REI REVIEW
PART 1
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SCS Annual Osteopathic Review Course
April 2, 2019

About HNC

- Part 1: Reproductive Physiology
- Part 1: Fertility workup
- Part 2: Endometriosis
- Part 3: Polycystic ovary disease PCOS
- Part 4: Ectopic pregnancy
Female Anatomy Highlights

Ovary
- Max 6 - 7 million germ cells at 16-20wks gestation
- At birth = 500,000 to 2 million
- Onset of puberty = 300,000 to 500,000
- Next 35 – 40 reproductive years, 400 to 500 oocytes are ovulated
- Menopause = few hundred to a thousand remain

The Cycle
- Mean age
  - Menarche = 12.8
  - Menopause = 51
- 90% have cycles between 24 to 35 days
  - Follicular: variable length
  - Ovulation
  - Luteal: more constant ~14 days
Fallopian Tubes
- Fertilization
- Oocyte, sperm, and embryo transport

Uterus
- Endometrium – responds to hormones
  - Stratum functionalis
    - shreds with menstruation
  - Stratum basalis
    - Gives rise to new functionalis
    - Stem cells
    - Blood vessels
    - Glands

Endometrial Cycle Changes
- Proliferation
  - “Unopposed Estrogen”
- Secretory
  - Progesterone for implantation
- Menses
  - Withdrawal bleeding
Vagina and Cervix

- **Cervical Mucus**
  - Cervical glands
  - **High estrogen at mid-cycle**
    - Clear, copious, elastic, ferning properties
  - Optimal for sperm transport
  - Progesterone → thick, cloudy, decreased production

- **Vagina**
  - Estrogens, androgens and progestins – all thicken the vaginal mucosa

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**The Hypothalamic – Pituitary – Gonadal/Ovarian Axis**

- Hormones throughout the menstrual cycle, where they originate, and the effect they have on their targets

- **The Ovary**
  - Follicular and Luteal phases
  - Recruitment, development, and atresia of follicles

- **The Follicle**
  - Graafian follicle, the components of this follicle, and the fate of the graafian follicle

- **The Endometrium**
  - Proliferative and secretory phases: major hormones in action

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**Hypothalamic – Pituitary – Gonadal**
HORMONES

Female Hormone Production

<table>
<thead>
<tr>
<th>Functional Compartment</th>
<th>Location of Action</th>
<th>Hormone or Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus</td>
<td>Arcuate nucleus</td>
<td>GnrH</td>
</tr>
<tr>
<td>Anterior Pituitary</td>
<td>Gnradotropin</td>
<td>FSH, LH</td>
</tr>
<tr>
<td>Ovary</td>
<td>Follicle, Corpus Luteum</td>
<td>Estradiol (E2), Progesterone (P2) , Inhibin, Anti-mullerian hormone, FSH, LH</td>
</tr>
<tr>
<td>Uterus</td>
<td>Endometrium</td>
<td>Proliferative, Secretory, Menstrual</td>
</tr>
</tbody>
</table>

The Two-Cell Theory
FSH

- Granulosa cells → Estradiol
  - Suppressed by rising estradiol and by inhibin

LH

- Theca cells → Androgens

  Estradiol → LH surge → ovulation and resumption of meiosis
  *Egg arrested in prophase of meiosis I (diplotene stage)

  Egg released from follicle → follicle becomes the corpus luteum

- Stimulates the luteinized cells and increases progesterone and estrogen in the corpus luteum

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Ovulation

- LH surge
  - Prostaglandins
  - Metalloproteinases

- 1st meiotic division resumes → extrusion of 1st polar body

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Corpus Luteum

- Secretes Progesterone and Estrogen
- No fertilization → demise ~14 days lifetime
- hCG pregnancy → rescues the CL
  - hCG similar in function to LH
Fertilization
*Completion of second meiotic division
Post-fertilization
Fallopian tube: Embryo cleavage → blastocyst formation → Uterine implantation

FERTILITY WORKUP

Natural Fertility
- Fecundability: pregnancy per month
  - Young and Normal → 20% per month
  - 38yo with 3-years of infertility → 2% per month
  - Greatest in the first 3 months
  - 75% will conceive in the first 6 months

<table>
<thead>
<tr>
<th>Time</th>
<th>Conception rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 1 month</td>
<td>20%</td>
</tr>
<tr>
<td>After 3 months</td>
<td>50%</td>
</tr>
<tr>
<td>After 6 months</td>
<td>75%</td>
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<tr>
<td>After 12 months</td>
<td>90%</td>
</tr>
</tbody>
</table>
Fertility Rate

- Births / 1,000 females age 15-44yo
  - Declining
    - 1950: 106.2
    - 2015: 62.5

- Factors
  - Advanced education / career
  - Later marriage
  - Improved access to family planning

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Fertility and Aging

- Aging affects women > men
- Steeper decline starting at:
  - Women age 35
  - Men age 50

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Age and Eggs

- With every year
  - Decrease in QUANTITY and QUALITY
    - Increase risk of aneuploidy and spontaneous abortions
  - Increase risk of GYN disorders
    - Fibroids
    - Tubal disease
    - Endometriosis
Timing

- Men
  - Avoid abstinence greater than 5 days
  - Myth: Frequent ejaculation decreases sperm
- Fertile window
  - 6-day interval ending on the day of ovulation
- Recommend intercourse every 1 to 2 days
  - Reduce stress

"Sperm waiting for the egg"

INFERTILITY / SUBFERTILITY

Infertility / Subfertility

- Disease
  - Failure to conceive a successful pregnancy after 12 months or more of regular unprotected intercourse or exposure to sperm
  - Primary or Secondary
  - 85% conceive within one year
  - 10-15% of couples
Earlier Evaluation

Risk factors:
- Anovulation
- Ectopic
- PID
- Endometriosis
- Chemotherapy
- Known or suspected male infertility

Women > age 35, 6 months without conception

Women > age 40, immediate expedited care

It Takes TWO
Evaluate both female and male at the same time (when applicable)

Fertility Factors:
Ovary
Tubes
Uterus
Sperm
Unexplained

COUPLES WOMEN
Relevant Reproductive History

- **OB-GYN History**
  - Duration of infertility
  - Menstrual history
  - Dysmenorrhea
  - Pregnancy history
  - Time to conception
  - Complications (Infections, D&Cs)
  - Contraception history
  - Sexual function
  - Previous abnormal paps and treatment
- **Past Medical**
  - Chronic medical problems
  - Optimize HTN and DM
  - Thyroid disease
  - Medications
- **Past surgery**
  - Appendicitis, ruptured?
  - PID
  - Ovarian cyst
  - Tubal surgery

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Relevant Reproductive History

- **Family history**
  - Early menopause/premature ovarian insufficiency
  - Infertility
  - Genetic disorders
  - Early cancers
- **Occupation**
  - Exposure to environmental hazards
- **Social habits**
  - Tobacco, alcohol, drugs
  - Caffeine avoid >250 mg/d

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Focused Physical Examination

- BMI, Vitals
- Thyroid exam
- Breast exam
- Signs of androgen excess
- Pelvic exam
  - Uterine size and mobility
  - Adnexal masses or tenderness
Preconception Counseling

- Carrier screening
  - Cystic Fibrosis CF
  - Spinal muscular atrophy SMA
- CBC, Type and Screen
- Immunities
  - Rubella
  - Varicella
- If risk factors
  - Hemoglobin electrophoresis, sickle cell
  - Fragile X screen
  - Diabetes screen
  - Infectious labs

Vaccination Guidelines

- Flu vaccine
- Without confirmed immunity
  - MMR vaccination
  - Varicella vaccination, 2 doses
  - Avoid conception 1 month after vaccination
- Live vaccines contradicted in pregnancy
  - MMR
  - Varicella
  - Herpes zoster
  - Intranasal flu

Known Causes of Female Infertility

- Ovulatory dysfunction
  - PCOS
  - Hyperprolactinemia
  - Hypothalamic/pituitary dysfunction
- Tubal occlusive disease
  - Inflammatory disease
  - Ectopic pregnancy
- Uterine abnormalities
  - Developmental anomalies
  - Polyps/Myomas
  - Intrauterine synechiae
- Peritoneal factors
  - Endometriosis
  - Pelvic/adrenal adhesions
- Cervical factors
  - Chronic cervicitis
  - Cervical stenosis
# Diagnostic: Historical Elements

- **Ovulatory dysfunction**
  - BBT
  - Timed serum progesterone
  - OPK

- **Tubal occlusive disease**
  - Xray HSG

- **Uterine abnormalities**
  - Xray HSG
  - US
  - Endometrial histologic dating

- **Peritoneal factors**
  - Diagnostic Laparoscopy

- **Cervical factors**
  - Chronic cervicitis
  - Cervical stenosis

# Diagnostic: Contemporary Elements

- **Ovulatory dysfunction**
  - Timed serum progesterone
  - OPK
  - US

- **Ovarian Reserve / Reproductive Aging**
  - AMH
  - FSH/E2
  - AFC

- **Tubal occlusive disease**
  - Xray HSG
  - Infusion hysterosonography/SIS
  - HyCoSy

- **Uterine abnormalities**
  - Xray HSG
  - US

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# Ovarian Evaluation

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Ovulatory Function

- Regular cycle: 21-35 days
  - Variation common and normal
  - Predictable
- Obvious menstrual disturbance
  - Oligomenorrhea or amenorrhea
  - Can be subtle
- Ovulation ➔ Cervical mucus / vaginal secretion
  - Slippery and clear

Ovulation Monitoring

- Ovulation Predictor Kits, OPKs
  - Mid-cycle urine LH surge
  - Positive ≈ 24hr before ovulation
    - False-positive 7% cycle
    - False-negative 25% cycle
  - Timed intercourse, TIC 2 days after +

- After the fact
  - Basal Body Temperature, BBT
    - Rise in body temperature with ovulation
  - Serum Progesterone
    - Check about 1 week before expected menses
      - Cycle 21 of 28-day cycle
      - > 3 ng/dl confirms ovulation
      - does not reflect ovulation quality
  - Serial ultrasound
    - Limitations
Ovulatory Dysfunction

■ Common causes
  - PCOS
  - Obesity
  - Strenuous exercise
  - Thyroid dysfunction
    ■ Check TSH
    ■ Subclinical hypothyroid, TSH > 2.5 +/- antibodies
  - Hyperprolactinemia
    ■ Check Prolactin

■ Consider premature ovarian insufficiency POI

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Ovarian Reserve Testing – “Quantity”

- Indirect measure of the size of remaining eggs
- Ability of ovaries to produce eggs and respond to treatment
- Help estimate “the window of reproductive opportunity”
- Variation among women

Screening test

*Does not fully determine reproductive potential

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Ovarian Reserve Testing

■ AMH
  - Produced by granulosa cells of early follicles
  - Any day of cycle
    ■ Hormone use (OCP) some suppressive effect
    ■ Check Prolactin
  - Normal values vary by lab
  - Generally <1, concerning for diminished ovarian reserve DOR

■ Day 2-5 FSH, estradiol
  - High FSH values > 10-20 IU/L, poorer prognosis
  - High estradiol > 60-80 pg/ml, suppressing the FSH to “normal”
Ovarian Reserve Testing

- Early follicular phase
- Antral follicle count (AFC)
  - 2-10mm
  - Pelvic US
  - Generally <10, concerning for DOR

TUBAL EVALUATION

Tubal Factor

- Risk Factors:
  - STI
  - PID
  - Septic abortion
  - Ruptured appendix
  - Pelvic tuberculosis
  - Ectopic pregnancy
  - Tubal surgery (e.g., tubal reanastomosis, salpingostomy, etc.)
  - Endometriosis

- Incidence of infertility after PID
  - 1 episode: 10-12%
  - 2 episodes: 23-35%
  - 3 episodes: 54-75%
Tubal Patency

- **X-ray Hysterosalpingography (HSG)**
  - Water- or lipid-soluble contrast media
- **Evaluate**
  - Proximal occlusion
  - Intramural (SIN)
  - Distal occlusion
  - Hydrosalpinx
  - Contrast loculation

- **Tubal Patency**
  - **X-ray HSG Patency**
    - Sensitivity 65%
    - Specificity 83%
  - **Distal occlusion**
    - Generally accurate
  - **Proximal occlusion**
    - Often inaccurate
      - Cath placement
      - Myometrial contractions ("tubal/cornual spasms")

- **Alternative to X-ray HSG**
  - Sonohysterography (SIS)
    - Appearance of fluid in the cul-de-sac
      - At least one tube open
    - Hysterosalpinogram (HyCoSy)
      - Saline and air bubble contrast media
Tubal Patency
- Laparoscopic Chromopertubation
  - Distal occlusion
  - Proximal occlusion
  - Pitfalls similar to HSG
- Chlamydia Antibody Test
  - Limited clinical utility

UTERINE EVALUATION

Uterine
- Evaluate
  - Developmental anomalies
    - Septum vs. bicornuate
    - Consider renal ultrasound
  - Fibroids
  - Polyps
  - Scar tissue, uterine synechiae, Asherman's
Uterine

■ Pelvic ultrasonography
  - 2D
  - 3D, defines external and internal uterine contour

■ Hysterosalpingography
  HSG
  - Tubal patency
  - Larger fibroids/polyps
  - Septum vs. bicornuate

■ Sonohysterography
  - Saline infusion sonography, SIS
  - High positive predictive value PPV > 90%

■ Intracervical pathology

■ 3D ultrasound and/or pelvic MRI to further characterize findings
Uterine

- Hysteroscopy
  - Definitive method for diagnosis and treatment
  - More invasive approach

PERITONEAL FACTORS

Peritoneal Factors
- Laparoscopy
  - Not recommended for routine infertility evaluation
  - Indications
    - Pelvic pathology
    - Tubal pathology
    - Risk factors, such as severe dysmenorrhea/pelvic pain
- Evaluate
  - Endometriosis
  - Pelvic adhesions
SEMEN ANALYSIS

Male
- Check semen analysis
  - Count
  - Volume
  - Concentration
  - Motility
  - Morphology
- Total Motile Count, TMC
  - Volume x Concentration x Motility%

Semen Analysis
- Collection:
  - 2-3 days of abstinence
  - Masturbation directly into a clean container
  - Examined within 1 hour of collection
- If abnormal, repeat at least 1 week apart

<table>
<thead>
<tr>
<th></th>
<th>WHO 5th</th>
</tr>
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<tbody>
<tr>
<td>Volume</td>
<td>&gt; 1.5</td>
</tr>
<tr>
<td>pH</td>
<td>&gt; 7.2</td>
</tr>
<tr>
<td>Concentration</td>
<td>&gt; 15 million/mL</td>
</tr>
<tr>
<td>% Motility</td>
<td>&gt; 40%</td>
</tr>
<tr>
<td>Normal Morphology</td>
<td>&gt; 4% (strict criteria)</td>
</tr>
</tbody>
</table>
UNEXPLAINED INFERTILITY

Unexplained Infertility

- Patients with:
  - Normal semen analysis
  - Bilateral tubal patency
  - Normal uterine cavity
  - Regular ovulation

- Average cycle fecundity with unexplained infertility: 2-4%

Unexplained Infertility

- Infertility due to abnormalities not detected by current methods of evaluation
  - Egg quality
  - Fertilization, egg-sperm interactions
  - Tubal function

- Likelihood of pregnancy without treatment decreases with
  - Increasing female partner age
  - Duration of infertility
TREATMENT

Tubal Factor
- IVF
  - As IVF success rates improve, indications for tubal surgery decrease
- Tubal surgery
  - Open tubes does not mean functional tubes

Severe tubal distal disease
- Hydrosalpinx
  - Meta-analysis: decreased PR by 50% and increased SAb x2 (Camus 1999)
  - Salpingectomy or tubal blockage beneficial

Uterine Factor
- Hysteroscopy
  - Submucosal fibroids
  - Intrauterine adhesions
  - Uterine septum
- Myomectomy
  - Cavity involvement
- No therapy for most congenital malformations
Male Factor

- **Intrauterine insemination (IUI)**
  - Washed sperm introduced into uterus through thin catheter around time of ovulation
  - Ideal TMC > 5-10 million
  - Success varies depending on other factors, 5-15%
- **In vitro fertilization (IVF)**
  - Conventional fertilization
  - Intracytoplasmic sperm injection (ICSI)

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Male Factor

- Urology referral if severe male factor
- **Azoospermia**
  - Identify possible causes
    - Obstructive or nonobstructive
      - Congenital bilateral agenesis of the vas deferens (CSAVD) – think cystic fibrosis (CF), 70-80%
  - Surgically retrieved sperm → IVF with ICSI

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Unexplained Infertility

- **Goal**: Increase monthly fecundity
- **Methods**:
  - **Superovulation** followed by IUI or IVF
    - Ovarian stimulation
      - Clomiphene citrate (Clomid)
      - Letrozole (Femara)
      - Exogenous gonadotropins
  - **Diagnostic Laparoscopy** controversial
    - May confer benefit if treating mild endometriosis
### Unexplained Infertility

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cycle Fecundability</th>
<th>TWINS</th>
<th>TRIPLETS</th>
<th>COST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timed intercourse</td>
<td>1 – 4%</td>
<td>1-2%</td>
<td>&lt; 1%</td>
<td>Free</td>
</tr>
<tr>
<td>Clomid / Timed intercourse</td>
<td>4 – 6%</td>
<td>3%</td>
<td>1 – 3%</td>
<td>$15</td>
</tr>
<tr>
<td>Clomid / IUI</td>
<td>5 – 8%</td>
<td>3%</td>
<td>1 – 3%</td>
<td>$1,000</td>
</tr>
<tr>
<td>Gonadotropin / IUI</td>
<td>15 – 17%</td>
<td>7 – 8%</td>
<td>3 – 5%</td>
<td>$1,500</td>
</tr>
<tr>
<td>IVF</td>
<td>&gt; 42 - 50%</td>
<td>Depends on # transferred</td>
<td>Depends on # transferred</td>
<td>$15,000</td>
</tr>
</tbody>
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### Third Party Reproduction

- Donor eggs
- Donor sperm
- Donor embryo
- Gestational Carrier

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  - TSH, PRL
- Ovarian Reserve / Reproductive Aging
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- Tubal occlusive disease
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- Uterine abnormalities
  - Xray HSG
  - US
- Male
  - Semen analysis
Fertility Highlights

- Optimize natural fertility
  - OPK, intercourse next two days
  - Don’t use BBT for intercourse timing
  - Peak fertility before ovulation
  - Common modifiable lifestyle changes
    - Smoking
    - Caffeine

- Age matters!

Fertility Treatment Options

- Ovulation Induction
  - Oral
  - Injectable gonadotropins
  - Intrauterine insemination IUI
  - IVF with or without ICSI

QUESTIONS?

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THANK YOU!