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Pre-IVF treatment with a GnRH antagonist in women with endometriosis (PREGnant): Study protocol for a prospective, double-blind, placebo-controlled trial

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Abstract

Introduction: Infertility is a common complication of endometriosis. While in vitro fertilization-embryo transfer (IVF-ET) successfully treats endometriosis-associated infertility, pregnancy rates are diminished in women seeing fertility treatment for endometriosis-associated infertility compared to other etiologies of infertility. The use of gonadotropin releasing hormone (GnRH) agonist prior to IVF has been suggested to improve success, however studies have been small and rarely reported live birth rates. Recent approval of an oral GnRH antagonist for endometriosis provides a novel option for women with endometriosis who are undergoing IVF. There have been no studies on the efficacy of GnRH antagonists for the treatment of endometriosis-related infertility.

Methods and Analysis: This study is a multi-center, prospective, randomized, double-blind, placebo-controlled trial to study the efficacy of GnRH antagonist pre-treatment for women with endometriosis who are undergoing IVF. A total of 814 patients with endometriosis undergoing fertility treatment will be enrolled and randomized 1:1 into two groups: elagolix 200 mg bid or placebo for 8 weeks, prior to undergoing IVF. All participants will then undergo IVF treatment per local protocols. The primary outcome is live birth. Secondary outcomes include oocyte number, fertilization rate, embryo morphology, and implantation rates, as well as rates of known endometriosis-related obstetrical outcomes (pregnancy-induced hypertension, antepartum hemorrhage, cesarean delivery, and preterm birth).

Ethics and Dissemination: This protocol is undergoing Institutional Review Board approval at Johns Hopkins University, pending a minor modification, with reliance agreements at all participating sites. Findings will be published in peer-reviewed journals.

Trial Registration: ClinicalTrials.gov Identifier NCT04173169

FDA IND: 152645

Key words: endometriosis; in vitro fertilization; IVF; gonadotropin releasing hormone; GnRH; elagolix; GnRH antagonist; Live birth

Strengths and Limitations of this Study

- Limited evidence suggests that pre-treatment with GnRH agonists may improve IVF outcomes in patients with endometriosis; however, the recently available oral GnRH antagonist has not yet been studied for this purpose.
- This study is a multi-center, prospective, randomized, double-blind, placebo-controlled study, randomizing 814 patients with endometriosis undergoing fertility treatment 1:1 to elagolix 200 mg bid or placebo for 8 weeks prior to undergoing IVF.
- This study uses a selective inclusion criteria requiring a documented diagnosis of endometriosis via direct surgical visualization or standardized sonographic evidence.
- Participants will undergo routine IVF protocols at each study site, improving the generalizability of results.
- Participants will not be stratified by endometriosis severity or treatment history, and both fresh and frozen embryo transfers will be included in this study, which is not powered to detect differences in effect within these clinical subgroups.

Introduction

Endometriosis is a disease of ectopic endometrial glands outside the uterus, commonly involving the adnexa and pelvic peritoneum. In addition to being a common cause of chronic pelvic pain, endometriosis is also associated with poorer reproductive outcomes. While endometriosis affects 10-15% of reproductive aged women [1,2], it is present in 25-50% of women with infertility and conversely, 30-50% of women with endometriosis struggle with infertility [3]. The fecundity of normal reproductive age couples without infertility is estimated to be around 15% to 20% per month, while the fecundity of women with untreated endometriosis is estimated at 2%-10% [4,5]. Women with mild endometriosis have a significantly lower probability of pregnancy over 3 years compared to women with unexplained fertility (36% vs.

55%, respectively) [6]. Endometriosis is also associated with obstetrical complications, including obstetrical hemorrhage, cesarean delivery, pre-eclampsia and pregnancy-induced hypertension, and preterm birth [7–12]. While the mechanism remains controversial and unclear, endometriosis is thought to contribute to reduced fertility via adnexal scarring and poor endometrial receptivity, though studies also suggest with women with advanced endometriosis also have poor ovarian reserve, low oocyte and embryo quality, and poor implantation [1,13–15].

While IVF is currently the most effective treatment for endometriosis-associated infertility, endometriosis is also associated with poorer IVF outcomes. One meta-analysis from 2002 including 22 non-randomized trials reported that the chances of achieving pregnancy with IVF in women with endometriosis was almost half that of those with tubal infertility (odds ratio [OR] = 0.56, 95% confidence intervals [CI] = 0.44–0.7) and women with severe disease had about half the pregnancy rate of those with mild disease [16]. A more recent study published in 2018 confirmed that women with endometriosis still have a 24% lower likelihood of live birth after IVF than women with unexplained infertility [17]. These data support the notion that when endometriosis is present, both spontaneous and ART-facilitated pregnancy rates are reduced, and that there is a dose-response effect in that those with worse disease have a worse prognosis.

As a hormone-dependent disorder, medical management of symptomatic endometriosis has targeted ovarian estrogen production, including combined oral contraceptives, progestins, danazol and gonadotropin-releasing hormone (GnRH) agonists or antagonist [18]. While these therapies have been helpful in managing endometriosis-associated pelvic pain, they have not been shown to treat endometriosis-associated infertility in the absence of IVF [19].

In the IVF setting, prolonged GnRH agonist treatment prior to IVF has been shown to improve fertility rates in women with advanced endometriosis [20–22]. Proposed mechanisms are by means of increased retrieved oocytes, higher implantation rates, and reduced preclinical

abortions [15,20]. A Cochrane review of 3 RCTs in 165 women with endometriosis concluded that GnRH agonist administration for a period of 3-6 months prior to IVF or ICSI increases the odds of clinical pregnancy (OR 4.28, 95% CI 2.00–9.15) [23]. However, none of those studies were placebo controlled, only one reported live birth rates and none provided sufficient data to investigate important secondary outcomes such as multiple or ectopic pregnancies, miscarriage, fetal abnormalities, or other complications.

Since then, the GnRH antagonist elagolix has recently become available for use, with a number of advantages over GnRH agonists: the convenience of oral rather than parenteral administration, improved tolerability and reduced severity of vasomotor symptoms, rapid onset of action with suppression of endogenous estradiol levels within 24 hours, and lack of initial gonadotropin stimulation ("flare" effect) seen with GnRH agonists [24]. However, elagolix has not yet been studied as an adjunctive treatment prior to IVF for women with endometriosis. Based on limited evidence from GnRH agonist trials, we hypothesize that GnRH antagonist therapy may also benefit women with endometriosis undergoing IVF treatment, possibly with a shorter course of treatment compared to what has been studied with GnRH agonists (3-6 months) [23].

Methods and Analysis

This is a multicenter, prospective, randomized controlled trial to study the effect of GnRH antagonist pre-treatment for women with endometriosis who are undergoing IVF.

Participants

Participants will be recruited based on the following inclusion criteria:

- Women aged 18-38
- Planning to undergo a cycle of IVF for treatment of infertility
- Surgical or sonographic diagnosis of endometriosis

- Body Mass Index (BMI) 18-38 kg/m^2 (inclusive) at time of screening
- Anti-Mullerian hormone (AMH) > 0.8 ng/ml within 6 months of planned IVF cycle start
- Uterine cavity assessment by sonohysterogram or hysteroscopy within 6 months indicating adequacy for embryo transfer
- Presence of at least one ovary with no clinically significant abnormalities (other than endometrioma)
- Negative urine or cervical swab for gonorrhea and chlamydia within 12 months of recruitment
- Willingness and ability to comply with trial procedures, including reporting of obstetrical outcomes after delivery

A diagnosis of endometriosis must be confirmed by surgical visualization of endometriosis (at the time of laparoscopy or laparotomy) within the last 10 years of initial trial visit, or by sonographic documentation of an ovarian endometrioma >2 cm, or two or more smaller endometriomas that total >2 cm in diameter. If a diagnosis of endometriosis was made sonographically, serial transvaginal ultrasounds must have documented the same unambiguous endometrioma on two separate occasions in more than one menstrual cycle. Images will be read centrally by the same investigator to assure uniform diagnostic criteria are applied.

Women will be excluded from the study if there was:

- Use of GnRH agonists or antagonists within 6 months of study start, except for antagonist use as part of an IVF cycle
- Use of depot medroxyprogesterone acetate (MPA) or subdermal contraceptive implant (e.g. Implanon® or Nexplanon®) within 10 months of study start
- Continuous use of oral progestins (MPA, NETA) within 3 months of study start

- Use of aromatase inhibitors, danazol or hormonal contraceptives (including combined oral contraceptive pill, progestin-only pill, transdermal patch or contraceptive ring) within 1 month of study start
- Pregnancy greater than 8 weeks in length within the last 6 months
- History of three or more prior IVF/ICSI attempts
- Presence of hydrosalpinx >2cm on ultrasound, untreated endometrial polyps, submucosal uterine leiomyomata, or intrauterine adhesions
- Abnormal cervical cytology other than low-grade within last year
- History of malignancy within 5 years of the start of screening, except for adequately managed basal cell carcinoma and squamous cell carcinoma of the skin
- History of suicide attempt within the last year of recruitment
- Hypersensitivity to study drugs
- Planned surgical treatment of endometriosis or planned surgery in the abdominal-pelvic area within the duration of the trial
- Untreated abnormal prolactin or TSH
- Presence of any condition for which pregnancy is precluded

Participants will be recruited from the population of patients already committed to pursuing IVF at one of the five participating clinical centers in the trial (Yale University, University of Colorado - Denver, Northwestern University, Johns Hopkins and University of North Carolina). Additional clinical centers may be added for enrollment if needed. All participants will provide written, informed consent for their participation in this study. The Food and Drug Administration has granted permission for the study to proceed using elagolix as an Investigational New Drug (IND 152645) for this indication.

Intervention

GnRH antagonist pre-treatment

Participants will be randomized 1:1 into one of two treatment groups: GnRH antagonist (elagolix 200 mg bid) or placebo for 8 weeks, prior to undergoing IVF. While using GnRH antagonists, hot flashes and other vasomotor symptoms may occur. If indicated, use of paroxetine mesylate will be allowed. No sex steroids or other hormone modifying treatments are permitted.

IVF treatment

All participants will then undergo IVF treatment per local protocols, with agreed upon standards. All sites will use standard FSH stimulation and GnRH antagonist in each cycle with the exception that additional LH activity will always be supplied at the outset of stimulation, since half of the participants will have been on GnRH antagonist pre-treatment and will be expected to have suppressed LH. Non-conventional IVF therapies outside of those following standard protocols at each site will not be performed.

The standard IVF treatment for the study will be a GnRH antagonist protocol (cetrotide or ganirelix). Gonadotrophin stimulation with recombinant human follicle stimulating hormone and menotropin (supplying 75IU FSH and 75 IU LH activity per vial) will be started at a daily dose ranging 150-375 IU depending on patient characteristics including age, early follicular phase FSH, AMH, antral follicle count and BMI. Each patient will receive at least 75 IU of LH activity daily as part of the initial stimulation protocol to counteract the LH suppression by the GnRH antagonist. The oral GnRH antagonist will be discontinued at the start of stimulation; addition of subcutaneous injections of GnRH antagonist will be based on each sites' standard IVF protocol. When at least two leading follicles measuring ≥18 mm are seen on ultrasound, the trigger injection of u-hCG (10,000 IU) or r-hCG (250 mcg) is administered, followed by oocyte retrieval 37h later. Depending on sperm parameters following preparation on the day of oocyte retrieval, fertilization will be achieved either by conventional IVF or ICSI [25].

Embryo culture and transfer

ET is performed between Days 3 and 5 of development depending on morphological assessment and the woman's age, following ASRM guidelines allowing for transfer of up to two embryos, with an elective single embryo transfer preferred [26,27]. Pre-implantation Genetic Testing for aneuploidy (PGT-A) will be allowed. Frozen embryo transfers are included in this study but must be preceded by the same pre-treatment with GnRH antagonist or placebo for 8 weeks, repeating the same treatment as initially assigned at randomization.

Luteal support will be initiated 1 day after oocyte retrieval with intramuscular or vaginal micronized progesterone and continued for 14 days, when a urine pregnancy test is performed. If pregnant, luteal support is continued until 10 weeks of pregnancy. A transvaginal ultrasound scan is scheduled to confirm a viable intrauterine pregnancy and determine number of gestations. Women are then discharged from the care of the IVF unit to their obstetrician for further prenatal care and delivery. Participants will have been consented for access to comprehensive pregnancy outcome and birth data at the time of enrollment.

Randomization

Eligible women will be randomized in a 1:1 fashion to one of two treatments:

- Elagolix 200 mg BID daily for 8 weeks prior to undergoing IVF.
- Placebo, BID daily for 8 weeks prior to undergoing IVF.

A computer-generated randomization list will be created and randomization will be performed prior to the first dose of elagolix or placebo. Randomization will have random sizes (2,4, or 6) of blocks, stratified by site and age group (<35 versus ≥35 years). Both participants and investigators will be blinded to the treatment assignment during the trial duration (except for serious safety concerns). The assigned treatment (GnRH antagonist vs. placebo) applied during the fresh cycle will also be used for subsequent frozen embryo transfers resulting from the initial

'fresh' egg retrieval cycle. Most women using elagolix menstruate in the first 2 months with only a 50% amenorrhea rate after 1 year in the Phase III clinical trial, enabling blinding to remain intact.

Outcome measures

The primary outcome measure will be live birth rate per cycle start, defined as live birth at ≥24 weeks of gestation.

As secondary outcome measures, we will also analyze a number of IVF cycle parameters: 1. Estradiol (E2) level on the day of human chorionic gonadotrophin (hCG) administration; 2. Progesterone (P) level on the day of hCG administration; 3. The number of oocytes retrieved; 4. Gonadotropin dosage and duration; 5. Number and percent of mature metaphase II (MII) oocytes; 6. Fertilization (2PN) rate; 7. Blastocyst rate; 8. Incidence of moderate-to-severe ovarian hyperstimulation syndrome (OHSS); 9. Implantation rate; 10. Clinical pregnancy rate; 11. Miscarriage rate (defined as pregnancy loss prior to viability scan and including those confirmed on ultrasound scan up to ≤23w6d gestation); 12. Rate of ectopic pregnancy or pregnancy of unknown location; 13. Ongoing pregnancy rate; 14. Multiple pregnancy rate.

We will also measure pregnancy-related parameters to determine the effect of pre-treatment with GnRH antagonist on pregnancy related complications associated with endometriosis: pre-eclampsia and pregnancy-induced hypertension, preterm birth, intrauterine growth restriction, cesarean delivery, and obstetric hemorrhage.

Finally, quality of life will be assed using the FertiQOL, a validated questionnaire that contains Emotional, Mind/Body, Relational and Social domains [28].

Statistical Analysis

Sample size and power calculations

The average live birth rate for women with endometriosis undergoing IVF is estimated to be 39%, based on 2016 SART data showing a live birth rate of 44.7% per cycle in women with endometriosis under the age of 35 and 34.0% in women ages 35-37. We conservatively estimate an effect of 10% absolute improvement in live birth rate to 49% in the GnRH antagonist arm, based on prior randomized trials using GnRH agonists. Thus, using 386 participants per arm (N=772) would provide an alpha of 0.05 and power of 80%. We will aim to enroll and randomize 814 participants (407 per treatment group), to account for an estimated drop-out rate of 5%.

Analysis of outcome measures

An intention-to-treat analysis will be performed on primary and secondary outcome measures. The primary outcome, cumulative live birth rate, will be compared between the two intervention arms using Pearson's chi-square test of independence. Baseline patient characteristics and secondary outcome measures will also be analyzed with Pearson's chi-square test and logistic regression as needed.

Based on prior experience, we expect a data completion rate of at least 99.5% and we do not expect missing data to significantly affect trial analysis or results. In the unlikely event of unexpectedly high rates of missing data, the potential mechanisms for missing data (missing completely at random, missing at random, or missing not at random) will be examined. We will compare the available characteristics of those with missing data to those with complete data. If necessary, imputation techniques may be used.

Patient and Public Involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Trial status and registration

The study was conceived and designed in 2019. Recruitment is expected to begin in April 2021. This study is registered on ClinicalTrials.gov Identifier NCT04173169. This manuscript describes the latest version, last updated Dec 10, 2020.

Ethics and Dissemination

The PREGnant trial is undergoing Institutional Review Board approval at Johns Hopkins University, pending a minor modification, with reliance agreements at all participating sites.

Protocol modifications will be reviewed by the IRB and reported to the funder. Participating investigators, providers, and study staff will be informed of protocol changes via email. Significant protocol modifications will also be noted on ClinicalTrials.gov.

Elagolix has had increasing use in treating endometriosis-related pain, and the findings of this trial can be easily adopted into the IVF setting. The results of this trial may reveal a new way to optimize outcomes for women with endometriosis seeking fertility treatment.

Safety and adverse events monitoring

The safety of the intervention medication elagolix has been previously investigated and found to be tolerable [24]. All adverse events are collected regardless of their grade of severity and reported based on established criteria. Data Safety Monitoring Board (DSMB) will receive unblinded data and advise on potential safety issues. The choice of continuing therapy or trial participation based on adverse events is at the discretion of the investigator and DSMB determinations.

Data management and sharing

The trial is conducted in accordance with relevant regulations and standard operating procedures, including data protection. Each subject is assigned a unique code for de-identification. Data will be collected electronically and abstracted from the electronic medical

record in a de-identified manner. Any medical information that is obtained in connection with this program that could identify a subject will remain confidential and will be disclosed only as required by law. All persons responsible for the quality control of the data take all necessary precautions to ensure the confidentiality of information regarding trial participants and in particular the identity of the participants and the results obtained. The final trial dataset will be available to study investigators and Research Ethic Boards at all participating sites. Results of the trial will be published in peer-reviewed journals.

Author Contributions

HST, HJL, SC, VF, LP, JR, NS, JS, DS, HH, SY, HZ each made substantial contributions to the conception or design of the study protocol, design of the study intervention, study outcomes, study procedures, and/or revised the protocol critically for important intellectual content and approved the final version to be published. HZ made substantial contributions to the conception or design of the study protocol and wrote the first draft of the protocol. HJL wrote the first draft of this manuscript. All authors approved the final version to be published.

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Competing Interests

The authors have no competing interests to report.

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Reporting checklist for protocol of a clinical trial.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-5, 8
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5-9

Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9-10
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention	9-10

		during the trial	
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7, 10-11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make	12

		the final decision to terminate the trial	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7, 9
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	12
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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Pre-IVF treatment with a GnRH antagonist in women with endometriosis (PREGnant): Study protocol for a prospective, double-blind, placebo-controlled trial

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Pre-IVF treatment with a GnRH antagonist in women with endometriosis (PREGNANT): Study protocol for a prospective, double-blind, placebo-controlled trial

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Abstract

Background: Infertility is a common complication of endometriosis. While in vitro fertilization-embryo transfer (IVF-ET) successfully treats endometriosis-associated infertility, pregnancy rates are diminished in women seeing fertility treatment for endometriosis-associated infertility compared to other etiologies of infertility. The use of gonadotropin releasing hormone (GnRH) agonist prior to IVF has been suggested to improve success, however studies have been small and rarely reported live birth rates. Recent approval of an oral GnRH antagonist for endometriosis provides a novel option for women with endometriosis who are undergoing IVF. There have been no studies on the efficacy of GnRH antagonists for the treatment of endometriosis-related infertility.

Methods/Design: This study is a multi-center, prospective, randomized, double-blind, placebo-controlled trial to study the efficacy of GnRH antagonist pre-treatment for women with endometriosis who are undergoing IVF. A total of 814 patients with endometriosis undergoing fertility treatment will be enrolled and randomized 1:1 into two groups: elagolix 200 mg bid or placebo for 8 weeks, prior to undergoing IVF. All participants will then undergo IVF treatment per local protocols. The primary outcome is live birth. Secondary outcomes include oocyte number, fertilization rate, embryo morphology, and implantation rates, as well as rates of known endometriosis-related obstetrical outcomes (pregnancy-induced hypertension, antepartum hemorrhage, cesarean delivery, and preterm birth).

Discussion: We hypothesize that GnRH antagonist pre-treatment increases the live birth rate among women with endometriosis undergoing IVF-ET.

Trial Registration: ClinicalTrials.gov Identifier NCT04173169

FDA IND: 152645

Key words: endometriosis; in vitro fertilization; IVF; gonadotropin releasing hormone; GnRH; elagolix; GnRH antagonist; Live birth

Strengths and Limitations of this Study

- Limited evidence suggests that pre-treatment with GnRH agonists may improve IVF outcomes in patients with endometriosis; however, the recently available oral GnRH antagonist has not yet been studied for this purpose.
- This study is a multi-center, prospective, randomized, double-blind, placebo-controlled study, randomizing 814 patients with endometriosis undergoing fertility treatment 1:1 to elagolix 200 mg bid or placebo for 8 weeks prior to undergoing IVF.
- This study uses a selective inclusion criteria requiring a documented diagnosis of endometriosis via direct surgical visualization or standardized sonographic evidence.
- Participants will undergo routine IVF protocols at each study site, improving the generalizability of results.
- Participants will not be stratified by endometriosis severity or treatment history, and both fresh and frozen embryo transfers will be included in this study, which is not powered to detect differences in effect within these clinical subgroups.

Introduction

Endometriosis is a disease of ectopic endometrial glands outside the uterus, commonly involving the adnexa and pelvic peritoneum. In addition to being a common cause of chronic pelvic pain, endometriosis is also associated with poorer reproductive outcomes. While endometriosis affects 10-15% of reproductive aged women [1,2], it is present in 25-50% of women with infertility and conversely, 30-50% of women with endometriosis struggle with infertility [3]. The fecundity of normal reproductive age couples without infertility is estimated to be around 15% to 20% per month, while the fecundity of women with untreated endometriosis is estimated at 2%-10% [4,5]. Women with mild endometriosis have a significantly lower probability of pregnancy over 3 years compared to women with unexplained fertility (36% vs.

55%, respectively) [6]. Endometriosis is also associated with obstetrical complications, including obstetrical hemorrhage, cesarean delivery, pre-eclampsia and pregnancy-induced hypertension, and preterm birth [7–12]. While the mechanism remains controversial and unclear, endometriosis is thought to contribute to reduced fertility via adnexal scarring and poor endometrial receptivity, though studies also suggest with women with advanced endometriosis also have poor ovarian reserve, low oocyte and embryo quality, and poor implantation [1,13–15].

Multiple effective treatments exist for the management of endometriosis-associated infertility, including laparoscopic destruction of endometriotic disease, ovulation induction, and intrauterine insemination [1,16,17]. While some studies show that conservative treatment alone may be effective in improving fertility for women with endometriosis and potentially helps avoid obstetrical complications associated with IVF [17], IVF remains the most direct and effective treatment for endometriosis-associated infertility, especially in patients who have failed conservative interventions.

There is some evidence that endometriosis is also associated with poorer IVF outcomes, though this is controversial. One meta-analysis from 2002 including 22 non-randomized trials reported that the chances of achieving pregnancy with IVF in women with endometriosis was almost half that of those with tubal infertility (odds ratio [OR] = 0.56, 95% confidence intervals [CI] = 0.44–0.7) and women with severe disease had about half the pregnancy rate of those with mild disease [18]. A more recent study published in 2018 showed via retrospective comparison of 531 women with endometriosis and 737 women with unexplained subfertility found that women with endometriosis still have a 24% lower likelihood of live birth after IVF than women with unexplained infertility [19]. However, a larger retrospective study in 2017 comparing 3583 women with endometriosis and 18,833 women without endometriosis found that endometriosis was associated with fewer oocytes retrieved, but no significant difference in live birth rates [20]. Similarly, a metanalysis of 33 studies published in 2015 examined the effect of endometrioma

on IVF/ICSI outcomes and also found that women with endometrioma had fewer oocytes retrieved, but similar live birth rates [21]. A large metanalysis of 78 studies published in 2014 also found a difference in number of oocytes retrieved but no significant difference in live birth rates between women with and without endometriosis [22]. It is important to note, however, that the effect of endometriosis on IVF outcomes may be underestimated, especially in more recent studies, due to a likely underdiagnosis of endometriosis in the IVF population as laparoscopy is no longer a routine practice in infertility evaluations [4]. As endometriosis commonly presents in conjunction with other infertility diagnoses (e.g. male factor, tubal factor, diminished ovarian reserve), it has been suggested that endometriosis, when associated with other barriers to fertility, contributes to poorer IVF outcomes in the general IVF population, even if this effect is not seen with endometriosis in isolation [23].

As the association between endometriosis and poorer IVF outcomes remains biologically plausible despite mixed clinical evidence [1,13–15,23], pre-treatment with GnRH agonist therapy has been investigated as a method to improve IVF outcomes, though with mixed evidence. As a hormone-dependent disorder, medical management of symptomatic endometriosis has targeted ovarian estrogen production, including combined oral contraceptives, progestins, danazol and gonadotropin-releasing hormone (GnRH) agonists or antagonist [24]. While these therapies have been helpful in managing endometriosis-associated pelvic pain, they have not been shown to treat endometriosis-associated infertility in the absence of IVF [5]. In the IVF setting, prolonged GnRH agonist treatment prior to IVF has been shown by several studies to improve fertility rates in women with advanced endometriosis [25–27], though a recent Cochrane review of 8 RCTs was unable to determine whether prolonged GnRH agonist treatment improved subsequent IVF outcomes, partly due to low quality of available evidence [28].

Since then, the GnRH antagonist elagolix has recently become available for use, with a number of advantages over GnRH agonists: the convenience of oral rather than parenteral

administration, improved tolerability and reduced severity of vasomotor symptoms, rapid onset of action with suppression of endogenous estradiol levels within 24 hours, and lack of initial gonadotropin stimulation ("flare" effect) seen with GnRH agonists [29]. However, elagolix has not yet been studied as an adjunctive treatment prior to IVF for women with endometriosis. Based on limited evidence from GnRH agonist trials, we hypothesize that GnRH antagonist therapy may potentially benefit women with endometriosis undergoing IVF treatment, possibly with a shorter course of treatment compared to what has been studied with GnRH agonists (3-6 months) [28,30].

Methods and Analysis

This is a multicenter, prospective, randomized controlled trial to study the effect of GnRH antagonist pre-treatment for women with endometriosis who are undergoing IVF.

Participants

Participants will be recruited based on the following inclusion criteria:

- Women aged 18-38
- Planning to undergo a cycle of IVF for treatment of infertility
- Surgical or sonographic diagnosis of endometriosis
- Body Mass Index (BMI) 18-38 kg/m^2 (inclusive) at time of screening
- Anti-Mullerian hormone (AMH) > 0.8 ng/ml within 6 months of planned IVF cycle start
- Uterine cavity assessment by sonohysterogram or hysteroscopy within 6 months indicating adequacy for embryo transfer
- Presence of at least one ovary with no clinically significant abnormalities (other than endometrioma)

- Negative urine or cervical swab for gonorrhea and chlamydia within 12 months of recruitment
- Willingness and ability to comply with trial procedures, including reporting of obstetrical outcomes after delivery

A diagnosis of endometriosis must be confirmed by surgical visualization of endometriosis (at the time of laparoscopy or laparotomy) within the last 10 years of initial trial visit, or by sonographic documentation of an ovarian endometrioma >2 cm, or two or more smaller endometriomas that total >2 cm in diameter. If a diagnosis of endometriosis was made sonographically, serial transvaginal ultrasounds must have documented the same unambiguous endometrioma on two separate occasions in more than one menstrual cycle. Images will be read centrally by the same investigator to assure uniform diagnostic criteria are applied.

Women will be excluded from the study if there was:

- Use of GnRH agonists or antagonists within 6 months of study start, except for antagonist use as part of an IVF cycle
- Use of depot medroxyprogesterone acetate (MPA) or subdermal contraceptive implant (e.g. Implanon® or Nexplanon®) within 10 months of study start
- Continuous use of oral progestins (MPA, NETA) within 3 months of study start
- Use of aromatase inhibitors, danazol or hormonal contraceptives (including combined oral contraceptive pill, progestin-only pill, transdermal patch or contraceptive ring) within 1 month of study start
- Pregnancy greater than 8 weeks in length within the last 6 months
- History of three or more prior IVF/ICSI attempts
- Presence of hydrosalpinx >2cm on ultrasound, untreated endometrial polyps, submucosal uterine leiomyomata, or intrauterine adhesions
- Abnormal cervical cytology other than low-grade within last year

- History of malignancy within 5 years of the start of screening, except for adequately managed basal cell carcinoma and squamous cell carcinoma of the skin
- History of suicide attempt within the last year of recruitment
- Hypersensitivity to study drugs
- Planned surgical treatment of endometriosis or planned surgery in the abdominal-pelvic area within the duration of the trial
- Untreated abnormal prolactin or TSH
- Presence of any condition for which pregnancy is precluded

Participants will be recruited from the population of patients already committed to pursuing IVF at one of the five participating clinical centers in the trial (Yale University, University of Colorado - Denver, Northwestern University, Johns Hopkins and University of North Carolina). Additional clinical centers may be added for enrollment if needed. All participants will provide written, informed consent for their participation in this study. This study was approved by a central Institutional Review Boards (IRB) as well as local IRBs at all five participating centers. In addition, the Food and Drug Administration gave permission for the study to proceed using elagolix as an Investigational New Drug (IND 152645) for this indication.

Intervention

GnRH antagonist pre-treatment

Participants will be randomized 1:1 into one of two treatment groups: GnRH antagonist (elagolix 200 mg bid) or placebo for 8 weeks, prior to undergoing IVF. While using GnRH antagonists, hot flashes and other vasomotor symptoms may occur. If indicated, use of paroxetine mesylate will be allowed. No sex steroids or other hormone modifying treatments are permitted. The GnRH antagonist will be administered during the routine evaluation conducted prior to the IVF cycle.

IVF treatment

All participants will then undergo IVF treatment per local protocols, with agreed upon standards. All sites will use standard FSH stimulation and GnRH antagonist in each cycle with the exception that additional LH activity will always be supplied at the outset of stimulation, since half of the participants will have been on GnRH antagonist pre-treatment and will be expected to have suppressed LH. Non-conventional IVF therapies outside of those following standard protocols at each site will not be performed.

The standard IVF treatment for the study will be a GnRH antagonist protocol (cetrotide or ganirelix). Gonadotrophin stimulation with recombinant human follicle stimulating hormone and menotropin (supplying 75IU FSH and 75 IU LH activity per vial) will be started at a daily dose ranging 150-375 IU depending on patient characteristics including age, early follicular phase FSH, AMH, antral follicle count and BMI. Each patient will receive at least 75 IU of LH activity daily as part of the initial stimulation protocol to counteract the LH suppression by the GnRH antagonist. The oral GnRH antagonist will be discontinued at the start of stimulation; addition of subcutaneous injections of GnRH antagonist will be based on each sites' standard IVF protocol. When at least two leading follicles measuring ≥18 mm are seen on ultrasound, the trigger injection of u-hCG (10,000 IU) or r-hCG (250 mcg) is administered, followed by oocyte retrieval 37h later. Depending on sperm parameters following preparation on the day of oocyte retrieval, fertilization will be achieved either by conventional IVF or ICSI [31].

Embryo culture and transfer

ET is performed between Days 3 and 5 of development depending on morphological assessment and the woman's age, following ASRM guidelines allowing for transfer of up to two embryos, with an elective single embryo transfer preferred [32,33]. Pre-implantation Genetic Testing for aneuploidy (PGT-A) will be allowed. Frozen embryo transfers are included in this

study but must be preceded by the same pre-treatment with GnRH antagonist or placebo for 8 weeks, repeating the same treatment as initially assigned at randomization. No more than two embryo transfers will be performed under this protocol, limiting administration of study drug to a maximum of three 8-week courses (one prior to IVF, and one prior to each embryo transfer).

Luteal support will be initiated 1 day after oocyte retrieval with intramuscular or vaginal micronized progesterone and continued for 14 days, when a urine pregnancy test is performed. If pregnant, luteal support is continued until 10 weeks of pregnancy. A transvaginal ultrasound scan is scheduled to confirm a viable intrauterine pregnancy and determine number of gestations. Women are then discharged from the care of the IVF unit to their obstetrician for further prenatal care and delivery. Participants will have been consented for access to comprehensive pregnancy outcome and birth data at the time of enrollment.

Randomization

Eligible women will be randomized in a 1:1 fashion to one of two treatments:

- Elagolix 200 mg BID daily for 8 weeks prior to undergoing IVF.
- Placebo, BID daily for 8 weeks prior to undergoing IVF.

A computer-generated randomization list will be created by staff at the PREGnant Data Coordinating Center (DCC) and randomization will be performed prior to the first dose of elagolix or placebo. Randomization will have random sizes (2,4, or 6) of blocks, stratified by site and age group (<35 versus ≥35 years). Both participants and investigators will be blinded to the treatment assignment during the trial duration (except for serious safety concerns). Treatment allocation information will not be accessible to investigators (except for serious safety concerns), trial staff at the site or central laboratory personnel during the trial. The assigned treatment (GnRH antagonist vs. placebo) applied during the fresh cycle will also be used for subsequent frozen embryo transfers resulting from the initial 'fresh' egg retrieval cycle. Most women using

elagolix menstruate in the first 2 months with only a 50% amenorrhea rate after 1 year in the Phase III clinical trial, enabling blinding to remain intact.

Outcome measures

The primary outcome measure will be live birth rate per cycle start, defined as live birth at ≥24 weeks of gestation. As a secondary outcome measure, we will also analyze the live birth rate per embryo transfer.

For exploratory analysis, we will examine a number of IVF cycle parameters: 1. Estradiol (E2) level on the day of human chorionic gonadotrophin (hCG) administration; 2. Progesterone (P) level on the day of hCG administration; 3. The number of oocytes retrieved; 4. Gonadotropin dosage and duration; 5. Number and percent of mature metaphase II (MII) oocytes; 6. Fertilization (2PN) rate; 7. Blastocyst rate; 8. Incidence of moderate-to-severe ovarian hyperstimulation syndrome (OHSS); 9. Implantation rate; 10. Clinical pregnancy rate; 11. Miscarriage rate (defined as pregnancy loss prior to viability scan and including those confirmed on ultrasound scan up to ≤23w6d gestation); 12. Rate of ectopic pregnancy or pregnancy of unknown location; 13. Ongoing pregnancy rate; 14. Multiple pregnancy rate.

We will also measure pregnancy-related parameters to determine the effect of pre-treatment with GnRH antagonist on pregnancy related complications associated with endometriosis: pre-eclampsia and pregnancy-induced hypertension, preterm birth, intrauterine growth restriction, cesarean delivery, and obstetric hemorrhage.

Finally, quality of life will be assed using the FertiQOL, a validated questionnaire that contains Emotional, Mind/Body, Relational and Social domains [34].

Statistical Analysis

Sample size and power calculations

The average live birth rate for women with endometriosis undergoing IVF is estimated to be 39%, based on 2016 SART data showing a live birth rate of 44.7% per cycle in women with endometriosis under the age of 35 and 34.0% in women ages 35-37. We conservatively estimate an effect of 10% absolute improvement in live birth rate to 49% in the GnRH antagonist arm, based on prior randomized trials using GnRH agonists. Thus, using 386 participants per arm (N=772) would provide an alpha of 0.05 and power of 80%. We will aim to enroll and randomize 814 participants (407 per treatment group), to account for an estimated drop-out rate of 5%.

Analysis of outcome measures

An intention-to-treat analysis will be performed on primary and secondary outcome measures. The primary outcome, cumulative live birth rate, will be compared between the two intervention arms using Pearson's chi-square test of independence. Baseline patient characteristics and secondary outcome measures will also be analyzed with Pearson's chi-square test and logistic regression as needed.

Based on prior experience, we expect a data completion rate of at least 99.5% and we do not expect missing data to significantly affect trial analysis or results. In the unlikely event of unexpectedly high rates of missing data, the potential mechanisms for missing data (missing completely at random, missing at random, or missing not at random) will be examined. We will compare the available characteristics of those with missing data to those with complete data. If necessary, imputation techniques may be used.

Trial status and registration

The study was conceived and designed in 2019. Recruitment is expected to begin in December 2021. This study is registered on ClinicalTrials.gov Identifier NCT04173169. This manuscript describes the latest version, last updated November 29, 2021.

Ethics and Dissemination

The PREGnant trial was approved by the Institutional Review Board at Johns Hopkins University School of Medicine (JHM IRB) on August 12, 2021, application #IRB00236742, with reliance agreements at all participating sites.

Protocol modifications will be reviewed by the IRB and reported to the funder. Participating investigators, providers, and study staff will be informed of protocol changes via email. Significant protocol modifications will also be noted on ClinicalTrials.gov.

Elagolix has had increasing use in treating endometriosis-related pain, and the findings of this trial can be easily adopted into the IVF setting. The results of this trial may reveal a new way to optimize outcomes for women with endometriosis seeking fertility treatment.

Safety and adverse events monitoring

The safety of the intervention medication elagolix has been previously investigated and found to be tolerable [24]. All adverse events are collected regardless of their grade of severity and reported based on established criteria. Data Safety Monitoring Board (DSMB) will receive unblinded data and advise on potential safety issues. The choice of continuing therapy or trial participation based on adverse events is at the discretion of the investigator and DSMB determinations.

Data management and sharing

The trial is conducted in accordance with relevant regulations and standard operating procedures, including data protection. Each subject is assigned a unique code for de-identification. Data will be collected electronically and abstracted from the electronic medical record in a de-identified manner. Any medical information that is obtained in connection with this program that could identify a subject will remain confidential and will be disclosed only as required by law. All persons responsible for the quality control of the data take all necessary

precautions to ensure the confidentiality of information regarding trial participants and in particular the identity of the participants and the results obtained. The final trial dataset will be available to study investigators and Research Ethic Boards at all participating sites. Results of the trial will be published in peer-reviewed journals. We will submit data and samples collected by the trial to NICHD DASH. The informed consent will include permission to bank these samples. The processes included initial data and documentation preparation (e.g., codebooks, protocols, informed consent for data sharing), data quality control, and submission.

Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Author Contributions

HST, HJL, SC, VF, LP, JR, NS, JS, DS, HH, SY, HZ each made substantial contributions to the conception or design of the study protocol, design of the study intervention, study outcomes, study procedures, and/or revised the protocol critically for important intellectual content and approved the final version to be published. HZ made substantial contributions to the conception or design of the study protocol and wrote the first draft of the protocol. HJL wrote the first draft of this manuscript. All authors approved the final version to be published.

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Competing Interests

The authors have no competing interests to report.

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Reporting checklist for protocol of a clinical trial.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-5, 8
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5-9

Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9-10
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention	9-10

		during the trial	
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7, 10-11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make	12

		the final decision to terminate the trial	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7, 9
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	12
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Pre-IVF treatment with a GnRH antagonist in women with endometriosis (PREGnant): Study protocol for a prospective, double-blind, placebo-controlled trial

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Pre-IVF treatment with a GnRH antagonist in women with endometriosis (PREGNANT): Study protocol for a prospective, double-blind, placebo-controlled trial

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Abstract

Introduction: Infertility is a common complication of endometriosis. While in vitro fertilization-embryo transfer (IVF-ET) successfully treats endometriosis-associated infertility, there is some evidence that pregnancy rates may be diminished in women seeing fertility treatment for endometriosis-associated infertility compared to other etiologies of infertility. The use of gonadotropin releasing hormone (GnRH) agonist prior to IVF has been suggested to improve success, however studies have been small and rarely reported live birth rates. Recent approval of an oral GnRH antagonist for endometriosis provides a novel option for women with endometriosis who are undergoing IVF. There have been no studies on the efficacy of GnRH antagonists for the treatment of endometriosis-related infertility.

Methods and analysis: This study is a multi-center, prospective, randomized, double-blind, placebo-controlled trial to study the efficacy of GnRH antagonist pre-treatment for women with endometriosis who are undergoing IVF. A total of 814 patients with endometriosis undergoing fertility treatment will be enrolled and randomized 1:1 into two groups: elagolix 200 mg bid or placebo for 8 weeks, prior to undergoing IVF. All participants will then undergo IVF treatment per local protocols. The primary outcome is live birth. Secondary outcomes include oocyte number, fertilization rate, embryo morphology, and implantation rates, as well as rates of known endometriosis-related obstetrical outcomes (pregnancy-induced hypertension, antepartum hemorrhage, cesarean delivery, and preterm birth).

Ethics and dissemination: The PREGnant trial was approved by the Institutional Review Board at Johns Hopkins University. Results will be published in a peer-reviewed journal.

Trial Registration: ClinicalTrials.gov Identifier NCT04173169

FDA IND: 152645

Key words: endometriosis; in vitro fertilization; IVF; gonadotropin releasing hormone; GnRH; elagolix; GnRH antagonist; Live birth

Strengths and Limitations of this Study

- Limited evidence suggests that pre-treatment with GnRH agonists may improve IVF outcomes in patients with endometriosis; however, the recently available oral GnRH antagonist has not yet been studied for this purpose.
- This study is a multi-center, prospective, randomized, double-blind, placebo-controlled study, randomizing 814 patients with endometriosis undergoing fertility treatment 1:1 to elagolix 200 mg bid or placebo for 8 weeks prior to undergoing IVF.
- This study uses a selective inclusion criteria requiring a documented diagnosis of endometriosis via direct surgical visualization or standardized sonographic evidence.
- Participants will undergo routine IVF protocols at each study site, improving the generalizability of results.
- Participants will not be stratified by endometriosis severity or treatment history, and both fresh and frozen embryo transfers will be included in this study, which is not powered to detect differences in effect within these clinical subgroups.

Introduction

Endometriosis is a disease of ectopic endometrial glands outside the uterus, commonly involving the adnexa and pelvic peritoneum. In addition to being a common cause of chronic pelvic pain, endometriosis is also associated with poorer reproductive outcomes. While endometriosis affects 10-15% of reproductive aged women [1,2], it is present in 25-50% of women with infertility and conversely, 30-50% of women with endometriosis struggle with infertility [3]. The fecundity of normal reproductive age couples without infertility is estimated to be around 15% to 20% per month, while the fecundity of women with untreated endometriosis is estimated at 2%-10% [4,5]. Women with mild endometriosis have a significantly lower probability of pregnancy over 3 years compared to women with unexplained fertility (36% vs.

55%, respectively) [6]. Endometriosis is also associated with obstetrical complications, including obstetrical hemorrhage, cesarean delivery, pre-eclampsia and pregnancy-induced hypertension, and preterm birth [7–12]. While the mechanism remains controversial and unclear, endometriosis is thought to contribute to reduced fertility via adnexal scarring and poor endometrial receptivity, though studies also suggest with women with advanced endometriosis also have poor ovarian reserve, low oocyte and embryo quality, and poor implantation [1,13–15].

Multiple effective treatments exist for the management of endometriosis-associated infertility, including laparoscopic destruction of endometriotic disease, ovulation induction, and intrauterine insemination [1,16,17]. While some studies show that conservative treatment alone may be effective in improving fertility for women with endometriosis and potentially helps avoid obstetrical complications associated with IVF [17], IVF remains the most direct and effective treatment for endometriosis-associated infertility, especially in patients who have failed conservative interventions.

There is some evidence that endometriosis is also associated with poorer IVF outcomes, though this is controversial. One meta-analysis from 2002 including 22 non-randomized trials reported that the chances of achieving pregnancy with IVF in women with endometriosis was almost half that of those with tubal infertility (odds ratio [OR] = 0.56, 95% confidence intervals [CI] = 0.44–0.7) and women with severe disease had about half the pregnancy rate of those with mild disease [18]. A more recent study published in 2018 showed via retrospective comparison of 531 women with endometriosis and 737 women with unexplained subfertility found that women with endometriosis still have a 24% lower likelihood of live birth after IVF than women with unexplained infertility [19]. However, a larger retrospective study in 2017 comparing 3583 women with endometriosis and 18,833 women without endometriosis found that endometriosis was associated with fewer oocytes retrieved, but no significant difference in live birth rates [20]. Similarly, a metanalysis of 33 studies published in 2015 examined the effect of endometrioma

on IVF/ICSI outcomes and also found that women with endometrioma had fewer oocytes retrieved, but similar live birth rates [21]. A large metanalysis of 78 studies published in 2014 also found a difference in number of oocytes retrieved but no significant difference in live birth rates between women with and without endometriosis [22]. It is important to note, however, that the effect of endometriosis on IVF outcomes may be underestimated, especially in more recent studies, due to a likely underdiagnosis of endometriosis in the IVF population as laparoscopy is no longer a routine practice in infertility evaluations [4]. As endometriosis commonly presents in conjunction with other infertility diagnoses (e.g. male factor, tubal factor, diminished ovarian reserve), it has been suggested that endometriosis, when associated with other barriers to fertility, contributes to poorer IVF outcomes in the general IVF population, even if this effect is not seen with endometriosis in isolation [23]. This finding may be due to a primary effect of endometriosis on reproductive biology, but may also be secondary to epidemiologic or iatrogenic factors associated with an endometriosis diagnosis: greater exposure to prior gynecologic surgery resulting in ovarian injury, diminished reserve, or impaired folliculogenesis) [24–26], or an effect of subsequent adhesive disease on the technical difficulty of oocyte retrievals. These factors, however, have not been well studied as potential mechanisms by which endometriosis may compromise IVF outcomes.

As the association between endometriosis and poorer IVF outcomes remains biologically plausible despite mixed clinical evidence [1,13–15,23], pre-treatment with GnRH agonist therapy has been investigated as a method to improve IVF outcomes, though with mixed evidence. As a hormone-dependent disorder, medical management of symptomatic endometriosis has targeted ovarian estrogen production, including combined oral contraceptives, progestins, danazol and gonadotropin-releasing hormone (GnRH) agonists or antagonist [27]. While these therapies have been helpful in managing endometriosis-associated pelvic pain, they have not been shown to treat endometriosis-associated infertility in the absence of IVF [5]. In the IVF setting, prolonged GnRH agonist treatment prior to IVF has been

shown by several studies to improve fertility rates in women with advanced endometriosis [28–30], though a recent Cochrane review of 8 RCTs was unable to determine whether prolonged GnRH agonist treatment improved subsequent IVF outcomes, partly due to low quality of available evidence [31].

Since then, the GnRH antagonist elagolix has recently become available for use, with a number of advantages over GnRH agonists: the convenience of oral rather than parenteral administration, improved tolerability and reduced severity of vasomotor symptoms, rapid onset of action with suppression of endogenous estradiol levels within 24 hours, and lack of initial gonadotropin stimulation ("flare" effect) seen with GnRH agonists [32]. However, elagolix has not yet been studied as an adjunctive treatment prior to IVF for women with endometriosis. Based on limited evidence from GnRH agonist trials, we hypothesize that GnRH antagonist therapy may potentially benefit women with endometriosis undergoing IVF treatment, possibly with a shorter course of treatment compared to what has been studied with GnRH agonists (3-6 months) [31,33].

Methods and Analysis

This is a multicenter, prospective, randomized controlled trial to study the effect of GnRH antagonist pre-treatment for women with endometriosis who are undergoing IVF.

Participants

Participants will be recruited based on the following inclusion criteria:

- Women aged 18-38
- Planning to undergo a cycle of IVF for treatment of infertility
- Surgical or sonographic diagnosis of endometriosis
- Body Mass Index (BMI) 18-38 kg/m^2 (inclusive) at time of screening

- Anti-Mullerian hormone (AMH) > 0.8 ng/ml within 6 months of planned IVF cycle start
- Uterine cavity assessment by sonohysterogram or hysteroscopy within 6 months indicating adequacy for embryo transfer
- Presence of at least one ovary with no clinically significant abnormalities (other than endometrioma)
- Negative urine or cervical swab for gonorrhea and chlamydia within 12 months of recruitment
- Willingness and ability to comply with trial procedures, including reporting of obstetrical outcomes after delivery

A diagnosis of endometriosis must be confirmed by surgical visualization of endometriosis (at the time of laparoscopy or laparotomy) within the last 10 years of initial trial visit, or by sonographic documentation of an ovarian endometrioma >2 cm, or two or more smaller endometriomas that total >2 cm in diameter. If a diagnosis of endometriosis was made sonographically, serial transvaginal ultrasounds must have documented the same unambiguous endometrioma on two separate occasions in more than one menstrual cycle. Images will be read centrally by the same investigator to assure uniform diagnostic criteria are applied.

Women will be excluded from the study if there was:

- Use of GnRH agonists or antagonists within 6 months of study start, except for antagonist use as part of an IVF cycle
- Use of depot medroxyprogesterone acetate (MPA) or subdermal contraceptive implant (e.g. Implanon® or Nexplanon®) within 10 months of study start
- Continuous use of oral progestins (MPA, NETA) within 3 months of study start
- Use of aromatase inhibitors, danazol or hormonal contraceptives (including combined oral contraceptive pill, progestin-only pill, transdermal patch or contraceptive ring) within 1 month of study start

- Pregnancy greater than 8 weeks in length within the last 6 months
- History of three or more prior IVF/ICSI attempts
- Presence of hydrosalpinx >2cm on ultrasound, untreated endometrial polyps, submucosal uterine leiomyomata, or intrauterine adhesions
- Abnormal cervical cytology other than low-grade within last year
- History of malignancy within 5 years of the start of screening, except for adequately managed basal cell carcinoma and squamous cell carcinoma of the skin
- History of suicide attempt within the last year of recruitment
- Hypersensitivity to study drugs
- Planned surgical treatment of endometriosis or planned surgery in the abdominal-pelvic area within the duration of the trial
- Untreated abnormal prolactin or TSH
- Presence of any condition for which pregnancy is precluded

Participants will be recruited from the population of patients already committed to pursuing IVF at one of the five participating clinical centers in the trial (Yale University, University of Colorado - Denver, Northwestern University, Johns Hopkins and University of North Carolina). Additional clinical centers may be added for enrollment if needed. All participants will provide written, informed consent for their participation in this study. This study was approved by a central Institutional Review Boards (IRB) as well as local IRBs at all five participating centers. In addition, the Food and Drug Administration gave permission for the study to proceed using elagolix as an Investigational New Drug (IND 152645) for this indication.

Intervention

GnRH antagonist pre-treatment

Participants will be randomized 1:1 into one of two treatment groups: GnRH antagonist (elagolix 200 mg bid) or placebo for 8 weeks, prior to undergoing IVF. While using GnRH antagonists, hot flashes and other vasomotor symptoms may occur. If indicated, use of paroxetine mesylate will be allowed. No sex steroids or other hormone modifying treatments are permitted. The GnRH antagonist will be administered during the routine evaluation conducted prior to the IVF cycle.

IVF treatment

All participants will then undergo IVF treatment per local protocols, with agreed upon standards. All sites will use standard FSH stimulation and GnRH antagonist in each cycle with the exception that additional LH activity will always be supplied at the outset of stimulation, since half of the participants will have been on GnRH antagonist pre-treatment and will be expected to have suppressed LH. Non-conventional IVF therapies outside of those following standard protocols at each site will not be performed.

The standard IVF treatment for the study will be a GnRH antagonist protocol (cetrotide or ganirelix). Gonadotrophin stimulation with recombinant human follicle stimulating hormone and menotropin (supplying 75IU FSH and 75 IU LH activity per vial) will be started at a daily dose ranging 150-375 IU depending on patient characteristics including age, early follicular phase FSH, AMH, antral follicle count and BMI. Each patient will receive at least 75 IU of LH activity daily as part of the initial stimulation protocol to counteract the LH suppression by the GnRH antagonist. The oral GnRH antagonist will be discontinued at the start of stimulation; addition of subcutaneous injections of GnRH antagonist will be based on each sites' standard IVF protocol. When at least two leading follicles measuring ≥18 mm are seen on ultrasound, the trigger injection of u-hCG (10,000 IU) or r-hCG (250 mcg) is administered, followed by oocyte retrieval 37h later. Depending on sperm parameters following preparation on the day of oocyte retrieval, fertilization will be achieved either by conventional IVF or ICSI [34].

Embryo culture and transfer

ET is performed between Days 3 and 5 of development depending on morphological assessment and the woman's age, following ASRM guidelines allowing for transfer of up to two embryos, with an elective single embryo transfer preferred [35,36]. Pre-implantation Genetic Testing for aneuploidy (PGT-A) will be allowed. Frozen embryo transfers are included in this study but must be preceded by the same pre-treatment with GnRH antagonist or placebo for 8 weeks, repeating the same treatment as initially assigned at randomization. No more than two embryo transfers will be performed under this protocol, limiting administration of study drug to a maximum of three 8-week courses (one prior to IVF, and one prior to each embryo transfer).

Luteal support will be initiated 1 day after oocyte retrieval with intramuscular or vaginal micronized progesterone and continued for 14 days, when a urine pregnancy test is performed. If pregnant, luteal support is continued until 10 weeks of pregnancy. A transvaginal ultrasound scan is scheduled to confirm a viable intrauterine pregnancy and determine number of gestations. Women are then discharged from the care of the IVF unit to their obstetrician for further prenatal care and delivery. Participants will have been consented for access to comprehensive pregnancy outcome and birth data at the time of enrollment.

Randomization

Eligible women will be randomized in a 1:1 fashion to one of two treatments:

- Elagolix 200 mg BID daily for 8 weeks prior to undergoing IVF.
- Placebo, BID daily for 8 weeks prior to undergoing IVF.

A computer-generated randomization list will be created by staff at the PREGnant Data Coordinating Center (DCC) and randomization will be performed prior to the first dose of elagolix or placebo. Randomization will have random sizes (2,4, or 6) of blocks, stratified by site and age group (<35 versus ≥35 years). The randomization list will not be available to any

person involved in the conduct and evaluation of the trial until the trial is complete and database is declared clean and is released by the DCC. Randomization and treatment allocation will be initiated by study staff according to the randomization list following enrollment and prior to the first dose of elagolix or placebo, but participants, investigators, trial staff, and central laboratory personnel will be blinded to the treatment assignment during the trial duration (except for serious safety concerns). The assigned treatment (GnRH antagonist vs. placebo) applied during the fresh cycle will also be used for subsequent frozen embryo transfers resulting from the initial 'fresh' egg retrieval cycle. Most women using elagolix menstruate in the first 2 months with only a 50% amenorrhea rate after 1 year in the Phase III clinical trial, enabling blinding to remain intact.

Outcome measures

The primary outcome measure will be live birth rate per cycle start, defined as live birth at ≥24 weeks of gestation. As a secondary outcome measure, we will also analyze the live birth rate per embryo transfer.

For exploratory analysis, we will examine a number of IVF cycle parameters: 1. Estradiol (E2) level on the day of human chorionic gonadotrophin (hCG) administration; 2. Progesterone (P) level on the day of hCG administration; 3. The number of oocytes retrieved; 4. Gonadotropin dosage and duration; 5. Number and percent of mature metaphase II (MII) oocytes; 6. Fertilization (2PN) rate; 7. Blastocyst rate; 8. Incidence of moderate-to-severe ovarian hyperstimulation syndrome (OHSS); 9. Implantation rate; 10. Clinical pregnancy rate; 11. Miscarriage rate (defined as pregnancy loss prior to viability scan and including those confirmed on ultrasound scan up to ≤23w6d gestation); 12. Rate of ectopic pregnancy or pregnancy of unknown location; 13. Ongoing pregnancy rate; 14. Multiple pregnancy rate.

We will also measure pregnancy-related parameters to determine the effect of pre-treatment with GnRH antagonist on pregnancy related complications associated with

endometriosis: pre-eclampsia and pregnancy-induced hypertension, preterm birth, intrauterine growth restriction, cesarean delivery, and obstetric hemorrhage.

Finally, quality of life will be assed using the FertiQOL, a validated questionnaire that contains Emotional, Mind/Body, Relational and Social domains [37].

Statistical Analysis

Sample size and power calculations

The average live birth rate for women with endometriosis undergoing IVF is estimated to be 39%, based on 2016 SART data showing a live birth rate of 44.7% per cycle in women with endometriosis under the age of 35 and 34.0% in women ages 35-37. Using 386 participants per arm (N=772) would provide an alpha of 0.05 and power of 80% to detect an effect of 10% absolute improvement in live birth rate to 49% in the GnRH antagonist arm. This effect is conservatively estimated from prior randomized trials using GnRH agonists [28–30], and what investigators deemed to be sufficient to recommend the routine use of GnRH antagonists in IVF protocols for this population. However, we acknowledge that the study may be underpowered to detect smaller but still relevant effects (5-10% improvement). We will aim to enroll and randomize 814 participants (407 per treatment group), to account for an estimated drop-out rate of 5%.

Analysis of outcome measures

An intention-to-treat analysis will be performed on primary and secondary outcome measures. The primary outcome, cumulative live birth rate, will be compared between the two intervention arms using Pearson's chi-square test of independence. Baseline patient characteristics and secondary outcome measures will also be analyzed with Pearson's chi-square test and logistic regression as needed.

Based on prior experience, we expect a data completion rate of at least 99.5% and we do not expect missing data to significantly affect trial analysis or results. In the unlikely event of

unexpectedly high rates of missing data, the potential mechanisms for missing data (missing completely at random, missing at random, or missing not at random) will be examined. We will compare the available characteristics of those with missing data to those with complete data. If necessary, imputation techniques may be used.

Safety and adverse events monitoring

The safety of the intervention medication elagolix has been previously investigated and found to be tolerable [24]. All adverse events are collected regardless of their grade of severity and reported based on established criteria. Data Safety Monitoring Board (DSMB) will receive unblinded data and advise on potential safety issues. The choice of continuing therapy or trial participation based on adverse events is at the discretion of the investigator and DSMB determinations.

Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Ethics and Dissemination

The PREGnant trial was approved by the Institutional Review Board at Johns Hopkins University School of Medicine (JHM IRB) on August 12, 2021, application #IRB00236742, with reliance agreements at all participating sites.

Protocol modifications will be reviewed by the IRB and reported to the funder. Participating investigators, providers, and study staff will be informed of protocol changes via email. Significant protocol modifications will also be noted on ClinicalTrials.gov.

Elagolix has had increasing use in treating endometriosis-related pain, and the findings of this trial can be easily adopted into the IVF setting. The results of this trial may reveal a new way to optimize outcomes for women with endometriosis seeking fertility treatment.

The trial is conducted in accordance with relevant regulations and standard operating procedures, including data protection. Each subject is assigned a unique code for de-identification. Data will be collected electronically and abstracted from the electronic medical record in a de-identified manner. Any medical information that is obtained in connection with this program that could identify a subject will remain confidential and will be disclosed only as required by law. All persons responsible for the quality control of the data take all necessary precautions to ensure the confidentiality of information regarding trial participants and in particular the identity of the participants and the results obtained. The final trial dataset will be available to study investigators and Research Ethic Boards at all participating sites. Results of the trial will be published in peer-reviewed journals. We will submit data and samples collected by the trial to NICHD DASH. The informed consent will include permission to bank these samples. The processes included initial data and documentation preparation (e.g., codebooks, protocols, informed consent for data sharing), data quality control, and submission.

Trial status and registration

The study was conceived and designed in 2019. Recruitment is expected to begin in December 2021. This study is registered on ClinicalTrials.gov Identifier NCT04173169. This manuscript describes the latest version, last updated November 29, 2021.

Author Contributions

HST, HJL, SC, VF, LP, JR, NS, JS, DS, HH, SY, HZ each made substantial contributions to the conception or design of the study protocol, design of the study intervention, study outcomes, study procedures, and/or revised the protocol critically for important intellectual

content and approved the final version to be published. HZ made substantial contributions to the conception or design of the study protocol and wrote the first draft of the protocol. HJL wrote the first draft of this manuscript. All authors approved the final version to be published.

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Competing Interests

The authors have no competing interests to report.

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Reporting checklist for protocol of a clinical trial.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-5, 8
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5-9

Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9-10
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention	9-10

		during the trial	
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7, 10-11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make	12

		the final decision to terminate the trial	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7, 9
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	12
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Pre-IVF treatment with a GnRH antagonist in women with endometriosis (PREGnant): Study protocol for a prospective, double-blind, placebo-controlled trial

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Pre-IVF treatment with a GnRH antagonist in women with endometriosis (PREGNANT): Study protocol for a prospective, double-blind, placebo-controlled trial

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Abstract

Introduction: Infertility is a common complication of endometriosis. While in vitro fertilization-embryo transfer (IVF-ET) successfully treats endometriosis-associated infertility, there is some evidence that pregnancy rates may be diminished in women seeing fertility treatment for endometriosis-associated infertility compared to other etiologies of infertility. The use of gonadotropin releasing hormone (GnRH) agonist prior to IVF has been suggested to improve success, however studies have been small and rarely reported live birth rates. Recent approval of an oral GnRH antagonist for endometriosis provides a novel option for women with endometriosis who are undergoing IVF. There have been no studies on the efficacy of GnRH antagonists for the treatment of endometriosis-related infertility.

Methods and analysis: This study is a multi-center, prospective, randomized, double-blind, placebo-controlled trial to study the efficacy of GnRH antagonist pre-treatment for women with endometriosis who are undergoing IVF. A total of 814 patients with endometriosis undergoing fertility treatment will be enrolled and randomized 1:1 into two groups: elagolix 200 mg bid or placebo for 8 weeks, prior to undergoing IVF. All participants will then undergo IVF treatment per local protocols. The primary outcome is live birth. Secondary outcomes include oocyte number, fertilization rate, embryo morphology, and implantation rates, as well as rates of known endometriosis-related obstetrical outcomes (pregnancy-induced hypertension, antepartum hemorrhage, cesarean delivery, and preterm birth).

Ethics and dissemination: The PREGnant trial was approved by the Institutional Review Board at Johns Hopkins University. Results will be published in a peer-reviewed journal.

Trial Registration: ClinicalTrials.gov Identifier NCT04173169

FDA IND: 152645

Key words: endometriosis; in vitro fertilization; IVF; gonadotropin releasing hormone; GnRH; elagolix; GnRH antagonist; Live birth

Strengths and Limitations of this Study

- Limited evidence suggests that pre-treatment with GnRH agonists may improve IVF outcomes in patients with endometriosis; however, the recently available oral GnRH antagonist has not yet been studied for this purpose.
- This study is a multi-center, prospective, randomized, double-blind, placebo-controlled study, randomizing 814 patients with endometriosis undergoing fertility treatment 1:1 to elagolix 200 mg bid or placebo for 8 weeks prior to undergoing IVF.
- This study uses a selective inclusion criteria requiring a documented diagnosis of endometriosis via direct surgical visualization or standardized sonographic evidence.
- Participants will undergo routine IVF protocols at each study site, improving the generalizability of results.
- Participants will not be stratified by endometriosis severity or treatment history, and both fresh and frozen embryo transfers will be included in this study, which is not powered to detect differences in effect within these clinical subgroups.

Introduction

Endometriosis is a disease of ectopic endometrial glands outside the uterus, commonly involving the adnexa and pelvic peritoneum. In addition to being a common cause of chronic pelvic pain, endometriosis is also associated with poorer reproductive outcomes. While endometriosis affects 10-15% of reproductive aged women [1,2], it is present in 25-50% of women with infertility and conversely, 30-50% of women with endometriosis struggle with infertility [3]. The fecundity of normal reproductive age couples without infertility is estimated to be around 15% to 20% per month, while the fecundity of women with untreated endometriosis is estimated at 2%-10% [4,5]. Women with mild endometriosis have a significantly lower probability of pregnancy over 3 years compared to women with unexplained fertility (36% vs.

55%, respectively) [6]. Endometriosis is also associated with obstetrical complications, including obstetrical hemorrhage, cesarean delivery, pre-eclampsia and pregnancy-induced hypertension, and preterm birth [7–12]. While the mechanism remains controversial and unclear, endometriosis is thought to contribute to reduced fertility via adnexal scarring and poor endometrial receptivity, though studies also suggest with women with advanced endometriosis also have poor ovarian reserve, low oocyte and embryo quality, and poor implantation [1,13–15].

Multiple effective treatments exist for the management of endometriosis-associated infertility, including laparoscopic destruction of endometriotic disease, ovulation induction, and intrauterine insemination [1,16,17]. While some studies show that conservative treatment alone may be effective in improving fertility for women with endometriosis and potentially helps avoid obstetrical complications associated with IVF [17], IVF remains the most direct and effective treatment for endometriosis-associated infertility, especially in patients who have failed conservative interventions.

There is some evidence that endometriosis is also associated with poorer IVF outcomes, though this is controversial. One meta-analysis from 2002 including 22 non-randomized trials reported that the chances of achieving pregnancy with IVF in women with endometriosis was almost half that of those with tubal infertility (odds ratio [OR] = 0.56, 95% confidence intervals [CI] = 0.44–0.7) and women with severe disease had about half the pregnancy rate of those with mild disease [18]. A more recent study published in 2018 showed via retrospective comparison of 531 women with endometriosis and 737 women with unexplained subfertility found that women with endometriosis still have a 24% lower likelihood of live birth after IVF than women with unexplained infertility [19]. However, a larger retrospective study in 2017 comparing 3583 women with endometriosis and 18,833 women without endometriosis found that endometriosis was associated with fewer oocytes retrieved, but no significant difference in live birth rates [20]. Similarly, a metanalysis of 33 studies published in 2015 examined the effect of endometrioma

on IVF/ICSI outcomes and also found that women with endometrioma had fewer oocytes retrieved, but similar live birth rates [21]. A large metanalysis of 78 studies published in 2014 also found a difference in number of oocytes retrieved but no significant difference in live birth rates between women with and without endometriosis [22]. It is important to note, however, that the effect of endometriosis on IVF outcomes may be underestimated, especially in more recent studies, due to a likely underdiagnosis of endometriosis in the IVF population as laparoscopy is no longer a routine practice in infertility evaluations [4]. As endometriosis commonly presents in conjunction with other infertility diagnoses (e.g. male factor, tubal factor, diminished ovarian reserve), it has been suggested that endometriosis, when associated with other barriers to fertility, contributes to poorer IVF outcomes in the general IVF population, even if this effect is not seen with endometriosis in isolation [23]. This finding may be due to a primary effect of endometriosis on reproductive biology, but may also be secondary to epidemiologic or iatrogenic factors associated with an endometriosis diagnosis: greater exposure to prior gynecologic surgery resulting in ovarian injury, diminished reserve, or impaired folliculogenesis) [24–26], or an effect of subsequent adhesive disease on the technical difficulty of oocyte retrievals. These factors, however, have not been well studied as potential mechanisms by which endometriosis may compromise IVF outcomes.

As the association between endometriosis and poorer IVF outcomes remains biologically plausible despite mixed clinical evidence [1,13–15,23], pre-treatment with GnRH agonist therapy has been investigated as a method to improve IVF outcomes, though with mixed evidence. As a hormone-dependent disorder, medical management of symptomatic endometriosis has targeted ovarian estrogen production, including combined oral contraceptives, progestins, danazol and gonadotropin-releasing hormone (GnRH) agonists or antagonist [27]. While these therapies have been helpful in managing endometriosis-associated pelvic pain, they have not been shown to treat endometriosis-associated infertility in the absence of IVF [5]. In the IVF setting, prolonged GnRH agonist treatment prior to IVF has been

shown by several studies to improve fertility rates in women with advanced endometriosis [28–30], though a recent Cochrane review of 8 RCTs was unable to determine whether prolonged GnRH agonist treatment improved subsequent IVF outcomes, partly due to low quality of available evidence [31].

Since then, the GnRH antagonist elagolix has recently become available for use, with a number of advantages over GnRH agonists: the convenience of oral rather than parenteral administration, improved tolerability and reduced severity of vasomotor symptoms, rapid onset of action with suppression of endogenous estradiol levels within 24 hours, and lack of initial gonadotropin stimulation ("flare" effect) seen with GnRH agonists [32]. However, elagolix has not yet been studied as an adjunctive treatment prior to IVF for women with endometriosis. Based on limited evidence from GnRH agonist trials, we hypothesize that GnRH antagonist therapy may potentially benefit women with endometriosis undergoing IVF treatment, possibly with a shorter course of treatment compared to what has been studied with GnRH agonists (3-6 months) [31,33].

Methods and Analysis

This is a multicenter, prospective, randomized controlled trial to study the effect of GnRH antagonist pre-treatment for women with endometriosis who are undergoing IVF.

Participants

Participants will be recruited based on the following inclusion criteria:

- Women aged 18-38
- Planning to undergo a cycle of IVF for treatment of infertility
- Surgical or sonographic diagnosis of endometriosis
- Body Mass Index (BMI) 18-38 kg/m^2 (inclusive) at time of screening

- Anti-Mullerian hormone (AMH) > 0.8 ng/ml within 6 months of planned IVF cycle start
- Uterine cavity assessment by sonohysterogram or hysteroscopy within 6 months indicating adequacy for embryo transfer
- Presence of at least one ovary with no clinically significant abnormalities (other than endometrioma)
- Negative urine or cervical swab for gonorrhea and chlamydia within 12 months of recruitment
- Willingness and ability to comply with trial procedures, including reporting of obstetrical outcomes after delivery

A diagnosis of endometriosis must be confirmed by surgical visualization of endometriosis (at the time of laparoscopy or laparotomy) within the last 10 years of initial trial visit, or by sonographic documentation of an ovarian endometrioma >2 cm, or two or more smaller endometriomas that total >2 cm in diameter. If a diagnosis of endometriosis was made sonographically, serial transvaginal ultrasounds must have documented the same unambiguous endometrioma on two separate occasions in more than one menstrual cycle. Images will be read centrally by the same investigator to assure uniform diagnostic criteria are applied.

Women will be excluded from the study if there was:

- Use of GnRH agonists or antagonists within 6 months of study start, except for antagonist use as part of an IVF cycle
- Use of depot medroxyprogesterone acetate (MPA) or subdermal contraceptive implant (e.g. Implanon® or Nexplanon®) within 10 months of study start
- Continuous use of oral progestins (MPA, NETA) within 3 months of study start
- Use of aromatase inhibitors, danazol or hormonal contraceptives (including combined oral contraceptive pill, progestin-only pill, transdermal patch or contraceptive ring) within 1 month of study start

- Pregnancy greater than 8 weeks in length within the last 6 months
- History of three or more prior IVF/ICSI attempts
- Presence of hydrosalpinx >2cm on ultrasound, untreated endometrial polyps, submucosal uterine leiomyomata, or intrauterine adhesions
- Abnormal cervical cytology other than low-grade within last year
- History of malignancy within 5 years of the start of screening, except for adequately managed basal cell carcinoma and squamous cell carcinoma of the skin
- History of suicide attempt within the last year of recruitment
- Hypersensitivity to study drugs
- Planned surgical treatment of endometriosis or planned surgery in the abdominal-pelvic area within the duration of the trial
- Untreated abnormal prolactin or TSH
- Presence of any condition for which pregnancy is precluded

Participants will be recruited from the population of patients already committed to pursuing IVF at one of the five participating clinical centers in the trial (Yale University, University of Colorado - Denver, Northwestern University, Johns Hopkins and University of North Carolina). Additional clinical centers may be added for enrollment if needed. All participants will provide written, informed consent for their participation in this study (see Supplementary File). This study was approved by a central Institutional Review Boards (IRB) as well as local IRBs at all five participating centers. In addition, the Food and Drug Administration gave permission for the study to proceed using elagolix as an Investigational New Drug (IND 152645) for this indication.

Intervention

GnRH antagonist pre-treatment

Participants will be randomized 1:1 into one of two treatment groups: GnRH antagonist (elagolix 200 mg bid) or placebo for 8 weeks, prior to undergoing IVF. While using GnRH antagonists, hot flashes and other vasomotor symptoms may occur. If indicated, use of paroxetine mesylate will be allowed. No sex steroids or other hormone modifying treatments are permitted. The GnRH antagonist will be administered during the routine evaluation conducted prior to the IVF cycle.

IVF treatment

All participants will then undergo IVF treatment per local protocols, with agreed upon standards. All sites will use standard FSH stimulation and GnRH antagonist in each cycle with the exception that additional LH activity will always be supplied at the outset of stimulation, since half of the participants will have been on GnRH antagonist pre-treatment and will be expected to have suppressed LH. Non-conventional IVF therapies outside of those following standard protocols at each site will not be performed.

The standard IVF treatment for the study will be a GnRH antagonist protocol (cetrotide or ganirelix). Gonadotrophin stimulation with recombinant human follicle stimulating hormone and menotropin (supplying 75IU FSH and 75 IU LH activity per vial) will be started at a daily dose ranging 150-375 IU depending on patient characteristics including age, early follicular phase FSH, AMH, antral follicle count and BMI. Each patient will receive at least 75 IU of LH activity daily as part of the initial stimulation protocol to counteract the LH suppression by the GnRH antagonist. The oral GnRH antagonist will be discontinued at the start of stimulation; addition of subcutaneous injections of GnRH antagonist will be based on each sites' standard IVF protocol. When at least two leading follicles measuring ≥18 mm are seen on ultrasound, the trigger injection of u-hCG (10,000 IU) or r-hCG (250 mcg) is administered, followed by oocyte retrieval 37h later. Depending on sperm parameters following preparation on the day of oocyte retrieval, fertilization will be achieved either by conventional IVF or ICSI [34].

Embryo culture and transfer

ET is performed between Days 3 and 5 of development depending on morphological assessment and the woman's age, following ASRM guidelines allowing for transfer of up to two embryos, with an elective single embryo transfer preferred [35,36]. Pre-implantation Genetic Testing for aneuploidy (PGT-A) will be allowed. Frozen embryo transfers are included in this study but must be preceded by the same pre-treatment with GnRH antagonist or placebo for 8 weeks, repeating the same treatment as initially assigned at randomization. No more than two embryo transfers will be performed under this protocol, limiting administration of study drug to a maximum of three 8-week courses (one prior to IVF, and one prior to each embryo transfer).

Luteal support will be initiated 1 day after oocyte retrieval with intramuscular or vaginal micronized progesterone and continued for 14 days, when a urine pregnancy test is performed. If pregnant, luteal support is continued until 10 weeks of pregnancy. A transvaginal ultrasound scan is scheduled to confirm a viable intrauterine pregnancy and determine number of gestations. Women are then discharged from the care of the IVF unit to their obstetrician for further prenatal care and delivery. Participants will have been consented for access to comprehensive pregnancy outcome and birth data at the time of enrollment.

Randomization

Eligible women will be randomized in a 1:1 fashion to one of two treatments:

- Elagolix 200 mg BID daily for 8 weeks prior to undergoing IVF.
- Placebo, BID daily for 8 weeks prior to undergoing IVF.

A computer-generated randomization list will be created by staff at the PREGnant Data Coordinating Center (DCC) and randomization will be performed prior to the first dose of elagolix or placebo. Randomization will have random sizes (2,4, or 6) of blocks, stratified by site and age group (<35 versus ≥35 years). Randomization sequences within each study site and

age stratum will be generated randomly and independently. The randomization list will not be available to any person involved in the conduct and evaluation of the trial until the trial is complete and database is declared clean and is released by the DCC. Randomization and treatment allocation will be initiated by study staff according to the randomization list following enrollment and prior to the first dose of elagolix or placebo, but participants, investigators, trial staff, and central laboratory personnel will be blinded to the treatment assignment during the trial duration (except for serious safety concerns). The assigned treatment (GnRH antagonist vs. placebo) applied during the fresh cycle will also be used for subsequent frozen embryo transfers resulting from the initial 'fresh' egg retrieval cycle. Most women using elagolix menstruate in the first 2 months with only a 50% amenorrhea rate after 1 year in the Phase III clinical trial, enabling blinding to remain intact.

Outcome measures

The primary outcome measure will be live birth rate per cycle start, defined as live birth at ≥24 weeks of gestation. As a secondary outcome measure, we will also analyze the live birth rate per embryo transfer.

For exploratory analysis, we will examine a number of IVF cycle parameters: 1. Estradiol (E2) level on the day of human chorionic gonadotrophin (hCG) administration; 2. Progesterone (P) level on the day of hCG administration; 3. The number of oocytes retrieved; 4. Gonadotropin dosage and duration; 5. Number and percent of mature metaphase II (MII) oocytes; 6. Fertilization (2PN) rate; 7. Blastocyst rate; 8. Incidence of moderate-to-severe ovarian hyperstimulation syndrome (OHSS); 9. Implantation rate; 10. Clinical pregnancy rate; 11. Miscarriage rate (defined as pregnancy loss prior to viability scan and including those confirmed on ultrasound scan up to ≤23w6d gestation); 12. Rate of ectopic pregnancy or pregnancy of unknown location; 13. Ongoing pregnancy rate; 14. Multiple pregnancy rate.

We will also measure pregnancy-related parameters to determine the effect of pre-treatment with GnRH antagonist on pregnancy related complications associated with endometriosis: pre-eclampsia and pregnancy-induced hypertension, preterm birth, intrauterine growth restriction, cesarean delivery, and obstetric hemorrhage.

Finally, quality of life will be assed using the FertiQOL, a validated questionnaire that contains Emotional, Mind/Body, Relational and Social domains [37].

Statistical Analysis

Sample size and power calculations

The average live birth rate for women with endometriosis undergoing IVF is estimated to be 39%, based on 2016 SART data showing a live birth rate of 44.7% per cycle in women with endometriosis under the age of 35 and 34.0% in women ages 35-37. Using 386 participants per arm (N=772) would provide an alpha of 0.05 and power of 80% to detect an effect of 10% absolute improvement in live birth rate to 49% in the GnRH antagonist arm. This effect is conservatively estimated from prior randomized trials using GnRH agonists [28–30], and what investigators deemed to be sufficient to recommend the routine use of GnRH antagonists in IVF protocols for this population. However, we acknowledge that the study may be underpowered to detect smaller but still relevant effects (5-10% improvement). We will aim to enroll and randomize 814 participants (407 per treatment group), to account for an estimated drop-out rate of 5%.

Analysis of outcome measures

An intention-to-treat analysis will be performed on primary and secondary outcome measures. The primary outcome, cumulative live birth rate, will be compared between the two intervention arms using Pearson's chi-square test of independence. Baseline patient characteristics and secondary outcome measures will also be analyzed with Pearson's chi-square test and logistic regression as needed.

Based on prior experience, we expect a data completion rate of at least 99.5% and we do not expect missing data to significantly affect trial analysis or results. In the unlikely event of unexpectedly high rates of missing data, the potential mechanisms for missing data (missing completely at random, missing at random, or missing not at random) will be examined. We will compare the available characteristics of those with missing data to those with complete data. If necessary, imputation techniques may be used.

Safety and adverse events monitoring

The safety of the intervention medication elagolix has been previously investigated and found to be tolerable [24]. All adverse events are collected regardless of their grade of severity and reported based on established criteria. Data Safety Monitoring Board (DSMB) will receive unblinded data and advise on potential safety issues. The choice of continuing therapy or trial participation based on adverse events is at the discretion of the investigator and DSMB determinations.

Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Ethics and Dissemination

The PREGnant trial was approved by the Institutional Review Board at Johns Hopkins University School of Medicine (JHM IRB) on August 12, 2021, application #IRB00236742, with reliance agreements at all participating sites.

Protocol modifications will be reviewed by the IRB and reported to the funder. Participating investigators, providers, and study staff will be informed of protocol changes via email. Significant protocol modifications will also be noted on ClinicalTrials.gov.

Elagolix has had increasing use in treating endometriosis-related pain, and the findings of this trial can be easily adopted into the IVF setting. The results of this trial may reveal a new way to optimize outcomes for women with endometriosis seeking fertility treatment.

The trial is conducted in accordance with relevant regulations and standard operating procedures, including data protection. Each subject is assigned a unique code for de-identification. Data will be collected electronically and abstracted from the electronic medical record in a de-identified manner. Any medical information that is obtained in connection with this program that could identify a subject will remain confidential and will be disclosed only as required by law. All persons responsible for the quality control of the data take all necessary precautions to ensure the confidentiality of information regarding trial participants and in particular the identity of the participants and the results obtained. The final trial dataset will be available to study investigators and Research Ethic Boards at all participating sites. Results of the trial will be published in peer-reviewed journals. We will submit data and samples collected by the trial to NICHD DASH. The informed consent will include permission to bank these samples. The processes included initial data and documentation preparation (e.g., codebooks, protocols, informed consent for data sharing), data quality control, and submission.

Trial status and registration

The study was conceived and designed in 2019. Recruitment is expected to begin in December 2021. This study is registered on ClinicalTrials.gov Identifier NCT04173169. This manuscript describes the latest version, last updated November 29, 2021.

Author Contributions

HST, HJL, SC, VF, LP, JR, NS, JS, DS, HH, SY, HZ each made substantial contributions to the conception or design of the study protocol, design of the study intervention, study outcomes, study procedures, and/or revised the protocol critically for important intellectual

content and approved the final version to be published. HZ made substantial contributions to the conception or design of the study protocol and wrote the first draft of the protocol. HJL wrote the first draft of this manuscript. All authors approved the final version to be published.

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Competing Interests

The authors have no competing interests to report.

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Lead Study Investigator: Dr. Hugh Taylor
Master Informed Consent Approval Date: April 20, 2021
Site Specific Consent Information Approval Date: April 20, 2021
JHM IRB Application No.: IRB00236742

JOHNS HOPKINS MEDICINE

Approved April 20, 2021

RESEARCH PARTICIPANT INFORMED CONSENT AND PRIVACY AUTHORIZATION FORM

Master Informed Consent Form

Protocol Title: **Pre-IVF treatment with a GnRH antagonist in women with endometriosis – A prospective double-blind placebo-controlled trial (PREGnant)**

Application No.: **IRB00236742**

Sponsor By: **National Institutes of The Eunice Kennedy Shriver Institute of Child Health and Human Development (NICHD)**

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You are being asked to take part in a research study. Participation in this study is voluntary. Even if you decide to join now, you can change your mind later.

This is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study this informed consent form includes two parts. The first part of this document includes information that applies to all study sites. The second part of the consent form includes information specific to the study site where you are being asked to enroll.

1. Research Summary (Key Information):

The information in this section is intended to be an introduction to the study only. Complete details of the study are listed in the sections below. If you are considering participation in the study, the entire document should be discussed with you before you make your final decision. You can ask questions about the study now and at any time in the future.

We are asking you to be in this research because you have been diagnosed with endometriosis and are seeking to undergo in vitro fertilization with an embryo transfer (IVF-ET). This research is being done to find out if pre-treatment with an GnRH antagonist, elagolix, also known as ORILISSA™, will increase the chance of having a baby with IVF-ET.

Long term complete female hormone suppression with an injectable drug has been shown to improve pregnancy rates in women with endometriosis undergoing IVF. Elagolix treatment is an oral

mechanism to lower hormones, however the repression is not as drastic as seen with the injectable drug. Elagolix is shown to treat endometriosis is a more gentle way without the severe side effects seen with the complete suppression. Here, we will determine if elagolix similarly improves pregnancy rates in women with endometriosis undergoing IVF.

In this study, we will provide you with study medication, either elagolix 200 mg twice a day or a placebo (which is like a sugar pill) twice a day, for 60 days prior to the start of your IVF cycle. You may receive the elagolix or placebo up to 14 additional days for the convenience of your IVF cycle scheduling. You will then undergo IVF-ET as planned with your reproductive endocrinologist. We will collect information about your IVF cycle and your embryo transfer.

If you did not get pregnant after the first IVF cycle, we will provide you with a second course of study drug for another 60 days prior to a second fresh IVF cycle or a frozen embryo transfer (FET), depending upon the availability of embryos. We will collect information about your IVF cycle, but after 2 embryo transfers there will be no more courses of study drug.

If you did not have an embryo transfer after the first IVF cycle and chose to freeze embryos, we will provide you with a second course of study drug for another 60 days of treatment prior to a frozen embryo transfer (FET).

If you did not become pregnant after the first frozen embryo transfer, you will have a third 60 days course of study drug prior to your second frozen embryo transfer. Up to three 60 days courses of treatment with study drug are allowed if you do not become pregnant and your first cycle was a "freeze all" cycle. In this case of frozen embryo transfer, will collect information about your IVF cycle, but after 2 embryo transfers there will be no more courses of study drug.

If you have an embryo transfer immediately following your IVF cycle, a "fresh" cycle, and become pregnant, there will be a total of 5 study visits. If you have a frozen transfer, do not get pregnant and have a subsequent frozen transfer, you could have as many as 11 study visits. Study visits include questionnaires, physical exam, pregnancy testing, and blood sample collection. There are risks associated with taking elagolix that are described later in this document.

2. Why is this research being done?

This research is being done to see if women who have been diagnosed with endometriosis who are planning on undergoing in vitro fertilization-embryo transfer (IVF-ET) who are pre-treated with a minimum of 60 days of elagolix have improved live birth rates compared to those who receive a minimum of 60 days of placebo.

Are there any investigational drugs/devices/procedures?

ORILISSA™ (elagolix) which has Food and Drug Administration (FDA) for treating pain related to endometriosis. It is not approved for use as part of the IVF-ET regimen. The FDA is allowing the use of elagolix in this research study.

Who can join this study?

Women between the ages of ≥18-≤38 years with ultrasound, pathology or surgical diagnosis of endometriosis who plan to undergo IVF-ET for infertility management may join the trial.

How many people will be in this study?

About 814 women with endometriosis will be in this study across four main sites (Yale University,

University of Colorado, University of North Carolina, Northwestern University) and a satellite enrolling site (Johns Hopkins University). Ancillary sites may be added if needed. All sites are within the United States.

3. What will happen if you join this study?

If you agree to be in this study, we will ask you to do the following things:

Screening Visit

This visit can take place on the same day that you and your regular doctor decide that you will undergo IVF-ET. After you review and sign the consent form, your study doctor will make sure you qualify for this study. This visit will take about 2 hours.

- This consent form will be reviewed by you and with the study staff. You will have an opportunity to read this consent form in full and ask any questions you may have about the procedures involved, risks and time commitments related to this study. Once all of your questions have been answered, and if you are willing to participate, you will be asked to sign this consent form. A copy will be provided to you for your records and a copy will be uploaded into your Electronic Medical Record.
- Your past medical and menstrual history will be recorded. This form will ask a series of questions about your medical health, family health history, reproductive and gynecological history, pregnancy history, and current use of medications.
- Your height, weight, vital signs (blood pressure and pulse) and hip and abdominal circumference will be collected. Your BMI (body mass index) will be calculated.
- Your demographic information will be recorded, such as age, race and ethnicity.
- A physical exam will be performed by the physician if one was not done in the last 90 days.
- You will be given two questionnaires to complete, one concerns your infertility, the other asks about your endometriosis symptoms.
- You will receive counseling on double barrier methods of contraception.
- A transvaginal ultrasound which involves inserting an ultrasound probe into your vagina to visualize your ovaries and uterus. Measurements and ultrasound pictures will be recorded of your ovaries and uterus.

The following procedures done for IVF treatment and would be performed as part of your IVF work up even if you were not a participant in the study:

- Uterine cavity assessment by either hysteroscopy or sonohysterogram.
- A pap smear if you are 21 or older and have not had one within the time period specified by current guidelines.
- Urine or cervical swabs for gonorrhea and chlamydia.
- Collect blood for Safety Laboratory tests (Comprehensive Metabolic Panel, CMP) for your physician to review if not in your medical record. This blood work will consist of checking hormone levels and that you are not anemic (a condition where your blood lacks healthy red blood cells).

Randomization Visit – Visit 1

After the Screening Visit, if you are eligible to continue in the research, you will return to the study Center to begin study regimen. You will be randomized by a computer system to receive either elagolix or placebo. A placebo is a pill that looks just like the elagolix pill but does not contain any active study

drug. Randomization means whichever study regimen you receive it will be determined purely by chance, like a flip of a coin. You will have an equal chance to receive either elagolix or placebo. Neither you nor your physician will be able to decide to which group you are assigned. Neither you nor your study team will know which study drug (elagolix or placebo) you will receive but this information can be made available in case of an emergency. Half of study participants are expected to receive placebo.

In addition to dispensing 30 days of study drug and giving instructions on how to take it, the study doctor or study staff will do the following:

- You will have about 2 teaspoons of blood drawn. The purpose of the blood collection is to store the serum in our biorepository so that we can look at biomarkers in your blood in hopes that we can determine which women with endometriosis will benefit from GnRH antagonist pre-treatment.
- A urine pregnancy test will be performed.

- You will be asked about any medication changes you may have made since the Screening Visit.

Study Visit 2

You will return 30 days after your Study Visit 1 (with window up to 37 days) where the following will occur:

- A qualified member of the research team will collect and count any remaining study drug.
- An additional 30 days of study drug will be dispensed.
- You will be asked about any adverse events or any medication changes

Study Visit 3

You will return about 30 days after Study Visit 2, and up to 74 days post-Visit 1, depending on the timing of your IVF cycle start.

- A qualified member of the research team will collect and count any remaining study drug.
- You will be asked about any adverse events or any medication changes.
- You will be given two questionnaires to complete, one concerns your infertility, the other asks about your endometriosis symptoms.
- Blood will be collected. About 2 teaspoons of blood will be drawn for safety labs (CMP) and remaining serum will be stored as in Visit 1.
- A urine pregnancy test will be performed.
- A transvaginal ultrasound which involves inserting an ultrasound probe into your vagina to visualize your ovaries and uterus. Measurements and ultrasound pictures will be recorded of your ovaries and uterus.

IVF Cycle

You will then undergo your IVF cycle which is standard of care and not a part of the study. We will record information about your IVF cycle and if you are having the embryos transferred within a week of retrieval, (a Fresh Embryo Transfer cycle), we will record the information about your embryo transfer. If you become pregnant, we will record information about your pregnancy.

Study Visit 4

This visit as well as Study Visits 5 and 6, will only occur when you are eligible for an Embryo Transfer (ET) under one of the following circumstances:

- If you had a Fresh Embryo Transfer and did not become pregnant or had a pregnancy loss prior to 10 weeks, and have frozen embryos banked and are returning for a Frozen Embryo Transfer.

- If you had a Fresh Embryo Transfer and did not become pregnant or had a pregnancy loss prior to 10 weeks, and do not have any frozen embryos and are returning for a second Fresh IVF cycle.
- If you are having a Frozen Embryo Transfer, this visit will occur 2 months prior to the transfer.
- If you had a Frozen Embryo Transfer and did not become pregnant or had a pregnancy loss prior to 10 weeks and are returning for a second Frozen Embryo Transfer.

This visit provides you with another 60 days of study drug prior to your planned FET or second IVF-ET start. You will come in about 60 days prior to when the FET or IVF will start. In addition to dispensing 30 days of study drug and giving instructions on how to take it, the study doctor or study staff will do the following:

- You will be dispensed 30 days of study drug. This will be the same study drug that you were given when you were randomized.
- A urine pregnancy test will be performed.
- A transvaginal ultrasound will be performed.
- Blood will be collected. About 2 teaspoons of blood will be drawn for safety labs (CMP) and remaining serum will be stored as in Visit 1.
- You will be asked about any medication changes you may have made since your last study visit.

Study Visit 5

You will return 30 days after your Study Visit 4 where the following will occur:

- A qualified member of the research team will collect and count any remaining study drug.
- An additional 30 days of study drug will be dispensed.
- You will be asked about any adverse events or any medication changes since your last study visit.

Study Visit 6

You will return about 30 days after Study Visit 5, up to 74 days post-Visit 4, depending on the timing of your transfer or IVF cycle start.

- A qualified member of the research team will collect and count any remaining study drug.
- You will be asked about any adverse events or any medication changes since your last visit.
- Blood will be collected. About 2 teaspoons of blood will be drawn for safety labs (CMP) and remaining serum which will be stored as in Visit 1.
- A urine pregnancy test will be performed.
- A transvaginal ultrasound will be performed.

End of Study (EOS) Visit

This visit will occur when either you have:

- An ongoing pregnancy at the time of discharge to Obstetrics.
- A negative pregnancy test following a second embryo transfer.
- A spontaneous pregnancy loss prior to 10 weeks gestation following a second embryo transfer.
- If 6 months pass from completion of the first cycle without beginning Visit 4 OR if 6 months pass from the completion of the first frozen transfer without starting the repeat of Visit 4.

This visit will include the following:

- A qualified member of the research team will ask you about any medication changes since your last study visit.
- You will be given two questionnaires to complete, one about your infertility and the other about your endometriosis symptoms.

Pregnancy Follow-up

We will follow up the outcome of your pregnancy. If you become pregnant after enrolled in the study, we will collect information related to your pregnancy outcomes including data on your newborn from your physician and delivery records from your labor and delivery hospital.

While you are in the study, you agree to:

- follow the instructions you are given,
- come to the study clinic for all visits with the study doctor or a member of the research team,
- tell the study doctor or a member of the research team about any changes in your health or the way you feel,
- or tell the study doctor or a member of the research team if you want to stop being in the study at any time.

Incidental Findings

As part of this research study, you will undergo imaging procedures. A qualified professional will review your research imaging. This research imaging will not include the full diagnostic information that you would get if your primary doctor referred you for imaging.

There is a possibility that while reviewing your imaging we may see an unexpected abnormality. This is called an "incidental finding."

We will let you know if we see such an incidental finding. Depending on the type of incidental finding, we may contact you by mail, email, or phone. In the case of a potential serious emergency, someone may go to your home.

A qualified person (usually a member of the research team) will talk to you if there is an incidental finding. You do not have an option to decline information about an incidental finding from an imaging procedure.

If you want, we will give information about this incidental finding to your primary doctor or we will refer you to an appropriate doctor for further evaluation.

What could happen if there is an incidental finding?

- An incidental finding may cause you to feel anxious.
- Since a report of the incidental finding will be part of your medical record, it will be available to those accessing your medical record for your clinical care and may affect your current or future life or health insurance coverage. This risk will vary depending on the type of insurance plan involved.

The costs for any care that may come from the incidental finding, such as the need to see a doctor to diagnose or treat an incidental finding, will not be paid for by this research study. These costs would be your or your insurance company's responsibility.

How long will you be in the study?

If you decide to be in this study and the study doctor says you are eligible for the study, your participation will be 15 months if you do not become pregnant and undergo two embryo transfers. Your participation will be up to 24 months if you undergo two embryo transfers and become pregnant with the second transfer.

4. What happens to data and biospecimens that are collected in the study?

If you join this study, your data and biospecimens will be used to answer the research question and your data will be used to publish the findings of this study. Biospecimens may include any of the following: blood, tissue, saliva, urine, bone marrow, cells, etc. Most biospecimens contain DNA, which is the genetic code for each person.

You will not own the data and/or biospecimens collected from you as part of this research study. If researchers use them to create a new product or idea, including those that may have commercial value, you will not benefit financially from those efforts.

Johns Hopkins researchers and their collaborators may use the data/biospecimens collected in this study for future research purposes and may share some of the data/biospecimens with others.

Because science constantly advances, we do not yet know what future use of research data or biospecimens may include. This future research may be unrelated to the current study and may include outside collaborators.

Sharing data and/or biospecimens is part of research and may increase what we can learn from this study. Often, data/biospecimen sharing is required as a condition of funding or for publishing study results. It also is needed to allow other researchers to validate study findings and to come up with new ideas. Your data and/or biospecimens may be shared with researchers at Johns Hopkins and other institutions, for-profit companies, sponsors, government agencies, and other research partners. Your data and/or biospecimens may also be put in government or other databases/repositories.

We (Johns Hopkins) will do our best to protect and maintain your data/biospecimens in a safe way. One of the ways we protect data/biospecimens is by limiting the uses of the information and the type of information that is shared, especially your personal information. This may occur through data/specimen sharing agreements and review by oversight groups within Johns Hopkins.

If data/biospecimens are used or shared with types of information that may be likely to identify you, such as your name, address or medical record number, further institutional review and approval would be required. In these cases, Johns Hopkins will review whether additional consent from you is required. Generally, if your data/biospecimens are used/shared without any personal identifiers or with information that is less likely to identify you (such as the date of a procedure), further review and approval is not needed.

Data/biospecimen sharing could change over time, and may continue after the study ends.

The use and sharing of your data and biospecimens is required for participation in this research study. If you are not comfortable with the use and sharing of your data/biospecimens in future research without further consent, you should not participate in this study.

5. What are the risks or discomforts of the study?

If you decide to participate in this study, you will not change your regular medical care, which includes your IVF cycle or embryo transfer.

Ask any member of the research team if you have questions about the signs or symptoms of any side effects that you read about in this consent form. Please tell the study doctor or a member of the research team right away if you have any side effects. Please tell them if you have any other problems with your health or the way you feel during the study, whether you think these problems are related to the study or not.

Risks of taking ORILISSA™ (elagolix)

The very common side effects of elagolix observed in women include:

- hot flashes (21.1% or about 21 in 100)
- headache (16.2% or about 16 in 100)
- feeling sick to one's stomach (nausea)(11.8% or about 12 in 100)

Mood Change:
During the endometriosis and uterine fibroids clinical trials, some subjects experienced mood changes, including mood swing, depression, depressed mood and anxiety during elagolix administration. In the endometriosis elagolix studies, depression was reported in 1.9% (about 2 in 100) subjects and depressed mood was reported in 0.8% (about 1 in 100) subjects. A number of subjects who reported depression had a history of depression. In the endometriosis program, four cases of suicidal thought, and one case with a history of depression reported suicidal thoughts while on elagolix . One case of depression with suicidal thought was reported while on placebo. There was one case of completed suicide which was considered by the study doctor not related to study drug but rather related to potential life stress. There was one case of suicidal ideation in the uterine fibroids program in a woman who received placebo.

If you have history of depression, other psychiatric related conditions or taking an anti-depressant, please let your study doctor know. If you have any of the above symptoms, please contact your study doctor immediately.

Effects on Menstrual Bleeding:
While you are taking elagolix you may experience changes in your menstrual cycle and bleeding pattern. Your menstrual bleeding may be more or less, or occur for fewer days or no days. The time between each period may also be shorter or longer and your periods may not be predictable. At higher doses, elagolix may completely suppress your periods. This effect is reversible after stopping elagolix.

Bone Mineral Density and the Risk of Fractures:
Similar to other medications that reduce female hormone levels in the body, particularly estrogen levels, elagolix has been shown to reduce bone mineral density and affect laboratory values that measure bone health and strength. The data suggest that higher doses and longer exposure to elagolix result in greater bone loss. Bone loss can place a woman at risk for osteoporosis (softening of the bones) and fractures (broken bones). Inform the study doctor if you or family members have been diagnosed with osteoporosis, if your mother had a hip fracture, if you are a smoker, if you have used or are now using drugs such as corticosteroids or drugs to treat epilepsy (convulsions or seizures), and if you have ever had any fractures.

Because the risk of fractures depends on many factors (including your age, overall health status, overall bone strength), you should discuss the possible risk of fractures specific to you with your study doctor. There is evidence that the bone loss associated with the use of elagolix is reversible.

Effects on Liver:
Increased levels of some liver function tests have been reported in subjects receiving elagolix. These increases were temporary, were generally not accompanied by any symptoms and were usually noted within the first 3 months of elagolix. The liver function tests improved in all subjects whether they continued to take elagolix or not. Your liver function tests will be routinely monitored during this study.

Drug Interaction Risks:
It is very important that you tell the study doctor about any other medicines (either prescription or over the counter) or supplements such as vitamins or herbs that you are taking.

Unknown risk
There may be side effects and discomforts that are not yet known.

Risks of giving blood for this study

The study doctor or study staff will take your blood by sticking a needle in your arm. Some problems you might have from this are:

- pain at the site of the needle placement
- bruising at the site of the needle placement
- dizziness
- infection

You should get medical help and contact the study doctor or study staff if you have any of these or any other side effects during the study.

Transvaginal Ultrasound
This type of ultrasound uses a probe that is inserted in the vagina. You may feel discomfort from the probe.

Other potential risks of being in this study

Filling out the questionnaire about your pelvic pain, menstrual cycle, and history of pregnancy and infertility could lead you to feel uncomfortable or upset. Please tell the study doctor or study staff if you feel uncomfortable or upset while filling out the questionnaire. You have the right to refuse to answer any questions.

There is a risk that information about you may become known to people outside of this study. You will read more about the protection of your information later in this form under the heading "How will your privacy be protected?" Please ask the study doctor or study staff if you would like to know more about how your information will be protected while you are in this study.

6. Are there risks related to pregnancy?

There are no known risks.

7. Are there benefits to being in the study?

There may or may not be a direct benefit to you from this research. The results of this research may guide the future of treatment for women with endometriosis undergoing in vitro fertilization.

8. What are your options if you do not want to be in the study?

You do not have to participate in this study to receive treatment for your endometriosis-related infertility. Choosing not to participate will not have any effect on your clinical care.

You do not have to join this study. If you do not join, your care at any of the study clinics (Northwestern University, University of Colorado, Yale University, University of North Carolina, and Johns Hopkins University) will not be affected.

9. Will you be paid if you join this study?

No, you will not receive any payment or compensation if you join this study

10. Can you leave the study early?

- You can agree to be in the study now and change your mind later.
- If you wish to stop, please tell us right away.
- Leaving this study early will not stop you from getting regular medical care.

If you drop out of the study early, the study team (at Northwestern University, University of Colorado, Yale University, University of North Carolina, or Johns Hopkins University) may use your health information that it has already collected if the information is needed for this study or any follow-up activities**.**

11. Will the study require any of your other health care providers to share your health information with the researchers of this study?

As a part of this study, the researchers may ask to see your health care records from your other healthcare providers.

12. What is a Certificate of Confidentiality?

Your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

13. What other things should you know about this research study?

During the study, we will tell you if we learn any new information that might affect whether you wish to continue to participate.

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. If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the

ClinicalTrials.gov study registration number.

What is the Institutional Review Board (IRB) and how does it protect you?
This study has been reviewed by an Institutional Review Board (IRB), a group of people that reviews human research studies. The IRB can help you if you have questions about your rights as a research participant or if you have other questions, concerns or complaints about this research study. You may contact the IRB at 410-502-2092 or jhmeirb@jhmi.edu.

What should you do if you have questions about the study, or are injured or ill as a result of being in this study?
Call the principal investigator for your study site, which is listed in the "Site-specific Consent Information" (Part 2 of this consent). If you wish, you may contact the principal investigator by letter. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at 410-502-2092.

If you have an urgent medical problem or think you are injured or ill because of this study, call 911 or go to your local emergency department. You should also call the study site physician at the number listed in the "Site-specific Consent Information" (Part 2 of this consent).

JOHNS HOPKINS MEDICINE

Approved April 20, 2021

SITE SPECIFIC CONSENT INFORMATION

Site Name: **Johns Hopkins Hospital**

Study Title: **Pre-IVF treatment with a GnRH antagonist in women with endometriosis – A prospective double-blind placebo-controlled trial (PREGnant)**

JHM IRB Application Number: IRB00236742

Site Principal Investigator: **Dr. James Segars**

Site Principal Investigator Contact Information:

Dr. James Segars
Professor and Director
Division of Reproductive Sciences & Women's Health Research
Department of Gynecology and Obstetrics
Johns Hopkins School of Medicine
720 Rutland Avenue, Ross Research Building Room 624
Baltimore, MD, 21205
Phone: 410-614-2000 Fax: 410-614-7060

Emergency Contact: **Mobile: 301-512-1556**

Introduction:

This study is being done at multiple sites. This part of the consent form includes information about your site and is specific to participation at your site only. Before making your decision, both the site-specific information and general study information will be reviewed with you. You will have the opportunity to discuss any questions, including questions about this portion of the consent document, with your site's study team.

Will it cost you anything to be in this study?

You will receive a separate Insurance and Research Participant Financial Responsibility Information Sheet (Sheet).

This Sheet will give you the following information:

- The procedures, tests, drugs or devices that are part of this research and that will be paid for by the study (no cost to you).
- The procedures, tests, drugs or devices that will be billed to you and/or your health insurer. If you have health insurance, you will be responsible for any co-pays or deductibles not covered by your insurance.

Compensation for Research-Related Injury:

Johns Hopkins and the federal government do not have programs to pay you if you are hurt or have other bad results from being in the study. However, medical care at Johns Hopkins is open to you as it is to all sick or injured people.

The costs for any treatment or hospital care you receive as the result of a study-related injury that are not covered by a health insurer will be billed to you.

By signing this form, you will not give up any rights you have to seek compensation for injury.

Site IRB Contact Information:

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. If you would like to review the information for this study, or a summary of the results, ask the study team doctor for the ClinicalTrials.gov study registration number.

During the study, we will tell you if we learn any new information that might affect whether you wish to continue to participate.

What should you do if you have questions about the study, or are injured or ill as a result of being in this study?

Call the principal investigator, Dr. James Segars at 410-614-2000. If you wish, you may contact the principal investigator by letter. The address is on page one of this consent form. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at 410-502-2092.

If you have an urgent medical problem or think you are injured or ill because of this study, call 911 or go to your local emergency department. You should also call Dr. James Segars at 410-614-2000 during regular office hours and at 301-512-1556 after hours and on weekends. If this doctor is not available, the operator will page the "on call physician."

How will your privacy be maintained and how will the confidentiality of your data be protected?

HIPAA Authorization for Disclosure of Protected Health Information

What information is being collected, used, or shared?

To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both Johns Hopkins Medicine and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Who will see, use or share the information?

The people who may request, receive or use your private health information include the researchers and their staff who may be a part of Johns Hopkins Health System, Johns Hopkins University or the Johns Hopkins

Applied Physics Laboratory. Additionally, we may share your information with other people at Johns Hopkins, for example if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Johns Hopkins. This may include the sponsor of the study and its agents or contractors, outside providers, study safety monitors, government agencies, other sites in the study, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?
You do not have to sign this Authorization, but if you do not, you may not join the study.

How long will your information be used or shared?
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

How will your information be protected?
All hard copy data contained in the participants' study will be maintained in a locked office. Whenever possible you will be identified only by the Study Identification Number (SID) to maintain confidentiality. All other study records will be kept in a locked file cabinet. Your data entered into the YNHH Oncore system is a secure password protected database system which meets all the HIPAA required security. Clinical information will not be released without your written permission, except as necessary for monitoring by the IRB, the DCC, OHRP, the sponsor, or the sponsor's designee.

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Optional Study Components:

Future Contact

We would like your permission for our research team to contact you in the future. Please note that your decision below does not prevent other researchers at Johns Hopkins from contacting you about other research.

Please sign and date your choice below:

YES ☐ _____ _____
Signature of Participant Date

NO ☐ _____ _____
Signature of Participant Date

Site IRB Contact Information:

What should you do if you have questions about the study, or are injured or ill as a result of being in this study?

Call the principal investigator, Dr. James Segars at 410-614-2000. If you wish, you may contact the principal investigator by letter. The address is on page one of this consent form. If you cannot reach the principal investigator or wish to talk to someone else, call the IRB office at 410-502-2092.

If you have an urgent medical problem or think you are injured or ill because of this study, call 911 or go to your local emergency department. You should also call Dr. James Segars at 410-614-2000 during regular office hours and at 301-512-1556 after hours and on weekends. If this doctor is not available, the operator will page the "on call physician."

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Approved April 20, 2021

Signature Lines

What does your signature on this consent form mean?

Your signature on this form means that you have reviewed the information in this form, you have had a chance to ask questions, and you agree to join the study. You will not give up any legal rights by signing this consent form.

WE WILL GIVE YOU A COPY OF THIS SIGNED AND DATED CONSENT FORM

Signature of Participant	(Print Name)	Date/Time

Signature of Person Obtaining Consent	(Print Name)	Date/Time

I have received the separate Insurance and Research Participant Financial Responsibility Information Sheet.

Signature of Participant	(Print Name)	Date/Time

Signature of Interpreter/Witness to Consent Procedures	(Print Name)	Date/Time

(Required for studies enrolling non-English speakers using the short form process or otherwise as determined required by the IRB)

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR AND A COPY MUST BE GIVEN TO THE PARTICIPANT. IF APPROPRIATE FOR THIS STUDY, A SCANNED COPY OF THE SIGNED CONSENT FORM SHOULD BE UPLOADED TO THE PARTICIPANT'S EPIC/EMR RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

DOCUMENTATION OF PHYSICIAN/MID-LEVEL PROVIDER CONSENT PROCESS

My signature below indicates that I have discussed the risks, benefits, and alternatives, answered any questions, and believe the participant is able to make an informed choice to join the study.

Signature of Physician/Mid-Level Provider (Print Name) Date/Time

Signature of Participant (Print Name) Date/Time

NOTE: A COPY OF THE SIGNED, DATED CONSENT FORM MUST BE KEPT BY THE PRINCIPAL INVESTIGATOR AND A COPY MUST BE GIVEN TO THE PARTICIPANT. IF APPROPRIATE FOR THIS STUDY, A SCANNED COPY OF THE SIGNED CONSENT FORM SHOULD BE UPLOADED TO THE PARTICIPANT'S EPIC/EMR RECORD (UNLESS NO MEDICAL RECORD EXISTS OR WILL BE CREATED).

Reporting checklist for protocol of a clinical trial.

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-5, 8
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5-9

Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9-10
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9-10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention	9-10

		during the trial	
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7, 10-11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make	12

		the final decision to terminate the trial	
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	7, 9
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	12
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a