Use of donor semen in the treatment of male infertility

Where is the evidence?

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Zwolle, The Netherlands
## Strength of evidence

<table>
<thead>
<tr>
<th>Evidence Type</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic review</td>
<td>1A</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>1A</td>
</tr>
<tr>
<td>RCT</td>
<td>1B</td>
</tr>
<tr>
<td>Well designed non-randomized controlled trial</td>
<td>2A</td>
</tr>
<tr>
<td>Well designed quasi experimental</td>
<td>2B</td>
</tr>
<tr>
<td>Descriptive / cases</td>
<td>3</td>
</tr>
<tr>
<td>Expert</td>
<td>4</td>
</tr>
</tbody>
</table>
Intra-Uterine versus Intra-Cervical


Comparison of intrauterine and intracervical insemination with frozen donor sperm: a meta-analysis

IUI is superior over ICI: The pooled OR was 2.4
95% CI: 1.5-3.8
Intra-Uterine versus Intra-Cervical

Besselink et al., Cochrane Database of Systematic Reviews, 2, 2009

Cervical insemination versus intra-uterine insemination of donor sperm for subfertility
Intra-Uterine versus Intra-Cervical

Besselink et al., Cochrane Database of Systematic Reviews, 2, 2009

Cervical insemination versus intra-uterine insemination of donor sperm for subfertility

IUI is superior to ICI in terms of:

- Pregnancy rate
- Live birth rate

With no difference in:
- Miscarriage rate
- Multiple pregnancies
Single or double insemination

Cantineau et al., *Cochrane Database of Systematic Reviews*, 2, 2009

Single versus double intrauterine insemination (IUI) in stimulated cycles for subfertile couples
Single or double insemination

Cantineau et al., *Cochrane Database of Systematic Reviews*, 2, 2009

Single versus double intrauterine insemination (IUI) in stimulated cycles for subfertile couples

Note: fresh partner semen

IUI performed on consecutive days is superior over a single insemination
Single or double insemination

Matilsky et al., J Androl., 1998; 19(5):603-7

Two-day IUI treatment cycles are more successful than one-day IUI cycles when using frozen-thawed donor sperm.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PR per cycle</th>
<th>PR per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single insemination</td>
<td>5%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Double insemination</td>
<td>17.9%</td>
<td>37.9%</td>
</tr>
</tbody>
</table>

The results of this study support the use of 2-day IUI treatment cycles when using frozen-thawed donor sperm.
Swim-up versus gradient

Boomsma et al., Cochrane Database of Systematic Reviews, 2, 2009
Semen preparation techniques for intrauterine insemination
Swim-up versus gradient

Boomsma et al., Cochrane Database of Systematic Reviews, 2, 2009

Semen preparation techniques for intrauterine insemination

Note: fresh partner semen

No evidence of a difference between either swim-up, gradient or wash and centrifugation was observed.
Number of motile spermatozoa to inseminate

Performance of the postwash total motile sperm count as a predictor of pregnancy at the time of intrauterine insemination: a meta-analysis

Note: fresh partner semen

- at cut-off levels between 0.8 to 5 million motile spermatozoa, the postwash TMC provided a substantial discriminative performance
- the cut-off value for a postwash TMC during the fertility workup should be based on the clinic’s own population and sperm-preparation technique
### Number of motile spermatozoa to inseminate

**Curfs, unpublished results**

**Number of motile spermatozoa:**

<table>
<thead>
<tr>
<th>Number of Spermatozoa</th>
<th>PR (%)</th>
<th>OPR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 million</td>
<td>11.8%</td>
<td>8.6%</td>
</tr>
<tr>
<td>&gt;1 and ≤ 2 million</td>
<td>13.7%</td>
<td>11.6%</td>
</tr>
<tr>
<td>&gt;2 million</td>
<td>14.1%</td>
<td>9.6%</td>
</tr>
</tbody>
</table>
Fresh versus frozen

Keel and Webster, Ferti. Steril., 1989; 52(1):100-5

Semen analysis data from fresh and cryopreserved donor ejaculates: comparison of cryoprotectants and pregnancy rates.

the number of motile sperm of cryopreserved ejaculates are dramatically reduced compared with the fresh counterparts.

if a minimum criteria for ejaculate quality is established, the use of cryopreserved semen can offer a viable, effective, and relatively safe alternative to artificial insemination by donor with fresh semen.

Low patient numbers
Fresh versus frozen

Successful sperm storage for 28 years.

Artificial insemination with semen cryopreserved for 21 and 28 years resulted in two live births.
Fresh versus frozen

COMMISSION DIRECTIVE 2006/17/EC of 31 March 2004 implementing Directive 2004/23/EC ... as regards certain technical requirements for the ... testing of human tissues and cells

Annex III, 4.3: Sperm donations other than by partners will be quarantined for a minimum of 180 days, after which repeat testing is required.
Number of treatment cycles?

De Brucker et al., Hum. Reprod., 2009; 24(8):1891-1899

*Cumulative delivery rates in different age groups after artificial insemination with donor sperm*
Number of treatment cycles?

Ferrara et al., Hum. Reprod., 2002; 17(9):2320-4
Intrauterine insemination with frozen donor sperm. Pregnancy outcome in relation to age and ovarian stimulation regime.
Number of treatment cycles?

Custers et al., Hum. Reprod., 2008; 23(4):885-888

*Intrauterine insemination: how many cycles should we perform?*

Note: fresh partner semen
Intrauterine insemination (IUI) pregnancy outcome is enhanced by shorter intervals from semen collection to sperm wash, from sperm wash to IUI time, and from semen collection to IUI time.

Note: fresh partner semen
Time to inseminate

Song et al., *Fertil. Steril.*, 2007; 88 (6), 1689-1691

Location of semen collection and time interval from collection to use for intrauterine insemination

Note: fresh partner semen

**TABLE 1**

| Semen values and time intervals from semen collection to insemination of intrauterine insemination (IUI) cycles (mean ± SD) in the groups with clinic versus home collection of semen or in the pregnant versus nonpregnant groups. |
|---|---|---|---|
| **Collection place** | **Pregnancy** |
| | Clinic (n = 397) | Home (n = 236) | Pregnant (n = 88) | Nonpregnant (n = 545) |
| Age of female patient (years) | 34 ± 4.3 | 35 ± 4.9a | 34 ± 4.7 | 34 ± 4.9 |
| Semen parameters | | | | |
| Sperm count (million/mL) | 59 ± 40 | 58 ± 40 | 65 ± 43 | 58 ± 40 |
| Sperm motility (%) | 44 ± 19 | 41 ± 17 | 45 ± 20 | 43 ± 18 |
| Progressive (velocity) | 31 ± 7 | 30 ± 7a | 32 ± 7 | 30 ± 7 |
| Total motile sperm (million) | 81 ± 84 | 67 ± 73 | 88 ± 93 | 71 ± 75 |
| Time intervals (min) | | | | |
| Collection to washing | 14 ± 8 | 29 ± 15a | 20 ± 11 | 20 ± 13 |
| Washing to insemination | 21 ± 14 | 18 ± 11a | 18 ± 12 | 20 ± 13 |
| Collection to insemination | 69 ± 15 | 81 ± 20a | 70 ± 19 | 73 ± 18 |
| Ongoing pregnancy rate | 7.3% (29/397) | 10.6% (25/236) |

aP value <.05; n = the number of cycles.
## Time to inseminate

Curfs, unpublished results  
Retrospective analysis, 1796 cycles

<table>
<thead>
<tr>
<th>Interval from gradient centrifugation to insemination</th>
<th>Pregnant</th>
<th>Total</th>
<th>Pregnancy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 h</td>
<td>66</td>
<td>592</td>
<td>11.1</td>
</tr>
<tr>
<td>&gt;3 h</td>
<td>101</td>
<td>1204</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>
Conclusions

• There is strong evidence that Intra Uterine Insemination is superior to Intra Cervical Insemination
• There is evidence that a double insemination on consecutive days is superior to a single insemination
• The evidence is inconclusive to which method is optimal for processing semen (after thawing)
• There is evidence that the minimal number of motile sperm to inseminate is between 0.8 and 5 million. However, each laboratory should determine its own cut-off level
• There is no evidence that fresh semen yields better results than frozen-thawed semen. European legislation prohibits the use of fresh donor semen
Conclusions

• There is no evidence of decreased pregnancy rates up until 8-12 cycles
• There is evidence that increasing the interval from sperm processing to insemination results in decreased pregnancy rates
• We need more and stronger data on almost every aspect of the treatment with donorsperm