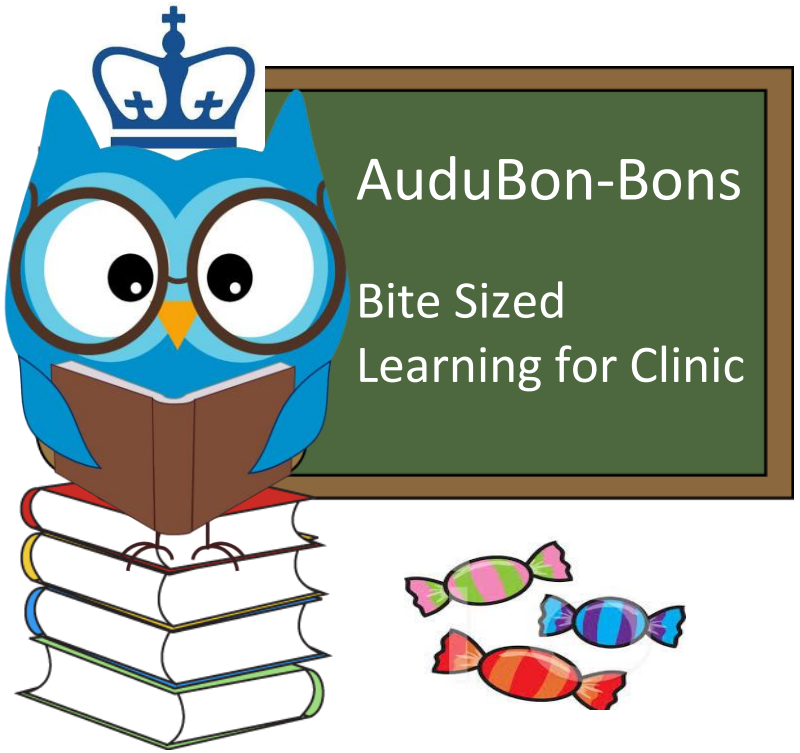
SECONDARY AMENORRHEA
PRIMARY OVARIAN INSUFFICIENCY (POI)



Week 97

Prepared by: **Hemangi P. Shukla, DO,MS**

Homework Assignment:
Podcast: Dr. Chapa's ObGyn Pearls, *"POI" in Young Women,* December 13, 2018

LEARNING OBJECTIVES

- To gain comfort describing why secondary amenorrhea should prompt an evaluation for Primary Ovarian Insufficiency (POI) and describing its pathophysiology
- To gain an understanding of other evaluations to be done once a diagnosis of POI is established
- To review the recommendations for management of symptoms and associated sequelae of POI
- To gain comfort with counseling a patient about the diagnosis and its implications

CASE VIGNETTE

- Ms. D. Or is a 30 y.o. G0P0 presents with complaints of no menses for 4 months. She had been on combined oral contraceptives for several years and discontinued them 4 months ago to conceive. Prior to initiating COCs 5 years ago, she had regular menses.

- She has been having unprotected intercourse, but is unable to use ovulation predictor kits as she is not menstruating.

FOCUSED HISTORY

- What will be pertinent in her history?
  - POB: G0
  - PGYN: LMP 4 months ago
    Menarche 15y.o./Cycle length 28-30d/Duration 3-4d
    No STIs; No known hx Cysts/Fibroids; No abnormal paps, last pap 2 years ago
    Sexual history: sexually active with 1 male partner for last 6 years; currently using no contraception
  - PMH: Denies
  - PSH: Denies
  - Meds: Multivitamin, COCs until self d/c'd 4 months ago
  - All: Shellfish - hives
  - Soc: Denies toxic habits; lives with her husband, feels safe; works as a teacher
  - FHx: No significant family history; no Gyn cancer

PERTINENT PHYSICAL EXAM FINDINGS

- What will be pertinent in her physical exam?
  - P: 80 BP: 120/70 Wgt: 58kg Hgt: 160cm BMI: 22.7
  - HEENT: Thyroid – no masses/enlargement
  - Skin No acanthosis nigricans; no hirsutism
  - Abd: soft, NT/ND
  - Pelvic: Vulva: Normal external female genitalia; Normal hair distribution on mons and labia; No clitoromegaly; No lesions
    Vagina: Healthy-appearing mucosa, No discharge
    Cervix: Nulliparous os; L/C/P
    Uterus: NT, ~8wk size, anteverted
    Adnexae: No mass/tenderness b/l
  - Ext: NT b/l

DIFFERENTIAL DIAGNOSIS

- What is your differential diagnosis?

  - Pregnancy
  - Primary ovarian insufficiency
  - PCOS
  - Hypothalamic amenorrhea
  - Thyroid disease
  - Prolactin disorder

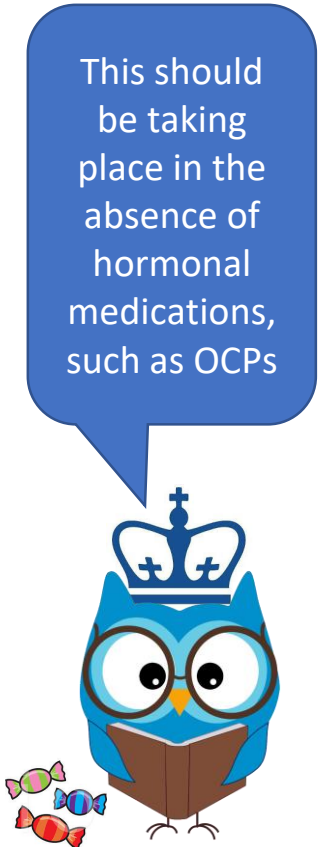
DIAGNOSTIC EVALUATION

- A pregnancy test is negative. What are the most useful initial diagnostic tests for a patients with secondary amenorrhea?

- FSH
- Estradiol
- TSH
- Prolactin

DIAGNOSIS

- **What clinical presentation should prompt an evaluation for POI?**
  - ≥3 consecutive months of lack of cycles or menstrual irregularities before the age of 40 years
- **What biochemical criteria can establish a diagnosis of POI?**
  - Follicle-stimulating hormone
    - > 30-40 mIU/mL (menopausal range)
  - Estradiol levels
    - < 50 pg/mL (hypoestrogenism)
  - 2 random tests at least 1 month apart



PATHOPHYSIOLOGY

- **What are the two major mechanisms through which POI occurs?**
  - **Follicle dysfunction**
    - Ovary still has follicles within, but normal function is prevented
  - **Follicle depletion**
    - Ovary doesn’t contain primordial follicles
      - Inadequate initial pool
      - Accelerated expenditure
      - Destruction

PATHOGENESIS

- **What are etiologies that give rise to POI?**
  - Idiopathic (90%)
  - Chromosomal abnormalities
  - Cancer therapy
    - Chemotherapy
    - Radiation
  - Fragile X Syndrome
  - Autoimmune process

EVALUATION

- **You find the patient's labs are notable for FSH of 45 and Estradiol of 30. Repeat testing in 1 month yields similar results confirming a diagnosis of POI. What further testing will you order?**

- Karyotype
  - e.g. Turner syndrome

- FMR-premutation

- Adrenal autoantibodies
  - If (+) → annual corticotropin stimulation testing

- PUS

- TSH (if not already checked) & TPO → Screen for thyroid disease every 1-2 years

- Others to consider: DM, pernicious anemia, myasthenia gravis, RA

Presence of adrenal autoimmunity confers a 50% chance of adrenal insufficiency

20% with POI of idiopathic etiology have hypothyroidism (mainly Hashimoto's)

MANAGEMENT

What are factors to consider regarding hormone replacement?

Breast development absent/incomplete

- Initiate estrogen therapy & increase slowly before graduated progesterone administration until development is complete to avoid tubular breast formation

Pubertal growth/ sexual maturity not complete

- PAG consult

Once development is complete

- Maintenance level of estrogen (100mcg daily, PO, PV, or TD) to mimic physiological range & symptom relief
- Cyclic progesterone 10-12 days/month to prevent endometrial hyperplasia/malignancy

Treatment should continue until the age of natural menopause (50-51 years old)

MANAGEMENT

Table 1. Bioequivalent Hormonal Dosages for Hormone Therapy for Primary Ovarian Insufficiency*

Estrogen	Progestogen	
	Continuous	Sequential
1–2 mg micronized 17β-estradiol (oral)	2.5–5 mg medroxyprogesterone acetate daily (oral)	10 mg medroxyprogesterone acetate daily (oral) for 12 days each month
100 micrograms 17β-estradiol (transdermal) 0.625–1.25 mg conjugated equine estrogen (oral)	100 mg micronized progesterone daily (oral)	200 mg micronized progesterone daily (oral) for 12 days each month

*Select one of the estrogen options to be combined with one of the progestogen options.

Committee Opinion No. 698. Hormone therapy in primary ovarian insufficiency. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;129:e134–41.

MANAGEMENT

- Other sequelae considerations
  - Fertility/Contraception
    - Referral to REI guided by patient
    - Fertility may persist
      - 5-10% chance of spontaneous pregnancy
      - Reliable contraception should still be discussed
  - Cardiovascular health
    - Help patients optimize CV health

Assessment
- Annual BP checks
- Q 5 year lipid levels

Prevention
- Tobacco avoidance
- Appropriate diet and exercise

  - Bone loss
    - Insufficient evidence to recommend routine screening

COUNSELING

- **How will you counsel this patient about her diagnosis?**

- Delivery of diagnosis
  - Sensitive and caring manner
  - POF should not be used
  - Be anticipatory of range of emotions

- Fertility
  - Offer psychologic counseling
  - Possibility of intermittent resumption of function

- Comorbidities
  - Risk of associated conditions
    - Cardiovascular health
    - Bone health
    - Endocrine disorders

SOCIAL DETERMINANTS OF HEALTH

Underrepresented minority women experience a delay in time to diagnosis of POI:

- Recent case series from reproductive endocrinology clinic at University Hospital in Newark, NJ showed a **6 year mean time of symptoms to diagnosis of POI**

Of 524 new patients:

19 (3.6%) diagnosed with POI

17/19 **(89.5%) Hispanic and/or Black**

This study reflects the need for a more proactive approach to oligo/amenorrhea in underrepresented minority women by improving access to care

- Decrease the delay in diagnosis
- Mitigate the impact of POI sequelae

EPIC .PHRASE

.BBonPOIWUandcounseling

Description: POI workup and counseling

The patient was counseled about the diagnosis of primary ovarian insufficiency. She was offered referral for support services to support emotional health. In addition, she was advised regarding the health risks associated with the diagnosis regarding endocrine disorders, cardiovascular health and bone health. The following will be ordered

[] TSH, TPO

[] Adrenal autoantibodies

[] Karyotype

[] FMR- premutation

[] Pelvic ultrasound

Additionally, the patient was told that although this diagnosis significantly decreases the likelihood of pregnancy, the possibility of spontaneous ovulation and conception still exists and contraception should continue to be considered to prevent undesired pregnancy.

CODING/BILLING

Diagnosis	ICD-10
Secondary Amenorrhea	N91.1
Primary Ovarian Failure	E28.3

EVIDENCE

References

- Primary ovarian insufficiency in adolescents and young women. Committee Opinion No. 605. American College of Obstetricians and Gynecologists. Obstet Gynecol 2014;123:193–7
- Nelson, L.M., 2009. Primary ovarian insufficiency. New England Journal of Medicine, 360(6), pp.606-614.
- Hormone therapy in primary ovarian insufficiency. Committee Opinion No. 698. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;129:e134–41.
- Sullivan, S.D., Sarrel, P.M. and Nelson, L.M., 2016. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. Fertility and sterility, 106(7), pp.1588-1599.
- Webber, L., Davies, M., Anderson, R., Bartlett, J., Braat, D., Cartwright, B., Cifkova, R., de Muinck Keizer-Schrama, S., Hogervorst, E., Janse, F. and Liao, L., 2016. European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI. ESHRE Guideline: management of women with premature ovarian insufficiency. Hum Reprod, 31(5), pp.926-37
- Bhatt, S.J., O'Besso, V.S., Douglas, N.C., Mcgovern, P., Loughlin, J. and Morelli, S.S., 2019. Prolonged time to diagnosis of primary ovarian insufficiency (POI) in an urban reproductive endocrinology (RE clinic. Fertility and Sterility, 112(3), p.e354.