Genetics Basis of Infertility

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Summer Class

Lecture 10

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Outline

- What is Infertility
- Genetic Basis of Infertility in Men
- Genetic Testing in Male Infertility
- Genetic Basis of Infertility in Females
- Reproductive Implications and Management

Objectives

- By the end of this lecture, students should be able to:
- Define infertility and its genetic underpinnings.
- Identify key genetic causes of male and female infertility.
- Explain how chromosomal abnormalities, single-gene mutations, and epigenetic factors contribute to reproductive failure.

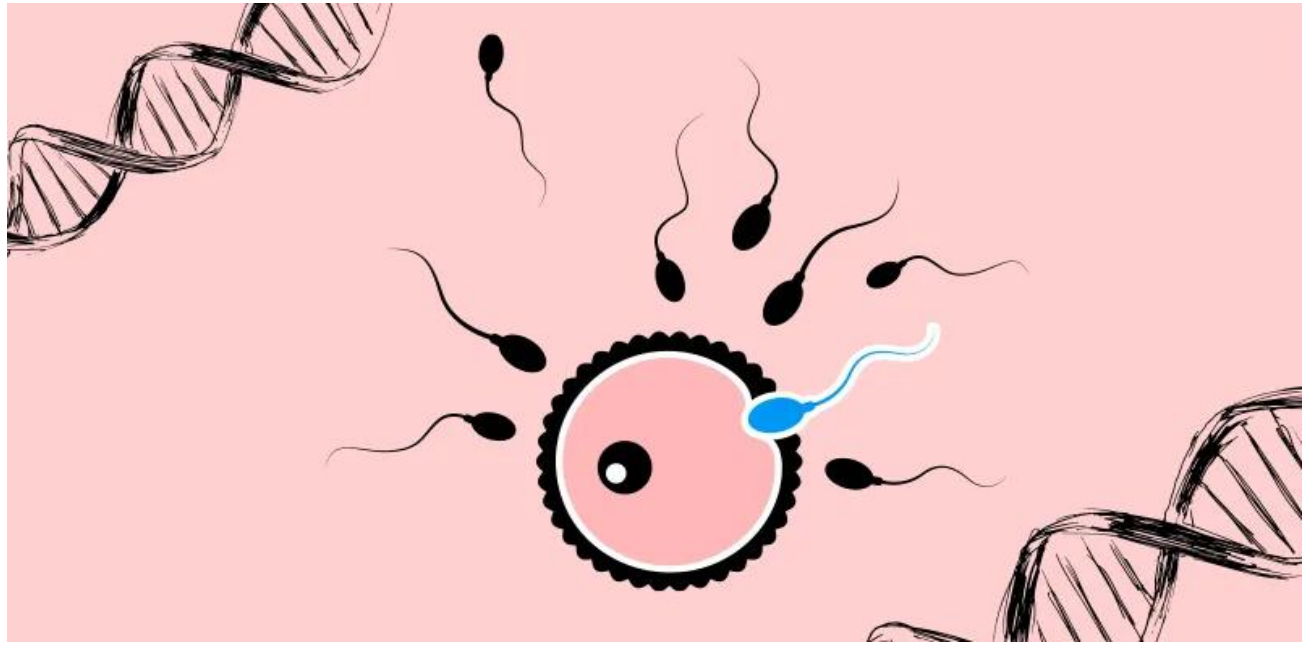
❑ What is Infertility?

- Infertility is defined as the inability to **conceive after 12 months** of **regular unprotected intercourse**.

- Prevalence: Approximately 15% of couples globally; 50% of cases have a genetic component.

- Primary Infertility.

- Secondary Infertility.



❑ Genetic Basis of Infertility in Men:

- Male infertility accounts for ~**30–50% of all infertility cases**.
- Genetics is a major underlying cause in men with **low sperm count** or **abnormal sperm function**.
- It involves:
- **Chromosomal abnormalities**
- **Gene mutations**
- **Epigenetic changes**.

❖ Chromosomal Abnormalities:

i. Numerical Abnormalities.

Condition	Karyotype	Effect
Klinefelter Syndrome	47,XXY	Small testes, azoospermia, low testosterone
XX Male Syndrome	46,XX (SRY+)	Testicular development with infertility

ii. Structural Abnormalities

Abnormality	Effect
Robertsonian translocations	Can impair meiosis → reduced fertility
Inversions (e.g. Y inv)	May disrupt sperm production
Y chromosome deletions	Lead to azoospermia

iii. Y Chromosome Microdeletions

- Found in ~10–15% of men with non-obstructive azoospermia.

- Affects AZF regions (Azoospermia Factor) on the long arm of the Y chromosome:

✓ **AZFa:** Sertoli cell-only syndrome (no sperm production)

✓ **AZFb:** Arrested spermatogenesis

✓ **AZFc:** Reduced sperm count

❑ Single-Gene Disorders:

i. CFTR Gene Mutations.

- Seen in men with Congenital Bilateral Absence of the Vas Deferens (CBAVD)

- CFTR mutation: Abnormal chloride channels, infertility without respiratory symptoms.

ii. **Androgen Receptor (AR) Gene Mutations**

- Lead to Androgen Insensitivity Syndrome (AIS)
- Can present as infertility or ambiguous genitalia depending on severity

iii. Other Genes Involved:

- **NR5A1 (SF-1) mutations**: Testicular dysfunction
- **DMRT1**: Testis development
- **SYCP3**: Meiotic arrest

❑ Epigenetic and Mitochondrial Factors

- DNA Methylation Errors: Disrupt imprinting (e.g., MEST, H19 genes)
- Histone Modification Defects: Affect sperm chromatin packaging
- Mitochondrial DNA Mutations: Impair sperm motility due to low ATP.

❑ Genetic Testing in Male Infertility:

Test	Indication
Karyotype analysis	Azoospermia, oligospermia
Y chromosome microdeletion	Non-obstructive azoospermia
CFTR gene mutation	CBAVD
FISH/SNP array	Chromosome aneuploidy screening in sperm
Gene panels	When idiopathic infertility is suspected

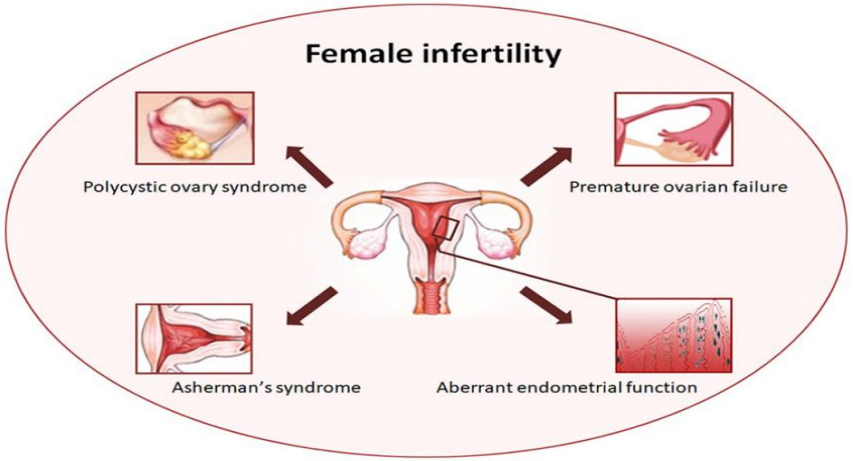
❑ Clinical and Reproductive Implications

- Informed genetic counseling is essential.
- Men with certain deletions (e.g., AZFc).
- Sperm banking is advised before surgical or radiation treatments.
- Ethical issues include transmission of defects and need for preimplantation genetic testing.

❑ Genetic Basis of Infertility in Females

- Female infertility contributes to ~40–50% of infertility cases worldwide.

- Genetics plays a significant role in disorders of ovarian function, hormonal regulation, developmental anomalies, and implantation failure.



❖ Chromosomal Abnormalities:

i. Numerical Abnormalities.

Condition	Karyotype	Effect
Turner Syndrome	45,X	Streak ovaries, amenorrhea, infertility
Mosaic Turner	45,X/46,XX	Variable fertility depending on mosaicism
Triple X Syndrome	47,XXX	Often fertile, may have early menopause

ii. Structural Abnormalities

Type	Effect
Deletions/Translocations on X	Affects ovarian development/function
Balanced translocations	May cause recurrent pregnancy loss or infertility

❑ Single-Gene Disorders:

Gene	Associated Disorder	Impact on Fertility
FMR1	Fragile X premutation	Premature Ovarian Insufficiency (POI)
FSHR, LHR	Receptor mutations	Poor response to FSH/LH → anovulation
CYP19A1	Aromatase deficiency	Estrogen deficiency → abnormal sexual development
BMP15	Oocyte maturation defects	POI or anovulation

❖ Developmental and Syndromic Causes:

Syndrome	Genetic Basis	Effect on Fertility
Müllerian Agenesis (MRKH)	Unknown/complex	Congenital absence of uterus/vagina
Congenital Adrenal Hyperplasia	21-hydroxylase mutation (CYP21A2)	Excess androgens → anovulation, ambiguous genitalia
Androgen Insensitivity Syndrome (AIS)	AR gene mutation (in XY)	Female phenotype with absent uterus, infertility

❖ Polygenic and Multifactorial Conditions:

a) Polycystic Ovary Syndrome (PCOS)

- Most common genetic reproductive disorder in women
- Genes involved: FSHR, LHCGR, INS, AMH
- Characterized by anovulation, hyperandrogenism, and insulin resistance

b) Endometriosis

- Hereditary component (familial clustering)

- Polymorphisms in genes related to inflammation and estrogen metabolism (e.g., VEGF, ESR1)

❖ Genetic Testing and Evaluation in Female Infertility:

Test	Purpose
Karyotype analysis	Detect chromosomal anomalies (e.g., Turner)
FMR1 gene testing	Assess risk for Fragile X-associated POI
Gene panels	Evaluate suspected monogenic infertility cases
Carrier screening	Identify risks for inherited diseases pre-conception

❖ Reproductive Implications and Management:

- Genetic Counseling is crucial for patients with:

✓ Known chromosomal or single-gene disorders

✓ Family history of early menopause, congenital anomalies, or recurrent miscarriages

- Assisted Reproductive Technologies

✓ Egg donation may be considered in POI or Turner syndrome

References

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3. Vafai SB, Mootha VK. "Mitochondrial disorders as windows into an ancient organelle." Nature, 2012.

Thanks