

# Infertility, In Vitro Fertilization (IVF) and Genetic Testing

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**Do you have any friends or family members  
that have struggled with infertility?**

**a. Yes**

**b. No**



**Do you think that you are fertile?**

**a. Yes**

**b. No**



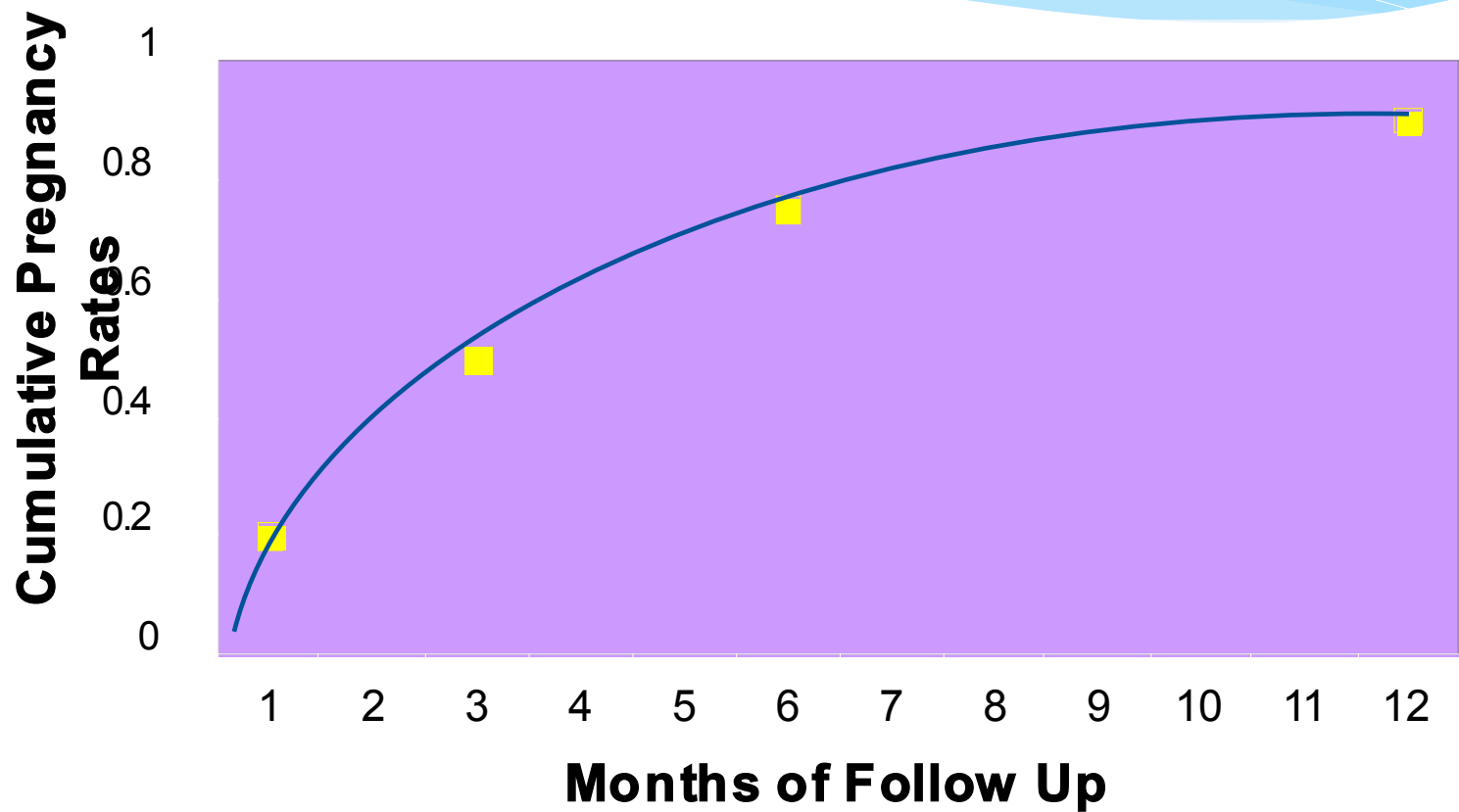
**What percentage of the population is subfertile or infertile?**

- a. 1-2%**
- b. 5-10%**
- c. 10-15%**
- d. 15-20%**
- e. 20-25%**

# Outline

- **Infertility**
- **Treatment Options**
  - **In Vitro Fertilization**
  - **Egg Freezing**
  - **Surrogacy**
- **Genetic Testing**
  - **Preconception**
  - **Preimplantation**
  - **Prenatal**
- **Controversies**

# Normal Fertility





# **Infertility**

# Overview of Infertility

- Definition: 1 year of well-timed, unprotected intercourse without a pregnancy
- 10-15% of population is infertile (subfertile)

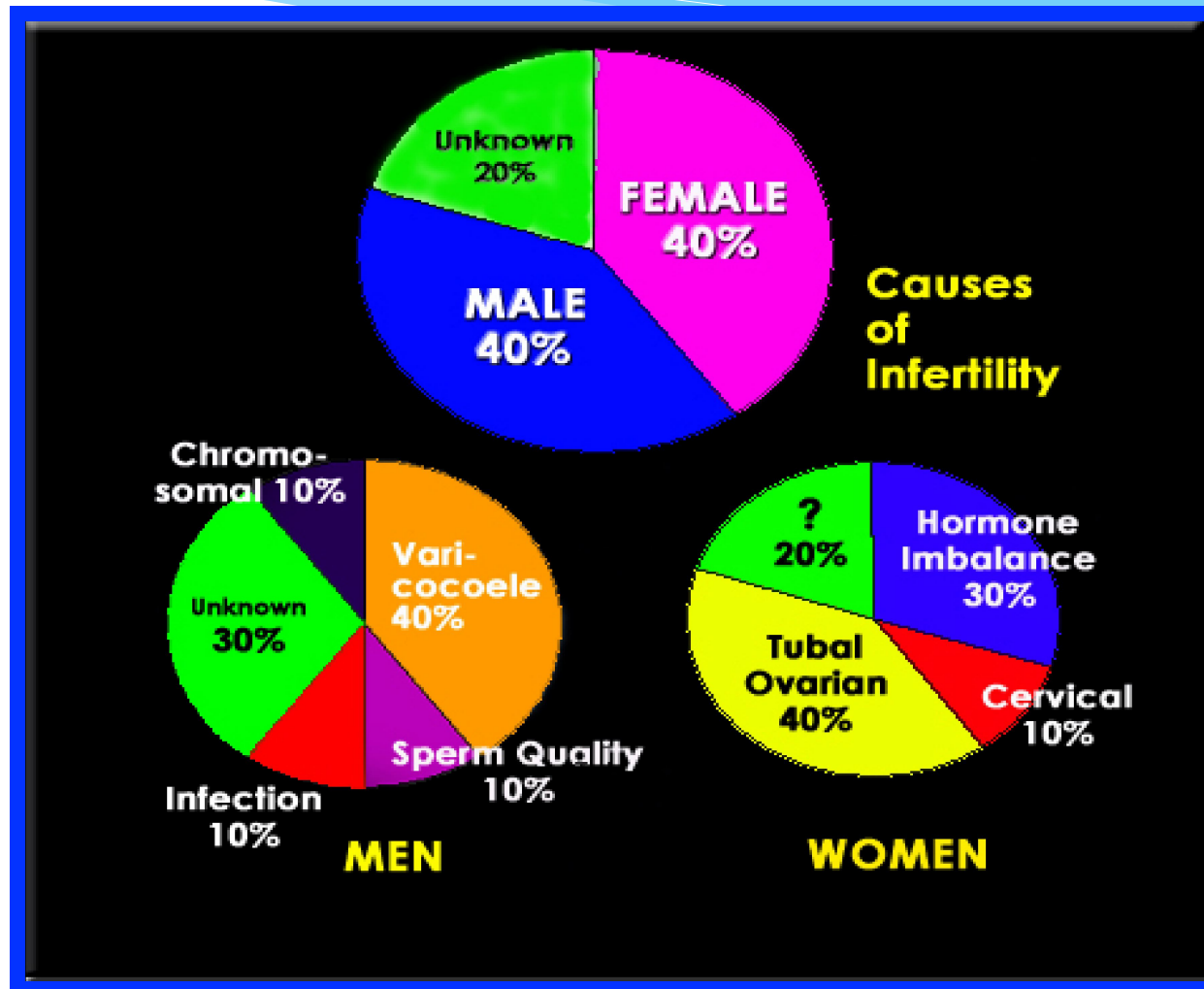




**What factor might cause problems with fertility?**

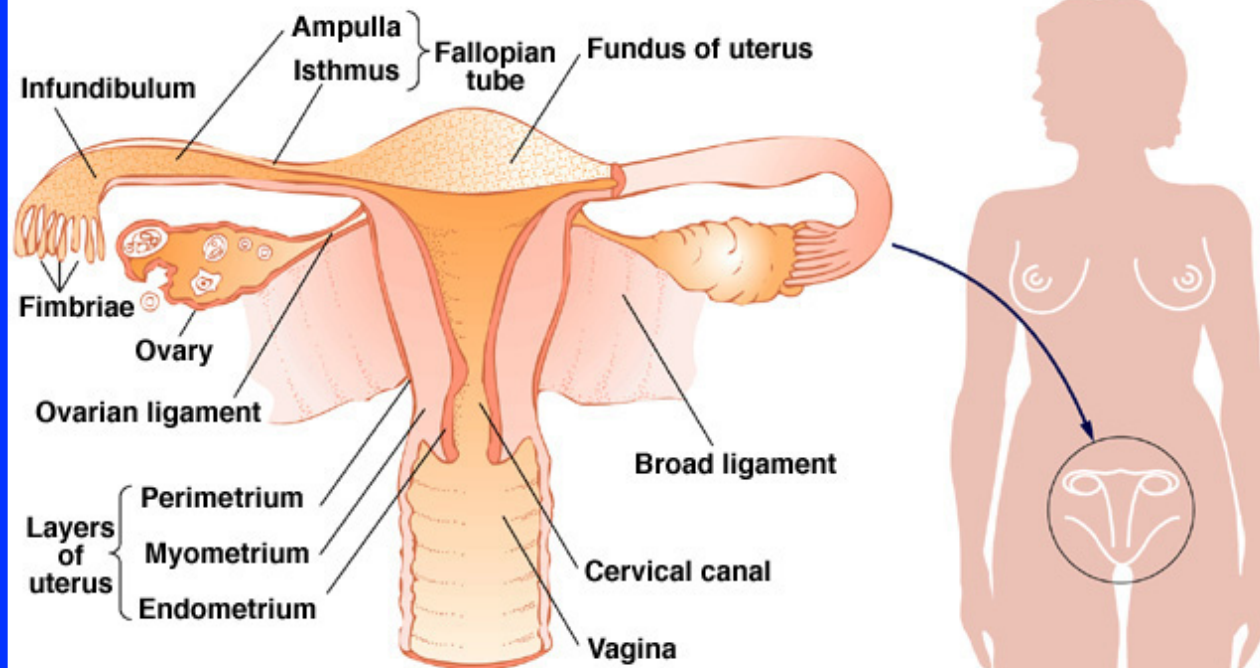
- a. boxer shorts**
- b. drinking a glass of wine every day**
- c. eating disorder**
- d. hiking for 30 minutes per day**
- e. history of yeast infections**

# Causes of Infertility

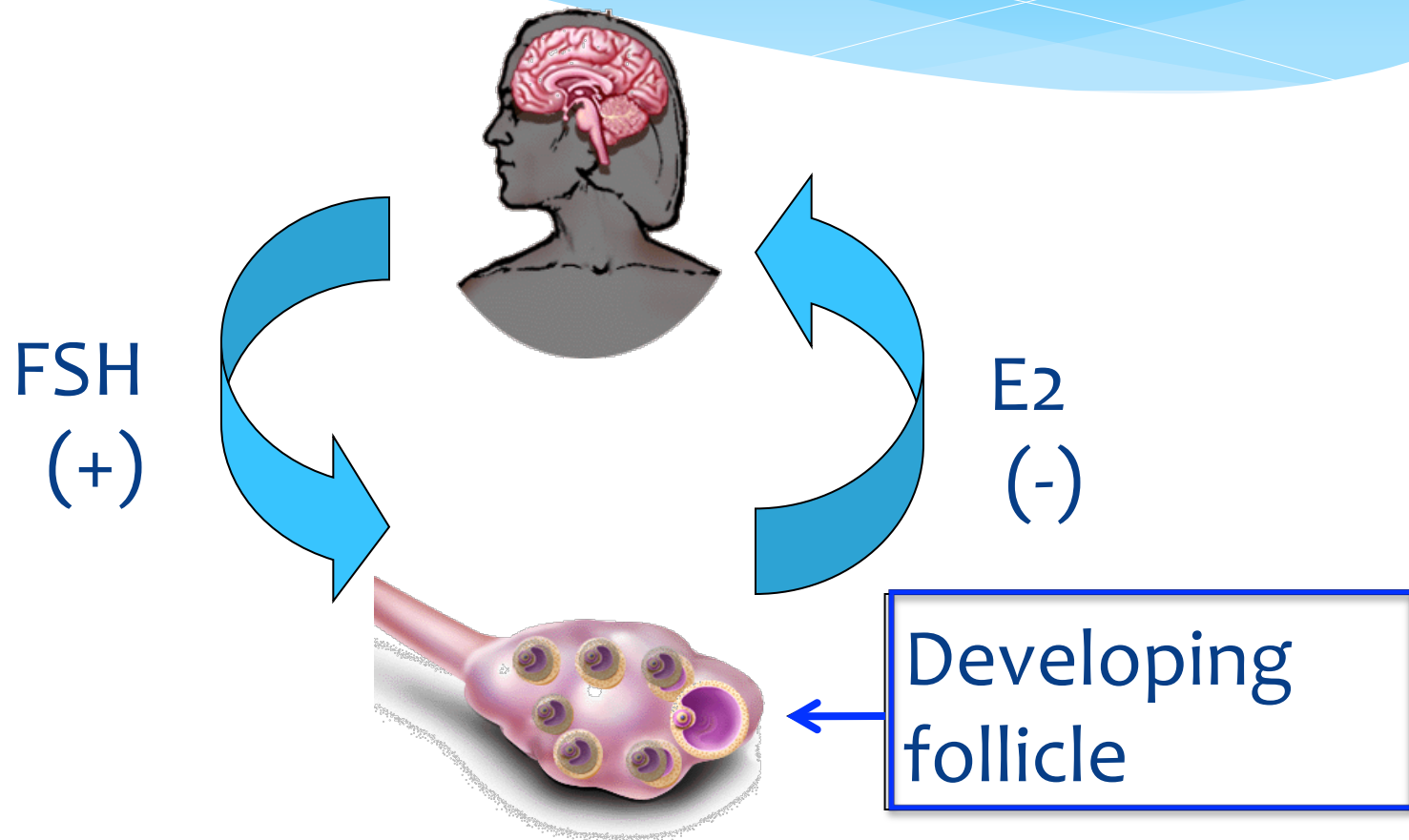


# Female Reproductive Organs

## Internal Sexual & Reproductive Organs(F)



# Physiology



FSH=Follicle Stimulating Hormone


E2=Estradiol

# Causes of Female Infertility

- Ovary
- Tubes
- Uterus
- Cervix
- Hormones
- Chromosomes

# Causes of Female Infertility - Ovary

- AGE
- Problems with ovulation
- Premature ovarian failure



**Do women continue to produce eggs throughout their life (*i.e.*, from puberty until death)?**

**a. Yes**

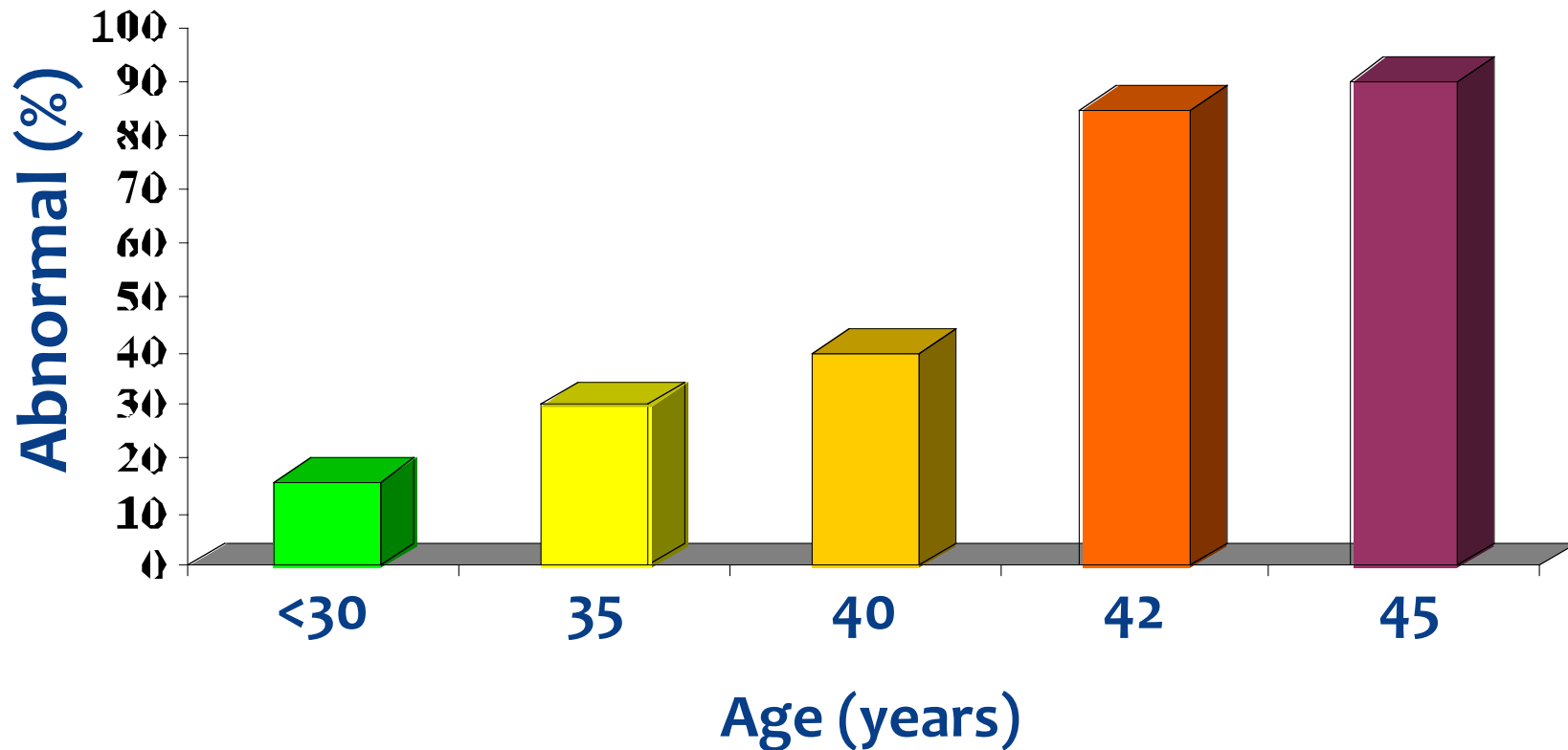
**b. No**

# Ovary - Female Age

- Women are born with their lifetime egg supply
  - 4 million at 20 weeks gestation
  - 400,000 at birth
- 100,000 eggs left at time of puberty
- Fertility initially declines at age 27
- Significant decline at age 37-38
- Rare pregnancies after age 44



# Prevalence of genetically abnormal oocytes in infertile women



# Ovary - Causes of Anovulation

- Hormone imbalance
- Obesity
- Anorexia
- Significant stress
- Patients display:
  - ❑ Irregular menstrual cycles
  - ❑ Skipped cycles
  - ❑ Minimal or absent premenstrual symptoms

# Ovary – Premature Ovarian Failure

- Menopause prior to age 40
  - Decreased Estrogen
  - Increased FSH
- Causes
  - Autoimmune
  - Genetic
  - Idiopathic
- 1-2% pregnancy rate



**What factor would not cause a woman's fallopian tubes to be blocked?**

- a. diabetes**
- b. ruptured appendix**
- c. endometriosis**
- d. chlamydia infection**
- e. tubal ligation**

# Causes of Female Infertility – Fallopian Tubes

- Infection (chlamydia)
- Endometriosis
- Tubal ligation (female sterilization)

# Open Tubes



# Blocked Tubes

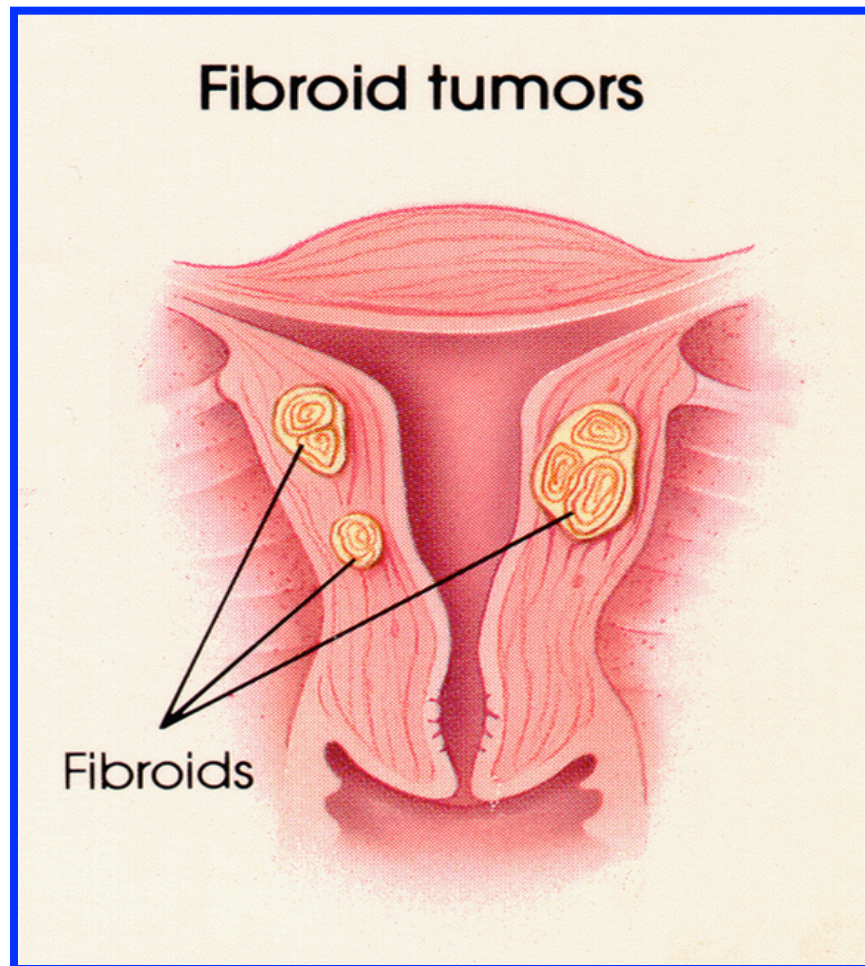


# Female Infertility - Uterus

- **Uterus**
  - **Fibroids**
  - **Polyps**
- Mullerian (congenital) defects
  - Absent
  - Bicornuate/Septum



# Female Infertility - Uterus

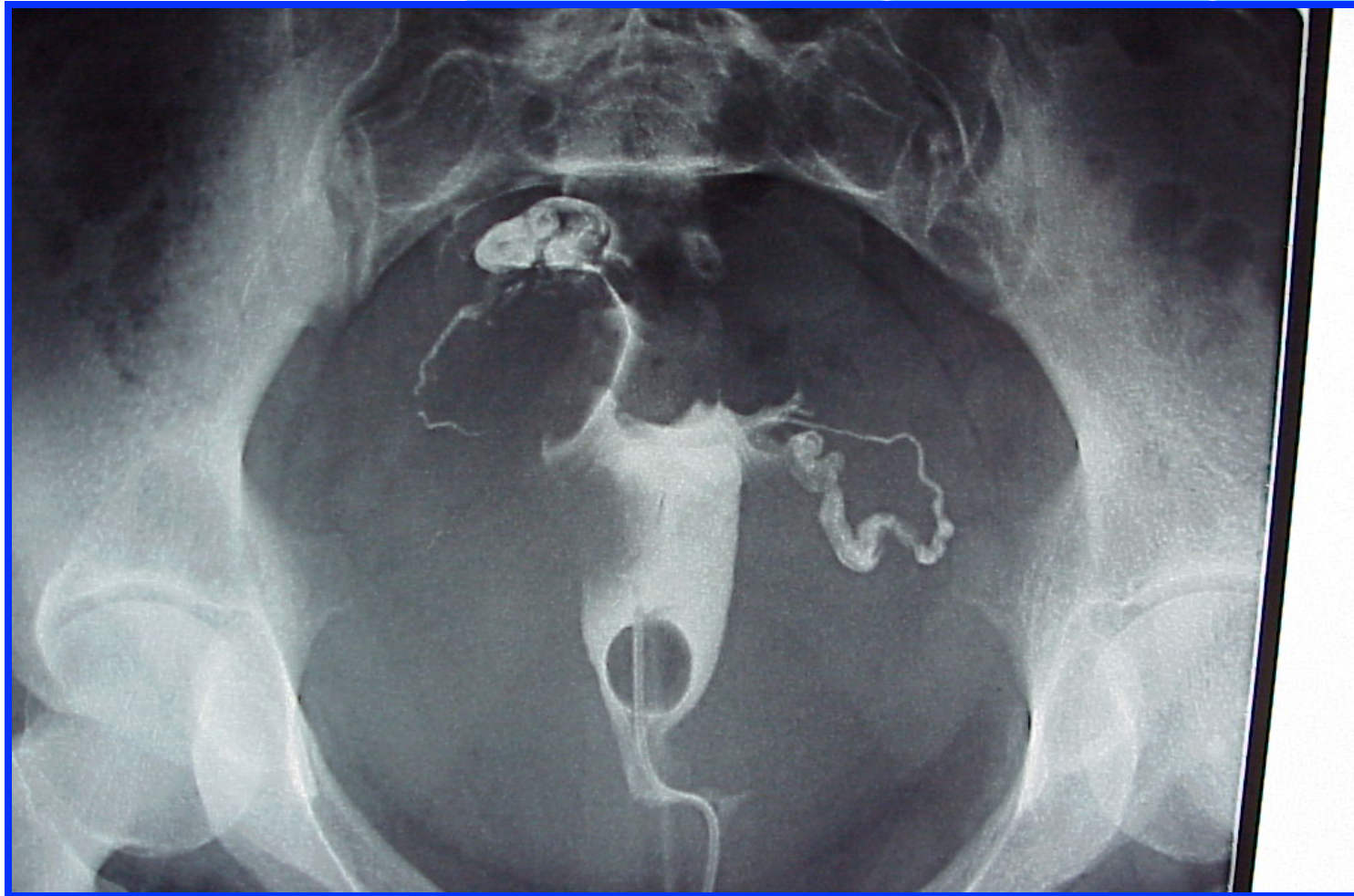


- Uterine muscle tumor
- Benign (>95%)
- 25-30% of women

# Normal Shape of Uterus



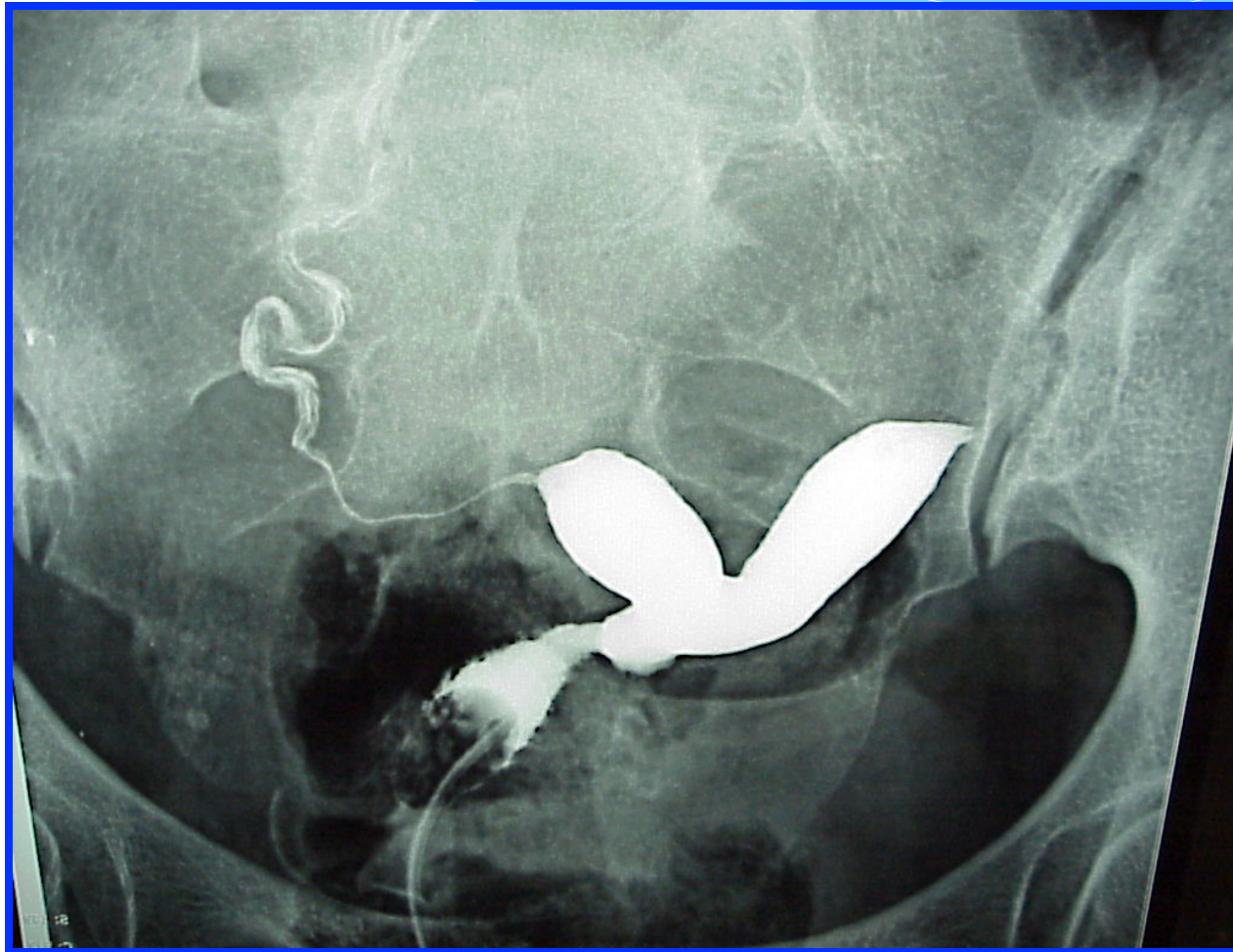
# Fibroid Uterus



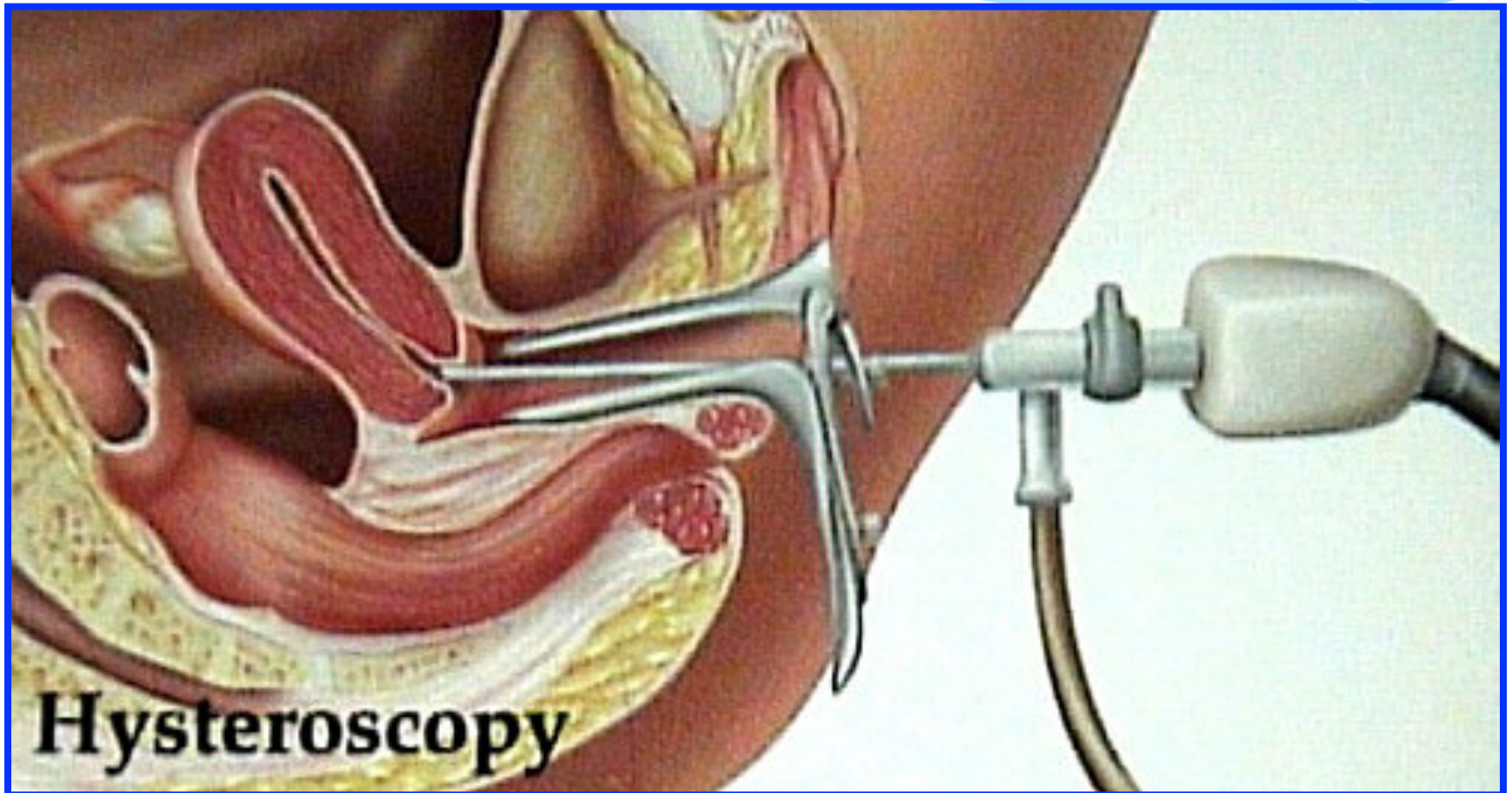
# Female Infertility - Uterus

- Uterus
  - Tumors
    - Fibroids
    - Polyps
  - **Mullerian defects (congenital)**
    - **Absent uterus**
    - **Bicornuate/septate**

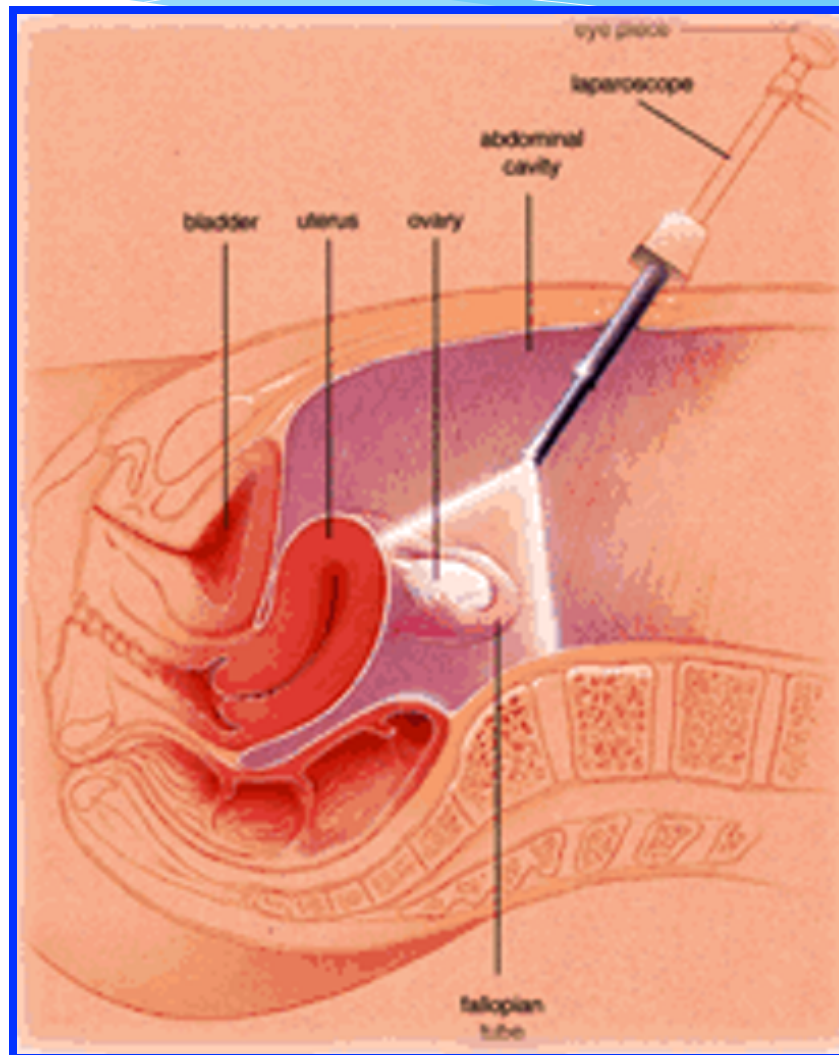
# Mullerian Defect



# Treatment with Hysteroscopy



# Treatment with Laparoscopy





# Surrogate Mothers, Inc.

*Alternatives to Infertility since 1984. ©*





# Female Infertility - Cervix

- Cervix
  - Post-surgical
    - Stenosis
    - Mucus changes

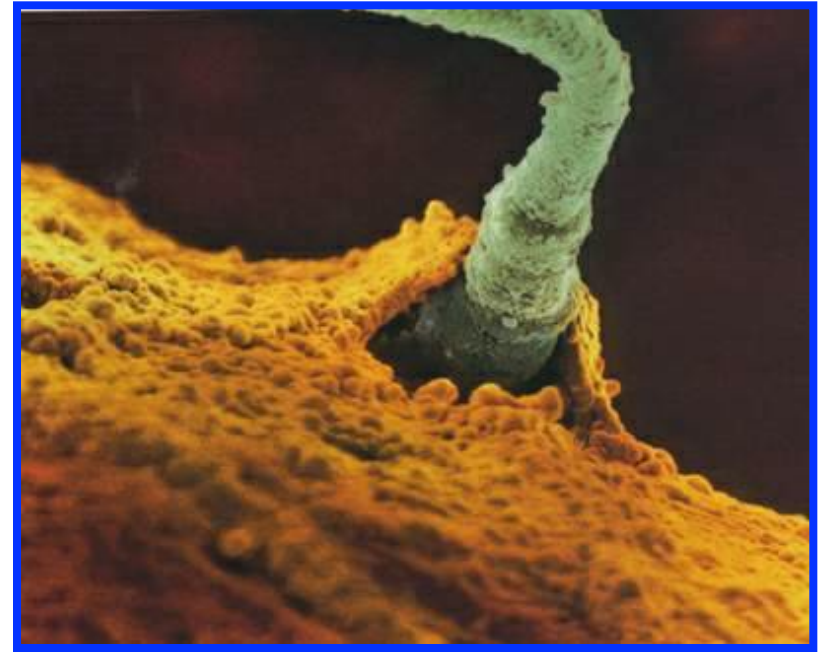
# Female Infertility - Hormones

- Endocrine abnormality (hormones)
  - Thyroid
  - Prolactin
  - Polycystic ovary syndrome (PCOS)
    - Estrogen, insulin
  - Hypothalamic hypogonadism
    - Stress
    - Exercise (ballet dancer)

# Other Causes of Female Infertility

- Other Causes
  - Chromosome abnormalities
    - Turner's syndrome (XO)
    - Androgen Insensitivity (XY)
      - Male pseudohermaphrodite
      - Female phenotype
      - Blind vaginal canal
      - Inguinal hernia (50%)

# Sperm Are Also Required!!





**Do men continue to produce sperm throughout their life (from puberty until death)?**

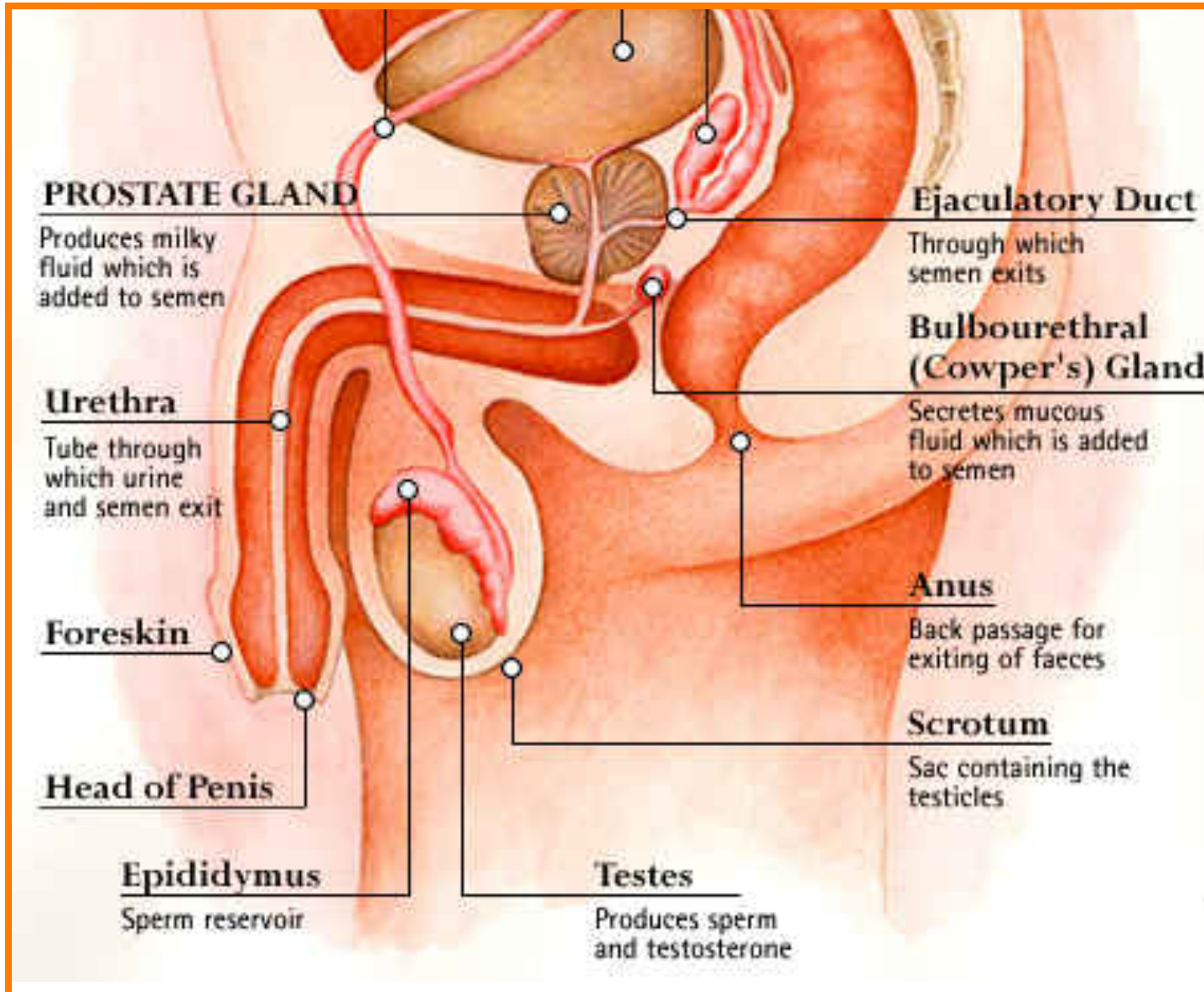
**a. Yes**

**b. No**

# Causes of Male Infertility

- Abnormality in sperm production
- Abnormality in sperm function
- Obstruction in the ductal system

# Male Reproductive Organs

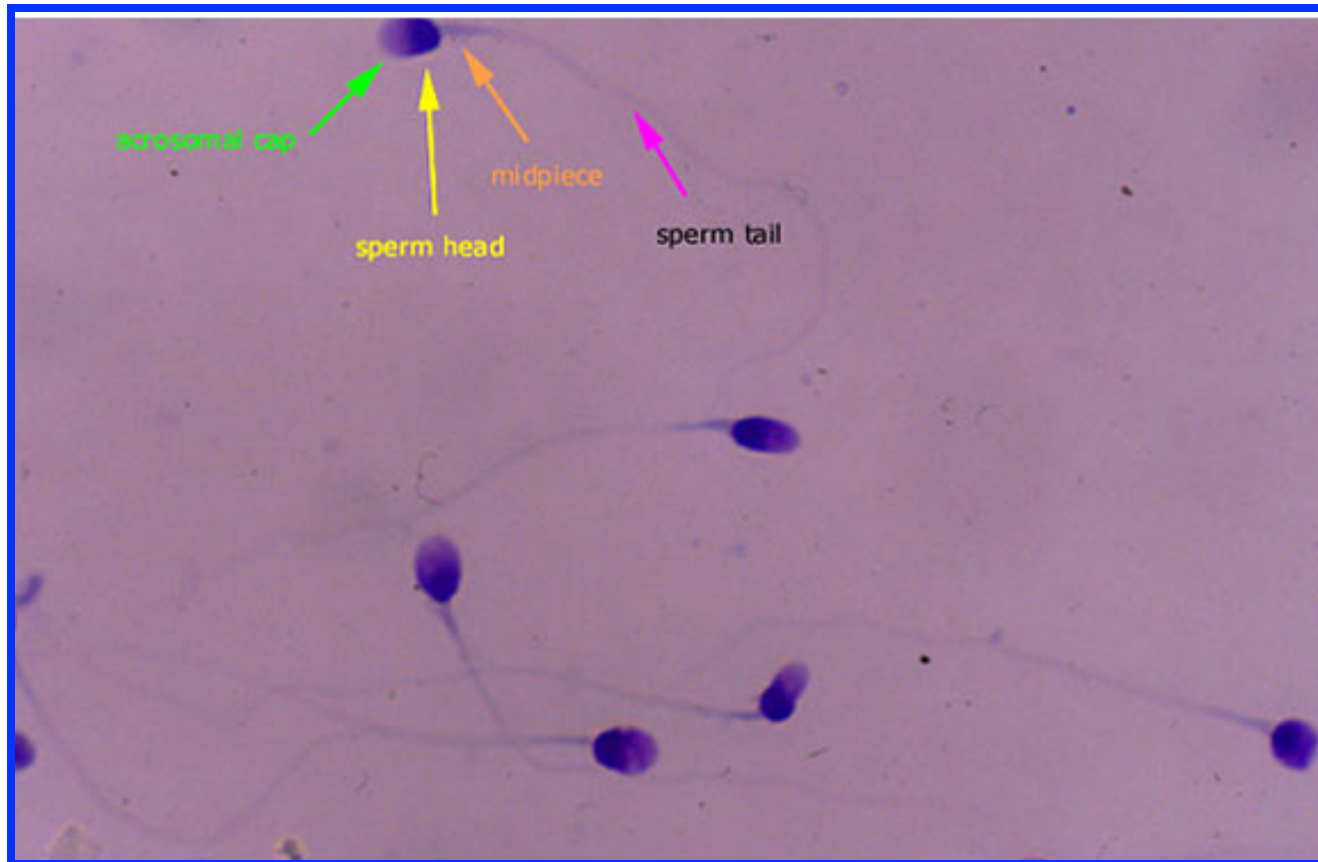


# Sperm: Semen Analysis

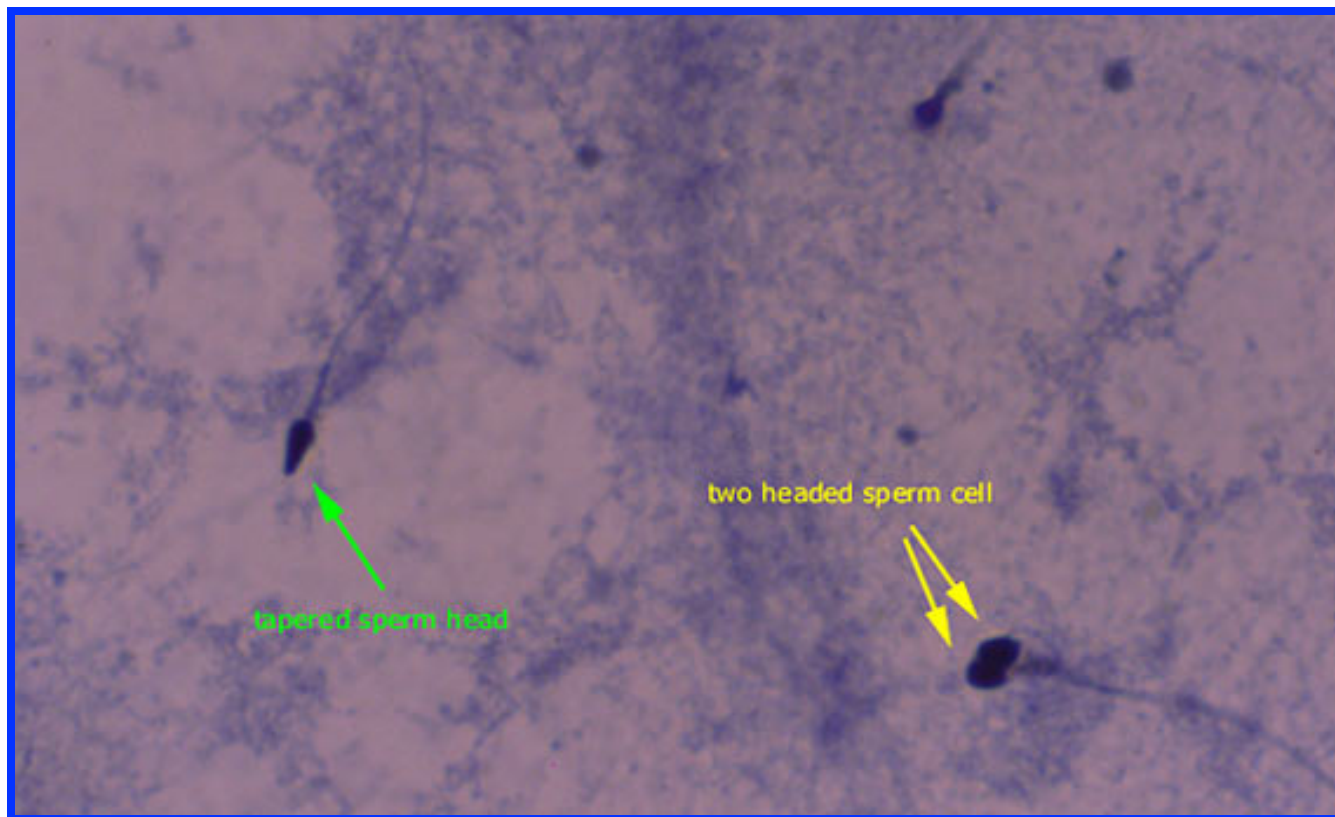
- Volume:  $\geq 2$  mL
- Concentration:  $\geq 20,000,000$  per mL
- Motility:  $\geq 50\%$
- Normal morphology:  $\geq 40\%$  normal
  - Krueger strict criteria:  $\geq 14\%$  normal
  - Best predictor of fertilizing ability



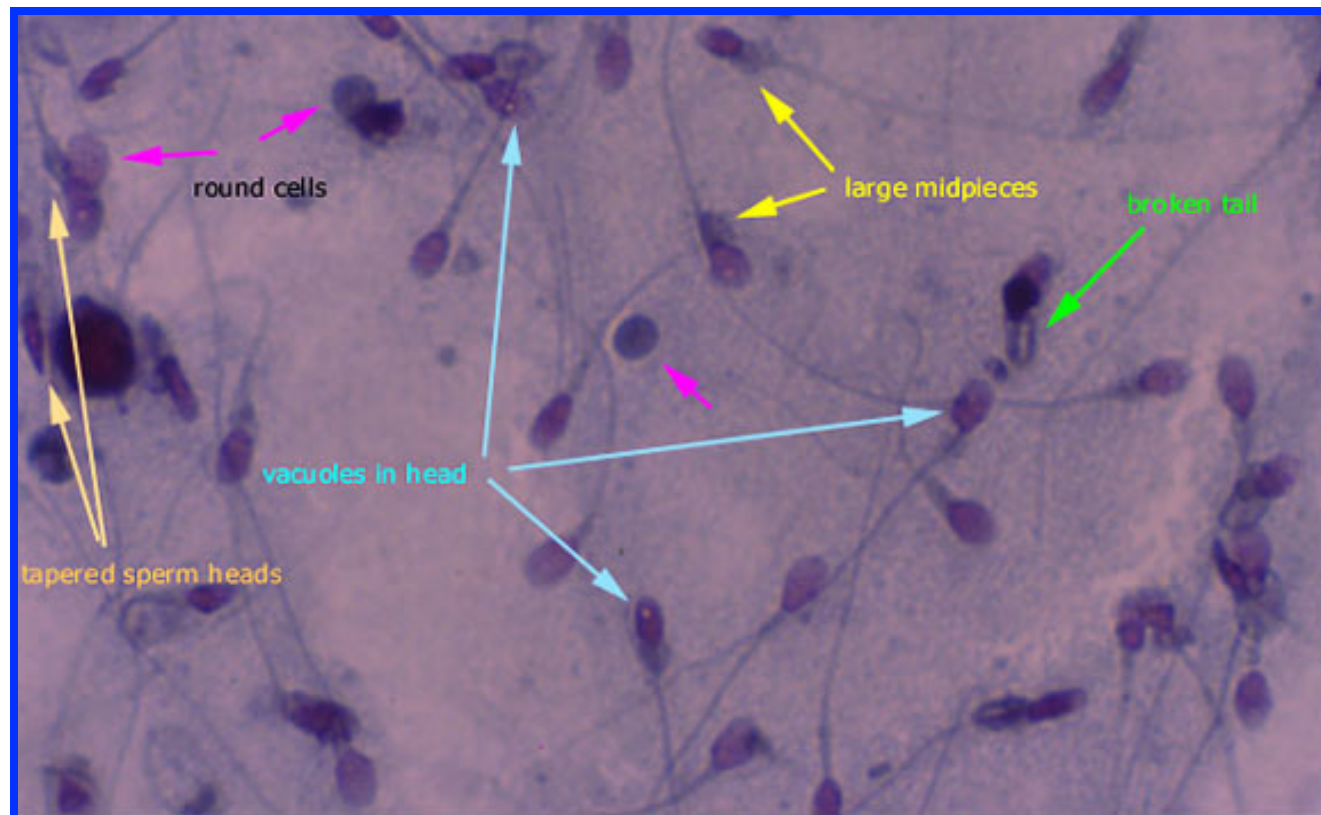
# Normal Sperm Morphology



# Abnormal Morphology



# Abnormal Morphology



# Sperm

- **How many are needed for fertilization?**
- Natural conception
  - 20,000,000
- Intra-uterine insemination
  - 1,000,000
- In-vitro fertilization (IVF)
  - 10,000
- Intra-cytoplasmic sperm injection (ICSI)
  - 1

# Causes of Male Infertility

- Abnormality in sperm production
- Abnormality in sperm function
- Obstruction in the ductal system

# Abnormalities of Sperm Production

- Genetic
  - Y chromosome microdeletions
- Damage to testes – anatomical
  - Cryptorchidism
  - Varicocele
- Infection
  - Mumps orchitis
- Gonadotoxins

# Abnormalities of Sperm Function

- Antisperm antibodies
- Genital tract inflammation
  - prostatitis
- Varicocele
- Failure of acrosome reaction
- Problems with sperm binding/penetration

# Obstructions in Ductal System

- Vasectomy
- Congenital bilateral absence of the vas deferens
- Epididymis/ejaculatory ducts
  - Congenital or acquired





What percentage of men desire another pregnancy after having a vasectomy?

- a. 1%
- b. 5%
- c. 10%
- d. 25%
- e. 100%

# Male Infertility - Lifestyle

- Tobacco
- Marijuana
- Alcohol
- Cocaine
- Steroids (can be permanent)
- Heat
- Exercise

# Infertility: Initial Evaluation

- Eggs
  - Ovulation
  - Egg quality
- Sperm
  - Presence
  - Quality
- Gamete transport/Implantation
  - Hysterosalpingogram

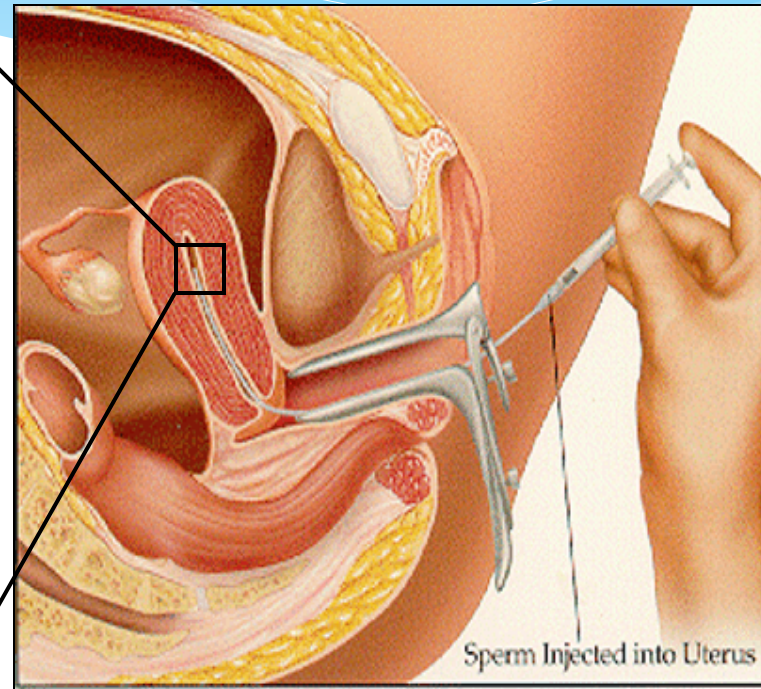
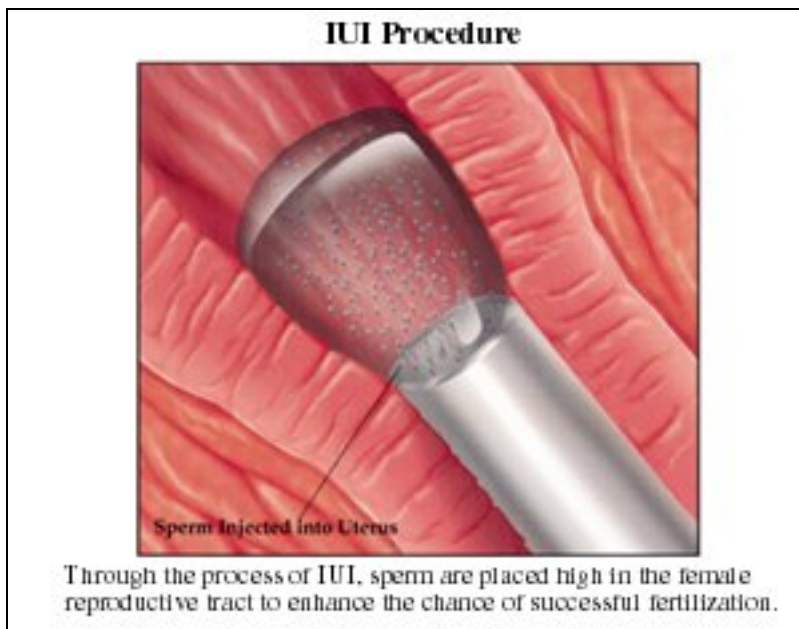
# Unexplained Infertility

- Work-up is negative
- 15-20 % of couples

# Infertility Treatments

- Improve Timing of Intercourse
- Intrauterine insemination (IUI)
  - Clomiphene citrate + IUI
  - FSH + IUI
- In Vitro Fertilization (IVF)
  - “Standard” IVF
  - Egg donation + IVF
  - Egg Freezing + IVF

# Intrauterine Insemination (IUI)



## Goal is to Maximize the Chance of Fertilization

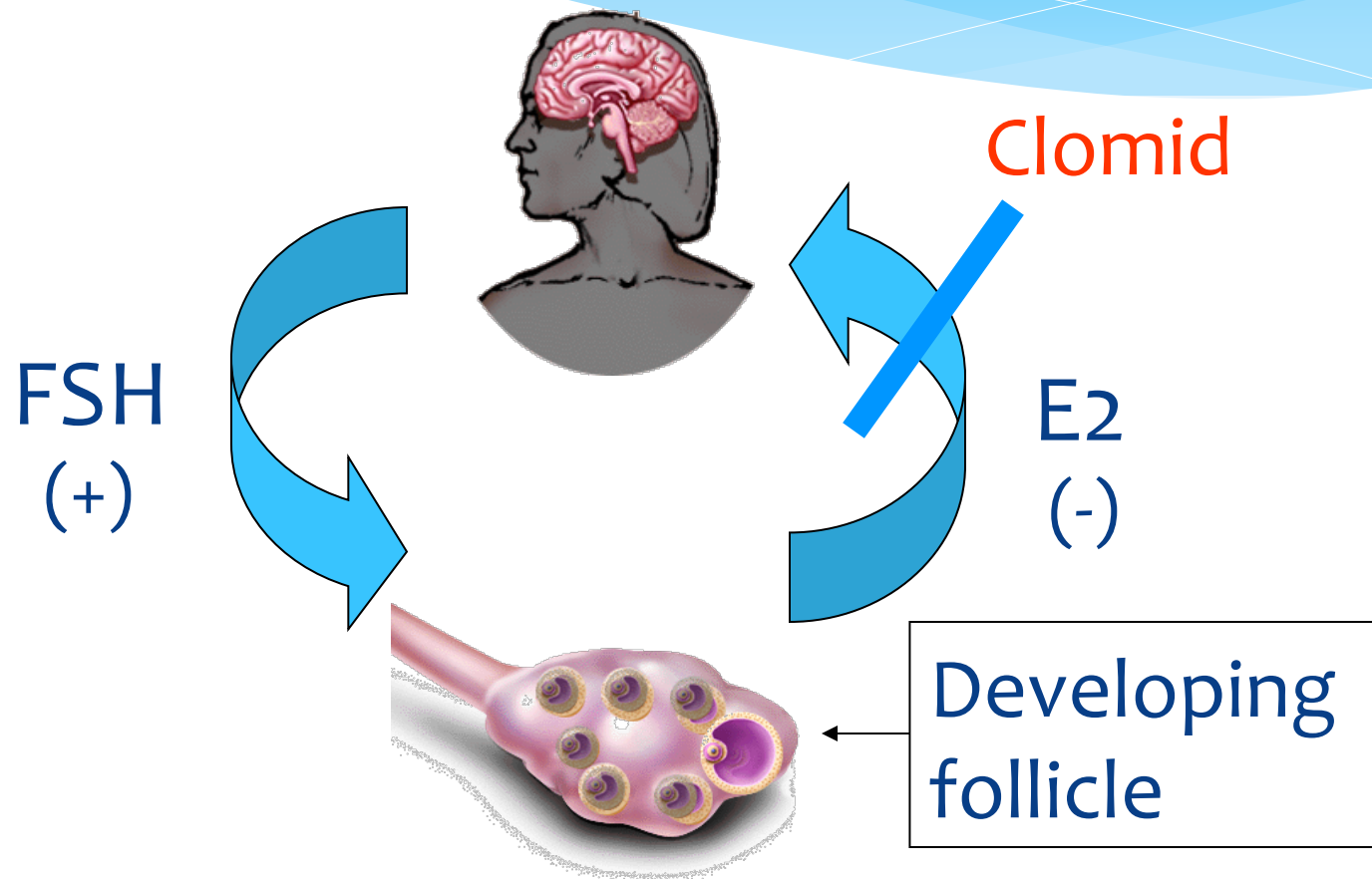
- Increase Number of Eggs
- Position Sperm Closer to Eggs

# Infertility Treatment Options

- IUI, FSH or FSH + IUI
- Patients with unexplained infertility

<b>Treatment</b>	<b>Cycles</b>	<b>Pregnancy</b>	<b>Pregnancy per cycle</b>
<b>IUI</b>	<b>30</b>	<b>1</b>	<b>2.7%</b>
<b>FSH</b>	<b>49</b>	<b>3</b>	<b>6.1%</b>
<b>FSH+IUI</b>	<b>34</b>	<b>9</b>	<b>26.4%</b>

# How Does Clomid Work To Increase Egg Number?

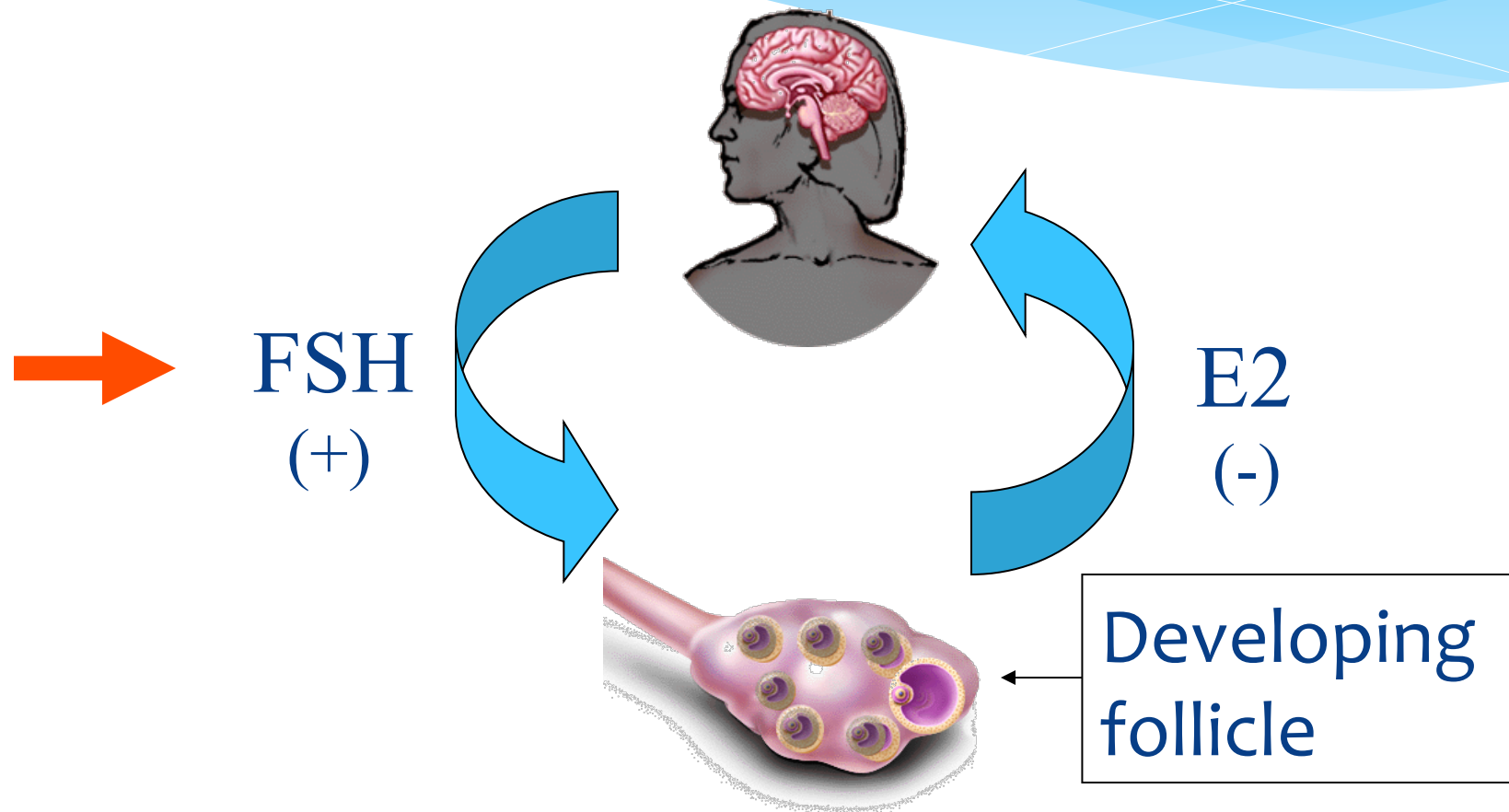


FSH=Follicle Stimulating Hormone

E2=Estradiol



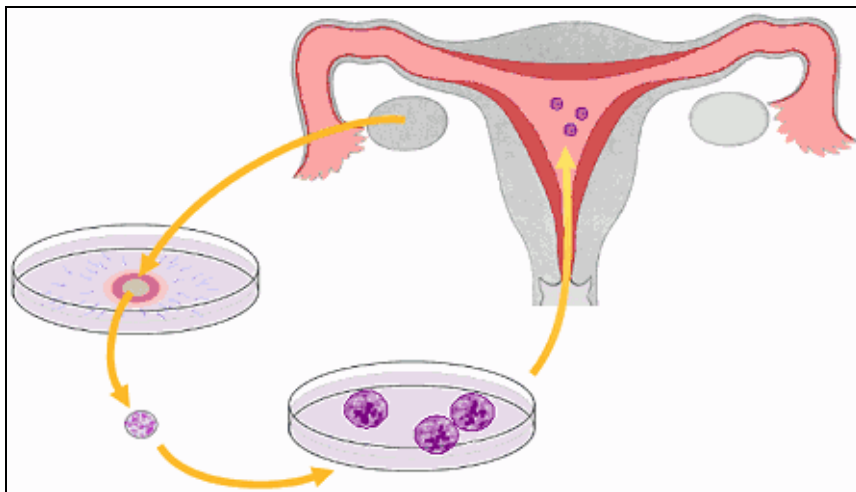
# How Does Recombinant FSH Work To Increase Egg Number?



FSH=Follicle Stimulating Hormone

E2=Estradiol

# In Vitro Fertilization



# Why In Vitro Fertilization?

- **Infertility**
- **DNA Testing**
  - **Genetic Disorders**
  - **Gender Selection**
- **Lesbian-Gay Couples**



**Who should decide if a couple/person can have infertility treatment?**


- a. state governments**
- b. national fertility agencies (ASRM)**
- c. reproductive specialists**
- d. psychologists/psychiatrists**
- e. the couple/person**



**Should a 52 year old postmenopausal woman be able to use her daughter's eggs to have a child with her new 28 year old husband?**

**a. Yes**

**b. No**



**Should a woman be able to have sperm  
extracted from her husband's newly dead  
body so that she can have "their child"?**

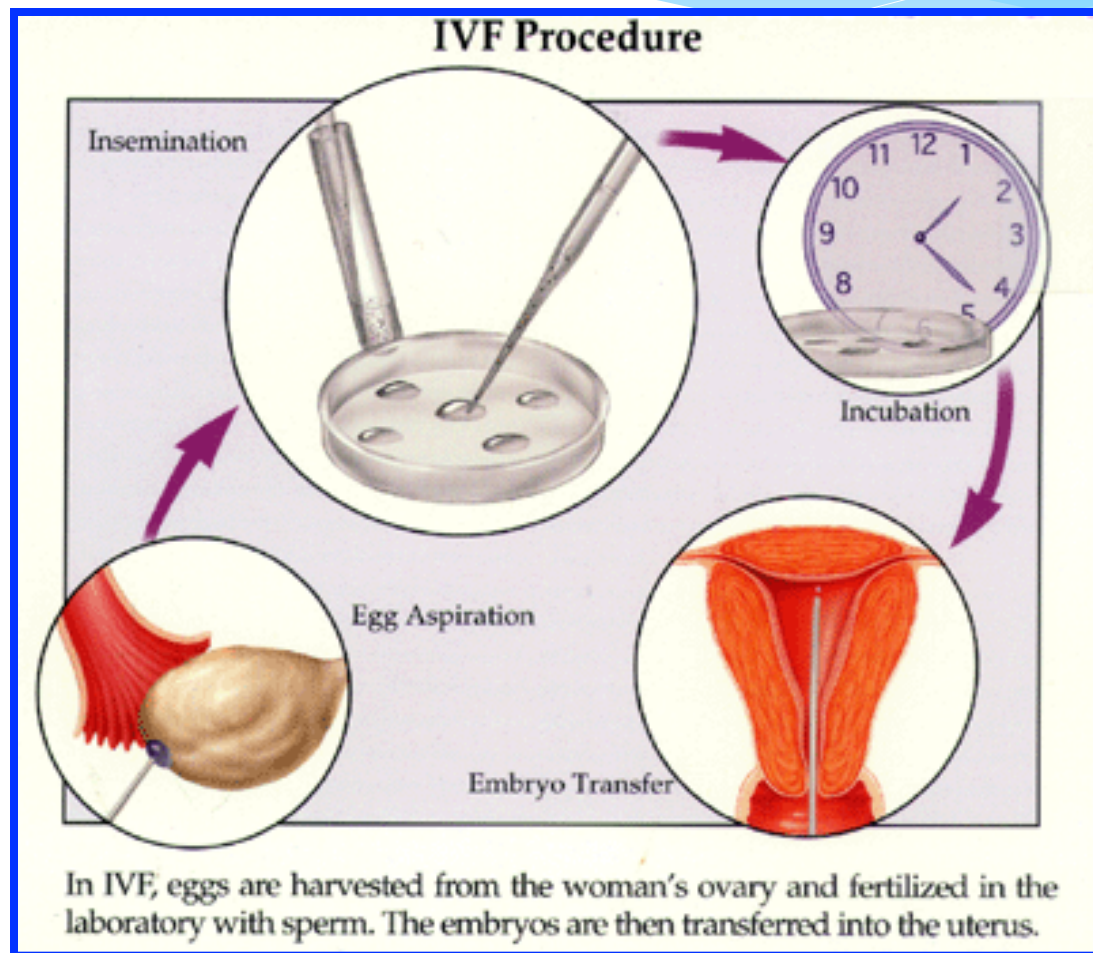
**a. Yes**

**b. No**

# In Vitro Fertilization - History

- 1978 – First “test tube” baby was born in England
- 1981 – IVF in U.S.
- Started with GIFT and ZIFT
- 2008 - >98% IVF with transfer of embryo to uterus

# In Vitro Fertilization (IVF)





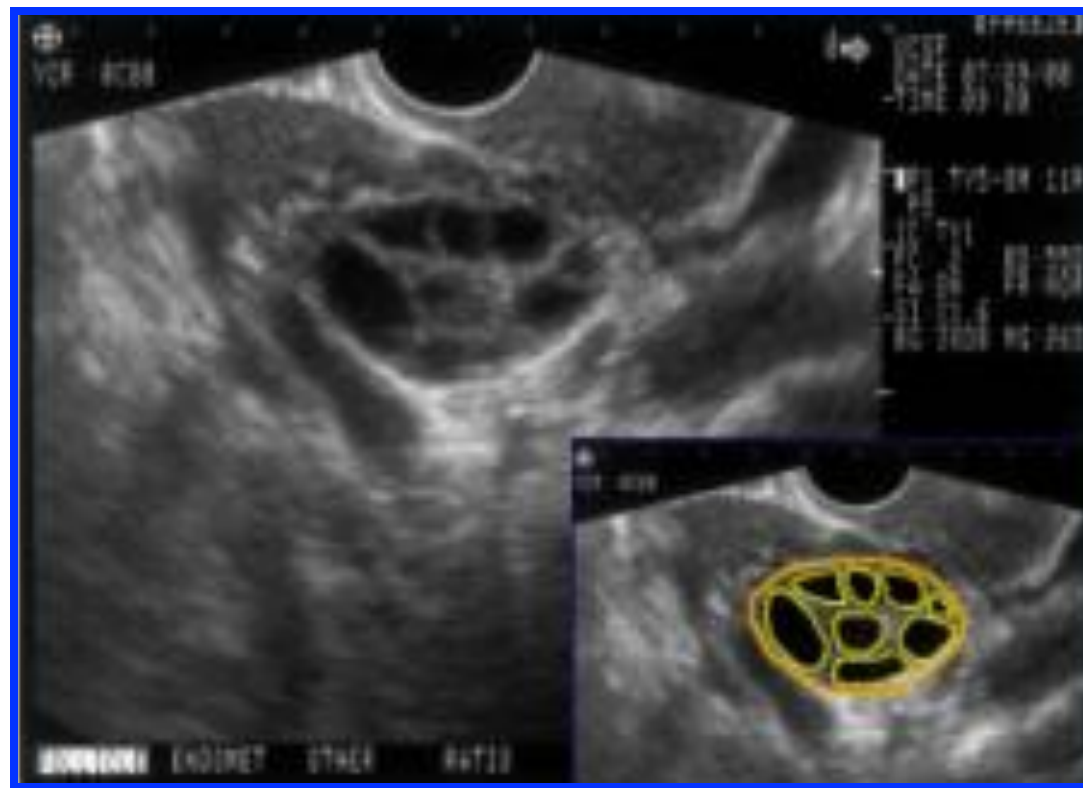
# IVF Statistics-2008

- **475 U.S. clinics offer IVF** (436 reporting data to CDC)
- **148,055 cycles of ART treatment**
- **9,649 donor oocyte cycles**
- **46,626 deliveries (birth of 61,426 infants)**

# Who Needs IVF?

- Failed other treatments
- Tubal damage
- Significant male factor
- Absent uterus
- Carriers of genetic diseases
- Gender selection
- Cancer patients
- Lesbian-Gay Couples

# Ovarian Hyperstimulation



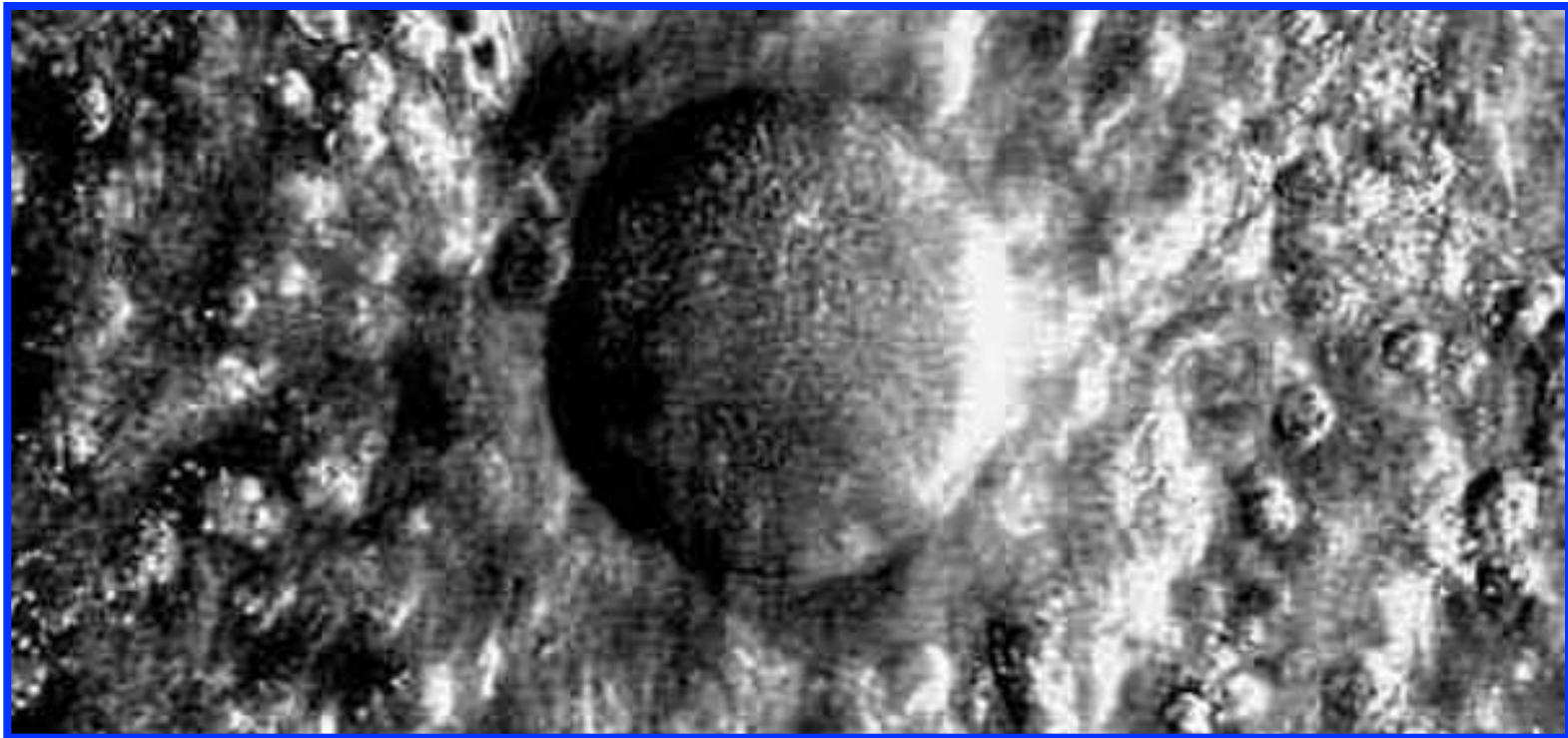
# Egg Retrieval



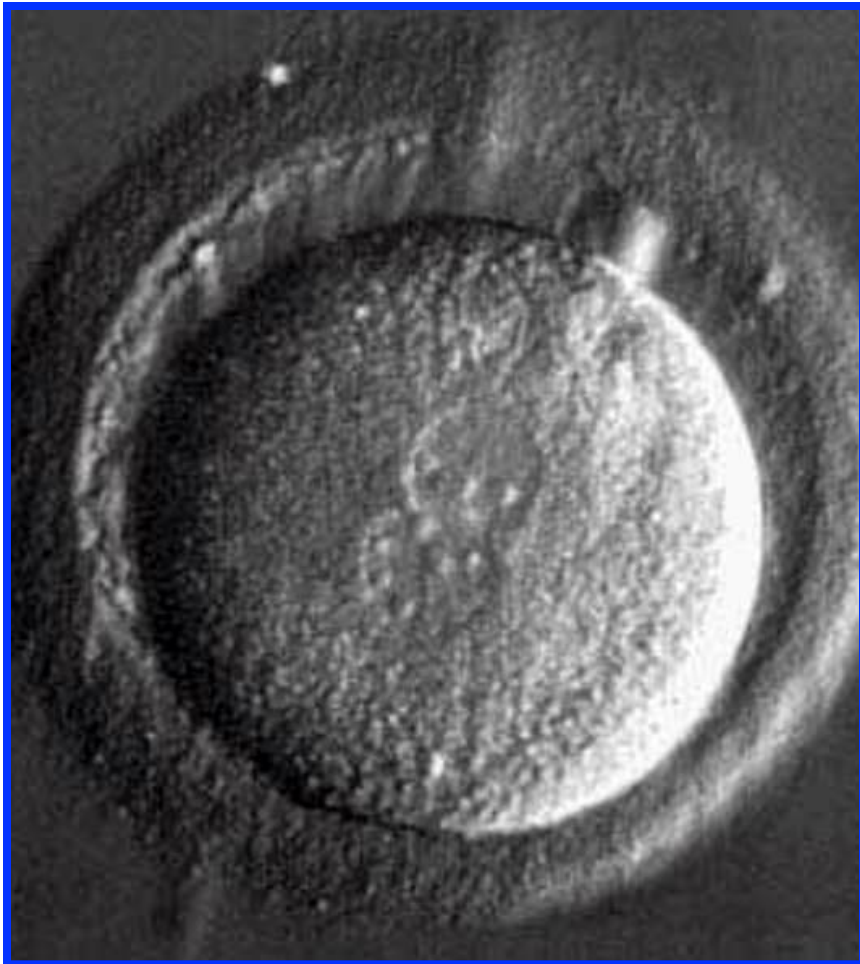
# Good Egg



# Bad Egg

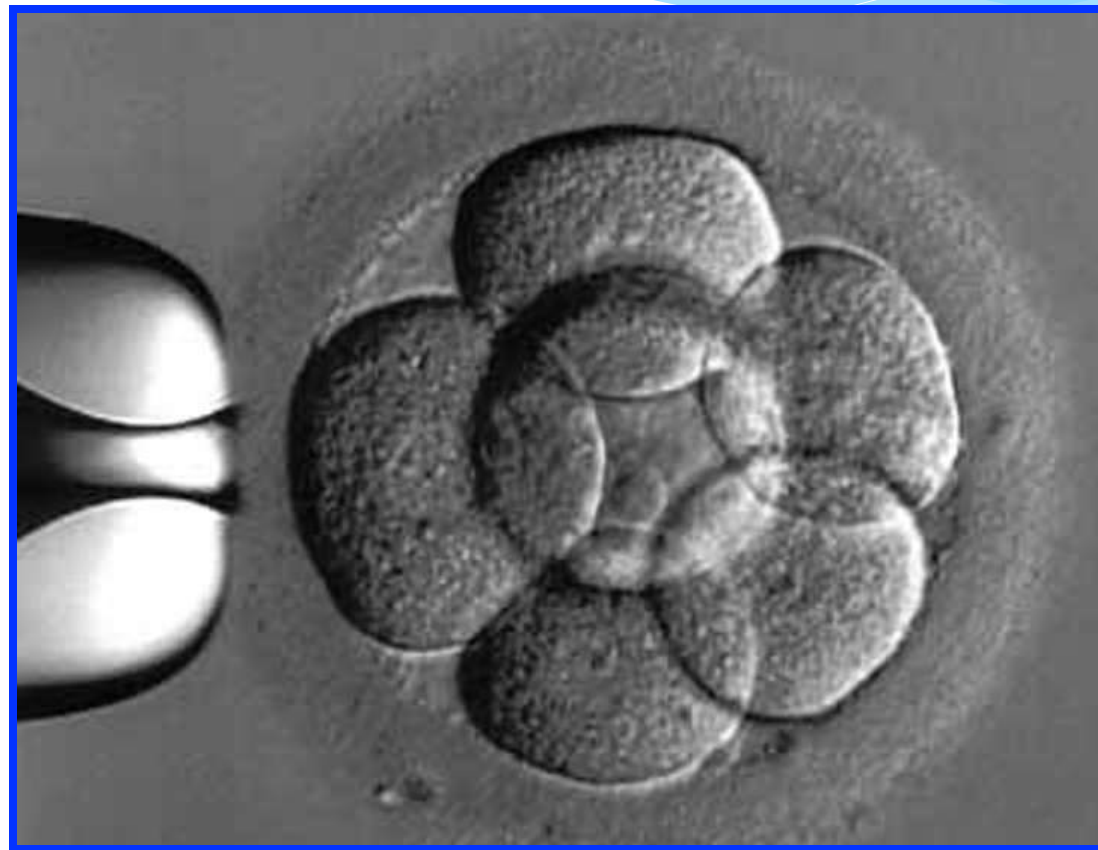


# Fertilization



- 2 Pronuclei (2PN)
- 1 day after egg retrieval

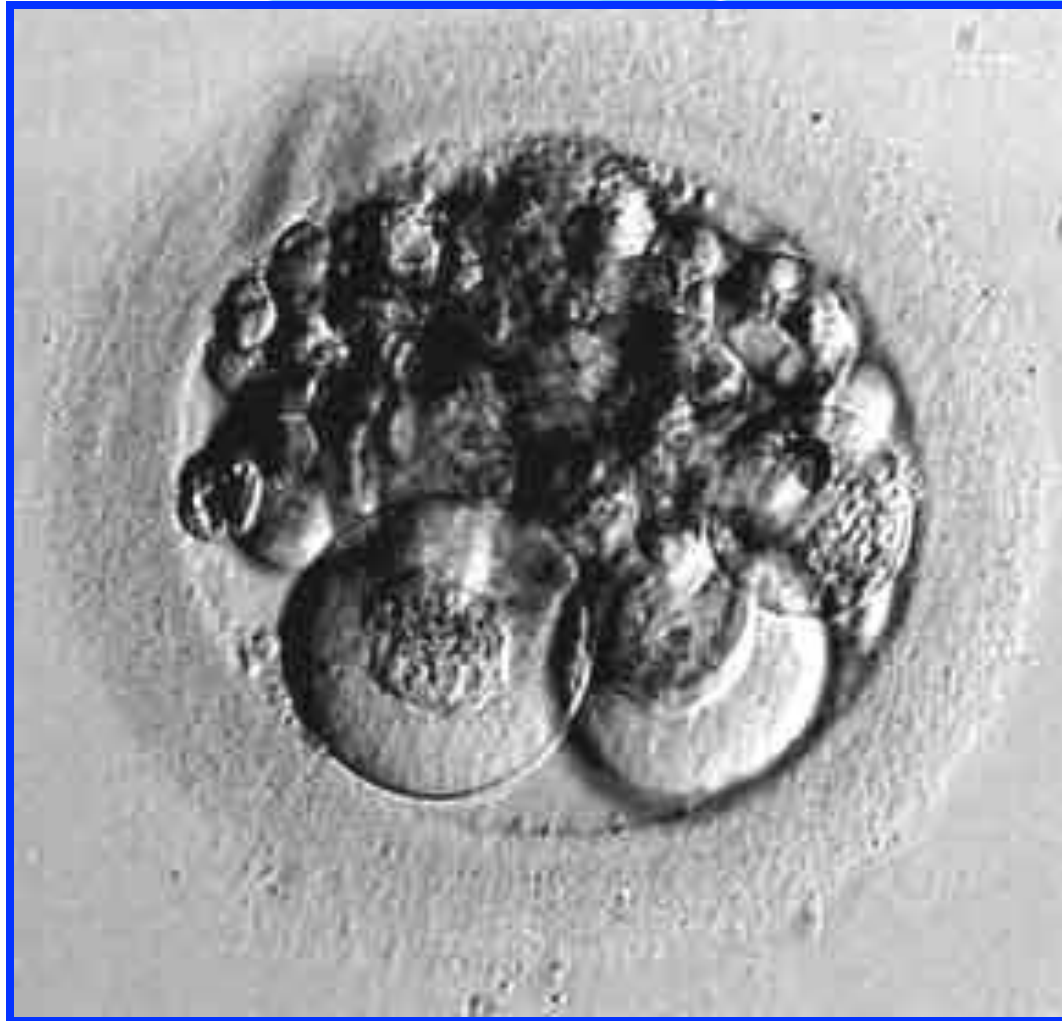
# Day 3 Embryo



**Pre-Implantation Genetic Testing Stage**



# Day 3 Embryo



# Blastocyst – Day 5

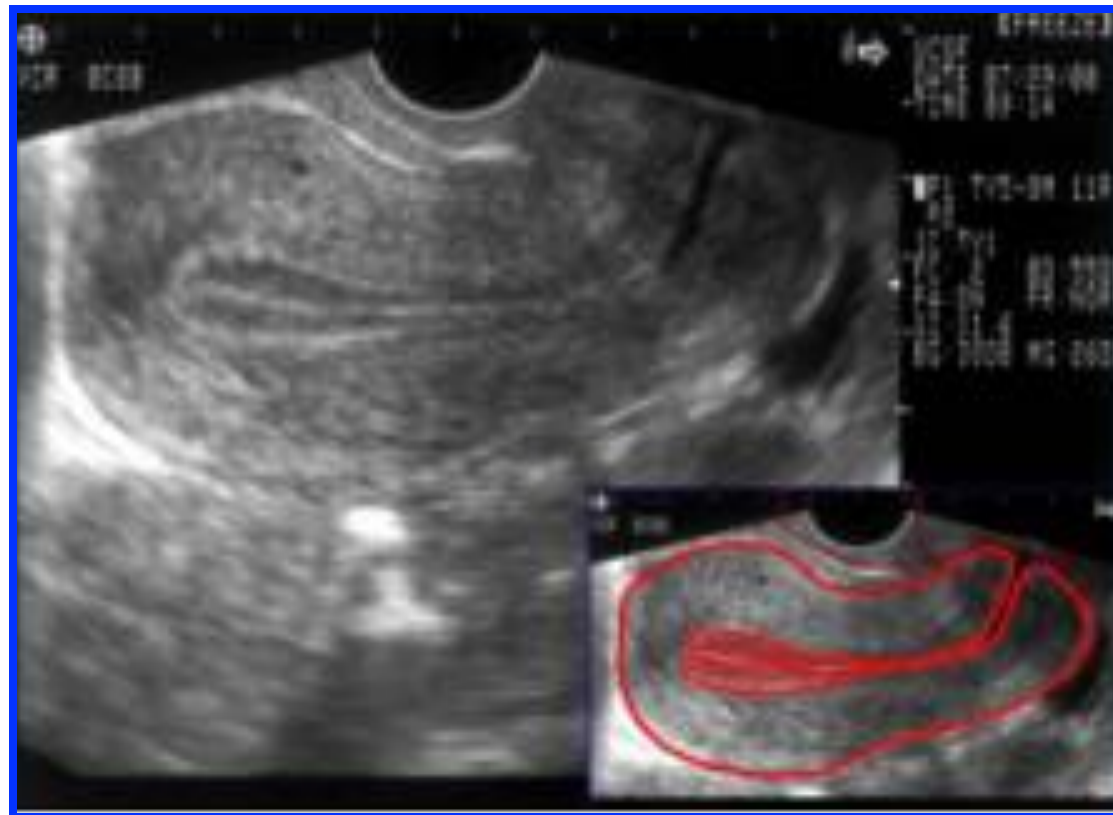


**Source of Stem Cells**

# Hatching Blastocyst



# Embryo Transfer



# Special IVF Procedures

- Assisted hatching
- Intracytoplasmic sperm injection (ICSI)
- Preimplantation genetic diagnosis (PGD)
- Freezing
- Egg donation
- Surrogacy

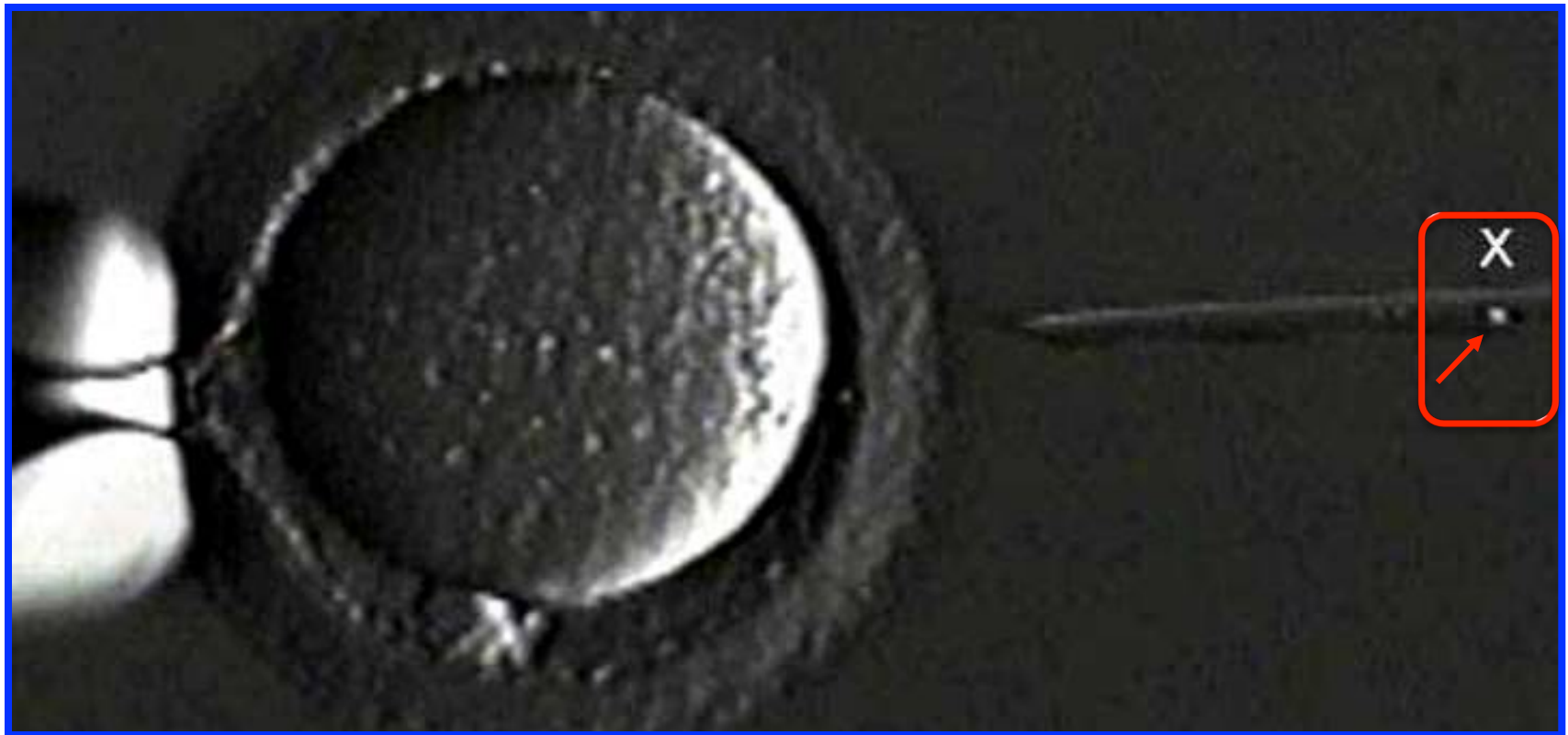
# Assisted Hatching



# Empty Zona

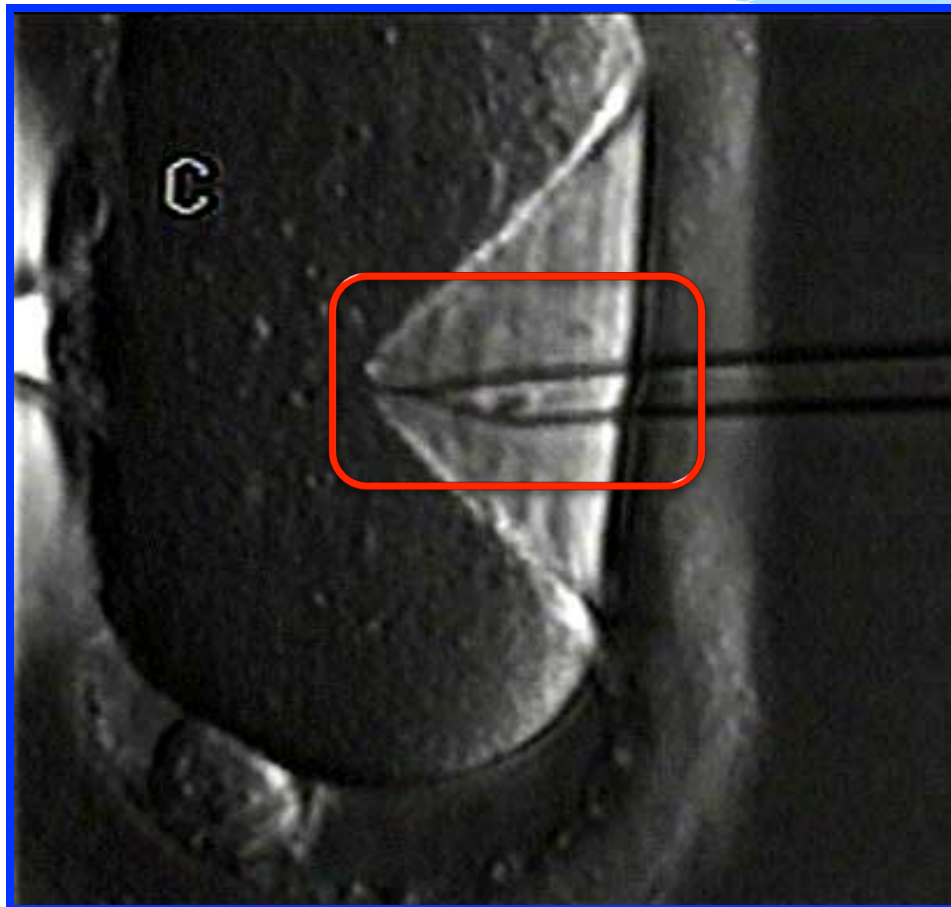


# ICSI

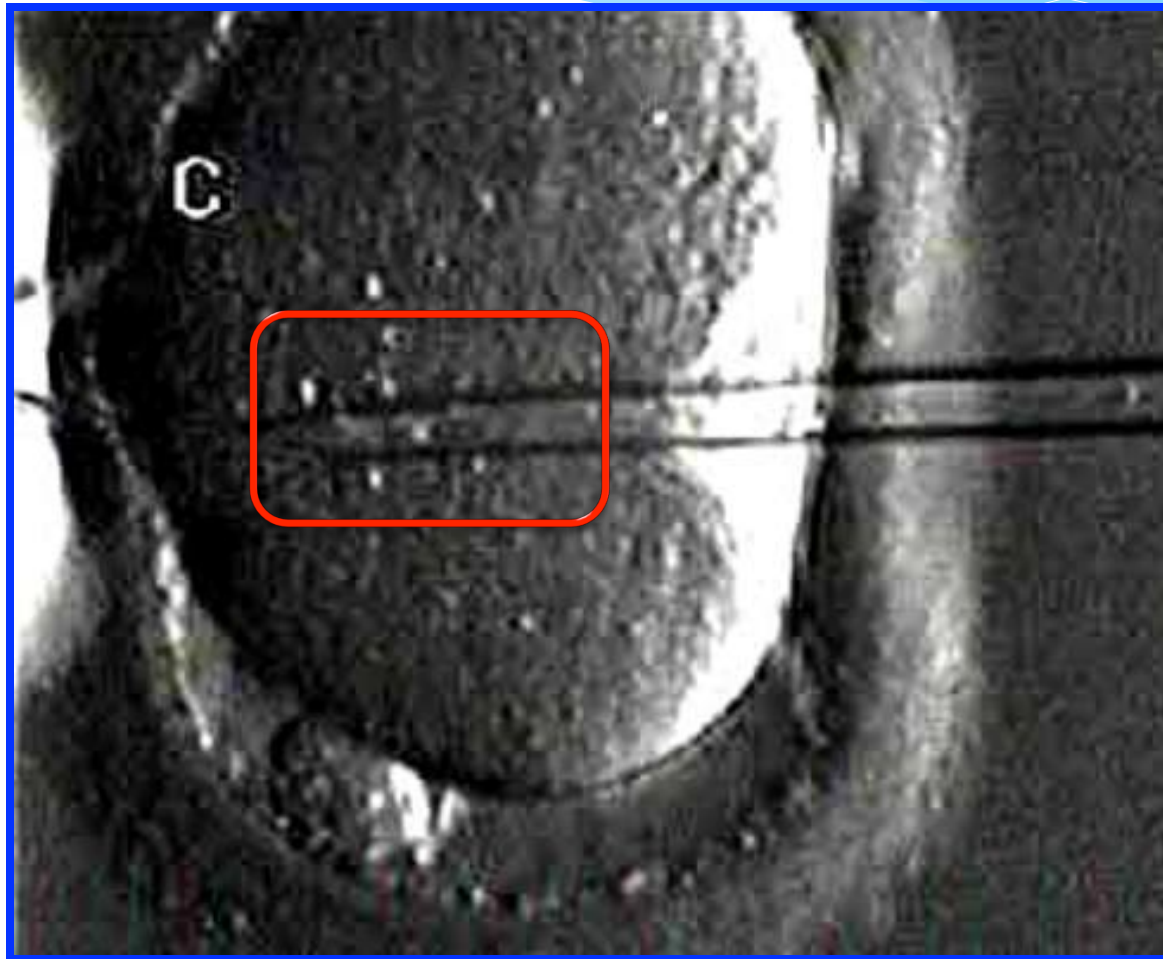




# ICSI



# ICSI





## **What are the risks of IVF?**

- a. bleeding requiring blood transfusion**
- b. pelvic infection**
- c. increased risk of congenital anomalies**
- d. multiple pregnancies**
- e. all of the above**



**How many embryos are recommended to transfer into a 42 year old woman's uterus?**

- a. 1**
- b. 2**
- c. 3**
- d. 4**
- e. 5**



## **Who should decide how many embryos are transferred?**

- a. The Doctor**
- b. The Couple/Person**
- c. American Society of Reproductive Medicine**
- d. Government**
- e. Religious Leaders**

# How Many Embryos are Transferred?

- **Related to age and embryo quality**
  - **<35 = 2**
  - **35-37 = 2-3**
  - **38-40 = 3-4**
  - **>40 = up to 5**
  - **For patients with 2 or more failed IVF cycles, or a poor prognosis, can add more based on clinical judgment**

# What Happens to the Other Embryos?

- **Freeze Embryos**
- **Donate For Research/Stem Cells**
- **Embryo Adoption**
- **Discard**



## **What Would You Do With Your Embryos?**

- a. Freeze and Store Them**
- b. Donate For Research (e.g., Stem Cells)**
- c. Donate To Others For Adoption**
- d. Discard**



# IVF Success Rates - 2008

- **U.S. Fertility Centers From SART/CDC**
- **Female age**
  - **25 – 47%**
  - **30 – 48%**
  - **35 – 41%**
  - **40 – 27%**
  - **44 – 8%**
  - **> 44 – 3%**

# IVF Statistics - 2008

- **68% singletons (41,770)**
- **32% twins (19,566)**
- **2% triplets (1,229)**
- **0.2% higher order multiples (123)**



# Twin Pregnancy



# Triplet Pregnancy



# IVF and Multiple Pregnancy

- **Maternal complications**
- **Fetal complications**
- **Cost**
- **“Selective reduction”**
- **Single embryo transfer vs. success rates**
- **Divorce**

# Cost of IVF

- IVF cycle + medications = \$10,000-15,000
- Assisted hatching = \$500
- ICSI = \$1,500
- Freezing = \$650
- Storage = \$360
- PGD = Minimum \$3,000
- Egg Donor = Minimum \$5,000
- Surrogate = Minimum \$20,000

**Not Covered By Insurance In Most States!**

# Egg Donation

Give The Gift Of Life...  
And Make A Difference



## EXCEPTIONAL DONORS

Exceptional Donors, Inc. was founded to help couples struggling with the pain of infertility in the Portland, Oregon area and throughout the United States. Egg donation is a wonderful way for families to grow. And we can help. Allow us to assist you as you begin your journey toward becoming a parent.

We are always searching for exceptional donors. If you are between 19 and 32 years of age, healthy, intelligent, athletic, artistic, musically talented, attractive, or possess other exceptional qualities, you could be a candidate for our program.

We offer \$5,000 compensation for first-time donors, and more for subsequent donations.

*Call 866.296.1015 or visit [www.exceptionaldonors.com](http://www.exceptionaldonors.com)  
to learn more about becoming an exceptional egg donor.*





**Would you consider being an egg or sperm donor?**

**a. Yes**

**b. No**



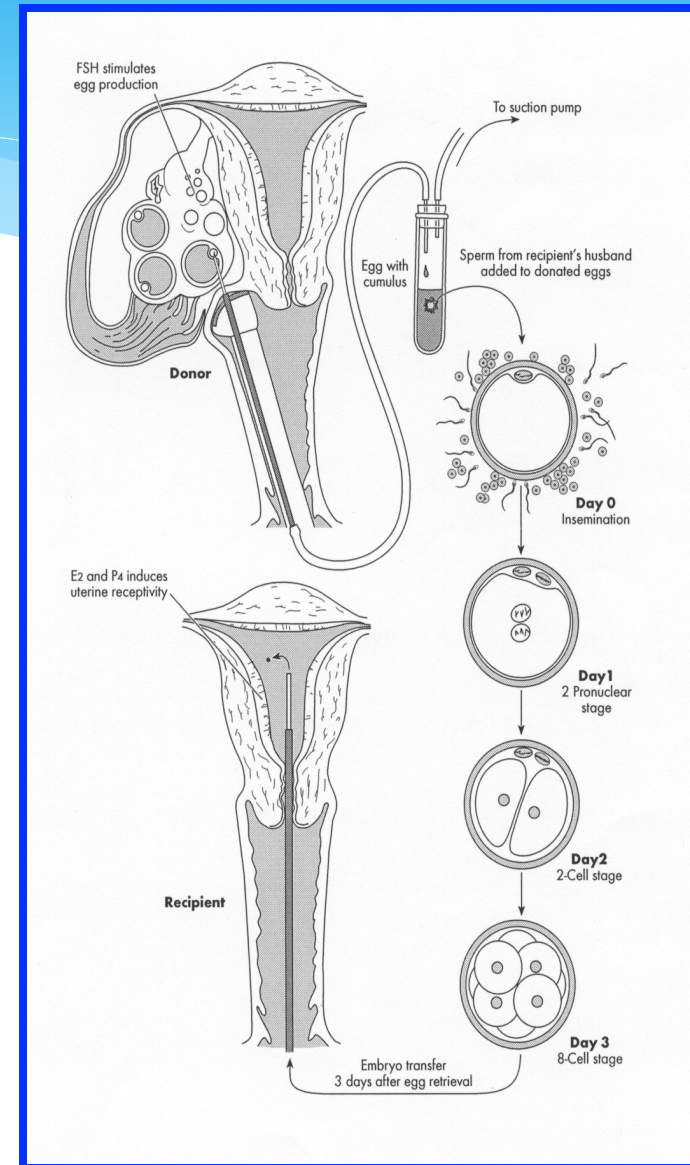
**Have you ever been an egg or sperm donor?**

**a. Yes**

**b. No**

# Egg donation

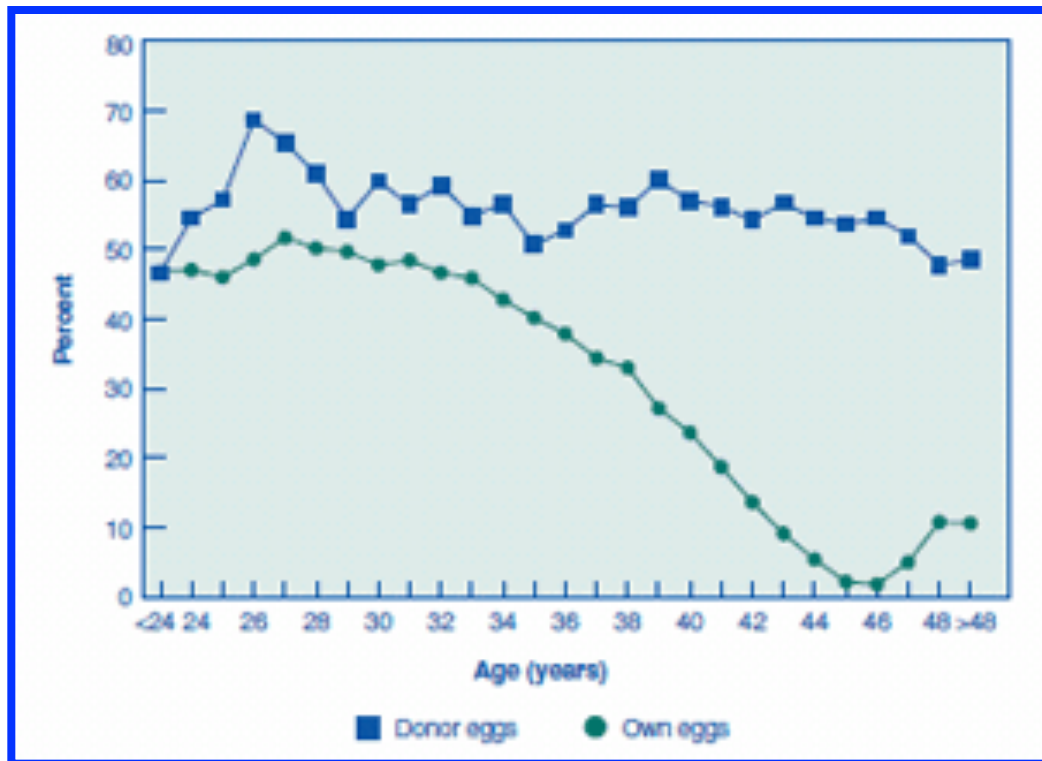
- IVF for two
  - Standard controlled ovarian hyperstimulation
  - Egg retrieval
- Donor
  - Standard controlled ovarian hyperstimulation
  - Egg retrieval
- Recipient
  - Embryo transfer



# Who are candidates to be an egg donor?

- 21-31 years old (older if a friend or relative)
- FSH <10
- Negative donor
- Good health and genetic history
- Preferably prior egg donation experience
  - How many eggs were produced?
  - Did pregnancy result?

# Current status of ART in the USA



Live birth rates per transfer for fresh embryos from own and donor eggs, by age of recipient

# Egg Donation

- October 23, 1999
- Selling Fashion Models' Eggs Online Raises Ethics Issues  
By CAREY GOLDBERG
- CAMBRIDGE, Mass. -- To the horror and disgust of mainstream infertility groups, a longtime fashion photographer has begun offering up models as egg donors to the highest bidders, auctioning their ova via the Internet to would-be parents willing to pay up to \$150,000 in hopes of having a beautiful child.

# Egg Donation - Ethical Issues

- Egg Donor
  - Known or anonymous
  - How many times to donate?
- Recipient
  - How old is too old?

# Pregnancy in the Sixth Decade of Life

- USC experience: 1991-2000
  - 77 recipients of egg donation
  - Mean age 52.8 + 2.9 years
- Of the 77 women, 42 (54.5%) had live births
- 45 deliveries in 42 women



# Pregnancy in the Sixth Decade of Life: Obstetric Complications

- Pre-eclampsia
  - 35%
- Background Incidence
  - 3-10%
- Gestational Diabetes
  - 20%
- Background Incidence
  - 5%

# How old is too old?

- Is 55 a “physiological limit” ?
  - Marked increase in pre-eclampsia
  - Increase in diabetes



## How old is too old to carry a pregnancy?

- a. 44 (rare natural pregnancies occur later)
- b. 51 (average age of menopause in U.S.)
- c. 65 (social security/retirement)
- d. No limit

# Genetic Testing



- Preconception
- Preimplantation
- Prenatal
- Postnatal



# Preconception Counseling

- Offered to all women
  - ❑ Prenatal vitamins – 400 micrograms folic acid/day
  - ❑ Rubella immunity
  - ❑ Varicella immunity
  - ❑ Blood Type/Rh status
  - ❑ HIV
  - ❑ Hepatitis B and C screening
  - ❑ Genetic screening for over 100 mutations

# Preconception Counseling

- Offered to certain ethnic groups
  - Mediterranean – thalassemia
  - African-American – sickle-cell anemia
  - Caucasian/Hispanic – cystic fibrosis, SMA
  - Ashkenazi Jews – 7 autosomal recessive disorders
    - Gaucher disease (1/13), Tay-Sachs (1/30), Familial dysautonomia (1/30), Canavan disease (1/40), Fanconi anemia (1/89), Niemann-Pick disease (1/90), Bloom syndrome (1/100)

# The Universal Genetic Test



# The Universal Genetic Test



January 29, 2010 New York Times

## Firm Brings Gene Tests to Masses

By [ANDREW POLLACK](#)

REDWOOD CITY, Calif. — The new movie “Extraordinary Measures” is based on the true story of a father who starts a company to develop a treatment for the rare genetic disease threatening to kill two of his children before they turn 10.

Now, a Silicon Valley start-up is making the bold claim that it can help eradicate that disease and more than 100 others by alerting parents-to-be who have the carrier genes.

The company, Counsyl, is selling a test that it says can tell couples whether they are at risk of having children with a range of inherited diseases, including [cystic fibrosis](#), Tay-Sachs, [spinal muscular atrophy](#), [sickle cell disease](#) and Pompe disease (the one afflicting the children in the movie).

Once informed, Counsyl says, couples can take steps like using in vitro fertilization with genetic testing of the embryos, to avoid bearing children who would have the diseases, many of which are incurable and fatal in childhood.

Some genetic testing of prospective parents is done now, but only for a few diseases like cystic fibrosis and Tay-Sachs, and only for certain ethnic groups. Each test can cost hundreds or even thousands of dollars.

Counsyl’s test, which analyzes DNA from saliva samples, costs \$349 for an individual or \$698 for a couple. Similar tests from others are on the way, experts say. The trend shows that new technology could make possible widespread screening for the risk of passing on rare diseases, something that was simply not practical before.



# ACOG Carrier Screening Guidelines



Couples  
planning a  
pregnancy



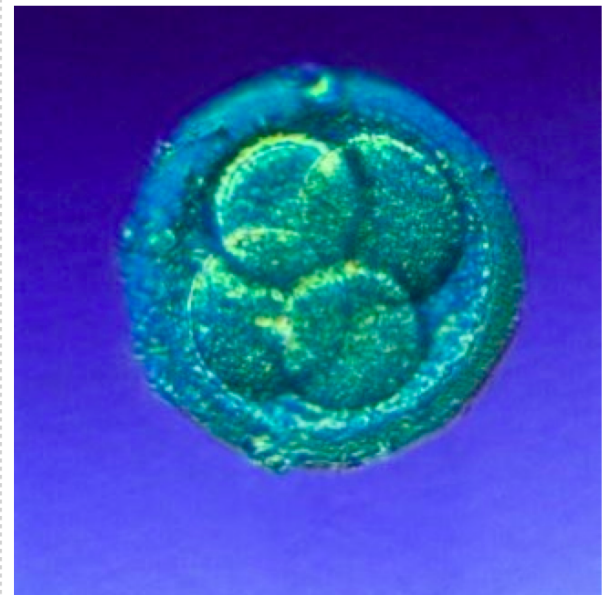
Women in first  
or second  
trimester



Individuals with  
family history

# Counsyl and IVF

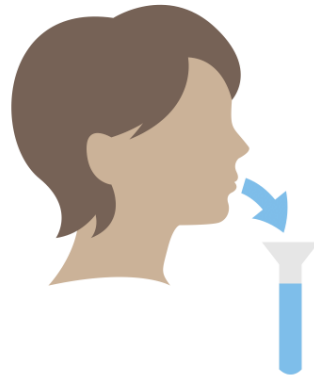
- Quickly identify couples able to benefit from PGD
- Free consultations with board-certified Genetic Counselors



# How the test works



Order online  
and we'll send  
you kits



Patients spit  
into collection  
tubes



Send the kit to  
Counsyl's lab



MD gets an  
email when  
results are  
ready

# Saliva is the new Gold Standard

- Results from saliva (99.9%) are equivalent or superior to results from blood (99.9%)
- Collection kits can be stored at room temperature
- Collected saliva **stable at room temperature (24C) for 1 year**, owing to chemical released by lid during collection



# Instant setup at your clinic



All you need is a  
web browser



Saliva collection  
takes only a few  
minutes



## *Papa Hen*

- ⌘ Papa is Ashkenazi Jewish. He has no known family members with genetic disease.
- ⌘ Papa's DNA Test shows that he is a carrier for Familial Dysautonomia.

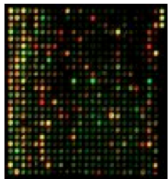
Clear, easy-to-  
read results  
available online

# How the chip works



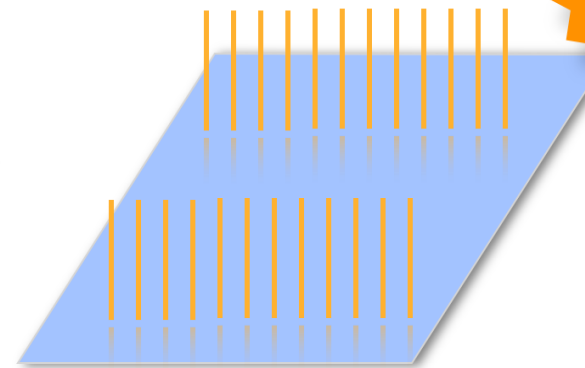
## Screen for 100+ Genetic Disorders

Extracted  
and  
Amplified



**Gene Chip**

• Strands are complementary  
DNA fragments for the mutation  
of interest



↑  
Chip Surface

1000s  
of strands  
per chip



*Jane Doe*



Jane Doe's DNA test shows that she is a carrier of familial dysautonomia.



*John Doe*



John Doe's DNA test shows that he is a carrier of familial dysautonomia.



## *Child Risk Summary*



Based on your DNA test results and ethnicities, your child is at increased risk to inherit the disease below. The following pages contain detailed information about your results as well as next steps to take.



### **Familial Dysautonomia**

Child Risk: 1 in 4. Risk before testing: 1 in 3,800.

Sample Report - Front Page

# Counsyl by the Numbers

100+

One test, 100+ serious Mendelian disorders

99.9%

99.9%+ accuracy for targeted mutations



Deep coverage for all ethnicities



# Result Distribution

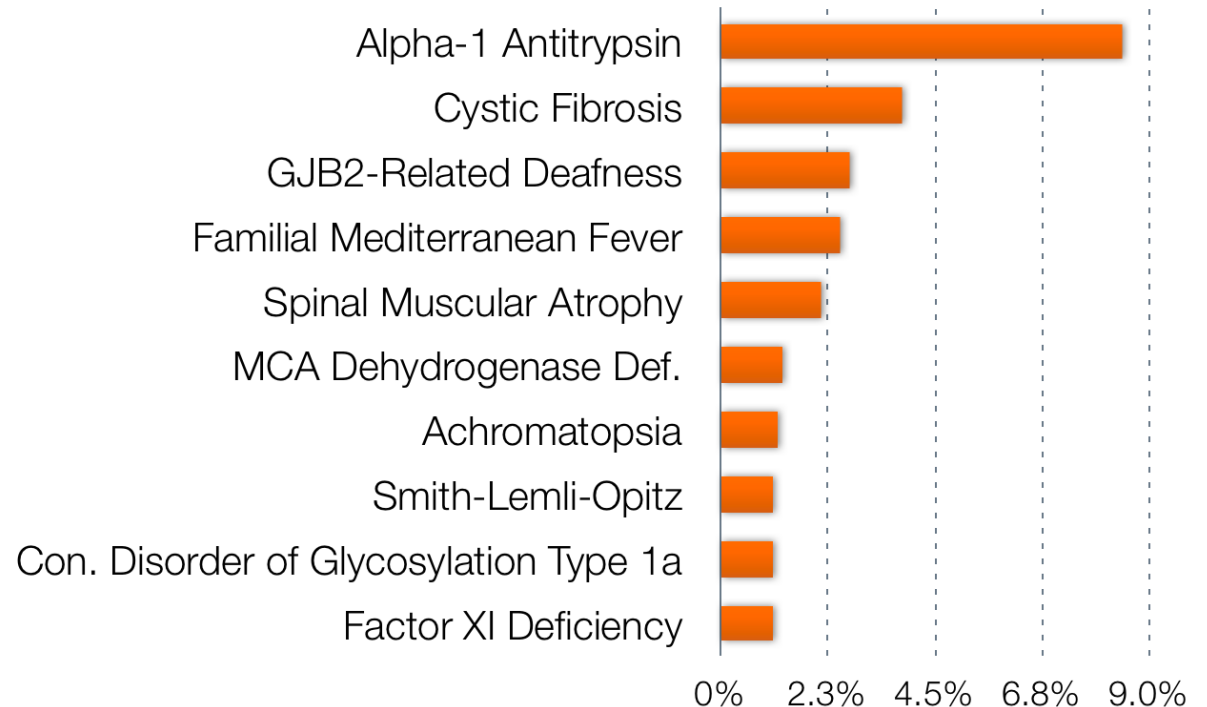
20-31% of individuals testing positive for at least one condition

Top 5 conditions account for 62% of positives

Top 10 conditions account for 80% of positives

Complimentary genetic counseling available

Distribution of Positives



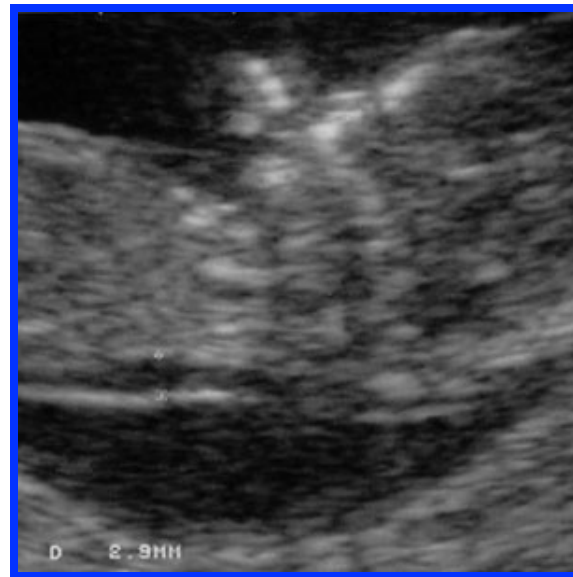
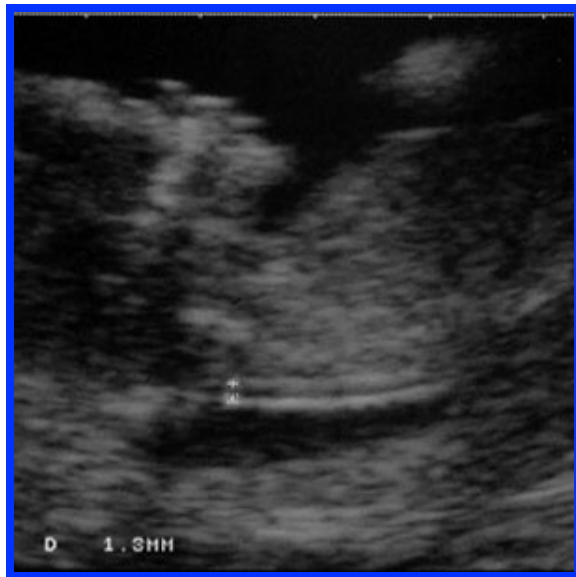
# Prenatal Testing

- Ultrasounds
- Serum screens
- Chorionic villus sampling (CVS)
- Amniocentesis

# Prenatal Tests - Ultrasound

- Nuchal translucency screening
  - Performed between 10-13 weeks gestation
  - Screen for Down Syndrome

# Nuchal Translucency



# Prenatal Tests - Ultrasound

- Second trimester ultrasound
  - Detailed exam
  - Down Syndrome, other trisomies
  - Cardiac, renal, spinal, limb, brain deformities
  - Cleft lip/palate

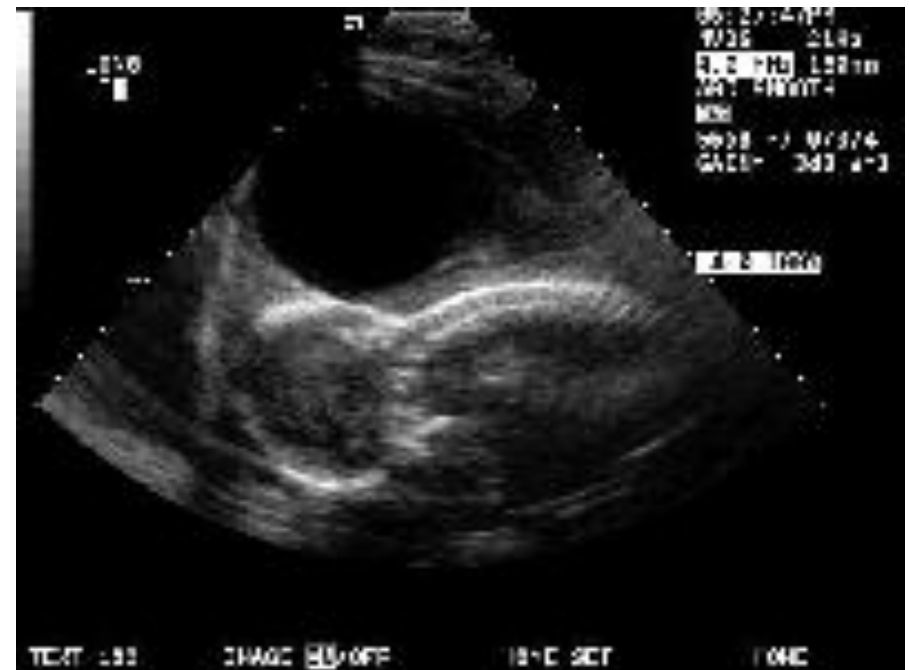
# Ultrasound Abnormalities



Echogenic bowel loops



# Ultrasound Abnormalities



# Prenatal Tests - Serum

- 15-20 weeks gestation
- Quad Screen
  - Tests for AFP, hCG, uE<sub>3</sub> and inhibin A
  - Neural tube defects, Down syndrome, Trisomy 18, Abdominal wall defects
  - Readjusts age-related risks



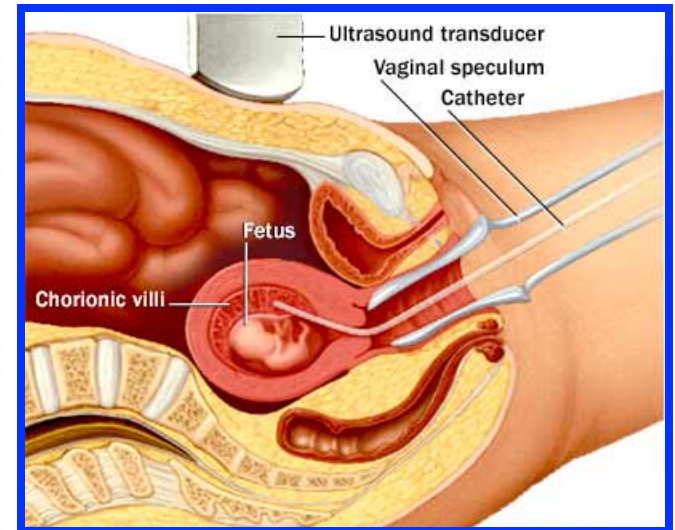
# Prenatal Tests

- **Who is offered further testing?**
  - ❑ Advanced maternal age
  - ❑ Previous child or pregnancy with birth defect
  - ❑ Suggestive screening test results
  - ❑ Family history
  - ❑ Positive parental genetic screening

# Prenatal Tests – CVS

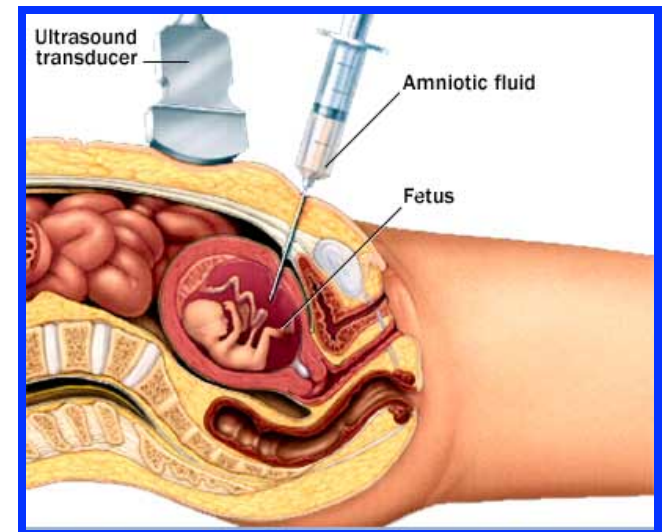
- **Chorionic Villus Sampling**

- ❑ 11-13 weeks gestation
- ❑ Catheter/needle biopsy of placental cells
- ❑ Performed through cervix or abdomen
- ❑ Can test for chromosome and gene defects
- ❑ 1-2% miscarriage rate
- ❑ Digit/limb deficiencies (10 weeks)



# Prenatal Tests - Amniocentesis

- Performed at 15-18 weeks gestation
- 10 cc amniotic fluid
- Living cells from fetus in amniotic fluid
- Cells grown in lab for 1-2 weeks
- Results in 3 weeks
- Chromosome and gene defects



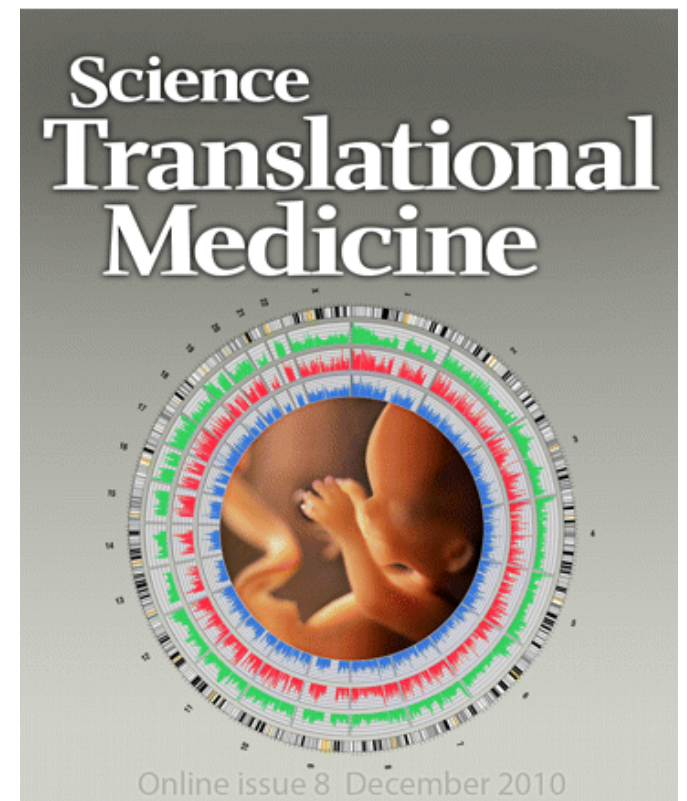
# Maternal Plasma DNA Sequencing Reveals the Genome-Wide Genetic and Mutational Profile of the Fetus

Science Translational Medicine, December 8, 2010 (61,1-12)

Sequencing DNA From the Blood of a Pregnant Woman Allows the Complete Genome Of the Fetus to Be Decoded!

*~10% of DNA in Maternal Plasma is From the Fetus*

**A New Era in DNA Testing!!**



# Postnatal Testing

- Most done during first day of life
- Heel stick
- California (mandatory)
  - ❑ Galactosemia
  - ❑ Hypothyroidism (congenital)
  - ❑ Phenylketonuria (PKU)
  - ❑ Sickle Cell Disease (SCD) and Hemoglobinopathies
  - ❑ + 35 Others as of July, 2005

# Postnatal Screening – Tandem Mass Spectrometry Screening Program

## Fatty Acid Oxidation Disorders

Carnitine/Acylcarnitine Translocase Deficiency (Translocase)  
Carnitine Palmitoyl Transferase Deficiency Type I (CPT-I)<sup>2</sup>  
3-Hydroxy Long Chain Acyl-CoA Dehydrogenase Deficiency (LCHAD)  
2,4-Dienoyl-CoA Reductase Deficiency<sup>2</sup>  
Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCAD)  
Multiple Acyl-CoA Dehydrogenase Deficiency (MADD or Glutaric Acidemia-Type II)  
Neonatal Carnitine Palmitoyl Transferase Deficiency-Type II(CPT-II)  
Short Chain Acyl-CoA Dehydrogenase Deficiency (SCAD)  
Short Chain Hydroxy Acyl-CoA Dehydrogenase Deficiency (SCHAD)  
Trifunctional Protein Deficiency (TFP Deficiency)  
Very Long Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD)

## Organic Acid Disorders

3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency (HMG)  
Glutaric Acidemia-Type I (GA I)  
Isobutyryl-CoA Dehydrogenase Deficiency  
Isovaleric Acidemia (IVA)  
    Acute onset  
    Chronic  
2-Methylbutyryl-CoA Dehydrogenase Deficiency  
3-Methylcrotonyl-CoA Carboxylase Deficiency (3MCC Deficiency)  
3-Methylglutaconyl-CoA Hydratase Deficiency  
Methylmalonic Acidemias  
    Methylmalonyl-CoA Mutase Deficiency 0  
    Methylmalonyl-CoA Mutase Deficiency +  
    Some Adenosylcobalamin Synthesis Defects  
    Maternal Vitamin B12 Deficiency  
Mitochondrial Acetoacetyl-CoA Thiolase Deficiency  
    (3-Ketothiolase Def.)  
Propionic Acidemia (PA)  
    Acute onset  
    Late onset  
Multiple-CoA Carboxylase Deficiency  
Malonic Aciduria

## Amino Acid Disorders

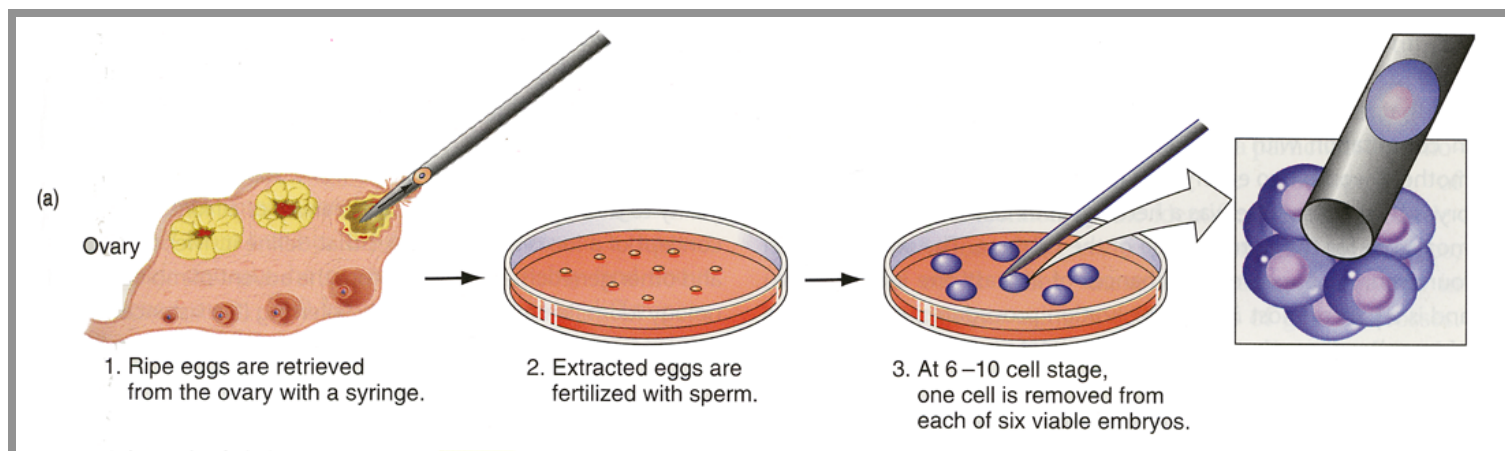
Argininemia  
Argininosuccinic Aciduria (ASA Lyase Deficiency)  
    Acute onset  
    Late onset  
Carbamoylphosphate Synthetase Deficiency (CPS Def.)<sup>2</sup>  
Citrullinemia (ASA Synthetase Deficiency)  
    Acute onset  
    Late onset  
Homocystinuria  
Hypermethioninemia  
Hyperammonemia, Hyperornithinemia, Homocitrullinemia  
    Syndrome (HHH)<sup>2</sup>  
Hyperornithinemia with Gyral Atrophy<sup>2</sup>  
Maple Syrup Urine Disease (MSUD)  
    Classical MSUD  
    Intermediate MSUD  
5-Oxoprolinuria (pyroglutamic Aciduria)<sup>2</sup>  
Phenylketonuria (PKU)  
    Classical PKU  
    Hyperphenylalaninemia  
    Biotpterin Cofactor Deficiencies (4)  
Tyrosinemia  
Transient Neonatal Tyrosinemia  
    Tyrosinemia Type I (Tyr I)<sup>2</sup>  
    Tyrosinemia Type II (Tyr II)  
    Tyrosinemia Type III (Tyr III)

## Other Abnormal Profiles

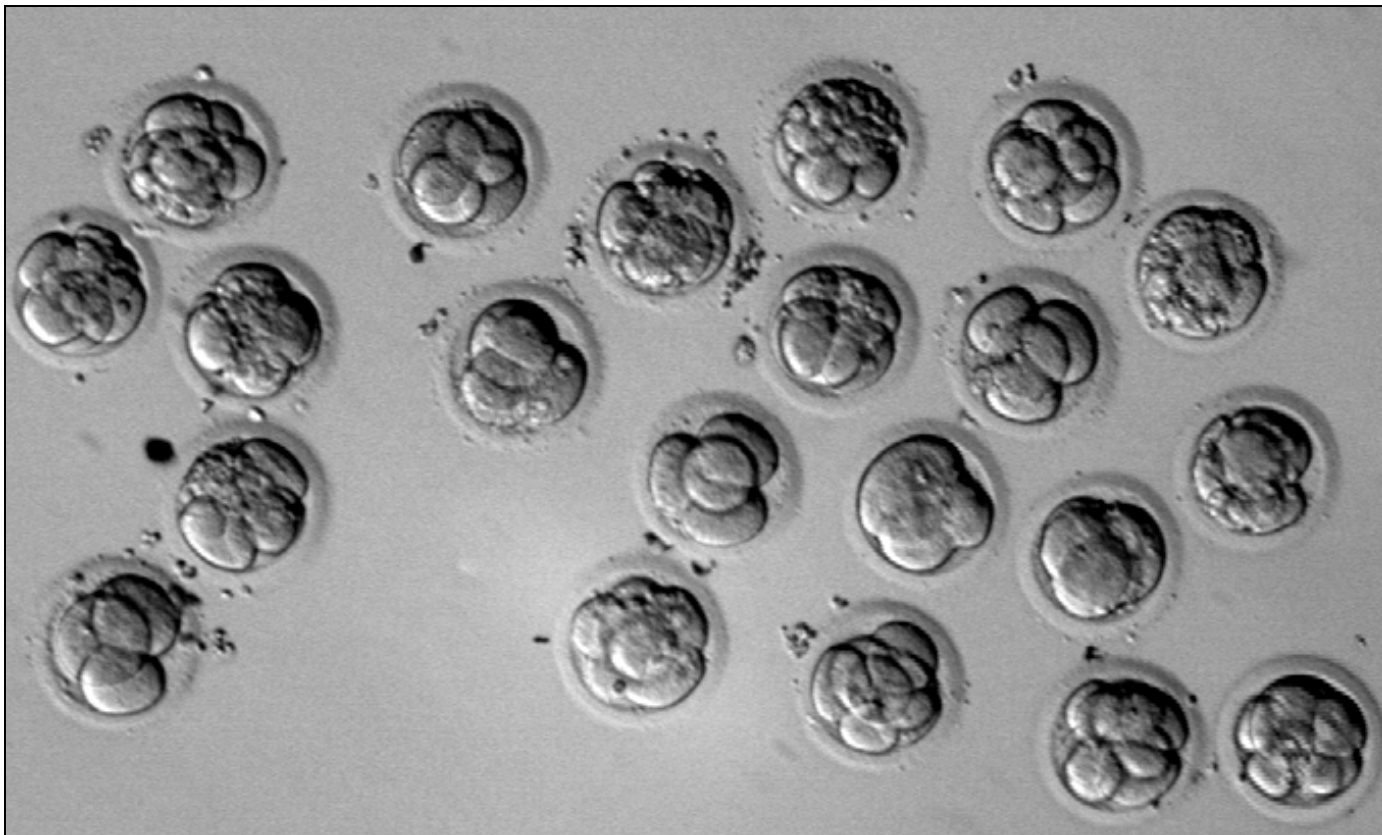
Hyperalimentation  
Liver Disease  
Medium Chain Triglyceride (MCT) Oil Administration  
Presence of EDTA Anticoagulants in blood specimen  
Treatment with Benzoate, Pyvalic Acid, or Valproic Acid  
Carnitine Uptake Deficiency<sup>2</sup>

# Preimplantation Genetic Screening (PGS)

- Can test embryos for genetic abnormalities prior to implantation
- Uses single cell (blastomere) at 8-cell stage



# Which Embryo is Disease-Free?





# PGS – Clinical Indications

- Single gene defects
- Balanced translocations
- Advanced maternal age (aneuploidy)
- Repetitive IVF failure
- Recurrent pregnancy loss
- Embryo selection

# PGS

- Fluorescence in situ hybridization (FISH)
  - Aneuploidy/translocations and sexing (5-9 chromosomes)
- PCR
  - specific single gene disorders
- Gene Chips (genome “scan”)
  - many gene disorders & chromosomal abnormalities at one time

# Genetic Disorders Assayed by PGS & Gene Chips

- Achondroplasia
- ADPKD1
- ADPKD2
- Adrenoleukodystroph
- Age-related aneuploidies
- Alpha-thalassemia
- Alpha-1-antitrypsin
- Alport disease
- Amyloid precursor protein (APP) mutation
- ARPKD
- Becker muscular dystrophy
- Beta-thalassemia
- Charcot Marie Tooth disease
- Chromosomal translocations
- Congenital adrenal hyperplasia
- Cystic fibrosis
- Down syndrome
- Duchenne muscular dystrophy
- Dystonia
- Epidermolysis bullosa
- Familial dysautonomia
- Fanconi anemia
- FAP
- Fragile X syndrome
- Gaucher disease
- Hemophilia A and B
- HLA genotyping
- HSNF5 mutation
- Huntington disease
- Hypophosphatasia
- Incontinentia pigmenti
- Kell disease
- Klinefelter syndrome
- LCHAD
- Lesch Nyhan syndrome
- Marfan syndrome
- Multiple epiphysial dysplasia
- Myotonic dystrophy
- Myotubular myopathy
- NF1 and NF2
- Norrie disease
- Osteogenesis imperfecta
- OTC deficiency
- P53 mutations
- PKU
- Retinitis pigmentosa
- SCA6
- Sickle cell anemia
- Sonic hedgehog mutations
- Spinal muscular atrophy (SMA)
- Tay-Sachs disease
- Tuberous sclerosis
- Turner syndrome
- Von Hippel Lindau
- X-linked hydrocephaly
- X-linked hyper IgM syndrome

# PGS for Single Gene Disorders - Advantages

- Safer than elective termination
- More psychologically acceptable for couples
- Provides couples with another option
  - Adoption
  - Sterilization
  - Donor gametes

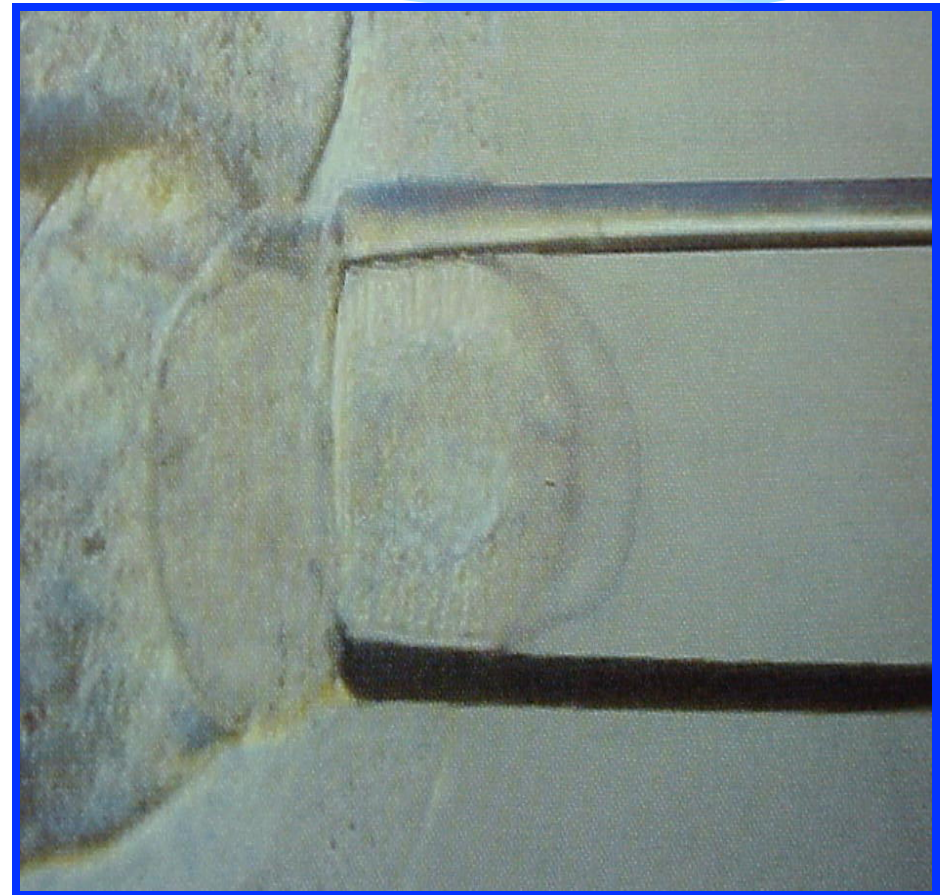
# PGS

- *Pre-implantation genetic screening (PGS)* has been successfully used in diagnosing and preventing inherited genetic diseases like Cystic Fibrosis, Tay Sachs, Thalassemia, Sickle Cell Anemia and may be potentially used to screen for cancer mutations.

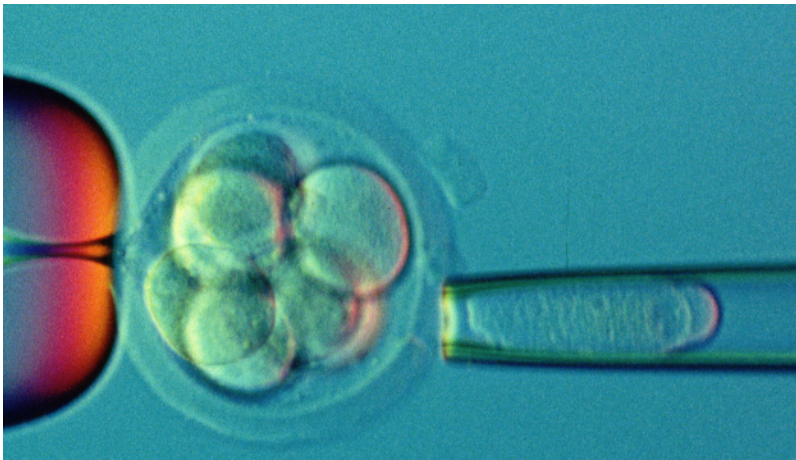


# PGS

- After a cycle of in-vitro fertilization, biopsy of a single cell can be performed from an 8 cell embryo obtained after 3 days of culture in the laboratory.



# PGS – Timing of Biopsy



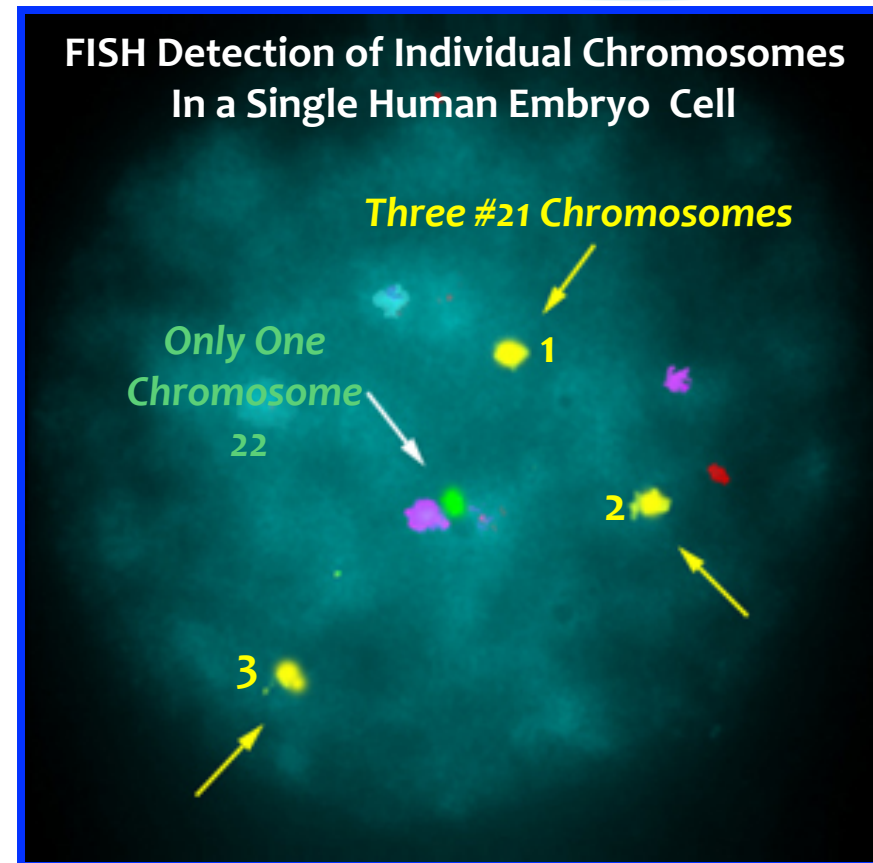
- <67 hours post-retrieval
- Implantation rates significantly lower if >70 hours



- Probably represents technical issues with compacting embryo

# PGS

- The genetic material of this single cell can be amplified by PCR and a *chromosomal mutation or an aneuploidy* (gain or loss of a chromosome) can be identified in the embryo that underwent a biopsy.





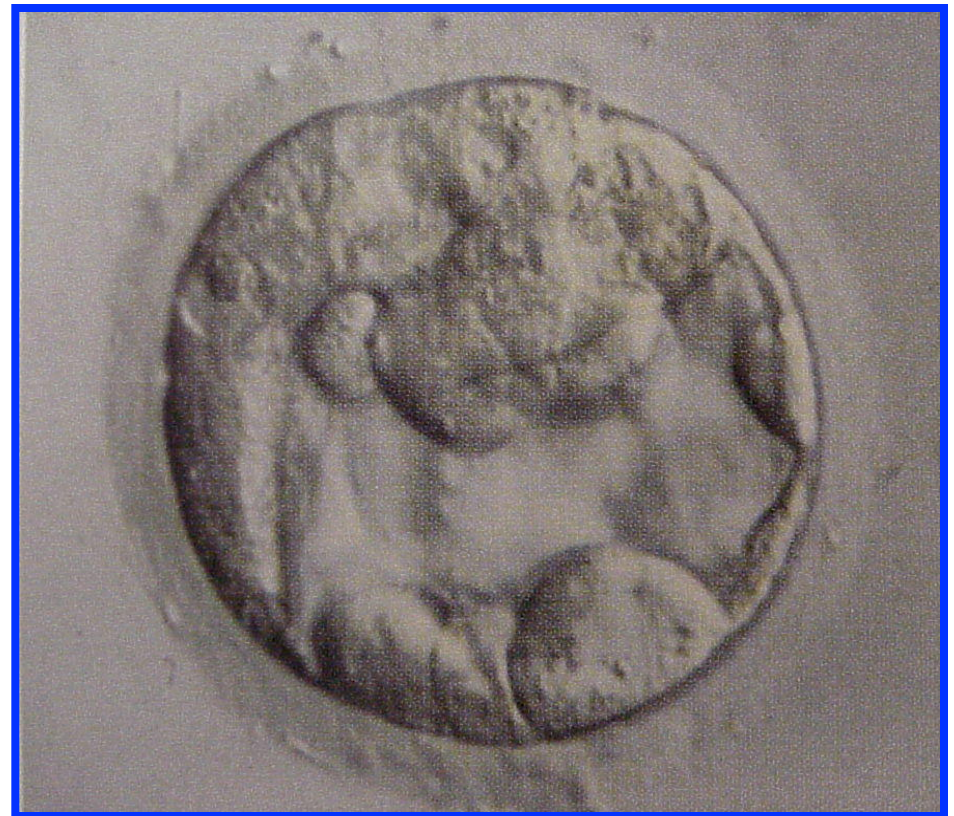
# PGS

- The embryos would continue to grow for 2 more days in the laboratory, awaiting genetic analysis, and confirmation of which embryos were unaffected with the mutation or aneuploidy.



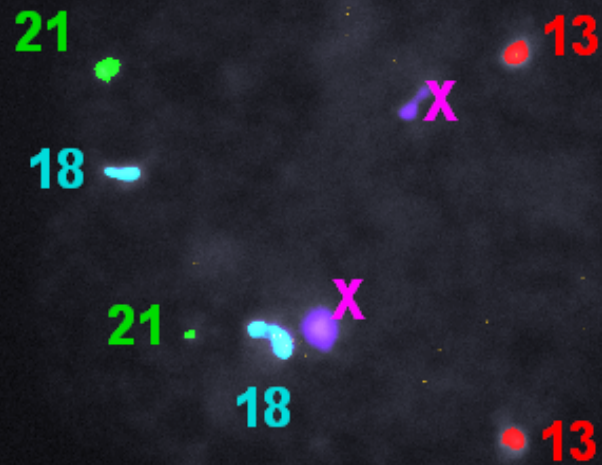
# PGS

- The unaffected embryos are then transferred to the uterus at the blastocyst stage on day 5 of embryo culture and subsequently a child would be born unaffected from the screened genetic disease.

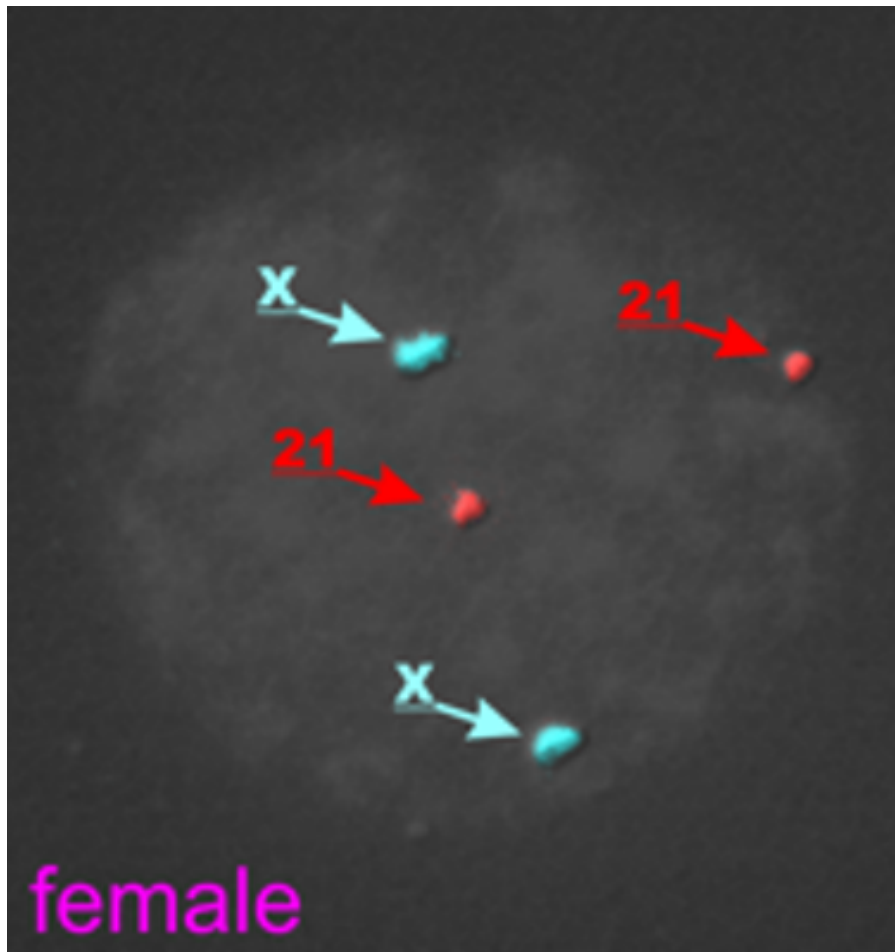


# Five Chromosome PGS

Normal Female.

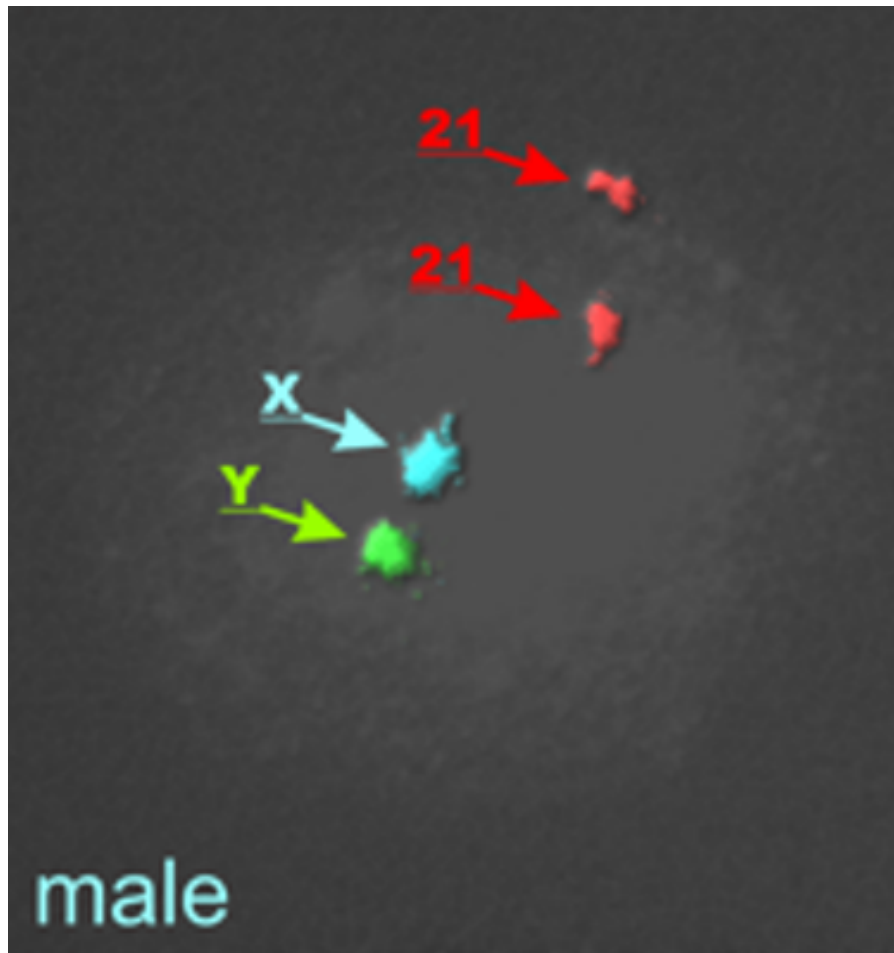


# PGS – Female Embryo



- Uses fluorescence in-situ hybridization (FISH) technique to identify XX
- Sex-linked diseases
- “Family balancing”

# PGS – Male Embryo



- Uses FISH to identify XY embryo



**If you had one or more children of the same sex, would you like to be able to choose the gender of your next child?**

**a. Yes**

**b. No**

# Prenatal vs. Preimplantation Diagnosis

	<u>PND</u>	<u>PGS</u>
<b>Cells</b>	<b>&gt;100,000</b>	<b>1</b>
<b>Time</b>	<b>2 weeks</b>	<b>6-10 hrs</b>
<b>Accuracy</b>	<b>99%</b>	<b>99%</b>
<b>Cost</b>	<b>Covered</b>	<b>~\$5,000</b>

# Who Would Benefit From PGS?

Couples with a history of --

- Abnormal numbers of chromosomes
- Single gene disorders
- Balanced translocations

Couples who --

- Desire an offspring of a certain sex

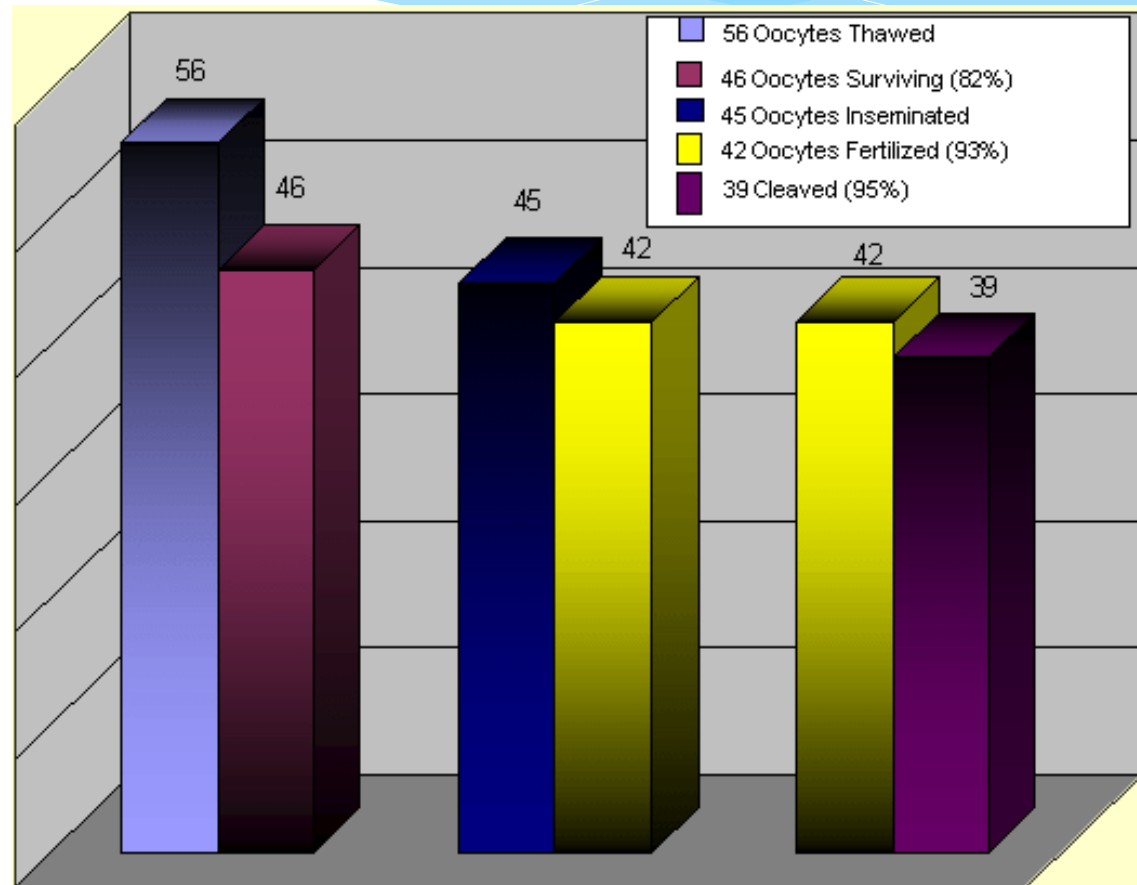




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**EGGFREEZING.COM**

*Egg Banking Now Available to Preserve Your Fertility*



# Cases

- Sperm donor
- Female couple
- Huntington's disease
- Single woman
- Sex-linked disease
- Family balancing
- “Wrongful death” of discarded embryo
- Implantation of the wrong embryo

# Thank you

