FEMALE INFERTILITY

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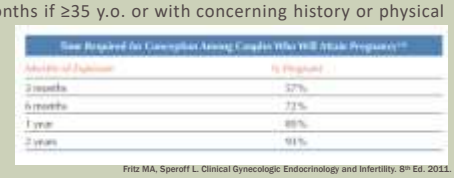
OBJECTIVES

- Understand definition of infertility
- Describe methods to optimize natural fertility
- List causes of infertility
- Describe an infertility evaluation
- Understand treatment options
- Describe psychosocial issues
- Know when to refer to Reprod Endo & Infertility

DEFINITION OF INFERTILITY

- **Infertility**: failure to achieve pregnancy
  - >12 months if <35 y.o.
  - >6 months if ≥35 y.o. or with concerning history or physical exam

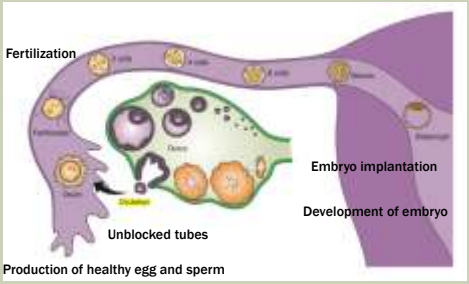


Duration of Exposure	% Pregnant
3 months	37%
6 months	72%
1 year	85%
2 years	91%

Fritz MA, Speroff L. Clinical Gynecologic Endocrinology and Infertility. 8th Ed. 2011.

- **Fecundability**: probability of conception per cycle
  - Average 20%. Does not exceed 35% even with carefully timed coitus

CONCEPTION

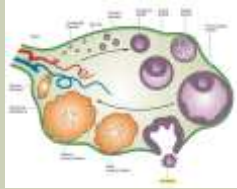


OPTIMIZING NATURAL CONCEPTION

OVULATION PREDICTION KITS

OPTIMIZING NATURAL CONCEPTION

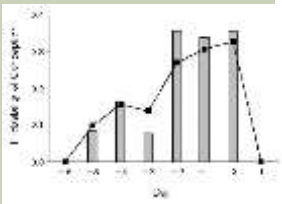
- **Detect Luteinizing Hormone (LH) surge**
  - Most reliable indicator of impending ovulation
  - Onset of LH surge occurs ~36 hours prior to follicle rupture
  - Ovulation usually occurs 14-26 hours (up to 48 hours) after detection of LH surge with OPK
- **LH surge initiates**
  - Meiosis in the oocyte
  - Luteinizes granulosa cells (progesterone)
  - Prostaglandin synthesis for follicle rupture
- **False positive** (~7%)
  - Fertility medications
  - Polycystic ovary syndrome (PCOS)
  - Menopausal state



COITAL FREQUENCY

OPTIMIZING NATURAL CONCEPTION

- Once the event of ovulation has occurred, the fertilizable life of the oocyte is 12 – 24 hours
- Fertile window closes the day of ovulation
- Great majority of pregnancies occur when coitus takes place in the 3 day interval just before ovulation



Probability of Conception on specific days near the day of ovulation

N ENGL J MED 1995;333:1517-1521

SPERM SHOULD BE WAITING FOR THE EGG!

LUBRICANTS

OPTIMIZING NATURAL CONCEPTION

- NOT OPTIMAL
  - Some commercial water-based lubricants (e.g. Astroglide, K-Y Jelly) can inhibit sperm motility by 60-100%
  - Olive oil, saliva, K-Y Jelly can dilute concentrations of sperm
- PREFERRED IF NEEDED
  - **Mineral oil, canola oil** appear to be OK for sperm concentration and motility
  - Hydroxyethylcellulose-based lubricants (e.g. Pre-Seed, ConceivEase) do not demonstrate adverse impact on sperm

LIFESTYLE

OPTIMIZING NATURAL CONCEPTION

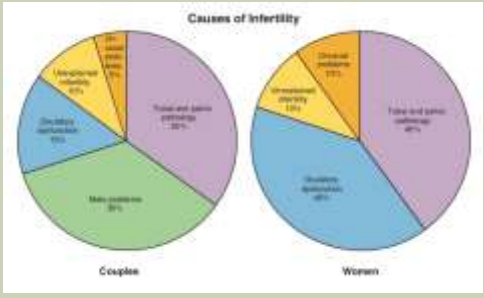
- Smoking
  - Menopause occurs 1 to 4 years sooner (accelerate egg reserve depletion)
  - Increase in miscarriage
  - Decreased sperm concentration and motility
- Alcohol
  - > 2 drinks/day associated with infertility
- Weight
  - Obesity: associated with ovulatory dysfunction and irregular menses, miscarriage rate, birth defects, reduced embryo quality
  - Obesity (BMI > 35) increased time to conception 2-fold. Altered endometrial function.
  - Underweight (BMI < 19) increased time to conception 4-fold
- Caffeine
  - > 500 mg/day (> 5 cups of coffee) increased risk for infertility
  - > 200 mg/day (> 2 cups of coffee) increase risk for miscarriage in pregnancy
- Marijuana
  - Discouraged in couples trying to conceive. Harmful effects to fetus.

IMMUNE SYSTEM

OPTIMIZING NATURAL CONCEPTION

- **Recommend vaccinations prior to conception**
  - Flu vaccine annually
  - Rubella (MMR x1 dose) if not immune.
    - Delay conception for at least 4 weeks after.
  - Varicella (x2 doses 4-6 weeks apart) if not immune.
    - Delay conception for at least 4 weeks after.
- **Zika**
  - www.cdc.gov/zika
  - Recommend no traveling to a zone with Zika if trying to conceive
  - Asymptomatic individuals with travel or possible exposure should wait *8 weeks for women* and *3 months for men* to conceive AND use condoms or abstain during that time.

CAUSES OF INFERTILITY

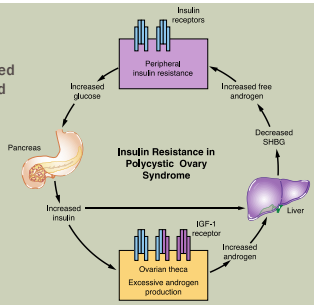


Fritz MA, Speroff L. Clinical Gynecologic Endocrinology and Infertility. 8th Ed. 2011.

OVULATORY DYSFUNCTION (PART 1 OF 3)

CAUSES OF INFERTILITY

- Polycystic ovary syndrome (PCOS)
  - 6-12% of reproductive aged patients (will be discussed later today)
  - Oligo/anovulation, hyperandrogenism, polycystic ovaries
- Obesity-related anovulation



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OVULATORY DYSFUNCTION (PART 2 OF 3)

CAUSES OF INFERTILITY

- Hypothalamic amenorrhea
  - Inadequate response from hypothalamus/pituitary (low FSH, LH). Ovaries are OK.
  - Extreme stress, anorexia, athletes, underweight
- Premature ovarian failure (POF)/Primary ovarian insufficiency (POI)
  - Over response from pituitary (high FSH, LH) due to decreased egg reserve. Ovaries NOT OK.
  - Idiopathic, prior gonadotoxic treatment (chemo, radiation), ovarian surgery, autoimmune, genetic (will be discussed later today)

Fritz MA, Speroff L. Clinical Gynecologic Endocrinology and Infertility. 8th Ed. 2011.

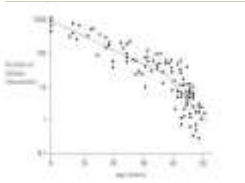
OVULATORY DYSFUNCTION (PART 3 OF 3)

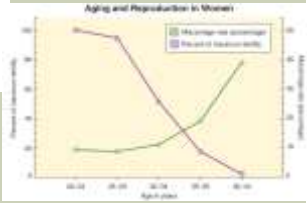
CAUSES OF INFERTILITY

- Thyroid disorder
  - Hypothyroid and hyperthyroid
- Hyperprolactinemia
  - Prolactin is produced by lactotrophs in the pituitary gland
  - Elevated prolactin usually due to pituitary adenoma
  - Other causes: hypothyroidism, medication (antipsychotics, metoclopramide, OCPS), pregnancy

DIMINISHED OVARIAN RESERVE

CAUSES OF INFERTILITY





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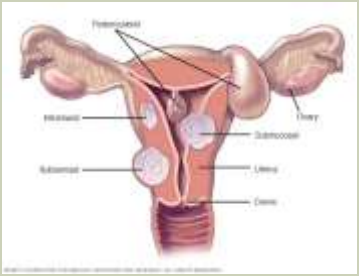
UTERINE

CAUSES OF INFERTILITY

- Fibroid
  - Submucosal or large intramural fibroids (>5-6 cm) can impact fertility
  - Decision for surgery has to be taken in context with remaining history



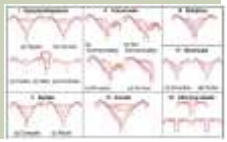
UTERINE

CAUSES OF INFERTILITY

- Intrauterine adhesions
  - Prior uterine surgery (e.g. D&C, myomectomy)
  - Hypomenorrhea, amenorrhea, or asymptomatic

- Polyps
  - Conflicting studies

- Uterine anomalies (unicornuate, bicornuate, septate, didelphys)
  - Associated with pregnancy loss and obstetric complications but NOT infertility



TUBAL

CAUSES OF INFERTILITY

- Varying degrees of abnormalities
  - Occlusion with normal caliber
  - Dilation with patency
  - Hydrosalpinx
  - Periadnexal adhesions

- May impair ovum capture and/or inhibit sperm and embryo transport
- Often due to prior pelvic inflammatory disease, prior surgery, endometriosis, pelvic TB (outside US)

ENDOMETRIOSIS

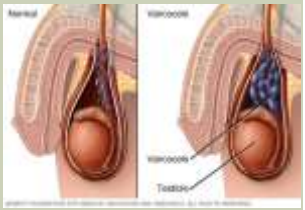
CAUSES OF INFERTILITY

- Presence of endometrial tissue outside the uterus
- Prevalence is 3-10% in reproductive aged women but 30-40% of women with infertility and pelvic pain
- Distort anatomy, reduced egg quality, tubal disease

MALE

CAUSES OF INFERTILITY

- Mostly unknown
- Varicocele
- Testicular failure
- Hypogonadism
- Urogenital infection
- Genetic causes



UNEXPLAINED

CAUSES OF INFERTILITY

- Limitations of testing
  - Could be cervical factor or mild endometriosis or pelvic adhesions
- Questions not addressed during initial evaluation
  - Egg quality
  - Sperm quality
  - Endometrial receptivity
- Much more we still don't understand

HISTORY

- FEMALE
  - Duration of infertility
  - Prior pregnancies
  - GYN history: menstrual history
  - Changes in hair growth, body weight, nipple discharge
  - Medical and surgical history including pelvic surgery
  - Medications
  - History of chemo and radiation
  - History of sexually transmitted infection
  - Social history (recreational drugs, tobacco, alcohol)
  - Frequency of intercourse
  - Family history mental retardation or reproductive failure
- MALE
  - Duration of infertility
  - Fertility in other relationships
  - Medical and surgical history, including testicular surgery
  - Medications
  - History of chemo or radiation
  - History of sexually transmitted infection
  - Social history (anabolic steroids, recreational drugs, tobacco, alcohol)
  - Frequency of intercourse
  - Sexual dysfunction
  - Family history mental retardation or reproductive failure

PHYSICAL EXAM

- Vitals, BMI
- Thyroid exam
- Breast exam

- Signs of androgen excess
  - Hirsutism (excess terminal hair)
  - Acne
  - Androgenic alopecia
- Signs of insulin resistance
  - Acanthosis nigricans
  - Skin tags
  - Centripetal fat distribution

- Pelvic exam
  - Cervical/vaginal abnormalities
  - Tenderness/masses in the adnexa/cul de sac
  - Uterine enlargement, lack of mobility

WORK UP

WORK UP

- Evaluate both female and male concurrently

OVARIAN RESERVE TESTING (1 OF 2)

- **Day 3 FSH and estradiol**
  - Basal FSH increases with advancing reproductive age
  - High FSH (>10 IU/L) values are associated with poor ovarian stimulation and failure to conceive
  - Low estradiol (<60-80 pg/ml) allow for interpretation of basal FSH
- **Anti-mullerian hormone (AMH)**
  - Produced by early follicles in ovary
  - Low levels (<1-1.5 ng/ml)
  - Lower AMH levels are associated with poor ovarian stimulation, poor embryo quality, and poor pregnancy outcomes in IVF

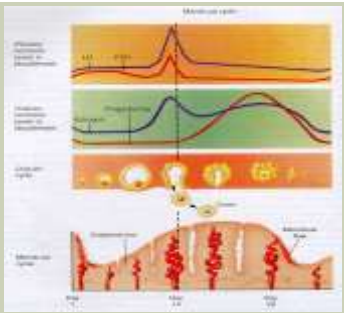
******JAMA 2017 study showed ovarian biomarkers (AMH, FSH) in women without infertility indicating diminished ovarian reserve were NOT associated with reduced fertility******

OVARIAN RESERVE TESTING (2 OF 2)

- **Antral follicle count (AFC)**
  - Transvaginal ultrasound to count number of follicles 2-10 mm in each ovary
  - Low AFC (<10) is associated with poor response to IVF stimulation but not failure to conceive

ASSESSING OVULATION

- Not always required based on history
- Mid-luteal progesterone (~cycle day 21) >3 ng/ml confirms ovulation



FALLOPIAN TUBES

- Hysterosalpingogram (gold standard)
  - Scheduled ~cycle day 5-11 (after completion of menses and prior to ovulation)
  - Preemptive ibuprofen 600-800 mg
  - Prophylactic doxycycline
  - Higher pregnancy rate for 1-2 months

FALLOPIAN TUBES

- Femvue (alternative)
  - Scheduled ~cycle day 5-11 (after completion of menses and prior to ovulation)
  - Preemptive ibuprofen 600-800 mg
  - Prophylactic doxycycline
  - Performed in office
  - Ultrasound evaluation

UTERUS

- Transvaginal ultrasound (initial evaluation)
- Further uterine cavity evaluation if needed
  - Sonohysterogram or 3-D ultrasound or MRI pelvis


SEMEN ANALYSIS

SEMEN ANALYSIS	PARAMETERS
PH	≥ 7.2
VOLUME	≥ 1.5 ML
CONCENTRATION	≥ 15 MILLION/ML
MOTILITY	≥ 40%
MORPHOLOGY	≥ 4%

TREATMENT OF INFERTILITY

- Attempt to address the underlying problem(s)
- Ovulation Induction + Timed Intercourse (TIC)
- Superovulation + intrauterine insemination (IUI)
- In vitro fertilization (IVF)
  - Preimplantation genetic testing (PGT)
  - Egg donation
  - Surrogacy
  - Fertility preservation

CONTROLLED OVARIAN STIMULATION

- **Ovulation Induction**
  - Patients with ovulation disorders (e.g. PCOS, hypothalamic amenorrhea)
  - Goal to stimulate growth and release 1-2 mature eggs
- **Superovulation**
  - Patients who ovulate and are not conceiving (e.g. unexplained, diminished ovarian reserve, endometriosis, mild male factor, unilateral tubal blockage)
  - Goal to stimulate growth and release of 2-3 mature eggs

CONTROLLED OVARIAN STIMULATION

- Use of oral medications and/or injectable medications to stimulate growth of follicle(s)
  - Clomiphene citrate (Clomid)
  - Letrozole (Femara)
  - Gonadotropins (Menopur, Gonal F, Follistim)
- Use of ultrasound monitoring to assess growth of follicles in response to medications
- Use of hcg to release eggs
  - Hcg (Ovidrel, Novarel)


- Coupled with timed intercourse (TIC) or intrauterine insemination (IUI)

INTRAUTERINE INSEMINATION (IUI)

- Washing sperm
- Concentrating motile sperm
- Insertion of catheter with sperm into the uterus to increase # that reach fallopian tubes

NATURAL CYCLE + IUI

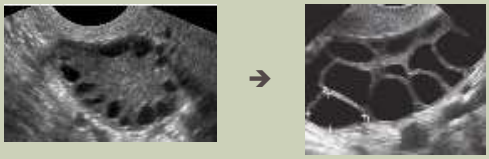
- Donor sperm
  - Same sex couples or single women
- Logistical obstacles
  - Partner lives far away, unable to tolerate intercourse, erectile dysfunction
- Women with severe diminished ovarian reserve unable to respond to controlled ovarian hyperstimulation

IN VITRO FERTILIZATION (IVF)

- Stimulate ovaries to grow multiple follicles
- Ultrasound monitoring
- Egg retrieval
- Embryo transfer

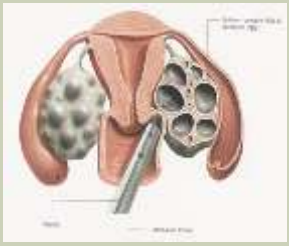
OVARIAN STIMULATION + ULTRASOUND

- Various protocols to synchronize and promote follicular growth and prevent premature ovulation
- Daily injections (usually subcutaneous) ~8-12 days



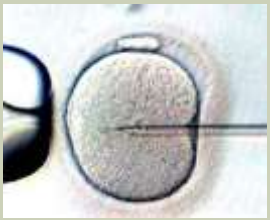
EGG RETRIEVAL

- 15-20 min
- Intravenous anesthesia
- Transvaginal ultrasound guidance

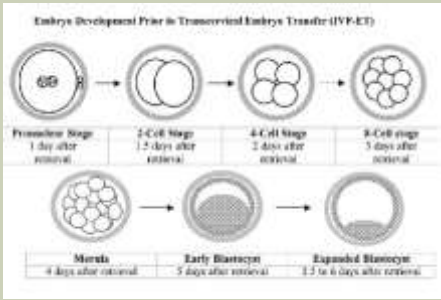


FERTILIZATION

- Standard insemination
- Intracytoplasmic sperm injection (ICSI)



EMBRYO DEVELOPMENT



EMBRYO TRANSFER

- Transabdominal ultrasound guidance
- Transcervical catheter insertion

LIVE BIRTHS

PREIMPLANTATION GENETIC TESTING (PGT)

- Biopsy cells from a day 5 (blastocyst)
  - screen for abnormalities
  - transfer unaffected embryos

- PGT-A (aneuploidy)
  - Test for chromosome number (loss or gain). (e.g. trisomy 21 = down's syndrome). Also sex chromosomes.
- PGT-M (monogenic disorder)
  - Probe created specifically for patient's mutation. (e.g. cystic fibrosis delta508 mutation)
- PGT-SR (structural rearrangement)
  - Screening for unbalanced translocations transmitted from a parent with balanced translocation.

OOCYTE DONATION AND SURROGACY

- Oocyte donation:
  - Donor is a fertile young woman
  - Eggs are donated with IVF to intended parents to use
- Gestational carrier
  - Maintain pregnancy achieved by IVF for intended parents

PSYCHOSOCIAL ISSUES

- Causes
  - Basic desires for child/family. Perpetuation of cultural values.
  - Shift from economic necessity. Now seen as source of fulfillment and happiness.
  - Financial costs especially when financially out of reach
  - Interference in sexual relationship (pleasurable → chore)

PSYCHOSOCIAL ISSUES

- Results
  - Sense of loss of control over body and destiny
  - Social and emotional withdrawal
  - Stress on primary relationship. Shifting of blame.
  - For men, damage to sense of masculinity, embarrassment, performance anxiety.
- Infertility can trigger anger, guilt, shame, depression, anxiety

RESOURCES

- 1 in 8 couples will have trouble conceiving. They are not alone.
- PROVIDERS
  - www.asrm.org
  - Your local Kaiser REI physician
- PATIENTS
  - Reproductivefacts.org
  - Resolve.org (support groups)
  - Social workers, psychologists, psychiatrists
  - Acupuncture

WHEN TO REFER TO REPROD ENDO & INFERTILITY

- Infertility
  - >12 months if <35 y.o.
  - >6 months if ≥35 y.o.
  - Preexisting medical condition
    - Anovulatory
    - Prior gonadotoxic therapy
    - Prior ovarian surgery
    - Inability to have timed intercourse
- Conception with donor sperm
  - Same sex couples or single women
- Need for preimplantation genetic testing (PGT)
  - Screen out embryos positive for serious medical conditions (e.g. cystic fibrosis, hemophilia, translocations, etc)
- Fertility preservation
  - Egg freezing or embryo freezing

WHERE ARE WE?

- Downey 562-657-2176
- Fontana 909-427-5711
- Los Angeles 323-783-2254
- Orange County 949-932-2450
- San Diego
- Woodland Hills 818-719-2317

THANK YOU

- Questions?

RISK FOR CHROMOSOMAL ABNORMALITY

Table. Risk of Down's Syndrome and Chromosomal Abnormalities at Live Birth, According to Maternal Age.*

Maternal Age at Delivery (yr)	Risk of Down's Syndrome	Risk of Any Chromosomal Abnormality
20	1/1667	1/526
25	1/1200	1/476
30	1/952	1/385
35	1/378	1/192
40	1/106	1/66
45	1/30	1/21