Find out the facts, period!
Evaluation of Amenorrhea and Menstrual Irregularity in Teenagers

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Presenter Disclosure

Presenter: Preetha Krishnamoorthy

Relationships with commercial interests:

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Learning Objectives

At the conclusion of this presentation, participants will be able to:

1. Determine the most common causes of amenorrhea and menstrual irregularity in teenagers

2. Review the evaluation of amenorrhea and menstrual irregularity in teenagers

3. Describe the management of polycystic ovarian syndrome in adolescent girls.

Case

- A 14 year old girl has not had her period yet.
- Is this NORMAL?
- The simple answer…

It all depends!

Definitions

- Primary amenorrhea
  - Absence of menarche by age 16
  - Absence of menarche within 2 years of onset of thelarche – not anymore!
- Secondary amenorrhea
  - Absence of 3 consecutive periods in a post-menarchal girl (2 years post menarche)
- Delayed puberty
  - Absence of secondary sexual characteristics (thelarche) by age 13 in girls

Case

- A 14 year old girl has not had her period yet.
- Is this NORMAL?
- Maybe!
- If no breast development → delayed puberty
- If onset of thelarche <10-11 years old → it's about time!

Which is ABNORMAL?

1. A 12 year old girl had her first period 12 months ago and nothing since.
2. A 12 year old girl had her first period 12 months ago, then periods every 2-3 months since.
3. A 12 year old girl had her first period 12 months ago, regular periods for 6 months, and nothing since.

Which is ABNORMAL?

1. A 12 year old girl had her first period 12 months ago and nothing since.
2. A 12 year old girl had her first period 12 months ago, then periods every 2-3 months since.
3. A 12 year old girl had her first period 12 months ago, regular periods for 6 months, and nothing since.

Most likely all NORMAL!

Caveat: Entire clinical picture

FUN FACT

- We do not expect menstrual regularity in the first 2 years following menarche
- Even if you have menarche and nothing after for 2 years, that can be normal
- Anovulatory cycles
- CUTOFF POINT 2 years

DUB (Dysfunctional Uterine Bleeding)

- If a girl is bleeding excessively → menorrhagia
- If a girl is bleeding more frequently → metrorrhagia

- If >1 pad/per hour soaked → ER!

- From an endocrine standpoint → hypothyroidism
- Pregnancy
- Spotting from inadequate estrogen (low dose OCP)

- MOST DO NOT NEED ENDO!

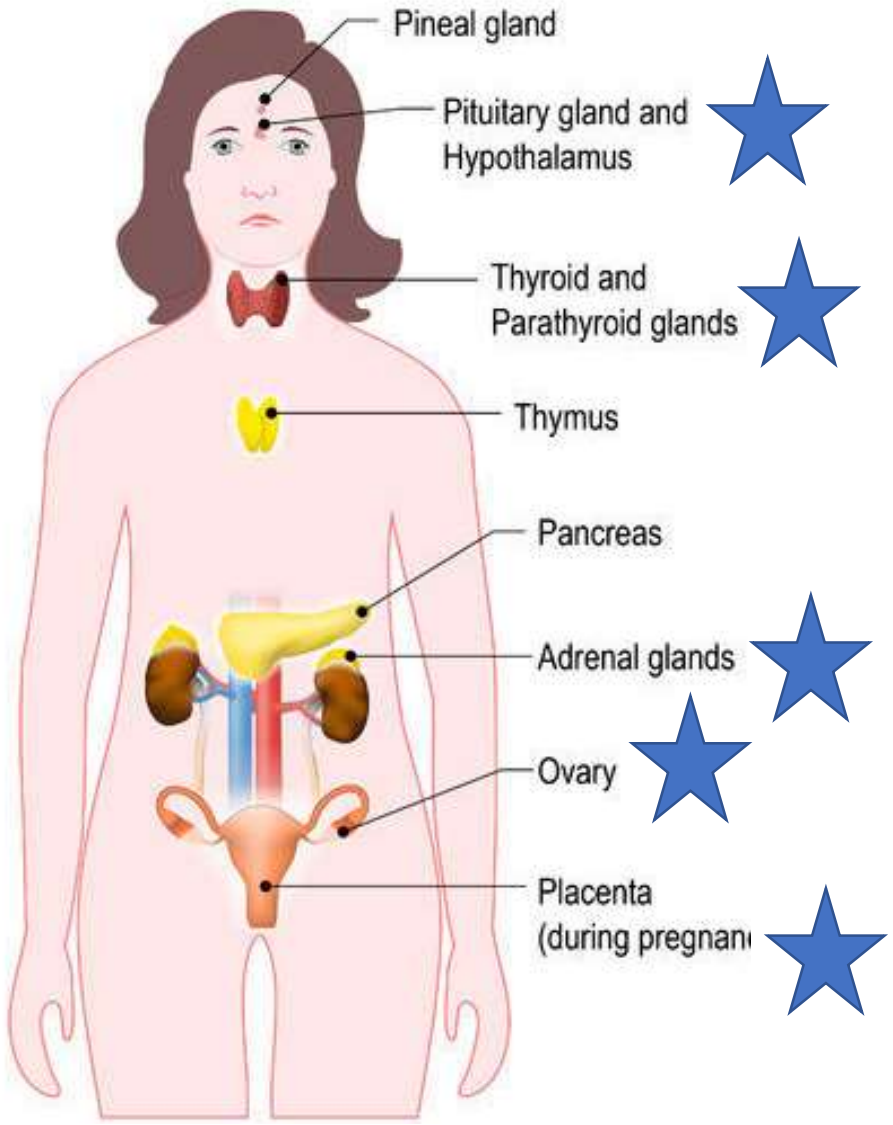
Case

- A 16 year old has not had a period yet
- A 16 year old had her menarche at age 12, had regular periods and now no periods for 1 year

- What is our approach?

Primary versus Secondary

- There is only 1 difference in our approach
- Anatomical anomalies are a part of our differential diagnosis in primary amenorrhea
- Rest of differential diagnosis is the same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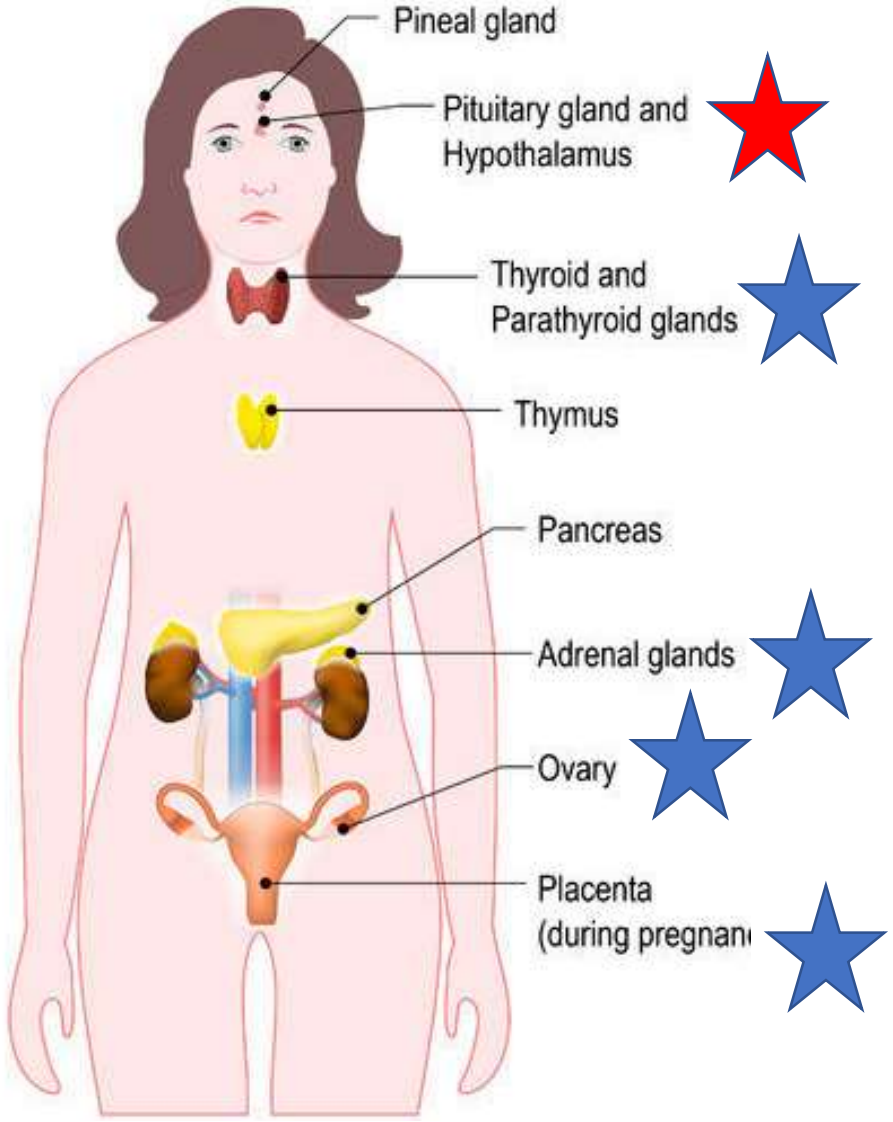
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Hypothalamic-Pituitary Axis

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Hypothalamic-Pituitary Axis

- Invasive
- Idiopathic (congenital hypopituitarism)
- Iatrogenic
- Infiltrative
- Ischemia (post-partum → Sheehan's)
- Immune
- Injury (classically presents with DI)
- Infection

FUN FACT

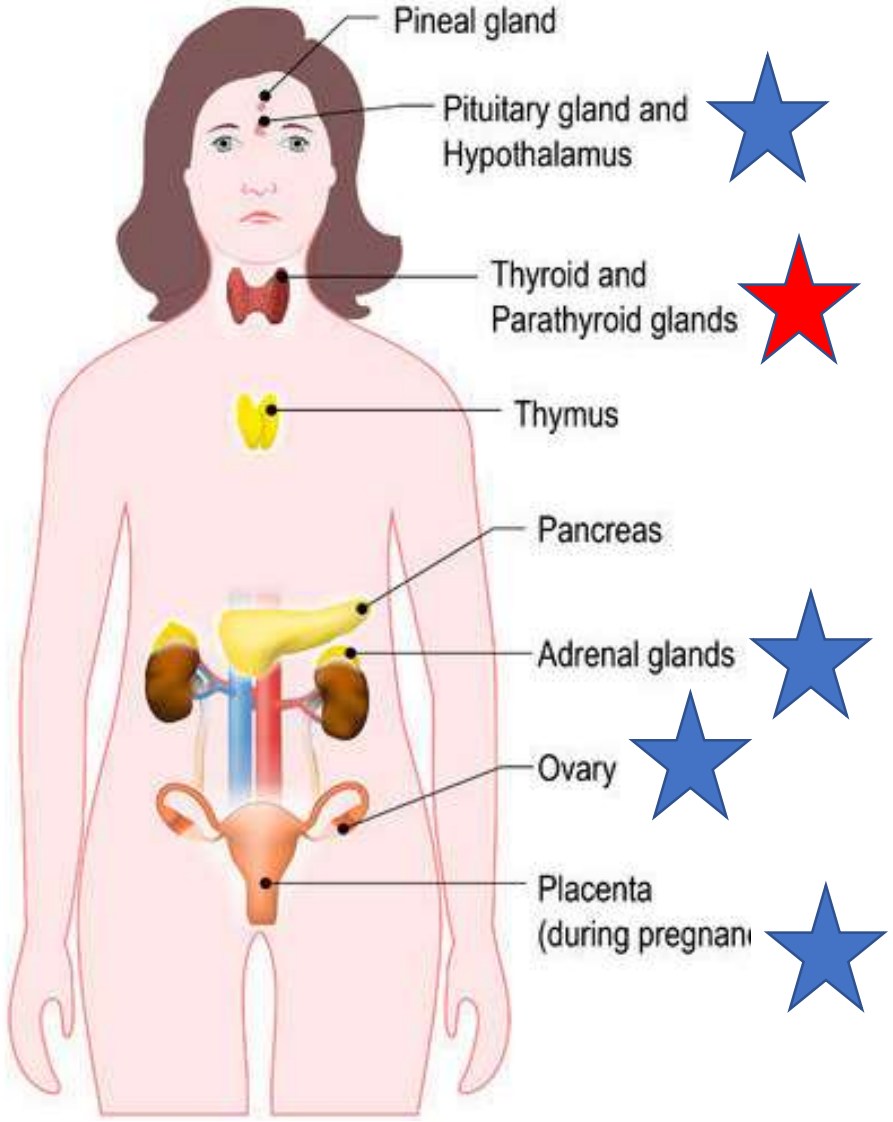
- Some of the same conditions that cause delayed/puberty or amenorrhea can cause precocious puberty
- Sex hormones like to be turned on!
- Examples: invasive, iatrogenic, infection

Do not forget…

- Constitutional delay
- Functional hypogonadotropic hypogonadism
  - Chronic illness
  - Eating disorders/weight loss
  - Excessive exercise
- Prolactinoma

Back to the Basics

- PMHx
- Family Hx
- Nutrition/habits
- Neuro symptoms
- Evidence of other pituitary dysfunction
  - Growth hormone
  - Thyroid
  - Cortisol
  - Prolactin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Thyroid

- Hypothyroid
  - Classically causes menorrhagia
  - Severe hypothyroidism → delayed bone age
- Hyperthyroidism
  - Oligomenorrhea

FUN FACT

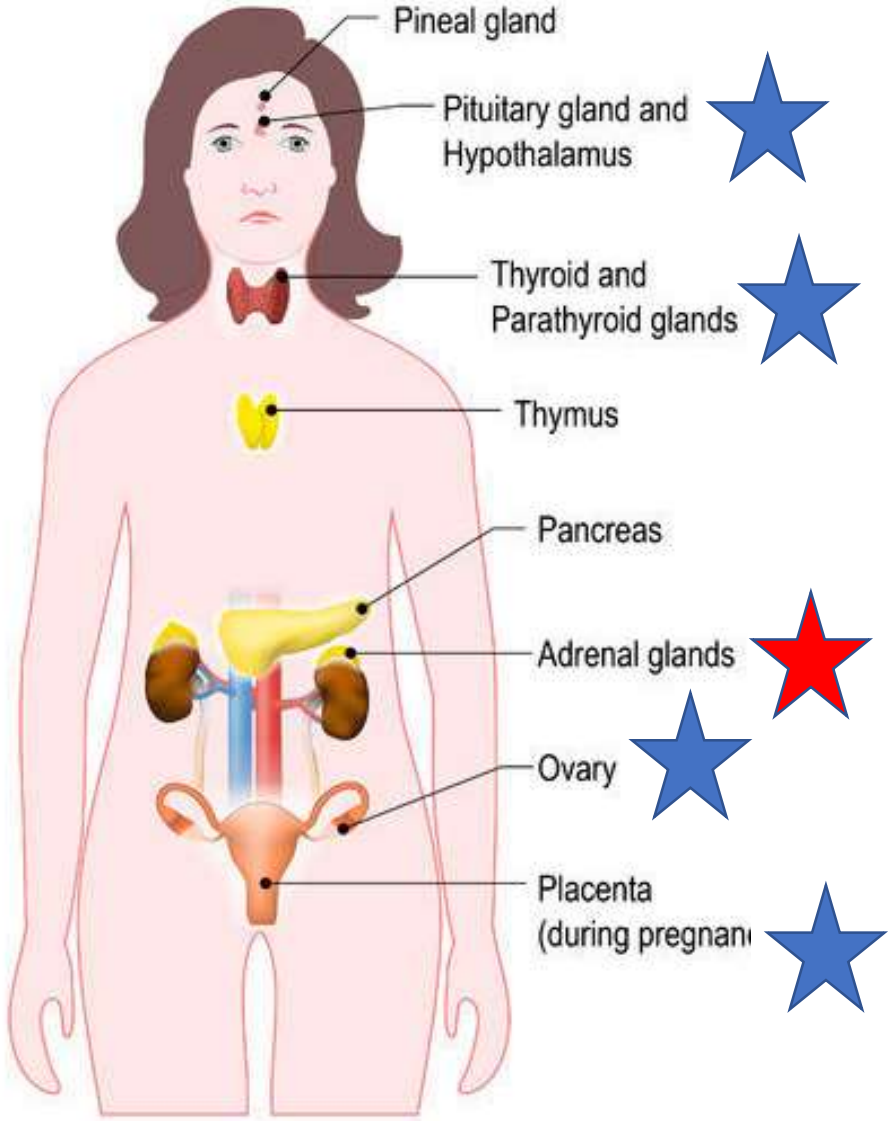
- Severe hypothyroidism can also cause precocious puberty
- Elevated TSH is the culprit
- Receptors are promiscuous
- Van Wyk-Grumbach syndrome

(I have seen it once!)

Back to the basics

- Hypothyroidism
  - Growth, delayed bone age and delayed secondary sexual characteristics
  - Weight gain, dry skin, constipation, cold intolerance

- Hyperthyroidism
  - Goiter, eye findings
  - Difficulty concentrating, insomnia, weight loss, palpitations, heat intolerance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Adrenal Glands

- Excessive adrenal androgens

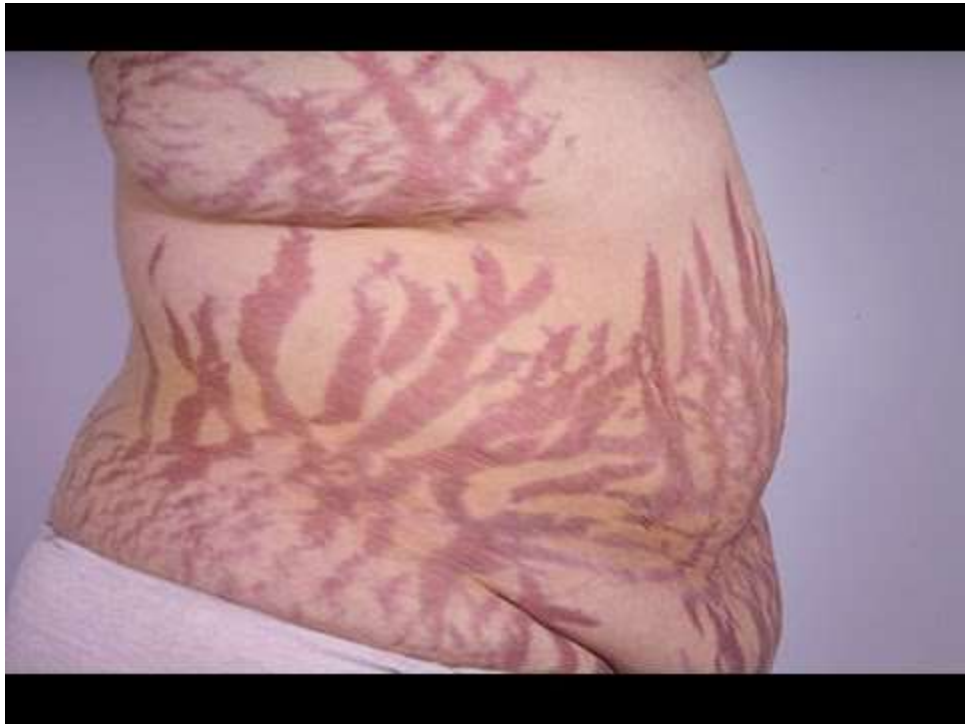
- Adenoma or carcinoma (rare)
- Congenital adrenal hyperplasia → clinically can look exactly like PCOS

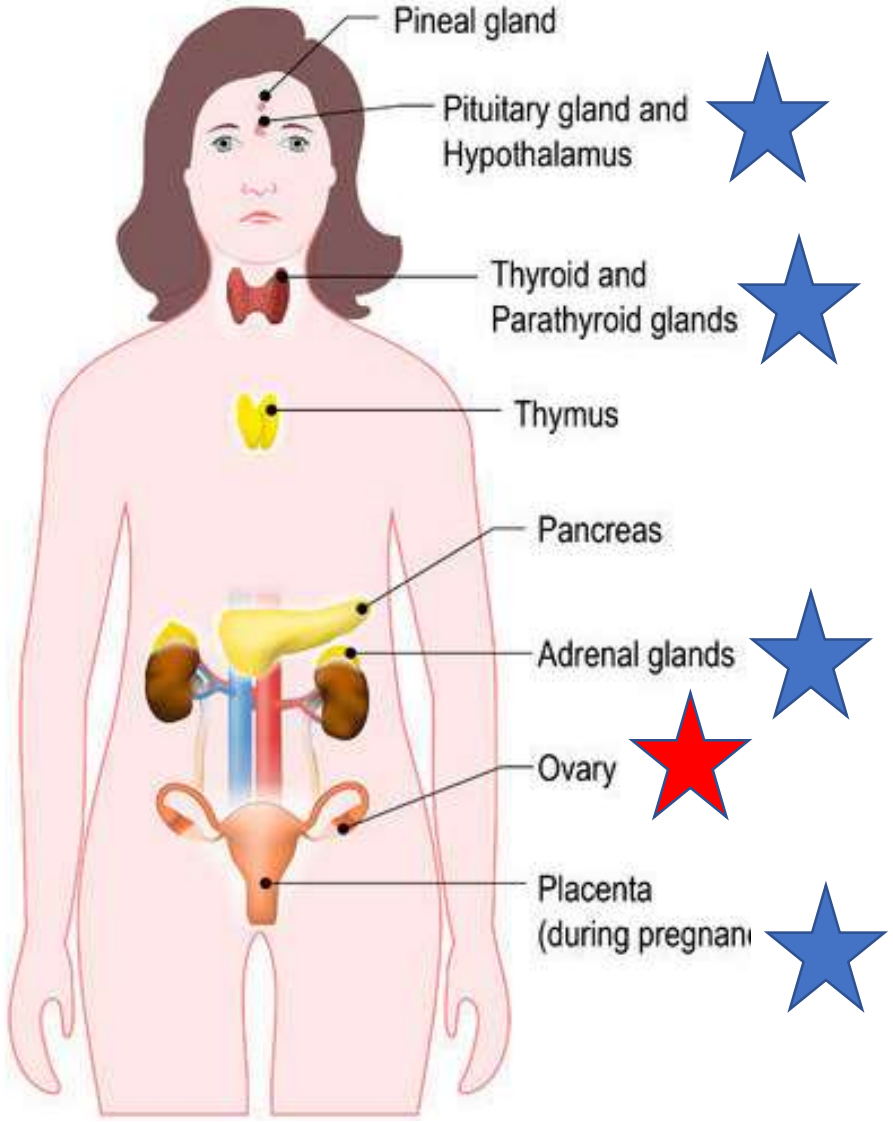
Back to the Basics

- Hirsutism
- Acne (severe, not only on the face)
- Male-pattern hair loss
- Clitoromegaly
- Cushing’s
  - Classic features: truncal obesity, striae, HTN, easy bruising, proximal muscle weakness, dorsocervical fat

FUN FACT

- Most cases that are R/O Cushing's are not in fact Cushing's
- Clinical features of dorsocervical fat and striae are associated with obesity
- Supraclavicular fat**
- Striae violaceous and > 1cm
- Don't bother with a morning cortisol → dexamethasone suppression test (1 mg dexamethasone at 11 pm with an early morning cortisol)

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Ovaries

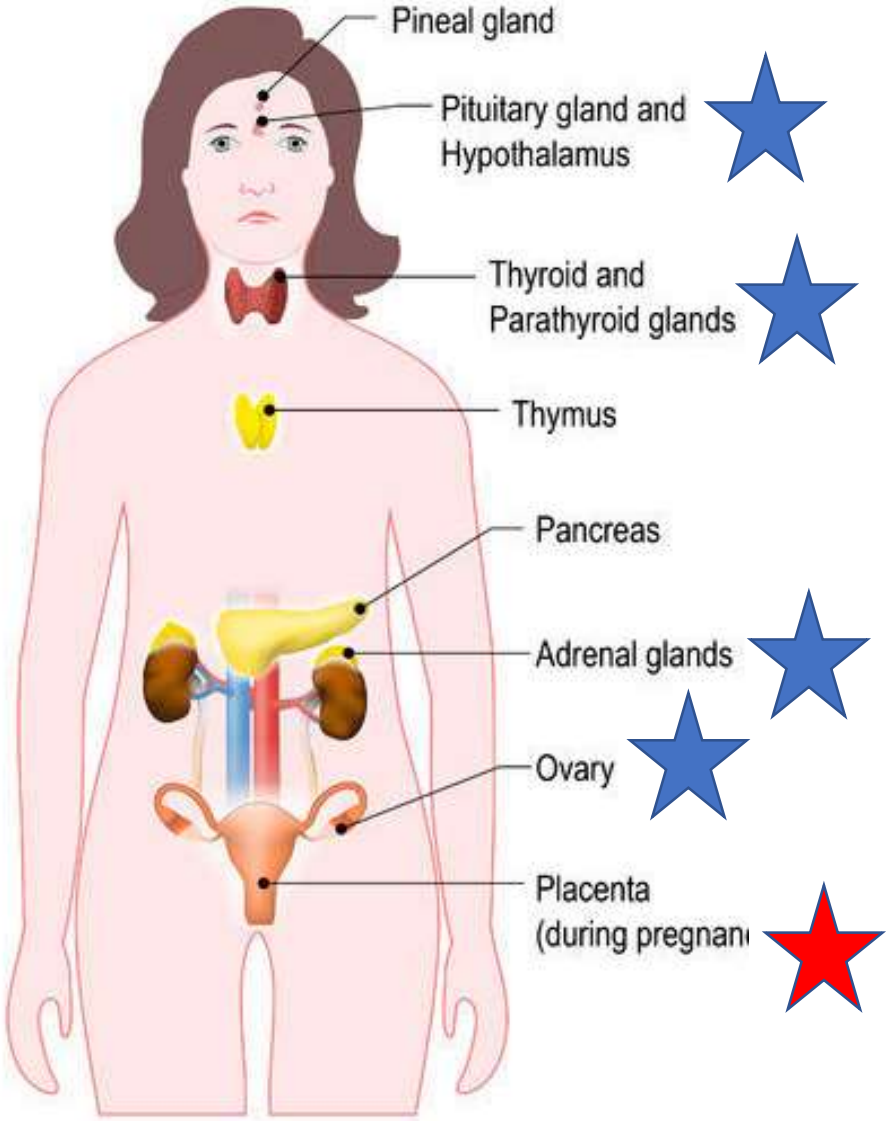
- PCOS
- Dysgenesis (Turner)
- Premature ovarian failure (autoimmune or other)
- Torsion
- Chemo (alkylating agents) or radiation
- Infection (mumps oopharitis)
- What if the ovaries are not really ovaries…?
  - Androgen insensitivity syndrome

Androgen Insensitivity Syndrome

- 46 XY karyotype
- Testosterone is unable to exert its effect
- No pubic or axillary hair
- Testosterone → estrogen → breast development
- Testes → AMH → no uterus → no period
  - Anatomic (primary amenorrhea)

Back to the basics

- Features of Turner syndrome
- Autoimmunity
- PMHx
- PCOS
  - Hirsutism, acne, male-pattern alopecia, insulin resistance, family history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Uterus

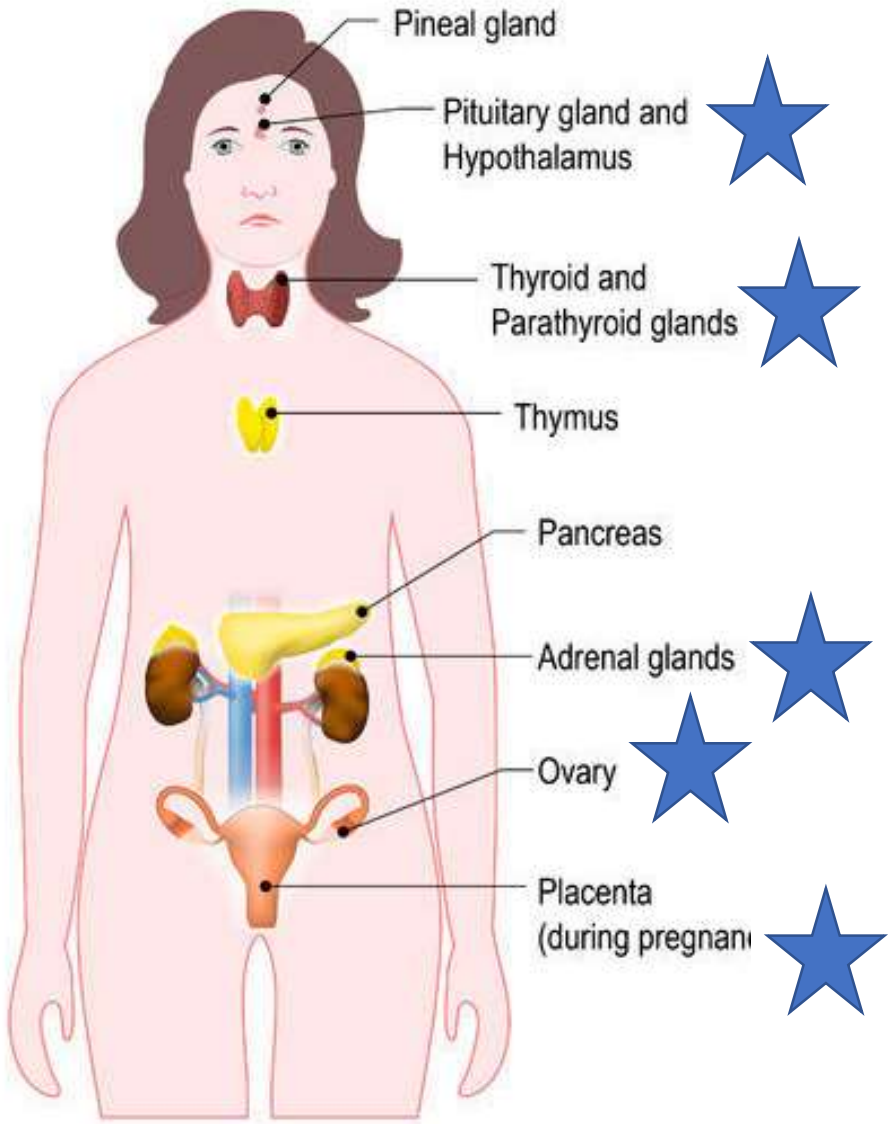
- Absent uterus
- Asherman’s
- Anatomic anomalies
- Imperforate hymen

NEVER FORGET

PREGANCY

Case

- A 16 year old without a period yet
- What do you want to know?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Key questions

- Onset of breast development and presence of pubic and axillary hair
- Family Hx (delayed puberty, fertility issues)
- PMHx
- Neuro symptoms/other pituitary hormones
- Galactorrhea
- Symptoms of thyroid disease
- Hirsutism or acne
- Sexual activity and contraception
- Vaginal discharge

Physical Exam

- Vital signs (BP)
- Growth parameters and BMI
- Thyroid
- Neuro exam, visual fields and fundoscopy
- Hirsutism and acne
- Acanthosis
- Tanner staging
- Palpate the breast tissue- is it estrogenized?
- Clitoromegaly

Case

- Unremarkable history
- Started breast development at age 12
- +Vaginal discharge
- Overall well
- 20 lb weight loss – now has a normal BMI
- Normal physical exam but breast tissue is soft

Likely diagnosis?

- Likely functional hypogonadotropic gonadism in the context of weight loss

- But we cannot with certainty rule out any of the other causes

Work-up

- LH, FSH, estradiol
- TSH
- DHEAS, total testosterone, 17-OHP
- Prolactin
- Pregnancy test
- If you suspect something central:
  - Free T4 and morning cortisol

Case

- All results normal
- LH 2.1, FSH 4.3, estradiol 95 pmol/L

- Next step?
- Provera challenge
  - 10 mg po qhs x 10 days
  - Bleed after completion of Provera, usually within the week after

Diagnosis?

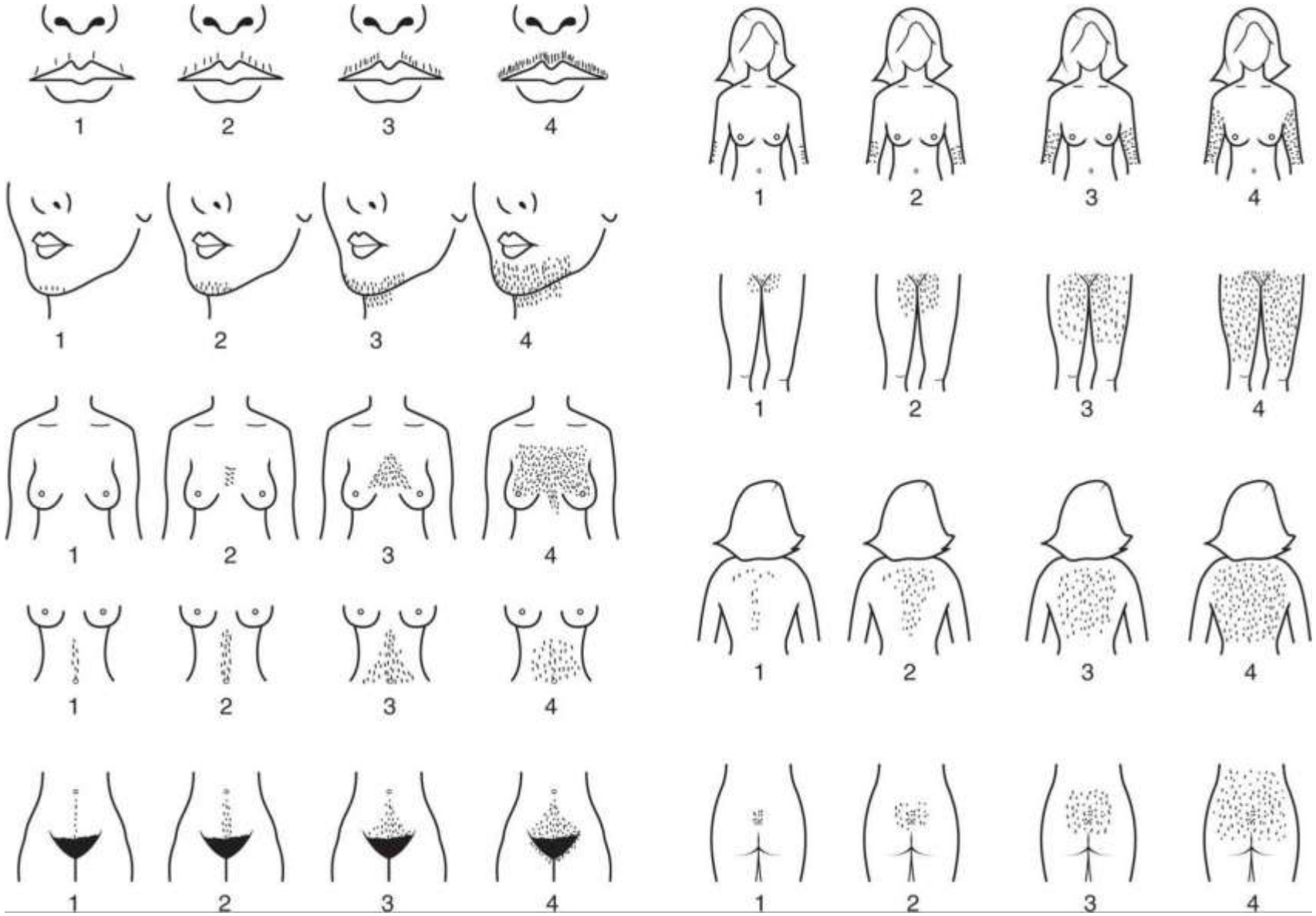
- Functional hypogonadotropic hypogonadism
- Likely recovering
- Wait and watch
- OCP

Case

- 15 year old girl
- Menarche at age 12
- Menses monthly x 1 year, then progressively irregular
- Menses every 3-6 months, LMP 6 months ago
- Acne, seen by dermatologist
- Excessive hair on sideburns, chin, lower abdomen
- Family Hx
  - mom had irregular menses
  - paternal grandfather T2DM

Case

- BMI 27
- Normal BP
- Mild hirsutism
- Facial acne and back acne
- No acanthosis
- Breasts Tanner 5, estrogenized
- Prominent clitoral hood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Is this enough to make a diagnosis?

- Likely PCOS

- 2/3 criteria
  - Anovulatory cycles
  - Clinical or biochemical evidence of hyperandrogenism
  - U/S findings consistent with PCOS

Enough, but…

- Still need to exclude other pathology
- Work-up is needed

Work-up

- LH, FSH, estradiol
- TSH
- DHEAS, total testosterone, 17-OHP
- Prolactin
- Pregnancy test
- If you suspect something central:
  - Free T4 and morning cortisol
  - Not needed here!

Case

- LH 18.5 IU/L, FSH 7.6 IU/L, estradiol 137 pmol/L
- Testosterone 2.3 nmol/L, DHEAS 8.5 umol/L, 17-OHP 4.2 nmol/L
- All else normal

Diagnosis?

- PCOS
- OGTT
- Lipid profile, liver enzymes
- Insulin resistance (2 hour insulin > 500 pmol/L)

FUN FACTS

- You do not need an ultrasound to diagnose PCOS!
- You can have PCOS with a normal BMI
- You can have insulin resistance with normal BMI PCOS

Treatment options

- HEALTHY ACTIVE LIVING
- Metformin if insulin resistance
  - May help with menses, but won’t help with acne or hirsutism
- OCP +/- antiandrogen
  - Will help menses and will likely help with acne
  - May help hirsutism but it can take 9-12 months
- Cyclic provera
  - Will help menses, but won’t help with acne or hirsutism
- Cosmetic hair removal

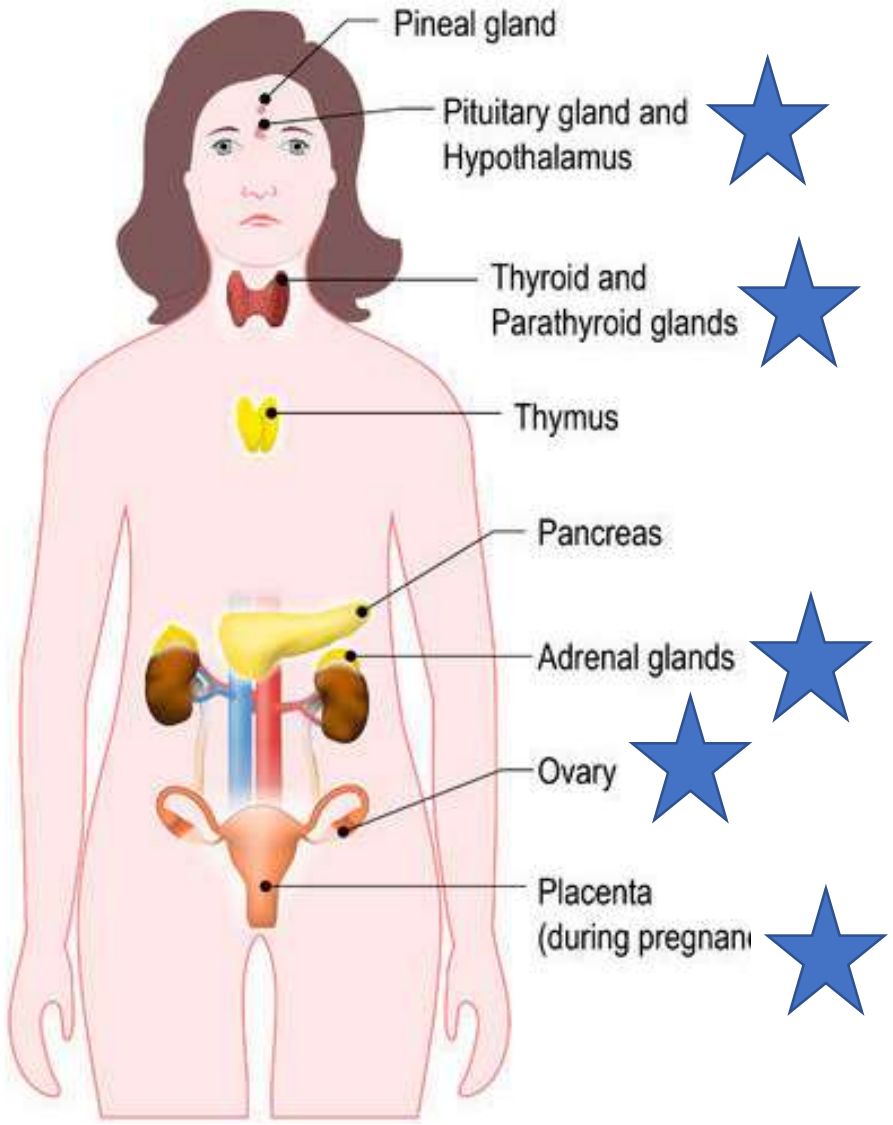
Case

- 14 year old girl
- Secondary amenorrhea
- Menarche at age 10
- Menses never regular
- Initially q4-6 months, nothing since age 13
- No vaginal discharge
- No hirsutism or acne
- PMHx and family hx unremarkable

Case

- Well-looking
- Normal BMI
- Tanner 4 breasts, soft
- Rest of exam normal

THOUGHTS?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Work-up

- LH, FSH, estradiol
- TSH
- DHEAS, total testosterone, 17-OHP
- Prolactin
- Pregnancy test
- If you suspect something central:
  - Free T4 and morning cortisol
  - NOW we need this!

Case

- LH 45.7 IU/L
- FSH 97.2 IU/L
- Estradiol < 37 pmol/L
- Rest of work-up normal

Diagnosis?

- Premature ovarian failure
- But WHY?

- Mosaic Turner syndrome
- Autoimmune
- Fragile X

- Microarray, anti-ovarian antibodies, Fragile X testing, POF panel

- In this patient → no diagnosis

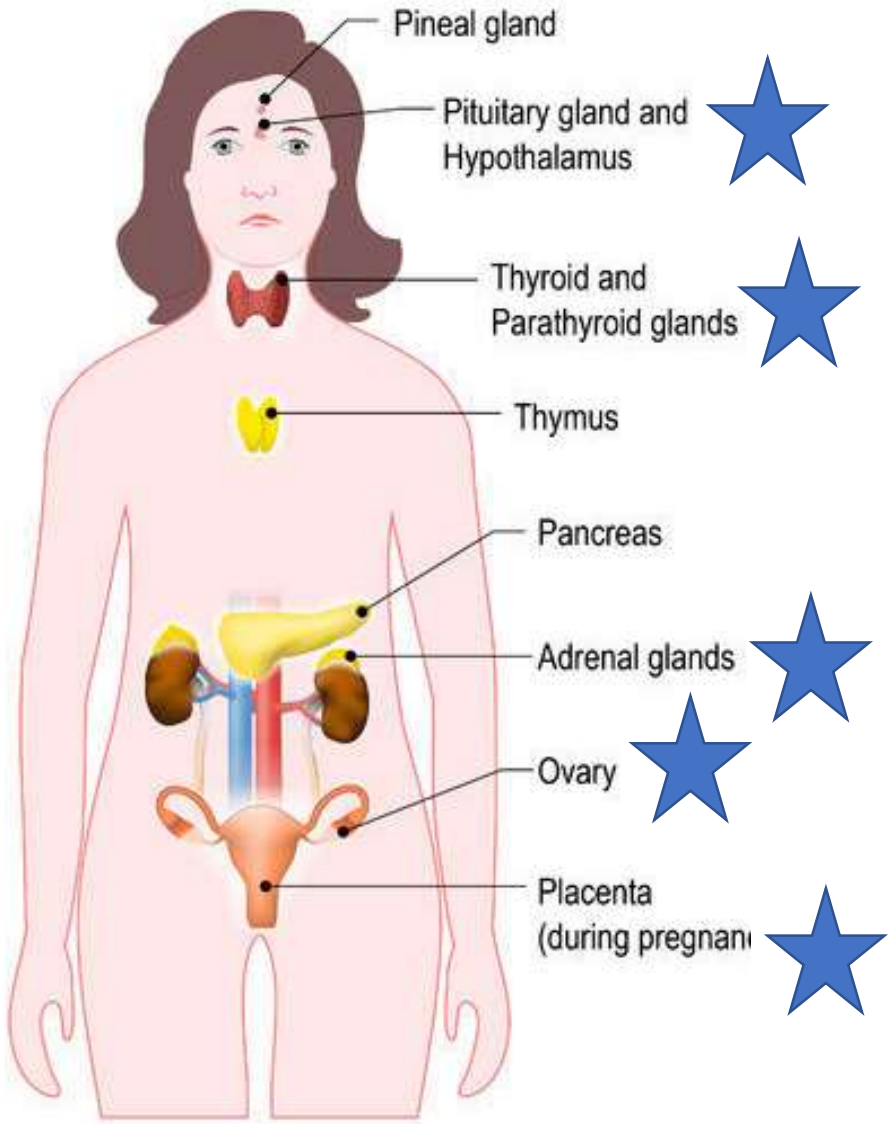
Treatment

- If patient is fully developed → OCP
- If patient has delayed puberty, gradual pubertal induction over about 2 years
  - Estrace 0.5 mg q2days x 6 months
  - Estrace 0.5 mg qday x 6 months
  - Estrace 1 mg qday x 6 months
  - Estrace 2 mg qday x 6 months
  - Switch to OCP
  - Estrogen patch protocols

Case

- 16-1/2 year old girl
- Menarche at age 13 with monthly menses
- Started on fluoxetine 2 years ago for anxiety
- Last period 1 year ago
- 5 lb weight loss
- PMHx and family hx unremarkable
- No other symptoms
- Normal exam
- Tanner 5 breasts, soft

THOUGHTS?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Work-up

- LH, FSH, estradiol
- TSH
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- Prolactin
- Pregnancy test
- If you suspect something central:
  - Free T4 and morning cortisol
  - NOW we need this!

Case

- LH 5.2 IU/L, FSH 6.8 IU/L, estradiol < 73 pmol/L
- Prolactin 60.8 nmol/L
- All else normal including TFTs and cortisol

- Next step?

- MRI

Diagnosis

- Pituitary macroadenoma

- For suspected microprolactinomas → dopamine agonists
- For macroadenomas → usually surgery

Case

- 16 year old girl
- Primary amenorrhea
- PMHx unremarkable
- Breast development since age 10
- +Axillary and pubic hair
- +Facial acne
- +Mild acanthosis
- BMI 31

THOUGHTS?

Case

- PCOS
- Cannot exclude adrenal pathology
- So let’s go ahead and do our work up…

Work-up

- LH, FSH, estradiol
- TSH
- DHEAS, total testosterone, 17-OHP
- Prolactin
- Pregnancy test
- If you suspect something central:
  - Free T4 and morning cortisol
  - Not needed here!

Case

- Everything comes back normal
- Normal estradiol level
- Enough to call it PCOS?

- Next step?
- Provera challenge

Case

- No bleed
- Abdominal imaging
- No uterus visualized
- Microarray

- Mayer-Rokitansky-Kuster-Hauser syndrome (Mullerian agenesis)

Take-Home Points

- It may take 2 years for periods to become regular post-menarche
- Work up for primary and secondary amenorrhea is almost identical
- Work your way down systematically
  - HPA
  - Thyroid
  - Adrenals
  - Ovaries
  - Uterus

Take-Home Points

- The basic work-up is always the same
- The most common causes
  - Constitutional delay
  - Functional hyogonadotropic hypogonadism
  - PCOS
- But even if you think you know, you may be fooled, so do the work-up!

Merci!

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