

Evaluation of the Patient with Menstrual Irregularities

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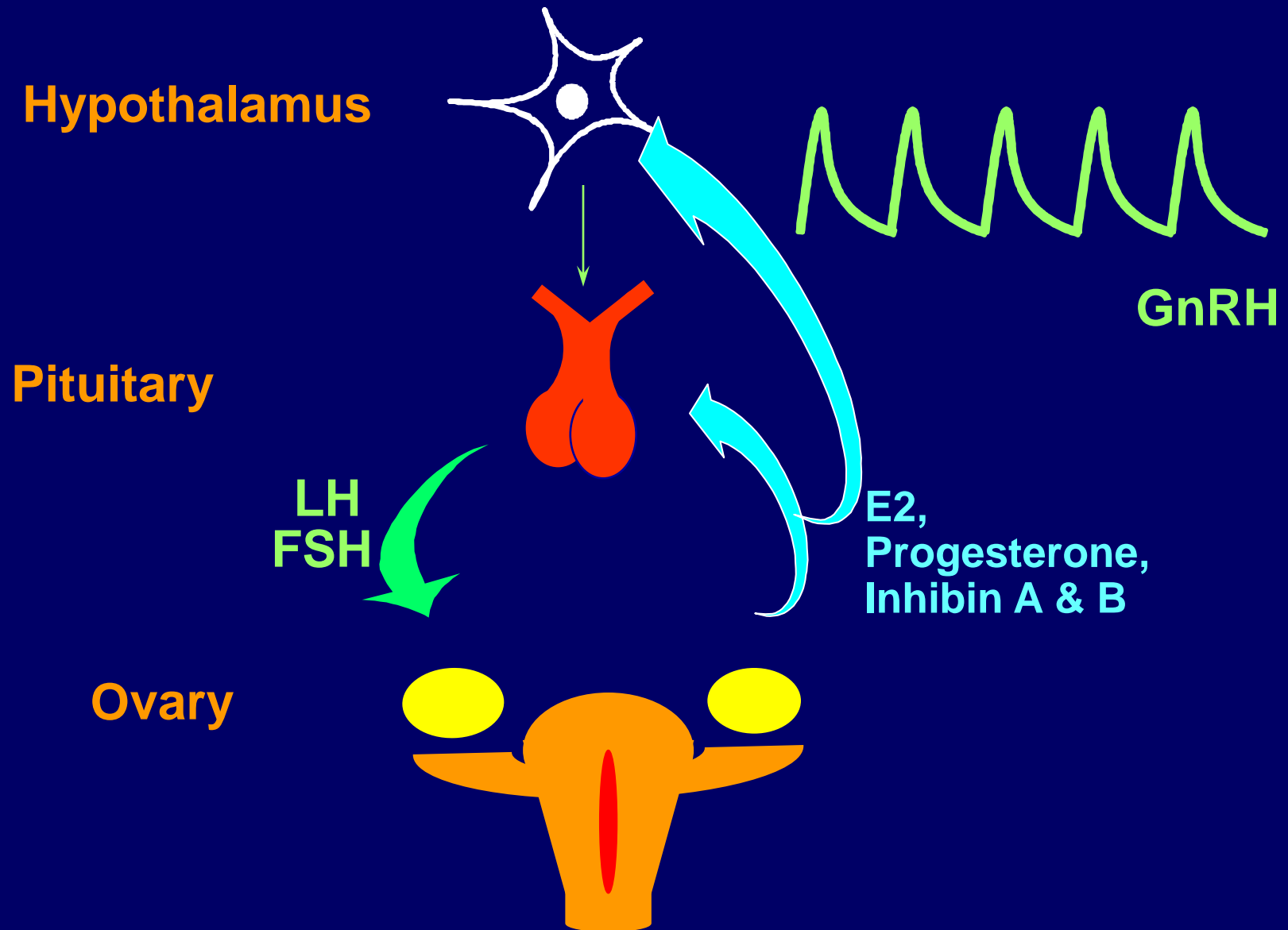
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 - Clinical focus: Primary Care & Endocrinology
 - Research focus: Medical Education

I have no conflicts of interest to report.

Objectives

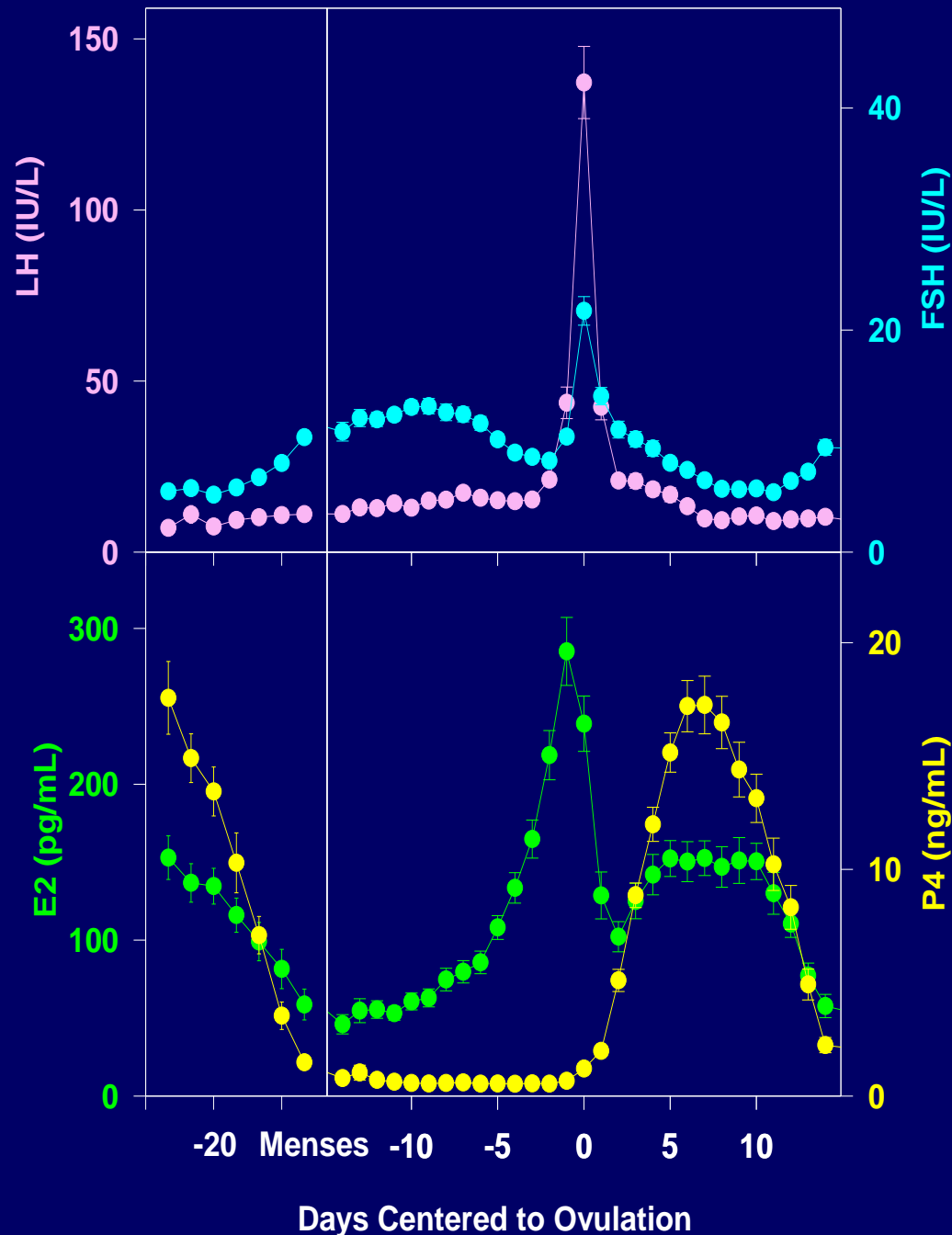
- Use case vignettes to highlight challenges in:
 - Evaluation of amenorrhea and irregular menses
 - Management of common etiologies of amenorrhea and irregular menses

Female Hypothalamic-Pituitary-Gonadal Axis



Hormone Secretion in the Normal Menstrual Cycle

Length 25-35 days
Luteal phase 12-14 days
Follicular phase variable



Case #1: History

- 19 year old woman presents to your clinic for evaluation because she has had no menses for 8 months.
- Her menarche was at age 13, and she had regular menses until 8 months ago.
- About one year ago, she increased her aerobic exercise with a 20 lb weight loss.

Case #1: History

- She has not had any headaches, vision changes, hot flushes, or night sweats.
- She has no history of an eating disorder.
- Her thyroid review of systems are negative.

Case #1: Physical Exam

- BMI 18 BP 100/60 P60
- Skin with no hirsutism, acne, or alopecia.
- Visual fields full.
- Thyroid size is normal. No nodules.
- No galactorrhea.
- Pelvic exam normal.

**What is her diagnosis and
what labs would you order?**

Amenorrhea

- Primary Amenorrhea
 - Absence of menses by age 16
- Secondary Amenorrhea
 - Absence of menses for 3 months

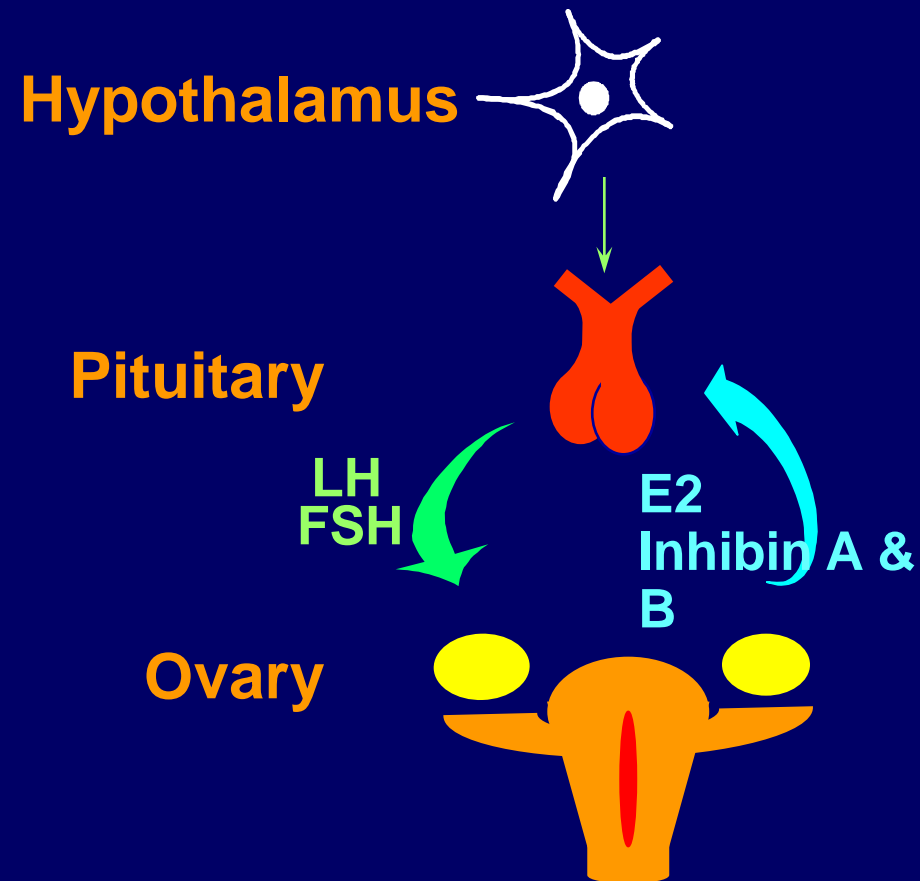
Pathophysiologic considerations are the same for both.

Incidence of genetic & anatomic abnormalities higher with primary amenorrhea.

Etiologies

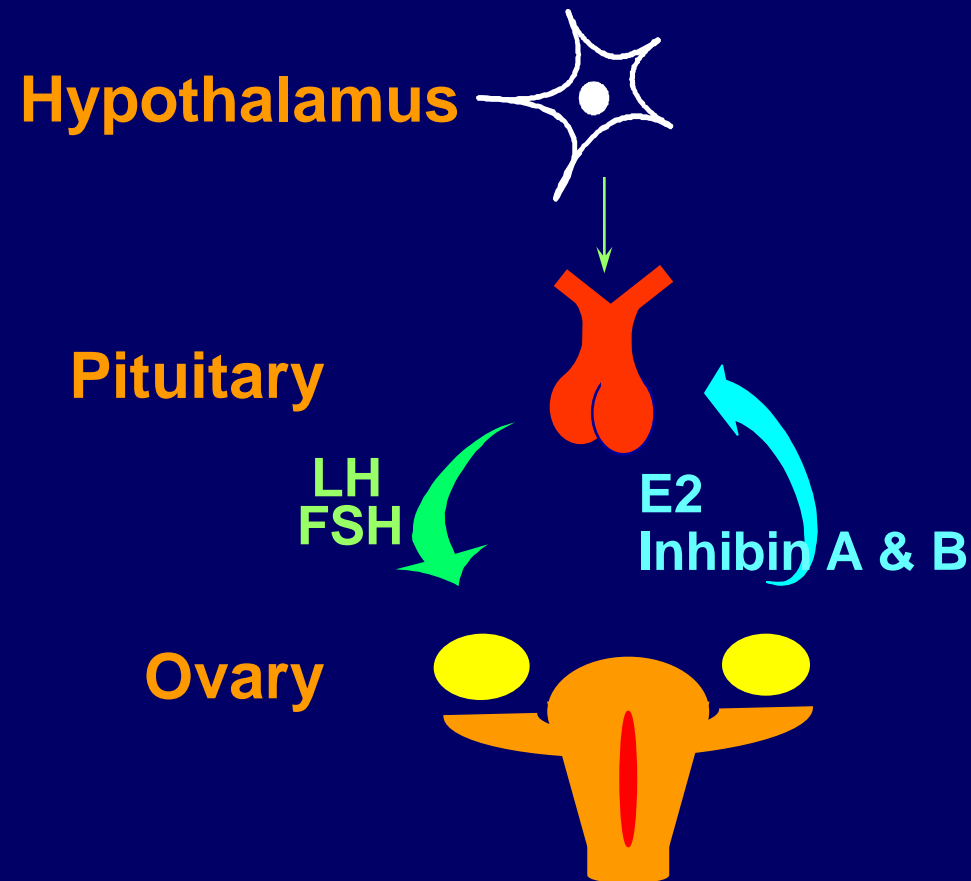
- Pregnancy
- Uterine or Outflow Tract Disorders
- Ovulatory Disorders

Causes of Primary Amenorrhea



- Hypothalamus 27%
- Pituitary 2%
- PCOS 7%
- Ovary 43%
- Uterus/Outflow Tract 19%

Causes of Secondary Amenorrhea



- Hypothalamus 36%
- Pituitary 15%
- PCOS 30%
- Ovary 12%
- Uterus/Outflow Tract 7%

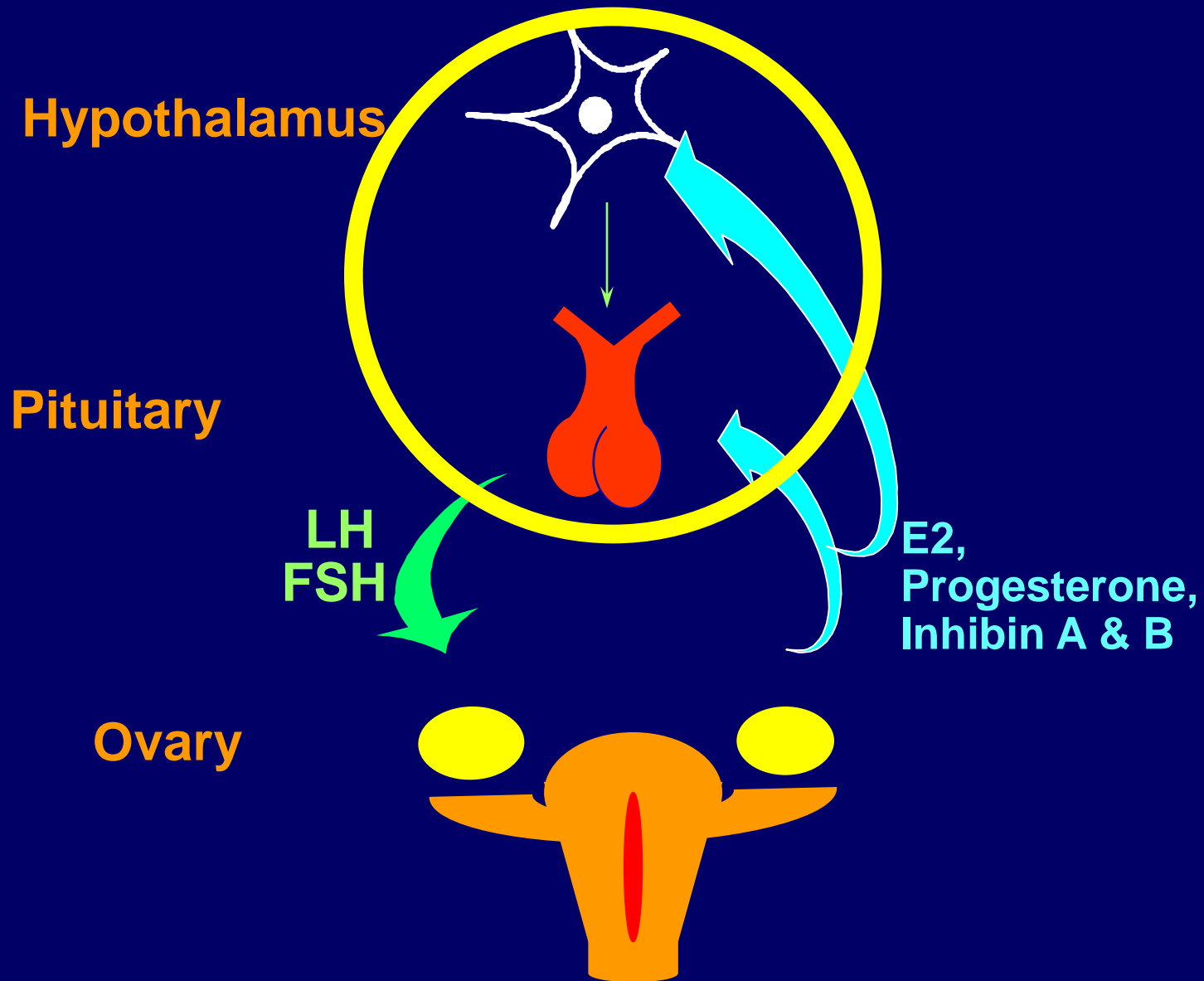
Diagnostic Lab Evaluation

- β hCG (rule out pregnancy!)
- FSH and estradiol (tests for ovarian insufficiency)
- Prolactin
- TSH

Case #1: Labs

- FSH 3.2 IU/L
 - Estradiol 20 pg/ml
 - Prolactin 6.3 ng/mL
 - TSH 2.6 μ U/mL
 - β hCG neg
-
- Medroxyprogesterone challenge was negative for a withdrawal bleed.

What is her diagnosis?



Hypothalamic & Pituitary Etiologies

- Hypothalamic Amenorrhea (HA)
- Hyperprolactinemia
- Tumors and Destructive/Infiltrative Lesions
- Genetic: IHH, Kallmann syndrome
- Cranial Irradiation
- Others: hypo- or hyperthyroidism, excess cortisol
- Pituitary tumor (mass effect)
- Lymphocytic hypophysitis
- Pituitary infarction
- Empty-sella syndrome

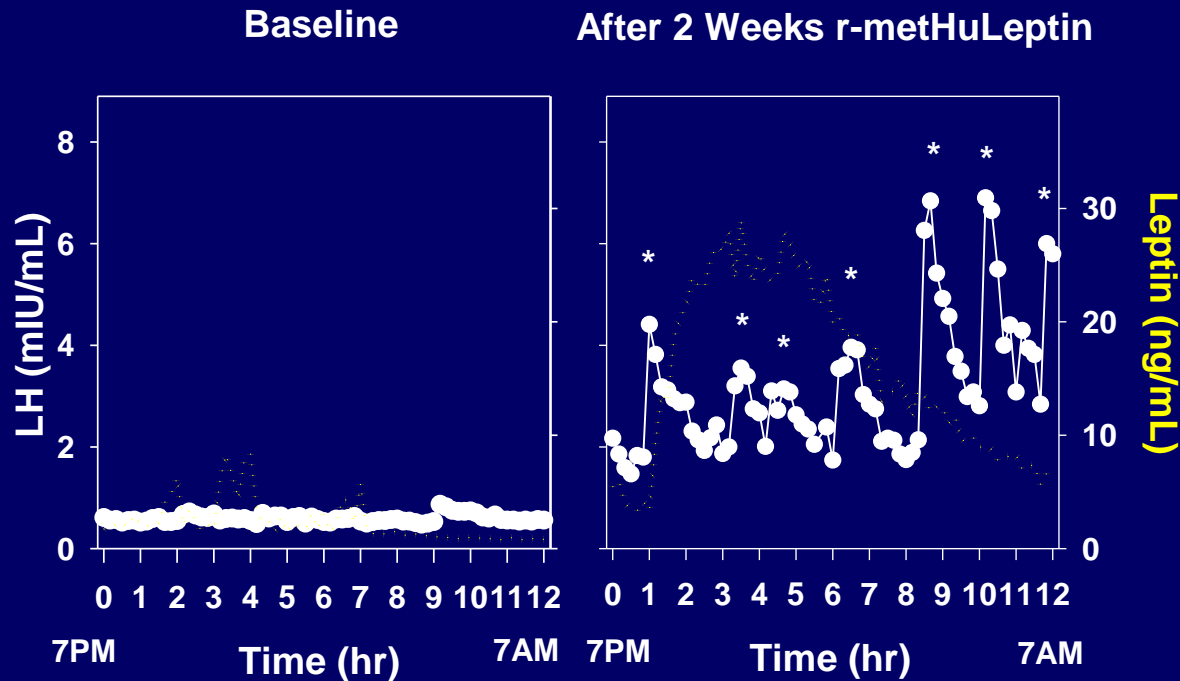
Hypothalamic Amenorrhea

- Etiology
 - Energy Output > Energy Input
 - Weight loss
 - Eating Disorders
 - Excessive exercise
 - Stress
 - Psychological
 - Physical

Hypothalamic Amenorrhea

- Leptin

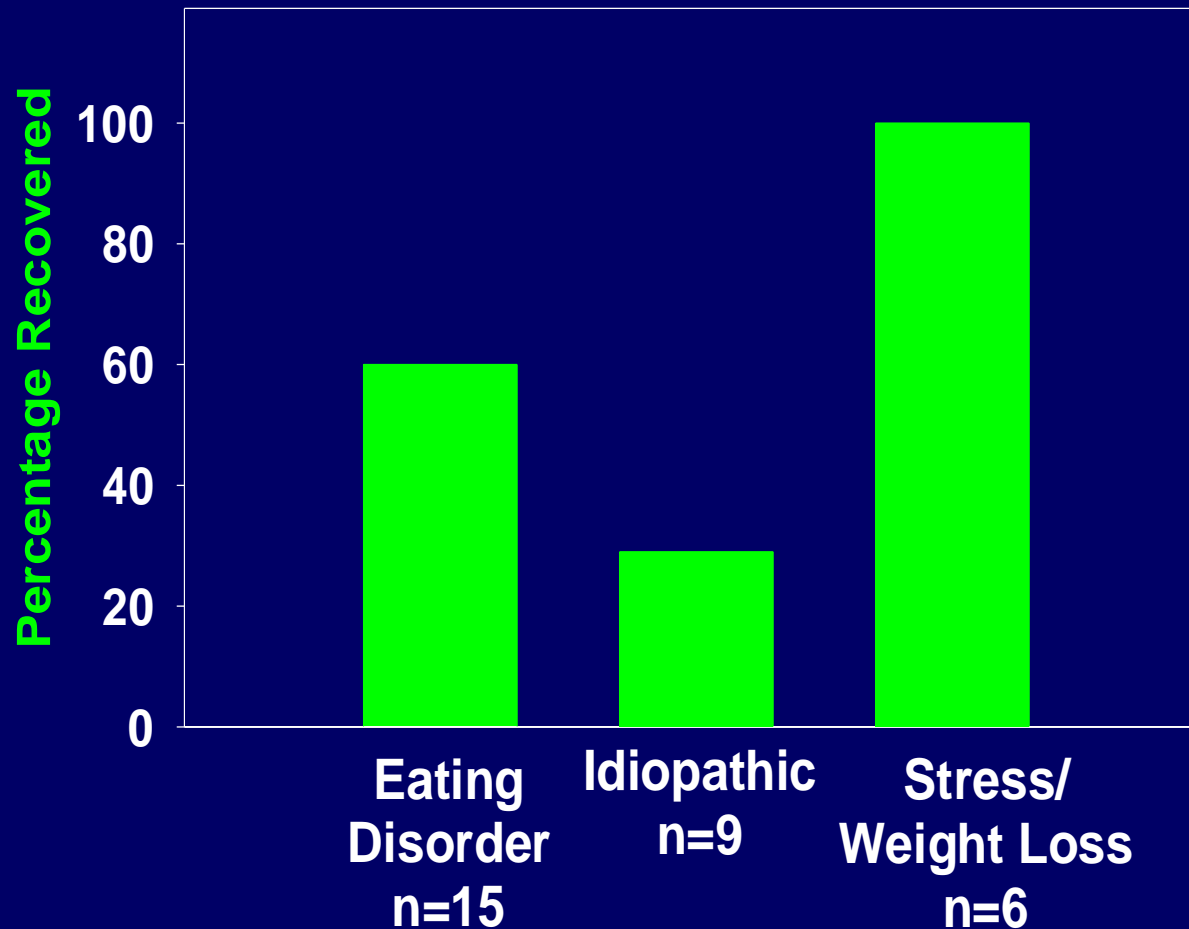
Peripheral signal indicating sufficient energy stores for reproduction.



Management Questions

- Does this patient need a MRI?
 - Headaches or neurological symptoms
 - Elevated prolactin
 - History unclear
 - Primary amenorrhea
- How about a Bone Mineral Density Scan?
 - amenorrhea >6 months

Hypothalamic Amenorrhea: Recovery



(Perkins et al., 2001)

Hypothalamic Amenorrhea: Treatment

- Weight gain, decrease exercise
- Hormone replacement therapy or oral contraceptives
- Calcium and Vitamin D

Case #2

- 27 yo with 3 months amenorrhea
- Moderate exercise, no eating disorders
- Insomnia
- No hirsutism, mild acne
- History of hypothyroidism on thyroid hormone replacement

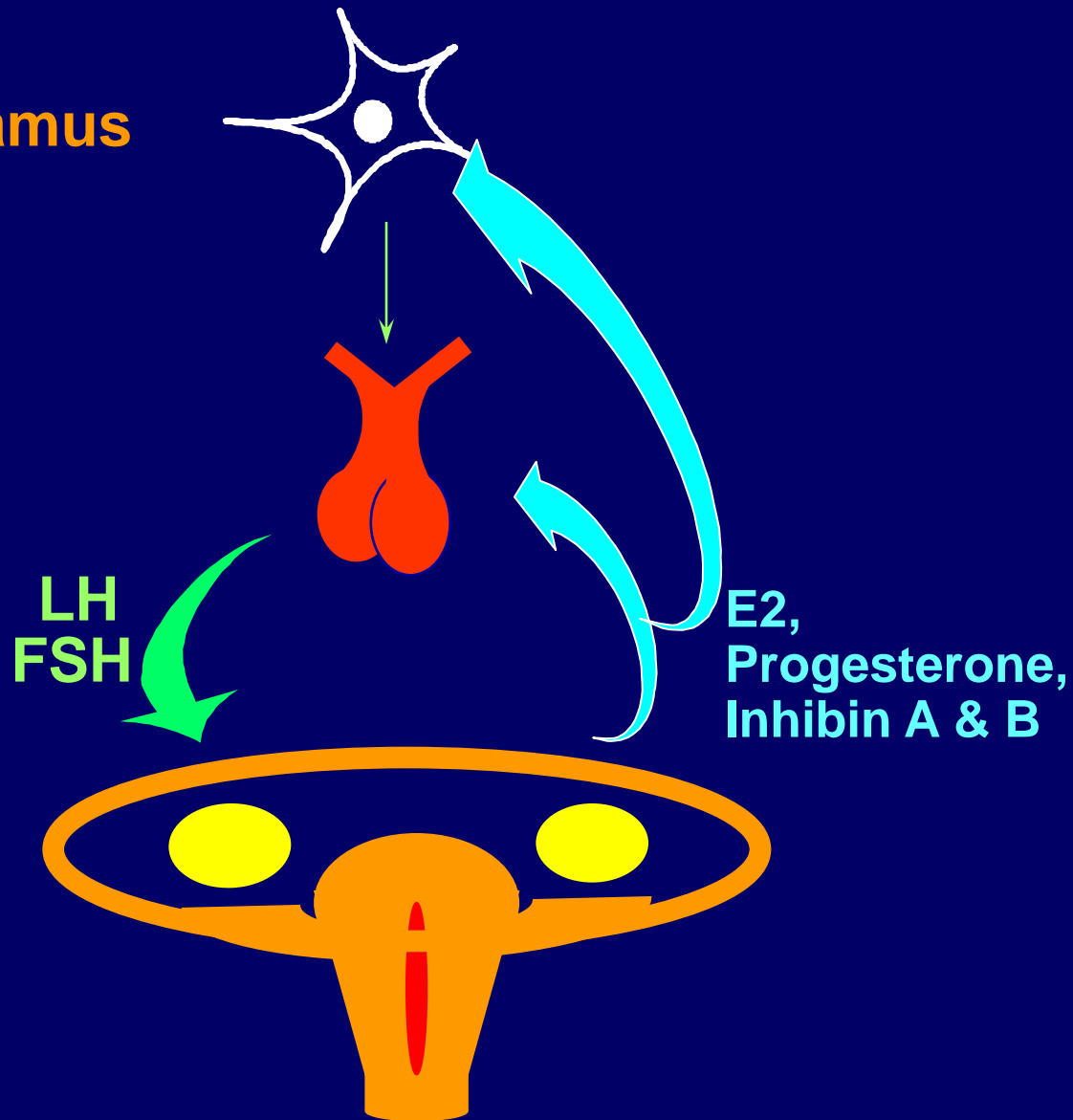
Case #2

- Family history of early menopause
- Physical exam unremarkable
- Labs:
 - FSH 56 IU/L, TSH 3.7 μ U/mL, neg β hCG, prl 10.8 ng/mL
- Diagnosis?
- Further workup?

Hypothalamus

Pituitary

Ovary



Primary Ovarian Insufficiency

- Elevated FSH, age < 40 yrs
- Repeat testing important: follicular phase
- Causes:
 - Turner's syndrome
 - X chromosome deletions, translocations
 - Fragile X premutations
 - Autoimmune
 - Chemotherapy or radiation therapy
 - Galactosemia, FSH/LH receptor mutations, blepharophimosis, BMP 15 mutations

Primary Ovarian Insufficiency: Diagnostic Tests

- Karyotype
 - Age <30 yrs, familial cases, ?everyone
 - Turner's features
- Fragile X Premutation screen
- Anti-thyroid and anti-adrenal antibodies
- Anti-ovarian antibodies poor test
- Ovarian biopsy is not helpful

Primary Ovarian Insufficiency: Treatment

- Oral contraceptive pills or hormone replacement therapy
- Calcium and vitamin D

Case #3: History

- 28 year old woman presents to your clinic for evaluation of irregular menses
- She describes irregular menses since age of menarche which was at 14 years of age
- She has also had problems with increased hair growth on her upper lip and chin

Case #3: History

- She does not have hot flashes, night sweats, galactorrhea, or positive thyroid review of systems
- She is on no meds currently and has a family history of type 2 diabetes.

Case #3: Physical Exam

- BMI of 29
- Skin with hirsutism of the upper lip, chin, and sides of her face. No acanthosis.
- No clitoromegaly.

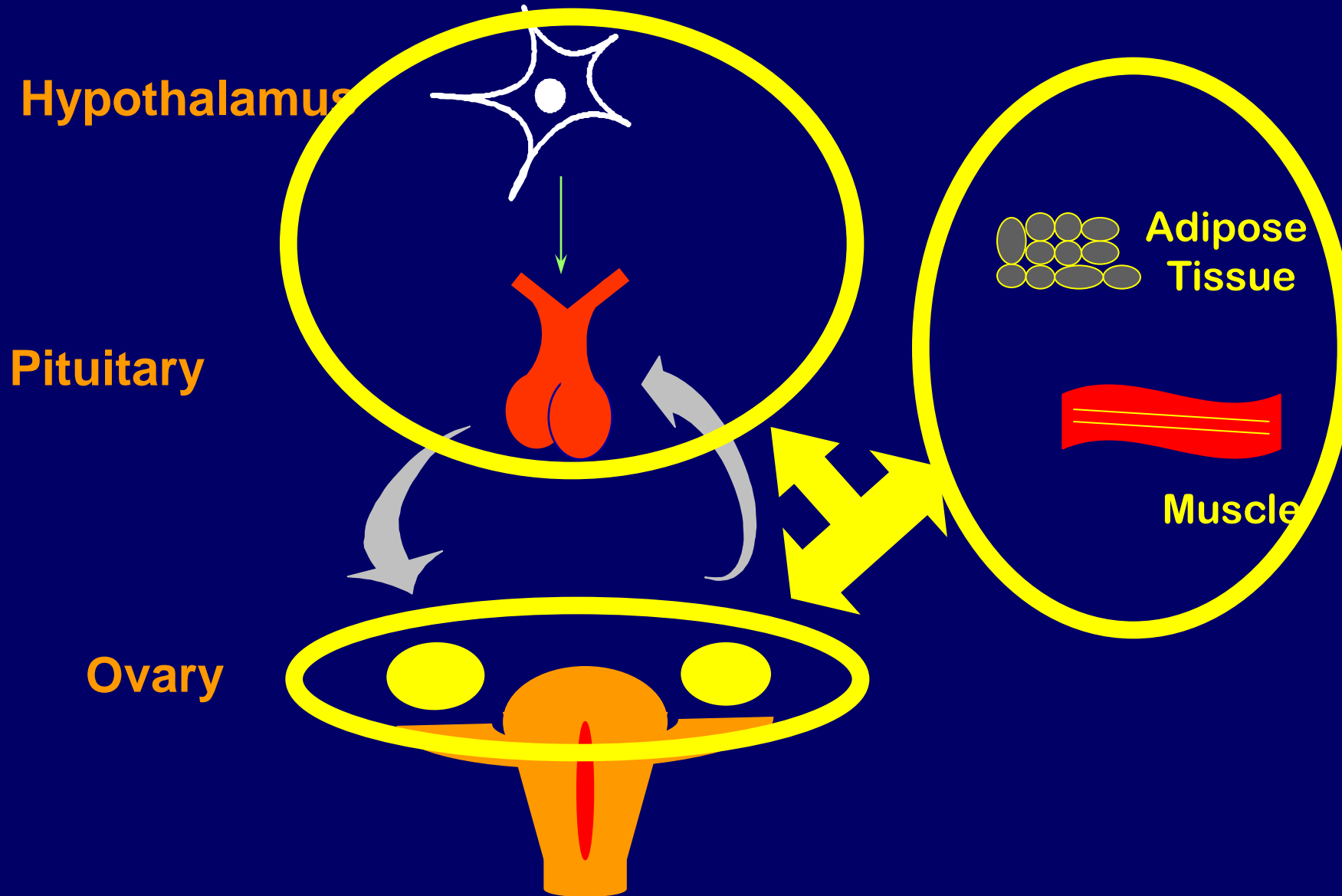
What labs/studies would you order?

Case #3: Labs

- Laboratory testing reveals normal
 - TSH
 - Prolactin
 - FSH
 - Androgen levels (total testosterone)

What is the diagnosis?

Polycystic Ovarian Syndrome



PCOS: Epidemiology

- 4.7-6.8% of women have PCOS as defined by the NIH criteria

(Knockenhauer et al., JCEM 1998; Diamanti-Kandarakis, JCEM, 1999; Asuncion, JCEM 2001)

- Most common cause of female infertility (50-60%)
- May be the most endocrinopathy in young women

PCOS: Rotterdam Definition

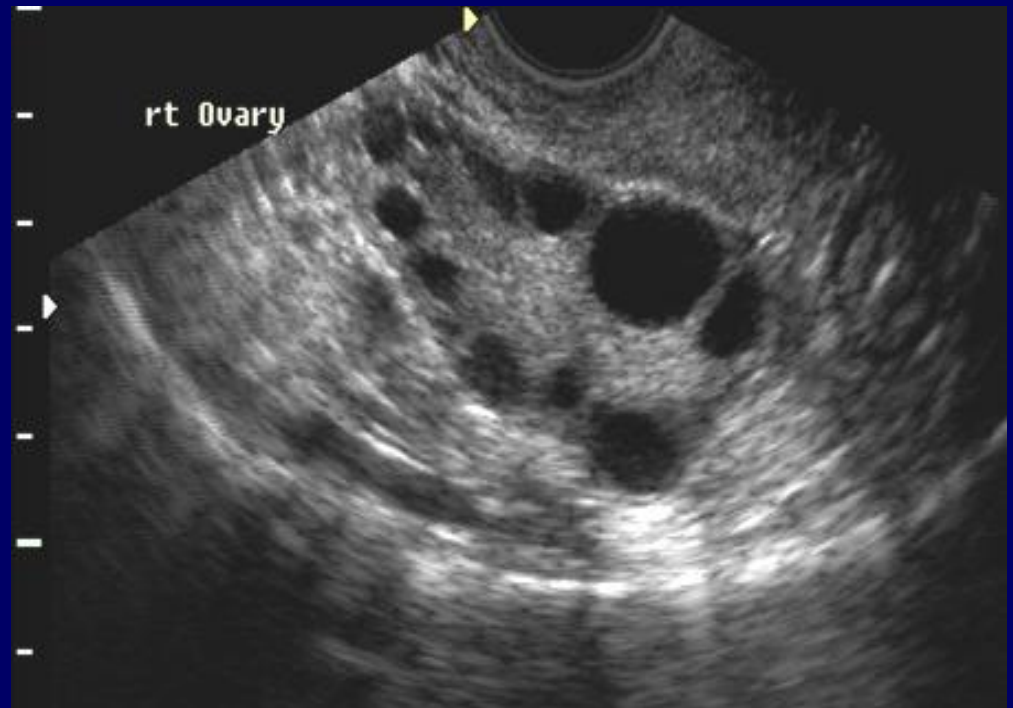
- 2 out of 3 of the following must be true:
 - Oligo- or anovulation
 - Clinical and/or biochemical signs of hyperandrogenism
 - Polycystic Ovaries

Exclusion of other etiologies (e.g. hyperprolactinemia, CAH, androgen secreting tumors)

Polycystic ovary (PCO):

- ▢ multiple small (2 – 9 mm) follicles
- ▢ peripheral distribution
- ▢ increased stromal volume
- ▢ ovaries usually enlarged

*(Adams et al, 1985,
Fert and Ster, 2004)*



Normal ovary:

- fewer follicles
- random distribution
- no increased stroma

(images courtesy of Judy Adams)

Polycystic Ovarian Morphology (PCOM)

- 100% of women with PCOS have PCOM
(Taylor et al JCEM 1997)
- 23% of normally cycling women will have PCOM
(Polson et al, Lancet, 1988)
- Present in other ovulatory disorders
(hyperprolactinemia, late onset CAH, adolescence)
(Azziz R. JCEM 2006)

Clinical Manifestations

- Oligo- or anovulation
- Hyperandrogenism
- Infertility
- Insulin Resistance

Treatment of PCOS

Hyperandrogenism

- Weight loss
- Cosmetic measures
- Hormonal therapy

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Oligo-amenorrhea

- Weight Loss
- Hormonal therapy
- Metformin

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Infertility

- Weight Loss
- Metformin
- Ovulation Induction/IVF

Treatment of PCOS

Hyperandrogenism

- Weight loss
- Cosmetic measures
- Hormonal therapy

Infertility

- Weight Loss
- Metformin
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Oligo-amenorrhea

- Weight Loss
- Hormonal therapy
- Metformin

Insulin Resistance

- Weight Loss/ Exercise
- Metformin
- Monitor BPs, lipids

Treatment of PCOS

Hyperandrogenism

- Weight loss
- Cosmetic measures
- Hormonal therapy

Infertility

- Weight Loss
- Metformin
- Ovulation Induction/IVF

Oligo-amenorrhea

- Weight Loss
- Hormonal therapy
- Metformin

Insulin Resistance

- Weight Loss/ Exercise
- Metformin
- Monitor BPs, lipids

Summary

- Hypothalamic Amenorrhea
 - Diagnosis
 - Low estrogen state of energy output > energy input
 - FSH low or inappropriately normal
 - Management
 - Rarely need MRI for diagnosis
 - Consider BMD after 6 months of amenorrhea
 - Treatment
 - Lifestyle measures-decrease exercise and/or increase po intake
 - HRT or OCPs. HRT preferred.

Summary

- Primary Ovarian Insufficiency
 - Definition
 - Elevated FSH, <40 years of age
 - Repeat testing important: follicular phase
 - Diagnostic evaluation
 - Karyotype
 - Fragile X premutations
 - Anti-adrenal and anti-thyroid antibodies
 - Treatment options
 - HRT or OCPs. HRT preferred.

Summary

- PCOS
 - Epidemiology : very common
 - Diagnosis
 - 2 out of 3: oligo-or anovulation, hyperandrogenism, PCOM
 - Clinical Manifestations: anovulation, hyperandrogenism, fertility, insulin resistance
 - Treatment options: weight loss, OCPs, spironolactone, metformin

Question #1

24 year old woman with a 6 month history of amenorrhea comes in for evaluation. Her thyroid review of systems are negative. She does not have hot flushes, night sweats, or galactorrhea. She is on no medications. Physical exam is unremarkable. hCG negative. FSH and TSH normal. Prolactin is slightly elevated at 30 ng/mL (<18 ng/mL) and confirmed on repeat evaluation.

Question #1

What is the next best step?

- A) Treat with bromocriptine/cabergoline
- B) Treat with an oral contraceptive pill
- C) Give a progesterone challenge
- D) Obtain a pituitary MRI
- E) Repeat the prolactin in 3 months. No treatment for now.

Question #1

What is the next best step?

- A) Treat with bromocriptine/cabergoline
- B) Treat with an oral contraceptive pill
- C) Give a progesterone challenge
- D) Obtain a pituitary MRI
- E) Repeat the prolactin in 3 months. No treatment for now.

Question #2

34 year old woman with a 4 month history of amenorrhea comes to see you for evaluation. Her menses had occurred every 2 months before they stopped. Her exercise routine is unchanged; she runs about 25 miles per week. She has had no hot flushes or night sweats. Her thyroid review of systems are negative. Physical exam reveals some terminal hair growth of her face. TSH, FSH, and prolactin are normal. hCG negative.

Question #2

What would you do next?

- A) Medroxyprogesterone challenge
- B) Treat with OCPs
- C) Treat with metformin
- D) MRI of the pituitary gland
- E) Pelvic ultrasound

Question #2

What would you do next?

- A) Medroxyprogesterone challenge
- B) Treat with OCPs
- C) Treat with metformin
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References

- Gordon CM, et al. 2017 Functional hypothalamic amenorrhea: An Endocrine Society Clinical Practice Guideline. JCEM 102:1413.
- Legro RS, et al. 2013 Diagnosis and Treatment of Polycystic Ovarian Syndrome: An Endocrine Society Clinical Practice Guideline. JCEM 98:4565.
- Stuenkel CA, et al. 2023. Primary ovarian insufficiency. NEJM 388:154.

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