CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: PIANO: A Multicenter National Prospective Study of Pregnancy and Neonatal Outcomes in Women with Inflammatory Bowel Disease

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Study Sponsor: The Crohn's and Colitis Foundation of America

This is a medical research study. Your study doctor, Uma Mahadevan, M.D., or her associates from the Gastroenterology Faculty Practice at UCSF, will explain this study to you.

Medical research studies include only people who choose to take part. Take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you are a pregnant female with either Crohn's disease (CD) or Ulcerative Colitis (UC), who received azathioprine/6MP, infliximab (Remicade®), adalimumab (Humira®), ustekinumab (Stelara®), certolizumab (Cimzia™), natalizumab (Tysabri®), golimumab (Simponi®), vedolizumab (Entyvio®), tofacitinib (Xeljanz®), or any other therapy for Inflammatory Bowel Disease (IBD) during pregnancy. You may also be one of 10 pregnant women who do not have IBD and are participating in the vaccine component of the study.

Why is this study being done?

This study is conducted to determine whether the rates of birth defects, miscarriages, premature births and other outcomes in women with inflammatory bowel disease (IBD) taking azathioprine/6MP or biologic therapy (i.e. Remicade®, Humira®, Cimzia™, Tysabri®, Stelara®, Simponi®, Entyvio®) or small molecules (i.e. Xeljanz®) are different from those among IBD-affected women not taking these medications.
We are interested in studying the role of these medications on pregnancy outcomes and will also study whether the level of biologic or other IBD drug transferred across the placenta to the infant by the time of birth predicts the risk of infection. We will determine whether the achievement of developmental milestones (being able to do simple tasks at age appropriate times), rates of growth by height and weight, and protection against infections are reduced in the children of women with IBD. As many women receive these drugs during their prime reproductive years, this information will be valuable in guiding therapy of women with CD or UC who wish to have children while receiving this therapy for their illness. While we now have more information about the immediate safety of these medications, we do not know what happens later in childhood, so we are continuing to follow children until adulthood.

How many people will take part in this study?

This study will be a multi-site study conducted by the members of the Crohn's Colitis Foundation Clinical Alliance – a group of hospitals that specialize in the care of patients with IBD. About 3000 women will take part in this study. Approximately 800 subjects will be enrolled at UCSF. Additionally, 10 non-IBD patients will be enrolled for our vaccine control group.

What will happen if I take part in this research study?

- Women with IBD who become pregnant and receive care at a participating center will be eligible for this study.
- If you agree to take part in this study, you will provide verbal consent for the study questionnaires as well as sign this Informed Consent Form before all other study procedures are performed.
- You will be asked to complete an intake questionnaire when you enter the study. Additionally, you will be asked to complete additional questionnaires during each trimester of your pregnancy, at delivery, at 4, 9, 12, 24, 36, and 48 months, and annually for up to 18 years after the birth of your baby. You may opt out at any point.
- The questionnaires can be completed by telephone, during your clinic visit if they fall within the appropriate time frame, or using our online patient portal. An automated email with a link specific to you will be sent to you at the time your questionnaire is due with two reminder emails.
- Both yours and your infant's charts may be reviewed. The data collected will be related to your IBD history, pregnancy history and course, paternal and maternal medical history, medications used, IBD disease activity, complications of pregnancy, your child's health and development, and environmental factors. Additionally, we will be collecting information on tobacco, alcohol and drug use before/during/after pregnancy. If an event occurs for which we need further information on your medical history or that of your child, we will contact your physician or pediatrician for further information only if you sign a HIPPA release form giving us permission to do so.
- As this is a study investigating the effects of certain medications used to treat IBD on pregnancy outcome and newborn outcome to fifteen years of age, both pregnant women and infants will be enrolled.
- No changes in your medical care will be made as a result of your participation in this study. However, if your child is found to have a developmental delay shown by scores on the questionnaire, we will alert you so you can share the results with your pediatrician, and he can intervene as needed.
- We will send you a kit with instructions for collecting your blood sample in the second trimester when the concentration of biologic drug in your blood is lowest. A blood sample will be taken from you by placing a needle in your vein; this will be done by lab

staff. Approximately 2mL (1/2 teaspoon will be obtained for this sample). Samples will be packaged by lab staff and prepared to be shipped to UCSF Gastroenterology.

- If you were taking Remicade®, Humira®, Cimzia™, Tysabri®, Stelara®, Simponi®, Entyvio®, Xeljanz®, or newer biologics and small molecules during your pregnancy then we will obtain blood samples to measure levels of drug from you, umbilical cord blood, and your infant (optional) at the time of delivery. A kit will be sent to you prior to delivery with instructions for obtaining all three blood samples. A blood sample will be taken from you and your infant by placing a needle in your/your infant's vein by the local hospital staff. Approximately 2 ml (or about ½ a teaspoon) of blood will be obtained from you and your infant at birth and, if needed, approximately 2 ml (or about ½ a teaspoon) of blood will be obtained from your infant at month 3 and at month 6. Samples will be packaged by hospital staff and prepared to be shipped to UCSF Gastroenterology. We will recheck your infant's blood at month 3 and month 6 as appropriate. A blood kit will be sent to you prior to the blood draw (similar to the one sent before delivery) with instructions for obtaining the blood sample at a local commercial lab or your pediatrician's office.
- If you were not taking Remicade®, Humira®, Cimzia™, Tysabri®, Stelara®, Simponi®, Entyvio, or Xeljanz® (or new biologics or small molecules that are introduced during the course of the study) during your pregnancy then we will not collect blood samples for drug measurement.
- In the second trimester you will submit a stool sample at your local Quest Diagnostics for fecal calprotectin testing. This will be an objective measure of disease activity.

Optional tests:

- Subjects taking part in this study have the option to give a breast milk sample for testing. If you choose to take part in this part of the study, we will take about 2 teaspoons of your breast milk on 8 occasions: 1, 12, 24, 48, 72, 96, 120, and 168 hours after your drug administration. You can choose not to give breast milk samples for tests and still take part in this study.

- Subjects taking part in this study have the option of checking response to vaccines (Haemophilus influenza, tetanus toxoid) when their child is 7 months or older. This is part of the standard of care to ensure that your infant had an appropriate response to vaccines. If you choose to take part in this part of the study, a blood sample will be taken from your child by placing a needle in his/her vein. Approximately 2 ml or ½ of teaspoon of blood will be obtained. You can choose not to give your infant's blood sample for this test and still take part in this study.

- Subjects taking part in this study have the option of checking their infant's blood at month 12 to determine if development of T and B cells is affected by the drug which they are taking. The development of T and B cells is very important for keeping your child healthy and preventing infections. If you choose to participate in this part of the study, a blood collection kit will be sent to you prior to the blood draw. This blood draw can be

done at a local commercial lab or pediatrician's office. The blood sample will be taken from your child by placing a needle in their vein. Approximately 2 ml or ½ of a teaspoon of blood will be obtained. You can choose not to give your infant's blood sample for this test and still take part in this study.

- Subjects taking part in this study have the option of submitting their infant's meconium and stool sample at birth, months 3, 6, and 9, and annually between ages 1-15 for analysis. A stool collection kit will be sent to you if you choose to take part in this optional study. The kit will include instructions for obtaining your infant's first bowel movement of the day as well as instructions for packaging and shipping. All postage will be prepaid.

- Subjects who received the COVID-19 vaccine have the option of measuring response to the COVID-19 vaccine. If you choose to participate in this study, a blood collection kit will be sent to you prior to your first dose of the COVID-19 vaccine. This blood draw can be done at a local commercial lab or at UCSF. The blood sample will be taken from you by placing a needle in your vein. Approximately 2 ml or ½ of a teaspoon of blood will be obtained. Another kit will be sent to you prior to delivery with instructions for obtaining blood samples from you and your umbilical cord. Approximately 2 ml (or about ½ a teaspoon) of blood will be obtained from you, your umbilical cord and if you wish your infant. Samples will be packaged by hospital staff and prepared to be shipped to UCSF Gastroenterology.

- Subjects who received the COVID-19 vaccine have the option of submitting breastmilk for testing. If you choose to participate in this study, we will take about 2 teaspoons of breastmilk in the morning and in the evening from two different days.

- Pregnant women without IBD (Control) just participating in the vaccine portion of the study will still have the opportunity to answer questionnaires during pregnancy and the first year post-partum. We will also measure pre-vaccine bloodwork as well from your blood, umbilical cord blood, and (optional) infant blood on the day of birth as noted above. Breastmilk samples can also be submitted as noted above, but only 2 samples on 2 separate days will be needed.

How long will I be in the study?

Participation in the study will take a total of about 20 hours over a period of approximately 225 months (9 months of pregnancy and 216 months after the birth of the baby, until your child is 18 years old). The intake questionnaire takes approximately 15-20 minutes to complete. All subsequent questionnaires take approximately 5-10 minutes plus additional time to collect the blood samples.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop.

The study doctor may stop you from taking part in this study at any time if she believes it is ibn your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

Blood drawing (venipuncture) risks:

The risks of blood draw include bruising, mild pain and rarely infection. There is also the possibility that the results of the blood tests may be distressing to you. You will have the ability to be seen in consultation by Dr. Mahadevan for advice regarding your IBD medications. Communication with your child's pediatrician will also be conducted.

Risk for emotional distress:

There is a risk for emotional distress by answering questions about potential negative outcomes in your pregnancy or in your child.

Risk of loss of privacy:

There is a risk of loss of privacy based on data collection. However, the information about you will be handled as confidentially as possible. Your name will not be used in any published reports or shared with any outside institution. When you fill out a questionnaire you will be identified in the computer records by a number only. Your primary hospital site and UCSF will have your name, but all computerized study records will only use your study number.
UCSF will use your name and address to ship the containers for blood collection to you. Your doctor or your child's pediatrician may also become aware of your participation in this study if they are assisting with the blood collection.

Are there benefits to taking part in the study?

The potential benefit to you is that you will know how much biologic drug is being passed on to your child and when those levels are no longer detectable in your baby.

This will also help pregnant IBD patients in the future, as it may define appropriate dosing intervals of biologic drug to minimize exposure of the infant to the drug.

Another benefit to you is that you will know if your child responded appropriately to their childhood immunizations.

If the questionnaires suggest your child has delayed development, we will inform you so you can discuss it with your child's pediatrician to get further testing. This may result in earlier intervention, which may benefit your child.

What other choices do I have if I do not take part in this study?

As an alternative, you can elect not to participate in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record is kept private. You will be assigned a unique identification number as a measure to protect your privacy. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The study doctors, other research team members, the Institutional Review Board (UCSF Committee on Human Research)
- The U.S. Food and Drug Administration (FDA) and other government agencies, involved in keeping research safe for people.

Because of the need to release information to these parties, absolute confidentiality cannot be guaranteed. The results of this research project may be presented at meetings or in publications; however, your identity will never be disclosed in such presentations.

Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. A medical record will be created because of your participation in this study. Your consent form and some of your research test results will be included in this record. Therefore, your other doctors may become aware of your participation. Hospital regulations require that all health care providers treat information in medical records confidentially.

All computerized study information will be labeled with a code number and will not include your name or other information that directly identifies you. A physical letter, identifying your participation in this study, may be sent to your doctor or your child's pediatrician to request assistance in the blood collection.

What are the costs of taking part in this study?

You will not be charged for any of the study activities. If you choose to check your infants, response to vaccinations this is considered standard of care and will be covered by your insurance, not the study.

Will I be paid for taking part in this study?

You will not be paid for taking part in this study.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Uma Mahadevan, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call her at 415/502-4444.

Treatment and Compensation for Injury: If you are injured as a result of being in this study, treatment will be available. The costs of the treatment may be covered by the University of California depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at 415- 476-1814.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor Uma Mahadevan at 415/502-4444.

For questions about your rights while taking part in this study, call the office of the **Committee on Human Research**, UCSF's Institutional Review Board (a group of people who review the research to protect your rights) at **415-476-1814**

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.

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CONSENT

Please read each sentence below and think about your choice. After reading each sentence, put your initials in the "Yes" or "No" box.

If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

- **Someone may contact me in the future to ask me to take part in more research.**

YES	*NO*

- **I freely agree to give a breast milk sample for IBD drug testing after 1, 12, 24, 48, 72, 96, 120, and 168 hours after my drug administration.**

YES	*NO*

- **I freely agree to give my baby's blood sample for checking response to vaccines (Haemophilus influenza, tetanus toxoid), as described in this form.**

YES	*NO*

- **I freely agree to give my infant's blood sample for checking my infant's blood at month 12 to determine if development of T and B cells is affected by the drug, which I am taking.**

YES	*NO*

- **I freely agree to give my infant's meconium and stool sample at birth, months 3, 6, and 9, annually between ages 1-18.**

YES	*NO*

- **I freely agree to give a blood sample from me prior to my COVID-19 vaccine and from me, my infant (optional) and my umbilical cord at my delivery.**

YES	*NO*

- **I freely agree to give 2 breast milk samples for COVID-19 related testing.**

YES	*NO*

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep. You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you as well as a separate form for your child.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

_____ _____
Date Participant's Signature for Consent

_____ _____
Date Parent's Signature for Child's Consent

_____ _____
Date Person Obtaining Consent