OPIOID-INDUCED AMENORRHEA – EXPLORING THE IMPACT OF CHRONIC OPIOID USE ON REPRODUCTIVE HEALTH

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DISCLOSURES

- No disclosures or conflicts of interest to report.

LEARNING OBJECTIVES

- Discuss history-taking for amenorrhea/oligomenorrhea in patients with chronic opioid use
- Explain the role of chronic opioids in the hypothalamic-pituitary axes and recall diagnostic investigations for evaluating secondary amenorrhea
- Discuss the management of secondary amenorrhea in patients with chronic opioid use

HISTORY OF PRESENT ILLNESS

- **46F, pseudonym Maria**
- **Chief complaint: irregular menstrual cycles since starting SL buprenorphine**
  - Amenorrhea following buprenorphine initiation (6 months post-initiation of buprenorphine, still no period).
  - Denied perimenopausal symptoms
  - Lower abdominal bloating/discomfort intermittently.
  - Denied abnormal vaginal discharge, denied nipple discharge.
  - Denied dietary changes, eats wide range of food, no excessive exercise (BMI 23).
  - No acne, or hirsutism, but endorsed hair loss.

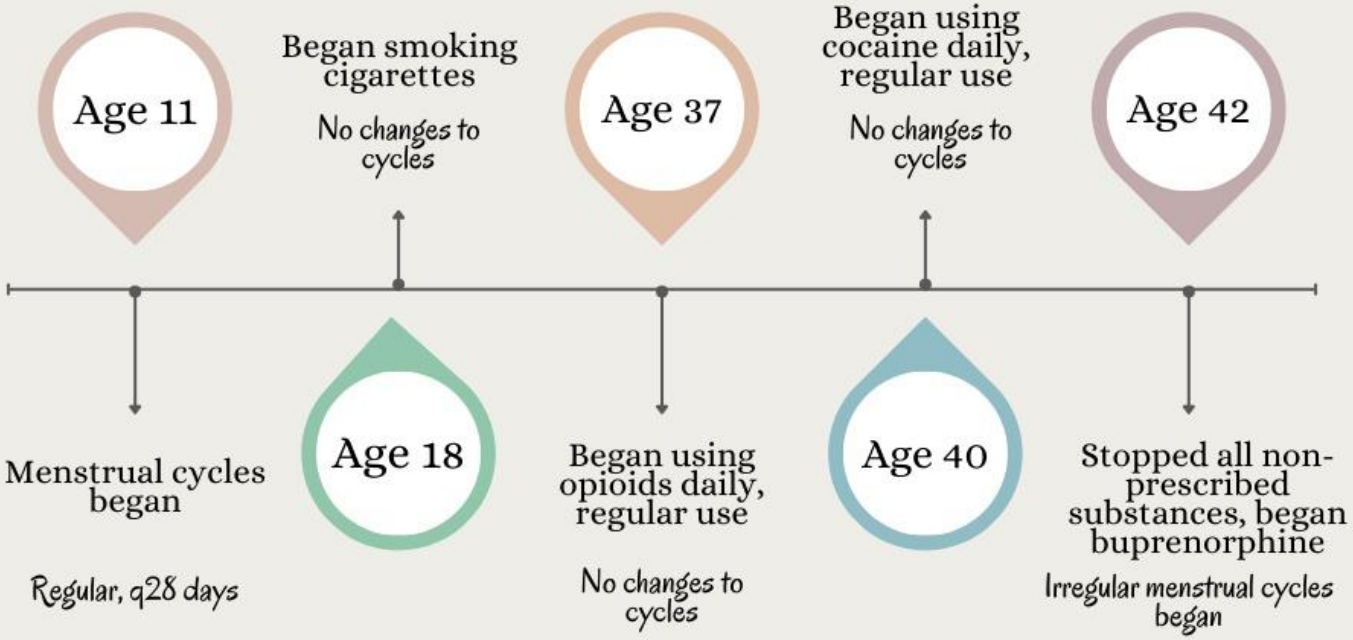
PAST MEDICAL HISTORY/SOCIAL HISTORY

- **PMHx:** deviated septum, carpal tunnel
- **Pregnancy Hx:** G3P0A3 (all therapeutic abortions, required D+C for one of them)
- **Social Hx:** from MA, Bachelor's degree; supportive close family; short term of incarceration in past few years
- **Race/Ethnicity:** Black, African American
- **Sexual Hx:** no current partner, last sexual encounter 2 years prior to jail
- **Pertinent Fam Hx:** menopause in 50's for all direct female family members, no breast cancer
- **Medications at initial visit:**
  - Buprenorphine-naloxone films 8mg, 8mg, 8mg (total 24mg) per day
  - Prior had been on oral combined contraceptive medications and depo-provera injections, but nothing in the last few years

SUBSTANCE USE HISTORY AND TREATMENT

- **Substance Use History:**
  - **Moderate Nicotine Use Disorder** – smokes 5 cigarettes/day, started at age 18
  - **Severe Opioid Use Disorder In Remission** – began use at age 37, used heroin (intranasal) and oral Percocets, last use 4 years ago.
  - **Severe Cocaine** Use Disorder In Remission – started at age 40, intranasal use, multiple times a day, last use 2019
- **Treatment History:**
  - Went to jail in 2019 for 3 months, there was started on buprenorphine 4mg →12mg
  - Connected to OBAT in Boston, titrated to 24mg
  - No trials of methadone or naltrexone.
- No other substances, alcohol only occasionally.
- No known or documented history of overdose.

Menstrual Cycle History with Substance Use History



DEFINITIONS

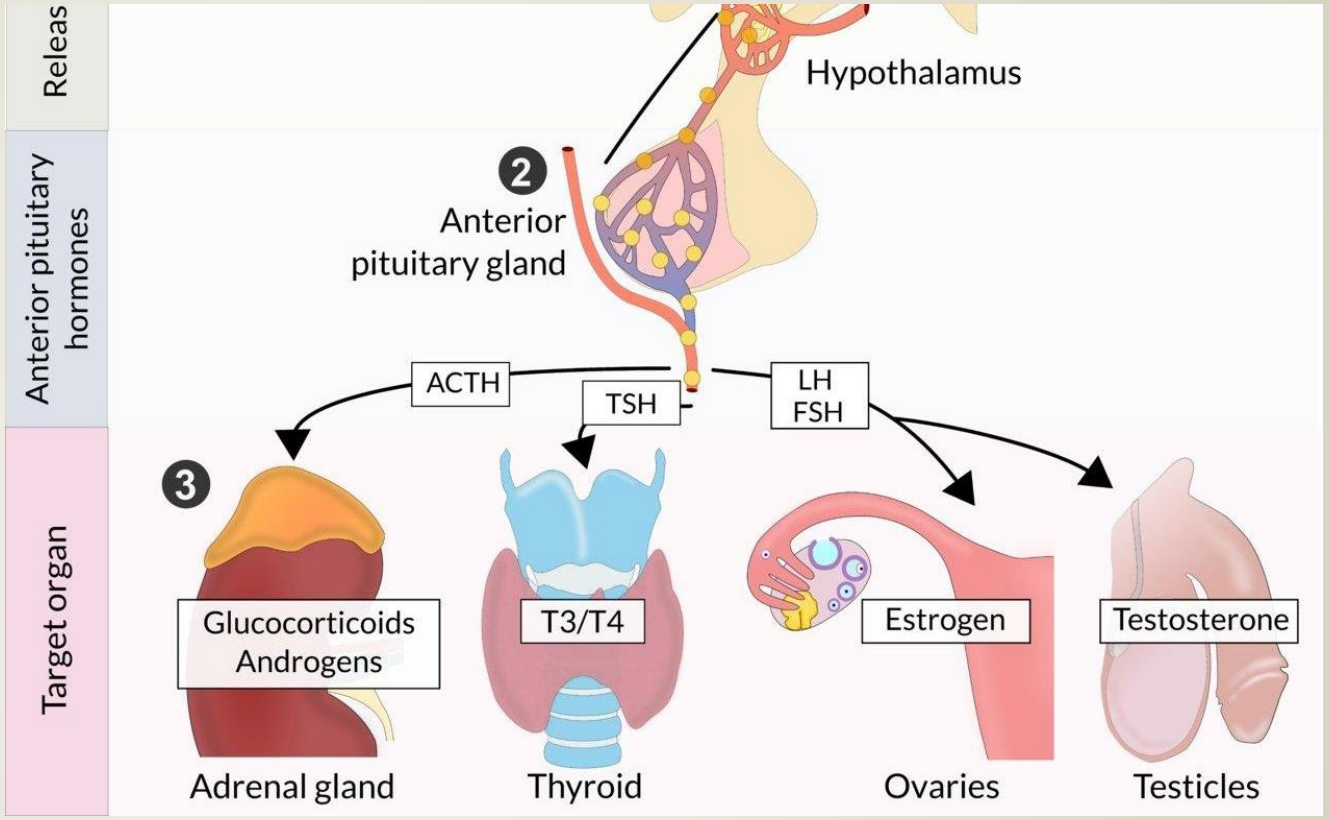
- **Secondary Amenorrhea:**
  - Absence of three or more periods in a row by someone who has had periods in the past.
- **Secondary Oligomenorrhea:**
  - Infrequent menstrual periods (fewer than six to eight periods per year) in someone who has had periods in the past.

Ref: UpToDate

HISTORY TAKING FOR SECONDARY AMENORRHEA/OLIGOMENORRHEA

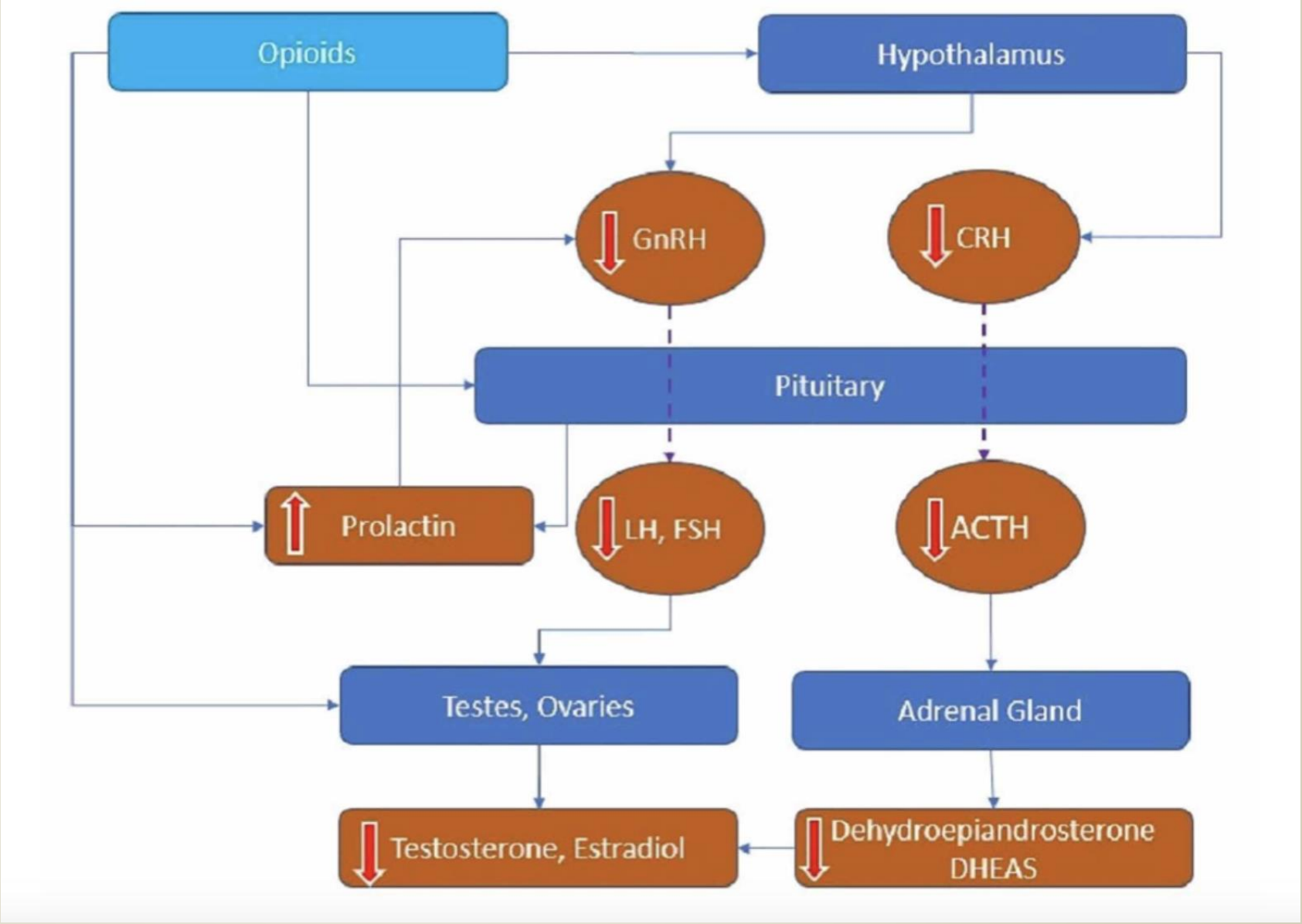
Endocrinopathy history	Reproductive/gynecologic history	Medications
• Stress • Changes to eating habits (restriction) • Excessive exercise • Headaches, visual field defects, fatigue, polyuria, polydipsia • Galactorrhea	• Menstrual history (age of onset, cycle length, what is "normal" for them) • Rule out pregnancy • Hirsutism, acne, history of irregular menses • Perimenopausal symptoms (hot flashes, vaginal dryness, decreased libido, poor sleep, etc) • Any history of obstetrical trauma, severe bleeding, D+C or endometritis or other infection that might have caused endometrial scarring	• Oral contraceptives • Metoclopramide • Anti-psychotics • Androgenic drugs like danazol or high dose progestin • Chronic opioid use

ENDOCRINE PATHWAYS



Ref: https://www.insidemedicine.co.uk/learning/basic-physiology-hypothalamic-pituitary-end-organ-axis

OPIOIDS AND THE HP-AXIS



WORKUP FOR AMENORRHEA/OLIGOMENORRHEA

- TSH – 2.51, FSH – 5.2, estradiol - 64, prolactin 12.1, serum T 13.1
- TVUS completed – normal
- Mammogram completed – normal
- Pap test completed – normal

Next steps:
- Referral to Obstetrics/Gynecology

CONSULT WITH OBSTETRICS-GYNECOLOGY

- Repeated labs, all normal again, not even in perimenopausal range
- No changes to health otherwise during all investigations over 2 years

DIAGNOSIS: functional hypothalamic amenorrhea secondary to opioid therapy

CONSULT WITH OBSTETRICS-GYNECOLOGY

- **Treatment options:** reduce dose of buprenorphine or trial of cyclical hormone therapy to induce menses.
- **Recommendations:** repeat labs again (third time), with repeat TVUS and possible endometrial biopsy and r/o other endocrine causes of amenorrhea/oligomenorrhea. No further medication recommendations.

NALTREXONE AS A TREATMENT OPTION

- Treatment can induce a normalization of the menstrual cycle and even successful pregnancies
- Resulted in an increase in the frequency/amplitude of gonadotropin pulses secondary to an increase in hypothalamic pulsatile GnRH secretion
- Naltrexone has also been shown to be effective for inducing ovulation and pregnancy in a patient with hyperprolactinemia who was resistant to dopamine agonist treatment
- Pilot studies administering 50 mg daily naltrexone to women with PCOS and insulin resistance showed a dramatic decline in insulin levels after 3–7 weeks of treatment

(Böttcher et al 2017)

STRUCTURAL BARRIERS & HEALTH INEQUITIES

- **Patient is Black/African-American**
  - Black women in the US are more than 3x more likely to experience a pregnancy-related death than White women
  - Black women suffer disproportionately more morbidity and mortality rates from cervical, endometrial, and ovarian cancers with worse overall survival in all major gynecological malignancies compared with White women
  - Black women experience a higher incidence of infertility (Wellons et al 2008), and lower odds of achieving pregnancy, and live birth through assisted reproductive technology

(Creanga et al 2017, Temkin et al 2018, Humphries et al 2016)

STRUCTURAL BARRIERS & HEALTH INEQUITIES

- National surveys demonstrate Black and LatinX people who menstruate (PWM) have younger menarche and earlier ages at menopause
- Black and LatinX PWM have longer and more varied cycle lengths than White PWM
- The differences in age at menarche and menopause and cycle regularity are important because these characteristics are associated with chronic diseases like endometriosis, polycystic ovary syndrome, breast cancer, and cardiovascular disease, thus, exacerbating existing health disparities

(National Health Statistics Reports, Number 146, September 10, 2020, 2020; Srikanth et al., 2023; Appiah et al., 2021, Boston & Ma 02115, 2022; Blanken et al., 2022; Golub et al., 2008; Titus-Ernstoff et al., 1998)

CURRENT UPDATES ON MARIA

- I personally met this patient in 2023 (now age 46), right after repeat testing/imaging was completed.
- Again, transvaginal and abdominal ultrasound normal, with normal labs.
- Continues to have some abdominal bloating/cramping, sensitivity (pre-menstrual symptoms) intermittently but no period.
- Patient has tried to decrease dose of buprenorphine and is at 20mg (initially at 24mg when starting in the program), however this has been difficult for her with cravings – risk/benefits discussion.

TAKE HOME POINTS

- Chronic opioid use including MOUD can have significant side effects on patients.
- Periodic evaluation of the hypothalamic-pituitary axes is advised for patients who are taking chronic opioids.
- The availability of antagonists such as naltrexone provide a possible treatment option and should be considered.
- Ensure a patient-centered approach, that aligns treatment/care with patient goals and priorities.

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