Natural, mild and conventional ovarian stimulation for IVF

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Mild ovarian stimulation

Lecture Outline

- The bigger picture
- Implications ovarian stimulation
- What is mild ovarian stimulation
- Room for improvement?

Numerator

- Biochemical pregnancy
- Ongoing pregnancy
- Live birth
- Term birth (singleton)

Denominator

- Intention to treat
- Oocyte pick-up
- Fresh ET
- Cumulative fresh and frozen ET
- Started IVF treatment

“Dr LookGood vs Dr HelpAll”
Mild ovarian stimulation

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Follicle recruitment and dominant follicle selection

Pache, FS 1990
vSantbrink, FS 1995
Schipper, FS 1998

Conventional superovulation strategy for IVF

Sequela of ovarian stimulation for IVF

Consequences for:
- Luteal phase endocrinology
- Endometrial receptivity
- Embryo aneuploidy
Arguments against "the more eggs the better"

- Reduced egg quality
- Reduced implantation rates
- Increase burden of treatment
- Increased complication rates
- Increased drop-out rates
  (successive IVF cycle approaches)
- Effects on children outcomes?
- Increased cost

Objective: Assess efficiency oocyte utilization after controlled ovarian stimulation for IVF

Design: Retrospective comparison Bourn Hall IVF; Compare early 80s versus year 2000
(women < 38 yrs)

Results: Number oocytes utilized per live birth;
- 25.1; in women 6-16 oocytes retrieved
- 51.5; in women > 16 oocytes

Conclusion: Efficiency of oocyte utilization is poor, and did not improve despite 25 yrs experience

Objective: Compare chromosome error rate from oocytes generated for ICSI
(subset in women < 35 yrs)

Patients: N=933 couples undergoing ICSI (total)

Methods: Polar body testing (chromosomes: 13, 16, 18, 21, 22)

Conclusions: High yield of oocytes after superovulation is associated with increased chromosome error rate

Results: chromosome error rate in relation to Oocyte No.

<table>
<thead>
<tr>
<th>Oocyte #</th>
<th>1-5</th>
<th>6-10</th>
<th>&gt; 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosome error rate</td>
<td>23±5%</td>
<td>35±4%</td>
<td>51±6%</td>
</tr>
</tbody>
</table>
Conclusions

Summary reported reasons for IVF discontinuation

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balancing treatment and work</td>
<td>Osamangceoglu’99</td>
</tr>
<tr>
<td>committment</td>
<td></td>
</tr>
<tr>
<td>Distance from clinic</td>
<td>Malcolm’04</td>
</tr>
<tr>
<td>Undergone agreed number of cycles</td>
<td>De Vries’99</td>
</tr>
<tr>
<td>Physical burden,</td>
<td>Vd Broeck’08</td>
</tr>
<tr>
<td>Financial burden</td>
<td></td>
</tr>
<tr>
<td>Perceived lack of staff expertise</td>
<td></td>
</tr>
<tr>
<td>Poor prognosis</td>
<td>Brandes’09</td>
</tr>
<tr>
<td>Toll on relationship</td>
<td>Domar’09</td>
</tr>
<tr>
<td>Being too anxious or depressed</td>
<td></td>
</tr>
<tr>
<td>Burden of treatment</td>
<td>Verberg’08</td>
</tr>
</tbody>
</table>


HR 2010

<table>
<thead>
<tr>
<th>Aim</th>
<th>Collect information regarding death within 1 year (and related to IVF, 1984-2008, The Netherlands)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results</td>
<td>- Total ~100,000 IVF treatment cycles - 6 death directly related to IVF - 3 OHSS - 3 thrombosis and sepsis after oocyte pick-up - 17 death directly related to IVF pregnancy</td>
</tr>
<tr>
<td>Conclusions</td>
<td>- Overall mortality related to IVF pregnancy increased - World-wide underreporting IVF related mortality - Importance national registry and reporting</td>
</tr>
</tbody>
</table>
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What mild??

Definition of mild ovarian stimulation for IVF
The administration of low doses (fewer days) of exogenous gonadotrophins in GnRH antagonist co-treated cycles, and/or oral compounds (like anti-estrogen, or aromatase inhibitors) for ovarian stimulation for IVF, aiming to limit the number of oocytes obtained to less than eight.
### RCTs involving natural cycle IVF

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Design</th>
<th>Outcomes (ongoing preg)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nil cycle</td>
<td>22 Natural/hCG vs 26 Agonist/HMG</td>
<td>0 vs 23%</td>
<td>Levy '91</td>
</tr>
<tr>
<td>&lt; 38 yrs, Nil cycle</td>
<td>14 Natural/hCG vs 16 CC/hCG</td>
<td>0 vs 13%</td>
<td>McDougall '94</td>
</tr>
<tr>
<td>Previous poor response</td>
<td>114 Natural/hCG vs 11 CC/hCG</td>
<td>3.5 vs 18%</td>
<td>Ingerslev '01</td>
</tr>
<tr>
<td>&lt; 38 yrs, ICSI</td>
<td>114 Natural/hCG vs 101 Agonist/HMG</td>
<td>6.1 vs 6.9%</td>
<td>Morgia '94</td>
</tr>
</tbody>
</table>

### RCTs involving CC stimulation for IVF

<table>
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<tr>
<th>Inclusion</th>
<th>Design</th>
<th>Outcomes (ongoing preg)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous IVF</td>
<td>151 CC vs 152 agonist/HMG</td>
<td>25 vs 37%</td>
<td>Dhont '95</td>
</tr>
<tr>
<td>Nil cycle</td>
<td>296 CC/HMG/agonist vs 291 CC/HMG</td>
<td>23 vs 21%</td>
<td>Fiedler '01</td>
</tr>
<tr>
<td>No IFV</td>
<td>154 CC/FSH/LH vs 140 agonist/FSH</td>
<td>35 vs 29%</td>
<td>Weigtner '02</td>
</tr>
<tr>
<td>&lt; 38 yrs, Nil cycle</td>
<td>8 Antagonist/CC/FSH vs 8 Antagonist/CC/HMG</td>
<td>40 vs 20% (live birth)</td>
<td>Engel '03</td>
</tr>
<tr>
<td>First ICSI</td>
<td>60 CC/HMG/agonist vs 60 agonist/HMG</td>
<td>42 vs 40%</td>
<td>Lin '06</td>
</tr>
</tbody>
</table>
Ovarian stimulation for IVF - comparison of agonist vs antagonist co-treatment

Ovarian stimulation regimen:
- FSH-HMG
- GnRHa (agonist, L Packaging)
- NCG/LH/GnRHa

Cycle day 1:
- Non-pregnant
- Pregnant

Cumulative pregnancies:
- A
- B
- C

JCEM 2003

Observations:
- P < 0.01

Note: The diagrams illustrate the comparison between spontaneous cycles and conventional and mild stimulated cycles, highlighting the differences in follicular dynamics and cumulative pregnancies.
Figure 2: Proportions of pregnancies leading to clinical outcomes from drill biopsy.

GnRH agonist (long prt)
- rFSH (225 IU/d)

GnRH antag
- rFSH (150 IU)

CD 2 5
- foll > 14 mm

2 blastomeres
- 10 chromosomes
- 1, 7, 15, X, and Y
- 13, 16, 18, 21, 22

111 Patients
- 528 fertilized oocytes
- 302 embryos FISHed

RCT
Mild ovarian stimulation

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Transition from mild stimulation to mild response

- reduced response
- more homogeneous response
- higher cancellation rate
- some too high response

Individualized mild stimulation approaches

SWOT analysis

<table>
<thead>
<tr>
<th>S</th>
<th>Strength</th>
<th>Internal</th>
</tr>
</thead>
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<tr>
<td>W</td>
<td>Weakness</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>Opportunities</td>
<td>External</td>
</tr>
<tr>
<td>T</td>
<td>Threats</td>
<td></td>
</tr>
</tbody>
</table>
“Mild stimulation for IVF; 10 years later”

**Strenght**
- GnRH antagonist
- Similar live birth/treatment
- Reduced complexity, discomfort, risk
- Reduced cost
- Beneficial oocyte/embryo quality

**Weakness**
- Lower pregnancy rate/cycle
- Lower "success" rate in registries
- Still excessive response
- Cost of medication still high
- Less margin suboptimal lab performance
- Fewer embryos for cryostorage
- Difficult programming
- No individualized FSH dosing yet
- Lack of robustness

Fauser, Nargund, Nyboe Andersen, Norman, Tzatzizis, Boivin, Ledger
Human Reproduction, 2010, Accepted for debate

The need for more patient tailored ovarian stimulation for IVF

Hyperresponse = danger

Hyporesponse = poor outcome

Individualization:
- Female age
- BMI
- Smoking
- AMH / AFC
- Genetic markers

Why mild???

**Why would you**
- Less discomfort
- Less complications
- Shorter / cheaper
- Less drop outs
- Same results per treatment

**Why wouldn’t you**
- Lower "success" rates
- (1 cycle max approach)
- No data on agonist
- Less planning
- Fixed price per cycle paradigm
In vitro fertilization
- the true balance -

Substitute outcome parameters
- Oocyte number
- Follicle number
- Embryo number
- Implantation rate
- Pregnancy rate

Healthy term live birth per treatment

Risks / complications
Patient discomfort
Costs

Reproductive Research Group
PhD students, and collaborators

Rotterdam
Pache, Schoot, vSantbrink, Schipper, Imani, de Jong, vHeusden, Eijkemans, Mulders, Hohmann, Heijnen, Baart, de Klerk, vdGaast, Blok, Laven, Macklon

Utrecht
Verberg, Knauff, vDisseldorp, Janse, Voorhuis, Kasius, Verhulst, Broer, Hamdin, Sterrenburg, Goverde, Broekmans, Heijnen

International collaborations:
Devroye (Brussels), Bouchard (Paris), Tarlatzis (Greece), Hsieh (Stanford)