Tranexamic Acid to Reduce Contraceptive-related Bleeding Side Effects

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Background:

Side effects and health concerns are frequently cited as a reason for non-use of hormonal contraceptive methods. This BoW seeks to describe the current state of provision and use of adjunct therapies to manage bleeding effects (the leading cause of discontinuation for progestin-only injectables and implants) and define the opportunity for further investment in these therapies to impact contraceptive use rates. Initial exploratory work will support a decision on whether to invest in clinical testing to inform guidelines and/or bring a product to market registered for the treatment or prevention of bleeding irregularities associated with progestin-only methods. The goal is to improve voluntary uptake and/or continued use of progestin-only contraceptive methods through strong evidence, changes to clinical guidelines, and access to adjunct therapies.

The etonogestrel (ENG) subdermal contraceptive implant (ENG implant) is a highly effective method of preventing pregnancy for up to 5 years. Given that the ENG implant is 20 times more effective at pregnancy prevention than oral contraceptive pills, strategies to increase its acceptability will translate into improved prevention of unplanned pregnancies. The primary reason for dissatisfaction and discontinuation of the ENG implant are the contraceptive induced menstrual changes (CIMC) that include irregular, bothersome bleeding.[1] While, many medications have been studied to treat CIMC caused by progestin-only contraceptives, most have been only marginally effective or have other draw backs.[2–5] Concurrent use of oral contraceptives (OCs) with the implant does stop bleeding but bleeding returns when OCs are stopped and continued usage of an OCP may not be acceptable or may be medically contraindicated for some patients.[4,6] A short course of the selective estrogen receptor modulator (SERM), tamoxifen, demonstrates a sustained reduction in bleeding in users of the implant.[2,7] However, tamoxifen carries a small increased risk of venous thromboembolism (VTE) with continuous use and its use in cancer care makes many concerned about using it.

Tranexamic acid (TXA) is an antifibrinolytic drug that has proven efficacy for heavy menstrual bleeding and obstetric hemorrhage.[8,9] TXA reversibly blocks the lysine binding site on plasminogen preventing plasmin from conversion of plasminogen to plasmin and subsequent plasmin degradation of the fibrin clot. In people with heavy menstrual bleeding, the excess bleeding is hypothesized to be related to the critical role of endometrial fibrinolytic enzymes and menstrual hemostasis, tissue shedding and repair. In the case of CIMCs, progestins down regulate estrogen receptor in the endometrium. As results, proliferative activities are inhibited and instead both glands become underdeveloped and eventually atrophic. Meanwhile, vessels have been shown to be thin-walled, ectatic and dilated with abnormal density—in short vascular formulation and vascular structures are pathologic with the end result of angiogenesis, “leaky” fragile vasculature and “break through bleeding”. This bleeding in turn activates the clotting cascade and thrombin formation thus a plausible mechanism for TXA to decrease CIMCs is through stabilization of the thrombin clot in microvasculature.

Due to its clear mechanism of action, TXA has been widely studied and utilized to manage various forms of obstetrical and gynecological hemorrhage including both acute and chronic bleeding.[10] TXA is available in both oral formulation and parental formulations and because of a relatively short half-life (2-11 hours), TXA is often dosed three times daily or even four times daily.[11] Food intake had no influence on TXA pharmacokinetics which also makes its less challenging for actual use.

TXA has been extensively studied for heavy menstrual bleeding (HMB) and currently FDA approved for this purpose under a regimen of 1300 g three times daily for up to 5 days during a heavy bleeding episode. Overall menstrual bleeding is reduced by 40-60% in these TXA studies.[12,13] In contrast to the significant number of studies evaluating TXA for HMB, few studies exist for TXA and CIMC. One depot medroxyprogesterone acetate study showed both significant improvement in bleeding while on a TXA 250 mg four times daily regimen as well as a higher likelihood of a 20 day bleeding-free interval compared to control.[14] Another study with the levonorgestrel implant (Norplant) and TXA (500 mg, twice daily for 5 days), demonstrated a high rate of cessation of bleeding while it is being used, but no extended benefit or significant overall reduction in bleeding.[15] No studies exist for TXA and CIMC bleeding associated with the ENG implant. Given the differences in both progestin steroid as well as the unique steady state pharmacokinetics of the slow releasing ENG implant, we do not know what the efficacy of TXA will be for managing ENG implant related bleeding.

TXA is well tolerated, widely available, inexpensive and is typically used for a short course of treatment that can be safely repeated; in the case of heavy menstrual bleeding, it is repeated monthly. **In order to determine if TXA is an efficacious treatment for CIMC due to the ENG implant, we propose a double-blind randomized clinical trial to evaluate TXA 1300 mg TID x 5 days as compared to placebo in users experiencing irregular bleeding. And if a positive impact on bleeding is found, then we will perform a subsequent trial investigating TXA over 90 days instead of the initial 30-day pilot.**

We expect that these studies will determine if TXA is efficacious as a treatment for CIMC for users of the ENG-implant experiencing significant problematic bleeding. Due to the likely shared pathophysiology of CIMC, these results could also guide clinical practice and research for CIMC due to any progestin-based contraceptive method such as injectables, hormonal IUDs or pills or any level of CIMC whether problematic or just bothersome.

Objectives:

To determine if TXA is a safe and effective treatment for troublesome bleeding and spotting in users of the ENG contraceptive subdermal implant.

Study Arms (randomized to treatment):

- TXA 1300 mg oral TID x 5 days
- Placebo

Primary Hypothesis:

In ENG implant users who report either a frequent or prolonged bleeding patterns, treatment with 1300 mg oral TID x 5 days (the current FDA-approved regimen for heavy menstrual bleeding) will result in more bleeding/spotting-free days than placebo in a 30-day reference period.

Study Design:

We are proposing a randomized, double-blind placebo-controlled clinical trial over a 30-day reference period for treatment of individuals seeking care for bothersome bleeding while using the ENG contraceptive implant.

The primary outcome of the study will be the total number of amenorrhea days in a 30-day reference period. The study has a number of secondary outcomes (see below, study objectives) focused around the efficacy of oral TXA to stop bleeding/spotting and for how long.

The study will evaluate TXA 1300 mg oral TID x 5 days. The first dose will be taken at the start of enrollment if the participant is on the 3rd day of active bleeding or if not bleeding, on day 3 of the next bleeding episode.[7] The study will be conducted at Oregon Health & Science University (OHSU) in Portland, Oregon

Each participant's involvement will be up to approximately 60 days as study drug will not be initiated at the time of enrollment unless they are experiencing bleeding/spotting that day plus two days prior to enrollment. Study drug will be started on the 3rd day of an active bleeding/spotting episode, which will serve as the first day of the 30-day reference period. If no active bleeding episodes happen in the first 30 days from enrollment then the participant will be withdrawn from the study. Our prior studies[7,16] have utilized these same strategies: 1) to confirm an eligible pattern of bleeding/spotting, 2) stringent screening practices to ensure enrollment of individuals with significant bleeding patterns. These practices combined with the use of a randomized double-blind study design aids in decreasing the risk of hindsight bias – a bias the affects many non-randomized trials of treatments for implant bleeding as the bleeding pattern starts and stops intermittently at random and thus many incorrectly attribute the cessation of bleeding to the treatment. We have only had to withdraw 1-2 participants who had no bleeding events over 30-days in prior studies. The study will consist of 3 in-person study visits [screening (V1), enrollment (V2), and a close out visit or study exit (V3)], as well as a daily response to a text or email message about bleeding and use of study medication. Additional phone and email contact may occur with the participant to ensure clarity of diary entry or completion, to ensure drug initiation and compliance, or to address questions/concerns of participants. The electronic diary only takes a few seconds to complete and we have had good success with very little missing data in studies where we have used it.

Data for this project will be stored in OCTRI's installation of REDCap, a highly secure and robust web-based research data collection and management system.
Features of REDCap that protect participants' privacy and data security include:

- Physical Security: OCTRI's REDCap software is housed on servers located in ITG's Advanced Computing Center providing locked physical security
- Electronic Security: The REDCap servers are housed behind both the OHSU firewall and a second ACC firewall. All transmissions of data from the application are encrypted over HTTPS with the industry standard TLS 1.2/1.3 protocol (AES 256-bit encryption).
- Controlled User Access: REDCap employs a robust multi-level security system that enables researchers to easily implement "minimum necessary" data access for their research staff, including specification of data fields that are identifiers. This feature includes "single click" ability to provide completely deidentified (removing all identified data fields and shifting dates) for analysis or other purposes. User activities are logged to enable auditing of all data access. Access is integrated with OHSU's network such that users who are also OHSU employees are authenticated against their OHSU network credentials.
- Data Integrity: REDCap is jointly managed in accordance with OHSU Information Security Directives by ACC staff and members of OCTRI's Biomedical Informatics Program, ensuring fidelity of database configuration and back-ups. User activities are logged to enable auditing of all data changes.

Study Population:

Our primary outcome is the total number of amenorrhea days in a 30-day reference between TXA and placebo groups. Our prior tamoxifen study demonstrated a 5-day difference in overall amenorrhea days in the first 30-day reference period.

A sample of 24 participants per group (n = 48 total) will provide more than 80% power to detect a mean 5-day difference between the TXA treatment and placebo groups. This power calculation assumes a two-sample t-test with a significance level of 0.05 and a common standard deviation of 6 days based on our previous study of CIMC treatment in a 30-day reference period (https://pubmed.ncbi.nlm.nih.gov/37116825/). If the assumptions for parametric testing are not met, this sample size will still provide adequate statistical power to detect the same difference using Wilcoxon's rank-sum test. To account for drop out, individuals with more than 3 doses of missing diary data or those who deviate from the protocol (non-adherent to treatment), we have increased the sample size for a total sample size of up to 80. This accounts for participants who did not experience a bleeding episode while on study and therefore did not take study drug. It allows for complete data of 48 participants who have confirmed treatment adherence and qualifying bleeding. Once 48 participants meeting those criteria have completed treatment enrollment will end.

Inclusion Criteria

- English or Spanish speaking women 15-45 years of age in good general health currently using the ENG implant who have experienced frequent or prolonged bleeding while using the device:
    - To be eligible, women will need to have >7 days of continuous bleeding/spotting in the last 30 days, OR 2 or more episodes of bleeding/spotting in the last 30 days.
- Implant use for at least 30 days prior to screening visit.
- Willing to continue using the implant for at least 30 days from study enrollment.
- Access to a reliable cell phone and must be willing to receive and respond to a daily text or email message to assess bleeding and use of study drug
- Implant must be palpable to prove that an ENG implant is in place at time of screening and enrollment.
- Negative gonorrhea/chlamydia screening performed at screening visit

Exclusion Criteria

- Centers for Disease Control Medical Eligibility for Contraceptive use category 3 or 4 for contraceptive usage
- Currently pregnant
- < 6 months postpartum, < 6 weeks post abortion, not breast/chest feeding (cessation of lactation at least 6 weeks prior to enrollment)
- Undiagnosed abnormal uterine bleeding pre-dating placement of contraceptive implant
- Bleeding dyscrasia
- Anticoagulation use
- Active cervicitis
- Allergy to TXA
- Known renal insufficiency
- History of venous thromboembolism
- Current or past breast or uterine malignancy
- Concurrent use of P450 pathway inducing drug
- Implant is due to be switched out in 2 months or less from enrollment
- Routine or chronic use of non-steroidal anti-inflammatory drugs (NSAIDs once daily or more >=14 days/month)

- Currently using oral contraceptives in addition to implant (to be eligible, needs to have a 4-6 week washout period)
- Prior pregnancy occurred while Nexplanon/Implanon was in place
- Chronic use of Cannabidiol, THC, or marijuana (>3 times per week). Of note, patients could have used Cannabidiol, THC, or marijuana chronically in past, but must have a washout time period of no use for at least one month prior to the study.
- Chronic use of cigarettes (>1 cigarette per week). Of note, patients could have used cigarettes chronically in past, but must have a washout time period of no use for at least six months prior to the study.

Vulnerable Populations

This study will not recruit or enroll vulnerable populations. Neonates, children and pregnant women are specifically excluded. Decisionally impaired individuals and prisoners will also be excluded.

Setting

This study will be conducted in the OHSU Women's Health Research Unit (WHRU).

Recruitment Methods

We will recruit from the Portland Metropolitan area. The OHSU WHRU has a dedicated recruitment specialist and our research team has successfully recruited subjects for treatment of implant related bleeding. We will utilize our normal recruitment efforts which include but are not limited to flyers, social media advertisements, the CWH webpage/WHRU contact form, the OHSU Study Participation Opportunities webpage, O2 promos, EPIC cohort discovery and a research listserv. We will also utilize a platform specific to clinical trial recruitment, BuildClinical LLC, for which we have obtained a professional service contract. BuildClinical advertisements will run on digital ad platforms such as: Facebook, Instagram, TikTok, Twitter, Snapchat, YouTube, Google Search, Bing Search, dating applications, etc. These recruitment materials are included in the study related documents for IRB approval.

Individuals who express interest in participating will be telephone screened to assess initial eligibility. A telephone screening script is included in the recruitment materials for this study. This will allow study staff to contact potential participants about the study. In order to collect protected health information (PHI) prior to participants signing consent, a Waiver of Authorization (WoA) will be requested. Participants will also be asked whether or not they prefer to receive a secure or non-secure emails from the study team. Secure emails would be sent when message includes PHI while non-secure would be for study visit reminders.

To further encourage recruitment we will compensate participants for their time. We will use the 'ClinCard' debit card system to provide compensation. Compensation will be prorated to support study completion and compliance.

Consent Process

All study procedures will be approved by the Oregon Health & Science University (OHSU) Institutional Review Board. Individuals will be screened for eligibility and if they meet the basic criteria and agree to participate, they will undergo informed written consent. Study participants may also be asked to review the consent with study staff virtually in order to limit time spent in clinic during the COVID-19 pandemic. In this case, a copy of the consent form will be emailed to study participants prior to the consenting process. After fully reviewing the consent with a participant and answering all study-related questions, study staff will note on the verbal consent memo both the date and time that the virtual consent was obtained or denied. In the case that verbal consent is given, participants

will wet-sign the consent form and the attestation of verbal consent memo when coming in for required in-person activities.

The protocols and consent will be reviewed and approved by the OHSU IRB prior to initiation of the study. Information we collect and create in order to conduct and oversee this research study may be stored in the Women's Health Research Unit repository (IRB# 6748) for possible future research if the participant opts to participate in the repository

Repository

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Procedures Involved:

Screening (Visit 1, V1). Estimated 1 hour

Eligibility and study consent will be signed at this visit. Baseline demographic, health and behavioral information will be collected by interview, including menstrual history, contraception history including timing of implant placement, sexual and pregnancy history, BMI/weight, ethnicity, age, and baseline use of panty liners (This is included as use or need of a panty liners or sanitary protection is part of the definition for "bleeding" and thus this becomes confounding in women who already use such a product at baseline).[17] A series of questions will be asked to retrospectively quantify number of bleeding and spotting days and frequency and duration of bleeding episodes over the preceding three months of implant use (or since placement, if less than three months, with at least one month of usage). Current implant use will be confirmed via palpation.

Physical exam including blood pressure check, pelvic examination, urine pregnancy test, cervical cytology evaluation (if not completed within the ASCCP recommended screening interval), and testing for gonorrhea and chlamydia. A baseline assessment of satisfaction with baseline bleeding pattern will also be performed using a Likert scale-based question ("how satisfied are you with your current bleeding pattern while using the Implant").

Once negative results from the participant's gonorrhea and chlamydia testing are demonstrated, visit 2 can be scheduled (enrollment).

Enrollment (V2), estimated 30 minutes

This visit could be combined with the screening visit. Pregnancy test will be performed. If negative, randomization will occur at this visit. The Study Drug Information Handout will be provided and explained. Study drug will be provided and the participant will be instructed to only start study drug at this visit if they are experiencing an active bleeding episode and this is the 3rd day of bleeding/spotting. Study coordinator will instruct how to start tracking bleeding via text message. Participants will receive training on the use of the electronic bleeding diary procedures. This includes instruction on use of the text message bleeding diary.

End of study (V3), estimated 30 minutes

The final visit will take place approximately 60 days after enrollment or at the time of study withdrawal/exit. Repeat STI testing only if indicated by a change in partners during the study. Vital signs will be performed and a review of bleeding diary, medications, AEs, and health changes. A short satisfaction questionnaire will be performed. Participation is complete after this visit. Unused study drug will be returned at these visits.

Visit	Details
Visit 1-Screening	• Informed consent • Baseline interview • Review current medications • Confirm implant use • Physical exam with vitals (blood pressure, pulse, weight, height) • Urine pregnancy test • Review eligibility criteria • Gonorrhea and chlamydia test • Pap (if indicated) • Baseline questionnaire
Visit 2– enrollment	• Review bleeding diary instructions with staff • Review medications • Vitals (blood pressure, pulse, weight, height) • Confirm implant use • Urine pregnancy test • Receive placebo or study drug and instructions • Review any health changes
Visit 3- end of study	• Urine pregnancy test if indicated • Repeat Gonorrhea and chlamydia test if change in partner occurs during study. • Review medications • Return any unused medication • Vitals (blood pressure, pulse, weight, height) • Confirm implant use • Review bleeding diary with staff • Review health changes • Exit questionnaire

Description of intervention/study drug

Participants receive study drug at enrollment. We will instruct participants to start study drug the next time they experienced three consecutive days of bleeding or spotting (initiating drug on the third day) or immediately if they have bleeding or spotting for at least consecutive 3 days at the time of enrollment, and to complete the full 5-day treatment regardless of subsequent bleeding patterns. If participants report no bleeding or spotting in the first 30 days after enrollment, we will withdraw the participant from the study. At follow up visits, participants will return unused drug and counts will be compared to reports. We will also collect information on side effects.

The OHSU research pharmacies will maintain the computer-generated randomization scheme and treatment assignments in a locked database and assigned the intervention during the enrollment visit in a 1:1 fashion in block sequence determined by the research pharmacy. Study staff and participants will be masked to treatment assignments. The randomization code will only be broken after completion of all data collection and entry or in the case of an adverse event and deemed necessary by the Data Safety and Monitoring Board.

Failure to complete the texting diary (see below) will prompt a phone call or email from the study coordinator. If we are unable to reach a participant by phone, email, letter over a 2-week time period, their participation will be terminated. Any data obtained up to this point will be analyzed in accordance to with intention to treat for time to event analyses.

Study procedures and data collection other than side effects and AEs will last 30-days from first day of study drug.

Bleeding Diary:

We plan to use an automated daily text message service (Mir3, San Diego, CA, USA) to collect daily data bleeding beginning on the day of enrollment with paper diaries as a back-up form of data collection if the text message-based data is incomplete. We have successfully used this text message service with other previous studies. We will define bleeding as a day that required the use of protection with a pad, tampon, or liner, spotting as a day with minimal blood loss that did not require the use of any protection, and amenorrhea as a day without bleeding or spotting.[2] For missing data, we will use the following rule: if bounded on both sides by no-bleeding days, we considered the day a no-bleeding day. If bounded on one or either side by a bleeding or spotting day, we coded the missing days to match the surrounding days. Our previous study experience demonstrates high participant compliance with the text-message diaries and rare missing data.[2] In cases with missing data that cannot be imputed using the approach outlined above, we will use multiple imputation to impute any potential missing data, categorizing days with missing values as bleeding or non-bleeding days.

Outcomes:

Primary outcome:

- **Total number of amenorrhea days in a 30-day reference period between treatment and placebo**

Secondary objectives:

- **Each 30-day reference period outcomes between treatment and placebo (double blind placebo-controlled RCT):**
    - Total number of bleeding/spotting days
    - Total number of consecutive bleeding/spotting-free (amenorrhea) days
    - Total number of spotting days
    - Total number of bleeding days
    - Total number of bleeding days while on active treatment
    - Time (days) to 3 consecutive days without bleeding/spotting
    - Time (days) to 5 consecutive days without bleeding/spotting
    - Time (days) to restart bleeding/spotting after completing treatment

- **Overall outcomes:**
    - Drop out
    - Patient satisfaction with bleeding pattern
    - Continuation of implant or anticipation of continuation
    - Acceptability/satisfaction with study drug
    - What treatment group participants think they are in and why
    - Side effects/adverse events

Analysis Plan

Our primary analysis will be based on intention-to-treat (ITT) for all participants who complete the 30-day reference period. We will compare treatment groups using student's t-test for normally distributed continuous outcomes. If assumptions for parametric testing are not met, we will use Wilcoxon's rank-sum test instead. We will use Pearson's chi-squared or Fisher's exact test, as appropriate, to compare categorical outcomes (e.g., plans for

implant continuation). For time-to-event outcomes, we will create Kaplan-Meier curves and compare groups using the log-rank test, including data from all participants regardless of completion status.

We will also perform a secondary per protocol analysis, excluding participants who missed more than 3 pills over the 5-day treatment period. Additionally, we will compare participants with perfect adherence to those with any missed pills, and assess potential differences between groups, with the understanding that we may not achieve statistical power to detect significant differences.

Finally, we will perform two sensitivity analyses: 1) excluding any participants who did not provide study staff with missing bleeding diary information within one week of the missing date to minimize the potential impact of recall bias, and 2) excluding any participants whose implants have been in place for less than 90 days. Based on our previous study using a similar design, we expect to have sufficient statistical power to detect between-group differences for both sensitivity analyses, as we experienced low numbers of participants meeting these exclusion criteria. If treatment groups differ by key baseline characteristics (baseline bleeding, age, BMI), we will also consider using multivariable regression models (linear, Poisson, or negative binomial, as appropriate based on data distributions) adjusted for these characteristics, with the understanding that we may not have statistical power given the sample size. However, the planned randomized design and our previous work suggest that groups will not be meaningfully different.

Sharing of Results with Subjects

We will share with subjects the results of their screening pap test, if performed, and/or STI tests. These tests will be performed by the CLIA-certified OHSU CORE Lab. Results will be placed in their OHSU medical record. We will also share the results of subject pregnancy tests done throughout the study.

Privacy, Confidentiality, and Data Security:

Participants will be contacted by the study team only if they have contacted our recruitment team for information regarding the study. They will have as much time as they need to review the consent form and for counselling with study staff about the nature of the project. They will retain the right to opt out of participation at any time without compromising medical care.

Confidentiality of personal health information will be maintained according to HIPAA requirements for research. All participants will be assigned a study ID at the screening visit to which all subsequent data will refer. Personal identifiers will not be on questionnaires, data, abstract sheets, or in the main database. All data will be kept in locked files or a password protected computer in secure area with limited access. Only the study investigators and staff will have access to these files. No identifying information will be included in the storage, use, or transfer of specimens or during statistical analysis.

If any safety/privacy concerns arise, a data safety monitoring board will be convened to review the study. An independent chart audit by a qualified individual will be performed after the first 5 participants have been enrolled and then at regular 6 months intervals to ensure data integrity and completeness.

Provisions to Monitor the Data to Ensure the Safety of Subjects:

Dr. Edelman will be identified lead PI overseeing the overall clinical aspects of the study procedures detailed in this proposal with Dr. Han the identified co-PI leading the basic science aspect of the sample analysis. Drs. Edelman and Han are experienced clinical investigators and practicing physicians. The coPIs will adhere to IRB policies regarding protection of human subjects and the reporting of study deviations and adverse events. In the rare case of a

serious adverse event, the OHSU WHRU data safety monitoring board (DSMB) will be activated to review the event and rule on a course of action. The WHRU DSMB is made up of individuals knowledgeable about women's reproductive health and therapies and will have no conflict of interest with the study or its outcomes.

The PIs will also oversee study procedures to ensure they are being carried out per the approved protocol. They will closely supervise conduct of study visits and will communicate with study staff frequently. The PIs will also conduct initial assessments and periodic assessments of the study and its procedures. Participants who appear to be experiencing an adverse event requiring clinical care will be referred back to either their identified health care provider or to the health system in which the PIs are located and will make direct contact with the provider seeing the patient to ensure that they have the appropriate information necessary to treat the patient. If incidental findings are discovered on screening evaluations, the patient will be informed and referred to their primary provider, or if they have no primary provider, a list of referral providers will be given to them.

The PIs and study staff are responsible for recording data and verifying data accuracy throughout the study. The PIs will conduct an in-depth review of the data upon completion of each subject and again at the conclusion of the clinical study.

Risks and Benefits:

This proposal includes a randomized clinical trial. Participants will be randomized to placebo or two doses of study drug. Study subjects will undergo some or all of the following procedures and exams:

- Daily diary collection
- Self-collection of urine sample at research clinic in order to perform urine pregnancy testing

Risks to Subjects

Study drug: With TXA there is a theoretical risk based on mechanism that it could increase the risk for venous thromboembolism. However, in its current applications where it is most widely used there is no increased risk found with TXA usage.[20] In many countries TXA is an over the counter medication sold for the treatment of heavy menstrual bleeding (e.g. UK and Japan).

Urine collection and pregnancy testing: There are no known harmful effects from obtaining a urine pregnancy test but there might be emotional distress if the test is positive or false positive. Patients will be referred to appropriate clinical treatment if a positive test occurs while on study – which would be unusual given the high efficacy of both of these contraceptive methods.

Potential Benefits to Subjects

There are no direct benefits to study participants. We have crafted a study protocol with attention to patient safety and utilizing a study medication with a good safety profile at its approved FDA dose.

This study will increase the knowledge regarding improving the acceptability of a highly effective contraceptive method. It may help to increase awareness regarding an additional health concern specific to certain individuals using these methods of contraception which when left untreated do increase the risk of dissatisfaction and discontinuation. It may go beyond the identification of a problem, but also help in providing the potential mechanism of action and intervention for this phenomenon.

Drugs or Devices:

We are using the FDA approved doses in a population of health individuals with no contraindications to use of these drugs. Women will undergo screening for any known contraindications to the study drugs prior to any drug exposure. Research Pharmacy will not be utilized; the contraceptive implants and injectable will be obtained through Outpatient Pharmacy.

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