

## ILLUSTRATED REVIEW

# Menstruation, anticoagulation, and contraception: VTE and uterine bleeding

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**Funding information**

BSB receives support from NIH grant L30 HL154449

**Handling Editor:** Alisa Wolberg.

**Abstract**

Abnormal or excessive menstrual bleeding affects one-third of reproductive-aged women. This number increases to 70% among women on direct oral anticoagulants (DOACs). While there is some variation in frequency of heavy menstrual bleeding (HMB) with different DOAC options, all menstruating individuals should receive counseling about the risk of HMB at the time of DOAC initiation. Management options include progestin-only therapies such as the levonorgestrel intrauterine system and etonogestrel subdermal implant or the progestin-only pill. Combined hormonal contraceptives and depot medroxyprogesterone acetate are associated with increased rates of thrombosis in nonanticoagulated women but may be continued, or even initiated, so long as therapeutic anticoagulation is ongoing. Procedural therapies, such as endometrial ablation, uterine artery embolization, or hysterectomy, are considerations for women who have completed childbearing and for whom more conservative measures are objectionable or ineffective. Given the high rates of HMB in women on DOACs, management strategies should be discussed even before heavy bleeding is diagnosed, particularly in women who experienced HMB prior to DOAC initiation. As iron deficiency with or without anemia is a common complication of HMB, complete blood count and ferritin levels should be monitored periodically, and iron deficiency should be treated with oral or intravenous iron supplementation.

**KEYWORDS**

anticoagulants, bleeding, heavy menstrual bleeding, menstruation, women's health

**Essentials**

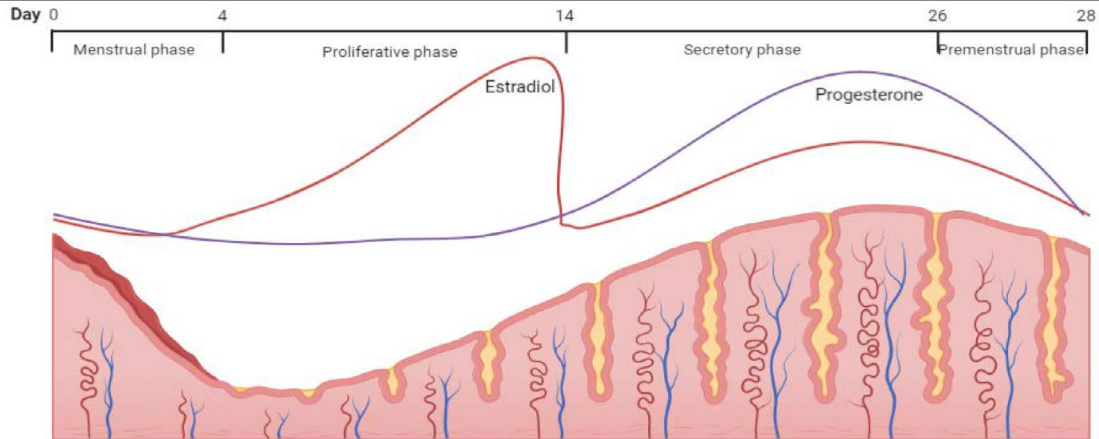
- Heavy menstrual bleeding (HMB) is bleeding that interferes with physical, social, emotional, or material quality of life.
- Seventy percent of women taking warfarin will experience HMB; rates are higher with rivaroxaban.
- Both hormonal contraceptives and tranexamic acid are effective treatments for HMB.
- Menstruating individuals on anticoagulation should be screened for HMB and iron deficiency.

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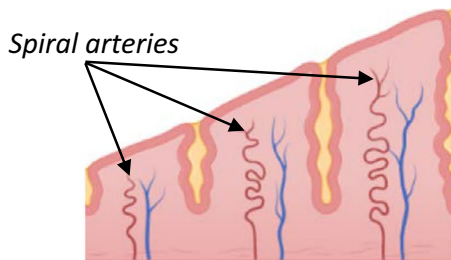
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For References 1-15

# Menstrual Bleeding and Hemostasis

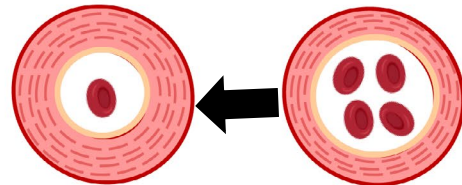


Menstrual bleeding is the process of shedding the endometrial lining which is built over the first half of the cycle while estrogen levels are rising.



The second half of the cycle is characterized by **increased vascularity** as the spiral arteries grow under the influence of rising progesterone levels.

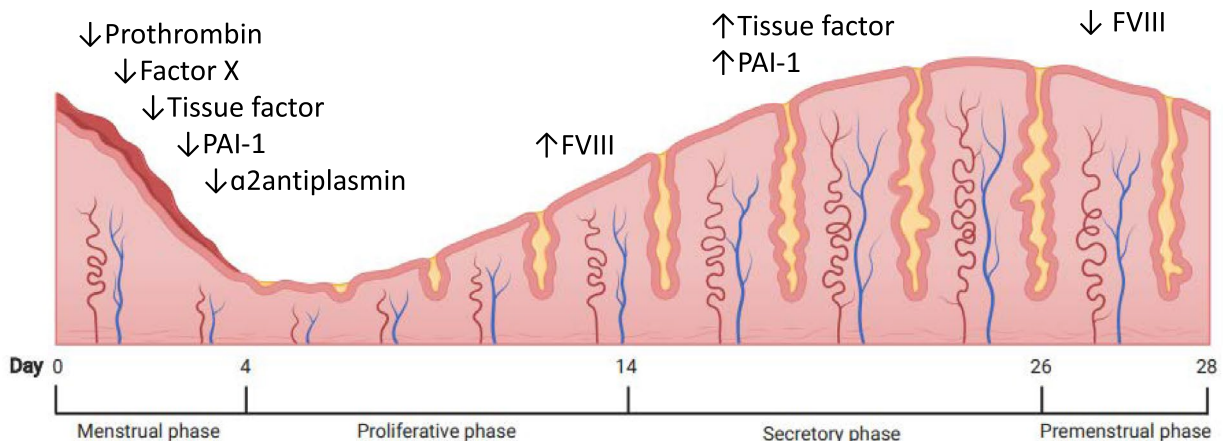
*Vasoconstriction of spiral arteries*



If implantation fails to occur progesterone levels drop rapidly and **intense vasoconstriction** occurs in the spiral arteries, resulting in **tissue ischemia** and shedding of the endometrial lining as menstrual blood. Fibrinolysis is key in this process

Differences in endometrial coagulation factor levels, such as tissue plasminogen activator, have been associated with HMB. How this is regulated in a tissue specific way remains unknown and additional basic science studies are needed. [1]

## Endometrial coagulation changes during the menstrual cycle[1-4]



# Abnormal Uterine Bleeding

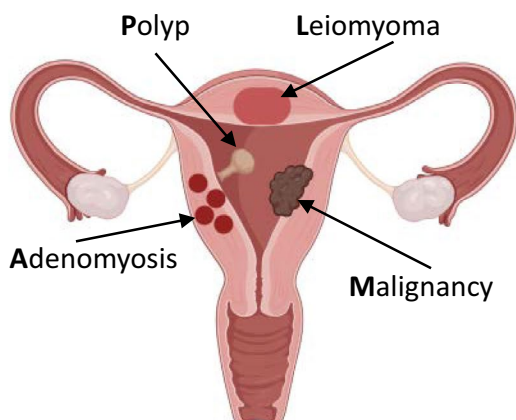
## Normal menstrual cycle

- Cycle length: 28 (21-35) days
- Duration of bleeding: 2-7 days
- Median blood loss: 53mL/cycle

## Heavy menstrual bleeding (HMB):

- >80mL menstrual blood loss (MBL)/cycle
- excessive menstrual blood loss that interferes with a woman's physical, social, emotional, or material quality of life.

## Structural causes of AUB: PALM[5]



**2.8cm = 1.1in**

## Clinical/laboratory signs of HMB

- Changing pad/tampon more often than hourly
- Leaking/soaking through clothing or having to change pads/tampons overnight
- Periods lasting >7 days
- Passing clots >2.8 cm

## Abnormal uterine bleeding (AUB)

### includes:

- Heavy menstrual bleeding
- Intermenstrual bleeding
- Postmenopausal bleeding
- Bleeding after sex
- Menstrual cycle <24 days or >38 days
- Irregular periods (cycle length varies by >7-9 days)

## Non-structural causes of AUB: COEIN[5]

Coagulopathy



Ovulatory



Endometrial

Iatrogenic



Not otherwise classified



## Consequences of HMB

- Iron deficiency with or without anemia
- Impaired quality of life
- Missed work or school
- Missed social obligations
- Hysterectomy
- Missed doses/increased recurrent venous thrombosis in anticoagulated women

# Anticoagulation and HMB

HMB/AUB effects:

- 30% of women at some point
- 70% of women on warfarin

*Which medicine should I take?*



Observational studies of rivaroxaban have demonstrated[6]:

- Prolonged menstrual bleeding >8 days (27%)
- Unscheduled contact with a provider for vaginal bleeding (41%)
- Medical or surgical interventions for vaginal bleeding (25%)
- Adaptation of anticoagulant treatment (15%)

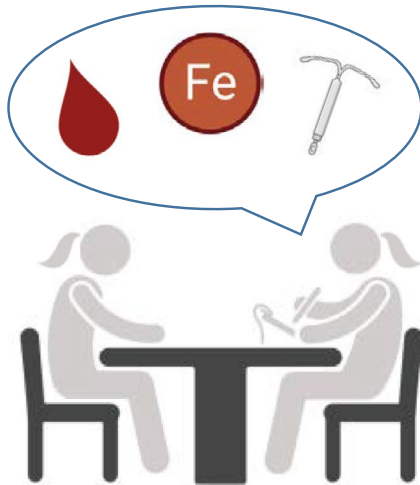
## Incidence of Major or Clinically Relevant Nonmajor Uterine Bleeds in Randomized Controlled Trials of Direct Oral Anticoagulants[7,8]

Drug	Incidence	OR (vs warfarin)
Rivaroxaban	9.5%	2.1
Edoxaban	9.0%	1.26
Apixaban	5.4%	1.18
Dabigatran	5.9%	0.59

## Proportion of Women Requiring Medical or Surgical Therapy for Uterine Bleeding Within Six Months of Anticoagulant Initiation[9]



# Starting, Monitoring and Stopping Anticoagulation in Menstruating People



When starting:

**Ask about:**

- History of heavy or abnormal bleeding
- History of iron deficiency

**Check:**

- CBC & ferritin

**Counsel on:**

- Anticoagulant options & risk of HMB
- Signs and symptoms of HMB
- Contraception

## Did you know?

You **do not have to stop oral contraceptives** in therapeutically anticoagulated patients. Anticoagulation prevents VTE and continuing OCPs may prevent HMB.[10]



At future visits

**Ask about:**

- Changes in periods
- Symptoms of anemia

**Check:**

- CBC & ferritin at least every 6 months

**Discuss:**

- Plan for stopping anticoagulation
- Possible need to transition from combined contraceptives to progesterone-only options



When stopping

**Discontinue:**

- Estrogen therapies 1 month in advance

**Offer:**

- Effective, estrogen-free contraception

**Discuss:**

- Planning for future pregnancies if desired, including preconception counseling with obstetrics or perinatology

# Combined Hormonal Contraceptives for Menstrual Management

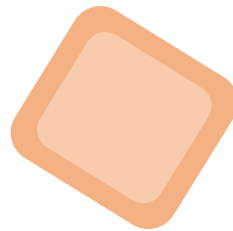
## Combined hormonal contraceptives (CHCs)

- Combination of estrogen and progestin which typically prevents ovulation
- Doses of estrogen vary from 10-30mcg
- Side effect profile varies by progestin type
- May be administered with or without “placebo” days
- Continuous administration allows avoidance of menses
- CHCs can be administered as pills, patches or the vaginal ring



### Contraceptive pills

- Up to 90% reduction in median menstrual blood loss[11]
- 91% effective for prevention of pregnancy[12]



### Contraceptive patch

- Reduction in menstrual blood loss not studied
- 91% effective for prevention of pregnancy[12]



### Contraceptive ring

- Up to 72% reduction in median menstrual blood loss[13]
- 91% effective for prevention of pregnancy[12]

## Risk of VTE in Anticoagulated Women on Hormonal Therapies[10]

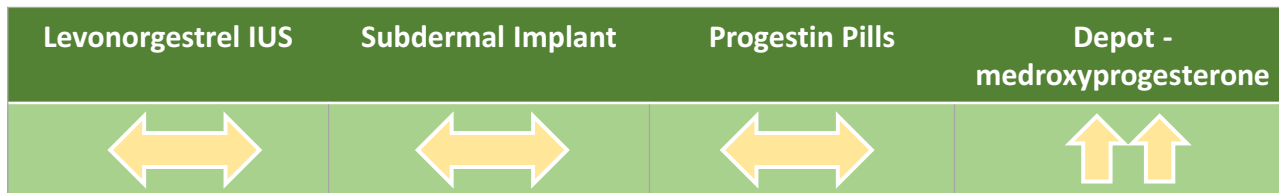
Hormonal Therapy	VTE Risk (%/year)
None	4.7
Estrogen-containing	3.7
Progestin-only	3.8
Any therapy	3.7



*CHCs prevent ovulation and may reduce hemorrhagic cysts!*

# Progestin-only Contraceptives for Menstrual Management

## Changes in VTE Risk with Addition of Progestin Only Contraceptives

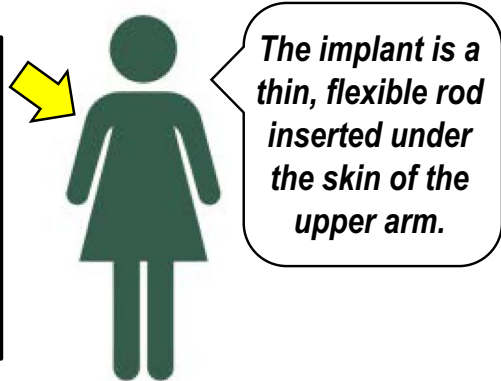


The levonorgestrel intrauterine system (LNG-IUS) is associated with:

- 86% reduction in blood loss at 3 months
- 97% reduction at 12 months[14]
- High rates (>20%) of amenorrhea
- >99% effective for prevention of pregnancy[12]

The etonogestrel subdermal implant is associated with:

- Amenorrhea in 22%
- Infrequent bleeding in 34%
- Prolonged 9 (17.7%) or frequent (6.7%) bleeding/spotting [15]
- >99% effective for prevention of pregnancy

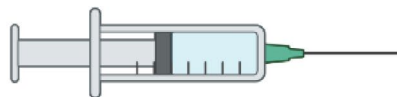


**POPs should be taken at the same time every day to prevent pregnancy**



Progestin-only pills (POPs) are associated with:

- 87% reduction in menstrual blood loss
- Lower satisfaction as compared to LNG-IUS
- 92% effective for prevention of pregnancy



Depot medroxyprogesterone acetate (DMPA) is associated with:

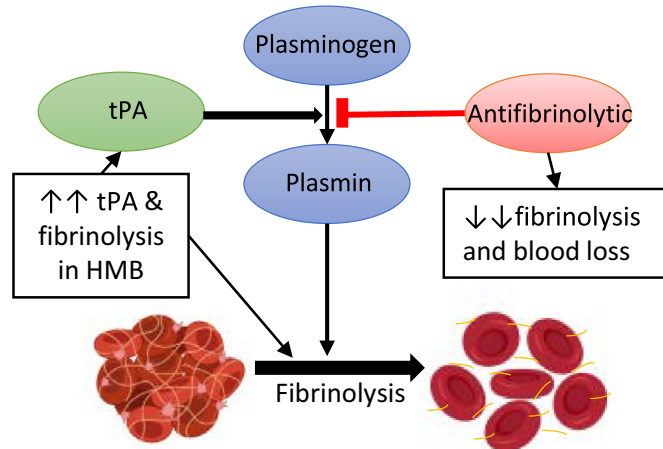
- Amenorrhea in 55+%
- Infrequent bleeding in 34%
- 96% effective for prevention of pregnancy

# Additional Approaches to Menstrual Management

Tranexamic acid is effective for the treatment of HMB

- 40% reduction in menstrual blood loss
- Improved quality of life
- Contraindicated in the setting of acute thrombosis
- Not studied in women on anticoagulation or with a history of VTE

## Fibrinolysis and Menstrual Bleeding



Holding or discontinuing anticoagulation early

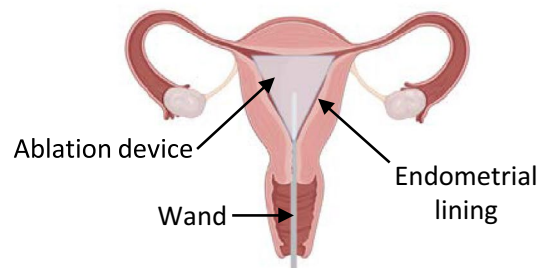
- Increases the risk of recurrent VTE
- Is not proven to reduce menstrual blood loss
- Is not recommended

Possible benefit of switching from a “higher risk” anticoagulant such as rivaroxaban to a “lower risk” anticoagulant such as dabigatran or apixaban is the subject of ongoing studies.

Procedural therapies for HMB include

- Endometrial ablation
- Uterine artery embolization
- Hysterectomy

## Endometrial Ablation



## Did you know?

Procedural therapies are restricted to women who have completed childbearing. Non-hysterectomy procedures require highly effective (sometimes permanent) contraceptive methods in order to prevent pregnancy related morbidity.

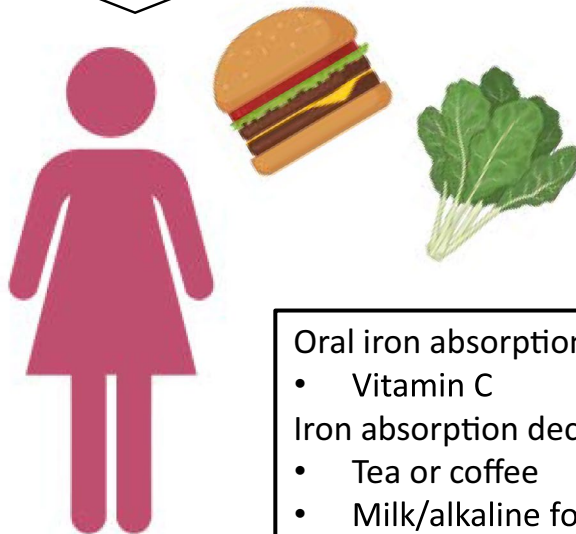
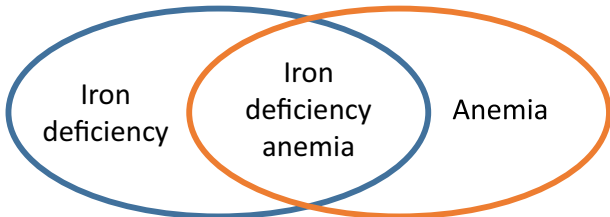


# Management of Iron Deficiency in HMB + Anticoagulation

- Iron deficiency effects up to 48% of reproductive age women
- Pregnancy and menstrual bleeding are contributing factors
- Risk of iron deficiency increases significantly with HMB

- Iron deficiency is associated with:
- Fatigue
  - Loss of concentration
  - Headaches
  - Easy bruising
  - Restless legs
  - Hair loss
  - Pica

*Ferritin is the best measure of iron stores. Serum iron levels vary with many factors including recent food intake and time of day.*



**Did you know?**  
Patients may be symptomatic from iron deficiency without anemia. Ferritin should always be checked in addition to the CBC in menstruating individuals.

- Oral iron absorption improves with
- Vitamin C
- Iron absorption decreases with
- Tea or coffee
  - Milk/alkaline foods



Oral Supplementation		Parenteral Supplementation	
Pros	Cons	Pros	Cons
<ul style="list-style-type: none"> <li>• Low cost</li> <li>• Widely available</li> </ul>	<ul style="list-style-type: none"> <li>• Long time to response</li> <li>• GI intolerance</li> </ul>	<ul style="list-style-type: none"> <li>• Immediate response</li> <li>• Limited availability</li> </ul>	<ul style="list-style-type: none"> <li>• Expensive</li> <li>• Rare but serious side effects</li> </ul>

## AUTHOR CONTRIBUTIONS

BSB, CM, and PJ wrote the manuscript.

## RELATIONSHIP DISCLOSURE

The authors have no conflicts to report.

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**How to cite this article:** Samuelson Bannow B, McLintock C, James P. Menstruation, anticoagulation, and contraception: VTE and uterine bleeding. *Res Pract Thromb Haemost*. 2021;5:e12570. <https://doi.org/10.1002/rth2.12570>