

ASRM RESIDENT POCKET GUIDE



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Assessment of Ovulation

EPIDEMIOLOGY



- Ovulatory disorders identified in 18-25% of infertile women
- Most women with ovulatory dysfunction can be induced to ovulate though pregnancy may not occur due to coexisting factors affecting fertility

BEGIN WITH HISTORY GUIDED EVALUATION & DIAGNOSIS



- Serum TSH, serum prolactin
- Cycle day 3 FSH/LH/estradiol
- OGTT or HbA1c glycemic status

If patient is interested in fertility

- Semen analysis
- HSG & transvaginal ultrasound imaging

DIAGNOSIS OF ANOVULATION: HISTORY



- Irregular, unpredictable, or infrequent menses
- If the patient's medical history is consistent with ovulatory dysfunction, then patient does not require further workup



Assessment of Ovulation

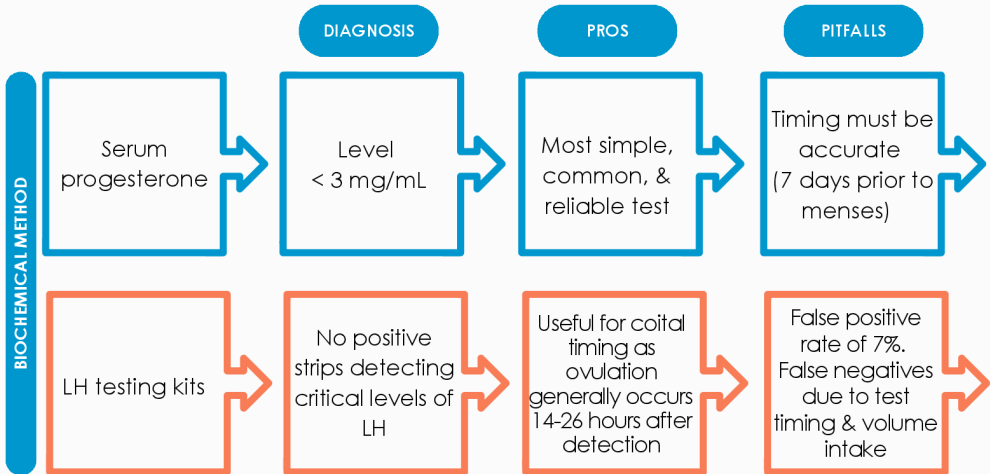
Physical Assessment

There are historical, physical, and laboratory methods to evaluate ovulation

	DIAGNOSIS	PROS	PITFALLS
Basal Body Temperature	No sustained temperature elevation before menses	Cheapest available	Requires daily testing. ↑ basal body temperature occurs after ovulation
Endometrial Biopsy	No secretory endometrium present	May be indicated in patients with chronic anovulation due to unopposed estrogen & risk of hyperplasia	Invasive & expensive Timing must be accurate (7 days prior to menses)
Serial transvaginal ultrasound	No visualization of dominant follicle & collapse	Most accurate estimate of when ovulation occurs. Provides detailed follicle development information	Invasive & expensive



Assessment of Ovulation



Polycystic Ovary Syndrome (PCOS) Treatment for the Non-Pregnant Patient

EPIDEMIOLOGY



- Most common endocrinopathy affecting reproductive aged women
- Prevalence of 6-15% depending on criteria used

DEFINITION



Rotterdam PCOS Diagnostic Criteria: Need 2 of 3 (Oligo/Anovulation, Clinical &/or Biochemical Hyperandrogenism, Polycystic Ovaries on ultrasound)

*In adolescents ultrasound criteria not recommended for diagnosis.

SCREENING



- Oligo/Anovulation: Cycles > 35 days (3yrs post menarche)
- Biochemical Hyperandrogenism: Total & Free Testosterone, Androstenedione, Dehydroepiandrosterone Sulfate (DHEAS)
- Clinical Hyperandrogenism: Acne, Alopecia, Hirsutism
- Ultrasound: Transvaginal Ultrasound (if > 8yrs post menarche) ³ 20 follicles or ovarian volume ³ 10mL

INFERTILITY TREATMENT FOR PCOS/ANOVULATION INFERTILITY (OVULATION INDUCTION)



- 1st Line** Consider Letrozole > Clomiphene, Metformin
- 2nd Line** Consider Gonadotropins
- 3rd Line** IVF where ovulation induction therapies have failed

Polycystic Ovary Syndrome (PCOS) Treatment for the Non-Pregnant Patient

PHARMACOLOGIC INTERVENTIONS (TOGETHER WITH LIFESTYLE MODIFICATIONS)



- cOCs are 1st Line for Menstrual Irregularity & Hyperandrogenism.
- Consider Metformin for management of metabolic features
- Can use cOCs together with metformin

NON-PHARMACOLOGIC INTERVENTIONS

OBESITY

- ✓ Education
- ✓ Self-empowerment
- ✓ Lifestyle intervention for prevention/management of excess weight

INSULIN RESISTANCE/ METABOLIC SYNDROME

- ✓ Blood Pressure
- ✓ Cardiovascular Risk
- Factors should be monitored yearly
- ✓ Fasting Lipid Profile should be done initially, with f/u dependent on results

IMPAIRED GLUCOSE TOLERANCE

- ✓ Glycemic Status (oGTT or HbA1C) assessed at baseline, 1-3 years thereafter, & preconception

NON-PHARMACOLOGIC INTERVENTIONS

CANCER

- ✓ Increased risk of Endometrial Cancer
- ✓ Consider lower threshold to screen for AUB

QUALITY OF LIFE

- ✓ Screen for depression & anxiety at diagnosis

OBSTRUCTIVE SLEEP APNEA

- ✓ Screen for OSA signs & consider referral to specialist

Induction of Ovulation - Diagnosis

FINDINGS

- Low FSH
- Low estradiol

- Stress, weight loss, excessive exercise, anorexia nervosa
- Kallmann syndrome
- Isolated gonadotropic deficiency
- Compressing lesion

Hormones

Causes

Group 1 (5-10%)

Group 2 (75-85%)

- Normal FSH
- Normal estradiol
- Normal to high LH

- PCOS

Differential Diagnosis

- High FSH
- Low AMH

- Premature ovarian insufficiency

Hormones

Causes

Group 3 (10-20%)

Group 4 (5-10%)

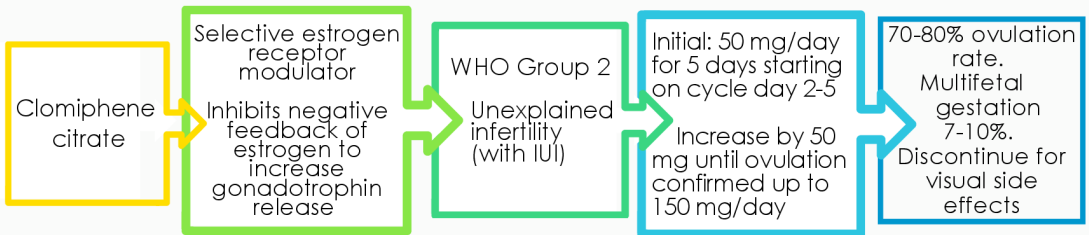
- High prolactin
- Low FSH
- Low – normal estradiol

- Hypothyroidism Iatrogenic
- Pituitary lesion

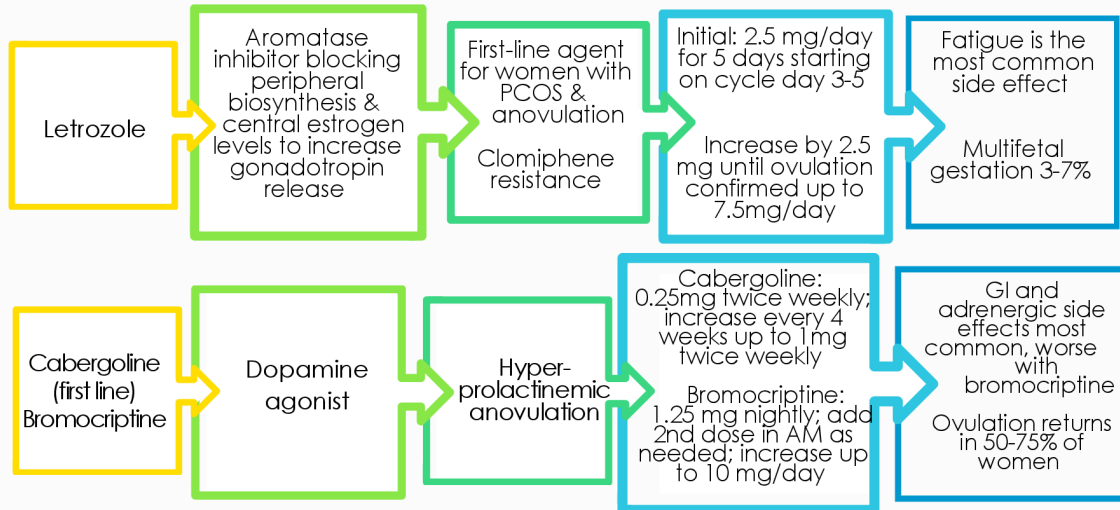
Induction of Ovulation

Treatment

- Target the underlying diagnosis
- In obese women & those with PCOS, weight loss of 5-10% of body weight can restore ovulatory cycles & improve sensitivity to induction agents
- Assess progesterone on cycle day 22-25 to evaluate for ovulation when using clomiphene citrate or letrozole; levels <3 ng/mL indicated anovulation
- Assess prolactin after four weeks when using cabergoline & after at least one week with bromocriptine



Induction of Ovulation



Preconception Counseling & Optimizing Natural Fertility

THREE GOALS OF PRECONCEPTION CARE



- Identify potential risks to mother, fetus & pregnancy
- Educate about these risks
- Initiate interventions to optimize maternal, fetal & pregnancy outcomes

"ONE KEY QUESTION" INITIATIVE



- Every patient encounter is an opportunity to counsel about wellness & healthy habits to improve reproductive & obstetric outcomes
- "Would you like to become pregnant in the next year?"
- Avoid interpregnancy intervals < 6 months, patients to be aware of risks if repeat pregnancy is < 18 months, though may be advisable if pursuing ART

REVIEW ALL HISTORY



- Chronic medical conditions should be optimally managed prior to pregnancy; consider referral to MFM
- Review ALL medications (eRx & non eRx), eliminate any medications with potential teratogenic effects in collaboration with prescribing provider
- Review genetic & family history of patient & partner

IMMUNIZATIONS



- Assess immunization status yearly (think Tdap, MMR, Hep B, varicella), give vaccines > 2 months in advance of conception
- All patients should receive influenza yearly



SCREENINGS

- Gonorrhea, chlamydia, syphilis, HIV: based on age & risk factors
- TB: based on risk factors, treat before pregnancy
- Toxoplasmosis: assess exposure & counsel
- Zika: as of 5/2024, FDA has determined it as RCDAD
- Substance use: assess dependence & offer supportive cessation services
- Intimate partner violence: screen confidentially, assess safety, provide community resources
- Nutritional status: prepregnancy folic acid supplementation to reduce risk of NTDs; confirm pts are meeting recommended daily allowances for nutrients; avoid high mercury fish, foods with high risk of listeria
- Healthy body weight: high AND low BMIs are associated with infertility & maternal/fetal pregnancy complications; weight should be optimized before pregnancy
- Oral disease: refer to dentist as appropriate
- Exercise/physical activity: patients should aim for 30min/day 5 days a week
- Teratogens/environmental occupational exposures: prepregnancy history & identification of exposures are encouraged; avoid exposures and/or refer to occupational medicine

Preconception Counseling & Optimizing Natural Fertility

Chronic hypertension

↑ Preeclampsia + IUGR; discontinue ACEIs/ARBs

Untreated hypothyroidism

↑ SAB, preeclampsia, PTB, placental abruption, IUFD; tx if thyrotropin is above upper level of normal

Bariatric surgery

Avoid pregnancy in the 12-24 mo after surgery due to effects on fetal growth

Mood disorders

↑ Impaired maternal/infant bonding, maternal-self harm or neglect; antidepressants & antipsychotic meds increase anovulation & decrease fecundability; emphasize collaborative decision making when managing medications as risk of relapse may be higher in pregnancy

HIV

↑ Vertical transmission; do NOT discontinue HAART; counsel serodiscordant couples on risks of transmission & safe methods for achieving pregnancy; consider PEP in the right patient; VL should be undetectable, co-manage with HIV health care provider

Thrombophilia

↑ DVT or PE during pregnancy/postpartum; consider thromboprophylaxis during pregnancy

Testing & Interpreting Measures of Ovarian Reserve

Which test is best?

AMH is more sensitive for diminished ovarian reserve & simpler to administer than cycle dependent tests. With experienced providers, AFC has been shown to be equivalent to AMH

Do markers of ovarian reserve predict pregnancy?

Studies show that cumulative pregnancy rate was similar between women with low AMH (<0.7 ng/mL) or high FSH (10 IU/L) & women with normal levels in the absence of a history of infertility or known risk factors. In women with a history of infertility, ovarian reserve tests did not predict unassisted pregnancy better than existing age-based prediction models.

Do markers of ovarian reserve predict outcomes in IVF?

Numerous studies indicate that AMH and AFC predict oocyte yield in assisted reproductive technologies. Whether they reliably predict pregnancy & live birth is less clear.

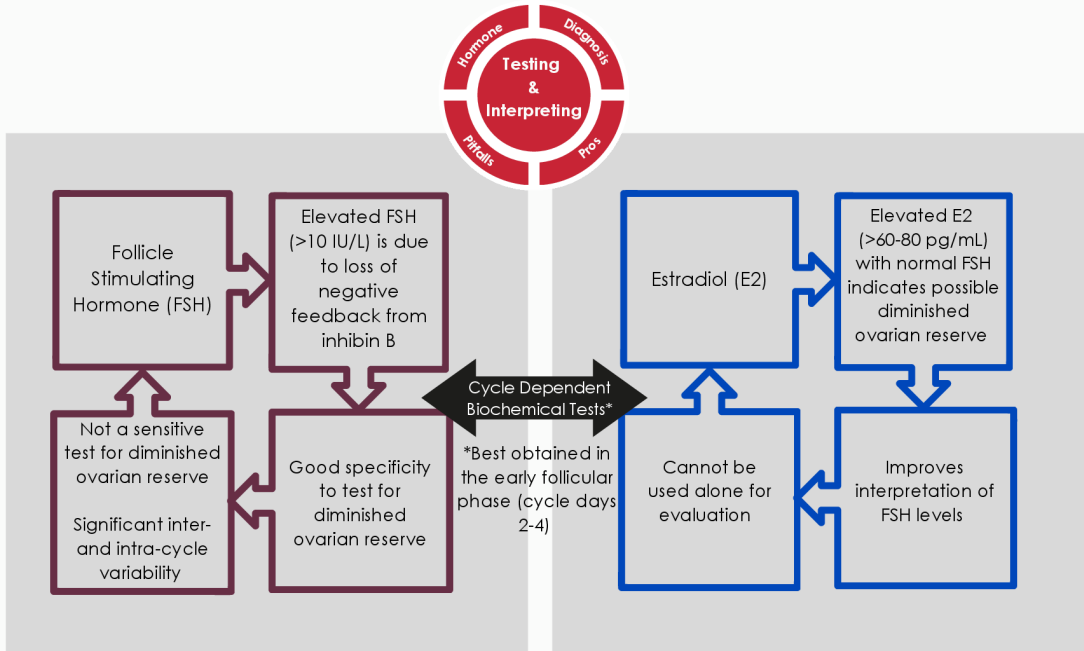
Which patients should undergo ovarian reserve testing?

Patients at increased risk for diminished ovarian reserve (age over 35, unexplained infertility, family history of early menopause, previous ovarian surgery/chemotherapy/radiation, smoking, poor response to exogenous gonadotropin stimulation). It should not be used as a fertility test in women who are not infertile.

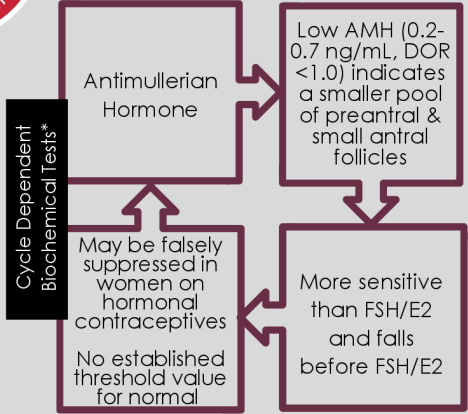
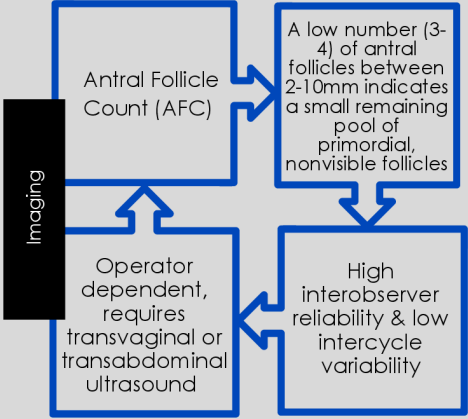
How should ovarian reserve tests be interpreted?

Ovarian reserve testing may add prognostic value in counseling infertile couples. Markers of ovarian reserve should not be used in promoting planned oocyte cryopreservation. This discussion should be guided by the woman's age & reproductive plans.

Testing & Interpreting Measures of Ovarian Reserve



Testing & Interpreting Measures of Ovarian Reserve



*Best obtained in the early follicular phase (cycle days 2-4)

Treatment for Pre & Post- Menopausal Patient Symptoms

SCREENING



- Change in cycle pattern (>60 days)
- Dyspareunia
- Depression, anxiety
- hair thinning
- Sleep disturbances
- Headaches
- Vasomotor symptoms
- Changes in weight distribution
- Vulvovaginal symptoms
- Change in memory, concentration
- Supportive lab values: FSH > 25 IU/L, Low AMH, Inhibin B

NON HORMONE RELATED THERAPIES



- Vasomotor Symptoms:
 - Paroxetine
 - Other SSRI, SNRI, Gabapentin, Clonidine (Off Label)
- Genitourinary Syndrome of Menopause:
 - Moisturizers, Lubricants, Pelvic Floor Therapy, Topical Lidocaine, Fractional CO2 Laser

Treatment for Pre & Post- Menopausal Patient Symptoms

HORMONAL THERAPY



- Vasomotor Symptoms:
 - Estrogen Therapy
 - Estrogen-Progestosterone Therapy (Need Progestogen if patient still has uterus!)
 - SERM Agonist/Antagonist Therapy
- Genitourinary Syndrome of Menopause:
 - Low-Dose Vaginal Estrogen, Vaginal DHEA, Oral SERM
 - Systemic HT (if VMS also)

HOW DO HORMONES HELP WITH MENOPAUSE?

- Reduce Vasomotor Symptoms (Hot flashes)
- Reduce Genitourinary Syndrome of Menopause (Vaginal atrophy, dryness, dyspareunia)
- Slow down osteoporosis



Treatment for Pre & Post- Menopausal Patient Symptoms

CONTRAINDICATIONS TO HT



- Unexplained vaginal bleeding
- Hx of VTE/PE
- Liver disease or dysfunction
- Estrogen-dependent neoplasia
- Known or suspected pregnancy
- Arterial thromboembolic disease (12 mo)
- Porphyria cutanea tarda

SIDE EFFECTS TO HT



- Uterine bleeding
- Breast tenderness
- Nausea
- Bloating
- Mood changes
- Pancreatitis
- Headaches

SHOULD HORMONE THERAPY BE USED TO...



- Prevent strokes or protect heart... NO ✗
- Prevent memory loss/Alzheimer's Disease... NO ✗
- Treat sleep disturbances... NO ✗

DOSING



- Should be started within 10 years of onset of menopause & before 65
- Consider using for the lowest effective dose for shortest amount of time needed

Evaluation of Secondary Amenorrhea

Amenorrhea lasting three months or more & oligomenorrhea (fewer than nine menstrual cycles per year or cycle length > 35 days) require investigation

HISTORY & PHYSICAL EXAM

- ? Changes in diet or exercise habits
- ? Headaches, visual changes or field defects
- ? Fatigue, polyuria, or polydipsia
- ? Recent uterine instrumentation
- ? BMI/weight changes
- ? Acne, hirsutism
- ? Galactorrhea
- ? Signs of estrogen deficiency

LABORATORY TESTING

Initial serum labs

- ✓ hCG
- ✓ FSH
- ✓ Estradiol
- ✓ TSH
- ✓ Prolactin

Total testosterone +/- 17-OHP if signs of hyperandrogenism

Evaluation of Secondary Amenorrhea

LABORATORY TESTING

- If prolactin elevated → Repeat fasting in AM
 - If still elevated, Pituitary MRI to evaluate for hyperprolactinoma
- If TSH abnormal → Evaluate for presence of thyroid disease with thyroid function tests
- If FSH elevated → Evaluate for primary ovarian insufficiency, particularly in the setting of low estradiol & symptoms
- If FSH low/normal → Low Estradiol
 - Evaluate for causes of hypogonadotropic hypogonadism
 - Consider Pituitary MRI
- Normal FSH & E2 → If signs of hyperandrogenism, PCOS likely
 - Serum T > 150 ng/dL or virilization should prompt further evaluation

NORMAL EVALUATION

If normal serum labs & no localizing symptoms, consider progestin withdrawal test

- Consider pelvic ultrasound as part of initial workup
- If no uterine bleeding, repeat with estrogen priming
- If no bleeding despite estrogen priming, consider cervical stenosis & evaluation of uterine cavity for intrauterine adhesions via saline infusion sonogram or hysteroscopy

Evaluation of Secondary Amenorrhea

OTHER ETIOLOGIES

Functional Hypothalamic Amenorrhea

- Traumatic brain injury, brain tumors, infiltrative diseases of hypothalamus
- Eating disorders, acute stress, severe or prolonged illness

Pituitary Dysfunction

- Pituitary infarct/apoplexy
- Cushing's Disease

Chemotherapy, radiation, autoimmune disease, type 1 & type 2 diabetes, androgen use

MANAGEMENT GOALS

- ✓ Correct the underlying pathology
- ✓ Restore fertility if desired
- ✓ Prevent complications of disease process

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Developed by the ASRM Education Committee

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