An ICSI strategy too far?

Testicular or ejaculated sperm (when both are available) in Oligozoospermia and ICSI failure

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Importance of Sperm DNA damage

- Higher prevalence of Sperm DNA damage in infertile men
- Sperm DNA damage associated with lower Pregnancy rate and higher pregnancy loss
- Concern of sperm genetic defect transferred to offspring via ICSI

WHY Testicular Sperm over Ejaculated Sperm for ICSI
(when both are available)

Experimental evidence
- Suganuma et al, 2005
  - Sperm DNA damage increase during transit through epididymis
  - Decline in fertility with abnormal chromatin during epididymal passage

Greco et al, 2005
- No specific treatment for SDF
  - Less SDF in testicular vs ejaculated sperm
  - Use of testicular sperm improved ICSI clinical outcomes
Testicular sperm should be offered to ICSI candidates with high Sperm DNA Fragmentation (SDF) in semen

1. SDF negatively impacts ART outcomes
2. SDF is lower in testicular than ejaculated sperm of non-azoospermic infertile men with high SDF in neat semen
3. Testicular sperm (therefore with lower SDF than ejaculated sperm) improves ICSI pregnancy outcomes in couples whose male partners have high SDF in semen
Premise # 1
Sperm DNA Fragmentation (SDF) negatively impacts ART outcomes

Review: Diagnosis and impact of sperm DNA alterations in assisted reproduction

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Translating the impact of SDF to Clinical Practice

IVF/ICSI Miscarriage:

- By fertilization method
  - IVF studies: OR 1.15 (95% CI 1.05-1.27); P=0.003
  - ICSI studies: OR 1.12 (95% CI 1.01-1.25); P=0.025

- By SDF assay type
  - TUNEL: OR 1.85 (95% CI 1.52-2.28); P<0.0001
  - SCD: OR 1.16 (95% CI 1.02-1.32); P=0.023
  - Comet: OR 4.15 (95% CI 3.04-5.68); P<0.0001
  - SCSA: OR 1.14 (95% CI 1.04-1.25); P=0.004

- Female infertility factors excluded
  - 1704 cycles: OR 1.37 (95% CI 1.11-1.68); P=0.003 (irrespective of method)

70 studies; 9363 IVF; 6260 ICSI; 2121 mixed IVF/ICSI

RR: 2.2 16 studies; 2959 couples (95% CI: 1.54–3.03); P<0.00001

Robinson et al, Hum Reprod 2012
Simon et al, Best Pract Res Clin Obstet Gynaecol 2017

OR~2.3 14 studies; 2756 couples (95% CI: 1.55–3.35; P<0.001)

Zhao et al, Fertil Steril 2014

ICSI only: OR 2.7

(95% CI: 1.40–5.14; P=0.003)
Premise #2:
SDF is lower in testicular than ejaculated sperm of non-azoospermic infertile men with high SDF in neat semen
Premise #3:
Testicular sperm improves ICSI pregnancy outcomes in couples whose male partners have high SDF in semen

### A. Fertilization rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fertilization - oligospermia / non-ICSI failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradley 2015</td>
<td>155</td>
<td>979</td>
<td>20%</td>
<td>1.19 (0.94, 1.50)</td>
<td></td>
</tr>
<tr>
<td>Addin 2015</td>
<td>418</td>
<td>1,105</td>
<td>39%</td>
<td>1.07 (0.90, 1.26)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>553</td>
<td>2,084</td>
<td>44%</td>
<td>1.14 (1.01, 1.28)</td>
<td></td>
</tr>
<tr>
<td><strong>Fertilization - nonoligospermia / repeat ICSI failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seco 2005</td>
<td>140</td>
<td>187</td>
<td>22.9%</td>
<td>1.11 (0.83, 1.48)</td>
<td></td>
</tr>
<tr>
<td>Farkas 2016</td>
<td>147</td>
<td>106</td>
<td>22%</td>
<td>1.25 (0.80, 1.99)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>287</td>
<td>293</td>
<td>41%</td>
<td>1.14 (0.88, 1.48)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1,140</td>
<td>2,377</td>
<td>100%</td>
<td>0.81 (0.59, 1.15)</td>
<td></td>
</tr>
</tbody>
</table>

### C. Miscarriage rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Misscarriage - oligospermia / non-ICSI failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradley 2016</td>
<td>4</td>
<td>11</td>
<td>37%</td>
<td>1.26 (0.63, 2.53)</td>
<td></td>
</tr>
<tr>
<td>Seco 2005</td>
<td>4</td>
<td>40</td>
<td>12</td>
<td>33</td>
<td>0.21 (0.05, 0.89)</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>8</td>
<td>51</td>
<td>26%</td>
<td>0.32 (0.13, 0.80)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>196</td>
<td>55</td>
<td>100%</td>
<td>0.28 (0.13, 0.66)</td>
<td></td>
</tr>
</tbody>
</table>

### B. Clinical pregnancy rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical pregnancy - oligospermia / non-ICSI failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradley 2015</td>
<td>8</td>
<td>18</td>
<td>44%</td>
<td>3.18 (1.35, 7.63)</td>
<td></td>
</tr>
<tr>
<td>Addin 2015</td>
<td>90</td>
<td>55</td>
<td>67%</td>
<td>3.75 (1.85, 7.59)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>98</td>
<td>243</td>
<td>93%</td>
<td>3.88 (2.16, 6.97)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical pregnancy - nonoligospermia / repeat ICSI failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seco 2005</td>
<td>1</td>
<td>1</td>
<td>100%</td>
<td>1.00 (0.34, 2.95)</td>
<td></td>
</tr>
<tr>
<td>Farkas 2016</td>
<td>11</td>
<td>2</td>
<td>55%</td>
<td>0.46 (0.06, 3.49)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>12</td>
<td>13</td>
<td>92%</td>
<td>0.57 (0.14, 2.15)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>110</td>
<td>256</td>
<td>100%</td>
<td>0.26 (0.11, 0.62)</td>
<td></td>
</tr>
</tbody>
</table>

### D. Live birth rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live Birth Rates - oligospermia / non-ICSI failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradley 2016</td>
<td>11</td>
<td>19</td>
<td>58%</td>
<td>2.83 (1.26, 6.38)</td>
<td></td>
</tr>
<tr>
<td>Addin 2015</td>
<td>13</td>
<td>18</td>
<td>78%</td>
<td>2.34 (1.21, 4.51)</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>24</td>
<td>37</td>
<td>62%</td>
<td>2.58 (1.54, 4.33)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>134</td>
<td>253</td>
<td>100%</td>
<td>2.14 (1.35, 3.39)</td>
<td></td>
</tr>
</tbody>
</table>
Evidence to date

**Arafa 2018**
Prospective: 36 oligozoospermic and normozoospermic men with history of ICSI failure
- SCD (30%)
- LBR 36% (T) vs. 8% (E) (P<0.0001)

**Zhang 2018**
Prospective: 102 oligozoospermic and normozoospermic men; No history of ICSI failure
- SCSA (30%)
- LBR 36% (T) vs. 10% (E) (P=0.001)

**Harrero 2019**
Retrospective: 145 couples with ICSI failure
- SCSA (25%)
- TUNEL (36%)
  - CLBR 22% (T) vs. 9% (E) (P<0.01; SCSA)
  - CLBR 20% (T) vs. 0% (E) (P<0.02; TUNEL)

**ANDROLOGY**

Intervention improves assisted conception intracytoplasmic sperm injection outcomes for patients with high levels of sperm DNA fragmentation: a retrospective analysis


Live Birth in High SDF Patients by Intervention

- None: 24.9%
- IMSI: 24.0%
- PICSI: 32.7%
- Testi-ICSI: 43.7%

**Testicular vs Ejaculated Sperm in Men with High Sperm DNA Fragmentation (April 2019)**

8 studies
Five retrospective & three prospective cohort studies

8 countries

796 patients
826 ICSI cycles

100%
Ongoing PR or live birth rate significantly higher with testicular sperm than ejaculated sperm

2-3x higher
Conclusion

WHERE DO WE GO FROM HERE?

Need more Basic Research & Good Clinical Studies (RCT)

To Determine if Testi-ICSI is
1. A valid approach (superior to Ejac-ICSI)
2. A safe approach (late complications)

To Establish Clinical Indications
1. Sperm profile (eg. High SDF)
2. Clinical profile (eg. prior ICSI failure, all ICSI candidates)