



437 Team: Obstetrics and Gynecology

Infertility

Objectives:

- Define infertility.
- List the causes of male and female infertility.
- Describe the evaluation and initial management of an infertile couple.
- Describe the psychosocial issues associated with infertility.
- Describe management options for infertility.
- Describe ethical issues confronted by patients with infertility.
- Identify the impact of genetic screening and testing on infertility associated treatments.

References:

- Kaplan USMLE step 2 CK - Obstetrics and Gynecology
- Online Meded videos
- Team 435

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What is infertility?

The inability to achieve pregnancy with frequent and unprotected sexual intercourse for **12 months** if woman **age <35** or **6 months** if woman **age ≥35**. Both male and female factors have to be evaluated in the patient with infertility.

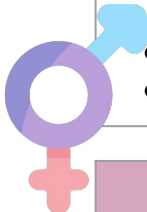
Fecundability is the likelihood of conception occurring with one cycle of appropriately timed mid-cycle intercourse. With the female partner age 20, the fecundity rate is 20%. By age 35, the rate drops to 10%.

Factors that may contribute to infertility:

- Medical problems
- Ethical
- Financial
- Psycho-social

Who's responsible?

- Male 20% **more common in our region than in the west.**
- Female 65%
- Unexplained 15%



Male Infertility	
Causes	Detection for good sperms
<ul style="list-style-type: none"> • Male factor (30%) – decreased sperm count, decreased motility or low normal forms. • Unexplained (15%) • Unusual problems (5%) 	<p>Semen analysis</p> <ul style="list-style-type: none"> • Abnormal > Repeat > Abnormal again? > refer to be assisted by urologist or reproductive endocrinologist.

Female Infertility	
Causes	Detection for good oocyte
<ul style="list-style-type: none"> • Ovulatory dysfunction (20%) – anovulation due to: <ul style="list-style-type: none"> ○ PCOS, Thyroid disorders, age and hyperprolactinemia. • Tubal and pelvic (30%) <ul style="list-style-type: none"> ○ Endometriosis, pelvic adhesions, pelvic inflammatory diseases and abdominal or pelvic surgeries • Unusual problems (5%) – Uterine anomalies but in case of: Abnormal bleeding, pregnancy loss, preterm delivery, previous uterine surgery. Uterine assessment must be done. • Unexplained (15%). 	<ul style="list-style-type: none"> • History of regular menses suggest ovulatory cycles. • Ovulation predictor kit: To assess ovulation based on the increase LH production which can be detected by urine. • Basal body temperature charting: Women can monitor her ovulation by checking her daily body temperature which is the effect of high levels of progesterone during the luteal phase of the cycle.

Initial noninvasive test

1) Semen analysis : The first step in the infertility evaluation is a semen analysis, which should be obtained after 2–3 days of abstinence and examined within 2 h.

Normal values

- volume >2 ml.
- pH 7.2–7.8.
- sperm density >20 million/ml.
- sperm motility >50%.
- sperm morphology >50% normal.



If values are abnormal, repeat the semen analysis in 4–6 weeks because semen quality varies with time.

Minimally abnormal

- If sperm density is mild to moderately lower than normal.
- intrauterine insemination may be used -> Washed sperm are directly injected into the uterine cavity.
- Idiopathic oligozoospermia is the most common male infertility factor.

Severely abnormal

- If semen analysis shows severe abnormalities.
- intracytoplasmic sperm injection may be used in conjunction with in vitro fertilization and embryo transfer.

No viable sperm

With azoospermia or failed ICSI, artificial insemination by donor (AID) may be used.

2) Anovulation

Of all causes of infertility, treatment of anovulation results in the greatest success.

History

Typically history is irregular, unpredictable menstrual bleeding, most often associated with minimal or no uterine cramping.

Objective data

- A basal body temperature (BBT) chart will not show the typical mid cycle temperature elevation.
- A serum progesterone level will be low.
- An endometrial biopsy shows proliferative histology.

Correctable causes

Hypothyroidism or hyperprolactinemia.

Initial Management of an Infertile couple

Ovulation induction

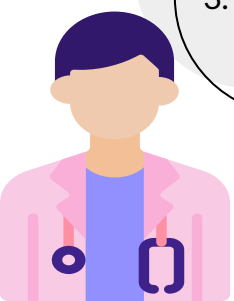
1. The agent of choice is **clomiphene citrate** (Selective estrogen receptor modulator) administered orally for 5 days beginning on day 5 of the menstrual cycle.
2. **HMG**: administered parenterally and used to induce ovulation if clomiphene fails.

Careful monitoring of ovarian size is important because ovarian hyperstimulation is the most common major side effect of ovulation induction.

Both Clomiphene and HMG work by stimulating the ovaries to increase follicular development. Clomiphene carries 10% risk of multiple gestation and HMG 25%.

- When a patient is given clomiphene, her own pituitary is being stimulated to secrete her own gonadotropins, whereas when a patient is administered HMG, the patient is being stimulated by exogenous gonadotropins.

3. **Intrauterine insemination**: Ejaculated semen is washed and introduced to uterine cavity by a catheter.



Assisted reproductive technologies

In vitro fertilization: 30% risk of multiple gestation.

Indications:

1. Blocked or absent fallopian tubes .
2. History of tubal sterilization.
3. Severe pelvic adhesions.
4. Severe endometriosis.
5. Poor ovarian response to stimulation.
6. Severe male factor infertility.
7. Failed treatment with less aggressive therapies.

❖ Preimplantation genetic diagnosis:

Genetic profiling of embryo **prior to implantation**; if the couple know that they are carriers of any inherited disease such as: cystic fibrosis or tay-sachs disease embryo can be tested for this prior implantation.

❖ Psycho-social stress:

Social support that patients receive can have significant effect in stress level. Compared to white & Asian women black women are less likely to report encouragement for treatment from their partners & family members.

FOLLOW-UP INVASIVE TESTS

Assessment of fallopian tube abnormalities is the next step if the semen analysis is normal and ovulation is confirmed.

Hysterosalpingogram (HSG)	<ul style="list-style-type: none">● A catheter is placed inside the uterine cavity, and contrast material is injected and the contrast material should be seen on x-ray images spilling bilaterally into the peritoneal cavity.● It should be scheduled during the week after the end of menses after prophylactic antibiotics to prevent causing a recurrent acute salpingitis.● No further testing is performed if the HSG shows normal anatomy.● If abnormal findings are seen, the extent and site of the pathology are noted and laparoscopy considered.
Laparoscopy	<ul style="list-style-type: none">● If potentially correctable tubal disease is suggested by the HSG, the next step in management is to visualize the oviducts and attempt reconstruction if possible (tuboplasty).● If tubal damage is so severe surgical therapy is futile, then IVF should be planned.
Chlamydia antibody	A negative IgG Antibody test for chlamydia virtually rules out infection induced tubal adhesions.

UNEXPLAINED INFERTILITY

- A diagnosis of unexplained fertility is reserved for couples in which the semen analysis is normal, ovulation is confirmed, and patent oviducts are noted.
- Approximately 60% of patients with unexplained infertility will achieve a spontaneous pregnancy within the next three years.



Management

- Controlled ovarian hyperstimulation (COH) with clomiphene, and appropriately timed preovulatory intrauterine insemination (IUI).
- The fecundity rates for six months are comparable with IVF with a significantly lower cost and risk.
- With IVF, eggs are aspirated from the ovarian follicles using a transvaginal approach with the aid of an ultrasound.
- They are fertilized with sperm in the laboratory, resulting in the formation of embryos. Single embryo transfer is recommended for most patients to avoid iatrogenic high-order multiple pregnancy.

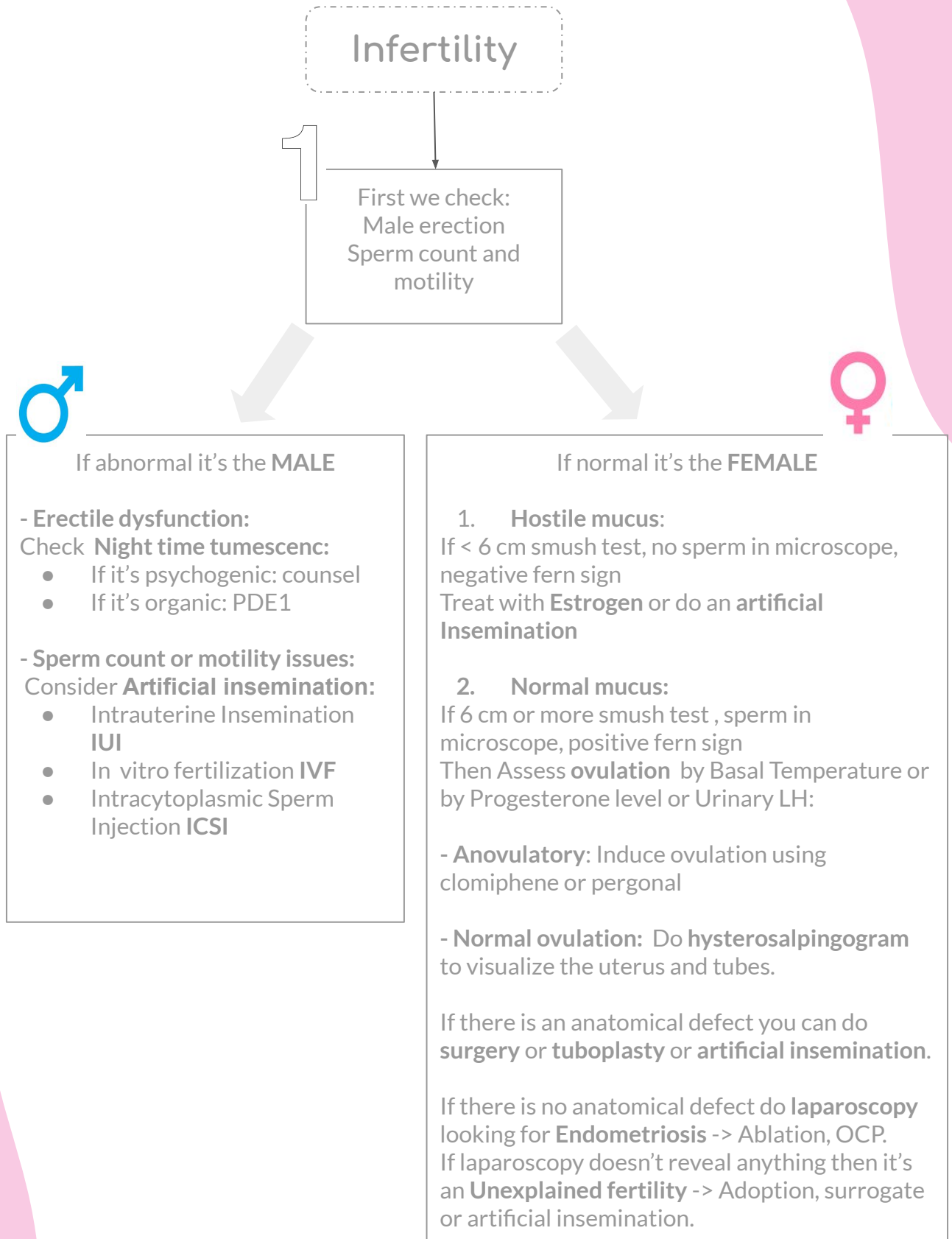
OVARIAN RESERVE TESTING

- Ovarian reserve testing (ORT) (mostly reserved for infertile women age ≥ 35) refers to assessment of the capacity of the ovary to provide eggs that are capable of fertilization.
- It is a function of (a) the number of follicles available for recruitment, and (b) the health and quality of the eggs in the ovaries.
- The most significant factor affecting ORT is a woman's chronological age, with a major decrease around age 35.
- The ORT tests help predict whether a woman will respond to ovarian stimulation or whether it would be best to proceed directly to in vitro fertilization (IVF).

Day 3 FSH level (most commonly used)	<ul style="list-style-type: none">• Is expected to be low due to the feedback of estrogen from the stimulated follicles.• An increased FSH occurs if there is follicle depletion.
Anti-Müllerian hormone (AMH)	<ul style="list-style-type: none">• This glycoprotein is produced exclusively by small antral ovarian follicles and is therefore a direct measure of the follicular pool.• As the number of ovarian follicles declines with age, AMH concentrations will decline.
Antral follicle count (AFC)	<ul style="list-style-type: none">• Is the total number of follicles measuring 2–10 mm in diameter that is observed during an early follicular phase transvaginal sonogram.• The number of AF correlates with the size of the remaining follicle pool retrieved by ovarian stimulation.• AFC typically declines with age.



Diagnostic workup should start at first 1 year.



Teaching case (video case)

A 37-year-old woman and her 37-year-old male partner present with the complaint of a possible fertility problem. The couple has been married for 2 years. The patient has a 4-year-old daughter from a previous relationship. The patient used birth control pills until one-and-a-half years ago. The couple has been trying to conceive since then and report a high degree of stress related to their lack of success. The patient reports good health and no problems in conceiving her previous pregnancy or in the vaginal delivery of her daughter who has cystic fibrosis. She reports that her periods were regular on the birth control pill, but have been irregular since she discontinued taking them. She reports having periods every 5-7 weeks. She works as a cashier, runs 12-24 miles each week for the last 2 years, and has no history of STIs, abnormal Paps, smoking, alcohol or other drugs. She has had no surgery. She has been taking a multivitamin with folic acid since trying to conceive. The patient's partner also reports good health and reports no problems with erection, ejaculation or pain with intercourse. He has had no prior urogenital infections or exposure to sexually transmitted infections. He has had unprotected sex prior to his current relationship, but has not knowingly conceived. He has no medical problems or past surgery. The couple has vaginal intercourse 3-5 times per week when he is at home. The female patient is 5'9" and weighs 130 pounds. Head and neck examination is unremarkable. Specifically there is no evidence of thyromegaly. Breast exam reveals no tenderness or masses, but she has bilateral galactorrhea on compression of the areola. Pelvic exam reveals normal genitalia, well-estrogenized vaginal mucosa and cervical mucus consistent with the proliferative phase. The uterus is anteflexed and normal in size without masses or tenderness. Several tests were ordered.



1- What is the definition of infertility?

- Inability to become pregnant despite 12 months of trying to conceive without using contraception in women <35-years-old.
- Six months of unprotected intercourse defines infertility in women 35 years and older.
- About 15% of couples experience this problem.
- At age of 35 we have sharp decline in fertility

2- What are the etiologies of infertility?

- Ovulatory dysfunction (20%) - anovulation.
- Male factor (30%) - decreased sperm count, decreased motility or low normal forms(morphology).
- Tubal and pelvic (30%) - tubal damage due to pelvic infection, or pelvic factors such as endometriosis or pelvic adhesions.
- Unexplained (15%).
- Unusual problems (5%).

3- What is the **initial work-up** for infertile couples and what tests would you add for this particular couple?

- Normal TSH.
- Prolactin 60 ng/ml (normal range < 20 ng/ml).
- Evaluation for ovulation: Progesterone (day 21) was 1.2 ng/ml (≥ 3 ng/ml will indicate ovulation).
- **Transvaginal pelvic ultrasound looking for any abnormalities of the uterine cavity, ovaries and the cervix.**
- **Hysterosalpingogram demonstrated a normal uterine cavity with spill of radiopaque dye from both fallopian tubes. The primary purpose is to assess the tubal patency which is the most important function, secondary purpose is to assess the integrity of the uterine cavity.**
- Saline infusion sonohysterography (SIS): same as HSG but with the advantage of using ultrasound, can be done at the clinic and Avoiding the use of dye.
- Semen analysis with 2 ml of semen (normal >1.5) **the most important thing is the volume**, 4 million sperm/ml (normal >15), 20% motility (normal >40%), 2% normal morphology (normal >4%).
- Discussion regarding frequency and timing of intercourse.
- Ovarian reserve testing: Day 3 FSH 8.3 mIU/ml, estradiol <20 pg/ml (**both FSH & Estradiol have specific days for measurement**), anti-müllerian hormone (AMH) (**Index of ovarian reserve**) **how much primary oocyte are available** 1.1 ng/ml which are considered normal **no specific day to measure it we can measure it at any day.**
- Could also review basal body temperature charting or have patient use ovulation Predictor kits. **This is a work up**

4- Offer genetic counseling and testing for cystic fibrosis mutations. Given the results of the tests, what is the differential diagnosis for the etiology(ies) of this couple's infertility?

- Anovulation secondary to hyperprolactinemia from a potential prolactinoma
- Oligospermia – repeat semen analysis once and consider referral to a urologist.

5- What is the appropriate management for etiology of this couple's infertility?

1. For anovulation secondary to a possible prolactinoma, the patient should have a head MRI to rule out a pituitary lesion. Treat with bromocriptine **dopamine agonist** to lower prolactin levels, which will usually result in regular ovulation.
2. If she remains anovulatory after management of her prolactinoma with bromocriptine to normalize her prolactin level, ovulation induction may be offered with clomiphene citrate **selective estrogen receptors modulator**.
3. For oligospermia **we repeat the semen analysis more than two times**, refer to a urologist **better to refer to andrologist because it is specialized in male infertility** for evaluation for correctable causes **if the problem persists**. However, if oligospermia remains after evaluation and treatment then options include in vitro fertilization with intracytoplasmic sperm injection, intrauterine insemination (**IUI Laboratory selection of perfect sperm and insert it in the uterus**) with partner's sperm, intrauterine insemination with donor sperm, adoption.

6- The husband elects to undergo testing for common cystic fibrosis mutations and is determined to be a carrier. What options are available to them to achieve a pregnancy that is less likely to lead to a child affected by cystic fibrosis? Discuss the ethical issues associated with these choices.

- The couple could elect to use donor sperm or donor eggs. In both cases one of the parents would not be genetic parents.
- The couple could elect to use IVF with preimplantation genetic diagnosis.
- The couple could elect to achieve a pregnancy with none of the above techniques and accept a 1:4 risk of having a child affected with CF. They could elect to undergo antepartum testing (chorionic villi sampling, amniocentesis, etc.) to determine if the pregnancy is affected with CF.

Treatment steps :

1. Treat the underlying cause anovulation due to high prolactin give bromocriptine , if she has PCO give her oral contraceptives .
2. If the patient wants to get pregnant from the first visit I will prescribe her folic acid.
3. Step two if she didn't get pregnant we give her clomiphene citrate
4. If she is not pregnant do IVF

Step 2 the doctor said it during the mentorship.