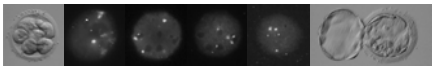
## Ovarian stimulation and consequences for oocyte/embryo quality

Esther Baart



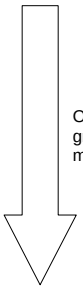
University Medical Center Utrecht

## Presentation outline

- Follikel development and oocyte quality
- Embryo quality assessment
  - *Morphology and development*
  - *Chromosomal constitution*
- Effect of ovarian stimulation approaches
  - *GnRH agonist versus GnRH Antagonist*
  - *Recombinant FSH versus hMG*
- New techniques in embryo quality assessment

## What is a good oocyte/ embryo?

- Competent to undergo fertilization
  - *Chromatin remodeling*
  - *DNA repair*
- Supports timely completion of cleavage divisions
- Reliably segregates chromosomes
  - *Spindle formation*
  - *Checkpoint functions*
- Activates the embryonic genome (8 cell stage)
  - *Chromatin remodeling*
  - *Establishment of genomic imprinting*



## How to assess embryo quality? - The classical approach -

- Implantation potential, ongoing PR and live birth
- Morphology and development:
  - *Assessment of pronucleate embryos*
  - *Timing of cleavage*
  - *Assessment on day 3 after fertilization*
  - *Development to the blastocyst stage*

## The perfect embryo (based on morphology and development)


Papanikolaou et al., NEJM, 2006

Successful implantation after SET in 49% of patients ≤36 yrs

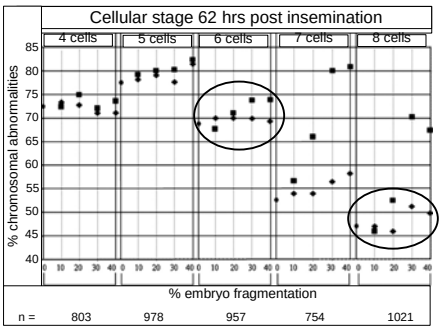
⇨ At least 50% of embryos are chromosomally abnormal

## Day 3: cleavage stage and chromosome abnormalities

- 662 patients, 916 cycles
- Poor prognosis patients
- PGS on day 3
- XY,13, 14, 15, 16, 18, 21, 22
- Cleavage stage assessment

Magli et al., Fertil Steril, 2007

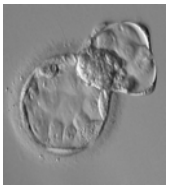
## Day 3: fragmentation and cell number




Magli *et al.*, Fertil Steril 2007

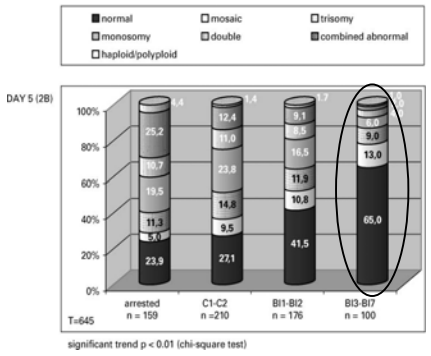
## Development to the blastocyst stage and chromosomal abnormalities

- 148 patients, 148 cycles
- patients ≥37 years
- IVF and ICSI
- PGS on day 3, two cells
- XY, 13, 16, 18, 21, 22
- Assessment of blastocyst development



Staessen et al., Hum Reprod, 2004

## FISH diagnosis on day 3 and development on day 5

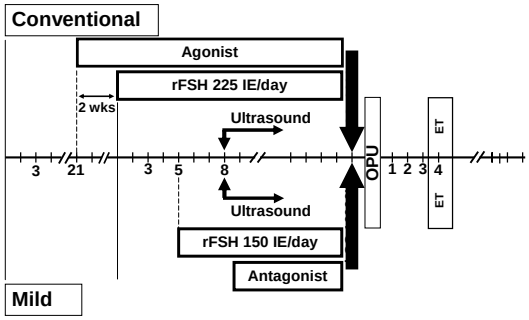


## Randomized comparison of two ovarian stimulation approaches

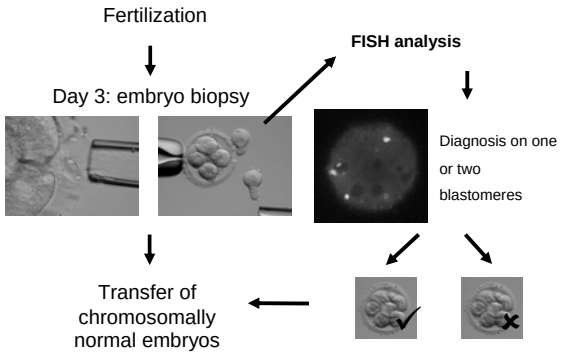
- Determine the incidence of aneuploidy and mosaicism in embryos from younger IVF patients
- Can PGS be used as an extra parameter to assess embryo quality?

## Comparison of stimulation approaches

Randomization of 111 patients:



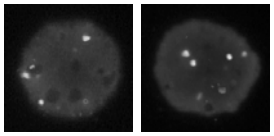

## Preimplantation genetic screening



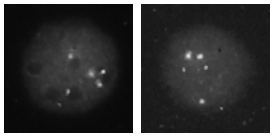
## Fixation and analysis of blastomeres

Method using HCl/Tween and Methanol/Acetic acid

First round of FISH:
chromosomes
1, 7, 15, X & Y



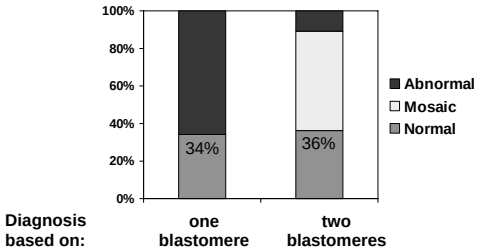
Second round of FISH:
chromosomes
13, 16, 18, 21, 22



Baart et al., Hum Reprod, 2004

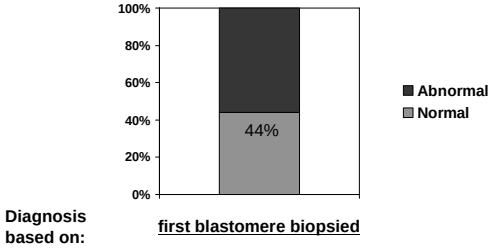
## PGS Diagnosis in young IVF patients

**Analysis of 265 embryos:**

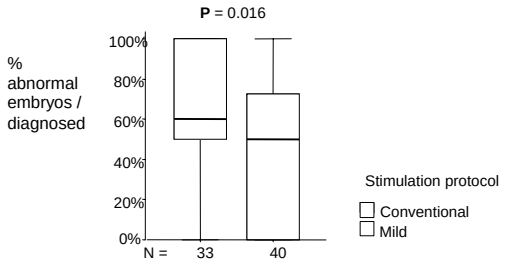



## PGS Diagnosis for statistical analysis

**Analysis of 265 embryos:**



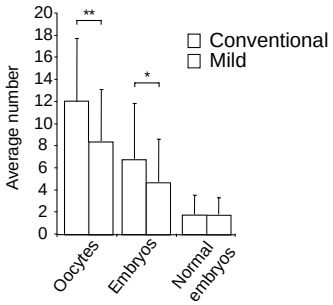
## Lower aneuploidy rate after mild stimulation




Good quality embryo rate per patient:

35% 51% P= 0.04

## Average number per patient



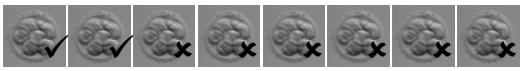

## What could it mean to the embryologist?

Conventional ovarian stimulation:

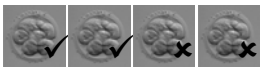
Mild ovarian stimulation:

## What could it mean to the embryologist?

Conventional ovarian stimulation:



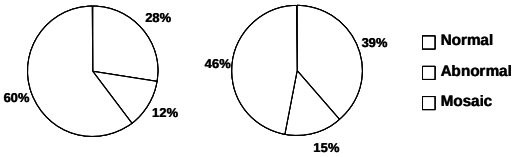
Mild ovarian stimulation:



## Chromosomal mosaicism after analysis of two cells

Conventional stimulation
(98 embryos)

Mild stimulation
(96 embryos)

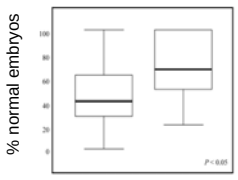



Rate of mosaic embryos per patient:

65% 37% P= 0.004

## Effect of LH/hCG containing gonadotropins

- Retrospective analysis
- recFSH vs. hMG
- Long agonist protocol
- PGS analysis on day 3
- Reduction in the number of oocytes
- Similar no. of normal embryos (3.1 vs. 3.3)

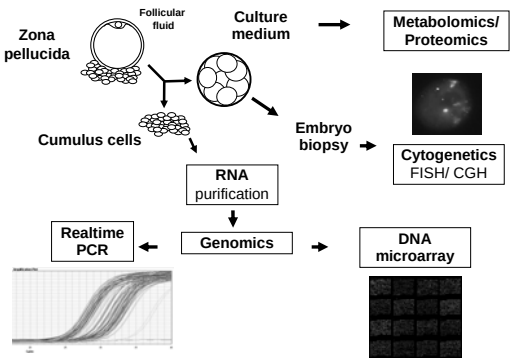



Weghofer et al., Hum Reprod, 2008

## PGS and embryo quality: conclusions

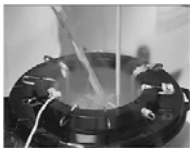
- Ovarian stimulation has an impact on the proportion of aneuploid/mosaic embryos
- PGS provides an additional marker of embryo quality
- PGS is invasive, costly and time consuming

## New techniques in embryo quality assessment



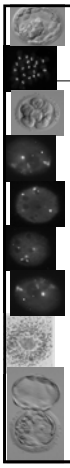

## Freeze 'm all?

- Improvements in cryopreservation protocols
- Single embryo transfer in the natural cycle
- Sequential thawing and transfer of all embryos
- Timing of transfer?



## Conclusions

- Assessment of chromosome constitution provides an additional marker for embryo quality
- Ovarian stimulation has an impact on the proportion of good quality embryos
- Ovarian stimulation should not aim at maximizing oocyte yield but at optimizing embryo quality
- Further improvements in embryo quality assessment are needed



## Acknowledgments

Dept. of Reproductive Medicine and Gynaecology
University Medical Center Utrecht, The Netherlands

Prof. Nick Macklon
Prof. Bart Fauser

Dept. of Reproductive Biology, Gyn/Ob
Stanford University School of Medicine, Stanford/CA, USA

Prof. Aaron Hsueh