The 7th Vital Sign: the Menstrual Cycle

DATE: February 7, 2017  PRESENTED BY: Amanda S. Bruegl, MD
Disclosures

• None
Menstrual Cycle

- Endometrial polyps/fibroids/hyperplasia
- Brain Tumors
- Ovarian Insufficiency (Fragile X)
- PID/Cervicitis
- PCOS
- Adrenal Dysfunction (congenital adrenal hyperplasia)
- Androgen secreting tumors
- Hyperprolactinemia
- Endometrial Cancer
- Cervical Dysplasia/Cancer
- Hypothyroidism
- Abnormal Karyotype (45X; 46 XY)
- Mullerian Agenesis
- Mullerian polyps/fibroids/hyperplasia
Today’s Agenda

I. Premenstrual Development
II. The Menstrual Years – Normal and Abnormal
III. Menopause
Premenstrual Development
Maturation of the HPO Axis (Hypothalamic-Pituitary-Ovary)
Maturation of the HPO Axis (Hypothalamic-Pituitary-Ovary)
# Pubertal Changes in Girls

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Hormones</th>
<th>Median Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thelarche</td>
<td>Breast Development</td>
<td>Estrogen from ovaries</td>
<td>9-10</td>
</tr>
<tr>
<td>Adrenarche</td>
<td>Axillary and pubic hair</td>
<td>DHEA, DHEA-S from adrenal glands</td>
<td>11.5</td>
</tr>
<tr>
<td>Peak Height Velocity</td>
<td>Growth spurt</td>
<td>Growth Hormone</td>
<td>---</td>
</tr>
<tr>
<td>Menarche</td>
<td>Onset of menses</td>
<td>FSH/LH, Estrogen, Progesterone</td>
<td>11-12</td>
</tr>
</tbody>
</table>
Educational Opportunity at Preventive Health Care Visits

- ACOG recommends initiating discussion of pubertal development to children and their caregivers at the 7 year and 8 year visits.
- Visit should include standard history and physical as well as an inspection of external genitalia.
- If breast development noted an exam, inform patient and caregiver that menses often follow within 2-3 years afterward.
Case #1: No menses

Chief Complaint: 16 yo female presents with her mother and states that her periods have not started

History:
- normal birth and childhood development
- breast development started at age 12
- not sexually active

PE:
- normal BMI
- Tanner 3 breast development and presence of axillary and pubic hair, normal external
Case #1: No menses

DDx:

- Constitutional Delay
- Gonadal Dysgenesis
- Endocrine Disorder (TSH/PRL)
- Pregnancy
- Primary Ovarian Insufficiency
- Eating disorder/elite athlete/malnutrition
- ...
Case #1: No Menses

Breast Development

Yes: Ovaries producing estrogen

No: Issue within HPO Axis
Case #1: No Menses

+ Breast Development

U/S

+ Uterus

MRI vs Referral OB/Gyn or REI

- Uterus

Referrals:
Genetic Counseling
OB/Gyn or REI
SW
Case #1: No Menses

**Hypergonadotrophic, Hypogonadism**
1. Gonadal Dysgenesis (e.g. Turner’s Syndrome, 46 X)
2. Premature ovarian insufficiency
3. Galactosemia

**Hypogonadotrophic, Hypogonadism**
1. Thyroid Disease or Prolactinoma
2. Athlete’s Triad/Eating Disorder
3. Constitutional Delay
4. Kallman’s Syndrome (Impaired GnRH)
Maturation of the HPO Axis (Hypothalamic-Pituitary-Ovary)
Case #1: No Menses
When to start a work up

• No menarche within 3 years of thelarche
• No menses by age 14 with signs of hirsutism
• No menses by age 14 and history/exam concerning for eating disorder
• No menarche by age 15

- History/Physical Exam
  - TSH/PRL
  - hCG
  - Abdominal ultrasound

- MRI
  - FSH
  - Testosterone
  - Genetics/Karyotyping
Case #2: Irregular Menses

Chief Complaint: 17 yo female presents with complaint of irregular cycles

History:
- normal birth and childhood development
- menarche at age 15; cycles have never been regular, q
  27-40 days lasting 4-8 days duration

PE: Sexually active, no intercourse
- BMI 95th %; normal breast development and hair growth pattern
Case #2: Irregular Menses

DDx:

- Pregnancy
- Immature HPO Axis
- Polycystic Ovary Syndrome (PCOS)
- PID/Cervicitis
- ...

OHSU
Case #2: Irregular Menses
What is regular for an adolescent?

<table>
<thead>
<tr>
<th>Normal Menstrual Cycles in Adolescent Girls</th>
</tr>
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<tbody>
<tr>
<td>Menarche (median age)</td>
</tr>
<tr>
<td>Mean cycle interval</td>
</tr>
<tr>
<td>Menstrual flow length</td>
</tr>
<tr>
<td>Menstrual product use</td>
</tr>
</tbody>
</table>

ACOG Committee Opinion 651: Menstruation in Girls and Adolescents
Case #2: Irregular menses
When to start a work up

- Menses occur more frequently than q 21 days or less frequently than q 45 days
- Last more than 7 days
- Occur 90 days or more apart

- History/Physical Exam
- TSH/PRL
- hCG
- Pelvic Exam +/- U/S

- STI Testing
- Free Testosterone/SHBG (biochemical hyperandrogenism)
- Start eval for congenital adrenal hyperplasia
# Case #2: Irregular menses

## Management Options

<table>
<thead>
<tr>
<th>Condition</th>
<th>Management Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immature HPO Axis</td>
<td>Education, Expectant Management</td>
</tr>
</tbody>
</table>
| Pregnancy            | 1. Evaluation for safety, sexual trauma  
                        2. Continuation of pregnancy vs termination  
                        3. Decision to parent vs adoption |
| PID/Cervicitis       | Antibiotics per CDC guidelines |
| PCOS                 | 1. Evaluation of weight: nutrition counseling and exercise if overweight/obese  
                        2. Diabetes screening  
                        3. Regulation of menses: OCP (can help decrease hirsutism), progesterone IUD  
                        4. Fasting Lipids as applicable |
Case #3: Heavy Menses

Chief Complaint: 16 yo female heavy periods

History:
- Menarche at age 13 with cycles occurring q 29 days
  lasting 5 days duration; uses 8-10 menstrual products per day

PE:  - Not sexually active
     - Normal height/weight;
     - Normal breast development and hair growth pattern
Case #3: Heavy menses
When to start a work up for a bleeding disorder

- Menses requiring frequent pad or tampon changes (soaking every 1-2 hours)
- Heavy Bleeding since menarche
- Subjectively heavy and associated with history of bruising or bleeding (≥ 2 episodes/month of epistaxis, bruising, gingival bleeding)
- Family history of a bleeding disorder
Case #3: Heavy menses
Initial work up for a bleeding disorder

Screen + for increased risk of bleeding disorder

CBC
PT/PTT
Fibrinogen/Thrombin Time

Suspected vWD:
vWF Antigen
vWF ristocetin cofactor activity
Factor VIII activity

WNL
Abnormal Results

Hormonal Manipulation of cycles
Hematology Referral
The Menstrual Years: Normal and Abnormal
The Menstrual Years: Normal Menstruation

The menstrual cycle
- Follicular phase
  - Menstruation
  - Follicular development
- Luteal phase
  - Ovulation
  - LH
  - Progesterone

Hypothalamus
GnRH
Anterior Pituitary
FSH/LH
Ovaries
E/P
Uterus
The Menstrual Years: Normal Menstruation

<table>
<thead>
<tr>
<th>Normal Menstrual Cycles in the mature HPO Axis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle interval</td>
</tr>
<tr>
<td>Menstrual flow length</td>
</tr>
<tr>
<td>Menstrual product use</td>
</tr>
</tbody>
</table>
Abnormal Uterine Bleeding

**Structural**
- PALM
  - P: Polyps
  - A: Adenomyosis
  - L: Leiomyoma
  - M: Malignancy/Hyperplasia

**Non-Structural**
- COEIN
  - C: Coagulopathy (vWD, coumadin)
  - O: Ovulatory Dysfunction
  - E: Endometrial
  - I: iatrogenic/Infection
  - N: NOS
Case #1

Chief Complaint:  35 G3P2013 presents with intermenstrual bleeding

History:
- menarche at 12
- Typical cycles: q 31 days lasting 4 days, regular
- Last two cycles: spotting in between cycles
- No history of STIs or abnormal paps, last pap 1 year ago
- monogamous relationship, negative screen for intimate
Case #1

PE:

- BMI 28, VSS
- Normal external genitalia, vaginal epithelium intact and free from lesions
- Cervix normal in appearance, non-friable
- Bimanual exam reveals 8 week sized retroverted uterus, no CMT, no palpable masses
Case #1

Evaluation:

- Labs: hCG, TSH, PRL, +/- CBC, +/- STI testing
- Endometrial Biopsy
  Risk Factors: BMI > 24, irregular bleeding
- TVUS
  Good initial screen for structural factors
**AUB – Structural Causes**

<table>
<thead>
<tr>
<th>Structural Anomaly</th>
<th>TVUS Findings</th>
<th>Management Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial Polyps</td>
<td>Nonspecific endometrial thickening</td>
<td>Hysteroscopy, D&amp;C</td>
</tr>
<tr>
<td></td>
<td>Endometrial mass</td>
<td></td>
</tr>
<tr>
<td>Adenomyosis</td>
<td>Normal uterus</td>
<td><strong>Medical Management</strong>: Hormonal Agents</td>
</tr>
<tr>
<td></td>
<td>Globular shaped uterus</td>
<td><strong>Surgical Management</strong>: Hysterectomy</td>
</tr>
<tr>
<td></td>
<td>Enlarged uterus</td>
<td></td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>Fibroids</td>
<td><strong>Medical Management</strong>: Hormonal Agents</td>
</tr>
<tr>
<td>Submucosal</td>
<td></td>
<td><strong>Surgical Management</strong>: Myomectomy</td>
</tr>
<tr>
<td>Subserosal</td>
<td></td>
<td><strong>Surgical Management</strong>: Hysterectomy</td>
</tr>
<tr>
<td>Hyperplasia/Malignancy</td>
<td>Thickened endometrial stripe</td>
<td><strong>Hyperplasia without Atypia</strong>: Progesterone</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity of uterine lining</td>
<td><strong>Hyperplasia with atypia</strong>: Hysterectomy vs medical management</td>
</tr>
</tbody>
</table>
Case #2

Chief Complaint: 29 G2P2002 presents with heavy periods.

History:
- Menarche at 11
- Typical cycles: q 27 days X 5 days
- No history of STIs or abnormal paps
- Hx of NSVD X 2 with 1 L PPH with birth of each child

PE:
- BMI 30, VSS
- Normal uterus, no masses
Next Steps:

- Consider Endometrial Biopsy
  Risk Factors: BMI > 24, heavy bleeding
- CBC, PT, PTT, Fibrinogen, TT +/- vWD labs
Screening for Hemostasis Disorder

- Heavy menses since menarche
- One of the following:
  - History of Postpartum Hemorrhage
  - Surgery-related bleeding (post op hematoma, excessive blood loss during surgery)
  - Bleeding associated with dental work
- Two or more of the following:
  - Epistaxis, 1-2X per month
  - Frequent gum bleeding
  - Family history of bleeding symptoms

ACOG Committee Opinion #580
Abnormal Uterine Bleeding – Ovulatory Dysfunction

Physiologic
- Lactation
- Adolescence
- Pregnancy
- Perimenopause

Iatrogenic
- Chemotherapy
- Radiation
- Surgery

Pathologic
- Hypothalamic Dysfunction
- Primary Pituitary Disease
- Hyperprolactinemia
- Thyroid disease
- PCOS
- Congenital Adrenal Hyperplasia
- Androgen Secreting Tumors
- Premature Ovarian Insufficiency
Case #3 – Ovulatory Dysfunction

Chief Complaint: 36 yo presents for well woman exam

History:

- menarche at 11
- cycles regular at first, now 3-4/year lasting ~10 days
- no symptoms of breast tenderness, cramping with menses or other PMS symptoms
- No history of STIs or abnormal paps

PE:

- BMI 35, VSS
- mail pattern hair growth on chin
- Skin: acne on face, chest, back
Next Steps:
- EMB
  < RF: Obesity, anovulatory bleeding
- TSH/PRL/hCG
- +/- FSH
- +/- 17-OH-P (suspicion of CAH)
- +/- 24 hour urinary free cortisol (suspicion of Cushing’s Disease)
- Consider TVUS
Case #3 – Ovulatory Dysfunction

PCOS
# PCOS – Diagnostic Criteria

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<tbody>
<tr>
<td>3/3</td>
<td>2/3</td>
<td>3/3</td>
</tr>
</tbody>
</table>

- **Menstrual irregularity:** oligo- or anovulation
- **Clinical and/or biochemical signs of hyperandrogenism**
- **Exclusion of other disorders (e.g. CAH, androgen secreting tumors, Cushing’s Syndrome)**
- **Oligo- or anovulation**
- **Clinical and/or biochemical signs of hyperandrogenism**
- **Polycystic ovaries (ultrasound)**
- **Clinical and/or biochemical signs of hyperandrogenism**
- **Ovarian dysfunction: oligo- or anovulation or polycystic ovaries on ultrasound**
- **Exclusion of other disorders**
PCOS – Polycystic ovaries

At least one ovary with:

≥ 12 follicles, ≥ 2 - 9 mm diameter OR ovarian volume > 10 mL

At least one ovary with:

≥ 25 follicles if an ultrasound transducer is used with ≥ 8 MHz frequency
PCOS – Hyperandrogenism

Clinical
- Hirsutism
- Acne
- Alopecia

Laboratory
- Elevated testosterone
PCOS – Comorbid Conditions

- 2 h OGTT
- Exercise, Weight Loss
- Fasting Lipids
- Progesterone
- Diabetes
- Obesity
- Dyslipidemia
- Endometrial Proliferation/Hyperplasia/Cancer
Be Seen AND Heard!

My periods have always been all over the place. Then I gained, like, twenty five pounds all at once, got horrible acne and other awful stuff that did nothing for my self confidence! I went to my gynecologist and was finally diagnosed with PCOS, Polycystic Ovary Syndrome. Now I know what the problem is, and I can work with my doctor to treat it.

Left unchecked, PCOS can lead to obesity, diabetes, high blood pressure, metabolic disorder, infertility and depression. Early diagnosis and treatment is advantageous.
Non-PCOS: Hyperandrogenism

Androgen Secreting Tumor

Physical Findings
- Rapid onset hirsutism
- Deepening of voice
- Clitoromegaly
- Increased muscle mass

Evaluation
- DHEA-S (adrenal source)
- Testosterone
- CT A/P (adrenal mass, ovarian mass)
Non-PCOS: Non Classical Congenital Adrenal Hyperplasia

Britten et al. Primary amenorrhea with hypertension; Med J Aust 2013; 199 (8)
Non-PCOS:
Non Classical Congenital Adrenal Hyperplasia

Risk Factors
- Eastern European Jewish women (1:27)
- Hispanic (1:40)
- Slavic (1:50)
- Italian (1:300)

Evaluation
- Morning 17-OH-P > 200
- ACTH challenge test
Ovulatory Dysfunction and Abnormal Uterine Bleeding – Regulating Cycles

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Options to Regulate</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-18</td>
<td>OCPs</td>
</tr>
<tr>
<td>19-39</td>
<td>OCPs, Progesterone containing IUD, Weight loss and Exercise</td>
</tr>
<tr>
<td>40-menopause</td>
<td>Cyclic progesterone, progesterone containing IUD, OCPs</td>
</tr>
</tbody>
</table>

ACOG practice bulletin on Bleeding due to Anovulation
Abnormal Uterine Bleeding – When to Biopsy

<table>
<thead>
<tr>
<th>Age Range</th>
<th>EC Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-19</td>
<td>0.2/100,000</td>
</tr>
<tr>
<td>20-34</td>
<td>1.6%</td>
</tr>
<tr>
<td>35-44</td>
<td>6.2%</td>
</tr>
<tr>
<td>40-menopause</td>
<td>13-24/100,000</td>
</tr>
</tbody>
</table>

ACOG practice bulletin on Bleeding due to Anovulation

- Endometrial biopsy if:
  - Age 45 or older
  - Age 35 with other risk factors for Endometrial Cancer
  - Not responding to hormonal regulation
  - Any point after menopause
# Endometrial Cancer Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing Age</td>
<td>2-3</td>
</tr>
<tr>
<td>Residency in North America or Northern Europe</td>
<td>3-18</td>
</tr>
<tr>
<td>Higher level of education or income</td>
<td>1.5-2</td>
</tr>
<tr>
<td>White Ethnicity/Race</td>
<td>2</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>3</td>
</tr>
<tr>
<td>History of Infertility</td>
<td>2-3</td>
</tr>
<tr>
<td>Menstrual Irregularities</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Unopposed Estrogen</strong></td>
<td><strong>10-20</strong></td>
</tr>
<tr>
<td>Tamoxifen Use</td>
<td>2-3</td>
</tr>
<tr>
<td>Obesity</td>
<td>2-5</td>
</tr>
<tr>
<td>Diabetes, HTN, Gallbladder disease, thyroid disease</td>
<td>1.3-3</td>
</tr>
<tr>
<td>Lynch Syndrome</td>
<td><strong>22-50% lifetime risk</strong></td>
</tr>
</tbody>
</table>
Abnormal Uterine Bleeding – What is in a biopsy?

- EMB samples ~ 4% of the endometrial cavity
- Sensitivity for detecting abnormalities
  - EMB: 68%
  - Hysteroscopy, D&C: 78%
Abnormal Uterine Bleeding – How often to biopsy?

- Persistent or recurrent bleeding needs to be evaluated
- TVUS as an adjunctive tool
  - Premenopausal
    - Proliferative Phase: EMS = 4-8 mm
    - Secretory Phase: EMS = 8-14 mm
  - Postmenopausal
    - EMS ≤ 4 mm
Postmenopausal Bleeding
Postmenopausal bleeding

- EMB
  - Benign
  - CAH or Cancer

- TVUS
  - ≤ 4mm: Observe
  - > 4mm: EMB
Be Seen AND Heard!

Did you tell your doctor about everything that's been worrying you?

No I didn’t tell him! He never understands what I'm saying!

Well, did he examine you?

I'm not taking my clothes off! He is not going to look at me down there!

How about if we get you an appointment with a gynecologist, mom? You pick, man or woman, and I'll go with you, okay?

YOU'LL SEE... IT'LL BE EASY...

EASY FOR WHO, MISSY?

If you have a hard time communicating with your doctor, take control of the situation. You can go to a different doctor, take a friend or family member with you, write down your questions.
Menstrual Cycle

- Endometrial polyps/fibroids/hyperplasia
- Mullerian Agenesis
- Brain Tumors
- Abnormal Karyotype (45X; 46 XY)
- Cervical Dysplasia/Cancer
- Hypothyroidism
- Endometrial Cancer
- Hyperprolactinemia
- Androgen secreting tumors
- Ovarian Insufficiency (Fragile X)
- PID/Cervicitis
- PCOS
- Adrenal Dysfunction (congenital adrenal hyperplasia)
- Mullerian Agenesis
- OHSU
Thank You