

## ANMC Infertility Guidelines

### Background

- Infertility is defined as the inability to become pregnant after attempting for one year. The diagnosis is based on the patient's report of attempting for this duration and can be primary (never pregnant) or secondary (prior history of pregnancy, but inability to conceive for more than a year). Infertility is most frequently caused by derangements of ovulation, tubal disease, or male factors.
- Infertility affects about 15% of couples.
- 30% diagnosed with unexplained infertility.
- In approximately 40 % of infertility couples the male partner is either the sole cause or a contributing cause of infertility.

### Definitions:

**Infertility:** Affects up to 15% of couples. Defined as failure to achieve pregnancy within 12 months of unprotected intercourse or therapeutic donor insemination in women younger than 35 years or within 6 months in women older than 35 years,

**Ovarian reserve:** The total number of healthy, immature eggs in the ovaries. It represents the number of oocytes available for potential fertilization at that point in time. It may be assessed by serum tests or ultrasonography. The presence of decreased ovarian reserve predicts future response to ovarian stimulation.

**Antral Follicle Count:** Ultrasonographic assessment of the antral follicle count is determined by the number of follicles that measure 2–10 mm in both ovaries. Low antral follicle count may be defined as fewer than 5–7 follicles and is associated with poor response to ovarian stimulation.

**Ovulatory dysfunction:** history of oligomenorrhea or amenorrhea or as luteal progesterone levels repeatedly less than 3 ng/mL, or both

**Oligo-Ovulation:** Infrequent ovulation.

**Anovulation:** Absence of ovulation

**Amenorrhea:** Absence of menses

**Leiomyoma:** Uterine fibroids

**Mullerian Anomalies:** Developmental anomalies of the female reproductive tract. Classified into: Mullerian agenesis, Bicornuate uterus, cervical agenesis and unicornate uterus to name a few.

## Screening and diagnostic procedures / Initial evaluation:

**Offer infertility evaluation for those who meet the criteria or are at high risk of infertility.**

1. Failure to achieve pregnancy within 12 months of unprotected intercourse in women under 35 years old. OR within 6 months in women older than 35 years.
2. Expedited Evaluation: Women older than 35 years should receive an expedited evaluation and undergo treatment after 6 months of failed attempts to become pregnant or earlier.
3. women older than 40 years, more immediate evaluation and treatment are warranted.
4. If a woman has a condition known to cause infertility, the obstetrician–gynecologist should offer evaluation.

### **Indications for OB/GYN evaluation:**

1. oligomenorrhea or amenorrhea
2. known or suspected uterine, tubal, or peritoneal disease.
3. stage III or stage IV endometriosis
4. known or suspected male infertility.

## Components of Initial Work-up

### **FEMALE:**

#### Medical Hx:

A) Duration of Infertility and previous tests and treatment.

B) Menstrual history ((including age at menarche, cycle interval, length, and characteristics; presence of molimina [mild premenstrual symptoms and changes]; and onset and severity of dysmenorrhea), signs or evaluation of ovulation including positive ovulation tests, cervical mucus changes, or biphasic basal body temperatures, patterns

C) Pregnancy Hx

D) Previous methods of contraception

E) Coital Frequency and Timing

F) Sexual Dysfunction

G) Previous surgeries focusing on abdominal / pelvic region

H) Gynecologic and Sexual Hx (PID, STI, Endometriomas, Fibroids)

I) review of organ systems, including history of thyroid disease, galactorrhea, hirsutism, pelvic or abdominal pain, and dyspareunia

J) previous abnormal cervical cancer screening tests and any subsequent treatment

K) current medications and supplements, with an emphasis on identifying allergies and potential teratogens

H) family history of birth defects, developmental delay, early menopause, / reproductive problems, occupation / exposure to known environmental hazards, use of nicotine products, alcohol, and recreational or illicit drugs.

Physical Exam- focus on vital signs, thyroid, breast, and pelvic examinations.

### Additional Tests

**Labs:** HCG, ovarian reserve, ovulatory function.

HCG: POC or serum

OVARIAN RESERVE: Ovarian reserve tests are good predictors of response to ovarian stimulation, but poor results do not necessarily predict inability to achieve a live birth. This can be assessed by measuring estradiol and FSH between cycle days 2–5.

AMH- Serum AMH is produced by the granulosa cells of antral follicles and, therefore, is another serum marker of ovarian reserve. Because AMH levels remain relatively stable throughout the menstrual cycle, they can be assessed on any day of the menstrual cycle.

FSH- Follicle Stimulating Hormone. Follicle-stimulating hormone values greater than 10 IU/L obtained on cycle day (CD) 2-5 are associated with poor response to ovarian stimulation and failure to conceive. See ovarian reserve.

Estradiol- Estradiol serves as an aid for interpreting FSH results. Basal estradiol levels typically should be less than 60–80 pg/mL; elevated estradiol levels may have a suppressive effect on FSH levels and are indicative of decreased ovarian reserve.

Prolactin- Stimulates growth of mammary tissue to secrete milk. Elevated prolactin in premenopausal women is linked to symptoms that include infertility, oligomenorrhea, or amenorrhea.

Tips: Prolactin increases slightly during sleep, strenuous exercise, and occasionally with emotional or physical stress, intense breast stimulation, and high-protein meals. Therefore, if an initial prolactin level is only borderline high, the test should be repeated

-Obtain while fasting (nothing to eat or drink anything but water) for 12 hours

-Avoid nipple stimulation for 24 hours prior to prolactin testing.

PRECONCEPTION LABS:

- Rubella and Varicella titers
- Infectious diseases (HIV, Hep B and Hep C, Syphilis)
- CBC and Fasting blood sugar

## OVULATORY DYSFUNCTION

Serum Progesterone – Provide a reliable and objective measurement of ovulatory function if obtained at appropriate time in the cycle. Generally obtained 1 week before expected onset of next menses or 1 week after peak LH surge (e.g., CD 21). A concentration level of 3ng/mL shows evidence of recent ovulation. Ref: ASRM Learning module Infertility Evaluation MD 013.

LH – Luteinizing hormone tests. Using Ovulation predictor kits (OPK).

### **STRUCTURAL ABNORMALITIES- Imaging studies:**

Imaging modalities can detect tubal patency and pelvic pathology and assess ovarian reserve.

Pelvic Ultrasound: Transvaginal Ultrasonography (TVUS) assists in detection of uterine leiomyomas, present in the uterine cavity as well as detection of mullerian anomalies.

HSG: The hysterosalpingogram (HSG) helps assess tubal patency. Radiopaque contrast is injected through the cervix during fluoroscopy to view the uterus and the fallopian tubes. Proximal and tubal occlusion, peri tubal adhesions and salpingitis may be seen.

Sonohysterography: Ultrasonographic visualization of the uterus and adnexa with infusion of fluid through a transcervical catheter.

Diagnostic Laparoscopy (not part of initial work-up)

## **MALE:**

40-50% of infertility can be attributed to Male Factor origins. Given the high statistics, a basic medical history and evaluation of the male partner are warranted from the beginning.

1. Male partner's medical history
  - Intercourse frequency and timing
  - Evidence of sexual dysfunction
  - Prior fertility or duration of infertility
  - Childhood illness (mumps) and developmental history
  - Chronic medical conditions
  - Previous pelvic surgery (cryptorchidism with or w/o surgery)
  - Medication use and allergies.
  - Sexual history, incl: STI
  - Exposure to gonadal trauma or toxins

## 2. Semen analysis

- For optimal analysis, it is advised to abstain 2-5 days from intercourse or ejaculation. Sample is to be transported warm, or body temperature and must be submitted for evaluation within 30 min to 1 hr (depending on facility)

Refer to Male infertility patients to male reproductive medicine specialist.

## Diagnosis:

### Diminished Ovarian Reserve:

- antimüllerian hormone (AMH) value less than 1 ng/mL
- antral follicle count less than 5–7 and
- follicle-stimulating hormone (FSH) greater than 10 IU/L or
- a history of poor response to in vitro fertilization stimulation (fewer than four oocytes at time of egg retrieval).

**Unexplained infertility:** Unexplained infertility occurs when the definition of infertility is met, the basic infertility evaluation is performed, and all the tests results are normal. At a minimum, these patients should have evidence of ovulation, tubal patency, and a normal semen analysis. May be diagnosed in as many as 30% of infertile couples.

**Ovulatory Dysfunction (25%):** up to one third of women with normal menstrual cycles are anovulatory.

- Evidence of anovulation
- Progesterone less than 3 ng/mL during midluteal phase
- Negative LH surge
- Dry or no cervical mucus
- No changes on BBT

Anovulation may be related to obesity, hypothalamic and pituitary dysfunction, PCOS, and other etiologies. Polycystic ovary syndrome is the most common cause of ovulatory infertility.

Thyroid Disease and Hyperprolactinemia: Can cause ovulatory dysfunction, ranging from an inadequate luteal phase to oligo-ovulation to amenorrhea.

If a woman has unexplained ovarian insufficiency or failure or an elevated FSH level before age 40 years, fragile X carrier screening is recommended to determine whether she has an FMR1 premutation

**Tubal Factor (11 %)** Tubal occlusion caused by previous PID, STI, pelvic adhesions. Dx by HSG or Sonohysterogram.

**Endometriosis (15 %):** Can contribute to distortion of pelvic anatomy from pelvic adhesions, damage to ovarian tissue, production of cytokines and growth factors affecting ovulation, fertilization and implantation.

**Uterine Factor:** Uterine factors associated with infertility include endometrial polyps, synechiae, müllerian anomalies, and leiomyomas/fibroids. Leiomyomas with a surgically modifiable effect on fertility include those with a submucous or endometrial cavity-distorting component.

**Male Factor Infertility (40-50%):** Lower than normal limits on Sperm volume, concentration, motility, morphology.

## Management

- **Anovulation:** Ovulation induction therapy with the use of Clomiphene Citrate or Letrozole
  - 1) Clomiphene Citrate: Selective Estrogen Receptor Modulator. Increases chance of pregnancy of 2.5% compared with no treatment. Increases production and secretion of FSH and LH.
    - Start at 50 mg/day on CD 2,3,4 or 5 (for 5 days).
    - Ovulation is then confirmed with CD 21 Progesterone blood draw.
    - If no ovulation, dosage is increased by 50 mg increments.
    - Max dose is 150 mg. Can proceed for 3 months on dose with confirmed ovulation.
    - If patient is amenorrheic, medroxyprogesterone is often given to induce withdrawal bleed prior to cycle start.
    - Counsel on risk of multiple gestations (8% for anovulatory women and 2.6%-7.4% if unexplained infertility).
  - 2) Letrozole: Aromatase inhibitor. Alternative to Clomid.
    - May be preferred for women with PCOS.
    - Decreased risk of multiples. However, not FDA approved for ovulation induction.
    - Start with 2.5 mg on CD 2,3,4,5 (5 days total).
    - Ovulation is confirmed with CD 21 Progesterone blood draw.
    - If no ovulation, dosage is increased by 2.5 mg increments. Max dosing is 7.5 mg.
    - Counsel on risk of multiple gestations.
    - No negative effects on endometrial lining and cervical mucus.

### SIDE EFFECTS of OVULATION STIMULATION:

Clomiphene Citrate side effects:

- Blurred or double vision

- Pelvic pain
- Ovarian cysts
- Enlarged ovaries
- PMS symptoms
- Can thicken cervical mucus due to anti-estrogenic effects.
- May inhibit endometrial growth (resulting in thin lining)
- Hot flashes

#### Letrozole side effects

- Minor hot flashes and gastrointestinal upset
- Not FDA approved for ovulation induction.

Additional management is treatment based on identified cause of anovulation.

- Obesity:** Optimize diet and lifestyle. If still anovulatory, the consensus for ovulation induction treatment is BMI <40, also at provider discretion.
- PCOS:** All women in whom PCOS is diagnosed should be screened for metabolic syndrome with measurements of waist circumference, blood pressure, fasting lipid panel, and glucose tolerance testing.
- Thyroid dysfunction and Hyperprolactinemia:** Serum thyrotropin should be measured in women with ovulatory dysfunction, infertile women, or those with signs of thyroid disease.  
-Serum prolactin should be measured in infertile women with irregular menses or other signs and symptoms of hyperprolactinemia. (See Tips if first prolactin is elevated. above)

- **Uterine or Tubal Factors:** Refer to GYN surgeon for appropriate management.
- **Male Factor Infertility:** Ideally and for expedited management, a semen analysis (SA) is obtained prior to referral. If SA needs optimization, refer to Urologist or male reproductive medicine specialist.

## MAXIMIZING NATURAL FERTILITY:

- Encourage track cycles to identify patterns and irregularities. One good app is FEMM (Fertility Education Medical Management)
- Fertile Window:** Can be identified by using ovulation predictor kits. Can be up to 6 days from the last day of ovulation, hence, intercourse prior to ovulation is more important.
- Frequency of Intercourse:** Highest pregnancy rates achieved with intercourse every 1-2 days, although there is nearly equal rates with intercourse 2-3x/week.
- Use of lubricants:** Be mindful of sperm friendly lubricants. Avoid spermicides.

- E. Diet and Exercise: Obesity shown to impair fertility. Goal is a healthy weight.
- F. Lifestyle: Tobacco is also known to decrease fertility. Alcohol intake should be consumed in moderation and avoided completely during the luteal phase.

## ASSISTED REPRODUCTIVE TECHNOLOGY (ART)

**(IUI) Intra-Uterine Insemination:** An in-office procedure in which prepared sperm is introduced directly in the uterus via catheter at the time of ovulation. This procedure can help increase the chances of pregnancy by ensuring there is a good amount of motile sperm. Protocols vary per provider. May involve: Ovulation stimulation, trigger injections, follicle monitoring ultrasounds. At Customer Owners Expense. Cost estimate: may start at \$2000-\$2,500.

**(IVF) In-Vitro Fertilization:** More involved procedure. Entails ovulation stimulation, egg harvesting, sperm preparation. Oocytes are then fertilized outside the human body, ideally in lab by an embryologist. Identified viable fertilized Oocytes are then transplanted back in the uterus. At Customer Owners Expense. Cost estimate: may start at \$20,000.

### Summary

- Early detection, referral and optimization of co-morbidities in relation to fertility increases chances of healthy pregnancy.
- Initial work up entails evaluation of both male and female parties.
- Offer infertility evaluation to females under age 35 who have been trying to conceive for 12 months of unprotected and frequent intercourse.
- Offer earlier evaluation for women over age 35 or with a history of oligo/amenorrhea, known or suspected tubal disease, endometriosis or when the partner has known male factor infertility.
- Components of initial evaluation include history and physical examination, diagnostic tests, semen analysis, assessment of ovulatory status, assessment of ovarian reserve, determination of tubal patency.



## REFERENCES

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