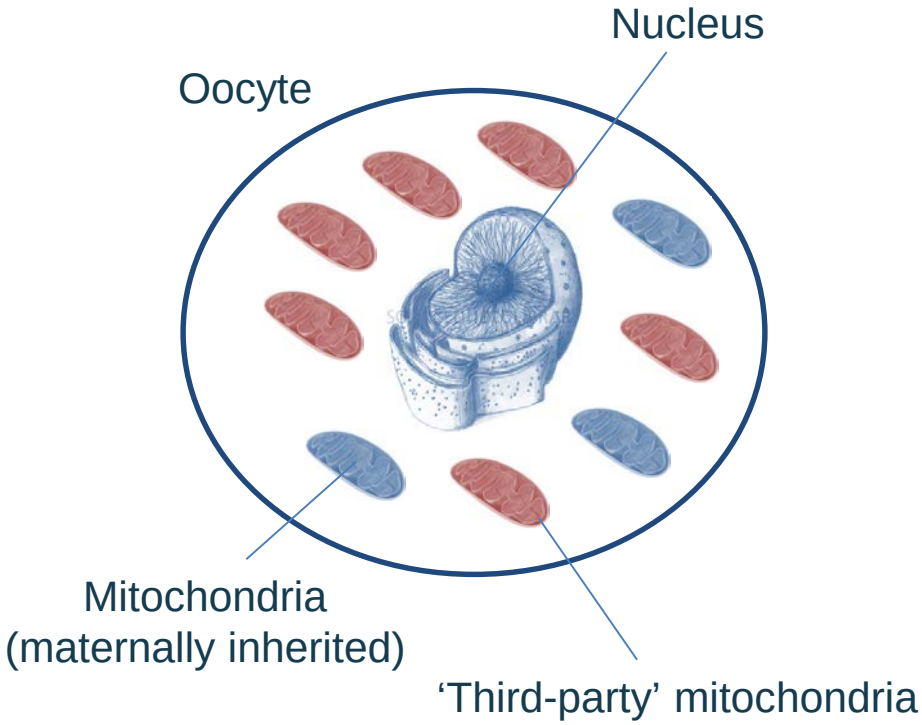
Cohen et al, Mol Hum Reprod 1998

Ooplasmic Transfer Process



Cohen et al, Mol Hum Reprod 1998

Heteroplasmy from Third-Party Mitochondrial Transfer



Donor Cytoplasm: Clinical Implications

- Long term effects of neutral mitochondrial heteroplasmy have not been studied
- Ooplasmic transfer is currently not sanctioned internationally

Lane and Nisker, J Obstet Gynecol, Canada 2016 (ePUB ahead of print)

Preclinical Support for Safety and Efficacy of Mitochondrial Transfer

Species	Cytoplasm (Cyto) or Mitochondria (Mito) Transfer	Safe for Oocyte	Increased Fertiliz-ation Rate	Viable Blastocyst	Healthy Live Births	Reference
Murine	Cyto and Mito	✓	✓	✓	✓	Yi, et al., 2007 Pinckert, et al., 1997 Acton, et al., 2007 Nagai, et al., 2004 Takeda, et al., 2005 Ishihara, et al., 2003 Cheng, et al., 2009 Ebert, et al., 1989 Van Blerkom, et al. 1998 Levron, 1998 Meirelles, et al., 1998
Porcine	Cyto	✓	✓	✓	Not reported	El Shourbagy, et al., 2006 Cagnone Tsai et al. 2016
Bovine	Mito	✓	✓	✓	Not reported	Chiaratti, et al., 2011 Hua, et al., 2007 Ferreira, et al., 2010

New Option for Repeated IVF Failure

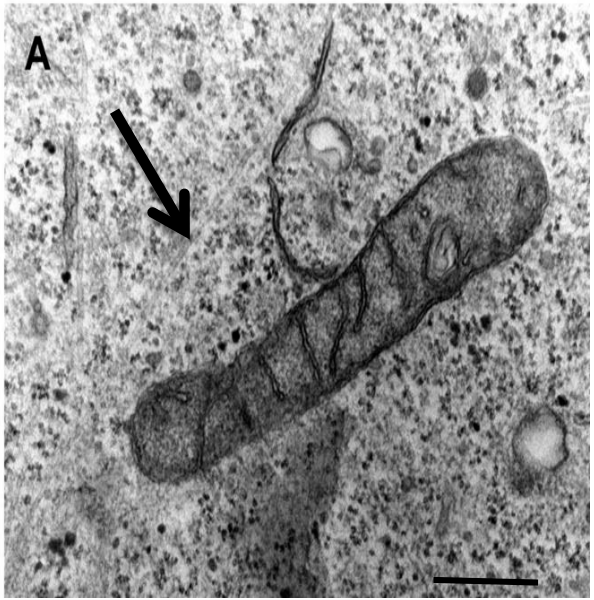
- Convincing evidence that adequate oocyte mitochondrial activity is necessary for embryo development to blastocyst and for successful implantation
- New Option for Repeated IVF Failure?
  - Autologous Mitochondrial Injection
- Goals:
  - Improve oocyte and embryo quality
  - Increase healthy live birth rate

Egg Precursor Cells

- Egg precursor cells in cortical tissue of the ovary are in a quiescent state
- Unlike stem cells, egg precursor cells are unipotent, germline cells
- Appear to be “younger”, not aged like somatic cells in the body
- Multiple independent investigators have published their research on egg precursor cells

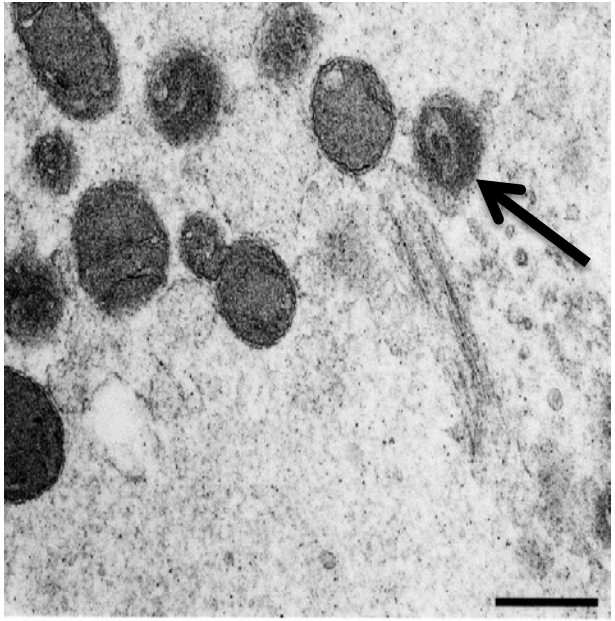
Egg Precursor Cell Mitochondria

Human Brain Cell



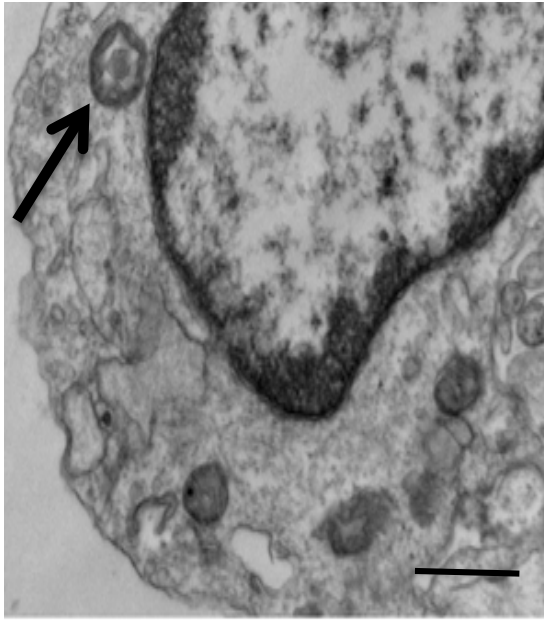
500 nm

Human Oocyte



500 nm

Human EggPC Cell



500 nm

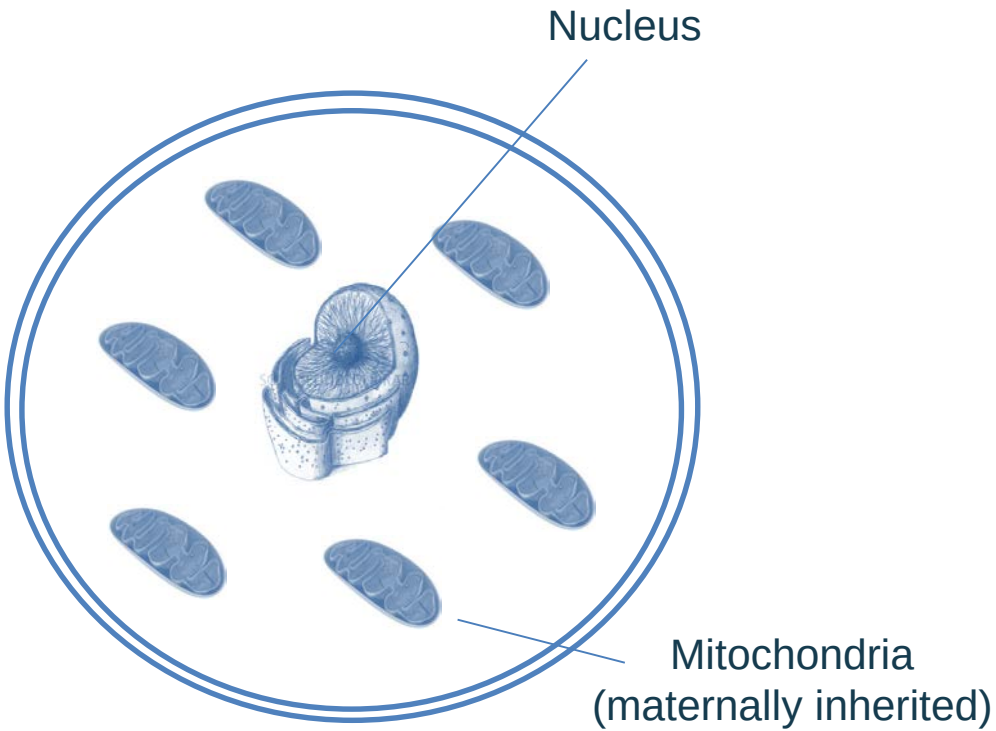
Human Brain cell: Bannwarth et al., Brain 2014: 137; 2329-2345

Human oocyte: Nottola et al., Human Reproduction 2007: 22; 1123-1133

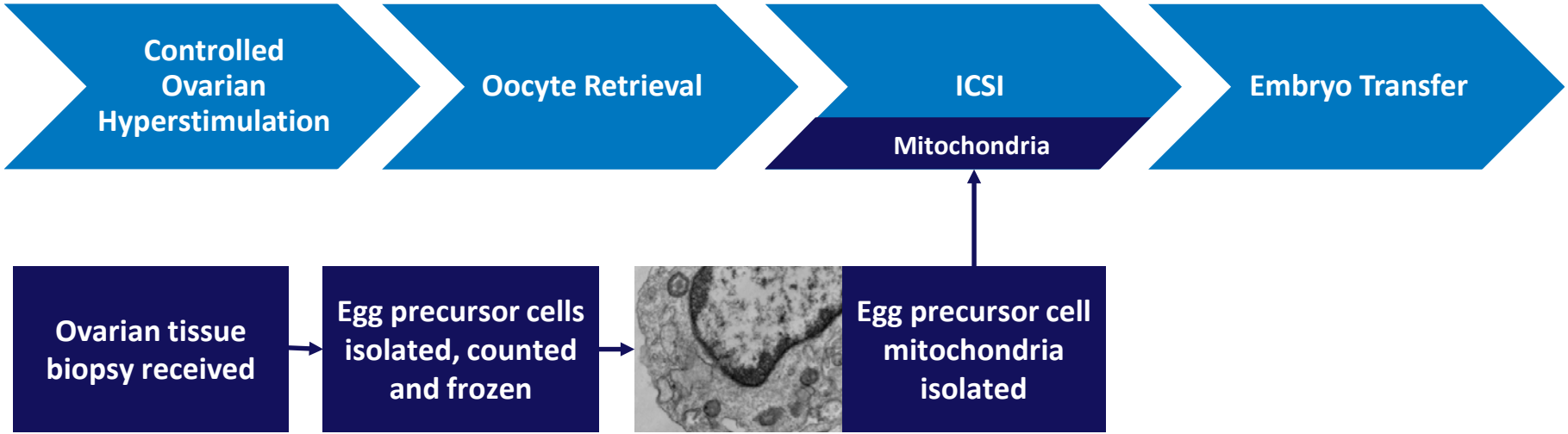
Human EggPC: Bonkowski et al., Ovarian Club VII Meeting 2016, Hong Kong: Poster 0009

Autologous Mitochondrial Transfer

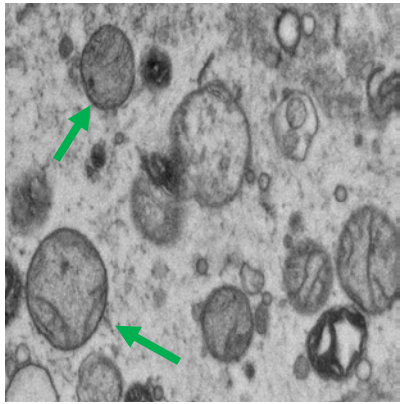
- Mitochondria obtained from egg precursor cells
- Maintains mitochondrial homoplasmy and nuclear and mitochondrial DNA communications



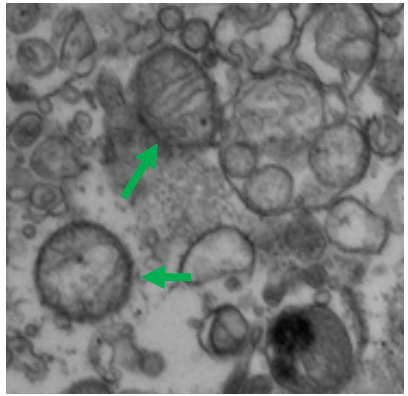
Autologous Mitochondrial Injection (AUGMENT^{SM} treatment) Process



EM of human EggPC mitochondria after processing



Pre-Freezing

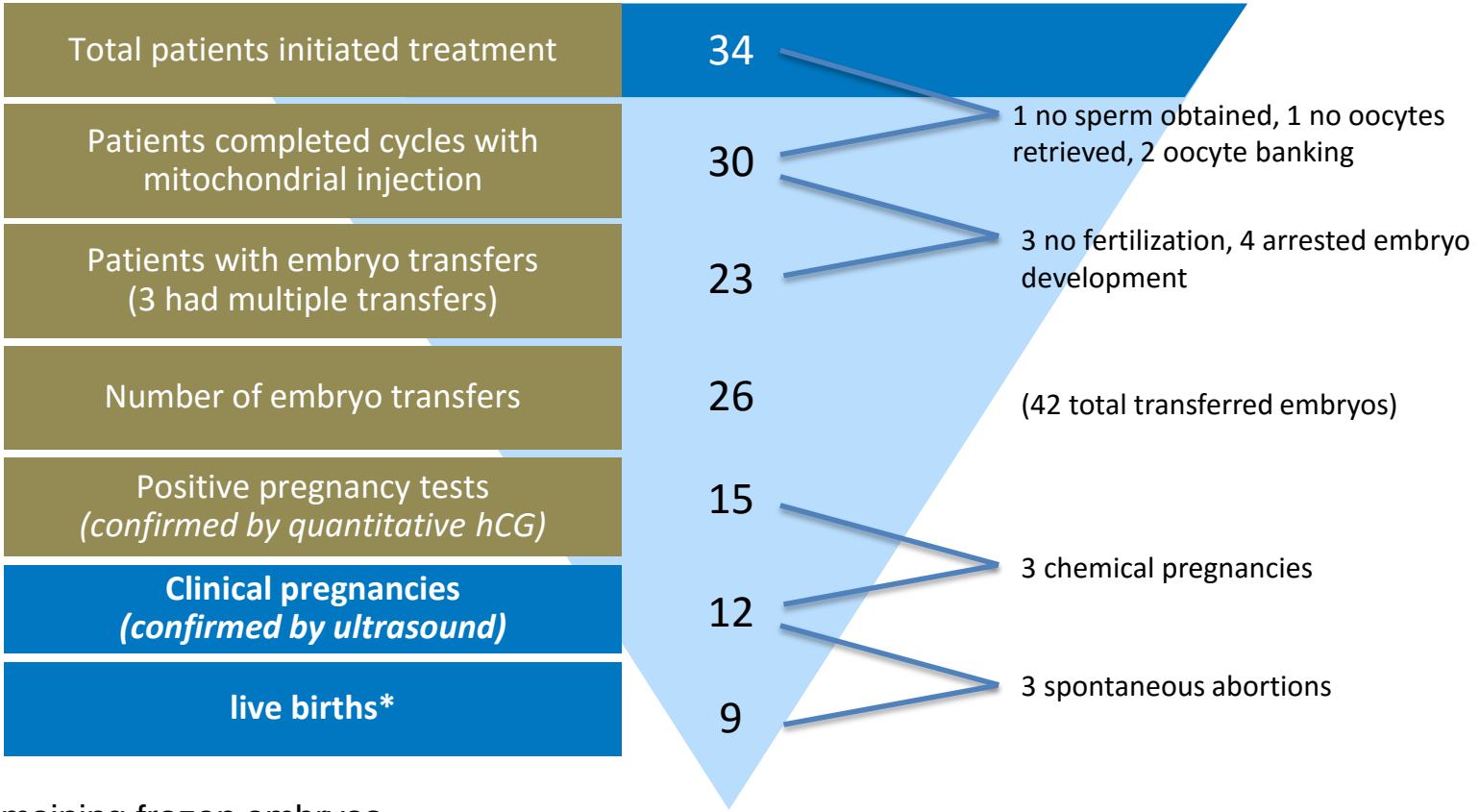


Post-Thaw

June 2015: Baseline Historical Pregnancy Rate

Metric	Previous IVF History Data
Number of patients	34
Average current age	36.0 (Range: 26-44)
Background/Diagnoses	Poor oocyte & embryo quality with one of the following diagnoses: Diminished Ovarian Reserve, Ovulatory Dysfunction, Polycystic Ovarian Syndrome, Tubal Factor, Endometriosis, Unexplained
Total previous IVF cycles initiated	71
Average cycles per patient	2 (Range: 1-5)
Total previous embryo transfers (fresh & frozen)	79
Historical clinical pregnancy rate: • **per cycle initiated** • **per embryo transfer**	 **11% (8/71)** **10% (8/79)**
Historical live birth rate: • **per cycle initiated** • **per embryo transfer**	 **1.4% (1/71)** **1.3% (1/79)**

June 2015: Clinical Experience with Autologous Mitochondrial Injection



* Remaining frozen embryos

June 2015: Clinical Experience with Autologous Mitochondrial Injection

Metric	Mitochondrial Injection
Number of patients	34
Average current age	36.0 (Range: 26-44)
Background/Diagnoses	Poor oocyte & embryo quality with one of the following diagnoses: Diminished Ovarian Reserve, Ovulatory Dysfunction, Polycystic Ovarian Syndrome, Tubal Factor, Endometriosis, Unexplained
Total mitochondrial injection cycles initiated	34
Average cycles per patient	1
Total embryo transfers (fresh & frozen)	26
Clinical pregnancy rate: • **per cycle initiated** • **per embryo transfer**	 **35% (12/34)** **46% (12/26)**
Live birth rate: • **per cycle initiated** • **per embryo transfer**	 **26% (9/34) *9 live births*** **35% (9/26) *9 live births***

9 patients have frozen embryos remaining for transfer

Updated Clinical Experience with Autologous Mitochondrial Injection

Metric	Mitochondrial Injection	
	< 40	≥40
Number of patients	26	23
Average age	35 years	42.5 years
Previous cycles	51	>70
Total mitochondrial injection cycles initiated	26	23
Total embryo transfers (fresh & frozen)	18 + 18	15 + 14
Ongoing Pregnancy per fresh ET	3/18 (17%)	0/15 (4 SAB)
Ongoing Pregnancy per FET	11/18 (61%)	1/14 (2 SAB)
Ongoing clinical pregnancy and live birth rate: per cycle initiated per embryo transfer	 54%* (14/26) 39% (14/36)	 4.3% (1/23) 3.4% (1/29)

* 12 live births, and frozen embryos remaining for transfer

CARTR/BORN Data 2014

Metric	Mitochondrial Injection		
	< 35	35-39	≥40
# of cycle starts	6444	5992	3706
Clinical pregnancy rate / cycle rate	38.2%	31.5%	18%
Live birth rate / cycle start	31.2%	23.4%	10.3%
Life birth rate / embryo transfer	38.4%	28.8%	13.8%
Percent single embryo transfer	57.8%	39.6%	24.1%
Multiple birth rate	16.8%	16.4%	15.2%

https://cfas.ca/cartr-annual-reports/

Conclusion

- Clinical experience with autologous mitochondrial injection during ICSI appears promising

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