IUI: State of art

Review literatuur

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6-6-2017
De spreker heeft:
Geen financiële banden met de IVD industrie
Geen sponsoring door belanghebbende industrie
Geen honoraria van belanghebbende industrie
Geen aandeelhouder van belanghebbende industrie
Geen andere relaties met belanghebbende industrie die gezien kunnen worden als belangenverstrengeling
Introduction

Ongoing discussion: when to apply IUI or IVF/ICSI (NICE 2013)
• Evidence factors: clinical and financial
Introduction

Impact technical aspects of IUI: more or less unclear

Laboratory manuals:
- WHO
- ESHRE
- NICE

Lack of standardization:
- Limited willingness
- Impractical recommendations
Semen collection
- Ejaculatory abstinence
- Semen collection place
- Time interval: semen production - processing
- IUI devices

Semen processing
- Semen separation method
- Centrifugation medium
- Centrifugation temperature
- Storage temperature
- Time interval: semen processing - insemination
- IUI devices

Insemination (IUI)
- Timing method of IUI
- Time between ovulation and insemination
- Time interval: semen production – insemination
- Bed rest after IUI
- IUI devices

Recommendations by:
- WHO
Ejaculatory abstinence

WHO: EA of 2-7 days

- **<2 days**
  - ↑ % Normal Morphology

- **2-7 days**
  - ↑ Semen volume
  - ↑ TMSC

- **>7 days**
  - ↑ Exposure to ROS
  - ↓ Fertility rate

<table>
<thead>
<tr>
<th>≤ 2 days (n=372)</th>
<th>≤ 3 days (n=407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation: EA of up to 3 days</td>
<td></td>
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</tbody>
</table>

Radboudumc
Time intervals

WHO:
• private room near laboratory
• collection at home: delivery within 1 hour
**Time intervals**

- **Semen production - IUI**
  - Semen production - processing
  - Semen processing - IUI

**Time interval**
- 15-30 minutes (n=37)
- Other time intervals
- >60 minutes

- ↑PR (hMG-treated)
- No differences
- No pregnancies
Time intervals

- Shorter interval: less DNA damage

- < 30 min and 31-60 min (n=37)
- 40-80 min (n=862)
- >30 min (n=1125)
- No differences (n=633 / 2154)
Time intervals

- < 90 min (n=132)
- No differences (n=633)

Recommendation: sample delivery <1 hour, avoid long time intervals
Semen separation method

Wide variance of products and methods

WHO: selection based on nature of semen sample

Pregnancy rates:
• 10 RCTs in total
• 6 RCTs in systematic review (Boomsma et al.)

Meta-analysis: no difference in pregnancy rates

Contradicting results

Difference in study designs:
• population
• methods of separation

Recommendation: selection of method based on semen sample
Centrifugation medium

WHO: based on used incubator
• atmospheric air: zwitterion-buffered
• atmosphere of 5% CO2: bicarbonate-buffered

Recommendation: follow WHO
Temperature during centrifugation

No recommendations

Room temperature commonly used

Body/testis vs. room temperature:
• no difference DNA damage (n=50)
• ↑ % motile sperm cells (n=10)

Recommendation: room temperature
Temperature during storage

No recommendations

Usually at body temperature
• long-term storage?

↓ motility
↓ sperm quality
↓ normal morphology

↓ motility
longer survival

Recommendation: ???
avoid long-term storage
Method of timing IUI

No recommendations

Pregnancy rates: 18 RCTs in systematic review (catineau et al.)
• hCG vs. LH detection: no differences
• other comparisons: no differences
• low/ very low evidence

Time interval: ovulation induction – insemination
• 24-48 hours
• no differences in PRs

Recommendation: method own preferences
Bed rest after IUI

NICE: bed rest >20 minutes does not improve IVF outcome
• immediate mobilization
• bed rest (10 / 15 minutes)

Bed rest:
- 10 minutes
- 15 minutes

- ↑ PRs (n= 95)
- ↑ PR (n= 391)
- No impact (n=479)

Recommendation: bed rest of 10-15 min or direct mobilization
Discussion

Technical aspects of IUI:
• lack of evidence
• contradictory findings
• low degree of standardization
<table>
<thead>
<tr>
<th>Variable</th>
<th>Level of evidence</th>
<th>Number of studies</th>
<th>Main conclusions in literature; reported procedure with highest PRs</th>
<th>Recommendations based on literature and WHO guideline</th>
<th>Next steps in research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejaculatory abstinence</td>
<td>3</td>
<td>2</td>
<td>EA up to 2 // 3 days</td>
<td>EA ≤ 3 days</td>
<td>Evaluation in RCTs, with stratification for oligo- and normozoospermic men</td>
</tr>
<tr>
<td>Collection place (clinic versus at home)</td>
<td>3#</td>
<td>2</td>
<td>Collection in the clinic // no difference</td>
<td>Either in the clinic or at home</td>
<td>Evaluation in RCTs, with stratification for oligo- and normozoospermic men</td>
</tr>
<tr>
<td>Time intervals</td>
<td>3#</td>
<td>4</td>
<td>Avoid short and long TIs // no impact</td>
<td>Sample delivered within 1 h after collection, avoid long TIs between semen collection-insemination and semen processing-insemination</td>
<td>In first instance in multi-center retrospective studies, separately for oligo- and normozoospermic men</td>
</tr>
<tr>
<td>Semen preparation technique</td>
<td>1a#</td>
<td>6 †@</td>
<td>No superior method</td>
<td>Method selection should be based on semen sample</td>
<td>Identification of methodologies with best IUI results in retrospective studies (e.g. number of layers, volume of medium)</td>
</tr>
<tr>
<td>Buffer of wash medium</td>
<td>1b</td>
<td>1</td>
<td>HEPES buffer better than bicarbonate buffer</td>
<td>Selection of the medium buffer should be based on used incubator</td>
<td>Additional evaluation in RCTs, with stratification for oligo- and normozoospermic men</td>
</tr>
<tr>
<td>Centrifugation temperature</td>
<td>1b</td>
<td>1</td>
<td>No difference between body // tests and room temperature</td>
<td>Non-controlled centrifugation temperature, for reasons of ease</td>
<td>None</td>
</tr>
<tr>
<td>Storage temperature</td>
<td>2*</td>
<td>4</td>
<td>Storage at room temperature better than body temperature*</td>
<td>Avoid body temperature, especially during long-term storage</td>
<td>Evaluation of impact on PRs in RCTs, with stratification for oligo- and normozoospermic men</td>
</tr>
<tr>
<td>Method of timing IUI</td>
<td>1a</td>
<td>18 †</td>
<td>No superior method</td>
<td>No recommendable method</td>
<td>Evaluation in RCTs with standardized methods</td>
</tr>
<tr>
<td>Time between ovulation and insemination</td>
<td>1b</td>
<td>7</td>
<td>No superior time interval</td>
<td>Inspermation 24–48 h after ovulation induction</td>
<td>Evaluation in RCTs with standardized methods, including insemination &lt;24 h after ovulation induction, With stratification for oligo- and normozoospermic men</td>
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<tr>
<td>IUI devices</td>
<td>–</td>
<td>–</td>
<td>Some devices were reported as cytotoxic</td>
<td>Avoid the use of IUI devices that cause reproductivity</td>
<td>Development of well-described tests to identify safe and effective devices</td>
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<tr>
<td>Bed rest after IUI</td>
<td>1b</td>
<td>3</td>
<td>Bed rest of 10 // 15 min // no difference between bed rest and immediate mobilization</td>
<td>Either bed rest of 10–15 min or direct mobilization</td>
<td>Additional evaluation in RCTs, with stratification for oligo- and normozoospermic men</td>
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</tbody>
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Discussion

Technical aspects of IUI:
• lack of evidence
• contradictory findings
• low degree of standardization

Recommendations introduced for:
• standardization
• ease / costs
• quality control

Further research is needed!
Conclusion

Further research: RCTs
- Wash medium buffer
- Storage temperature
- Timing of insemination
- Bed rest

Guidelines updated
Implementation strategies