Heavy Menstrual Bleeding in Adolescents and Modern Management

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Mission

“The Foundation for Women and Girls with Blood Disorders seeks to ensure that all women and adolescent girls with blood disorders are correctly diagnosed and optimally treated and managed at every life stage.”

Disclosures

For Dr. Sokkary
- No Conflicts of interest or disclosures

For Dr. Francis
- No Conflicts of interest or disclosures
Pre-Test

• Please take a few minutes to fill out the answers to the questions provided.

• Your responses will be collected before this presentation begins.

• A post-test will be administered after the presentation

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**Case 1**

12-year-old patient comes to your office with HMB since menarche. She soaks 8-10 pads/day and bleeds for up to 2 weeks.

- What additional history do you want and what labs (if any)?
- When and why would you refer her to hematology?

**Case 2**

15-year-old sexually active female with von Willebrand Disease is referred to you for HMB?

- What contraceptive options would control her bleeding?
- What would you do if she had breakthrough bleeding while on contraception?
Heavy Menstrual Bleeding in Adolescents

- Background
- Differential Diagnosis
- Workup
- Treatment

Background

- Abnormal uterine bleeding is the most common complaint of adolescents reporting to gynecologists
- Heavy Menstrual Bleeding
  - The most common presenting symptom in women with bleeding disorders
  - 40% of adolescents report having heavy periods
  - 10-48% of adolescents with menorrhagia have a bleeding disorder
- Bleeding disorders are under-recognized and under-treated
  - Screening performed in <25% of women with HMB

Background

- Normal cycle
  - Interval 21-45 days
  - Length 7 days
  - Flow 6 pads/tampons daily or < 80 ml per cycle
  - Pictorial Blood Loss Assessment Chart (PBAC) < 100
Background

Dysfunctional Uterine bleeding = Abnormal Uterine bleeding

Menorrhagia = Heavy menstrual bleeding
- > 8 days of bleeding
- > 80 ml of blood loss per cycle
- Need to change pad < every 2 hours
- PBAC>100

ACOG, 2012

Heavy Menstrual Bleeding in Adolescents

Differential Diagnosis

- Polyp
- Adenomyosis
- Leiomyoma
- Malignancy/hyperplasia
- Coagulopathy
- Anovulatroy
- Endometrial
- Iatrogenic
- Not yet classified

Emans, 2005

PREGNANCY
Differential Diagnosis

- von Willebrand Disease
  - General population prevalence is 1%
  - Study of 500 adolescents with menorrhagia
  - Prevalence range: 3-36% depending on setting
- Bleeding symptoms
  - Menorrhagia: 80%
  - Easy bruising: 80%
  - Dental related: 50%
  - Epistaxis: 50%
  - Surgical related: 50%
  - Postpartum Hemorrhage: 30%

Mikhail, 2010

Differential Diagnosis: Bleeding Disorders

- Platelet Disorders
  - Decreased platelets (thrombocytopenia)
    - ITP, TTP
    - Chemotherapy, leukemia, aplastic anemia, hereditary macrothrombocytopenia
  - Platelet Dysfunction
    - Primary secretion and signal transduction
    - Bernard-Soulier: deficiency of plt glycoprotein Ib
    - Glanzmann: deficiency in plt glycoprotein IIb-IIIa
    - Platelet granule disorders
    - Inherited macrothrombocytopenia

Philip, 2010

Differential Diagnosis: Bleeding Disorders

- Factor Deficiency
  - Factor II
  - Factor V
  - Factor VII
  - Factor X
  - Factor XI
  - Hemophilia A/B

[Diagram of Blood Clotting Process]
Clot formation

- Platelet
- VWF
- Factor VIII
- Fibrinogen
- Fibrin
- Thrombin
- GpIb
- GpIIb/IIIa

Bernard-Soulier
Glanzmann

The Workup

Heavy Menstrual Bleeding in Adolescents

Workup: History

- Menses
  - Menarche
  - Interval, days of bleeding, pads per day
  - Soiling/Clothing

- Bleeding specific history
  - Easy bruising
  - Nose bleed
  - Gum bleeding
  - Prolonged bleeding with small wounds
  - Bleeding complication with operation/procedure
  - Unexplained blood in stool
  - Anemia requiring blood transfusion

Bowman, 2008
PBAC Score

Menstrual Calendar

Workup: History

- PMH:
  - Bleeding disorders
- FH:
  - Bleeding disorders
  - Heavy menses, postpartum hemorrhage
- SH:
  - Sexual activity
- Medication:
  - Aspirin, anticoagulation, contraception
- ROS:
  - Change in weight, stress, acne, unwanted hair growth, breast discharge
Workup

- Ultrasound
  - Better define pelvic anatomy
  - Polyp/Fibroids
  - Ovarian tumors
    - Granulosa cell
  - Patient's with bleeding disorders
    - No increase in EML
    - No increase in hemorrhagic cysts

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Fowler, et al. Ultrasound findings in adolescent with heavy menstrual bleeding. Publication in process

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Workup: Labs

- Pregnancy test
- CBC
- Type and Screen
- TSH
- +/- PCOS labs
- +/- Prolactin

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Workup: Labs

Bleeding Disorder

- INR, PT, PTT, fibrinogen
- VW Panel-SSSS
  - von Willebrand Factor Antigen
  - Ristocetin cofactor activity
  - Factor VIII
  - May need to repeat
  - Platelet Function Analyzer-100 (PFA-100)*

Adolesan, 2015
Workup: Labs

- Hematology consult
- Platelet aggregation studies
- Electron microscopy
  - High suspicion for bleeding d/o
- Factor deficiency
- Blood smear

Adolesan, 2015

Workup: Labs
Bleeding Disorder

- +VWF deficiency do further analysis to subtype
  - VWF multimer analysis
  - RIPA: Ristocetin Induced Platelet Aggregation

Workup: Labs
Bleeding Disorder

- UPT, CBC, T&G, TSH, Prolactin
- Coags, VWP
- Heme consult
- Plt agg, electron microscopy, bid smear
  - VWF multimer, RIPA
Heavy Menstrual Bleeding in Adolescents

Modern Management

Establish goals and expectations

- Within the context of the individual medical history:
  - Does this patient:
    - prefer to have a period every month?
    - have other menstrual symptoms including dysmenorrhea, or acne?
    - feel they are reliable at taking something at home?
    - also need contraception?

Estrogen-containing options: COCs

- Regimen can be cyclic, extended, or continuous
- Continuous tends to work best for menstrual suppression
- Variety of doses can be used but traditionally a 30mcg pill is used
- There is a higher rate of BTB with continuous or extended use
  - 50% amenorrhea rate after 1 year in one trial

Altshuler, 2014; Teichmann, 2009
Estrogen-containing options: the vaginal ring

- Etonogestrel/ethinyl estradiol containing ring that is placed in the vagina typically for 3 weeks but can be used continuously
- Unscheduled spotting may be more common with extended/continuous use
- This method is not as popular with teens based on route of administration
- May be more appealing in patient who also needs contraception

Miller, 2005

Estrogen-containing methods: the patch

- Norelgestromin/ethinyl estradiol transdermal patch intended for weekly administration
- Extended regimen (12 consecutive weeks) resulted in fewer bleeding days and fewer bleeding episodes
- More spotting days but overall satisfaction remained similar
- Extended cycle arm reported more breast discomfort, headache, and nausea
  - Only adverse event was 1 pregnancy with spontaneous abortion

Stewart, 2005

Progesterone-only options: the POP

- Norethindrone 35 mcg is not appropriate for treatment of heavy menstrual bleeding due to the half-life which requires near perfect compliance
- Amenorrhea is achieved in about 10% of patients

Altshuler, 2014
Progesterone-only options: the implant

- Also not recommended due to side effect profile of unpredictable bleeding
- Can’t reliably offer menstrual suppression in cases of heavy menstrual bleeding
- Appropriate if patient refuses other options and needs reliable contraception

Progesterone-only options: DMPA

- Most widely recognized for achieving amenorrhea
- 60% after 1 year and 70% after 2 years of use
- Advantage of not requiring a trained provider to administer (compared to IUD)
- Frequency of visits and side effects may be a barrier

Treatment: Maintenance

- Progestin only
  - Medroxyprogesterone acetate
  - May use more frequently
  - IM (150 mg) vs. subcutaneous (104 mg)
  - Randomized evaluator blinded study evaluating safety and efficacy of subcutaneous injection
  - Followed 225 women (18-35) over 2 years
  - No difference in pregnancy rate (0% vs. 0.8%, CI 0-2.37)
  - No difference in change in BMD between the two groups
  - No difference in percentage of participants that gained weight (12% vs. 14%)
  - No difference in amenorrhea (71% vs 80%)

Kauertz, 2009
Progesterone-only options: the IUD

- The levonorgestrel-intrauterine system is not only appropriate for use in adolescents but recommended as first line contraception
- Takes an average of 4 months to reduce amount of monthly blood loss
- Amenorrhea in 50% after 1 year of use and 60% after 5 years of use
- If insertion is a barrier, can be placed under sedation or anesthesia in the OR

IUD

- Progesterone only
- Intrauterine device
- Decreases median blood loss by up to 90% after 1 year
- Amenorrhea in 80% of users after 2 years
- Report of 5 adolescents with bleeding disorders refractory to COC, DDAVP and tranexamic acid (4 VWD, 1 hemophilia A)
- All had light or no bleeding at 3- and 12-month follow up
- No adverse effects

Chi, 2010

Nonhormonal options: NSAIDs

- 2013 Cochrane review showed NSAIDs are more effective than placebo at reducing menstrual blood loss in women with regular menstrual cycles
- Reviewed 18 RTCs
- Less effective than tranexamic acid and the LNG-IUS
- Dose regimens vary in different studies
  - Naproxen 250-500 up to 4 times daily
  - Ibuprofen 600-1200 daily

Lethaby, 2013
Nonhormonal options: antifibrinolytics

- Have not been FDA approved in patients younger than 18 years of age
- Shown to be effective in adult women for treatment of heavy menstrual bleeding
- Still should be considered in cases of refractory heavy menstrual bleeding

Bennett, 2014

Special Considerations

- Treating menorrhagia in patients undergoing treatment for cancer:
  - Bleeding may be related to a hematologic malignancy, effects of chemotherapy/radiation/bone marrow transplantation, or disruption of the HPO axis
  - Gynecologists often consulted prior to initiation of therapy, as well as during an episode of heavy bleeding

Therapy for Patients with Cancer

- Several studies but data limited
- Therapy is individualized based on platelet count, course of treatment, time to expected nadir, risk of VTE, and need for contraception
- Collaboration with patient’s oncologist is highly recommended

ACOG Committee Opinion 606
Prophylactic menstrual suppression
- COCs used continuously (20 mcg pill) resulted in light bleeding or amenorrhea by 3 months in 68% of participants
  - 88% at 12 months
  - Study done in ages 18-45; none in adolescents
- Use of estrogen-containing products may be indicated in this circumstance even in patients for whom it would otherwise be contraindicated for contraception

Higher dose (50 mcg) pills have been used to treat bleeding but not for menstrual suppression in patients undergoing BMT
- Some have observed hyperbilirubinemia and hepatic venoocclusive disease
- Vaginal ring and transdermal patch may not be appropriate due to potential for mucositis or skin reactions while undergoing therapy for cancer

POP options include:
- Norethindrone acetate 5-15 mg/d
- Norethindrone 0.35 mg/d
- Norgestrel 0.075 mg/d

Injectable option:
- DMPA is reasonable but amenorrhea is not immediate and irregular bleeding makes it less reliable for rapid menstrual suppression
What about LARC?

- Currently no evidence to support use of levonorgestrel IUD in adolescents undergoing cancer therapy
  - Efficacy in immunocompromised adults with heavy menstrual bleeding has been established
  - Initial irregular bleeding limits use for menstrual suppression
  - Increased expulsion rate during episodes of heavy bleeding limits emergency placement

Patients with Cancer: GnRH agonist

- Leuprolide acetate has been proven to work very well in multiple studies
- Has been studied in ages 12-51, with the best bleeding profile when compared to DMPA and those left untreated
- Ideally should be started prior to induction of myelosuppressive therapy and at least 4 weeks prior to expected onset of thrombocytopenia

GnRH agonists and preservation of ovarian function

- These data are inconclusive
  - Don’t recommend for fertility preservation but patients may ask about this
  - Meta-analysis including data from 6 RTCs evaluated incidence of new onset POF, resumption of ovulation and occurrence of pregnancy
  - Showed higher resumption of menses and ovulation but no difference in pregnancy rates with GnRH

Fertil Steril, 2011
Management of acute heavy bleeding episode

- Detailed algorithm in ACOG Committee Opinion 606
- Again, weigh the risks and benefits of estrogen use, as combined pills and IV estrogen may be your best option due to rapid onset of action
- Antifibrinolytics may be used in refractory cases but data is limited
- Surgical options may be necessary and include uterine curettage, ablation, and even hysterectomy

ACOG Committee Opinion 606

Case 1

- 12-year-old patient comes to your office with HMB since menarche. She soaks 8-10 pads/day and bleeds for up to 2 weeks
  - What additional history do you want and how would you work her up?
  - When and why would you refer her to hematology?

Case 2

- 15-year-old sexually active female with von Willebrand Disease is referred to you for HMB?
  - What contraceptive options would control her bleeding?
  - What would you do if she had breakthrough bleeding while on contraception?
Question #1

Approximately what percent of adolescents complain of heavy menstrual bleeding?

a. 5%

b. 10%

c. 20%

d. 40%

Question #2

Which of the following is the most common cause of abnormal uterine bleeding among adolescents?

a. Anovulation

b. Cervical cancer

c. Fibroids

d. Medication
Question #3

In an adolescent with heavy menstrual bleeding, which of the following should be checked at their initial visit:

a. CBC and Type and Screen
b. CBC, Type and Screen, Coag, von Willebrand Panel, TSH
c. CBC, electron microscopy, Platelet aggregometry
d. Both B and C

Question #4

Antifibrinolytics have been FDA approved for use in adolescents.

a. True
b. False

Question #5

The intra-uterine devise can be used in adolescents with heavy menstrual bleeding disorders due to a bleeding disorder.

a. True
b. False
Question #6

Amenorrhea rates after 1 year of DMPA use are approximately:

a. 10%

b. 30%

c. 60%

d. 80%

References

- JOSPER 401E: Diagnosis of Abnormal uterine bleeding in reproductive aged women. 2012
- Resnik M. Screening Bleeding Disorders in Adolescents and Young Women with Menorrhagia. Turkish J Haemat. 2015; 30:168-176
References


