Abnormal Uterine Bleeding

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Definition

- Menstrual bleeding of abnormal quantity, duration, or schedule
- Occurs in up to 35% of women
- Accounts for 1/3 of visits to gynecologist
- The most common etiologies are endometrial hyperplasia (23%), submucosal myoma (11%), endometrial polyps (22%), endometrial atrophy (2%), adenocarcinoma (1%), adenomyosis, anovulation, disorders of hemostasis, or neoplasia

Normal Menstruation

- Occurs at regular intervals
- Frequency of 21-35 days
- Volume of blood <80ml
- Duration is 7 days
- Molimina symptoms are usually present including: thin cervical mucus secretions at mid cycle, premenstrual cramps, premenstrual breast tenderness, premenstrual fluid retention, and appetite or mood changes
- 5% of women will have mid cycle spotting likely due to a rapid decrease in estradiol while progesterone levels are still low

PALM-COEIN

- In 2011, the International Federation of Gynecology and Obstetrics introduced revised terminology
- Polyp, adenomyosis, leiomyoma, malignancy, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified,
- Otherwise known as the acronym PALM-COEIN

Descriptions of Abnormal Uterine Bleeding

- Heavy Menstrual Bleeding
- Intermenstrual Bleeding
- Ovulatory Dysfunction
- Postmenopausal Bleeding

Heavy Menstrual Bleeding

- Refers to ovulatory (cyclic) menses that are heavy or prolonged
- It does not include heavy or prolonged menses in women who have an ovulatory dysfunction
- It is present in situations of anemia or when it interferes in a patient's quality of life such as the need to change pads frequently, when bleeding stains clothes or bedding, or prevents a patient from participating in events in her life due to fear of consequences from bleeding.

Heavy Menstrual Bleeding

- The most common etiologies of HMB are:
  - Uterine leiomyomas-mainly submucosal leiomyomas
  - Adenomyosis
  - Cesarean scar defect- usually in the case of multiple cesarean sections, women experience cyclical postmenstrual bleeding which is mostly spotting due to blood being trapped in the scar and expelled intermittently after menstruation is completed
  - Endometrial hyperplasia, carcinoma or sarcoma
  - Endometrial polyps
  - Endometritis or PID (also can present with intermenstrual bleeding)
  - Uterine arteriovenous malformation

Intermenstrual Bleeding

- Intermenstrual bleeding occurs in between otherwise regular menses
- Small volume of blood loss, anemia does not usually result
- Usual etiologies are endometrial polyps, chronic endometritis
- Diagnosis is usually found by ultrasound, sonohystogram, or endometrial biopsy

Intermenstrual Bleeding

- Common causes of intermenstrual bleeding include:
  - Endometrial polyps
  - Contraception
  - Endometrial hyperplasia or malignancy
  - Endometritis or PID
  - Ovulatory bleeding
  - Cervical cancer, cervical polyps, cervicitis, ectropion

Ovulatory Dysfunction

- Irregular, non-ovulatory (noncyclic) bleeding where prolonged, heavy, or hemorrhagic bleeding may occur
- It is typically characterized by phases of absence of menstruation for 2 or more months and then other phases with either spotting or heavy bleeding. Molimina is typically absent
- More often at extremes of reproductive age
- Usually occurs due to chronic estrogen production unopposed by adequate progesterone, endometrium outgrows blood supply, has areas focal necrosis and shedding
- Common etiologies include thyroid disease, hyperprolactinemia, and PCOS.
- If etiology found, that is treated first, goal is to restore a cyclic bleeding pattern, prevent heavy bleeding, and prevent endometrial hyperplasia or cancer.

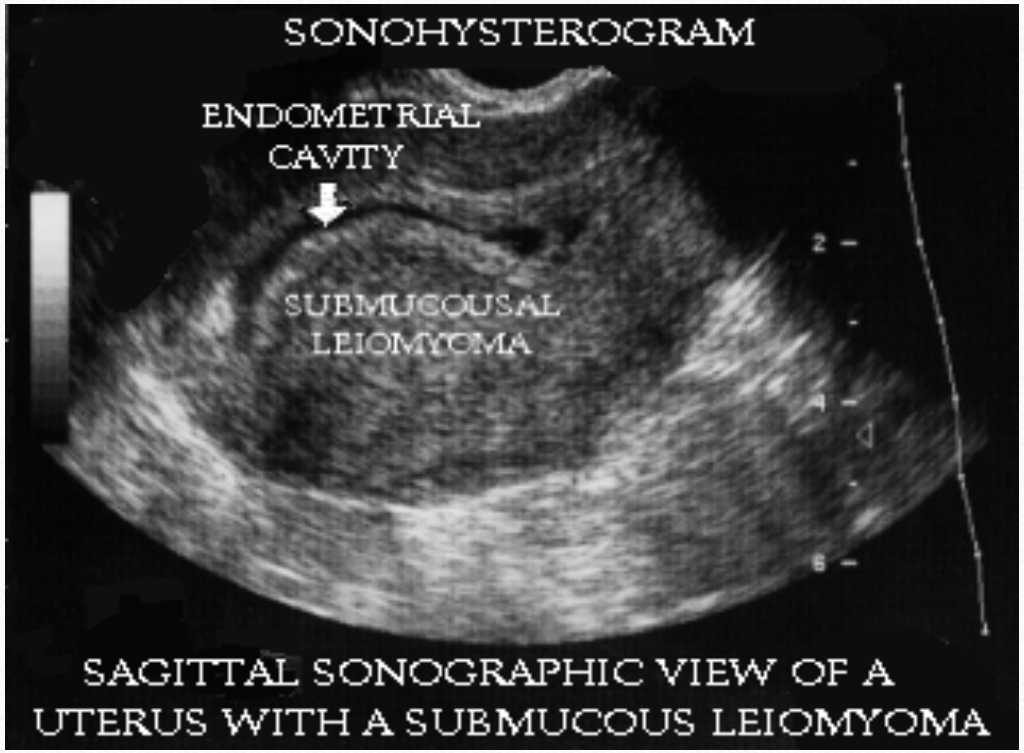
Ovulatory Dysfunction

- Common causes of ovulatory dysfunction include:
  - Polycystic ovarian syndrome
  - Hyperthyroidism or Hypothyroidism
  - Chronic liver or renal disease
  - Hyperprolactinemia
  - Congenital adrenal hyperplasia
  - Cushings
  - Medications: progestins, corticosteroids, antidepressants or antipsychotic drugs

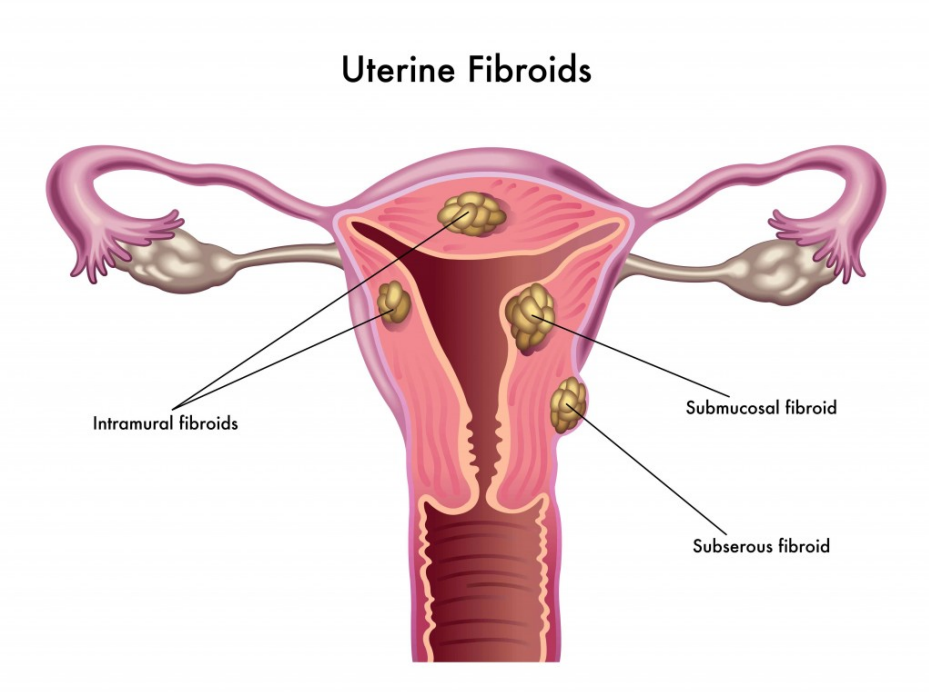
Leiomyoma

- They are benign monoclonal tumors arising from the smooth muscle cells of the myometrium
- Typically found in up to 25% of reproductive aged women
- They occur in 3 locations: submucosal, intramural, and subserosal
- Intramural and submucosal myomas can distort the endometrial cavity resulting in heavy or prolonged menstrual periods
- Risk of malignancy is extremely low

Leiomyoma


SONOHYSTEROGRAM
ENDOMETRIAL CAVITY
SUBMUCOUSAL LEIOMYOMA
SAGITTAL SONOGRAPHIC VIEW OF A UTERUS WITH A SUBMUCOUS LEIOMYOMA

Leiomyoma


Uterine Fibroids
Intramural fibroids
Submucosal fibroid
Subserous fibroid

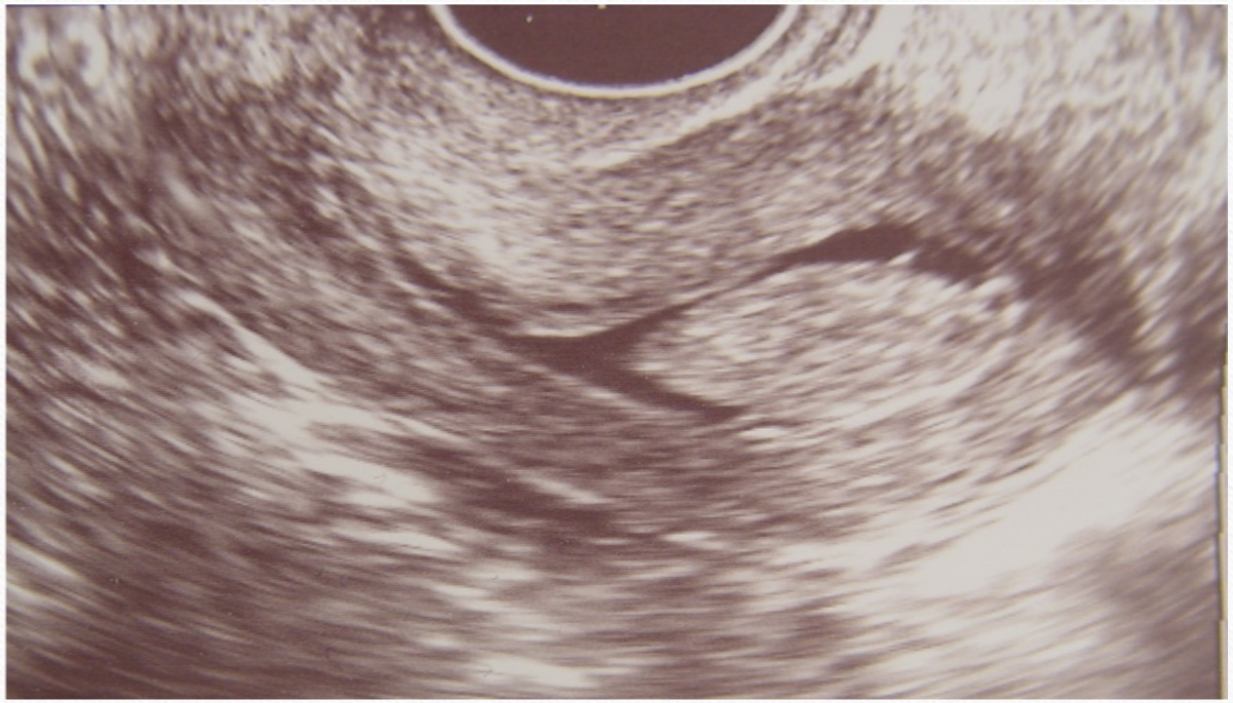
Arteriovenous Malformation

- Can be congenital from failure of embryonic differentiation leading to abnormal vascular connections or from uterine instrumentation where new abnormal vascular connections occur
- Typically present with uterine bleeding refractory to hormonal treatment
- Should also be suspected if an invasive procedure exacerbates the problem, even up to more than a year later as the vessels erode through the endometrium
- If suspected, can diagnose with pelvic ultrasound with Doppler or MRI
- Uterine artery embolization is an effective treatment

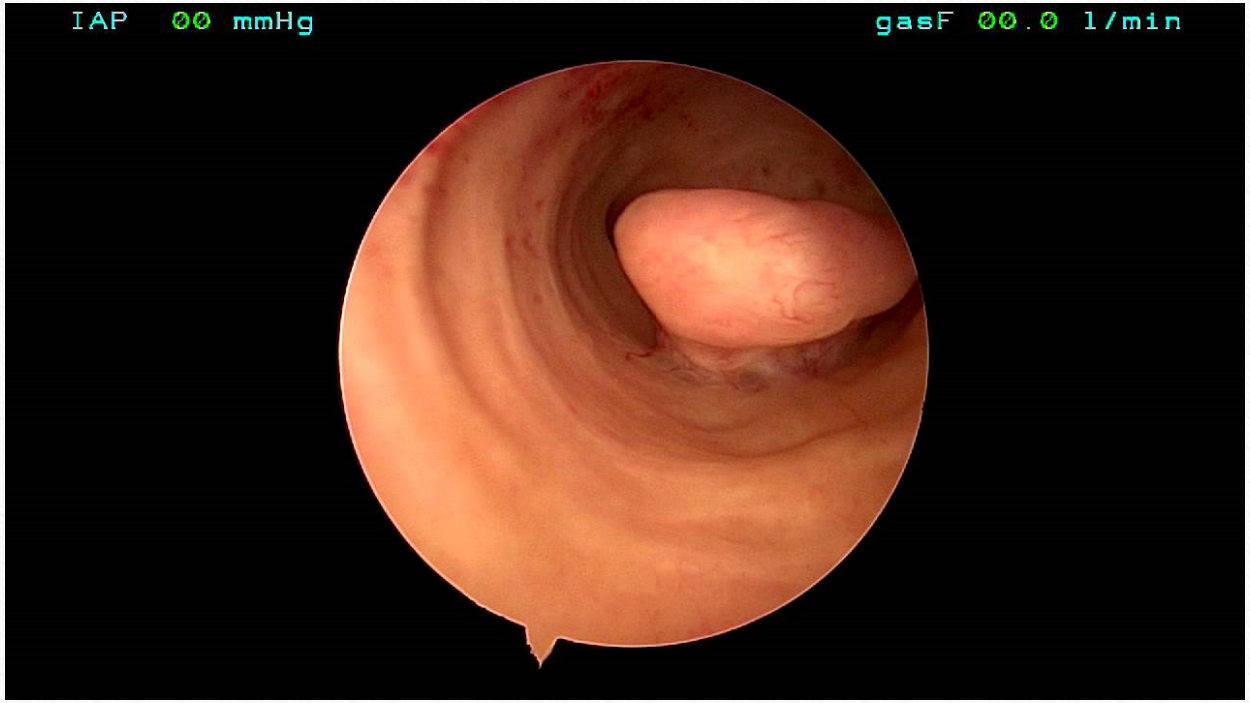
Endometrial polyp

- Hyperplastic overgrowths of the endometrial glands and stroma that form a projection on the surface of the endometrium
- Endometrial polyps occur in 6% of reproductive aged women
- Endometrial polyps are usually benign, risk of malignancy increases with age, especially in postmenopausal patients, with the risk being 5% in a postmenopausal patient and 1-2% in a premenopausal pt.
- Polyp size greater than 1.5cm also increase risk of malignancy

Endometrial Polyp



Endometrial polyp



Adenomyosis

- It is a disorder in which endometrial glands and stroma are present within uterine myometrium
- It affects 20% of women
- It is more common in parous than in nulliparous women
- The endometrium causes the muscular layer to hypertrophy, which results in a diffusely enlarged uterus and heavy, painful periods
- It is usually only diagnosed on hysterectomy.

Coagulopathy

- 15-29% of women who present with heavy vaginal bleeding have some sort of bleeding coagulopathy
- One of the most common being Von Willebrand disease, immune thrombocytopenia, or platelet dysfunction
- Excessive bleeding may also be due to leukemia, liver or renal failure, or anticoagulant therapy
- Often present at menarche or later reproductive years
- Von Willebrand disease worsens with decreasing estrogen as estrogen promotes von Willebrand factor synthesis

Iatrogenic

- Combination OCPs can cause irregular bleeding due to atrophy of the endometrium causing it to breakdown while it is fragile
- Prolonged or irregular bleeding is a common side effect of progestin-only contraceptives also due to endometrial atrophy from insufficient estrogen
- The copper IUD causes an inflammatory reaction which may cause the endometrium to hypertrophy and cause intermenstrual bleeding

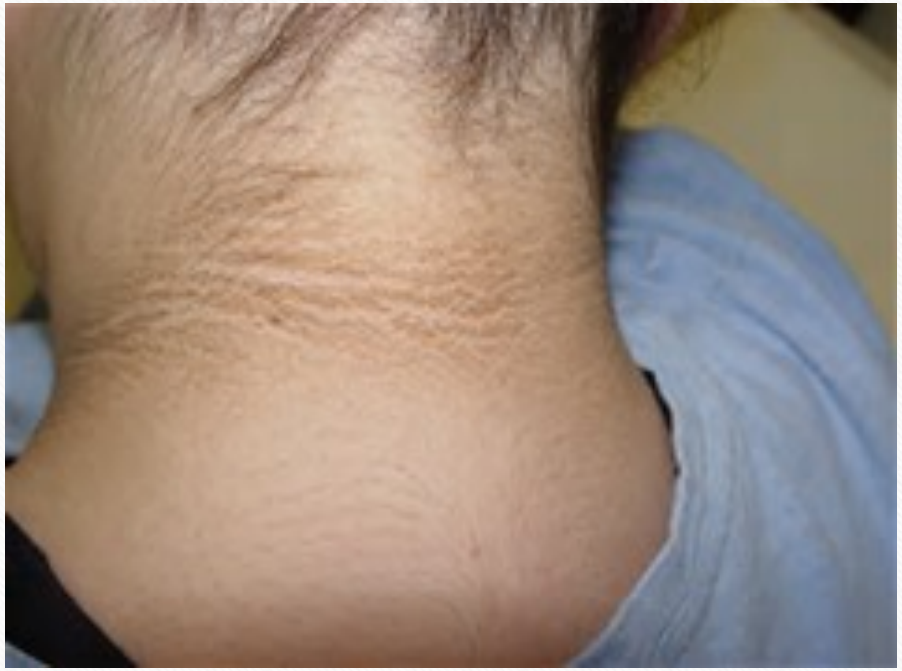
Endometrial

- Chronic endometritis can present with intermenstrual bleeding, spotting, post-coital bleeding, or heavy prolonged bleeding associated with vague crampy lower abdominal pain
- Acute endometritis usually occurs postpartum or after instrumentation of uterine cavity and is associated with fever, uterine tenderness, foul discharge, and leukocytosis
- PID can also have an associated endometritis, especially after placement of an IUD and often occurring after menses

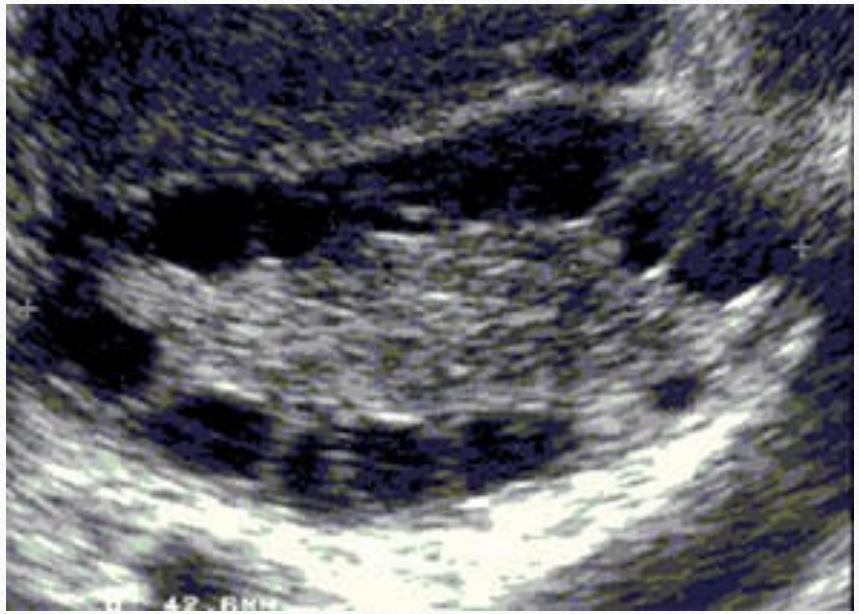
Ovulatory Dsyfunction

- Immaturity of the hypothalamic-pituitary-ovarian axis at postmenarche where as ovulatory cycles will not consistently occur
- Menopausal transition with fluctuations n the hypothalamic-pituitary-ovarian axis and intermittent periods of anovulatory cycles
- Polycystic ovarian syndrome- chronic unopposed estrogen stimulating the endometrium with irregular shedding and is accompanied by obesity, hirsutism, acne, acanthosis nigricans, and characteristic findings on ultrasound
- Thyroid disease, hyperprolactinemia
- Stress and poor nutrition

Acanthosis Nigricans



Ovary in a PCOS patient



Initial Evaluation

- Physical exam:
  - Fever, ecchymoses, enlarged thyroid gland, hyperandrogenism (acne, hirsutism, acne, male pattern balding), acanthosis nigricans, galactorrhea, severe persistent headaches, new onset vision changes.
- Laboratory evaluation:
  - HCG/UPT (7vs14), CBC, TSH (mainly ovulatory), prolactin (ovulatory), androgen levels, consider FSH/LH and estradiol
  - Coagulation tests- 15-24% of women will have bleeding diathesis (VonWillebrand disease, immune thrombocytopenia, or platelet dysfunction defect) and present at menarche or late reproductive years (decreasing estrogen can impact Von Willdebrand factor synthesis), pap, GC/CT, and looking for other causes cervicitis such as trichomonas and herpes
  - Age >45: bleeding that is less than 21 days, more than 5, or heavy, needs endometrial sampling and age <45 with unopposed estrogen (risk endometrial cancer 19% ages 45-54 versus 6% ages 35-44)

Initial Evaluation

- Indications for imaging:
  - If exam finds enlarged or globular uterus or adnexal mass, or symptoms persist despite treatment
  - May omit if bleeding is felt to be due to endocervical polyp, anovulation, or infection
- Pelvic ultrasound is first line imaging study and more specifically, transvaginal pelvic ultrasonography
- If intracavitary pathology is suspected from transvaginal ultrasound, can proceed with saline infusion sonography or hysteroscopy. Besides being able to diagnose intracavitary lesions, SIS can assess the depth of extension of leiomyomas into the myometrium for surgical planning and can identify asymmetric or focal endometrial thickening, an important marker of endometrial neoplasm

Risk Factors for Endometrial Cancer

- Increasing age (age 50-70 have a 1.4% risk endometrial cancer)
- Unopposed estrogen therapy: 2-10 RR
- Tamoxifen therapy: 2 RR
- Late menopause: 2 RR
- Nulliparity: 2 RR
- PCOS: 3 RR
- Obesity: 2-4 RR
- Diabetes: 2 RR
- Lynch syndrome: 22-50% lifetime risk
- Cowden syndrome: 13-19% lifetime risk

Women requiring endometrial sampling

- Postmenopausal bleeding- any bleeding including spotting with a transvaginal ultrasound endometrial thickness greater than 4mm
- Women age 45 or older with intermenstrual bleeding, less than 21 days apart, heavy, or prolonged
- Women younger than 45 with bleeding that is persistent, occurs in the setting of unopposed estrogen, failed medical management, or with other risk factors
- Women who have had a pap smear with atypical glandular cells

Postmenopausal Bleeding

- Refers to any uterine bleeding in a menopausal women.
- Vaginal bleeding occurs in 4-11% of postmenopausal women.
- The likelihood of bleeding decreases with time since menopause
- Postmenopausal bleeding accounts for 5% of office gynecology visits
- Endometrial carcinoma will be the etiology in 10%
- The most common cause of bleeding will be atrophy of the vaginal mucosa or endometrium and other causes are endometrial hyperplasia, polyps, and submucosal fibroids

Postmenopausal Bleeding

- In a study of 454 women with postmenopausal bleeding, etiologies were: carcinoma (6%), atypical hyperplasia (0.2), hyperplasia without atypia (2%), polyp (37%), fibroid (6%), proliferative/secretory endometrium (14%), hypertrophy/atrophy (30%)

Postmenopausal Bleeding

- Atrophy: hypoestrogenism causes atrophy of the endometrium, the walls of the uterus collapse against itself and there is friction of the endometrial surfaces with microerosions, a chronic inflammatory response that leads to chronic endometritis and light bleeding or spotting

Evaluation of postmenopausal bleeding

- One can either start with transvaginal ultrasound or endometrial biopsy
- Office endometrial biopsy has high sensitivity (99.6%), low complication rate and low cost
- Transvaginal ultrasound findings indicating need for endometrial bx:
  - Endometrial thickness greater than 4mm
  - Endometrium with diffuse or focal increased echogenicity
  - Endometrium cannot be adequately visualized
  - Persistent bleeding
- Cervical pap smear
- If a patient has persistent bleeding with endometrial biopsy, then proceed to hysteroscopy

Asymptomatic thickening of endometrium

- If postmenopausal patient has transvaginal ultrasound with incidental finding of endometrium greater than 5mm, a biopsy is warranted if the endometrium is thicker than 11mm as they have the same risk as a postmenopausal bleeding patient with endometrium of 5mm or more.
- No bleeding is found in 5-20% of patient's with endometrial cancer

Postmenopausal bleeding on HRT

- TVUS is not a useful modality for evaluating women with postmenopausal bleeding on hormone replacement therapy as there are no established standards
- Bleeding can be common with initiation of hormone replacement therapy but it should decrease over time and eventually stop and if it does not, then an endometrial biopsy is warranted.

Postmenopausal Bleeding on Tamoxifen

- Endometrial biopsy is always warranted for any abnormal bleeding with patients on tamoxifen therapy
- They always tend to have endometrium with a thickened cystic appearance and therefore transvaginal ultrasound is not a useful modality

Treatment of Abnormal Uterine Bleeding

- Treatment should not be initiated until the etiology has been evaluated and premalignant or malignant disease excluded
- The goal of therapy is to control bleeding, treat anemia, and restore quality of life
- Any underlying disorders should be treated first such as chronic endometritis or PCOS and structural lesions removed via hysteroscopy such as endometrial polyp or submucosal fibroid

Treatment of Abnormal Uterine Bleeding

- The initial approach of chronic abnormal uterine bleeding is pharmacologic approach and the mirena IUD is often first line therapy
- 58% of women with medical treatment with choose definitive surgical intervention after 2 years
- Heavy menstrual bleeding can be treated medically or surgically
- Ovulatory bleeding should be treated medically

Treatment of Heavy Menstrual Bleeding

- Common etiologies are uterine leiomyomas and adenomyosis
- Medical therapy is an appropriate first therapy
- Combination OCPs (35-69% reduction) or mirena IUD (71-95% reduction) are best first line therapies
  - Both are well-tolerated
  - Low side effects
- Depo-provera and cyclic provera (87% reduction) is reasonable alternative
- Nexplannon nay not be effective

Treatment of Heavy Menstrual Bleeding

- Ultra-low dose postmenopausal hormone therapy formulations if contra-indication to OCPs
- Expectant management
- Tranexamic acid (26-54% reduction) and NSAIDs (10-52% reduction)

Treatment Ovulatory Dysfunction

- Combination OCPs, oral progestin therapy, and the mirena IUD are first line therapy options as they decrease bleeding and reduce the risk of endometrial cancer
- Cyclic progesterone using provera for 10-14 days each month can give a predictable withdrawal bleed
  - Does not provide contraception
- Mirena IUD reduces overall bleeding

Combination OCPs

- Advantages are bleeding is lighter, regular, and periods are less painful
- Provides contraception
- Other routes administration
  - Patch: Ortho-Evra
  - Vaginal contraceptive ring: Nuvaring
- Formulations with 4 or fewer hormone free days per pill pack are associated with less bleeding
  - Natazia was approved by the FDA for treatment HMB (26 day pill pack)
- Can prescribe in a cyclic, extended, or continuous regimen

Combination OCPs to Treat AUB

- Contraindications:
  - Age >35 and smoking more than 15 cigarettes/day
  - HTN
  - Venous Thromboembolism
  - Known thrombogenic mutations
  - Known ischemic heart disease
  - Stroke
  - Pulmonary HTN, Atrial fibrillation, Subacute bacterial endocarditis
  - Migraine with aura at any age

Use of HRT to treat Abnormal Uterine Bleeding

- Ultra low dose estrogen-progesterone hormone replacement therapy formulations used for menopausal women can be used for AUB is the patient has contra-indication to COCPs.
  - Such as obesity, HTN, tobacco use, diabetic
- Do not provide contraception
- Often result in amenorrhea
- Example is Jinteli 1/5 (5mcg ethinyl estradiol and 1 mg norethindrone acetate

Mirena IUD to treat AUB

- Approved by the FDA for treatment heavy menstrual bleeding
- Releases levonorgestrel 20mcg/day
- Reduces blood loss by 71-95%
- Comparable to endometrial ablation
- 3 Months after placement, most common bleeding is spotting
- At 6 months, the majority of patients have amenorrhea
- Increased expulsion rate with fibroids
- Helps manage dysmenorrhea even with adenomyosis
- Best choice in women with increased thrombosis risk

Depo-Provera to Treat AUB

- 50% of women are amenorrheic after 4 injections (1 year)
- 75% are amenorrheic after 8 injections (2 years)
- After 2 months, there is a 49% reduction in menstrual blood loss
- Some studies suggest it reduces fibroid size due to decrease in exogenous estradiol levels, fibroid volume decreases by 33% in 6 months
- In 6 months therapy, all women experienced an improvement in bleeding, 30% amenorrheic

Oral Progestins for Treating AUB

- Norethindrone acetate- 5mg 1-3 tablets daily
- Provera 5-30 mg daily
  - Can cause bloating, breast tenderness, dysphoria, increased appetite
- Continuous rather than cyclic therapy works best

Tranexamic acid for AUB

- It is an anti-fibrinolytic agent that competively blocks the conversion of plasminogen to plasmin thereby reducing fibrinolysis
- Can be used in patient's trying to conceive
- FDA approved it for use with HMB in 2009 but lists elevated risk of thrombosis as a contraindication however studies do not confirm that it is associated with an increased risk of thrombosis
- It reduces blood loss by 26-54%
- Adverse effects are menstrual cramps, headache, back pain, and nausea
- 1300mg (two tablets) up to three times daily for 5 days per month

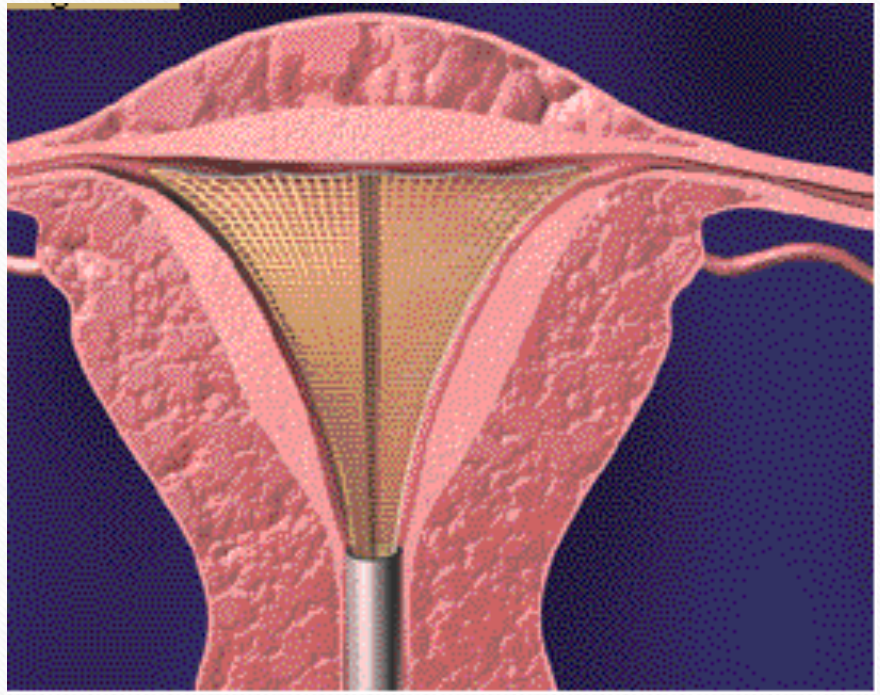
NSAIDs for treatment of AUB

- Does not typically treat Ovulatory dysfunction
- Decreases the rate of prostaglandin (PGE2 and PGF2) synthesis in the endometrium, leading to vasoconstriction and reduced bleeding
- Start the first day of bleeding and stop 5 days after bleeding starts
- Dosing:
  - Mefenamic acid: 500mg three times per day
  - Naproxen: 500mg at onset and 3-5 hours later, then 250-500mg BID
  - Ibuprofen: 600mg once per day
- Helps manage dysmenorrhea
- If trying to conceive, need to stop once conception occurs

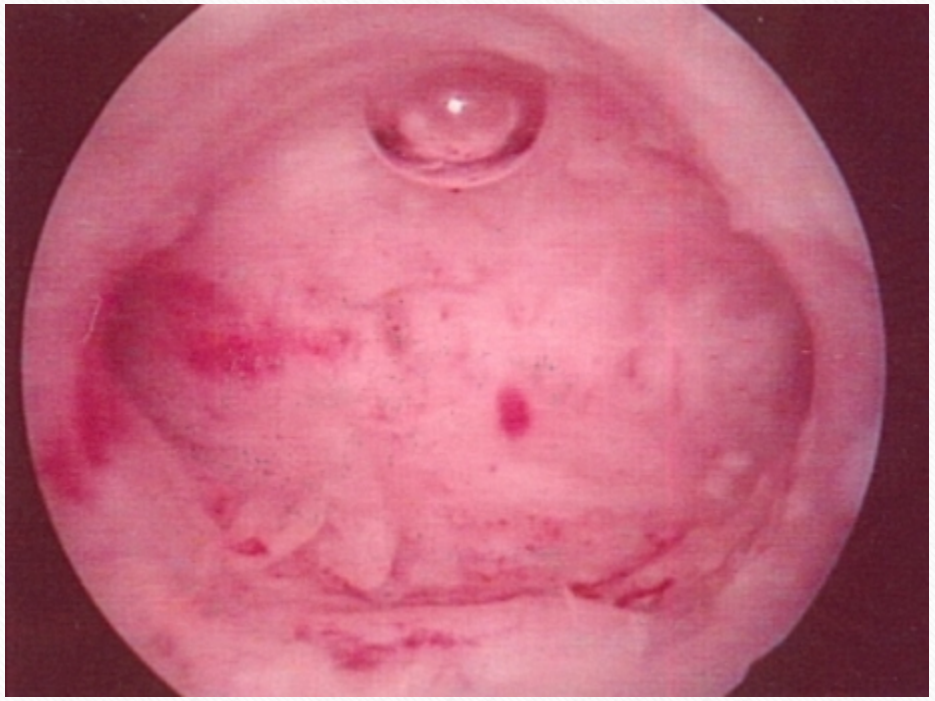
Surgical Intervention for Treatment AUB

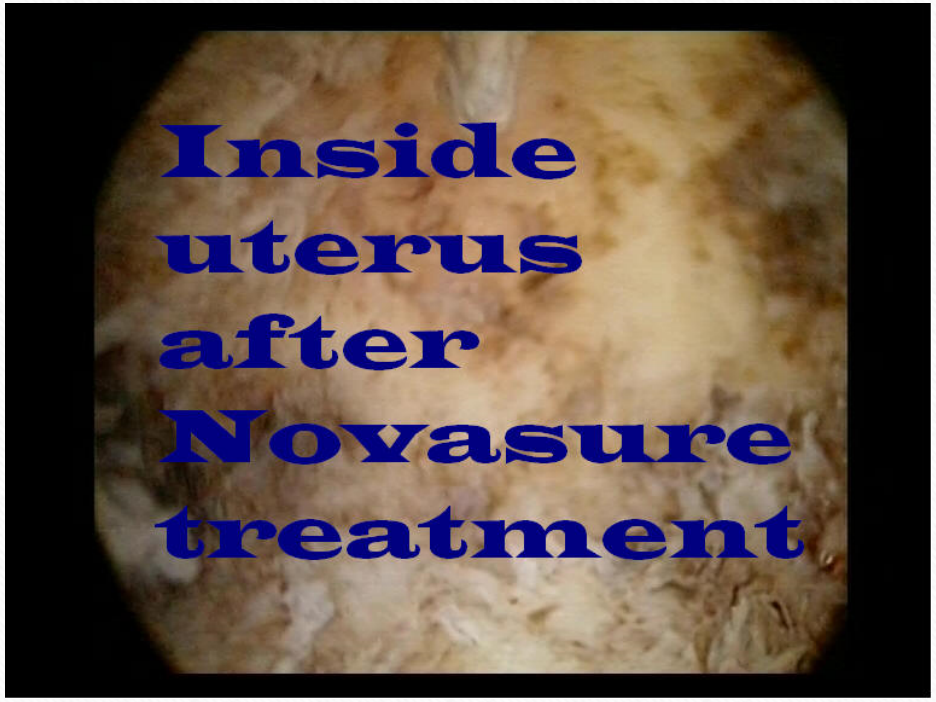
- Endometrial ablation- should not conceive afterward and therefore should be sterilized, Mirena IUD has equal efficacy
- Myomectomy- If one desires to maintain fertility or for hysteroscopic myomectomy which is minimally invasive
- Uterine artery embolization- useful for women with fibroids, but safety of childbearing has not been established
- Hysterectomy- definitive treatment, high rate of patient satisfaction

Endometrial Ablation



Endometrial Ablation

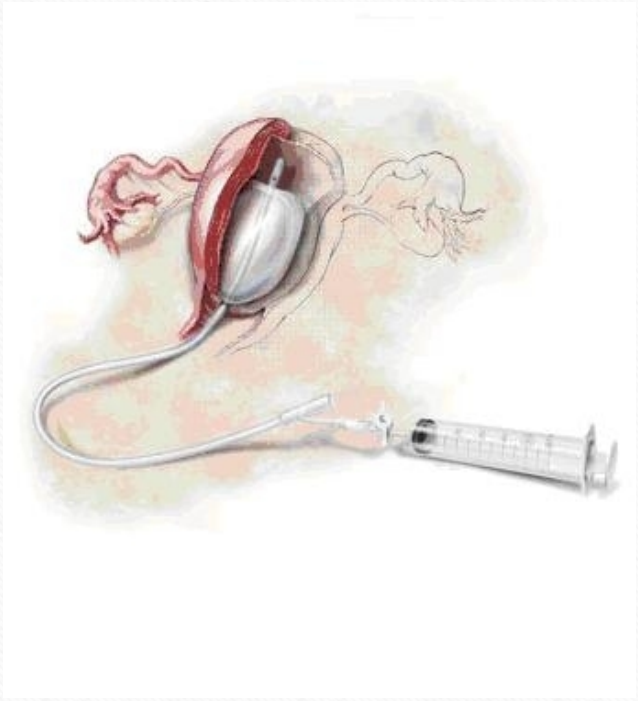




Profuse Uterine Bleeding

- All patient should have endometrial sampling (pregnant?)
- Hemodynamic Unstable
  - IVF
  - Uterine tamponade (30cc foley, bakri balloon, kerlix with thrombin
  - Uterine curettage
  - High dose IV estrogen (Premarin 25mg in 5ml NS, repeat every 3-5 hours), after about 8 hours, can switch to oral estrogen either premarin 2.5mg four times daily for 21-25 days, then provera 10mg /day for 10 days or COCP with 35mcg estrogen 2 pills daily for 5 days, then 1 pill per day for 20 days.
  - Uterine artery embolization
  - Endometrial ablation
  - Hysterectomy

Bakri Balloon



Profuse Bleeding

- Hemodynamically Stable
  - First line therapy in high dose estrogen
  - Premarin 2.5mg 2-4 times daily until bleeding subsides at most 21-25 days, then provera 10mg/day for 10 days
    - May have to give an anti-emetic with it
  - 35mcg COCP 1 pill 2-4 times daily bleeding usually subsides in 48 hours, or can use a cascading regimen (5 pills day 1, 4 pills day 2, 3 pills day 3, 2 pills day 4, 1 pill day 5 and continue 1 pill daily for 1 week, then have a withdrawal bleed). Pt will need an antiemetic.
  - Ovulatory bleeding can be treated with high dose progestins (provera 10-20 mg BID for 5-10 days, norethindrone 5mg 1-2 times daily for 5-10 days, megestrol acetate 60mg BID for 10 days)

Adolescents

- Average age of menarche in the United States is 12 years
- The first 5-7 years after menarche there is considerable variability in the menstrual cycle
- In the first year after menarche, 50% of cycle are anovulatory
- By the third year, 95% of cycles are if the 21-45 days range and lasting 2-7 days
- Time to regular ovulatory cycles depends on age of menarche, <12 years, 50% cycles ovulatory in 1 year, 12-13 3 years, and >13 4.5 years

Adolescents

- Anovulatory bleeding is the most common cause of excessive menstrual flow with irregular bleeding
- Blood dyscrasias and structural anomalies (polyps/fibroids) are more common in cyclic bleeding
- Anovulatory bleeding- delayed maturation of normal negative feedback and estrogen does not suppress FSH so estrogen secretion is maintained, FSH is increased and endometrium grows until is becomes unstable

Adolescents

- Evaluation to consider:
  - Day 3 FSH, LH, Prolactin, also TSH, free and total testosterone, DHEAS, CBC, and VWF panel

Adolescents

- Management anovulatory bleeding
  - If increased bleeding is mild and hbg is normal, (cycles shortened for >2 months, moderately increased flow)
  - If increased bleeding is moderate and hbg >10 (bleeding is more than 7 days, occurring every 1-3 weeks, and moderate in amount)
    - can do reassurance, start iron, or initiate medical therapy reassurance is fine
    - Start at least 30mcg ethinyl estradiol OCPs
      - 1 pills every 8 hours until bleeding stops, then every 12 hours for 5 days, then daily for 21 days
      - If bleeding recurs, increase to BID for 21 days
  - If not bleeding, can try oral micronized progesterone, 200mg nightly for 12 days

Adolescents

- Longterm therapy
  - Hbg <10g/dL- COCP with ethinyl estradiol 50mcg per day monophasic for 3 months continuous
  - Hbg >10g/dL- COCP with ethinyl estradiol 30mcg per day monophasic for 3 months cyclically for 3-6 months

Thank You