european society of human reproduction & embryology

Organisation of the PGD Centre

Joyce Harper

Chair of the ESHRE PGD Consortium

Overview

- Setting up a PGD Centre
- Organisation of the PGD Centre
- The patient
- Workup
- PGD cycle
- Misdiagnosis
- Accreditation
- EQA
- What makes a good PGD Centre?

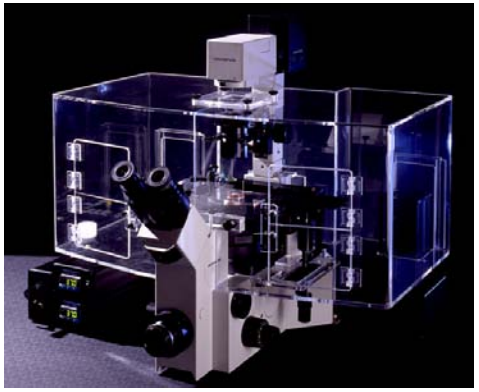
Setting up a PGD centre

- Two ways

- IVF centre and PGD centre in the same institute – preferred
- Transport PGD

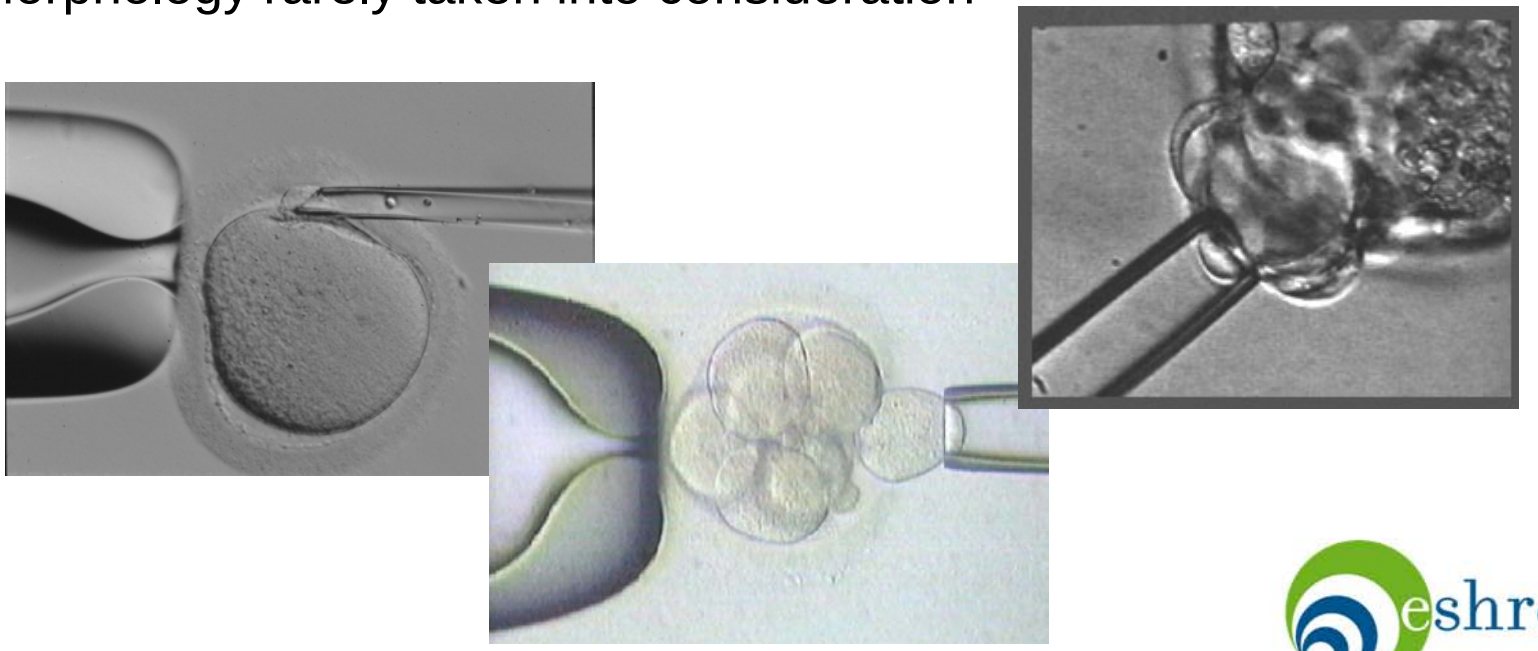
Organisation of the PGD Centre

- Highly successful IVF unit
- Patients need genetic and specific PGD counselling
- Biopsy performed by trained embryologist
- Diagnosis performed by molecular biologist/cytogeneticist
- Accredited lab
- Patient information leaflets and consents
- Excellent communication between IVF centre and diagnosis lab
- Join the PGD Consortium



Successful IVF Unit

- No point doing PGD in an IVF unit with poor results
- Need experience in biopsy
- Selecting embryos on genetic and chromosomal status
- Morphology rarely taken into consideration

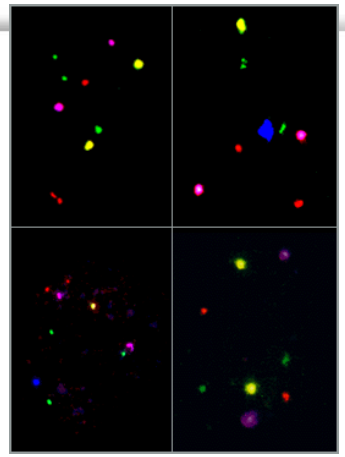


Evaluation of the patient

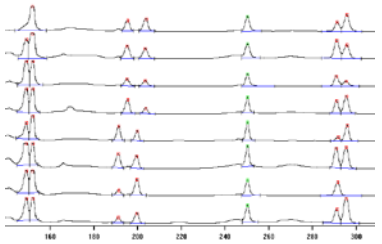
- Full report from genetics centre (and genetic counselling)
- IVF and PGD specific information
- Standard IVF workup
- Competent at embryo biopsy
- Confirm patients diagnosis
- Suitable diagnostic workup
  - FISH
  - PCR
  - Arrays

Pretreatment workup

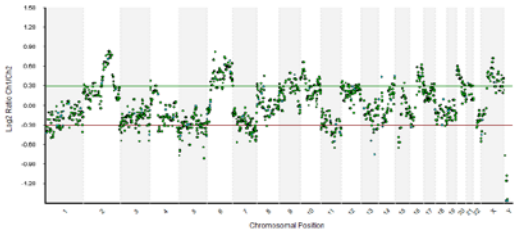
- FISH
  - Sexing need to check for polymorphisms
  - Translocation protocols developed by cytogeneticist
  - For PGS – polymorphic sites



- PCR
  - Confirmation of mutation on proband and relatives
  - Suitable informative markers to detect contamination
  - Experienced molecular biologist



- Arrays
  - Depends if for molecular or cytogenetic
  - Validation of WGA and array
  - Experienced clinical scientist



eshre

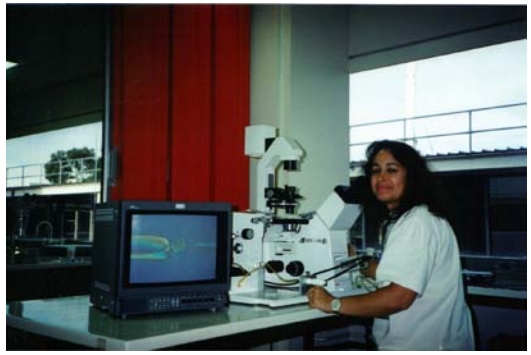
european society of human reproduction & embryology

Work-up of diagnosis

- Validation of method
- Full authorised report
- Protocol logged into lab system
- Prior to cycle – internal quality assessment of all reagents and equipment

Clinical cycle

- Full consultation, information leaflets, relevant consents
- Need good number oocytes/embryos
- Patients must not have unprotected sex
- All cumulus cells removed (maternal contamination)
- ICSI for all molecular diagnosis (paternal contamination)
- Medium to support blastocyst growth
- Clear identification of biopsied cell and embryo number
- Ensure correct embryo transferred
- Appropriate witnesses throughout diagnosis
- Full authorised report logged in PGD and IVF centre



Misdiagnosis

- Analysis of untransferred embryos
- Prenatal diagnosis
- Follow up of pregnant patients
- Follow up of babies born
- Wilton et al, 2009

Cumulative data I-X: FISH misdiagnosis - 1

Sexing for X linked disease

45,XO Haemophilia A	PND	TOP
46,XY Haemophilia A	Post	Born
46,XY Retinitis Pigmentosa (twins)	Post	Born

Translocations

T13 after 45,XY,der(13;14)(q10;q10)	Mis	Mis
47,XX,+der(22)t(11;22)(q23.3;q11.2)	PND	TOP
46,XY,der(15)t(13;15)(q25.1;q26.3)pat	PND	TOP

Cumulative data I-X: FISH misdiagnosis - 2

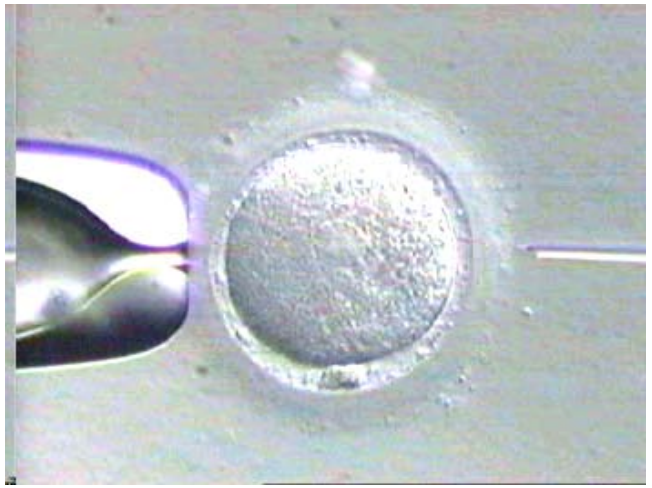
PGS		
T16 after 1st PB biopsy only	Mis	Mis
T16 after 1st PB biopsy only	Mis	Mis
Trisomy 16	Mis	Mis
Trisomy 16	Mis	Mis
Trisomy 21	Post	Born
Trisomy 21	PND	TOP
47,XXX	PND	Lost to follow-up
Normal/Trisomy 18	PND	TOP
Social Sexing		
Requested male but female foetus	PND	TOP

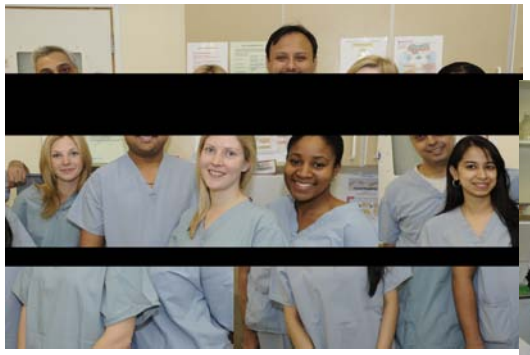
Cumulative data I-X: PCR misdiagnosis

Monogenics		
Myotonic dystrophy type 1	PND	TOP
SMA	Post	Born
ß-thalassemia	PND	TOP
ß-thalassemia	PND	TOP
Familial amyloid polyneuropathy	PND	Born
Cystic fibrosis	PND	Born
Cystic fibrosis (1 of twins)	Post	Born
CMT1A	PND	Born
CMT1A (twins)	PND	TOP of both twins
Fragile X	PND	Born
Sexing for X-linked disease		
46,XY in retinitis pigmentosa	PND	Born
46,XY in Duchenne muscular dystrophy twin	PND	TOP of one twin

Key points for biopsy/diagnosis lab

- Counselling
- Appropriately trained staff
- Aware of misdiagnosis possibilities
- Quality control
- Records
- ISO/accreditation





eshre

european society of human reproduction & embryology

Accreditation for diagnostic lab

- ISO 15189
- How can the consortium help?
- QM workshop
- Paper on accreditation of a PGD laboratory, Harper et al, 2010
- Establish an accreditation advisory panel
  - Discussion with national accreditation bodies
  - Offer centres help with accreditation process

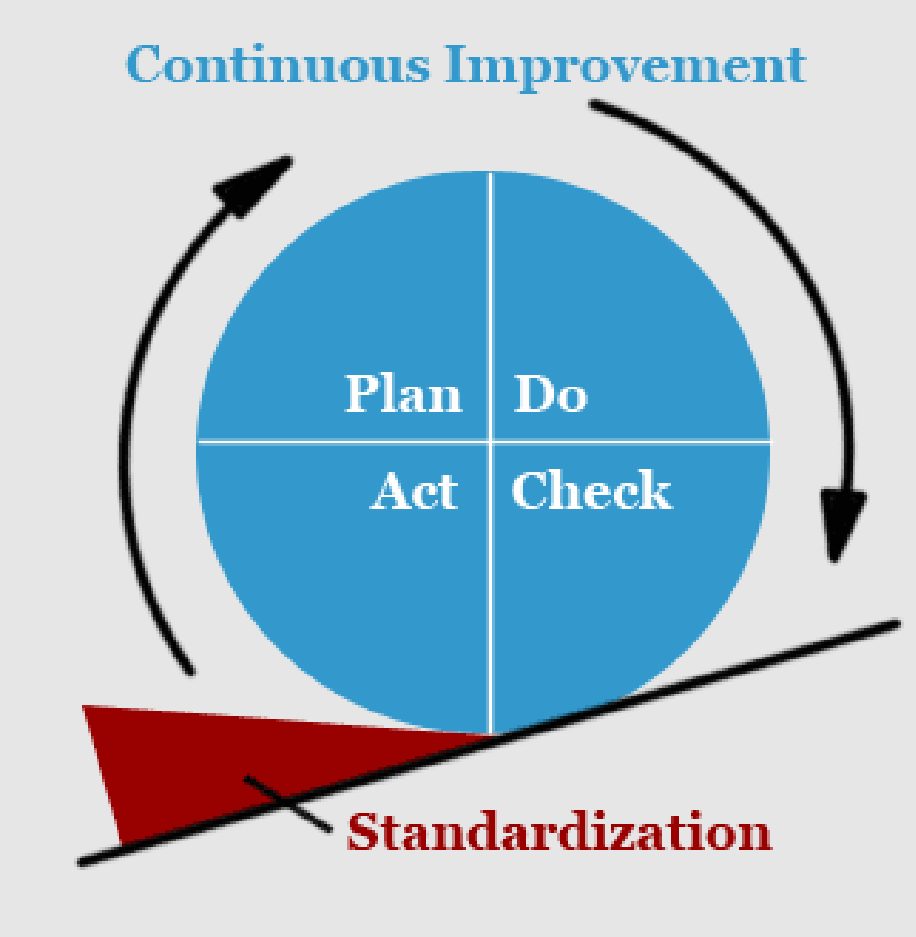
ISO 15189

- **Management requirements**
- Organization and quality management
- Quality management system
- Document control
- Review of contracts
- Examination by referral laboratories
- External services and supplies
- Advisory services
- Resolution of complaints
- Identification of control of non conformities
- Corrective action/Preventative action
- Continual improvement
- Quality and technical records
- Internal audits
- Management review

ISO 15189

- **Technical requirements**
- Personnel
- Accommodation and environmental conditions
- Laboratory equipment
- Pre-examination procedures
- Examination procedures
- Assuring quality of examination procedures
- Post-examination procedures
- Reporting results

Deming or PDCA cycle



External quality assessment (EQA) FISH

- web: www.ceqa-cyto.eu
- Cytogenetics European Quality Assessment scheme (CEQA)
- Ros Hastings, Joyce Harper, Edith Coonen, Paul Scriven

  - 2008 – pilot in three stages: PGD and PGS on line analysis and submission of retrospective case.
  - 2009 – 27th June, participants meeting
  - 2009 – EQA. Robertsonian and reciprocal translocation cases in two stages

Pilot EQA for Molecular PGD

UK NEQAS

- Pilot
- Labs sent ‘parental’ &‘affected relative’ DNA samples from cell lines
  - Test DNA, report data and state if can offer PGD to couple
- Labs sent single cells representing 5 embryos
  - test cells and report results in regular format
  - interpret results into ‘transfer’ / ‘no transfer’

- 2009/2010
  - Repeat pilot to determine performance criteria for full EQA scheme

eshre
european society of human reproduction & embryology

What makes a good PGD centre?

COMMUNICATION

Excellent IVF Platform

Excellent Diagnostics Laboratory

Integration of Services

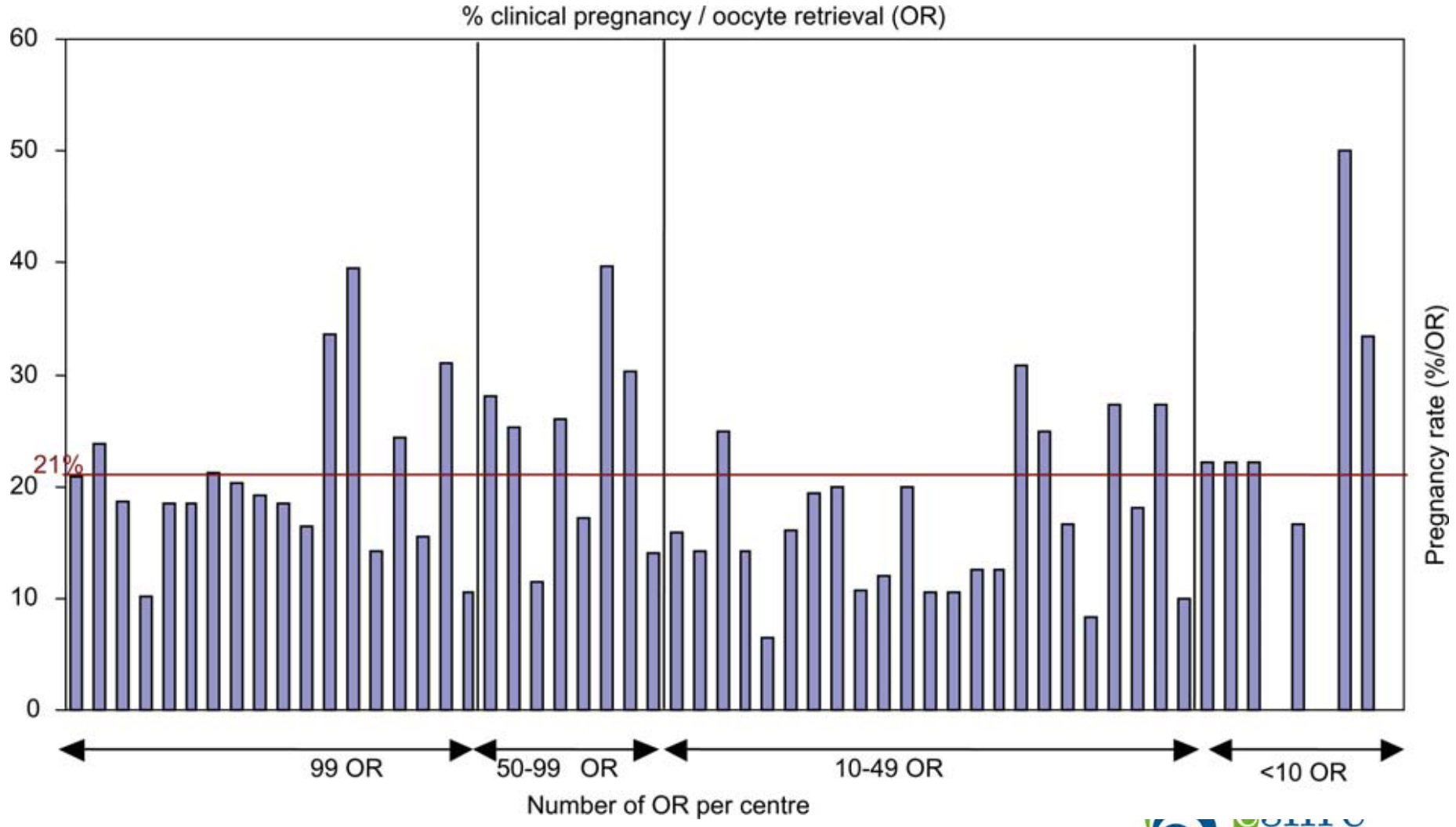
Rigorous Quality Control/Quality Assurance

Commitment to Follow-up

Comprehensive Ethical Review

TRANSPORT PGD

Success rates by number of ORs



eshre

european society of human reproduction & embryology