Washington University in St. Louis

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INFORMED CONSENT DOCUMENT- Female

Project Title: Prophylactic antibiotics prior to embryo transfer: a randomized controlled trial

Principal Investigator: Ashley Eskew, MD.

Research Team Contact: Caitlin Ashby, 314-286-2458

This consent form describes the research study and helps you decide if you want to participate. It provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights and responsibilities as a research participant. By signing this form you are agreeing to participate in this study.

- You should read and understand the information in this document including the procedures, risks and potential benefits.
- If you have questions about anything in this form, you should ask the research team for more information before you agree to participate.
- You may also wish to talk to your family or friends about your participation in this study.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We invite you to participate in this research study because you are completing a fresh in vitro fertilization (IVF) cycle and embryo transfer.

The purpose of this research study is to compare no antibiotic prophylaxis (no antibiotics given prior to the embryo transfer) to routine administration of antibiotics prior to embryo transfer in a fresh IVF cycle in relation to clinical pregnancy rate, spontaneous miscarriage rate, embryo development and live birth. Receiving antibiotic prophylaxis is standard of care at Washington University's Division of Reproductive Endocrinology and Infertility (REI). We will use the antibiotic called azithromycin.

Azithromycin is approved by the U.S. Food and Drug Administration to treat certain mild to moderate infections. However, the use of azithromycin is considered investigational in this study.

Depending on when you enroll into the study we will ask you for your permission to obtain vaginal swabs at 3 time points to better characterize alterations (changes) in the vaginal microbiome (i.e.: the profile of communities of microorganisms that populate the human body) throughout IVF and prior to embryo transfer. Alterations in the microbiome have been linked to general health and pregnancy outcomes, however, have not been well studied in the IVF patient population. It is unknown whether the human virome (the collection of all viruses that are found in or on humans) impacts pregnancy outcomes and will be obtained and evaluated through these samples as well.

WHAT WILL HAPPEN DURING THIS STUDY?

If you agree to participate in this study, you will be asked to come to the REI, which is located at 4444 Forest Park Avenue, in Suite 3100. Once at REI, the following will occur:

- After you sign the consent form, your chart will be marked to designate participation in the study.
- Fifty couples going through their first IVF cycle will be offered enrollment into a pilot study (a smaller exploratory study) as a part of the ongoing randomized control trial to evaluate the reproductive track microbiome and virome (as described above). You and your partner will be notified prior to review of this consent if you will be offered enrollment in the pilot study.
- You will be randomly assigned (by a computer) to either receive prophylactic antibiotics or no antibiotics. You will have a 50% chance of being in either group. Neither you nor your doctor or the study team can decide which group you are in.
    - Your partner (if male) will also be asked to participate in this study and will be assigned to the same group. Your partner will provide their own consent on a separate consent form.
- Patients randomly assigned to the antibiotic group will receive our current standard of care: 1g azithromycin (the antibiotic) orally one time the day of gonadotropin start.
- Patients randomly assigned to the no antibiotic treatment group will not be prescribed oral antibiotic prophylaxis.

This visit will take approximately 30 minutes.

IVF outcomes data will be collected, including: clinical pregnancy rate, spontaneous miscarriage rate, embryo development, and live birth which is routinely tracked in our clinic.

Depending on when you enroll into the study we would like to obtain vaginal swabs from you at three time points during your regular clinic visit. The first collection would be at the time of your baseline testing, the second prior to egg retrieval, and the third at the time of embryo transfer. The physician will obtain the sample with a cotton swab from the mid-vagina via a speculum exam. We would like to use these vaginal swabs to better characterize alterations (changes) in the vaginal microbiome (i.e.: the profile of communities of microorganisms that populate the human body) throughout IVF and prior to embryo transfer.

I agree to have vaginal swabs collected for research as described above.

_____ Yes	_____ No	___ N/A
Initials	**Initials**	**Initials**

Will you save my samples or research data to use in future research studies?

As part of this study, we are obtaining data from all participants and vaginal swabs for some participants. We would like to use this data and vaginal swabs for studies going on right now as well as studies that are conducted in the future. These studies may provide additional information that will be helpful in understanding fertility, or other diseases or conditions, including research to develop investigational tests, treatments, drugs, or devices that are not yet approved by the U.S. Food and Drug Administration. It is unlikely that what we learn from these studies will have a direct benefit to you. There are no plans to provide financial compensation to you should this occur. By allowing us to use your data and vaginal swabs you give up any property rights you may have in the data and vaginal swabs.

We will share your data and vaginal swabs with other researchers. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at Washington University, at other research centers and institutions, or industry sponsors of research. We may also share your research data with large data repositories (a repository is a database of information) for broad sharing with the research community. If your individual research data is placed in one of these repositories only qualified researchers, who have received prior approval from individuals that monitor the use of the data, will be able to look at your information.

If you change your mind and do not want us to store and use your data and/or vaginal swabs for future research you should contact the research team member identified at the top of this document. The data and/or vaginal swabs will no longer be used for research purposes. However, if some research with your data and/or vaginal swabs has already been completed, the information from that research may still be used. Also, if the data and/or vaginal swabs have been shared with other researchers it might not be possible to withdraw the data and/or vaginal swabs to the extent it has been shared.

Please place your initials in the blank next to Yes or No for each of the questions below:

My data and vaginal swabs (if collected) may be stored and used for future research as described above.

_____ Yes **_____ No**
Initials **Initials**

My data and vaginal swabs (if collected) may be shared with other researchers and used by these researchers for the future research as described above.

_____ Yes **_____ No**
Initials **Initials**

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 350 couples will take part in this study conducted by investigators at Washington University. Approximately 50 of these couples will also be asked to participate in the pilot study.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement will last for 1 year.

- The visit where you are randomly assigned to your group should take approximately 30 minutes to complete.
- Pilot Study Participants: The visits where vaginal swabs are collected will be done at your standard of care appointments. The collection of vaginal swabs will add little time to the visit (1-3 minutes).

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

Some risks described in this consent document, if severe, may cause death.

Azithromycin (antibiotic)

Likely / Common

Mild

- Nausea
- Abdominal pain
- Loose stool

Less Likely / Less Common

Mild

- Vomiting
- Vaginitis (yeast infection)

Rare

Life Threatening

- Anaphylaxis (a life threatening allergic reaction)

Serious

- Allergic reaction

No antibiotic prophylaxis

Potential theoretical risks to consider with no antibiotic prophylaxis is lack of treatment of an asymptomatic (shows no symptoms) pelvic infection which may impact your IVF plan and outcome.

Vaginal swabs

As swab collection requires a speculum exam you may experience some mild discomfort from the speculum itself. The swab collection itself should not cause any additional discomfort.

Breach of Confidentiality

One risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure. Please see the section in this consent form titled *"How will you keep my information confidential?"* for more information.

WHAT ARE THE BENEFITS OF THIS STUDY?
You may or may not benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because results from this study may be applied to improve and optimize our care for patients going through fresh IVF cycles.

WHAT OTHER TREATMENT OPTIONS ARE THERE?
Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you could receive the antibiotic prophylaxis without being in the study.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?
As part of this study you will receive tests and procedures that are identical to what you would receive during routine clinical care of your condition. Your health plan/insurance company will be billed for some or all of these costs, and you will be responsible for any co-pays and deductibles that are normally required by your health plan/insurance. Not all insurance plans cover the costs associated with being in a study. Even if they do, you may be responsible for more out-of-pocket expenses, such as co-pays and deductibles, when there are more tests and procedures or more expensive tests and procedures involved in the study than if you were to receive routine clinical care outside the study. If you wish to know whether there are more tests and procedures or more expensive tests and procedures in the study, you should ask your study doctor.

If you wish to know whether your insurance will pay, you should contact them directly, or speak with the study team about obtaining a financial pre-certification prior to enrolling in the study.

WILL I BE PAID FOR PARTICIPATING?
You will not be paid for being in this research study.

WHO IS FUNDING THIS STUDY?
The Children's Discovery Institute of Washington University, St. Louis Children's Hospital, and the National Institutes of Health are funding this research study. This means that Washington University is receiving payments from the Children's Discovery Institute of Washington University, St. Louis Children's Hospital, and NIH to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from the Children's Discovery Institute of Washington University, St. Louis Children's Hospital, nor NIH for conducting this study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?
Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator at 314-286-2458 and/or the Human Research Protection Office at 1-(800)-438-0445.

Decisions about whether payment for medical treatment for injuries relating to your participation in research will be made by Washington University. If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

HOW WILL YOU KEEP MY INFORMATION CONFIDENTIAL?

Other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you. We will keep your participation in this research study confidential to the extent permitted by law.

- Government representatives, (including the Office for Human Research Protections) to complete federal or state responsibilities
- The U.S. Food and Drug Administration
- The National Institutes of Health
- Hospital or University representatives, to complete Hospital or University responsibilities
- Information about your participation in this study may be documented in your health care records and will be available to anyone with access to your health care record, including your health insurance company. This information may also be released as part of a release of information request.
- The last four digits of your social security number may be used in hospital or University systems to track billing information for research procedures
- Washington University's Institutional Review Board (a committee that oversees the conduct of research involving human participants) and the Human Research Protection Office. The Institutional Review Board has reviewed and approved this study.

To help protect your confidentiality, all paper records will be stored in a double-lock system (in a locked drawer and behind a locked door). All electronic data will be stored on a password protected database/computer in a password protected database/network folder. The swabs will be stored in a secure freezer in our office and care will be taken to protect information when transferred for analysis by identification with date of birth and medical record number. Only study team members will have access to this information. Any report or article that we write will not include information that can directly identify you. The journals that publish these reports or articles require that we share your information that was collected for this study with others. Sharing this information will allow others to make sure the results of this study are correct and help develop new ideas for research. Your information will be shared in a way that cannot directly identify you.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

To further protect your privacy, this research is covered by a Certificate of Confidentiality from the federal government. This means that the researchers can refuse to disclose information that may identify you in any legal or court proceeding or to anyone who is not connected with the research except if:

- there is a law that requires disclosure, such as to report child abuse and neglect, or harm to self or others*;*
- you give permission to disclose your information, including as described in this consent form; or
- it is used for other scientific research allowed by federal law.

You have the right to share your information or involvement in this study with anyone at any time. You may also give the research team permission to disclose your information to a third party or any other person not connected with the research.

If information about you or your involvement in this research is placed in your medical record the information may no longer be protected under the Certificate. However, information in your medical records is protected in other ways.

Are there additional protections for my health information?

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form. The research team will follow state and federal laws and may share your health information with the agencies and people listed under the previous section titled, "How will you keep my information confidential?"

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form or as permitted or required by law. When possible, the research team will make sure information cannot be linked to you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

Although you will not be allowed to see the study information, you may be given access to your health care records by contacting your health care provider.

If you decide not to sign this form, it will not affect

- your treatment or the care given by your health provider.
- your insurance payment or enrollment in any health plans.
- any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research
- This authorization does not expire.
- You may later change your mind and not let the research team use or share your information (you may revoke your authorization).
    - To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ or you may request that the investigator send you a copy of the letter.
        - **If you revoke your authorization:**
            - The research team may only use and share information already collected for the study.
            - Your information may still be used and shared as necessary to maintain the integrity of the research, for example, to account for a participant's withdrawal from the research study or for safety reasons.
            - You will not be allowed to continue to participate in the study.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. Any data that was collected as part of your participation in the study will remain as part of the study records and cannot be removed.

If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I decide to withdraw from the study?

You may withdraw by telling the study team you are no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ under Withdrawing from a Research Study.

Will I receive new information about the study while participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can someone else end my participation in this study?

Under certain circumstances, the investigator might decide to end your participation in this research study earlier than planned. This might happen for no reason or because in our judgment it would not be safe for you to continue, because funding for the research study has ended, or because the sponsor has decided to stop the research.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Ashley Eskew, MD, at 314-286-1384**.** If you experience a research-related injury, please contact: Ashley Eskew, MD, at 314-286-1384.
If you have questions, concerns, or complaints about your rights as a research participant, please contact the Human Research Protection Office at 660 South Euclid Avenue, Campus Box 8089, St. Louis, MO 63110, 1-(800)-438-0445, or email hrpo@wustl.edu. General information about being a research participant can be found on the Human Research Protection Office web site, http://hrpo.wustl.edu. To offer input about your experiences as a research participant or to speak to someone other than the research staff, call the Human Research Protection Office at the number above.

This consent form is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by agreeing to participate in this study. As a participant you have rights and responsibilities as described in this document and including:

- To be given enough time before signing below to weigh the risks and potential benefits and decide if you want to participate without any pressure from the research team or others.
- To understand all of the information included in the document, have your questions answered, and receive an explanation of anything you do not understand.
- To follow the procedures described in this document and the instructions of the research team to the best of your ability unless you choose to stop your participation in the research study.

- To give the research team accurate and complete information.
- To tell the research team promptly about any problems you have related to your participation, or if you are unable to continue and wish to stop participating in the research study.

Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a signed and dated copy of this form.

Do not sign this form if today's date is after EXPIRATION DATE: 11/07/19.

_____ _____
(Signature of Participant) (Date)

_____
(Participant's name – printed)

Statement of Person Who Obtained Consent

The information in this document has been discussed with the participant or, where appropriate, with the participant's legally authorized representative. The participant has indicated that they understand the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)

_____
(Name of Person who Obtained Consent - printed)