بسم الله الرحمن الرحيم

Human fertility
&
In Vitro Fertilization

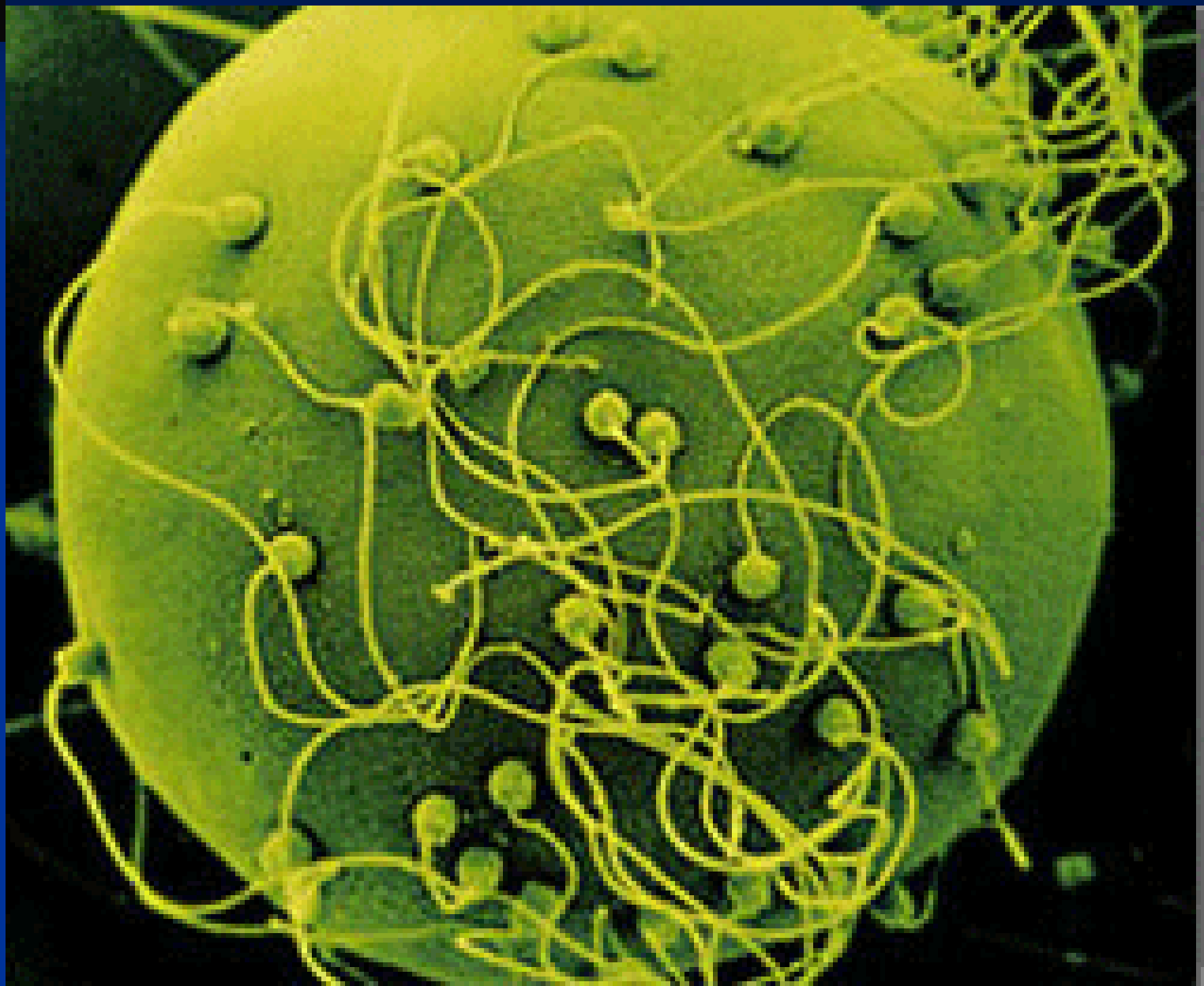
By:

Mustafa Hussien Ali

6th stage

Diyala university_college of medicine

Normal fertilization



Overview of Infertility

- If 100 just married couples begin having sexual relations (with no previous use of contraceptives) then within one year, 80 % of the women would be pregnant.
- Of the remainder, 10 % would be classified as subfertile
- But **10 % would be infertile.**

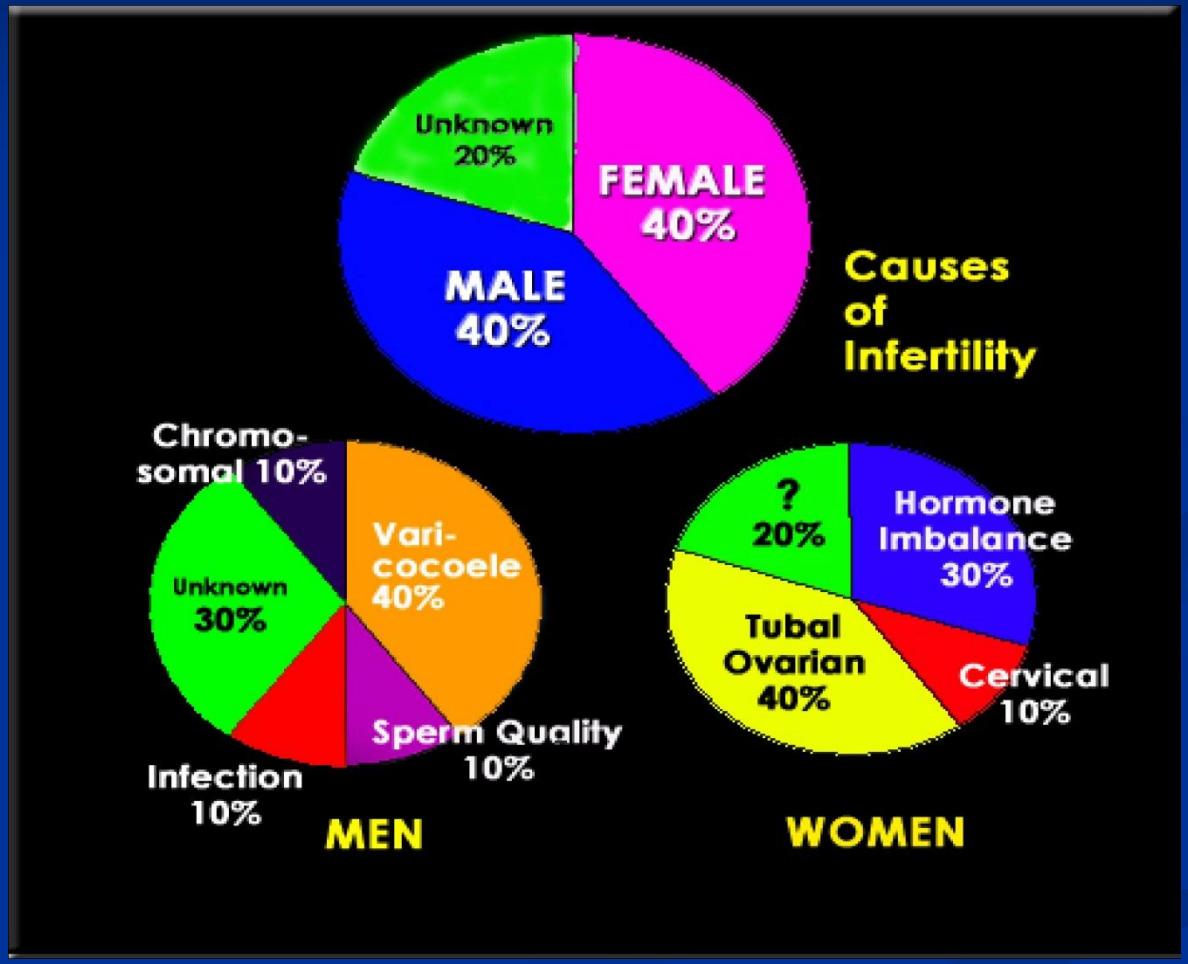
Infertility

- Problems in the male account for 25% of cases of infertility
- In the female 40 %
- And combined male/female problems in the remaining 35%.

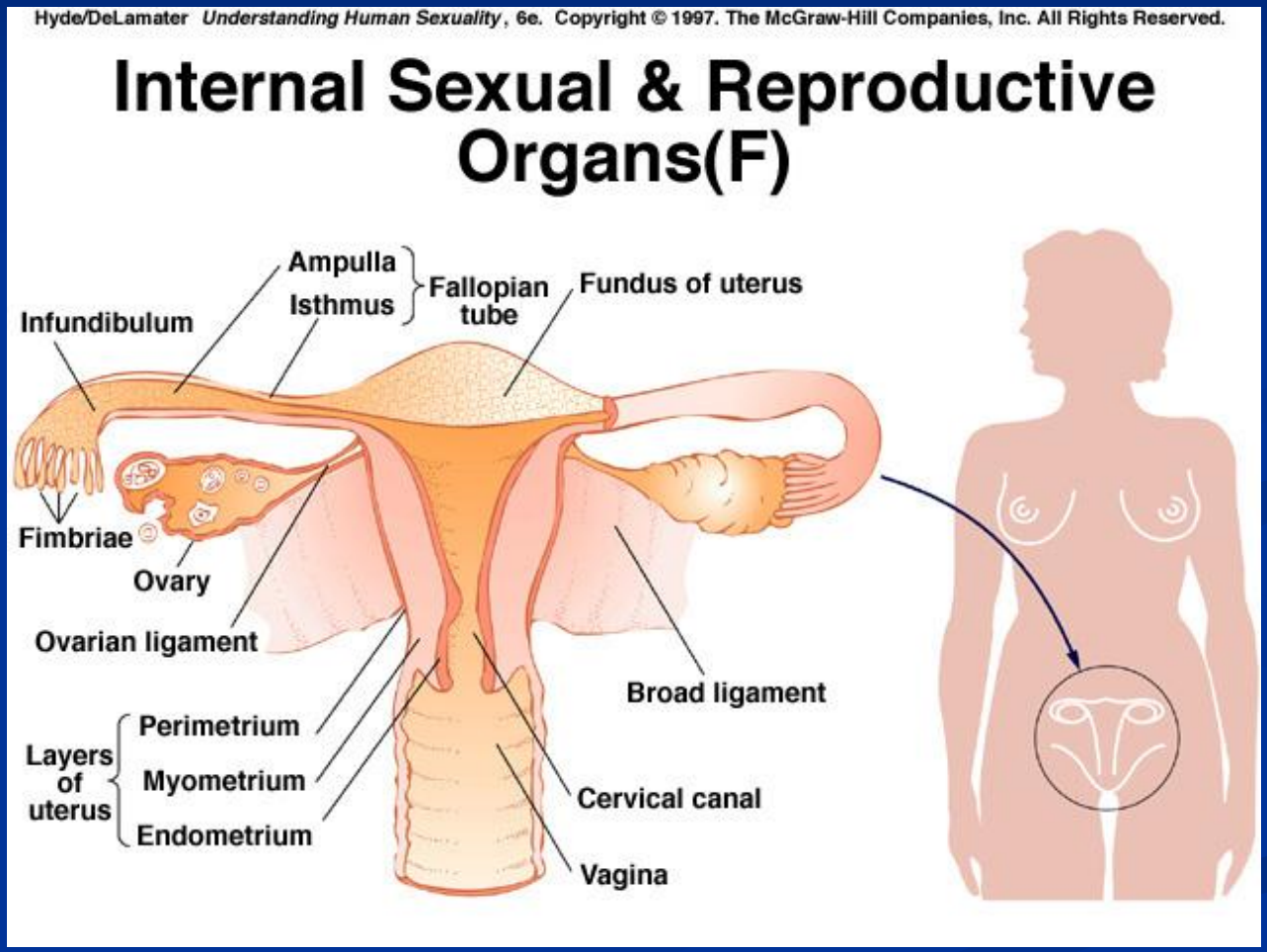
Causes of infertility(in general)

- Delayed marriages and later childbearing
- Sexually transmitted diseases
- Pollution
- Diet
- Lack of exercise
- Previous contraceptive use leading to sterility
- Sterility from previous abortion
- Falling sperm count in males (medicines, alcohol etc)

Causes of Infertility



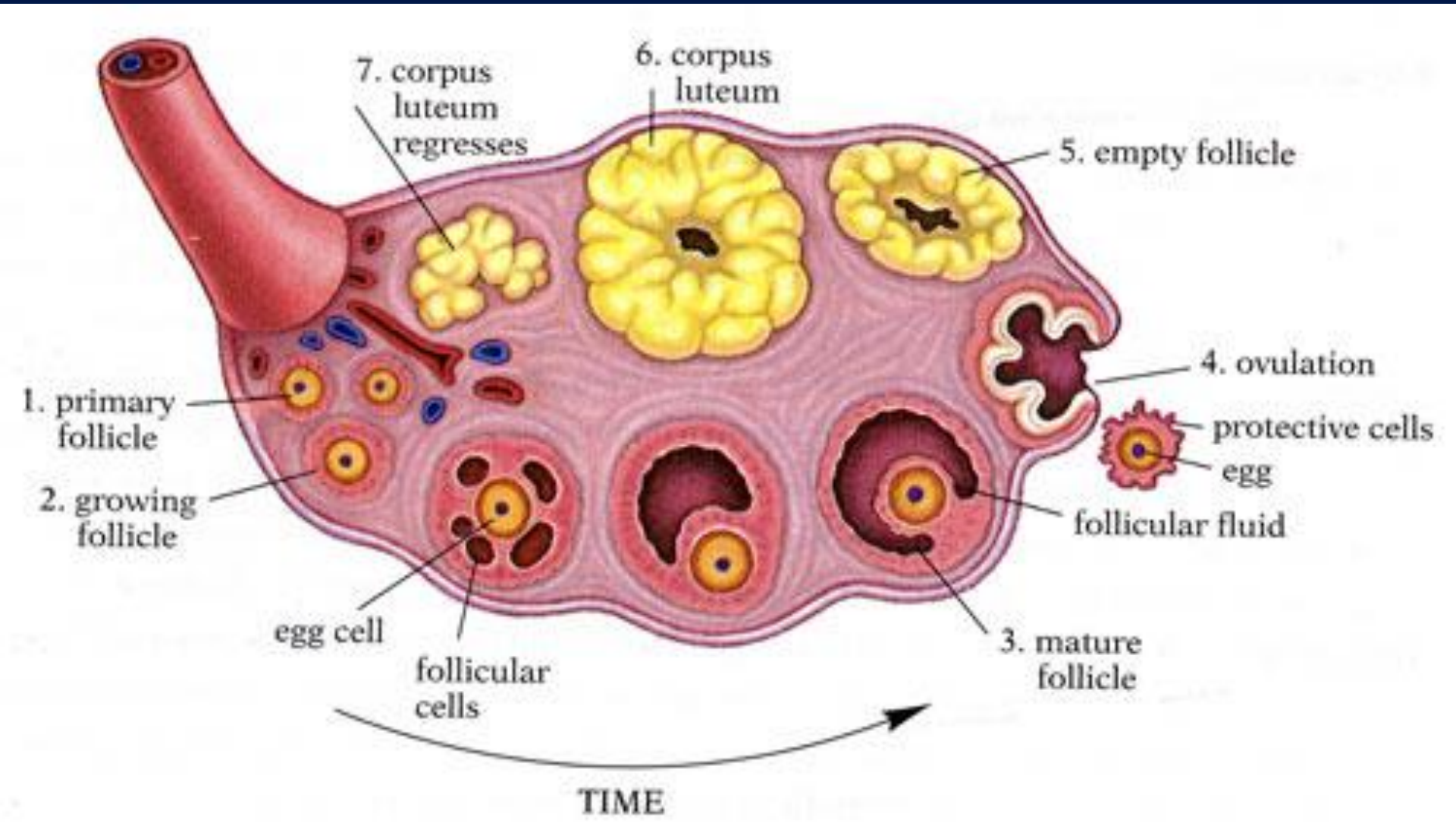
Female Reproductive Organs



Causes of Female Infertility

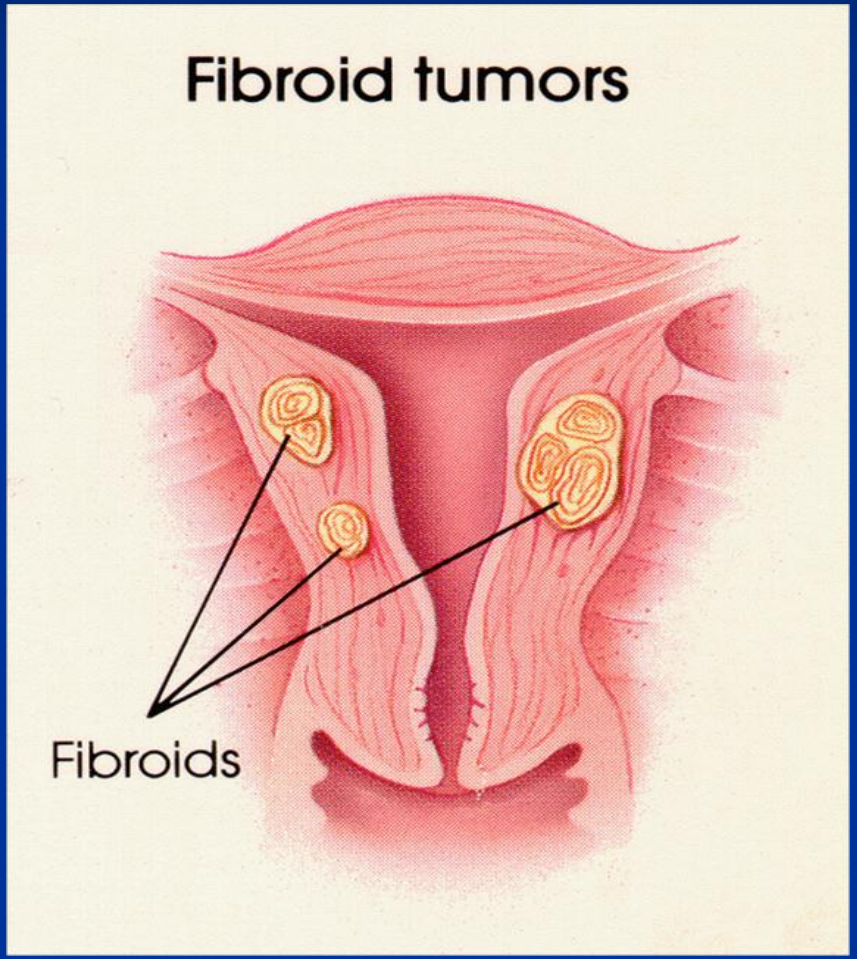
- Ovary
- Tubes
- Uterus
- Cervix
- Hormones
- Chromosomes

Normal ovulation



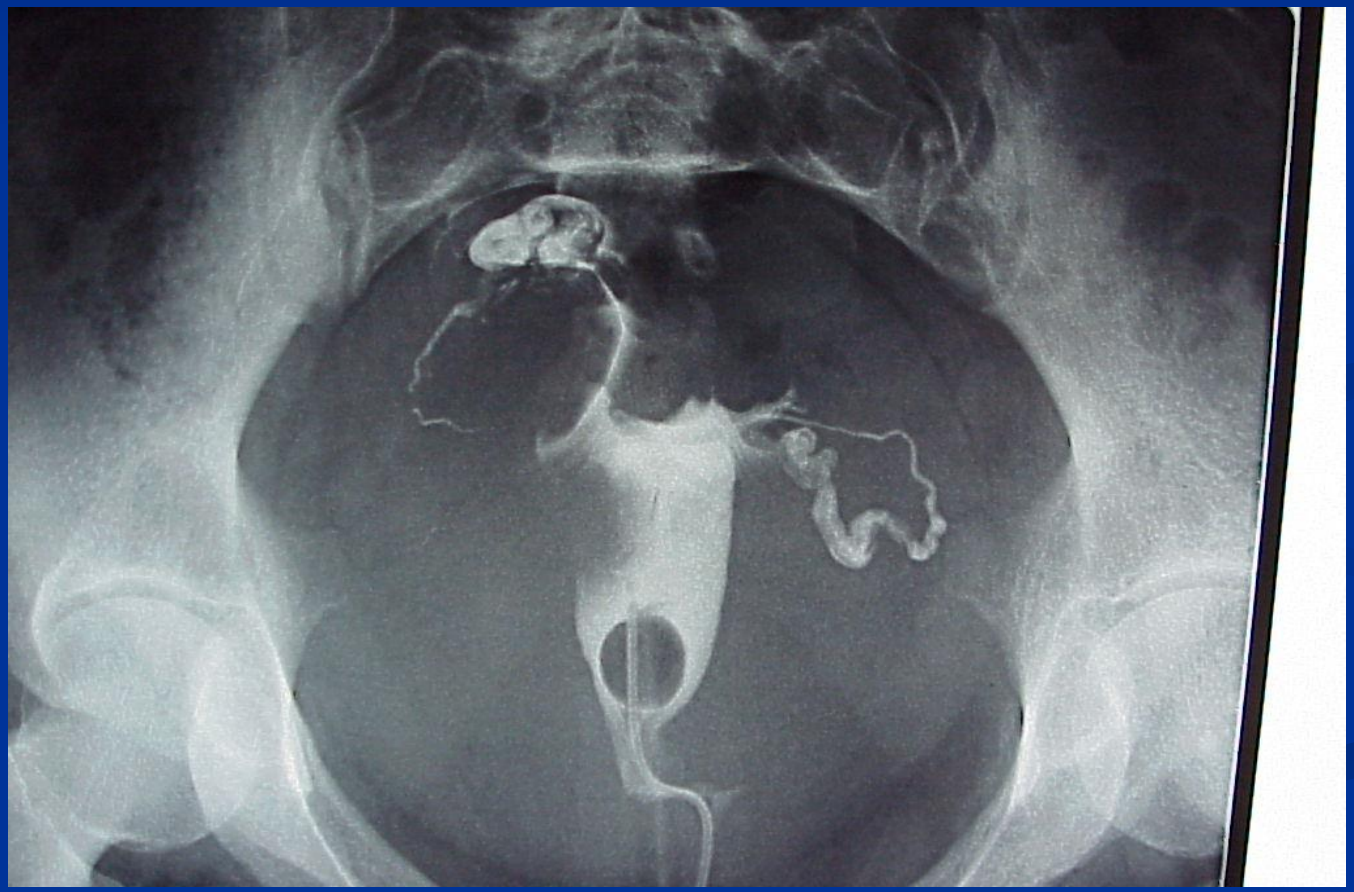
Blocked tubes

Female Infertility

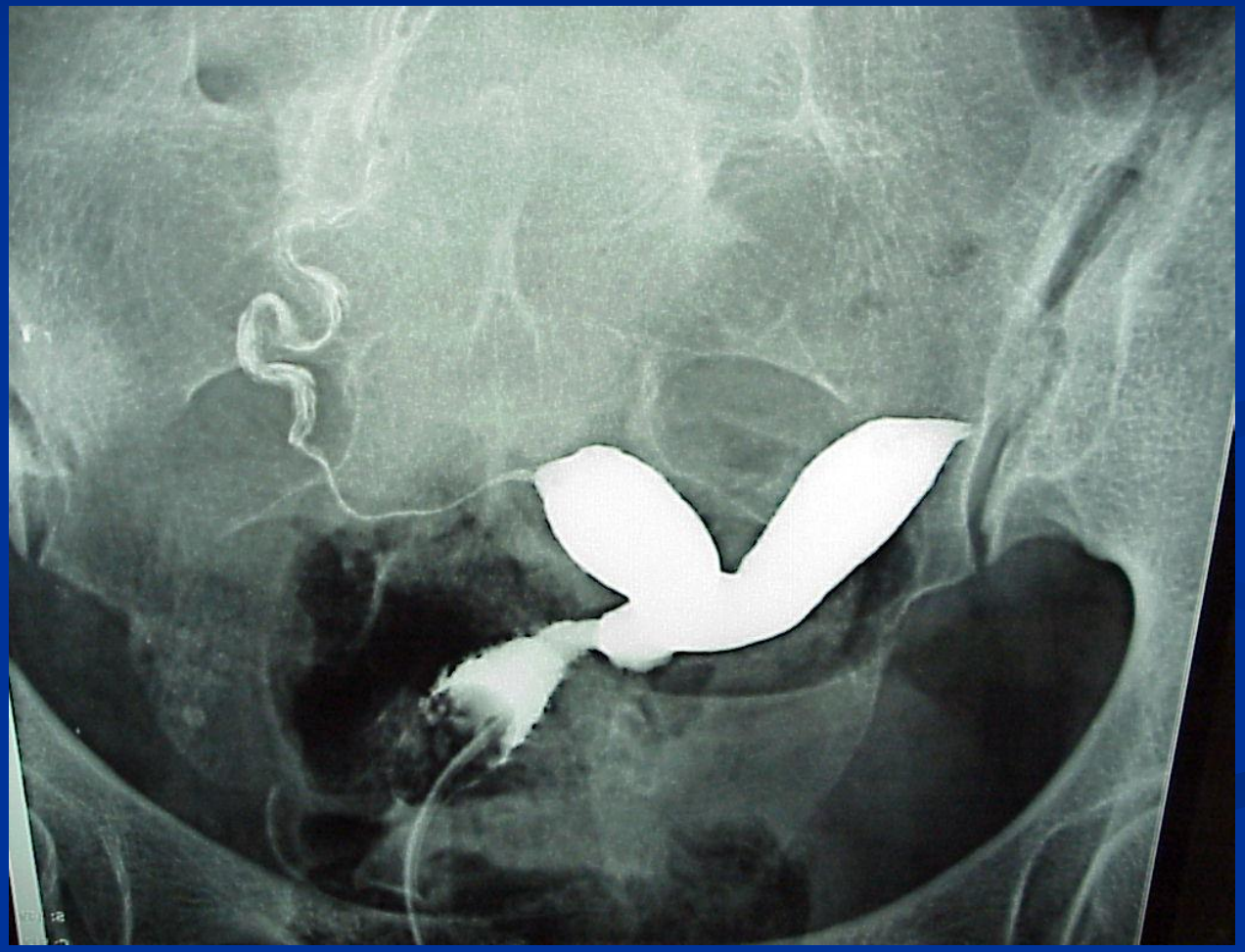


- Uterine muscle tumor
- Benign (>95%)
- 25-30% of women

Fibroid Uterus



Mullerian Defect

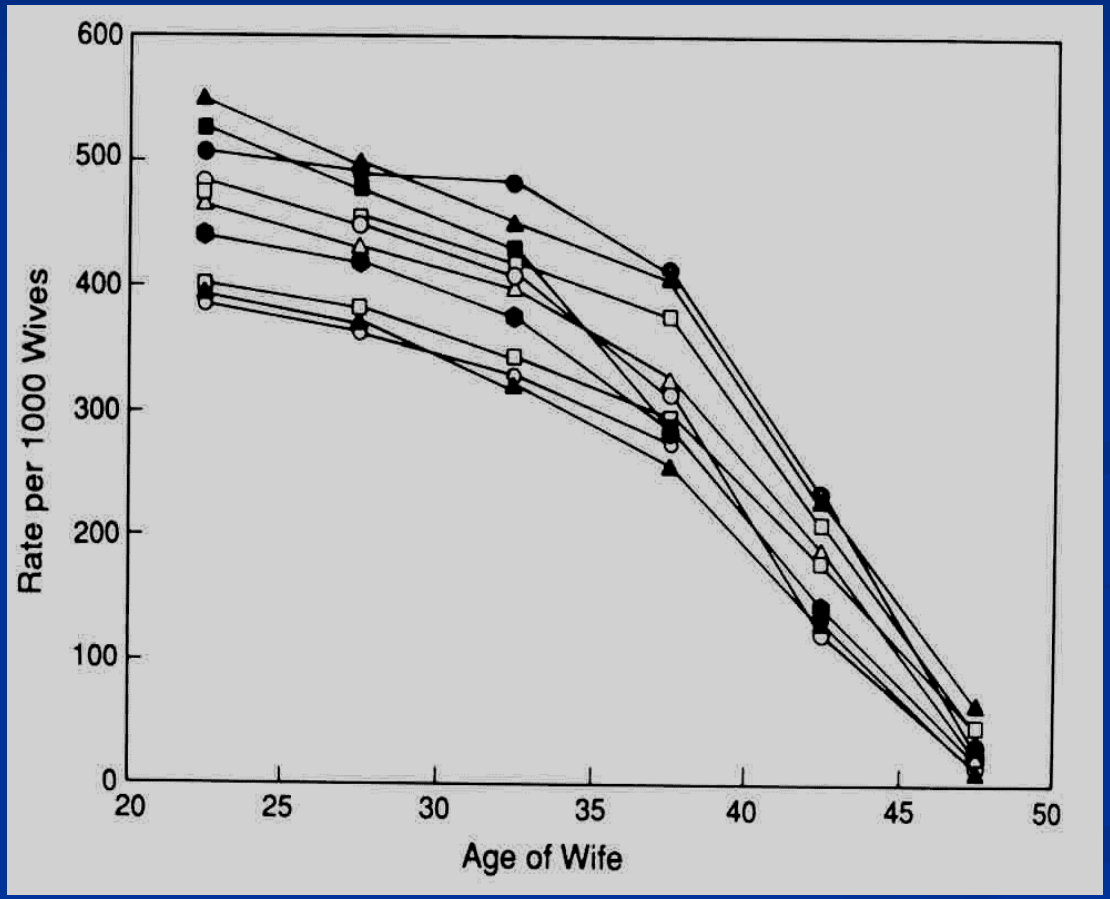


Percentage of Married Women Who are Infertile

From 3 national U.S. surveys

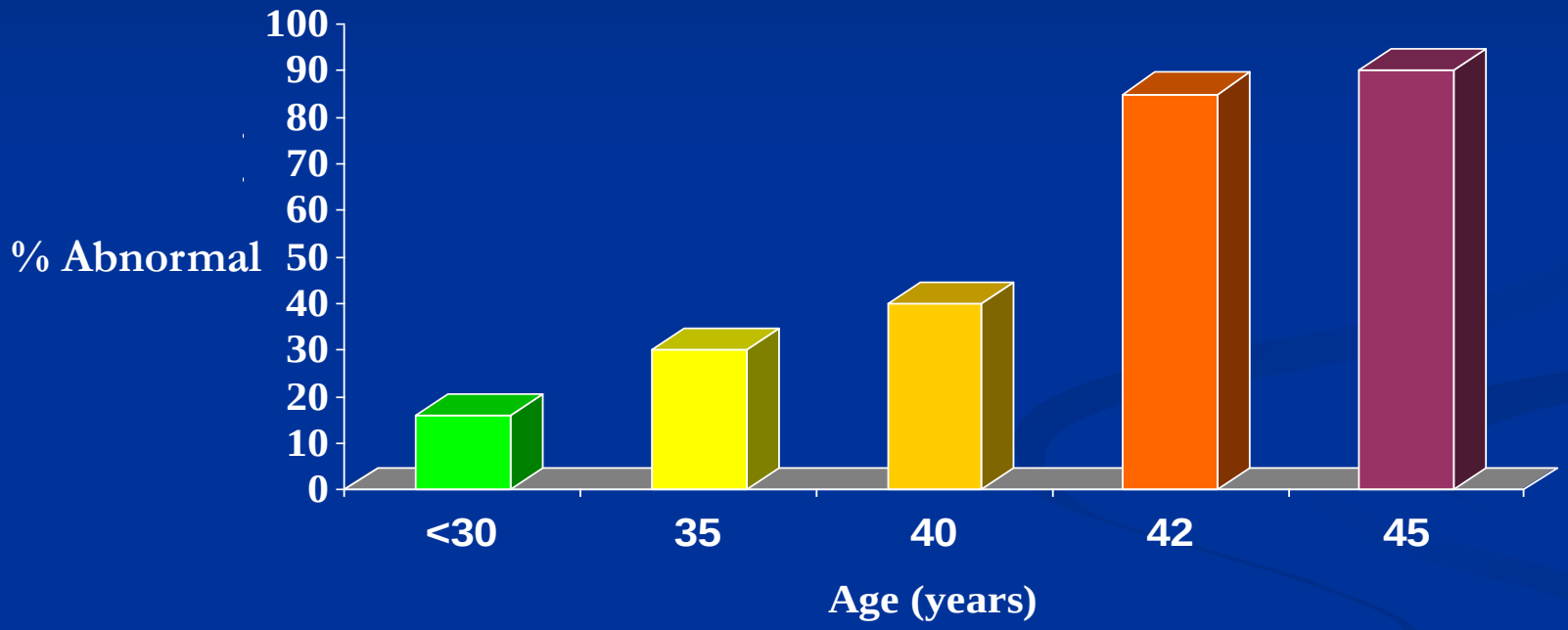
Age (years)	Infertile
20-24	7.0
25-29	8.9
30-34	14.6
35-39	21.9
40-44	28.7

Fertility and age: natural populations

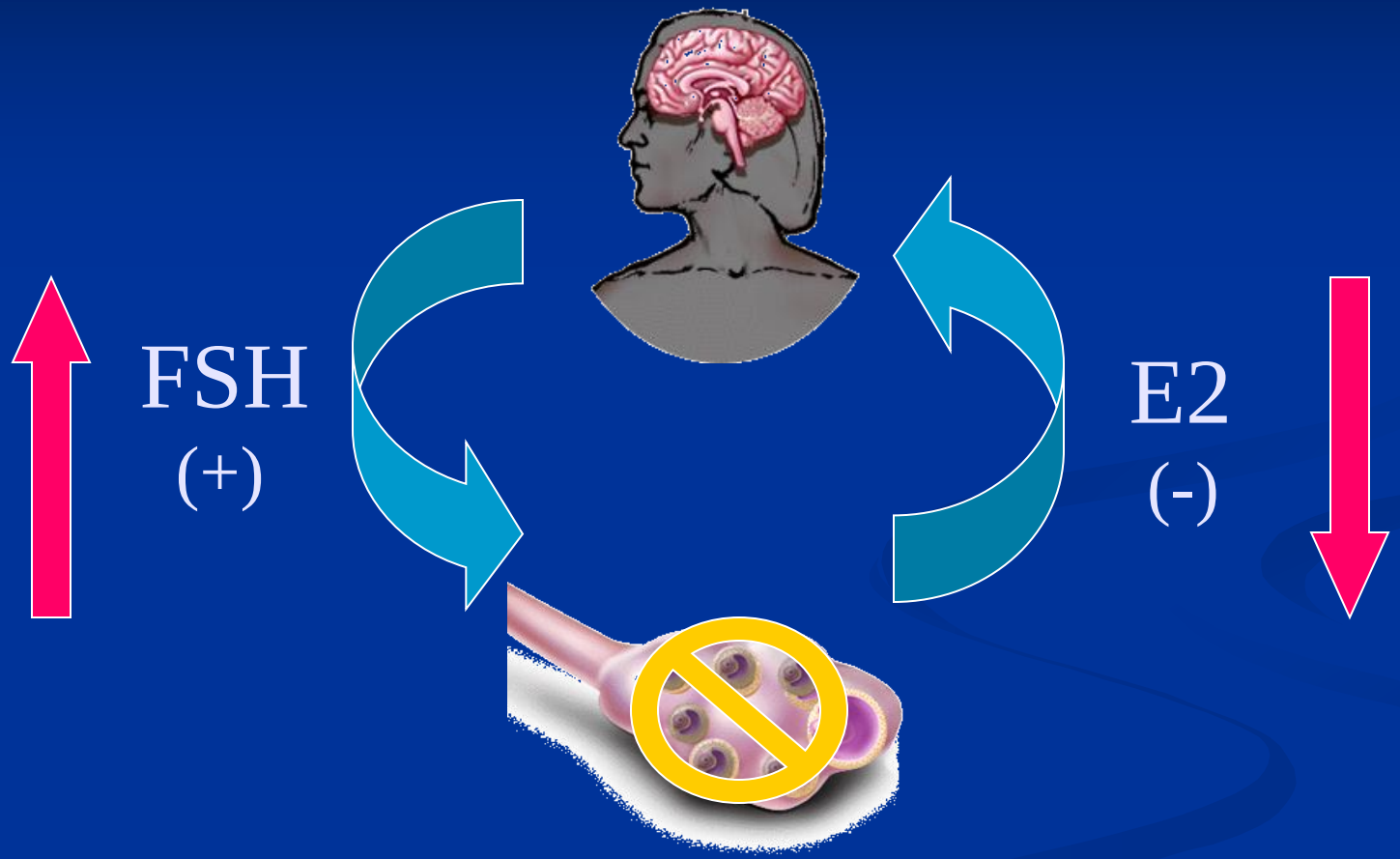


Marital fertility rates in natural populations (no contraception) as a function of age of wife

Prevalence of genetically abnormal oocytes in infertile women



Effects of Aging on the Ovary



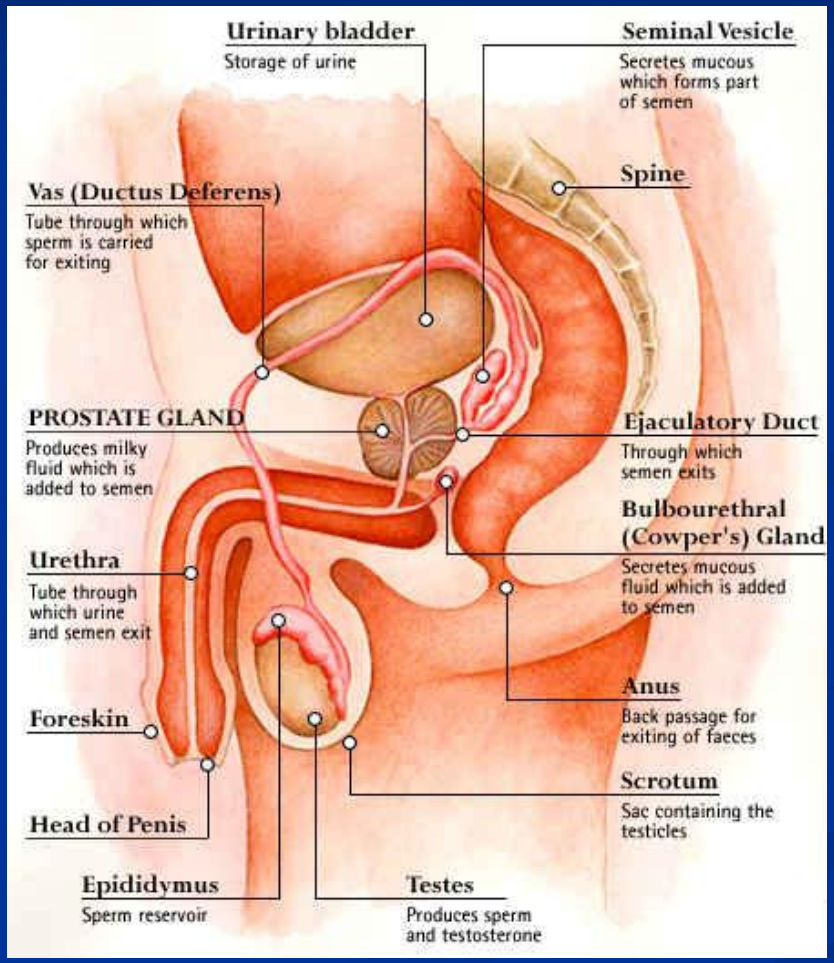
FSH=Follicle Stimulating Hormone

E2=Estradiol

Causes of Male Infertility

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

Male Reproductive Organs



Male Infertility_ lifestyle

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

Abnormalities of Sperm Production

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

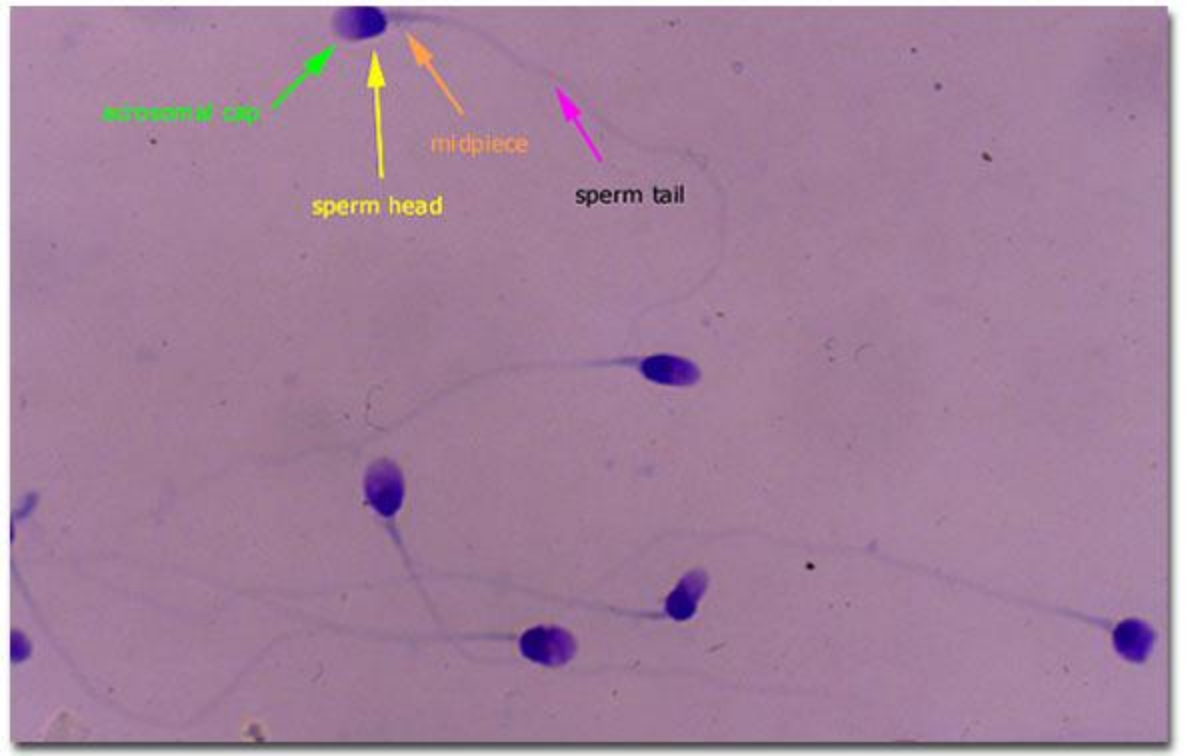
Abnormalities of Sperm Function

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

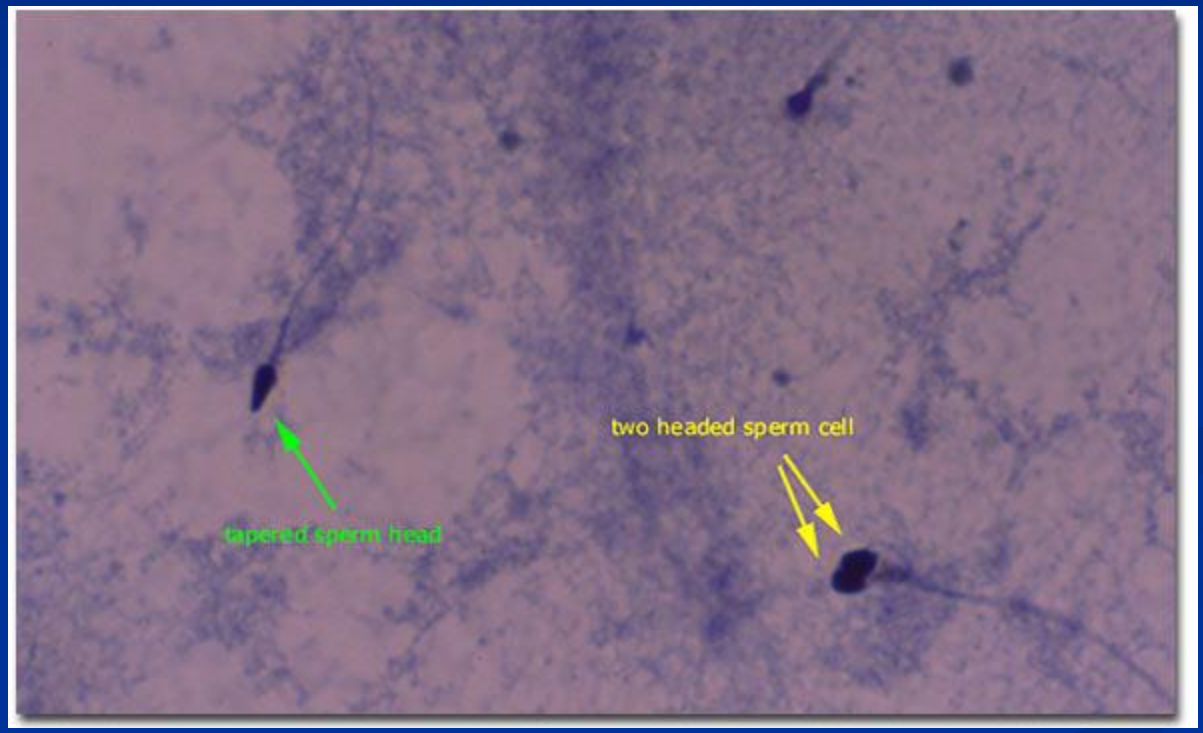
Obstructions in Ductal System

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

Normal Sperm 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

Sperm: Semen Analysis

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

Infertility Treatments

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

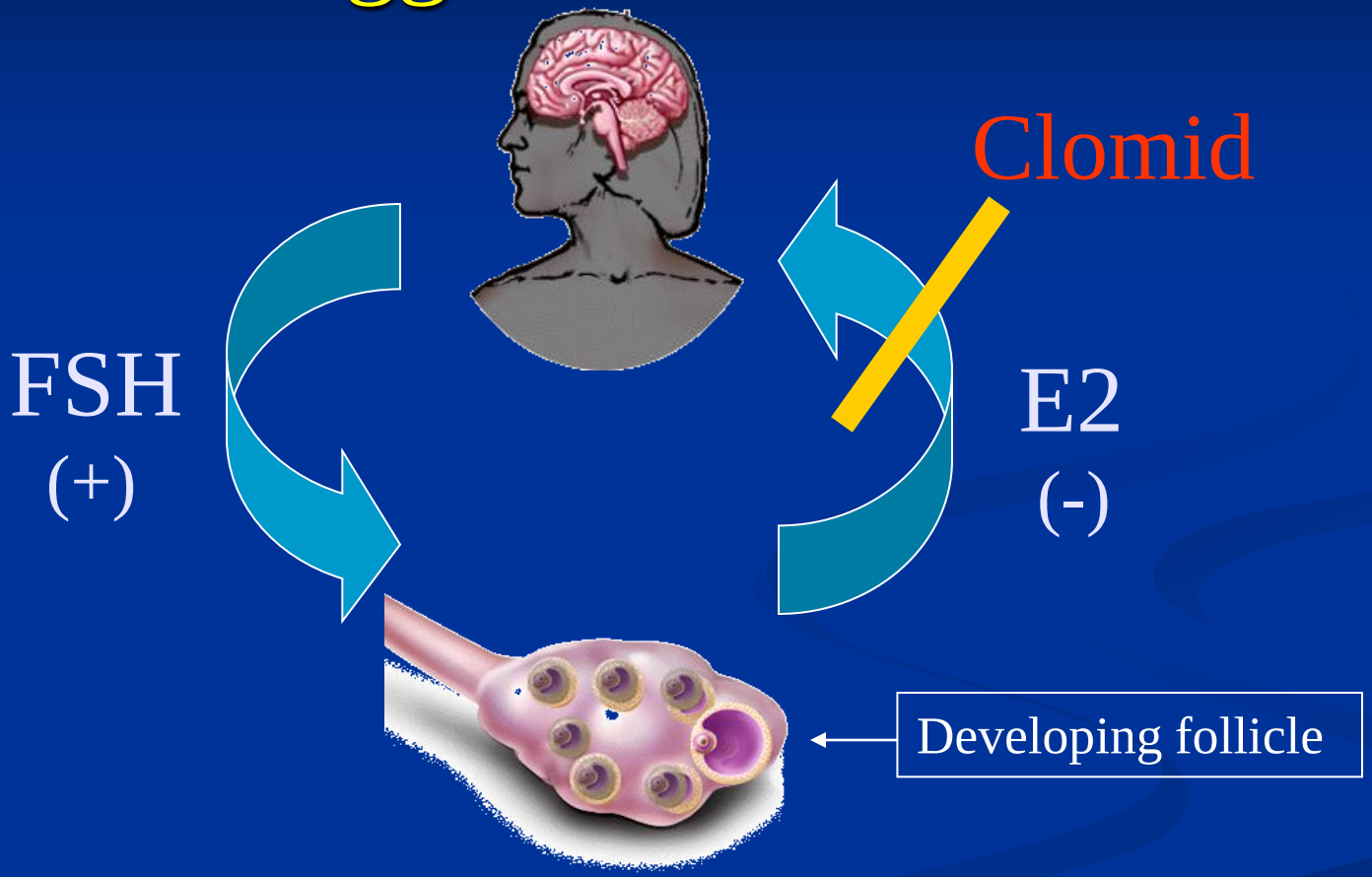
Infertility Treatment Options

- 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%

Serhall et al, Fertil Steril 1988;49:602

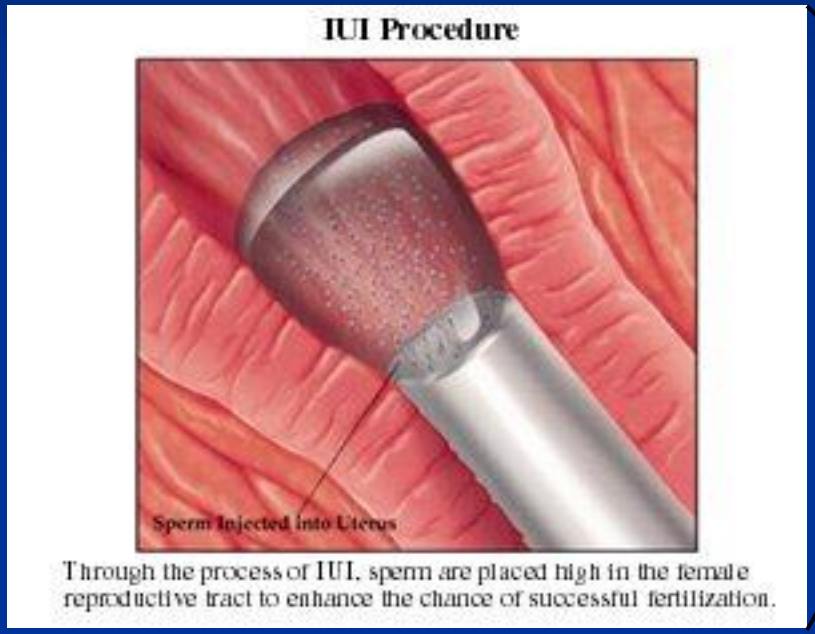
How Does Clomid Work To Increase Egg Number?

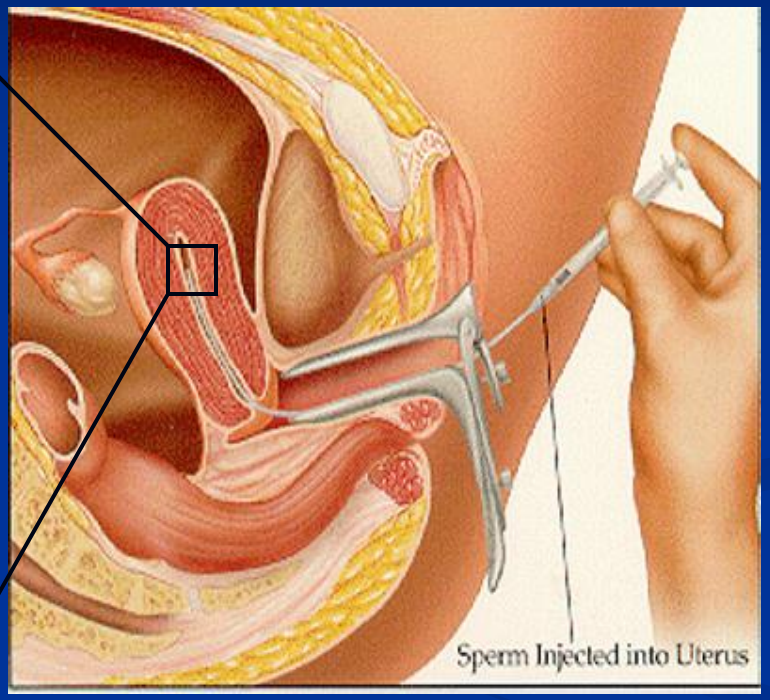


FSH=Follicle Stimulating Hormone

E2=Estradiol

Intrauterine Insemination (IUI)





Goal is to Maximize the Chance of Fertilization

- **Increase Number of Eggs**
- **Position Sperm Closer to Eggs**

I.V.F.

In

Vitro: glass

Fertilization: sperm + ova

"Test tube babies"

Louise Brown, 1978

BRITAIN'S BIGGEST EVENING SALE

Evening News

LATE SPECIAL CITY PRICES

LONDON: THURSDAY JULY 27 1978

Meet Louise, the world's first test-tube arrival

SUPERBABE

Wide-eyed Louise Brown pictured in hospital 18 hours after she was born. Today she's doing well. See Page Three

Today there are more than 3 million IVF babies

Indications of IVF

- In cases of unexplained infertility when anatomy and function appear to be normal.
- Pt. with endometriosis.
- Tubal dis.
- When the sperm count is low but not so low that fertilization is impossible.
- Pt. showing cervical hostility to sperm.
- Absent uterus
- Carriers of genetic diseases
- Family Balancing

Success rate of IVF

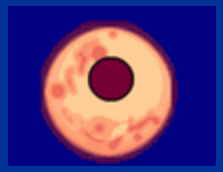
- Success rates vary and are often exaggerated
- Probably around **20-25 %** successful between **1995-2003**.

Basic Principle of IVF

Hormonal treatment

Female

Harvest the ovum



Mature Ova

Mix in a test tube

Keep to develop embryo

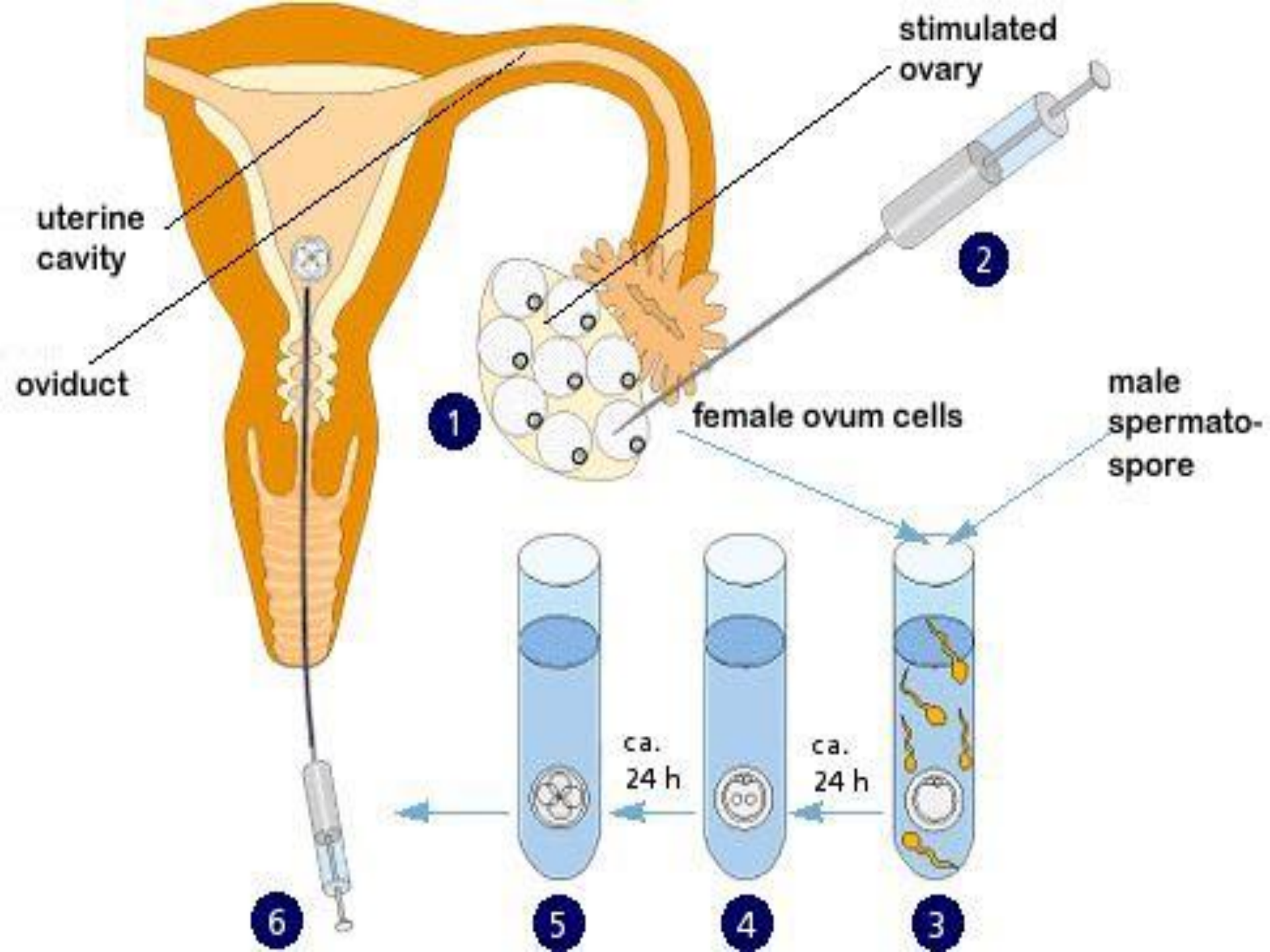
Motile sperms

Collect semen

Transfer to mother

Male

Natural ejaculation


stimulated ovary
uterine cavity
oviduct
2
1
female ovum cells
male spermato-spore
ca. 24 h
ca. 24 h
6
5
4
3

Hormonal Treatments

Drugs currently in use include:

- **clomiphene citrate**
- **human menopausal gonadotrophin (hCG)**
- **gonodotrophin releasing hormone (GnRH) analogue called leuprolide**

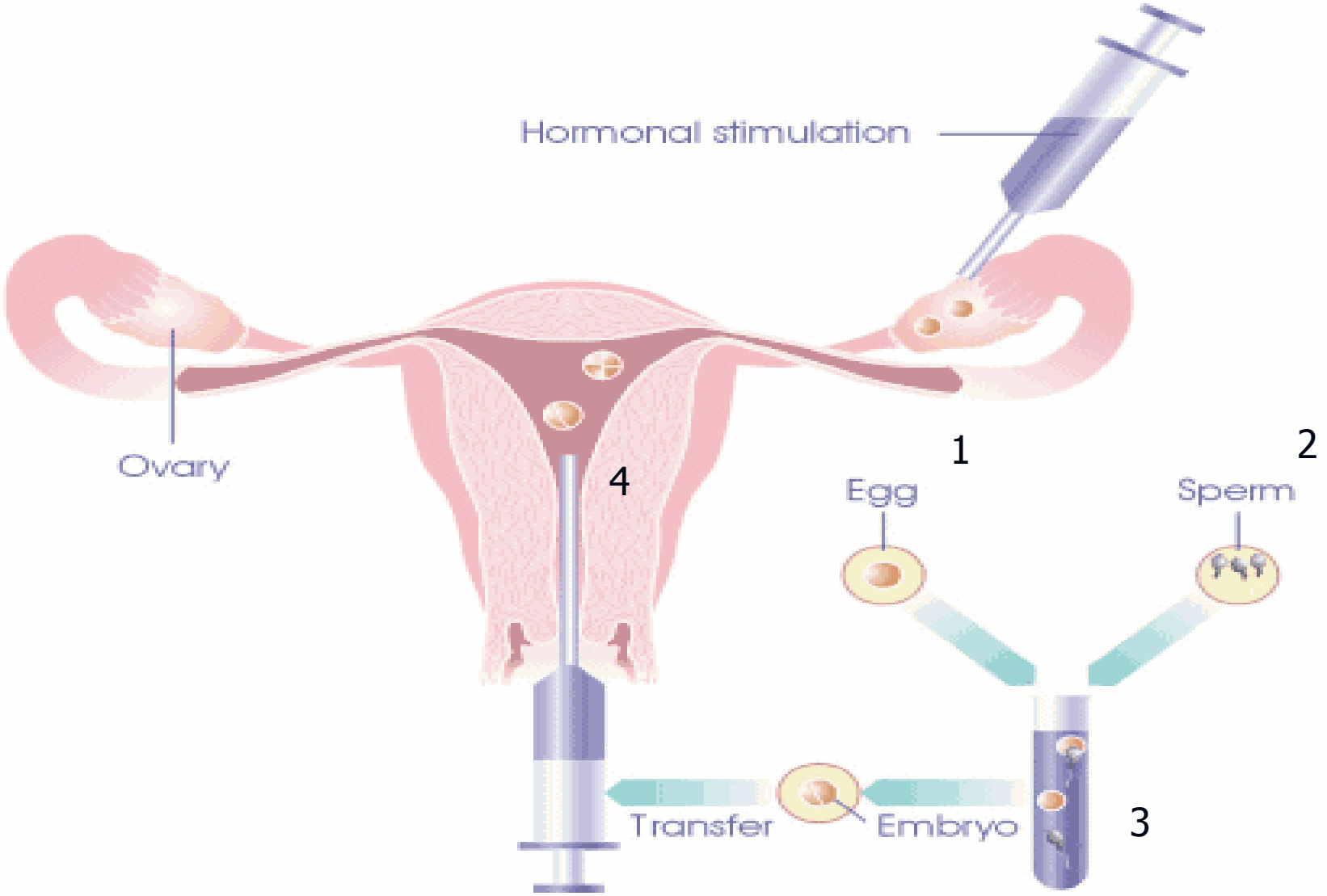
Most of these drugs may be used alone or in a combination with others.

THE TECHNIQUE OF IVF

There are generally four major steps in the process of IVF:

1. Collect eggs from the woman
2. Obtain sperm from the man
3. In the laboratory place eggs and sperm together to allow for fertilization, to create embryos. (ICSI-Intra-cytoplasmic sperm injection since 1990's.)
4. Transfer embryos into uterus of woman

THE TECHNIQUE OF IVF



1. Collect eggs from the woman

The woman is given drugs to hyper-ovulate (produce many eggs). The drugs can cause side effects such as abdominal pain, nausea etc.

2. Obtain sperm from the man

- Obtaining sperm by masturbation may be morally objectionable
- Sometimes donor sperm may be used

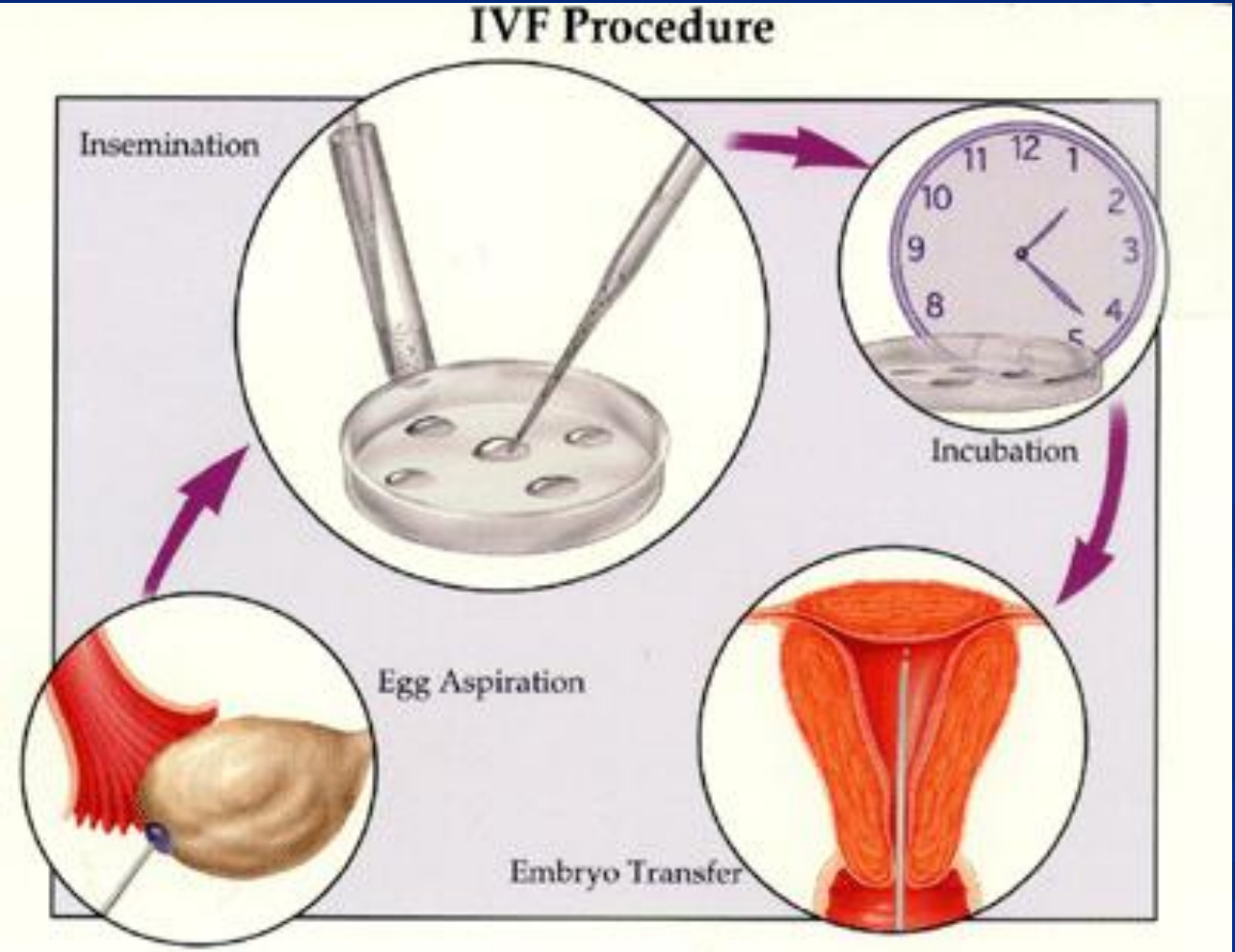
3. In the laboratory place eggs and sperm together to allow for fertilization, to create embryos

- Embryos are created in the laboratory (the test tube) thus human fertilization occurs apart from sexual intercourse and outside the human body.

4. Transfer embryos into uterus of woman

- Many embryos implanted in mother's womb (usually 2-4) to increase chance of pregnancy.
- Should too large a number of embryos start to grow, the 'excess' embryos are usually aborted (called "pregnancy reduction").

IVF procedure

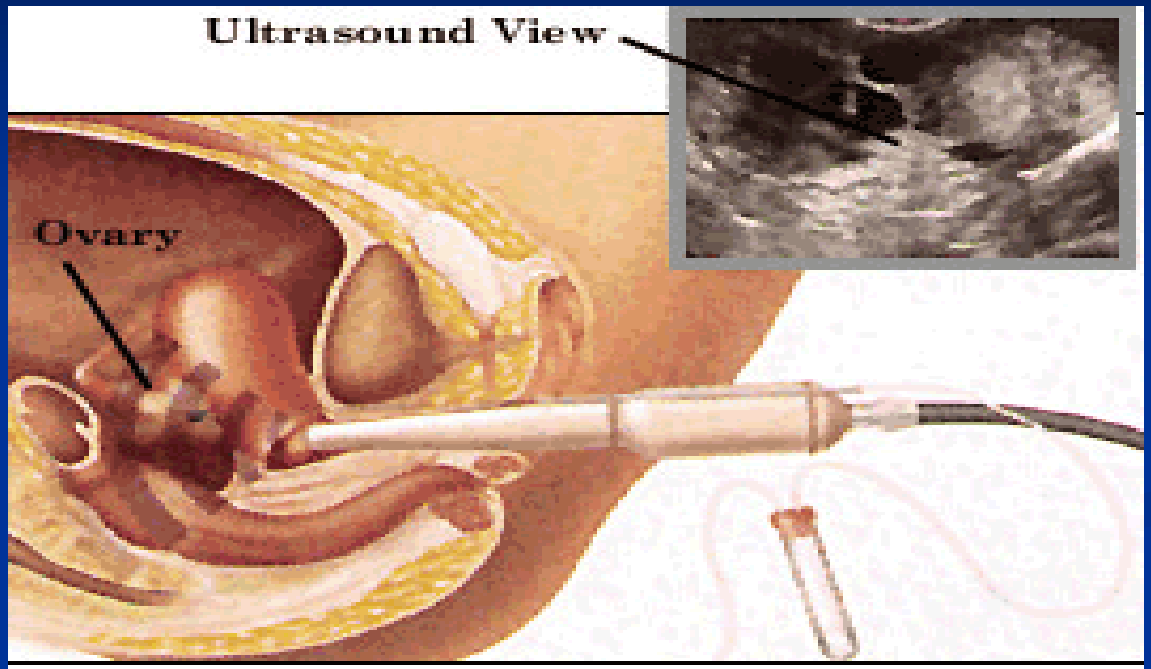


Egg Harvest

1. **Ultra Sound Guided Aspiration**

2. **Laproscopy**

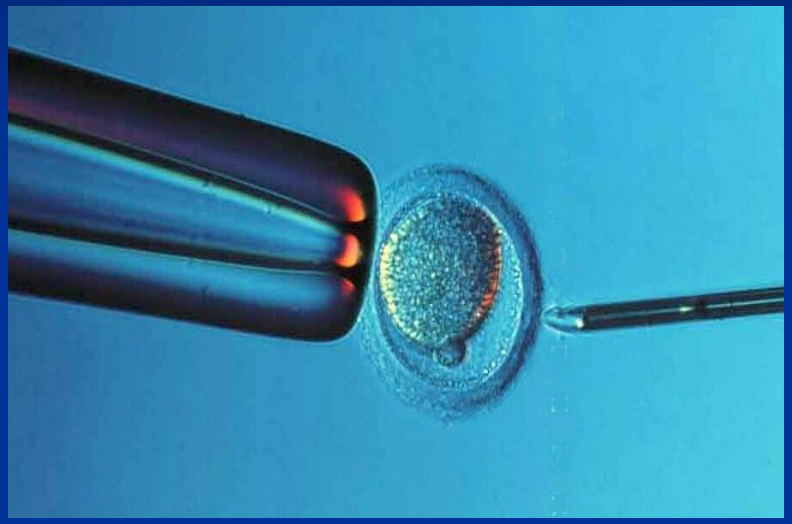
Egg Retrieval

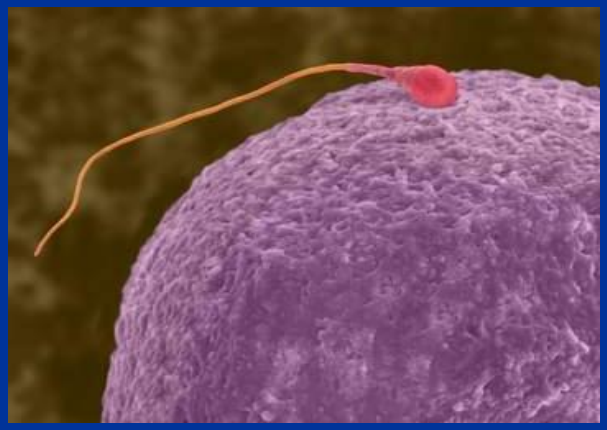


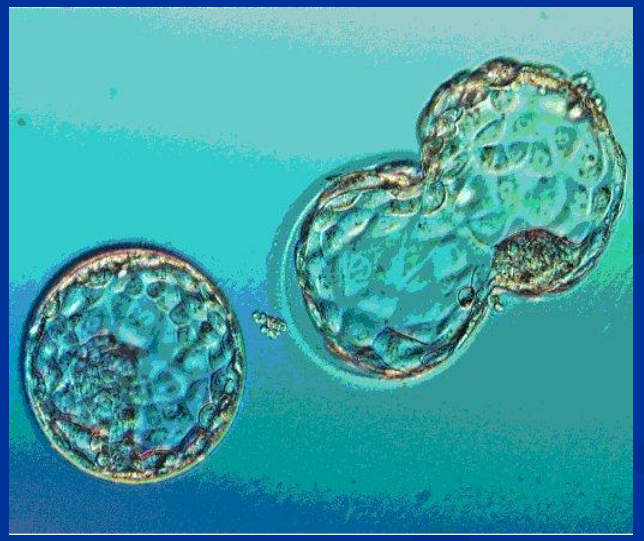
Using ultrasound to view the ovary, the physician inserts the needle that runs alongside the ultrasound probe through the wall of the vagina into the ovary and removes the egg for use in IVF or GIFT.

Egg Retrieval

Fertilization







Fertilization

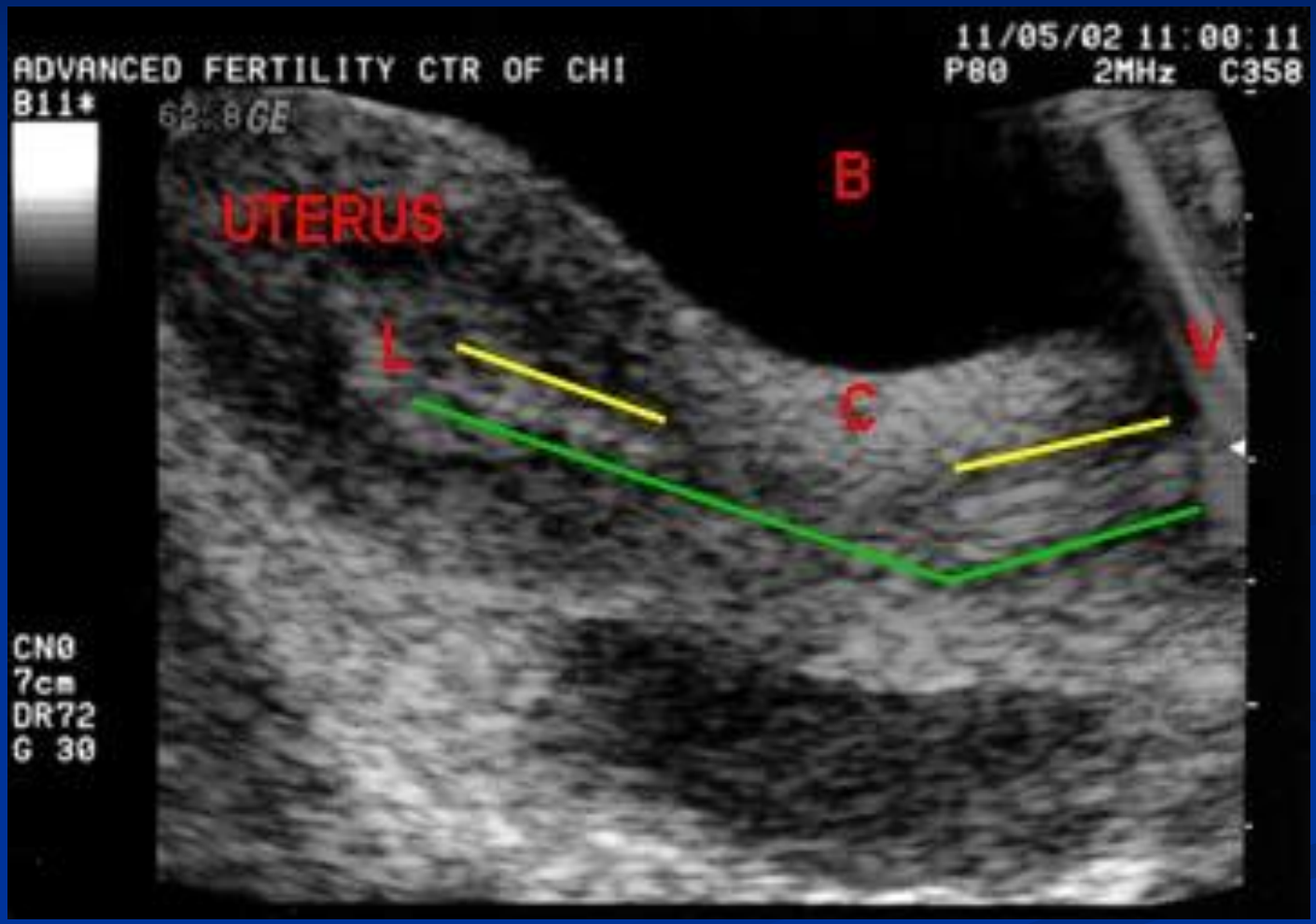
- 2 Pronuclei (2PN)
- 1 day after egg retrieval

8-cell embryo for transfer

Blastocyst for transfer

Implantation

Embryo Transfer



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

What Happens to the Other Embryos?

- Freeze Embryos
- Donate For Research/Stem Cells
- Embryo Adoption
- Embryo destruction

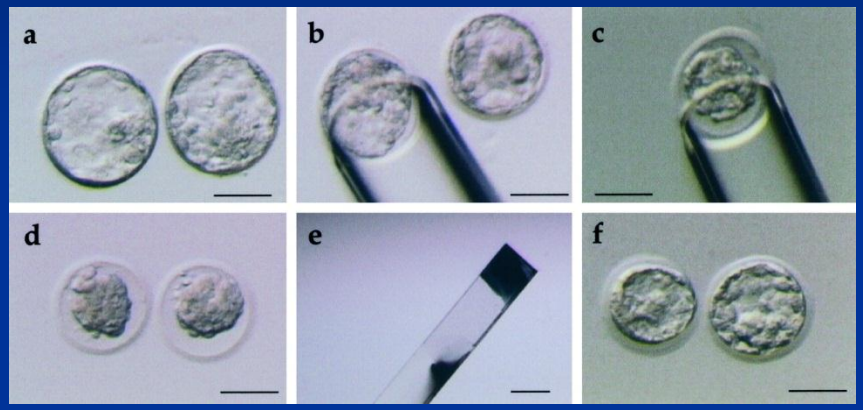
- Healthy embryos can be transferred to woman or they can be frozen for use at later date. Sometimes they are experimented on.

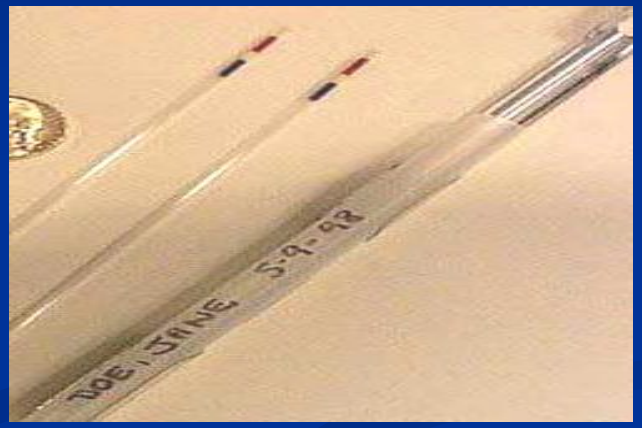
Cryopreservation of ova, sperm& embryo

The problem of frozen embryos

- In USA there are >400,000 frozen embryonic persons, a kind of "hell of ice".
- In thawing them 50 % will die.
- Worldwide there are up to 1 million frozen embryos

Oocyte Cryopreservation





- **Slow-freeze Technique**
- **Vitrification (Rapid Freeze) Technique**

The destruction of embryos

- Many embryos created. Healthy ones kept but defective embryos are destroyed.

Alternates of IVF

Gamete intrafallopian transfer (GIFT):

GIFT is similar to IVF. It is used when a woman has at least one normal fallopian tube. Eggs are placed in this tube along with a man's sperm to fertilize there.

Zygote intrafallopian transfer (ZIFT):

ZIFT is tubal embryo transfer in which a woman's eggs are taken from her ovaries, fertilized in the laboratory, and put back in the fallopian tubes rather than the uterus.

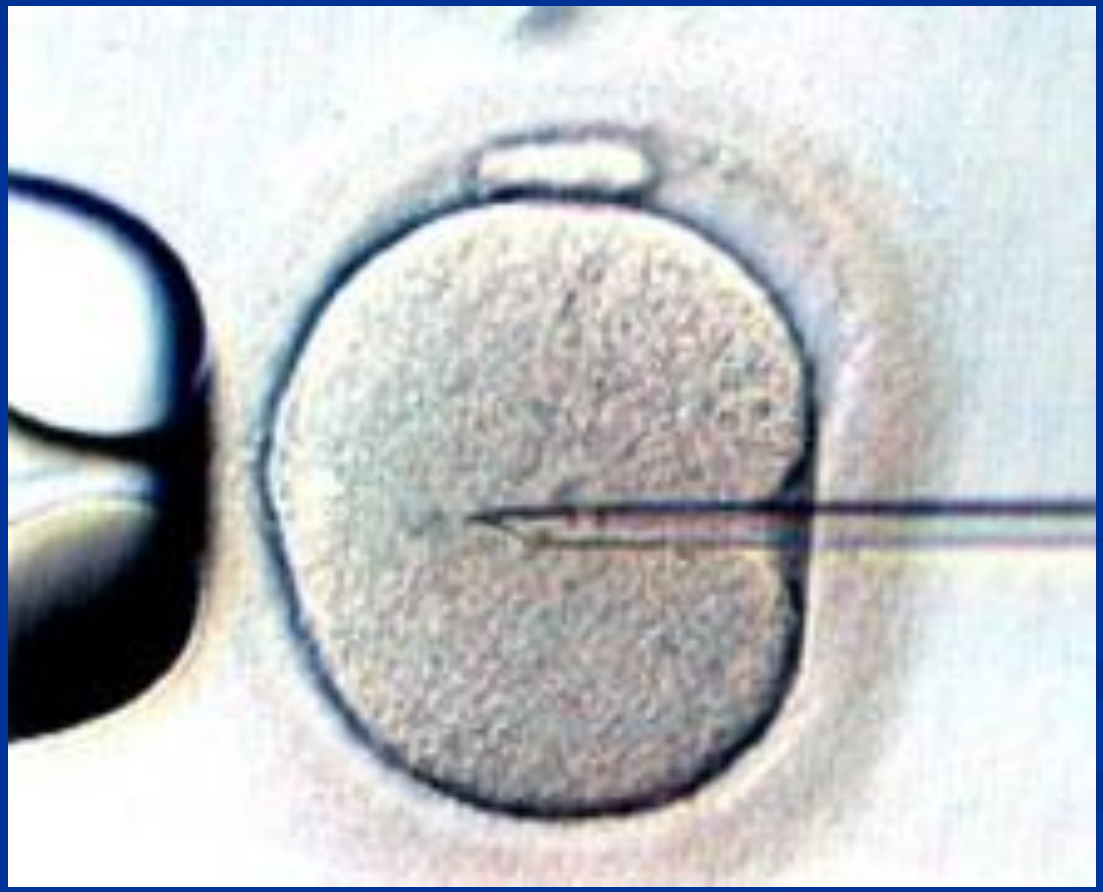
Assisted fertilization techniques

when not enough sperm are available or sperm quality is not sufficient to fertilize include the following:

- **Partial zona dissection**
- **Subzonal sperm injection**
- **Intracytoplasmic sperm injection**
- **Embryo cryopreservation (frozen fertilized egg and sperm)**

Intra Cytoplasmic Sperm Injection (ICSI)

Stands for intracytoplasmic sperm injection. This process is used to inject a single sperm into each egg before the fertilized eggs are put back into the woman's body. The procedure may be used if the male has a low sperm count.



Complication of IVF

- There is a considerable increase in the fetal morbidity & mortality associated with **multiple pregnancy**, mainly related to prematurity.

Risks

Super ovulation Stimulates Egg Development

Ovarian Hyper stimulation Syndrome (OHSS)

Other Risks

- There may be a failure to recover an egg because:
  - follicles that contain mature eggs may not develop in the treatment cycle
- - ovulation has occurred before time of egg recovery
  - one or more eggs cannot be recovered
  - pre-existing pelvic scarring and/or technical difficulties prevent safe egg recovery
- The eggs that are recovered may not be normal;
- There may be insufficient semen to attempt fertilization of the recovered eggs because the man is unable to produce a semen specimen, because the specimen contains an insufficient number of sperm to attempt fertilization, because the laboratory is unable to adequately process the specimen provided, or because the option to use a donor sperm as a "backup" was declined
- The embryos may not develop normally or may not develop at all. Embryos that display any abnormal development will not be transferred;
- Embryo transfer into the uterus may be difficult/impossible, or implantation(s) may not occur after transfer, or the embryo(s) may not grow or develop normally after implantation

Genetic testing

- A kind of quality control selection

- To create the perfect baby – disease free, blond hair, blue eyed, good footie player …

Genetic Testing

- Preconception
- Preimplantation
- Prenatal
- Postnatal

Preimplantation Genetic Diagnosis (PGD)

- Can test embryos for genetic abnormalities prior to implantation
- Has been successfully used in diagnosing and preventing inherited genetic diseases like Cystic Fibrosis, Thalassemia, Sickle Cell Anemia and may be potentially used to screen for cancer mutations.
- Uses single cell (blastomere) at 8-cell stage

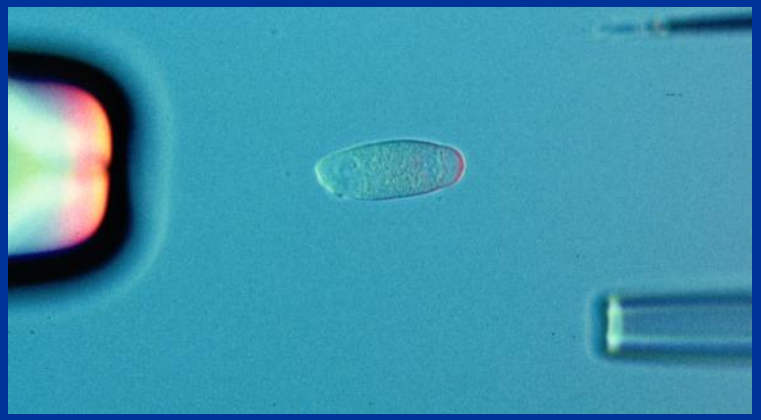
PGD

- First clinical application described by Handyside, Winston in 1990
- By 2003, estimated >1000 PGD-defined live births.

PGD – Clinical Indications

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

PGD – Timing of Biopsy



- Biopsy of a single cell can be performed from an 8-cell embryo after 3 days of culture in the laboratory

PGD

- The embryos would continue to grow for 2 more days in the laboratory, awaiting genetic analysis.
- 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.

PGD Chromosome Panels

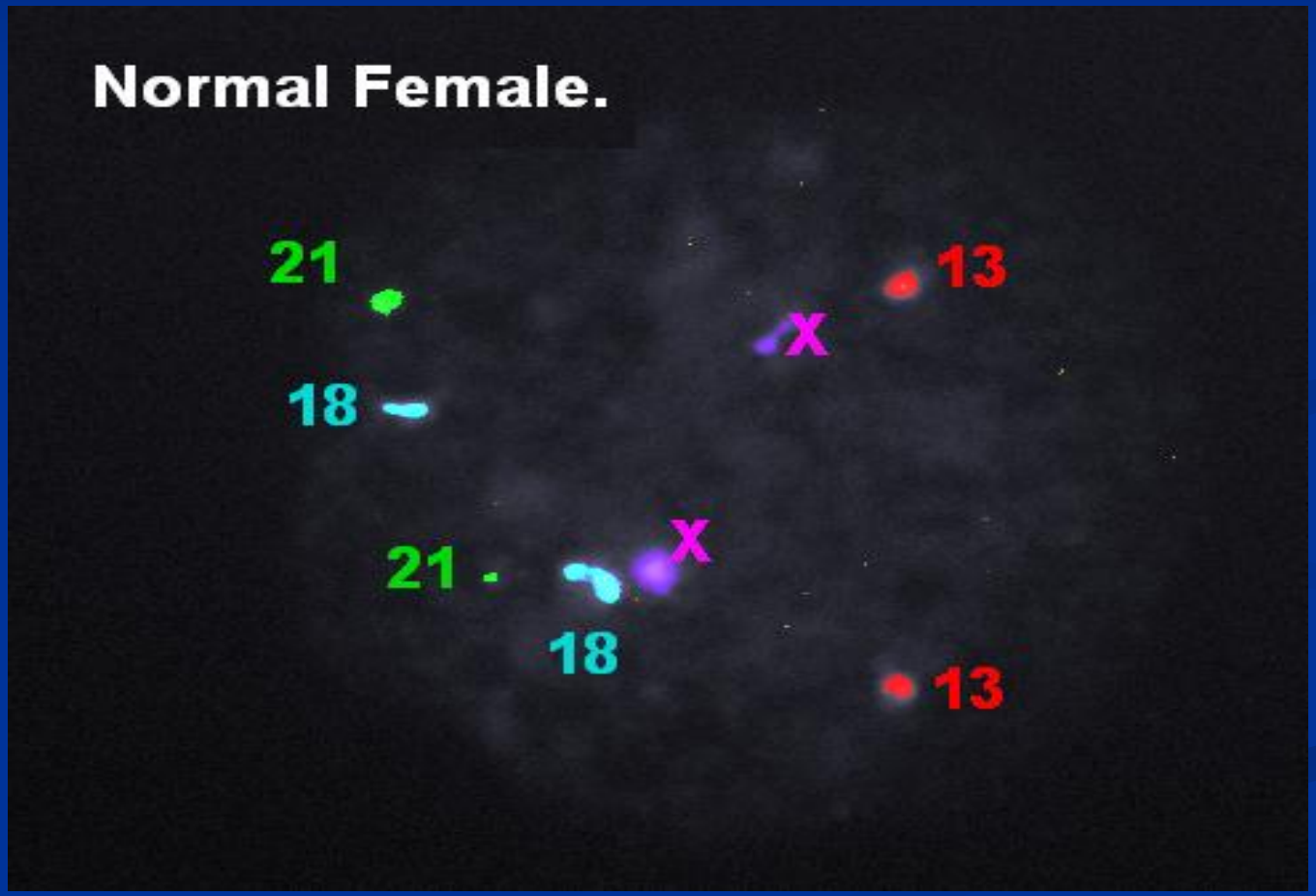
Five Chromosome PGD

- 13, 18, 21, X, Y

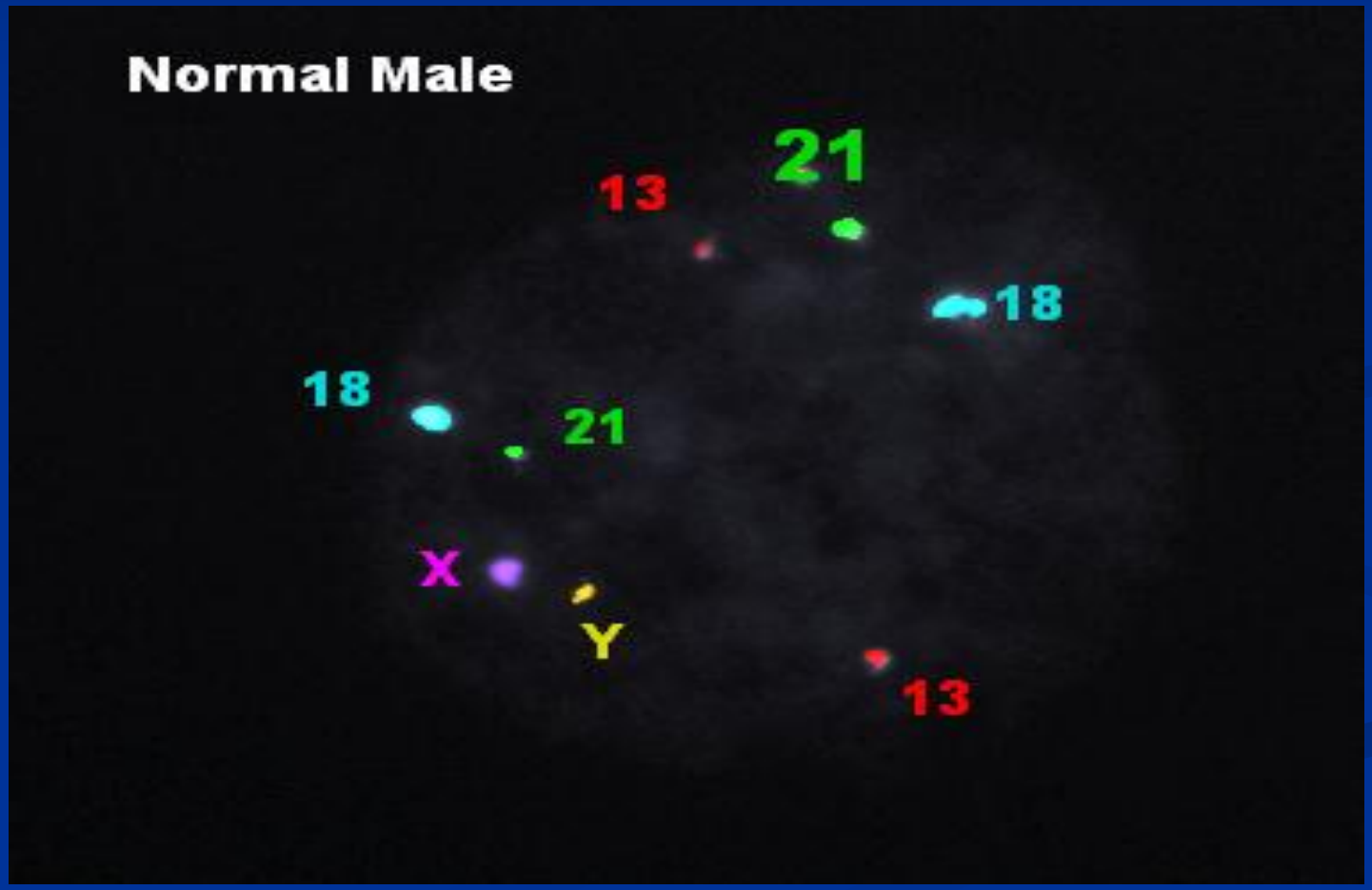
Ten Chromosome PGD

- 8, 9, 13, 15, 16, 18, 21, 22, X, Y

Five Chromosome PGD



Five Chromosome PGD



Prenatal vs. Preimplantation Diagnosis

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

PGD

Gender Selection:

A Big Controversy!

Athics

- Bypassing the natural method of conception.
- The creation of life in the laboratory.
- Fertilization of more embryos than will be needed.
- Discarding of excess embryos.
- Creation of embryos, then freezing them, and keeping them "in limbo".
- Exposure of embryos to unnatural substances.
- Infertility is treated as a disease and not as a symptom of underlying medical problems.
- Religious objections

Thank you!