HYPER-PROLACTINEMIA

SANDERS 3.24.15

Learning Objectives

- To understand the physiologic role of prolactin
- To understand the clinical presentation and physiologic/ pathologic causes of hyperprolactinemia
- To discuss how hyperprolactinemia relates to amenorrhea and oligomenorrhea
- Prerequisites
  - None
- See also – for closely related topics
  - Primary amenorrhea
  - Secondary amenorrhea
  - Oligomenorrhea

FUNCTION OF PROLACTIN

- Prolactin is a peptide hormone secreted from the anterior pituitary in pulsatile fashion
  - Highest levels at night and decreased during the day
- Also secreted by decidual and endometrial tissue, and the chorion during pregnancy
- Normal range in non-pregnant women: 0-20 ng/mL
- Prolactin release is STIMULATED by serotonin & thyroid releasing hormone (TRH)
- Prolactin release is INHIBITED by dopamine

FUNCTION OF PROLACTIN

- Known for its role in lactogenesis
  - Stimulation of the nipple from the baby results in down stream signaling to hypothalamus and anterior pituitary to release prolactin
  - While prolactin promotes the milk production, oxytocin, released from the posterior pituitary, promotes milk let down
- However, if elevated outside of pregnancy, it can produce some undesirable symptoms

SYMPTOMS OF HYPER-P

- An increase in prolactin can lead to symptoms of galactorrhea AND/OR gynecomastia
- Further, an increase in prolactin inhibits GnRH → ↓ in gonadotropin (LH and FSH) release which can then lead to abnormal menses, amenorrhea, infertility, hot flashes, vaginal dryness, decreased libido, or decreased bone density
- If a pituitary adenoma is the cause, it can lead to headache and visual changes

PHYSIOLOGIC CAUSES OF HYPER-P

- PREGNANCY
  - The high estrogen state of pregnancy promotes hyperplasia of the lactotroph cells in the anterior pituitary → an ↑ in prolactin
  - Prolactin reaches peak at delivery, and by 6 weeks post-partum, prolactin levels return to normal (even in a breastfeeding mother)
- Notably, the amount of estrogen in contraceptive modalities does not lead to elevated prolactin

PHYSIOLOGIC CAUSES OF HYPER-P

- There are both physiologic and pathologic causes. Some physiologic causes include:
  - PHYSICAL and MENTAL STRESS
  - EXERCISE (especially in the situation of a poorly-fitted bra causing nipple stimulation)
  - SEXUAL INTERCOURSE (…with nipple stimulation)
- These physiologic stimuli will rarely raise prolactin to more than ~30-40 ng/mL, however PREGNANCY can increase the prolactin level to 35-600 ng/mL

PATHOLOGIC CAUSES OF HYPER-P

Three broad pathologic categories:

1) OVERPRODUCTION OF PROLACTIN

Ex. Lactotroph adenoma = Prolactinoma

2) DECREASED INHIBITION OF PROLACTIN SECRETION BY DOPAMINE

3) DECREASED CLEARANCE OF PROLACTIN

OVERPRODUCTION OF PROLACTIN

- PROLACTINOMA
  - Benign tumor of anterior pituitary lactotroph cells
  - Serum prolactin can range from 40 ng/ml to 50,000 ng/mL
  - More common in women than men, usually aged 20-40 years
  - Usually sporadic but may be associated with multiple endocrine neoplasia type 1 syndrome (MEN1)[2]

DECREASED INHIBITION OF PROLACTIN SECRETION

- Dopamine normally inhibits the release of prolactin through negative feedback, thus, less dopamine → increase in serum prolactin
- Three main causes of reduction of dopamine:
  - USE OF PHARMACOLOGIC AGENTS THAT BLOCK DOPAMINE RECEPTORS (classic = antipsychotics)
  - DAMAGE TO THE HYPOTHALAMUS (specifically the dopaminergic neurons)
  - LESION AT THE INFUNDIBULUM (pituitary stalk)

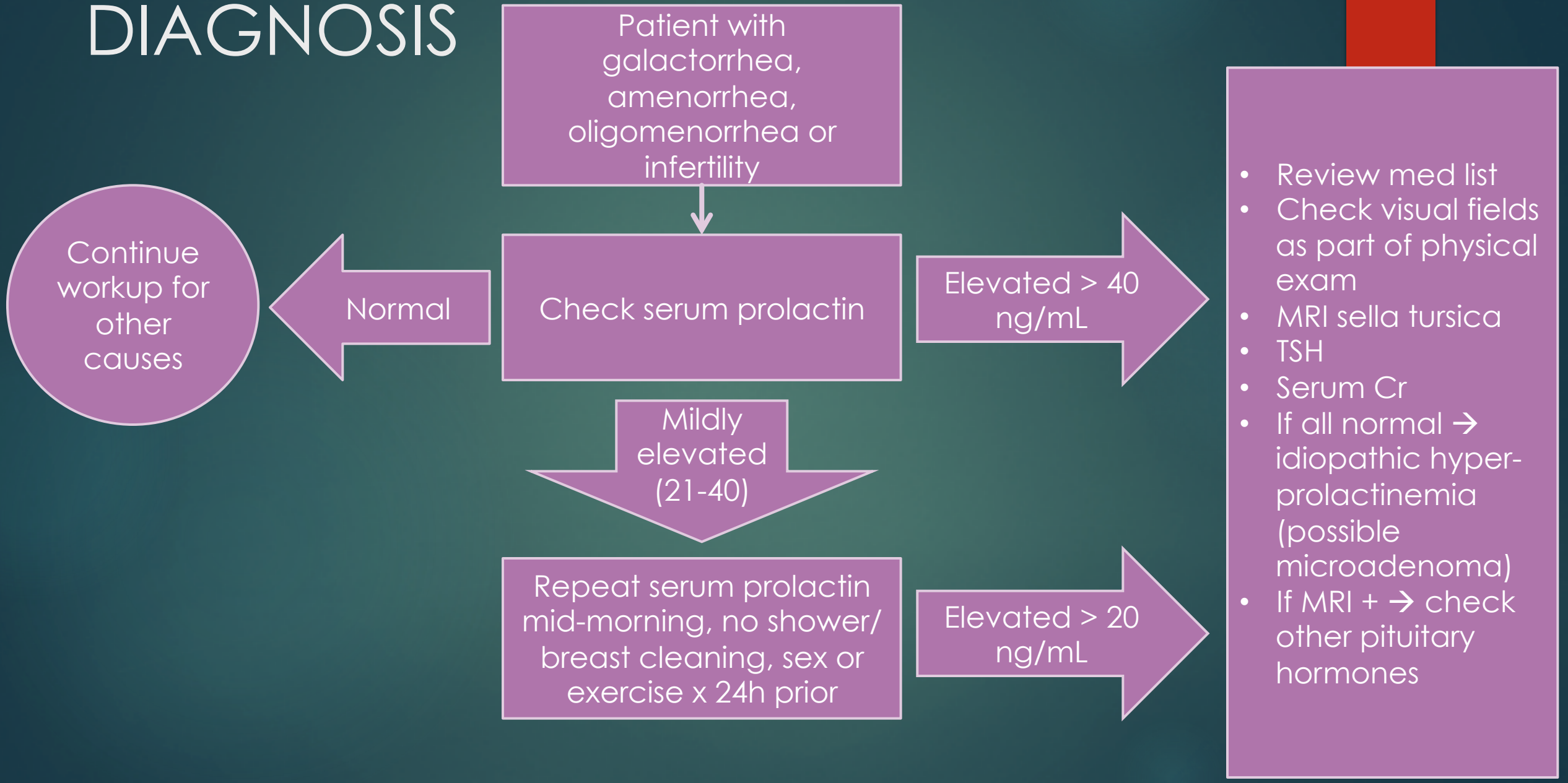
PHARMA CAUSES OF HYPER-P

- Some antipsychotics and gastric motility agents can increase prolactin by antagonizing D2 receptors. Examples include:
  - Risperidone, atypical antipsychotic[1]
  - Haloperidol, typical antipsychotic[1]
  - Metoclopramide, gastric motility agent[3]
- Some anti-hypertensives increase prolactin in other ways
  - Methyldopa – inhibits dopamine synthesis
  - Reserpine - inhibits dopamine storage
  - Verapamil – not well understood; specific to this medication

OTHER CAUSES OF HYPER-P

- Hypothyroidism
  - Remember that thyrotropin releasing hormone (TRH), is reflexively increased in hypothyroidism, which stimulates prolactin release from the lactotrophs[1]
  - Prolactin levels are normal in most patients with hypothyroidism[2], and for the patients who do have elevated prolactin, the levels will return to normal with treatment of the hypothyroidism[3]
- Chronic renal failure, chest wall injury, genetic mutation, autoimmune, idiopathic

DIAGNOSIS


Patient with galactorrhea, amenorrhea, oligomenorrhea or infertility
Check serum prolactin
Normal
Continue workup for other causes
Elevated > 40 ng/mL
Mildly elevated (21-40)
Repeat serum prolactin mid-morning, no shower/ breast cleaning, sex or exercise x 24h prior
Elevated > 20 ng/mL
• Review med list
• Check visual fields as part of physical exam
• MRI sella tursica
• TSH
• Serum Cr
• If all normal → idiopathic hyper-prolactinemia (possible microadenoma)
• If MRI + → check other pituitary hormones

TREATMENT

- If symptomatic, discontinue the offending drug OR start treatment with dopamine agonists
  - Cabergoline (first line) – ergot dopamine agonist
  - Bromocriptine – ergot, associated with ↑ nausea
  - Pergolide – ergot, associated with ↑ in valvular heart disease (higher than the other two)
- For prolactinomas, if medical mgmt fails or adenoma is large/ symptomatic → transsphenoidal surgery +/- radiation
- OCPs PRN cycle control or hypogonadism
- Continue meds while trying to conceive, stop with + pregnancy test

SOURCES

- Uptodate.com “Causes of Hyperprolactinemia” 2/2015
- Uptodate.com “Clinical manifestations and evaluation of hyperprolactinemia” 2/2015
- Uptodate.com “Treatment of hyperprolactinemia due to lactotroph adenoma and other causes” 2/2015

OTHER SOURCES

- Rock JA, Jones HW. Te Linde's Operative Gynecology.
- Tyson JE, Hwang P, Guyda H, Friesen HG. Am J Obstet Gynecology. 1972.
- Kleinber DL, Noel GL, Frantz AG. N Engl J Med. 1977.
- Prosser et al 1979: PUBMED ID 37794
- David DR, Taylor CC, Kinon BK, Breier A. Clin Ther. 2000.
- Rivera JK, Lal S, Ettigi P, Hontela S, Muller HF, Friesen HG. Clin Endocrinology. 1976.
- McCallum RW, Sowers JR, Hershman JM, Studrvant RA. J Clin Endocrin Metab. 1976.
- Sowers JR, Sharp B, McCallum RW. J Clin Endocrin Metab. 1982
- Kleinberg DL, Noel GL, Frantz AG. N Engl J Med. 1977.
- Honbo KS, van Herle AJ, Kellett KA. Am J Med. 1978.
- Grubb MR, Chakeres D, Malarkey WB. Am J Med. 1987.