The Plan

Amenorrhea—mostly secondary
1. Broad differential
2. Simple, stepwise, work-up

Focus on PCOS
1. Clinical features
2. Diagnostic criteria
3. Treatment approach—short and long term sequelae

Goal: Efficient (fewest visits) and cost-effective (targeted testing) work-up

Case 1

A 26 yo P0 with previously normal periods now reports no period for 5 months. She is normal weight and is not on any medications. She denies hot flashes.

1. What term describes her symptoms?
2. Physiologically, what causes this type of bleeding pattern?
3. What is the differential?
Q1: In addition to a urine pregnancy test and TSH, which of the following is the most appropriate test to obtain at this time?

1. Prolactin
2. FSH
3. Total testosterone and DHEAS
4. Transvaginal Ultrasound (TVUS)
5. All of the above
6. None of the above

Amenorrhea, Oligomenorrhea

- **Amenorrhea** –
  - Primary amenorrhea
    - No menarche by age 14 without secondary sexual characteristics
    - No menarche by age 16 with secondary sexual characteristics
  - Secondary amenorrhea – absence of menses in a previously menstruating woman
    - No menses for > 3 cycle lengths in previously cycling woman
    - No menses > 6 months in women with irregular cycles

- **Oligomenorrhea** – <9 periods per year

Normal: Cycle= 28 days +/- 7 d (21-35); Length=2-7 days; Heaviness=self-defined

Primary Amenorrhea, approach

- Wide differential that includes anatomic, genetic and hormonal causes.
- Includes physiologic delay, karotype abnormalities, congenital malformations as well as all of the causes of secondary amenorrhea.

Key questions in the work-up include:

1. Secondary sexual characteristics present?
2. Level of gonadotropins (FSH/LH)
3. Uterus present?
4. Karyotype XX, Xo or XY
5. Patent outflow tract?

Reference: Primary Amenorrhea: workup
Secondary amenorrhea: differential diagnosis

In order of frequency:
1. Pregnancy (by far most common)
2. Polycystic ovarian syndrome (PCOS) & chronic anovulation due to obesity (40% of non-pregnant)
3. Hypothalamic amenorrhea (weight loss / exercise) (35%)
4. Hyperprolactinemia (20%, not incl brst feeding)
   - Breastfeeding
   - Hypothyroid
   - Prolactinoma
   - Neuroleptic meds
5. Asherman’s syndrome <5%
6. Premature ovarian failure <5%

Hypothalamic amenorrhea

- "Hypogonadotropic hypogonadism"
- Stress, low body weight/fat, low calorie intake, severe systemic illness alters the GnRH pulsatility of the hypothalamus (via increased CRH)
- Low FSH, LH ∴ no ovulation, low estrogen state b/c low FSH
- Worry re: bone health
- Treat: underlying cause, replace estrogen (OCP)

Hyperprolactinemia causes

- Pituitary adenoma: Micro (<1cm) or Macro (>1cm). Secrete prolactin.
- Hypothyroid: Increased TRH stimulates prolactin secretion
- Neuroleptics: blocks dopamine which increases prolactin
- Breast feeding (and nipple stim)
Hyperprolactinemia

- Similar presentation as Hypothalamic: "Hypogonadotropic hypogonadism"
- High prolactin alters the GnRH pulsatility of the hypothalamus
- Low FSH, LH → no ovulation, low estrogen state b/c low FSH
- Galactorrhea not a reliable sign—many do not have it.
- Worry re: bone health, macroadenoma causing visual impairment

Pituitary adenoma

- Level of prolactin generally proportional to size (<1 cm = <200 ng/ml)
- Microadenomas: little risk of visual effects, can be treated conservatively or expectantly; Macroadenomas require treatment to prevent visual effects
- Get MRI if prolactin >100 or HA or visual field defects (some say MRI for all with no other known reason for elevation eg meds, nipple stim; hypothyroid)
- Treatment: dopamine antagonist: decreases PLN secretion and size of adenoma

Pituitary adenoma treatment

- Microadenoma:
  - Old way: Bromocriptine was the only dopamine antagonist available and poorly tolerated so gave OCP for menstrual regulation and to preserve bone. Reserved bromo for galactorrhea and pregnancy.
  - Now: Cabergoline—few side effects → first line treatment for symptomatic hyperprolactinemia and infertility. OCP if can’t tolerate or needs contraception.
- Macroadenoma—always treat w dopa agonists, possible surgery

Reference: hyperprolactinemia

- Drugs that can cause hyperprolactinemia (partial list)
  - Antipsychotics (haloperidol, chlorpromazine, fluphenazine many others): Antiemetic (Metoclopramide): Opioids (Methadone)
- Treatment prolactinoma: Cabergoline (dopa agonist)
  - Start low to minimize side effects: 0.25 mg twice a week or 0.5 mg once a week.
  - Increase slowly titrating to prolactin level up to 1.5 mg twice weekly. (Caution: Higher doses assoc with valvuloplasty)
  - Main side effect = nausea (can give intravag)
  - May be able to decrease or dc after 1-3 yrs but often can recur
Premature ovarian failure/primary ovarian insufficiency

- Hypergonadotropic hypogonadism:
  - Diagnosis made if repeated FSH level >30, <40 years old
- Etiology:
  - Karyotype abnormality (X0, mosaic X0, fragile X)
  - Ovarian damage (chemo, xrt, surgery)
  - Auto-immune
  - Unknown in >50%
- Low estrogen state → OCP to prevent osteoporosis, treat hot flashes
- Infertility: egg donor, adoption

Case 2

A 28 yo woman reports very heavy periods about every 5 months since menarche. LMP 4 months ago

- PMH significant for HTN, on no meds
- Had one child at age 25, required clomiphene to become pregnant, pregnancy complicated by gestational diabetes
- On further questioning, has had to wax her upper lip and chin for many years for “stubborn hair” and has acne

For this patient, what additional testing is required to diagnose PCOS?

a. Ultrasound
b. Total testosterone
c. DHEA-S
d. LH/FSH ratio
e. All of the above
f. None of the above

(28 yo heavy periods every 5 months since menarche, hirsutism, h/o infertility, h/o GDM)

Case 2

How would you classify her bleeding pattern?

Physiologically, what causes this type of bleeding pattern?
What is the differential?
Pathophysiology: Anovulatory Bleeding

**Bricks & Mortar**

**Estrogen** = Bricks, build endometrium

**Progesterone (P)** = Mortar, stabilize it, only have P if ovulate

Normal menses: withdrawal of P causes wall to fall down, all at once (orderly bleed)

Anovulation: No P so when wall grows too tall, it falls. Bleed is heavy because wall is tall. Bricks can also fall intermittently & incompletely ie irregularly irregular

PCOS

- Affects 4-12% of reproductive aged women
- Associated with obesity (50%) and insulin resistance (48% with abn GTT)
- A common cause of infertility; once pregnant, higher risk of SAab, GDM
- Increased risk of: diabetes, endometrial cancer, cardiovascular disease, sleep apnea, lipid abnormalities, nonalcoholic steatohepatitis, metabolic syndrome, mood disorders, eating disorders.

Clinical features

- Oligomenorrhea 30-50%
- Amenorrhea 20-50%
- Hirsutism 65-70%
- Polycystic ovary 80%
- Insulin resistance 30-70%
- Acne 27-35%
- Alopecia 3-5%
- Infertility 20-75%
- Overweight 40-85%

Pathophysiology

- **Androgen overproduction**
  - Increased circulating LH
  - Sex Hormone Binding Globulin
  - Estrogen without Progesterone
  - Free Androgen
  - Acanthosis nigracans
  - T2DM, CVD
  - Hirsutism, Acne

- **Risk of Endometrial hyperplasia/cancer**
- **Subfertility**
- **Failed growth of Dominant Follicle**
- **Anovulation amenorrhea**
**PCOS diagnosis**

2 of the following 3:
1. Hyperandrogenism (clinical or biochemical)
2. Oligo- or anovulation
3. Polycystic ovaries (by ultrasound)

AND: Absence of pituitary or adrenal disease (eg, nonclassic congenital adrenal hyperplasia, Cushings, adrenal tumor)

Many can be diagnosed with history and PE alone (no labs, no sono)

Rotterdam criteria, confirmed by NIH consensus conference 2012

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**Rule out other diagnoses**

1. Rule out other causes of amenorrhea/irregular bleeding (we do routinely)
   - Pregnancy → pregnancy test
   - Hypothyroidism → TSH
   - Hyperprolactinemia → prolactin
   - (Premature Ovarian failure → FSH (only if suspected eg has hot flushes and prolonged amenorrhea))

2. Rule out other causes of hyperandrogenism in select patients

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**What's in a Name?**

- NIH consensus panel 2012: “We believe the name ‘PCOS’ is a distraction…. The name focuses on polycystic ovarian morphology which is neither necessary nor sufficient to diagnose the syndrome.

- It is time to expeditiously assign a name that reflects the complex metabolic, hypothalamic, pituitary, ovarian and adrenal interactions that characterize the syndrome—and their reproductive implications.
Menstrual Dysfunction

- Oligo or amenorrhea
  - Typically begins in the peripubertal period
  - Periods typically very heavy with spotting between

- Since no ovulation—no progesterone

- Chronic unopposed estrogen stimulation of the endometrium leads to
  - Intermittent breakthrough bleeding
  - Heavy periods
  - Endometrial hyperplasia and/or cancer (3x increased risk)
    - Low threshold to do EMB after 2-5 years of untreated chronic anovulation, even in young women
    - Need to induce at least 4 periods per year to prevent

Hyperandrogenism

- Most women have BOTH clinical and biochemical hyperandrogenism
  - Clinical: Hirsutism, acne
  - Chemical: Elevated total testosterone and/or DHEA-S. (Labs not necessary for diagnosis however many consultants will want them)
  - Should not have virilization: rapid onset of hirsutism, increased muscle mass, deepening voice, clitoromegaly (search for underlying androgen producing neoplasm with DHEA-S and Total-T)

Hirsutism: don’t just look, ask about shaving, plucking

- Classic polycystic ovaries: >12 follicles in one ovary
- NOT SPECIFIC for PCOS. Can be seen in normally cycling women
- No need for u/s if has other 2 criteria
Other TESTING?

- LH/FSH ratio — No longer recommended, not sensitive or specific
- Tests of insulin resistance (not recommended, no reliable tests available, not sensitive or specific)
- Testosterone/DHEA-S — get if oligomenorrhea but no clinical signs of hyperandrogenism.
- Pelvic ultrasound: Get if has 1 of oligomenorrhea or hyperadrogenism (clinical or chemical)

Note: other tests (fasting glucose, oral GTT, lipids) are recommended to detect complications of PCOS but these are not necessary for diagnosis.

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(28 yo heavy periods every 5 months since menarche, hirsutism, h/o infertility, h/o GDM)

Meets diagnostic criteria with oligomenorrhea plus clinical hyperandrogenism

Aims of managing PCOS

- Manage the presenting problem(s):
  - Infertility
  - Hirsutism
  - Oligo/amenorrhea
- Manage longterm risk:
  - DM
  - CVD
  - Endometrial hyperplasia and ca

Don't forget contraception if not ready to conceive now! High risk pregnancies so want to plan them!
#1 WEIGHT LOSS
- Weight loss, Weight loss, Weight loss!
- Even modest weight loss (5 to 10 percent reduction in body weight) may result in restoration of normal ovulatory cycles
  - If ovulatory: resolution of abnormal menses, infertility, hyperandrogenism and prevention of endometrial cancer
- Normalizes glucose metabolism and decreases risk of long term complications (DM, CVD)

#2 OCP
- Combination OCP (patch or ring) first line treatment when fertility not desired
  - Regular, light, withdrawal bleeds
  - Prevention of endometrial hyperplasia
  - Decreases hirsutism via:
    - Decrease LH → decrease androgen from ovary
    - Increase sex-hormone binding globulin → decreases free testosterone
  - Caution DVT risk: BMI>30 + age>40
- If OCP contraindicated → progestin only method, will need separate treatment for hirsutism
- Hirsutism (and acne)
  - Need 6 month OCP trial to determine if effective (see prescribing guide)
  - Decrease testosterone action: if OCP fail or not OCP candidate: spironolactone (caution—it’s a teratogen so need contraception)
  - Mechanical: hair removal
  - Decrease growth of hair: Vaniqa cream (eflornithine hydrochloride) only works while taking it, not reliably covered by insurance
  - What about metformin? Not effective for decreasing hirsutism
Metformin?

#4 (after wt loss, ocp, progestin only):
- May reduce insulin levels, reduce ovarian androgens
- Allows ovulation in ~50% with PCOS
- Unknown if it protects endometrium (need to prove ovulation with D21 progesterone)
- Despite lower androgen levels, no change in hirsutism
- Lots of GI side effects

Metformin?

- May be reasons to use it....
- Improved weight loss, esp in obese women (~10% decrease BMI in 6 mos)
  - Prevent T2DM? ADA says consider in BMI>35, <60yo and impaired fasting and abnormal GTT. (Diet and exercise more effective)
  - Esp beneficial in women w prior GDM
  - Is it safe for many many years of use? No long term RCT’s looking at safety
  - Could consider short term use ie during reproductive years

Reference: Prescribing Guide PCOS: OCP

- OCP: 2nd line treatment (after wt loss).
- For higher risk VTE (bmi>30 or age>40), choose ocp with one of original progestins ie norethindrone
- If not higher risk VTE: choose OCP with minimal androgenicity: gestodene, norgestimate, drospirenone

Reference: Prescribing Guide Hirsutism

- Spironolactone : for hirsutism not responsive to OCP (or can’t take ocp):
  - 50 to 100 mg twice a day.
  - Caution hyperkalemia, dehydration, somnolence, teratogen (need reliable contraception).
- Efllornithine_cream 13.9% (Vaniqa)
  - Inhibits hair growth (not a depilatory), must use indefinitely to prevent regrowth.
  - 32% had marked improvement
  - Results in 6-8 wk; if stop, regrowth in 8 wks
**Reference: Prescribing Guide**  
**PCOS: Progestins**

- Progestin contraception: Can’t take OCP
  - Mirena IUD, Implant, DMPA (caution with DMPA: 1 yr to return to fertility)
  - “Mini-pill”: norethindrone daily
  - Achieve endometrial protection but not treatment of hirsutism
- Cyclic Progestin: Don’t want contraception but need endometrial protection
  - Induce withdrawal bleed every 2-3 months (4 bleeds per year to prevent cancer)
  - Provera 10 mg daily for 10 days

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**Reference: Prescribing Guide**  
**PCOS: Metformin**

- 3rd line treatment: induces ovulation in ~50%, lots of side effects but does improve wt loss in obese women
- May not protect endometrium, may not improve hirsutism
- Dose goal is 500 mg tid or 850 bid with meals. Start 500 qd with meal and increase by 500mg every 1-2 wks.
- Up to 6 months for ovulation to occur
- Confirm ovulation with day 21 progesterone

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**Infertility**

- Weight loss, weight loss, weight loss
- Treatment of choice: Clomid. 80% ovulate, ~33% pregnancy rate
- Metformin?
  - Metformin alone no better than placebo for live birth rate. Clomid plus metformin no better than Clomid alone.
  - Often use if unable to induce ovulation with Clomid alone
- Laparoscopic ovarian diathermy
- Gonadotropin ovarian stimulation (high rate multiples, risk of ovarian hyperstimulation)
- IVF

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**Laparoscopic ovarian diathermy?**

- Destroy ovarian cortex (theca cells → decreased androgens → increased FSH → normal follicular development → ovulation
- Use in PCOS unresponsive to clomid and clomid+metformin (~30%)
- As effective and cheaper than gonadotropin therapy with fewer multiple gestations
  - ~50% ovulate; 37% live birth in 12 mos

Farquhar, Cochrane, 2012
Reduce T2DM & CV risks

- 10-20% will develop Type 2 DM by middle age
  - Risk greatest if obese, FH of DM + PCOS
  - PCOS alone (without obesity) independent risk factor for DM: 2-5 fold increase
- Undiagnosed DM in up to 10% of those with PCOS important to diagnose pre-pregnancy to optimize pregnancy outcomes
- Great opportunity for lifestyle change, especially if desiring pregnancy:
  - Weight Loss
  - Nutrition counselling
  - Exercise

Recommendations (ACOG, other orgs)

- BP, BMI each visit, fasting lipids at diagnosis
- 2 hour OGTT q 2 yrs
  - more sensitive for impaired glucose tolerance than fasting glucose
  - if abnormal: screen annually with FBG + HBA1C to detect T2DM
- Consider Metformin if impaired glucose tolerance and obese, h/o GDM
- Pregnancy planning: contraception until ready, prenatal vitamins, remove teratogens, optimize health

Conclusions: PCOS

- Diagnosis: 2 of 3 of oligoovulation, hyperandrogenism, polycystic ovaries
- Rule out other causes amenorrhea: Upreg, TSH, PLN
- Weight loss prevents and/or corrects all short and long term issues
- Low androgenic OCP’s mainstay for women not desiring fertility
- Long term issues: Screen for impaired glu tolerance, CV disease RFs, low threshold for EMB, induce bleed with OCP or progestins at least quarterly

Asherman’s Syndrome

- Excessive uterine scarring and loss of basalis of endometrium
  - Typically due to D&C PLUS infection or hysteroscopic surgery
  - D&C alone not typically associated (eg induced abortions)
  - Only scenario in which you ovulate without menses therefore have minimal sx (sx of ovulation)
- Diagnose: failure to bleed after E plus P (can’t form endometrium): hysteroscopy to confirm.
- Treatment: Hysteroscopic lysis of adhesions
Back to the differential...

In order of frequency:
1. Pregnancy (by far most common) → Upreg
2. Polycystic ovarian syndrome (PCOS) & chronic anovulation due to obesity (40% of non-pregnant)
3. Hypothalamic amenorrhea (weight loss / exercise) (37%)
4. Hyperprolactinemia (20%, not incl breast feeding)
   - Breastfeeding
   - Hypothyroid → TSH
   - Prolactinoma → Prolactin
   - Neuroleptic meds
5. Asherman’s syndrome <5%
6. Premature ovarian failure <5% → FSH

Step 1 Amenorrhea Work-up

- Always: Urine pregnancy test. If Neg: TSH & PLN
- If hot flashes: FSH

How can we distinguish between a 35 yo with ...

1. Hypothalamic amenorrhea (low estrogen state)
2. PCOS in a normal weight woman who does not have hirsutism (normal estrogen)
3. Asherman’s Syndrome (normal estrogen)

Step 2: does she have estrogen (bricks)?

Challenge tests

- Progesterin challenge test (10 mg Provera x 10 days) determines if endogenous estrogen is present (ie does she have bricks?)
  - Distinguishes hypothalamic amenorrhea (no bleeding or just spots) from PCOS and obesity induced anovulation (full withdrawal bleed)
  - Serum estradiol level is not diagnostic

- Estrogen challenge test (Premarin 2.5 mg qd x 3 wks then Provera x 10 days) distinguishes hypothalamic amenorrhea (full withdrawal bleed) from Asherman’s (no bleeding or just spots) (ie can she make bricks, and is the outflow tract patent?)
Obtain HCG First

First Check FSH, Prolactin, TSH

FSH High

TSH High

Prolactin high

Rule out thyroid, drugs, consider MRI

Abnormally thin

Obese or clinical hyperandrogenism

Evaluate for Asherman’s

History of Uterine Surgery

Stepwise Diagnosis

2 visit amenorrhea workup

1. Visit 1: Good medication history, Ureg, TSH, PLN, FSH (unless you suspect PCOS by phenotype), and progestin challenge.

2. Visit 2: Get results and begin treatment. This will diagnose vast majority of cases

3. Visit 3: estrogen challenge—only necessary if progestin challenge negative and labs normal (leaving you with Asherman’s vs hypothalamic).

Q1: In addition to a urine pregnancy test and TSH, which of the following is the most appropriate test to obtain at this time?

1. Prolactin
2. FSH
3. Total T + DHEAS
4. Transvaginal Ultrasound
5. All of the above
6. None of the above

Recap: Amenorrhea Treatment

1. PCOS—Weight loss and protect the endometrium! (from hyperplasia due to unopposed E2) → combined contraceptives, progestin. OCP also treats hirsutism.

2. Obesity induced anovulation → same

3. Hyperprolactinemia due to microadenoma → Cabergoline (OCP’s if can’t tolerate to protect bone)

4. Functional hypothalamic amenorrhea— protect the bones! (from lack of E2) → estrogen containing contraceptives

5. Premature ovarian failure → same

6. Asherman’s syndrome → Hysteroscopy if desires pregnancy
Questions.....