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 fertilisation-embryo transfer (IVF) 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 with 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-associated infertility.

Methods and analysis This study is a multicentre, prospective, randomised, double-blind, placebo-controlled trial to study the efficacy of GnRH antagonist pretreatment for women with endometriosis who are undergoing IVF. A total of 814 patients with endometriosis undergoing fertility treatment will be enrolled and randomised 1:1 into two groups: elagolix two times per day 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, fertilisation rate, embryo morphology and implantation rates, as well as rates of known endometriosis-related obstetrical outcomes (pregnancy-induced hypertension, antepartum haemorrhage, caesarean 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 number NCT04173169.

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%–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 with women with unexplained fertility (36% vs 55%, respectively).5 Endometriosis is also associated with...
with unexplained infertility 24% lower likelihood of live birth after IVF than women with endometriosis still have a worse 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 epidemiological or iatrogenic factors associated with an endometriosis diagnosis: greater exposure to prior gynaecological 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,12–15 pretreatment with gonadotropin releasing hormone (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 oestrogen production, including combined oral contraceptives, progestins, danazol and GnRH agonists or antagonist.22 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 randomised controlled trials (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 hypothesise that GnRH antagonist therapy may potentially benefit women with endometriosis undergoing IVF treatment, possibly with a shorter course of treatment compared with what has been studied with GnRH agonists (3–6 months).31–33

METHODS AND ANALYSIS
This is a multicentre, prospective, RCT 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 sonographical diagnosis of endometriosis.

Body mass index (BMI) 18–38 kg/m² (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 (ET).

Presence of at least one ovary with no clinically significant abnormalities (other than endometrioma).

Negative urine or cervical swab for gonorrhoea 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 visualisation of endometriosis (at the time of laparoscopy or laparotomy) within the last 10 years of initial trial visit, or by sonographical 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 (eg, Implanon or Nexplanon) within 10 months of study start.
- Continuous use of oral progestins (MPA, norethindrone acetate) within 3 months of study start.
- Use of aromatase inhibitors, danazol or hormonal contraceptives (including combined 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 >2 cm 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 thyroid stimulating hormone (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 centres in the trial (Yale University, University of Colorado-Denver, Northwestern University, Johns Hopkins and University of North Carolina). Additional clinical centres may be added for enrollment if needed. All participants will provide written, informed consent for their participation in this study (see online supplemental file). This study was approved by a central Institutional Review Boards (IRB) as well as local IRBs at all five participating centres. In addition, the Food and Drug Administration gave permission for the study to proceed using elagolix as an Investigational New Drug (152645) for this indication.

**Intervention**

**GnRH antagonist pretreatment**

Participants will be randomised 1:1 into one of two treatment groups: GnRH antagonist (elagolix 200 mg two times per day) 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 on standards. All sites will use standard follicle stimulating hormone (FSH) stimulation and GnRH antagonist in each cycle with the exception that additional luteinizing hormone (LH) activity will always be supplied at the onset 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 75 IU 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 site’s standard IVF protocol. When at least two leading follicles measuring ≥18 mm are seen on ultrasound, the trigger injection of human chorionic gonadotrophin (hCG) (10 000 IU) or r-hCG (250 mcg) is administered, followed by oocyte retrieval 37 hours later. Depending on sperm parameters following preparation on the day of oocyte retrieval, fertilisation 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 American Society for Reproductive Medicine (ASRM) guidelines allowing for transfer of up to two embryos, with an elective single ET preferred.35 36 Preimplantation Genetic Testing for aneuploidy will be allowed. Frozen ETs 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 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 ETs resulting from the initial ‘fresh’ egg retrieval cycle. Most women using elagolix menstruate in the first 2 months with only a 50% amenorrhoea 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 analyse the live birth rate per ET.

For exploratory analysis, we will examine a number of IVF cycle parameters: (1) Estradiol (E2) level on the day of 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 per cent of mature metaphase II oocytes; (6) Fertilisation (2PN) rate; (7) Blastocyst rate; (8) Incidence of moderate-to-severe ovarian hyperstimulation syndrome; (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 ≤23 weeks 6 days gestation); (12) Rate of ectopic pregnancy or pregnancy of unknown location; (13) Ongoing pregnancy rate and (14) Multiple pregnancy rate.

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

Finally, quality of life will be assessed 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 randomised 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 differences.
effects (5%–10% improvement). We will aim to enrol and randomise 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 $\chi^2$ test of independence. Baseline patient characteristics and secondary outcome measures will also be analysed with Pearson’s $\chi^2$ 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. 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 12 August 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 optimise 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 deidentification. Data will be collected electronically and abstracted from the electronic medical record in a deidentified manner. Any medical information that is obtained in connection with this programme 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 the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Data and Specimen Hub (DASH). The informed consent will include permission to bank these samples. The processes included initial data and documentation preparation (eg, 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 on November 2021.

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Competing interests
None declared.

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

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Supplemental material
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