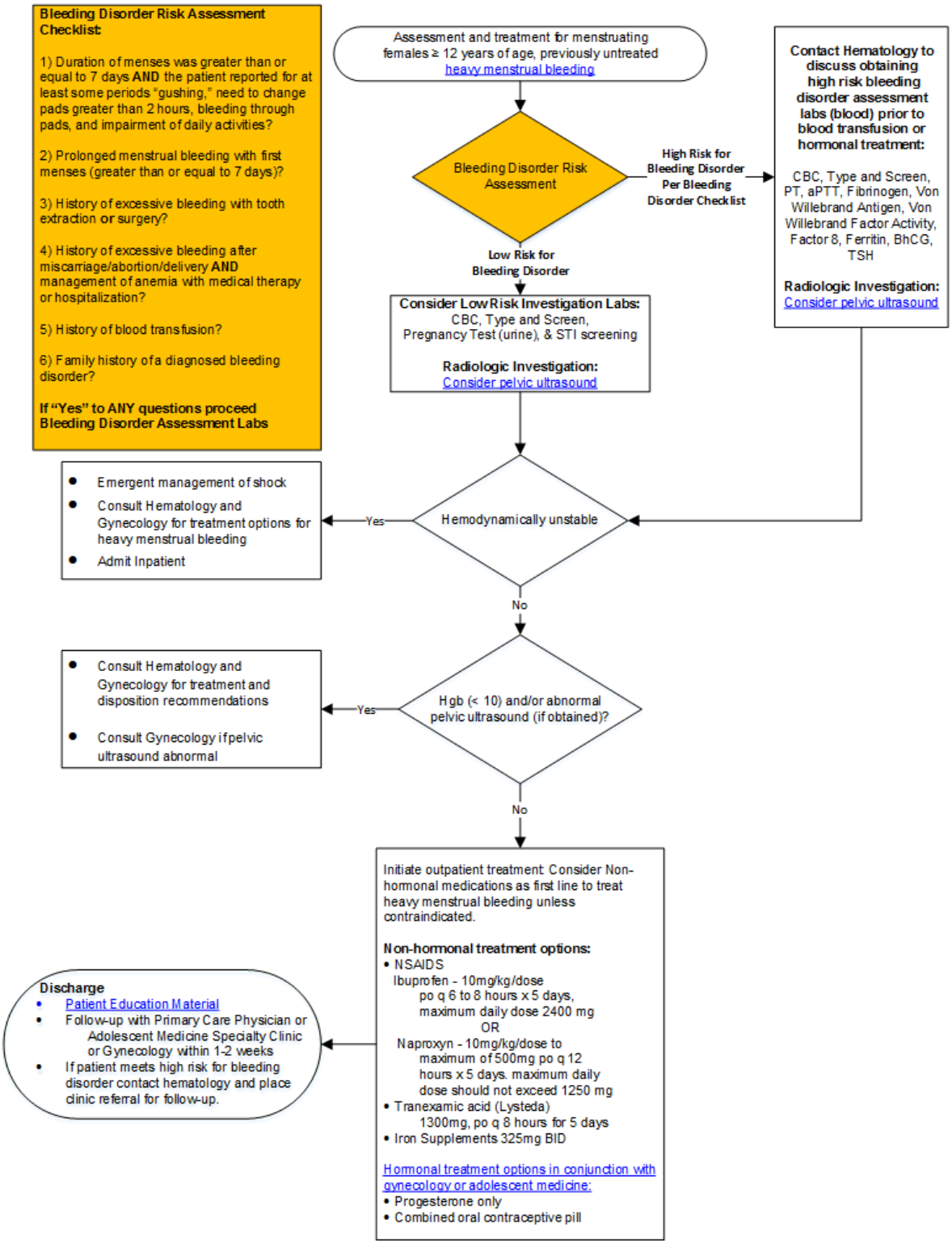
Children's Mercy

December 2017

Children's Mercy Hospitals and Clinics
Evidence Based Practice Care Process Model

Evaluation and Treatment of Pre-Teen and Adolescent Heavy Menstrual Bleeding



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Objective:

1. Management of heavy menstrual bleeding potentially mitigating the need for hormonal medications for menstruating females 12 years and older.
2. Help to identify those patients with heavy menstrual bleeding possibly due to an undiagnosed bleeding disorder needing further subspecialty care.

Target Users:

- Emergency Department
- Urgent Care Center
- Inpatient Units
- Teen Clinic
- PCC
- Gynecological consultants
- Adolescent medicine consultants
- House Staff

Guideline Inclusion Criteria:

- Adolescents ≥ 12 years old who present with heavy menstrual bleeding.

Guideline Exclusion Criteria:

- Hormonal bleeding with contraception
- Pregnancy
- Known trauma
- Sexual assault
- Genital injury
- Known bleeding disorders
- Hemodynamic instability

Outcome Measures:

- Tranexamic acid use
- Hormonal medication use
- Consultation with gynecology or hematology prior to parenteral hormone treatment and/or blood products

Process Measures:

Heavy Menstrual Bleeding PowerPlan utilization

Balance Measures:

- 72 hour acute care return visit
- Readmissions within 7 days with same diagnosis
- Consultations – Gynecology and Hematology

Potential Cost Implications:

- Cost of medication to patients

Potential Barriers:

- Access to medication
- Access to follow up

Supporting Tools:

- Power Plan
- Heavy menstrual bleeding algorithm with Bleeding Disorder Risk Assessment Checklist Based on Phillip Questionnaire
- Education Material

Questions:

1) In adolescents ≥ 12 years old who present with heavy menstruation is non-hormonal versus hormonal medication treatment better in the resolution of acute bleeding?
2) In adolescent patients with heavy menstruation is oral vs. intravenous tranexamic acid better in the resolution of acute bleeding?
3) What is the recommended dose for hormonal treatment of pre-teen or adolescent patients with heavy menstruation?
4) In preteen or adolescent patients with heavy menstrual bleeding, does ultrasound versus no ultrasound result in improved patient diagnosis and outcomes?

Definition

- Volume (equates to needing to change a heavy absorbent pad/tampon due to saturation more frequently than every two hours) **OR** excessive menstrual flow duration (>7 days)
- Bleeding causing symptomatic anemia or lifestyle disturbance
- Bleeding unlikely to be due to ongoing hormonal contraception

Bleeding Disorder Risk Assessment

High risk bleeding disorder screen as adapted from Phillip (Philipp 2008, Cincinnati Children's Hospital Medical Center, 2011).

Screening may be considered positive for bleeding disorder if any one of the following five conditions are met

1) Duration of menses was greater than or equal to 7 days AND the patient reported for at least some periods "gushing," bleeding through pads, and impairment of daily activities.
2) History of excessive bleeding with tooth extraction or surgery.
3) History of excessive bleeding after miscarriage/abortion/delivery AND management of anemia with medical therapy or hospitalization.
4) History of blood transfusion
5) Family history of a diagnosed bleeding disorder

Patient assessment

History:

- Menstrual history (menarche, last menstrual period, frequency, duration, flow, pain, sexual history)
- Bruising or other bleeding
- Galactorrhea
- Fatigue, dizziness/light headedness, lethargy, headache
- Sexual activity
- Sexual assault/abuse
- Medication use

Examination:

- Pallor
- Signs of abnormal bleeding (e.g., petechia and/or bruising)
- Palpation of the abdomen for uterine or ovarian mass

- Genital exam, speculum if indicated

Investigations:

Low Risk Bleeding Disorder Assessment:
- ✓ Pregnancy Test
- ✓ Consider: CBC, Type and Screen, STI testing
- ✓ Measurement of serum TSH to exclude thyroid abnormalities

High Risk Bleeding Disorder Assessment:
- ✓ Pregnancy Test
- ✓ Type and screen, CBC and Ferritin
- ✓ Coagulation screen (PT, aPTT, Fibrinogen, Von Willebrand Antigen, Von Willebrand Factor Activity, Factor 8)
- ✓ Measurement of serum TSH to exclude thyroid abnormalities

Radiology:
- Consider discussing patient's condition with GYN to evaluate the need for pelvic ultrasound if history or exam is accompanied by pain or palpable mass (to exclude structural causes, such as fibroids, polyps, and/or ovarian tumors)

Management
- **Single or combination of non-hormonal treatment (for example NSAIDS & Tranexamic acid) should be considered for first line treatment for those who are hemodynamically stable**
- Hormonal treatment may be used in consultation with gynecology or adolescent medicine specialist if clinically indicated or first line therapy is contraindicated.
-

Non-hormonal forms of treatment:
- NSAIDS and Tranexamic acid are first line to decrease flow unless contraindicated:
  1) **NSAIDS**
     - Decreases flow up to 30% if taken regularly during the first 48 hours of menstruation (Lethaby, Duckitt et al., 2013)
     - Ibuprofen - 10mg/kg/dose po q 6 to 8 hours x 5 days, maximum single dose 800 mg. Maximum daily dose should not exceed 2400 mg
     - Naproxyn - 10mg/kg/dose to maximum of 500mg po q 12 hours x 5 days. Maximum daily dose should not exceed 1250 mg

  2) **Tranexamic acid**
     - Tranexamic acid is a non-hormonal antifibrinolytic medication that decreases menstrual flow by 50%, does not reduce the duration of menses or regulate the menstrual cycle, and is taken for 3 to 5 days following cessation of bleeding (Buggy, Sheppard et al., 1994)
     - Menstruating females $\geq$ 12 years: 1300 mg by mouth every 8 hours for 5 days

  3) **Iron supplements**
     - 325 mg BID
     - If anemic or recurrent/severe bleeding

Hormonal forms of treatment in conjunction with gynecology or adolescent medicine specialist consult:

1) **Progesterone** (Norethindrone 5mg)
   - Good with anovulation (infrequent periods) due to the lack of progesterone
   - Acute treatment: 10 mg by mouth, once daily for 21 days

- Prophylactic treatment: 7-10 days/month

2) **Combined oral contraceptive pill**
   - Decreases flow by 50%. Good with anovulation/irregular menses
   - Sprintec 1 tablet daily until follow-up, **Do not take placebos.**
   - Ethinyl estradiol 35mcg/norgestimate 25mcg

Discharge Criteria & Follow up:

- Education materials:
  - Medication to treat heavy menstrual bleeding
  - Heavy menstrual (vaginal) bleeding
- Follow up with PCP, GYN or Adolescent Medicine Specialty Clinic within 1-2 weeks, with good return precautions to an acute care facility as needed prior to their follow up visit.
- Follow up with hematology per recommendations if consulted.

Care Process Model Preparation: This care process model was prepared by The Office of Evidence Based Practice (EBP) in collaboration with content experts at Children's Mercy—Kansas City. Development of this care process model supports the Department of Clinical Effectiveness's initiative to promote care standardization that builds a culture of quality and safety that is evidenced by measured outcomes. If a conflict of interest is identified the conflict will be disclosed next to the team members name.

The recommendations are based upon synthesized evidence from two clinical practice guidelines (Cincinnati Children's Hospital, 2011; Royal Children's Hospital, 2016) and three individual studies (Lukes, Moore et al., 2010; Srivaths, Dietrich et al., 2015; Fillingham, Kayupov et al., 2016). The guidelines were appraised using the AGREE II instrument (Brouwers, Kho et al. 2012):

	Cincinnati Children's Best	Royal Children's Hospital
Domain 1 - SCOPE AND PURPOSE	78%	33%
Domain 2 - STAKEHOLDER INVOLVEMENT	56%	30%
Domain 3 - RIGOR OF DEVELOPMENT	47%	15%
Domain 4 - CLARITY AND PRESENTIATION	46%	52%
Domain 5 - APPLICABILITY	42%	4%
Domain 6 - EDITORIAL INDEPENDENCE	61%	0%

Menorrhagia Team Members:
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• Jacqueline A. Bartlett, PhD, RN, EBP Director

Guideline Development Funded By: Departmental funding.

The Office of Evidence Based Practice, 2017
Center of Clinical Effectiveness

Approval Process: Care process models are reviewed and approved by Content Expert Team, the Office of EBP, and other appropriate hospital committees as deemed suitable for the guidelines intended use. Care processes are reviewed and updated as necessary every 3 years within the Office of EBP at CMH. Content expert teams will be involved with every review and update.

Disclaimer:

The Content Experts and the Office of EBP are aware of the controversies surrounding care process models. When evidence is lacking or inconclusive, options in care are provided in the document and the power plans that accompany the guideline.

These guidelines do not establish a standard of care to be followed in every case. It is recognized that each case is different and those individuals involved in providing health care are expected to use their judgment in determining what is in the best interests of the patient based on the circumstances existing at the time.

It is impossible to anticipate all possible situations that may exist and to prepare guidelines for each. Accordingly, these guidelines should guide care with the understanding that departures from them may be required at times.

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Specific Care Question: In adolescent patients with heavy menstruation is non-hormonal vs. hormonal medication better in the resolution of acute bleeding?

Question Originator:
Julie Strickland, MD, MPH and Shannon Carpenter, MD, MS

Evidence Summary from The Office of Evidence Based Practice: A weak recommendation based on very low quality of evidence supports the use of the non-hormonal medication tranexamic acid as a treatment option for adolescent patients with heavy menstrual bleeding.

Lukes, Moore et al. (2010) showed women who received tranexamic acid (TA) (n = 115) had a significantly greater reduction in menstrual blood loss of -69.6 mL compared with -12.6 mL (8.2%) in the 72 women who received placebo ($P < .001$). Compared with women receiving placebo, women treated with tranexamic acid experienced significant improvements in limitations in social or leisure and physical activities, work inside and outside the home, and self-perceived menstrual blood loss ($P < .01$). The majority of adverse events were mild to moderate in severity, and the incidence of gastrointestinal adverse events was comparable with placebo.

Srivaths, Dietrich et al. (2015) patients were randomized to a TA to combined oral contraceptives (COC), each for 3 cycles, with crossover to the second arm after 1-month washout. Nine subjects completed both arms of the study (mean age 14.2 years, range 11.7 to 16.8 years). Eight patients withdrew from the study due to adverse events or noncompliance. Ten patients (58%) experienced adverse events that were possibly drug related (TA: n = 3, 30%; COC: n = 7, 64%). Significant improvement ($P < 0.05$) was demonstrated by TA and COC in MBL (mean Pictorial Blood Assessment Chart score decrease: TA, 536.4; COC, 430.6) and quality of life (mean Pediatric Quality of Life Inventory version 4.0 Generic Scales score increase: TA, 15.6; COC, 16.75), but no significant difference was noted between TA and COC ($P > 0.05$). Length of menstrual cycle for COC had a statistically significant reduction (mean reduction 5.3 days; $P = 0.04$). Reduction in length of menstrual cycle for TA was not statistically significant ($P = 0.18$).

Search Strategy and Results:
("Menorrhagia"[Mesh] OR "menorrhagia"[tiab] OR "heavy menstrua*"[tiab] OR "acute menstrua*"[tiab]) AND (contraceptive*[tiab] OR contraception[tiab] OR "Tranexamic Acid"[Mesh] OR "tranexamic acid"[All Fields] OR "Contraceptives, Oral, Hormonal"[Mesh] OR "Contraceptive Agents, Female"[Pharmacological Action] OR "Contraceptives, Oral, Combined"[Mesh] OR "Contraceptive Agents"[Pharmacological Action] OR "Contraceptive Agents"[Mesh] OR "Estrogens"[Mesh] OR "Estrogens"[Pharmacological Action] OR "Estrogen Replacement Therapy"[Mesh] OR "Progestins"[Mesh] OR "Progestins"[Pharmacological Action])) AND (adolescent*[tiab] OR adolescent[Mesh] OR adolescence[tiab] OR "puberty"[MeSH Terms] OR puberty[tiab] OR pubescent OR pubescence OR teen[tiab] OR teenage*[tiab] OR "youth"[tiab] OR pediatric*[tiab] OR paediatric*[tiab] OR pediatrics[Mesh]) AND ("2006/10/01"[PDat] : "2016/12/31"[PDat])

Studies included in this review:
Lukes, Moore et al. (2010)
Srivaths, Dietrich et al. (2015)

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (RevMan 5.3) was used to synthesize the one included study

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EBP Scholar's responsible for analyzing the literature:
Jeanette Higgins, RN, MSN, CPNP
Kelly Huntington, RN, BSN, CPN

EBP team member responsible for reviewing, synthesizing, and developing this literature:
Jarrod Dusin, MS, RD, LD, CNSC

Specific Care Question: In adolescent patients with heavy menstruation is oral vs. intravenous tranexamic acid better in the resolution of acute bleeding?

Question Originator: Julie Strickland, MD, MPH and Shannon Carpenter, MD, MS

Evidence Summary from The Office of Evidence Based Practice: This study suggests equal efficacy to control post-operative bleeding due to adult total knee replacement surgery between oval and IV TA. Current studies specifically answering this question for heavy menstrual bleeding in adolescent females is unavailable. Current expert consensus, with extrapolation to the care of adolescents with heavy menstrual bleeding supports oral tranexamic acid versus IV tranexamic acid as first line option unless contraindicated.

One study (Fillingham, Kayupov et al., 2016) was identified that compared oral versus intravenous tranexamic acid (TXA) in a double-blinded, placebo-controlled trial, adult patients undergoing primary total knee were randomized to receive 1.95g of TXA orally 2 hours preoperatively or 1g IV bolus before wound closure. Thirty-four patients received oral TXA and 37 patients received IV TXA. There was no difference in the mean reduction of hemoglobin between oral and IV groups (3.45g/dL vs 3.31g/dL, respectively; $P > .001$, equivalence), and total blood loss was equivalent at 1281 mL vs 1231 mL, respectively ($P < .02$, equivalence). Oral TXA provides equivalent reductions in blood loss, at a cost of $14 compared with $47-$108 depending on the IV formulation selected.

Search Strategy and Results:

("Menorrhagia"[Mesh] OR "menorrhagia"[tiab] OR "heavy menstrua*"[tiab] OR "acute menstrua*"[tiab]) AND (contraceptive*[tiab] OR contraception[tiab] OR "Tranexamic Acid"[Mesh] OR "tranexamic acid"[All Fields] OR "Contraceptives, Oral, Hormonal"[Mesh] OR "Contraceptive Agents, Female"[Pharmacological Action] OR "Contraceptives, Oral, Combined"[Mesh] OR "Contraceptive Agents"[Pharmacological Action] OR "Contraceptive Agents"[Mesh] OR "Estrogens"[Mesh] OR "Estrogens"[Pharmacological Action] OR "Estrogen Replacement Therapy"[Mesh] OR "Progestins"[Mesh] OR "Progestins"[Pharmacological Action])) AND (adolescent*[tiab] OR adolescent[Mesh] OR adolescence[tiab] OR "puberty"[MeSH Terms] OR puberty[tiab] OR pubescent OR pubescence OR teen[tiab] OR teenage*[tiab] OR "youth"[tiab] OR pediatric*[tiab] OR paediatric*[tiab] OR pediatrics[Mesh]) AND ("2006/10/01"[PDat] : "2016/12/31"[PDat])

Studies included in this review:
Fillingham, Kayupov et al. (2016)

Method Used for Appraisal and Synthesis:
The Cochrane Collaborative computer program, Review Manager (RevMan 5.3).

EBP Scholar's responsible for analyzing the literature:
Erin Lindhorst, MS, RD, LD

EBP team member responsible for reviewing, synthesizing, and developing this literature:
Jarrod Dusin, MS, RD, LD, CNSC.

Specific Care Question: What is the recommended dose for hormonal treatment of adolescent patients with heavy menstruation?

Question Originator: Julie Strickland, MD, MPH and Shannon Carpenter, MD, MS

Evidence Summary from The Office of Evidence Based Practice:
No current literature could be identified that provided the recommended dose for hormonal treatment of adolescent patients with heavy menstruation. Current dose recommendations are based on Lexicomp® Online (2016).

Search Strategy and Results
'oral contraceptive agent'/exp OR 'contraceptive agent'/exp OR 'estrogen'/exp OR 'estrogen therapy'/exp OR 'gestagen'/exp OR 'tranexamic acid':ab,ti OR 'contraceptive*':ab,ti OR 'contraception':ab,ti'adolescent*':ab,ti OR 'adolesence':ab,ti OR 'teen':ab,ti OR 'teenage*':ab,ti OR 'youth':ab,ti OR 'pubesence':ab,ti OR 'pubescent':ab,ti OR'pediatr*':ab,ti OR 'paediatr*':ab,ti OR 'adolescent'/exp OR 'adolescent' OR 'juvenile'/exp OR 'puberty'/exp OR 'puberty':ab,ti OR'pediatric'

Studies included in this review:
Lexicomp Online®, Pediatric & Neonatal Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; Accessed October, 18, 2016.

Method Used for Appraisal and Synthesis: No appraisal required for this question.

EBP team member responsible for reviewing, synthesizing, and developing this literature:
Jarrod Dusin, MS, RD, LD, CNSC

Specific Care Question:
In adolescent patients with heavy menstruation, does ultrasound vs. no ultrasound result in improved patient diagnosis and outcomes?

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Question Originator:
Julie Strickland, MD, MPH and Shannon Carpenter, MD, MS

Evidence Summary from The Office of Evidence Based Practice:
No current literature could be identified that determined if ultrasound improved diagnosis and outcomes of pediatric patients with heavy menstruation.

Based on expert opinion, it is recommended that a pelvic ultrasound be performed if accompanied by pain or palpable mass (to exclude structural causes, such as fibroids, polyps, and/or ovarian tumors).

Search Strategy and Results:
("Menorrhagia/ultrasonography"[Majr]) OR (("Menorrhagia/diagnosis"[Majr] OR "menorrhagia"[tiab]) AND (ultrasound[tiab] OR "Ultrasonography"[Mesh] OR ultrasonography[tiab])) AND ("2006/10/01"[PDat] : "2016/12/31"[PDat])

Method Used for Appraisal and Synthesis:
No appraisal required for this question.

EBP team member responsible for reviewing, synthesizing, and developing this literature:
Jarrod Dusin, MS, RD, LD, CNSC

Lukes 2010

Methods	Randomized, double-blind, parallel-group study
Participants	**Setting:** 40 clinical sites in the United States **Randomized into Study:** *N* = 196 • **Group 1:** Tranexamic acid (*n* = 123) • **Group 2:** Placebo (*n* = 73) **Completed Study:** *N* = 148 • **Group 1:** Tranexamic acid (*n* = 94) • **Group 2:** Placebo (*n* = 54) **Age, mean years (Standard Deviation):** • **Group 1:** Tranexamic acid 38.7 (6.4) • **Group 2:** Placebo 38.7 (6.8) **Inclusion Criteria:** • Adult women age 18-49 years • History of 3 or more consecutive days of heavy menstrual bleeding over at least 4 of their last 6 menstrual periods • During a 2-cycle pretreatment baseline phase, menstrual blood loss < 60mL during first menstrual period and had to average < 80mL over both pretreatment cycles • Normal findings on pelvic examination • No clinically important cervical cytology abnormalities • No clinically important uterine pathologic findings by transvaginal ultrasonography: Abnormal if, endometrial thickness was greater than 12mm or if the endometrial thickness was 5 to 12 mm and the patients clinical history suggested long-term unopposed estrogen exposure • History of regularly occurring menstrual periods of no more than 10 days in duration and 21-35 days from start of one period until the start of the next menstrual period • Women of childbearing potential who utilize non-hormonal method of birth control • Normal color vision **Exclusion Criteria:** • Endometrial biopsy (warranted for abnormal transvaginal ultra-sonogram) that shows presence of a sufficient number and size of leiomyomas that warrant surgical management • History or presence of significant medical problems (eg, thromboembolic disease, coagulopathy, subarachnoid hemorrhage, endocrinopathy, or ocular disease) • Had severe anemia (hemoglobin less than 8 g/dL) • Pregnant or lactating • History or presence of endometrial abnormalities or cervical carcinoma • Had anovulatory dysfunctional uterine bleeding, metrorrhagia, menometrorrhagia, or polymenorrhea • Glaucoma, ocular hypertension, macular degeneration, or retinopathies **Power Analysis:** Initial power analysis said they needed 92 subjects for treatment group and 46 for Placebo group. A secondary power analysis performed by Data Safety Monitoring

	Board resulted in an increase in the planned sample size to 120 participants in the tranexamic acid treatment group and 64 participants in the placebo treatment group to achieve appropriate power for detecting between-group differences in the pre-specified secondary variables.
Interventions	Women were instructed to begin treatment at the onset of heavy menstrual bleeding and to take the study medication 3 times daily at least 6 hours apart for up to 5 days per cycle over the course of 6 menstrual cycles. **Group 1 (Tranexamic acid)**: Received tranexamic acid (LYSTEDA) 1.3g per dose (two 650mg tablets) 3 times a day equaling a total daily dose of 3.9g. **Group 2 (Placebo):** Received a matching placebo • Participants self-collected and returned all menses captured, and it was measured objectively using a validated alkaline hematin method. • During a two-cycle pretreatment baseline phase, menstrual blood loss was collected. • The change in menstrual blood loss was calculated by subtracting mean blood loss during the two pretreatment cycles from the man blood loss during four of the on-treatment cycles (first, second, third, and sixth cycles). • Secondary outcome measurements included change from baseline in health-related quality-of-life parameters and the occurrence of large blood stains. • Qualitative health-related quality-of-life assessments were based on responses to the MIQ, a disease-specific, validated patient-reported outcome instrument that was completed by participants after all screening and treatment cycles. • Among the parameters measured by the MIQ were limitations on social or leisure activities, limitations on physical activities, limitation in work outside or inside the home, and patient perception of treatment-induced changes in menstrual blood loss. • The number and size of blood stains were recorded by participants in menstrual bleeding diaries.
Outcomes	**Primary Outcome:** Menstrual Blood Loss 1. Significantly greater than that of the placebo group 2. Greater than 50mL from baseline 3. Greater than a reduction in menstrual blood loss previously established to be perceived as meaningful to women (> 36mL; unpublished data) **Secondary Outcome:** Quality of Life 1. Change from baseline in health-related quality-of-life parameters 2. Occurrence of large blood stains
Results	Use of acetaminophen, analgesic opioids, oral iron therapy, and vitamins were permitted throughout study. **Primary Outcome Results:** 1. Tranexamic Acid (Group 1) mean menstrual blood loss of -69.6 mL (40.4% reduction) and Placebo (Group 2) mean menstrual blood loss of -12.6mL (8.2% reduction); p<.001.Tranexamic Acid (Group 1) least-squares mean change in blood loss -66.3mL (38.5% reduction) and Placebo (Group 2) least-squares mean change in blood loss -17.8mL (11.6% reduction); p<.001. 2. Tranexamic Acid (Group 1) had 56% of cycles with a reduction of at least 50mL and Placebo (Group 2) had 19% reduction of at least 50mL; p<.001. 3. Tranexamic Acid (Group 1) had 69% of cycles with clinically meaningful reduction in menstrual blood loss of at least 36mL and Placebo (Group 2) had 29% of cycles with clinically meaningful reduction in blood loss; p<.001 **Secondary Outcome Result (Occurrence of large blood stains):**

	1. The percentage of women who experienced reductions in the number of large stains reported from baseline (large stain responder) was slightly higher among women treated with tranexamic acid than with placebo; however, the difference was not statistically significant

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	A randomization schedule was generated for packaging, labeling, and treatment group assignment using a permuted block randomization scheme.
Allocation concealment (selection bias)	Low Risk	Study drug was individually packaged for each visit and labeled with the study code. The tranexamic acid and placebo tablets were identical in appearance.
Blinding of participants and personnel (performance bias)	Low Risk	Participants, investigators, sponsor, statisticians, clinical data management staff, and clinical monitors were blinded to study group allocation.
Blinding of outcome assessment (detection bias)	Unclear Risk	Authors did not address
Incomplete outcome data (attrition bias)	High Risk	They used a "modified" intent-to-treat population, which included only participants who had sufficient data at baseline and for at least one treatment cycle.
Selective reporting (reporting bias)	Low Risk	Primary and secondary outcomes were reported on.
Other bias	Low Risk	The study appears to be free of other sources of bias.

Srivaths 2015

Methods	Randomized Crossover Trial
Participants	**Setting:** USA, Texas Children's Hospital hematology or gynecology clinic **Number randomized:** 17 **Number who completed the study:** 10 completed the TA (tranexamic acid) and 11 completed the COC (combination oral contraceptive) arm **Gender:** 0 males **Age:** mean age 14.2 years (range 11.7 to 16.8 years) **Inclusion criteria:** Postmenarchal girls aged 21 years or younger with HMB (heavy menstrual bleeding) including both menorrhagia and menometrorrhagia with PBAC (pictorial blood assessment chart) score greater than 100 for 2 consecutive cycles, normal pelvic ultrasound that excluded pelvic pathology that can cause HMB within 12 months, normal external genitalia examination and

	normal TSH within 6 months, and a negative urine pregnancy test within 4 weeks, before study participation. **Exclusion criteria:** the presence of an intrauterine device, presence of a diagnosed bleeding disorder based on a comprehensive hemostatic laboratory workup including complete blood count, prothrombin time, partial thromboplastin time, fibrinogen, von Willebrand panel and platelet function analysis or platelet aggregometry, intake of medications and herbal products with increased risk of bleeding, sexually active status, and a body weight less than 40 kg.
Interventions	**Group A** received oral TA (tranexamic acid) at 1300 mg TID days 1-5 on menstrual cycle for 3 consecutive cycles. **Group B** received COC (Combined oral contraceptive pills) with 3 weeks of hormonal pills and 1 week of placebo pills for 3 consecutive cycles. Each medication was prescribed for 3 menstrual cycles with a 1 month washout between medications. Subsequently, the groups crossed over; group A patients, who initially received TA, crossed over to receive COC; and group B patients who initially received COC, then received TA.
Outcomes	Menstrual cycle length, PBAC scores for MBL (menstrual blood loss) estimation, and QOL (quality of life) assessment with the PedsQL instrument (The Pediatric Quality of Life Inventory version 4.0 Generic scales score) were obtained at baseline and at the end of each medication arm.
Notes	Significant improvement (P <0.05) was demonstrated by both TA and COC in reduction of MBL and QOL. Although there was a trend for greater reduction of MBL with TA from baseline compared with COC, this was not statistically significant. QOL improvement was similar for both medications. There was statistically significant reduction in length of menstrual cycle compared with baseline on COC only. Although the menstrual cycle length was reduced from baseline to end of therapy on TA this was not statistically significant (P=.18). There was statistically significant differences between TA and COC in MBL reduction as measured by PBAC scores or improving QOL. Of note, patients on TA reported 100% compliance, while 57% on COC reported periods of non-compliance. 10 patients (58% out of the original 17) experienced adverse events that were possibly drug related, 2 on TA, and 8 on COC.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomized manually by blinded draw of cards labeled with study arms, to 1 of 2 treatment groups, group A versus group B.
Allocation concealment (selection bias)	Unclear risk	Author did not report
Blinding of participants and personnel (performance bias)	Unclear risk	Author did not report
Blinding of outcome assessment (detection bias)	Unclear risk	Author did not report

Incomplete outcome data (attrition bias)	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Low risk	Author reported all outcomes
Other bias	Unclear risk	None

Fillingham 2016

Methods	A single-center, prospective, double-blinded, randomized, placebo-controlled trial
Participants	**Setting:** Department of Orthopedic Surgery and Department of Anesthesia, Rush University Medical Center, Chicago, Illinois **Randomized into study:** • **Group 1:** Oral Tranexamic Acid *n* = 40 • **Group 2:** IV Tranexamic acid *n* = 38 **Completed Study:** • **Group 1:** Oral Tranexamic Acid *n* = 34 • **Group 2:** IV Tranexamic Acid group *n* = 37 **Gender, males:** • **Group 1:** *n* = 13 • **Group 2:** *n* = 11 **Age, years (mean):** • **Group 1:** 62 (11) • **Group 2:** 63 (10) **Inclusion Criteria:** • Patients, male or female, undergoing a Total Knee Arthroplasty (TKA). **Exclusion Criteria:** • Patients were excluded if they had a known allergy to TXA, history of renal failure or kidney transplant, a history of arterial thromboembolic event (eg, myocardial infarction, stroke) within the past year, placement of an arterial stent within the past year, a history of thromboembolic event, or refusal to receive blood products. **Power Analysis:** It was determined that 58 total subjects were needed.
Interventions	• **Group 1: Oral TXA:** 1950mg TXA (3 tablets of 650mg) plus placebo of 10ml normal saline • **Group 2: IV TXA:** 1 g TXA (diluted in 10ml normal saline) plus 750mg of ascorbic acid (3 tablets of 250mg)2 **Group 1** was given the tablets approximately 2 hours before incision and was given the placebo immediately before wound closure. **Group 2** was given the IV TXA immediately before wound closure and received the ascorbic acid approximately 2 hours before the incision.
Outcomes	**Primary outcome(s):** • Postoperative drop in hemoglobin **Secondary outcome(s)**

	• Postoperative blood loss, postoperative hemoglobin loss, drain output, number of blood units transfused, length of hospital stay, and thromboembolic events
Results	**Cost Savings Report:** • Oral TXA provides equivalent reductions in blood loss, at a cost of $14 compared with $47-$108 depending on the IV formulation selected. • As approximately 700,000 primary TXA are performed in the United States annually, a switch to oral TXA could yield a total cost savings of between 23 million and 67 million dollars per year for our health care system. • When accounting for all hospital costs including operating room, laboratory, transfusion, room and board, and pharmacy costs, the authors found the use of TXA reduced costs by $879 per patient. • The authors noted two different power analysis numbers in the study. 29 participants per group were noted in 1 section of the study and 30 participants per group were noted in another section of the study. **Table 2 report:** • Group 1 had a 3.45 g/dL reduction in hemoglobin, while group 2 had a 3.31g/dL reduction. Overall P-Value of .0001. • Group 1 had a total blood loss of 1281ml. Group 2 blood loss was 1231ml. P-value of .02. • Group 1 had a 177g total hemoglobin loss. Group 2 had 168g loss. P-value of .01. • Group 1 had 301ml of drain output. Group 2 had 288ml of drain output. P-value of .83. • Groups 1's rate of transfusion was 2.9%, while group 2's was 2.7%. P-value of .99. • Group 1 had a hospital stay of 3 (1) days. Group 2 had a stay of 3 (1) days. P-value of .99.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The researchers state that patients were randomly allocated between the 2 treatment groups of oral and IV TXA using a random number algorithm to provide a binary output to assign the patients treatment.
Allocation concealment (selection bias)	Low risk	The article states group assignments were prepared by research assistant and were kept blinded from the study participants and clinical staff involved in decisions regarding study outcomes. Research pharmacists, not involved in patient care, prepared the study medications and placebos to ensure identical appearance and blinding between the medications and placebos.
Blinding of participants and personnel (performance bias)	Low risk	All study participants, surgeons, and clinical staff participating in treatment were blinded to the study group allocation throughout the study period.

Blinding of outcome assessment (detection bias)	Low risk	All study participants, surgeons, and clinical staff participating in treatment were blinded to the study group allocation throughout the study period.
Incomplete outcome data (attrition bias)	Low risk	All outcome measures were recorded within the results sections under "primary outcome measures" and "secondary outcome measures." The article noted that all outcome measures were recorded after the patient has been discharged from the hospital by a research assistant, who was not involved in the clinical management of the study participants.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were clearly noted within the results section of the article.

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Appendix A

Education Material

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Medicine to Treat Heavy Menstrual Bleeding

Females who have problems with heavy periods (heavy menstrual bleeding also known as menorrhagia mene raj e), may need medication to help with getting a period to stop or slow down the bleeding. There are several options that may be offered to you. Please understand, not all options are available to everyone for a lot of different reasons.

One option that you may be asked to try is called Lysteda. Lysteda is not a hormone, and only has to be taken when your period starts. This is a nice option for some, so that you don't have to take a medicine all the time. Lysteda also lets the health care team to be able to get more blood work later, if it is needed. When hormonal medications are used, often more blood work may be harder to be used to diagnose a problem.

Another option is hormonal medications. Your body naturally makes hormones such as estrogen and progesterone. Sometimes your health care team may have you take medications that have these hormones in them. When the hormones are given as a medication, they help to take over for your body's hormones and can help control your bleeding.

If you are given a prescription for a medication, please be sure to take it as you were told. It is very important that you don't suddenly stop, or just not take it all.

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Heavy Menstrual (Vaginal) Bleeding

Heavy periods in teen girls can occur one time, or very often. This is also known as menorrhagia (mene raj e), but now it is mostly called heavy vaginal bleeding.

Heavy vaginal bleeding is described as having a period that lasts more than 7 days, changing a pad or tampon hourly, passing clots (clumps of blood), bigger than 1 inch. There have been a lot of people studying about this, and there is a chart that we use sometimes to help us know how much of a concern this heavy bleeding will be for you. You may be given this chart and asked to fill it out, and bring it back with you to a clinic appointment. If you are asked to do this, it is very important that you complete it and bring it to your next clinic appointment.

There are some concerns for females with heavy vaginal bleeding. One of the concerns is that you have a bleeding disorder. A bleeding disorder is when there is a delay in your blood clotting. Some bleeding disorders are very mild and might not be known until periods start. Other bleeding disorders can be more severe and need more help and more clinic visits. In order to find out if you have a bleeding disorder, blood work may need to be done. Sometimes, that blood work has to be done more than once.

If you don't have a bleeding disorder, your heavy bleeding might be because you don't have a monthly period, and the lining of your uterus is built up. In that case, medication might be very helpful for you. In this case, you may or may not need medicine, but this is something you and your provider can decide together.

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References

Brouwers, M. C., et al. (2012). "The Global Rating Scale complements the AGREE II in advancing the quality of practice guidelines." Journal of clinical epidemiology **65**(5): 526-534.

Buggy, F., et al. (1994). "The effect of tranexamic acid on measured menstrual loss and endometrial fibrinolytic enzymes in dysfunctional uterine bleeding." Acta obstetricia et gynecologica Scandinavica **73**(3): 274-277.

Cinicinnati Childrens Hospital Medical Center. (n.d.) Retrieved October 28, 2016, from https://www.cincinnatichildrens.org/service/j/anderson-center/evidence-based-care/recommendations/topic

Fillingham, Y. A., et al. (2016). "A Randomized Controlled Trial of Oral and Intravenous Tranexamic Acid in Total Knee Arthroplasty: The Same Efficacy at Lower Cost?" The Journal of arthroplasty.

Lethaby, A., et al. (2013). "Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding." The Cochrane Library.

Lukes, A. S., et al. (2010). "Tranexamic acid treatment for heavy menstrual bleeding: a randomized controlled trial." Obstetrics & Gynecology **116**(4): 865-875

Royal Children's Hospital Melbourne. (n.d.). Retrieved October 28, 2016, from http://www.rch.org.au/clinicalguide/guideline_index/Adolescent_Gynaecology_Menorrhagia/

Srivaths, L. V., et al. (2015). "Oral tranexamic acid versus combined oral contraceptives for adolescent heavy menstrual bleeding: a pilot study." Journal of Pediatric and Adolescent Gynecology **28**(4): 254-257.