Cover Page:

Title: A Phase II study to evaluate the delay in ovulation following oral levonorgestrel plus meloxicam compared to placebo in normal menstruating women

NCT number: NCT05695352

Document date: November 8, 2021

Study Protocol:

1. Objective: This clinical trial determines 1) if an oral medication taken within 2 days of anticipated ovulation will delay ovulation by 7 days, 2) compare the incidence of unscheduled bleeding and interval between menses, 3) evaluate sitting blood pressure between cycles with placebo compared to treatment, and 4) treatment emergent adverse events between a placebo and a treatment cycle in normal menstruating women.

2. Design: The study compares placebo tablets (control) to a combination of levonorgestrel, a synthetic hormone plus meloxicam, a non-steroidal anti-inflammatory drug (treatment) in 22 healthy women between the ages of 18 to 40. The control and treatments are each taken orally 48 hours apart in the first and second menstrual cycle, respectively when the ovarian follicle has a diameter of 17 ± 1.0 mm measured by transvaginal ultrasound. This follicle diameter is found 2 ± 1.0 days before ovulation. Each study participant has approximately 9 visits during each of two menstrual cycles. The visits are between 3 to 6 from menstrual day 9 (first visit) to largest follicle depending upon follicle growth. A blood sample to measure serum estradiol and luteinizing hormone and a transvaginal ultrasound to measure ovarian follicle diameter are obtained at each visit. The appropriate first dose of medication (placebo first cycle and levonorgestrel plus meloxicam in the second cycle) is taken when the largest diameter of the lead ovarian follicle is 17 ± 1.0 mm in any dimension. The second dose is taken 2 days later with interim and final visits at 5 and 10 days following first dose. Each participant collects 4.0 mL of her first morning urine from menstrual day 9 to 23. This aliquot of morning urine is placed in a labelled storage tube and kept in the refrigerator freezer section until returned to the clinical site at a scheduled visit and stored frozen until analyzed a central laboratory.

3. Methods: Ovulation is determined using the change in ratio of the urinary metabolites of estradiol and progesterone known as the Day of follicular-Luteal Transition (DALT). The estradiol and progesterone metabolites are estrogen glucuronide and pregnanediol glucuronide, respectively. They are measured in the urine using specific antibodies to each metabolite using a specific ELISA kit. A published algorithm based on a moving day to day average of the metabolites ratio is used to determine the day of ovulation (DALT). The Investigators anticipate that the control cycle will have an interval to ovulation of ≤ 3 days from the first placebo dose to ovulation while a delay of ≥7 days will be found between the first treatment dose to ovulation. Treatment emergent side effects between control versus treatment cycles are based on symptoms such as nausea or

abdominal cramping, change in sitting blood pressure and the interval between menstrual bleeding and /or unscheduled bleeding between menses.

4. Outcomes: The primary outcome compares the interval in days from first dose of each medication to ovulation between placebo and treatment. Secondary outcomes are changes in mean blood pressure, unscheduled vaginal bleeding, and interval between menstrual periods, adverse events such as nausea, headache, and abdominal and /or menstrual cramps in placebo cycle compared to the treatment cycle.

5. Statistical Analysis: We expect that two doses of a levonorgestrel plus meloxicam combination, dosed 48h apart with the first dose administered when the dominant follicle has reached 17±1.0 mm in size, will result in the "Day of follicular-Luteal Transition" (**DALT**) being delayed by at least 7 days vs the time to DALT ≤3 days when a woman received two doses of placebo. The DALT following determination of the ratios of the urinary metabolites of estrone conjugates and progesterone will be identified using published algorithms. Survival analysis/LogRank method was applied to calculate the required sample size. The outcome event is the time until ovulation (DALT) and censored observations (subjects for whom ovulation did not occur during the 10-day follow-up time) are probable. The aim is to compare the survival curves for the 2-doses placebo to the 2-doses treatment group using the length of follow-up for each patient and the Log-Rank Test. The Null Hypothesis is that there will be no significant difference between the two survival curves. The sample size is obtained for a power of 80% and a two-sided test size alpha of 5%. We assume that the ovulation rate in the placebo group is approximately 95% by 10 days after the first dose of placebo. If we want to increase the success rate (failure to ovulate) from 5% in the placebo group to 80% in the treatment group by 10 days after the first dose of drug combination, we will need to recruit to complete 22 subjects. We plan to enroll 26 or more participants to complete a minimum of 22 participants in this study.

Informed Consent:

Participant Consent Form And Authorization to Use and Disclose Protected Health Information

Sponsor / Study Title:	**InnovaGyn, Inc. / "A Phase II study to evaluate the delay in ovulation following oral levonorgestrel plus meloxicam compared to placebo in normal menstruating women"**
Protocol Number:	**IG-20-001**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**

Address: **«PiLocations»**

KEY SUMMARY OF INFORMATION

You are invited to take part in a research study evaluating levonorgestrel plus meloxicam (LNG/MEL) as a possible "on-demand" contraceptive, sponsored by InnovaGyn, Inc. The use of LNG/MEL in this study is investigational. An investigational use is one that is not approved by the United States Food and Drug Administration (FDA). It is important that you do not become pregnant while in the study; you must use effective methods of birth control throughout the study. This page provides key information to help you decide whether to participate. The detailed consent form follows this page. If you have questions, please ask the research team, or contact the principal investigator in charge of this study.

WHAT IS THE PURPOSE, WHAT ARE THE PROCEDURES, AND WHAT IS THE DURATION OF THIS STUDY?

The purpose of this study is to find out if ovulation is delayed when using LNG/MEL compared to placebo (inactive substance); if there are any effects of the LNG/MEL study drug on menstrual periods and unscheduled vaginal bleeding; the effects the study drug has on the function of the ovaries and uterus; if there are side effects from this study drug; if the side effects from this study drug are more or less serious than the side effects from other hormonal contraceptives. Your total time in the study is expected to include up to 18 visits over 3 months, including a screening period, control cycle, study treatment cycle, and follow up after the end of study treatment. The exact number of site visits is unknown.

WHAT ARE SOME REASONS YOU MIGHT CHOOSE TO PARTICIPATE IN THIS STUDY?

You will receive medical and gynecological exams, laboratory assessments and satisfaction of participating in the possible development of a new "on-demand" contraceptive option for women. You will receive compensation for travel and costs that are associated with participation in the study.

WHAT ARE SOME REASONS YOU MIGHT CHOOSE NOT TO PARTICIPATE IN THIS STUDY?

You might choose not to participate in this study if you have any health problems or conditions or are taking any medicines with contraindications to the study drug and study requirements, or if you are planning to become pregnant. You will need to consider the exposure to research related risks as well as potential side effects. For a complete description of the risks of this study, please refer to the detailed consent form.

DO YOU HAVE TO TAKE PART IN THIS STUDY?

Participation in this study is voluntary. If you do not want to be in this study, you will still receive any of the services otherwise available to you at this study site. You are free to withdraw from the study at any time.

WHAT IF YOU HAVE QUESTIONS OR CONCERNS?

For questions about the study, contact the investigator at the phone number listed on page one of this form.

Please continue for detailed information about the study.

SPONSOR
The costs of this study, including administrative fees paid to the investigator(s), are being paid by InnovaGyn, Inc., who developed the experimental on-demand contraceptive containing levonorgestrel and meloxicam being studied.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to find out:

- If ovulation is delayed when using LNG/MEL compared to placebo.
- If there are any effects of the LNG/MEL study drug on menstrual periods and unscheduled vaginal bleeding.
- The effects the study drug has on the function of the ovaries and uterus.
- If there are side effects from this study drug that are different from what we know about side effects from other hormonal contraceptives.
- If the side-effects from this study drug are more or less serious than the side-effects from other hormonal contraceptives
- Sexually experienced women have indicated a need for a discreet oral product that is a highly effective contraceptive method with limited side effects, to be taken immediately before or after intercourse. This approach has been termed on demand or pericoital contraception when the product is taken within 24 hours before or after intercourse. This method reduces the need for motivation to take continuous oral medication and potentially reduces the exposure to daily exogenous hormones used with long-acting reversible methods.

WHY ARE YOU BEING ASKED TO TAKE PART?
You are being asked to participate in this research project because you are a woman who is generally healthy with no chronic medical conditions, 18 through 40 years old, have a regular menstrual cycle that starts every 24-32 days, and have a uterus and both ovaries.

This is a research study. This study includes only people who choose to take part. Please take your time to make your decision and feel free to ask any questions you might have.

WHAT ARE SOME IMPORTANT DETAILS ABOUT THIS STUDY?
At this local site 22 people will take part in this study at one (1) site in the United States. We will need you to be in the study for approximately 3 months.

Clinically relevant research results will not be disclosed to participants.

WHEN SHOULD YOU NOT TAKE PART?

To join the study, you should not be pregnant and must not have had any unprotected heterosexual intercourse during the previous 10 days. If you have intercourse you or your partner should use a condom, or diaphragm, or you could have a copper intrauterine device for contraception. You should not currently be using hormonal contraception (a pill, vaginal ring, patch, or injection and the levonorgestrel releasing intrauterine device). Also, you must understand what is required to take part in the study and be willing to meet the study requirements.

If you have any of the following health problems or conditions or are taking any of the medicines listed below, you should not take part in this study:

1. Known hypersensitivity or allergies to progestins and non-steroidal anti-inflammatory drugs such as Advil/Ibuprofen.
2. Abnormal transvaginal ultrasound or safety laboratory results evaluated during the screening period recognized as clinically significant by the investigator or medically qualified designee.
3. Known or suspected alcohol or marijuana abuse.
4. Undiagnosed abnormal genital bleeding.
5. Undiagnosed vaginal discharge, lesions, or abnormalities. Potential participants diagnosed with Chlamydia or Gonorrhea at screening may be included in the clinical study if treatment was completed. Women with a history of genital herpes can be included if the outbreaks are infrequent and antiviral prophylaxis is allowed if used.
6. Uncontrolled thyroid disorder.
7. Current use of hormonal contraception or a levonorgestrel releasing intrauterine device.
8. Use of a long-acting injectable hormonal contraceptive within the past 6 months and must have had at least one spontaneous menstrual cycle (two menstrual bleeding episodes) since the last injection.
9. Breastfeeding women or those within 30 days of discontinuing breast-feeding or those who have discontinued and had not had a spontaneous menstrual bleed.
10. Women who plan a major surgical procedure during the study.
11. Women (couples) who plan to become pregnant during the months of the study procedures.
12. Women who smoke greater than 15 cigarettes per day or who use greater than 1 mL/day of nicotine-containing liquid for electronic cigarettes should be evaluated for the impact of this use on its impact on increasing the risk of cardiovascular disease and thromboembolism.
13. Current or history of ischemic heart disease or stroke while pregnant or during use of hormonal contraception.
14. Current or past deep vein thrombosis (blood clot) or thromboembolic disorder.
15. History of thrombophilia in a first degree relative less than 45 years of age suggesting a defect in the blood coagulation system. The Principal Investigator's opinion of the risk with hormonal contraception should be considered.
16. History of retinal vascular lesions, partial or complete loss of vision.
17. Known or suspected cancer of the breast, endometrium, or other suspected progestin sensitive neoplasia.

18. History of other carcinomas excluding basal cell cancers unless in remission for greater than 5 years.
19. Current or past medically diagnosed severe depression unless the potential participant is on stable medication and in the opinion of the Principal Investigator could be exacerbated using a hormonal contraceptive.
20. History of headaches with focal neurologic symptoms.
21. Have a current need for exogenous hormones or therapeutic anticoagulants.
22. History of jaundice during a pregnancy or jaundice with prior steroid hormone use.
23. Other benign or malignant liver tumors or active liver disease.
24. Systolic blood pressure (BP) greater than or equal to 145 mm Hg and /or diastolic BP greater than or equal to 96 mm Hg after 5 -10 minutes of rest in a sitting position. Systolic BP greater than 145 mm Hg and/or diastolic BP greater than 95 mm Hg is exclusionary. If the initial BP values are above these cut-offs a total of 3 measurements may be taken and the results averaged. If the average BP is below the cut off levels the participant may be allowed into the study. Hypertension that is treated and controlled may in the judgment the Investigator are good candidates for the study require a waiver.
25. Clinically significant abnormal blood chemistry values of liver or kidney function based on the Investigator judgement.
26. Participation in another clinical trial involving an investigational drug or device within the past two months before anticipated enrollment or is planning to participate in another clinical study during this study.
27. Use of any liver enzyme inducers or plans to use such medication during the study (See Appendix).
28. Known HIV infection.
29. History of a gastrointestinal ulcer or bleeding.
30. Women who are using medication on the exclusionary medication list (See Appendix).
31. Have issues or concerns in the opinion of the Investigator that may compromise the study or confound the reliability of compliance and information that is required in this study.
32. Have a known hypersensitivity to either levonorgestrel or a non-steroidal anti-inflammatory drug.
33. Use of any medication that could interfere with the metabolism of a hormonal contraceptive or the non-steroidal anti-inflammatory drugs or any drug that falls in FDA Pregnancy and Lactation narrative subsections (Formerly Category D or X medications)
34. Be a site member with delegated study responsibilities or a family member of, or have a close relationship with, a site staff member will be delegated study responsibilities.

WHAT IS INVOLVED IN THE STUDY?

Your total time in the study is expected to last up to 3 months. The screening period will be approximately 2 weeks, the control cycle will be 1 month, the study treatment cycle will be 1 month, and follow up will occur approximately 3 weeks after the end of study treatment. The exact number of site visits is unknown as the study drug is given based on the largest size of the ovarian follicle (cyst) reaching a pre-determined size using a transvaginal ultrasound scan of

your ovaries. It is estimated there will be approximately 18 scheduled visits over 3 months that will need to be completed during the study.

During the study, a total of approximately 100 mL of blood (about 20 teaspoons or less than one-half of a cup) will be drawn from you over 3 months. The most blood drawn in a single day will be 18 mL, or less than 4 teaspoons. You will be asked to collect your first morning urine from menstrual day 9 to 23 and place a teaspoonful of this urine in a vial for storage. The vial is kept frozen in your refrigerator until returned to the clinical site.

If you are enrolled and agree to participate, you must not be at risk of becoming pregnant for your entire time of study participation. If you are sexually active in a heterosexual relationship, either your partner must be surgically sterile with a vasectomy, you must have previously had your tubes tied (tubal ligation) or you must use another non-hormonal method of birth control to prevent pregnancy (such as condoms, diaphragm plus spermicide, or a copper IUD).

Once you have decided to participate in the study, you will first be sent the informed consent to review before your scheduled appointment. This should provide a minimum of 24 hours before your appointment in order to read and consider participation in the study. On the day of your first visit you will be asked to sign and date this Informed Consent Form indicating you have read and understood the study and all of your questions have been answered before any study procedures will be done.

If you agree to be in this study, you will be asked to give your consent by signing and dating this form. Participation is expected to consist of approximately 18 study visits over 3 months. The details of these visits are described below. A table of these visits has also been provided later in this form.

At most visits, study staff will review your study diary, in which you will be asked to record daily occurrence of vaginal bleeding or spotting and collect vital signs. At pre-study treatment visits and during each menstrual cycle, you will have your blood drawn and a pelvic ultrasound (US) test will be performed. At post-study treatment visits you will drop off your daily morning urine collection.

During visits where blood is drawn (screening and pre-study treatment) about 1-3 teaspoons of blood will be drawn. During the study a total of approximately 100 mL of blood (about 20 teaspoons or less than one-half of a cup) will be drawn. Urine pregnancy tests will be performed at screening, at your first control cycle visit and your first study treatment cycle visit. This test must be negative in order for you to continue in the study.

You will have one screening visit. This visit will occur between the twentieth and twenty-fourth day (20^{th} and 24^{th} day) of your menstrual cycle. The following will occur at the first visit:

1. Read the informed consent form and ask questions about things you do not understand. Before you sign and date the consent form, make sure you understand what this study is about and what you will be asked to do.

2. The study site staff needs to make sure the study is right for you. They need to obtain the following:
   a. Information about you, including your date of birth, ethnicity, and race.
   b. Your medical history, including all past and current medical problems, surgeries and gynecological (female reproductive) history. The information collected will include smoking history, history of alcohol or drug use (if you have used either), menstrual cycle history, pregnancy history and current sexual activity information.
   c. Your family history of certain health conditions like blood clots.
   d. Your blood pressure will be measured after you have rested by sitting for 5-10 minutes. It will be measured three times with a five-minute rest period between the measurements.
   e. Your pulse, weight, and height will be recorded. The study staff will tell you what your body mass index (BMI) is.
   f. Tell the study staff about the medicines you are taking or have taken in the previous two weeks. This includes prescriptions, over-the-counter medicines, vitamins, and herbal products.
   g. You will have a complete physical examination, including a breast exam, a pelvic exam (internal female exam), and a cervical Pap smear (unless you have had one recently and the study doctor can obtain the results, or if you are under 21 years old). You will also be screened for Gonorrhea, Chlamydia and Trichomonas.

      During the pelvic exam, you will lie on your back with your feet in stirrups. Your study doctor will insert a speculum into your vagina. The speculum gently spreads apart the vaginal walls, allowing your study doctor to see the inside of the vagina and the cervix (opening to the womb). You may feel some slight discomfort when the speculum is placed. Swabs will be used to collect samples from your vagina and cervix for testing.

      A pelvic ultrasound (US) test will be performed. Before the study procedure, you will be asked to empty your bladder. For the ultrasound, the tip of a small, thin ultrasound instrument (probe) is lubricated with a small amount of gel and inserted in your vagina. Only two to three inches of the instrument are inserted into the vagina. Ultrasound imaging uses sound waves to produce pictures of the inside of the uterus and ovaries. The ultrasound pictures will be shown on a computer monitor. The study doctor will be looking at the thickness of the endometrium (lining of the womb) and number and size of ovarian follicles (fluid filled sacs located just beneath the ovary's surface that contain the immature eggs).

      The Pap test is a test of a sample of cells taken from a woman's cervix (opening of the womb). This test is used to look for changes in the cells of the cervix that show

cervical cancer or conditions that may develop into cancer. If you are due for a Pap, this test will be done while the speculum is inserted during the pelvic exam. If you have a vaginal infection, you may be given medicine for it before you can enroll in the study.

h. Regular blood and urine tests, including urine pregnancy tests.
i. You will be given a diary to fill out and instructions on urine collection.

After the screening visit is complete, you will contact your study coordinator on the first day of your next menses. Your study coordinator will schedule you to come in on the ninth day (9th day) of your menstrual cycle to begin the control/study treatment cycle procedures. Refer to the visit flow chart below for additional information.

Appendix: On Demand Visit Flow Chart

	Screen[a]	**Control Cycle Pre-Study Treatment Visits [b]**	**Control Cycle DOSE 1[c]**	**Control Cycle DOSE 2[d]**	**End of Cycle Urine Collection CD 22**	**Study Treatment Cycle Pre-Study Treatment Visits[b]**	**Study Treatment Cycle 2 DOSE 1[c]**	**Study Treatment Cycle 2 DOSE 2[d]**	**End of Cycle Urine Collection**	**EXIT visit[H]**
Procedures										
Informed Consent Form (ICF)	X									
Med HX	X									
Con Med	X	X		X	X	X			X	X
Adverse Events (AEs)	X	X		X	X	X			X	X
Vitals[e]	X	X		X	X	X			X	X
Height and Weight	X								X	
Complete blood count (CBC)	X									
Chemistries	X									
P4	X									
Estradiol		X				X				
Luteinizing hormone		X				X				
Physical Examination	X									
Urine Pregnancy Test (UPT)	X	X				X				X
Transvaginal Ultrasound (TVU)	X	X				X				
Study Drug Dispensing			X	X			X	X		

Daily Urine Collection[f]		X			X				X	
Dispense Diary and Collect[G]		X				X			X	X

[a] Screening to occur on CD 20-24

[b] Pre-study treatment visits will start on CD 9. Frequency and number of visits is dependent on follicle monitoring and up to the discretion of the PI. Each visit has a blood draw for estradiol and luteinizing hormone and a transvaginal ultrasound for uterine stripe and ovarian follicle size.

[c] Initial dose will occur when dominant follicle measures 17±1.0 mm in the largest diameter and after all pre-study treatment visit procedures are completed

[d] Second dose to occur 48 hours after initial dose

[e] Vitals consist of sitting blood pressure and pulse

[f] Collect daily first void morning urine beginning cycle day 9 and ending 10 days after first dose. Aliquot urine into supplied capped tube and refrigerate.

[G] Dispense daily diary at first visit day 9 in both cycles and collect on second cycle day 9 and at exit visit.

[H] Exit visit between day 5 to 10 after study treatment cycle 2 menstrual bleed.

WHAT ARE THE RISKS OF THE STUDY?

You may have some side effects we do not expect because we are still learning about this study drug. The side effects listed below have been reported in people who used LNG (levonorgestrel) in pills, implants or IUDs (intrauterine devices). LNG is a drug that is similar to LNG/MEL study drug. Because the LNG is the active component of LNG/MEL in the body, we expect that the side effects from LNG/MEL will be similar to those seen in women using LNG. MEL (meloxicam) can cause indigestion, nausea, vomiting or bleeding from your bowel. Meloxicam has also been associated with heart attacks, blood clots in the leg, and stroke, mainly in older men and women. There may be other unknown side effects of the LNG/MEL study treatment.

It is not known if a woman using this LNG/MEL study treatment is at a higher risk of serious side effects than she would be if she used an FDA approved birth control.

Risks and side effects related to the LNG/MEL study drug may include:

- Irregular menstrual spotting or bleeding 23%
- More frequent or prolonged or heavy bleeding 30.9%
- Frequent onset of bleeding and/or very light or absent menstrual bleeding 52%
- Headache 12%
- Vaginal irritation/inflammation 20%
- Breast tenderness or pain 8.2%
- Abdominal pain 13.3%
- Mood changes 4%
- Nausea 13.7%
- Acne 15%
- Discomfort with menstruation 9%
- Back or pelvic pain 6%
- Elevations in liver function tests 1%

Less likely side effects may include:

- Migraine headache 2%
- Abnormal hair growth (increased hair growth and/or hair loss) 1%
- Pelvic cramping 6%
- Ovarian cysts symptoms include: 13%
    - Pelvic pain
    - Nausea
    - Vomiting
    - Fullness in the abdomen
    - Pressure on your rectum or bladder

Rare but serious side effects may include:

- Severe allergic reactions less than 1%. Symptoms may include:
    - Rash
    - Hives
    - Itching
    - Difficulty breathing
    - Tightness in the chest
    - Swelling of the mouth, face, lips, or tongue

Meloxicam is a well-known non-steroidal anti-inflammatory drug (NSAID) used to treat and reduce the pain of arthritis. It is principally taken daily by older men and women for chronic arthritic or muscular pain. There is an increased risk of cardiovascular disease such as deep vein thrombosis and myocardial infarction with chronic daily administration of non-steroidal anti-inflammatory drugs that is also age related. Gastric ulcers and gastrointestinal bleeding are associated with chronic administration of an NSAID at any age. Skin reactions are infrequent but can be life threatening. Stevens Johnson Syndrome and Toxic epidermolysis are rare but can have serious or fatal side effects. Common side effects occurring in more than 5% of users are:

- Diarrhea 7.8%
- Upper respiratory tract infection 6.1%
- Dyspepsia (indigestion) 4.45%
- Influenza like symptoms 5.8%

You should contact your study staff and study doctor immediately if any of these serious events occur. If your study doctor cannot be reached, you should seek medical treatment at the nearest medical facility available to you.

There may be other side effects that are unknown and that we cannot predict.

WHAT ARE THE RISKS OF THE STUDY PROCEDURES?

- Blood Collection (Venipuncture): Venipuncture is taking blood from a vein by needle. There is a risk of fainting, infection, bruising, swelling and pain at the site of the blood

drawing. Blood samples will be taken with each ultrasound visit. Fasting blood samples will be taken at the screening visit.

- Gynecological Exams and Pap Smears: Gynecological exams and pap smears may cause some slight pain or cramping. Some women may experience temporary spotting or bleeding afterward.
- Diary, Acceptability Questionnaire and Medical History Questions: Some of the questions you will be asked may seem personal or embarrassing. They may upset you. You may refuse to answer any of the questions that you do not wish to answer. If the questions make you very upset, we will help you find a counselor.

A risk associated with allowing your data to be saved is the release of personal information from your study record. We will strive to protect your records so that your personal information (like name, address, social security number and phone number) will remain private.

While on the study, you are at risk for these side effects. You should discuss these with the investigator and/or your regular doctor or healthcare provider. Other drugs may be given to make side effects less serious and make you more comfortable. Many side effects go away shortly after the LNG/MEL is stopped, but in some cases side effects can be serious, long lasting and/or permanent.

Reproductive risks: Because the study drugs in this study can affect an unborn baby, you should not become pregnant while on this study. You should not breastfeed your baby while on this study. Ask about counseling and more information about preventing pregnancy. Acceptable methods of birth control include: either your partner must be surgically sterile with a vasectomy or you must have previously had your tubes tied (tubal ligation) or you must use another non-hormonal method of birth control to prevent pregnancy (such as condoms, diaphragm plus spermicide, or copper IUD). You will have to use one of these methods the whole time you are in this study. You should consider this before you decide to take part in this study. This study is <u>NOT</u> intended to find out how well the study drug works to prevent pregnancy, so if you are sexually active with a male partner, you <u>must</u> use other means of birth control while you are in the study.

The LNG/MEL study treatment should not be considered a form of birth control. The LNG/MEL study treatment must not be relied upon as a method of birth control. To take part in this study, you must not be at risk of becoming pregnant. You do not have to be sexually active to take part in this study.

Talk to the study doctor or study nurse about what you might do if you become pregnant and do not wish to continue the pregnancy. If you become pregnant, LNG has not been shown to affect the fetus. MEL has inconclusive information on early pregnancy, but near delivery it can affect the fetus only if you continue to take it during the pregnancy. You should understand what you could do before you give consent to take part in this study.

If you become pregnant during the study, you will be discontinued from the study and complete the study procedures for the Exit Visit. You will be informed about pregnancy options and referral for appropriate care. The study staff will monitor the pregnancy until the pregnancy outcome is known or 6- or 12-month follow-up after delivery. The study staff will attempt to estimate the date of conception by performing a pelvic ultrasound and/or pelvic and/or abdominal examination and by looking at your diary information and blood hormone levels.

For more information about risks and side effects, ask the investigator.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be a direct benefit to you. There is no guarantee that you will personally benefit from taking part in this study. We hope the information learned from this study will benefit other women with the development of a new "on-demand" contraceptive option in the future.

WHAT ABOUT CONFIDENTIALITY?

In conducting this research study, it may be necessary for the research team to send information about you and your health to persons in other organizations. For example, the investigator or members of the research team will report the results of your study-related data to InnovaGyn, Inc., the sponsor of the study. This information may include what we call "protected health information (PHI)," which includes personal information about you. It will be shared with others only as described below:

Description of Your PHI to Be Disclosed	Organization and Person (or their title) Disclosing Your PHI	Organization and Person (or their title) Receiving Your PHI	Purpose of Disclosure
Name, Social Security #, Participant #, Initials	Investigator and/or research center	David F. Archer, MD and InnovaGyn, Inc.	Identification and reporting laboratory results and issuance of an IRS 1099 form for reimbursed for participating in the study
Date of Birth, Demographics, Medical History and Acceptability Questionnaire	Investigator and/or research center	David F. Archer, MD and InnovaGyn, Inc.	Data management and analysis; To protect the rights and safety of participants and make sure applicable laws are followed

All protected health information will be maintained in strict confidence as required by law. However, your protected health information may be disclosed if required by law. Once your protected health information is disclosed for research, such as to the sponsor, federal privacy laws may no longer protect the information.

- If you refuse to give your approval for your personal information to be shared as described in this consent form, you will not be able to be in this study. However, your choice will not affect any medical benefits to which you are entitled.
- By signing and dating this consent form to participate in the study, you are allowing the research team to share PHI, as described in this consent form.
- You have the right to cancel your approval for the sharing of PHI. If you cancel your approval, you will have to leave the study. All information collected about you before the date you cancelled will not be used. To cancel your approval, you must notify the investigator.
- Your approval for the sharing of personal information about you for this study does not expire at the end of the study.
- You also have the right to review your research records, or someone you designate may review your research records on your behalf once the study has ended unless prohibited by law.
- Any research information in your medical record will become a permanent part of that document.

Your study records may be reviewed and/or copied in order to meet state and/or federal regulations. Reviewers may include, for example, the Institutional Review Board, Representatives of InnovaGyn Inc., The Food and Drug Administration (FDA) and other US governmental agencies, Government agencies to whom certain diseases (like HIV, hepatitis, and STDs) must be reported, Governmental agencies of other countries, Labs working with the sponsor on this study, and other authorized users.

To ensure that your information collected for this study will be kept private, your name will not be used whenever possible. A code will be used instead of your name. All of your study data will be kept in a secure location.

Your health data needs to be shared for the research and other reasons. Therefore, complete privacy of your health data cannot be promised. However, sharing your health data will be guided by professional standards and the law.

Information from this study may be presented at meetings or published in medical journals. The information included at meetings or in journals will not include your name or information that can easily be traced back to you.

Information learned from this research may be used in reports, presentations and publications. None of these will personally identify you.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the agency which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of, for instance, child abuse or neglect, harm to self or others, and communicable diseases.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

WHAT WILL PARTICIPATION IN THE STUDY COST OR PAY?

There are no additional costs to you associated with taking part in this study.

You could receive up to $910.00 if all study visits are completed. You will be paid $100 for the Screening Visit. At the End of Cycle 1, you will be paid $380. At the end of Cycle 2, which includes the Exit Visit, you will be paid $430.

You will be paid following each completed visit (Screening, Cycle 1, and Cycle 2) or at the end of your participation in the research study. If you do not finish the study, you will only be paid for the visits you completed.

If the amount exceeds $600 within a calendar year, an IRS Form 1099 will be filed with the Internal Revenue Service, with a copy going to you.

If any new products, tests, or discoveries resulting from the research have potential commercial value, you will not be compensated or benefit financially.

ALTERNATIVES TO PARTICIPATION
This research study is for research purposes only. The only alternative is to not participate in this study.

WHAT IF YOU GET INJURED?
In the case of injury or illness resulting from this study, please seek emergency medical treatment. Financial compensation for a research related injury or illness, lost wages, disability, or discomfort is not available. However, you do not waive any legal rights by signing and dating this consent form.

WHAT ABOUT THE COLLECTION OF DATA/TISSUE/SPECIMENS?
Researchers can look closely at large amounts of your genetic information by sequencing, or "reading," every letter in your DNA (your genome). Reading a person's entire genetic code is called whole genome sequencing. The research **will not include** whole genome sequencing (for example, sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

You are in a study where data and blood samples are collected as part of your participation in the research study. These data and blood samples will not be used or distributed for future research studies by the investigator or other researchers. After all of the study testing is complete, the data and specimens will be destroyed.

To ensure that your identifiable data collected for this study will be kept private, your name will not be used whenever possible. A code will be used instead of your name. All your study data will be kept in a secure location. Your health data needs to be shared for the research and other reasons. Therefore, complete privacy of your health data cannot be promised. However, sharing your health data will be guided by professional standards and the law. For more detailed information, please refer to the section of this consent titled "What about confidentiality?"

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?
Taking part in this study is your choice. If you decide not to take part, your choice will not affect any medical benefits to which you are entitled. You may choose to leave the study at any time. If you do leave the study, discuss it with the investigator who will help you do so in the safest way. If you leave, the study it will not result in any penalty or loss of benefits to you.

The investigator may decide to take you off this study if you cancel your approval or if it is in the best interest of your health, if your condition worsens, if funding it stopped, or in the case of non-compliance with study requirements. We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Virginia law says that if you or anyone associated with the study is exposed to the other person's body fluids that might transmit the virus that causes AIDS or the Hepatitis B or C virus:

- The person whose body fluids were involved is deemed to have consented to testing for those viruses so that no further consent is necessary to test the person for these diseases; and,
- Those test results will be released to the person who was exposed and to the health department as required by Virginia law.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact:

- By mail:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00059583.

FDA CLINICAL TRIAL REGISTRATION

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.

SIGNATURE		
You will get a copy of this signed and dated form. You may also request information from the investigator. By signing and dating your name on the line below, you agree to take part in this study and accept the risks.		
_____ Typed or Printed Name	_____ Signature of Participant	___/___ /___ MM/ DD/ YY

STATEMENT OF THE INVESTIGATOR OR APPROVED DESIGNEE	
I certify that I have explained to the above individual the nature and purpose of the study, potential benefits, and possible risks associated with participation in this study. I have answered any questions that have been raised and have witnessed the above signature. I have explained the above to the participant on the date stated on this consent form.	
_____ Signature of Investigator or Approved Designee	_____ / _____ / _____ MM/ DD/ YY

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

If you decide to be in this study, the investigator and study staff will use and share health data about you to conduct the study. Health data may include:

- Your name.
- Address.
- Phone number.
- Date of birth.
- Medical history.
- Information from your study visits, including all test results.

Health data may come from your study records or from existing records kept by your doctor or other health care workers.

For this study, the study staff may share health data about you with authorized users. Authorized users may include:

- Representatives of InnovaGyn, Inc.
- Representatives of Advarra IRB (an Institutional Review Board that reviews this study).
- The Food and Drug Administration (FDA) and other US federal and state agencies.
- Government agencies to whom certain diseases (like HIV, hepatitis, and STDs) must be reported.
- Governmental agencies of other countries.
- Outside individuals and companies, such as laboratories and data storage companies, who work with the researchers and sponsor and need to access your information to conduct this study.
- Other research doctors and medical centers participating in this study, if applicable.
- A data safety monitoring board which oversees this study, if applicable.

Your health data will be used to conduct and oversee the research, including for instance:

- To see if the study drug works and is safe.
- To compare the study drug to other drugs.
- For other research activities related to the study drug.

Once your health data has been shared with authorized users, it may no longer be protected by federal privacy law and could possibly be used or disclosed in ways other than those listed here.

Your permission to use and share health data about you will end in 50 years unless you revoke it (take it back) sooner.

You may revoke (take back) your permission to use and share health data about you at any time by writing to the investigator at the address listed on the first page of this form. If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered

after your written request is received. However, health data about you that has already been gathered may still be used and given to others as described in this form.

Your right to access your health data in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health data.

If you decide not to sign and date this form, you will not be able to take part in the study.

STATEMENT OF AUTHORIZATION		
I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing and dating this form.		
_____ Typed or Printed Name	_____ Signature of Participant	___/___ /___ MM/ DD/ YY