Abnormal Uterine Bleeding in Midlife Women

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Objectives

Following this presentation, participants will be able to:

1. Identify the most common causes of abnormal uterine bleeding among midlife women
2. Evaluate a midlife woman with abnormal uterine bleeding
3. Develop a management plan for presented causes of AUB in a midlife woman

Disclosures

- Consultant, Speaker's Bureau and/or Presentation (within past 12 months) for:
  - PDR Network
  - Medscape
  - NPACE, CT APRN Society, NPWH
  - Engage
  - Amgen
  - Datamonitor
  - Pfizer

PHYSIOLOGY

Characteristics of Normal Menses

	Average	Range
Menarche	12-13 yrs	8-16 yrs
Interval	28-30 days	24-35 days
Duration	4-5 days	2-8 days
Amount of flow	30-40 mL	20-80 mL
Menopause	50-52 yrs	40-60 yrs

Shwayder JM. *Obstet Gynecol Clin North Am*. 2000;27:219-234; Oehler MK, Rees MC. *Acta Obstet Gynecol Scand*. 2003;82:405-422; Speroff L., Fritz MA. Clinical Gynecologic Endocrinology and Infertility, 8th Ed. 2008.; Stenchever MA, et al. Mishell D. *Comprehensive Gynecology. 2001.*

Actions of Estrogen

- Stimulates development of ovaries, fallopian tubes, uterus, vagina, and of secondary sexual characteristics; eg, growth of the breasts during puberty
- Interacts with hypothalamic and pituitary hormones to regulate normal menstrual cycle
- Promotes cyclic proliferation of endometrium

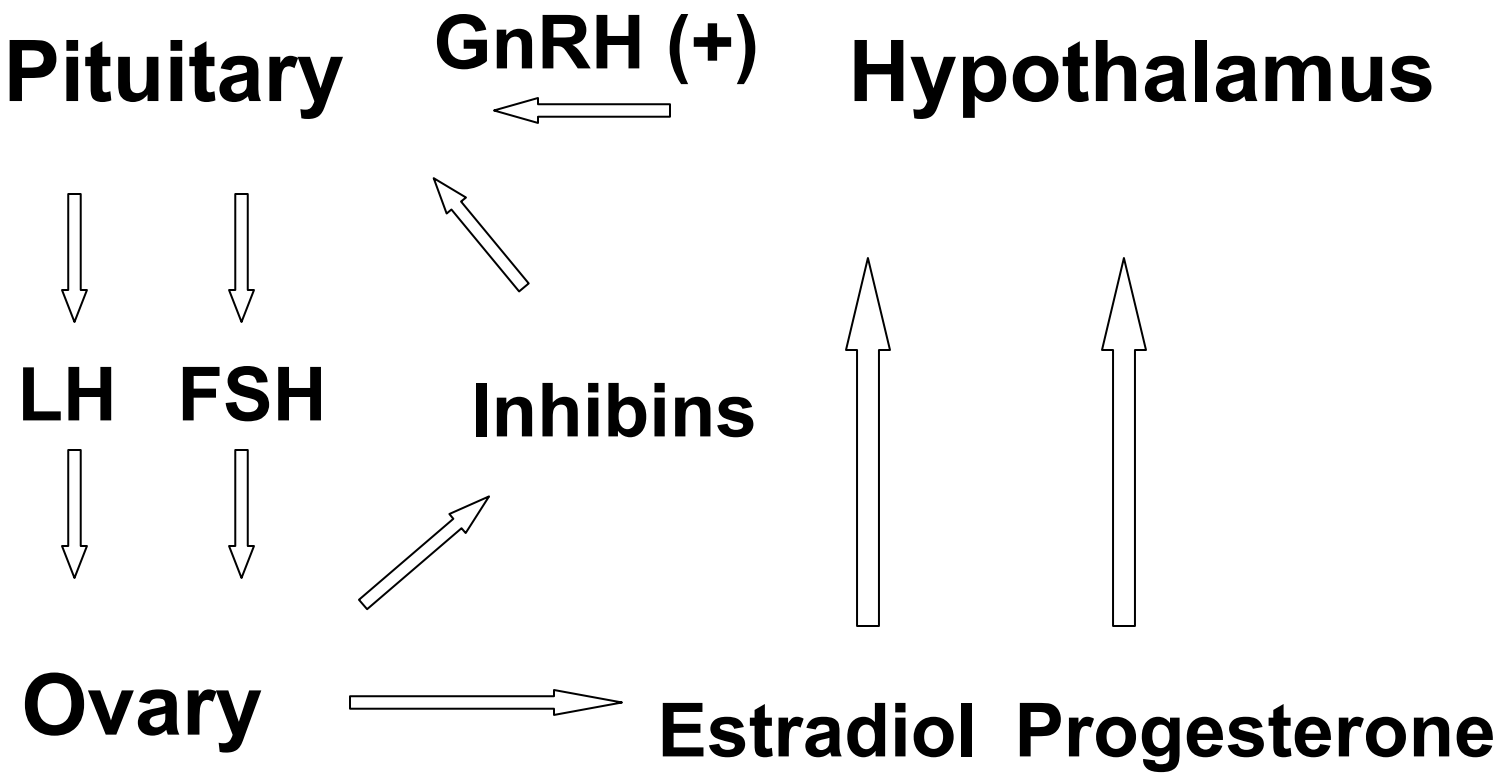
Goldfien. *Basic and Clinical Pharmacology*. 1998; Shwayder JM. *Obstet Gynecol Clin North Am*. 2000;27:219-234; Oehler MK, Rees MC. *Acta Obstet Gynecol Scand*. 2003;82:405-422; Speroff L., Fritz MA. Clinical Gynecologic Endocrinology and Infertility, 8th Ed. 2008.; Stenchever MA, et al. Mishell D. *Comprehensive Gynecology. 2001.*

Actions of Progesterone

- Interacts with hypothalamic and pituitary hormones to regulate normal menstrual cycle
- Induces secretory changes in the endometrium to prepare for possible pregnancy
- Increases viscosity of cervical mucus
- Prepares breasts for lactation

Goldfien. *Basic and Clinical Pharmacology*. 1998; Shwayder JM. *Obstet Gynecol Clin North Am*. 2000;27:219-234; Oehler MK, Rees MC. *Acta Obstet Gynecol Scand*. 2003;82:405-422; Speroff L., Fritz MA. Clinical Gynecologic Endocrinology and Infertility, 8th Ed. 2008.; Stenchever MA, et al. Mishell D. *Comprehensive Gynecology. 2001*.; Williams, Stancel. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 1996.

Hypothalamic-pituitary-ovarian axis



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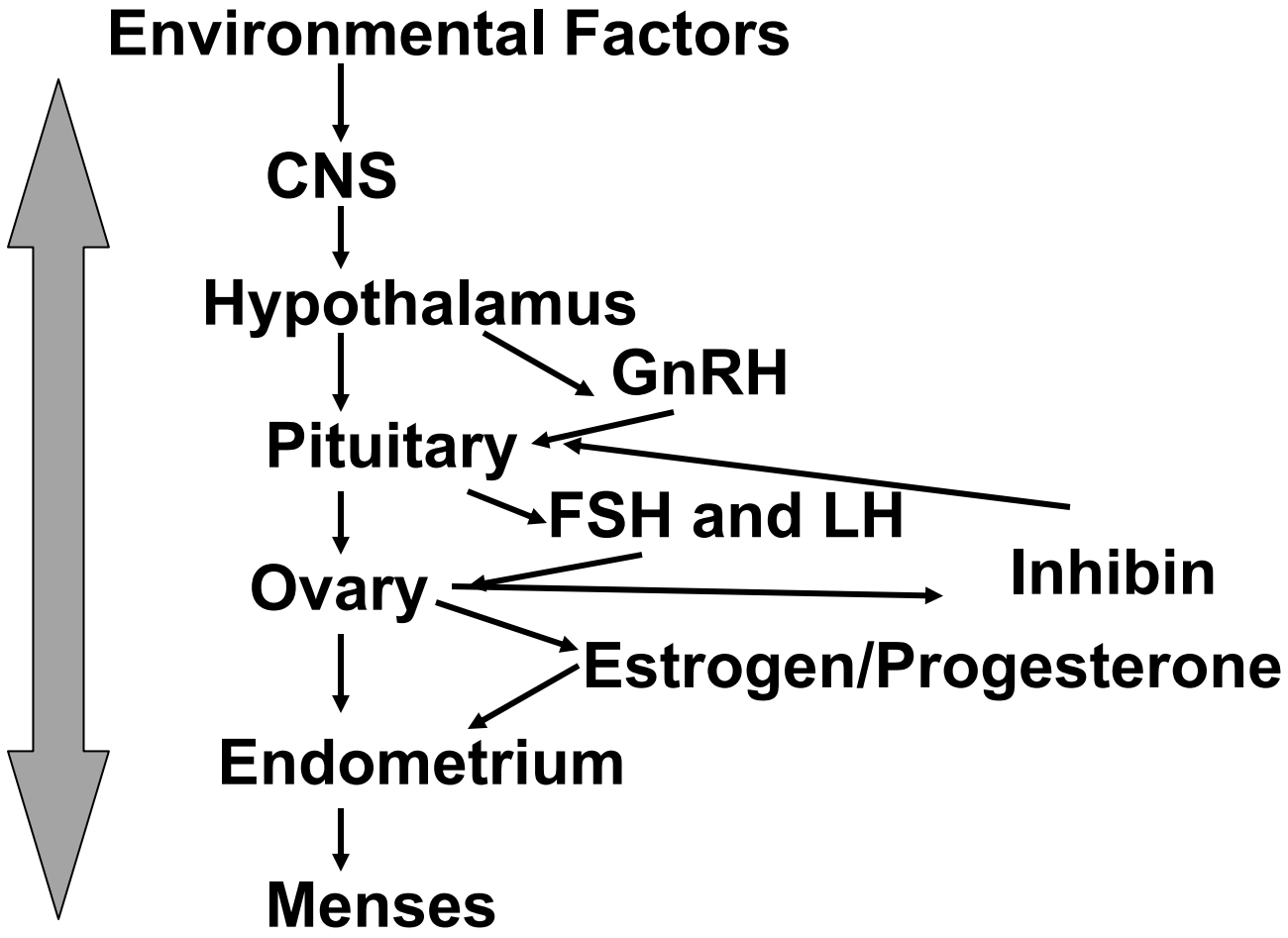
Endocrinologic Factors of Normal Menses



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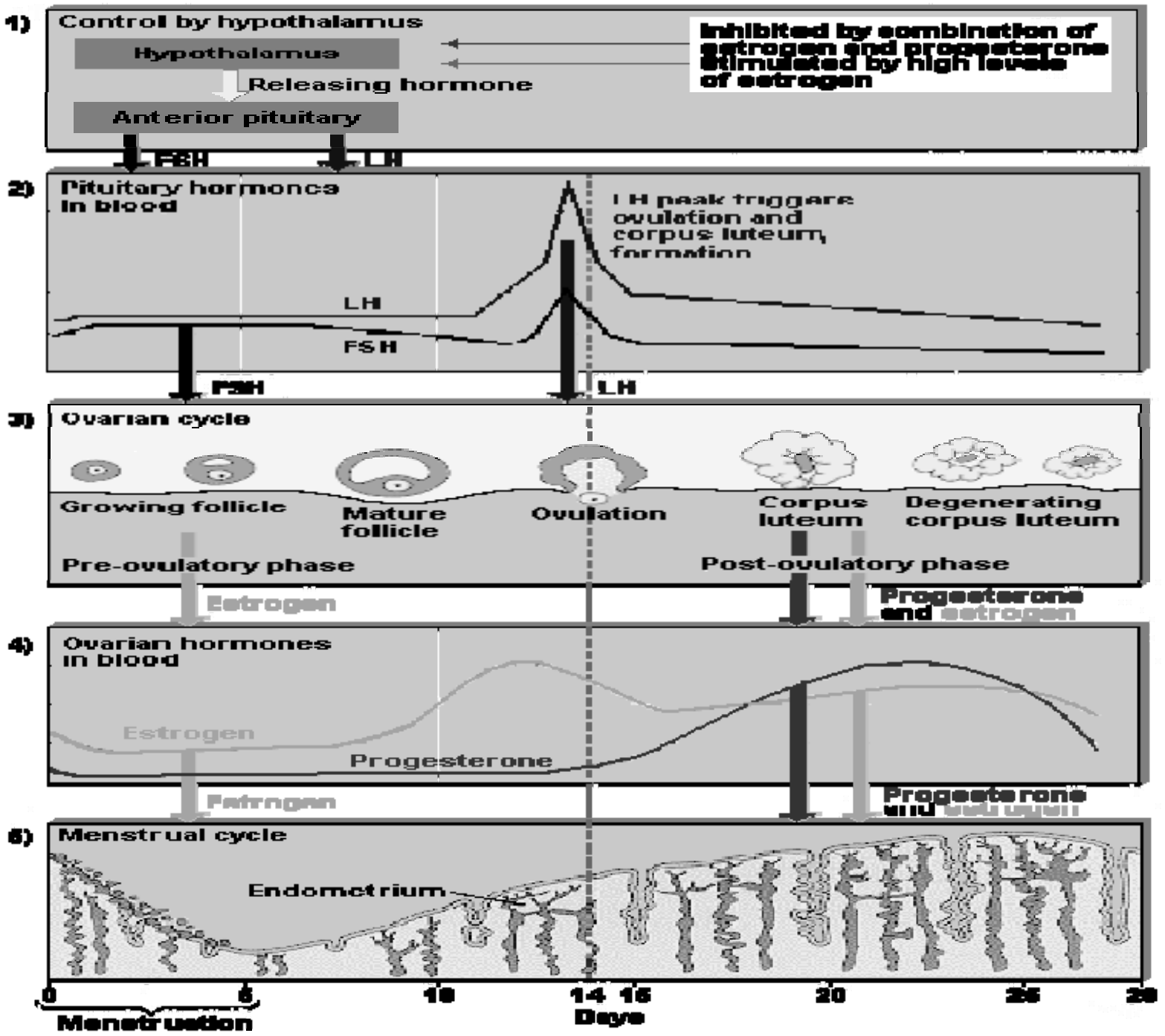
1)
Control by hypothalamus
Hypothalamus
Releasing hormone
Anterior pituitary
Inhibited by combination of estrogen and progesterone
Stimulated by high levels of estrogen
FSH
LH
2)
Pituitary hormones in blood
LH peak triggers ovulation and corpus luteum formation
LH
FSH
FSH
LH
3)
Ovarian cycle
Growing follicle
Mature follicle
Ovulation
Corpus luteum
Degenerating corpus luteum
Pre-ovulatory phase
Post-ovulatory phase
Estrogen
Progesterone and estrogen
4)
Ovarian hormones in blood
Estrogen
Progesterone
Estrogen
Progesterone and estrogen
5)
Menstrual cycle
Endometrium
0
5
10
14
15
20
25
28
Menstruation
Days

AUB: DEFINITION

Def: Abnormal Uterine Bleeding

- Uterine bleeding outside of the normal menstrual parameters
  - duration: <2 or >7 days
  - heavier than normal flow, or flow > 80 ml (Chronic loss of > 80 mL /cycle → anemia)
  - cycle length <24 or >35 days
  - intermenstrual bleeding or postcoital spotting

Speroff L., Fritz MA. Clinical Gynecologic Endocrinology and Infertility, 8th Ed. 2008.

Abnormal Uterine Bleeding Includes...

- Dysfunctional uterine bleeding (DUB)
- Oligomenorrhea
- Menorrhagia
- Intermenstrual bleeding
- Amenorrhea
- Polymenorrhea
- Metrorrhagia
- Menometrorrhagia
- Premenstrual spotting
- Hypermenorrhea / Hypomenorrhea

Speroff L., Fritz MA. Clinical Gynecologic Endocrinology and Infertility, 8th Ed. 2008.

The Fe′de′ration Internationale de Gyne′cologie et d'Obste′′trique (FIGO) – 2011

Munro, MG., Critchley, HOD., Fraser IS., & FIGO Menstrual Disorder Working Group. 2011. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertility & Sterility. 95(7): 2204-2208

Definitions per FICO

- Provides clarity and consistency in identification of root causes of genital bleeding
- Recommend retiring the terms menorrhagia, metrorrhagia and dysfunctional uterine bleeding (DUB)

Munro, MG., Critchley, HOD., Fraser IS., & FIGO Menstrual Disorder Working Group. 2011. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertility & Sterility. 95(7): 2204-2208; Fraser IS, Critchley HO, Munro MG, Broder M. A process designed to lead top international agreement on terminologies and definitions used to describe abnormalities of menstrual bleeding. Fertil Steril 2007;87:466-76

Nine (9) Categories per FIGO: PALM-COEIN

- P – Polyp
- A – Adenomyosis
- L – Leiomyomas (Submucosal, Other)
- M – Malignancy & Hyperplasia
- C – Coagulopathy
- O – Ovulatory disorders
- E – Endometrium
- I – Iatrogenic
- N – Not classified

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PALM-COEIN Categorization

- Structural Problems
- Measured by
  - direct Visualization
  - Imaging
  - use of Histopathology

Munro, MG., Critchley, HOD., Fraser IS., & FIGO Menstrual Disorder Working Group. 2011. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertility & Sterility. 95(7): 2204-2208

PALM-COEIN Categorization

- Nonstructural
- Not defined via histopathology or imaging

Munro, MG., Critchley, HOD., Fraser IS., & FIGO Menstrual Disorder Working Group. 2011. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertility & Sterility. 95(7): 2204-2208

PALM COEIN Categorization

- Not yet classified

Munro, MG., Critchley, HOD., Fraser IS., & FIGO Menstrual Disorder Working Group. 2011. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertility & Sterility. 95(7): 2204-2208

PALM-COEIN Categorization

- Recognizes that a woman may have one or more entities that could cause bleeding
- May have entities that are asymptomatic and not contributing to presenting problem
  - leiomyomas, adenomyosis, polyps

Munro, MG., Critchley, HOD., Fraser IS., & FIGO Menstrual Disorder Working Group. 2011. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertility & Sterility. 95(7): 2204-2208

AUB: PREVALENCE

AUB: Prevalence

- Abnormal bleeding is the most common reason for non-annual gyn visit
  - 10-35% of all women have heavy bleeding
  - 11% of postmenopausal women have spontaneous bleeding
  - Annovulation and irregular cycles very common among adolescent and perimenopausal women

AUB: PATHOPHYSIOLOGY

AUB: DDx (Pathophysiology)

- Pathophysiology of AUB = DDx
- DDx affected by:
  - Age
  - Menstrual status
  - Pregnancy
- Most common DDx are:
  - Anovulation
  - Pregnancy
  - Structural Prob
  - Devices
  - Cancer
  - Systemic Dz
  - Infxn/STI
  - Trauma
  - Medications

Pathophysiology of Anovulatory Cycles

- Abnormal Estradiol stimulation of endometrium
- E_2 levels either too high or too low to start cascade leading to ovulation
- Altered E_2 effects cause:
  - long periods of amenorrhea
  - polymenorrhea
  - hemorrhage
  - spotting

Pathophysiology of Anovulatory Cycles con't

- Minor deficiency in the E_2 signal can result in:
  - subnormal central response
  - impaired or inappropriate degree of follicular growth and function
  - disturbed feedback mechanisms

Pathophysiology of Anovulatory Cycles con't

- Abnormal feedback upsets the synchrony of the cycle
  - E_2 levels must fall enough to allow sufficient FSH response for the initial growth stimulus
  - E_2 levels may be inadequate to produce the positive stimulatory effects for an LH surge

AUB: PRESENTATION & ASSESSMENT

Presentation

- Altered bleeding pattern:
  - Longer, shorter, or irregular cycle
  - Heavier or lighter flow
  - Longer or shorter length of flow
  - Change in flow characteristics (mid-cycle bleeding, spotting, etc)

Munro, MG., Critchley, HOD., Fraser IS., & FIGO Menstrual Disorder Working Group. 2011. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertility & Sterility. 95(7): 2204-2208

Presentation (con't)

- Acute
  - Episode of heavy bleeding; requires intervention to stabilize woman and prevent further blood loss
- Chronic
  - Altered bleeding pattern (amount, timing, regularity) for most of a 6 month period
- Intermenstrual
  - Bleeding in between predictable menses and defined cycles; can be random or predictable (replaces "metrorrhagia")

Munro, MG., Critchley, HOD., Fraser IS., & FIGO Menstrual Disorder Working Group. 2011. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertility & Sterility. 95(7): 2204-2208; Fraser IS, Critchley HO, Munro MG, Broder M. A process designed to lead top international agreement on terminologies and definitions used to describe abnormalities of menstrual bleeding. Fertil Steril 2007;87:466-76

Evaluating a Woman with Abnormal Bleeding

History

Physical Exam

Diagnostic Evaluation

History: Key Questions

- Usual menses? Signs of ovulation?
- Nature of the abnormal bleeding?
  - Frequency
  - Duration
  - Volume
  - Relationship to activities (eg, coitus, exercise)
  - When occurs
  - Associated symptoms

Goodman, A. Initial Approach to the premenopausal woman with abnormal uterine bleeding. *UpToDate*, 2010.

History: Key Questions, con't

- What is her age?
- Where does blood originate?
- Is she sexually active? Pregnant?
- Systemic illness(es)?
- Medications?
- Personal or Family Hx of bleeding d/o?
- Weight change – eating d/o, excessive stress, excessive exercise or illness?

Goodman, A. Initial Approach to the premenopausal woman with abnormal uterine bleeding. *UpToDate*, 2010.

History: Quantifying Patient Measures of Abnormal Bleeding

- An increase of ≥ 2 pads or tampons/day
- Menstrual bleeding lasting 3 days longer than usual
- Blood clots that have increased in size and/or number
- Sanitary product needs that interfere with her usual activities, need to change pad at night

History: Screening for Bleeding Disorders

1. + if Heavy bleeding since menarche
2. + if Postpartum hemorrhage; Surgical related bleeding; and /or Bleeding associated with dental work
3. + if ≥2: Bruising 1-2x/ms; Epistaxis 1-2x/ms; frequent Gum Bleeding; Family hx of bleeding sxs

- Positive screen → consider further evaluation

Munro, MG., Critchley, HOD., Fraser IS., & FIGO Menstrual Disorder Working Group. 2011. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertility & Sterility. 95(7): 2204-2208

History: Documenting AUB

- Regularity
  - Regular, irregular, absent
- Duration of Flow
  - Normal, prolonged, shortened
- Frequency
  - Normal, frequent, infrequent
- Volume
  - Normal, heavy, light

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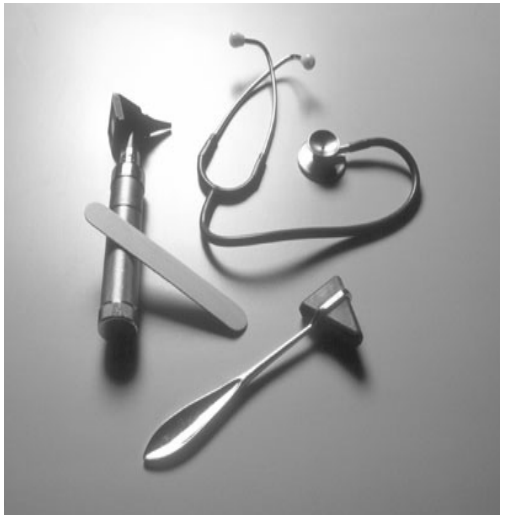
PE: Identify Pathology, Identify Bleeding Source

- General appearance, BMI, sexual maturity
- Systemic eval for Sx of systemic cause:
  - Body habitus, skin and hair (distribution, hirsute), mucosal color, petechaie
- Head / Neck, Thyroid exam
- Breast exam
- Genital / Pelvic (cerv cytol, cxs)
- Rectal exam (hemoccult stool)
- Blood on toilet tissue or sanitary pad may not be uterine



AUB: DIAGNOSTICS

AUB: Diagnostic Studies

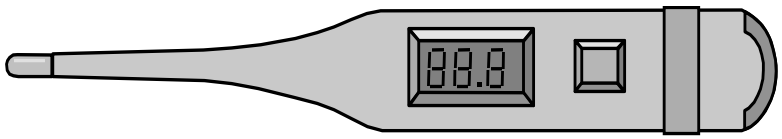
Age	Laboratory Tests
13-18 years	■ Coag studies (INR, PT/PTT, fibrinogen, von Willebrand Factor, ristocetin cofactor) ■ CBC with platelet count to id coag defects, leukemia, anemia
19-50 years	■ HCG, cervical cytology, cultures ■ TSH – hypo- / hyperthyroidism, esp if untested in 5 years ■ FSH (controversial) , maybe with E_2 Pg and LH ■ CBC with platelet count and serum Fe, blood drawn early in cycle (day 3) – coag defects, anemia ■ UA – UTI, renal calculi, bladder cancer ■ Guiac – colon polyps, diverticula, GI cancer, ulcer, hemorrhoids, fissures ■ Ultra Sound – leiomyomata , structural abn; ?endometrial Bx ■ ?Fasting serum prolactin – pituitary adenoma (if bleeding is infrequent or minimal), ?CNS imaging ■ ?Coag studies, ?LFTs, ?Renal Function Studies

ACOG. *Int J Gynaecol Obstet*. 2001;73:263-271; Speroff L, Fritz MA. *Clinical Gynecologic Endocrinology and Infertility*. 8th ed. 2008; James AH, et al. *Hematology Am Soc Hematol Educ Program*. 2006:474-485. Munro et al 2011 Fert Ster.

AUB: DDX

Secondary Work-up and When No Signs of Ovulation

- Determine ovulatory status
  - cycle charting
  - basal temperature monitoring
  - progesterone testing
  - OTC test kits
  - EMBx



DDx of AUB: Pregnancy-Related Conditions

- Pregnancy is a common cause of bleeding
  - >33% of women experience bleeding during the first 20 weeks
- Pregnancy-related conditions:
  - Ectopic pregnancy
  - Trophoblastic disease
  - Miscarriage – incomplete, threatened, or missed abortion

Shwayder JM. *Obstet Gynecol Clin North Am*. 2000;27:219-234.

DDx of AUB: Systemic Causes

- Endocrine disorders – Thyroid dz, Hyperprolactinemia, Polycystic ovary syndrome
- Hematologic disorders – up to 20% have coagulopathy, most often von Willebrand[1]
- Adrenal hyperplasia/Cushing disease
- Renal / Liver disease
- Mucosal diseases (Chron's, Bechet's)
- Stress
- Extreme exercise
- Medications
- Eating Disorders (obesity, anorexia)
- Weight loss

[1]James AH, et al. *Hematology Am Soc Hematol Educ Program*. 2006;474-485.

DDx of AUB: PALM (Structural Abnormalities)

- Infections
  - STIs, cervicitis, vaginitis, endometritis
- Benign structural abnormalities
  - Polyps, ectropian, cysts, etc
  - Leiomyomata (eg, submucosal)
- Premalignant/malignant lesions
- Trauma/irritation
  - Intercourse, Sexual assault
  - Presence of a foreign body

DDx of AUB: Iatrogenic (Other Causes, Medications, Devices)

- Oral contraceptives (esp intermenstrual, oligo- / amenorrhea)
- Intrauterine devices
- Hormone replacement
- Selective serotonin reuptake inhibitors
- Antipsychotics
- Anticoagulants
- Corticosteroids
- Herbal supplements

Diagnostic Reasoning

- Primary or secondary?
- Is she pregnant?
- Is it drug related?
- Is there a problem with the HPO?
- Is there a problem with the uterus?
- Is there a structural problem?
- Is there a chronic endocrine problem?

AUB – Not Specified

- Diagnosis of exclusion – no organic or structural cause for bleeding identified
- Defined as: periodic uterine blood loss >80 mL /cycle that occurs in the absence of structural uterine abnormalities
- Negatively impacts her quality of life
- Associated with increased healthcare costs

Bongers MY, et al. *Maturitas*. 2004;47:159-174; Cote I, et al. *Am J Obstet Gynecol*. 2003;188:343-348; Cote I, et al. *Obstet Gynecol*. 2002;100:683-687; Munro MG et al, F+S 2011; Fraser IS et al, F+S 2011.

AUB – Not Specified in a Premenopausal Adult Woman

- What is your most important rule out?
  - pregnancy
- What will you include for PE?
  - General survery, thyroid, pelvic exam
- Will you order any diagnostics?
  - HCG
  - Cervical cytology, cultures
  - TSH, LFTs
  - ?coag studies, prolactin

DDx by Age

- Reproductive Years
  - anovulation
  - pregnancy
  - benign growths
  - medication induced
  - endocrine dz
  - bleeding disorder
  - liver dz
  - infection
- Perimenopausal
  - anovulation
  - cancer
  - benign growths
- Postmenopause
  - cancer
  - medication induced
  - atrophy
  - benign growths

Consider Common Lesions

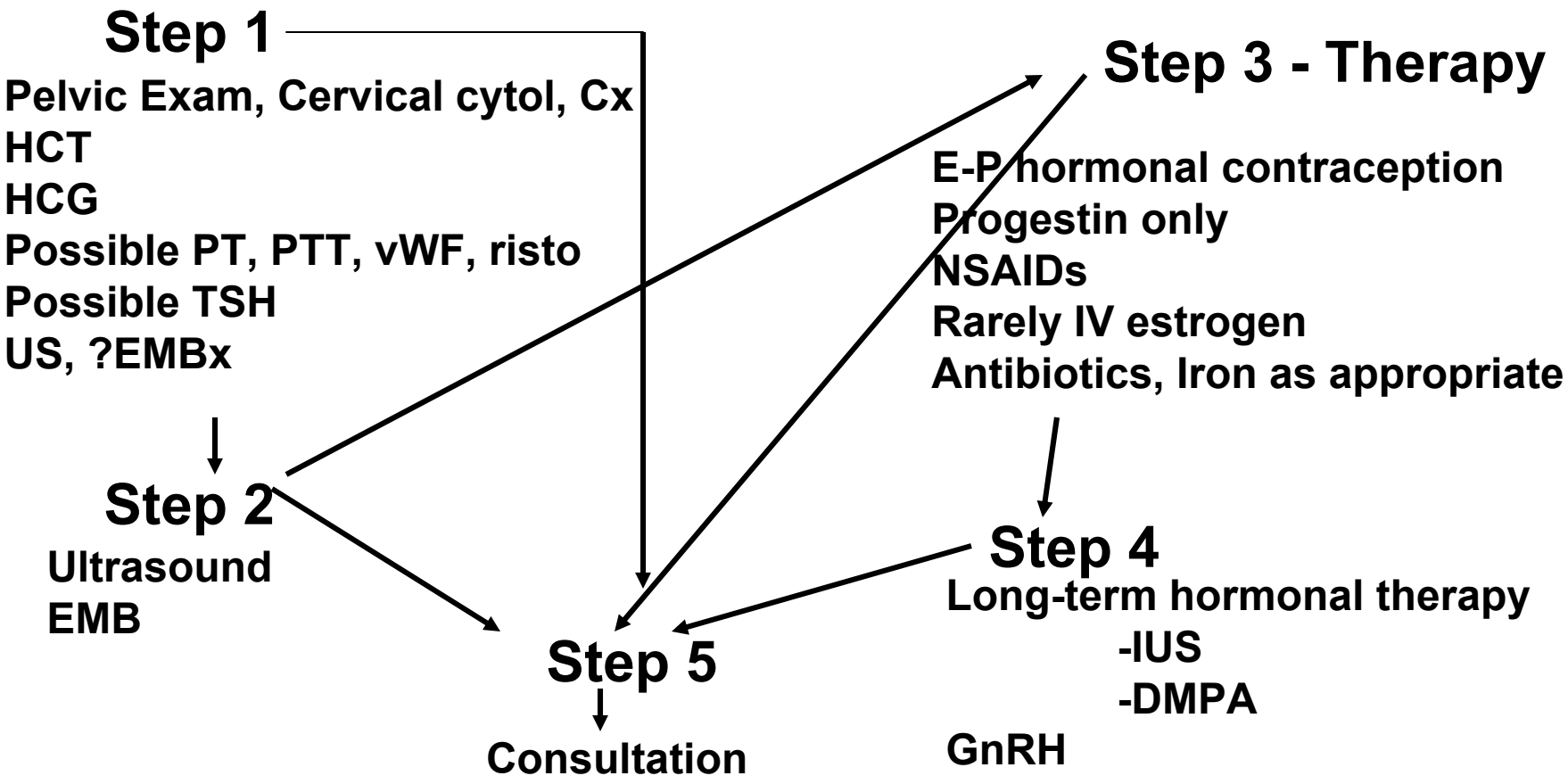
- Benign pelvic lesions
  - leiomyomata / fibroids
    - Heavy menstrual bleeding
  - polyps
    - intermittent spotting
    - post coital bleeding
  - Adenomyosis
    - ectopic endometrial glands within the myometrium

CHRONIC AUB: MANAGEMENT

Chronic AUB Management

- Adjust medications (esp, OCs)
- Treat infection
- Manage systemic disease
- Refer as needed for systemic disease or coagulopathy management

Chronic AUB Management

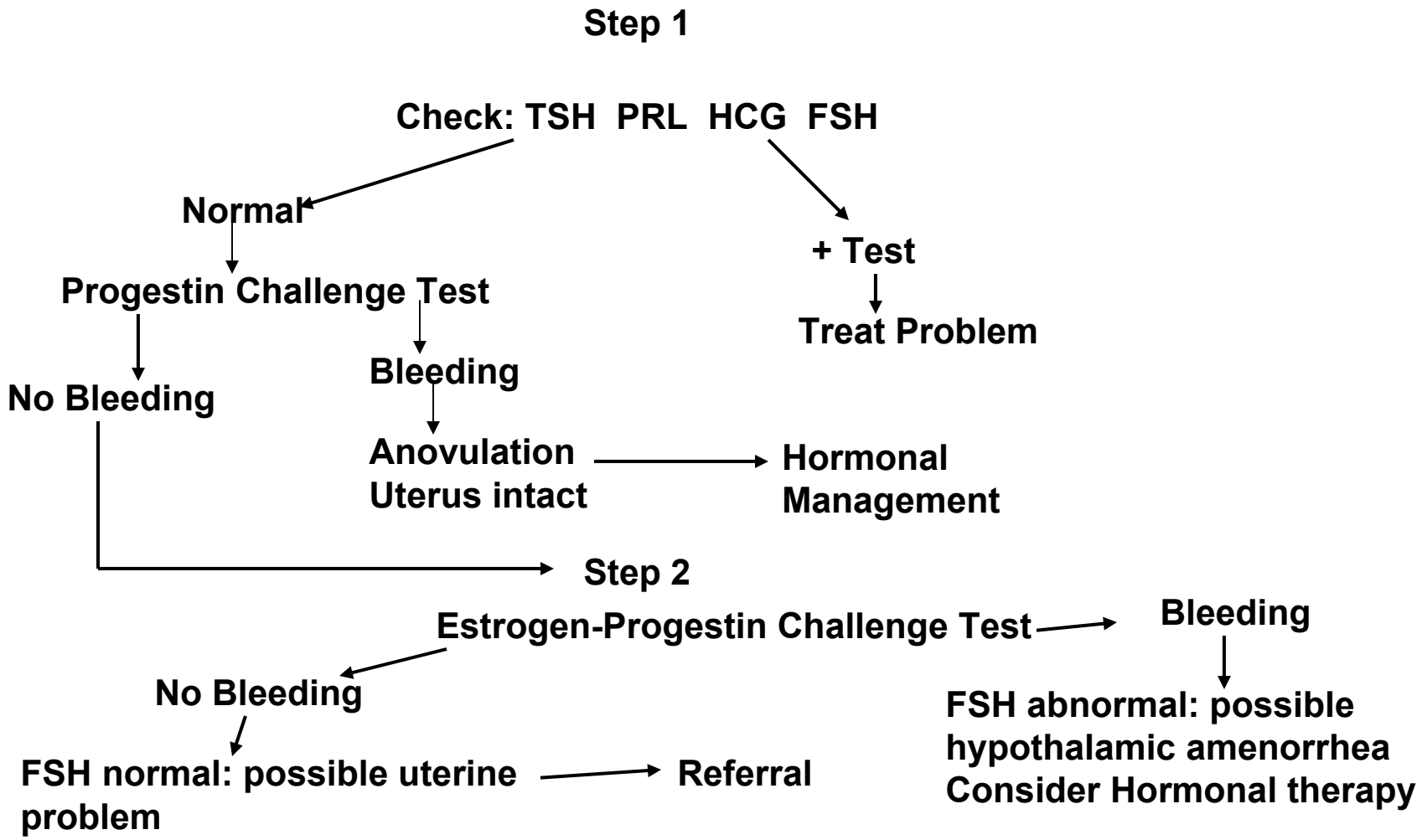


Amenorrhea and Oligomenorrhea

Essentials of Diagnosis: Amenorrhea and Oligomenorrhea

- Exclude pregnancy
- Rule-out endometrial neoplasia, hormonal abnormality
- Exclude hypothalamic causes
  - Anorexia
  - Exercise
  - Stress

Amenorrhea Management



Progestin Therapy

- Oligomenorrhea
  - Progestin Challenge Test
    - absence of withdrawal bleed requires work-up
  - monthly administration of 5-10 mg MPA or 200-400mg Prometrium for minimum of 10 days
  - some women prefer P Rx less often: Why?
  - OCPs better choice if contraception needed

E_2 Add Back: Depo, Norplant, POPs

- Endometrium shrinks from pharmacologically induced pseudoatrophy
  - endometrium consists of pseudodecidual stroma and blood vessels with minimal glands
  - more like the fragile tissue typical of pure estrogen stimulation → bleeding
- Rx: Add CEE 1.25 mg or Estradiol 2 mg for 7 days to OCs or depo

Anovulatory Cycles

Essentials of Dx: Anovulation

- Rule-out Central Causes
  - GnRH levels (production, stress, anxiety, anorexia, excessive exercise, etc)
  - Hyperprolactinemia
  - PCOS
  - Systemic Disease affecting E clearance (thyroid,liver disease)
- Rule-out ovarian causes
  - Infection, endometriosis, abnormal receptors
- Usually multi-factorial, id of precise etiology unnecessary in most instances
- Can be normal at midlife approaching menopause

Physical Characteristics Accompanying Anovulation

- Hirsutism
- Acne
- Galactorrhea
- Thyroid enlargement
- Evidence of an eating disorder
- Bruises
- Abnormalities on pelvic exam such as?

Anovulatory Bleeding: Evaluation

- History, PE
- Cervical cytology
- Pregnancy
- CBC
- TSH
- ?LFT, renal panel
- ?Prolactin level
- ?EMB
- ?TVS

Anovulatory Bleeding: Management

- PCOS
- Systemic disease
- OC
- Cyclic progestin
- Progestin IUD
- GnRH agonist

Progestin Therapy: When? Who?

- Teens and premenopausal women
  - may not ovulate or sustain corpus luteum function or duration
- Usual presentation?
  - Oligomenorrhea followed by heavy bleeding
- Progestin acts like an antiestrogen
  - diminishes effect of E on target cells

AUB: Ovulatory

Essentials of DDx – AUB: Ovulatory (Hvy Menstrual Bldg)

- Adolescents
  - (usually anovulatory)
  - coagulopathy
  - systemic illness
- Adult Women
  - benign growths
  - coagulopathy
  - systemic disorder
  - chronic endometritis
  - neoplasia

AUB – Ovulatory: Evaluation

- History, PE
- Cervical cytology
- Beta-HCG
- CBC
- Coagulation studies
- TSH
- LFTs
- Renal function tests
- Endometrial biopsy
- Transvaginal Ultrasound

Pre-Menopausal AUB: When to Biopsy?

Age Group	Endometrial CA Incidence (per 100,000 women)	ACOG Recommendations for Biopsy
13-18 years	0.1	Only consider if anovulatory >2 years and obese
19-34 years	2.3	Consider if chronic anovulation or unresponsive to medication
35-39 years	6.1	
40-49 years	36.0	Biopsy unless pregnant or another clear reason to avoid sampling the endometrium

ACOG. *Int J Gynaecol Obstet*. 2001;73:263-271.

Endometrial Biopsy

- To identify endometrial cancer or premalignant lesions
- Women >35
- Women 18-35 if risk factors for endometrial cancer
- Performed at or after cycle day 18

Transvaginal Ultrasound

- To measure endometrial thickness & identify structural lesions
- ?before or after EMB
- Performed on cycle day 4, 5, or 6

Endometrial Cancer

- Absence of growth limiting influence of progesterone
- no regular shearing of the lining
- endometrium achieves abnormal height without structural support
- fragile tissue suffers spontaneous superficial breakage and bleeding
- one site heals/ another breaks down

Hyperplasia vs Neoplasia

Two distinct and biologically unrelated diseases

- Hyperplasia without atypia = endometrial hyperplasia (not usually a precursor to CA)

  Treatment → Hormones

- Hyperplasia with cytologic atypia = Endometrial intraepithelial neoplasia (EIN)

  Treatment → Surgery

Management of Acute Bleeding

- Moderate to severe → not hemodynamically stable
  - hospitalize
  - IV CEE and antiemetics
- Moderate to severe → hemodynamically stable
  - outpatient treatment
  - high dose OCs

Should You Rx: Estrogen Alone?

- Use E alone after prolonged bleed
  - scant lining of basalis layer, atrophic endometrium
  - biopsy reveals little tissue
- When patient has been on a progestin
  - POPs, depoprovera
- When follow up is uncertain because E will stop all categories of bleeding

Unopposed E Therapy

- High doses can precipitate…
  - thrombotic event
- Little data to quantify risk, dose
- Risk benefit ratio individualized
- Avoid in woman with past history of idiopathic venous thromboembolism

Medical Therapies for AUB – Ovulatory (Hvy Menstrual Bldg)

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
  - If bleeding does not improve with NSAIDs, consider the possibility of a coagulation disorder, or liver or kidney dz
- Combination oral contraceptives
- Progestins
  - Cyclic or continuous administration
  - Levonorgestrel intrauterine system
- Danazol
- Gonadotropin-releasing hormone agonists
- Antifibrinolytics
- Desmopressin

Working Party for Guidelines for the Management of Heavy Menstrual Bleeding. *NZ Med J*. 1999;112:174-177; Lethaby A, et al. *Cochrane Database Syst Rev*. 2002;(1):CD000400.

Medical Therapy for Heavy Menstrual Bleeding: Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- Systematic review of studies evaluating NSAIDs versus placebo
  - Mefenamic acid, meclofenamic acid, diclofenac, ibuprofen, and naproxen were compared
  - Treatment was given only during menses
- All NSAIDs, except ibuprofen, reduced menstrual flow when compared to placebo
  - Reduction in flow averaged 35 mL (95% CI: 27-43)
  - Pain relief was an additional benefit
- Adverse effects
  - Gastrointestinal symptoms (i.e., nausea, vomiting, indigestion)

Working Party for Guidelines for the Management of Heavy Menstrual Bleeding.
NZ Med J. 1999;112:174-177; Lethaby A, et al. *Cochrane Database Syst Rev*. 2002;(1):CD000400.

Medical Therapy for Heavy Menstrual Bleeding: Oral Contraceptives

- Oral contraceptives reduce endometrial thickness as visualized by uterine ultrasonography
- Paucity of data on use of oral contraceptives for heavy menstrual bleeding
- One small, randomized clinical trial (Fraser & McCarron, 1991) reported a 43% reduction in menstrual blood loss with a low-dose monophasic combined oral contraceptive

Iyer V, et al. *Cochrane Database Syst Rev*. 2000;(2): CD000154;
Fraser IS, McCarron G. *Aust N Z J Obstet Gynaecol*. 1991;31:66-70.

Medical Therapy for Heavy Menstrual Bleeding: Oral Progestins

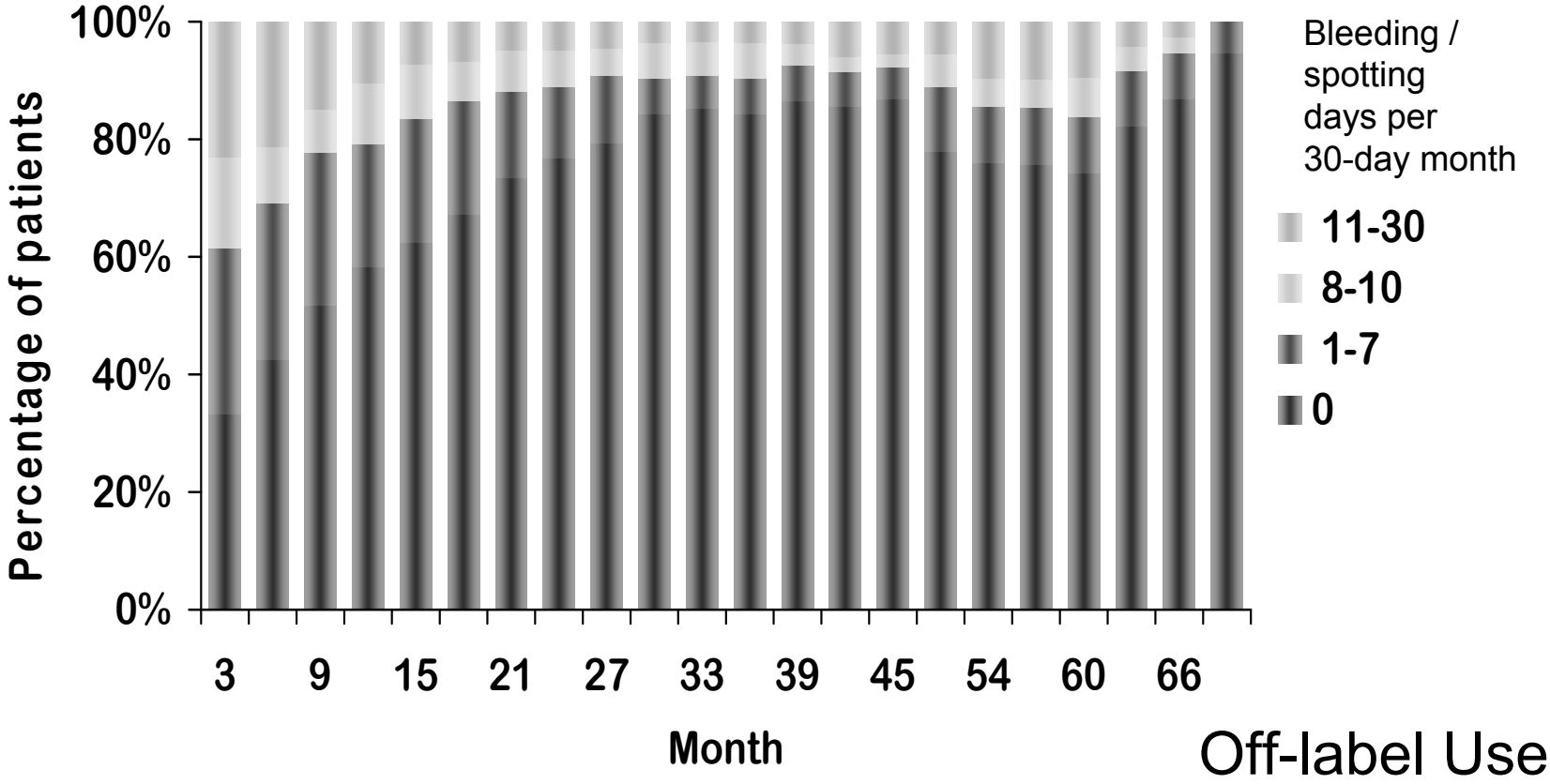
- Administration during the luteal phase of the menstrual cycle is less effective than other methods of administration
- Progestin therapy for 21 days of the menstrual cycle is more effective but causes more side effects
- In practice → progestins for 10-14 days q mo
  - Induces stabilizing predecidual stromal changes
  - Followed by a withdrawal bleed (“medical D&C”)
  - If no correction then reevaluate/ refer

Lethaby AE, et al. *Cochrane Database Syst Rev*. 2005;(4):CD002126.

Oral Progestin Dosages

Medroxyprogesterone acetate	5 to 10 mg daily for 5-10 days. Give monthly
Norethindrone acetate	2.5 to 10 mg daily for 5 –10 day. Give monthly
Micronized progesterone	200 mg daily for 12 days. Give monthly

Medical Therapy for Heavy Menstrual Bleeding: Injectable Depot Medroxyprogesterone Acetate



Off-label Use

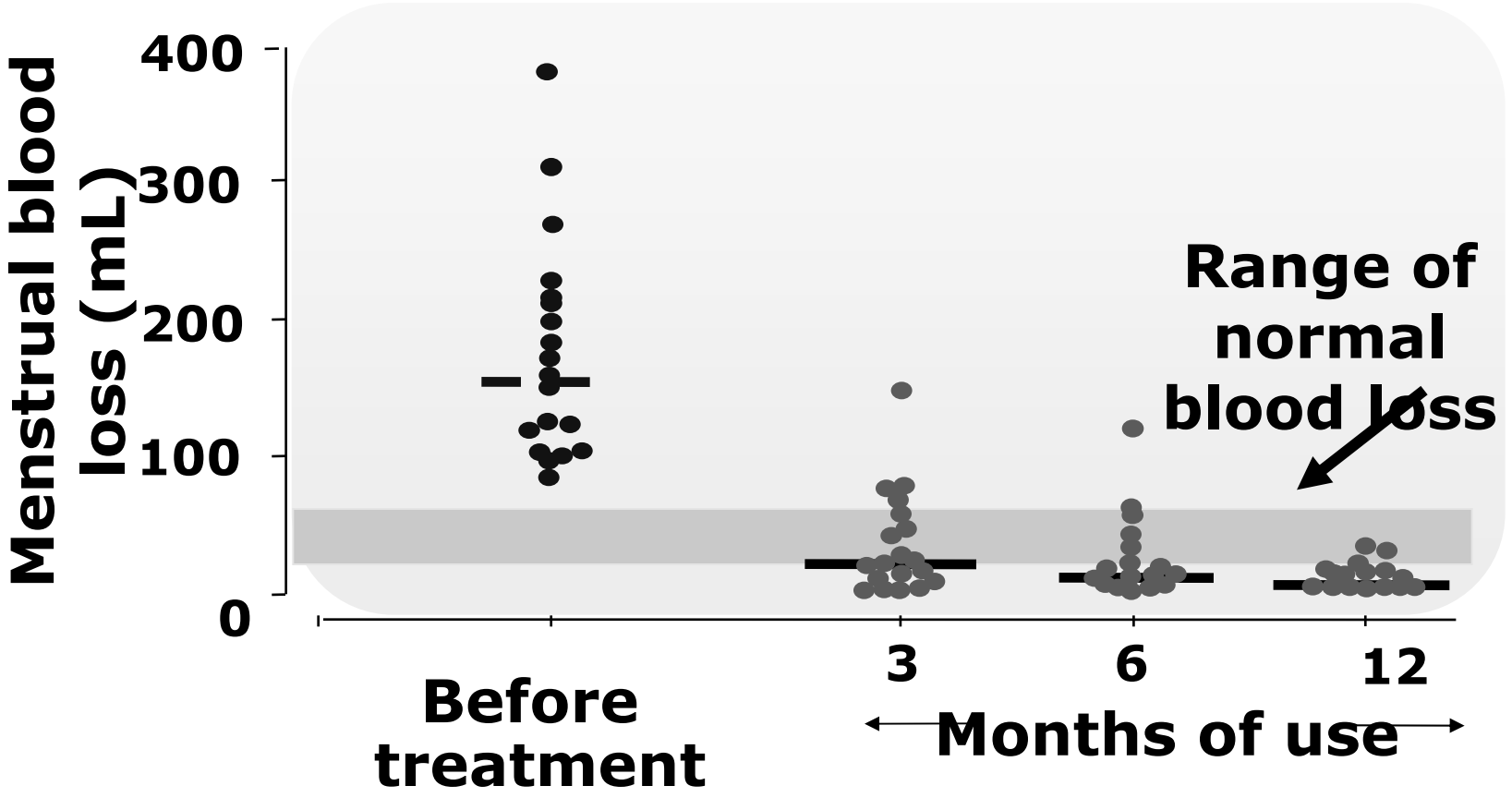
Schwallie PC, Assenze JR. *Fertil Steril* 1973;24:331-339; Greydanus DE, et al. *Pediatrics*. 2001;107:562-573; Kaunitz AM. *J Reprod Med*. 2002;47:785-789; Jain J, et al. *Contraception*. 2004;70:269-275; Scholes D, et al. *Arch Pediatr Adolesc Med*. 2005;159:139-144.

Medical Therapy for Heavy Menstrual Bleeding: Levonorgestrel IUS

- Releases 20 μg of levonorgestrel every 24 hrs
- ↓ amount of menstrual blood loss
- Consider a bleeding disorder if she does not respond to treatment
- FDA approved for contraception and to treat heavy menstrual bleeding in IUD users; also used off-label for endometrial protection in PM women taking estrogen

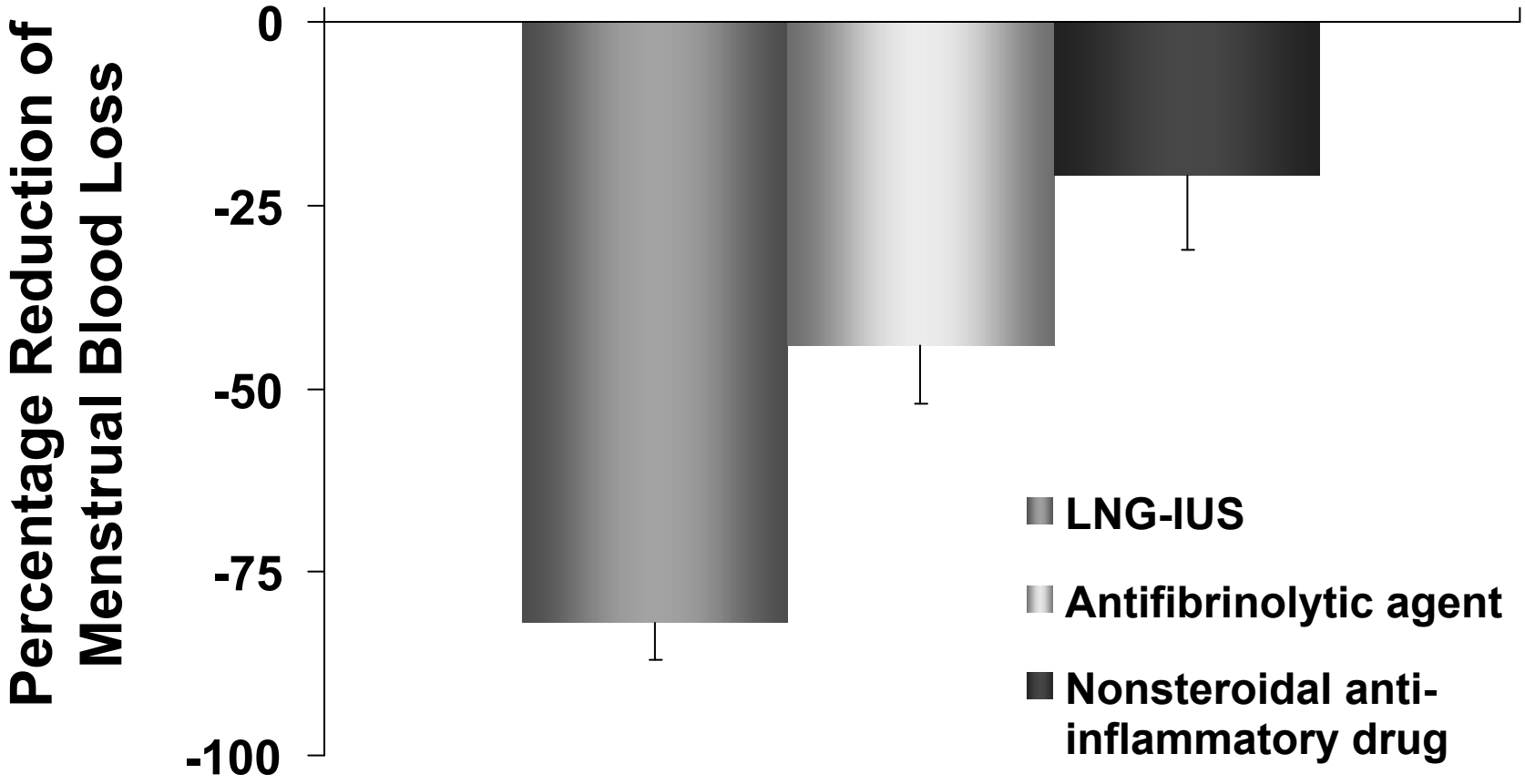
Andersson JK, Rybo G. *Br J Obstet Gynaecol*. 1990;97:690-694.

Medical Therapy With the Levonorgestrel Intrauterine System Reduces Heavy Menstrual Bleeding



Andersson JK, et al. *Br J Obstet Gynaecol*. 1990;97:690-694. Fedele L, et al. *Fertil Steril*. 1997;68:426-429; Soysal S, Soysal ME. *Gynecol Obstet Invest*. 2005;59:29-35.

Levonorgestrel Intrauterine System Decreases Menstrual Blood Loss



LNG-IUS = levonorgestrel-releasing intrauterine system

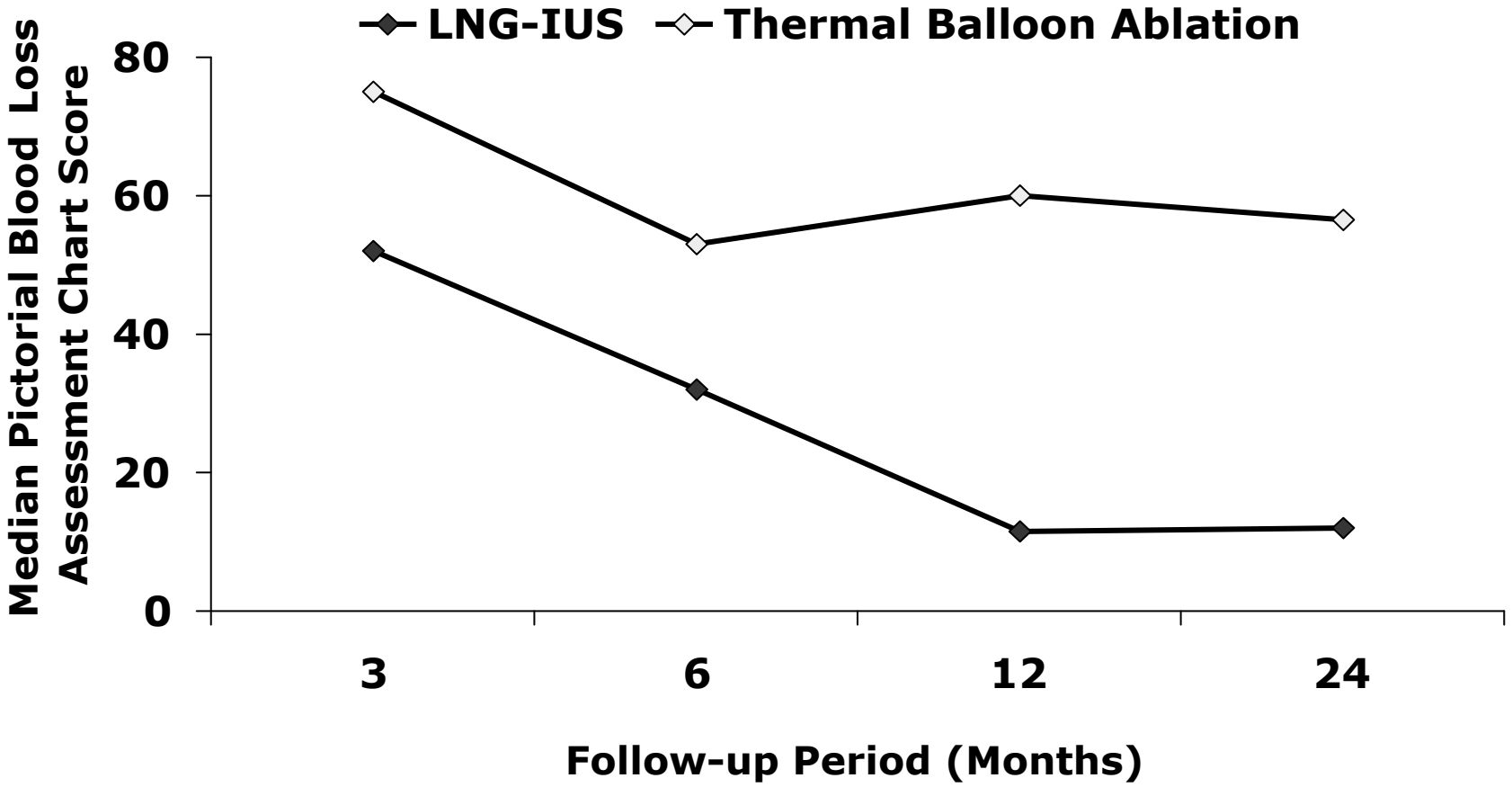
Milsom I, et al. *Am J Obstet Gynecol*. 1991;164:879-883.

Surgical Therapies for Heavy Menstrual Bleeding

- Dilation and curettage (acute bleeding)
- Endometrial ablation techniques
  - First-generation techniques
    - Rollerball ablation
    - Transcervical resection
  - Second-generation techniques
    - Bipolar impedance
    - Cryoablation
    - Balloon ablation
    - Hydrothermal ablation
- Hysterectomy
- Myomectomy

Bongers MY, et al. *Maturitas*. 2004;47:159-174. Sowter MC, et al. *Cochrane Database Syst Rev*. 2002;(3):CD001124.

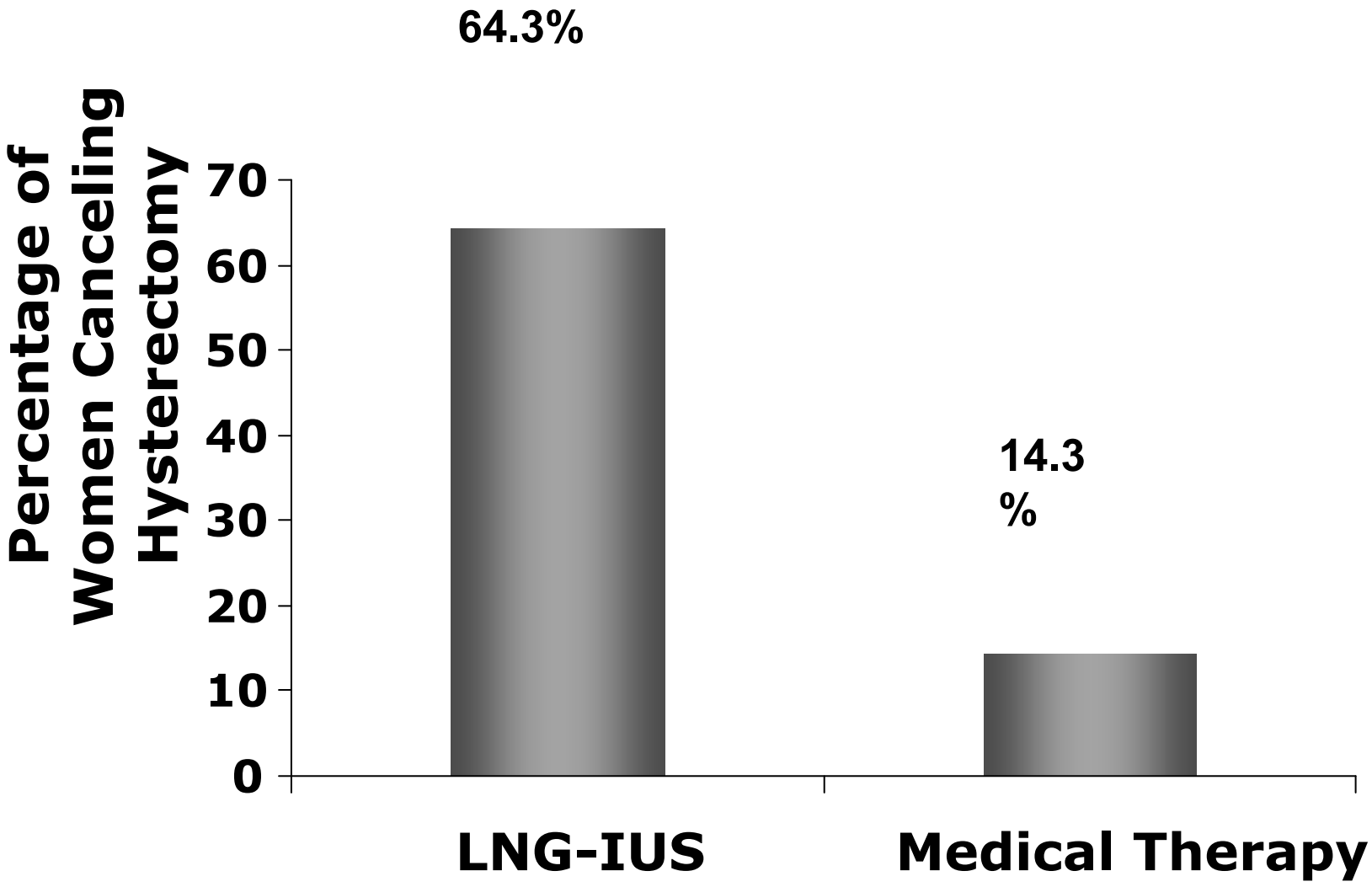
Levonorgestrel Intrauterine System Versus Endometrial Ablation



LNG-IUS=levonorgestrel intrauterine system

Busfield RA, et al. *Br J Obstet Gynaecol*. 2006;113:257-263.

Levonorgestrel Intrauterine System as an Alternative to Hysterectomy for Heavy Menstrual Bleeding



Lahteenmaki P, et al. *BMJ*. 1998;316:1122-1126; Hurskainen R, et al. *Lancet*. 2001;357:273-277.

AUB – Ovulatory (Hvy Menstrual Bldg): Management con't

- Consider risk of repeat hemorrhage
- May need periodic P if not on OC
- May require treatment change or re-eval
- If persistent DUB, consider:
  - submucus fibroids
  - polyps
  - missed diagnosis of serious pathology
  - wrong diagnosis on endometrial biopsy

Intermenstrual Bleeding

Essentials of Dx: Intermenstrual Bleeding

- OC misuse / problem
- STIs
- Pregnancy
- Ovulatory bleeding
- Endometrial cancer / premalignant lesion

Progesterone Related Intermenstrual Bleeding

- Progesterone withdrawal bleeding
  - When stop exogenous source of P
    - Eg, COCs, P challenge
  - Occurs as normal menstrual bleed
- Progestin breakthrough bleeding
  - Unfavorable high ratio of P to E
  - Not enough E or too much P
    - Eg, depoprovera, COCs

Intermenstrual Bleeding: Evaluation

- History, PE
- Cervical cytology
- Beta-HCG
- Wet prep
- Cultures
- ?CBC
- ?LFT, renal studies
- TSH
- ?EMB
- ?TVS

Intermenstrual Bleeding: Management

- Educate / adjust OC
- Treat infection
- Pregnancy management or termination
- Surgery

Not Classified AUB: Management

Essentials of Diagnosis

- Exclude pregnancy
- Quantify amount of bleeding with HCT
- Evaluate for neoplasia, structural abnormalities and hormone abnormalities
- Rule out coagulopathy
  - Usually identified in younger women

Estrogen Effects

- Estrogen withdrawal bleeding
  - low levels = intermittent spotting
    - may be prolonged
    - light
  - high levels = sustained availability leading to
    - prolonged periods of amenorrhea
    - followed by acute episodes of profuse bleeding

Management

- Same as for ovulatory menorrhagia
- Hormone management as first line
- Reserve surgical treatment for refractive

Perimenopause: *Contraception*

- Despite a doubling in the use of OCs since the 1970s, the incidence of unintended pregnancy in women aged ≥40 years is >50%
- Because pregnancy is still possible, contraception remains a concern
  - consider OCs, barrier methods, IUDs
- ACOG: The lowest effective estrogen dose should be used

ACOG, American College of Obstetricians and Gynecologists.

ACOG Educational Bulletin 247. *Int J Gynecol Obstet.* 1998; Henshaw. *Fam Plann Perspect*. 1998; North American Menopause Society. www.menopause.org/edumaterials/guidebook/mgtoc.html.

Physiology of the Menopausal Transition

- Variable cycle length[1]
- Endocrinologic milieu shifts
  - ↓ Inhibin[2-4]
  - ↑ FSH[2-4]
  - Variable changes in E_1[5]
  - Testosterone: no change[3,6]

1. Treolar et al. *Int J Infertil.* 1967;12:77.
2. Burger. *Hum Reprod.* 1993;8(suppl 2):129.
3. Burger et al. *J Clin Endocrinol Metab.* 1995;80:3537.
4. Lenton et al. *J Clin Endocrinol Metab.* 1991;73:1180.
5. Santoro et al. *J Clin Endocrinol Metab.* 1996;81:1495.
6. Bancroft et al. *Clin Endocrinol.* 1996;45:577.

AUB Evaluation in Post-Menopausal Women

- History
  - How long since any bleeding has occurred?
- PE
  - Maturation index
- Labs
  - EMBx

DDx in Post-Menopausal Women

- Cancer – until proven otherwise
- Medication induced (HT, other systemic medications)
- Systemic disease (liver, renal, coagulopathies)
- Atrophy
- Benign growths

Remember:

Postmenopausal bleeding
is endometrial cancer
until proven otherwise

AUB Management in Post-Menopausal Women

- If new onset HT, may be related – consider US prior to EMBx
- If no HT – EMBx
- Management based on results of Hx, PE and Diagnostic evaluation (infection treatment, atrophy management, systemic disease management, medication adjustment, etc)

Post-Menopausal Atrophy Management

- Start with local estrogen – is Progestin needed?
- If significant systemic symptoms consider systemic HT
- Later management – lubricants, moisturizers, titrate local estrogen dose

Summary

- The diagnosis of AUB bleeding involves elimination of other causes such as pregnancy, pregnancy-related conditions, systemic diseases, medication side effects, iatrogenic causes, genital tract pathology and malignancy.
- Hormonal therapy should be the first-line option for most pre-menopausal women
- Surgical techniques should be reserved for women in which medical therapy fails and childbearing is no longer desired

ACOG practice bulletin. *Int J Gynaecol Obstet*. 2001;72:263-271.

CASES

Case – Cheryl

Cheryl comes to your office complaining of increasingly heavy menses. She is a 45 year old Black woman. Cheryl describes increasing cramping with her periods and significantly increased flow, but her periods remain regular (q 30 days, 7 days flow). She wants to know if she is beginning “the change.”

Case – Martha

Martha is 57. She had her last menses 2.5 years ago. She is managing her hot flashes with lifestyle changes – avoidance of caffeine, alcohol, and sugar; wearing layered breathable fabrics, etc. Today she presents because she got her period last evening.

Resources

- NIH - National Heart, Lung, and Blood Institute
  - http://www.nhlbi.nih.gov/
- The Hormone Foundation
  - http://www.hormone.org/
- Nat'l Center for Complimentary and Alt Medicine
  - http://nccam.nih.gov/
- Herbal Product Information
  - http://consumerlabs.com
- North American Menopause Society
  - http://www.menopause.com

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  - NAMS (purchased slide set)
  - NOF
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  - Council on Hormone Education
  - Colleagues