Basics of infertility
Student Lecture
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Definitions

- **Infertility**
  - One year of 'frequent' unprotected intercourse without conception (U.S. ACOG)
  - > 2 years (WHO)
  - Primary infertility: no prior pregnancy
  - Secondary infertility: Prior pregnancy by woman or man

- **Fecundity**
  - The ability/chance of achieving a live birth during any one menstrual cycle

- **Fecundability**
  - The ability/chance of achieving a pregnancy during any one menstrual cycle

Time To Conception In Fertile Women

<table>
<thead>
<tr>
<th>Time</th>
<th>% pregnant</th>
</tr>
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<tbody>
<tr>
<td>1 month</td>
<td>50%</td>
</tr>
<tr>
<td>6 months</td>
<td>72%</td>
</tr>
<tr>
<td>12 months</td>
<td>85%</td>
</tr>
<tr>
<td>24 months</td>
<td>93%</td>
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Prevalence of Infertility in US women age 18-45

<table>
<thead>
<tr>
<th></th>
<th>1985</th>
<th>1988</th>
<th>1995</th>
</tr>
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<tbody>
<tr>
<td>All</td>
<td>13.3</td>
<td>13.9</td>
<td>11.9</td>
</tr>
<tr>
<td>Primary</td>
<td>2.2</td>
<td>6.0</td>
<td>5.7</td>
</tr>
<tr>
<td>Secondary*</td>
<td>11.1</td>
<td>7.7</td>
<td>6.2</td>
</tr>
</tbody>
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Definition: Inability to conceive >1 year, within past 3 years. NSFG 1965 – 1995

Source: Chandra. Infertil Repro Clin North Amer 1995;5:283

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

Age and Fertility

- Peak fertility age 20-24
- Decrease starting age 30-32
- Rapidly declines after age 40
- Due to decline in quantity and quality of oocytes
Always remember!

- Uterus and tubes
  - Are tubes patent?
  - Is the uterus normal?

- Egg
  - Are eggs ovulated on a regular basis?

- Sperm
  - Are the sperm swimming?
  - Are there enough sperm?

Investigations for Infertility

The Basic Infertility Work-up

Uterine/Tubal Factor

30% of all infertile couples
Tools to diagnose Tubal Factor

Basic infertility workup

Uterus and tubes

- Hysterosalpingogram
- Sonohysterogram
- Laparascopy with dye test
- Hysteroscopy
- Pelvic ultrasound

Diagnosing tubal factor

- Hysterosalpingogram:
  - Most utilized method (TFC first step)
  - Not useful for peritubal adhesions/endometriosis
  - Not as useful for intrauterine adhesions/filling defects
  - Sens. 65%, spec. 83% (Worse for proximal tubal factor)
  - Therapeutic benefit: 12 RCT
    - PR with HSG: (OR 3.3)

Pelvic Inflammatory Disease and Infertility

1. Cervical infection (C. trachomatis and/or N. gonorrhoeae)

2. Alteration of cervicovaginal microenvironment, increased pH
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.

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

<table>
<thead>
<tr>
<th>Episode of PID</th>
<th>Risk of Tubal disease</th>
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<tbody>
<tr>
<td>1st</td>
<td>10-12%</td>
</tr>
<tr>
<td>2nd</td>
<td>25-35%</td>
</tr>
<tr>
<td>3rd</td>
<td>75%</td>
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**Salpingitis and PID**

**Uterine Anatomical Factors**
- Polyps
- Fibroids
- Septums
- Adhesions
Sonohysterography

- Advantage of assessing tubes/ovaries/uterine cavity over HSG
- Compared to HSG: Metanalysis Holtz 1997.
  - 83% concordant with HSG for tubal factor
- Compared to hysteroscopy for uterus:
  - Sensitivity 93%, specificity of 89%

Endometriosis & Fecundity

- The monthly fecundity rate in subfertile women with endometriosis vs. Fertile is
  
  2-10% vs. 15-20%
  
  The Practice Committee of the American Society for Reproductive Medicine, 2004

Endometriosis

Prevalence is part of the enigma

- Laparoscopy for infertility: 38%
- Laparoscopy for pelvic pain: 20-70%
- Laparoscopy for a pelvic mass: 0-5%
- Incidental finding 2-18%
- In the general population 7-10%

Canadian Consensus on Endometriosis, SOGC 1999
ACOG Guidelines

Gold standard(s)

- **Tubal Factor: Laparoscopy/Chromotubation:**
  - Cost/Benefit analysis does not favour global approach in all couples.
  - HSG compared to Lap/CTB
    - FP 12.5%, FN 11.2%
  - SHG compared to Lap/CTB
    - FP 10.3%, FN 6.7%
- **Hysteroscopy:**
  - Advantage of site, endometrial evaluation, treatment
  - Evidence of enhanced IVF outcomes following scope.
    - < 6months, Best < 50 days.

Hystero-laparoscopy

Egg

30-35% of all infertile couples
Basic infertility workup

**Egg**
- Assess folliculogenesis and ovarian reserve
- Menstrual history
  - Day 3 Hormonal profile: FSH, LH, Estradiol
  - TSH, Prolactin
- Document ovulation
  - Day 21 progesterone
  - BBT, LH kits

How many eggs are we dealing with?

- 5 months in utero: 2-5 million primordial follicles arrested at prophase I of meiosis.
- Birth: 1-2 million
- Puberty: 300,000
  - Majority will be lost to atresia
- Ovulate: 400-500 lifetime cycles
- Menopause: < 1000

Ovarian reserve tests
- Intended to help predict future fecundability and provide help in predicting likelihood of successful IVF
- Day 3 FSH (normal < 10)
  - Normal FSH < 10 mIU/mL
  - Borderline FSH 10-15 mIU/mL
  - High FSH > 15 mIU/mL
- Day 3 Estradiol level:
  - Day 3 ultrasound antral follicle count
  - AMH

Tests Utilized
- Antral Follicle Count (AFC):
  - Usually measured Day 3
  - US to measure follicles (2-10mm)
  - Poor AFC: 4-10 total
  - In poor AFC: Anytime of cycle is equally prognostic
  - Not predictive:
    - Oocyte quality
    - Pregnancy outcome
Anti-Mullerian Hormone

- AMH is expressed by granulosa cells of the ovary during the reproductive years
- Produced by small pre-antral and early antral follicles prior to the attainment of FSH responsiveness
- In essence, produced by the pool of follicles that are ready for recruitment each cycle (ovarian reserve)
- Level independent of the cycle, can be measured any day

Tests of Ovulation

- Ovulation Kits
  - Urine detection of LH (approx. 1-2 days of the true surge)
  - Web-based temperature charts
    - Retroactive of the true surge by at least 2 days
    - Do not increase chance of conceiving over regular timed intercourse
- Day 21 Progesterone:
  - Indicative of ovulation (Don’t produce Progesterone without CL)
  - Ultrasound/blood work monitoring

Male Factor

35% of Infertility couples

Basic infertility workup

Sperm

- Semen analysis
  - 2 to 5 days of abstinence
  - Sample in the lab within 45 minutes
  - In Canadian weather, has to be kept warm
  - Always repeat if borderline result

Semen analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
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<tbody>
<tr>
<td>Volume</td>
<td>1.5-5.0 ml</td>
</tr>
<tr>
<td>pH</td>
<td>&gt;7.2</td>
</tr>
<tr>
<td>Concentration</td>
<td>&gt;15 x 10^6/ml</td>
</tr>
<tr>
<td>Total sperm count</td>
<td>&gt;40 x 10^6</td>
</tr>
<tr>
<td>motility</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>Morphology</td>
<td>&gt;30% normal forms</td>
</tr>
</tbody>
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Variability in sperm count in one individual!
Male Factor

- Advanced Semen analysis (Monash)
- 20-30% discordant from CBSA
- Separation of sperm from semen
- Motility
- Morphology
- Predicts success in ART

Follow up (6 weeks)

- Go over:
  - D3, D21 bloodwork
  - Tubal Tests
  - Sonohysterogram
  - SA
- Or findings from hysteroscopy, laparoscopy, tubal dye tests

ART

- IUI (10-25%)
- IVF (40-50%)
- IVF +/- ICSI (40-50%)

The major discriminator is sperm quality!

The minor discriminators are:
- Cost
- Female parameters (TP, Age)
- not anovulation

Tubes open, Sperm normal, Not ovulating

Options:
1. Oral ovulation (Clomiphene Citrate, Letrezole) + TI
   - ovulating: allow 6 months
   - not-ovulating: increase dose, add metformin
   - Still not ovulating: LOD (80%) or IUI
2. IUI (PO or SC ovulation medication)

Tubes open, Sperm normal, ovulating
(unexplained infertility 5-20%)

Options:
1. Investigate for endometriosis and treat
2. IUI

Tubes open, Sperm abnormal, +/- ovulating

Options:
1. Refer to urology: search and treat a correctable factor
2. IVF +/- ICSI
3. IVF with Donor Sperm
4. IUI with Donor Sperm
**Tubes Blocked, sperm/ovulation +/- normal**

- IVF

**Uterine Anomalies**

- Minor: correct
- Major: Gestational Carrier
- IVF with both parents gametes

**Advanced Reproductive Age, no eggs**

- Donor eggs: Known or anonymous
- Embryo Adoption
- Child Adoption

**Thank You**

- Questions?