PRE-Congress Course 7

Ovarian stimulation for ART: how to achieve efficacy and safety?

Special Interest Group Reproductive Endocrinology
London - UK, 7 July 2013
Ovarian stimulation for ART: how to achieve efficacy and safety?

London, United Kingdom
7 July 2013

Organised by
The ESHRE Special Interest Group Reproductive Endocrinology
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Course coordinators

Georg Griesinger (Germany)

Course description

Ovarian stimulation remains an essential part of ART. Inter-individual variation in ovarian response represents a significant clinical and economical challenge. Undoubtedly, there is a need to reliably predict ovarian response to stimulation, to tailor stimulation protocols optimizing the probability of pregnancy and keep at the same time the risks of complications and costs at a minimum. Special emphasis needs to be given on how to avoid excessive response and predict the occurrence of ovarian hyperstimulation syndrome (OHSS), as well as on maximizing tolerability of treatment from a patient’s perspective. Topics to be covered include ovarian stimulation strategies; primary, secondary and tertiary prevention of OHSS; development of protocols for patients with diminished ovarian reserve; ovarian reserve testing and its practical implications; mild stimulation and financial implications; segmentation of IVF treatment; impact of ovarian stimulation on the endometrium; and emergency stimulation for oncofertility patients.

Target audience

Physicians and scientists in reproductive medicine
Scientific programme

Session 1: Cost implications of ovarian stimulation in expected normal responders
Chairman: Daniela Romualdi - Italy

09:00 - 09:15  Introduction and E-system voting
09:15 - 09:45  Conventional stimulation & cryopreservation of surplus oocytes or embryos is the most cost-effective treatment
Filippo Ubaldi - Italy
09:45 - 10:15  Repetitive natural cycles or mild stimulation offer most benefit per € spent
Michael von Wolff - Germany
10:15 - 10:30  E-system voting & Discussion

10:30 - 11:00  Coffee break

Session 2: Poor response to ovarian stimulation: three short sketches and a mini-debate
Chairman: Frank J. Broekmans - The Netherlands

11:00 - 11:15  Is the clinical impact of a poor response female age dependant?
Simone Broer - The Netherlands
11:15 - 11:30  Is manipulating intra-ovarian androgen conditions effective in upgrading ovarian response?
Renato Fanchin - France
11:30 - 11:45  Will application of stimulation dosages over 225 IU per day prevent a poor response?
Frank J. Broekmans - The Netherlands
11:45 - 12:00  Mini - Debate: A first cycle poor responder after adequate FSH dosing should not be allowed further ART treatment
11:45 - 12:00  Pro
Petra De Sutter - Belgium
12:00 - 12:15  Con
Pia Saldeen - Sweden
12:15 - 12:30  E-system voting

12:30 - 13:30 Lunch

Session 3: Excessive response
Chairman: Georg Griesinger - Germany

13:30 - 13:40  Introduction and E-system voting
13:40 - 14:00  How should we stimulate patients with polycystic ovaries
Efstratios Kolbianakis - Greece
14:00 - 15:00  Debate: Excessive ovarian response affects oocyte quality, endometrial receptivity and child health
14:00 - 14:22  Pro
Nicholas Macklon - United Kingdom
14:22 - 14:44  Con
Karin Middelburg - The Netherlands
14:45 - 15:00  E-system voting & Discussion

15:00 - 15:30 Coffee break
Session 4: Individualisation of ovarian stimulation: can it impact the outcome?
Chairman: Efstratios Kolibianakis - Greece

15:30 - 15:45  Introduction and E-system voting
15:45 - 16:15  Maximising success rates by stimulation individualization
               Ernesto Sr. Bosch - Spain
16:15 - 16:45  Individualisation of ovarian stimulation has little impact on outcome
               Georg Griesinger - Germany
16:45 - 17:00  E-system voting & Discussion
Conventional stimulation and cryopreservation of surplus oocytes or embryos is the most cost-effective treatment

Filippo Maria Ubaldi
M.D. M.Sc.

Outline / learning objectives

- Definition of poor and high responders
- Description of different stimulation protocols
- Literature review of comparisons between conventional stimulation and mild stimulation
- Retrospective analysis of our data
- Conclusions

Conflict of interest

I declare no conflict of interest related to this presentation
Definition of poor and high responders

Consensus Building

The lack of a uniform definition of poor responders makes it difficult to compare treatment outcomes and develop and assess protocols for prevention and management (Surrey 2000; Kailasam 2004; Franco 2006)

FSH >10, E2 <800, <5 mature oocytes (Akman 2001)
Age >37, FSH >9 (De Placido 2006)
<4 oocytes when >300 IU FSH for >14 d. (Malmusi 2005)
E2 >600, <3 oocytes (Mené 2003)
FSH >10, <3 mature follicles (Cheung 2005)
E2 >850, <4 follicles >15 mm (Schmidt 2005)

Agenda

- Definition of poor and high responders
- Description of different stimulation protocols
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- Retrospective analysis of our data
- Conclusions

ESHRE consensus on the definition of ‘poor response’ to ovarian stimulation for in vitro fertilization: the Eilapen criteria

A.P. Fareedah1, A. La Manc2, G.C.M. Factor1, P. Turkington1, G. Roquejoffre, and L. Guise2 on behalf of the ESHRE working group on Poor Ovarian Response Definition

Poor Ovarian Response definition

At least two of the following three features must be present:
(i) Advanced maternal age (≥40 years) or any other risk factor for POR;
(ii) A previous POR (<3 oocytes with a conventional stimulation protocol);
(iii) An abnormal ovarian reserve test ( AFC 5–7 follicles or AMH 0.5–1.1 ng/ml)
**Agenda**

- Definition of poor and high responders
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**Different stimulation protocols**

**Long luteal GnRH-a protocol:**

- GnRH antagonist
- r-FSH
- hCG

Suprefact s.c. 0.2 ml twice daily from mid luteal phase to menstrual cycle than 0.05 ml s.c. twice daily until hCG

From cycle day 3, with "basal" ovaries, gonadotropins with a patient tailored dose

**Mild GnRH-antagonist protocol:**

- Leading follicle >14 mm
- GnRH antagonist
- hCG

Ultrasound performed on cycle day 3-5. If the ovaries were "basal" with follicles 1-10 mm, ovarian stimulation was started on day 4 with a patient tailored dose.

GnRH-ant was started when the leading follicle was 14-15 mm with serum LH<10 IU/ml
Cost-effectiveness analysis
Heijnen et al., 2007; Polinder et al., 2008

STUDY DESIGN (patients < 38 yr old):
MILD STIMULATION + SINGLE EMBRYO TRANSFER (up to 4 cycles in 1 yr)
vs
CONVENTIONAL STIMULATION + DOUBLE EMBRYO TRANSFER (up to 3 cycles in 1 yr)

OUTCOMES: term live births after 1yr & costs* of the 2 strategies

* Treatment costs (up to the outcome of the last IVF cycle) + antenatal, peripartum, postpartum care (until 6 weeks after delivery) [alternatively miscarriage or ectopic pregnancy costs were considered]

COST-EFFECTIVENESS DEFINITION

Difference in average costs
difference in average effects between STANDARD and MILD

Lower rate of cancellation of the started cycles, higher ongoing pregnancy rate and term live birth rate (fresh cycles) through the standard stimulation protocol

No significant differences in depression, anxiety, physical discomfort and subjective sleep quality

Cost-effectiveness analysis
Heijnen et al., 2007

Cost-effectiveness analysis
Polinder et al., 2008

Parameters
Cost-effectiveness analysis
Polinder et al., 2008

The overall increase in costs is determined by summing up small differences (often not even significant) in indirect costs, intramural care or delivery care (at least double for the standard strategy), without considering that the study design contemplate only SET in the mild stimulation protocol and double ET in the standard stimulation protocol. The latter obviously involves higher peripartum and postpartum care costs.

Cost-effectiveness analysis
Polinder et al., 2008

The MILD STIMULATION effectiveness increases thanks to a higher number of cycles, BUT also due to the costs.

Cost-effectiveness analysis
Letter to the editor (Craft and Hodgson)

STUDY DESIGN:
Why did they compare MILD STIMULATION + SINGLE ET vs CONVENTIONAL STIMULATION + DOUBLE ET and not SINGLE ET for both the strategies?

STUDY DESIGN (2):
Why did they consider up to 4 cycles for the MILD STIMULATION group vs up to 3 cycles for the CONVENTIONAL STIMULATION group in a 12-month period and not up to 3 cycles in a 10-month period for both the strategies?

OUTCOME:
Is it fair for patients to achieve a lower live-birth rate with the mild stimulation protocol than with standard?

CONCLUSION:
Biological variance should be addressed before promoting mild stimulation protocol as a fixed philosophy. Age, basal FSH and antral follicle counts should be considered.
Correlation between euploidy and stimulation protocol Baart et al., 2007

Milder ovarian stimulation for in-vitro fertilization reduces aneuploidy in the human preimplantation embryos: a randomized controlled trial

Enrolment and randomization

Enrolment and randomization

PRIMARY OUTCOME:
- Ovarian response & proportion of chromosomally abnormal embryos/patient

SECONDARY OUTCOME:
- Proportion of fertilized oocytes, proportion of embryos with normal morphology & proportion of embryos biopsied and diagnosed

Correlation between euploidy and stimulation protocol Labarta et al., 2012

Primary care

Primary care

Secondary care

Secondary care

Tertiary care

Tertiary care

Conclusions: Moderate ovarian stimulation does not increase the incidence of human embryo aneuploidy in in-vitro fertilization cycles.

In young normo-ovulatory women does not significantly increase the embryos aneuploidy rate in in-vitro fertilization derived human embryos as compared with an unstimulated cycle.

Page 14 of 155
Correlation between euploidy and stimulation protocol

The scientific soundness of both studies is limited by the fact that 9chr FISH is an inappropriate strategy to perform PGS and that blastomere stage is subjected to a number of problems among which mosaicism is the most critical. These results could then be misleading and the analysis might be better reconducted at the blastocyst stage through 24chr platforms (aCGH, qPCR, ...)

Relationship between response to the stimulation and implantation rate
Verberg at al., 2009

The clinical significance of the retrieval of a low number of oocytes following mild ovarian stimulation for IVF: a meta-analysis
M.J.G. Verberg, P.J.C. Eijkemans, N.S. Macklon, R.M.W. Holm, J.B. Bot, J.P. Hekmans, and F.J. Brockmans

Meta-analysis of 3 RCTs comparing mild to conventional stimulation protocol

Relationship between response to the stimulation and implantation rate
Verberg at al., 2009

It has been estimated that among patients undergoing IVF treatment, the prevalence of poor ovarian response is 9 to 24%

MILD STIMULATION PROTOCOLS elicit better results in poor responders
WHILE
STANDARD STIMULATION PROTOCOLS elicit better results in good responders
The number of eggs to maximize the LBR is 15.

**Number of oocytes needed to maximize live birth rate**

- **Observed live birth rate**
- **Predicted live birth rate**


**15 eggs in all patients population**


**Agenda**

- Definition of poor and high responders
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- Literature review of comparisons between conventional stimulation and mild stimulation
- Retrospective analysis of our data
- Conclusions
Retrospective analysis of our data

Good responders

Fresh cycles characteristics

<table>
<thead>
<tr>
<th></th>
<th>Antagonist</th>
<th>Long</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles (N)</td>
<td>226</td>
<td>233</td>
</tr>
<tr>
<td>Age (m+SD)</td>
<td>36.2±3.0</td>
<td>36.5±3.2 ns</td>
</tr>
<tr>
<td>Previous IVF cycle performed (m+SD)</td>
<td>1.7±1.2</td>
<td>1.6±0.4 ns</td>
</tr>
<tr>
<td>Baseline FSH (m+SD)</td>
<td>7.9±2.4</td>
<td>7.2±3.0 ns</td>
</tr>
<tr>
<td>Gonadotropins (m+SD)</td>
<td>184.0±84.5</td>
<td>207.4±92.87 P&lt;0.001</td>
</tr>
<tr>
<td>Days of Stimulation (m+SD)</td>
<td>11.0±1.8</td>
<td>12.8±1.7 P&lt;0.001</td>
</tr>
<tr>
<td>CDC retrieved (m+SD)</td>
<td>8.6±3.3</td>
<td>12.6±5.7 P&lt;0.001</td>
</tr>
<tr>
<td>Metaphase II (m+SD)</td>
<td>6.4±4.1</td>
<td>9.4±5.7 P&lt;0.001</td>
</tr>
<tr>
<td>Vitrified oocytes (m+SD)</td>
<td>3.3±4.0</td>
<td>4.9±15.5 P=0.01</td>
</tr>
<tr>
<td>Obtained embryos (m+SD)</td>
<td>3.8±2.1</td>
<td>4.4±2.0 P&lt;0.001</td>
</tr>
<tr>
<td>Top quality embryos (m+SD)</td>
<td>2.2±1.8</td>
<td>2.7±1.9 P&lt;0.005</td>
</tr>
<tr>
<td>Vitrified embryos (m+SD)</td>
<td>1.1±1.6</td>
<td>1.7±1.7 P=0.005</td>
</tr>
</tbody>
</table>

Retrospective analysis of our data

Good responders

Cumulative ongoing PR/cycle

<table>
<thead>
<tr>
<th></th>
<th>Antagonist</th>
<th>Long</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh cycles (%)</td>
<td>61/226 (27.8)</td>
<td>84/233 (36.1) ns</td>
</tr>
<tr>
<td>I warming (%)</td>
<td>70/226 (31.1)</td>
<td>106/233 (45.5) P&lt;0.005</td>
</tr>
<tr>
<td>II warming (%)</td>
<td>73/226 (32.3)</td>
<td>112/233 (48.1) P&lt;0.005</td>
</tr>
</tbody>
</table>

Conclusions

- Mild protocols of stimulation are less expensive than standard stimulation ones, but need more cycles to reach a comparable outcome.

- A putative influence of stimulation protocols on embryo euploidy is yet to be described through a reliable analysis method and an appropriate biopsy strategy.

- The number of retrieved oocytes associated with the highest implantation rate in every category of patients is 15.

- Standard protocols of stimulation for good responder patients seem to be more effective than mild ones, in particular when considering also embryo transfers carried out after thawing: the delivery rate per started cycle becomes significantly higher with a standard stimulation protocol than with a mild one.

HIGHER COST-EFFECTIVENESS OF MILD STIMULATION PROTOCOLS IS YET TO BE PROPERLY DEMONSTRATED IN ORDER TO REACH A GENERALLY ACCEPTED CONSENSUS AMONG PHYSICIANS.
Repetitive natural cycles or mild stimulation protocols offer most benefit per spent

Prof. Michael von Wolff, MD

I hereby confirm that we do not have any commercial and financial relationships related to this presentation and its contents
Repetitive natural cycles or mild stimulation protocols offer most benefit per spent

Learning objectives:
- What are natural cycle or mild stimulation protocols?
- What kind of benefits offer these kind of treatments?
- What does an optimized NC-protocol look like?
- What are the pregnancy rates one can expect?
- How long does the treatment take to achieve a pregnancy?
- How much does an optimized cycle cost the IVF-center?
- What are the costs per pregnancy?

Rotterdam ISMAAR (International Society for Mild Approaches in Assisted Reproduction) Consensus Group-Classification (Nargund et al., 2007):

Conventional IVF:
- IVF with gonadotropin dosages to receive the highest possible number of oocytes with low risk of OHSS

Mild IVF:
- Conventional stimulation IVF with low dosages of gonadotropins or clomifenictrate
- Natural Cycle IVF:
  - IVF without any stimulation
  - Modified Natural Cycle IVF
  - Natural Cycle IVF with HCG to induce ovulation

Mild IVF and Natural Cycle-IVF (NC-IVF) are completely different techniques concerning:
- Costs (in mild IVF but not in NC-IVF: expensive HMG/FSH)
- Downregulation (in mild IVF but not in NC-IVF: GnRHa or GnRHant)
- Aspiration (in mild IVF but not in NC-IVF: Aspiration with anaesthesia)

Conclusion:
Mild IVF and NC-IVF are different techniques and can not be combined for a comparison with conventional IVF
To visualize the problem

You cannot compare a Mercedes with both, a Golf and a Smart. You have to choose the car you want to compare the Mercedes with.

Mercedes  Golf  Smart

= cIVF  = Mild IVF  = Modified NC-IVF

Definitions in this presentation

Therefore: Definitions used in this presentation:

- Mercedes = cIVF: Conventional IVF with high dosages of HMG/FSH
- Smart = Mod. NC-IVF: Any IVF without HMG/FSH and without high dosages of CC, allowing repetitive, monthly IVF-cycles (i.e.: high dosages of CC frequently require a break of one month due to formation of ovarian cysts)

Another question: What does „benefit per spend“ mean?

A list of 10 possible benefits:
1. Fewer consultations?
2. No injections?
3. Treatment without side effects?
4. Faster aspiration?
5. Aspiration without anaesthesia?
6. No complications such as OHSS?
7. No twins or triplets?
8. Lower costs per cycle?
9. Lower costs per pregnancy?
10. Pregnancy in the shortest possible treatment time?
The „Smart“-treatment chosen for the comparison with the „Mercedes“-treatment:

1 consultation with sono and blood test (E2, LH):
Calculation of the time of HCG-application and aspiration
HCG, i.e. 5,000U s.c.

The name of this treatment in this presentation:
Modified Natural Cycle IVF = „Mod. NC-IVF“

Day of cycle (only regular cycles, 28-35 days)
Clomafen citrate 25mg/day

Why Mod. NC-IVF and not NC-IVF?
Each patient, with a maximum of one previous cIVF received a NC-IVF cycle followed by a Mod. IVF-cycle

<table>
<thead>
<tr>
<th></th>
<th>NC-IVF</th>
<th>Mod. NC-IVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles (n)</td>
<td>55</td>
<td>49</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35.1</td>
<td>30.1</td>
</tr>
<tr>
<td>Premature ovulations / cycle (%)</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Transfers / cycle (%)</td>
<td>39</td>
<td>61</td>
</tr>
<tr>
<td>Clinical pregnancy rate / cycle (%)</td>
<td>12</td>
<td>44</td>
</tr>
<tr>
<td>Multiple pregnancies (%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusion: Mod. NC-IVF is much more efficient, resulting in much higher transfer rates / cycle

NC-IVF in previous studies

<table>
<thead>
<tr>
<th></th>
<th>Janssen et al., 2000</th>
<th>Polyzos et al., 2012</th>
<th>Roesner et al., 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycles (n)</td>
<td>47</td>
<td>300</td>
<td>591</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37.3 ± 3.9</td>
<td>37.3 ± 3.9</td>
<td>23%</td>
</tr>
<tr>
<td>Premature ovulations / cycle (%)</td>
<td>47%</td>
<td>42%</td>
<td>4%</td>
</tr>
<tr>
<td>Clinical pregnancy rate / cycle (%)</td>
<td>4.6% (low responder)</td>
<td>4.2%</td>
<td></td>
</tr>
</tbody>
</table>
Benefit 1: fewer consultations?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cumulative pregnancy rate</th>
<th>Cumulative number of required consultations (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cIVF 1 cycle without cryo cycles</td>
<td>30%</td>
<td>4</td>
</tr>
<tr>
<td>cIVF 2 cycles without cryo cycles</td>
<td>51%</td>
<td>5</td>
</tr>
<tr>
<td>1 cryo cycle following cIVF</td>
<td>20%</td>
<td>4</td>
</tr>
<tr>
<td>cIVF plus 1 cryo cycle</td>
<td>42%</td>
<td>5</td>
</tr>
<tr>
<td>Mod. NC-IVF 1 cycle</td>
<td>12%</td>
<td>2</td>
</tr>
<tr>
<td>Mod. NC-IVF 2 cycles</td>
<td>22%</td>
<td>3</td>
</tr>
<tr>
<td>Mod. NC-IVF 3 cycles</td>
<td>37%</td>
<td>4</td>
</tr>
<tr>
<td>Mod. NC-IVF 4 cycles</td>
<td>41%</td>
<td>5</td>
</tr>
<tr>
<td>Mod. NC-IVF 5 cycles</td>
<td>47%</td>
<td>6</td>
</tr>
</tbody>
</table>

Calculations are based on a transfer rate of 100% in cIVF and cryo cycles and 60% in NC-IVF.

Conclusion: Mod. NC-IVF require around 40-50% more consultations / achieved pregnancy than cIVF.

Benefit 2: No injections?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>cIVF</th>
<th>Mod. NC-IVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 injection / cycle</td>
<td>≥15 injections / cycle</td>
<td>≤1-2 injections / day</td>
</tr>
<tr>
<td>Injections to achieve a 50% cumulative pregnancy rate: 6 injections</td>
<td>Injections to achieve a 50% cumulative pregnancy rate: ≥20-30 injections</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Mod. NC-IVF require much fewer injections than cIVF.

Benefit 3: Treatment without side effects?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>cIVF</th>
<th>Mod. NC-IVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>No side effects</td>
<td>Dyscomfort due to low and high estrogen concentrations</td>
<td></td>
</tr>
</tbody>
</table>

13 patients received both: Mod. NC-IVF and cIVF.

Question: Which kind of treatment did you find more unpleasant until aspiration?

Conclusion: Mod. NC-IVF has less side effects than cIVF and women experience the time until aspiration less unpleasant.
Benefit 4: Faster aspiration?

<table>
<thead>
<tr>
<th>Mod. NC-IVF</th>
<th>cIVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration time: 2 min.</td>
<td>Aspiration time: ≥ 5 min.</td>
</tr>
<tr>
<td>Patient is allowed to eat before aspiration</td>
<td>Patient is not allowed to eat anything beforehand</td>
</tr>
<tr>
<td>Anaesthesia required</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Aspiration in Mod. NC-IVF is easier and faster than in cIVF.

Benefit 5: Aspiration without anaesthesia and analgetics?

13 patients received both: an aspiration in cIVF with anaesthesia and an aspiration in NC-IVF without any anaesthesia and analgetics.

Question: Which kind of aspiration did you find more unpleasant?

<table>
<thead>
<tr>
<th>%</th>
<th>cIVF</th>
<th>NC-IVF</th>
<th>equal</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>0</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: Aspiration in Mod. NC-IVF without anaesthesia is less unpleasant than cIVF with anaesthesia.

Benefit 6: No complications such as OHSS?

<table>
<thead>
<tr>
<th>Mod. NC-IVF</th>
<th>cIVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berne: OHSS: 0%</td>
<td>Berne: OHSS without hospitalisation: around 2% OHSS III° requiring hospitalisation: around 1% (Antagonist protocols)</td>
</tr>
</tbody>
</table>

Conclusion: Mod. NC-IVF is a therapy without any OHSS.
Benefit 7: No twins and triplets?

<table>
<thead>
<tr>
<th>Mod. NC-IVF</th>
<th>cIVF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twins / pregnancy:</td>
<td>Twins / pregnancy:</td>
</tr>
<tr>
<td>Berne: &lt;1%</td>
<td>Europe*: Twins: 21% / pregnancy</td>
</tr>
<tr>
<td>Janssens et al., 2000: ?</td>
<td>Polyzos et al., 2012: ?</td>
</tr>
<tr>
<td>Roecker et al., 2012: ?</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion:
Mod. NC-IVF is a therapy almost without any multiple pregnancies

Benefit 8: Lower costs per cycle?

<table>
<thead>
<tr>
<th></th>
<th>JAN-1 fresh cycle</th>
<th>cIVF-1 fresh cycle</th>
<th>NC-IVF-1 fresh cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total required consultations cycle (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Required labour - physician (4)</td>
<td>105</td>
<td>60</td>
<td>75</td>
</tr>
<tr>
<td>Required labour - secretaries and nurses (4)</td>
<td>90</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td>Required labour - IVF-laboratory staff (4)</td>
<td>250</td>
<td>120</td>
<td>195</td>
</tr>
<tr>
<td>Required medication (€)</td>
<td>1200,-</td>
<td>70,-</td>
<td>40,-</td>
</tr>
<tr>
<td>Required blood tests (E2, LH) (€)</td>
<td>60,-</td>
<td>0</td>
<td>35,-</td>
</tr>
<tr>
<td>Required consumables IVF-laboratory (€)</td>
<td>184,-</td>
<td>191,-</td>
<td>179,-</td>
</tr>
<tr>
<td>Anaesthesia and postoperative care (€)</td>
<td>500,-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total required consultations, consumables, anaesthesia, blood tests (€)</td>
<td>1744,-</td>
<td>261,-</td>
<td>254,-</td>
</tr>
<tr>
<td>Total labour (min.)</td>
<td>445</td>
<td>225</td>
<td>330</td>
</tr>
<tr>
<td>Total costs (€)</td>
<td>2188,-</td>
<td>383,-</td>
<td>431,-</td>
</tr>
</tbody>
</table>

1 cIVF including gonadotropins and GnRH agonists/antagonists
2 NC-IVF with clomiphene citrate
3 NC-IVF with luteal phase support
4 According to treatment protocol in Berne
5 1/3 of cycles fertilization by ICSI, 2/3 by insemination. Gas for incubators, laboratory equipment etc. not included
6 Physician € 40,-/hour, secretaries & nurses € 30,-/hour

Conclusion: Mod. NC-IVF is much cheaper per cycle than cIVF

Benefit 9: Lower costs per pregnancy?

<table>
<thead>
<tr>
<th>Pregnancy rate per money spent</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVF-1 ET / stimulation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Start</th>
<th>1000,-</th>
<th>2000,-</th>
<th>3000,-</th>
<th>4000,-</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>%</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>%</td>
<td>80</td>
<td>90</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

von Wolff et al., submitted
**Benefit 10: Pregnancy in the shortest possible treatment time?**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cumulative pregnancy rate (initiated cycles)</th>
<th>Cumulative required treatment time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cIVF 1 cycle without cryo cycles</td>
<td>30%</td>
<td>1</td>
</tr>
<tr>
<td>cIVF 2 cycles without cryo cycles</td>
<td>51%</td>
<td>3</td>
</tr>
<tr>
<td>cIVF plus 1 cryo cycle</td>
<td>44%</td>
<td>3</td>
</tr>
<tr>
<td>NC-IVF, 1 cycle</td>
<td>12%</td>
<td>1</td>
</tr>
<tr>
<td>NC-IVF, 2 cycles</td>
<td>23%</td>
<td>2</td>
</tr>
<tr>
<td>NC-IVF, 3 cycles</td>
<td>32%</td>
<td>3</td>
</tr>
<tr>
<td>NC-IVF, 4 cycles</td>
<td>40%</td>
<td>4</td>
</tr>
<tr>
<td>NC-IVF, 5 cycles</td>
<td>47%</td>
<td>5</td>
</tr>
</tbody>
</table>

1. Including a break of 1 month following a classical IVF-cycle (fresh transfer) and no break between NC-IVF cycles
2. Approximated according to pregnancy rates in the ESHRE register (Ferraretti et al. 2012)
3. Approximated according to pregnancy rates in Berne (12%, table 1): >1 cycle calculated i.e. 2 cycles: 100/88 * 100 = 114%

**Conclusion:** Mod. NC-IVF require more time / achieved pregnancy than cIVF

---

**In which category does Mod. NC-IVF offer more benefits?**

1. Fewer consultations/achieved pregnancy? No
2. No injections? Yes
3. Treatment without side effects? Yes
4. Faster aspiration? Yes
5. Aspiration without anaesthesia? Yes
6. No complications such as OHSS? Yes
7. No twins or triplets? Yes
8. Lower costs per cycle? Yes
9. Lower costs per achieved pregnancy? Yes
10. Pregnancy in the shortest possible treatment time? No

* Mod. NC-IVF only in women with regular menstrual cycles.
Summary

- NC-IVF require some modifications ("Mod. NC-IVF") and needs to be performed under optimized conditions to be a real alternative for conventional IVF ("cIVF")
- Mod. IVF can only effectively be performed in women with regular menstrual cycles
- Mod. NC-IVF provides many benefits in comparison to cIVF
- Costs per achieved pregnancy seem to be lower in Mod. NC-IVF
- Treatment time per achieved pregnancy seems to be higher in Mod. NC-IVF
- Mod. NC-IVF should not be performed in women around the age of 40 with a high ovarian reserve as treatment time is essential

References


Roesner S, Pfahler M, Gerres A, Mentz M, Brossard T, Tisch B. Natural Cycle IVF evaluation in 591 cycles. Arch Gynecol Obstet. 2012 PO-Endo 04.15
Is the clinical impact of a poor response female age dependant?

Simone Broer, MD, PhD
Reproductive Medicine
University Medical Center Utrecht
The Netherlands

Conflicts of interest

No potential conflicts of interest

Learning objectives

• The influence of age on the pregnancy prospects for poor responders
• Integration of quality and quantity aspects for individualizing pregnancy prospects
• Predictive possibilities for pregnancy prospects of poor responders
Overview

- Definitions
- Poor responders and pregnancy prospects
- Poor responders in age categories
- Quality aspects
- Prediction of prospects for poor responders
- Quantity vs quality
- Conclusions

Poor responders

- Diminished ovarian reserve / ovarian ageing?

- Sub Optimal stimulation?

Suboptimal exposure to gonadotrophins

150 IU/d versus 200-250 IU/d

Number of oocytes per ORU
Number of cryopreserved embryos
Total amount of mFN (IU)

Chance of ORU
Chance of pregnancy
Chance of DMRG

Steensma et al., HRU 2011
Poor ovarian response

At least 2 of the 3 features must be present:
1. Advanced maternal age (≥40) or any other risk factor for POR
2. A previous POR (≤3 oocytes) with conventional stimulation protocol
3. Abnormal ovarian reserve test

Incidence of poor response

Percentage of poor responders increases with age

Pregnancy rates in Poor vs Normal responders

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Poor responders</th>
<th>Normal responders</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biljan et al.</td>
<td>828</td>
<td>11.9%</td>
<td>29.4%</td>
<td>0.015</td>
</tr>
<tr>
<td>Hendriks et al.</td>
<td>222</td>
<td>7.0%</td>
<td>25.9%</td>
<td>0.001</td>
</tr>
<tr>
<td>Saldeen et al.</td>
<td>1803</td>
<td>9.0%</td>
<td>32.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Zhen et al.</td>
<td>472</td>
<td>14.8%</td>
<td>36.7%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pooled estimate</td>
<td>14338</td>
<td>14.8%</td>
<td>34.5%</td>
<td></td>
</tr>
</tbody>
</table>

Oudendijk et al., HRU 2012
### Pregnancy rates in Poor Responders

#### Female Age categories

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>28</th>
<th>29</th>
<th>30</th>
<th>31</th>
<th>32</th>
<th>33</th>
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<th>36</th>
<th>37</th>
<th>38</th>
<th>39</th>
<th>40</th>
<th>41</th>
<th>42</th>
<th>43</th>
<th>44</th>
<th>45</th>
<th>&gt;46</th>
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</thead>
<tbody>
<tr>
<td>Zhen et al.</td>
<td>472</td>
<td>18.5%</td>
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<tr>
<td>Rooij, van et al.</td>
<td>47</td>
<td>13.0%</td>
<td>4.0%</td>
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<tr>
<td>Biljan et al.</td>
<td>42</td>
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<tr>
<td>Oudendijk et al., HRU 2012</td>
<td>290</td>
<td>14.0%</td>
<td>3.0%</td>
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<tr>
<td>Saldeen et al.</td>
<td>290</td>
<td>13.0%</td>
<td>4.0%</td>
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<tr>
<td>Inge et al.</td>
<td>39</td>
<td>27.1%</td>
<td>12.7%</td>
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<tr>
<td>Sutter, de et al.</td>
<td>1280</td>
<td>23.0%</td>
<td>12.0%</td>
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<td>Galey‐Fontaine et al.</td>
<td>163</td>
<td>14.6%</td>
<td>4.9%</td>
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</tr>
<tr>
<td>Ulug et al.</td>
<td>290</td>
<td>19.5%</td>
<td>7.2%</td>
<td>1.5%</td>
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<tr>
<td>Hanoch et al.</td>
<td>143</td>
<td>19.3%</td>
<td>6.0%</td>
<td>6.5%</td>
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</tr>
<tr>
<td>Yih et al.</td>
<td>4862</td>
<td>35%</td>
<td>21%</td>
<td>17%</td>
<td>11%</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

#### Pregnancy prospects per number of oocytes retrieved

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baka et al.</td>
<td>96c</td>
<td>0.0%</td>
<td>15.3%</td>
<td>12.5%</td>
<td></td>
<td></td>
<td>p=0.41</td>
</tr>
<tr>
<td>Gaast, van der et al.</td>
<td>7422w</td>
<td>7.0%</td>
<td>11.5%</td>
<td>15.4%</td>
<td>16.0%</td>
<td>21.7%</td>
<td>-</td>
</tr>
<tr>
<td>Timeva et al.</td>
<td>975w</td>
<td>0.0%</td>
<td>10.8%</td>
<td>8.7%</td>
<td>11.5%</td>
<td>22%</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Hug et al.</td>
<td>290</td>
<td>2.3%</td>
<td>4.5%</td>
<td>11.3%</td>
<td>13.9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* N = number of women (w)/cycles (c) included, PR = pregnancy rate.

### Live birth rate per number oocytes

[Graphs showing live birth rate per number oocytes]

*Sunkara et al., HRU 2011*
Nomogram for the prediction of live birth

Quantity versus Quality?

OR

Are they related?

Miscarriage rates
Trisomic pregnancy rates

<table>
<thead>
<tr>
<th>Parameter of outcome</th>
<th>Control (n = 100)</th>
<th>Case (n = 100)</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>50 (50.0%)</td>
<td>50 (50.0%)</td>
<td>1.0 (0.85-1.15)</td>
<td>0.803</td>
</tr>
<tr>
<td>Total number of severely retarded children</td>
<td>100 (100.0%)</td>
<td>150 (150.0%)</td>
<td>1.50 (1.30-1.73)</td>
<td>0.000</td>
</tr>
<tr>
<td>Female</td>
<td>50 (50.0%)</td>
<td>50 (50.0%)</td>
<td>1.0 (0.85-1.15)</td>
<td>0.803</td>
</tr>
<tr>
<td>Male</td>
<td>50 (50.0%)</td>
<td>50 (50.0%)</td>
<td>1.0 (0.85-1.15)</td>
<td>0.803</td>
</tr>
</tbody>
</table>

Odds Ratio of at least one severely retarded child by gender

Euploidy rates – day 3 embryo

<table>
<thead>
<tr>
<th>Odds Ratio of at least one euploid embryo by female age</th>
<th>0.79 (95%CI 0.75-0.83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds Ratio of at least one euploid embryo by every additional embryo available</td>
<td>1.33 (95%CI 1.24-1.43)</td>
</tr>
</tbody>
</table>

Every year increase female age = decrease 2.4% euploidy rate

Cohort size not significantly associated with euploidy rate

Euploidy rates – blastocysts

<table>
<thead>
<tr>
<th>Odds Ratio of at least one euploid embryo by female age</th>
<th>0.82 (95%CI 0.70-0.94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds Ratio of at least one euploid embryo by every additional embryo available</td>
<td>1.55 (95%CI 1.25-1.95)</td>
</tr>
</tbody>
</table>

Every year increase female age = decrease 2.9% euploidy rate

Cohort size not significantly associated with euploidy rate
Quality and female age

Table 5: Effect of females ageing on chromosomes alignment in MI oocytes

<table>
<thead>
<tr>
<th>Age of mice</th>
<th>No. of mice examined</th>
<th>No. of oocytes examined</th>
<th>Chromosomal alignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young</td>
<td>10</td>
<td>70</td>
<td>Normal: 58.12%</td>
</tr>
<tr>
<td>Middle aged</td>
<td>13</td>
<td>62</td>
<td>Abnormal: 41.88%</td>
</tr>
<tr>
<td>Aged</td>
<td>13</td>
<td>94</td>
<td>Normal: 58.79%</td>
</tr>
</tbody>
</table>

Chromosomal aneuploidy mostly due to non-disjunction and meiotic errors.

Chromosomal aneuploidy is increased with female age.

Quality and biological age

Table 4: Chromosomal aneuploidy in 16 day embryos in Balb/c mice: variation according to maternus age and fetal sex

<table>
<thead>
<tr>
<th>Environmental group</th>
<th>Maternal age</th>
<th>Embryonic sex</th>
<th>20</th>
<th>21</th>
<th>22x</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>26</th>
<th>27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>50-50</td>
<td>Male</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>50-50</td>
<td>Female</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td>1</td>
<td>1</td>
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</tr>
<tr>
<td>Male</td>
<td>50-70</td>
<td>Male</td>
<td>1</td>
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<td>1</td>
<td>1</td>
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<tr>
<td>Female</td>
<td>50-70</td>
<td>Female</td>
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</tr>
<tr>
<td>Male</td>
<td>70-70</td>
<td>Male</td>
<td>1</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Female</td>
<td>70-70</td>
<td>Female</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Independent of female age, aneuploidy occurs more often in mice who underwent ovariectomy.

Aneuploidy is related to biological age.

Integration of quantity and quality

Diagram showing changes in oocyte quality and quantity with age.
Can we predict which poor responder will become pregnant?

Univariable Models

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.96</td>
<td>0.90 - 1.02</td>
<td>0.178</td>
</tr>
<tr>
<td>BMI</td>
<td>0.97</td>
<td>0.88 - 1.08</td>
<td>0.622</td>
</tr>
</tbody>
</table>

AUC 95%CI n=

| Age                     | 0.54 | 0.40 - 0.69  | 0.387   |
| Duration of subfertility | 0.51 | 0.32 - 0.69  | 0.039   |
| AMH                     | 0.57 | 0.38 - 0.75  | 0.020   |

Ongoing Pregnancy Prediction

<table>
<thead>
<tr>
<th>Age &amp; AFC</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &amp; AFC</td>
<td>0.55</td>
<td>0.36 - 0.74</td>
</tr>
</tbody>
</table>

Nomogram of AFC and age

Percentage of ongoing pregnancies across AFC categories

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>AFC 2-10</th>
<th>AFC 11-20</th>
<th>AFC 21-40</th>
<th>AFC &gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>10.0%</td>
<td>15.6%</td>
<td>25.3%</td>
<td>17.3%</td>
</tr>
<tr>
<td>30-34</td>
<td>15.6%</td>
<td>20.0%</td>
<td>30.0%</td>
<td>21.3%</td>
</tr>
<tr>
<td>35-39</td>
<td>20.0%</td>
<td>25.6%</td>
<td>35.3%</td>
<td>26.3%</td>
</tr>
</tbody>
</table>

Dolleman, Broer et al., on behalf of the IMPORT & EXPORT study group, manuscript in writing.
Nomogram of AMH and Age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>&lt;0.4</th>
<th>0.4-0.8</th>
<th>0.8-1.6</th>
<th>1.6-2.8</th>
<th>&gt;2.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;31</td>
<td>17.8%</td>
<td>18.5%</td>
<td>30.3%</td>
<td>25.6%</td>
<td>40.2%</td>
</tr>
<tr>
<td>31-35</td>
<td>19.8%</td>
<td>16.4%</td>
<td>24.2%</td>
<td>20.2%</td>
<td>24.8%</td>
</tr>
<tr>
<td>35-40</td>
<td>8.1%</td>
<td>9.6%</td>
<td>16.5%</td>
<td>12.8%</td>
<td>12.0%</td>
</tr>
<tr>
<td>&gt;40</td>
<td>2.2%</td>
<td>2.8%</td>
<td>2.5%</td>
<td>2.8%</td>
<td>6.5%</td>
</tr>
<tr>
<td>&lt;31</td>
<td>13.4%</td>
<td>19.7%</td>
<td>27.3%</td>
<td>29.8%</td>
<td>18.5%</td>
</tr>
<tr>
<td>31-35</td>
<td>5.6%</td>
<td>6.4%</td>
<td>12.0%</td>
<td>4.5%</td>
<td>12.7%</td>
</tr>
<tr>
<td>&gt;40</td>
<td>0.0%</td>
<td>0.3%</td>
<td>2.3%</td>
<td>1.2%</td>
<td>10.3%</td>
</tr>
<tr>
<td>&lt;31</td>
<td>2.7%</td>
<td>3.7%</td>
<td>6.3%</td>
<td>3.4%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

Dolleman, Riss et al., on behalf of the IMPORT & EXPORT study group, Manuscript in writing

Answers...

Is the clinical impact of a poor response female age dependant?

ABSOLUTELY!

Counseling poor responders

- Age
- Actual number of oocytes
- AMH/AFC prior

INDIVIDUALISE.....
Conclusions

- Poor response must be evaluated in the perspective of a woman's age.
- Poor responders have lower pregnancy rate/live birth rate compared to normal responders.
- Age negatively influences the quality of the oocyte/embryos and thereby the pregnancy prospects.
- Still, age, actual number of oocytes, AFC and AMH can not predict non-pregnancy.
  > but we can use them for counseling!

Acknowledgements

- Frank Broekmans
- Madeleine Dolleman
- Bart Fauser
- Jeroen van Disseldorp
- Ben Willem Mol
- Brent Opmeer
- Rene Eijkemans
- IMPORT study group
- EXPORT study group

References

Is manipulating intra-ovarian androgen conditions effective in upgrading ovarian response?

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INSERM U752
Clamart-France
renato.fanchin@abc.aphp.fr

Conflict of Interest

The presenter has no conflict of interest regarding the content of this course

Learning objectives

- Understanding why androgens are likely to be involved in the regulation of ovarian follicle growth
- Understanding what are the strategies that have been used to improving intra-ovarian androgen concentrations
- Awareness of main results of clinical approaches trying to enhance intra-ovarian androgen concentrations
Ovarian function defect

Clinically sizable features:
- Less FSH-sensitive follicles
- Inadequate response to FSH
- Early follicle selection
- Poor oocyte competence
- Reduced likelihood of pregnancy

Proposed approaches

- Increasing gonadotropin dose
- Reducing GnRH agonist dose
- Using GnRH antagonists
- Administering growth hormone
- Administering aspirin
- Doing ICSI…

Management perspectives

Non-FSH strategies

Androgen hypothesis
Increased folliculogenesis in:

**Androgen hypothesis**

- Erickson & Yen, Semin Reprod Endocrinol, 1984
- Lobo, JCE&M, 1984
- Kase et al, Acta Endocrinol, 1983
- Puttanewal & Deligdisch, JCE&M, 1986
- Pache et al, Histopathology, 1991

Female-to-male transsexuals

- Lobo, JCE&M, 1984
- Kase et al, Acta Endocrinol, 1963
- Futterweit & Deligdisch, JCE&M, 1986
- Pache et al, Histopathology, 1991

Specific immunostaining for androgen receptors in the ovary:

- 4.2-fold as high in immature as in preovulatory GCs

Hillier et al, Hum Reprod, 1997
Androgen hypothesis

Increased folliculogenesis in androgen-treated rhesus monkeys

Androgens promote initial follicle recruitment in rhesus monkeys

Vendola et al, J Clin Invest, 1998

Vendola et al, Biol Reprod, 1999
Androgen hypothesis

Increase in FSHR expression in androgen-treated rhesus monkeys

Weil et al, JCE&M, 1999

Serum androgen levels correlated with small AFC in PCOS

Jonard et al, Hum Reprod, 2003
Enhancing androgen availability

Finding the best way of increasing ovarian androgen availability:

Androgen administration

Providing LH activity

Aromatase inhibition

Dehydroepiandrosterone

2.9 ± 0.5-fold increase

6 "poor responders"
DHEA, 80 mg/day for 2 months

Casson et al, Hum Reprod, 2000
Androgen administration

25 "poor responders", DHEA, 75 mg/day for 4 months

Barad et al, Hum Reprod, 2006

Androgen administration

5 "poor responders", DHEA, 50-75 mg/day for 1-6 months


Androgen administration

62 "poor responders"

DHEA (75 mg/d) 16 wks

(n=17) (n=16)

RCT 2 COH cycles

Wiser et al, Hum Reprod, 2010
Androgen administration

Yeung et al, J Clin End Metab, 2013

22 POF patients

DHEA (75 mg/d) 16 wks (n=10)

Placebo (n=12)

T patches
25 "poor responders"
T patches (20 µg/d) for 5 days

62 "poor responders"
T patches (20 µg/d) 5 days (n=31)
No treatment (n=31)

12 women, aged 38-45 years
T patches (2.5 mg/d) 12 days
Placebo (Crossover study)
Androgen administration

T gels

49 "poor responders"

T gel (10 mg/d) 15-20 days (n=24)
Placebo (n=25)

Massin et al, Hum Reprod, 2006

Androgen administration

T gel (12.5 mg/d) pretreatment for 21 days

n=110 poor responders

Kim et al, Fertil Steril, 2011
Androgen administration

![Graph showing DHEA or T pretreatment x pregnancy rate in IVF-ET](Sunkara & Coomarasamy, Fertil Steril, 2011)

Enhancing androgen availability

Finding the best way of ovarian androgen availability:

- Androgen administration
- Aromatase inhibition
- Providing LH activity

![Diagram showing Aromatase inhibition](Mitwally et al, Hum Reprod, 2006)

Aromatase inhibition

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean ± SD</th>
<th><em>p</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA 75 mg/d for 5 days</td>
<td>10.2 ± 1.5</td>
<td>0.05</td>
</tr>
<tr>
<td>DHEA 200 mg/d for 5 days</td>
<td>10.7 ± 1.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Letrozole (2.5 mg/d) for 5 days</td>
<td>10.9 ± 1.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

12 "poor responders", 34 cycles

Letrozole (2.5 mg/d) for 5 days

Mitwally et al, Hum Reprod, 2006
### Aromatase inhibition

**Garcia-Velasco et al, Fertil Steril, 2005**

OCP + Letrozole (2.5 mg/d) during the first 5 days of FSH treatment

**Schoolcraft et al, Fertil Steril, 2008**

OCP + Micro-flare (n=355)

Letrozole (2.5 mg/d) during the first 5 days of FSH (n=179)

### Providing LH activity
**Providing LH activity**

*Cédrin-Durnerin et al., Hum Reprod, 2008*

<table>
<thead>
<tr>
<th>Cycle day</th>
<th>Day</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 - 22</td>
<td>0.1</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.1</td>
<td>0.1</td>
<td>0.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>

LH priming

**Providing LH activity**

*Cédrin-Durnerin et al., Hum Reprod, 2008*

**Table 1.** Parameters due to LH-ox and LH-primed patients of a group.

<table>
<thead>
<tr>
<th>Type of Patients</th>
<th>Parameter</th>
<th>Mean</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH-ox</td>
<td>Age</td>
<td>34.2</td>
<td>33.5</td>
<td>22.0</td>
<td>45.5</td>
</tr>
<tr>
<td></td>
<td>Height</td>
<td>168.5</td>
<td>165.5</td>
<td>150.0</td>
<td>180.0</td>
</tr>
<tr>
<td></td>
<td>Weight</td>
<td>68.5</td>
<td>65.5</td>
<td>45.0</td>
<td>90.0</td>
</tr>
</tbody>
</table>

**Providing LH activity**

*Cédrin-Durnerin et al., Hum Reprod, 2008*

**Table 2.** Parameters for LH-promoted patients.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34.2</td>
<td>33.5</td>
<td>22.0</td>
<td>45.5</td>
</tr>
<tr>
<td>Height</td>
<td>168.5</td>
<td>165.5</td>
<td>150.0</td>
<td>180.0</td>
</tr>
<tr>
<td>Weight</td>
<td>68.5</td>
<td>65.5</td>
<td>45.0</td>
<td>90.0</td>
</tr>
</tbody>
</table>

103 "normal" patients (androgen priming, n=53)

Loszló et al., Hum Reprod, 2008
Providing LH activity

Losel et al, Hum Reprod, 2008

103 "normal" patients (androgen priming, n=53)

Beretsos et al, Reprod Biol Endocrinol, 2009

46 "normal" patients, one previous ICSI failure

hCG (200 IU/d) for 7 days after pituitary suppression (before FSH?)

Motta et al, J Assist Reprod Genet, 2009

100 "normal" patients, one previous IVF-ET failure

hCG (250 µg) on day 1, FSH administration starting on day 3
Providing LH activity

<table>
<thead>
<tr>
<th>LH (%)</th>
<th>Control</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryonic survival (mean ± SD)</td>
<td>3.8 ± 1.6</td>
<td>2.5 ± 1.3</td>
</tr>
<tr>
<td>Embryonic pregnancy/ET (%)</td>
<td>27%</td>
<td>45%</td>
</tr>
<tr>
<td>% sign pregancy/ET (%)</td>
<td>40%</td>
<td>41%</td>
</tr>
<tr>
<td>HCG (IU/L)</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>LH at HCG (%)</td>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td>Multiple pregnancy (%)</td>
<td>25</td>
<td>27</td>
</tr>
</tbody>
</table>

100 "normal" patients, one previous IVF-ET failure

hCG (20 µg) on day 1, FSH administration starting on day 3


Conclusions

1. Alleviating reproductive implications of ovarian aging constitutes one of the single most important challenges in reproductive medicine for the next years.

2. Whereas the relationship between increased androgen availability and the bulk of growing follicles in the ovaries is likely, the best way to provide such an activity remains to be set.

3. Recent trials indicate that androgen administration, in particular DHEA, are effective in increasing the number of ovarian follicles, but further RCT are needed to confirm and/or expand these first observations.

4. In the light of these first results, and in the absence of other effective treatments, clinical use of androgens should be considered to enhance ovarian function in selected cases.
“Will application of stimulation dosages over 225 IU per day prevent a poor response?”

Frank Broekmans
Helen Torrance

Disclosures

Member external advisory board Merck Serono,
Member external advisory board Gideon Richter
Consultancy work MerckSharpDome
Educational activities Ferring BV
Consultancy work Roche

LEARNING OBJECTIVES

1. APPRECIATE KNOWLEDGE ON PHARMACODYNAMICS OF GONADOTROPIN OVARIAN STIMULATION
2. ACKNOWLEDGE EXPLANATIONS FOR POOR OVARIAN RESPONSE
3. ACCEPT THE CURRENT INABILITY TO ALTER FATE OF A POOR RESPONDER
Answer to Take Home

...the ovaries... are no oranges...

---

Agenda

Poor Ovarian Response

- Definition
- Significance
- Causes
- Forecasting
- Prevention– Dose adjustments
- Conclusions

---

Definition

Operational:

≤3 oocytes with conventional stimulation protocol

And/or

Advanced maternal age (≥40) and/or Abnormal Ovarian Reserve Test

---

Ferraretti et al, Hum Reprod 2011
Agenda

Poor Ovarian Response

- Definition
- Significance
- Causes
- Forecasting
- Prevention – Dose adjustments
- Conclusions

Significance

Sunkara HFSA
N=400,000
HR 2011

Agenda

Poor Ovarian Response

- Definition
- Significance
- Causes
- Forecasting
- Prevention – Dose adjustments
- Conclusions
Causes - Folliculogenesis

- Genetic variants FSH receptor
- FSH underdosing
- Small cohort
- Variation

Agenda

Poor Ovarian Response

- Definition
- Significance
- Causes
- Forecasting
- Prevention – Dose adjustments
- Conclusions

Forecasting

- AUC age: 0.60 (0.57-0.64)
- AUC age+FSH: 0.69 (0.66-0.72)
- AUC age+AFC: 0.76 (0.72-0.80)
- AUC age+AMH: 0.80 (0.76-0.84)
- AUC AMH: 0.81 (0.77-0.84)
- AUC age+AMH+AFC+FSH: 0.81 (0.75-0.86)

Broer, IMPORT study, HRU 2012
**Forecasting poor response**

- **ROC Curve**
  - Sensitivity
  - 1 - Specificity
  - Predicting false negatives and positives..

- **Personalising**
  - Can we increase the antral follicle number and egg yield

---

**Agenda**

- Poor Ovarian Response
  - Definition
  - Significance
  - Causes
  - Forecasting
  - Prevention – Dose adjustments
  - Conclusions

---

**Dose Response Curves by Age Level**

- Hypothetical
  - Oocyte Number
  - Dose FSH
  - response 30
  - response 35
  - response 40
Ovarian Response to COS

It is the cohort

And the size may vary...

Predicted Poor Response

Klinkert et al. Hum Rep 2005: n=52
P: IVF patients with AFC < 5 (Q. score)
I: 300 IU FSH/day
C: 150 IU FSH/day
O: oocyte yield and ongoing pregnancy

P: IVF patients with AMH < 14 pmol/L + age < 36 yrs
I: 300 IU FSH/day
C: 150 IU FSH/day
O: oocyte yield and ongoing pregnancy

Harrison et al. Fertil & Steril 2001: n=170
P: IVF/ICSI patients, with FSH > 8.5 U/L
I: 300 IU FSH/day
C: 150 IU FSH/day
O: oocyte yield and ongoing pregnancy

Berkkanoglu et al. Fertil & Steril: n=119
P: ICSI patients, with AFC < 12, and FSH < 12 U/L
I: 450 and 600 IU FSH/day
C: 300 IU FSH/day
O: oocyte yield and ongoing pregnancy

Oocyte Yield

Higer FSH dose: no effect on number of oocytes
Ongoing Pregnancies

Higher FSH dose: no effect on outcome Pregnancy

Predicted Normal response

Jayaprakasan et al BJOG 2010: n=131
P: IVF/ICSI patients aged < 39 jaar, FSH < 12 and AFC 8-21
I: 300 IU/day
C: 225 IU/day
O: oocyte number, ongoing pregnancy and live birth

Predicted Normal Response

Higher FSH dose: no effect on oocyte yield nor ongoing pregnancies nor live birth
Actual poor response

There is insufficient evidence to use of any particular intervention to improve treatment outcomes in poor responders in IVF.

ONLY one RCT on FSH dose adjustment: 225 versus 450 DURING poor response cycle

Agenda

Poor Ovarian Response

– Definition
– Significance
– Causes
– Forecasting
– Prevention– Dose adjustments
– Conclusions

Conclusion

...the ovaries... are no oranges...even if squeezed
Still,...hope ?.. Popovic et al

Individualised dosing:
not more oocytes, BUT more ongoing pregnancies...

The OPTIMIST trial
OPTIMisation of cost effectiveness through individualised FSH
Stimulation dosages for IVF Treatment: a randomised trial.
Dutch RM consortium

18 months treatment approach

ZonMw
Conflict of Interest / Disclosure Statement

Prof. dr. F.J. Broekmans receives monetary compensation:

Member of the external advisory board for Merck Serono, The Netherlands
Member advisory board Roche, Switzerland
Consultancy work for Gedeon Richter, Belgium
Consultancy work for MSD, The Netherlands
Educational activities for Ferring BV, The Netherlands
Educational activities for MSD, The Netherlands

19-03-2013
Mini - Debate: A first cycle poor responder after adequate FSH dosing should not be allowed further ART treatment: PRO!

Petra De Sutter
Centre for Reproductive Medicine
University Hospital Gent

Conflicts of interest

I have the following interests to declare (last three years):

- Institutional unrestricted research grants from Ferring and Merck-Serono
- Personal travel grants from Ferring, Merck-Serono, MSD
- Speaker allowances from Ferring, Ipsen
- Institutional training centre for Cook

Learning objectives

After this debate, the participants should be able to

- Understand the decision making process on whether or not to start/continue treatment
- Discuss the elements of importance in this decision making:
  - Medical indication for treatment
  - Health-economic aspects
  - Psychological / ethical aspects
  - Risks and complications
Introduction

ART: IVF and ICSI

Medical aspects: "indications for treatment"
Health economic aspects
Ethical/psychological aspects

When to start?
When to stop?

Different aspects may be conflicting

Non-medical aspects

- Health-economic/financial arguments
  (1 cycle expectant management = 0 Euro <> 1 IUI cycle = 300 Euro <> 1 IVF cycle = 4000 Euro)

- Psychological/ethical arguments
  (willingness-to-pay, impatience, autonomy to decide)

- To be balanced against risks and complications (psychosocial burden, OHSS, multiple pregnancies, procedure-related risks?)

When not to allow further treatment to a poor responder after adequate FSH dosing?
When to stop?

(Starting or) continuing IVF is not recommended if chances of pregnancy < financial burden (patient vs society) ± emotional burden ± risks and complications

Financial burden?

If society pays: legitimate ethical reasons for watchdog position of physician (5%/cycle = 42 yrs)
If patient pays: willingness-to-pay after realistic information about chances prevails

Emotional burden?

(+) Patient may want to continue/start treatment for Ψ reasons (even if chances are low)
(-) Patient may want to stop treatment for Ψ reasons (even if chances are high)

Risks and complications?

Even if patient pays and may have a "Ψ indication", IVF is not ethically defendable if chances of pregnancy are <1-2% ± incidence of complications ! (age limit 45 years)
What with younger patients with poor prognosis?

Continuing IVF is not recommended if chances of pregnancy < financial burden (patient vs society) ± emotional burden ± risks and complications

If chances are < 5% per cycle?
  e.g. (very) poor responders, bad embryo quality, failed implanters > 6 cycles?

Oocyte donation

---

Conclusion

The decision when to start and when to stop ART should be taken after informed consent (“colloque singulier”)

It should depend on available (medical) evidence of chances of pregnancy after expectant management ⇔ non-IVF ⇔ IVF treatment

It should be moderated by financial and emotional arguments

Decision to treat ≠ availability of reimbursement (fast IVF if reimbursement or no treatment if not reimbursed)

Emotional burden should be considered, both in the decision to treat and not to treat
A first cycle poor responder after adequate FSH dosing should not be allowed further ART treatment

Contra arguments

Pia Saldeen
MD, PhD
Malmö, Sweden

Disclosures

No conflict of interest within the topic presented in this lecture

Learning objectives

To understand why first time poor responders should be offered further IVF cycle/s
Poor response

- Prevalence 5.6-35.1% depending on the definition (Oudedijk et al, 2011)
- No universal consensus on definition until 2011
- 2011 ESHRE Bologna criteria: consensus on the definition of “poor response” (Ferraretti et al, 2011)
- Criteria based on risk factors, previous cycle and ovarian reserve test

Bologna criteria for poor ovarian response (POR)

Two of the three criteria must be present
- Advanced maternal age (≥ 40) or other risk factor for POR
- Previous cycle with ≤ 3 oocytes with a conventional stimulation
- Abnormal ovarian reserve test (i.e AFC < 5-7 or AMH < 0.5-1.1 ng/ml)

Two episodes of POR after maximal stimulation in the absence of advanced maternal age or abnormal ovarian reserve tests

Ferraretti et al, 2011

Prevalence of POR in relation to female age

Ferraretti et al, 2011

The relationship between age and POR (cycles cancelled because of absent or low ovarian response or pick up with ≤ 3 oocytes) in 2631 women undergoing the first IVF cycle in the Bologna S.I.S.Me.R unit and in the Modena University unit 2004-2009.
What is the problem with POR?

- Reduced pregnancy rates after IVF
- High cancellation rates

The prevalence
- High treatment costs per delivered child (high quantity of gonadotropins, reduced delivery rates)

Strategies
- No treatment strategy better than the other

Psychology
- High stress and burden on the patients
- Extensive counselling needed

Ethical issues
- Patient autonomy/preferences
- Potential conflicts

But..

- POR can be an occasional finding (Veleva et al, 2005)
- Not all POR have poor pregnancy prospects
- Even if reduced pregnancy prospects at a group level, women with POR do get pregnant and deliver after IVF.
- Since reduced pregnancy rates, reasonable to try more than one IVF cycle
- Cumulative ongoing pregnancy rates (3 cycles) of 11.5-19.0 % in expected poor responders (Veleva et al, 2005 and Hendriks et al, 2008).
- To reduce costs, natural cycle IVF might be an alternative
Natural cycle IVF in poor responders

- An alternative to conventional IVF or oocyte donation?
- Less expensive
- Lower treatment burden?
- As effective as ovarian hyperstimulation?

Naturcycle in in vitro fertilization in poor responder patients: a survey of 500 consecutive cycles

Schimberni et al., 2009

<table>
<thead>
<tr>
<th>Cycle #</th>
<th>PR/cycle</th>
<th>Cumulative PR</th>
<th># of pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>9.5%</td>
<td>12.9%</td>
<td>28</td>
</tr>
<tr>
<td>#2</td>
<td>9.7%</td>
<td>15.0%</td>
<td>10</td>
</tr>
<tr>
<td>#3</td>
<td>12.0%</td>
<td>16.3%</td>
<td>6</td>
</tr>
<tr>
<td>#4</td>
<td>10.2%</td>
<td>16.7%</td>
<td>4</td>
</tr>
<tr>
<td>#5</td>
<td>7.1%</td>
<td>16.7%</td>
<td>1</td>
</tr>
</tbody>
</table>

49 pregnancies in 294 women
Data on poor responder-natural cycle IVF- and age

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>≤ 35</th>
<th>36-39</th>
<th>≥ 40</th>
</tr>
</thead>
<tbody>
<tr>
<td># patients</td>
<td>294</td>
<td>90</td>
<td>69</td>
<td>165</td>
</tr>
<tr>
<td># cycles</td>
<td>500</td>
<td>105</td>
<td>120</td>
<td>275</td>
</tr>
<tr>
<td>PR/cycle</td>
<td>9.8%</td>
<td>18.1%</td>
<td>11.7%</td>
<td>6.8%</td>
</tr>
<tr>
<td>PR/patient</td>
<td>16.7%</td>
<td>31.7%</td>
<td>20.3%</td>
<td>9.7%</td>
</tr>
</tbody>
</table>

Live birth rates following natural cycle IVF in women with poor ovarian response according to the Bologna criteria

• Retrospective cohort trial
• 136 poor ovarian responders (Bologna criteria)
• 390 Natural cycle IVFs
• Mean age 37.3
• Mean # of previous cycles 3.8

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>≤ 35</th>
<th>36-39</th>
<th>≥ 40</th>
</tr>
</thead>
<tbody>
<tr>
<td># cycles</td>
<td>390</td>
<td>122</td>
<td>168</td>
<td>100</td>
</tr>
<tr>
<td>Oocyte retrieval rate</td>
<td>74.6%</td>
<td>77.9%</td>
<td>73.2%</td>
<td>73.0%</td>
</tr>
<tr>
<td>ET rate</td>
<td>42.1%</td>
<td>47.5%</td>
<td>43.5%</td>
<td>33%</td>
</tr>
<tr>
<td>LBR/cycle</td>
<td>10/390</td>
<td>3/122</td>
<td>4/168</td>
<td>3/100</td>
</tr>
<tr>
<td>LBR/patient</td>
<td>2.6%</td>
<td>2.5%</td>
<td>2.4%</td>
<td>3.0%</td>
</tr>
</tbody>
</table>
Although the best treatment for POR is oocyte donation.

A first cycle poor responder after adequate FSH dosing should be allowed further ART treatment, because...

- A single episode of POR can be an occasional finding
- Pregnancy prospects might vary within the group of poor responders
- Even a true poor responder can get pregnant and deliver after IVF
- If tubal factor or severe male factor, no other possibility than IVF
- Not all couples are willing to go for oocyte donation
- Patient autonomy and preferences should be respected
- Natural cycle IVF might be a cost-effective alternative to conventional IVF - results contradictory
- Further studies on the reproductive potential of Bologna criteria POR needed (after IVF with or without gonadotropin stimulation)

Further...

- The Bologna criteria was not set up to exclude poor prognosis patients from IVF
- Main purpose: research, homogenous population in future trials
References


How should we stimulate patients with polycystic ovaries

Stratis Kolibianakis
MSc MPhil PhD
Assistant Professor
in Obstetrics Gynaecology and Assisted Reproduction
Unit for Human Reproduction
1st Department of Obstetrics and Gynaecology
Aristotle University of Thessaloniki, Greece

Disclosure
No commercial and/or financial relationships with manufacturers of pharmaceuticals, mentioned in this presentation
Invited speaker for MSD, Serono, Ferring

Learning objectives
By the end of this presentation it should be clear:

What is the most efficient way to stimulate patients with PCOS

What is the most safe way to stimulate patients with PCOS
Infertility treatment in PCOS

First line treatment:
- Lifestyle changes
- Ovulation inducing agents (clomiphene citrate, insulin-sensitizing medications)

No conception:
- Gonadotrophin treatment
- Laparoscopic ovarian drilling

Ovarian stimulation for IVF in PCOS

- Understimulation
- Overstimulation
- Ovarian hyperstimulation syndrome (odds ratio 6.8, 95% CI: 4.9-9.6)

Maternal mortality rates from OHSS:
~3 deaths per 100,000 IVF cycles performed

Confidential Enquiry into Maternal and Child Health, 2007; Braat et al., 2010

Ovarian stimulation for IVF in PCOS

IVM

- Metformin pretreatment
- Gonadotrophin
- Analog
- Triggering signal
- Segmentation
Ovarian stimulation for IVF in PCOS

**IVM**

- Oocyte collection from the ovaries of women with PCOS in an unstimulated cycle
- Maturation in-vitro prior to insemination

**Siristatidis et al. 2011**

**IVM** is a feasible option for subfertile women with PCOS

- Favorable maturation, fertilization, pregnancy, and live birth rates
- Pregnancy complications, congenital anomalies, similar to those of conventional IVF
IVM

No data from randomised trials to support recommendations for clinical practice at present

Until more evidence is available, IVM may not be the preferred first line of treatment for subfertile women with PCOS

Pretreatment with metformin?

Rationale: to improve IVF outcome

Reduction of intraovarian androgens, leading to an improvement in oocyte quality and fertilization

Reduction in OHSS rate

Metformin

enhances insulin sensitivity

in the liver, where it inhibits hepatic glucose production,
in the peripheral tissues, where it increases glucose uptake and utilization into muscle tissue

reduces insulin resistance, intraovarian and hyperandrogenemia

Dunn and Peters, 1995
Ovarian stimulation for IVF in PCOS

Pretreatment with metformin

- 5 IVF trials
- 396 patients with PCOS
- Metformin + IVF vs. IVF

Less FSH required after metformin pretreatment

WMD = –290.4 IU
95% CI = –450.3 to –130.5

E2 on the day of hCG

WMD = –3.5 nmol/L
95% CI = –9.2 to +2.2
Ovarian stimulation for IVF in PCOS

COCs

WMD = -0.44
95% CI: -0.98 to +1.86

Costello et al 2006

OHSS rate

OR = 0.21
95% CI: 0.11–0.41
RD = -12%
95% CI: -24 to 0.0

Costello et al 2006

Pregnancy rate

OR = 1.29
95% CI: 0.84–1.98

Costello et al 2006
### Ovarian stimulation for IVF in PCOS

#### Metformin pretreatment

**Live birth rate**

<table>
<thead>
<tr>
<th>Group</th>
<th>Live Birth Rate</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>0.98</td>
<td>2.02</td>
<td>0.98–4.14</td>
</tr>
</tbody>
</table>

Costello et al. 2006

---

#### Gonadotrophin of choice?

No comparative data regarding the outcome of IVF in PCOS patients stimulated with different gonadotrophin preparations.

Data from ovulation induction cycles: no outcome differences in the gonadotrophin preparations.

Nugent et al., 2000; van Wely et al., 2003b

---

### Ovarian stimulation for IVF

#### Pregnancy rate

<table>
<thead>
<tr>
<th>Group</th>
<th>Pregnancy Rate</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>hMG versus rhFSH</td>
<td>1.04</td>
<td>1.04</td>
<td>0.89 to 1.15</td>
</tr>
</tbody>
</table>

Lehert 2010

---

hMG versus rhFSH
Which analogue?

Ovarian stimulation for IVF in PCOS

Agonists vs. antagonists

Duration of stimulation

<table>
<thead>
<tr>
<th>Method</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
<th>4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>agonists</td>
<td>0.85</td>
<td>0.75</td>
<td>0.65</td>
<td>0.55</td>
</tr>
<tr>
<td>antagonists</td>
<td>0.80</td>
<td>0.70</td>
<td>0.60</td>
<td>0.50</td>
</tr>
</tbody>
</table>

SD = -0.86

95% CI: -1.14 to -0.59

Griesinger 2006

Gonadotrophin consumption

<table>
<thead>
<tr>
<th>Method</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
<th>4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>agonists</td>
<td>0.30</td>
<td>0.25</td>
<td>0.20</td>
<td>0.15</td>
</tr>
<tr>
<td>antagonists</td>
<td>0.35</td>
<td>0.30</td>
<td>0.25</td>
<td>0.20</td>
</tr>
</tbody>
</table>

SD = -0.31

95% CI: -0.77 to +0.15

Griesinger 2006
### Ovarian stimulation for IVF in PCOS

#### Agonists vs. antagonists

<table>
<thead>
<tr>
<th>COC</th>
<th>peeled</th>
<th>peeled</th>
<th>peeled</th>
<th>peeled</th>
<th>peeled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**SD = 0.6**
95% CI: -0.49 to +0.60

---

**Griesinger 2006**

#### Clinical pregnancy

<table>
<thead>
<tr>
<th></th>
<th>peeled</th>
<th>peeled</th>
<th>peeled</th>
<th>peeled</th>
<th>peeled</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**OR = 0.82**
95% CI: 0.51 to 1.32

---

**Griesinger 2006**

#### OHSS rate

<table>
<thead>
<tr>
<th></th>
<th>peeled</th>
<th>peeled</th>
<th>peeled</th>
<th>peeled</th>
<th>peeled</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**OR = 0.73**
95% CI: 0.22 to 2.38

---

**Griesinger 2006**
### OHSS per woman randomized Cochrane 2011

<table>
<thead>
<tr>
<th>Study</th>
<th>OHSS-affected</th>
<th>OHSS-unaffected</th>
<th>Risk Difference</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>10</td>
<td>20</td>
<td>-10%</td>
<td>-14.0 to -7.0</td>
</tr>
</tbody>
</table>

- Risk difference: -10%
- 95% CI: -14.0 to -7.0

*Al-Inany et al. 2011*

### Cancellation or coasting due to OHSS risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancellation</th>
<th>Coast</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>10</td>
<td>20</td>
<td>0.50%</td>
<td>0.33 to 0.76</td>
</tr>
</tbody>
</table>

- Odds ratio: 0.50%
- 95% CI: 0.33 to 0.76

*Al-Inany et al. 2011*

### Ovarian stimulation for IVF in PCOS

#### Which triggering signal?
GnRHa-triggering of final oocyte maturation in GnRH-ant protocols in patients at risk of developing OHSS.

536 patients

<table>
<thead>
<tr>
<th>Trial type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>Acevedo et al 2006</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Bodri et al 2009</td>
</tr>
<tr>
<td>Observational, High risk</td>
<td>Griesinger et al 2007</td>
</tr>
<tr>
<td>Retrospective case-control, high risk</td>
<td>Manzanares et al 2009</td>
</tr>
<tr>
<td>Retrospective</td>
<td>Hernandez et al 2009</td>
</tr>
<tr>
<td>Retrospective, high risk: agonist arm only</td>
<td>Shapiro et al 2007</td>
</tr>
<tr>
<td>RCT</td>
<td>Sismanoglu et al 2009</td>
</tr>
<tr>
<td>RCT</td>
<td>Galindo et al 2009</td>
</tr>
<tr>
<td>RCT, high risk</td>
<td>Shahrokh et al 2010</td>
</tr>
</tbody>
</table>

1660 patients

<table>
<thead>
<tr>
<th>Trial type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>1660 patients</td>
</tr>
</tbody>
</table>

2196 patient : no severe OHSS

Why do we still use hCG for final oocyte maturation? Why do we still use agonists for controlling endogenous LH?
Replacement of hCG by GnRH agonist

GnRH agonist can replace hCG for induction of final oocyte maturation but luteal phase is insufficient and leads to a lower pregnancy rate

Griesinger et al. Hum Reprod Update 2005

Ovarian stimulation for IVF in PCOS

GnRHa triggering in GnRH-ant protocols in OHSS-risk patients

<table>
<thead>
<tr>
<th>LPS</th>
<th>Standard</th>
<th>Modified</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Ongoing</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>Pregnancy rate</td>
<td>72.0%</td>
<td>68.0%</td>
</tr>
</tbody>
</table>

Humaidan et al. 2010

Ovarian stimulation for IVF in PCOS

GnRHa triggering in GnRH-ant protocols in OHSS-risk patients

<table>
<thead>
<tr>
<th>LPS</th>
<th>Standard</th>
<th>Modified</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Ongoing</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>Pregnancy rate</td>
<td>72.0%</td>
<td>68.0%</td>
</tr>
</tbody>
</table>

Kolibianakis et al. 2011
GnRHa triggering in GnRH-ant protocols in OHSS-risk patients

Ovarian stimulation for IVF in PCOS

Elective cryopreservation of all pronuclear oocytes after GnRH agonist triggering of final oocyte maturation in patients at risk of developing OHSS

Griesinger et al 2007

20 patients at increased risk of developing OHSS

defined as:
- >20 follicles >10 mm or
- E2 >4000 pg/ml at the time of induction of final oocyte maturation or
- a history of cycle cancellation due to OHSS risk or
- the development of severe OHSS in a previous cycle
GnRHa triggering in GnRH-ant protocols in OHSS-risk patients

<table>
<thead>
<tr>
<th>% (n)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practice</td>
<td>0.3 (24)</td>
</tr>
<tr>
<td>Practice</td>
<td>33.0 (193)</td>
</tr>
<tr>
<td>Practice</td>
<td>24.5 (87)</td>
</tr>
<tr>
<td>Practice</td>
<td>27.2 (54)</td>
</tr>
</tbody>
</table>

PR: pregnancy rate

*Theoretical best is the cumulative pregnancy rate resulting from 24 ETs in 19 patients.

No patient developed signs or symptoms of clinically relevant OHSS II–III

0%, 95% CI: 0.0 - 1.6

---

**Ovarian stimulation for IVF in PCOS**

**GnRH antagonist for triggering final oocyte maturation**

in patients with polycystic ovaries

Unit for Human Reproduction
Medical School, Aristotle University of Thessaloniki

---

**Inclusion criteria**

- Indication for IVF
- Presence of PCO ovaries (volume >10cm³, >12 AF)
- ≥ 14 follicles ≥ 11mm on the day of triggering final oocyte maturation

**Stimulation:**

- rec FSH 150-300 IU/day

**Suppression of LH:**

GnRH antagonist daily,

fixed day 5 or flexible after day 5

**Criteria for triggering:**

- presence of ≥ 3 follicles of ≥ 17mm

**Triggering:**

triptorelin 0.2 mg

*Kolibianakis et al unpublished*
Fertilization method
ICSI, IVF, ICSI/IVF
Freezing at 2PN stage

Patients were instructed to report any symptoms associated with OHSS, in which case were examined at the clinic.
Admission in the hospital was performed in case of severe OHSS.

Thawing cycle:
Hormonal substitution with estrogen/progesterone
Transfer up to three embryos

Patient population
111 patients
PCO ovaries: 111 patients (100%)
PCOS: 61 patients (54.9%)

Male factor was also present in 34 patients (no testicular sperm was used)

Age: 32.4 ± 4.8 years
BMI: 24.3 ± 5.6 Kg/m²

Stimulation characteristics
Mean FSH starting dose:
171 ± 42 IU

Mean antagonist starting day
5.7 ± 1.4

Mean duration of stimulation
10.6 ± 2.3 days

Mean total dose of FSH required
1888 ± 655 IU
Hormonal values on the day of triggering final oocyte maturation

- LH: 2.3 ± 2.1 IU/L
- P: 1.4 ± 0.7 ng/ml
- E2: 4107 ± 1450 pg/ml
- Follicles: 26.1 ± 8.4

Embryological data

- COCs: 19.5 ± 10.3
- Fertilization rate: 54.9 ± 18.1%
- 2PN oocytes: 10.1 ± 5.6

OHSS

- Severe OHSS: 0 patients
- OHSS associated symptoms (nausea, abdominal pain-distention, oliguria, feeling unwell): 0 patients
- Duration of luteal phase: range 5-10 days

(Kolibianakis et al unpublished)
Thawing cycles

2PN oocytes: 847

Thawed embryos: 506

Still frozen 2PN oocytes: 341

FRET cycles:
158
mean: 1.4

Kolibianakis et al unpublished

<table>
<thead>
<tr>
<th>Biochemical</th>
<th>Ongoing pregnancy</th>
<th>Cumulative Ongoing pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>5% CI</td>
<td>%</td>
</tr>
<tr>
<td>Biochemical</td>
<td>Biochemical</td>
<td>Cumulative Ongoing pregnancy</td>
</tr>
<tr>
<td>%</td>
<td>5% CI</td>
<td>%</td>
</tr>
<tr>
<td>Biochemical</td>
<td>Biochemical</td>
<td>Cumulative Ongoing pregnancy</td>
</tr>
<tr>
<td>%</td>
<td>5% CI</td>
<td>%</td>
</tr>
<tr>
<td>Biochemical</td>
<td>Biochemical</td>
<td>Cumulative Ongoing pregnancy</td>
</tr>
<tr>
<td>%</td>
<td>5% CI</td>
<td>%</td>
</tr>
</tbody>
</table>

Conclusions

No association between the type of gonadotrophin used for ovarian stimulation and outcome differences can currently be supported in PCOS patients undergoing IVF

The use of GnRH antagonists as compared to GnRH agonists in PCOS patients undergoing IVF is associated with decreased duration of stimulation decreased gonadotrophin consumption and a similar probability of pregnancy
Conclusions

Pretreatment of PCOS patients with metformin does not appear to improve the probability of pregnancy after IVF.

In PCOS patients, segmentation of ovarian stimulation by replacement of hCG with GnRH agonist for triggering final oocyte maturation appears to be an attractive option, since it maintains the probability of pregnancy and eliminates the occurrence of OHSS.
Excessive ovarian response affects oocyte quality, endometrial receptivity and child health

Nick Macklon
Professor of Obstetrics and Gynaecology, University of Southampton, UK
Director, Complete Fertility Centre Southampton
Visiting Professor, University of Copenhagen and University of Adelaide

Conflicts of interest

• I have received consultancy and speaker fees from the following companies: Ferring, Organon, Schering Plough, MSD, Serono, Merck Serono, IBSA and Aeneova.

Learning Objectives

At the end of this debate I hope to have convinced the audience that:
• Excessive ovarian response affects oocyte quality, endometrial receptivity and child health
• We can ameliorate these effects.
• They should vote for the motion!
Implantation is the rate-limiting step in IVF.

The Iceberg of pregnancy loss:

- **Spontaneous**
  - Live Birth: 30%
  - Miscarriage: 15%
  - Pre-implantation loss: 25%
  - Post-implantation loss: 30%

- **IVF**
  - Live Birth: 30%
  - Miscarriage: 15%
  - Pre-implantation loss: 20%
  - Post-implantation loss: 30%

(Macklon et al., Hum Reprod Update, 2002)

(Boomsma et al., Hum Reprod, 2009)

(CONCEPTIONS)

(De Vos et al., Hum Reprod Update, 2010)
Optimal number of oocytes after long protocol?

![Graph showing live birth rate and oocyte yield.]

Optimal

Van der Gaast et al, RBM Online, 2006

Association between the number of eggs and live birth in IVF treatment: an analysis of 400 135 treatment cycles

Seth Komal Sanskara, Wulun Rittenberg, Nida Rana-Ferning, Shadys Bhattacharya, Javer Zaman, and Avni Gomnaran

![Graph showing the association between oocyte number and implantation.]

Verberg et al Hum Rep Update 2009

Number of oocytes and implantation after a mild stimulation protocol

Meta-analysis of studies with late start rFSH (Cn) and flexible start GnRH antagonist.

> 10 oocytes: significant decrease in chance on ongoing implantation

Conventional

Mild

Verberg et al Hum Rep Update 2009
Does mild stimulation reduce the rate of embryo aneuploidy?

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

111 Patients
528 fertilized oocytes
302 embryos FISHed

Baart et al, Hum Reprod 2007

![Diagram of GnRH agonist and GnRH antagonist with FSH levels and CD 2 follicle size](image)

Mild ovarian stimulation for in vitro fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial.

RCT

** 0 4 8 12**

Average per patient

0 4 8 12 16 20

- Conventional
- Mild

Mild Stimulation: helping the embryologist select.

Conventional ovarian stimulation

Mild stimulation

Page 94 of 155
What about the endometrium?

- Pubmed cited IVF papers

Ovarian stimulation damages the endometrium

- Natural cycle, day of ovulation
- When advanced >3 days NO IMPLANTATION

Stimulated cycle, day of OPU
- Secretory features present:
  - Subnuclear vacuoles displacing nucleus

- 25 natural cycles
- 25 stimulated cycles
- Biopsies on day 1, 3, 5, 7 after LH rise/hCG
What does the embryo see?

- Endometrial secretions
- Can be safely carried out prior to Embryo Transfer\(^1\)\(^2\)
- Demonstrates molecular fingerprint for implantation\(^2\)

---

Ovarian stimulation on intra-uterine cytokine profile

Multivariable analysis in 203 patients showed significant relations between the number of oocytes retrieved and secretion concentrations of IL-12, Dkk-1 (positive) and VEGF, IL-15 (negative).

---

WARNING!

Estrogen levels in this household may be toxic!!!
Estrogen is a critical determinant that specifies the duration of the window of uterine receptivity for implantation. This phenomenon is depicted in the scheme showing modulation of the window of receptivity in the P4-primed uterus in response to changing estrogen levels. This scheme shows that estrogen at low threshold level extends the window of uterine receptivity for implantation, but higher levels rapidly close this window, transforming the uterus into a refractory state.

**What about impact of high Progesterone levels?**

Most recent meta-analysis in GnRH antagonist cycles (n=585)

- Patients with progesterone elevation
  - higher serum estradiol levels on the day of hCG (p=0.008)
  - more COCs retrieved (+2.9, 95% CI +1.5 to +4.4, p < 0.001)
- Progesterone elevation on the day of hCG administration was associated with a significantly decreased probability of clinical pregnancy per cycle (-9%, 95% CI -17 to -2, p=0.005)
- In conclusion, in patients treated with GnRH antagonists and gonadotrophins, progesterone elevation on the day of hCG administration is significantly associated with a lower probability of clinical pregnancy.

When progesterone exceeded the threshold of 1.5 ng/ml, lower delivery rates:

- Rise >1.5 ng/ml in 24% of the antagonist group and 23% agonist group
- "9 out of 10 patients failed to achieve a clinical pregnancy whenever progesterone levels exceeded the threshold of 1.5 ng/ml"

<table>
<thead>
<tr>
<th></th>
<th>Antagonist</th>
<th>Agonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone level</td>
<td>34.3%</td>
<td>31.8%</td>
</tr>
<tr>
<td></td>
<td>P=0.07</td>
<td>P=0.03</td>
</tr>
</tbody>
</table>

Progesterone level (ng/ml on day of hCG)  

- Study group: 6 patients
- Control group: 6 patients

Endometrial receptivity is affected in women with high circulating progesterone levels at the end of the follicular phase: a functional genomics analysis.

- 12 oocyte donors

- Endometrial samples collected 7 days after the hCG injection
- Endometria compared with the control endometria, regardless of the GnRH analogue employed

- Of the 25 gene targets previously proposed as markers for endometrial receptivity:
  - >1.5 ng/ml (study group) 6
  - <1.5 ng/ml (control group) 6

Ovarian stimulation makes babies smaller by disrupting the endometrium
The endometrium and the baby

- Perinatal outcome of singleton siblings born after Assisted Reproductive Technology and spontaneous conception

Danish National Sibling-Cohort study

**AIM**: Separate the effects of the maternal characteristics and the effects of infertility

---

**Birthweight (g), adjusted**

- **IVF procedure or Ovarian Stimulation?**
- **Cryo: Birthweight (g), adj.**
What can we do to ameliorate the impact of ovarian stimulation on the endometrium?

Does milder stimulation reduce estradiol and progesterone levels at the end of the follicular phase?

Follicular Phase Endocrine Characteristics during Ovarian Stimulation and GnRH Antagonist Cotreatment for IVF: RCT Comparing rFSH Initiated on Cycle Day 2 or 5

Christophe Blockeel,† Marijke D. Sterrenburg,‡ Frank J. Bovendern,§ Marius I. C. Lijnen,¶ Jolien Sinte, Paul Uitterlinden, and Fem C. J. M. Evers∗

‘There is an alternative’ I said to Jean. ‘We could try freezing human embryos, and keep them in store until the effects of the fertility drugs have faded away and their menstrual cycles were back to normal. The womb would then be receptive, and capable of sustaining the growth of the fetus’.

The idea suddenly excited me. We could provide the mother with a whole family spaced in the way she wished, just thawing out each embryo when desired.

---

**Fresh embryo transfer versus frozen embryo transfer in in vitro fertilization cycles: a systematic review and meta-analysis**

- Three trials accounting for 693 cycles in women aged 27–33 years
- Mostly high responders

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events Total</th>
<th>Total Events</th>
<th>Total (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflatoonian 2010</td>
<td>73 187</td>
<td>52 187</td>
<td>46.0% 1.4 [1.05, 1.88]</td>
</tr>
<tr>
<td>Shapiro 2011 – Normal</td>
<td>39 70</td>
<td>27 67</td>
<td>24.4% 1.38 [0.97, 1.98]</td>
</tr>
<tr>
<td>Shapiro 2011 – High</td>
<td>38 60</td>
<td>34 62</td>
<td>29.6% 1.15 [0.86, 1.55]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>317 316</td>
<td>100.0% 1.32 [1.10, 1.59]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 1.03, df = 2 (P = 0.60); I² = 0%
Test for overall effect: Z = 3.00 (P = 0.003)

---

**Miscarriage**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events Total</th>
<th>Total Events</th>
<th>Total (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflatoonian 2010</td>
<td>5 187</td>
<td>6 187</td>
<td>33.2% 0.83 [0.26, 2.68]</td>
</tr>
<tr>
<td>Shapiro 2011 – Normal</td>
<td>6 70</td>
<td>7 67</td>
<td>39.6% 0.82 [0.29, 2.32]</td>
</tr>
<tr>
<td>Shapiro 2011 – High</td>
<td>4 60</td>
<td>5 62</td>
<td>27.2% 0.83 [0.23, 2.93]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>317 316</td>
<td>100.0% 0.83 [0.43, 1.60]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.00, df = 2 (P = 1.00); I² = 0%
Singleton pregnancies after the transfer of frozen thawed embryos were associated with better perinatal outcomes compared with those after fresh IVF embryos.

Lower relative risks (RR) and 95% confidence intervals (CI) after FET for:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antepartum haemorrhage</td>
<td>0.67 (0.55–0.81)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>0.84 (0.78–0.90)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>0.45 (0.30–0.66)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>0.69 (0.62–0.76)</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>0.68 (0.48–0.96)</td>
</tr>
</tbody>
</table>

Conclusions

- Despite embryo selection, implantation rates after IVF are lower than after spontaneous conceptions.
- Mild stimulation probably does not improve embryo quality; it just 'selects the best'.
- Ovarian stimulation disrupts the endometrium and intrauterine environment.
- No clinical intervention yet shown to ameliorate this.

Conclusions: Freeze all frees all.

- Doctor free to stimulate ovaries without disrupting endometrium.
- Women free of OHSS risk.
- Embryos free to implant in more physiological environment.
- Babies free of impact of ovarian stimulation on development.
Stimulate with gonadotropins in order to obtain 10-15 oocytes.

Freeze all embryos and transfer in FET cycle.

Further Reading


Excessive ovarian response affects oocyte quality, endometrial receptivity and child health


So does potentially any form of Assisted Reproductive Technology.

The statement is therefore potentially misleading so I am against it.

Disclosure statement

Nothing to disclose

None of the members of the research group have any commercial and/or financial relationship with manufacturers of pharmaceuticals, laboratory supplies and/or medical devices.
Conditions for treatment

Ovarian stimulation for ART: how to achieve efficacy and safety?
Pre-congress course 7
Special Interest Group Reproductive Endocrinology

Outline
Conditions for treatment: Effectiveness & Safety

- Safety of ART
  - Perinatal outcome
  - Long term follow-up
  } Potential mechanisms that may influence outcome
- Effectiveness of ART
  - Unexplained subfertility

Conclusions and reflections
Learning objectives

- What is known on safety of ART?
  - Perinatal outcome
  - Long term follow-up

- What mechanisms may influence outcome following ART?

- What is known on effectiveness of ART?
  - Indications

Perinatal outcome of singletons born following ART

<table>
<thead>
<tr>
<th>Outcome</th>
<th>% ART/C</th>
<th>n ART/C</th>
<th>RR / OR (95%CI)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth &lt; 37 wks</td>
<td>11% / 6%</td>
<td>5361 / 7038</td>
<td>RR 2.04 (1.80–2.32)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>12% / 5%</td>
<td>12114 / 410650</td>
<td>OR 1.95 (1.73–2.20)</td>
<td></td>
</tr>
<tr>
<td>Birth-weight &lt; 2500 g</td>
<td>11% / 6%</td>
<td>5361 / 7038</td>
<td>RR 1.70 (1.50–1.92)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>10% / 4%</td>
<td>10098 / 199342</td>
<td>OR 1.77 (1.40–2.22)</td>
<td>B</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>26% / 18%</td>
<td>5694 / 6616</td>
<td>RR 1.54 (1.44–1.65)</td>
<td>A</td>
</tr>
<tr>
<td>Admission NICU</td>
<td>17% / 12%</td>
<td>4442 / 5621</td>
<td>RR 1.27 (1.16–1.40)</td>
<td>A</td>
</tr>
<tr>
<td>Perinatal mortality</td>
<td>1.2% / 0.8%</td>
<td>4452 / 1641</td>
<td>RR 1.68 (1.11–2.55)</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>2.0% / 1.7%</td>
<td>5199 / 192993</td>
<td>OR 2.19 (1.81–2.68)</td>
<td>B</td>
</tr>
</tbody>
</table>

A: Helmerhorst et al 2004; B: Jackson et al, 2004

Birth defects in children born following ART

<table>
<thead>
<tr>
<th>Outcome</th>
<th>% ART/C</th>
<th>n ART/C</th>
<th>RR / OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All birth defects</td>
<td>7% / 5%</td>
<td>50671 / 3870760</td>
<td>RR 1.32 (1.24–1.42)</td>
</tr>
<tr>
<td>Major birth defects</td>
<td>3% / 2%*</td>
<td>50671 / 3870760</td>
<td>RR 1.42 (1.29-1.56)</td>
</tr>
</tbody>
</table>

* Risks are subject to population background risk
Impact

A Millennium NYs Baby from This Year

Patient factors related to subfertility

- Increased risk of obstetrical complications
  - Pre-eclampsia, antepartum haemorrhage, caesarean section
- Increased risk of adverse perinatal outcome
  - Preterm birth, low birth weight, perinatal death

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n TTP &gt;1y</th>
<th>n TTP &lt; 1y</th>
<th>RR / OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth &lt; 37 wks</td>
<td>7565</td>
<td>57618</td>
<td>OR 1.36 (1.22-1.50)</td>
</tr>
</tbody>
</table>

Draper et al, 1999; Thomson et al, 2005; Pandian et al, 2001; Pinborg et al, 2013

Potential mechanisms that may underlie poorer outcome

1) Patient factors related to subfertility
2) Early fetal losses
3) Aspects of the ART procedure
   a) Laboratory procedures involved in ART
   b) Ovarian stimulation

Increased risk of obstetrical complications
- Pre-eclampsia, antepartum haemorrhage, caesarean section

Increased risk of adverse perinatal outcome
- Preterm birth, low birth weight, perinatal death

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n TTP &gt;1y</th>
<th>n TTP &lt; 1y</th>
<th>RR / OR (95%CI)</th>
</tr>
</thead>
<tbody>
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<td>Preterm birth &lt; 37 wks</td>
<td>7565</td>
<td>57618</td>
<td>OR 1.36 (1.22-1.50)</td>
</tr>
</tbody>
</table>

Draper et al, 1999; Thomson et al, 2005; Pandian et al, 2001; Pinborg et al, 2013
Early fetal losses

- ~10% of ART-singletons originate from twin pregnancies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Early fetal loss</th>
<th>Controls</th>
<th>RR/ OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth &lt; 37 wks</td>
<td>1727</td>
<td>19608</td>
<td>OR 1.73 (1.54-1.94)</td>
</tr>
<tr>
<td>Birth weight &lt; 2500 g</td>
<td>1727</td>
<td>19608</td>
<td>OR 2.09 (1.82-2.39)</td>
</tr>
<tr>
<td>SGA</td>
<td>942</td>
<td>5237</td>
<td>OR 1.50 (1.03-2.20)</td>
</tr>
</tbody>
</table>


Laboratory procedures involved in ART

- Large-offspring syndrome in livestock, reduced birth weight in mice
- Animal studies not confounded by subfertility
- Culture conditions may lead to disturbed genomic imprinting

Young et al, 1998; Ceelen and Vermeiden, 2001; Dumoulin et al, 2010

Effect of in vitro culture of human embryos on birthweight of newborns

John C. Franssen(1,2), Joost de Vries(1,2), Dollar P. Van Meerveld(1), Eva C. Nilsen(1,3), Edith Cooremans(1), Jochen G. Deruyt(1), Inge L. Schreurs(1), Gerard A. Duemelmann(1,3), Arnold D. Kester(1), Joyce P. Gerards(1,3), and Johannes L. Evans(1,3)

1Department of Obstetrics and Gynaecology, University of Amsterdam, Amsterdam, The Netherlands
2Department of Obstetrics and Gynaecology, Academic Medical Center, Amsterdam, The Netherlands
3Department of Obstetrics and Gynaecology, Medical University of Graz, Graz, Austria

*Correspondence address: J. C. Franssen, j.c.franssen@amc.nl
Birthweight distributions of live born singletons resulting from embryo culture in either A or B sequential media. The graph depicts the percentage of newborns per birthweight category.


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Laboratory procedures involved in ART

Increase in birthweight with longer time in culture

| Group | Null (time 0) | P | T | P
|-------|--------------|---|---|---
| Null | 0.0008 | 0.002 | 0.002 | 0.002
| P | 0.0021 | 0.002 | 0.002 | 0.002
| T | 0.002 | 0.002 | 0.002 | 0.002
| P | 0.002 | 0.002 | 0.002 | 0.002

Mäkinen et al, 2013
Ovarian stimulation

Possible explanations

- Loss of natural selection of the dominant oocyte, resulting in reduced oocyte quality
- Impaired endometrial receptivity due to supraphysiological estradiol levels

Ertzeid and Storeng, 2001; van der Auwera and d'Hooghe, 2001

Ovarian stimulation

- Embryo donation model in mice.


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Ovarian stimulation

- Higher percentage of blastocysts on day 4 in control mice (61% vs. 41%; P < 0.001)
- Reduction of implantation rate of superovulated embryos in control mice (12% vs 25%; P < 0.001)
  → Reduced embryo developmental capacity
  - Higher implantation rate of control embryos in control recipients than in superovulated recipients (25% vs. 7%; \( p = 0.0001 \))
  - Lower birth weight in superovulated recipients than in control recipients (0.51g vs. 0.72g; \( p = 0.006 \))
  → Reduced endometrial receptivity

Ertzeid and Storeng, 2001
Ovarian stimulation
Obstetric and perinatal outcomes in singleton pregnancies resulting from the transfer of frozen thawed versus fresh embryos generated through in vitro fertilization treatment: a systematic review and meta-analysis

Maheswari et al. 2012

Long term consequences of poorer perinatal outcome

- Developmental Origins of Health and Disease
- Association birthweight and risk of chronic disease including coronary heart disease, hypertension, stroke, and type 2 diabetes in later life
  - Lower birth weight → higher risk
- Environmental influences acting during early development shape disease risk in later life
- Early environment in assisted reproduction

### Cardiovascular risk in ART-children

<table>
<thead>
<tr>
<th>Age</th>
<th>In ART/controls</th>
<th>Bp ART</th>
<th>Bp controls</th>
<th>p-value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>150 / 147</td>
<td>100 / 60</td>
<td>95 / 55</td>
<td>P &lt; 0.001</td>
<td>Belva et al, 2007</td>
</tr>
<tr>
<td>8-18</td>
<td>225 / 225</td>
<td>109 / 61</td>
<td>105 / 59</td>
<td>P &lt; 0.001</td>
<td>Ceelen et al, 2008</td>
</tr>
<tr>
<td>4-14</td>
<td>106 / 68</td>
<td>SDS +0.3±0.7</td>
<td>SDS +0.3±0.2</td>
<td>P &lt; 0.001</td>
<td>Sakka et al, 2010*</td>
</tr>
<tr>
<td>14</td>
<td>217 / 223</td>
<td>105 / 64</td>
<td>113 / 64</td>
<td>ns</td>
<td>Belva et al, 2012</td>
</tr>
<tr>
<td>11-12</td>
<td>65 / 57</td>
<td>113 / 70</td>
<td>FMD: 6.7</td>
<td>P &lt; 0.001</td>
<td>Scherrer et al, 2012*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PWV: 7.8 m/s</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CIMT: 410 μm</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pap: 30 mmHg</td>
<td>p &lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Measure for vascular function: FMD = flow-mediated dilation of the brachial artery, PWV = pulse-wave velocity, CIMT = carotid intima-media thickness, Pap = pulmonary artery pressure.

### Cerebral palsy in ART-children

**Multiplicty and early gestational age contribute to an increased risk of cerebral palsy from assisted conception: a population-based cohort study**

D. Heijlman1,2, J. Groen1, D. Schmidt, C. Barner1, L. St. Schrier1, P. Uldall1,2, E. Eric1, B. Jacobsson1, and P. Thoren1

Values of birth weight, length of gestation, duration of neonatal stay, and others were extracted from the registry of the Hospital Episode Statistics (HES) database in the United Kingdom. The diagnosis of cerebral palsy was based on the definition of the collaborating centers for the cerebral palsy registry. The study was approved by the ethics committee of the Hadassah-Hebrew University Medical Center.

**References**

Hvidtjørn et al. 2010

Neurodevelopmental outcome of singletons born following ART

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuromotor development</td>
<td>ART-children = naturally conceived</td>
</tr>
<tr>
<td>Cognition</td>
<td>ART-children = naturally conceived</td>
</tr>
<tr>
<td>Behaviour</td>
<td>ART-children = naturally conceived</td>
</tr>
</tbody>
</table>

Pertinent conclusions precluded due to:
- Limited methodological quality of controlled studies, problems with attrition, blinding, power
- Meta-analyses not possible due to large variety in age of testing and neurodevelopmental tests used
- Data on long term follow-up limited

Middelburg et al. 2008

Effects of ART and subfertility
ART in the Modified Natural Cycle

Effect of Ovarian Hyperstimulation

Ovarian hyperstimulation and neurodevelopment

Ovarian hyperstimulation and mental development and behaviour

<table>
<thead>
<tr>
<th>Age</th>
<th>n COH/ MNC</th>
<th>Measure</th>
<th>Outcome</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 y</td>
<td>66 / 56</td>
<td>Mental development*</td>
<td>98 / 101*</td>
<td>-1.9 (-6.6; 2.9)</td>
</tr>
<tr>
<td>2 y</td>
<td>66 / 55</td>
<td>Behaviour**</td>
<td>46 / 47**</td>
<td>-1.1 (-4.4; 2.2)</td>
</tr>
</tbody>
</table>

Measured with * BSID II, MDI, and **Child behaviour check list, Total problems scale

Jongbloed- Pereboom et al, 2011

Ovarian hyperstimulation and birth defects

<table>
<thead>
<tr>
<th>Age</th>
<th>n COH/ MNC</th>
<th>Measure</th>
<th>Outcome</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 y</td>
<td>66 / 56</td>
<td>Minor anomalies*</td>
<td>50% / 54%</td>
<td>1.13 (0.52–2.47)</td>
</tr>
<tr>
<td>2 y</td>
<td>66 / 56</td>
<td>Clinically relevant abnormalities*</td>
<td>11% / 4%</td>
<td>2.97 (0.49-18.21)</td>
</tr>
</tbody>
</table>

* Dysmorphic features according to Merks et al.

Seggers et al, 2012

Conclusions on safety of ART

Perinatal outcome

- Increased risk of preterm birth & low birth weight
- Uncertainty concerning the mechanism that underlies poorer perinatal outcome:
  - Patient factors related to subfertility
  - Early fetal losses
  - Ovarian hyperstimulation
  - Laboratory procedures involved in ART
Conclusions on safety of ART

Long term follow-up

- Concern about cardiovascular risk in ART children
- Neurodevelopmental outcome reassuring, but
  - Increased risk of cerebral palsy and neurodevelopmental disorders in ART children mediated by a higher rate of preterm birth
  - Long term follow-up limited and neurodevelopmental disorders may emerge as children grow older

→ Safety is not guaranteed yet

Outline

Conditions for treatment: Effectiveness & Safety

- Safety of ART
  - Perinatal outcome
  - Long term follow-up
- Effectiveness of ART
  - Unexplained subfertility

Conclusions and reflections

Indications

1990
- 50% tubal pathology
- 20% male factor
- 15% unexplained subfertility
- 15% other

2010
- 10% tubal pathology
- 35% male factor
- 25% unexplained subfertility
- 30% other

Annual reports AMC/VUmc
ART in unexplained subfertility

Figure 5. Forest plot of comparison 3 in vitro fertilisation (IVF) versus intracervical insemination plus ovarian stimulation (SO+IUI) contrast: 3.1 live birth rate per woman.

Pandian et al. 2012.

IVF vs. SO+IUI

A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial

Reindollar et al. 2010.
Conclusions on effectiveness of ART

- For the majority of indications of ART we are unsure on the effectiveness
- No comparative studies in unexplained, mild male?
### Impact

A 6-monthly IVF baby from this year

---

### Conditions for treatment

<table>
<thead>
<tr>
<th>Safety</th>
<th>Effectiveness</th>
<th>ARE THESE CONDITIONS FULFILLED??</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consider treatment</td>
<td>Offer treatment</td>
<td></td>
</tr>
<tr>
<td>Do not offer treatment</td>
<td>Consider treatment</td>
<td></td>
</tr>
</tbody>
</table>

---

### Conditions for treatment

<table>
<thead>
<tr>
<th>Safety</th>
<th>Effectiveness</th>
</tr>
</thead>
</table>
References

- Barker DJ. The fetal and infant origins of adult disease. BMJ. 1990;301:1111

References

- Jackson RA, Gibson KA, Wu YW and Crou

References

- Jackson RA, Gibson KA, Wu YW and Crou
References


Suggested presentations

- Sunday 7 July; Pre-congress course E: High standard psychosocial care in your clinic: how to implement new guidelines
  11:00 - 11:30: Patients and professionals’ barriers and facilitators of tailored expectant management
  Noorje Van Den Broek - The Netherlands

- Monday 8 July; Session 07: Female infertility: new developments
  11:00 - 11:15: Preliminary comparative effectiveness of IVF with single embryo transfer and repeated attempts with a natural cycle and IUI with hyperstimulation; a randomized trial (INeS trial)
  Alexandra Benenbroek - The Netherlands

- Tuesday 9 July; Session 29: Ovarian stimulation
  11:00 - 11:15: Continued treatment with clomiphene citrate in subfertile women with World Health Organization type II anovulation who are not pregnant after six ovulatory cycles
  Nienke Weiss, The Netherlands

- Tuesday 9 July; Session 45: Clinical female infertility
  15:15 - 15:30: An economic analysis comparing IVF with a single embryo transfer and IVF with a modified natural cycle to EU with hyperstimulation (the INeS trial)
  Raïssa Tjon-Kon-Fat, The Netherlands
Maximising success rates by stimulation individualization

Dr. Ernesto Bosch
Medical Director Human Reproduction Unit
Instituto Valenciano de Infertilidad
Valencia. Spain

Disclosure of Potential Conflicts of Interest

Dr. E. Bosch declares having received honoraria during the last 36 months for consultancy, participating in advisory boards and lectures including services in speakers bureaus by MSD, Merck-Serono and Ferring pharmaceuticals

Learning objectives

Primary:
- Understand the advantages of individualizing ovarian stimulation for optimizing IVF outcome

Secondary:
- Recognize the heterogeneity of population undergoing IVF
- Identify advantages and pitfalls of serum AMH
- Anticipate situations that may impact on ovarian response
- Consider the role of other ovarian response biomarkers
- Guidelines for choosing the personalized ovarian stimulation protocol
Patients are not all the same

Heterogeneity of population undergoing COS for IVF

<table>
<thead>
<tr>
<th>Age</th>
<th>≤ 35</th>
<th>36-40</th>
<th>&gt; 40</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>41.5%</td>
<td>5.8%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Anovulation/PCO</td>
<td>0.6%</td>
<td>0.3%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Low responders</td>
<td>0.6%</td>
<td>0.7%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>0.7%</td>
<td>0.6%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Maximising success rates by stimulation individualization

Nelson et al, Hum Reprod (2006), 24: 897-75

Arce et al, Fertil Steril (2013), Feb. 5 (Epub ahead of print)

Brodin et al, JCEM (2013), 98: 1107-1114
Maximising success rates by stimulation individualization

Le Marca et al. (2009) Hum Reprod 24: 2264-75

...Not everything is what it seems...

Maximising success rates by stimulation individualization

Hadlow et al. Fertil Steril (2013), Feb. 21 (Epub ahead of print)
Maximising success rates by stimulation individualization

Antimüllerian hormone levels decrease in women using combined contraception independently of administration route


The relationship of AMH with PCO morphology and PCO syndrome: A prospective cohort study


In women with endometriosis anti-Müllerian hormone levels are decreased only in those with previous endometrioma surgery


SUP: Superficial peritoneal lesion
OMA: Endometrioma
DIE: Deep infiltrating endometriosis
S-: No past surgery
S+: past surgery

Page 127 of 155
Impact of different factors on ovarian response, regardless of ovarian reserve

- Age
- Basal androgen levels
- Basal gonadotrophin levels
- BMI
- Hyperinsulism
- Hyperprolactinemia
- Gonadotropin receptor polymorphisms

Ovarian ageing: Endocrine features

- Total testosterone: ↓ 55%
- DHEAS: ↓ 77%
- Free testosterone: ↓ 49%
- Androstenedione: ↓ 64%

Davison et al. (2005) JCEM 90:3847

Welt et al. (2006) Hum Reprod;21:2189-93
Hypothalamic-pituitary failure: Endocrine features

- ↓ E2 levels (sometimes below detection level)
- FSH and LH < 1.2 IU/L (consider when FSH < 5 IU/L)
- Variable response to pulsatile GnRH
- Normal Inhibin-B
- AMH within normal limits

Hypothalamic-pituitary failure: Ovarian stimulation management

<table>
<thead>
<tr>
<th>FSH</th>
<th>Feto</th>
<th>E2 (pg/ml)</th>
<th>Fol</th>
<th>Endometrial thickness (mm)</th>
<th>% hCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 LH</td>
<td>0-1</td>
<td>28 ± 8</td>
<td>3 - 4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>25 LH</td>
<td>1-2</td>
<td>106 ± 59</td>
<td>3 - 4</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>75 LH</td>
<td>4-5</td>
<td>267 ± 54</td>
<td>7 - 8</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>225 LH</td>
<td>3-4</td>
<td>472 ± 213</td>
<td>7 - 8</td>
<td>85</td>
<td></td>
</tr>
</tbody>
</table>

The European Recombinant Human LH Study Group (1998), JCEM 83: 1507-14

Different impact of BMI on ovarian response in PCO than no PCO women

≤ 35 yr; Initial dose=225 IU; No PCO
≤ 35 yr; Initial dose=225 IU; PCO
Modulation by insulin of gonadotrophins action

Effects of PRL on basal and GnRH-stimulated LH release

FSH receptor polymorphisms
Suboptimal response to GnRHa long protocol is associated with a common LH polymorphism

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>GR agonist</th>
<th>LH receptor</th>
<th>FSH</th>
<th>E2</th>
<th>17β</th>
<th>AMH</th>
<th>E2</th>
<th>E2</th>
<th>E2</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>0.3</td>
<td>0.5</td>
<td>0.7</td>
<td>0.9</td>
<td>1.1</td>
<td>1.3</td>
<td>1.5</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>-</td>
<td>0.5</td>
<td>0.7</td>
<td>0.9</td>
<td>1.1</td>
<td>1.3</td>
<td>1.5</td>
<td>1.7</td>
<td>1.9</td>
<td>2.1</td>
</tr>
<tr>
<td>-</td>
<td>0.7</td>
<td>0.9</td>
<td>1.1</td>
<td>1.3</td>
<td>1.5</td>
<td>1.7</td>
<td>1.9</td>
<td>2.1</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Endocrine evaluation of infertile patients before COS for IVF

- Minimal
  - AMH
  - FSH
  - E2

- Recommended
  - LH
  - PRL
  - TSH, T3, T4

- Consider depending on the case
  - Total T
  - SHBG
  - Insulin
  - FSH/LH Polymorphisms

COS: Decision-making

- Type of gonadotrophin suppression
- Dose of FSH
- Administration of LH activity (LH, hMG, hCG)
- Choice of alternative protocols
GnRH agonists vs GnRH antagonists

Gonadotrophin-releasing hormone agonists for assisted reproductive technology (Review)

45 RCT (n=7511)

Live birth: OR=0.86 (0.69-1.08)
OHSS: OR=0.43 (0.33-0.57)


GnRH agonists vs GnRH antagonists in Endometriosis

FSH window
hCG if 2 or 3 follicles ≥17 mm
FSH window
hCG if 2 or 3 follicles ≥17 mm

GnRH agonist versus GnRH antagonist:
Follicular growth dynamics

FSH threshold
CD21 CD1 S1 S3 S5 S7 S9 S11 S13 hCGd CD21 CD1 S1 S3 S5 S7 S9 hCGd


IIVI
Study | LMH + LH | LH alone | Weight | LMH, fixed 95% CI | LH, fixed 95% CI
-- | -- | -- | -- | -- | --
Agonist | 1999 | 3/13 | 10/17 | 10 | 0.21 [0.04, 1.05]
Bl | 2001 | 0/16 | 1/14 | 23 | 0.02 [0.00, 0.72]
Humaidan | 2004 | 39/116 | 31/115 | 31 | 1.37 [0.78, 2.41]
Fabregues | 2006 | 24/60 | 25/60 | 22.5 | 0.93 [0.45, 1.93]
Tarlatzis | 2006 | 6/55 | 10/59 | 12.9 | 0.6 [0.2, 1.78]
Subtotal | 89/347 | 96/354 | 100 | 0.92 [0.65, 1.31]
Antagonist | Sauer | 2004 | 9/25 | 10/24 | 9.8 | 0.79 [0.25, 2.49]
Griesinger | 2005 | 8/62 | 9/65 | 11.4 | 0.92 [0.33, 2.56]
Subtotal | 17/87 | 19/89 | 21.2 | 0.86 [0.4, 1.85]
Total | 89/347 | 96/354 | 100 | 0.92 [0.65, 1.31]


Review: Recombinant Luteinising Hormone (rLH) for controlled ovarian hyperstimulation in assisted reproductive cycles
Comparison: LH and rFSH versus rFSH alone for COH in GnRH agonist downregulated IVF/CSI cycles in poor responders
Outcome: Ongoing pregnancy per woman randomised

Study | LMH + LH | LH alone | Weight | LMH, fixed 95% CI | LH, fixed 95% CI
-- | -- | -- | -- | -- | --
Barrenetxea | 2006 | 8/36 | 7/36 | 25.7 | 1.18 [0.38, 3.70]
DePlacido | 2005 | 19/65 | 13/65 | 43.5 | 1.65 [0.74, 3.71]
Ferraretti | 2004 | 22/54 | 11/54 | 30.8 | 2.69 [1.14, 6.33]
Total (95% CI) | 155 | 155 | 100.0 | 1.85 [1.10, 3.11]

Heterogeneity: Chi2=1.40, df=2 (P=0.50); I2=0.0%
Test for overall effect: Z=2.32 (P=0.020)
Ongoing pregnancy rate per started cycle transfer according to androgen levels

<table>
<thead>
<tr>
<th>Androgen Level</th>
<th>FSH+LH</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone ≤ 0.45 ng/mL</td>
<td>33.1 (25.4-41.7)</td>
<td>44.4 (36.1-53.2)</td>
<td>1.34 (0.98-1.85)</td>
</tr>
<tr>
<td>Testosterone &gt; 0.45 ng/mL</td>
<td>50.0 (37.5-62.5)</td>
<td>40.0 (28.6-52.6)</td>
<td>0.80 (0.53-1.20)</td>
</tr>
<tr>
<td>DHEAS ≤ 156 mcg/L</td>
<td>32.4 (24.3-41.7)</td>
<td>38.2 (29.6-47.5)</td>
<td>1.18 (0.82-1.69)</td>
</tr>
<tr>
<td>DHEAS &gt; 156 mcg/L</td>
<td>47.3 (36.3-58.1)</td>
<td>43.4 (32.9-54.6)</td>
<td>0.92 (0.65-1.30)</td>
</tr>
<tr>
<td>Δ4 ≤ 1.90 ng/mL</td>
<td>39.1 (30.5-48.4)</td>
<td>46.0 (37.1-55.2)</td>
<td>1.18 (0.87-1.60)</td>
</tr>
<tr>
<td>Δ4 &gt; 1.90 ng/mL</td>
<td>40.3 (29.7-51.8)</td>
<td>47.9 (36.9-59.2)</td>
<td>1.19 (0.82-1.72)</td>
</tr>
</tbody>
</table>

Bouch et al (2011),ESHRE.

Choices for COS according to possible combinations of GnRH analogs and stimulation drugs

<table>
<thead>
<tr>
<th>GnRH agonist</th>
<th>GnRH antagonist</th>
<th>No GnRH analogue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long</td>
<td>Short</td>
<td>Microflare</td>
</tr>
<tr>
<td>Natural</td>
<td>Mini</td>
<td>Modified natural</td>
</tr>
<tr>
<td>FSH</td>
<td>HMG</td>
<td>Others</td>
</tr>
<tr>
<td>Metformin</td>
<td>Clomiphene</td>
<td>Letrozole</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Estrogens</td>
<td>AMH</td>
</tr>
</tbody>
</table>

AMH tailored stimulation protocols improve outcomes whilst reducing adverse effects and costs of IVF.

Conclusions and reflections (I)

Reproductive medicine is not different than the rest of medical areas. Despite its clear and crucial benefits, the way to personalized medicine and customized therapy is still very large, with several barriers to overpass.

On one side, the pharmaceutical industry promotes a blockbuser model, focused on developing and marketing drugs for as broad a patient group as possible, while discourages the development of therapies aimed at smaller subpopulations and the diagnostic tests that can identify them.

Conclusions and reflections (II)

On the other side, the regulatory agencies cause too many resources to be devoted to phase-three clinical trials, and too few to monitoring and assessment after a particular drug has been approved.

On the top of that, clinicians’ daily practice is still based too often in a trial and error methodology, despite the availability of fine diagnostic tests that could help for a more personalized prescription of drugs and procedures.
To change the world, dear Sancho, it is not madness, neither utopia. It is just justice!

Don Quijote de La Mancha
Individualisation of ovarian stimulation has little impact on outcome

Georg Griesinger
University of Lübeck, Germany

Conflict of interest disclosure

within the last 36 months
➢ Consultancy: Glycotope, MSD, Merck-Serono
➢ Invited speaker: Merck-Serono, MSD, Ferring
➢ Participated in industry funded research:
  IBSA, Glycotope, MSD

Learning objectives

➢ Understand the association between oocyte numbers and outcome
➢ Understand promises and limits of prediction of ovarian response
➢ Understand natural occurring variation in ovarian response and how this affects outcome
Definitions

- Individualisation: discriminating the individual from the generic group
- Ovarian stimulation: retrieving multiple oocytes for IVF
- Outcome: live birth or cumulative live birth

What is the underlying assumption to individualisation?

- Oocyte numbers independently affect outcome (?)
  - Observation
  - Experiment
  - Uni-variate
  - Multi-variate
  - RCT

Observations
The association of oocyte numbers with outcome – a UNIVARIATE analysis

![Graph showing the association between oocyte numbers and a specific outcome.](image1)

Adjustment for: age, fecundity, cause of infertility, FSH dosage, type of luteal support, no. of embryos transferred

The association of oocyte numbers with outcome – a MULTIVARIATE analysis

![Graphs showing different outcomes based on the number of oocytes.](image2)

The association of oocyte numbers with outcome – a UNIVARIATE analysis

![Bar graph showing the percentage of OPR (%) per start.](image3)

Engage trial, n ~1500 patients, <38 yrs

*Note: Images and graphs are placeholders and need to be replaced with actual graphical representations.*
### The association of oocyte numbers with outcome – a MULTIVARIATE analysis

<table>
<thead>
<tr>
<th>Factors in the multi-variate model</th>
<th>Oocyte categories</th>
<th>Odds ratio for ongoing pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocytes</td>
<td>0-5 vs. 10-13</td>
<td>0.87 (0.58-1.30)</td>
</tr>
<tr>
<td></td>
<td>6-9 vs. 10-13</td>
<td>1.04 (0.74-1.44)</td>
</tr>
<tr>
<td></td>
<td>14-18 vs. 10-13</td>
<td>1.02 (0.74-1.42)</td>
</tr>
<tr>
<td></td>
<td>&gt;18 vs. 10-13</td>
<td>1.17 (0.84-1.65)</td>
</tr>
<tr>
<td>Age</td>
<td>Per year increase</td>
<td>0.96 (0.90-0.99)</td>
</tr>
<tr>
<td>Cycle-day FSH start (d2 vs. d3)</td>
<td>Day 3 vs. day 2</td>
<td>1.21 (0.87-1.68)</td>
</tr>
<tr>
<td>Region (NA vs. Europe)</td>
<td>NA vs. EUR</td>
<td>1.90 (1.58-2.30)</td>
</tr>
<tr>
<td>Progesterone on day of hCG</td>
<td>&gt;1.5 vs. ≤1.5 ng/mL</td>
<td>0.46 (0.30-0.70)</td>
</tr>
</tbody>
</table>

Fatemi, Doody, Griesinger et al. Hum Reprod 2012

---

### The association of oocyte numbers with cumulative outcome – univariate

Engage trial, n ~1500 patients, <36 yrs

![Graph showing OPR and cOPR per oocyte retrieved](Image)

Data on file, courtesy of MSD

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### Experiments

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---
low vs. high dose of FSH: effect on no. of oocytes (n=1,976 patients)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Year</th>
<th>Weight</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison A: Low vs. High</td>
<td>2000</td>
<td>34.9%</td>
<td>-6.6 (4.29, -8.9)</td>
</tr>
<tr>
<td>Comparison B: High vs. Low</td>
<td>2001</td>
<td>15.9%</td>
<td>-1.35 (1.23, -2.47)</td>
</tr>
<tr>
<td>Mean difference (95% CI)</td>
<td>2004</td>
<td>15.9%</td>
<td>-1.29 (0.03, -2.53)</td>
</tr>
<tr>
<td>Relative risk (95% CI)</td>
<td>2005</td>
<td>15.9%</td>
<td>-1.29 (0.03, -2.53)</td>
</tr>
<tr>
<td>Hypothesis:</td>
<td>2006</td>
<td>21.1%</td>
<td>-1.29 (0.03, -2.53)</td>
</tr>
</tbody>
</table>

Best estimate from multivariate analyses and RCTs: The relationship between oocyte numbers and pregnancy chance appears to be weak (as long as there are sufficient oocytes for an embryo transfer to happen).
Individualisation: two issues

- Variation! ("the play of chance")
- predict → individualise → alter outcome?

Variation!

1. Number of FSH sensitive follicles → Stimulation
2. Number of pre-ovulatory follicles
   but: inter-individual variation and intra-individual variation
3. Oocyte retrieval rate per follicle → Variation!
4. Fertilisation rate → Variation!
5. Good quality embryos formation → Variation!
All patients on the same protocol, no adaption allowed; Luebeck IVF, data on file.

Inter-individual variation in ovarian response: AFC by pre-ovulatory follicles


Inter-individual variation in ovarian response

Lee et al., ECERM 2012

Arce et al., Fertil Steril 2013

Intra-individual variation

Trust trial: repetitive stimulation in the same protocol

Differences in Number of Follicles Between Cycles for Subjects Who Underwent Three Cycles

There Is Considerable Inter-cycle Variation in Ovarian Response

- For women with a normal response (6–<18 follicles), in the first cycle the probability to switch to a low (0–<6 follicles) or high ovarian response (>18 follicles) in the second cycle was 19%.

- The probability for those with a low or high ovarian response in the first cycle to switch to a normal response in the second cycle was 39%.
**Prediction:** mostly on extremes of response

... will create many false positives and false negatives (because of variation?)

**Individualize (to avoid extremes)**

1. avoid poor response:
   - give higher FSH doses (concept failed?!)  
   - create more FSH sensitive follicles (how?)

2. avoid hyper response:  
   - allow only a part of the FSH-sensitive follicles to grow (?)

**Proven concept:
Individualisation to prevent OHSS**

- Predict risk by number of growing follicles  
- Replace hCG by Agonist trigger  
- Freeze all embryos
Conclusion

- Oocyte numbers and pregnancy rate have only a weak association
- There is enormous variation in ovarian response (as well as down-stream events), making response prediction (and even more so outcome prediction) a difficult task
- No measure has been found to increase the number of follicles in poor responders and no measure has been shown to be effective in avoiding excessive response (e.g. in patients with a high number of similarly FSH-sensitive follicles)

Thank you very much for your attention!

griesing@uni-luebeck.de
You can now register for these upcoming ESHRE Campus events:

- Application and challenges of emerging technologies in preimplantation and prenatal diagnosis  
  12-13 September 2013 - Prague, Czech Republic

- Female genital tract congenital malformations: new insights in an old problem  
  27-28 September 2013 - Thessaloniki, Greece

- Introducing new techniques into the lab  
  4-5 October 2013 - Barcelona, Spain

- Polycystic ovary syndrome: A new look at an old subject  
  25-26 October 2013 - Rome, Italy

- Infections from conception to birth: role of ART  
  7-8 November 2013 - Berlin, Germany

- Endoscopy in reproductive medicine  
  20-22 November 2013 - Leuven, Belgium

- From early implantation to later in life  
  28-29 November 2013 - Brussels, Belgium

Mark your calendar for:

- Premature ovarian insufficiency  
  6-7 December 2013 - Utrecht, The Netherlands

www.eshre.eu  
(see “Calendar”)  
Contact us at info@eshre.eu