Understanding Amenorrhea and PCOS

Michael Policar, MD, MPH
Professor of Ob, Gyn, and Repro Sciences
UCSF School of Medicine
policarm@obgyn.ucsf.edu

Disclosure

• I am a litigation consultant to a law firm contracted with Bayer Healthcare relating to the Mirena IUD
Amenorrhea: Definitions

- **Primary** Amenorrhea
  - Absence of menarche by
    - 16 yo with sexual development
      - ASRM: 15 yo or ≥ 5 years after breasts develop
    - 14 yo without sexual development
- **Secondary** Amenorrhea
  - No vaginal bleeding for at least
    - Three cycle lengths OR six months
  - ASRM: oligomenorrhea with < 9 menses/year

ASRM: American Society of Reproductive Medicine

Presentation Approach to Amenorrhea

- Most common diagnoses early in workup
- Minimize potentially unnecessary tests and office visits
- Separate evaluation schemes for
  - Spontaneous secondary amenorrhea
  - Post-surgical amenorrhea
  - Primary amenorrhea
  - Progestin-induced failure to withdraw
Reproductive Hormonal Axis

- HYPOTHALAMUS
  - GnRH

- ANTERIOR PITUITARY
  - FSH
  - LH

- OVARY
  - Estradiol (E$_2$)
  - Progesterone (P)

- ENDOMETRIUM

Amenorrhea: Causes

- Hypothalamic amenorrhea
- Pituitary amenorrhea
- Ovarian failure
- Outflow tract failure
- Anovulatory amenorrhea
- Pregnancy induced amenorrhea
2° Amenorrhea: Hypothalamic Amenorrhea

- **Athlete’s amenorrhea**
  - Critical ratio of muscle to body fat exceeded
  - Despite exercise, risk osteoporosis (and fracture)
- **Female athlete triad**: disordered eating, amenorrhea, and osteoporosis
  - Preoccupation with food and weight, frequent bathroom use during and after meals, laxative use, brittle hair or nails, dental cavities

2° Amenorrhea: Hypothalamic Amenorrhea

- **Anorexia nervosa**
- **Chronic stress**
- **Post-hormonal suppression**
  - Resolves within 3 months of method discontinuation
2° Amenorrhea: Pituitary Amenorrhea

- Hyperprolactinemia
  - Prolactinoma (prolactin-secreting adenoma)
  - Drugs, esp antipsychotics
  - Primary hypothyroidism
- Destructive pituitary lesions
  - Tumors, tuberculosis
  - Sheehan’s syndrome
    - Pituitary atrophy after post-partum hemorrhage
    - Hypothyroid sx, difficulty lactating, loss of pubic or underarm hair, low BP, fatigue, weight loss

2° Amenorrhea: Ovarian Failure

- > 40 years old: True menopause
- < 40 years old: Premature menopause
  - Premature ovarian failure
    - Autoimmune; follicles present
  - Resistant ovary syndrome
    - Non-autoimmune; follicles sparse
  - Gonadal dysgenesis (mosaic or Fragile X)
2° Amenorrhea: Outflow Tract Failure

- **Cervical Stenosis**
  - Occurs after TAB, cryotherapy, cone, or LEEP
  - Blockage of internal os with blood accumulation
  - Cyclic premenstrual symptoms *with uterine cramping*
- **Asherman's Syndrome**
  - Endometrial ablation (TAB or curettage) and uterine infection, leads to intrauterine synechiae
  - Cyclic premenstrual symptoms, but *no cramps*

Anovulatory Amenorrhea

- Compartments intact, but dyssynchronous
- Normal (or high) E₂ levels
- Will have progestin withdrawal bleeding because of estrogen-induced endometrial priming
- Causes
  - **Hyperandrogenic anovulation**
    - PCOS, adult onset CAH
  - **Hypothalamic anovulation**: stress, wt. loss
  - **Hyperprolactinemia**
Secondary Amenorrhea

<table>
<thead>
<tr>
<th>Hypothalamic Amenorrhea</th>
<th>Pituitary Amenorrhea</th>
<th>Ovarian Failure</th>
<th>Outflow Failure</th>
<th>Anovulatory Amenorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athlete's am. Stress Anorexia nervosa</td>
<td>Prolactinoma HypoT₄ Drugs Pit tumors Sheehans syn</td>
<td>Menopause Premat OF OIS Mosaic</td>
<td>Cervical stenosis Asherman’s syndrome</td>
<td>PCOS HyperPRL Stress</td>
</tr>
<tr>
<td>E: low</td>
<td>E: low</td>
<td>E: low</td>
<td>E: normal</td>
<td>E: normal</td>
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<tr>
<td>FSH: low</td>
<td>FSH: low</td>
<td>FSH: high</td>
<td>FSH: normal</td>
<td>LH &gt; FSH</td>
</tr>
</tbody>
</table>

Hx, PE, Preg test

Preg test POS

Pregnant

• Location
• GA Dating

Preg test NEG

TSH, PRL, MPA x10d

• Incr PRL
• Incr TSH

Evaluate, treat

• W/D Bleed

• NO W/D Bleed

Anovulation

FSH, LH

Incr FSH, LH

Ovarian Failure

NL, low FSH, LH

Central Failure

Speroff: Spontaneous 2° Amenorrhea
Amenorrhea: Clinical Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Suggestive of</th>
</tr>
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<tbody>
<tr>
<td>Pregnancy symptoms</td>
<td>• Pregnancy</td>
</tr>
<tr>
<td></td>
<td>• Missed SAB</td>
</tr>
<tr>
<td>Galactorrhea</td>
<td>• Hyperprolactinemia</td>
</tr>
<tr>
<td>Headache</td>
<td>• Hypothalamic, pituitary dz</td>
</tr>
<tr>
<td>Visual changes</td>
<td>• Pituitary tumor</td>
</tr>
<tr>
<td>Hirsuitism, acne</td>
<td>• Chronic anovulation/PCOS</td>
</tr>
<tr>
<td>Psychological stress</td>
<td>• Anovulation</td>
</tr>
<tr>
<td></td>
<td>• Hypothalamic amenorrhea</td>
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</tbody>
</table>

ASRM, Fertil Steril 2008; 90:S219
### Amenorrhea: Clinical Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Suggestive of</th>
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</thead>
<tbody>
<tr>
<td>Medications</td>
<td>• Anovulation</td>
</tr>
<tr>
<td></td>
<td>• Hypothalamic amenorrhea</td>
</tr>
<tr>
<td>Athletics, weight loss</td>
<td>• Hypothalamic amenorrhea</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>• Ovarian, central failure</td>
</tr>
<tr>
<td>Cervical or uterine surgery</td>
<td>• Cervical stenosis</td>
</tr>
<tr>
<td></td>
<td>• Asherman's syndrome</td>
</tr>
<tr>
<td>Cyclic premenstrual symptoms</td>
<td>• Cervical stenosis</td>
</tr>
<tr>
<td></td>
<td>• Asherman's syndrome</td>
</tr>
</tbody>
</table>

### Amenorrhea: Physical Examination

<table>
<thead>
<tr>
<th>Organ</th>
<th>Signs</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>• Hirsuitism</td>
<td>• PCOS</td>
</tr>
<tr>
<td></td>
<td>• Acne</td>
<td></td>
</tr>
<tr>
<td>Breasts</td>
<td>• Galactorrhea</td>
<td>• ↑ prolactin</td>
</tr>
<tr>
<td>Abdomen</td>
<td>• Uterus enlarged</td>
<td>• Pregnancy</td>
</tr>
<tr>
<td>Cervix</td>
<td>• Pinpoint os</td>
<td>• Cervical stenosis</td>
</tr>
<tr>
<td>Uterus</td>
<td>• Enlargement</td>
<td>• Pregnancy</td>
</tr>
</tbody>
</table>
2° Amenorrhea: Visit 1

- History, physical exam
- Highly sensitive urine pregnancy test

Findings
- Galactorrhea on hx, PE: galactorrhea W/U
- Pregnancy test result:
  - Positive: DX=PREGNANCY; locate, date
  - Neg, unprotected sex: Use BC, repeat 2 wk
  - Neg, protected or no sex: proceed to lab

2° Amenorrhea: Visit 1

- Order lab tests
  - Prolactin, TSH level (not TFT's)
  - If signs of androgen excess: testo, DHEAS
- Progestin challenge
  - MPA 10 mg PO QD x 10 days OR
  - Micronized progesterone 400 mg x10d
- Schedule F/U visit 3 weeks
2º Amenorrhea: Visit 2

- Review lab results
  - PRL elevated: hyperprolactinemia evaluation
  - TSH elevated: 1º hypothyroidism evaluation
  - Testosterone elevated: evaluate ovarian tumor
  - DHEAS elevated: evaluate for adrenal tumor
- Review result of P challenge
  - Withdrawal bleed: DX= ANOVULATION
  - No withdrawal bleed: order FSH

Anovulatory Amenorrhea

- Work up not necessary, unless virilization
  - If PCOS, check lipids and fasting +2º PGL glucose levels
- Management:
  - Desire contraception
    - Cycle on OC's
  - Desire pregnancy
    - Induce ovulation with clomiphene
  - Neither: cycle bleeding, prevent hyperplasia
    - MPA or microP x 10-14d every 1-2 months
    - LN-IUS (Mirena)
2° Amenorrhea: Visit 3

- Increased FSH, LH: **DX = OVARIAN FAILURE**
  - > 40 years old: Menopause
  - < 40 years old: Premature menopause
    - Karyotype: if < 30: gonadectomy if Y ch’some
    - Autoimmune POF: screen with TSH, anti-thyroid antibodies, FBG, electrolytes
    - Ovarian biopsy not indicated
      - If pregnancy is desired, refer for ART (ovum donation)

- Normal, low FSH, LH: **DX=CENTRAL FAILURE**
  - If explained by athletics, anorexia, poor nutrition, or stress, no further evaluation needed
  - If unexplained or CNS symptoms, exclude hypothalamic or pituitary tumor
    - “Pituitary MRI” or head CT with contrast
  - Provide estrogen replacement: low dose OC
  - Pregnancy desired: gain weight or induce ovulation with clomiphene, HMG, or pulsatile GnRH
Which feature is a clinical criteria for the diagnosis of PCOS?

a) Obesity  
b) Hyperinsulinemia  
c) Oligo-anovulation  
d) Glucose intolerance  
e) All of the above
PCOS: Overlapping Syndromes

* Hyperandrogenism (clinical or biochemical)
* Chronic oligo-anovulation
* Exclusion of other disorders

[PAO on ultrasound in Rotterdam criteria set]

PCOS Diagnostic Criteria

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<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Androgens</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Periods</td>
<td>Irregular, fewer than 8 per year</td>
<td>Irregular</td>
<td>Irregular OR</td>
</tr>
<tr>
<td>Ovarian morphology on ultrasonography</td>
<td>Not included in NIH criteria</td>
<td>Polycystic morphology</td>
<td>Polycystic morphology</td>
</tr>
</tbody>
</table>

AE-PCOS: Androgen Excess and PCO Society
PCOS: Chronic Oligo-Anovulation

- Menstrual irregularity
  - Amenorrhea, oligomenorrhea
  - Variable cycle length
  - DUB (dysfunctional uterine bleeding)
- Absence of menstrual symptoms
- Prior need for ovulation induction
- No ovulation can be documented with
  - Ovulation prediction kit
  - Basal body temperature measurement
  - Luteal phase progesterone level

PCOS: Hyperandrogenism

- Skin manifestations
  - Hirsutism (65%); peripubertally or adolescence
  - Acne (25%), seborrhea, alopecia
  - Mild to moderate acanthosis nigricans
  - Obesity (35% to 60%)
**Polycystic Appearing Ovaries (PAO)**

- A functional result of local ovarian hyperandrogenism... “not a disease”
- Low FSH results in “mid-antral arrest”
- Polycystic ovaries
  - 2.8 times normal size (volume > 10 mL)
  - Atretic follicles doubled
  - Ultrasound: “String of black pearls” (12 follicles/ovary)
- Prevalence of PAO
  - 75% with chronic anovulation
  - 16-23% of normal ovulatory women
  - 14% of OC users

**Not...Criteria for PCOS Diagnosis**

- Obesity is not a diagnostic criterion for PCOS, and approximately 20% of women with PCOS are not obese
- Insulin resistance
- Polycystic appearing ovaries (PAO) on ultrasound
- Gonadotropin levels or ratios
Causes of Hyperandrogenism

- Ovarian
  - Polycystic ovary syndrome - PCOS
  - Ovarian androgen tumors
- Adrenal
  - Congenital adrenal hyperplasia
  - Cushing’s syndrome
  - Adrenal androgen tumors
- Exogenous androgens; drug effects
- Idiopathic

Virilization: Danger Signs

- Rapid onset of thick, pigmented hair
- Male pattern baldness
- Clitoral hypertrophy
  - “Cliteromegaly” defined as > 1 cm at base
- Deepening of the voice
- Androgenic muscle development
- Breast atrophy, masculine habitus
Ovarian Tumors

- Androgen secreting tumors
  - Sertoli-Leydig cell
  - Hilar cell
  - Lipoid cell
  - Adrenal rest cell
- Total Testosterone > 200 ng/dL
  (in menopause, T > 100 ng/dL is abnormal)
- Diagnostic imaging
  - Pelvic/transvaginal ultrasound
  - Pelvic CT scan

Late Onset Congenital Adrenal Hyperplasia

- AKA: Non-classical CAH (NCCAH)
- Most common form is 21-hydroxylase deficiency
- First seen in childhood or adolescence
  - Late onset type is autosomal recessive
  - Most commonly seen in E European Jews (1/27), Hispanics (1/40), Jugoslavs (1/50), Inuits, Italians
- Laboratory confirmation
  - Fasting morning follicle phase 17-OHP > 2 ng/ml
  - Confirm high level with ACTH stimulation test
**Cushing’s Syndrome**

- Overproduction of cortisol + adrenal androgens
- **Caused by**
  - 1°: Adrenal tumors, hyperplasia
  - 2°: ACTH secreting adenoma
- **Presentation**
  - Hypertension
  - Moon facies, buffalo hump, easy bruising
  - Centripetal obesity, striae
  - Proximal myopathies, osteoporotic fractures
- **Laboratory**
  - 24° urinary free cortisol > 100 mcg/24 hours
  - Confirmed with low dose dexamethasone suppression test

**Adrenal Tumors**

- **Pathology**
  - Adrenal carcinomas: usually large
  - Adrenal adenomas: small, very uncommon
- Total Testosterone < 200 ng/dl
- DHEAS > 700 ug/dl
- Confirmation of diagnosis
  - CT or MRI scan
- Incidentally discovered adrenal masses require evaluation
Medications

• Anabolic Steroids (methyl-T or injected)
• Phenytoin – Dilantin®
• Cyclosporine – Neoral®
• Minoxidil – Loniten®, Rogaine®
• Danazol -Danocrine
• Glucocorticoids
• DHEA (food supplement)

Case Study

• 22 year old woman with unpredictable menses every 5-8 weeks, lasting 2-8 days since menarche
• Recent immigrant from Mexico
• Backache and cramps before menses, but no other molimenal symptoms
• BMI=28, BP 122/78
• PE: mild acne, upper lip has some hair growth, no galactorrhea
Which studies would you offer her?

a) 17 alpha hydroxy progesterone (17-OHP)
b) Total testosterone
c) FSH, LH levels
d) Pelvic ultrasound for PAO
e) All of the above
f) None of the above

Diagnosis of PCOS

- PCOS is a *clinical diagnosis*
  - Chronic oligo-anovulation + hyperandrogenism
- Lab tests may be necessary to...
  - Differentiate PCOS from other causes of
    - Virilization
    - Amenorrhea
  - Screen (or test) for sequelae of PCOS
    - Metabolic syndrome (DM, lipids, HTN)
    - Endometrial hyperplasia
  - Choose optimal drug for ovulation induction
Basic Evaluation of PCOS

• Check blood pressure
• Measure BMI + waist circumference (+ hip)
  – Waist circumference >35 inches
  – Waist/hip ratio > 0.72
• In women with “clinical PCOS”, screen for
  – T2DM: FBS+ 2⁰ post-glucose load test with 75-g glucose
    • Impaired glucose tolerance (IGT): 140-199 mg/dl
    • T2DM: > 200 mg/dl
  – Hyperlipidemia: fasting lipid panel
  – Screen both every 2 years; annually if IGT

Further Evaluation of PCOS

• If cycle irregularity, add
  – Prolactin, TSH
• If amenorrhea (≥ 3 missed menses or LMP ≥ 6 months), add
  – Prolactin, TSH, pregnancy test
  – Progestin challenge
  – If no withdrawal bleed, check LH, FSH
• If dysfunctional uterine bleeding, add
  – Pregnancy test, hematocrit
  – Endometrial biopsy if hyperplasia suspected
Further Evaluation of PCOS

- If hirsuitism, *add*
  - 17a-hydroxy progesterone (17-OHP), if risk factors for late onset CAH
  - Normal morning follicle phase level less than 2 ng/mL or random level less than 4 ng/mL
- If non-hirsute, *add*
  - Total testosterone
  - Some experts recommend free testosterone, but only from reliable lab

Further Evaluation of PCOS

- If virilization (in addition to hirsuitism), *add*
  - DHEAS (for adrenal tumor) *and*
  - Total testosterone (for ovarian tumor)
    - If ↑T, pelvic ultrasound for ovarian tumor
- If stigmata of Cushing’s Disease, *add*
  - Urinary 24 hour free cortisol *or*
  - Overnight dexamethasone suppression test
PCOS: Goals of Treatment

- Support lifestyle changes to achieve normal body weight
- Treat hirsuitism and acne by reducing androgen
- Protect the endometrium against unopposed E
- Induce ovulation to achieve pregnancy
- Minimize insulin resistance to prevent (or delay) type 2 diabetes
- Minimize the impact of metabolic syndrome on the development cardiovascular disease

Treatment of PCOS: Anovulation

- **Weight loss** (to BMI <27)
- **Combination oral contraceptives**
  - Regulates cycles
  - Prevents endometrial hyperplasia
  - Provides contraception
  - Decreases free T; controls acne and hirsuitism
  - *May prevent atheroma formation and reduce CV risk*
Treatment of PCOS: Anovulation

Cyclic progestins
- Given first 14 days of each *or every other* month
  - Regulates cycles
  - Prevents endometrial hyperplasia
  - No contraceptive effect (unless DMPA or POP)
  - No studies as treatment for hirsuitism

Treatment of PCOS

Improve (reduce) insulin resistance
- Metformin (Glucophage); insulin-sensitizing agent
  - Improves insulin sensitivity
  - Decreases LH, decreases free T
  - May increase SHBG
- Metformin use
  - 500 mg bid to tid (or 850 mg bid)
  - Do not use if creatinine > 1.4 mg/dl or risk of renal dysfunction (risk of lactic acidosis)
  - GI adverse effects
Metformin in Women with PCOS

- **Restores normal menses and ovulation** in 68-95% of women with PCOS; uses include
  - Ovulation induction
  - Treatment of Type 2 DM
  - Regularize menstrual cyclicity
- **Unproven uses** (and not currently recommended)
  - Treatment of hirsuitism or obesity
  - *Prevention* of diabetes or CVD morbidity
  - Routine treatment of PCOS without glucose intolerance

PCOS and Cardiovascular Risk

- Women with PCOS should be screened for
  - CV risk by determination of BMI
  - Fasting lipid and lipoprotein levels
  - Metabolic syndrome risk factors
- **Regular exercise and weight control are proven methods to reduce CV morbidity and mortality**
  - These modalities should be considered before prescription drugs are used

*ACOG Practice Bulletin Obstet Gynecol* 2009;114:936
PCOS and Cardiovascular Risk

- Exercise with dietary change consistently reduces diabetes risk comparable to or better than meds
- Recent studies have suggested little benefit to the addition of metformin above lifestyle therapy alone
- Currently, data are insufficient to recommend insulin-sensitizing agents prophylactically to prevent diabetes in women with PCOS

ACOG Practice Bulletin Obstet Gynecol
2009;114:936

Regional Hair Removal

- Bleaching – skin irritation
- Depilation (cut to skin surface)
  - Shaving – irritation, acne, hasten growth
  - Chemical depilatories – skin irritation
- Epilation (remove hair to dermal bulb)
  - Plucking – time consuming, scaring
  - Waxing – temporary
  - Epilatory device
Hair Removal – Permanent

- **Hair electrolysis**
  - Electric current - multiple treatments
  - $60 - $100 per hour, $1,000 to $3,000 per yr
- **Laser hair removal/ IPL (intense pulsed light)**
  - 20-80% of hair removed in 2-3 treatments
  - Average 50% less hair at 4 months
  - Nd: YAG laser
  - Long-pulse ruby or alexandrite
  - 1 to 3 hours per treatment

Hirsuitism: A Multidisciplinary Approach

- Clinician
- Aestetician
- Laser therapist
- Electrologist
- 3-6 months of treatment required before improvement for most patients
**Hirsuitism: Oral Contraceptives**

- **Mechanism**
  - Progestin reduces testosterone secretion
  - Estrogen increases SHBG; reduces free T
  - Drospirenone may block androgen receptor
- **Stop further hair growth; will not reverse hirsuitism**
- **Response is slow; > 6 months of treatment required to demonstrate impact**
- **Choice of progestin**
  - Preferred: drospirenone, desogestrel, norgestimate, ethinodiol diacetate
  - Avoid: l-norgestrel (relatively more androgenic)

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**Spironolactone**

- **Inhibits binding of DHT to androgen receptor**
- **Dosage of 75 mg to 200 mg per day**
  - Begin with 50 mg bid, if no response after 3 mo increase to 100 mg bid
- **Adverse effects**
  - Nausea, fatigue, headache
  - Hyperkalemia (if renal impairment or diabetes)
- **Change in Ferriman-Gallwey (hirsuitism) score**
  - Spironolactone alone ↓ 28%
  - Spironolactone+OC ↓ 41%
Anti-Androgen Drugs

- Both drugs indicated for prostate cancer
- **Finasteride (Proscar®)**
  - 5 mg/d for 6 mo in 17 hirsute women
  - T increased, DHT reduced
  - Ferriman-Gallwey score improvement = ↓ 47%
  - Finasteride + BCPs improvement = ↓ 60%
  - 2.5 mg/d = 5 mg/day PO in reducing hirsuitism scores
- **Flutamide (Eulexin®)**
  - F-G score: flutamide (↓ 71%) vs finasteride (↓ 41%)
  - Flutamide dose: 250 mg/day

References

References