Not Enough Pads!
Abnormal Uterine Bleeding

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Disclosures

- Except where noted, all illustrations were purchased from iStockPhoto
- Consultant to Hologic, AirExpanders, California Milk Ad Board, Bayer
- Vendor to Cord Blood Registry
Objectives

- Understand the hypothalamic pituitary axis interconnection with the ovaries & uterus
- Describe work up for amenorrhea and AUB
- Elucidate the PALM-COEIN diagnostic algorithm for AUB
- List pharmacologic treatments with risks/benefits for these conditions
Why Should You Care?

- Many of your patients have questions about:
  - Their periods – Pain? Length? Risks?
  - Anemic? Tranfusion? Surgery?
  - If they’re normal
  - If they can get pregnant
  - Are they too scared to ask?
Daniela

- 17 yr old high school student
- Acne severe, started OCPs at 14
- Went off OCPs 6 months ago, no periods until last week
- She presents in your office with her mom who is worried because her skin is dry and scaling and her hair is falling out
Amelia

- 28 year old woman desires pregnancy
- Amenorrhea x 6 months
- Hypothyroid
- Intermittent galactorrhea
Shivani

- 46 yr old woman with 4 month hx of periods lasting 10-17 days, with intermittent spotting in between
- Previously, periods were regular q month
- 2 healthy deliveries, partner had vasectomy
- A few rare night sweats
Start at the Beginning

A Quick Review
Review of Menstrual Cycle

- Hypothalamus/Pituitary
- Ovary
- Uterus & Endometrium
- Follicular Phase
- Ovulation
- Luteal Phase
- Menses
The Menstrual Cycle

- **3 feedback loops & 4 Stages**
- **Long** - target gland hormones
  - Estrogen, Progesterone
- **Short** - pituitary hormones on hypothalamus
- **Ultrashort** - inhibition of releasing hormone on itself
- **4 stages**: Proliferation, Ovulation, Luteal, Menstrual

Follicular Phase

- 1st - Primordial Follicle, an oocyte surrounded by granulosa cells: highly receptive to FSH and E₂

- Each woman has 6-7 million Primordial Follicles. Growth and atresia embyro to menopause.

- At birth, 2 million, by puberty 300,000

- Each month, 6-7 new follicles are recruited in each ovary

- One will eventually become dominant and the others will undergo atresia: regress, shrink and be resorbed

Beshay, VE & Carr, BR, 2013
Follicle growth depends on:

- Granulosa Cells responding to ↓ LH and ↑ FSH
- Conversion of androgens - estrogens
- One follicle becomes dominant, producing the greatest amt of E\textsubscript{2}
- This higher level E\textsubscript{2} feeds back to the pituitary to ↓ FSH.

Beshay, VE & Carr, BR, 2013
Dominant Follicle

- Identified by cycle day 5
- It survives and grows faster because of:
  - Greater numbers of FSH receptors
  - Increased Estrogen production in the granulosa cells
- Estrogen must rise, only then can LH surge

Beshay, VE & Carr, BR, 2013
Ovulation

- Occurs 24 - 36 hrs after peak Estradiol levels attained - leads to LH surge
- Occurs 10 - 12 hours after LH peak
- LH *must* be maintained for at least 14 hours for the full maturation of the follicle to occur

Beshay, VE & Carr, BR, 2013
Ovulation

- LH surge and Progesterone also act to stretch the follicular wall
- Estrogen levels drop as LH reaches its peak
- Prepares follicle for transition to Luteal Phase

Beshay, VE & Carr, BR, 2013
Luteal Phase

- Granulosa cells increase in size, accumulate a yellow pigment (lutein)
- Produces Progesterone which in turn inhibits FSH and new follicular growth
- Progesterone further acts on the endometrium making it thicker and more glandular

Beshay, VE & Carr, BR, 2013
Endometrium

- **Proliferative Phase** - follicular phase, Estrogen (E2) dominant
  - Endometrial growth from 0.5 to 3.5-5.0mm, relatively smooth surface

- **Secretory Phase** - luteal phase, Progesterone dominant
  - Height unchanged, becomes more glandular, sawtooth appearance

- **Menses** – decreased E2 and Progesterone

Menses

- Shrinkage of endometrial height
- ↓ blood flow \(\rightarrow\) vasoconstriction of spiral arteries (from ET-1 Endothelin-1) \(\rightarrow\) Relaxation \(\rightarrow\) endometrial blanching
- Leads to ischemia, prostaglandin production (high levels PG F2α)

Fritz MA & Speroff L, 2011
Hemostasis

- Tissue factor initiates intravascular clotting and sets in motion the production of thrombin from prothrombin.
- Then fibrinogen to fibrin
- At the same time, not too many clots, this is balanced by fibrinolytic activity.

Fritz MA & Speroff L, 2011
Endometrial Repair

- After hemostasis, and with the new follicle’s production of Estradiol, angiogenesis begins.
- Mediated by migratory leukocytes and a range of growth factors and cytokines.
- Remodeling and repair completed by day 4 to 5.

Fritz MA & Speroff L, 2011
Cervical Mucus

- Follicular is generally white and pasty

- Ovulatory - Estrogen dominant
  - is clear, looks like uncooked egg white, stringy, nourishes sperm on their journey

- Luteal - Progesterone dominant
  - pasty and may appear yellow
Normal Cycling

- Normal Interval: 21-35 days
- 15% of women have 28 day cycles
- Duration of flow 2 to 8 days, average is 4-6
- Normal volume is 30 ml
- Range: 20 - 80 ml
Can the Pill Mask Conditions?

- Combined Oral Contraceptives and NuvaRing
- Contain both Estrogen (E2) and Progesterone
- Together they suppress ovarian function
- Influence feedback loops masking thyroid and pituitary conditions
- Increase SHBG – Sex Hormone Binding Globulin - Reduce androgenic symptoms
Combined Contraception

- Many non-contraceptive benefits
- Reduce endometrial height
  - Decreases bleeding, cramping, pain
  - Reduced risk of PID
  -Suppresses endometriosis
- Reduces risk of ovarian cysts
- Suppress the hormonal roller coaster in PCOS
Disorders

What, How, Why and What
Adolescence

- Average age of menarche (1st period)
- Normal to have anovulation and skipped cycles
- Issues that may arise:
  - Dysmenorrhea
  - Bleeding disorders
  - Acne
  - Teratomas
  - PMS
  - Anemia
  - PCOS
  - Adenomas
Menstrual Disorders

- Amenorrhea
  - Primary & Secondary

- Dysmenorrhea – Painful periods

- Bleeding Disorders

- Endometriosis

- Abnormal Uterine bleeding: PALM - COEIN
Primary Amenorrhea

- Complete absence of menses by age 16
- Work up: Complete H & P
- Absence of secondary sex characteristics?
  - Genetic testing? Turners 45X
- Physical obstruction? Imperforate hymen?
- Labs: TSH, Prolactin, FSH, LH, Estradiol

Fritz MA & Speroff L, 2011
Secondary Amenorrhea

- Pt has had at least 1 cycle and then at some point stopped cycling
- Physical assessment: complete H & P
  - Drug use, exercise, weight, acne, hirsuit?
- Key point: Look at BMI: Hypothalamic or PCOS
Daniela

- 17 yr old high school student
- Acne severe, started OCPs at 14
- Went off OCPs 6 months ago, no periods
- She presents in your office with her mom who is worried because her skin is dry and scaling and her hair is falling out
Risk factors

- Recreational drug use
- Pituitary adenoma
- Eating disorder
- Over exercise
- Thyroid dysfunction
**Work UP**

- Complete H & P, 24 hour diet recall, BMI, Pregnancy test
- Labs: TSH, Free T-4, LH, FSH, Prolactin, $E_2$
  - Thyroid antibodies if you suspect Hashimoto’s
- Ultrasound if you suspect PCOS
- Vitamin D, B12, Folate if nutritional deficiency suspected

Fritz MA & Speroff L, 2011
Progesterone Challenge Test

- Theory: if endometrium has had any $E_2$ exposure, then 10 days of PG, *should convert proliferation to secretory*

- Once it stops, then within 10 days, you should see a withdrawal bleed
Progestin Options

- Medroxyprogesterone acetate (*Provera*)
  - 5 or 10 mg q hs x 10
  - Most studied

- Prometrium (*bioidentical micronized progestin*)
  - 100 mg q hx x 10
Daniela

- BMI: 17.3
- FSH 1.5, LH 1.9, E_2 32
- Prolactin, thyroid all wnl
- Thin atrophic lining
- Fails progesterone challenge test
Hypothalamic Amenorrhea

- Aka: Athletes Amenorrhea
  - Also occurs with anorexia

- Low BMI = Low peripheral fat & reduced aromatization of \( E_2 \)

- Suppressed FSH, LH and \( E_2 \)

- No proliferation, ovulation or progesterone

- Thin atrophic lining – nothing to slough

- High risk for Bone Health
Treatment: Hypothalamic

- Treat any underlying medical issue
- Gaining as little as 5 pounds may help
- Improving all nutritional status, vitamin deficiencies – check Vitamin D
- Combined OCs to provide some estrogen
- For anorexics – do not discuss weight
Estrogen and Serotonin

- E2 increases the production of tryptophan – the precursor to serotonin
- E2 increases the amount of time serotonin stays in the synapse
- E2 Increases density, distribution of serotonin receptors
- E2 increases serotonin transporter sites

Consider SSRIs & SNRIs

- Fluoxetine (*Prozac*) found to be helpful as many of these women also have mood disorders
- Can help with OCD behaviors and compulsivity
- Both SSRIs and SNRIs can be weight neutral
Amelia

- 28 year old woman desires pregnancy
- Amenorrhea x 6 months
- Hypothyroid
- Intermittent galactorrhea
Amelia

- No visual disturbances
- FSH: 6.3, LH 4.8, TSH: wnl
- Prolactin: 168
- MRI: small pituitary adenoma
Pituitary Adenoma

- Suspect when the Prolactin is > 60
- With or without galactorrhea
- MRI indicated when prolactin is > 150
- Tx: combined OCs, Cabergoline (*Dostinex*), Bromocriptine (*Parlodel*)
- Surgery rarely necessary unless visual disturbances

Lleva, RR and Inzucchi, SE. *Curr Opin Oncol*. Jan, 2011.
Why MRI and Ophthalmic Eval

- Preferred over CT – No radiation exposure
- Better visualization of soft tissues and vascular structures.
- Visual field testing recommended especially in tumors involving the optic chiasm.
- If there are visual defects: more aggressive treatment course may be warranted

Lleva, RR and Inzucchi, SE. Curr Opin Oncol. Jan, 2011.
Cabergoline

- Long-acting Dopamine receptor agonist
  - *Dostinex*

- High affinity for D2 receptors: increases activity

- Normalizes serum prolactin levels by:
  - Inhibiting hypothalmic stimulation of Ant Pituitary

- Thereby reduces prolactin secretion
Cabergoline

- Extremely long half-life: Once weekly dose
  - Peak levels within 2-3 hours
  - No interference with food

Do not use to suppress lactation: HTN, stroke, seizures

Do not use with D2 antagonists: metoclopramide, phenothiazines, butyrophenones, thioxanthenes
Cabergoline: Warnings

- Doses > 1.0 mg associated with orthostatic hypotension

- Contraindications:
  - Uncontrolled Hypertension
  - Known sensitivity to ergot derivatives
  - Hx of cardiac valvular disorders
  - Hx of pulmonary, pericardial or retroperitoneal fibrotic disorders
Bromocriptine

- *Parlodel* Original D 2 receptor agonist
- Taken 1 – 3 times/day
- Side effects: Dizziness, drowsiness, headache, depressed mood, insomnia, dry mouth, nausea, vomiting, stomach pain, of appetite, diarrhea, constipation
## Endpoints

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<tr>
<th></th>
<th>Cabergoline</th>
<th>vs</th>
<th>Bromocriptine</th>
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<tbody>
<tr>
<td><strong>NML Prolactin Levels</strong></td>
<td>83%</td>
<td>vs</td>
<td>59%</td>
</tr>
<tr>
<td><strong>Ovulatory cycles or pregnancy</strong></td>
<td>72%</td>
<td>vs</td>
<td>52%</td>
</tr>
<tr>
<td><strong>Amenorrhea Rates</strong></td>
<td>7%</td>
<td>vs</td>
<td>16%</td>
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<tr>
<td><strong>Discontinuation rates</strong></td>
<td>3%</td>
<td>vs</td>
<td>12%</td>
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Contraception

- Once prolactin levels normalize, women can get pregnant
- Use contraception
- Oral Contraceptives, NuvaRing, IUDs, Implants
Dysmenorrhea

- Dysmenorrhea – Painful periods
- Endometrial lining contains prostaglandins (PG F2α)
- These are released throughout the pelvis
- Cramping, nausea, diarrhea, constipation, urinary difficulty
- Treatment: NSAIDs
NSAIDs

- Prostaglandins higher in endometrium of women w AUB higher than in women w/o
- ↑’d levels of Nitric oxide ↑s prostaglandins via the cyclooxygenase (COX) pathway
- Inhibiting COX and reducing blood loss
- Few side effects

NSAIDs - Naproxen

- Also reduces the amount of bleeding
- OTC Naproxen 220mg
- Not to exceed 660 mg in 24 hours
- Prescription: Naproxen Sodium 550 mg
- 1 every 12 hours
- Not to exceed 1100 mg/day
NSAIDs - Mefenamic acid

- Mefenamic acid
- 250 to 500 mg taken 2 – 4 times/day
- Ibuprofen
- 600 mg every 4 – 6 hours
- All NSAIDs must be taken with food
- Contraindicated in women w Peptic Ulcer
Shivani
Shivani

- 46 yr old woman with 4 month history of periods lasting 10-17 days, with intermittent spotting in between

- Previously, periods were regular q month
- 2 healthy deliveries, partner had vasectomy
- A few rare night sweats
- Vegetarian, no medications
Shivani

- Pregnancy test neg
- TSH, T-4 wnl, FSH: 15, LH: 7.0
- E₂: 123, Prolactin: wnl
- Hgb A1C: 5.6
- HCT 26.9/ Hgb 8.7
- Ferritin, TIBC, Hgb Electrophoresis: wnl
Shivani

- Limiting her activities
- Passing big clots
- Ruining clothes, sheets
- Worried about hysterectomy
- Where do you begin?
Abnormal Uterine Bleeding

• Define Abnormal Uterine Bleeding?
• Causes of Abnormal Uterine Bleeding?
• How do we approach the Diagnosis?
• What treatments are available?
What is Abnormal Bleeding?

- > 1 pad/hour for more than 1 day
- > 7 days at a time
- < 20 days apart
- > 80 cc a month
- Enough to cause anemia
- Enough to cause disruption in life style

ACOG, Committee Opinion. April 2013 (reaffirmed 2015), number 557.
Prevalence

- 5% of women between 35 – 49\(^1\)
- Up to 50% of perimenopausal women will experience AUB\(^1\)
- 1.4 million women in the US annually\(^2\)
- 53% of women report that their periods interfered with their life, compared with 23% of age-matched community controls\(^2\)

Diagnostic Workup

- H & P, Pregnancy Test
- Blood tests: CBC, TSH, FSH, LH, E2, Prolactin
  - Depending upon history: Von Willebrands factor
- Vaginal ultrasound – endometrial thickness
- Endometrial biopsy
- Additional tests, such as saline infused sonohysterography & hysteroscopy

ACOG, Committee Opinion. April 2013 (reaffirmed 2015), number 557.
AUB: Old nomenclature

- Menorrhagia – excessive bleeding but occurs at regular intervals
- Metorrhagia – irregular intervals and/or intermenstrual bleeding
- Menometorrhagia – prolonged and irregularly timed bleeding

Throw these out!
AUB: PALM-COEIN

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

- **COEIN – Non-structural**
  - C - Coagulopathy
  - O - Ovulatory
  - E - Endometrial
  - I - Iatrogenic
  - N – Not Classified

Established by **FIGO** - Fédération Internationale de Gynécologie et d'Obstétrique (the International Federation of Gynecology and Obstetrics).

Munro, MG et al. *Int J Gynecol Obstet.* 2011
Uterine Structural Pathology

- Hyperplasia
- Polyp
- Fibroids
- Adenomyosis
Direct Visualization

- Hysteroscopy

EndoSee
AUB: Polyps

- Epithelial proliferations
- As many as 25% may resolve spontaneously
- Mostly associated with Intermittent bleeding
- Risk of malignancy - 1.7% for pre-menopause
- Risk of malignancy – 5.4% for post menopause
- Size not correlated with risk

Polyps
Polyp Treatment

- Intra-Uterine polypectomy via hysteroscope
- Up to 25% regress, particularly if less than 10 mm
- Symptomatic postmenopausal polyps should be excised for histologic assessment
- Removal in infertile women improves fertility
- Surgical risks associated with hysteroscopic polypectomy are low.

AAGL, *Min Invas Gynecol.* 2012
AUB: Adenomysis

- Uterine lining grows into the adjacent muscular tissue (myometrium)
- May have no signs or symptoms – difficult to diagnose
- Excessive menstrual bleeding
  - Painful menstruation and Intercourse
  - Uterus may be enlarged

Adenomysis

- Ultrasound or MRI
- Rx: NSAIDs
- Hormone therapy, such as oral contraceptives
- Hysterectomy
- Doesn't affect fertility
- Resolves with menopause

Pharmacologic Tx

- NSAIDs, which are effective at reducing the amount of bleeding, discomfort and cramping.
- Prescription anti-fibrinolytic medications such as Tranexamic acid (Lysteda) taken three times each day are also employed to help reduce excessive blood loss.
Adenomyosis Tx Options

- NSAIDs
- Anti-fibrinolytics – Tranexamic
- GnRH agonist
- OCs
- Progestin containing IUDs
- Depo Medroxyprogesterone Acetate (Depo Provera®)
NSAIDs & AUB

- Prostaglandins higher in endometrium of women w AUB higher than in women w/o
- ↑’d levels of Nitric oxide ↑⁷ s prostaglandins via the cyclooxygenase (COX) pathway
- Inhibiting COX and reducing blood loss
- Fewer side effects

Tranexamic acid

- Higher plasminogen activators in the endometrium of women with AUB
- Tranexamic acid is a synthetic lysine derivative that blocks lysine binding sites on plasminogen = preventing fibrin degradation
- More effective than mefenamic acid
- Over a few cycles reduces blood loss by 60%
Tranexamic acid

- 1 to 1.5 g tid – qid for 3 to 4 days on day 1
- Reduce the dose in pt with renal failure
- Side effects are dose dependent
- Increased risk of DVT, contraindicated w people with thromboembolic disease
- Nausea, vomiting, diarrhea, and dyspepsia, as well as disturbances in color vision.
Levonorgestrel (LNG) IUD

- Can reduce menstrual blood loss within 5-26 days by up to 96%
- Delivers 20 mcg of levonorgestrel q 24 hrs
- 50% of women using the 5 year system, Mirena will have amenorrhea
- There can be some variable spotting
Oral Contraceptives

- Suppress ovarian function
- Low dosages can reduce endometrial proliferation, prostaglandin production and pain
- Consider pills containing 20 mcg or less
Contraceptive Ring: NuvaRing

- Non Biodegradable, flexible vaginal ring
- Delivers 15 mcg of ethinyl estradiol per day
- 120 mcg of etonorgestrel/day
- Works in the same way as combined oral contraceptives to reduce endometrial stimulation and proliferation
Leiomyoma = Fibroids

- Benign Calcifications of the Uterus.
- In women w AUB: present in approx 50%
- Present in 1/3 of women > 30
- Estimated 50% in women > 50
- Asymptomatic or cause bladder, intestinal discomfort, bleeding & dyspareunia
- Tx depends on size, location & desire for fertility

ACOG, Practice Bulletin, 2012
Leiomyoma: Fibroid
Submucosal Leiomyoma

- AUB most likely from submucosal leiomyomas
- Impinge on Uterine cavity and endometrium
- Detected via transvaginal US, sonohysterography, MRI, EndoSee, computed tomography (CT), or hysteroscopy
Treatment options

- GnRH agonists (Lupron Depot) – abruptly withdraws E₂, fibroids regress
- Uterine Artery Embolization – interferes with blood supply leading to regression
- See & treat with Hysteroscopy used for fibroids within the endometrium
- Intrauterine morcellation – Myosure
- Laproscopic removal, hysterectomy

AAGL, J Min Invas Gynecol. 2012
GnRH agonist: Leuprolelin

- Competitive agonists at GnRH receptors in the pituitary

- This desensitizes the GnRH-releasing cells = a hypogonadotrophic state leads to:
  - Hypoestrogenism
  - Endometrial atrophy
  - Amenorrhea
Uterine Artery Embolization: UAE

- Option for women with AUB who are unresponsive to medical therapy and desire future fertility.\(^3,18\)

- Minimally invasive, catheter threaded to the specific Uterine Artery nourishing the fibroid.

- Magnetic Resonance–guided Focused Ultrasound (MRgFUS): Emerging radiologic technique which uses MRI to identify the location of fibroids and high-intensity focused ultrasound energy to destroy leiomyomas without injury to surrounding tissues.\(^19\)
Intra-Uterine Fibroid Removal

- New minimally invasive intra-uterine procedures are now being utilized
- Small telescoping instruments can be inserted through a hysteroscope to remove fibroids
- New technologies use reciprocating cutters to shave off fibroid tissue while sparing the myometrium
What not to do

- Blind D & C
  - No benefit
  - Will miss pathology or have incomplete removal

- Extra-uterine morcellation in the pelvic cavity via a laparoscope
  - Associated with an increased risk of seeding leiomyosarcoma into the pelvic cavity

Why treat?

- Interfering with life or lifestyle
- Pain, bleeding, pressing on other organs
- Rapid growth
- Rarely is Hysterectomy necessary
- Refer to a minimally invasive Gyn specialist
Shivani

- Has polyps and submucosal fibroids
- Elects to have both fibroids removed via the hysteroscope and to have endometrial ablation at same time
- Back to work after a weekend to recover
- Complete amenorrhea in 6 months
AUB – Malignancy
Endometrial Hyperplasia

- More common in younger women (< 50) with PCOS and chronic anovulation
- More common in post menopausal women with unopposed $E_2$ stimulation
- High index of suspicion with any bleeding
- Ultrasound to measure Endometrial stripe

Eileen

- Post menopausal x 7 years
- No menopausal hormone therapy, on thyroid replacement medication for years
- 6 month hx of intermittent spotting
- Busy caring for her elderly mom
How We Diagnose?

- H & P
- Labs: Urine HCG, CBC, TSH, Free T-4, Thyroid Antibodies, FSH, E₂, Coagulation Panel if indicated
- Ultrasound/ Sonohysterography
- Endometrial Biopsy for stripe > 8 mm for new onset.
  - > 3 mm for persistent
- Hysteroscopy: See and Treat with Surgical Sampling
Deciphering EMBs

- Reported as:
  - Benign Proliferative – Estrogenic
  - Benign Secretory – Indicates Progesterone and ovulation
  - Atypical Hyperplasia
  - Cancerous
Hyperplasia types

- Simple w/o atypia: 1% risk progress to CA
- Complex w/o atypia: 3% risk progress to CA
- Simple with atypia: 8% risk progress to CA
- Complex with atypia: 29% progress to uterine cancer

17 to 59% of cases have coexistent uterine cancer.
Endometrial Hyperplasia
Treating Hyperplasia

- Correct any hormonal imbalance
- Remember often seen with PCOS
- Being sure to add a progestin to her regimen if on Estrogen treatment
- Progestin containing IUD, Oral Progesterone, Medroxyprogesterone Acetate (Provera)
Eileen

- All labs wnl
- Endometrial stripe 13 mm
- EMB revealed endometrial cancer
- Pt elected to have a hysterectomy – Stage 1
Treating Malignancy

- Hysterectomy with BSO, lymph node sampling
- Treatment dependent upon the level of invasion
- May need radiation and/or chemotherapy
AUB - Coagulopathy

- Von Willebrands
- Hemophilia, Thrombocytopenia - rare
- Inherited deficiencies in prothrombin, fibrinogen, factor V, factor VII, factor X, and factor XIII
- Platelet function disorders: 98% of women with Bernard-Soulier syndrome or Glanzmann’s thrombasthenia
- Women on anticoagulant therapies
AUB – Von Willebrands

- Von Willebrands – A group of (generally) inherited disorders of coagulation related to a defect in von Willebrand factor, critical for the normal function of factor VIII

- Incidence: 13%

- History will suggest: prolonged bleeding, postpartum hemorrhage

Shankar M, BJOG, 2004
Katrina

- Age 17, plays soccer, few bruises on her arms
- Long Hx heavy periods since menarche
- On Fe for anemia from pediatrician
- History: frequent nosebleeds
Screening vWF

• Heavy menstrual bleeding since menarche

• One of the following conditions:
  • Postpartum hemorrhage
  • Surgery-related bleeding
  • Bleeding associated with dental work

OR

• Two or more of the following conditions:
  • Epistaxis, one to two times per month
  • Frequent gum bleeding
  • Family history of bleeding symptoms

ACOG Committee Opinion Von Willebrand Disease in Women, 2013
vWF

- vWF is essential for platelet adhesiveness and maintenance of nml levels of factor VIII.

- 3 recognized variants of vWD:
  - Type 1 - 60%–80% (mild), may be clinically insignificant, even in women with chronic AUB.
    - commonly overlooked, only be dx w certainty using specific testing for vWF levels.

  - Type 2 - qualitative deficiency that may manifest solely with bruising or AUB without impaired clotting – labs: vWF = 10 - 45% of nml.
vWF

• Type 3 – most severe, least common, usually presents at menarche.

• Labs: no measurable vWF

• Diagnosis should be considered in any woman with chronic HMB, especially if she does not pass simple screening tests

ACOG Committee Opinion Von Willebrand Disease in Women, 2013
Treatment Von Willebrands

- Consultation with hematologist
- Progestin containing IUD, Implant
- Progestin Only Pill, Combined OCPs
- Tranexamic acid – antifibrinolytic
  - Inhibit conversion of plasminogen to plasmin, which inhibits fibrinolysis helps to stabilize clots.
  - Reduces menstrual bleeding by 30–55%

Katrina

- Hgb 10.3, HCT 26.1
- vWF; 25% of normal
- Type 2 Von Willebrands
- Elects to use Progestin containing IUD
- Cautioned to avoid NSAIDs
Treatment von Willebrand

- **DDAVP** – *Desmopressin* – IV injection or via a nasal spray – Stimate
- Synthetic hormone similar to vasopressin
- Controls bleeding by stimulating more von Willebrand factor stored in the endothelium enhancing factor VIII levels
- Effective in type 1 and some subtypes of type 2 vWF
AUB: Ovulatory

Perimenopause

Changes in both menstrual flow and frequency are common and usually normal:

- Lighter bleeding
- Heavier bleeding
- Duration of bleeding
- Cycle length often changes
- Skipped menstrual periods
AUB: Ovulatory

- PCOS
- LOOP events
- Hypothyroidism
- Hyperprolactinemia
- Hyperandrogenism
- Lifestyle factors
- Medications: Tricyclic antidepressants, Phenothiazines
- Street drugs
- Stress
LOOP Events in Perimenopause

- LOOP (Luteal Out-Of-Phase) events – the development of follicles with release of high levels of estradiol in the luteal phase.
- This represents a 2\textsuperscript{nd} spike of $E_2$.
- At a time when levels should be declining.
- LOOP events are associated with sporadic episodes of AUB and breast tenderness.

Hale, GE et al. Menopause, 2009
Progesterone Vaginal Cream

- Not FDA approved
- 4% Crinone Cream 45 mg
- 12 days of cycle or twice weekly
- No cases of endometrial hyperplasia

Contraceptive implant

- Progestin containing contraceptive implant (Nexplanon®) – Subdermal, single rod
- Progestin only – Etonorgestrel
- Highly effective contraception, 0.05% failure rate
- 3 years of benefit
Progestin is released initially at a rate of 60–70 µg/day. This decreases to 35–45 µg/day at the end of 1 year of use. 30–40 µg/day at the end of 2 years. 25–30 µg/day by the end of the third year.
**Progestin Containing Implant**

- Bioavailability remains constant throughout the life of the device
- There is no evidence to suggest accumulation over time
- Half-life elimination time is approx 25 hr
- Immediate return to fertility when removed
Progestin Containing Implant

- Bleeding is irregular
- 22% amenorrhea rate
- 34% irregular bleeding (defined as 3+ episodes in 2 years)
- 7% frequent bleeding (> 5 episodes in 2 yrs)
- 18% prolonged bleeding (> 14 days)
**Progestin Containing Implant**

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<thead>
<tr>
<th>Bleeding pattern</th>
<th>Definition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amenorrhea</td>
<td>No bleeding and/or spotting in 90 days</td>
<td>22</td>
</tr>
<tr>
<td>Infrequent</td>
<td>Less than three bleeding and/or spotting episodes in 90 days (excluding amenorrhea)</td>
<td>34</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Any bleeding and/or spotting episode lasting more than 14 days in 90 days</td>
<td>18</td>
</tr>
<tr>
<td>Frequent</td>
<td>More than five bleeding and/or spotting episodes in 90 days</td>
<td>7</td>
</tr>
</tbody>
</table>

AUB - Endometrial

- The cause of AUB-E: Local disorders of the normal hemostatic mechanisms
- Combination of excesses of PA or vasodilating prostaglandins such as PG I\textsubscript{2} or PG E\textsubscript{2}, or deficiencies in vasoconstricting agents such as ET-1 and PG F2\textalpha{}.
- Or Infections, such as *Chlamydia trachomatis*.
- No commercially available tests to detect such disorders.

AUB - Iatrogenic

- Usually from estrogen & progestin containing contraceptives, especially progestin-only agents
- Missed pills
- Certain medications that impact cytochrome p-450 pathway: anticonvulsants or some antibiotics
- Cigarette smoking
- Street drugs
AUB – **N** *(Not otherwise classified)*

- Catch-all category includes the rare and poorly defined and/or poorly examined uterine conditions such as:
  - Cesarean section scar bleeding
  - Arteriovenous malformations
  - Myometrial hypertrophy.
Medical Options

- Treat vWF
- Combined Oral Contraceptives
- Progesterone – Oral, IUD or IM injection
- Hormonal implant
- GnRH agonists – Leuprolelin
- Antifibrinolytic medications - Tranexamic acid
- NSAIDs
Levonorgestrel Containing – Intrauterine System (Mirena®)

Levonorgestrel
- Office procedure
- 5 years
- Provides contraception
- May have 3-6 months of prolonged unscheduled bleeding

- 40% of women have amenorrhea
- If this is used for a Polyp or Fibroid – about 30% of women go on to other procedures

Gupta, JO et al. NEJM, 2013
Surgical Treatment

- Hysteroscopic polypectomy
- Hysteroscopic myomectomy
- Abdominal myomectomy
- Uterine Artery Embolization
- Endometrial Ablation
- Hysterectomy
Endometrial Ablation

- Minimally invasive alternative to Hysterectomy, used for:
  - AUB – Polyps
  - AUB-Adenomyosis
  - AUB-Leiomyoma
  - AUB-Coagulopathy
  - AUB-Ovulatory
  - AUB-Endometrial
Ablation

- Appropriate for women who have finished childbearing
- Perimenopausal women: post ablation pregnancies can be problematic, use contraception
- May normalize menstruation or produce amenorrhea.
- Not been studied in postmenopausal women
- Should not be used with suspected uterine cancer or hyperplasia

Ablation

- Impedance-guided bipolar radiofrequency: *NovaSure*
- Fluid-filled thermal balloon: *ThermaChoice*
- Microwave: *Microwave Endometrial Ablation*
- Cryoablation: *Her Option*
- Free-fluid thermal: *ThermAblator*
Hysterectomy

- Surgical removal of the uterus
- Most definitive Rx for abn bleeding
- Major procedure
- Abdominal, vaginal, LAVH, Robotic
- Significant Risks
- Recovery period of 6-8 weeks
- Psychological issues
Hysterectomy

- Most common non-obstetric major surgery
- Fibroids are most common reason
- Asymptomatic fibroids don’t require treatment
- Submucosal fibroids:
  - After hysteroscopic myomectomy: 16% had 2\textsuperscript{nd} surgery
  - After hysteroscopic myomectomy + Endometrial Ablation: 5% required a second surgery
Questions


References


References


References


References


References


- Munro MG, Critchley HOD, Broder MS, Fraser IS, for the FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. *Int J Gynecol Obstet.* 2011;113:3-13.


References


