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LECTURE 3.a.

Female and Male Infertility
Lecture Objectives

- Different definitions of infertility
- Time trends and geographic variations in infertility
- Etiology and treatment of male and female factor infertility
- Adverse effects of infertility treatment
Definitions of infertility

- Inability to achieve a recognized pregnancy after trying to conceive for:
  - > 1 year (U.S. ACOG) or
  - > 2 years (WHO)

- Primary infertility: no prior pregnancy

- Secondary infertility: Prior pregnancy by woman or man

- Infecundity: Inability to achieve a live birth
Prevalence of Infertility
Depends on the question

<table>
<thead>
<tr>
<th>Definition</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever waited &gt; 24 months</td>
<td>20.6</td>
</tr>
<tr>
<td>Tried for &gt; 24 months</td>
<td>12.5</td>
</tr>
<tr>
<td>Consulted a physician</td>
<td>9.6</td>
</tr>
<tr>
<td>Diagnosed infertility</td>
<td>6.1</td>
</tr>
</tbody>
</table>

- Prevalence of infertility depends on the specificity of the question asked
Demographic Definitions

- **Primary infertility:** Absence of a live birth at specific ages (e.g. > age 30) in non-contracepting population

- **Secondary infertility:** Absence of a live birth > 5 years in persons with prior births
# Prevalence of Infertility in U.S. 1965 - 1995

## U.S. Married Women Aged 15 – 44 years

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>13.3</td>
<td>13.9</td>
<td>13.7</td>
<td>11.9</td>
</tr>
<tr>
<td>Primary</td>
<td>2.2</td>
<td>5.8</td>
<td>6.0</td>
<td>5.7</td>
</tr>
<tr>
<td>Secondary</td>
<td>11.1</td>
<td>8.1</td>
<td>7.7</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Definition: Inability to conceive >1 year, within past 3 years. NSFG 1965 – 1995.

### Numbers of Infertile Women in US

<table>
<thead>
<tr>
<th>Number (millions)</th>
<th>1965</th>
<th>1982</th>
<th>1988</th>
<th>1995</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.0</td>
<td>2.4</td>
<td>2.3</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Excludes sterilized couples.

*Source: NSFG 1995.*
U.S. trends in primary infertility

- **Demographic:**
  - Delay in marriage (1968 24.9 vs 2002 25.1 yrs)
  - Delay in first birth 1968 21.4 vs 2002 25.1 yrs
  - Delayed childbearing → shifts first births to later ages when fertility is lower

- **Biologic:**
  - Possible effects of STDs and PID?
U.S. Trends in secondary infertility

- Decrease in Secondary Infertility
  - Decrease in family size since 1960’s
  - More couples adopt sterilization to terminate reproduction and do not recognize secondary infertility
Physician Office Visits
For Infertility
U.S. 1966-1988

Consultations (1000s)

Year

Center for Disease Control
Reference 1
Most data come from demographic sources
- Proportions childless age 25-34
- Proportions with no birth in past 5 years

Range of primary infertility, 3-20+% 

Regional variation: Historic “Infertility Belt” in central Africa
- Cameroon, Congo, Uganda
Trends in Developing Countries

- Infertility in Africa decreased in recent decades
  - Difficult to determine trends from surveys due to selective inclusion of currently married women (e.g. infertile women may often be divorced)
  - Variation in survey samples over time
Trends in Developing Countries

♦ Papua New Guinea
  - Tabar infertility 45% in 1940’s decreased to 18.5% in one generation following use of penicillin for presumptive therapy

♦ Zaire
  - Equater province infertility 42% in 1955, decreased to 9.7% in 1975

Source: WHO Technical Report 1975; No. 582
Etiology of Infertility

- Etiologic studies require invasive procedures and clinical evaluation

- Variability between clinics
  - Type of service (general, specialization)
  - Triage (selective referral)
  - Costs and socioeconomic barriers
  - Lack of standardization

- Female cause ~ 50-60%

- Male cause ~ 40-50%
Etiology of Infertility in Women

- Tubal occlusion due to Pelvic Inflammatory Diseases (PID)
  - Industrialized countries 33%
  - Africa 75%
- Ovulatory disorders
  - ~ 30%
- Endometriosis
- HIV
- Toxic exposures:
  - smoking, glycol ethers, nitrous oxide, pesticides
Pelvic Inflammatory Disease and Infertility

1. Cervical infection (C. trachomatis and/or N. gonorrhoeae)
2. Alteration of cervicovaginal microenvironment, increased pH
Pelvic Inflammatory Disease and Infertility

3. Overgrowth of vaginal and anaerobic flora, resulting in BV.
4. Progressive ascent of original cervical pathogen and/or BV anaerobes into the endometrium, fallopian tubes, and the peritoneal cavity.
Sequence of Extension

1. Cervix
2. Uterine Cavity
3. Fallopian Tubes
4. Abdominal Cavity
Clinical Features

- **Endocervicitis**: May be asymptomatic; vaginal discharge, cervical inflammation, or infection; local tenderness
- **Endosalpingitis**: Constant bilateral lower quadrant abdominal pain aggravated by body motion. Tenderness in one or both adnexal areas. Abscess formation may occur.
- **Endometriosis**: Menstrual irregularity
- **Peritonitis**: Nausea, emesis, abdominal distention, rigidity, tenderness. Pelvic or abdominal cavity abscess formation may follow.
Tubal Factor Infertility & PID

Percent of women with tubal factor infertility following PID, by number of episodes

Note: The relative standard error for these estimates of the total number of acute and chronic PID cases ranges from 6% to 18%. Data available through 2003.

**SOURCE:** National Hospital Discharge Survey (National Center for Health Statistics, CDC)
Pelvic Inflammatory Disease
Initial Visits to Physicians’ Offices


Note: The relative standard error for these estimates ranges from 19% to 30%.

SOURCE: National Disease and Therapeutic Index (IMS Health)
Ectopic Pregnancy
Hospitalizations of Women 15 to 44 United States, 1980–2003

Hospitalizations (in thousands)

Note: Some variations in 1981 and 1988 estimates may be due to changes in sampling procedures. The relative standard error for these estimates ranges from 8% to 12%. Data available through 2003.

SOURCE: National Hospital Discharge Survey (National Center for Health Statistics, CDC)
Smoking and Subfertility

- Risks of subfertility > 1 year
  - Mother smoker
    • RR = 1.5 (1.2-2.0)
  - Father smoker, mother non-smoker (passive smoking)
    • RR = 1.2 (1.0-1.4)

<table>
<thead>
<tr>
<th>EGE Exposure</th>
<th>Subfertility (Inability to conceive &gt; 1 year) (%)</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>9.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Low</td>
<td>13.3</td>
<td>1.5 (0.7-3.1)</td>
</tr>
<tr>
<td>Medium</td>
<td>13.3</td>
<td>1.8 (0.8-4.3)</td>
</tr>
<tr>
<td>High</td>
<td>27.3</td>
<td>4.6 (1.6-13.3)</td>
</tr>
</tbody>
</table>

Treatment of Female Infertility

- Tubal Occlusion
  - Assisted Reproductive Technologies (ART)
    - In vitro fertilization (IVF)
    - Gamete intrafallopian transfer (GIFT)
    - Zygote intrafallopian transfer (ZIFT)
  - Tubal surgery
In vitro fertilization (IVF)

(1) Once mature, the eggs are suctioned from the ovaries and (2) placed in a laboratory culture dish with the man's sperm for fertilization. (3) The dish is then placed in an incubator. (4) About 2 days later, 3 to 5 embryos are transferred to the woman's uterus.

United States: 1 in 80-100 births now IVF conceptions; 100,000 IVF cycles; 48,000 births
Live births per embryo transfer, by age of mother and age of donor

**Figure 2.** Effect of a Woman’s Age on the Rate of Live Births per IVF Embryo Transfer.
Data are for the United States in 2003.8

Preconception genetic diagnoses

- One or two blastomeres are removed from the embryo
- Chromosome identification and evaluation by fluorescence in situ hybridization (FISH)
- Current techniques allow evaluation of up to 10 chromosomes in a single cell
Treatment of Female Infertility

- Ovulation Disorders
  - Ovulation induction by Clomid, GnRH

- Endometriosis
  - Drug treatment (Danazol)
  - Surgery
Prognosis of Infertility

- Prognosis varies with:
  - Age
  - Primary vs. secondary infertility
  - Duration of infertility
  - Type and severity of pathology
  - Single vs. multiple causes
  - Male, female, or both affected
  - Smoking, caffeine, nutrition
### Delivery Rates with IVF

<table>
<thead>
<tr>
<th>Age</th>
<th>Delivery %</th>
<th>Age</th>
<th>Delivery %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>35.7</td>
<td>&lt;35</td>
<td>35.1</td>
</tr>
<tr>
<td>35-39</td>
<td>33.5</td>
<td>35-39</td>
<td>33.5</td>
</tr>
<tr>
<td>40+</td>
<td>10.3</td>
<td>40+</td>
<td>12.8</td>
</tr>
</tbody>
</table>

- **No male factor**
- **Male factor infertility**

ASRM/SART Registry *Fertil Steril* 2002;77:18-31
Outcomes of IVF: U.S.

- Live births per embryo transfer ~50%
- Pregnancy loss ~ 18%
- Multiple births per delivery
  - 31% twins
  - 3% triplets or more
  - (normal conception, 1% multiple gestations)


Bradley NEJM 2007;356:379
Percentage of twins after in vitro fertilisation by year of birth in Europe

IVF Pregnancy Outcomes
(Shevell Obstet Gybecol 2005;106:1039)

- Odds of adverse outcomes IVF vs no ART
  - Preeclampsia OR 2.7 (1.7-4.4)
  - Preterm labor OR 1.5 (1.0-2.2)
  - Placental abruption OR 2.4 (1.1-5.2)
  - Placenta previa OR 6.0 (3.4-10.7)
  - Cesarean section OR 2.3 (1.8-2.9)
Low Birth Weight and ART (US)
Schieve *NEJM* 2002;346:731-7

- N = 42,463 ART vs 3,389,098 natural conceptions

- Risk of low birth weight with ART RR = 2.6 (2.4-2.7)

- Very low birth weight (<1500 gm) RR = 1.8 (1.7-2.0)

- 4.3% of very low birth weight attributable to ART
Birth Defects and ART

- N = 837 IVF; 301 ICSI; 4000 natural conceptions

- **All Major Defects:**
  - IVF = 9.0%, ICSI = 8.6%, natural = 4.2%
  - IVF RR = 2.0 (1.5-2.9); ICSI RR = 2.0 (1.3-3.2)
  - Musculoskeletal defects: IVF = 3.3%, ICSI = 3.3%, natural = 1.1%
  - Chromosomal defects: IVF = 0.7%, ICSI = 1.0%, Natural = 0.2%

- **VLBW:** IVF = 4%, ICSI = 1%, natural = 1.0%

- Hansen *NEJM* 2002; 346: 725-30
**Costs of *in vitro* Fertilization**

<table>
<thead>
<tr>
<th>Service</th>
<th>Cost Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation induction</td>
<td>$1500-5000</td>
</tr>
<tr>
<td>Artificial insemination</td>
<td>$1000-2000</td>
</tr>
<tr>
<td>IVF woman’s own eggs</td>
<td>$12,500-25,000</td>
</tr>
<tr>
<td>IVF donor eggs</td>
<td>$20,000-35,000</td>
</tr>
</tbody>
</table>
Insurance Coverage and IVF: USA 2001

IVF primarily privately funded
- 3 states full coverage
- 5 states partial coverage
- 37 states no coverage

IVF per 1000 women
- Full coverage 3.8/1000
- Partial coverage 1.8/1000
- No coverage 1.4/1000

Jain NEJM 2002;347:661

IVF procedures 1996 = 64,036 vs 2001 = 107,587
Infertility and Pregnancy Loss

- Women with recurrent EPLs have no recognized pregnancy and report delayed conception. If delay >1 year classified as infertile.
- Increased SABs in women with infertility may reflect a common mechanism of damage to ovum and fetus such as toxic exposures.
  - e.g., Glycol ethers increase SAB (RR = 2.8) and infertility (RR = 4.6)
Infertility and Pregnancy Loss

- Early Pregnancy Loss (EPL)
  - No Infertility history  EPL = 21.1%
  - Infertility history    EPL = 69.7%

- Spontaneous Abortion (SAB)
  - No Infertility history  SAB = 14%
  - Infertility history    SAB = 23%

- Women with delays in conception have higher rates of EPLs and SABs
## Microchip Manufacturing: Female Workers
## Exposure to Ethylene Glycol Ethers (EGE)

<table>
<thead>
<tr>
<th>EGE Exposure</th>
<th>Spontaneous Abortion (%)</th>
<th>RR (CI)</th>
<th>Subfertility (%)</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>14.8</td>
<td>1.0</td>
<td>9.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Low</td>
<td>16.0</td>
<td>1.0</td>
<td>13.3</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>(0.6-0.7)</td>
<td></td>
<td>(0.7-3.1)</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>18.9</td>
<td>1.4</td>
<td>13.3</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>(0.8-2.6)</td>
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<td></td>
</tr>
<tr>
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<td>33.3</td>
<td>2.8</td>
<td>27.3</td>
<td>4.6</td>
</tr>
<tr>
<td></td>
<td>(1.4-5.6)</td>
<td></td>
<td>(1.6-13.3)</td>
<td></td>
</tr>
</tbody>
</table>
Infertility, SABs, and Age

- Infertility increases with age
- SABs increase with age
- Due to *ovum deterioration* with age
- IVF with donation of an ovum from young women to an older recipient increases pregnancy rates and decreases SABs
Male Infertility

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Etiology of Male Infertility

- Varicoele ~ 20-40% (importance?)
- Infections (e.g. mumps, STD orchitis & epididymitis, HIV)
- Undescended testis
- Toxins (e.g. DPCP, glycol ethers)
**Treatment of Male Infertility**

- **Varicocelectomy**
  - 7 Randomized trials no benefit
  - Pregnancy RR = 1.04 (0.7-1.4)
  - Evers & Collins Lancet 2003;361:1849

- **Artificial insemination by donor or self**

- **Hormone supplements**

- **Intracytoplasmic sperm injection (ICSI)**
Male fertility and time trends in semen quality
Factors influencing male fertility

- Male fertility and age, effect of endocrine status
- Secular trends in semen quality
- Testicular development and testicular cancer as a marker of adverse effects
- Possible effects of environmental factors including environmental estrogens, endocrine disruptors hypothesis
Male Fertility and Age

- Sexual activity declines with age
- Testosterone decline with age
- Semen quality and age
- Difficult to estimate male fertility with age, independent of female age-specific fertility
  - Correlation of partner’s age
  - Only women become pregnant
- Ireland and Bangladesh data suggest decline in male fertility > age 50
Male Sexual Activity and Age

Any sexual activity

Sexual intercourse

Number of sexual events per 5 years

Age groups
Birth rates by male age married to women aged 20-29, Ireland 1911

Birth per 1000 by male age

<table>
<thead>
<tr>
<th>Male Age</th>
<th>Birth/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>~40</td>
<td>425</td>
</tr>
<tr>
<td>~45</td>
<td>411</td>
</tr>
<tr>
<td>~50</td>
<td>356</td>
</tr>
<tr>
<td>~60</td>
<td>293</td>
</tr>
</tbody>
</table>
Assessment of Semen

- Requires sample from masturbation

- Assessed by:
  - Semen volume (normal 5 mL)
  - Sperm count (normal > 20 million/mL)
  - Motility (>40%)
  - Morphology (50% typical forms)
Problems in assessment of Semen

- Variation in semen quality
  - Between laboratories and regionally
  - Season (lower in hot months)
  - Age (lower with age)
  - Recent ejaculation (decreased if < 3 days)
## Semen Quality and Age

<table>
<thead>
<tr>
<th>Young (&lt;39)</th>
<th></th>
<th>Older men (&gt; 59)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>5.3 mL</td>
<td>Volume</td>
<td>2.3 mL</td>
</tr>
<tr>
<td>Count</td>
<td>325 mill</td>
<td>Count</td>
<td>208 mill</td>
</tr>
<tr>
<td>Motility</td>
<td>32.8%</td>
<td>Motility</td>
<td>23.8%</td>
</tr>
<tr>
<td>Abnormal morphology</td>
<td>11.0%</td>
<td>Abnormal Morphology</td>
<td>12.8%</td>
</tr>
<tr>
<td>Chromosomal abnormalities</td>
<td>11.9%</td>
<td>Chromosomal abnormalities</td>
<td>4.8%</td>
</tr>
</tbody>
</table>
Seasonal Variation in Sperm Count

Sperm concentration, millions/ml

Meta-analysis and some longitudinal studies suggest declines in sperm counts of “normal” males over time.

- Is this evidence for male reproductive damage?

- Are these trends real?
  - Consistency between studies
  - Selection effects
  - Definition of “normal”
  - Adjustment for recency of intercourse, age and season
Trends in Sperm Count over Time

"Environmental Estrogen Hypothesis"

- Environmental estrogens may act as hormonal disruptors:
  - Diet (fat, phytoestrogens)
  - Synthetic hormones
  - Estrogenic chemicals (e.g. pesticides, organochlorine and benzene derivatives)
  - Solvents
  - Fungicide causing azoospermia (DBCP)
Concentration of Sperm by Birth Cohort

Problems with Time Trends in Semen Quality

- Studies inconsistent
- Variations in definitions of “normal” (WHO definition decreased from 60 to 20 million/mL over time)
- Selection of “normal” men varies between studies (e.g. sperm donors, vasectomy cases)
Problems with Time Trends in Semen

- Lack of control for time since last ejaculation, season, and age
- Variation in laboratory methods, and inter-observer variation in sperm counts
- Confounding between regions