

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

Optimizing natural fertility: a committee opinion. *Fertility and Sterility*. 2017;107(1):52-58.

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How long should it take to conceive?

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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

Effects on the probability of conception, survival of the pregnancy, and sex of the baby. *N Engl J Med.* 1995;333(23):1517-1521.
 Relationship between the duration of sexual abstinence and semen quality: analysis of 9,489 semen samples. *Fertility and Sterility.* 2005;83(6):1680-1686.

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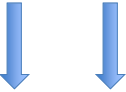
Coital Practice

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

The dynamics of rapid sperm transport through the female genital tract: evidence from vaginal sonography of uterine peristalsis and hysterosalpingoscintigraphy. *Hum Reprod.* 1996;11(3):627-632.

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Fertile Window



6 days up to and including ovulation day

Photo © Universal Images Group/Getty Image

Timing Intercourse



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Detecting Ovulation

1. Calendar
 - Corpus luteum lasts 12-14 days
2. Apps (essentially Calendar)
3. Basal Body Temperature
 - ↑ 0.5°C *after ovulation* from progesterone
4. Ovulation Predictor Kits
5. Egg white cervical mucous & Mittelschmerz
1. LH & Progesterone blood tests
 - > 10nmol/L

Infertility: When to investigate?

- **After 1 year of trying**

Earlier:

1. Age

- > 35 years (6 months trying)
- > 40 years (immediately)

2. Irregular cycles

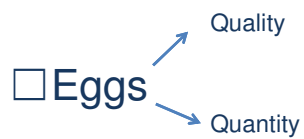
- E.g. PCOS, Perimenopause, Endocrine disease, Uterine pathology

3. Risk factors for tubal disease

- E.g. PID, Pelvic surgery, Ectopic pregnancy

4. Male factor suspected

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Uterus & Tubes

Sperm

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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

Martin et. al. (2010) Birth Data Natl Vital Stat Rep
<http://vancouver.24hrs.ca/2016/02/16/bc-moms-give-birth-later-than-rest-of-canada>

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Costs of delayed childbearing:

- Aneuploidy
- Miscarriage
- Infertility

Oocyte aneuploidy:

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

Double the aneuploidy in 5 years!

Fransiak. et al. Fertil Steril (2013):101:656

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Simulated model of 1000 couples:

32

27

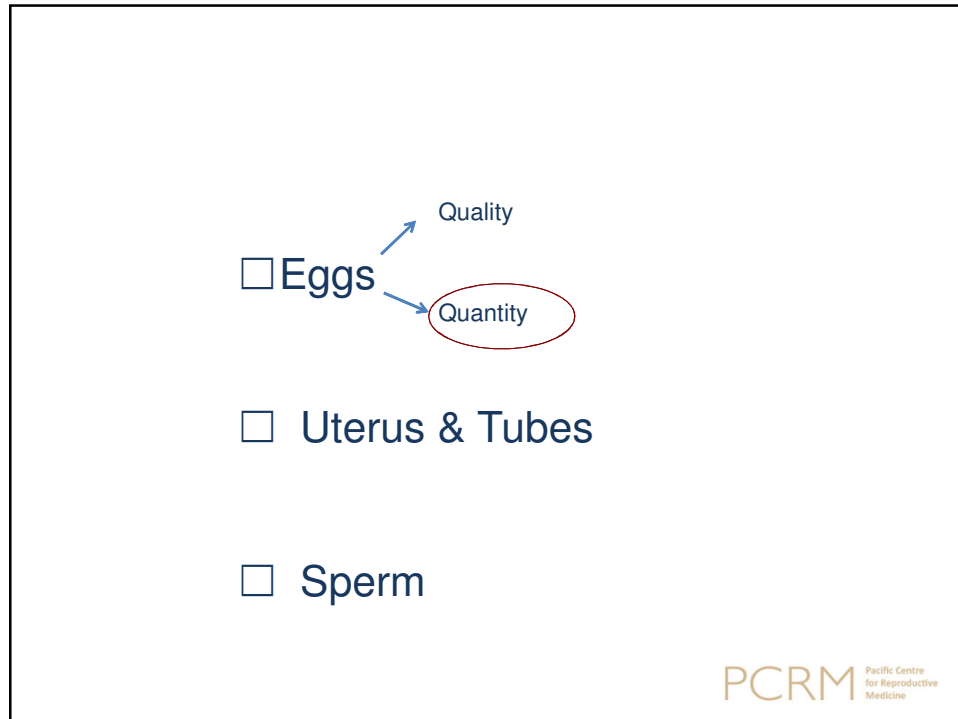
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Table 1 Maximum female age (years) at which couples should start building a 1-, 2- or 3-child family, for a 50, 75 and 90% chance of realizing the desired family size, with and without IVF.

| Chance of realization | 1-child family | 2-child family | 3-child family |
|-----------------------|----------------|----------------|----------------|
| Without IVF | | | |
| 50% | 41 | 38 | 35 |
| 75% | 37 | 34 | 31 |
| 90% | 32 | 27 | 23 |
| With IVF | | | |
| 50% | 42 | 39 | 36 |
| 75% | 39 | 35 | 33 |
| 90% | 35 | 31 | 28 |

Hum Reprod 2015; 30:2215 – 2221.

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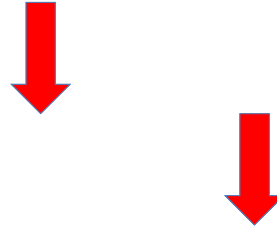


What is ovarian reserve?

- 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

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



Human Reproduction Vol.23, No.3 pp. 699-708, 2008

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Significant decline after age 35



Human Reproduction Vol.23, No.3 pp. 699-708, 2008

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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

Fertility and Sterility. Elsevier; 2008 Apr;89(4):868–78

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Anti-Müllerian Hormone (AMH)

- Dimeric glycoprotein
- Initially known for its role in sexual differentiation

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- 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

HSG

- 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

Consider: Pre-HSG pregnancy test ± STI screening PRN

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)

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Pelvic Ultrasound

- Not mandatory
- Useful to rule out structural lesions (E.g. fibroids, large polyps, ovarian cysts)
- Performed by PCRM doctors

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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

Clinical Gynecological Endocrinology, Fritz&Speroff, 8th ed.

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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*

ASRM. Unexplained Infertility. Fertility and Sterility Vol. 86, Suppl 4, November 2006

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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%

ASRM. Unexplained Infertility. Fertility and Sterility Vol. 86, Suppl 4, November 2006
Fertil Steril 2013;100:341, CPG: Use of CC in infertile women. ASRM.

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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

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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