Disclosure
None
Objectives

1. Fertility vs. Infertility
2. When to investigate
3. Age-related Infertility
4. Initial workup:
   • Day 3 FSH & Estradiol
   • AMH
   • HSG
   • Semen analysis
   • Pelvic ultrasound
5. Treatment of Unexplained Infertility

Infertility

• Failure to achieve a pregnancy after 12 months of unprotected intercourse

• 15% of couples
Infertility

- If couples do not conceive after the first 3 months, the chances of pregnancy decline substantially

How long should it take to conceive?
Timing Intercourse

• Frequency of intercourse
  • Study of 221 couples:
    • Every day (37%) *
    • Every other day (33%) *NSD
    • Weekly (15%)
  • Abstinence >5 days can have adverse effects
  • Even daily ejaculation can maintain normal sperm counts and motility


Coital Practice

• No evidence that coital position affects fecundability
• Sperm can be found within the:
  • Cervical canal within seconds
  • Fallopian tube within minutes of ejaculation

Fertile Window

6 days up to and including ovulation day

Timing Intercourse
Detecting Ovulation

1. Calendar
   - Corpus luteum lasts 12-14 days

2. Apps (essentially Calendar)

3. Basal Body Temperature
   - $0.5^\circ$ C after ovulation from progesterone

4. Ovulation Predictor Kits

5. Egg white cervical mucous & Mittelschmerz

   1. LH & Progesterone blood tests
      - $> 10$ nmol/L

http://www.huffingtonpost.ca/dr-caitlin-dunne/how-to-tell-if-you-are-ovulating_b_16562466.html
Infertility: When to investigate?

- After 1 year of trying

Earlier:

1. Age
   - > 35 years (6 months trying)
   - > 40 years (immediately)

2. Irregular cycles
   - E.g. PCOS, Perimenopause, Endocrine disease, Uterine pathology

3. Risk factors for tubal disease
   - E.g. PID, Pelvic surgery, Ectopic pregnancy

4. Male factor suspected

☐ Eggs
☐ Uterus & Tubes
☐ Sperm
Age-related infertility

- Women are choosing to have children later in life
- BC has the highest age of first birth in the country (30.5 years in BC vs. 30.3 years in ON)
- Canada: 2010 first time in history more women in their 30's were having children than women in their 20's

http://vancouver.24hrs.ca/2016/02/16/bc-moms-give-birth-later-than-rest-of-canada
Costs of delayed childbearing:

- Aneuploidy
- Miscarriage
- Infertility

Oocyte aneuploidy:

- < 35 years: 15-20%
- 40 years: 40-50%
- 45 years: 80-90%

Speroff 8th edition
http://physiologyonline.physiology.org/content/26/5/314
Double the aneuploidy in 5 years!

Simulated model of 1000 couples:

<table>
<thead>
<tr>
<th>Chance of realization</th>
<th>1-child family</th>
<th>2-child family</th>
<th>3-child family</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without IVF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>41</td>
<td>38</td>
<td>35</td>
</tr>
<tr>
<td>75%</td>
<td>37</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>90%</td>
<td>32</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>With IVF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>42</td>
<td>39</td>
<td>36</td>
</tr>
<tr>
<td>75%</td>
<td>39</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>90%</td>
<td>35</td>
<td>31</td>
<td>28</td>
</tr>
</tbody>
</table>

What is ovarian reserve?

- Technically it is the number of oogonia (eggs) remaining (in primordial follicles)
- We test ‘functional’ ovarian reserve by assessing hormone responsive pre-antral and antral follicles
- Function ovarian reserve provides a reasonable estimate of ‘true’ ovarian reserve
Oogonia

- 20\textsuperscript{th} week gestation = max (6-7 million)
- Birth = 1-2 million
- Puberty = 400k
  - 500 ovulate
- Menopause = <1000

Significant decline after age 35
How do we test ovarian reserve?

1. Day 3 Follicle-Stimulating Hormone (FSH)

2. Antral Follicle Count
   - PCO > 12 per ovary
   - Low < 5-7 total

3. Anti-Müllerian Hormone

Day 3 FSH

- Produced by the anterior pituitary
- Acts on granulosa cells (Sertoli cells in males)
- Stimulates ovarian folliculogenesis
- Can be suppressed by Estrogen & Inhibin B in the later follicular phase
  - Always measure estradiol (< 200 pmol/L) to ensure FSH is not being suppressed
IVF live birth rates:

- Maximal when FSH < 7 IU/L
- < 2% when FSH > 18 IU/L

Anti-Müllerian Hormone (AMH)

- Dimeric glycoprotein
- Initially known for its role in sexual differentiation
• SRY region (short arm of Y)
• SOX9: testis differentiation
• AMH from Sertoli cells after testicular differentiation
• Ipsilateral regression of the müllerian ducts by 8 weeks
• Emergence of testosterone and stimulation of the wolffian ducts.

Anti-Müllerian Hormone (AMH)
• Holy Grail of ovarian reserve testing?
• Discovered in 2002 to be associated with number of oocytes retrieved at IVF
• Produced by the granulosa cells of pre-antral and small antral follicles
• NOT produced by the dominant follicle so it is stable across the menstrual cycle
Anti-Müllerian Hormone (AMH)

- Life Labs charges $70
- Can be done on any day of the cycle, even on OCP
  - No appointment required
  - Results in ~5 days
- Normal range is highly age-specific
  - Higher = more oocytes
    - Note: There is no level diagnostic of PCOS
  - Low is generally < 8pmol/L (< 1.1ng/ml)
    - Conversion factor 0.14, beware of the units

---

Anti-Müllerian Hormone (AMH)

- Useful for:
  - Dose planning in IVF
  - Ovarian reserve assessment
    - E.g. pre/post chemotherapy or ovarian surgery
  - Confirming menopause/perimenopause
    - E.g. Oligomenorrhea – PCOS or perimenopause?
Eggs (Age, D3 FSH, AMH, AFC)

☐ Uterus & Tubes

☐ Sperm

Hysterosalpingography (HSG)
• Radio-opaque fluid and fluoroscopy

Hydrosalpinx
HSG

- HSG has good sensitivity and specificity for detecting fallopian tube pathology

- Less accurate when it comes to endometrial lesions
  - Confirmatory tests for endometrial polyps, adhesions or submucosal fibroids = Sonohysterography (SHG) & Hysteroscopy

- Uterine pathology such as bicornuate or septate uterus are sometimes picked up by HSG
  - Differentiation requires 3D ultrasound, MRI or concurrent laparoscopy/hysteroscopy
  - PCRM offers 3D ultrasound

- Risk factors for post-procedure infection (PID hx or hydrosalpinx) → antibiotic prophylaxis is recommended
  - Doxycycline 100mg PO BID for 3 – 5 days beginning the day before the procedure is a common regimen
HSG

British Columbia:
1. Laurel Radiology (604-879-7726) - #106-888 W. 8th Ave., Vancouver
2. UBC Hospital - Koerner Pavillion (604-822-1799) - 2211 Wesbrook Mall, Vancouver
3. Royal Columbian Hospital (604-520-4642) - 330 E. Columbia St, New Westminster
4. Eagle Ridge Hospital (604-469-3172) - 475 Guildford Way, Port Moody
5. Langley Memorial Hospital (604-533-6405) - 22051 Fraser Highway, Langley
6. Abbotsford Regional Hospital (604-851-4863) - 32900 Marshall Road, Abbotsford
7. Royal Jubilee Hospital (250-727-4455 ext 1) - 1952 Bay Street, Victoria

(Check with your local hospital)

Consider: Pre-HSG pregnancy test ± STI screening PRN

Pelvic Ultrasound

- Not mandatory

- Useful to rule out structural lesions (E.g. fibroids, large polyps, ovarian cysts)

- Performed by PCRM doctors
☑ Eggs (Age, D3 FSH, AMH, AFC)

☑ Uterus & Tubes (HSG, U/S)

☐ Sperm

Semen analysis

- Optimal sample is obtained after 2 – 5 days of abstinence
- Reference ranges in the WHO 5th Ed. established from a population of fertile men with a time to pregnancy of less than 12 months (lower 5th centile was used as a threshold for normal semen parameters)
- Most important results: concentration (> 15 million/ml), motility (> 40%) and progressive motility (> 32%)
- Morphology is of lesser importance
  - In the WHO 1st edition 80.5% normally shaped sperm were required… Then 50%… 30%… 15% over the next editions
  - Current 5th edition uses a cutoff of 4% for morphology
  - Even 0% morphology does not preclude a pregnancy
Semen analysis

- Need an appointment at Life Labs
- PCRM

☑ Eggs (Age, D3 FSH, AMH, AFC)

☑ Uterus & Tubes (HSG, U/S)

☑ Sperm (SA)
**Etiology of Infertility**

1. Male
   - Dr. Chow

1. Ovulatory
   - Dr. Havelock

1. Tubal/uterine
   - Dr. Bedaiwy & Dr. Mehra

1. Unexplained

---

**Unexplained infertility**

- Diagnosed when the basic evaluation fails to show an abnormality

- 10 – 30% of infertility is unexplained

- Average cycle fecundity 1.8 – 3.8%
  - Decreases with age and duration of infertility

---

Unexplained infertility

- Treatment is empiric
  - Intrauterine insemination (IUI)
  - Clomiphene
  - Clomiphene + IUI
  - Gonadotropins (FSH injections) + IUI
  - IVF

Unexplained infertility

1. IUI alone
   - PR 4.1% IUI vs. 2.4% intercourse (per cycle)
   - NNT = 37 IUIs for one additional pregnancy

2. Clomiphene citrate alone
   - Earlier evidence suggested small benefit
   - ASRM 2013: “CC and intercourse is no better than expectant management”
   - PR with clomiphene 5.6% vs. 1.3 – 4.2% with expectant management
Unexplained infertility

4. Clomiphene citrate and IUI
   • Modest treatment effect
   • PR ~8%
   • Lower with advanced age
     • Especially > 40 (~3%)
     • Common to try 3 cycles

5. IVF
   • Very effective but not insured by MSP
   • PR cumulative
     • < 35 years = 69%
     • 35 – 42 years = 49%

Conclusions:

• Talk to your patients about the effects of age and fertility

• Investigate after 1 year (6 months if >35 and immediately if >40)

• Basic evaluation includes: D3 FSH and Estradiol, AMH, HSG and SA
  • Note: If referring to PCRM, our referral coordinator will arrange all testing

• Clomiphene alone is likely not an effective treatment for unexplained infertility, clomiphene + IUI has a modest effect
Thank you for coming today!

Questions?

Ovarian stimulation cycle

• ~ 21 days of OCP
• FSH injections for ~10 days

• Ultrasounds (2-4 over the 10 days)
  – 7:15am – 8:30am

• Egg retrieval
  – Need this day off work