## DELAYED MENSES OR SECONDARY AMENORRHEA IN PREMENOPAUSAL WOMEN

### DEFINITION
The lack of spontaneous menstruation (bleeding or spotting) for at least 3 months in premenopausal women can be a presenting complaint for many different pathological conditions, some of which have profound long term health consequences. Pregnancy must always be evaluated first. The other most common causes are PCOS, hypothalamic amenorrhea, hyperprolactinemia and ovarian insufficiency, but there is a very long differential list for amenorrhea including medical, surgical, hormonal and psychosocial causes. This protocol will suggest appropriate work-ups to identify the appropriate cause for individual women and enable targeted therapies. If the underlying problem causes unopposed estrogen, the woman needs protection from endometrial cancer. If the woman’s problem causes hypoestrogenism, the woman needs protection from osteoporosis and other menopause-related symptoms. If the problem causes unwanted infertility, that also must be addressed.

### SUBJECTIVE
Must include:
1. LMP (date, duration, flow).
2. PMP (date, duration, flow).
3. Age of menarche and history of subsequent bleeding patterns (frequency, duration and flow) matched with patient’s corresponding weight over time.
4. Medication use, including prescription, over-the-counter and recreational drugs with emphasis on drugs that could induce amenorrhea.

May include:
1. Symptoms of pregnancy.
2. Hot flashes, dry vagina, night sweats.
3. Recent changes in weight, hair loss, fatigue, depression, nervousness, and appetite.
4. Spontaneous milky nipple discharge.
5. Obesity or overweight.
7. Thyroid diseases, diabetes, change in facial appearance, history of other chronic diseases (hepatitis C, celiac disease, renal failure, sarcoidosis etc.).
8. Complaints of acne, hirsutism or balding (androgen excess or sensitivity).
9. History of prior radiation or chemotherapy.
10. Strong family history of diabetes, early ovarian failure.
11. Recent life stressors.
12. Strenuous physical activity or exercise.
13. History of PCOS.
14. History of prior testing and treatments used to treat amenorrhea.
15. Previous pelvic surgery, including ovarian surgery, D&Cs and cervical treatments.

### OBJECTIVE
Must include: Weight, height, BMI.

May include:
1. Acne on face, chest, or back.
2. Facial hair, chest hair.
3. Male or female balding pattern on scalp.
4. Thyroid enlargement or nodule.
5. Easily expressible galactorrhea bilaterally.
6. Restricted fields of vision.
7. Enlarged liver or jaundice.
8. Unusually large hands and feet.
10. Clitoromegaly.
12. Short stature, webbed neck and wide carrying angle (young women only).
OBJECTIVE (Continued)  
13. Deep tendon reflexes-slow or brisk.  

LABORATORY  
Must include negative pregnancy test if any sexual activity since LMP.

ASSESSMENT  
Secondary amenorrhea (no spotting bleeding for at least 3 months).

PLAN  
1. For long established (>1 year) history of infrequent menses (<8 menses per year) in a woman who has no previous evaluation, perform the following tests. Selected items from this list may be needed if patient partially evaluated in past or if testing needs to be updated.  
   a. TSH, total testosterone.  
   b. If any concern about galactorrhea, add Prolactin.  
   c. If hirsutism is extreme or rapidly progressing or if there are signs of virilization, also test DHEA-S, especially if testosterone levels are not elevated.  
   d. If hirsutism is a major problem in women < 25 years, add 17-hydroxy progesterone test.  
   e. If family history of diabetes or personal history of GDM, offer 2 hour GTT (preferred test) or hemoglobin A1C.  
2. For new onset of infrequent menses (<1 year) in a woman not seeking pregnancy, consider offering some of the following tests, if indicated by history and exam: TSH, prolactin and total testosterone.  
3. For women <40 years with a history of spontaneous monthly menses, who present with no bleeding or spotting for at least 3 months and complaints of vasomotor symptoms but deny use of medications that might cause loss of menses, offer FSH, LH, E2.  
4. Provide medroxyprogesterone acetate (MPA) 5-10 mg one tablet orally each day for 10-12 days.  
5. Have patient keep menstrual calendar.  
6. Treat (or refer for treatment of underlying problem(s) (e.g. hypothyroidism, prolactinoma, androgen secreting tumor, diabetes, hepatitis, obesity). Provide progestin to prevent unopposed estrogen stimulation of endometrium until that treatment is successful and spontaneous monthly menses can be documented (see below for treatment options).  
7. If anovulatory cycling is cause of secondary amenorrhea, treat according to her fertility desires.  
   a. If patient seeking pregnancy, unless medically contraindicated, provide one of the following treatments:  
      1) Cyclic MPA* (only medical contraindication is recent breast cancer). MPA* 5-10 mg daily for first 10 days of each month. This option is good for women with more infrequent menses (<4 per year)  
      2) MPA 5-10 mg daily for 10 days whenever menses delayed (>35 days since LMP). This option is good for women who have less frequent episodes of amenorrhea.  
      * NOTE: NETA can be used in place of MPA by using Aygestin 5 mg.  
   b. If patient not seeking pregnancy, select one of above therapies and provide barrier or behavioral contraception or select one of the following methods:  
      1) Provide chronic progestin therapy with one of these methods, unless patient has US MEC category 4 condition for desired method.  
         a) Progestin only birth control pill daily.  
         b) DMPA.  
         c) LNG IUS-20 mcg/24 hours or LNG IUS-13.5 mg.  
         d) Contraceptive implant.  
      2) Provide combined estrogen/progestin contraceptive therapies with one of the following options (See Combination Hormonal Contraceptive Method: Identification of Candidate and Initial Start or Restart protocol). In general, these treatment options are preferred if the patient has androgen excess symptoms.  
         a) Oral contraceptive pills daily for monthly cycling or extended cycle use.  
         b) Vaginal contraceptive rings for monthly cycling or extended cycle use (new ring every month).  
         c) Contraceptive patch for monthly cycling.  
8. For women whose secondary amenorrhea is caused by low estrogen levels, provide both estrogen
PLAN (Continued) and progestin until she normalizes.

1. Use combination hormonal contraception, (See Combination Hormonal Contraceptive Methods: Identification of Candidate and Initial Start or Restart protocol).
2. Evaluate for eating disorders and athletic triad.
3. Prescribe calcium supplements to raise daily intake to 1200mg daily until her estrogen levels rise.

PATIENT EDUCATION

1. Reinforce need for patient to return 2-3 weeks after completion of progestin-only to report withdrawal bleeding.
2. Urge patient to use barrier contraception at each act of intercourse until workup is more complete (unless she is using a contraceptive method to treat her amenorrhea.)
3. Explain that regular withdrawal bleeding is necessary to prevent later problems with endometrial hyperplasia or cancer, unless she is using a method that suppresses her endometrium.
4. Advise women with hypoestrogenism as cause of secondary amenorrhea about concerns for bone health, poor healing, dry vagina symptoms, and vasomotor symptoms. 
   a. Recommend consumption of at least 1200mg of elemental calcium daily.
5. Inform patient that the most effective treatment for secondary amenorrhea due to anovulation is lifestyle therapy, with focus on diet, exercise and stress reduction.
6. Counsel that menstrual cycling often returns for overweight/obese anovulatory women with the loss of as little as 10-15% of body weight.
   a. Tell patient that no diet is preferred for weight loss. Help her choose one that she is most likely to maintain over the long term.
7. For patients who inquire, recommend against first line use of metformin in obese women for weight loss, unless the woman has prediabetes or had gestational diabetes. Agents such an orlistat are more effective than insulin sensitizing agents in achieving weight loss.
8. Advise patients with infrequent cycles that they may face challenges conceiving, but that they should not rely on their amenorrhea to protect them from pregnancy.
9. Cognitive behavioral therapy can be very helpful for women with secondary amenorrhea.

REFER to MD/ER

1. Women with significant medical problems.
2. Women who do not respond to progestin therapy.
3. Women with hirsutism or severe acne.
4. Women who have eating disorders or other severe behavioral causes of hypoestrogenism.
5. Women who are menopausal before age 35.

REFERENCES

10. Ladson G, Dodson WC, Sweet SD, et al. The effects of metformin with lifestyle therapy in