بسم الله الرحمن الرحيم
Human fertility & In Vitro Fertilization

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6th stage
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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

**MEN**
- Unknown 30%
- Infection 10%
- Sperm Quality 10%
- Varicocele 40%
- Chromosomal 10%

**WOMEN**
- Tubal Ovarian 40%
- Cervical 10%
- Hormone Imbalance 30%
- Unknown 20%
- Unknown 20%

**CAUSES OF INFERTILITY**
- Male 40%
- Female 40%
- Unknown 20%
- Other 10%
Female Reproductive Organs

Internal Sexual & Reproductive Organs (F)

- Infundibulum
- Ampulla
- Isthmus
- Fallopian tube
- Fundus of uterus
- Ovaries
- Ovarian ligament
- Fimbriae
- Ovary
- Layers of uterus:
  - Perimetrium
  - Myometrium
  - Endometrium
- Broad ligament
- Cervical canal
- Vagina
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

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Infertile</th>
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<tbody>
<tr>
<td>20-24</td>
<td>7.0</td>
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<tr>
<td>25-29</td>
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<td>14.6</td>
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<td>35-39</td>
<td>21.9</td>
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<tr>
<td>40-44</td>
<td>28.7</td>
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</table>
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

- **Urinary bladder**: Storage of urine
- **Seminal Vesicle**: Secretes mucous which forms part of semen
- **Vas (Ductus Deferens)**: Tube through which sperm is carried for exiting
- **Spine**: 
- **Prostate Gland**: Produces milky fluid which is added to semen
- **Ejaculatory Duct**: Through which semen exits
- **Bulbourethral (Cowper's) Gland**: Secretes mucous fluid which is added to semen
- **Urethra**: Tube through which urine and semen exit
- **Anus**: Back passage for exiting of faeces
- **Foreskin**: 
- **Scrotum**: Sac containing the testicles
- **Head of Penis**: 
- **Epididymus**: Sperm reservoir
- **Testes**: Produces sperm and testosterone
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**: $\geq 2 \text{ mL}$
- **Concentration**: $\geq 20,000,000 \text{ per mL}$
- **Motility**: $\geq 50\%$
- **Normal morphology**: $\geq 40\%$ normal
  - Krueger strict criteria: $\geq 14\%$ 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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cycles</th>
<th>Pregnancy</th>
<th>Pregnancy per cycle</th>
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<tbody>
<tr>
<td>IUI</td>
<td>30</td>
<td>1</td>
<td>2.7%</td>
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<tr>
<td>FSH</td>
<td>49</td>
<td>3</td>
<td>6.1%</td>
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<tr>
<td>FSH+IUI</td>
<td>34</td>
<td>9</td>
<td>26.4%</td>
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How Does Clomid Work To Increase Egg Number?

FSH (Follicle Stimulating Hormone) and E2 (Estradiol) are involved in the process.

**FSH**

(+)

Clomid

E2

(-)

Developing follicle

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
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

Motile sperms

Keep to develop embryo

Transfer to mother

Male

Collect semen

Natural ejaculation
Hormonal Treatments

Drugs currently in use include:

• clomiphene citrate
• human menopausal gonadotrophin (hCG)
• gonadotrophin 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

In IVF, eggs are harvested from the woman’s ovary and fertilized in the laboratory with sperm. The embryos are then transferred into the uterus.
Egg Harvest

1. Ultra Sound Guided Aspiration

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

Normal Female.
Five Chromosome PGD
# Prenatal vs. Preimplantation Diagnosis

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<th>PND</th>
<th>PGD</th>
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<tbody>
<tr>
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<tr>
<td>Time</td>
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<tr>
<td>Accuracy</td>
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<tr>
<td>Cost</td>
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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!