Protocol: A randomized controlled trial of three prophylactic antibiotic regimens for first trimester surgical abortion

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A randomized controlled trial of three prophylactic antibiotic regimens for first trimester surgical abortion

Fellow: Diane Horvath-Cosper, MD
Primary Mentor: Matthew Reeves, MD MPH
Additional Mentors: Jamila Perritt, MD MPH; Peggy Ye, MD MPH
Fellowship Site: Washington Medstar Hospital

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PROJECT SUMMARY

Justification for the project

Preoperative oral antibiotics have been shown to decrease infection rates for surgical abortion, and are universally recommended by the Society of Family Planning [1]. While data shows that that several different drug regimens appear to be effective in preventing perioperative infection,[2] we do not currently have data comparing side effects and patient tolerability of these various regimens. Data does suggest higher rates of nausea with doxycycline versus placebo,[3] but we lack sufficient evidence to recommend any one medication over another. Azithromycin 500 mg, doxycycline 200 mg, and metronidazole 500 mg are recommended for use before abortion by Planned Parenthood and the National Abortion Federation, and have been widely adopted since the previously most commonly used regimen (doxycycline 200 mg twice daily for 7 days post-procedure) became unreasonably expensive. Prior to doxycycline price increase, the standard of care had been post-procedure prophylaxis.

Proposed research

This double-blinded randomized controlled trial will consist of 180 participants undergoing first-trimester surgical abortion. Each subject will be randomized to one of four groups:
1. Azithromycin 500 mg – single dose
2. Doxycycline 200 mg – single dose
3. Metronidazole 500 mg – single dose
4. Placebo (with post-procedure antibiotics: azithromycin 1 g once or doxycycline 200 mg twice daily for 7 days)

The primary outcomes are nausea, vomiting, and pain. Subjects will be assessed for the presence of these symptoms before administration of study drug, immediately following the abortion procedure, and again in the recovery area.

A substudy will assess for serum drug levels and for the presence of viable bacteria within the endometrial cavity in 40 women.

New features

This will be the first study to compare side effect profile and patient tolerability for the three most commonly used prophylactic antibiotic regimens for first-trimester surgical abortion.

The substudy will be the first to examine the use of bacterial cultures from the endometrial cavity after abortion. If performing bacterial cultures is found to be useful, further studies will be warranted to evaluate this method as a potential surrogate for efficacy. An earlier landmark study by Mishell et al. employed culture of the endometrial cavity associated with use ofintrauterine devices.[4]

Problems anticipated

No major problems are anticipated in the main study. Six months should be sufficient for enrollment, as both project sites have high volumes of first-trimester surgical abortions.

For the pilot substudy, the anticipated findings are unclear. We intend to establish the methods to make cultures of the endometrial cavity a useful tool for use in future studies of antibiotics at abortion.

1.1 Rationale and objectives of the study

1.1.1 Rationale

Preoperative antibiotic prophylaxis has been proven effective in preventing infection in patients undergoing surgical abortion in multiple placebo-controlled studies.[5] All antibiotics given prior to abortion have been found to be effective in reducing infections. However, at present, published comparative data do not address side effects with various antibiotic regimens. Accordingly, from the perspective of side effects, clinicians cannot recommend any one agent over the others.

Anecdotally, doxycycline and metronidazole appear to be associated with higher levels of gastrointestinal side effects, including emesis. Patient experience and satisfaction may also be negatively impacted by a medication that has a higher rate of unpleasant side effects. If we are able to demonstrate a significant difference in side effect profiles and/or patient satisfaction for the study medications, then we may be able to improve patient experience.

Our substudy will examine endometrial bacterial culture following first-trimester surgical abortion, using samples collected by suction endometrial biopsy. A 2014 study that examined bacterial ecology in the vagina, cervix, and uterus did not show a significant change in bacterial species identified by PCR before and after levonorgestrel IUS insertion.[6] Predominant species were genus Lactobacillus and Burkholderia.[6] Since we are only interested in the types and amount of living bacteria, we will use a culture method (instead of PCR) for both anaerobic and aerobic species. As this will be performed after the completion of the procedure (involving multiple passes in and out of the cervix), we expect the cervical and uterine microbiota to be essentially the same.[4] Thus we do not plan to use a protective sheath over the endometrial biopsy device cannula.

1.1.2 Objectives and Hypotheses

This study aims to investigate the side effects of three different preoperative antibiotic regimens used for surgical abortion prophylaxis and a pre-operative placebo and to determine if any differences exist.

The primary objective is to determine if the side effects associated with individual medications are more similar to placebo than the others. We hypothesize that all study medications will cause more nausea than placebo. Primary outcome measures are nausea, emesis, and patient satisfaction.

We will assess pain in our questionnaires as a secondary study outcome. It is conceivable that the study interventions will alter pain perception either due to the influence of nausea or emesis on pain perception or, less likely, due to direct effects on perceived pain. We will note if the patient was in the endometrial assessment substudy as this may also affect pain perception.

The substudy aims to explore our ability to identify bacteria within the uterine cavity. The objective is to assess the feasibility of identifying bacteria within the uterus after abortion. We hypothesize that the

burden of bacteria will be higher in women receiving placebo, and that aerobic bacteria will not be decreased with metronidazole.

1.2 Previous similar studies

We could not identify any prior studies comparing the study medications to each other and to placebo. As noted above, azithromycin has been compared to erythromycin and found to cause fewer gastrointestinal side effects in pregnant patients.[7] Various doses of metronidazole have been compared to each other and the overall rate of GI side effects was found to be low.[8] Another study of metronidazole compared route of administration (oral v. vaginal) but side effects were not assessed as an outcome. [9] Gastrointestinal side effects are well-established in doxycycline vs. placebo studies,[10–12] and in the study that compared administration with and without food.[3]

Regarding the endometrial assessment substudy, a 2014 study that examined bacterial ecology in the vagina, cervix, and uterus did not show a significant change in bacterial species identified by PCR before and after levonorgestrel IUS insertion. Predominant species were genus Lactobacillus and Burkholderia.[6] Another study examined bacterial colonization in the endometrium and found a wide variety of bacterial species, even after using a technique designed to minimize contamination from the lower genital tract.[13] An older study showed mostly negative endometrial cultures at the time of hysterectomy.[14]

1.3 Design and Methodology

1.3.1 Research Design and General Methodological Approach

Primary study: We have designed a randomized controlled trial to be conducted at Washington Hospital Center (WHC) and Planned Parenthood of Metropolitan Washington (PPMW) over the course of 6-8 months. A total of 180 English-speaking women will be enrolled with 45 participants in each of the four groups.

The women will be randomized to receive single oral doses of azithromycin 500 mg, doxycycline 200 mg, metronidazole 500 mg, or placebo. Computer-generated randomization will be used to assign participants to one of the four treatment arms. Women receiving placebo will receive antibiotic prophylaxis after completion of the study.

Both the participants and the investigators will be blinded as to the treatment group. This will be accomplished by placing the study medication inside opaque gelatin capsules, a method that has been successful in prior studies.[3] We will randomize participants by assigning them to the next of the sequentially numbered sealed opaque study packets, containing the gelatin capsules with study medication inside. A second smaller opaque sealed envelope will also be inside the study packet. This envelope will be opened after completion of all study procedure and will only say if the participant received placebo, so that additional antibiotics can be given.

Participants will swallow the appropriate medication approximately 30-60 minutes prior to the surgical abortion. We will assess side effects via written questionnaire immediately before the start of the procedure and in the recovery room. Study population will be all eligible patients undergoing surgical abortion in the first trimester at PPMW and at WHC.

For the substudy 40 women will be recruited to undergo immediate post-procedure endometrial sampling using a suction-piston device. Due to the double-blind nature of this study, enrollment into the substudy will not be by group. Thus there are likely to be unequal group sizes. For a pilot substudy such as this, unequal numbers within groups will not detract from the utility of the results.

1.3.2 Criteria for selection of participants

We will enroll up to 200 women so that 180 women complete the final post-procedure questionnaire. We will enroll women who meet the following criteria (see Appendix H):

- Women in good general health
- Age 18 or over
- Seeking non-urgent surgical termination of pregnancy
- Gestational age of 5 0/7 to 13 6/7 weeks, confirmed by sonography
- English-speaking

Women who meet any of the following criteria will be excluded:

- Early pregnancy failure or fetal demise
- Intolerance, allergy, or contraindication to any of the study medications
- Inability to tolerate oral intake due to current nausea or vomiting
- Desire to use intravenous sedation.

For the substudy, women will be recruited until 40 samples have been obtained. The only inclusion criterion is eligibility for the main study. We will exclude women from the substudy if procedural complications such as perforation or hemorrhage occur that would make endometrial sampling unsafe or unadvisable.

1.3.3 Participant recruitment and allocation

The research coordinator, co-investigators, or other designated individual will recruit women to the study. WHC and PPMW serve representative samples of the Washington metropolitan area. Baseline characteristics of the outpatient center at WHC and at PPMW in 2012 are shown below:

Age (years)	WHC	PPMW
<20	4%	12%
20-24	11%	38%
25-29	11%	25%
30-39	68%	21%
40 or more	6%	5%
Race		
Black, non-Hispanic	22%	65%
White, non-Hispanic	61%	16%
Hispanic	11%	8%
Multiracial	0%	8%
Other/unknown	6%	3%

WHC patients are generally referred from their general obstetrician's office for abortion and are seen in the private outpatient office. We will recruit eligible patients on days when we are not recruiting at PPMW.

PPMW has a diverse patient population, with a majority of women being African American and age 20-

29 years old. We will recruit from the PPMW clinic in Washington DC on Wednesdays and Thursdays. If needed to meet the recruitment timeline, we can expand recruitment to the PPMW clinic in Silver Spring, Maryland, on Fridays.

The potential participant will be approached for study recruitment only after she has signed informed consent for the first-trimester surgical abortion. She will be approached by a research staff member or co-investigator and asked to participate in the study. A detailed explanation of the study will be provided and written informed consent will be obtained (Appendix A). The patient will be given a copy of her signed informed consent. After the consent is signed, eligibility for the study will be confirmed.

For randomization, a Medstar Research Institute statistician not involved in the conduct of the study will produce the allocation sequence using a computer generating pseudo-random sequence. The Medstar Research Pharmacy will prepare sequentially numbered sealed opaque allocation packets containing the appropriate study drugs placed within opaque gelatin capsules. The packets will not be assigned to a participant until eligibility is confirmed. To preserve blinding while allowing participants receiving placebo to be given antibiotics after study completion, a small sealed opaque envelope will be placed inside the packet with the gelatin capsules. The envelope will contain a folded piece of paper saying only "Placebo" or "Not placebo."

The patient will only open the randomization packet at take the study medication at the time of pre-medication for her abortion procedure. She will hand the small envelope to the research staff. The allocation number will be recorded twice on the participant's chart. At the time of allocation, the small envelope will be attached to the participant's chart, and will be opened by the PPMW or WHC staff after collection of the final post-procedure questionnaire. If the participant is in the placebo group, appropriate post-procedure antibiotics will be given, such as azithromycin 1 g or doxycycline 100 mg twice daily for 3 days.

1.3.4 Description of the drugs and devices to be studied

Doxycycline is almost completely absorbed with a bioavailability of >80%, and is only minimally affected by the presence of food in the gut. [15] The half-life of absorption is 0.85+/-0.41 h. Serum levels are detectable within 15 minutes and peak serum concentrations are reached 2-3 hours after oral administration.[15,16] Doxycycline levels within the endometrium are reached almost immediately.[16] The elimination half-life is between 12 and 25 hours.[15] A 2009 study showed that administering doxycycline with dinner the night before dilation and evacuation resulted in less emesis but lower serum concentration.[3] There was no difference in serum concentration in patients with emesis compared to patients without emesis.[3]

Azithromycin has lower bioavailability than doxycycline (37%). Peak serum concentrations are reached 2-3 hours after oral administration. Azithromycin exits the serum rapidly and has tissue concentrations 10 to 100 times higher than serum concentrations.[17] The estimated tissue half-life is greater than 60 hours for a single 500-mg dose, though the peak serum concentration is reached in 2-3 hours.[17] While gastrointestinal side effects are the most common side effects, azithromycin is associated with significantly less nausea and emesis than erythromycin in pregnant patients.[7,18]

Metronidazole has excellent bioavailability (>90%). Peak serum concentrations are reached 0.25-4 hours after oral administration of 500 mg.[19] Tissue penetration in pelvic organs is approximately 90% of serum concentration, and half-life is 6-10 hours.[19] Side effects are also primarily gastrointestinal, with 1.8% of 167 women in one study experiencing emesis.[8]

	Bioavailability	Time to peak serum concentration	Half-life
Doxycycline	>80%	2-3 hours	12-25 hours
Azithromycin	37%	2-3 hours	>60 hours (500 mg dose)
Metronidazole	>90%	0.25-4 hours (500 mg dose)	6-10 hours

1.3.5 Admission Procedure

After informed consent has been obtained and eligibility confirmed, the participant will complete a baseline survey of demographic, medical history, and baseline symptoms, notably nausea (Appendix C). If the participant is interested in the substudy, a second consent will be signed for the substudy. She will then be assigned the next of the sequentially numbered randomization packet. At the time of pre-medication with ibuprofen and other standard medications, the participant will take the study drug from the first envelope with water approximately 30-60 minutes prior to procedure (15-90 minutes acceptable range). Time of administration will be recorded on the patient's chart. All other medications given concurrently will be recorded. At PPMW and WHC, patients are typically given ibuprofen 800 mg, tramadol 50 mg, alprazolam 0.25 mg, and promethazine 25 mg. While we plan to use this for all study participants, medications will be tailored to the need of each woman, such as, for example, allergies to medications.

1.3.6 Follow-up Procedure

Immediately prior to procedure (acceptable range 0-15 minutes) the participant will complete a questionnaire (Appendix **D**) assessing the primary study outcomes. Time of questionnaire completion will be recorded on the patient's chart and on the questionnaire itself. The abortion procedure will be performed in the usual fashion at that facility. The details of the paracervical block will be recorded by the abortion provider: volume, local anesthetic concentration, and other agents added. Episodes of emesis during the procedure will be recorded by the provider.

For the patients enrolled in the substudy, immediately after completion of the uterine aspiration but before removal of tenaculum, the endometrial sample will be collected. The external os will be cleaned with chlorhexidine. The physician investigator will pass the endometrial samping device to the fundus and then withdraw the plunger to collect a sample at the fundus. If a second pass is needed to collect an adequate sample, a new sterile device will be used. The sample will be placed in appropriate medium for anaerobic and aerobic culture.

After completion of the procedure, substudy patients will have a blood sample collected via venipuncture before leaving the procedure room. This sample will be spun and frozen until the end of the study. After unblinding of the study data, the serum for each participant will be sent for the appropriate assay to determine the level of doxycycline, azithromycin, or metronidazole, as appropriate. No testing will be performed for participants receiving placebo.

Prior to discharge from the recovery room, the participant will complete a final questionnaire in the recovery area, again assessing the study outcomes (Appendix E). After completing the final questionnaire, the second envelope will be opened. Participants receiving placebo will be given azithromycin 1 g. If azithromycin is contraindicated, doxycycline 100 mg twice daily for 3 days will be given. Then participants will be given a $50 gift card. Participants in the substudy will be given an additional $50, for

$100 in total.

Each participant will also receive a telephone call 1-2 weeks after the abortion procedure to assess for evidence of infection (Appendix F). Date and time of completion of all questionnaires will be recorded.

1.3.7 Criteria for Discontinuation

Any participant who meets the following criteria after enrollment will be discontinued from the study: (1) decline further participation in the study, (2) receives IV sedation, or (3) decides not to proceed with surgical abortion.

For the substudy, (1) inability to confirm uterine evacuation, or (2) surgical complication that would make the endometrial assessment an unacceptable risk would disqualify a patient from continuing to participate in the study. Any patient disqualified from the substudy will continue in the main study.

1.3.8 Laboratory and Other Investigations

Endometrial samples will be sent to the University of Pittsburgh laboratory for processing. Serum sample will be sent to the appropriate commercial lab to perform the assays for doxycycline, azithromycin, or metronidazole, as appropriate. Serum placebo from participant receiving placebo will be discarded once the data is unblinded.

1.3.9 Data Management

Source documents will be stored in a locked room at the Medstar Research Institute. The study personnel who will be collecting and entering the data have extensive experience working with confidential medical information and will follow standard institutional procedures for data handling, verification, cleaning, and storage.

Data will be entered by study staff into a database and accessible only by the primary, co-investigators, and research coordinator via password protection. All source documents are maintained in locked files in a locked room. Appropriate firewall and virus scanning software are installed and updated routinely by the hospital support staff.

1.3.10 Data Analysis

Data analysis will be conducted using Stata. The baseline characteristics of the populations will be described. Primary outcomes will be recorded as described above in 1.1.2, 1.3.1, and 1.3.5. Outcomes will be assessed using parametric or non-parametric analysis as appropriate.

The primary analysis will be based on intention-to-treat analysis, as participants will be analyzed based on the randomization group they are assigned regardless of actual treatment. Although study discontinuation after enrollment is possible, we expect extremely low discontinuation in this one-day study.

1.3.11 Number of Subjects and Statistical Power

Sample size: 180 women for main study

To detect a 30% difference in a given outcome compared to the placebo group, we will need to enroll 45 women per group to achieve a power of 80% with alpha of 0.05.

For the endometrial sampling substudy, we will enroll 40 women. As this has not been done previously,

we cannot predict results with any accuracy. We expect that roughly 10 women per group will give us enough data to understand if this methodology will be fruitful for future research, without undue risk to a large number of women at this early stage. Enrollment in the sub-study may be more challenging but we need many fewer participants. To give a rough idea of power, the substudy will have 85% power with alpha of 0.05 to detect a reduction in positive culture (any bacteria detected) from 90% with placebo to 20% in a treatment group. This assumes 10 women per group.

1.3.12 Study Limitations

A study of this size will only be able to examine common outcomes such as emesis and nausea. A much larger study would be needed to look at outcomes such as adverse drug reactions or post-abortal infection.

Patients will be recruited from WHC and PPMW. While they are representative of women in this area, they may not be generalizable to women with different characteristics.

The use of the smaller envelope to be opened after completion of the study creates some risk that blinding will be lost. However, we feel that this risk is minimal. This method is the simplest solution for women receiving placebo antibiotics after the abortion.

1.3.13 Duration of Project

Recruitment is expected to begin in July 2015 and continue until 180 participants have completed the study. Based on surgical volumes and prior experience, this should be achievable within 6-8 months. Recruitment of subjects, data collection, follow-up of subjects (with the exception of the 1-2 week telephone call) and data entry will be completed on the same day of the initial consultation for the procedure. For a similar one-day study of second-trimester cervical preparation, we easily recruit 2-4 participants per week at PPMW on Thursdays, our maximum per day to avoid disrupting clinic flow. Since this proposed study is simpler, we anticipate enrolling 4-6 participants per day at PPMW with the option to enroll 2 days per week. At WHC, we expect to enroll 2-6 women per week at WHC, from the roughly 10-20 first-trimester procedures per week. Thus we feel that we can safely estimate enrolling 10-15 women per week. At 10 women per week, we would need 18 weeks or 4-5 months. However since delays seem inevitable, we estimate 6-8 months for enrollment.

Data analysis will follow and be completed prior to writing the final paper. Please see the timeline for graphical depiction.

1.4 Project Management

Diane Horvath-Cosper, the Family Planning fellow and the faculty research mentors will have ultimate responsibility for this research project. This study will not involve other institutions.

Regarding field training, the staff at PPMW and WHC have participated in two similar studies and are familiar with the data collection and study participation process. We will have pre-study meetings with the staff at both PPMW and WHC to explain the study and discuss work flow.

1.5 Links with Other Projects

This study has no formal links to other studies.

1.6 Main Problems Anticipated

No major problems are anticipated in the main study.

1.7 Expected Outcomes of the Study and Dissemination of Findings

If any one of the study drugs has a side effect profile that is significantly different from placebo or from the other study drugs, then it might be possible to apply that information to minimize unpleasant side effects and improve patient satisfaction. When medications are lost due to emesis, patients are sometimes given a second dose, which increases cost and risk. Choosing prophylactic medication more appropriately could both reduce cost and risk.

The substudy is a feasibility study that aims to investigate bacterial ecology following first-trimester induced abortion, about which we current lack data. If any of the groups are found to have bacterial populations that differ from placebo, it may indicate that this methodology could be useful with a larger study sample.

We plan to submit the results of this study for presentation at the North American Forum on Family Planning or a similar national conference. We intend to submit the final manuscript for publication in *Obstetrics and Gynecology* or *Contraception*.

1.8 References

1. Achilles SL, Reeves MF. Prevention of infection after induced abortion: release date October 2010: SFP guideline 20102. *Contraception*. 2011;83(4):295-309. doi:10.1016/j.contraception.2010.11.006.

2. Kapp N, Whyte P, Tang J, Jackson E, Brahmi D. A review of evidence for safe abortion care. *Contraception*. 2013;88(3):350-363. doi:10.1016/j.contraception.2012.10.027.

3. Reeves MF, Lohr PA, Hayes JL, Harwood BJ, Creinin MD. Doxycycline serum levels at the time of dilation and evacuation with two dosing regimens. *Contraception*. 2009;79(2):129-133. doi:10.1016/j.contraception.2008.09.006.

4. Mishell DR, Bell JH, Good RG, Moyer DL. The intrauterine device: a bacteriologic study of the endometrial cavity. *Am J Obstet Gynecol*. 1966;96:119-126.

5. Sawaya GF, Grady D, Kerlikowske K, Grimes DA. Antibiotics at the time of induced abortion: the case for universal prophylaxis based on a meta-analysis. *Obstet Gynecol*. 1996;87:884-890.

6. Jacobson JC, Turok DK, Dermish AI, Nygaard IE, Settles ML. Vaginal microbiome changes with levonorgestrel intrauterine system placement. *Contraception*. 2014;90:130-135. doi:10.1016/j.contraception.2014.04.006.

7. Bush MR, Rosa C. *Azithromycin and Erythromycin in the Treatment of Cervical Chlamydial Infection during Pregnancy.*; 1994:61-63.

8. Spence MR, Harwell TS, Davies MC, Smith JL. The minimum single oral metronidazole dose for treating trichomoniasis: A randomized, blinded study. *Obstet Gynecol*. 1997;89:699-703. doi:10.1016/S0029-7844(97)81437-8.

9. Mitchell CM, Hitti JE, Agnew KJ, Fredricks DN. Comparison of oral and vaginal metronidazole for treatment of bacterial vaginosis in pregnancy: impact on fastidious bacteria. *BMC Infect Dis*. 2009;9:89. doi:10.1186/1471-2334-9-89.

10. Story MJ, McCloud PI, Boehm G. Doxycycline tolerance study. Incidence of nausea after doxycycline administration to healthy volunteers: A comparison of 2 formulations (Doryx' vs Vibramycin'). *Eur J Clin Pharmacol*. 1991;40:419-421. doi:10.1007/BF00265856.

11. Freeman LD, Hooper DR, Lathen DF, Nelson DP, Harrison WO, Anderson DS. *Brief Prophylaxis with Doxycycline for the Prevention of Traveler's Diarrhea.*; 1983:276-280. doi:10.1097/00006534-198311000-00087.

12. Nadelman RB, Nowakowski J, Fish D, et al. *Prophylaxis with Single-Dose Doxycycline for the Prevention of Lyme Disease after an Ixodes Scapularis Tick Bite.*; 2001:79-84. doi:10.1177/000992280204100214.

13. Hemsell DL, Obregon VL, Heard MC, Nobles BJ. Endometrial bacteria in asymptomatic, nonpregnant women. *J Reprod Med*. 1989;34:872-874.

14. Teisala K. Endometrial microbial flora of hysterectomy specimens. *Eur J Obstet Gynecol Reprod Biol*. 1987;26:151-155. doi:10.1016/0028-2243(87)90050-5.

15. Agwuh KN, MacGowan A. Pharmacokinetics and pharmacodynamics of the tetracyclines including glycylcyclines. *J Antimicrob Chemother*. 2006;58:256-265. doi:10.1093/jac/dkl224.

16. Whelton A, Blanco LJ, Carter GG, et al. Therapeutic implications of doxycycline and cephalothin concentrations in the female genital tract. *Obstet Gynecol*. 1980;55:28-32.

17. McCarty JM. Azithromycin (Zithromax). *Infect Dis Obstet Gynecol*. 1996;4:215-220. doi:10.1002/(SICI)1098-0997(1996)4:4<215::AID-IDOG3>3.0.CO;2-Y.

18. Pitsouni E, Iavazzo C, Athanasiou S, Falagas ME. Single-dose azithromycin versus erythromycin or amoxicillin for Chlamydia trachomatis infection during pregnancy: a meta-analysis of randomised controlled trials. *Int J Antimicrob Agents*. 2007;30:213-221. doi:10.1016/j.ijantimicag.2007.04.015.

19. Freeman CD, Klutman NE, Lamp KC. Metronidazole. A therapeutic review and update. *Drugs*. 1997;54:679-708.

ETHICAL CONSIDERATIONS

2.1 Informed Decision-Making and Confidentiality

As soon as the preliminary proposal is submitted to the FFP reviewers, we will submit an application for this protocol to Washington Hospital Center IRB. PPMW will review the proposal and give approval to proceed as appropriate. PPFA approval will be obtained once WHC IRB approval is obtained.

BUDGET

3.1 Line-Item Budget

3.2 Budget Justification

A. Personnel

Diane Horvath-Cosper will lead the study. She will be responsible for subject recruitment, assist in data analysis, and dissemination of findings. Matthew Reeves will assist in data collection, data analysis and dissemination of findings. WHC and PPMW physicians will perform procedures for the study participants. The research coordinator, Arezou Akar will assist in subject recruitment, obtaining consent, treatment allocation and concealment. Budget will include salary support for the research coordinator.

For the substudy, only study investigators (Diane Horvath-Cosper, Matthew Reeves, Jamila Perritt, Peggy Ye) will obtain the pipelle samples.

Biostatistics support will be obtained through the research department at Washington MedStar Hospital, as needed.

B. Equipment

No additional equipment will be needed for the study.

C. Materials and Supplies

Biostatistics support: $100/hour x 10 hours = $1000

Pharmacy costs

Study drugs:

Azithromycin 250 mg x 100

Doxycycline 100 mg x 100

Metronidazole 250 mg x 100

Gelatin capsules x 400

Endometrial pipelles x 50

Culture media, 50 aerobic and 50 anaerobic.

Lab services at University of Pittsburgh

Shipping

Venipuncture supplies

Lab services for serum antibiotic testing

Shipping

Office supplies/copies

D. Participant Costs

180 participants will receive a $50 gift card for participation on the day of their procedure ($9,000). The 40 substudy participants will receive an additional $50 gift card ($2,000).

E. Travel

Travel will occur between the two sites of the study, WHC and PPMW, for both the research coordinator and the co-investigator. Estimated travel expenses are based on cost of mass transit and/or driving costs.

F. Other Costs

These costs will include copying and printing of consent and questionnaire forms, and the cost of materials and shipping.

Consultant Services

Medstar Washington Hospital biostatistician services will be obtained.

Contractual Costs

PPMW will receive $50 per study participant to cover costs incurred with study participation.

4. APPENDICES

A: Consent form – Main Study

B: Consent form – Substudy

C: Participant Questionnaire – Baseline (pre-medication)

D: Participant Questionnaire – Immediate Pre-Procedure

E: Participant Questionnaire – Final Post-Procedure

F: Participant Questionnaire – Telephone Call

G: Inclusion/Exclusion Screening Form