Gamete Assessment and Quality Perspectives.

QAPonline - the future for all IVF laboratories.

Dr James Stanger PhD.

FertAid - QAPonline

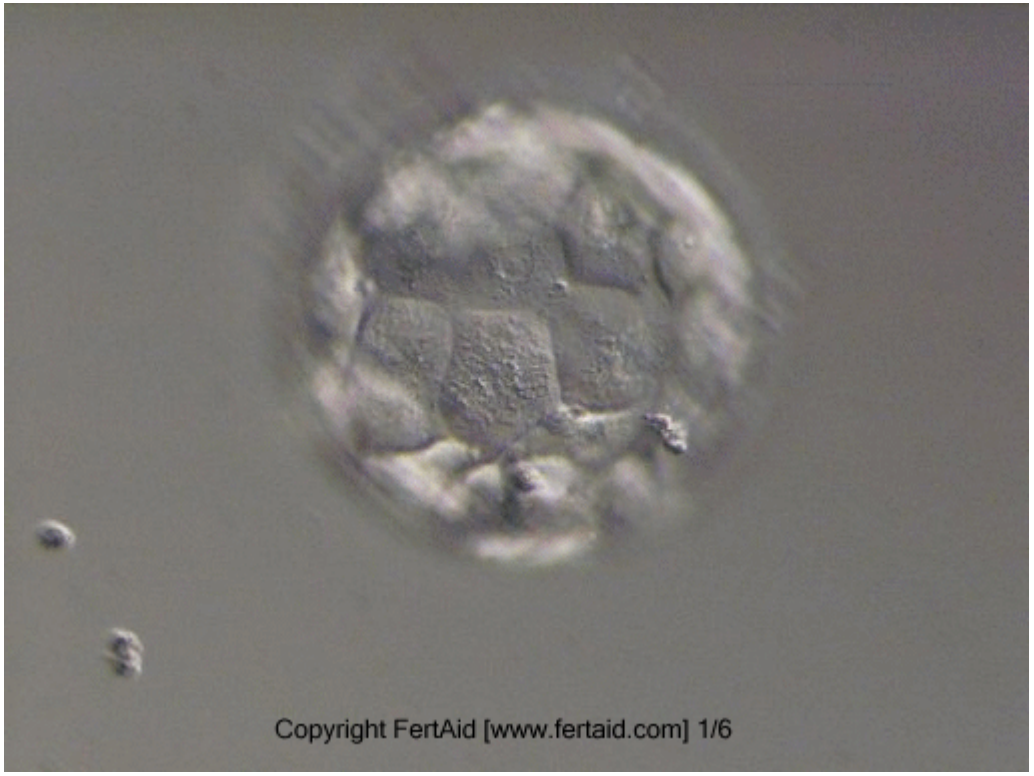
QAPonline

- I run an Internet based Quality Assurance scheme for Andrology and Embryology
- It is directed towards improving the professional skills of Embryologists
- Hope it would be part of a clinics QA system
- www.fertaid.com

What would you do this embryo?

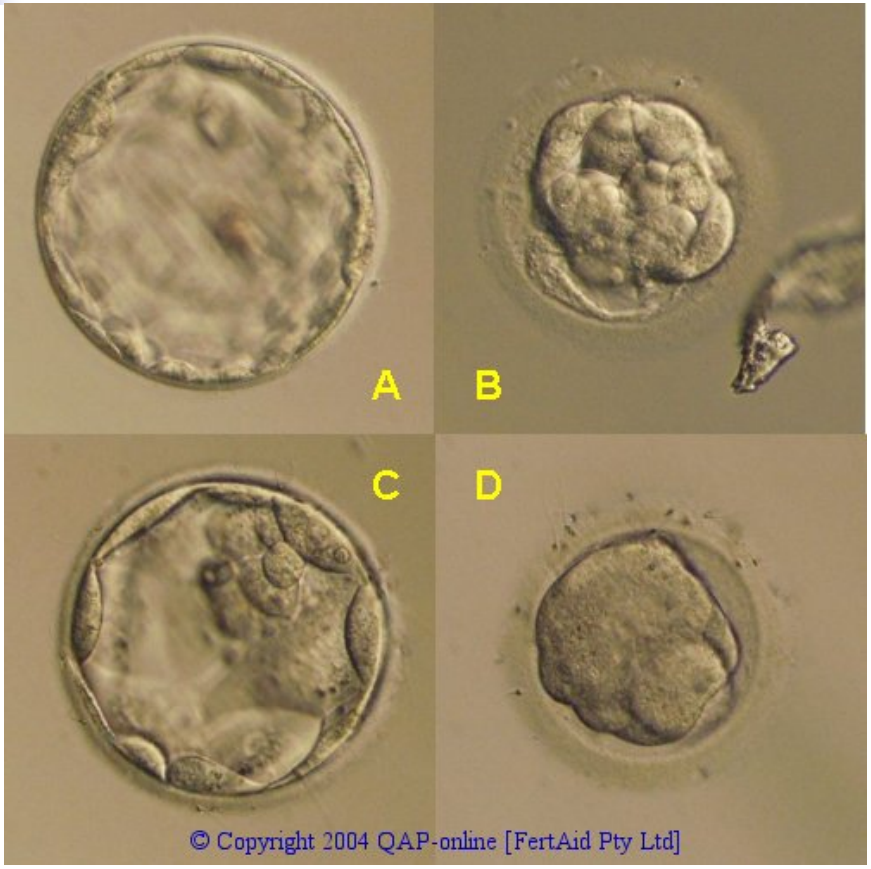
- Transfer
- Freeze
- Discard

What would you do this embryo?



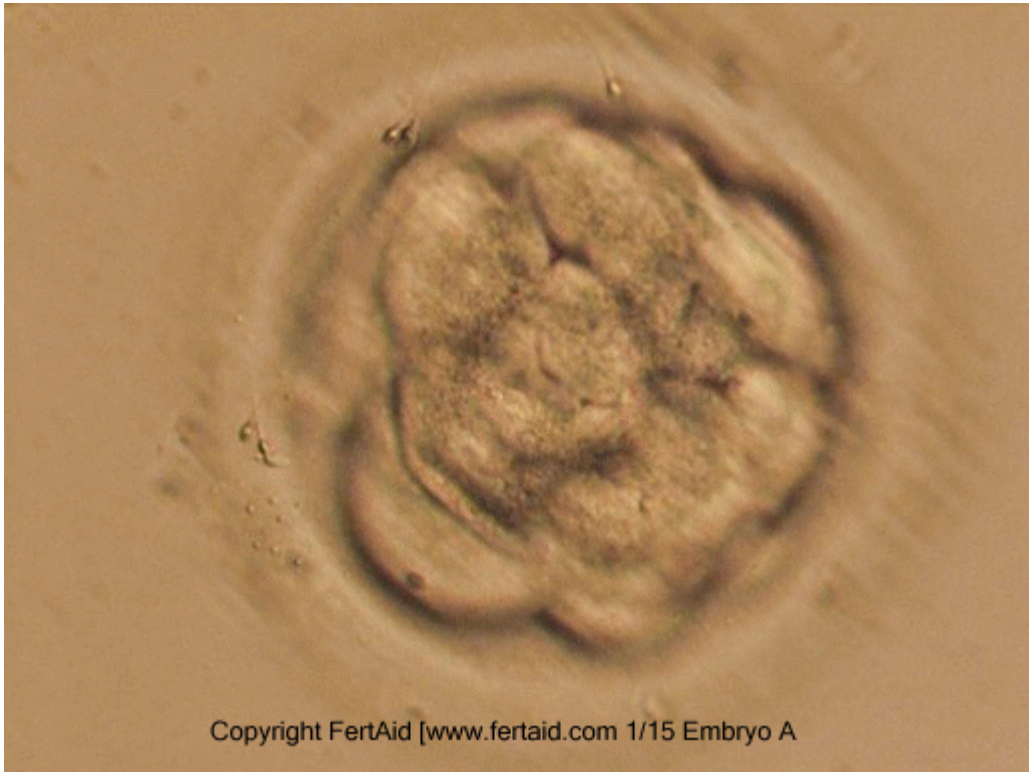
- Transfer
- Freeze
- Discard

How would your rank these embryos?



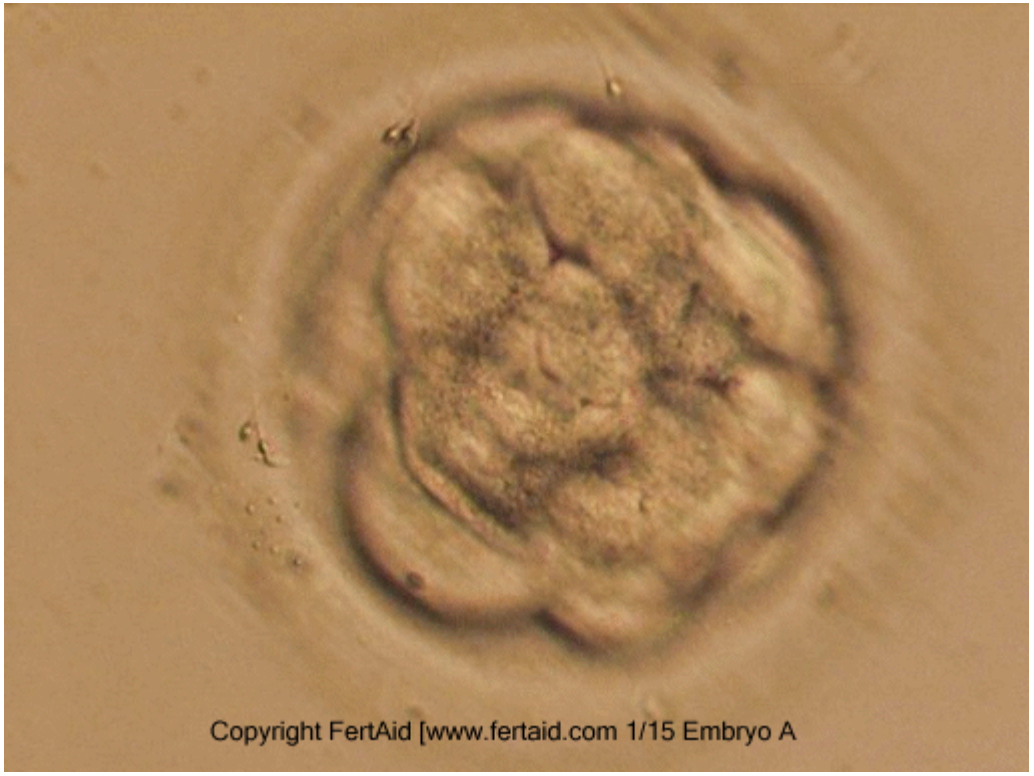
- Would you:
- Transfer
- Freeze
- Discard

How would your rank these embryos?



- Would you:
- Transfer
- Freeze
- Discard

How would your rank these embryos?



FROM QAPonline

- 1st
- 66% C
- 32% B
- 1% A

Freeze

12% A

80% B

89% C

Aim of the presentation

- Not about embryo grading
  - Would be a good talk
- It is about being an embryologist
- Implication from variations in assessment
- Quality Management of skills

IVF
a fusion of Andrology and Embryology

- IVF is a mixture of many disciplines
  - Gynaecology
  - Infertility
  - Endocrinology
  - Andrology
  - Embryology
  - Ultrasonography
  - Genetics
  - Counselling and support process.

Embryology – A visual process

- Embryology and Andrology are largely visual processes
- Recent physiological criteria not practical [at present] in a busy IVF laboratory
- Photographic systems under development but also not yet feasible as a routine procedure.. But coming..
- Require skilled assessment competency

What is required of embryologists?

- Essentially to make and transfer embryos for the establishment of pregnancy.
- To select embryos most likely to result in pregnancy
- To ensure that the patient receives the same embryos generated for their gametes.
- Do no harm to gametes and embryos – maintain viability.

The reality of embryology

- No real say in patients treated
- No real say in stimulation or follicle management
- No real tools to initiate selection of oocytes
- No real say in number and quality of gametes.
- Work under considerable pressure in a clinical environment where the clinics various timetable is primary.

The laboratory determines pregnancy rate however.....

- The proportion of younger to older women important
- The proportion of IVF to male factor important
- The competency of follicle recruitment and ova recovery important
- BUT the IVF laboratory is where the pregnancy rate is mediated !!
  - Culture systems
  - Equipment systems
  - Staff skill levels
  - Uniformity in gamete selection
    - Transfer
    - Freezing
    - discarding

Selection pressures

- Single embryo transfer
- Allocate embryos to cryopreservation.
- Commit remainder to the bin.
- In some countries, there are limits on the number of ova to be inseminated or number to be transferred.

Biological Pressures.

- Not all embryo are equal
- Controlled ovarian hyperstimulation generates a continuous recruitment of follicles.
- The mix of oocytes is a reflection of the matrix of follicle development
- Oocyte quality reflects early embryo development
  - Genetic
  - Cytoplasmic

Why grade/score embryos

- Historical documentation and records
- Rank embryos for transfer or storage
- Convey a summary to doctors and patients
- Use for QC purposes, eg % A grade/month
- Measure of toxicity
- **But most importantly – select embryo for transfer.**

High Embryonic Wastage (US)

- About 85-90% of all embryos fail to establish as a pregnancy.
- 25% implantation rate only for the “Best” – highly selected embryos for fresh transfer.
- Balance less likely to implant.

- Kovalevsky and Patrizio (2005) Fertil & Steril 84 (2):325-330

High Embryonic Wastage
Summary.

- While up to 25+% implantation rate for the “best” embryos at fresh transfer regularly reported.
- Only about 8-12% of all embryos transferred will implant
- Selection critical
- Clinic pregnancy rates may vary if
  - selection criteria limited and
  - if variation between staff members exits

Quality Issues with Embryology

- Clinic (and patients) needs to ensure that
  - All viable embryos are utilised.
    - Transferred
    - Frozen
    - Donated
- All staff will select the same embryos
  - Uniformity in grading
  - Uniformity if allocation to transfer, freezing or discarding.

Variations between clinicians

- Considerable data exists to demonstrate difference between clinicians in pregnancy rate /transfer.
- Minimised after training, review and uniformity
  - Ultrasound transfers
  - Clear protocols
  - Data reviews.

Variations between scientists

Internal Data Audits.

- All clinics should routinely collect performance statistics on all scientists including
  - Oocyte collection rates
  - Fertilisation rates – IVF and ICSI
    - ICSI lysis rates
  - Pregnancy rates per transfer
  - Thaw rates.

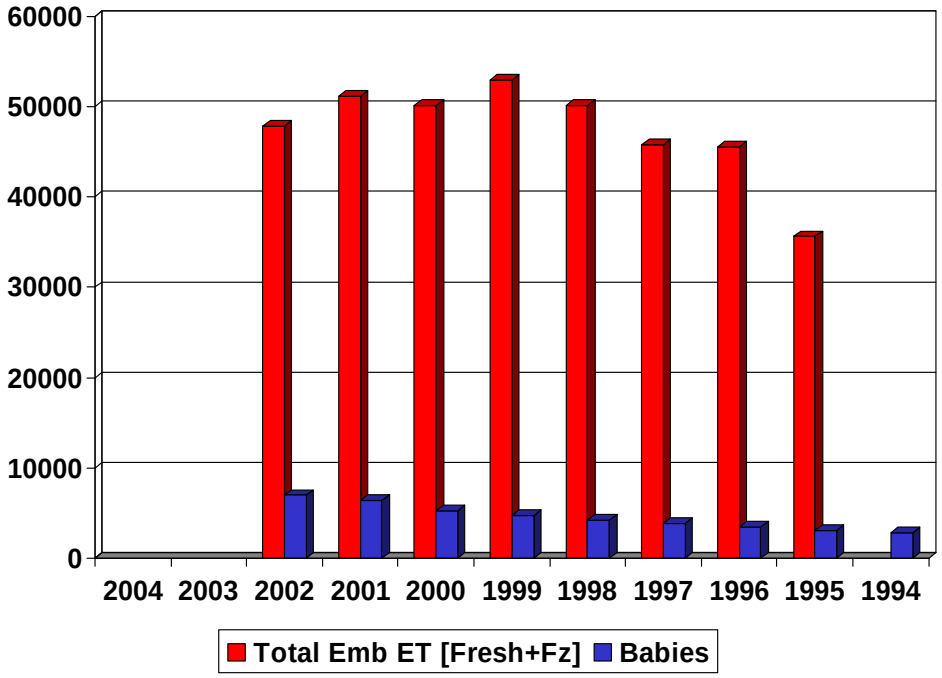
  Problems is that in many clinics each aspect is multifactorial

Variations between scientists

The problem.

- No data on variability between scientists in embryo selection and grading.
- Scientists largely
  - Work independently
  - Work at a relatively “pressured “ rate
  - Quality of imaging variable.
  - Largely taught by peer tutorials.
- Yet selection of a single embryo from a cohort of 1-20 embryos may be considered speculative in most centre.

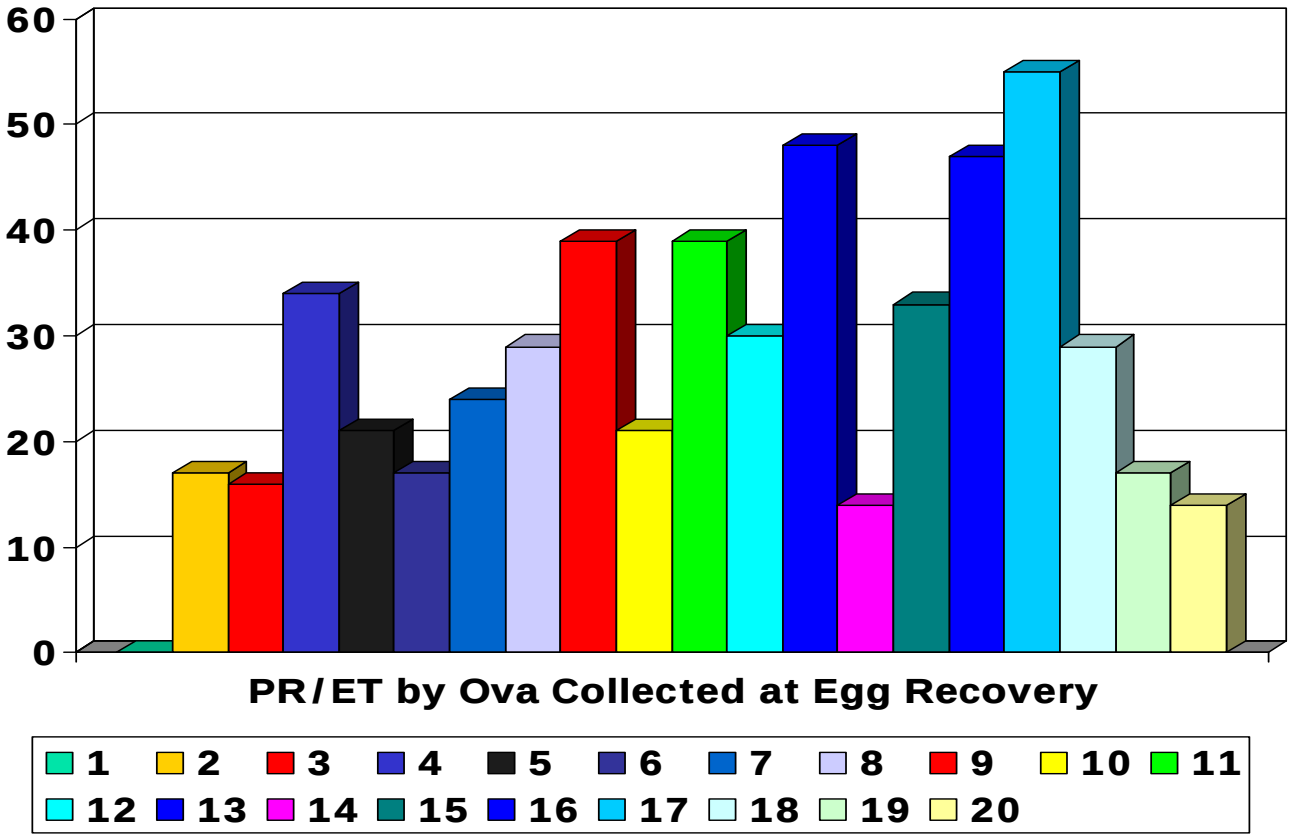
High Embryonic Wastage (Aus)



- Combined fresh and Frozen embryos transferred x number of babies 1994-2002 [NPSU data]
- 15% implantation of all embryos.
- 85% failed to implant

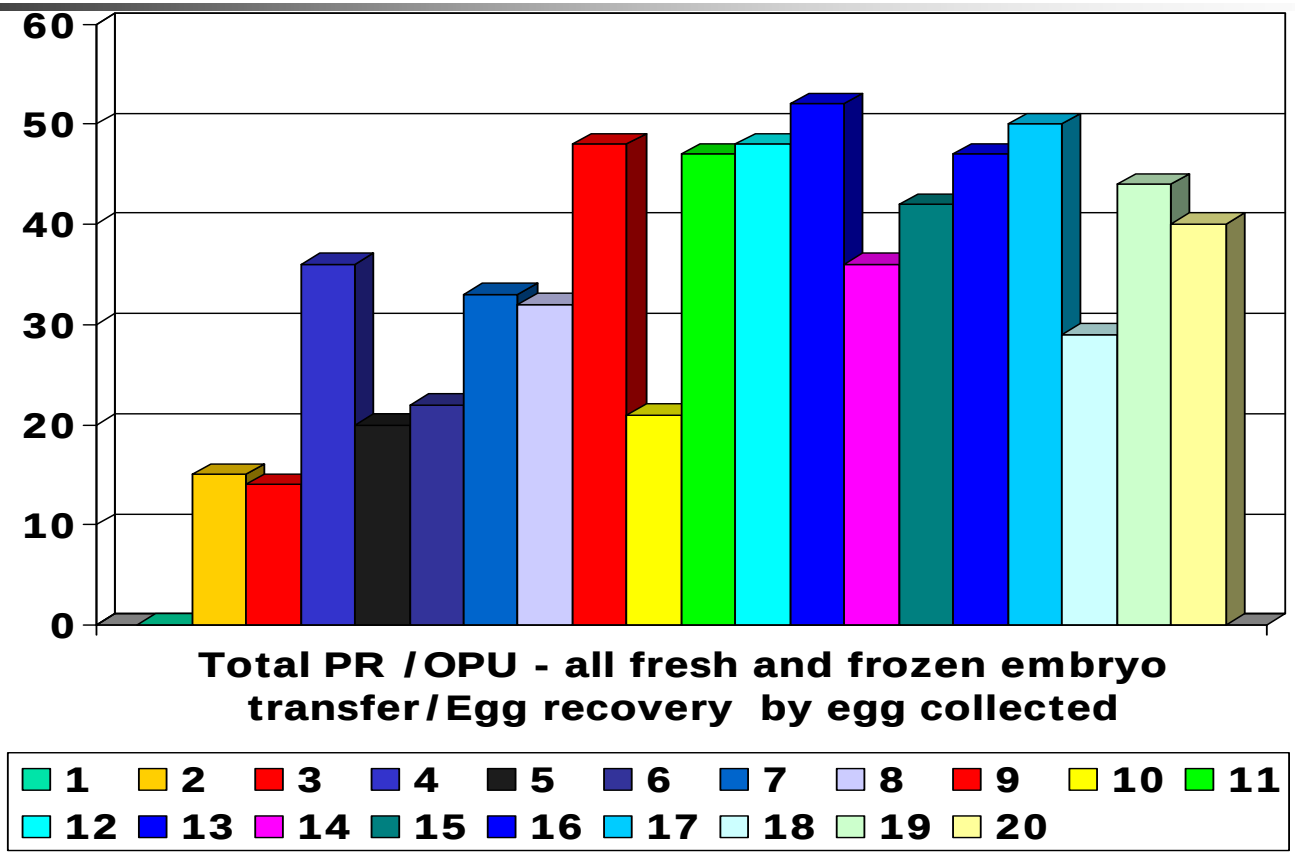
High Embryonic Wastage

All data Hunter IVF-2003-2005- fresh ET only



High Embryonic Wastage

All data Hunter IVF-2003-2005- All embryos/OPU



High Embryonic Wastage

- Data suggests that the pregnancy rate is not proportional to ova number.
- With increased ova number embryo selection for transfer increases.
- When all embryos fresh and frozen transferred over all age groups, the pregnancy rate flattens.
- Embryo selection is the key to good pregnancy rates

Variations between scientists
Does it matter – fresh or frozen

- If freezing available, the best will ultimately be transferred.
  - Cryopreservation has an inherent risk and diminution in quality
- Cost to patient –financial and emotional
- If freezing not available then.....
- Some clinics may consider some variability to be a good thing

Variations between scientists
Current efforts

- Most embryologist learn in “in-house” training
- Increasing post graduate studies important.
- Many clinics use pregnancy rate/transfer as a measure of variation between scientists
- This is subject to many contributing variables.
- Some clinics operate “in-house” Internal QC
- Some clinics participate in external schemes such as QAPonline.

Variations between scientists
Does it matter

- I argue that it does matter..
  - Professional approach requirement
  - Maximise pregnancy rate
  - Clinic and patient should expect all scientist will assess embryo quality the same.
  - Pregnancy rates/scientist may mask subtle differences in assessments between scientists.
  - Allows more advanced selection methodology such as sequential assessment to be effectively employed.

Accreditation Aspects

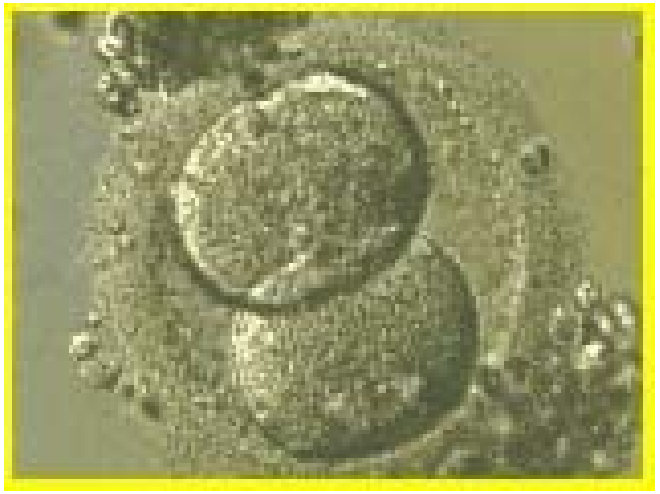
ISO 15189:2003

- ISO 15189:2003 Medical Laboratories
  - – Particular requirements for quality and competence.
- Section 5.6 – Assuring quality of examination procedures.
  - 5.6.1 Internal QC systems to verify attainment of intended results
  - 5.6.2 Laboratory will determine the uncertainty of results.
  - 5.6.3 calibration of measuring systems – if inappropriate then
    - Participant in suitable program for interlaboratory comparisons
    - Use of suitable reference material
    - Examination by another procedure
  - 5.6.4 Participate in external quality assessment schemes
  - 5.6.5 Use of challenging materials to test acceptability of methods
  - 5.6.6 With different procedures methods should be available to verify conformity
  - 5.6.7 EAQ to be recorded and deficiencies acted upon.

QAPonline
Internal QC and External QA

- What is it and how does it work?
- Internet based system of Images and questions.
- Participants linked as QA groups
  - Each participant answers compared
    - Within the group – Internal QC
    - Between all other participants – External QA.

The problem

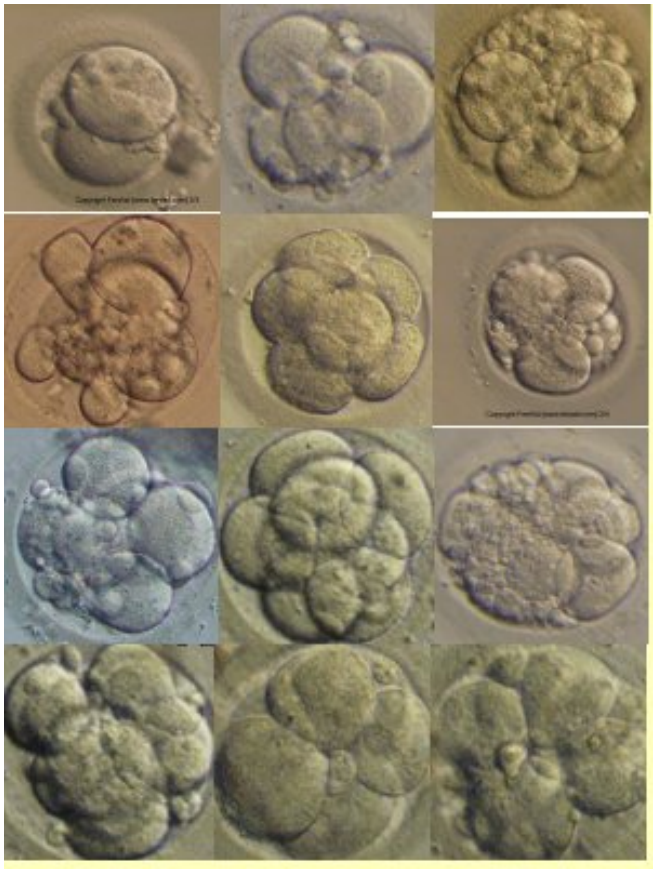


- Embryo quality will vary over time.
- The fate of an embryo may depend on
  - When it was observed
  - Who observed it.

Which embryo?

- In many cases, embryo selection is self evident
- "A" is clearly the preferred embryo for transfer
- "B" discard because of delay?
- "C" freeze or discard ?

Which Embryo?



- A more likely scenario
- Which embryo to transfer?
- Which to
  - Freeze
  - Discard
- Describe each embryo.

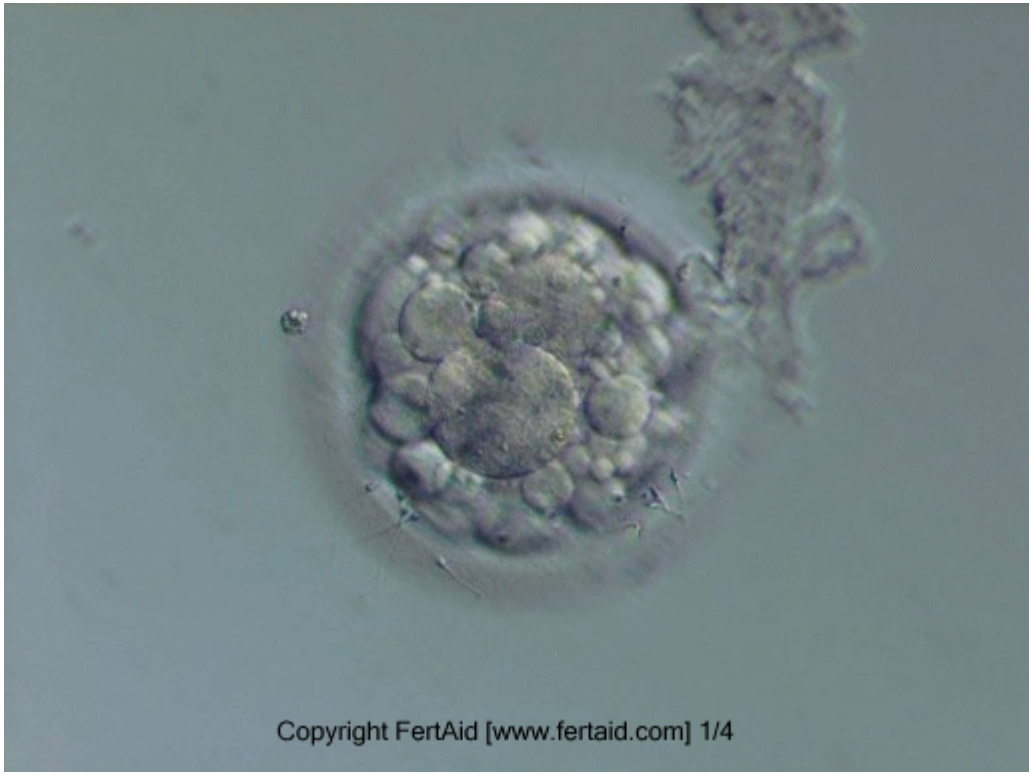
Pronuclear Scoring

- 42% Z1
- 48% Z2
- 10% Z3

Pronuclear Scoring

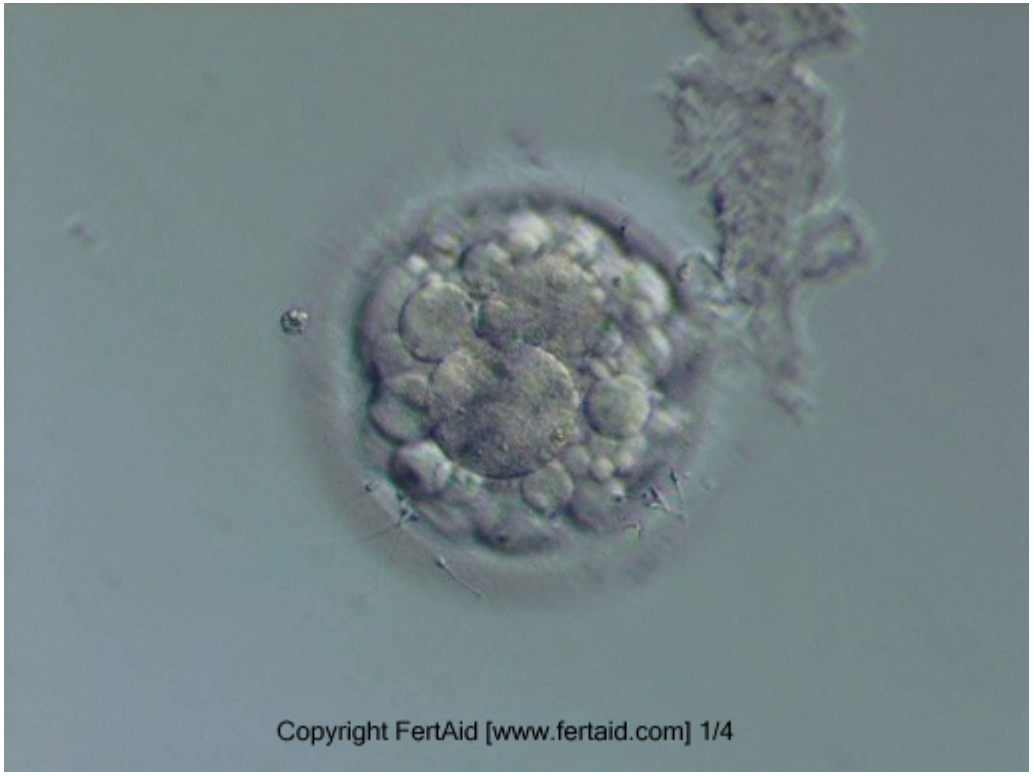
- 10% Z1
- 70% Z2
- 12% Z3
- 8% Z4

Fragmentation



- Mean=42%
- SD 14
- 66% replies between 28 & 56
- CV=33%

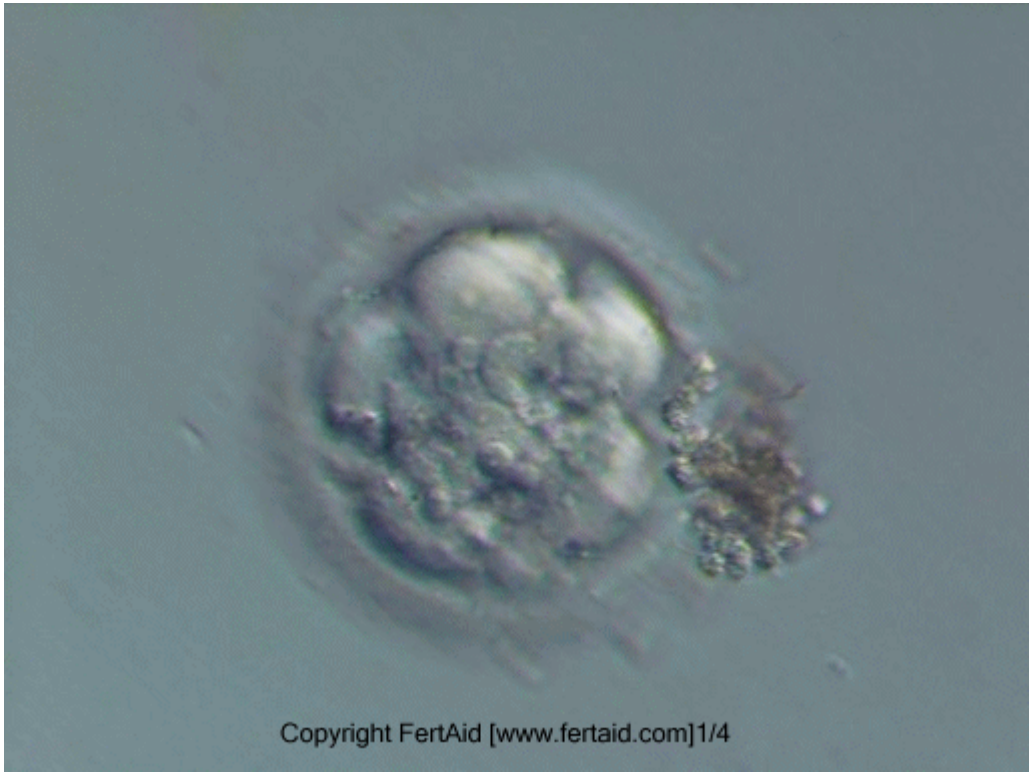
Fragmentation



- 5% localised
- 40% small even and distributed
- 55% large and random

- 10% freeze
- 90% discard

Fragmentation

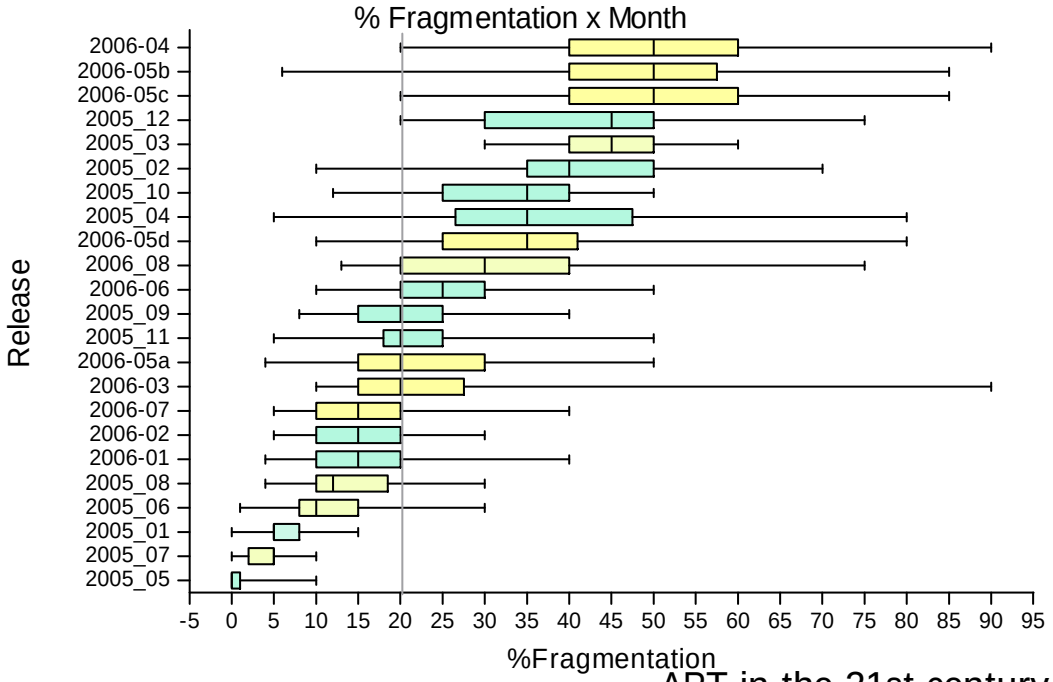


- 15% small localised
- 20% clustered
- 55% small even and distributed
- 10% large and random

- 75% freeze
- 25% discard

Variation in Assessment

- Variation in assessment of Fragmentation



Quality Management for Embryologists.

- As part of any Quality Management system, a lot of focus on
  - Equipment
  - Environment
  - Traceability
  - Risk Assessment
  - Less on Staff Professional Development

Pressure of Embryo Selection.

- Yet the selection of one embryo for transfer may be the key variable in a clinics pregnancy rate
- Embryos are largely invisible except for briefly to one examiner at only selected time frames.
- Age at transfer may influence the number of observations possible.
- Day 2 = 2-3 observations
- Day 5 = 3-6 observations.

Quality Management for Embryologists.

- Therefore a clinic needs to monitor the embryo selection skills of embryologists
- As part of quality management system
- Reduce variation in reporting
- Reduce variation in description
- Reduce variation in selection skills.

Quality Management for Embryologists.

- Staff experience changes over time
- Staff turnover bring different skills to clinic
- Training program.
- Increased professional knowledge
- Detect variation in environment [KPI]
  - Tissue culture
  - Environment.

Quality Management for Embryologists.

- Clinic size is important
  - A small clinic with 1-4 embryologists have good communication between staff but live in a very isolated world
  - A large clinic has many scientists. They may live in a large world but the capacity to monitor assessment skills is more problematic

Quality Management for Embryologists.

- So to finish, one aspect of QA that is frequently assumed to be OK is Gamete and Embryo Assessment skills.
- QAPonline has identified considerable variation in these skills
- Professional development / Competency is as important in a Laboratory QA system

Quality Management for Embryologists.

- Thank you.