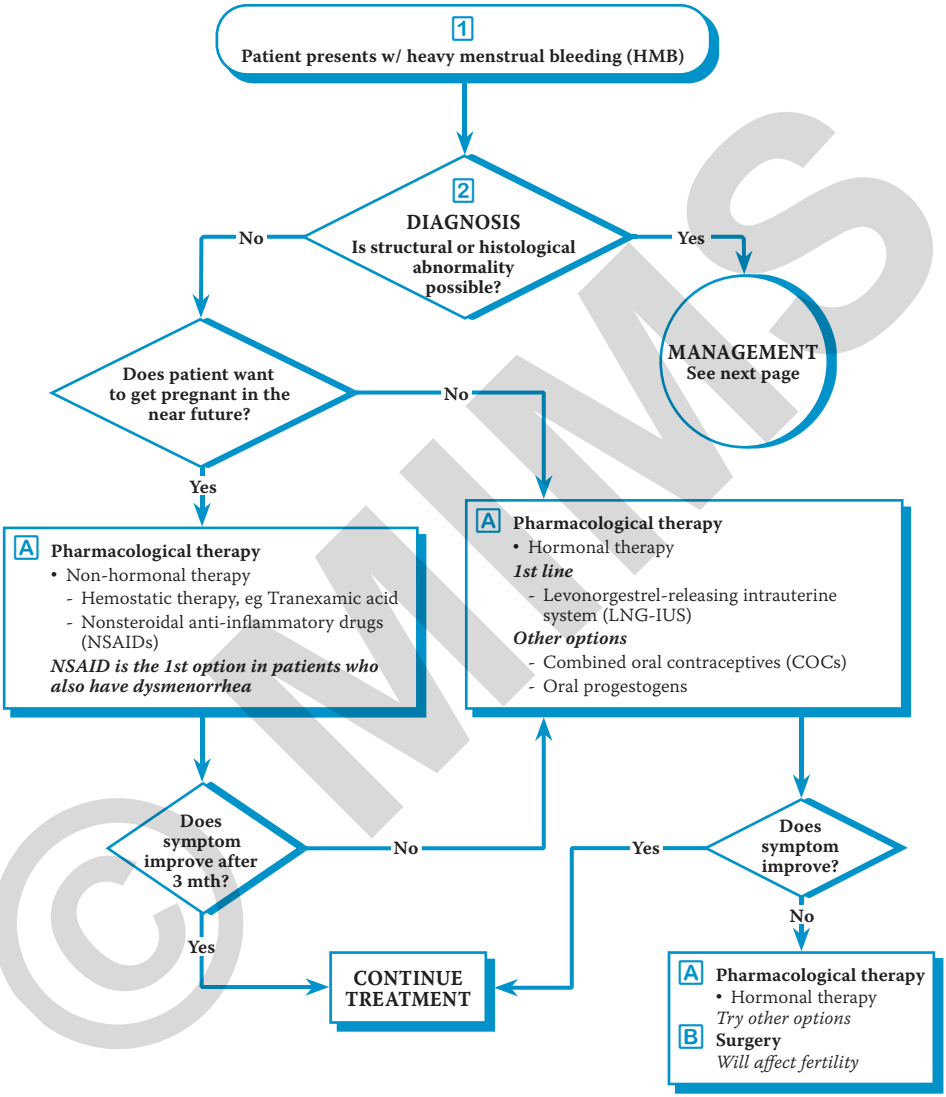
Heavy Menstrual Bleeding (1 of 10)



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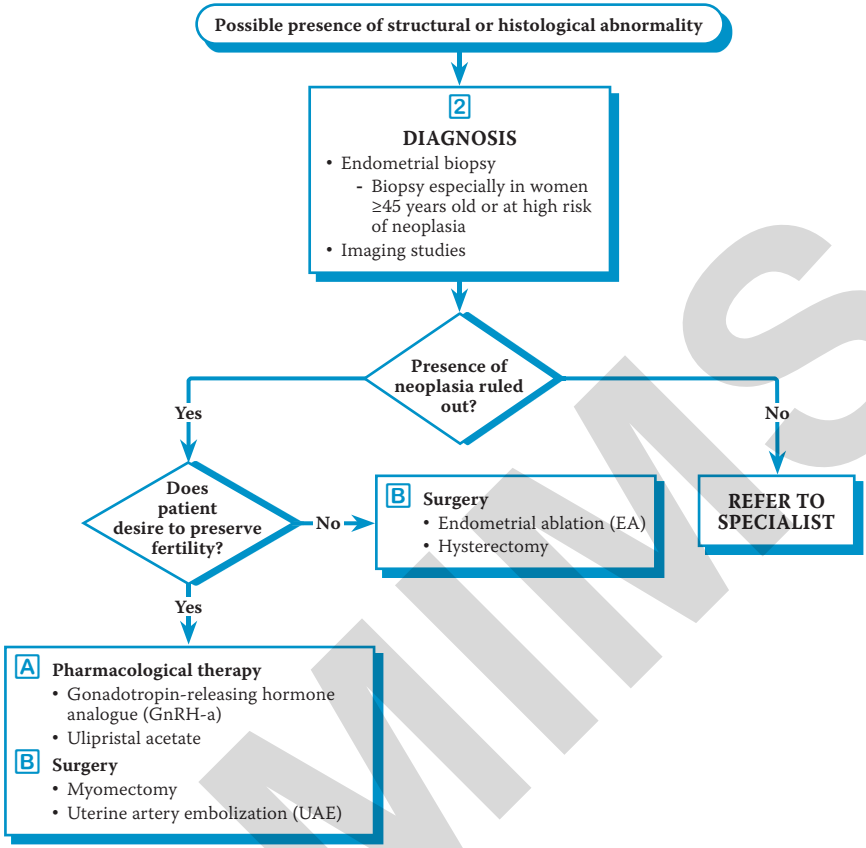

1 HEAVY MENSTRUAL BLEEDING (HMB)

- Prolonged (>7 days) or excessive (>80 mL) uterine bleeding occurring at regular intervals over several menstrual cycles
  - Menstrual blood loss that is excessive & interferes w/ patient's physical, emotional, social & quality of life
- Common problem in women of reproductive age (increases w/ age) which usually causes anemia
  - Most common symptom experienced by women w/ bleeding disorder
- Causes of abnormal uterine bleeding (AUB) are categorized into the following groups:
  - Discrete structural abnormalities that can be examined w/ imaging techniques &/or histopathology
    - PALM: **P**olyp, **a**denomyosis, **l**eiomyoma[1], **m**alignancy & hyperplasia
  - Non-structural abnormalities that cannot be defined by imaging or histopathology
    - COEIN: **C**oagulopathy, **o**vulatory dysfunction, **e**ndometrial, **i**atrogenic, **n**ot otherwise classified
    - Coagulopathy includes von Willebrand's disease (VWD) or platelet dysfunction
    - Iatrogenic causes include AUB associated w/ use of hormonal or non-hormonal medications (eg anticoagulation therapy), intrauterine systems or devices, or other local or systemic agents
    - Not otherwise classified causes include conditions that are rare or ill-defined that do not fit into any classification
  - Other causes include chronic endometrial infection, arteriovenous malformation, hypothyroidism, obesity
  - Patients may have >1 cause
- Anovulation is the most common cause in adolescents & perimenopausal women; structural lesions & malignancy are more common w/ increasing age

[1]Please see Leiomyomas disease management chart for further information.

2 DIAGNOSIS

- Main goals are to confirm HMB, rule out endometrial hyperplasia or cancer, & to identify other pathology

History

- Should be able to identify nature of bleeding, presence of any underlying pathology & other features (including family history of pathology) that may determine future action or treatment
  - Important to inquire about the frequency, duration, amount of bleeding & timing of changes in menstrual patterns
  - Features suggestive of excessive blood flow:
    - Changes sanitary pads every <3 hours or at night
    - Consumes >20 pads or tampons/cycle
    - Passes >1-inch blood clot
    - Bleeds >7 days
    - W/ or without iron-deficiency anemia (IDA)
  - Intermenstrual & postcoital bleeding may be suggestive of an anatomical cause
- Menstrual blood loss as a problem should be asked to the patient since direct (alkaline hematin) or indirect (pictorial blood loss assessment chart) measurement is not routinely recommended
- Coagulation disorder may be suggested by the following:
  - HMB since menarche
  - History of easy bruising (bruises >5 cm) or bleeding from mucosal surfaces (epistaxis once a month)
  - Personal or family history of coagulopathy
  - History of postpartum hemorrhage
  - Bleeding from surgery or dental procedures
- Pressure symptoms, eg urinary & bowel symptoms, may indicate a fibroid
- Abdominopelvic pain may be due to infections or structural lesions

Physical Exam

- Done through observation, abdominal palpation, visualization of the cervix & bimanual (internal) exam
- Identifies any underlying pathology, indication for further investigation & possible treatment options
  - Size of the uterus & location of fibroids, if present, should be assessed
- Assessment of hemodynamic instability (eg orthostatic blood pressure, pulse rate) should be done in the presence of acute HMB
- Examine for the presence of anemia, coagulopathy or thyroid disease

Lab Tests

- Not always recommended but may be useful in excluding other diagnosis
- Complete blood count (CBC) should be carried out on all women w/ HMB to assess presence of anemia & parallel w/ HMB treatment, to monitor response
- Coagulation studies should be done in patients w/ history suggestive of coagulation disorder
  - Platelet count, prothrombin time (PT) & partial thromboplastin time (PTT) may be an initial screening test for suspected bleeding disorders
  - Usually include assessment of quantity & activity of von Willebrand's factor (VWF) & factor VIII
    - VWD is seen in majority of cases
- Ferritin level is the most accurate test for determining IDA but is not routinely requested; normal level does not rule out HMB
- Hormonal examination [eg luteinizing hormone (LH) & follicle-stimulating hormone (FSH)] should not be routinely performed in women w/ HMB
- Thyroid function test is recommended only in patients w/ signs & symptoms suggestive of thyroid disease
  - Hypothyroidism can cause menstrual irregularities & HMB
- Pregnancy test should be done if pregnancy is a possibility or suspected

Endometrial Biopsy

- Should be done to exclude endometrial cancer or atypical hyperplasia w/ 91% sensitivity
- Recommended in women ≥45 years old w/ continuous intermenstrual bleeding or w/ treatment failure, in younger obese patients w/ prolonged periods of anovulation or unopposed estrogen stimulation, in women w/ ≥12-mm transvaginal endometrial thickness, or in younger women w/ endometrial cancer risk factors

Imaging Studies

- Carried out in patients w/ abdominally palpable uterus, pelvic mass of unknown origin seen on vaginal exam, or failed medical treatment
- Ultrasound (US) is the primary diagnostic imaging used for identifying structural abnormalities that is 60% sensitive & 93% specific
  - Useful if physical exam findings are abnormal or doubtful due to the women's habitus, or if reassurance & no treatment is needed
  - Can detect small ovarian cysts, leiomyoma, endometrial hyperplasia or carcinoma
  - Transvaginal US depicts endometrium better than transabdominal US
    - Transvaginal US is the 1st-line imaging procedure for AUB

2 DIAGNOSIS (CONT'D)

Imaging Studies (Cont'd)

- Hysteroscopy is used when US results show intrauterine abnormalities or are inconclusive, or when initial treatment has failed
  - Detects intrauterine lesion definitively w/ 86% sensitivity & 99% specificity
- Saline infusion sonohysteroscopy/sonohysterography/infusion sonography detects fibroids w/ sensitivity of 87% & specificity of 92%, & polyps w/ sensitivity of 86% & specificity of 81%
  - Should not be used as an initial diagnostic tool
- Magnetic resonance imaging (MRI) is used if menstrual bleeding is secondary to leiomyomas & myomectomy is contemplated, US is uncertain in differentiating adenomyosis from leiomyomas, when malignancy & adnexal pathology is suspected, or when US or instrumentation of the uterus (eg congenital anomalies) cannot be performed
  - Should not be used as an initial diagnostic tool

A PHARMACOLOGICAL THERAPY

- Recommended for patients w/ no structural or histological abnormalities, or w/ fibroids <3 cm in diameter that did not cause deformation of the uterine cavity
- Should include iron supplements if IDA is present secondary to HMB

Non-Hormonal Therapies

- Treatment of choice for patients who desire to maintain fertility & be pregnant in the near future
- Alternative treatment for patients who do not desire hormonal therapy or those awaiting workup & definitive treatment
- Used to treat HMB that is cyclic or has predictable timing
  - Should be taken from the start of menstruation until heavy blood loss has stopped
- Discontinue if no improvement in symptoms is seen after use for 3 cycles

Hemostatic Therapy

- Antifibrinolytic agents
  - Eg Tranexamic acid
  - Competitively inhibits plasminogen activation & other factors associated w/ blood clotting
  - Decreases breakdown of fibrin in a preformed clot
  - Used to treat HMB that is cyclic or has predictable timing
  - Studies showed that it reduced menstrual bleeding by 29-58% through reduction of liquefaction of clotted blood from spiral endometrial arterioles
  - High-dose Tranexamic acid may aid in reducing or stopping acute HMB
  - Does not reduce dysmenorrhea nor regulate cycles & not a contraceptive
- Desmopressin (DDAVP)
  - Stimulates release of VWF from endothelial cells
  - Given to patients w/ type 1 & some cases of type 2 VWD w/ HMB
  - Not recommended in patients w/ type 2B VWD due to possible worsening of thrombocytopenia & thrombosis
  - Not more effective than oral contraceptives in controlling HMB
- Coagulation factor replacement
  - Used in patients w/ VWD-related HMB where antifibrinolytics & DDAVP are not effective
  - VWF/factor VIII replacement therapy can be considered definitive therapy, particularly in massive hemorrhage (eg severe VWD)

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

- Reduce prostaglandin synthesis which is implicated in uterine bleeding & cramps
  - Cause 20-49% decrease in menstrual blood loss
  - Preferred treatment for patients w/ HMB & dysmenorrhea
- Not as effective as Tranexamic acid or Danazol but have less side effects than Danazol
- Not recommended for patients w/ HMB secondary to bleeding disorders

Hormonal Therapies

- Considered 1st-line therapy (combined w/ conservative medical management) if future fertility is desired but pregnancy is not wanted in the near future

Levonorgestrel-Releasing Intrauterine System (LNG-IUS)

- 1st line of treatment for patients suitable for pharmacological therapy, provided long-term use is expected
  - Reduces bleeding by 71-96% but full benefit may not be seen after at least 6 cycles
  - Bleeding patterns may vary for the 1st 6 months of use

A PHARMACOLOGICAL THERAPY (CONT'D)

Levonorgestrel-Releasing Intrauterine System (LNG-IUS) (Cont'd)
- A small plastic device placed in the uterus that slowly releases 20 mcg/day of Levonorgestrel
- Used for contraception, management of idiopathic HMB & as a progestogen content of hormone replacement therapy regimen
- Prevents proliferation of the endometrium & thickening of cervical mucus & suppresses ovulation in some women
- Approved for 5 years of use
- Preferred treatment option for long-term use or when patient opted for long-term reversible contraception
- May be considered as a treatment option for obese women
- Comparable w/ endometrial ablation in reducing menstrual blood loss up to 24 months
  - May be considered an option before surgery
- Most cost-effective approach in treating patients w/ HMB after 1 year of combined oral contraceptive (COC) use or when COC therapy has failed

Combined Oral Contraceptives (COCs)
- Contain estrogen & progestogen that inhibit ovulation & fertility through action on the hypothalamo-pituitary axis
  - Prevent proliferation of the endometrium
- Used in 21-day treatment cycle followed by 7 days' rest where breakdown & loss of endometrium occur
  - Regulate & reduce bleeding, also decrease breast pain & dysmenorrhea
- A study showed that COCs (Ethinyl estradiol & Levonorgestrel) reduced menstrual bleeding by 43%
- Most cost-effective approach in the 1st year of treatment for women w/ HMB w/ no pathological cause
- Not suitable for smoking women >35 years old & women w/ risk factors for cardiovascular (CV) disease
- High-dose estrogen may be used initially to treat HMB then transitioned within a few days to standard estrogen-progestin contraceptive pills
- Estrogen-progestin preparations may be given continuously for prevention of recurrent HMB

Oral Progestogens
- Eg Norethisterone, Medroxyprogesterone
- Prevent proliferation of the endometrium
- Use for 7-10 days during the luteal phase of the menstrual cycle showed no effect on menstrual bleeding
  - May reduce menstrual bleeding for up to 83% after long-term use
- A progestin, eg Megestrol acetate, can be given to prevent recurrent HMB
- A case series showed premenopausal women w/ symptomatic uterine fibroids had an improvement in AUB w/ 6 months of depot Medroxyprogesterone acetate therapy
- Option for women who cannot tolerate estrogen-containing therapy or if estrogen is contraindicated

Gonadotropin-Releasing Hormone Analogue (GnRH-a)
- Induces reversible hypogonadism secondary to deficient production of FSH or LH that causes poor follicular development & estrogen production, anovulation, lack of progesterone production & amenorrhea
  - Reduces menstrual blood loss in the form of amenorrhea
  - When treatment is discontinued, effects are not maintained
- May be given to patients w/ uterine fibroids prior to undergoing surgery, or when surgery or uterine artery embolization (UAE) is contraindicated
  - Causes reduction in fibroids' size making surgery easier
  - May be given to patients w/ enlarged or distorted uterus secondary to uterine fibroids 3-4 months prior to hysterectomy or myomectomy
- Associated w/ significant adverse effects (eg perimenopausal symptoms, headache, nausea), which prevent long-term use
  - Hormone replacement addback therapy may be given to prevent undesirable effects or if GnRH use is >6 months

Ulipristal acetate
- Used for preoperative management of women w/ moderate to severe symptoms of uterine fibroids
  - Has established efficacy in the management of HMB due to fibroids w/ reduction of fibroid size prior to surgery
- Patients w/ HMB may be offered up to 4 courses (20 months) of Ulipristal acetate if w/ fibroids of ≥3 cm in diameter & hemoglobin level of ≤102 g/L
- Benign & reversible changes occur in the endometrial tissue w/ use of Ulipristal acetate
- Data showed Ulipristal acetate is non-inferior to GnRH agonist w/ less menopausal side effects
- Monitor liver function tests (LFTs) before & during treatment; discontinue if w/ signs & symptoms of liver failure

Danazol
- Synthetic androgenic steroid w/ anti-estrogen & antiprogestogen activity
- Has antiproliferative effect on the endometrium & inhibitory effect on the production of gonadotropins by the pituitary gland causing anovulation
- Reduces menstrual bleeding by 50%
- Associated w/ significant androgenic adverse effects
  - Not routinely given for the treatment of HMB

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SUMMARY OF THERAPEUTIC EFFECTS OF DRUGS USED IN HMB

Drugs	Effects			
	Reduction in Blood Loss	Contraception	Dysmenorrhea	Fertility
Tranexamic acid	58%	No	No	No
NSAIDs	25%	No	Yes	No
LNG-IUS	95% after 6 months	Yes	No	No
COCs	43%	Yes	Yes	No
Oral Progestogens	83% in long-term	Yes	No	No
GnRH-a	amenorrhea	No	No	No
Ulipristal acetate	amenorrhea	Yes[1]	No	No

[1]Emergency contraceptive

B SURGERY

Considered in cases where patient does not desire future pregnancy or in the presence of pelvic disease (ie uterine fibroid tumors)

Endometrial Ablation (EA)

- Aims to destroy or remove the endometrium & the superficial myometrium which reduces or completely stops menstrual blood loss
- Should be considered in women who have a normal or ≤10-week pregnancy-sized uterus, those w/ <3-cm uterine fibroids, those wherein medical treatment has failed, who completed child-bearing or who are not candidates for major surgery
- After endometrial ablation, women are advised to avoid subsequent pregnancy & the need to use effective contraception, if required
- Results in faster return to normal activities compared w/ hysterectomy but is associated w/ a 22% reintervention rate
- Divided into 1st- or 2nd-generation methods, depending on whether direct visualization is needed or not

Hysteroscopic-Guided Endometrial Ablation

- First-generation methods, eg transcervical resection of the endometrium (TCRE), rollerball EA (REA)
- Performed through a hysteroscope
- Recommended in patients who will also undergo hysteroscopic myomectomy
- Involves distending the uterine cavity w/ fluid & then resecting the tissue w/ an electrosurgical loop (TCRE method) or burning the tissue w/ a heated rollerball (REA method)
- Takes more time to perform, requires regional or general anesthesia & is technically more difficult than 2nd-generation methods
- Not suitable for patients w/ cardiac or renal disease due to 4% risk of fluid overload

Non-Hysteroscopic Methods

- Second-generation technologies, eg thermal balloon endometrial ablation (TBEA), microwave EA (MEA), hydrothermablation, bipolar radiofrequency EA, endometrial cryotherapy
- Used when there is no structural or histological abnormality identified
- Not done under direct visualization of the uterine cavity
- Easier to learn & safer to use
  - Risks of complications are fewer & anesthetic requirement is lesser than hysteroscopic ablation

Hysterectomy

- Appropriate for women who have completed their family, have failed or are contraindicated for other treatment options, do not want to retain their uterus, fertility or menstrual bleeding, & are willing to assume the risks of surgery
- 3 main routes: Abdominal hysterectomy (AH), vaginal hysterectomy (VH) & laparoscopic hysterectomy (LH)
  - Choice of route depends on the size or mobility of the uterus, size & location of uterine fibroids, size & shape of the vagina, presence of other gynecological conditions & history of previous surgery
  - VH is the preferred route; contraindicated in patients w/ large uterus, presence of pathology & low uterine mobility
- Possible unwanted outcomes include infection & less commonly, intraoperative hemorrhage, damage to other abdominal organs & urinary dysfunction
- Bilateral oophorectomy is not recommended if patient has healthy ovaries

B SURGERY (CONT'D)

Myomectomy

- Recommended for women w/ >3-cm uterine fibroids who want to retain their uterus & fertility
- May be performed via an abdominal approach, laparoscopically, or hysteroscopically
- Possible unwanted outcomes include adhesions (which may result in pain &/or impaired fertility), infection, perforation & recurrence of fibroids

Uterine Artery Embolization (UAE)

- Advised in patients w/ >3-cm uterine fibroid who want to retain their uterus & fertility & avoid surgery
- Done by an interventional radiologist through injecting particles in the uterine arteries causing blockage & then shrinkage of the fibroids
- Studies showed that effect on HMB that is associated w/ uterine fibroid is similar to hysterectomy & myomectomy

Magnetic Resonance-Guided Focused Ultrasound Surgery (MRgFUS)

- Uses focused high-intensity ultrasound waves to destroy fibroid tissue
- A noninvasive approach w/ shorter recovery time
- Effective & safe to use for uterine fibroids in the short term

Dosage Guidelines

ANTIGONADOTROPIN

Drug	Dosage	Remarks
Danazol	200 mg PO 24 hrly for 12 wk	**Adverse Reactions** • CV effects (hypertension, edema, flushing); CNS effects (depression, dizziness, headache, sleep disorder); Dermatologic effects (acne, alopecia, mild hirsutism, rash); Endocrine effects (amenorrhea, decreased breast size, clitoris hypertrophy, increased LDL, menstrual disturbances); GI effects (N/V, wt gain, constipation); GU effects (vaginal dryness or irritation, pelvic pain); Hematologic effects (eosinophilia, leukocytosis, leukopenia); Other effects (hepatic adenoma, paresthesia, hematuria, voice change) **Special Instructions** • Use w/ caution in patients w/ diabetes mellitus (DM) or diseases exacerbated by fluid retention (eg asthma, epilepsy, migraine, cardiac or renal disease) • Avoid in patients w/ undiagnosed vaginal bleeding, porphyria, severe hepatic, renal or cardiac impairment, pregnancy, breastfeeding

Dosage Guidelines

HAEMOSTATICS

Drug	Dosage	Remarks
Ethamsylate	500 mg PO 6 hrly from start of bleeding until menstruation ceases	**Adverse Reactions** • Other effects (headache, skin rashes, nausea) **Special Instructions** • Avoid in pregnant patients, in patients w/ hypersensitivity, porphyria
Tranexamic acid	1 g PO 6-8 hrly starting at day 1 of menses for up to 5 days	**Adverse Reactions** • CNS effects (headache, migraine); GI effect (abdominal pain); Musculoskeletal effects (back pain, muscle pain, arthralgia); Resp effect (nasal symptoms); Hematologic effect (anemia); Other effect (fatigue) **Special Instructions** • Use w/ caution in patients w/ upper urinary tract bleeding or obstruction due to clot formation, disseminated intravascular coagulation, renal impairment, subarachnoid hemorrhage, in patients receiving hormonal contraceptives or Tretinoin • Avoid use in patients who are at risk of or w/ previous or active thromboembolic disease [eg hypercoagulopathy, retinal artery occlusion, cerebral thrombosis, deep vein thrombosis (DVT), pulmonary embolism]

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Drug	Dosage	Remarks
Anthranilic Acid Derivative		
Mefenamic acid	250-500 mg PO 8 hrly beginning w/ onset of menses & continuing for 5 days or until cessation of flow	**Adverse Reactions** • GI effects (abdominal cramps, heartburn, indigestion, N/V, gastric or duodenal ulcers, gastritis); Hematologic effect (bleeding); Hepatic effect (increased LFT); CNS effects (headache, nervousness, dizziness); Other rare effects (hypertension, tachycardia, urticaria, anaphylactic reactions, dyspnea, allergic rhinitis, hyperkalemia, tinnitus) **Special Instructions** • Should be taken w/ food • Use w/ caution in patients requiring mental alertness in performing tasks (eg driving or operating machineries), patients w/ coagulation disorders, hepatic impairment, hypertension, patients receiving anticoagulants or other agents causing hyperkalemia (eg ACE inhibitors) • Avoid in patients allergic to Aspirin or other NSAIDs, patients w/ active ulceration or chronic inflammation of the GI tract, patients w/ renal impairment, or in perioperative pain in the setting of coronary artery bypass graft (CABG) surgery - Associated w/ increased risk of myocardial infarction (MI) & stroke following CABG surgery • Withhold use for 8-12 hr (4-6 half-lives) prior to surgical or dental procedures
Propionic Acid Derivative		
Naproxen	825-1375 mg/day PO divided 12 hrly	

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Dosage Guidelines

PROGESTOGENS		
Drug	**Dosage**	**Remarks**
Levonorgestrel	1 IUS unit inserted into the uterine cavity within 7 days of the onset of menstruation	**Adverse Reactions** • CNS effects (headache, depression); Endocrine effects (amenorrhea after 1 yr of use, enlarged follicles, breast pain/tenderness); GI effect (abdominal pain); Dermatologic effect (acne); GU effects (uterine/vaginal bleeding/spotting, pelvic pain); Other effects [ectopic pregnancy, intrauterine device (IUD) expulsion] **Special Instructions** • Use w/ caution in patients w/ DM, coagulopathy, congenital or other heart disease, history of ectopic pregnancy, in patients receiving anticoagulants • Avoid in patients w/ uterine anomaly, acute pelvic inflammatory disease (PID), history of PID, uterine or cervical neoplasia, untreated cervicitis or vaginitis, unremoved IUD, undiagnosed AUB, active hepatic disease, breast cancer, pregnancy • Postpartum insertion should be postponed until 6 wk after delivery
Lynestrenol	10 mg/day PO for 10 days	**Adverse Reactions** • CV effects (fluid retention, edema); CNS effects (depression, migraine); Dermatologic effects (urticaria, rash); Endocrine effects (gynecomastia, menstrual flow changes, breast tenderness, change in libido); GI effects (change in wt/appetite); Other effects (LFT/lipid profile changes, anaphylactic reactions) **Special Instructions** • Use w/ caution in patients w/ DM, hypertension, migraine, depression, diseases exacerbated by fluid retention (eg asthma, epilepsy, migraine, cardiac or renal disease) • Avoid use in patients w/ history or active thromboembolic disorders, hepatic disease, breast cancer, undiagnosed vaginal bleeding, pregnancy
Medroxyprogesterone	2.5-10 mg/day PO for 5-10 days starting on the 16th day of menstrual cycle	**Adverse Reactions** • CNS effects (depression, dizziness, headache); Endocrine effects (irregular menses, decreased libido); GI effects (abdominal pain, wt gain); CV effect (edema); Dermatologic effects (acne, rash); Other effects (dysmenorrhea, vaginitis, arthralgia, bone mineral loss, anaphylactic reactions, ectopic pregnancy) **Special Instructions** • Use w/ caution in patients w/ DM, depression, diseases exacerbated by fluid retention (eg asthma, epilepsy, migraine, cardiac or renal disease) • Avoid use in patients w/ history or active thromboembolic disorders, cerebrovascular disease, hepatic disease, breast cancer, undiagnosed vaginal bleeding, pregnancy
Nomegestrol acetate	5 mg PO 24 hrly from 16th-25th day of cycle	**Adverse Reactions** • Endocrine effects (modification of menstruation, amenorrhea, intercurrent bleeding); Other effects (wt gain, insomnia) **Special Instructions** • Use w/ caution in patients w/ history of MI, cerebrovascular diseases, hypertension, DM, predisposition to thromboembolism • Avoid in patients w/ thrombophlebitis, liver dysfunction, undiagnosed genital hemorrhage

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Dosage Guidelines

PROGESTOGENS (CONT'D)		
Drug	**Dosage**	**Remarks**
Norethisterone (Norethindrone)	10-15 mg/day PO divided 8 hrly for 10 days, in a cyclical regimen	**Adverse Reactions** • CV effects (cerebral embolism, DVT, edema); CNS effects (depression, dizziness, migraine, mood swings); Dermatologic effects (acne, chloasma, rash); Endocrine effects (amenorrhea, menstrual flow changes, breast tenderness); GI effects (nausea, wt gain/loss); Other effects (LFT abnormalities, pulmonary embolism, anaphylactic reactions) **Special Instructions** • Use w/ caution in patients w/ DM, hyperlipidemias, high risk of thromboembolism, depression, diseases exacerbated by fluid retention (eg asthma, epilepsy, migraine, cardiac or renal disease) • Avoid use in patients w/ history or active thromboembolic disorders, hepatic disease, breast cancer, undiagnosed vaginal bleeding, pregnancy

PROGESTOGEN & ESTROGEN COMBINATIONS		
Drug	**Dosage**	**Remarks**
Dienogest/ estradiol valerate	1 tab/day PO starting on day 1 of menses for 28 days	**Adverse Reactions** • CV effects (edema, varicose vein aggravation); CNS effects (depression, migraine, mood swings); Dermatologic effects (chloasma, rash); Endocrine effects (amenorrhea, menstrual flow changes, breast tenderness, spotting); GI effects (bloating, abdominal cramps, N/V, wt change); GU effects (endocervical hyperplasia, fibroid enlargement, vaginal candidiasis); Hematologic effects (decreased folate, porphyria exacerbation); Other effects [contact lens intolerance, rhinitis, anaphylactic reactions, systemic lupus erythematosus (SLE) exacerbation] • Associated w/ arterial thromboembolism, cerebral hemorrhage, cerebral thrombosis, hypertension, MI, venous thrombosis, gallbladder disease, hepatic adenomas, retinal thrombosis, pulmonary embolism **Special Instructions** • Use w/ caution in patients w/ DM, familial defects of lipoprotein metabolism, high risk of thromboembolism, depression, diseases exacerbated by fluid retention (eg asthma, epilepsy, migraine, cardiac or renal disease) • Avoid use in patients w/ history or active thromboembolic disorders, cerebrovascular disease, coronary artery disease, valvular heart disease, uncontrolled hypertension, thrombophilias, DM w/ vascular involvement, severe headache w/ focal neurological symptoms, migraine, hepatic disease, breast or endometrial cancer, smoking ≥15 cigarettes/day, pregnancy
Levonorgestrel/ ethinyl estradiol[1]	1 tab/day PO starting on day 1 of menses for 21 days	

[1]Combination w/ Ferrous fumarate is available. Please see the latest MIMS for specific prescribing information.

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