Abnormal Uterine Bleeding
Adolescent Evaluation & Treatment

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Objectives
• Describe Normal Menstrual Cycle
• Correlate Menstrual History
• Comprehend Complexities
• Define: Abnormal Uterine Bleeding
  Dysfunctional Uterine Bleeding

Objectives
• Know the optimal imaging procedure
• Determine diagnosis
• Establish treatment plan

The Menstrual Cycle 101
Foundation
• Dysmenorrhea
• Premenstrual Syndrome
• Amenorrhea (Primary and Secondary)
• Abnormal Uterine Bleeding
• Endometrial - Uterine Pathology
• Menopause - Postmenopausal Bleeding
• Contraception - Infertility

The Menstrual Cycle 101
Key Concepts
• Cycle Purpose: To establish a pregnancy
• Hypothalamic-Pituitary-Ovarian Axis
• Dominant Follicle
• Endometrial Complexities

The Menstrual Cycle 101
Objectives
• Describe Normal Menstrual Cycle
• Correlate Menstrual History
• Comprehend Complexities
• Establish Foundation for Future Diagnosis and Treatment
• Quiz – ABFM Questions
“If he was wise in any respect, it was in the knowledge of his own ignorance”

Socrates (469-399 BC)

Hypothalamic-Pituitary-Ovarian-Uterine Axis

- The descriptions are eloquent
- The explanations of the initiation and propagation of the mechanisms are insufficient or absent

- What determines the selection of the dominant follicle?
- What makes the ova leave the ovary Day 14?
- How does the ovary and corpus luteum know that a pregnancy has occurred?
- Why does the corpus luteum involute?
Endometrium

The endometrium is one of the most complex tissues in the human body.

It is always changing.

Leon Speroff, M.D.
Clinical Gynecologic Endocrinology and Infertility

Endometrium

- Endocrine – regulatory substances from glandular organ to target cells
- Autocrine – produces regulatory substances that act on itself
- Paracrine – regulatory substances act on nearby cells

Endometrial Complexities

- The composition and function is determined by the dominant follicle
- Estrogen & Progesterone vary
- Cellular response varies
Endometrial Complexities

- Spiral arteries respond to estrogen, progesterone and prostaglandins
- Basal arteries do not respond
- PGF<sub>2α</sub> vasoconstriction
- PGE<sub>1</sub> vasodilation
- The dominant follicle determines the estrogen/progesterone ratios and the prostaglandin ratios

Endometrial Regulatory Substances

Estrogen, Progesterone, prostaglandins, prostacyclin, thromboxanes, leukotrienes, interleukins, gonadotropin releasing hormones, inhibin, activin, interferon, colony stimulating factor, prolactin, relaxin, renin, epidermal growth factor, insulin-like growth factor, corticotropin releasing factor, fibronectin, tumor necrosis factor, testosterone, endorphin, dopamine, serotonin, & norepinephrine.

Speroff, Glass & Kase
Clinical Gynecologic Endocrinology and Infertility

Abnormal Uterine Bleeding Definition

Any bleeding that differs in regularity, frequency, duration or volume from a patient’s usual menstrual flow

Definitions

Amenorrhea: absence of menstruation for at least three usual cyclic lengths
Oligomenorrhea: cyclic length > 35 days
Polymenorrhea: cyclic length < 22 days
Menorrhagia: regular, normal intervals with excessive volume and duration of flow
Metrorrhagia: irregular intervals with normal or reduced volume and duration of flow
Menometrorrhagia: irregular intervals and excessive volume and duration of flow

Abnormal Uterine Bleeding Definitions

- Polymenorrhea: < 22 day interval
- Hypermenorrhea: excessive volume
- Prolonged menses: > 8 days
Menstrual Cycle Interval

- Normal interval: 22 – 35 days
- Oligomenorrhea: > 35 day interval
- Polymenorrhea: < 22 day interval

The Menstrual Cycle Volume

- Average – 40 cc
- Over 95% < 60 cc
- Menorrhagia > 80 cc
- Anemia > 80 cc

Differential Diagnosis

Abnormal Uterine Bleeding

Adult

- Complications of pregnancy
- Infection
- Gynecologic cancer
- Benign pelvic pathology
- Systemic disease
- Medications

Adolescent Menstrual Cycles

- Average age menarche - 11.7 years
- Precocious puberty age varies
- White - Pubertal development before 7
- African American - before 6*
- Mean cycle interval 32.2 days in first few years after menarche**

**Hillard, PA “Menstruation in Adolescents: What is Normal?” Medscape 2008

Differential Diagnosis

Abnormal Uterine Bleeding

Adolescent**

- 80% Anovulatory
- 20% hypermenorrhea coagulation defects
- 50% hypermenorrhea with menarche vWD
- 6% Polycystic Ovary Syndrome

Dysfunctional Uterine Bleeding

**Definition**
Any bleeding that differs in regularity, frequency, duration or volume from a patient’s usual menstrual flow…
in which no clear systemic, anatomic or infectious etiology has been identified

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Ovulatory DUB*

- Diminished progesterone effect
- ↑ Ratio of PGE$_1$ : PGF$_{2\alpha}$
- ↑ Level of PGI$_2$
- ↑ Fibrinolytic activity


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Anovulatory DUB

- Common in adolescents
- Common with Polycystic Ovary Syndrome
- May be seen after discontinuing OCPs
- Common in peri-menopausal women
- Prolonged estrogen stimulation
- Absence of cyclic progesterone

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Anovulatory DUB

- Bleeding erratic in both timing and volume
- Hyperplastic, fragile endometrium prone to localized disruption and bleeding
- Endometrial thickness variable on sono
- Endometrial histology may be ‘disordered proliferative endometrium’
- Associated with functional ovarian cysts
- No moliminal symptoms

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Evaluation of AUB

- History
- Physical Exam
- Laboratory tests
- Ultrasound
Evaluation of AUB Laboratory tests

- Urine HCG
- Complete Blood Count
- Coagulation screen
- von Willebrand panel
- Thyroid Stimulating Hormone
- Follicle Stimulating Hormone
- Luteinizing Hormone
**Medical Treatment of DUB**

- Iron
- NSAIDs
- Antifibrinolytic*
- Progestins
- Estrogens + progestins
- Parenteral estrogen

*Tranexamic Acid FDA Approved November 2009

**Iron**

- Menstrual volume >80 cc may cause iron-deficiency anemia
- Primary symptom is fatigue
- Daily doses of oral iron

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**Surgical Treatment of DUB in Adolescents**

Surgical treatment with Dilation and Curettage is the last option.
**Non Steroidal Anti-inflammatory Drugs**

- NSAIDs have been shown to be effective in the treatment of menorrhagia although not superior to other medical therapies*
- Sodium Naproxen - Aleve 220 mg
- Preemptive treatment - start day prior to menses - need to clarify and identify premenstrual alert system
- 440 mg twice daily with meals for cycle


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**Tranexamic Acid**

- Worldwide use for over forty years
- Is available over the counter in Europe
- Injectable was approved by the FDA in USA in 1986 for use in patient with hemophilia and tooth extractions
- Used in severe trauma cases

**Tranexamic Acid**

- The first nonhormonal treatment for Dysfunctional Uterine Bleeding to be approved by the FDA Nov 2009
- Dosage: two 650 mg (1,300 mg) three times a day for five days
- Cost: $180.00
- Is on the Medicaid formulary

**Tranexamic Acid**

- Women with hypermenorrhea may have elevated levels of plasminogen activators in the endometrium*
- ‘Lysteda’ - Synthetic lysine derivative
- Reversibly blocks lysine binding sites on plasminogen to prevent fibrin degradation
- Inhibits fibrinolysis

*Kauntiz, AM. OBG Management Vol 22, No. 6 June 2010

**Tranexamic Acid**

- USA Study – multicenter, randomized, double-blind, placebo-controlled*
- 187 patients ages 18 to 49
- Precise measurements of menstrual flow and of evaluation impact on activities
- 70% therapeutic response rate
- 40% decrease in menstrual volume

It is important to evaluate
the endometrial lining
prior to hormonal treatment

Progestins

- Medroxyprogesterone acetate (MPA):
  North America (Provera)
- Prolonged hypermenorrhea with thickened endometrial lining - 10 mg daily for 7 days
- Anticipate cessation of flow within 48 hours
- Anticipate heavy menses after treatment
- Then initiate long term therapy

Progestins

- For chronic anovulation - cyclic MPA
- 5 mg, 7 mg or 10 mg daily 21 - 28 of cycle
- May consider withdrawal at longer intervals

Progestins

- Norethindrone acetate - NETA (Aygestin) 5 mg
- For prolonged hypermenorrhea with thin endometrial lining – taper down regimen
- Rx # 50
- Four daily for four days
- Anticipate cessation of flow within 48 hours
- Three daily for four days
- Two daily for eleven days then off seven days
- Anticipate withdrawal during those seven days

Estrogens + Progestins (OCs)

- Effective for ovulatory and anovulatory DUB
- Most commonly prescribed treatment
- Effective in adolescents with excessive bleeding

Estrogens + Progestins (OCs)

“Surprisingly, the use of combination oral contraceptives for DUB has had relatively little evaluation. Although OC use is widely perceived as effective to treat heavy menstrual bleeding, the data to support their efficacy are sparse.”*

Pathophysiology
DUB with long term Depo-Provera

- “Raw basalis layer”
- “Pseudoatrophy from long term progestin therapy”
- Ultrasound - thin endometrium
- Treat with taper down oral contraceptive pills or NETA

Parenteral Estrogens

- IV conjugated equine estrogens (Premarin): most widely prescribed emergent treatment for acute, excessive, & rapid uterine bleeding
- Very effective - adolescents with acute bleeding
- Prior to treatment: CBC, HCG & von Willebrand panel

Evidence Based Medicine

Use of IV Premarin in the treatment of dysfunctional uterine bleeding – randomized double-blind control study

• 34 patients (age range 16 - 49, mean age 27)
• Randomized, double-blind, placebo-controlled
• Yale-New Haven Hospital Emergency Department 1979-1980
• Excluded from study:
  - Gross uterine, cervical and ovarian pathology
  - History of thromboembolic coagulation disorders
  - Hormone dependent tumors
  - Suspected pregnancy
• Endometrial biopsy, CBC, PT, PTT

• Bleeding evaluated with pelvic examination every hour
• If bleeding stopped at 3 hours - stop
• If bleeding continued - dose repeated
• At the end of the fifth hour - If no bleeding - no further Rx If bleeding continued treatment was unblinded and IV Premarin given
• If bleeding after 8 hrs - surgery

Results

Bleeding stopped in 72% of patients who received IV Premarin series

Bleeding stopped in 38% of patients who received placebo

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<tr>
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<th>Premarin (18)</th>
<th>Placebo (16)</th>
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<tbody>
<tr>
<td>Stopped after 1st dose</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Stopped after 2nd dose</td>
<td>9</td>
<td>1</td>
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<tr>
<td>Unblinded &amp; stopped after additional dose</td>
<td>3</td>
<td>7</td>
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<tr>
<td>No effect</td>
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<td>3</td>
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Potential Complications

• Death – thromboembolic event
• Stimulate estrogen sensitive disease process
• Medical-legal consequences

Recommendations

• Ultrasound imaging is optimal
• Obtain labs before treatment initiated
• Resuscitate with blood as needed
• Check bleeding hourly
• Administer additional doses based on level of bleeding
Seven Case Studies

Peri-Menarchal DUB

- Menarche - January 21 – 4 days
- Moderately heavy for 14 days in February
- Moderately heavy for 3 days in March
- Heavy April 4 - 6 and 14 - 21
- Syncope and headaches
- Hgb 10.1 and Hct 29.5%
- Coagulation studies normal
- Endometrial lining less than 1 cm

Peri-Menarchal DUB

- Treated with daily iron
- Treated with NETA taper-down 2 cycles
- Preemptive Aleve 440 mg twice daily

von Willebrand Disease #1

- 14 yo female severe menorrhagia & syncope
- Transabdominal ultrasound normal
- CBC: Hgb 3.9, Hct 12.6%, WBC 10,300
- vWF Antigen 345 (59-150)
- Ristocetin 414 (47-150)
- Responded well to DDAVP* & transfusions

von Willebrand Disease #2

- 12 yo female severe menorrhagia & syncope with first menses
- History of severe epistaxis
- Mother with severe postpartum hemorrhage
- 5’ 95 pounds – Tanner 2
- Transabdominal ultrasound normal
- vWD Panel positive

*DDAVP – Stimate – synthetic analog of vasopressin – releases factor VII, vWF, Factor and plasminogen activator from storage sites
von Willebrand Disease #2

- Hgb 6.2 Hct 16.8%
- Did not respond to IV Premarin
- Did respond to Stimate (DDAVP)
- Received 8 units packed cells
- Recommend Yaz and preemptive Aleve

Polycystic Ovary Syndrome #1

- 14 yo with 4 year history hypermenorrhea, polymenorrhea and prolonged menses
- 5'2" 164 pounds BMI 30
- Typical PCO phenotype
- Hgb 3.6 Hct 14.8%
- Coagulation panel normal
- Ultrasound thin endometrial lining & PCO

Polycystic Ovary Syndrome #1

- Transfusion 3 units packed cells
- Life style changes
- Metformin 500 mg three times a day
- Iron
- Preemptive Aleve
- Yaz

Polycystic Ovary Syndrome #2

- 13 yo with 3 year history hypermenorrhea
- Menarche at 10
- 3 day cycles - four times a year
- Then at 6 month intervals
- Then 8 weeks of continuous bleeding

Polycystic Ovary Syndrome #2

- Born at 24 weeks gestation with significant mental and physical challenges – VP shunt
- Typical PCO phenotype
- Type II DM – Rx with Metformin
- PCO labs classic – LH/FSH: 16.4/4.4, Testosterone 62
- Hgb 10.3 Hct 31.2%
- Coagulation panel normal
- Sono: 1.2 cm endometrial lining & PCO
Polycystic Ovary Syndrome #2

- Treated with Provera 10 mg for ten days
- Bleeding stopped
- Then anticipated heavy four day period treated with preemptive Aleve
- Treated with Yaz cycles for three months
- Then Yaz extended cycle

Dysfunctional Uterine Bleeding

- 15 year old 10 day hypermenorrhea
- Menarche 14 with heavy irregular periods
- 5’2” 121 pounds BMI 22
- Syncope
- Hgb 7.0 Hct 24%
- Coagulation panel normal
- Endometrial lining 3mm - ovaries normal

Dysfunctional Uterine Bleeding

- Received IV Premarin - bleeding stopped
- Transfused with three units packed cells
- Iron
- Treated with NETA taper-down for 3 cycles
- Preemptive Aleve
- Menses still moderately heavy
- Converted to NETA 10 mg daily for 3 months

Acute Leukemia

- 14 yo G 0 with severe menorrhagia
- Profound anemia
- Acute leukemia

A 12-year-old female patient of yours presents to the emergency department with syncope after severe menorrhagia with her second menstrual period. She has a family history of women who are “bleeders.”

The hemoglobin is 4.4 and hematocrit is 10.5%.

The bleeding decreases significantly following a single dose of Premarin 25 mg intravenously.

Which of the following is correct?

A) IV Premarin for severe menorrhagia has been studied extensively
B) The most likely diagnosis is von Willebrand’s Disease
C) She should receive additional 25 mg doses of IV Premarin every four hours for twenty four hours
D) She will not require further treatment

Answer: B

- The most common coagulation disorder in young females with menorrhagia is von Willebrand’s Disease
- High-dose intravenous Premarin is very effective in adolescents with acute bleeding
- IV Premarin is the most widely prescribed emergent treatment for acute, excessive, & rapid uterine bleeding
- Only one clinical study for the use of IV Premarin

De Vore GR: Obstet Gynecol 1982
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