Autologous mitochondrial injection to increase energy in oocytes

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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
Preclinical Support for Safety and Efficacy of Mitochondrial Transfer

<table>
<thead>
<tr>
<th>Species</th>
<th>Cytoplasm (Cyto) or Mitochondria (Mito) Transfer</th>
<th>Safe for Oocyte</th>
<th>Increased Fertilization Rate</th>
<th>Viable Blastocyst</th>
<th>Healthy Live Births</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Murine  | Cyto and Mito                                   | ✓              | ✓                           | ✓                 | ✓                 | Yi, et al., 2007  
Pinckert, et al., 1997  
Acton, et al., 2001  
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 |
| Bovine  | Cyto and Mito                                   | ✓              | ✓                           | ✓                 | Not reported      | Chiaratti, et al., 2011  
Hua, et al., 2007  
Ferreira, et al., 2010 |
Convincing evidence that adequate oocyte mitochondrial activity is necessary for embryo development to blastocyst and for successful implantation\(^1\)

**Goals:**

- Improve oocyte and embryo quality
- Increase healthy live birth rate

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1. Chappel, Obst and Gyn Intl 2013; Tilly et al, Cell Metab 2013
Discovery of Egg Precursor Cells

Egg Precursor Cell Mitochondria are Similar to Oocyte Mitochondria

- Egg precursor cells are unipotent, germline cells in the outer cortex of the ovary

Human brain: [http://dx.doi.org/10.1093/brain/awu138](http://dx.doi.org/10.1093/brain/awu138), 2329-2345, 2014
Human egg precursor cell: Harvard Medical School
Autologous Mitochondrial Transfer Possible

- Maintains mitochondrial homoplasmy and nuclear and mitochondrial DNA communications

1. White et al., 2012
AUGMENT<sup>SM</sup> Process

1. Performed by OvaScience
Many Conditions are Prognostic for Live Birth

- Age
- Oocyte/embryo quality
- Antral follicle count
- Hormone levels: FSH (follicle stimulating hormone), AMH (anti-mullerian hormone)
- BMI (body mass index)
- Environmental factors
- Previous diagnoses: diminished ovarian reserve, endometriosis, etc.
- Previous failed IVF

Lack of agreement on how to rank significance of risk factors
## Baseline Clinical Pregnancy Rate

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

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<tr>
<td>Total mitochondrial injection cycles initiated</td>
<td>34</td>
</tr>
<tr>
<td>Average cycles per patient</td>
<td>1</td>
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<tr>
<td>Total embryo transfers (fresh &amp; frozen)</td>
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**Clinical pregnancy rate:**
- per cycle initiated: 35% (12/34)
- per embryo transfer: 46% (12/26)

**Ongoing clinical pregnancy and live birth rate:**
- per cycle initiated: 26% (9/34) includes 1 live birth
- per embryo transfer: 35% (9/26) includes 1 live birth

9 patients have 23 total frozen embryos remaining for transfer.
**Clinical Experience with AUGMENT™**

- **Total patients initiated treatment**: 34
- **Patients completed cycles with mitochondrial injection**: 30
- **Patients with embryo transfers (3 had multiple transfers)**: 22
- **Number of embryo transfers**: 26
- **Positive pregnancy tests (confirmed by quantitative hCG)**: 15
- **Clinical pregnancies (confirmed by ultrasound)**: 12
- **Ongoing clinical pregnancies and live births***: 9

* Includes 1 live birth

- 1 no sperm obtained, 1 no oocytes retrieved, 2 oocyte banking
- 3 no fertilization, 4 arrested embryo development, 1 pending frozen embryo transfer
- (42 total transferred embryos)
- 3 chemical pregnancies
- 3 spontaneous abortions
Clinical Experience Shows Improved Pregnancy Rates Compared to Baseline

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<td>Clinical pregnancies</td>
<td>8</td>
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<td>10%</td>
<td>46%</td>
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<tr>
<td>Ongoing clinical pregnancies and live births (rate per cycle initiated)</td>
<td>No ongoing and 1 live birth (1%)</td>
<td>9 including 1 live birth (26%)</td>
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Conclusion

• Clinical experience with AUGMENT\textsuperscript{SM} during ICSI appears promising
  – One live birth and 8 ongoing clinical pregnancies
  – Ongoing clinical pregnancy rate of 26% per cycle initiated and 35% per embryo transfer

• Women included in this clinical experience were poor prognosis for live birth
  – Failed previous IVF cycles, poor embryo development, and 1.4% live birth rate per previous cycle

• Nine patients have frozen embryos remaining for transfer
Acknowledgements

TCART Clinical
- Dr Yaakov Bentov
- Dr Paul Chang
- Dr Dan Nayot
- Deborah Myers
- Caroline Lux

First Steps
- Dr Marjorie Dixon
- Dr Fay Weisberg

TCART Lab
- Dr Navid Esfandiar
- Dr Julia Szeptycki
- Dennis De la Cruz
- Khalid Rao