Pre-Implantation Genetic Diagnosis

Bradley Kalinsky, MD
Amanda Kalinsky, RN, BSN

Our Clinical Vignette

- A young couple in the mid-to-late twenties presents to your clinic to discuss having children. The wife carries the gene for an AD, devastating neurodegenerative disease that is uniformly fatal in the 4th-5th decade. No treatments options available at present. They want to "have healthy kids." Do you have any advice?
- Options?
  - Don't have biological kids.
  - Surrogacy, adoption.
  - Take a 50% chance?
  - Do you test the child in utero? Do you abort the pregnancy?
  - Do you test the child at birth? Is that Ethical?
- What if they could prevent the disease from being inherited by their own biologic children?

Objectives

- PGD Background
- Process
- Safety
- Success Rate
- Expense
- Ethical Concerns
- Amanda's Experience

Pre-implantation Genetic Diagnosis

Testing done to screen eggs, sperm and embryos for chromosomal abnormalities (aneuploidy/translocations), single gene disorders, sex, and human leukocyte antigen (HLA) matching.

Brief PGD Background

- Today, PGD is a worldwide clinical option that combines ART, embryology, and genetics which has born over a 1000 healthy children at "high risk" for life-threatening genetic disorders.

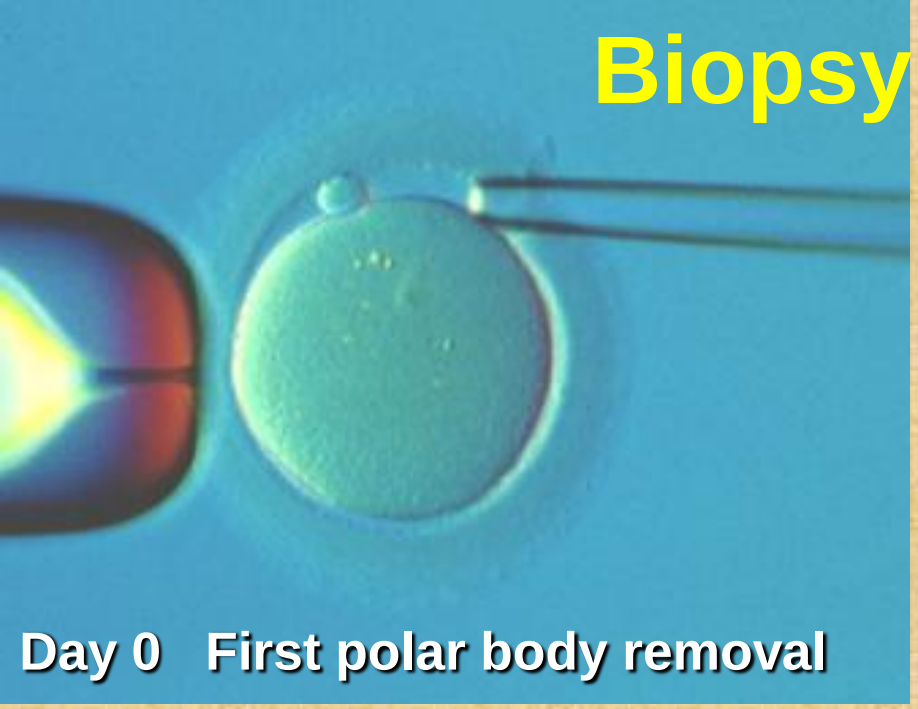
- Ever-expanding clinical implications (Down's Syndrome, CF, SC, HD, BRCA 1+2 and other cancer predisposition genes, repeated IVF failure, repeated loss of pregnancy, HLA genotyping and Savior Siblings, etc.) that are exciting and limitless.

- For our discussion, we will focus on the role of PGD in single gene defect diseases, such as fCJD, GSS, FFI, etc.

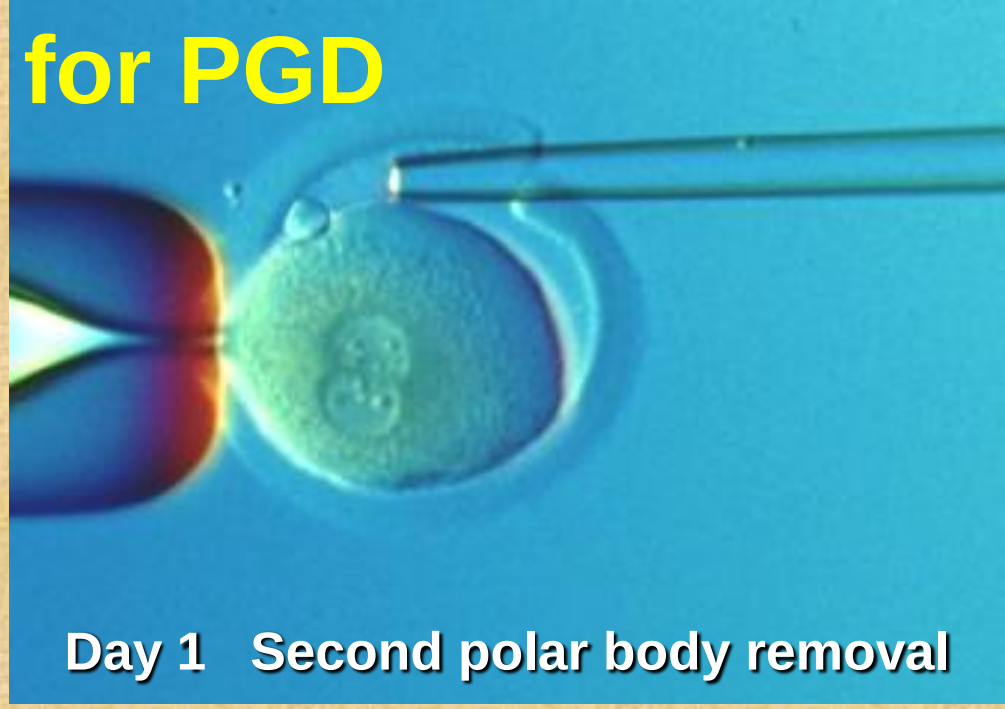
PGD Process

- Starts with Patient Counseling.
- Standard IVF cycle (follicular stimulation of with medication, egg harvest under anesthesia, injection with a single sperm).
- Once fertilized, the oocyte and/or embryo will undergo biopsy and testing by either polar body biopsy and/or blastomere biopsy.
- The biopsy technique involves removing one cell and either fixing it to a slide or releasing its DNA for further analysis.
- Typically the biopsy is done by the IVF facility and the genetic material is sent off to a genetic lab. If the genetic results become available within the next 48 hours, a fresh embryo transfer will usually be done 5 or 6 days after egg retrieval.
- If the results cannot be obtained within this time frame, the embryos can be frozen until the results are known. Then, a frozen embryo transfer can be performed.

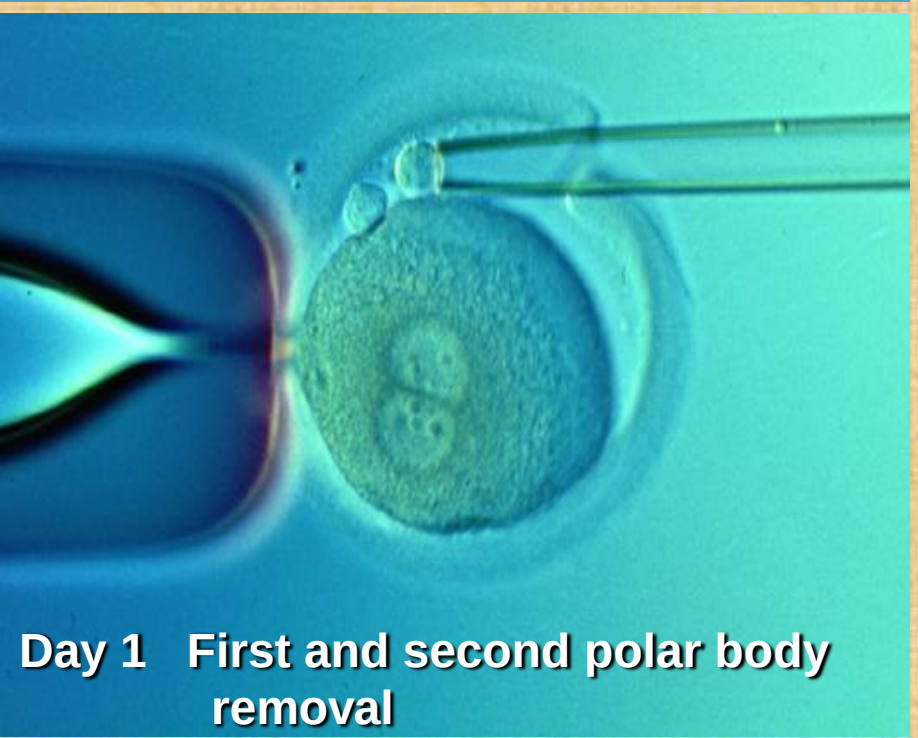
Biopsy for PGD



Day 0 First polar body removal



Day 1 Second polar body removal



Day 1 First and second polar body removal

Day 3 Embryo biopsy

Genetic Testing of Embryos: Practices and Perspectives of US IVF Clinics

- In 2008, PGD was offered by 74% of IVF clinics.
- PGD was used in about 5% of all IVF cycles in the US.
- Only few major PGD labs for single gene disorders, HLA, and translocations.

Baruch et al, Fertil Steril 2008;89:1053–8.

Biopsy for PGD: Is It Safe?

Blastocyst Rates after 1-3 Micromanipulations for PGD

January 2001 – March 2004

PGD	1,653 / 3,293 (50.2 %)
Non-PGD ICSI only	9,726 / 19,529 (49.8 %)

p=NS

Cieslak-Janzen, Tur-Kaspa, et al, Fertil Steril 2006

Health of Children Conceived after PGD

- 49 PGD children and 66 matched naturally conceived controls, age range, 3-56 months.
- Outcomes measured: neuro-developmental screening, health problems and parent-child relationships.

Conclusions:

- PGD children have health and development that is comparable with naturally conceived children.
- Families had no identifiable difficulties, and if anything, enjoyed warmer parent-child relationships.

Banerjee et al. RBM Online; March 2008

Multiple studies show that children born after PGD show no increase in congenital anomalies.

Strom, et al, 2000; Tur-Kaspa et al. 2005;

Munne et al, 2006; Banerjee et al 2008;

Ginsberg et al, 2009; Liebaers et al, 2010; Simpson JL, 2010

Is PGD for Single Gene Defects Accurate?

- Most important limitation for reliable testing is undetected allele drop out
- Also, AD vs. AR makes a difference
- Most studies report reliability of 95-98%
- Will never be 100%. False Negatives are well documented, as well as False Positives.
- The technology is ever-evolving and improving (multiple biopsies, linked polymorphic marker analysis, multiplex single cell PCR)
- All centers recommend Prenatal Testing (CVS, Amniocentesis) but most don't.

How Much Does it Cost?

- The average cost of IVF is $12,000 - $15,000.
- PGD typically adds $3,000 - $5,000.
- IVF minimally covered by insurance. PGD is not.

At the End of the Day: Limitations of PGD

- There may be few or no normal embryos available for transfer.
- There is no guarantee of pregnancy even in otherwise fertile couples with the transfer of normal good quality embryos.
- Cryopreserved biopsied embryos appear to have a lower implantation rate than non biopsied cryopreserved embryos.
- Embryos can only be diagnosed as "normal" for the defect(s) tested.
- There is a very low risk ~ 0.1% of damage to the embryo as a result of the biopsy.
- Analysis of a single cell has limitations and an error rate (1-5%) that allows for a small percentage of misdiagnosis .
- Ethical Concerns....

Ethical Concerns

- Life Begins at Conception? Destruction of Affected Cells
- Inaccuracy of genetic testing
- Reduced Penetrance of Certain Genetic Diseases (BRCA, etc)
- Non-Disclosure Cycles
- Weaning out Disabilities, Eugenics.
- Adult Onset Diseases. May be a cure?

Genetic Selection and Prenatal Diagnosis

- Prenatal diagnosis should be confined to "seeking genetic information in order to correct or avoid unambiguous disabilities or to improve the well-being of the fetus."

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, 1983

- "The use of genetic technology to avoid the birth of a child with a genetic disorder is in accordance with the ethical principles associated with physicians' therapeutic role."

American Medical Association. Prenatal Genetic Screening. CEJA Report D-1-92, February 8,2011

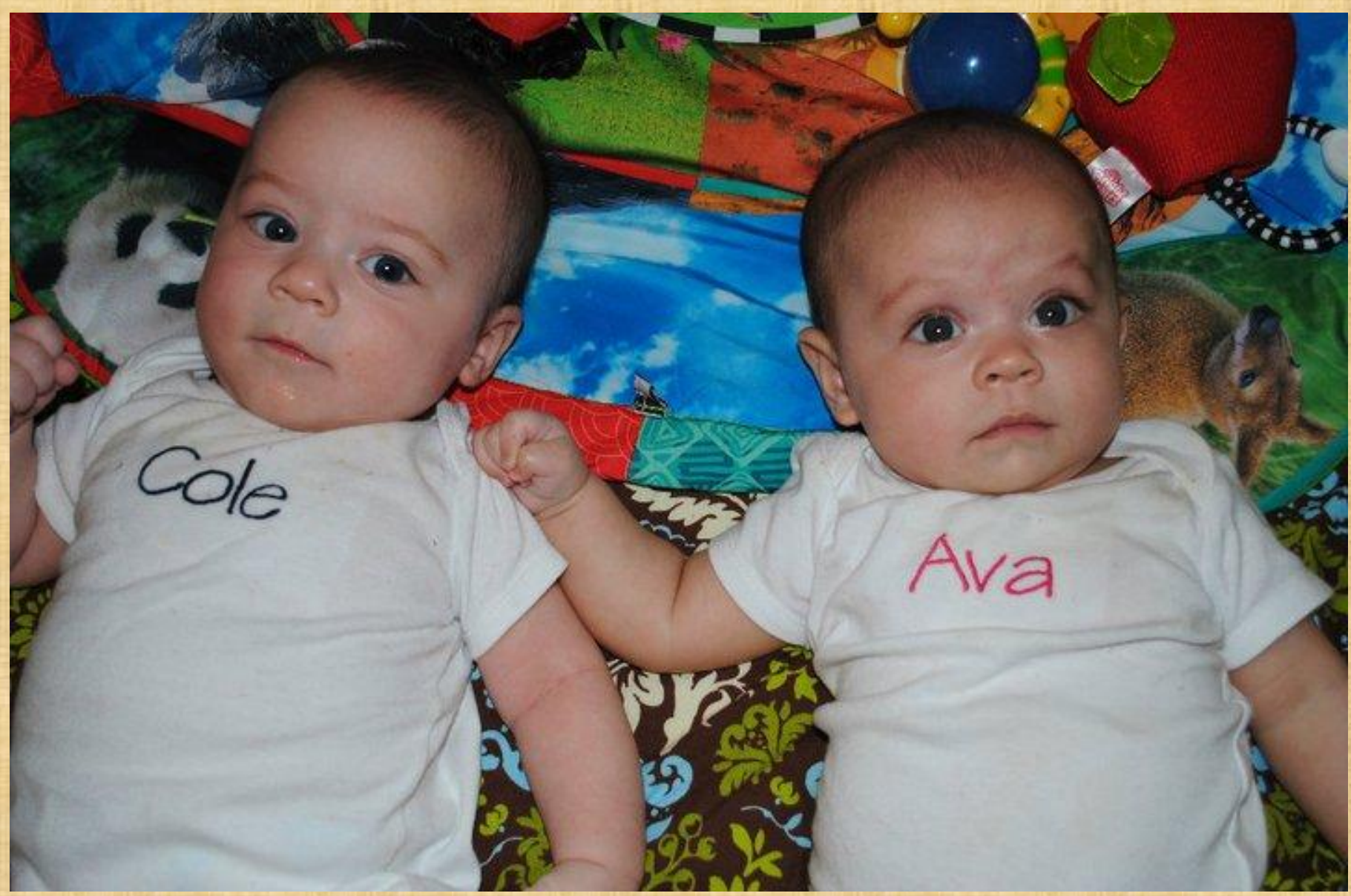
Regulation?

- In the UK, the HFEA oversees and licenses all procedures relating to embryo creation and manipulation.
- A license is required for each PGD center for each new condition to be tested.
- In Germany, only procedures of direct benefit to the embryo are allowed, and PGD is prohibited at any point following pronuclear fusion.
- PGD is banned in some other European countries, including Italy, where draconian legislation has been passed.
- In contrast, there is no federal regulation of PGD in the United States.

Braude et al. 2002

The Personal Side of Pre-Implantation Genetic Diagnosis


05 15 2008 08


Cole
Ava

Institute for Human Reproduction

2825 N. Halsted Street
Chicago, IL 60657

Phone: 773-472-4949

www.infertilityIHR.com