Is the era of PGS over?

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ESHRE Winter Course Early Pregnancy 6-7 December 2007

Universitair Ziekenhuis Brussel

I always avoid prophesying beforehand, because it is a much better policy to prophesy after the event has already taken place.
Winston Churchill

Is the era of PGS over?

1. Back to basics: where and when does aneuploidy arise?
2. Evidence based PGS - state of the art
3. The future of PGS
4. Conclusions - Key message

1. Etiology of aneuploidy

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Incidence of numerical chromosomal abnormalities

- First trimester miscarriage 50%
- 10 weeks gestation ongoing 5%

- Pre-implantation embryos 30-70%
- Embryos <36 years 25-64%
  → Baart et al HR 2006
- Embryos >36years 63%
  → Staessen et al HR 2004

1. etiology of aneuploidy

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

- early developmental abnormalities:

usually dysmorphisms
32-52% aneuploidy
typically fail to fertilize

- late developmental abnormalities

at or after formation of metaphase spindles
15% aneuploidy
not always dysmorphisms
Van Blerkom et al Hum Reprod 1992

1. etiology of aneuploidy

1. non-disjunction
2. anaphase lagging
3. premature centromeric dysjunction
4. abnormal follicular fluid biochemistry

temporal relation between oocyte dysmorphism and aneuploidy

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

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1. etiology of aneuploidy

1. age
2. homo Sapiens
3. male factor
4. infertility status
5. technical limitations
6. ovarian stimulation?

1. etiology of aneuploidy

induction of chromosomal abnormalities
or absence of natural selection

Boué et al, Lancet 1973
Kola, Birth 1988

'The incidence of chromosomal aneuploidy in stimulated and unstimulated (natural) uninseminated human oocytes.'

Gras et al, Human Reproduction 1992

'Does the magnitude of ovarian stimulation or IVF affect chromosomal competence of embryos as assessed by PGS?'

Baart et al, Human Reproduction 2005

1. etiology of aneuploidy

- ART is associated with an increased risk of rare imprinting disorders
- Methylation defects may occur at all stages
- Different stages of oogenesis and folliculogenesis may exhibit specific sensitivities to environmental chemicals
- Ovarian stimulation or in vitro maturation may induce epigenetic defects

Sato et al, Hum Reprod 2007

Study: aneuploidy in unstimulated cycle embryos

goal of the study:

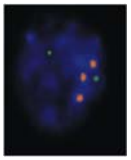
1. assessment of the **aneuploidy rate** in embryos of young women (<36y) in unstimulated (natural) cycle ICSI
2. assessment of the efficacy of natural cycle ICSI associated with preimplantation genetic screening (PGS) ie **clinical competence**
3. assessment of implantation potential of natural cycle embryos after biopsy ie **embryonic competence**

Study protocol

- natural cycle
- blood analysis and ultrasound on day 10 (cycle <28 days) or day 12
- hCG 5000IU at a follicle diameter of 16mm or larger
- oocyte pick-up (OPU) at hCG +32 hours
- ICSI
- single blastomere biopsy at day 3

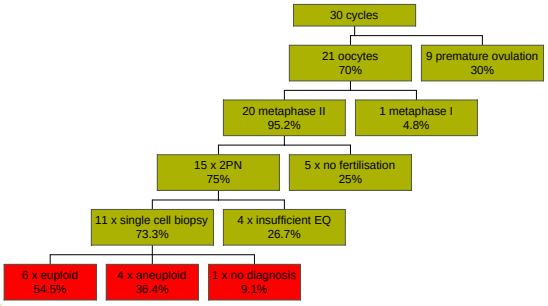
Study protocol

- PGS in two rounds C13, 16, 18, 21, 22, X and Y



- single embryo transfer (SET) at day 5

Results



Conclusion etiology of aneuploidy

- Multiple factors involved at multiple levels
  - → gamete level
  - → embryonic level
  - → self-correction
- Contradiction
  - → all ages
  - → natural cycle and stimulated cycles
  - → high prevalence of mosaics

2. PGS: state of the art

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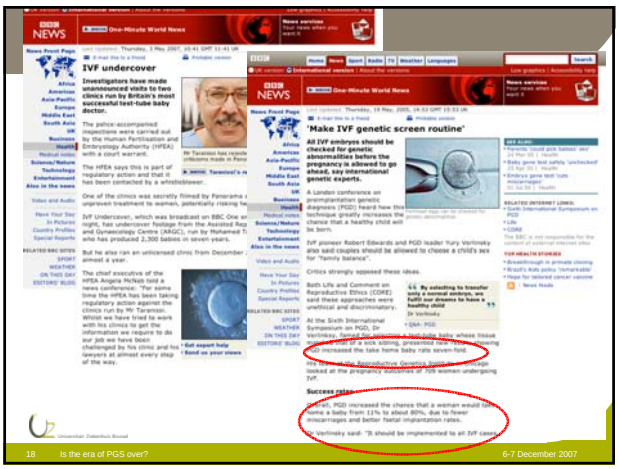
2. PGS: state of the ART

A lie gets halfway around the world before the truth has a chance to get its pants on.
Winston Churchill



2. PGS: state of the ART

High prevalence of numerical chromosomal abnormalities

- aneuploidy
- postmeiotic abnormalities

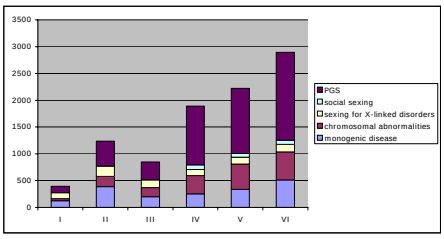
Age >37, recurrent miscarriage, recurrent implantation failure, azoospermia

Gianaroli et al, 1999; Munné et al, 1999; Kuliev et al, 2003; Munné et al, 2003; Munné et al, 2005; Ercelen et al, 2005; Platteau et al, 2005B; Pellicer et al, 1999; Gianaroli et al, 2005; Munné et al, 2005; Platteau et al, 2005; Kahraman et al, 2000; Gianaroli et al, 2001; *Gianaroli et al, 2002*; Pehlivan et al, 2002; Wilding et al, 2004

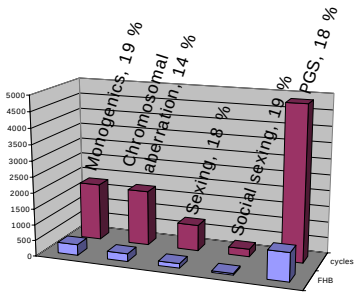
ESHRE Consortium data

- Established 1997
- 14000 cycles
- Over 2000 children born
- International working party on PGD

Evolution on number of cycles reported

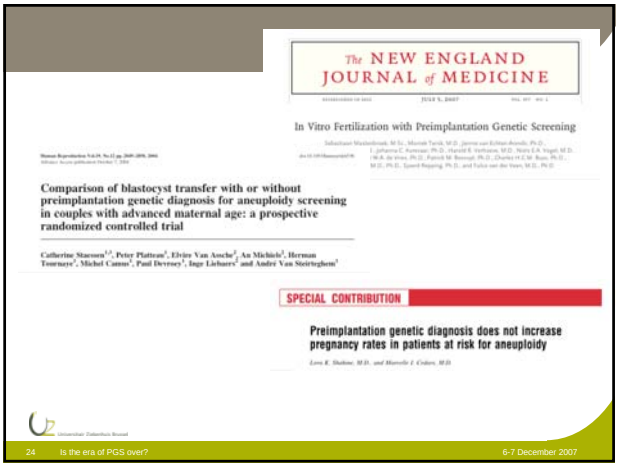


Pregnancies according to indication: data I-VI



ESHRE PGD consortium data VII

- 3530 cycles reported (+ 14 %)
- 3356 cycles to OR
  - → 535 monogenic (16 %)
  - → 5 HLA only (<1%)
  - → 552 chromosomal abnormalities (16 %)
  - → 1977 PGS (59 %)
  - → 90 sexing for X-linked disease (3 %)
  - → 80 social sexing (2 %)
  - → 117 unknown (3.5 %)


The NEW ENGLAND JOURNAL of MEDICINE

In Vitro Fertilization with Preimplantation Genetic Screening

Comparison of blastocyst transfer with or without preimplantation genetic diagnosis for aneuploidy screening in couples with advanced maternal age: a prospective randomized controlled trial

SPECIAL CONTRIBUTION

Preimplantation genetic diagnosis does not increase pregnancy rates in patients at risk for aneuploidy

2. PGS: state of the ART

Benefit unproven

- Staessen et al, 2004
- Shahine et al, 2006;
- Twisk et al, 2006
- Mastenbroek et al 2007

Potential benefit

1. if sufficient number of embryos
2. in reducing miscarriage
3. in explaining reproductive failure

- Munné et al, 2003 and 2005B; Platteau et al, 2005

2. PGS: state of the ART

- high incidence of numerical chromosomal abnormalities in young women
- 58-64% mainly mosaics
- mosaic embryos confirmed in only 50%!!
  - → Munné et al, 2004; Baart et al, 2006

- PGS in young women undergoing SET: prospective randomised study: no significant benefit of PGS
  - → Staessen et al ESHRE 2007

potential benefits of PGS

1. selection in high responders
2. selection when number of embryos transferred limited
3. reduction in miscarriage rate
4. reduction in viable aneuploid pregnancies/ avoiding amniocentesis
5. rationale for failure of ART

disadvantages of PGS

1. no proven benefit in improving live birth rate
2. few randomised studies
3. blastocyst culture very variable
4. unknown long-term effects

A person who never made a mistake never tried anything new.
Albert Einstein

3. The future of PGS

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New developments in genetic analysis of embryos

- Comparative genomic hybridisation (CGH)
  - → Wilton et al HRU 2005
  - → Le Caignec et al Nucl Ac Res 2006
- Whole genome amplification (WGA)
  - → Coskun et al Prenat Diagn 2007
- Return to
  - → Polar body analysis
  - → Sperm DNA analysis

Conclusion and key message

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conclusion

- Nature does not seem to allow us to interfere with natural selection, or at least we're not good at doing so
- PGS is dead, long live PGS
- PGS is useful in UNDERSTANDING biological mechanisms of embryology and early pregnancy
- future research is essential
  - → defining risk groups
  - → influence of ART techniques on genetic constitution of the embryo and offspring