

A celebration of 20 years of PGD
Paediatric follow up

ESHRE Rome 2010

Alison Lashwood
Centre for PGD, Guy's Hospital, London

This is what it is all about.....



And the big question is.....

- Is PGD safe?
- Does it cause any increase in abnormality rate?

Are couples concerned?

and is this any more important in PGD.....

PGD issues that warrant some thought

- Affected children already in family
- Potential parental health status
- Fertile couples



What follow up is recommended?

Need for paediatric follow up has been highlighted from early on in PGD history:

- In 1996 **Simpson and Liebaers** recommended a standardized approach to collating data at birth on PGD babies
- Human Genetics Commission- UK (**Making babies 2006**)
- In US **Baruch et al (2005)** reported on a working group to discuss the need for comprehensive data collection including birth outcome from PGD
- Huge variation in practice across the EU- impact on follow up (**Lawford Davies 2007**)

Following this:

- PGDIS- guidelines for good practice in PGD (PGDIS- 2008)
- ESHRE- best practice guidelines for clinical PGD (Thornhill 2005)

“What the papers say”

PGD Birth outcome:

- 109 babies from polar body biopsy at birth and 44 at a mean of 11 months
- no increase in abnormality rate *(Strom 2000)*
- 480 babies polar body & blastomere biopsy
- 4.4% minor abnormalities, 1.7% major abnormalities *(Tur Kaspas 2005)*
- 24 babies over 5 years PGD for CF- no increase in major abnormalities
(Keymolen 2007)
- ESHRE (1999-2006) indicated abnormality rate at birth 3.99%
(Goossens 2009)
- Case controlled study 2007 (Brussels) 581 babies
- increased perinatal death rate in multiple births
- major abnormality 2.13% <3.38%(ICSI) *(Liebaers et al 2010)*
- Remaining reports are small “case” reports

“What the papers say”

PGD Longer term outcome:

Little long term data on PGD babies

- 3 papers have reported longer term case controlled outcomes

- Mental & psychomotor development at 2 yrs- 70 children
(Nekkebroeck 2008)
- Auxological & medical follow up at 2 yrs- 70 children
(Desmyttere 2009)
- General health at 2 yrs- 49 children
(Banerjee 2008)

All report developmental parameters same as control groups

Malformations in context- background population risks

Major malformation-

“major structural anomalies have medical and social consequences”

(Stevenson & Hall- Human malformations & related anomalies)

- 2-3% at birth
- 5% at 5 years

Malformations in context- background population risks

Minor malformations

“minor anomalies are relatively frequent structural alterations that pose no significant health or social burden”

- 15% at birth

**What are the abnormalities in
PGD babies?**

Range of major abnormalities in PGD

(ESHRE 2009)

- Aorta coarction
- Absence of corpus callosum
- Absence of corpus callosum, haemivertebra
- Absence of corpus callosum, kidney dilatation, growth
- Retardation
- Absence of ductus venosus
- Bilateral clubfoot
- Cataract
- Choanal atresia
- Cleft lip unilateral
- Cleft lip and palate
- Congenital hip luxation
- Congenital ichthyosiform erythrodermia
- Fryns syndrome, neonatal death
- Hemangioma
- Hydrocephaly
- Large cavernous haemangioma
- Laryngomalacia, receding chin, strawberry naevus
- Left ventricular hypoplasia syndrome, Aorta stenosis
- Pes equinovarus
- Phocomelia and pulmonary deficiency
- Right ear- external meatus obstruction
- Sacral dimple without intestinal connections
- Pulmonary stenosis
- Rubinstein-Taybi
- Tachycardia of Courmel
- Tetralogy of Fallot
- Unilateral cryptorchidia
- Unilateral intrauterine torsio testis
- Ventricular septum defect
- Ventricular septum defect, retrognathia

Range of minor abnormalities in PGD

(ESHRE 2009)

- Bilateral hydrocoele
- Capillary haemangioma
- Cardiac septum defect
- Cerebral calcifications + limb malformation
- Congenital hip luxation
- Cryptorchidy
- Heart murmur
- Heart problems + 1 testicle + mental retardation
- Hypospadias
- Kidney and bladder problems
- Microcephaly
- Mongolian spot
- Positional talipes
- Pre-auricular tags
- Pyelourethral junctional stenosis
- Pyelo-caliectasy bilateral
- Sacral dimple
- Syndactyly digit iv-v
- Uni-umbilical artery

Review ESHRE PGD data

(Goossens et al 2009)

Birth data collection from January 1997
To December 2006 (& subsequent pregnancies)

- Data available on 3303/3841 babies (86%)
- No data available on **538/3841 babies (14%)**
- Multiple birth rate 23% (ESHRE 2009)
- Malformations reported in 132/3303 babies
 - Overall malformation rate = 3.99%
 - Major malformations= 68
 - Minor malformation= 65 (1 baby had more than 1 malformation)

Can we learn from ART ?

- In developed countries ART babies represent 1-4% of babies born
- There is a need to compare singleton pregnancies to control for confounding multiple birth factors
- It is difficult to assess whether the underlying cause of sub-fertility or ART is responsible

Paediatric follow up after ART

- 3 meta-analyses *(Hansen 2005, Lie 2005 & Rimm 2004)*
and a controlled study of nearly 3000 infants confirmed relative risk of
major abnormality of 1.24 in ART babies *(Bonduelle 2002)*
- Longer term studies on ICSI/IVF babies show a relative increase risk of
abnormality- ICSI (2.77) and IVF (1.8)
(Bonduelle 2005)
- Increase risk of imprinting disorders such as Beckwith Wiedemann,
Angelman and retinoblastoma
(Sutcliffe 2006, Maher 2003 & 2009, Moll 2003)
- Paper at ESHG >15,000 babies 4.24% major abnormality, increase in
BWS (5.1) & retinoblastoma (4.4) *(Viot 2010)*

Difficulties with PGD paediatric data collection?

- Numbers per centre are small- 700 children needed for power to detect major abnormalities
(Desmytere 2008)
- Easy to lose contact with families and fail to collect complete data
- Funding of paediatric follow up
- Distance to travel to PGD Centre & secrecy of PGD
- Ascertainment bias, requires control population



Number of variables to control for:

- Type of biopsy
- 1 versus 2 cell biopsy
- Singletons versus multiples
- PGD vs PGS as background reason for treatment is different
- Fresh vs cryopreserved embryos
- Fertile vs infertile couples
- Affected vs unaffected parents

The future

- Should we improve paediatric follow up?
- How can we do this?

- Collaborative effort is essential

EU 8th Framework PGD study

Multi faceted study. The main goals of the study are:

- to facilitate the collection of data relating to the use of reproductive technologies and their outcomes in EU member states through the use of common terminologies and data registers (the 'technical strand')
- to facilitate the referral of patients from one centre to another, particularly for patients at risk of rare monogenic diseases (the "clinical strand")
- **to enable the efficient follow-up of patients and their off-spring so as to monitor safety and efficacy through data collection and a data register (the 'monitoring strand')**
- to examine the relevant requirements of the EU Human Tissue and Cells Directive (2004/23/EC) and other relevant legal requirements at EU and member state level, and to address related ethical issues (the 'legal and ethical strand').

Two part study

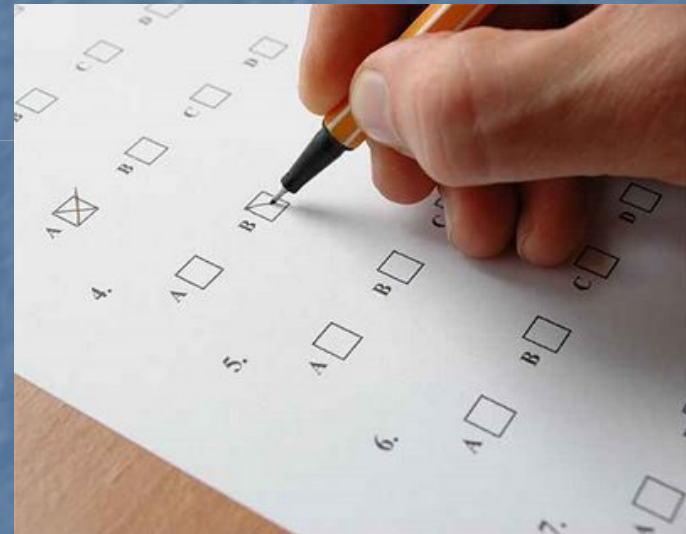
Part 1- PGD centre data

- Questionnaire sent to each ESHRE participating centre (118)
- Questions included:
 - Local paediatric follow up provision
 - Extent of information collected
 - Interest/willingness in prospective data collection
 - Legal and ethical obstacles

23 responders (19.5%)

Parental postal questionnaire

- Cross sectional sample
- 16 centres agreed to participate
- Approximately 2000 babies
- 6 centres actually participated
- Around 600 babies
- Data collection complete
- Data entry underway



Data management

- Data is stored on a new paediatric web based database created- EuroPGD Code project
- This database will form a prototype for possible future PGD data collection.
- Database is live and data is being entered centrally.
- Results reported by End of 2010

PGD babies- do we need to consider anything else?

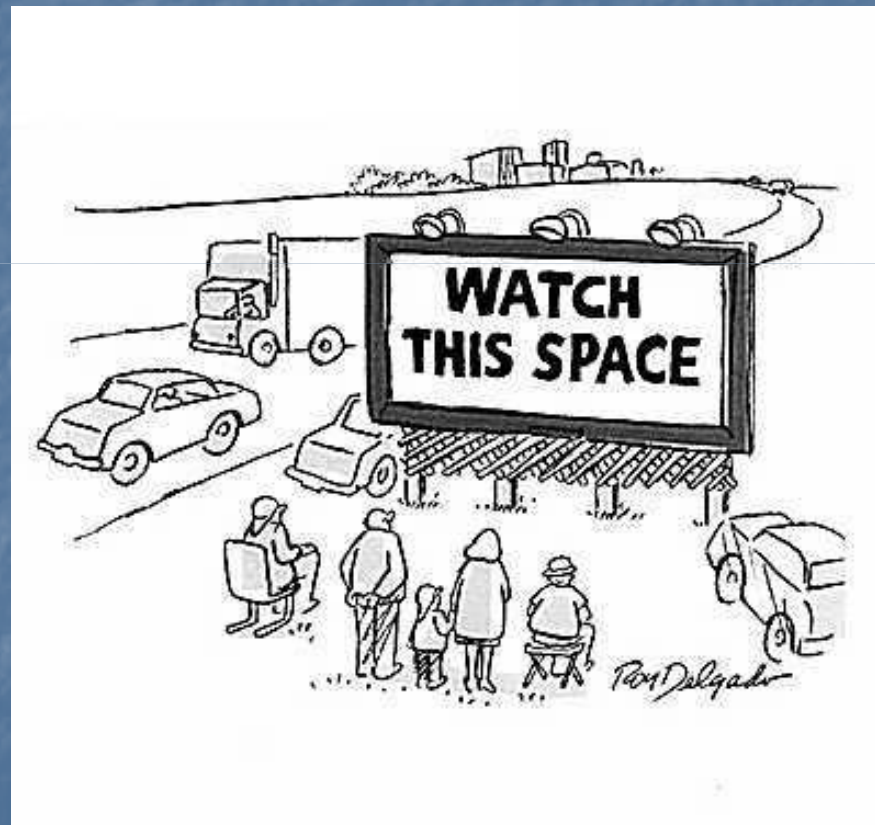
The health of babies born after PGD is important, but what else may impact on these children?

- PGD multiple births in “Genetic” families.
- maternal & paternal health factors-
 - during pregnancy
 - during infancy & childhood
- Do parents plan to tell their children about PGD and does it matter?

Summary

- Short and long term data on PGD babies is limited.
- At present the overall abnormality rate at birth appears to be no higher than abnormality rates for other ART procedures
- In future studies a number of variables will need to be considered and controlled for.
- A large collaborative, prospective case controlled study is required.
- Such a study is complicated by multicentre participation (in multiple countries), language, ethics, standardisation of terminology and cost.....

Can it be done?





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