LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

- Describe the indications for IVF and ICSI.
- Review the effectiveness of IVF and ICSI.
- Evaluate the pros and cons of IVF and ICSI.
- Analyze the cost-effectiveness of IVF and ICSI.

DISCLOSURE

- S.I.S.Me.R. srl - Direct Stockholder (Self)
Ever since the first live births with ICSI were reported in 1992, ICSI has been adopted as a powerful tool to treat almost all forms of male infertility as well as a method to overcome fertilization failure.

ICSI, as a component of in vitro fertilization (IVF), has assisted several million couples globally to conceive, resulting in the birth of over five million babies to date.

ICSI INDICATIONS

ICSI as the only treatment option for patients with
- Fertilization failure after conventional IVF
- Severe male factor
- Obstructive azoospermia
- Non-obstructive azoospermia

ART IN EUROPE, 2014:
RESULTS GENERATED FROM EUROPEAN REGISTRIES BY ESHRE
Delivery rate/oocyte pick-up >20%, almost doubled by adding FET
ICSI INDICATIONS

ICSI IN NON-MALE FACTOR

To prevent TFF

In PGT cycles

General Policy

In Specific Cases

Albania
Bosnia-Herzegovina
Czech Republic
Malta
Montenegro
Egypt
Lebanon

Poor Ovarian Responders
Advanced Maternal Age

Unexplained infertility

EIM 2018
ICMART 2018

Poor Ovarian Responders
Advanced Maternal Age
Unexplained infertility
ICSI IN POOR OVARIAN RESPONDERS

Represents analysis of 1305 cycles matched by age, FSH level, infertility type and duration

<table>
<thead>
<tr>
<th>No. retrieved oocytes</th>
<th>ICSI cycles</th>
<th>IVF cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>1</td>
<td>160</td>
</tr>
<tr>
<td>93</td>
<td>2</td>
<td>186</td>
</tr>
<tr>
<td>131</td>
<td>3</td>
<td>162</td>
</tr>
<tr>
<td>131</td>
<td>4</td>
<td>162</td>
</tr>
</tbody>
</table>

ICSI IN POOR OVARIAN RESPONDERS

- Fertilization rate significantly higher in ICSI
- Cleavage rate significantly higher in ICSI
- Cleavage rate significantly higher in IVF
- Implantation rate no differences
- Cycle cancellation rate no differences
- Clinical pregnancy rate no differences
- Cumulative clinical pregnancy rate no differences
- Live birth rate no differences
- Cumulative live birth rate no differences

Guo et al., Curr Med Sci 2018
ICSI IN NON-MALE FACTOR

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In Specific Cases

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Advanced Maternal Age
Poor Ovarian Responders
Unexplained infertility

ICSI IN ADVANCED MATERNAL AGE

A retrospective, single center study included women, aged 40–43 years, who underwent IVF treatments for non-male factor infertility between January 2012 until June 2015.

Exclusion criteria included: more than three previous IVF cycles, a history of fertilization failure or low fertilization (<50%), the use of donor or frozen oocytes and the use of donor or frozen sperm samples.

Primary outcome: live birth rate
Secondary outcomes: fertilization rates, fertilization failure and embryo quality

ICSI IN ADVANCED MATERNAL AGE

<table>
<thead>
<tr>
<th></th>
<th>IVF (n=255)</th>
<th>ICSI (n=490)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of oocytes retrieved</td>
<td>7.2 ± 5.5</td>
<td>6.5 ± 5.7</td>
<td>0.18</td>
</tr>
<tr>
<td>Fertilization rate / retrieved oocyte (%)</td>
<td>57*</td>
<td>52</td>
<td>0.037</td>
</tr>
<tr>
<td>Fertilization rate / MII oocyte (%)</td>
<td>64</td>
<td>67</td>
<td>0.25</td>
</tr>
<tr>
<td>Total fertilization failure (%)</td>
<td>9.0</td>
<td>9.7</td>
<td>0.73</td>
</tr>
<tr>
<td>Cycles with blastocyst stage transfer (%)</td>
<td>36*</td>
<td>26</td>
<td>0.005</td>
</tr>
<tr>
<td>Cycles with spare embryos to freeze (%)</td>
<td>26.4*</td>
<td>19.7</td>
<td>0.048</td>
</tr>
<tr>
<td>Number of embryos frozen</td>
<td>2.5 ± 1.9*</td>
<td>1.7 ± 1.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Pregnancy rate (%)</td>
<td>29.5</td>
<td>22.8</td>
<td>0.70</td>
</tr>
<tr>
<td>Clinical pregnancy rate (%)</td>
<td>21.1</td>
<td>16.7</td>
<td>0.82</td>
</tr>
<tr>
<td>Live birth rate (%)</td>
<td>11.9</td>
<td>9.6</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>IVF (n=72)</td>
<td>ICSI (n=164)</td>
<td>P-value</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------</td>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>Number of MII oocytes</td>
<td>1.76 ± 0.81</td>
<td>1.75 ± 0.74</td>
<td>0.90</td>
</tr>
<tr>
<td>Fertilization rate / MII oocyte (%)</td>
<td>57</td>
<td>58</td>
<td>0.91</td>
</tr>
<tr>
<td>Total fertilization failure (%)</td>
<td>26.3</td>
<td>22.5</td>
<td>0.40</td>
</tr>
<tr>
<td>Number of embryos transferred</td>
<td>1.25 ± 0.52</td>
<td>1.33 ± 0.51</td>
<td>0.32</td>
</tr>
<tr>
<td>Clinical pregnancy rate (%)</td>
<td>11.8</td>
<td>7.7</td>
<td>0.39</td>
</tr>
<tr>
<td>Live birth rate (%)</td>
<td>7.8</td>
<td>4.3</td>
<td>0.34</td>
</tr>
</tbody>
</table>

There is no advantage of ICSI over conventional IVF in women aged 40 years and over when used for non-male factor infertility, even when a reduced number of oocytes is available.

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<table>
<thead>
<tr>
<th></th>
<th>IVF (n=25253)</th>
<th>ICSI (n=38820)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles cancelled before transfer (%)</td>
<td>1970 (6.2)</td>
<td>2160 (5.6)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Clinical pregnancy rate (%)</td>
<td>48.1</td>
<td>46.6</td>
<td>0.99</td>
</tr>
<tr>
<td>Implantation rate (%)</td>
<td>25.2%</td>
<td>23.9%</td>
<td>0.62</td>
</tr>
<tr>
<td>Miscarriages (%)</td>
<td>15.0%</td>
<td>14.9%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Live birth rate (%)</td>
<td>40.0%</td>
<td>38.7%</td>
<td>0.99</td>
</tr>
<tr>
<td>Preterm delivery (%)</td>
<td>24.5%</td>
<td>25.5%</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Low birth weight in any infant (%)</td>
<td>25.7%</td>
<td>27.0%</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

Data from the US National Assisted Reproductive Technology Surveillance System during 1996-2012
ICSI IN NON-MALE FACTOR

To prevent TFF

In PGT cycles

General Policy

In Specific Cases

Albania
Bosnia-Herzegovina
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Poor Ovarian Responders

Advanced Maternal Age

Unexplained infertility

927 patients underwent IVF-PGD cycles for single-gene disorders

315 in the IVF group

565 in the ICSI group

47 in the mixed group

Aim of the study:

Accuracy of IVF vs. ICSI due to possible parental contamination

Investigation of the parental origin of abnormalities in 514 embryos diagnosed as abnormal for aneuploidy or UPD

ICSI should be indicated only in cases of male-factor infertility

Pre-implantation genetic diagnosis—should we use ICSI for all?

Barnach Feldman 1,2, Advie Ahuu 1, Marsha Brogari 1, Kerem Detan 1, Jacob Levin 1, Eyal Schif 1, Ronit Ornstein 1,2

927 patients underwent IVF-PGD cycles for single-gene disorders

315 in the IVF group

565 in the ICSI group

47 in the mixed group

No. analyzed embryos

IVF 196

ICSI 318

P-value

Relative parental contribution (%)

58 (29.6) 99 (31.1) NS

No. analyzed washing medium samples

2002

3091

Parental alleles detected (%)

17 (0.8) 22 (0.7) NS

56 IVF and 88 ICSI newborns were tested pre- or post-natally. No single case of misdiagnosis was observed.
To ICSI or Not to ICSI
Gianpiero Palermo, MD, PhD1 Queenie V. Neri, MS1 Ziv Rosenwaks, MD1
1Ronald O. Perelman and Glenda Cohen Center for Reproductive Medicine, Weill Cornell Medical College, New York, New York
Address for correspondence: Gianpiero Palermo, MD, PhD, Ronald O. Perelman and Glenda Cohen Center for Reproductive Medicine, Weill Cornell Medical College, 1305 York Avenue, Suite 730, New York, NY 10021 (e-mail: gpalermo@med.cornell.edu)

Intracytoplasmic sperm injection (ICSI) is the most effective assisted reproductive procedure enabling fertilization in severe forms of male factor indications and male gamete dysfunction. Reliability of ICSI has allowed the expansion of its application to other forms of infertility rendering it the most popular assisted reproduction technology (ART) insemination method worldwide. The concern related to the invasiveness of ICSI together with the arbitrary selection of the inseminating spermatozoa has induced the execution of studies to compare the performance of ICSI in non-male factor infertility with standard in vitro insemination approach. Not surprisingly, the outcome has evidenced that ICSI does not yield higher pregnancy rates than in vitro fertilization but functions invariably as a normalizer of fertilization modifying the absent or low fertilization.

REBUTTAL
IS ICSI FOR ALL?
in non-male factor

- There is no evidence supporting a superior clinical outcome after ICSI

We should consider cumulative data

ICSI CUMULATIVE DATA

A population-based cohort of 14,693 women, who had their first ever stimulated cycle with fertilization performed for at least one oocyte by either IVF or ICSI between July 2009 and June 2014 in Victoria, Australia was evaluated retrospectively.

3418 had no male factor indications
1792 IVF
1626 ICSI
ICSI CUMULATIVE DATA

<table>
<thead>
<tr>
<th>Fertilization rate per oocytes retrieved (%)</th>
<th>IVF</th>
<th>ICSI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.8*</td>
<td>56.2</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>59.9</td>
<td>69.9*</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fertilization rate per oocytes inseminated (%)</th>
<th>IVF</th>
<th>ICSI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. women Case of infertility</td>
<td>Cumulative live-birth (%)</td>
<td>No. women ICSI</td>
<td>Cumulative live-birth (%)</td>
</tr>
<tr>
<td>Non-male factor</td>
<td>1792</td>
<td>39.2</td>
<td>1626</td>
</tr>
<tr>
<td>female factor only</td>
<td>905</td>
<td>39.8</td>
<td>745</td>
</tr>
<tr>
<td>unexplained infertility</td>
<td>887</td>
<td>38.6</td>
<td>881</td>
</tr>
</tbody>
</table>

The observed conservative cumulative live birth rate was higher for women undergoing IVF cycles compared with ICSI cycles among all causes infertility groups except infertility attributed to male factor only.

ICSI CUMULATIVE DATA

IS ICSI FOR ALL?

in non-male factor

- There is no evidence supporting a superior clinical outcome after ICSI even when considering cumulative data.
IS ICSI FOR ALL?
in non-male factor

- There is no evidence supporting a superior clinical outcome after ICSI even when considering cumulative data.

- Position of scientific societies on the use of ICSI FOR ALL.

Intracytoplasmic sperm injection (ICSI) for non-male factor infertility: a committee opinion

The American Society for Reproductive Medicine and Society for Assisted Reproductive Technology

The Practice Committee of the ASRM: The use of ICSI

- ICSI for unexplained infertility does not improve clinical outcomes.
- ICSI for low oocyte yield and advanced maternal age does not improve clinical outcomes.
- ICSI may improve fertilization rates in a subsequent cycle following total failed fertilization in a prior IVF/conventional insemination cycle, although fertilization failure seems to correlate with poor ovarian stimulation.
- ICSI may be used for patients undergoing IVF with PGT, in vitro matured oocytes, and previously cryopreserved oocytes.

The Practice Committee of ASRM: The use of ICSI

THE PRACTICE COMMITTEE OF ASRM: THE USE OF ICSI

The ICSI “can”

- ICSI can provide a safe and effective therapy for the treatment of male factor infertility.
- ICSI can increase fertilization rates when lower than expected or failed fertilization has previously occurred with conventional insemination.

The ICSI “may”

- ICSI may improve fertilization rates in a subsequent cycle following total failed fertilization in a prior IVF/conventional insemination cycle, although fertilization failure seems to correlate with poor ovarian stimulation.
- ICSI for routine use may decrease the incidence of unexpected failed fertilization; however, more than 30 couples would have to undergo ICSI unnecessarily to prevent one failed fertilization.
- ICSI may be used for patients undergoing IVF with PGT, in vitro matured oocytes, and previously cryopreserved oocytes.

The ICSI “does not”

- ICSI for unexplained infertility does not improve clinical outcomes.
- ICSI for low oocyte yield and advanced maternal age does not improve clinical outcomes.

ART IN EUROPE, 2014:
RESULTS GENERATED FROM EUROPEAN REGISTRIES BY ESHRE

IVF cycles: 146,148
ICSI cycles: 362,285

108,448 extra ICSI cycles for non-male factor (PGT excluded)

Figure 1: Proportion of IVF versus ICSI in Europe, 1997–2014.
IS ICSI FOR ALL?

in non-male factor

- There is no evidence supporting a superior clinical outcome after ICSI even when considering cumulative data.

- Scientific societies do not sustain the use of ICSI FOR ALL.

- There is an increased cost related to the technique compared to conventional IVF

  - Human resources 50 min ≈70 Euros
  - Training ≈ 20-40 euros
  - Equipment & maintenance ≈ 50-80 euros
  - Disposables ≈ 70 euros
  - Media ≈ 75 euros

  TOTAL ≈ 400 euros

ART IN EUROPE, 2014:
RESULTS GENERATED FROM EUROPEAN REGISTRIES BY ESHRE

The European IVF-monitoring Consortium (EIM) for the European Society of Human Reproduction and Embryology (ESHRE). Hum Reprod 2018

IVF cycles: 146,148
ICSI cycles: 362,285
+ 43,379,200 €

+ 108,448 extra ICSI cycles for non-male factor (PGT excluded)

extra ICSI cycles for non-male factor (PGT excluded)

108,448
+ 43,379,200 €

IS ICSI FOR ALL?
in non-male factor

- There is no evidence supporting a superior clinical outcome after ICSI even when considering cumulative data.

- Scientific societies do not sustain the use of ICSI FOR ALL.

- There is an increased cost related to the technique compared to conventional IVF

  Supporting the non-justified use of ICSI would have important economical consequences on

  - The national health economy in those countries where ART is covered by the National Healthcare Service.
  - Patients that have to pay for their treatment both directly or through an insurance.
  - Developing countries where the unnecessary use of an expensive technique could preclude access to treatment.
We felt we had something to offer — done the “right way” in contrast to the increasing numbers of “for profit” meetings being advertised.
IS ICSI FOR ALL?