Influence ovarian stimulation on oocyte and embryo quality

Prof.Dr. Bart CJM Fauser
How to balance too much vs too little?

Lecture Outline

- Context ovarian stimulation
- Impact ovarian stimulation on oocyte / embryo
- Wider implications
Why ovarian stimulation?

- **Retrieve multiple oocytes for IVF procedure**
  - Have multiple embryos available to choose from
  - Compensate for suboptimal fertilisation and implantation
  - Have access embryos for cryostorage

- **Improve IVF outcomes**
<table>
<thead>
<tr>
<th>approaches</th>
<th>compounds</th>
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<tbody>
<tr>
<td>Stimulation</td>
<td>Gonadotropins (urine, rec) CC, aromatase inhibitors, insulin sensitizers</td>
</tr>
<tr>
<td>Co-treatment (1)</td>
<td>GnRH agonist, antagonist</td>
</tr>
<tr>
<td>Co-treatment (2)</td>
<td>LH, hCG, androgens, GH, etc</td>
</tr>
<tr>
<td>Oocyte maturation triggering</td>
<td>hCG, GnRH agonist bolus</td>
</tr>
<tr>
<td>Pre-stimulation</td>
<td>GnRH agonist flare, OC, Estrogens</td>
</tr>
<tr>
<td>Post-stimulation</td>
<td>Prog, Estrogens, hCG, GnRHa</td>
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</table>
The dominant ovarian follicle*

Gary D. Hodgen, Ph.D.

Pregnancy Research Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland

Ovulation

Recruitment → Selection → Dominance

Maturation

Cohort of Growing Follicles

N

DF

DF

N-1

Atresia

1  3  5  7  9  11  13  15

Day of the Menstrual Cycle
Conventional superovulation strategy for IVF

Sequela of ovarian stimulation for IVF

Consequences for
- luteal phase endocrinology
- Endometrial receptivity
- Embryo quality/aneuploidy

74% of failed IVF = failed implantation

IVF results, The Netherlands, 2010
Optimal number of oocytes for IVF
- *the more the better* ??

Society perspective

Patient perspective

Child perspective
# Relevant studies in mice

## Superovulation in mice causes

<table>
<thead>
<tr>
<th>Cause</th>
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<tbody>
<tr>
<td>Reduced oocyte quality</td>
</tr>
<tr>
<td>Reduced embryo quality</td>
</tr>
<tr>
<td>Delayed pre-implantation embryo development</td>
</tr>
<tr>
<td>Reduced implantation</td>
</tr>
<tr>
<td>Fetal growth retardation</td>
</tr>
<tr>
<td>Abnormal methylation of imprinted loci</td>
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<tr>
<td>Negative impacts on oviductal and uterine milieu</td>
</tr>
</tbody>
</table>

Laprise, Mol Reprod & Dev 2009
Reproductive potential of a metaphase II oocyte retrieved after ovarian stimulation: an analysis of 23,354 ICSI cycles

D. Stoop*, B. Ermini, N.P. Polyzos, P. Haentjens, M. De Vos, G. Verheyen, and P. Devroey

Figure 2: Live births (LB) per fresh cycle.

Live birth in relation to oocyte yield
Objective | Chromosome error rate from oocytes generated for ICSI in women < 35 yrs
---|---
Patients | N=933 couples undergoing ICSI
Methods | Polar body testing chromosomes 13, 16, 18, 21, 22
Conclusions | High yield of oocytes is associated with increased chromosome error rate

| Results; chromosome error rate in relation to Oocyte No. |
|---|---|---|---|
| Oocyte # | 1-5 | 6-10 | > 10 |
| Chromosome error rate | 23±5% | 35±4% | 51±6% |
**Objective**  
Study effects of FSH on aneuploidy in IVM oocytes

<table>
<thead>
<tr>
<th>Patients</th>
<th>Male factor infertility, ICSI (86 cycles, 252 oocytes)</th>
</tr>
</thead>
</table>
| Interventions | FSH; 0.5; 5.5; 22; 100; 2000 ng/ml  
Polar body biopsy; chrom 13, 16, 18, 21, 22 |
| Results | Aneuploidy rate; 27, 23, 37, 47, and 63%, respectively |
| conclusion | High FSH concentrations during IVM sign. increases first meiotic division error |

*Fertil Steril 2010*

Yan-Wen Xu, M.D., Ph.D., Yue-Ting Peng, M.D., Bin Wang, M.D., Yan-Hong Zeng, B.Sc., Guang-Liu Zhuang, M.D., and Can-Quan Zhou, M.D.
Clinical outcomes in relation to the daily dose of recombinant follicle-stimulating hormone for ovarian stimulation in in vitro fertilization in presumed normal responders younger than 39 years: a meta-analysis

M.D. Sterrenburg1,2, S.M. Veltman-Verhulst1, M.J.C. Eijkemans1,2, E.G. Hughes3, N.S. Macklon1,4, F.J. Broekmans1, and B.C.J.M. Fauser1

A 100 IU/d versus 200 IU/d

Number of oocytes per OPU
Number of cryopreserved embryos
Total amount of recFSH (IU)

St WMD

-4 -2 0 2 4

Chance of OPU
Chance of pregnancy
Chance of OHSS

OR

0.01 0.1 1 10 100

B 150 IU/d versus 200–250 IU/d

Number of oocytes per OPU
Number of cryopreserved embryos
Total amount of recFSH (IU)

St WMD

-4 -2 0 2 4

Chance of OPU
Chance of pregnancy
Chance of OHSS

OR

0.01 0.1 1 10 100
A Randomized Comparison of Two Ovarian Stimulation Protocols with Gonadotropin-Releasing Hormone (GnRH) Antagonist Cotreatment for in Vitro Fertilization Commencing Recombinant Follicle-Stimulating Hormone on Cycle Day 2 or 5 with the Standard Long GnRH Agonist Protocol

FEMKE P. HOHMANN, NICHOLAS S. MACKLON, AND BART C. J. M. FAUSER

JCEM 2003

P < 0.01

Pregnant
Non-pregnant
Cumulative pregnancies

Oocyte # / PU

A

B

C
Embryo quality in relation to ovarian stimulation, pregnancy chances in relation to embryo quality

Hohmann, JCEM 2003
Embryo quality and embryo selection
- the bigger picture

**Female age**
- PCOS
- Ovarian stimulation
- Follicle / oocyte development
- Sperm quality
- Embryo culture conditions

**Morphology criteria**
- Day of transfer
- Time laps monitoring
- Omics
- # embryos transferred
- Cryotechnology
- ET technology
- Endometrial receptivity
Preimplantation genetic screening reveals a high incidence of aneuploidy and mosaicism in embryos from young women undergoing IVF.

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

Esther B.Baart, Elena Martini, Marinus J.Eijkemans, Diane Van Opstal, Nicole G.M.Beekers, Arie Verhoeven, Nicolas S.Macklon, and Bart C.J.M.Fauser.

GnRH agonist (long prt)

rFSH (225 IU/d)

GnRH antag

rFSH (150 IU)

CD 2

5

foll ≥ 14 mm

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

111 Patients
528 fertilized oocytes
302 embryos FISHed
Correlation between oocyte number and embryo aneuploidy

Baart, HR 2007

Graphs showing the correlation between oocyte number and embryo aneuploidy under conventional and mild stimulation conditions.
Embryo aneuploidy for mild vs conventional stimulation

Conventional embryo aneuploidy for mild vs conventional stimulation

P = 0.016

N = 33

N = 40
Milder ovarian stimulation for *in-vitro* fertilization reduces aneuploidy in the human preimplantation embryo: a randomized controlled trial

Conventional

Mild

**Average per patient 12**

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oocytes</td>
<td><strong>12</strong></td>
<td>8</td>
</tr>
<tr>
<td>Embryos</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Normal embryos</td>
<td>4</td>
<td>2</td>
</tr>
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</table>

**HR 2007**
A mild treatment strategy for in-vitro fertilisation: a randomised non-inferiority trial

Esther M E W Heijnen, Marinus J C Eijkemans, Cora De Klerk, Suzanne Polinder, Nicole G M Beckers, Ellen R Klinkert, Frank J Broekmans, Jan Passchier, Egbert R Te Velde, Nick S Macklon, Bart C J M Fauser

Summary

Background Mild in-vitro fertilisation (IVF) treatment might lessen both patients’ discomfort and multiple births, with their associated risks. We aimed to test the hypothesis that mild IVF treatment can achieve the same chance of a singleton term live birth as standard IVF treatment.

![Graph showing the proportion of pregnancies leading to term live birth over time]

<table>
<thead>
<tr>
<th>Time since randomization (months)</th>
<th>Proportion leading to term live birth (%)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
</tr>
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</table>

**Number of patients**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time (months)</th>
<th>Patients</th>
</tr>
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<tbody>
<tr>
<td>Standard</td>
<td>199</td>
<td>152</td>
</tr>
<tr>
<td>Mild</td>
<td>205</td>
<td>174</td>
</tr>
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</table>

Lancet 2007; 369:743-49
The clinical significance of the retrieval of a low number of oocytes following mild ovarian stimulation for IVF: a meta-analysis


Figure 2: Ongoing pregnancy rate per embryo transfer (implantation rate) according to the number of oocytes retrieved following mild or conventional ovarian stimulation for IVF ($P = \ldots$).
Ovarian response to recombinant human follicle-stimulating hormone: a randomized, anti-Müllerian hormone–stratified, dose–response trial in women undergoing in vitro fertilization/intracytoplasmic sperm injection

F&S 2014

<table>
<thead>
<tr>
<th>Study objective</th>
<th>Evaluate dose response new rFSH</th>
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<td>Study influence of initial AMH</td>
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<tr>
<td>Design</td>
<td>RCT, 7 centers, 265 women undergoing IVF/ICSI, AMH stratified</td>
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</table>
Oocyte # retrieved in relation to rFSH dose

Arce, F&S 2014
Oocyte No in relation to No good quality blastocysts

Arce, F&S 2014
<table>
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<th>Study objective</th>
<th>Evaluate dose response new rFSH Study influence of initial AMH</th>
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<tr>
<td><strong>Design</strong></td>
<td>RCT, 7 centers, 265 women undergoing IVF/ICSI, AMH stratified</td>
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<tr>
<td><strong>Results</strong></td>
<td>Dose dependent increase in oocyte No in relation to rFSH dose</td>
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<td></td>
<td>Slope dose response differed in relation to AMH</td>
</tr>
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<td></td>
<td>Fertilization rate and blastocyst/oocyte ratio decreased with increasing rFSH</td>
</tr>
<tr>
<td></td>
<td>No linear relationship between rFSH dose and blastocyst No</td>
</tr>
<tr>
<td><strong>Conclusion</strong></td>
<td>Increasing rFSH results in linear increase in oocyte No</td>
</tr>
<tr>
<td></td>
<td>Increase in oocyte number dependent on initial AMH</td>
</tr>
<tr>
<td></td>
<td>Blastocyst number less dependent on rFSH or AMH</td>
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Ovarian hyperstimulation for IVF - the bigger picture

- Access to treatment
- Cost
- Complexity
- Monitoring
- Burden of treatment
- Complications (OHSS)
- Drop out (cum outcomes)

Contribute to success?
Recent papers in favour of mild stimulation IVF

NEW DEBATE

Coming soon to your clinic: patient-friendly ART

Guido Pennings1,3 and Willem Ombelet2

Perinatal outcome in singletons after modified natural cycle IVF and standard IVF with ovarian stimulation

Marie-José Pelinck a,*, Marjan H. Keizer a, Annemieke Hoek a, Arnold H.M. Simons a, Karin Schelling b, Karin Middelburg b, Maas Jan Heineman a, c

Mild/minimal stimulation for in vitro fertilization: an old idea that needs to be revisited

Shvetha M. Zarek, M.D., a and Suheil J. Muasher, M.D. a,b

How many eggs are needed to produce an assisted reproductive technology baby: is more always better?

Beth McAvay, M.D., M.S., a,b Athena Zapantis, B.S., a Sangita K. Jindal, Ph.D., a,b Harry J. Lieman, M.D., a,b and Alex J. Polotsky, M.D., M.S. a,c

Perspectives of mild cycle IVF: a qualitative study

Deborah Payne1,*, Sonja Goedeke2, Sarah Balfour1, and Guy Gudex3

Less is more: increased gonadotropin use for ovarian stimulation adversely influences clinical pregnancy and live birth after in vitro fertilization

Lubna Pai, M.B.B.S., M.R.C.O.G., M.S., a, b Sangita Jindal, Ph.D., a Barry R. Witt, M.D., b and Nanette Santoro, M.D. a,c
PhD’s thesis mild IVF