INFERTILITY

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Introductory Case

A 37-year-old G0 presents with a chief complaint of inability to become pregnant. She has been actively trying to conceive for the past 2 years. She reports a long history of infrequent menses, and her exam is significant for obesity, with a body mass index (BMI) of 43 kg/m^2 and facial acne. Her medical history is otherwise notable for hypothyroidism on Synthroid and a remote history of chlamydia as a teenager. Her partner is a 34-year-old male with no children of his own. He is generally healthy but smokes 2 packs cigarettes per day and reports occasional marijuana use. They are having unprotected intercourse approximately once a week. She is not using ovulation predictor kits.

Milestone-Based Focused Questions

LEVEL 1: DEMONSTRATE BASIC KNOWLEDGE ABOUT COMMON AMBULATORY GYNECOLOGIC PROBLEMS

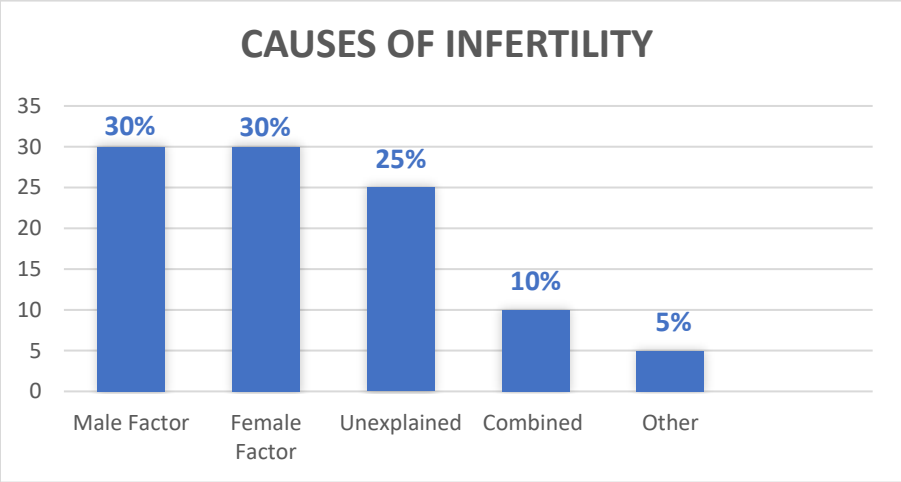
WHAT IS THE OVERALL EXPECTED LIKELIHOOD OF CONCEIVING WITHIN THE FIRST YEAR?

- 85% of couples conceive within the first year of regular unprotected intercourse
- The probability of pregnancy is highest in the first several months of unprotected intercourse (25% chance each month in the first three months), with a declining likelihood of success each subsequent month (15% per month thereafter)

HOW IS INFERTILITY DEFINED?

- Among women < 35 years old, infertility is the inability to conceive after *12 months* of regular unprotected intercourse (i.e. without the use of contraception)
- Among women ≥ 35 years old, this interval decreases to *6 months* of regular unprotected intercourse.

WHAT ARE THE CAUSES OF INFERTILITY?



- Causes of female infertility:
  - Ovulatory disorders 25%
  - Endometriosis 15%
  - Pelvic adhesions 12%
  - Tubal blockage 11%
  - Other tubal abnormalities 11%
  - Hyperprolactinemia 7%

LEVEL 2: PERFORMS THE INITIAL ASSESSMENT, FORMULATES A DIFFERENTIAL DIAGNOSIS, AND INITIATES TREATMENT FOR COMMON AMBULATORY GYNECOLOGIC PROBLEMS

BASED ON HER MENSTRUAL PATTERN, YOU SUSPECT THAT THIS PATIENT HAS POLYCYSTIC OVARIAN SYNDROME (PCOS). HOW IS PCOS DIAGNOSED?

Rotterdam criteria (requires at least two of the following):

1. Oligo/anovulation (fewer than 6-9 menstrual cycles per year)
2. Hyperandrogenism: clinical signs (hirsutism, acne, male pattern balding) or biochemical evidence
3. Polycystic ovaries on ultrasound: ≥12 follicles or increased ovarian volume (>10cm^3)

WHEN SHOULD AN INFERTILITY WORKUP BE INITIATED?

- Infertility evaluation should begin after *12 months* of unprotected intercourse in women < 35 or *6 months* of unprotected intercourse in women ≥ 35 years old
- Many experts also recommend initiating an infertility evaluation after 6 months among patients with risk factors for premature ovarian failure, advanced stage endometriosis, or suspected tubal disease

HOW DO YOU INITIATE THE INFERTILITY WORKUP FOR THIS PATIENT AND HER PARTNER?

The main elements that need to be evaluated are

- Female Factor
  - Ovulatory status and ovarian function
  - Tubal patency
- Male Factor
  - Semen Analysis

Female patient

- Key components of history
  - Infertility: Duration, previous infertility workup and treatment
  - Complete Gyn history: menstrual pattern (cycle frequency, length, and characteristics), contraception use (current and past), history of abnormal pap smears including any past cervical procedures
  - Molimina symptoms prior to menses: breast tenderness, bloating, fatigue

    - Sexual history: frequency of intercourse, sexual dysfunction, use of lubricants, home ovulation predictor kit use, basal body temperature measurements, sexually transmitted infections, pelvic inflammatory disease
    - Complete OB history: include management (medical vs surgical) of any pregnancy terminations or miscarriages, how were they performed (medically vs surgically)
    - Symptoms of thyroid dysfunction, galactorrhea, visual symptoms, hirsutism, pelvic and/or abdominal pain
    - Previous intra-abdominal infections and/or surgeries (for example, PID, ruptured appendicitis, diverticulitis, inflammatory bowel diseases)
    - History of chemotherapy or pelvic irradiation
    - Social history: Tobacco, illicit drug, alcohol use. Occupation and potential occupational or environmental exposures. Exercise, stress, changes in diet or weight.
    - Current medications and allergies
    - Family history of infertility, birth defects, developmental delays, early menopause
- Physical examination
    - Vital Signs including blood pressure and BMI
    - Evaluate for thyromegaly, signs of androgen excess (cystic acne, hirsutism, male pattern baldness), skin changes (acanthosis nigricans)
    - Abdominal Exam with assessment of obesity and presence of abdominal scars
    - Pelvic examination
        - Examine for signs of cervicitis (mucopurulent discharge, cervical motion tenderness)
        - Uterine size, shape, position, mobility
        - Adnexal masses
        - Cul-de-sac masses, nodularity, tenderness on exam
        - Vaginal or cervical structural abnormalities
- Diagnostic evaluation (see
    - Ovulatory function
        - Clinically, if the patient is having regular cycles, particularly if she is having molimina symptoms prior to menses, the patient is most likely ovulatory.
        - Labs to order: Mid luteal phase serum progesterone level (collected approximately 1wk before anticipated menses, typically day 21 in women with regular cycles).
        - Home ovulation predictor kits (OPK) can also detect the luteinizing hormone (LH) surge, which occurs just before ovulation.
    - Ovarian reserve
        - Labs to order: Anti-mullerian hormone (AMH), Day 3 Follicle stimulating hormone (FSH), Estradiol (E2)
            - AMH is produced by the granulosa cells of the ovary and reflects the primordial follicle pool. It can be obtained at any point in the menstrual cycle.
        - Antral follicle count
            - Assessed with transvaginal ultrasound. Count follicles measuring 2-10mm in mean diameter.
    - Tubal patency
        - Hysterosalpingogram (HSG). Performed cycle day 6-12 when endometrial lining is thin
            - Non-spillage may be due to tubal blockage or due to tubal spasm/myometrial contraction (particularly if proximal tubal occlusion is seen)
            - Diagnostic HSG also has a therapeutic effect – pregnancy rates higher among women after HSG
            - Laparoscopy with chromopertubation
            - Not considered part of initial infertility evaluation. May consider if there is concern for pelvic adhesions or endometriosis
    - Uterine cavity

        - HSG can provide information about uterine cavity but has low sensitivity for endometrial polyps and submucosal leiomyomas
        - Saline-infusion sonohysterography (SHG) is better for identifying intrauterine pathology
        - Hysteroscopy can be both diagnostic and therapeutic methodology
    - Additional tests:
        - Thyroid studies
        - Prolactin
        - Fragile X mutation
        - Karyotype
        - Androgen profile including testosterone, 17α-hydroxyprogesterone (screening for late onset congenital adrenal hyperplasia), dehydroepiandrosterone sulfate (DHEAS, screening for adrenal abnormality)
        - Glucose tolerance test, lipid profile for patients with evidence of PCOS
        - Consider Vitamin D levels

Table 1. Diagnostic Assessment for Infertility

	Clinical evaluation	Laboratory Evaluation	Additional Testing	
Ovulatory Function	Regular cycles with molimina symptoms	Day 21 Progesterone (mid luteal phase)	Ovulation Predictor Kits (assess for LH surge)	
Ovarian Reserve		AMH Day 3 FSH and Estradiol (E2)		
Tubal Patency			Hysterosalpingogram (HSG)	
Uterine Cavity			HSG SHG Hysteroscopy	
Additional assessments		Thyroid studies Prolactin Fragile X Karyotype 17α-hydroxyprogesterone DHEAS Glucose tolerance test Lipid profile Vitamin D	Semen Analysis in ***Male partner*** Additional Testing in ***Male partner*** as clinically indicated	

Male patient

- Relevant history
    - Any previous children, previous fertility assessments
    - Timing and onset of puberty
    - Medical comorbidities
    - History of head or pelvic trauma
    - History of mumps
    - Previous surgeries to the inguinal or scrotal areas.
    - Sexual function (assessment of libido, frequency of intercourse)

- Sexually transmitted infection history
- Environmental or chemical exposures
- Tobacco, illicit drug, alcohol, or exogenous androgen use
- Family history of infertility, birth defects, developmental delays, early menopause

- Physical exam
  - Body mass index
  - Signs of endocrinopathies (for example, thyroid dysfunction, Cushing's syndrome)
  - Findings of androgen deficiency (loss of secondary sex characteristics)
  - Genital exam for evidence of incomplete pubertal development
- Diagnostic evaluation
  - Semen analysis: Assesses semen volume, sperm concentration, count, motility, and morphology
  - Additional work up should be referred to a specialist in male infertility

Essential Orders

Order **Day 3 FSH (and/or AMH) E2, PRL, TSH, HSG, Semen analysis**, +/- **HSG** as part of the standard infertility work up

LEVEL 3: FORMULATES MANAGEMENT PLANS AND INITIATES TREATMENT FOR COMPLEX AMBULATORY GYNECOLOGIC PROBLEMS.

Interpretation:

- Mid luteal phase (day 21) progesterone**:** >3 ng/mL suggests recent ovulation
- FSH and E2
  - F*S*H: will be elevated in women with a reduced follicle pool because more *stimulation* is required to cause production of ovarian hormones.
    - A normal FSH is not useful for predicting fertility, but a *highly abnormal level* (FSH > 20 IU/L) suggests that spontaneous pregnancy is unlikely.
    - <10 IU/L suggests adequate ovarian reserve
    - 10-15 IU/L borderline
  - Estrogen (E2): will be elevated in women with poor ovarian reserve due to advanced premature follicle recruitment
    - <80 pg/mL suggestive of adequate ovarian reserve
    - >80 pg/mL associated with worse advanced reproductive technology outcomes
  - FSH and E2 should be assessed in relation to each other

FSH	E2	Interpretation
↑↑	↓↓	Hypergonadotrophic hypogonadism (ex, premature ovarian insufficiency)
↓ **or NL**	↑	Small pool of available oocytes
↓	↓	Hypogonadotrophic hypogonadism (ex, anorexia)

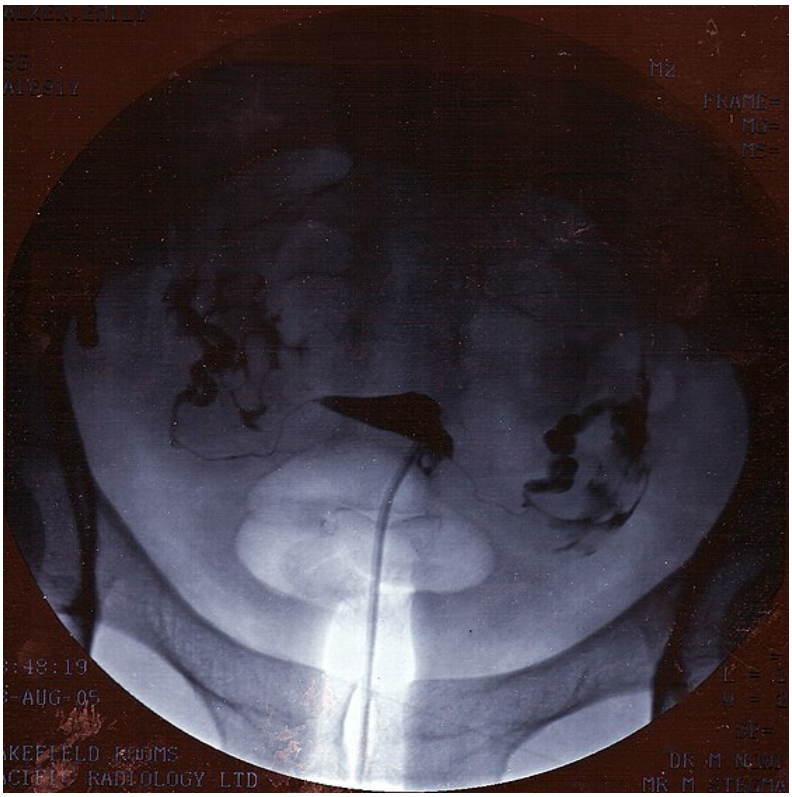
- AMH
  - <0.5 ng/mL predicts reduced ovarian reserve with <3 follicles in IVF cycles
  - <1.0 ng/mL associated with limited response to ovarian stimulation
  - Between 1.0-3.5 ng/mL suggests good response to stimulation
  - >3.5 ng/mL associated with a strong response to ovarian stimulation and may increase the risk of ovarian hyperstimulation syndrome

    - AMH will be falsely elevated in patients with PCOS. AMH can also be suppressed if on oral contraceptive pills. Obtain value after discontinuing pills for 2-3 months.
- Antral Follicle Count
    - 3-6 follicles associated with a poor response to ovarian stimulation
    - Normal antral follicle count ≥10
- TSH: Goal <2.5 mIU/L
- Prolactin

Serum concentration (ng/mL)	Clinical manifestations
>100	Overt hypogonadism
50-100	Oligo/amenorrhea
20-50	May not have menstrual abnormalities, although can still cause infertility

    - If only slightly elevated, repeat as a fasting, early morning value
    - If elevated or persistently slightly elevated, obtain MRI pituitary to look for prolactinoma
- Vitamin D: <20ng/mL considered vitamin D deficiency
    - Vitamin D replete patients have improved clinical pregnancy rates following IVF
- Semen analysis

	Lower Limit of Normal
Volume	1.5mL
pH	7.2
Concentration	15 million
Total sperm #	39 million
% motility	40%
Forward progression	32%
Normal morphology	4% normal forms
Sperm agglutination	Absent
Viscosity	≤ 2cm thread after liquefaction



Normal HSG: Bilateral spill of contrast into peritoneal cavity consistent with tubal patency
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LEVEL 4: EFFECTIVELY CARES FOR PATIENTS WITH COMPLEX PRESENTATIONS. USES A MULTI-DISCIPLINARY APPROACH AND MAKES APPROPRIATE REFERRALS WHEN CARING FOR PATIENTS WITH COMPLEX AMBULATORY GYNECOLOGIC PROBLEMS. LEADS AN INTER-PROFESSIONAL TEAM, INCLUDING SUPERVISION, EDUCATION, AND COORDINATION OF CARE.

WHAT IS THE MANAGEMENT OF PATIENTS WITH OVULATORY DYSFUNCTION RELATED TO PCOS?

Ovulation induction

Clomiphene citrate (clomid)

- A Selective Estrogen Receptor Modulator (SERM) that counteracts normal negative feedback inhibition of FSH/LH, leading to increased pulse frequency of GnRH, thus increased FSH and LH
- Regimen: 50mg/day x 5 days starting on cycle day 3-5. If ovulation does not occur, increase dose to 100mg/day with next cycle
  - LH surge should occur between 5-12 days after the last day of clomid administration
  - Monitor ovulation with ovulation predictor kit, mid-luteal progesterone, or ultrasound
  - May need to induce withdrawal bleed prior to clomid administration
- Side effects: hot flashes, mood changes, breast tenderness, pelvic pain, nausea, headaches
- Pregnancy rate per cycle:
  - 5-8% with timed intercourse starting 5 days after last dose
  - 10-12% with intrauterine insemination
- Risk of multiple gestation may be as high as 8% in anovulatory women
- Causes thinning of endometrial lining, which may negatively affect implantation success, thus long term use not recommended

Letrozole
- An Aromatase Inhibitor that blocks the conversion of testosterone and androstenedione to estradiol and estrone (respectively), reducing negative feedback and stimulating release of FSH
- First-line for ovulation induction in patients with **PCOS**, resulting in higher ovulation rate, clinical pregnancy rate, and live birth rate
  - May also be useful in clomiphene non-responders
- Regimen: 2.5mg/day x 5 days starting on cycle day 3-5. Max dose of 7.5mg/day
- Off-label use for ovulation induction
- Similar rate of multiple gestation compared to clomid
- No adverse effects on endometrial lining

Metformin
- Decreases circulating androgens, improves ovulation rate, improved glucose tolerance
- Should not be used as sole agent for ovulation induction. More beneficial when used in conjunction with clomid, especially in clomid-resistant patients
- Pre-treatment for 3 months prior to ovulation induction may have benefit in live birth rate
- Regimen: 1500-2000mg daily in divided doses

Weight modulation

Elevated body weight:
- Weight loss advised if BMI ≥ 27 and patient with anovulatory infertility
- Among obese women with PCOS, weight loss of 5-10% can restore ovulation and improve reproductive outcomes

Low body weight (BMI < 17), eating disorders, or strenuous exercise regimens are at risk for hypogonadotropic hypogonadism. Patients should be advised to gain weight, improve diet, and decrease exercise regimen.

Optimal coital timing

Highest probability of conception in the 1-2 days preceding ovulation. The "fertile window" is the five days prior to ovulation and the day of ovulation

Highest pregnancy rates are among couples who have intercourse every 1-2 days

Optimal semen quality noted when there have been 2-3 days of ejaculatory abstinence prior to coitus

Things that ***do not*** affect fertility: position during intercourse, presence of female orgasm, female position after intercourse (i.e. remaining supine)

Substance use

Cigarettes
- Dose-dependent association between smoking and infertility
- Women
  - Conception delay (possibly via adverse effects on the tubes or cervix), accelerated ovarian follicular depletion
  - Pregnancy complications, including increased miscarriage rate, ectopic pregnancy, preterm delivery, intrauterine growth restriction, placental abruption
  - Rate of IVF success remains lower among patients who smoke cigarettes
- Men
  - Reduced sperm concentration, motility, morphology

Alcohol
- Moderate alcohol intake likely has no or minimal effect on fertility. Studies regarding heavy alcohol intake (≥ 14 drinks/week) are mixed.

Marijuana
- Men: Marijuana use ≥ 1x/week can lower sperm count and concentration

Caffeine: No demonstrated effect on fertility

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