

# Pre-Implantation Genetic Diagnosis and Prion Diseases

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# Disclaimer:

- We are not Prion researchers. We are not Reproductive Endocrinologists/Geneticists.
- We do not have any financial relationships to disclose.

# 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 4<sup>th</sup>-5<sup>th</sup> decade. No treatments options available at present. They want to “have healthy children.” Do you have any advice?
- Options?
  - Don't have children.
  - 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?
- **BEST OPTION:** What if they could prevent the disease from being inherited by their own biologic children?

# Pre-implantation Genetic Diagnosis

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

# Objectives

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

# Brief PGD Background

- Pioneered from advances in ART and PCR technology (1980's-1990's)
- 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, 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.

1st PGD for FA & HLA

Verlinsky et al, JAMA 2001



Savior Siblings

# Popular Culture:

## The Match

“Savior Siblings” and  
One Family’s Battle to  
Heal Their Daughter



Beth Whitehouse

## MY SISTER'S KEEPER

a novel

“This beautifully crafted novel will grab  
readers with its stunning topic.”

—*People*

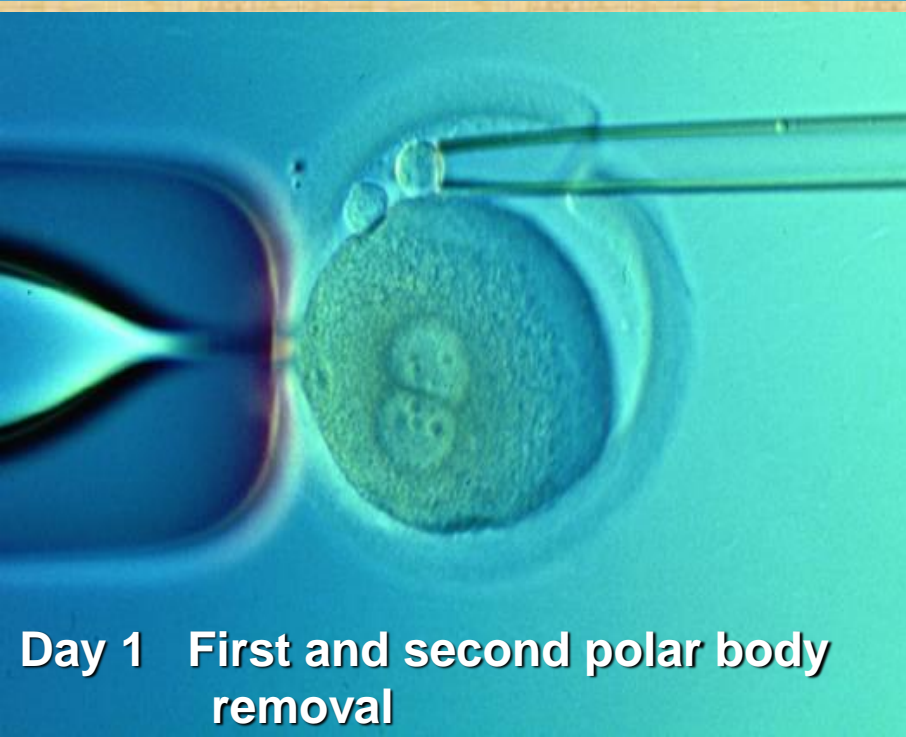
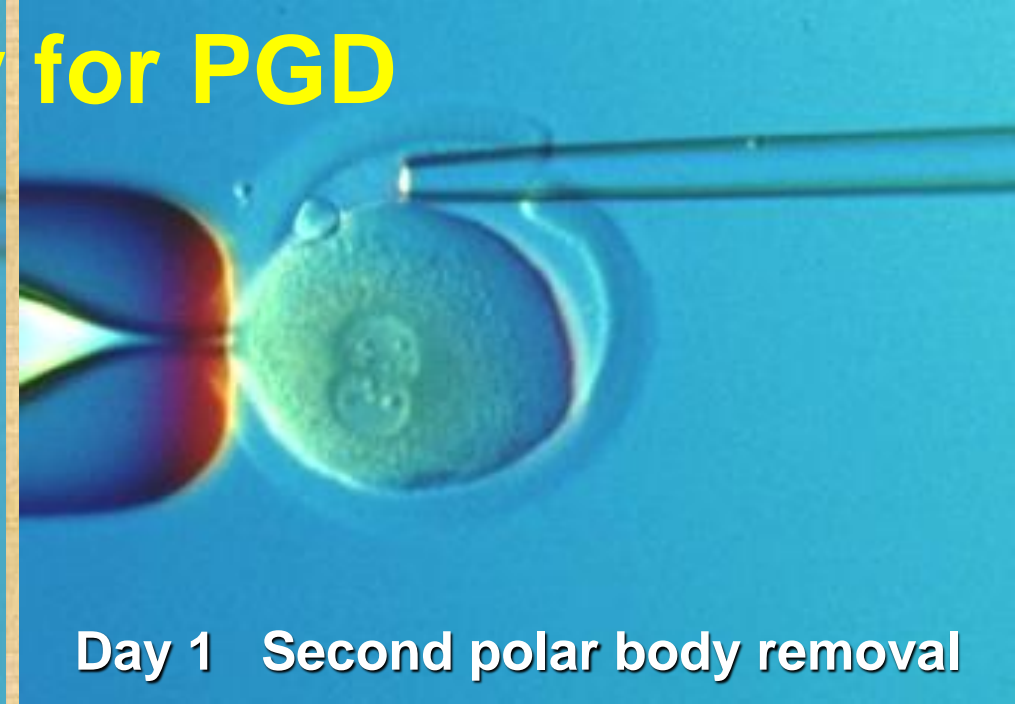
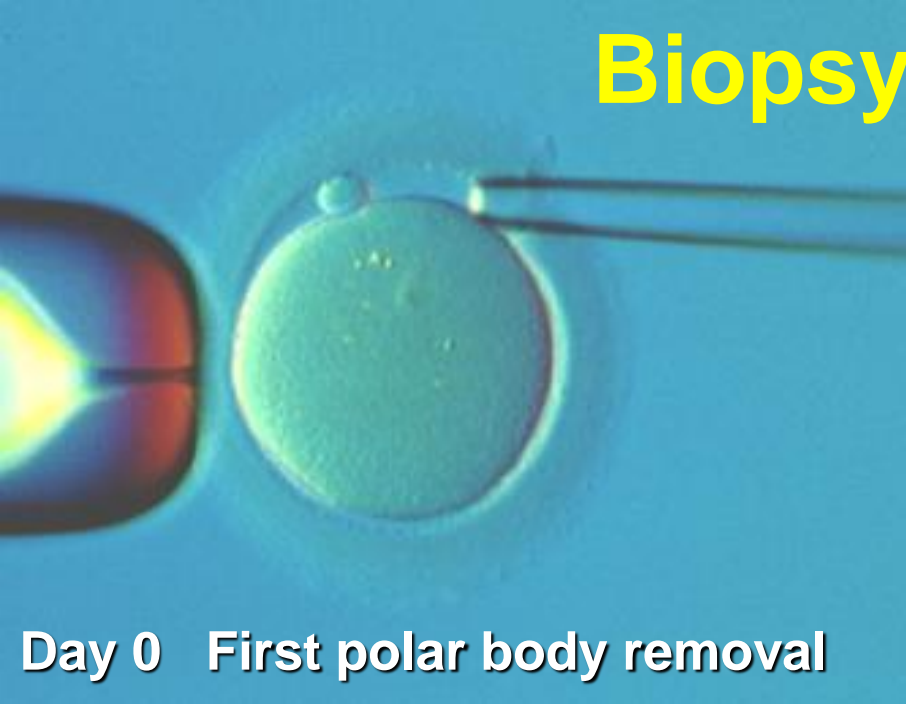




# Process and Time-course

- Months to Years Before Harvest:
  - Patient Counseling (doctors, genetic counselors, clergy, etc) +/- Genetic Testing
- 1-2 Months Before Harvest:
  - Standard IVF cycle (follicular stimulation of with medication, frequent US, bloodwork, etc)
- Day Zero:
  - egg harvest under anesthesia, sperm collection, injection with a single sperm
- Day Zero to Day Five:
  - once fertilized, the embryo will undergo biopsy and testing by polar body biopsy and/or blastomere biopsy

# Biopsy for PGD



# Process and Time-course

- Day Three to Day Six: await genetic analysis
  - if the genetic results become available within the next 48 hours, a FET will usually be done 5 or 6 days after egg retrieval.
  - if the results cannot be obtained within this time frame, the embryos will be cryopreserved until the results are known
- Day 10-12 After Implantation:
  - Continued medications and pregnancy test
- 4-6 Weeks After Implantation:
  - Stop medications and expectant management
- 12-20 Weeks After Implantation:
  - CVS vs Amniocentesis if preferred

# 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 (for the embryo  
and baby)?

# 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

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

# 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.

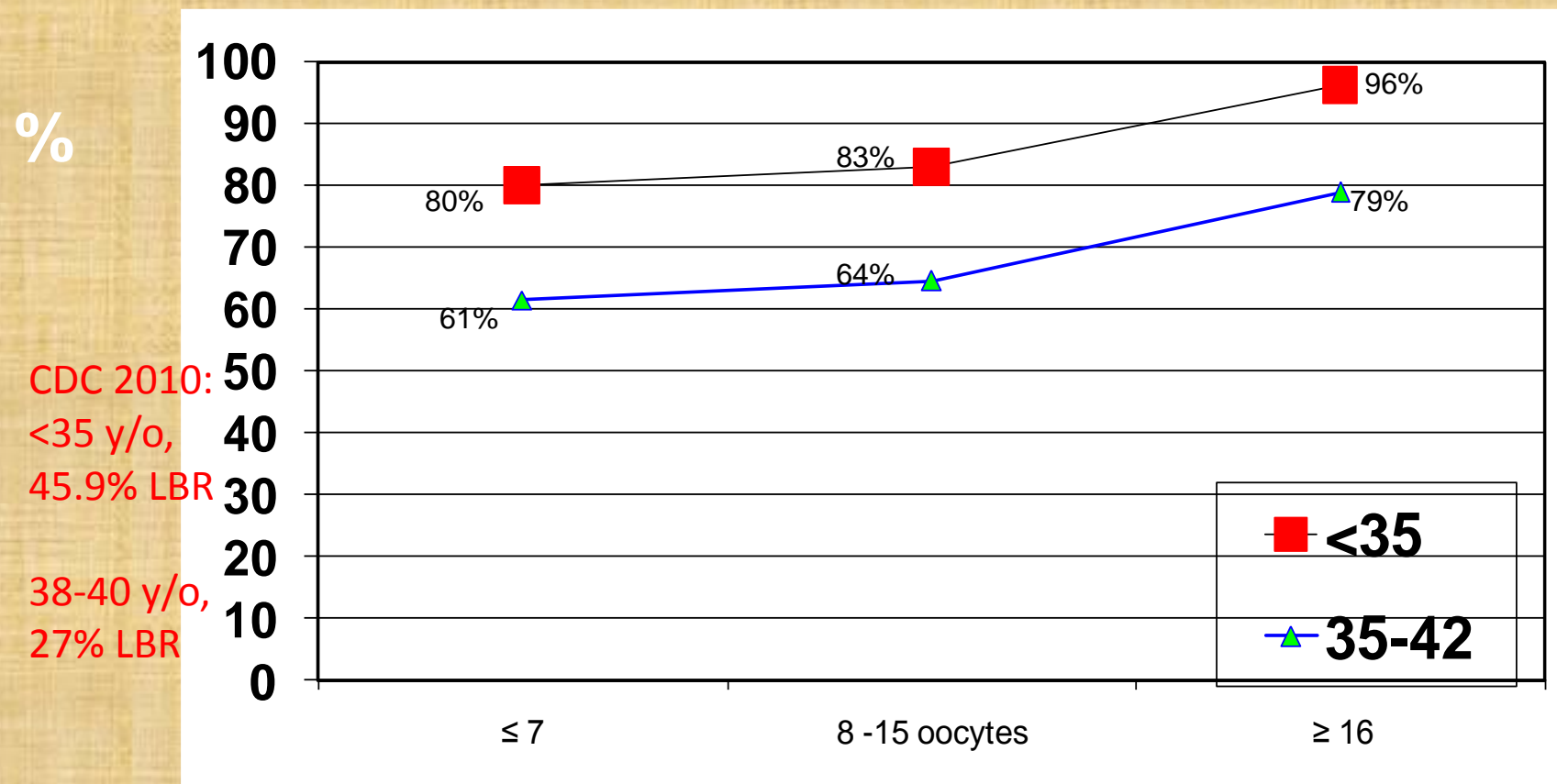
## Conclusions:

- 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.



# Factors that affect Embryo Transfer:

IVF-PGD for Single Gene Disorders: % Embryo Transfer at IHR by Number of Oocytes Retrieved and Woman's Age



# 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 94-98% with a low end being around 90%
- 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 coverage is mandated in some states, PGD is mostly not.
- Getting Cheaper though.

# How Many Couples with Single Gene Disorders Would Opt to Choose PGD Over Prenatal Diagnosis ?

- **74%** of couples preferred testing with PGD.
- **80%** preferred PGD when PGD could be performed without any significant delay.

Survey showed a need for high-risk patient and Physican/Nurse education about PGD options.

# Cryopreservation:

- 1983, 1<sup>st</sup> successful human pregnancy of a cryopreserved embryo
- Used in 20% of all ART cycles and has led to >200K live births
- Process: Slow freezing vs. Vitrification
  - slows metabolic activity to nothing
  - theoretically, can preserve living cells for 1,000 years

# Cryopreservation:

- Success Rate: 10-20% of embryos don't survive the freezing/thawing process. But, those that do seem to do better (than FET) in terms of obstetric and perinatal outcomes (Maheshwari et al) as 22%-35% result in live births.
- Safety: Wennerholm et al showed reassuring neonatal outcomes in comparison to FET (preterm birth, low birthweight, and malformation rates). Though, longer studies need to be done.
- Expense: \$400-1,000/year.
- Does storage time influence post-thaw survival and pregnancy outcome? Riggs et al showed "no" with successful pregnancies up to 9.2 years after of storage.

# 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 may not survive the thawing/unthawing process.
- Embryos can only be diagnosed as "normal" for the defect(s) tested.
- Analysis of a single cell has limitations and an error rate (1-5%) that allows for a small percentage of misdiagnosis .
- Unknown longterm risks to mother and conceived children
- 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?



# Can PGD used for designing your perfect baby ?

THE NEW YORK TIMES **OP-ED** FRIDAY, JANUARY 24, 2003

## YOUR PERFECT BABY® CHECK LIST

EYES  
COLOR \_\_\_\_\_  
SHAPE \_\_\_\_\_  
VISION \_\_\_\_\_

EARS  
COLOR \_\_\_\_\_  
SHAPE \_\_\_\_\_

PLEASE CHECK HERE IF YOU WANT FAMILY RESEMBLANCE

SEX CHECK ONE

MALE

FEMALE

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

HAIR  
COLOR \_\_\_\_\_  
TEXTURE \_\_\_\_\_

MOUTH  
SIZE \_\_\_\_\_  
SHAPE \_\_\_\_\_

FAT  
% \_\_\_\_\_

BONES  
DENSITY \_\_\_\_\_

INTELLIGENCE  
I.Q. \_\_\_\_\_  
REASONING \_\_\_\_\_  
CREATIVITY \_\_\_\_\_

TEETH  
SIZE \_\_\_\_\_  
NUMBER \_\_\_\_\_  
\*SEE DISEASE RESISTANT

BELLY  
BUTTON  
\*PLEASE CONSULT WITH YOUR PHYSICIAN

JOINTS  
SIZE \_\_\_\_\_ ROTATION \_\_\_\_\_

HEAD  
SIZE \_\_\_\_\_  
SHAPE \_\_\_\_\_

NOSE  
SIZE \_\_\_\_\_  
SHAPE \_\_\_\_\_

SKIN  
COLOR \_\_\_\_\_  
MELANIN% \_\_\_\_\_

HANDS  
SIZE \_\_\_\_\_  
FINGER LENGTH \_\_\_\_\_

FEET  
SIZE \_\_\_\_\_  
ARCH \_\_\_\_\_  
TICKLISH \_\_\_\_\_

HEIGHT/WEIGHT AT BIRTH

H \_\_\_\_\_ W \_\_\_\_\_

THIS CAN VARY 10-15%  
BASED ON NUTRITION IN UTERO

DISEASE RESISTANT \*ADDITIONAL CHARGE, PLEASE REFER TO  
"YOUR PERFECT BABY" HANDBOOK SECTION 32A.

# 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, recent allowance of selective cases of PGD has been permitted
- PGD is banned in some other European countries, including Italy, Switzerland, etc
- In contrast, there is no federal regulation of PGD in the United States.

Braude et al. 2002

# The Future of PGD for Prion Diseases:

- Goal is not that 100% of persons at risk for genetic prion diseases will undergo PGD. Rather that 100% of persons at risk are aware of their reproductive options.
- The technology and screening will continue to get better and cheaper.
- Insurance companies will start to cover these procedures.

# Take Home Message

- Professor Robert Edwards eloquently summarizes:

"A constant worry is the oft repeated charge that these techniques introduce eugenics to human populations rather than helping to avoid inherited diseases in fetuses. Great care is essential to avoid any impression that averting genetic disease in embryos casts any reflection of the value and equality of the handicapped in a modern society. And a final challenge to the democracy of science is that the rich will benefit most from these new advances because health authorities in many countries still crassly decline to fund IVF and PGD despite their overwhelming advantages to so many couples. ....There is no doubt that PGD is bound to offer ever widening opportunities while demanding the closest of ethical attention."

"An Atlas of Preimplantation Genetic Diagnosis"

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