

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



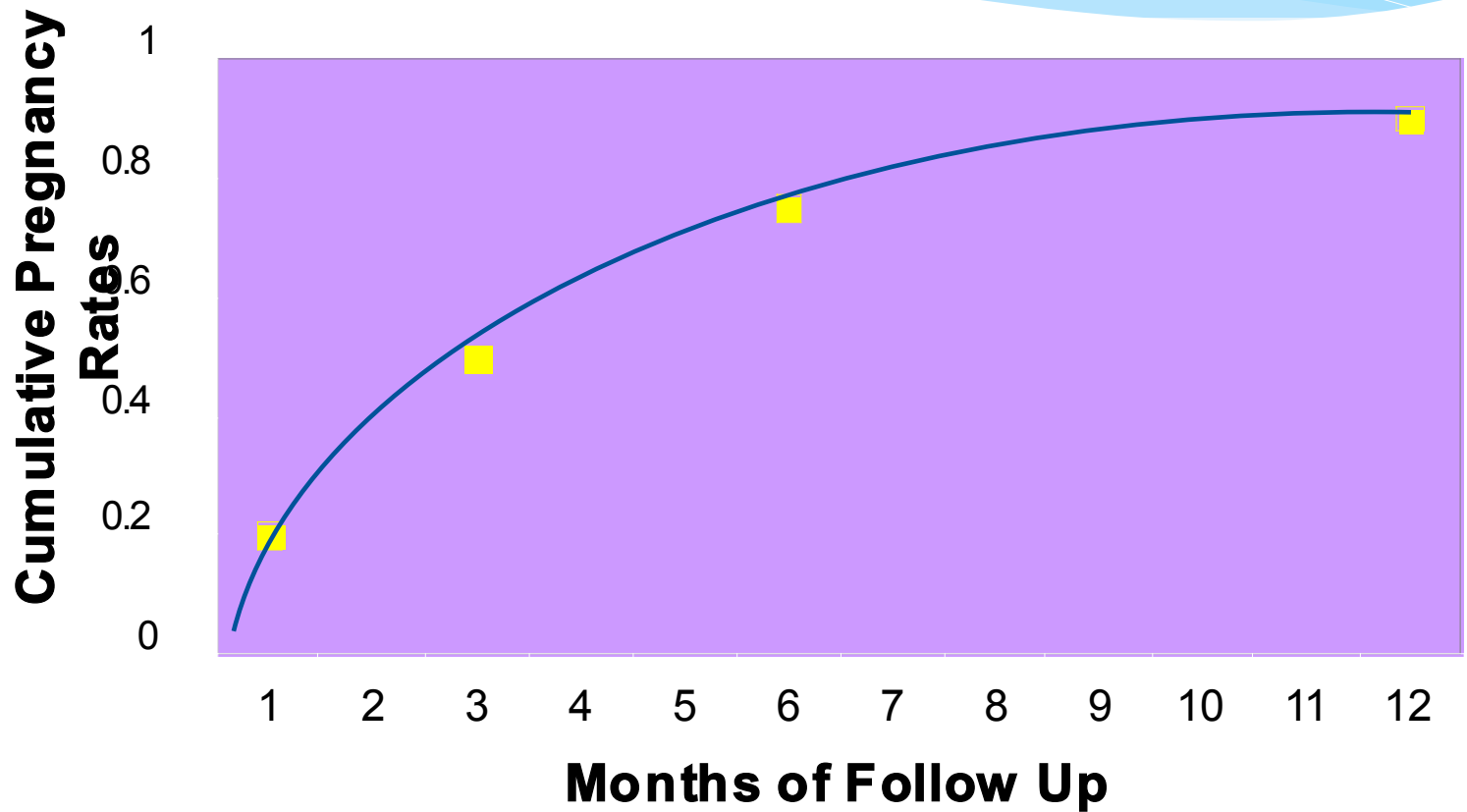
What percentage of the population is subfertile or infertile?

- 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**
 - **What Happens to Embryos?**
 - **Parent-Fertility Center Contracts**
- **Genetic Testing**
 - **Preconception**
 - **Preimplantation**
 - **Prenatal**
- **Controversies**

Normal Fertility





Infertility

Overview of Infertility

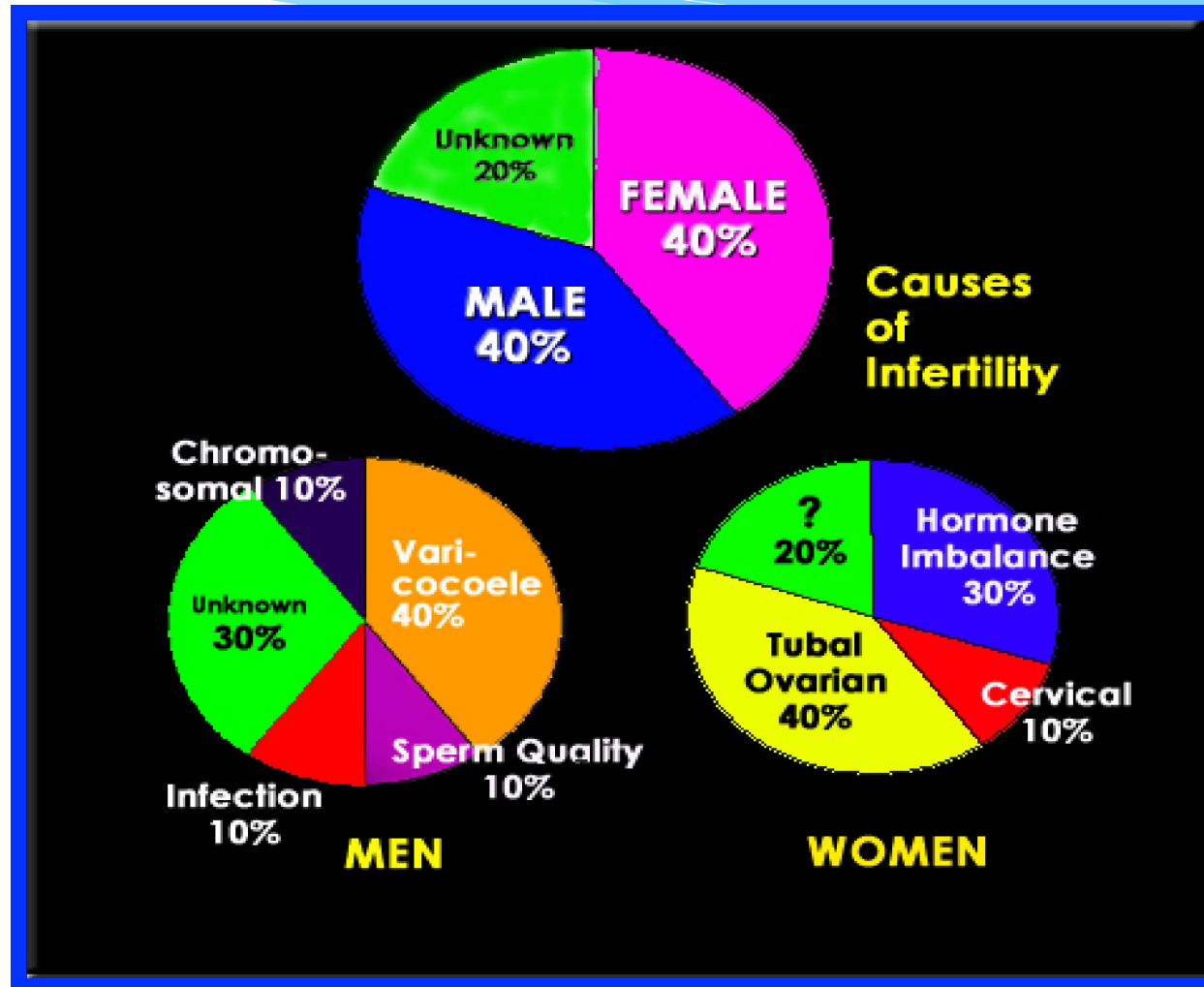
- Definition: 1 year of well-timed, unprotected intercourse without a pregnancy
- 10-15% of population is infertile (subfertile)



What factor might cause problems with fertility?

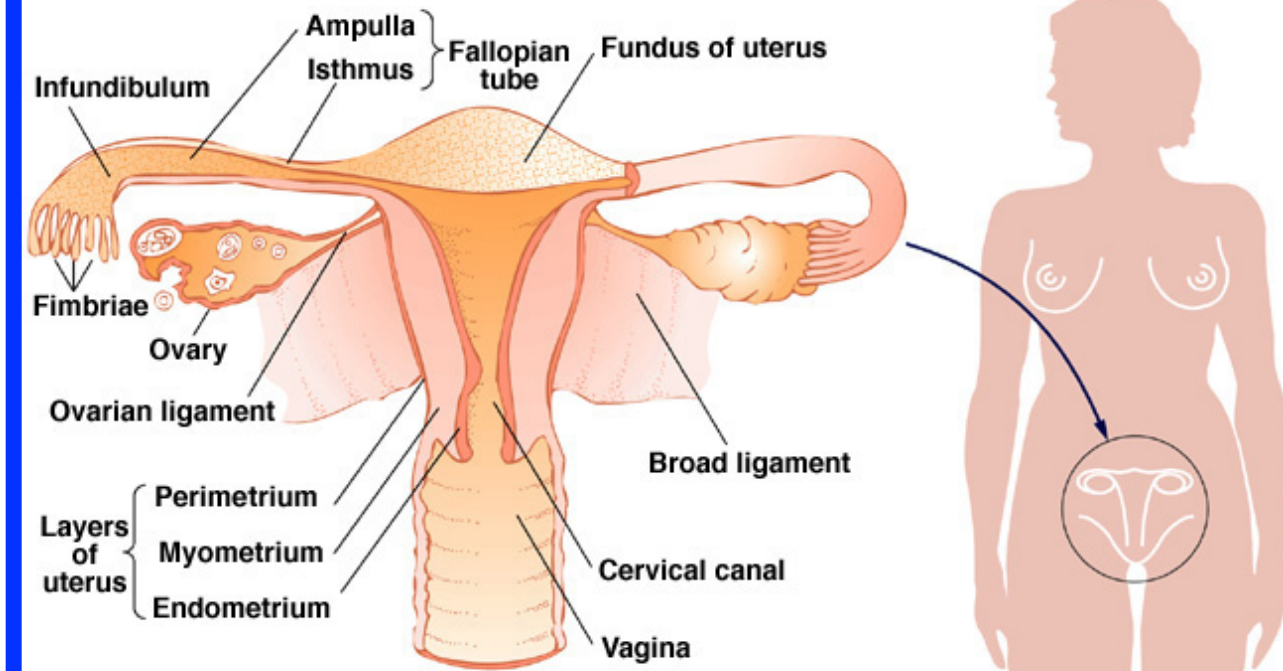
- a. boxer shorts**
- b. drinking a glass of wine every day**
- c. eating disorder**
- d. hiking for 30 minutes per day**
- e. history of yeast infections**

Causes of Infertility

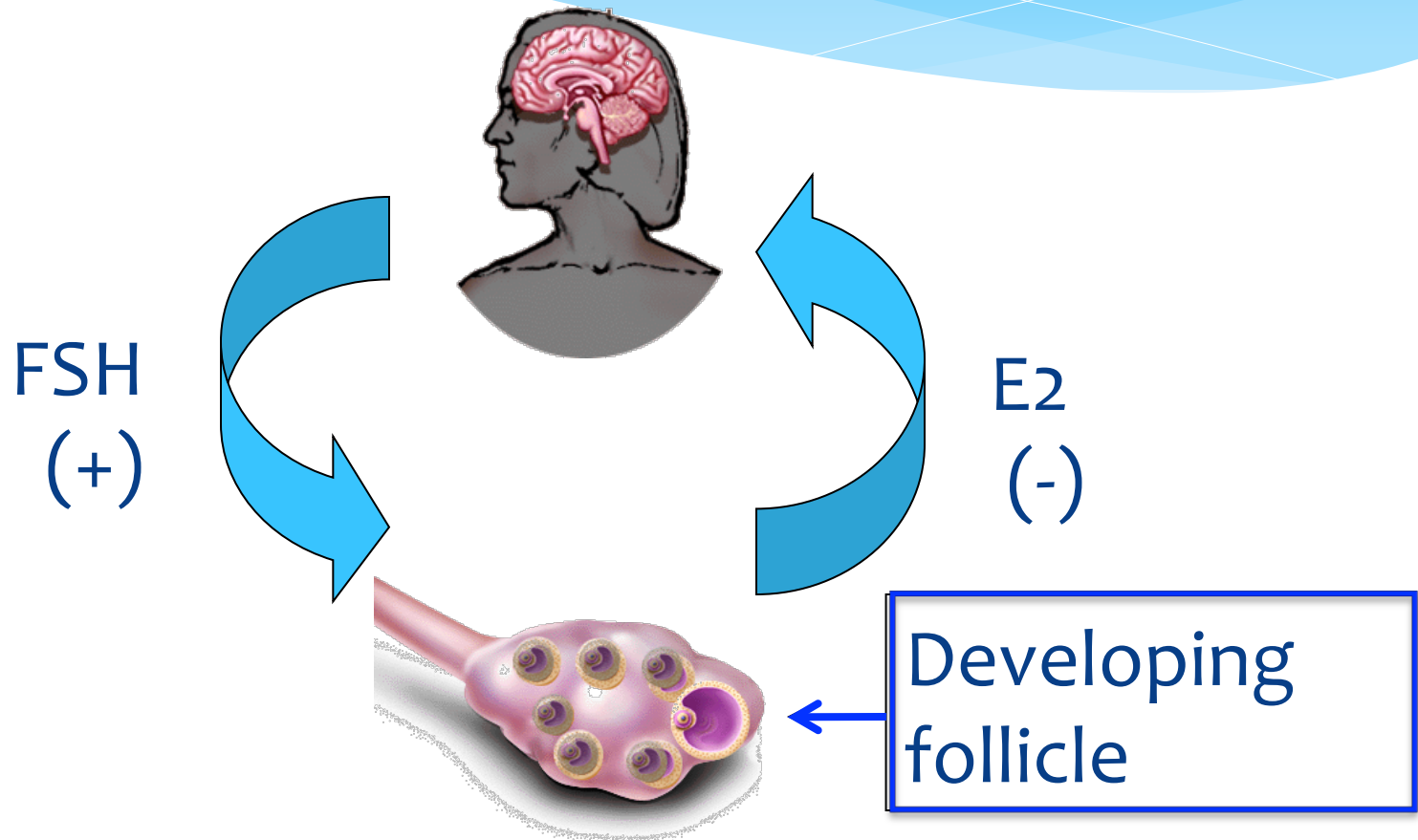


Female Reproductive Organs

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)?

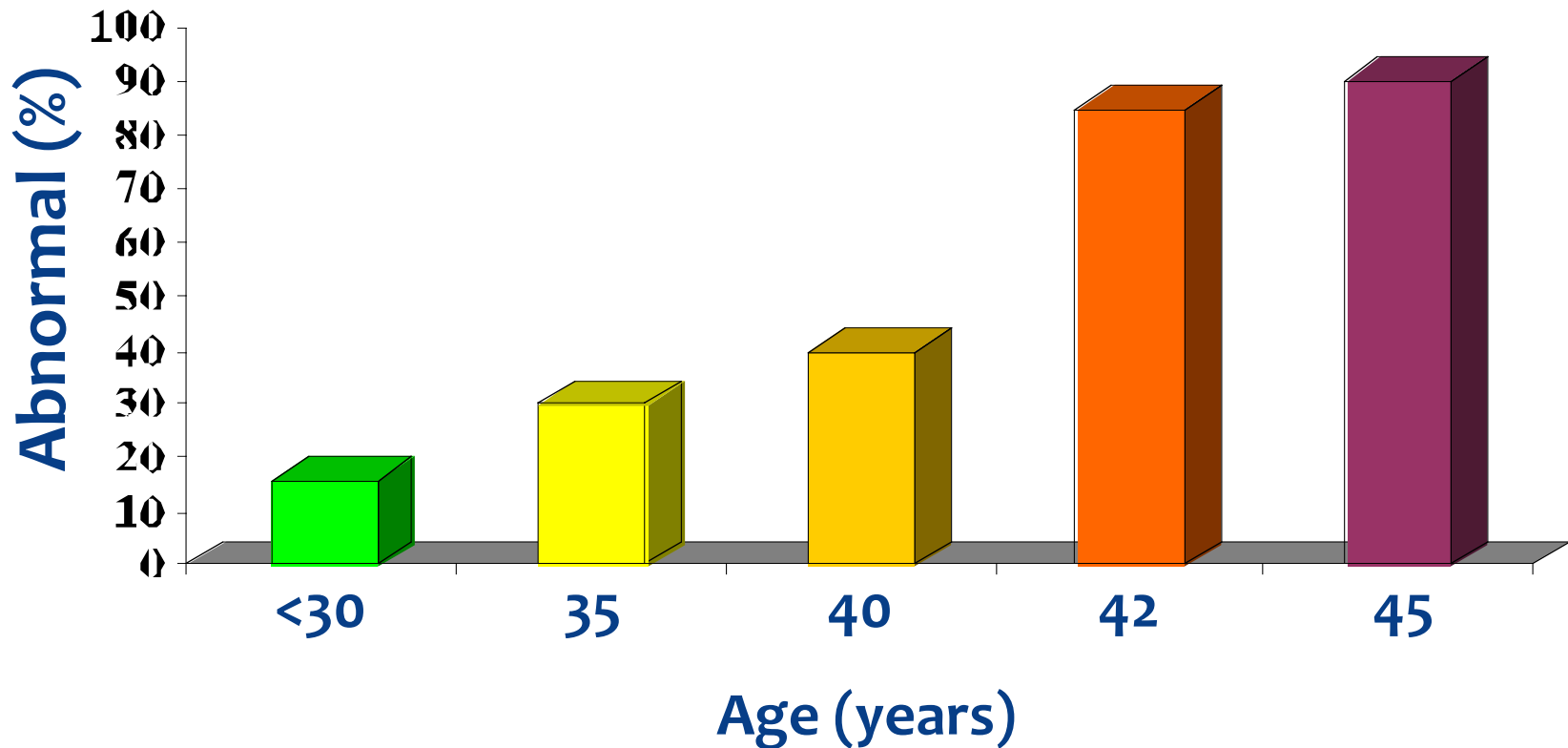
a. Yes

b. No

Ovary Problems - 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 Problems - Causes of Anovulation

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

Ovary Problems – 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

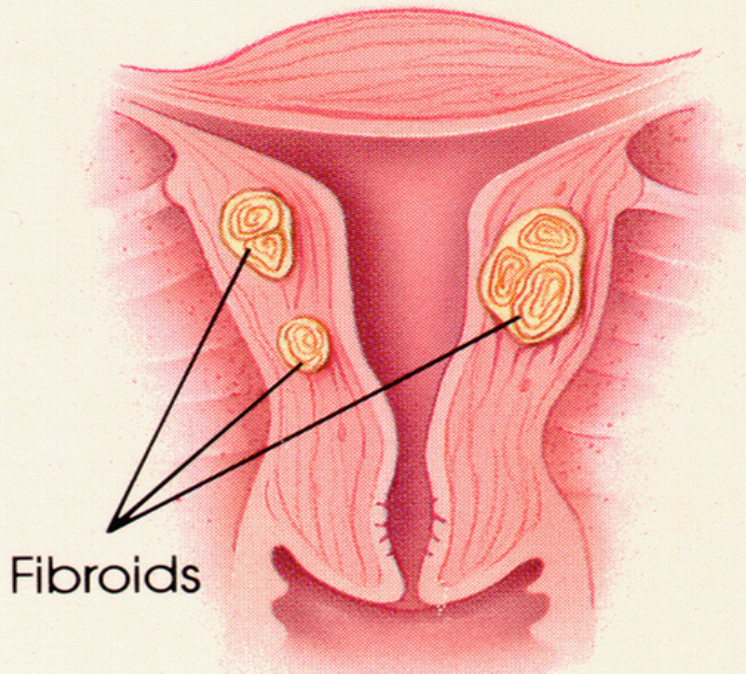


Female Infertility - Uterus

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

Female Infertility - Uterus

Fibroid tumors

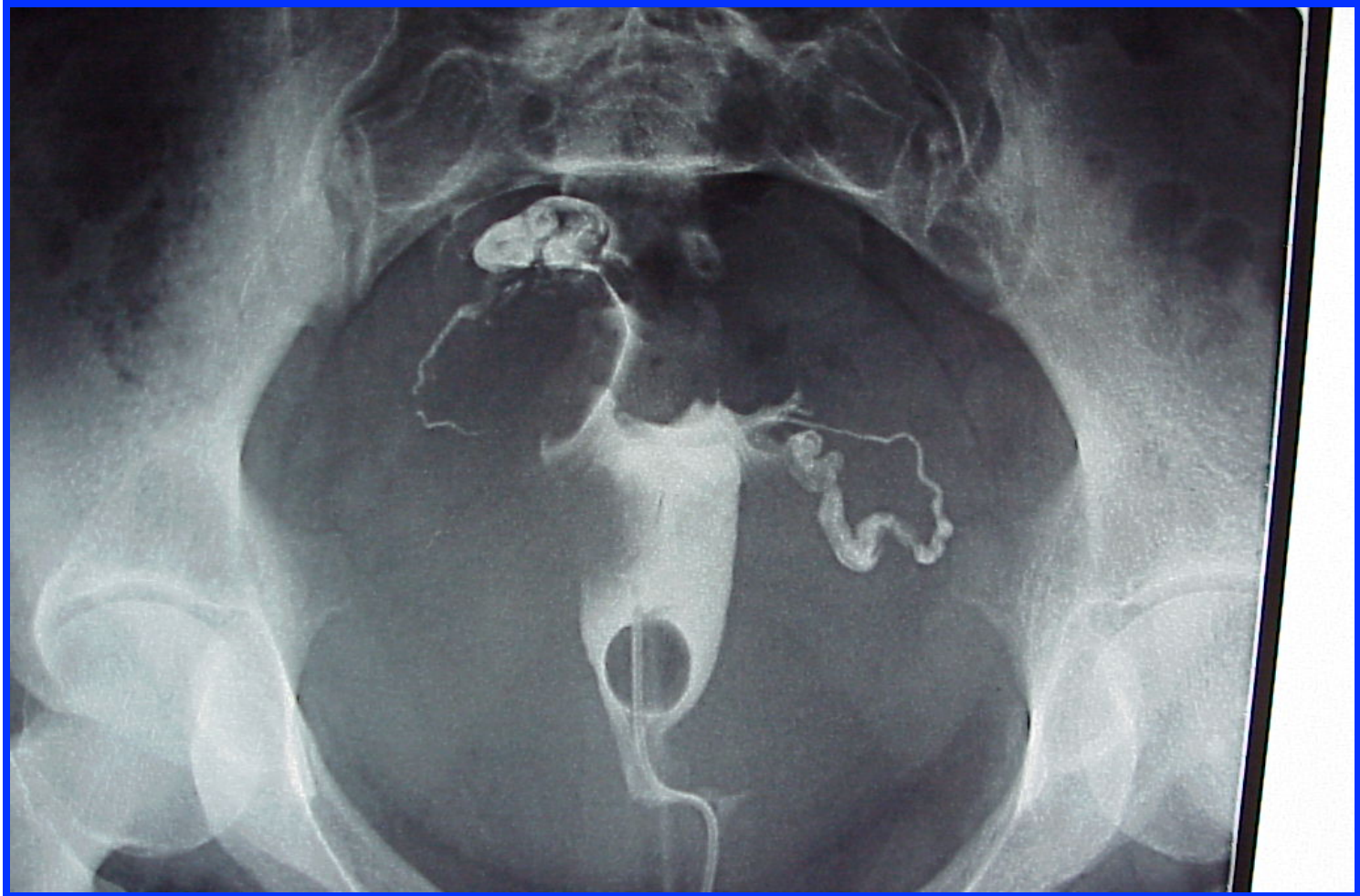


- Uterine muscle tumor
- Benign (>95%)
- 25-30% of women

Normal Shape of Uterus



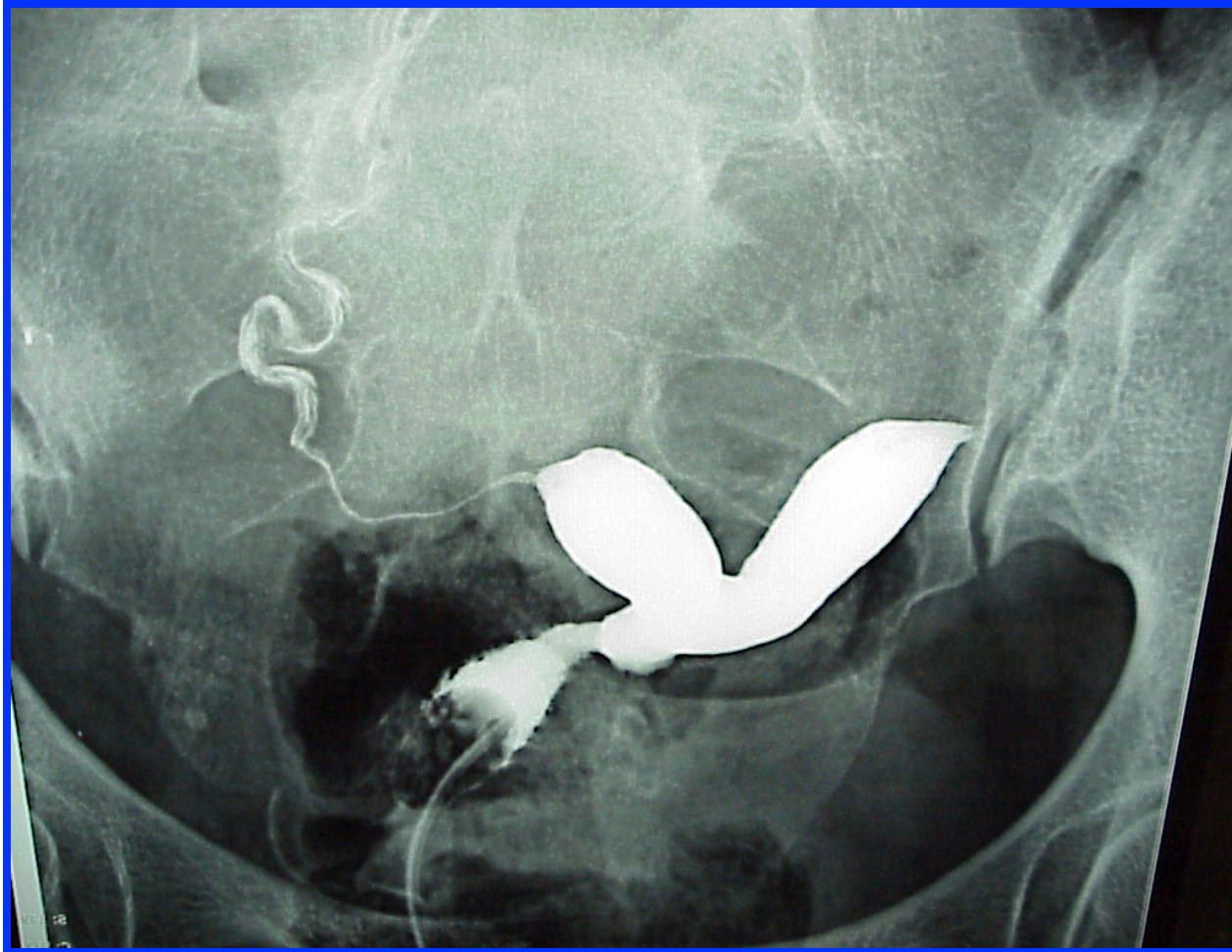
Fibroid Uterus



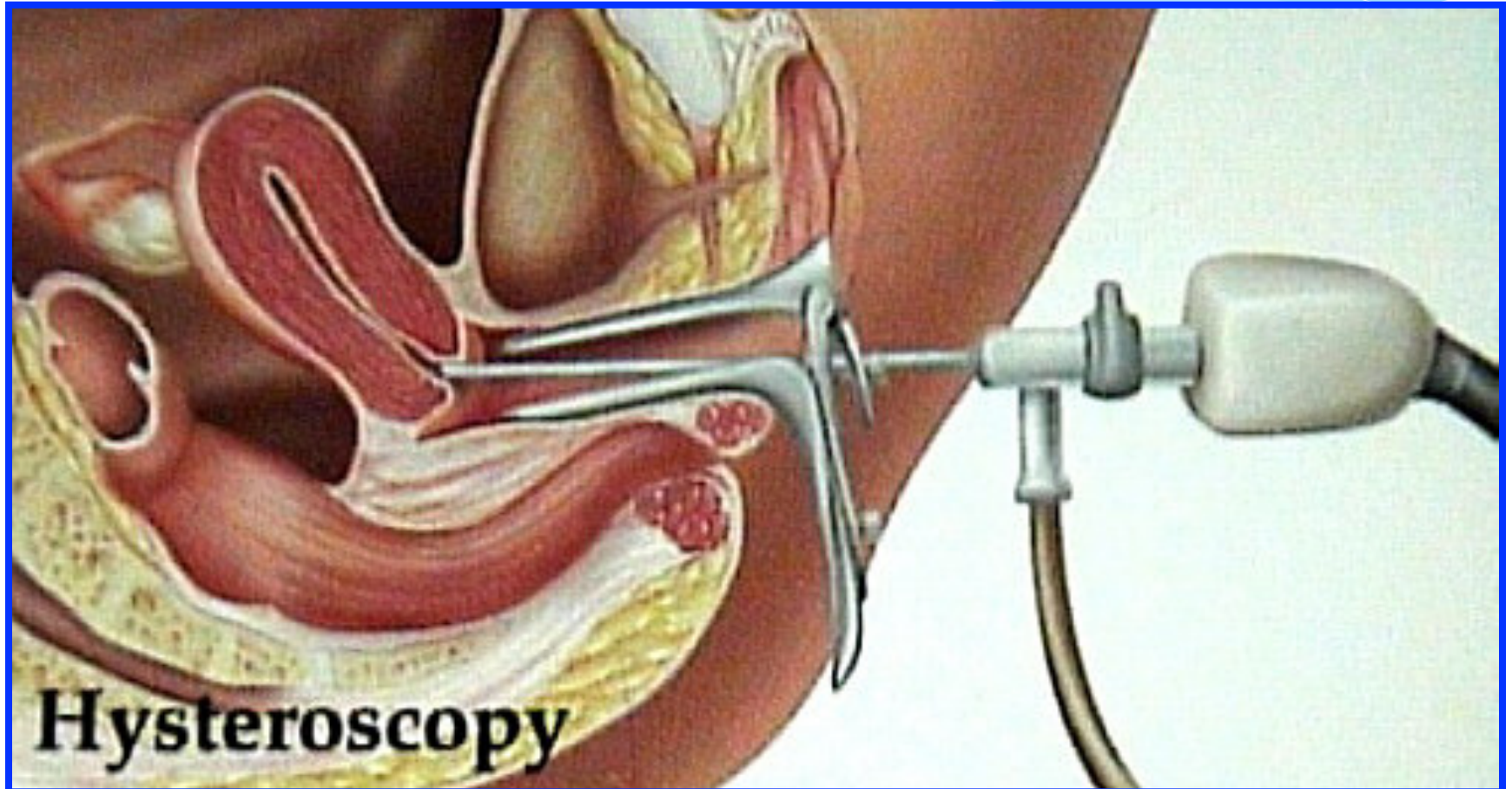
Female Infertility - Uterus

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

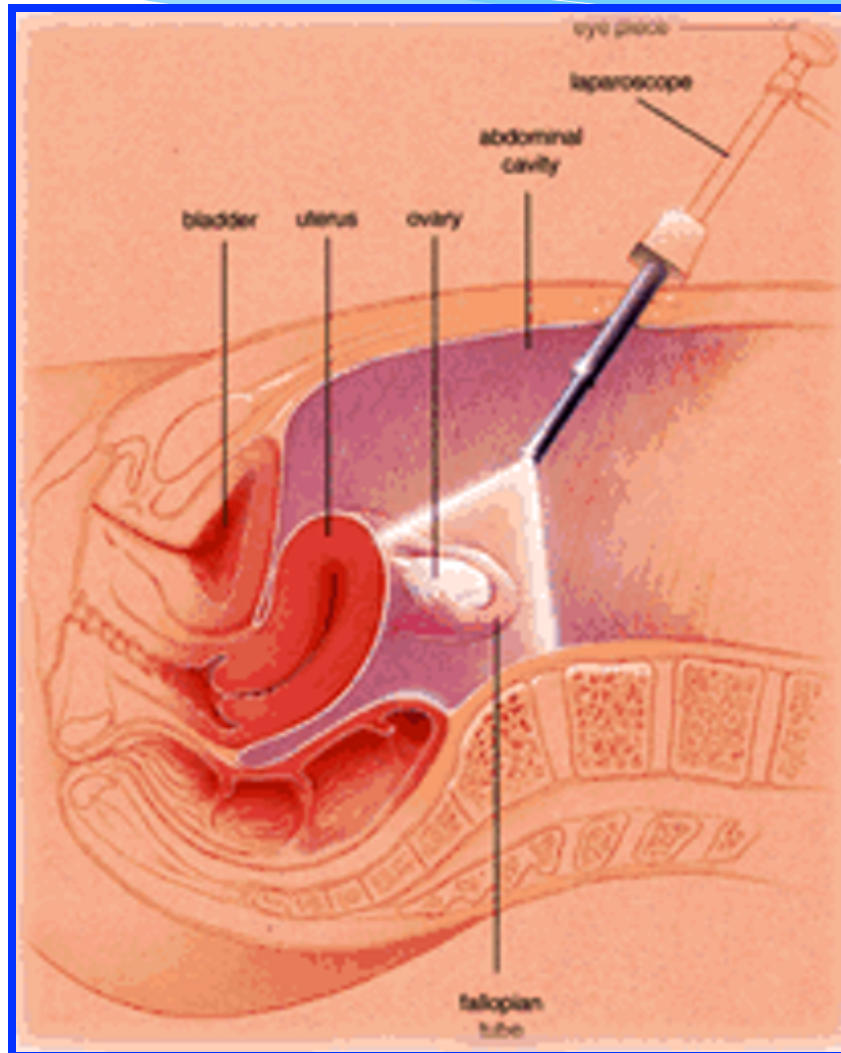
Mullerian Defect



Treatment with Hysteroscopy



Treatment with Laparoscopy





Surrogate Mothers, Inc.

Alternatives to Infertility since 1984. ©



When are Surrogates Used?

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)
 - Male pseudohermaphrodite
 - Female phenotype
 - Blind vaginal canal
 - Inguinal hernia (50%)
 - Androgen Insensitivity (XY)

Sperm Are Also Required!!





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

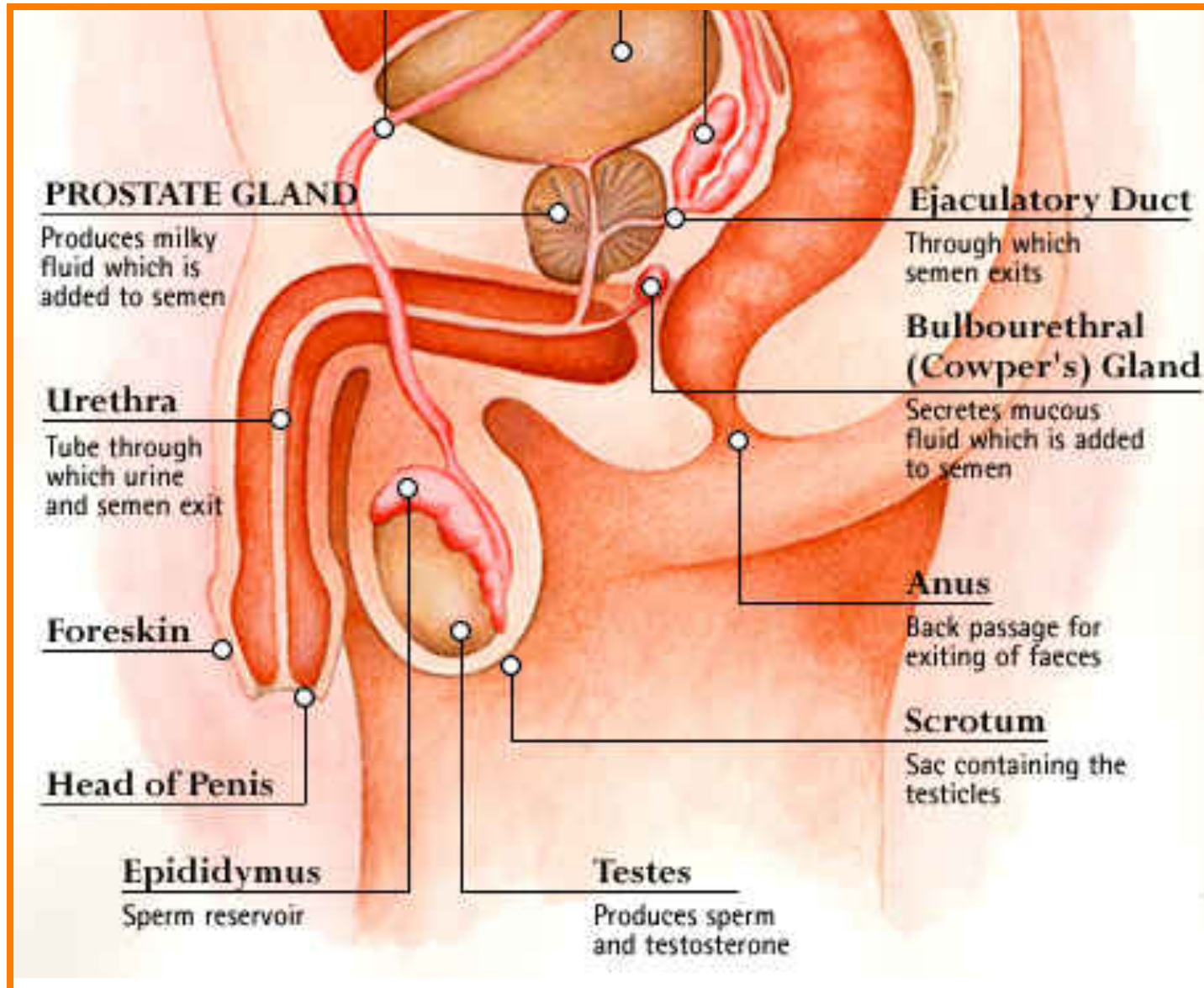
a. Yes

b. No

Causes of Male Infertility

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

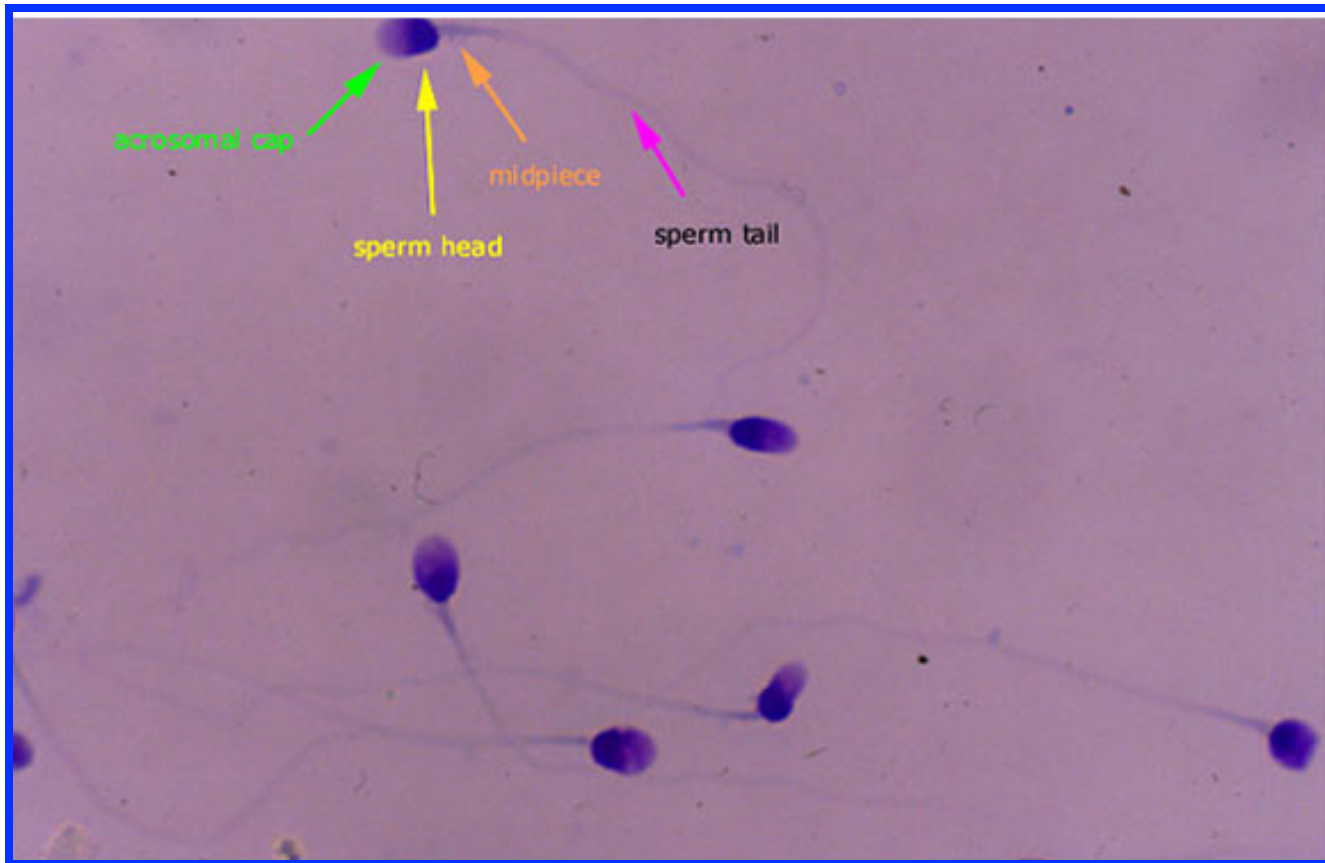
Male Reproductive Organs



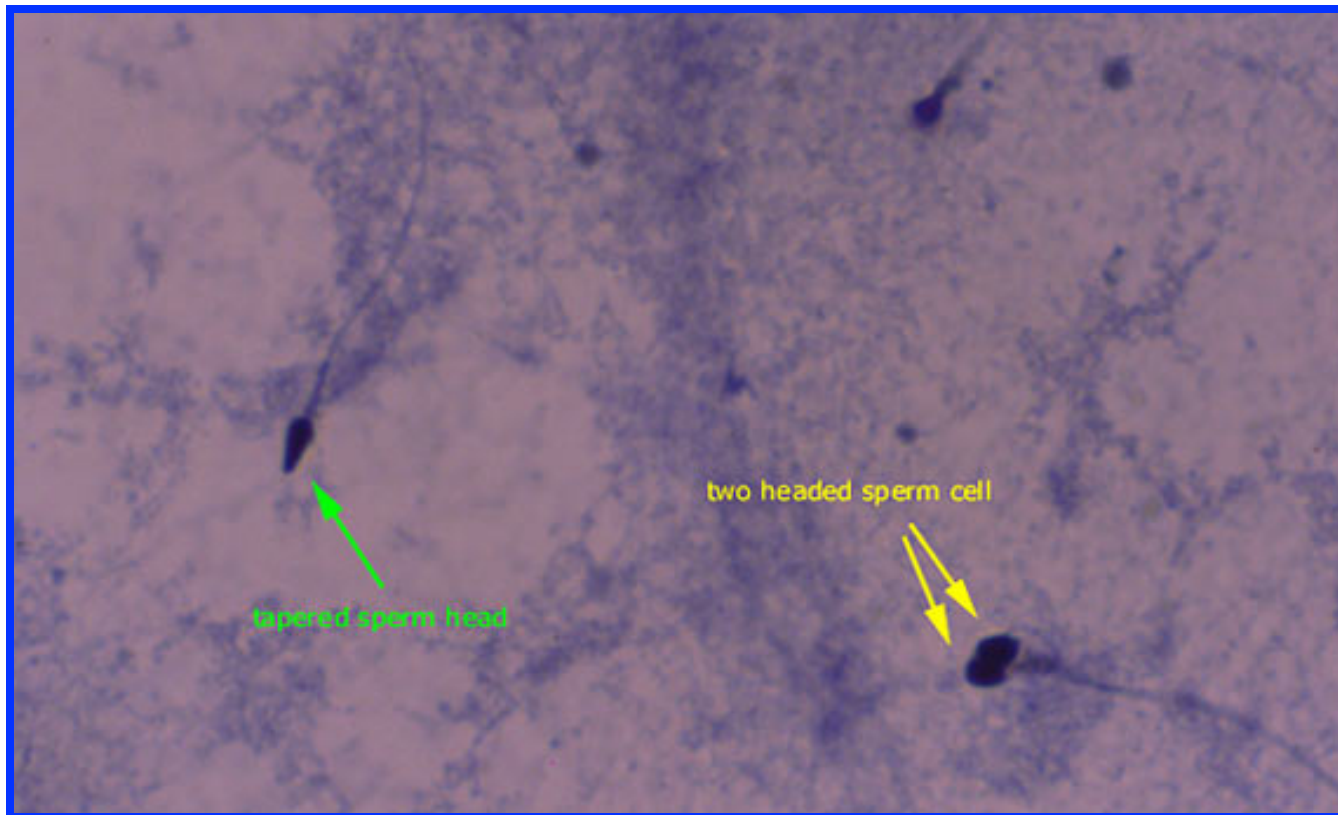
Sperm: Semen Analysis

- Volume: ≥ 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

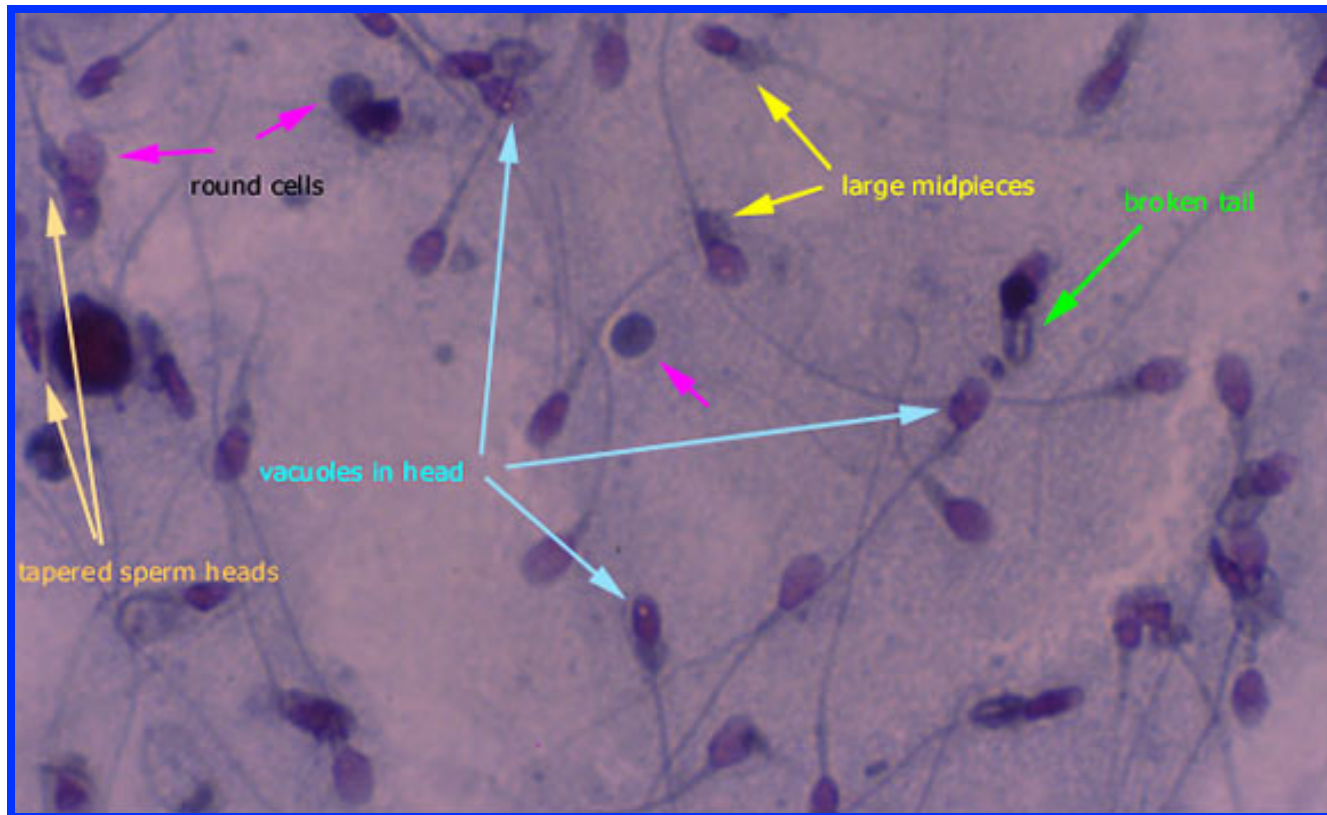
Normal Sperm Morphology



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

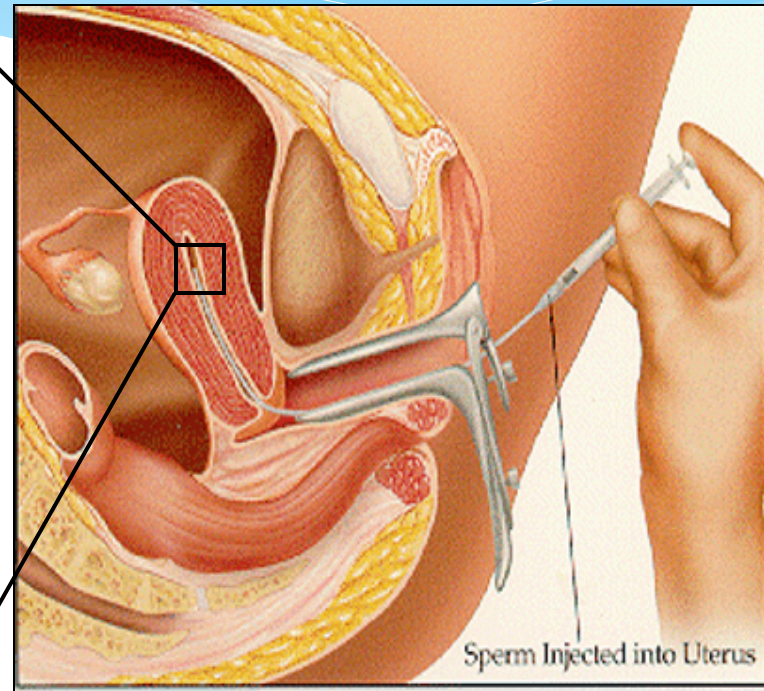
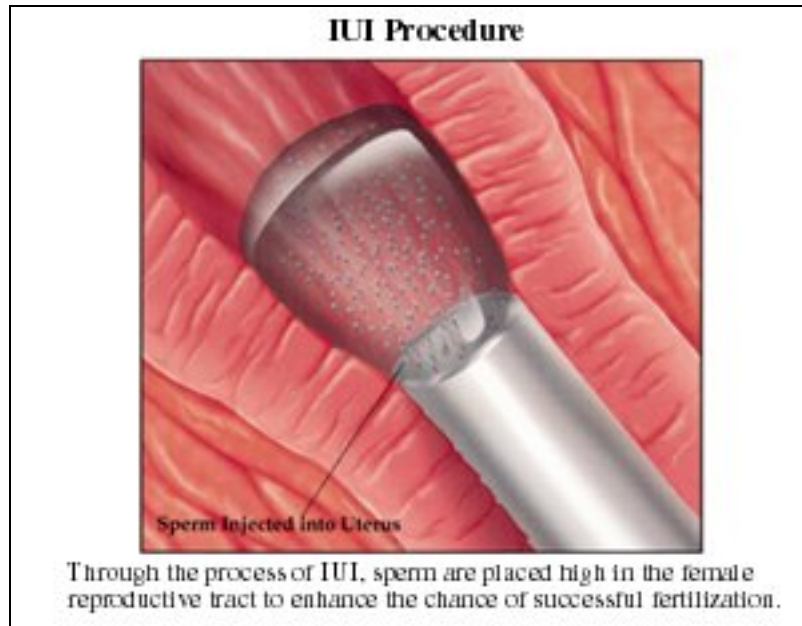
Unexplained Infertility

- 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

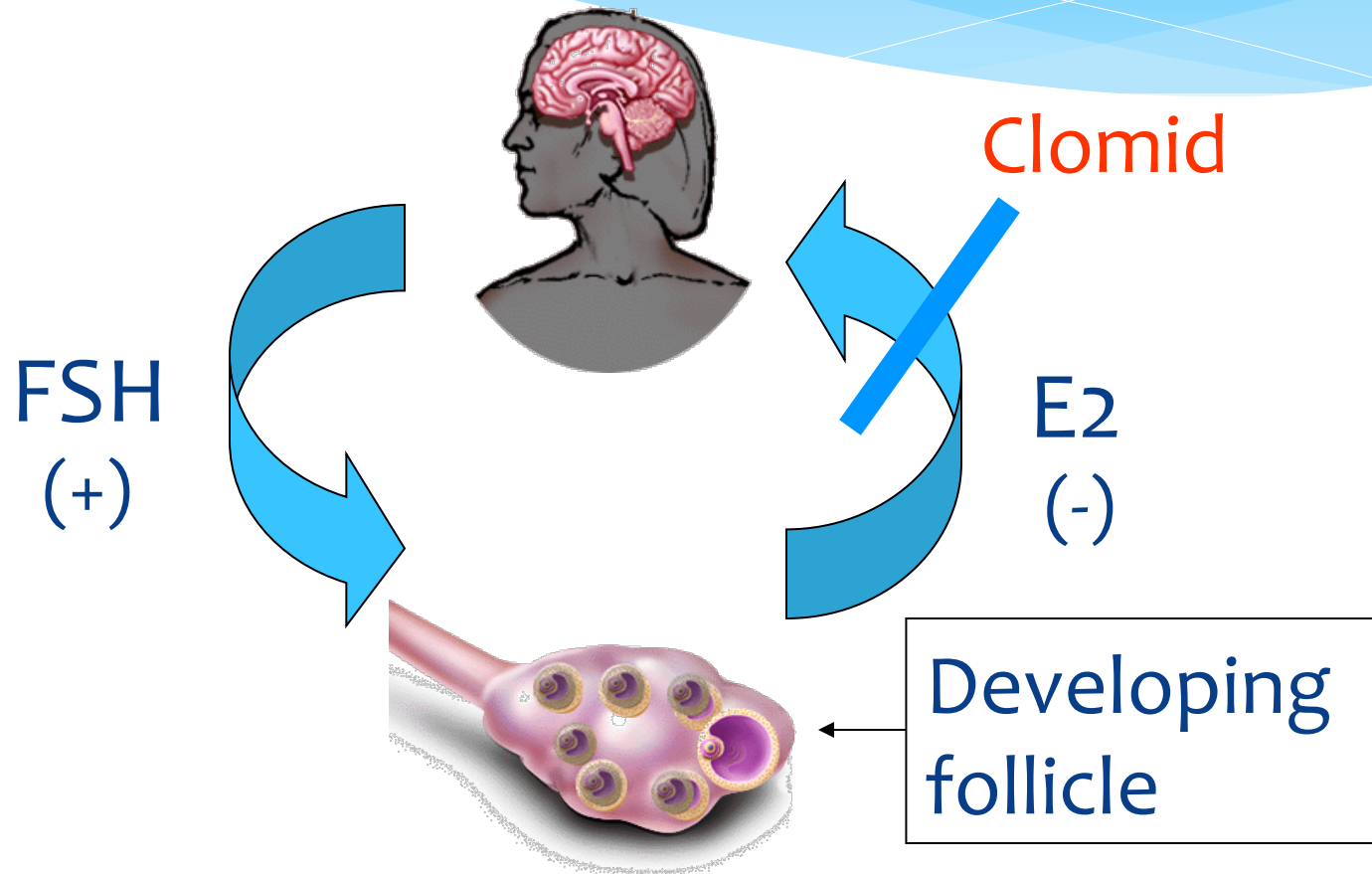
- Increase Number of Eggs
- Position Sperm Closer to Eggs

Infertility Treatment Options

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

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

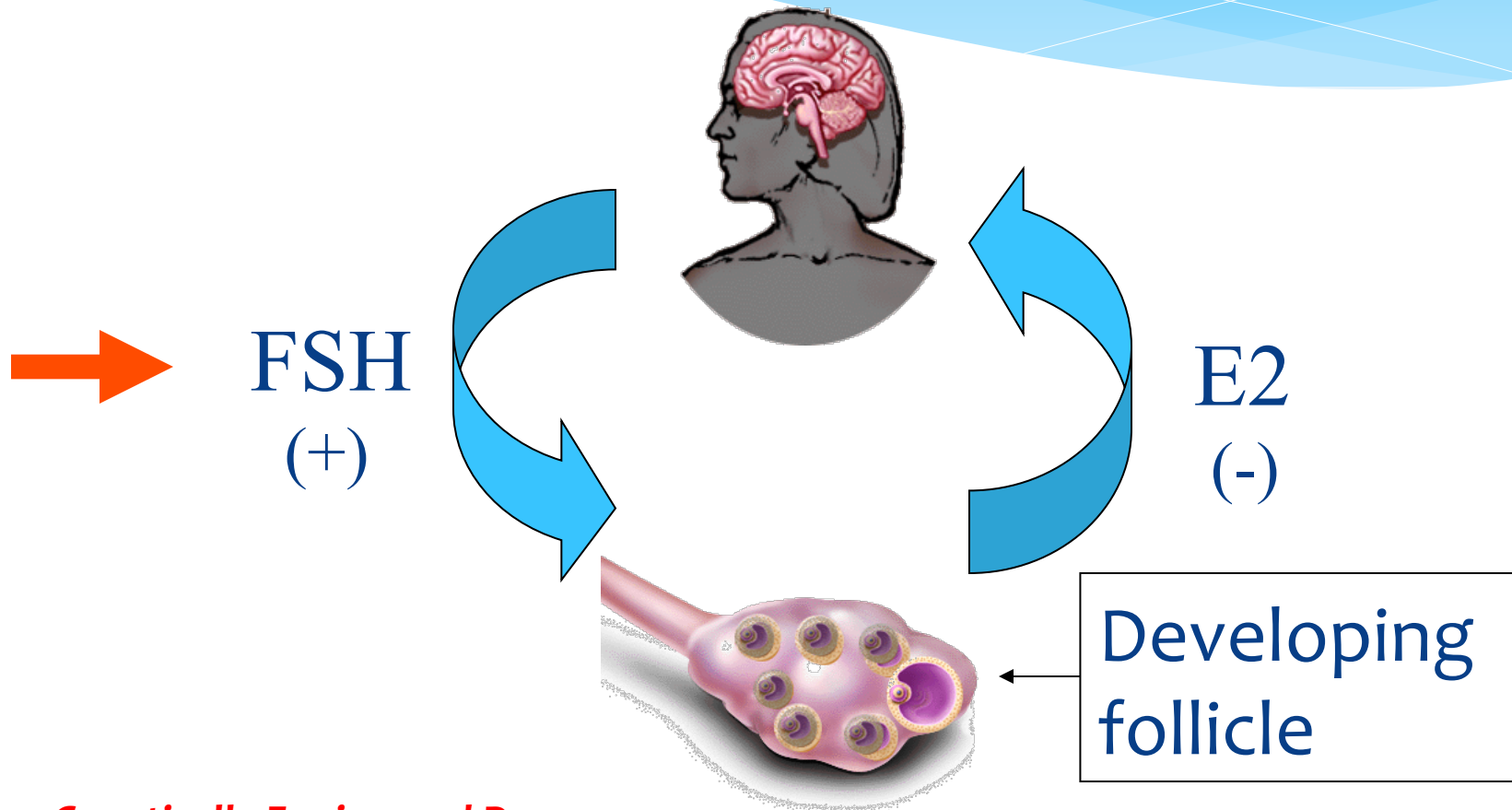
How Does Clomid Work To Increase Egg Number?



FSH=Follicle Stimulating Hormone

E2=Estradiol

How Does Recombinant FSH Work To Increase Egg Number?

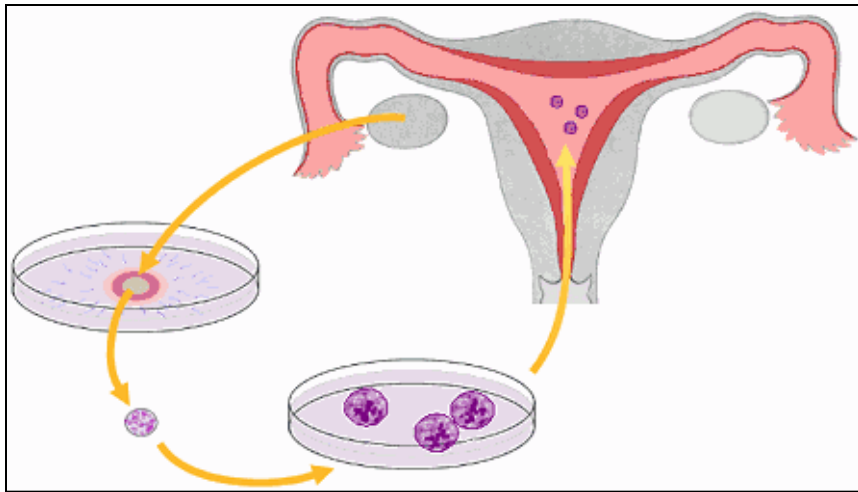


Genetically Engineered Drug

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"?

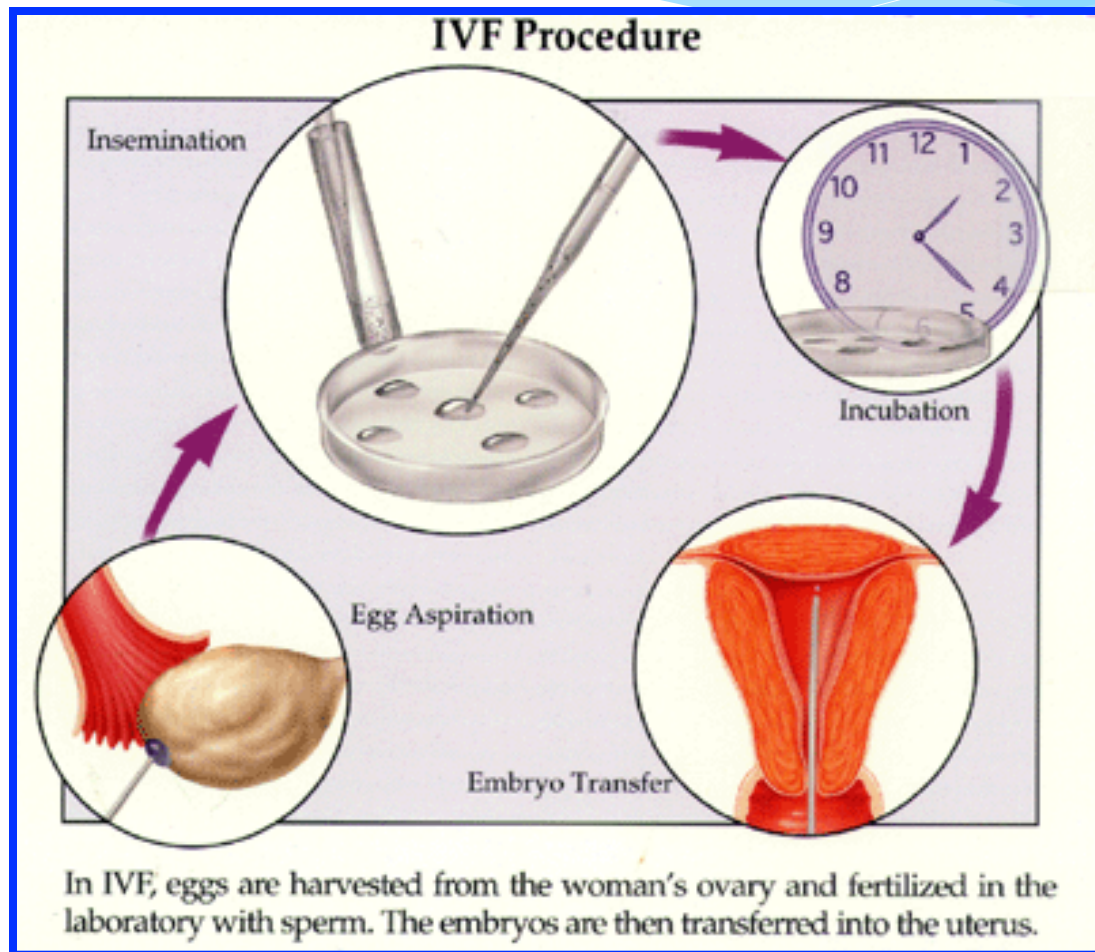
a. Yes

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)



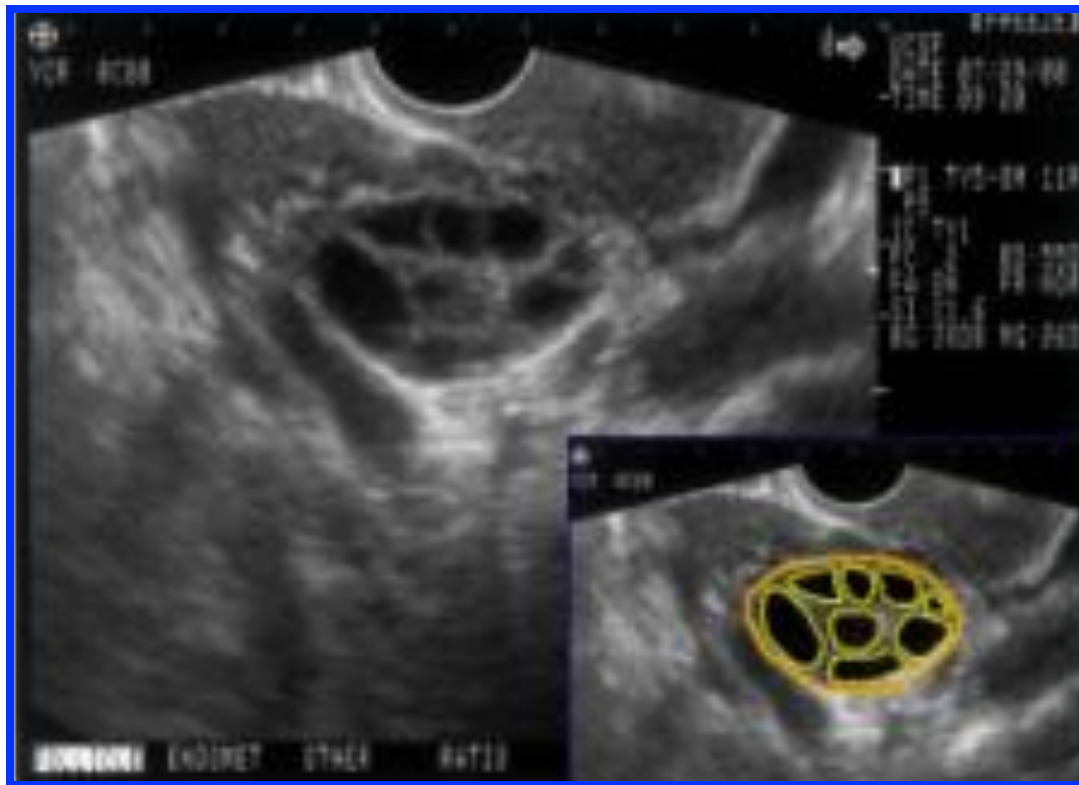
IVF Statistics-2009 (Latest Report)

- **475 U.S. clinics offer IVF** (441 reporting data to CDC)
- **146,256 cycles of ART treatment**
- **17,697 donor oocyte cycles**
- **45,870 deliveries (birth of 60,190 infants-1% of all infants born in US)**

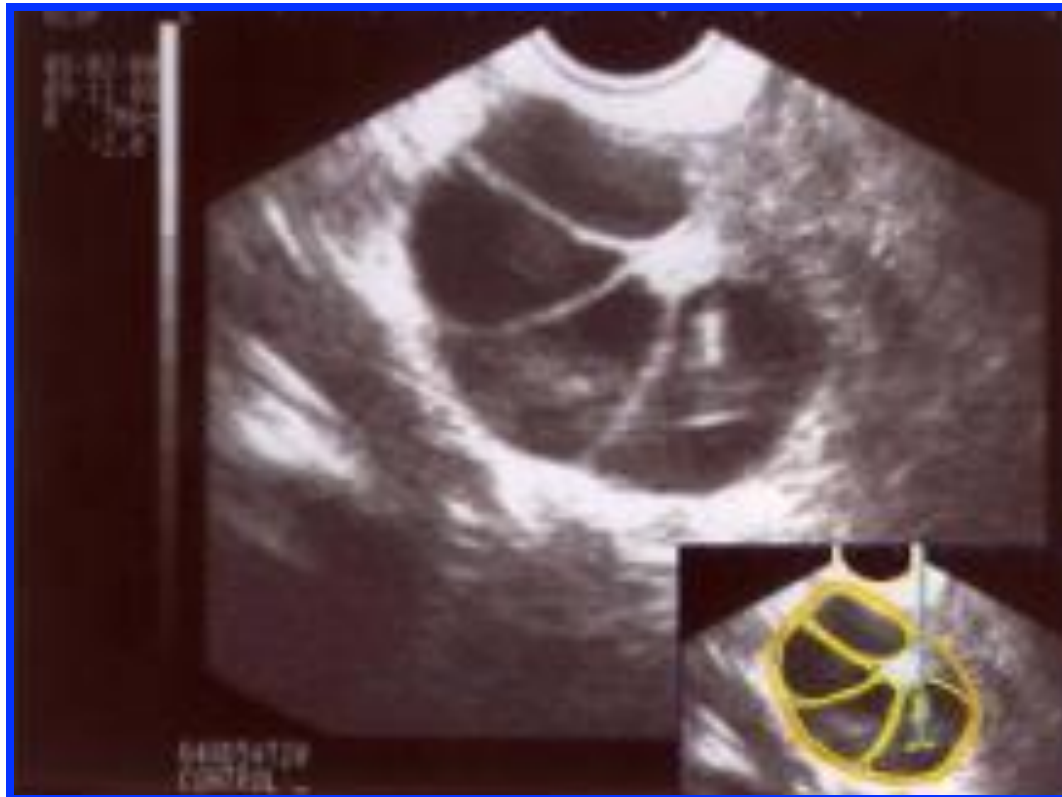
Who Needs IVF?

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

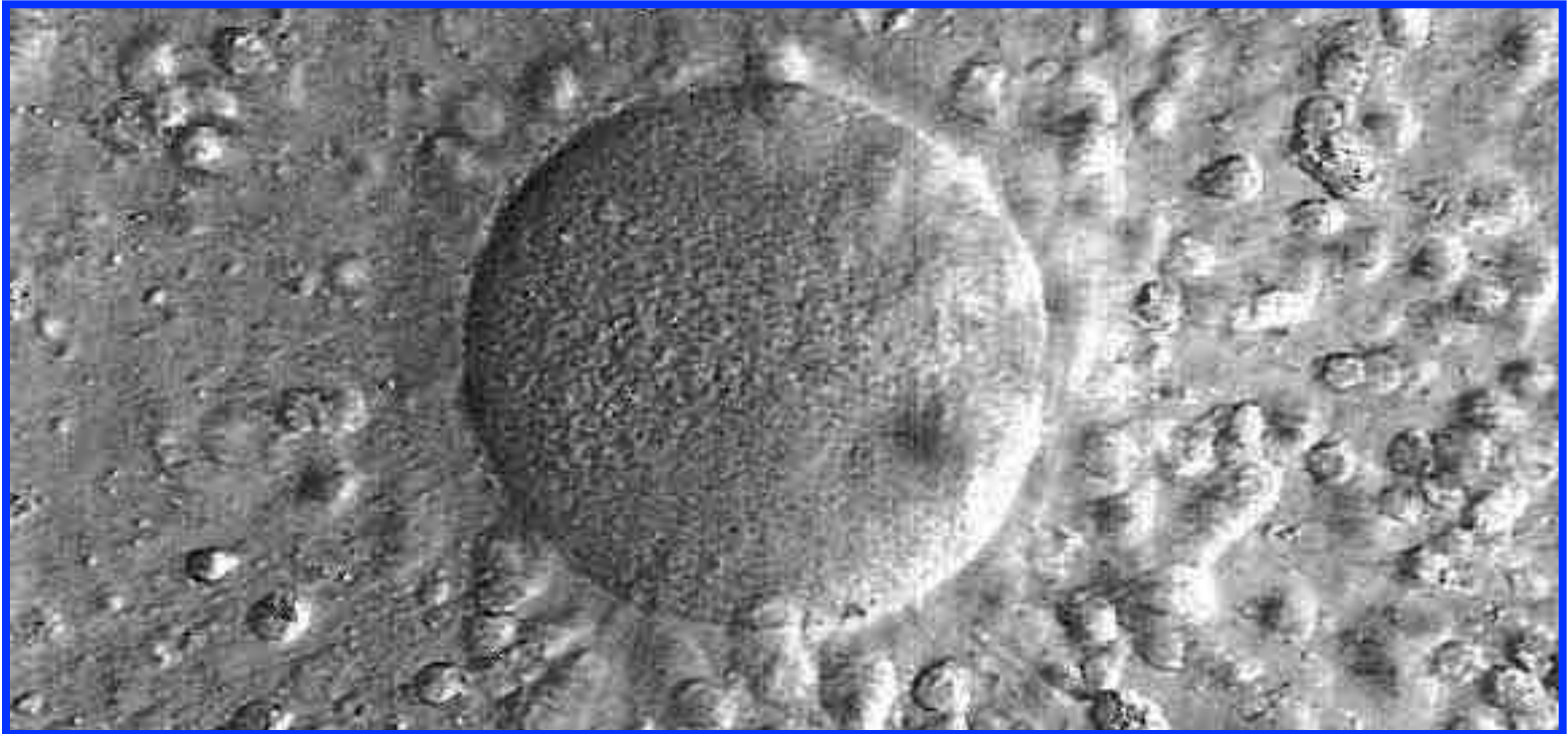
Ovarian Hyperstimulation



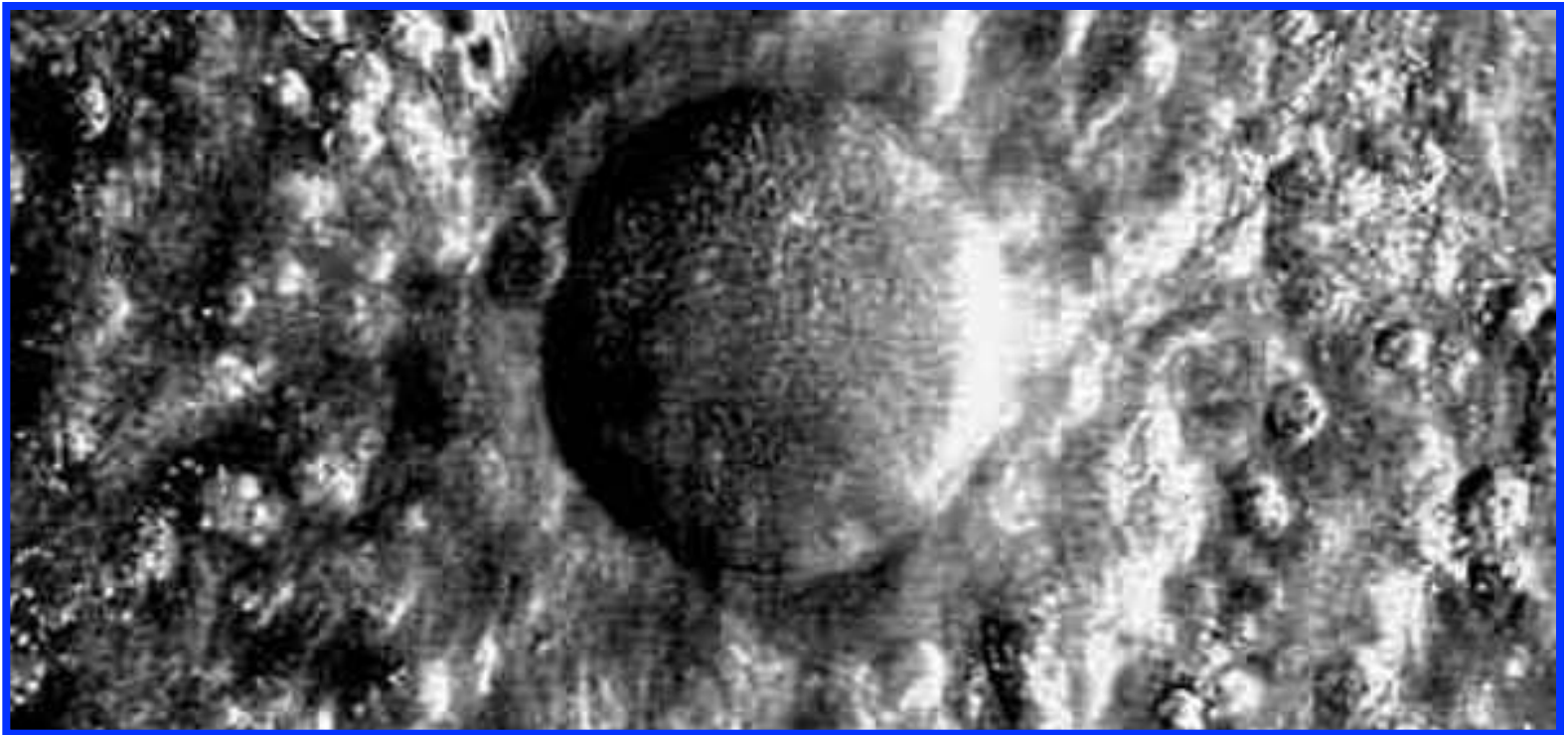
Egg Retrieval



Good Egg



Bad Egg

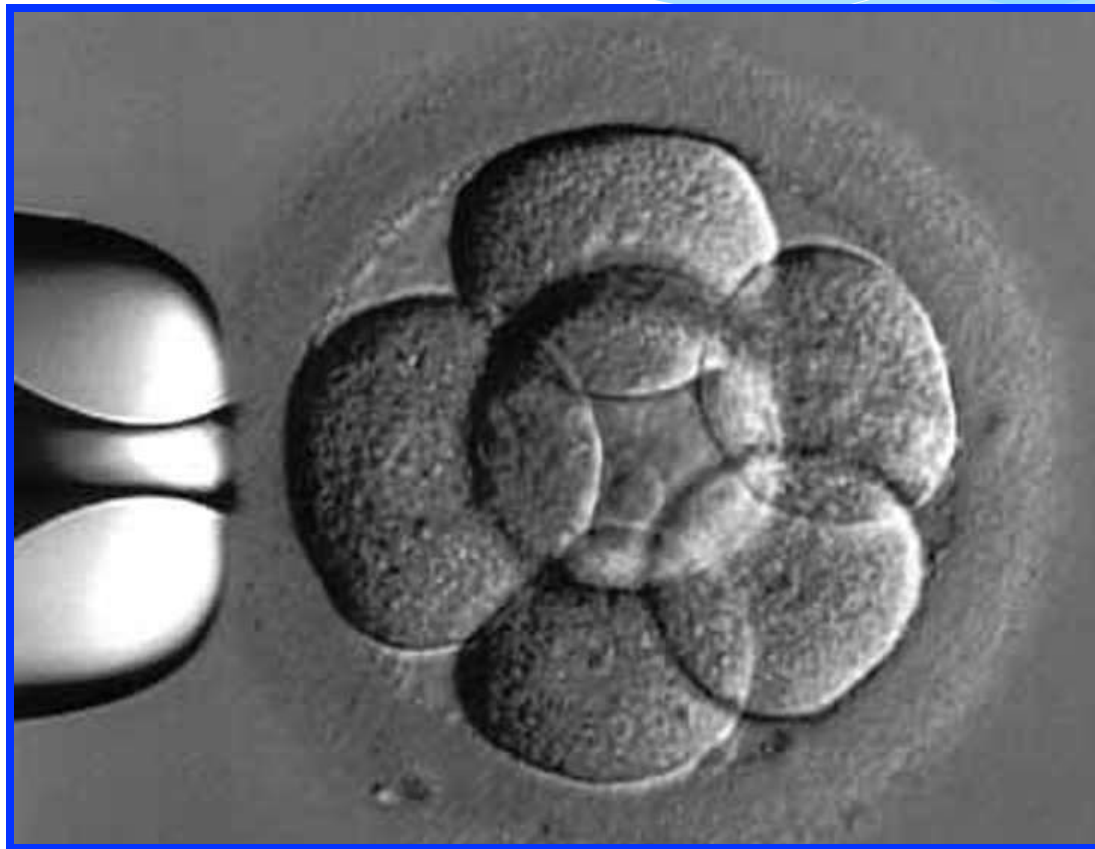


Fertilization



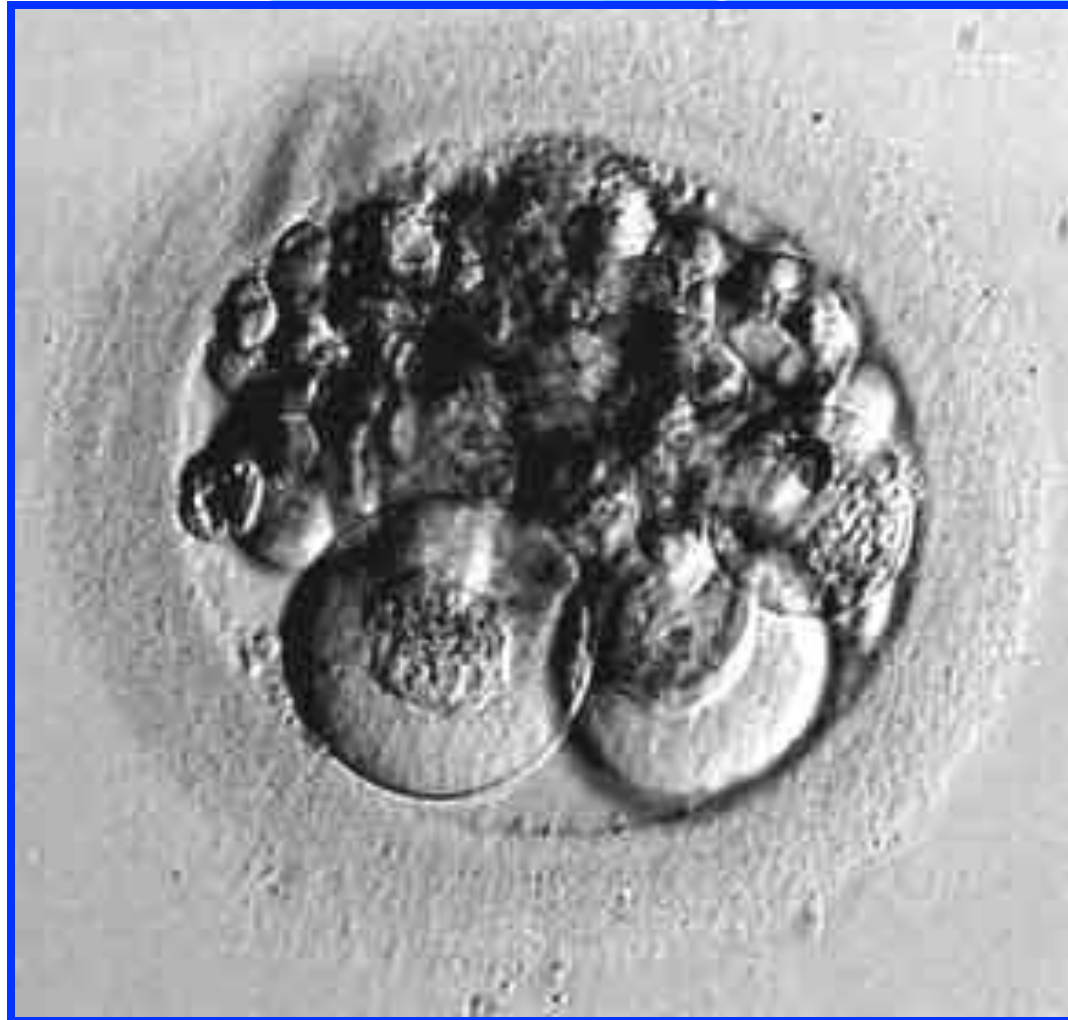
- 2 Pronuclei (2PN)
- 1 day after egg retrieval

Day 3 Embryo



Pre-Implantation Genetic Testing Stage

Day 3 Embryo



Blastocyst – Day 5

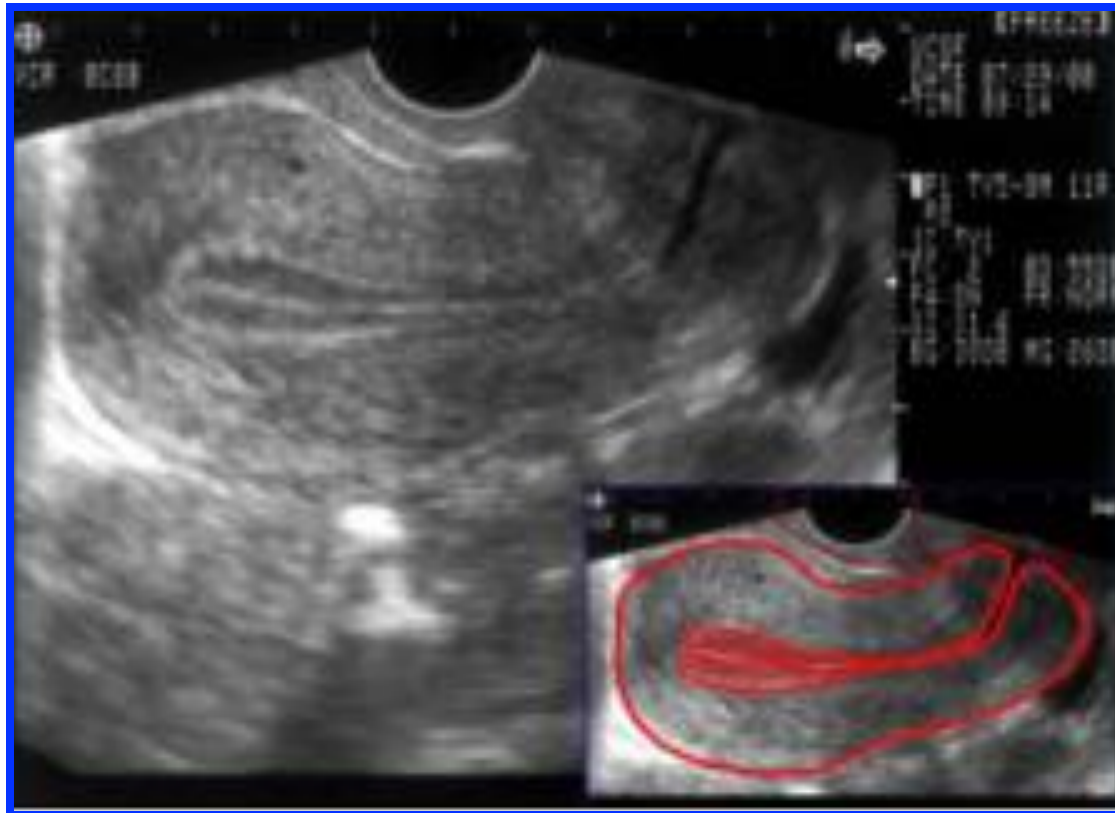


Source of Stem Cells

Hatching Blastocyst



Embryo Transfer



Special IVF Procedures

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

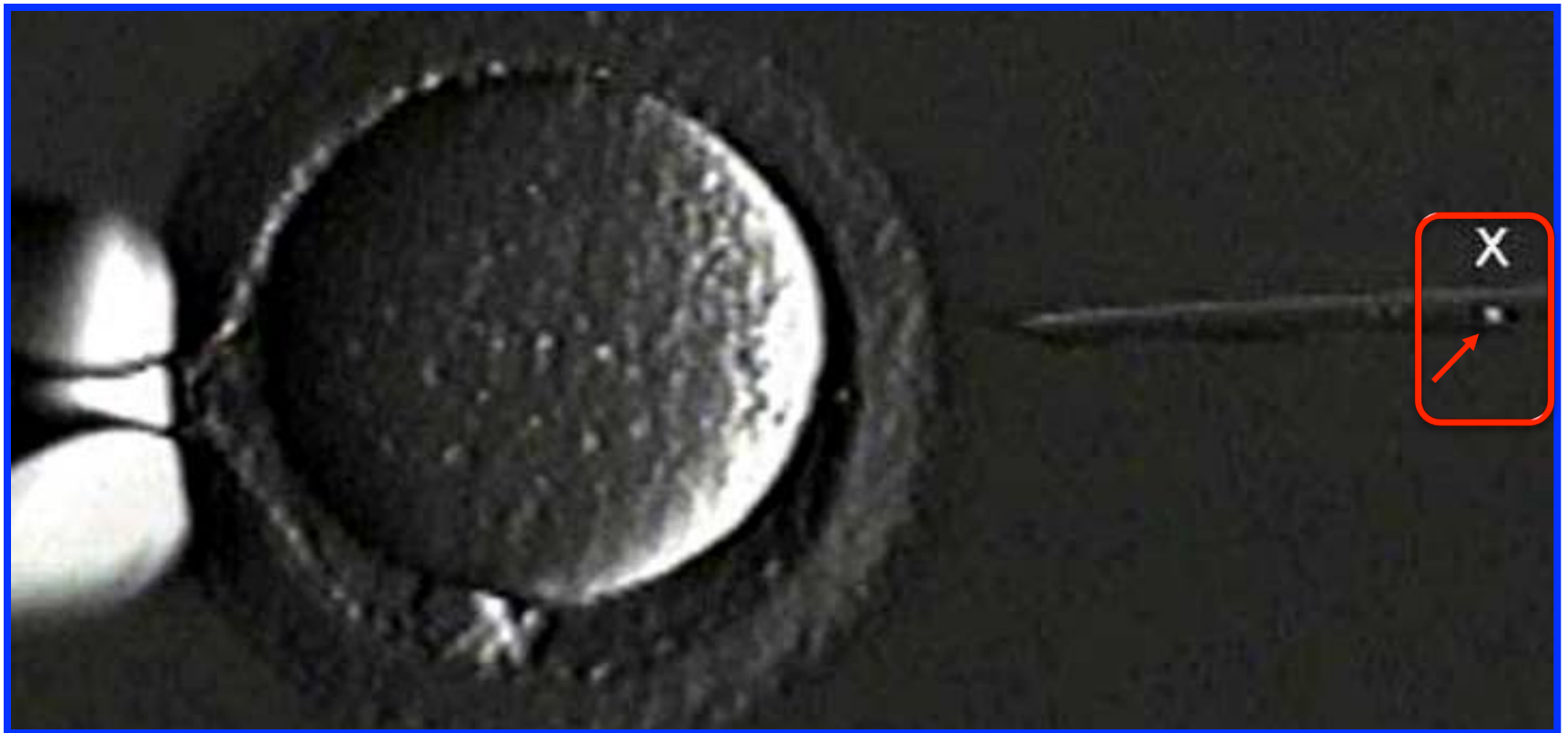
Assisted Hatching



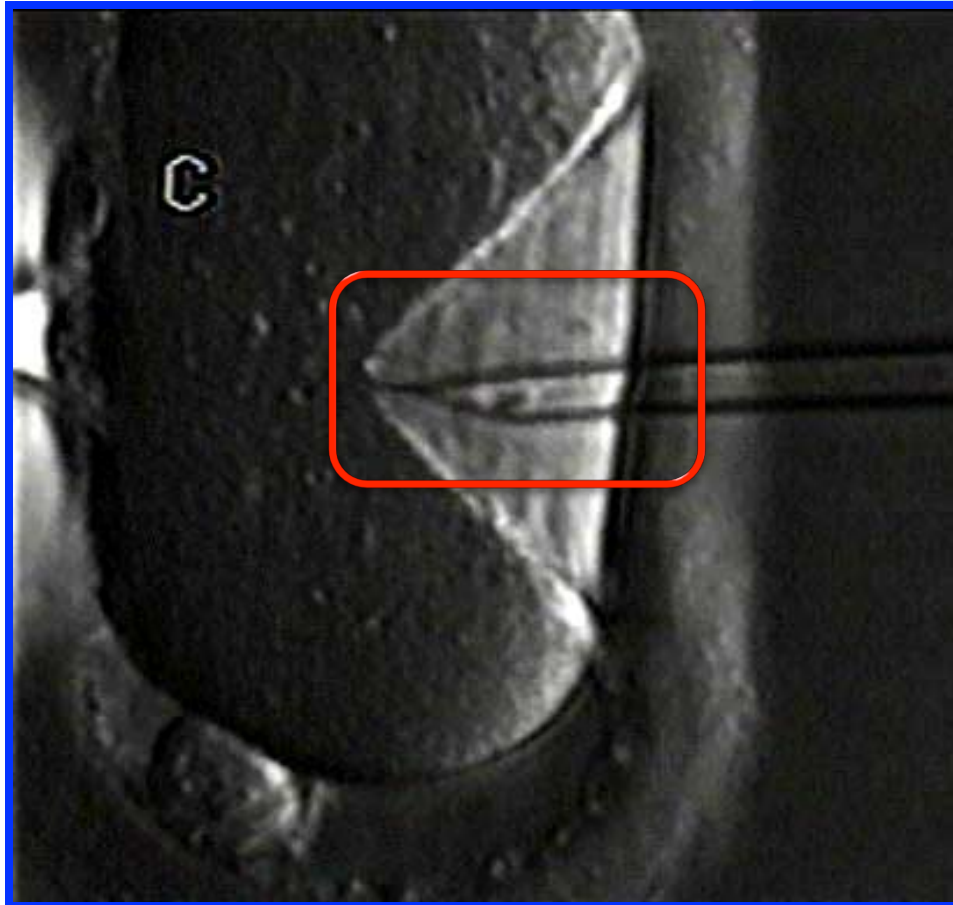
Empty Zona



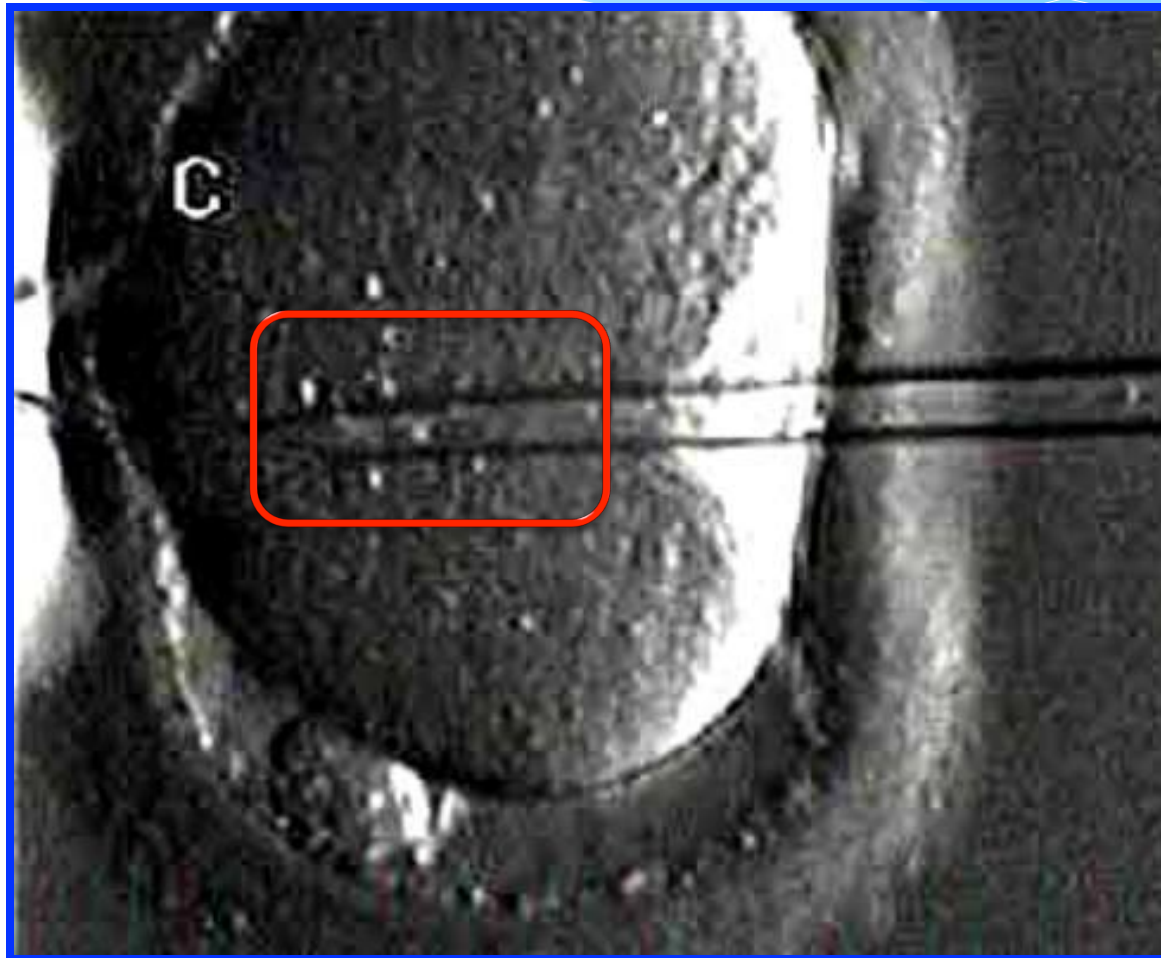
ICSI



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 - 2009

- **U.S. Fertility Centers From SART/CDC**
- **Female age**
 - **<35 – 43%**
 - **35-37 – 33%**
 - **38-40 – 22%**
 - **41-42 – 11%**
 - **43-44 – 4%**
 - **> 44 – 1-2%**

IVF Statistics - 2008

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

Singleton Pregnancy



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
to learn more about becoming an exceptional egg donor.*



Would you consider being an egg or sperm donor?

a. Yes

b. No



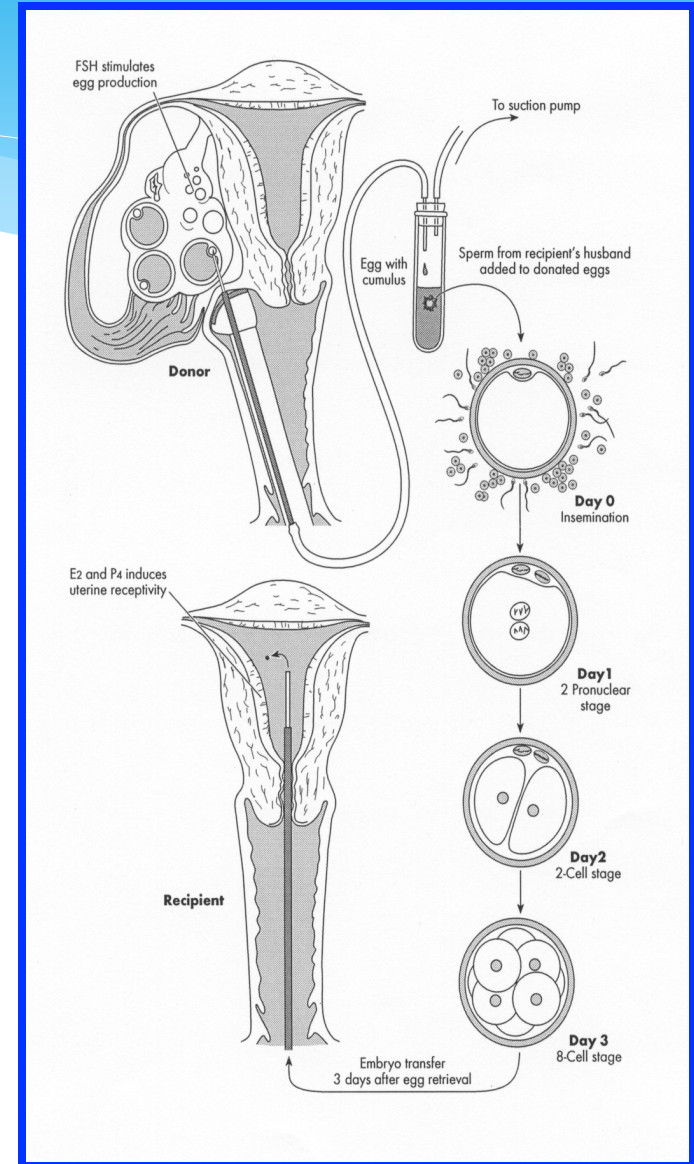
Have you ever been an egg or sperm donor?

a. Yes

b. No

Egg donation

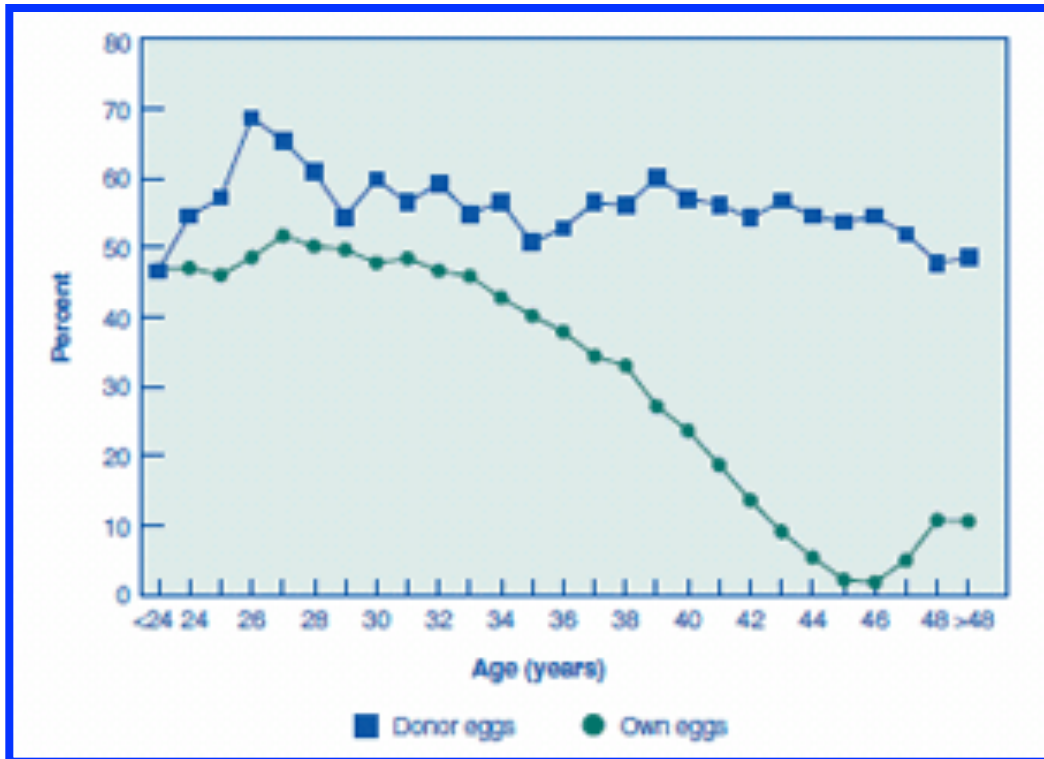
- IVF for two
- Donor
 - Standard controlled ovarian hyperstimulation
 - Egg retrieval
- Recipient
 - Embryo transfer



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



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.

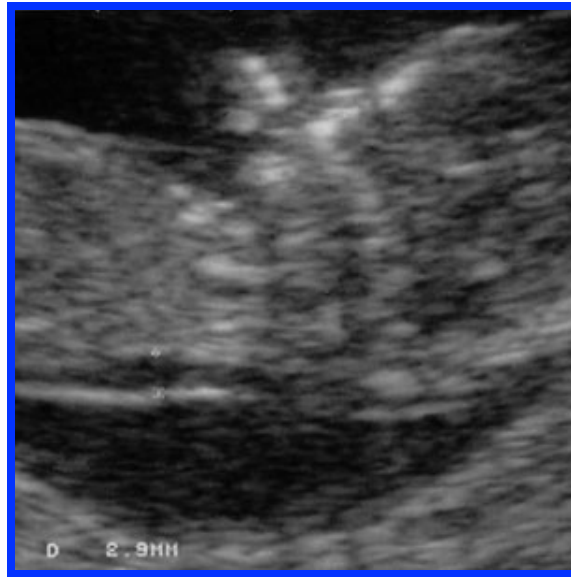
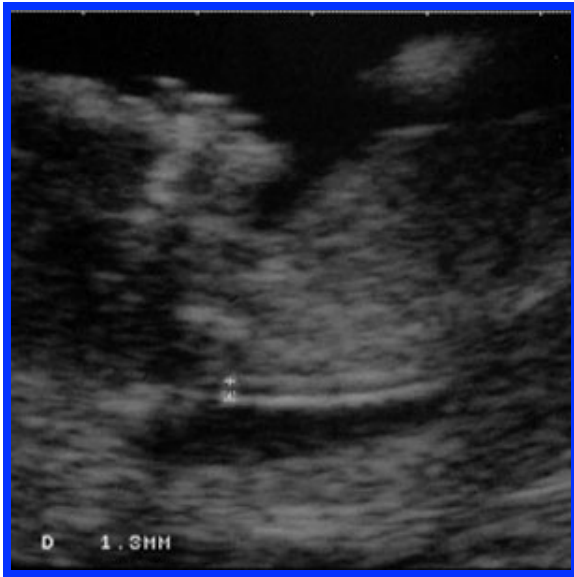
Prenatal Testing

- 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

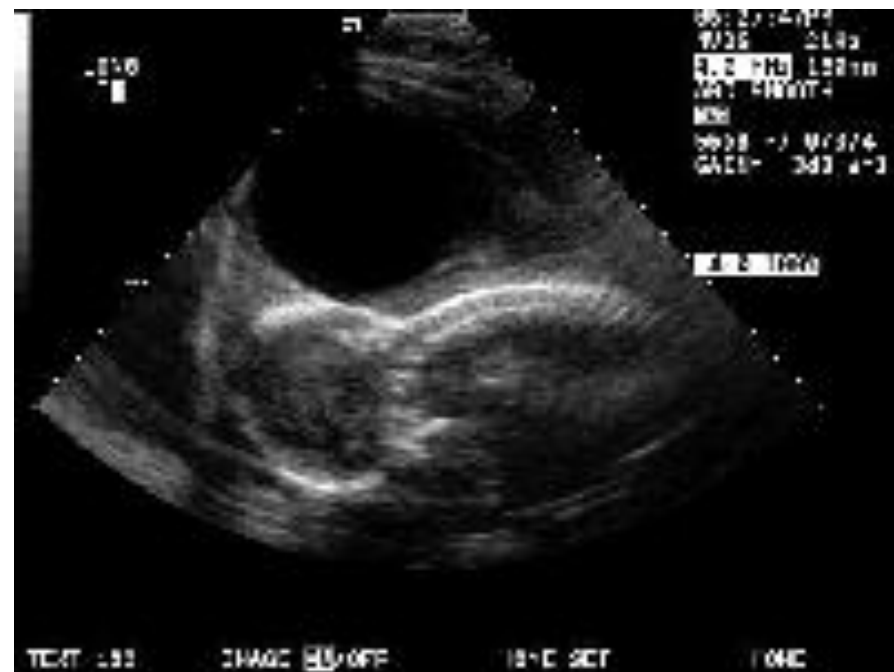
Ultrasound Abnormalities



Echogenic bowel loops



Ultrasound Abnormalities



Prenatal Tests - Serum

- 15-20 weeks gestation
- Quad Screen
 - Tests for AFP, hCG, uE₃ and inhibin A
 - Neural tube defects, Down syndrome, Trisomy 18, Abdominal wall defects
 - Readjusts age-related risks

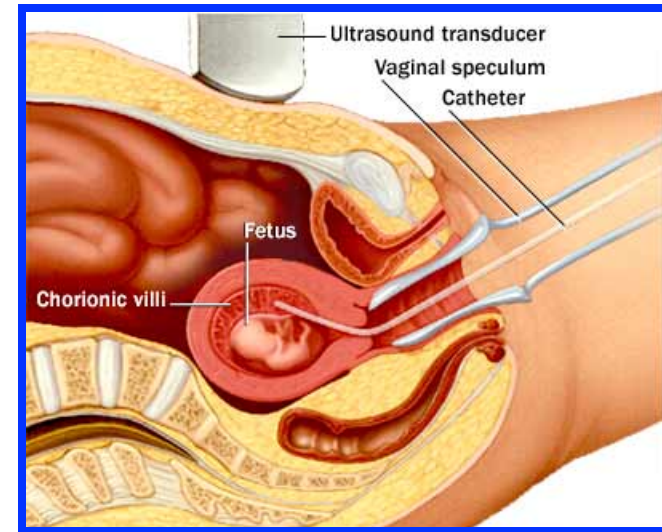
Prenatal Tests

- **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

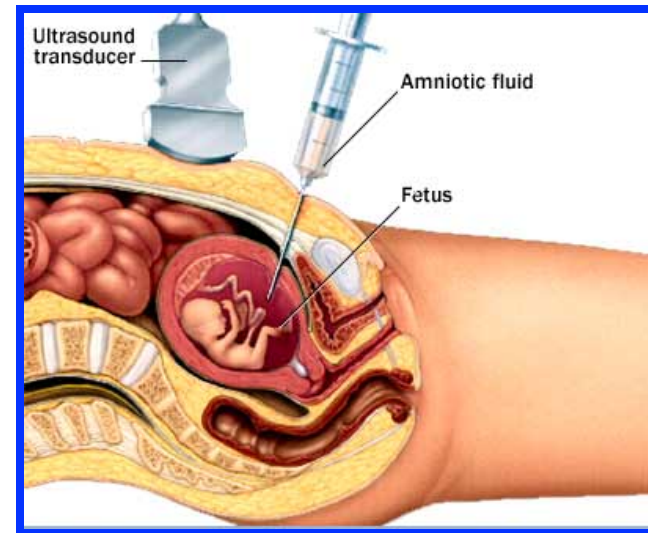
• Chorionic Villus Sampling

- ❑ 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



PRENATAL DIAGNOSIS

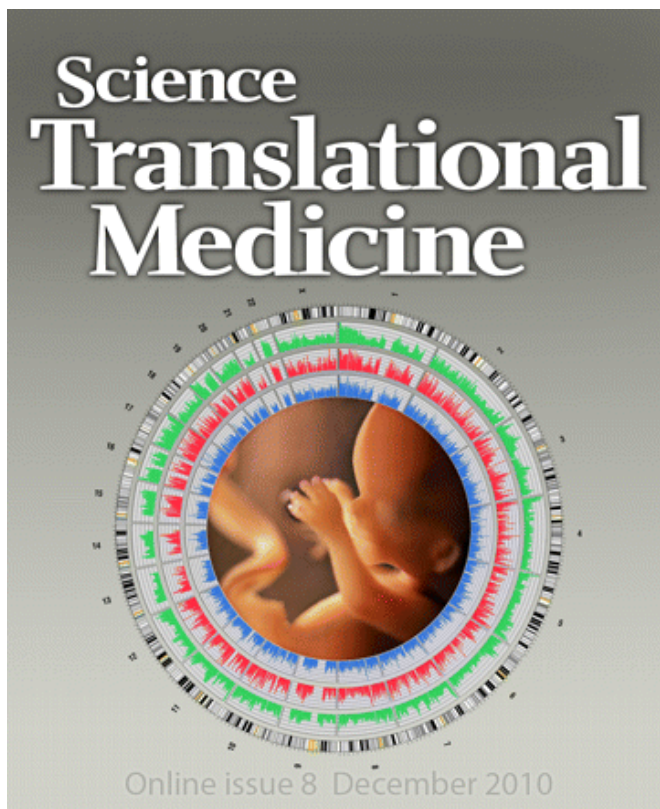
Maternal Plasma DNA Sequencing Reveals the Genome-Wide Genetic and Mutational Profile of the Fetus

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)²
3-Hydroxy Long Chain Acyl-CoA Dehydrogenase Deficiency (LCHAD)
2,4-Dienoyl-CoA Reductase Deficiency²
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

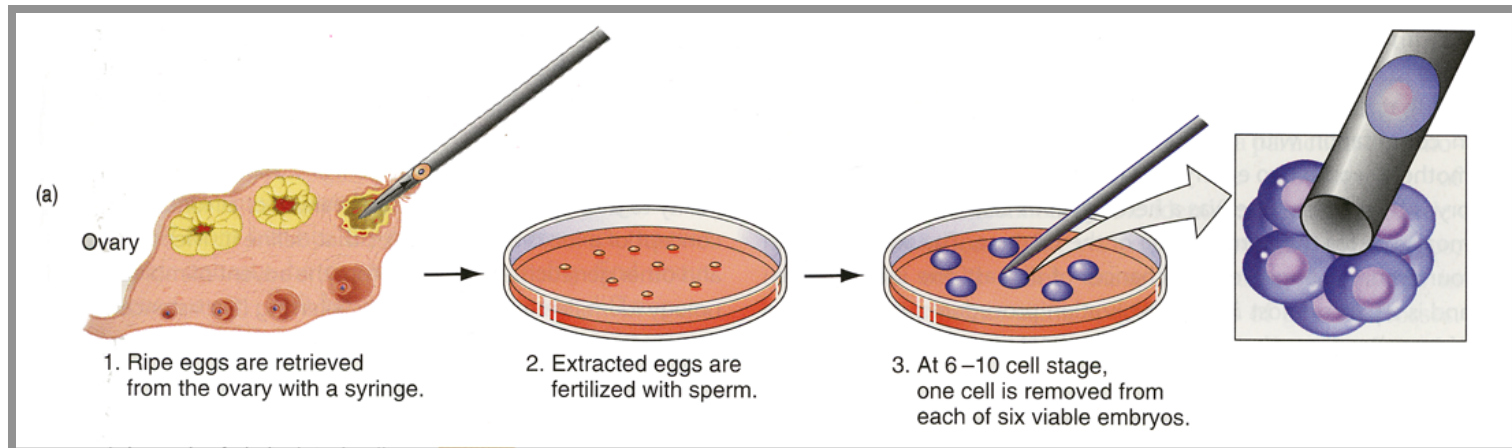
Argininemia
Argininosuccinic Aciduria (ASA Lyase Deficiency)
 Acute onset
 Late onset
Carbamoylphosphate Synthetase Deficiency (CPS Def.)²
Citrullinemia (ASA Synthetase Deficiency)
 Acute onset
 Late onset
Homocystinuria
Hypermethioninemia
Hyperammonemia, Hyperornithinemia, Homocitrullinemia
 Syndrome (HHH)²
Hyperornithinemia with Gyral Atrophy²
Maple Syrup Urine Disease (MSUD)
 Classical MSUD
 Intermediate MSUD
5-Oxoprolinuria (pyroglutamic Aciduria)²
Phenylketonuria (PKU)
 Classical PKU
 Hyperphenylalaninemia
 Biotpterin Cofactor Deficiencies (4)
Tyrosinemia
Transient Neonatal Tyrosinemia
 Tyrosinemia Type I (Tyr I)²
 Tyrosinemia Type II (Tyr II)
 Tyrosinemia Type III (Tyr III)

Other Abnormal Profiles

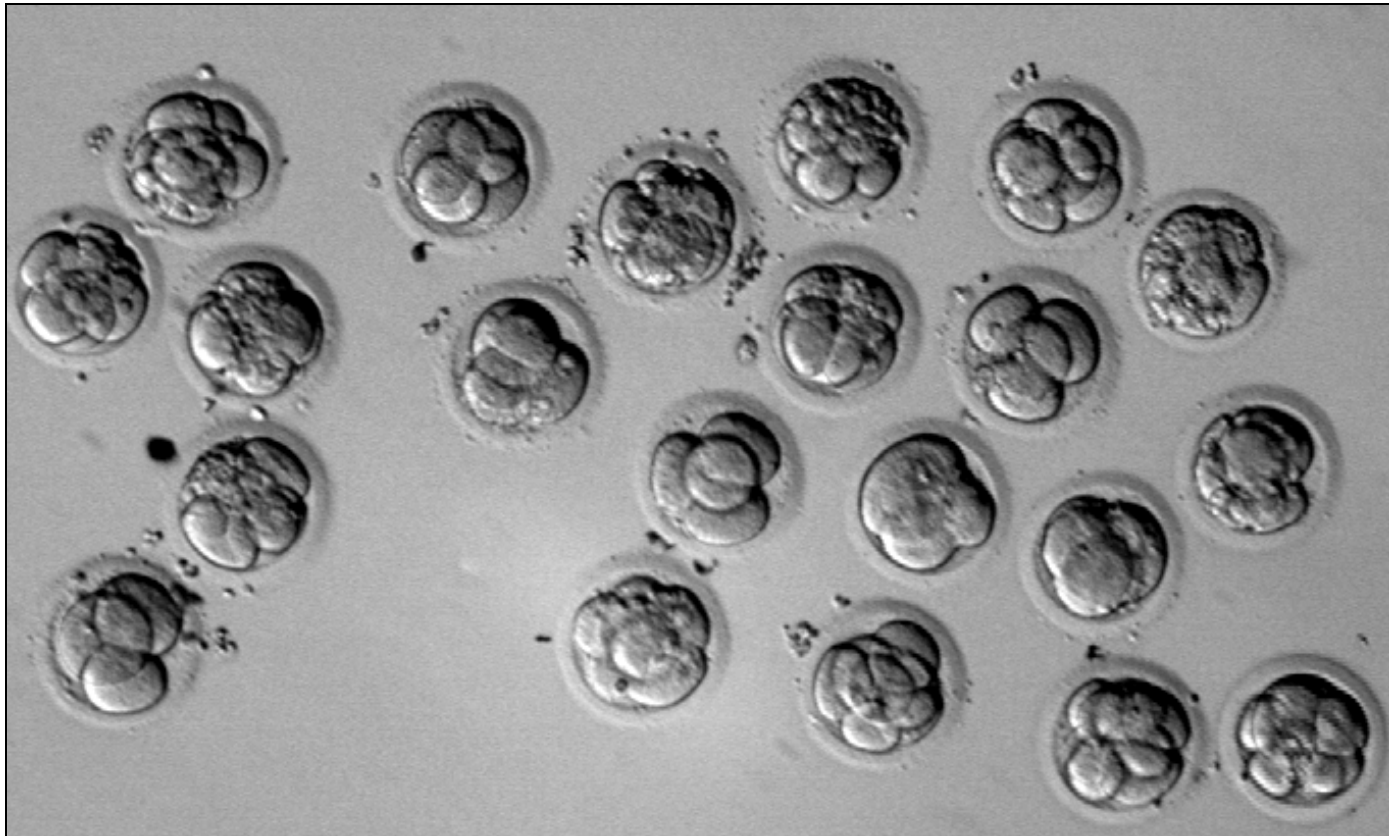
Hyperalimentation
Liver Disease
Medium Chain Triglyceride (MCT) Oil Administration
Presence of EDTA Anticoagulants in blood specimen
Treatment with Benzoate, Pyvalic Acid, or Valproic Acid
Carnitine Uptake Deficiency²

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

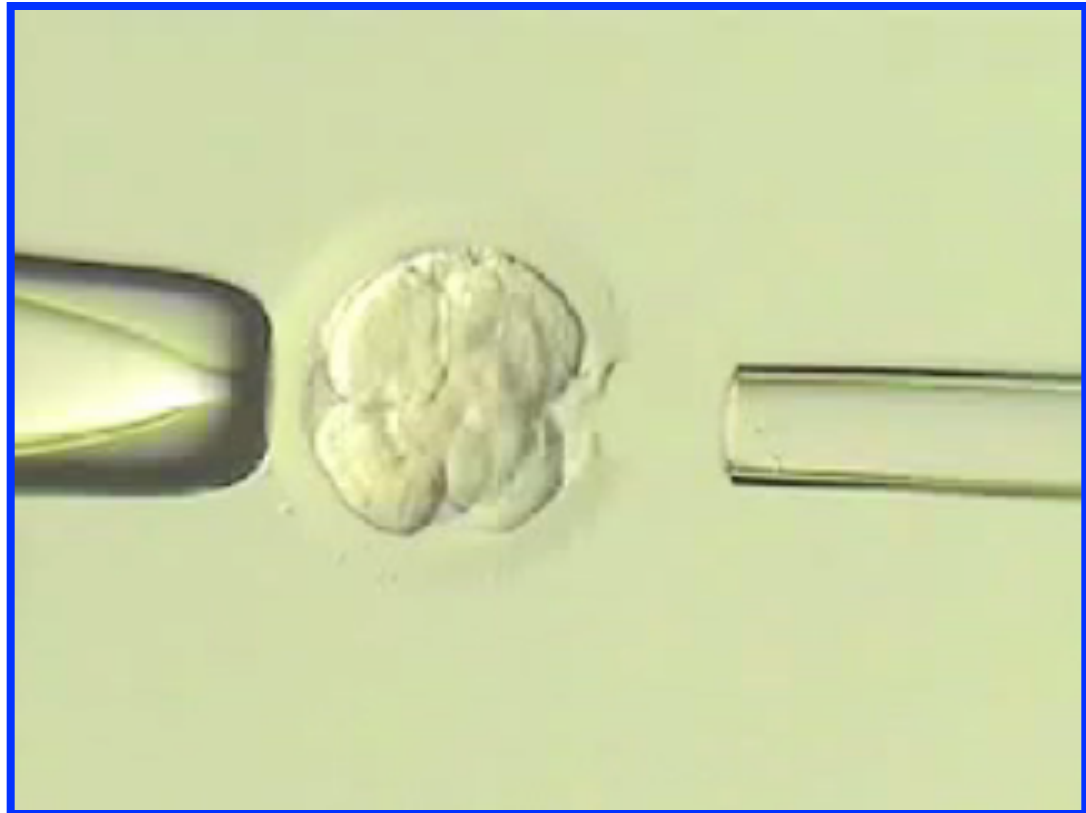
- Achondroplasia
- ADPKD1
- ADPKD2
- Adrenoleukodystroph
- Age-related aneuploidies
- Alpha-thalassemia
- Alpha-1-antitrypsin
- Alport disease
- Amyloid precursor protein (APP) mutation
- ARPKD
- Becker muscular dystrophy
- Beta-thalassemia
- Charcot Marie Tooth disease
- Chromosomal translocations
- 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

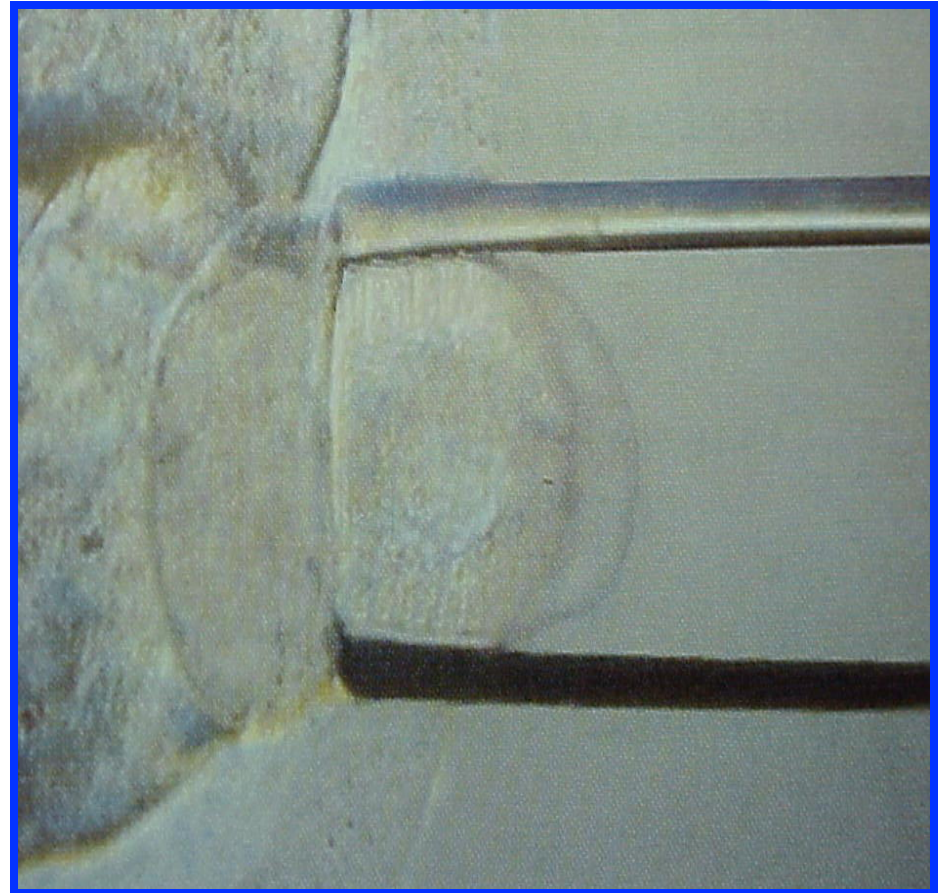
PGS

- *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.

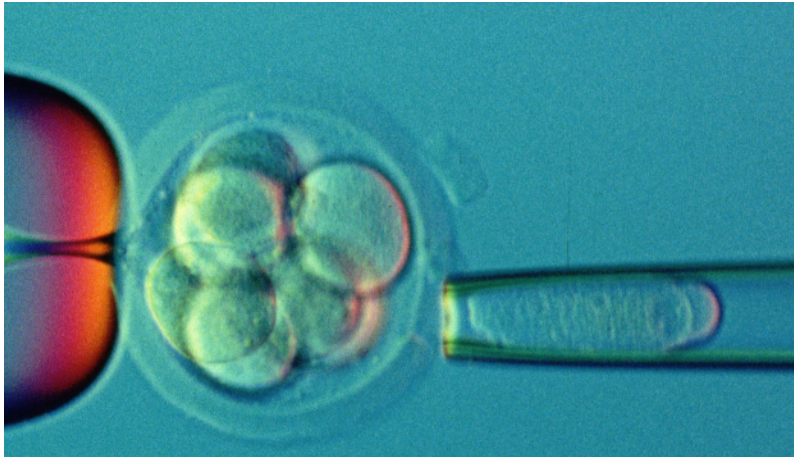


PGS

- 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



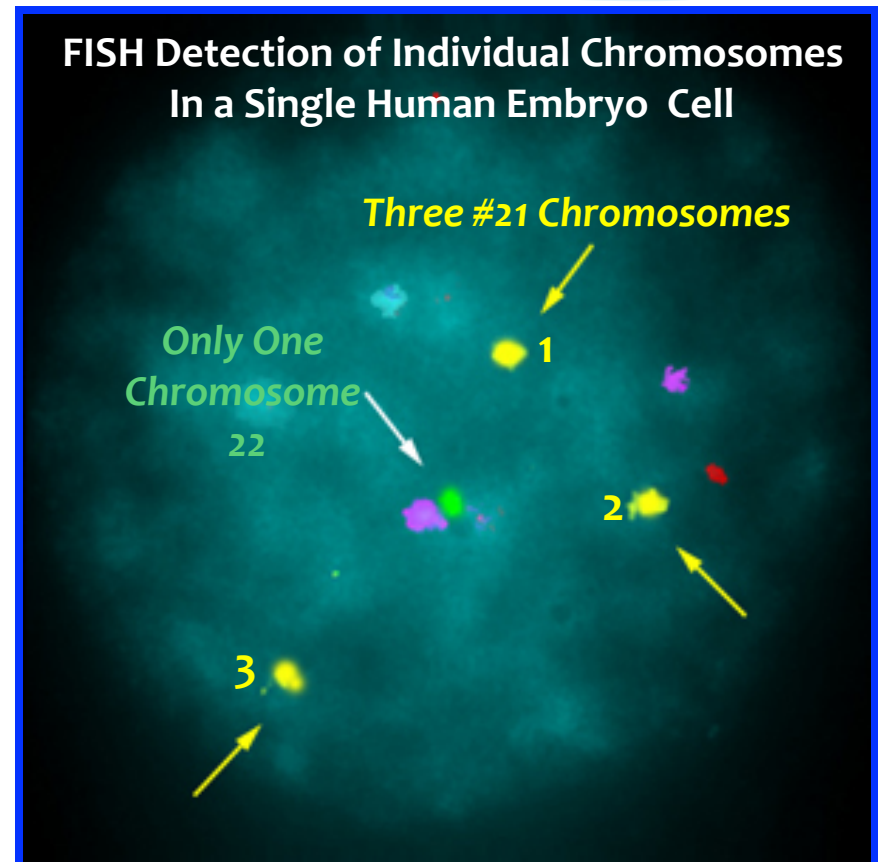
- <67 hours post-retrieval
- Implantation rates significantly lower if >70 hours



- 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.



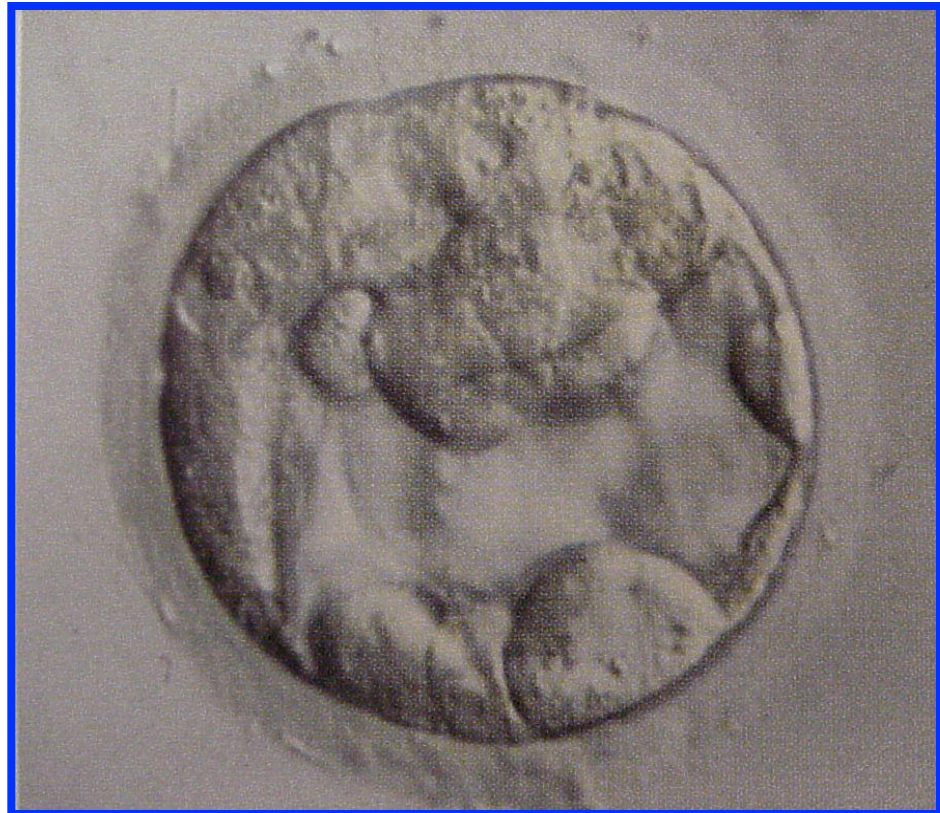
PGS

- 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.



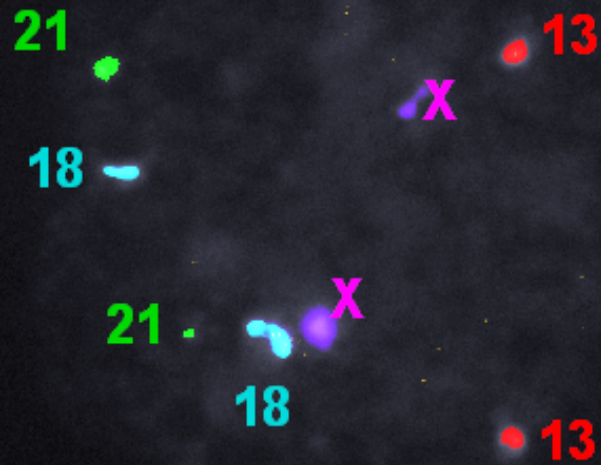
PGS

- 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.

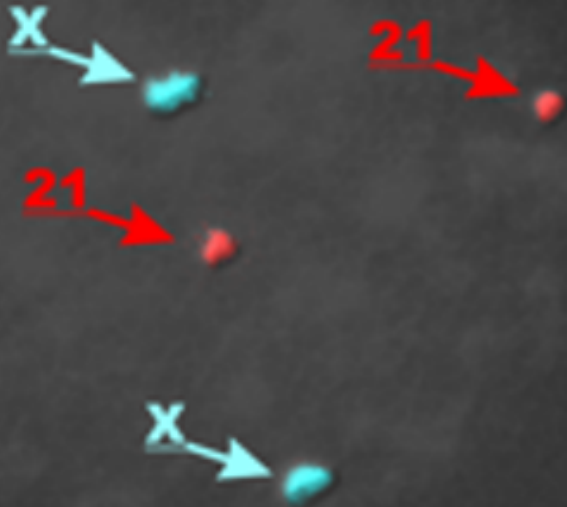


Five Chromosome PGS

Normal Female.



PGS – Female Embryo



female

- 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>
Cells	>100,000	1
Time	2 weeks	6-10 hrs
Accuracy	99%	99%
Cost	Covered	~\$5,000

Who Would Benefit From PGS?

Couples with a history of --

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

Couples who --

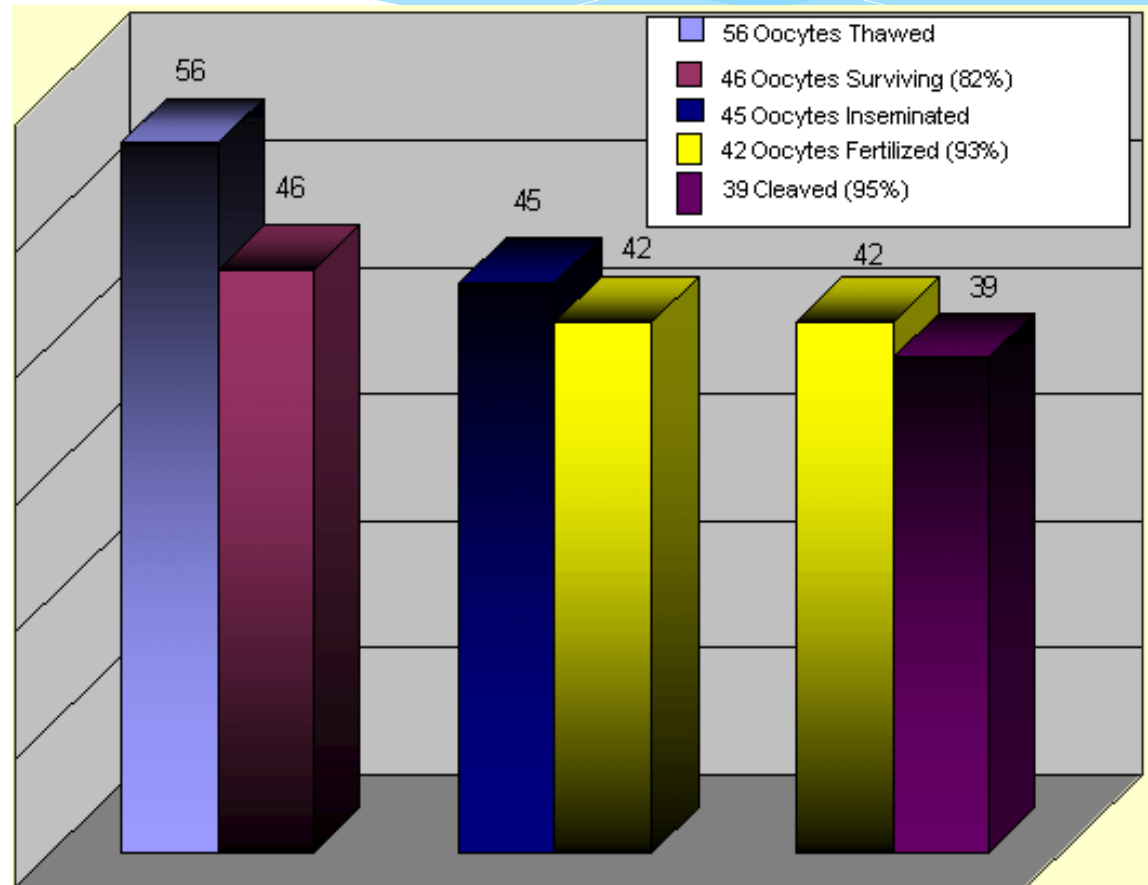
- Desire an offspring of a certain sex



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Specific 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

