Reproductive Technology, Gene Therapy, and Genetic Counseling

Chapter 16

Infertility Is a Common Problem

- In the US, about 13% of all couples are infertile
- Causes, include problems with gamete formation, and hormonal imbalances

Assisted Reproductive Technologies (ART) Expand Childbearing Options

- Assisted reproductive technologies (ART)
  - A collection of techniques used to help infertile couples have children
  - Techniques have developed ahead of legal and social consensus about their use

**Table 16.1 Some Causes of Fertility Problems**

<table>
<thead>
<tr>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems with ovulation (27%)</td>
<td>Testis vein enlargement (38%)</td>
</tr>
<tr>
<td>Pelvic adhesions (12%)</td>
<td>Unknown causes (23%)</td>
</tr>
<tr>
<td>Oviduct problems (22%)</td>
<td>Duct obstructions (13%)</td>
</tr>
<tr>
<td>Endometriosis (5%–15%)</td>
<td>Testicular failure (3%)</td>
</tr>
<tr>
<td>Pituitary malfunctions (7%)</td>
<td>Ejaculatory dysfunction (2%)</td>
</tr>
</tbody>
</table>

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Collecting Gametes

- Hormones can induce ovaries to produce many oocytes which can be collected, sorted, and frozen for future use.
- Sperm can be pooled, or retrieved through microsurgery and frozen.

Methods of Assisted Reproduction

- **In vitro fertilization (IVF)**
  - Gametes are collected and fertilized in a dish.
  - The resulting zygote is implanted in the uterus.

- **Gamete intrafallopian transfer (GIFT)**
  - Gametes are collected and placed into a woman’s oviduct.

- **Zygote intrafallopian transfer (ZIFT)**

- **Intracytoplasmic sperm injection (ICSI)**
  - An egg is fertilized by microinjection of a single sperm (for defects in sperm count or motility).

**New Ways to Make Babies**

<table>
<thead>
<tr>
<th>In Vitro Fertilization</th>
<th>Artificial Insemination and Embryo Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Father is infertile. Mother is married to donor and carries child. Egg from donor is fertilized by sperm from donor and implanted in mother.</td>
<td>1. Father is infertile but able to provide sperm. Egg from donor is fertilized in laboratory. (Donor is married to mother.)</td>
</tr>
<tr>
<td>2. Father is infertile but able to carry child. Donor egg is fertilized by father’s sperm. Fertilized egg is implanted in mother.</td>
<td>2. Father is infertile but able to provide sperm. Egg from donor is fertilized in laboratory. (Donor is married to mother.)</td>
</tr>
<tr>
<td>3. Father is infertile and does not carry child. Sperm from donor is fertilized by egg donated by a woman who carries child. Egg from donor is fertilized in laboratory.</td>
<td>3. Father is infertile and does not carry child. Sperm from donor is fertilized by egg donated by a woman who carries child. Egg from donor is fertilized in laboratory.</td>
</tr>
<tr>
<td>4. Both parents are infertile, but neither is able to carry child. Egg from donor is fertilized by sperm from donor and implanted in mother.</td>
<td>4. Both parents are infertile, but neither is able to carry child. Egg from donor is fertilized by sperm from donor and implanted in mother.</td>
</tr>
<tr>
<td>5. Father is infertile but unable to carry child. Egg from donor is fertilized by sperm from donor. Egg is transferred to mother.</td>
<td></td>
</tr>
<tr>
<td>6. Both parents are infertile, but neither is able to carry child. Egg from donor is fertilized by sperm from donor. Egg is transferred to mother.</td>
<td>6. Both parents are infertile, but neither is able to carry child. Egg from donor is fertilized by sperm from donor. Egg is transferred to mother.</td>
</tr>
<tr>
<td>7. Father is infertile. Mother is infertile but able to carry child. Egg from donor is fertilized by sperm from donor. Egg is transferred to mother.</td>
<td>7. Father is infertile. Mother is infertile but able to carry child. Egg from donor is fertilized by sperm from donor. Egg is transferred to mother.</td>
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</tbody>
</table>
ART (Assistive Reproductive Technology) and Older Mothers

- The age of the oocyte causes infertility as women age, not the age of the reproductive system.
- With hormonal treatment women in their 50s and 60s can become pregnant using donated eggs:
  - Increases risks of diabetes, stroke, high blood pressure and heart attacks.

70-y-old Indian mother
Grandmother gives birth to grandkids

In Vitro Fertilization in Women Over 40

Ethical Issues in Reproductive Technology

- Use of ART raises unresolved ethical issues:
  - Health risks to both parents and their offspring resulting from ART.
  - Use of preimplantation genetic diagnosis to select siblings who are suitable tissue or organ donors for other members of the family.

Use of ART Carries Risks to Parents and Children

- Risks of ART:
  - Threefold increase in ectopic pregnancies
  - Multiple births (35% in IVF)
  - Increased risk of low birth weight
  - Increased risk of transmitting genetic defects to male children (in ICSI)
Preimplantation Genetic Diagnosis (PGD) Has Several Uses

- **Preimplantation genetic diagnosis (PGD)**
  - Removal and genetic analysis of a single cell from a 3- to 5-day old embryo
  - Used to select embryos free of genetic disorders for implantation and development
  - Has been used to select embryos tissue-matched to siblings with Fanconi anemia or leukemia to serve as transplant donors

Controversial Reasons for Using PGD

- Controversial reasons for PGD include non-medical sex selection and selection for disabilities, such as deafness and dwarfism

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneuploidy</td>
<td>93%</td>
</tr>
<tr>
<td>Autosomal disorders</td>
<td>82%</td>
</tr>
<tr>
<td>Chromosomal rearrangement</td>
<td>67%</td>
</tr>
<tr>
<td>X-linked diseases</td>
<td>58%</td>
</tr>
<tr>
<td>Non-medical sex selection</td>
<td>42%</td>
</tr>
<tr>
<td>To avoid an adult-onset disease</td>
<td>28%</td>
</tr>
<tr>
<td>HLA typing with single gene test</td>
<td>24%</td>
</tr>
<tr>
<td>HLA typing w/o single gene test</td>
<td>6%</td>
</tr>
<tr>
<td>To select for a disability</td>
<td>3%</td>
</tr>
</tbody>
</table>

0 10 20 30 40 50 60 70 80 90 100
Percent of IVF-PGD clinics that provide each type of PGD

Sibling for a cure? (Fanconi Anemia, Molly Nash and brother Adam)
Hollywood Movie: My Sister’s Keeper

Genetic Journeys: Saving Cord Blood

- Umbilical cord blood contains stem cells used to treat immune disorders
- Cord blood is better for transplants than marrow; it has not been exposed to pathogens and is less likely to carry antibodies
- Mothers should consider donating cord blood to a cord blood bank to save lives

Genetics in Society: The Business of Making Babies

- IVF and ART have become a profitable business with revenues up to $3 billion per year
- This business has little or no government or industry oversight, and there is little consistency in state regulations or insurance coverage

Gene Therapy Promises to Correct Many Disorders

- Gene therapy transfers a normal gene copy into target cells of individuals carrying a mutant allele
- Gene therapy
  - The transfer of cloned genes into somatic cells as a means of treating a genetic disorder
What Are the Strategies for Gene Transfer?

- There are several methods for transferring cloned genes into human cells
  - Viral vectors
  - Chemical methods used to transfer genes across cell membranes
  - Physical methods such as microinjection or fusion of cells with vesicles carrying cloned DNA

Using Viral Vectors for Gene Therapy

Gene Therapy Showed Early Promise

- Ashanti de Silva remains the only success for severe combined immunodeficiency disease (SCID) gene therapy

David Vetter (Bubble Boy 1971-1984)
**Gene Therapy Trials**

Number of Gene Therapy Clinical Trials Approved Worldwide 1989–2007

- Cancer diseases 66.5% (n = 871)
- Cardiovascular diseases 9.1% (n = 119)
- Monogenic diseases 8.3% (n = 109)
- Infectious diseases 6.5% (n = 85)
- Neurological diseases 1.5% (n = 20)
- Ocular diseases 0.9% (n = 12)
- Other diseases 1.6% (n = 21)
- Gene marking 3.8% (n = 50)
- Healthy volunteers 1.7% (n = 22)

**Exon Skipping and Gene Therapy**

- Duchenne muscular dystrophy
  - Pre-mRNA: Deletion of exons 45-50
  - Splicing
  - mRNA: Reading frame of transcript disrupted
  - Protein: Dystrophin translation stops prematurely

- Exon skipping to reframe transcripts
  - AON hides exon 51 from splicing machinery
  - Exon 51 is skipped
  - mRNA: Reading frame of transcript restored
  - Protein: Translation continues

**Variations of Gene Therapy**

- **Somatic gene therapy**
  - Gene transfer to somatic cells to cure genetic disorders

- **Germ-line gene therapy**
  - Gene transfer to gametes to prevent genetic disease
  - The new gene will be passed onto the next generation
Some Gene Therapy Involves Stem Cells, Gene Targeting, and Therapeutic Cloning

- A blastocyst begins to implant in the uterine wall

Therapeutic Cloning

- Stem cells can also be created by transferring a somatic cell nucleus into an enucleated egg

  **Somatic cell nuclear transfer**
  - A cloning technique that transfers a somatic cell nucleus to an enucleated egg, which is stimulated to develop into an embryo
  - Inner cell mass cells collected from the embryo are grown to form a population of stem cells

Stem Cells are Classified by their Potential

- **Totipotent**
  - The ability of a stem cell to form a whole organism or every cell type in the body including extra-embryonic cells (e.g. zygote)

- **Pluripotent**
  - The ability of a stem cell to form all three germ layers (e.g. embryonic stem cells)

- **Multipotent**
  - The restricted ability of a stem cell to form a limited number of cell lineages (bone marrow stem cells, adult stem cells, umbilical cord stem cells)

iPS Cells

- Induced Pluripotent Cells are a type of pluripotent stem cells that are artificially derived from non-pluripotent cells, e.g. adult somatic cells

- iPS cells are induced via a “forced” expression of certain genes
**Gene Transfer**

- Adult stem cells modified by gene transfer are being developed to treat genetic disorders.
- Viral vectors were used to insert normal genes into cells with mutant genes.

**Gene Doping: Athletics and Enhancement Gene Therapy**

- Athletes have been suspended from competitions for using erythropoietin (EPO), a hormone that increases production of red blood cells to enhance athletic performance.
- Repoxygen, a form of gene therapy which results in increased synthesis and release of erythropoietin, may be impossible to detect.

**Genetic Counseling**

**Genes Assess Reproductive Risks**

- Counselors help people understand:
  - Medical facts, diagnosis, and treatment
  - How heredity contributes to the disorder and risk of having children with the disorder
  - Alternatives for dealing with the risk of recurrence
  - Ways to adjust to the disorder

- Genetic counselors have specialized graduate training in medical genetics, psychology, and counseling.
<table>
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<th>Why Do People Seek Genetic Counseling?</th>
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<tr>
<td>Counseling is recommended for</td>
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<tr>
<td>• Women who are or may be pregnant after age 35</td>
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<tr>
<td>• Couples who have a child with a genetic defect</td>
</tr>
<tr>
<td>• Couples seeking information about genetic defects that are common in their ethnic group</td>
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<tr>
<td>• Couples who are close blood relatives</td>
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<tr>
<td>• Individuals at risk through jobs or lifestyle</td>
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<tr>
<td>• Those concerned that they may have an inherited disorder or birth defect</td>
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<th>How Does Genetic Counseling Work?</th>
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<tbody>
<tr>
<td>Prenatal screening and cytogenetic or biochemical tests can be used along with pedigree analysis to determine risk</td>
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<tr>
<td>Decisions about whether to have additional children, to undergo abortion, or even to marry are always left to those being counseled</td>
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