

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-052043
Article Type:	Protocol
Date Submitted by the Author:	20-Apr-2021
Complete List of Authors:	Taylor, Hugh; Yale School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Li, Howard; Yale School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Carson, Sandra; Yale School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Flores, Valerie; Yale School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Pal, Lubna; Yale University School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Robbins, Jared; Northwestern University, Obstetrics and Gynecology Santoro, Nanette F. ; University of Colorado, Obstetrics and Gynecology Segars, James H. ; Johns Hopkins University School of Medicine, Gynecology and Obstetrics Seifer, David; Yale School of Medicine, Obstetrics, Gynecology, and Reproductive Sciences Huang, H; Yale University School of Public Health Young, Steven; The University of North Carolina at Chapel Hill, Obstetrics and Gynecology Zhang, Heping; Yale University School of Public Health
Keywords:	Sex steroids & HRT < DIABETES & ENDOCRINOLOGY, Subfertility < GYNAECOLOGY, Reproductive medicine < GYNAECOLOGY, Clinical trials < THERAPEUTICS

SCHOLARONE™
Manuscripts

1
2
3 1 **Pre-IVF treatment with a GnRH antagonist in women with endometriosis (PREGnant):**

4
5 2 **Study protocol for a prospective, double-blind, placebo-controlled trial**

6
7 3
8
9 4 Hugh S. Taylor¹, Howard J. Li¹, Sandra Carson¹, Valerie Flores¹, Lubna Pal¹, Jared Robbins²,
10 5 Nanette Santoro³, James Segars⁴, David Seifer¹, Hao Huang⁵, Steven Young⁶, and Heping
11 6 Zhang⁵

12 7
13 8 1. Yale School of Medicine, New Haven, CT

14 9 2. Northwestern University, Chicago, IL

15 10 3. University of Colorado, Aurora, CO

16 11 4. Johns Hopkins University, Baltimore, MD

17 12 5. Yale School of Public Health, New Haven CT

18 13 6. University of North Carolina, Chapel Hill, NC

19 14

20 15 **Correspondence:**

21 16 Hugh S. Taylor

22 17 Department of Obstetrics, Gynecology and Reproductive Sciences

23 18 Yale School of Medicine

24 19 333 Cedar Street

25 20 New Haven CT 06520 Phone: 203-785-4001

26 21 Email: hugh.taylor@yale.edu

27 22

28 23 **Word count:** 2926 words

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 seeking 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

50 **Strengths and Limitations of this Study**

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

65 **Introduction**

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

1
2
3 75 55%, respectively) [6]. Endometriosis is also associated with obstetrical complications, including
4
5 76 obstetrical hemorrhage, cesarean delivery, pre-eclampsia and pregnancy-induced hypertension,
6
7 77 and preterm birth [7–12]. While the mechanism remains controversial and unclear,
8
9 78 endometriosis is thought to contribute to reduced fertility via adnexal scarring and poor
10
11 79 endometrial receptivity, though studies also suggest with women with advanced endometriosis
12
13 80 also have poor ovarian reserve, low oocyte and embryo quality, and poor implantation [1,13–
14
15 81 15].

16
17
18 82 While IVF is currently the most effective treatment for endometriosis-associated
19
20 83 infertility, endometriosis is also associated with poorer IVF outcomes. One meta-analysis from
21
22 84 2002 including 22 non-randomized trials reported that the chances of achieving pregnancy with
23
24 85 IVF in women with endometriosis was almost half that of those with tubal infertility (odds ratio
25
26 86 [OR] = 0.56, 95% confidence intervals [CI] = 0.44–0.7) and women with severe disease had
27
28 87 about half the pregnancy rate of those with mild disease [16]. A more recent study published in
29
30 88 2018 confirmed that women with endometriosis still have a 24% lower likelihood of live birth
31
32 89 after IVF than women with unexplained infertility [17]. These data support the notion that when
33
34 90 endometriosis is present, both spontaneous and ART-facilitated pregnancy rates are reduced,
35
36 91 and that there is a dose-response effect in that those with worse disease have a worse
37
38 92 prognosis.

39
40
41 93 As a hormone-dependent disorder, medical management of symptomatic endometriosis
42
43 94 has targeted ovarian estrogen production, including combined oral contraceptives, progestins,
44
45 95 danazol and gonadotropin-releasing hormone (GnRH) agonists or antagonist [18]. While these
46
47 96 therapies have been helpful in managing endometriosis-associated pelvic pain, they have not
48
49 97 been shown to treat endometriosis-associated infertility in the absence of IVF [19].

50
51 98 In the IVF setting, prolonged GnRH agonist treatment prior to IVF has been shown to
52
53 99 improve fertility rates in women with advanced endometriosis [20–22]. Proposed mechanisms
54
55 100 are by means of increased retrieved oocytes, higher implantation rates, and reduced preclinical
56
57
58
59
60

1
2
3 101 abortions [15,20]. A Cochrane review of 3 RCTs in 165 women with endometriosis concluded
4
5 102 that GnRH agonist administration for a period of 3-6 months prior to IVF or ICSI increases the
6
7 103 odds of clinical pregnancy (OR 4.28, 95% CI 2.00–9.15) [23]. However, none of those studies
8
9 104 were placebo controlled, only one reported live birth rates and none provided sufficient data to
10
11 105 investigate important secondary outcomes such as multiple or ectopic pregnancies, miscarriage,
12
13 106 fetal abnormalities, or other complications.

15
16 107 Since then, the GnRH antagonist elagolix has recently become available for use, with a
17
18 108 number of advantages over GnRH agonists: the convenience of oral rather than parenteral
19
20 109 administration, improved tolerability and reduced severity of vasomotor symptoms, rapid onset
21
22 110 of action with suppression of endogenous estradiol levels within 24 hours, and lack of initial
23
24 111 gonadotropin stimulation (“flare” effect) seen with GnRH agonists [24]. However, elagolix has
25
26 112 not yet been studied as an adjunctive treatment prior to IVF for women with endometriosis.
27
28 113 Based on limited evidence from GnRH agonist trials, we hypothesize that GnRH antagonist
29
30 114 therapy may also benefit women with endometriosis undergoing IVF treatment, possibly with a
31
32 115 shorter course of treatment compared to what has been studied with GnRH agonists (3-6
33
34 116 months) [23].

36
37 117

38 39 118 **Methods and Analysis**

40
41 119 This is a multicenter, prospective, randomized controlled trial to study the effect of GnRH
42
43 120 antagonist pre-treatment for women with endometriosis who are undergoing IVF.

44
45 121

46 47 122 ***Participants***

48
49 123 Participants will be recruited based on the following inclusion criteria:

- 50
51 124
- 52 • Women aged 18-38
 - 53 • Planning to undergo a cycle of IVF for treatment of infertility
 - 54 • Surgical or sonographic diagnosis of endometriosis
- 55
56 126

- 1
2
3 127 • Body Mass Index (BMI) 18-38 kg/m² (inclusive) at time of screening
4
5 128 • Anti-Mullerian hormone (AMH) > 0.8 ng/ml within 6 months of planned IVF cycle
6
7 129 start
8
9 130 • Uterine cavity assessment by sonohysterogram or hysteroscopy within 6 months
10
11 131 indicating adequacy for embryo transfer
12
13 132 • Presence of at least one ovary with no clinically significant abnormalities (other
14
15 133 than endometrioma)
16
17 134 • Negative urine or cervical swab for gonorrhoea and chlamydia within 12 months of
18
19 135 recruitment
20
21 136 • Willingness and ability to comply with trial procedures, including reporting of
22
23 137 obstetrical outcomes after delivery
24
25

26 138 A diagnosis of endometriosis must be confirmed by surgical visualization of
27
28 139 endometriosis (at the time of laparoscopy or laparotomy) within the last 10 years of initial trial
29
30 140 visit, or by sonographic documentation of an ovarian endometrioma >2 cm, or two or more
31
32 141 smaller endometriomas that total >2 cm in diameter. If a diagnosis of endometriosis was made
33
34 142 sonographically, serial transvaginal ultrasounds must have documented the same unambiguous
35
36 143 endometrioma on two separate occasions in more than one menstrual cycle. Images will be
37
38 144 read centrally by the same investigator to assure uniform diagnostic criteria are applied.
39
40

41 145 Women will be excluded from the study if there was:
42

- 43 146 • Use of GnRH agonists or antagonists within 6 months of study start, except for
44
45 147 antagonist use as part of an IVF cycle
46
47 148 • Use of depot medroxyprogesterone acetate (MPA) or subdermal contraceptive
48
49 149 implant (e.g. Implanon® or Nexplanon®) within 10 months of study start
50
51 150 • Continuous use of oral progestins (MPA, NETA) within 3 months of study start
52
53
54
55
56
57
58
59
60

- 1
2
3 151 • Use of aromatase inhibitors, danazol or hormonal contraceptives (including
4
5 152 combined oral contraceptive pill, progestin-only pill, transdermal patch or
6
7 153 contraceptive ring) within 1 month of study start
8
9 154 • Pregnancy greater than 8 weeks in length within the last 6 months
10
11 155 • History of three or more prior IVF/ICSI attempts
12
13 156 • Presence of hydrosalpinx >2cm on ultrasound, untreated endometrial polyps,
14
15 157 submucosal uterine leiomyomata, or intrauterine adhesions
16
17 158 • Abnormal cervical cytology other than low-grade within last year
18
19 159 • History of malignancy within 5 years of the start of screening, except for
20
21 160 adequately managed basal cell carcinoma and squamous cell carcinoma of the
22
23 161 skin
24
25 162 • History of suicide attempt within the last year of recruitment
26
27 163 • Hypersensitivity to study drugs
28
29 164 • Planned surgical treatment of endometriosis or planned surgery in the
30
31 165 abdominal-pelvic area within the duration of the trial
32
33 166 • Untreated abnormal prolactin or TSH
34
35 167 • Presence of any condition for which pregnancy is precluded
36
37
38

39 168 Participants will be recruited from the population of patients already committed to
40
41 169 pursuing IVF at one of the five participating clinical centers in the trial (Yale University,
42
43 170 University of Colorado - Denver, Northwestern University, Johns Hopkins and University of
44
45 171 North Carolina). Additional clinical centers may be added for enrollment if needed. All
46
47 172 participants will provide written, informed consent for their participation in this study. The Food
48
49 173 and Drug Administration has granted permission for the study to proceed using elagolix as an
50
51 174 Investigational New Drug (IND 152645) for this indication.
52
53
54 175

55
56 176 **Intervention**
57
58
59
60

1
2
3 177 *GnRH antagonist pre-treatment*
4

5 178 Participants will be randomized 1:1 into one of two treatment groups: GnRH antagonist
6
7 179 (elagolix 200 mg bid) or placebo for 8 weeks, prior to undergoing IVF. While using GnRH
8
9 180 antagonists, hot flashes and other vasomotor symptoms may occur. If indicated, use of
10
11 181 paroxetine mesylate will be allowed. No sex steroids or other hormone modifying treatments are
12
13 182 permitted.
14

15
16 183
17
18 184 *IVF treatment*
19

20 185 All participants will then undergo IVF treatment per local protocols, with agreed upon
21
22 186 standards. All sites will use standard FSH stimulation and GnRH antagonist in each cycle with
23
24 187 the exception that additional LH activity will always be supplied at the outset of stimulation,
25
26 188 since half of the participants will have been on GnRH antagonist pre-treatment and will be
27
28 189 expected to have suppressed LH. Non-conventional IVF therapies outside of those following
29
30 190 standard protocols at each site will not be performed.
31

32
33 191 The standard IVF treatment for the study will be a GnRH antagonist protocol (cetrotide
34
35 192 or ganirelix). Gonadotrophin stimulation with recombinant human follicle stimulating hormone
36
37 193 and menotropin (supplying 75IU FSH and 75 IU LH activity per vial) will be started at a daily
38
39 194 dose ranging 150-375 IU depending on patient characteristics including age, early follicular
40
41 195 phase FSH, AMH, antral follicle count and BMI. Each patient will receive at least 75 IU of LH
42
43 196 activity daily as part of the initial stimulation protocol to counteract the LH suppression by the
44
45 197 GnRH antagonist. The oral GnRH antagonist will be discontinued at the start of stimulation;
46
47 198 addition of subcutaneous injections of GnRH antagonist will be based on each sites' standard
48
49 199 IVF protocol. When at least two leading follicles measuring ≥ 18 mm are seen on ultrasound, the
50
51 200 trigger injection of u-hCG (10,000 IU) or r-hCG (250 mcg) is administered, followed by oocyte
52
53 201 retrieval 37h later. Depending on sperm parameters following preparation on the day of oocyte
54
55 202 retrieval, fertilization will be achieved either by conventional IVF or ICSI [25].
56
57
58
59
60

203

204 Embryo culture and transfer

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

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

218

219 Randomization

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

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

223 A computer-generated randomization list will be created and randomization will be
224 performed prior to the first dose of elagolix or placebo. Randomization will have random sizes
225 (2,4, or 6) of blocks, stratified by site and age group (<35 versus ≥35 years). Both participants
226 and investigators will be blinded to the treatment assignment during the trial duration (except for
227 serious safety concerns). The assigned treatment (GnRH antagonist vs. placebo) applied during
228 the fresh cycle will also be used for subsequent frozen embryo transfers resulting from the initial

1
2
3 229 'fresh' egg retrieval cycle. Most women using elagolix menstruate in the first 2 months with only
4
5 230 a 50% amenorrhea rate after 1 year in the Phase III clinical trial, enabling blinding to remain
6
7 231 intact.
8

9 232

11 233 **Outcome measures**

13 234 The primary outcome measure will be live birth rate per cycle start, defined as live birth
14
15 235 at ≥ 24 weeks of gestation.

17 236 As secondary outcome measures, we will also analyze a number of IVF cycle
18
19 237 parameters: 1. Estradiol (E2) level on the day of human chorionic gonadotrophin (hCG)
20
21 238 administration; 2. Progesterone (P) level on the day of hCG administration; 3. The number of
22
23 239 oocytes retrieved; 4. Gonadotropin dosage and duration; 5. Number and percent of mature
24
25 240 metaphase II (MII) oocytes; 6. Fertilization (2PN) rate; 7. Blastocyst rate; 8. Incidence of
26
27 241 moderate-to-severe ovarian hyperstimulation syndrome (OHSS); 9. Implantation rate; 10.
28
29 242 Clinical pregnancy rate; 11. Miscarriage rate (defined as pregnancy loss prior to viability scan
30
31 243 and including those confirmed on ultrasound scan up to ≤ 23 w6d gestation); 12. Rate of ectopic
32
33 244 pregnancy or pregnancy of unknown location; 13. Ongoing pregnancy rate; 14. Multiple
34
35 245 pregnancy rate.
36
37

38
39 246 We will also measure pregnancy-related parameters to determine the effect of pre-
40
41 247 treatment with GnRH antagonist on pregnancy related complications associated with
42
43 248 endometriosis: pre-eclampsia and pregnancy-induced hypertension, preterm birth, intrauterine
44
45 249 growth restriction, cesarean delivery, and obstetric hemorrhage.
46

47 250 Finally, quality of life will be assessed using the FertiQOL, a validated questionnaire that
48
49 251 contains Emotional, Mind/Body, Relational and Social domains [28].
50

51 252

53 253 **Statistical Analysis**

54 254 *Sample size and power calculations*

1
2
3 255 The average live birth rate for women with endometriosis undergoing IVF is estimated to
4
5 256 be 39%, based on 2016 SART data showing a live birth rate of 44.7% per cycle in women with
6
7 257 endometriosis under the age of 35 and 34.0% in women ages 35-37. We conservatively estimate
8
9 258 an effect of 10% absolute improvement in live birth rate to 49% in the GnRH antagonist arm,
10
11 259 based on prior randomized trials using GnRH agonists. Thus, using 386 participants per arm
12
13 260 (N=772) would provide an alpha of 0.05 and power of 80%. We will aim to enroll and randomize
14
15 261 814 participants (407 per treatment group), to account for an estimated drop-out rate of 5%.
16
17
18 262

20 263 *Analysis of outcome measures*

21
22 264 An intention-to-treat analysis will be performed on primary and secondary outcome
23
24 265 measures. The primary outcome, cumulative live birth rate, will be compared between the two
25
26 266 intervention arms using Pearson's chi-square test of independence. Baseline patient
27
28 267 characteristics and secondary outcome measures will also be analyzed with Pearson's chi-square
29
30 268 test and logistic regression as needed.

31
32 269 Based on prior experience, we expect a data completion rate of at least 99.5% and we do
33
34 270 not expect missing data to significantly affect trial analysis or results. In the unlikely event of
35
36 271 unexpectedly high rates of missing data, the potential mechanisms for missing data (missing
37
38 272 completely at random, missing at random, or missing not at random) will be examined. We will
39
40 273 compare the available characteristics of those with missing data to those with complete data. If
41
42 274 necessary, imputation techniques may be used.
43
44
45 275

47 276 ***Patient and Public Involvement***

48
49 277 Patients and the public were not involved in the design, or conduct, or reporting, or dissemination
50
51 278 plans of this research.
52
53
54 279

56 280 **Trial status and registration**

1
2
3 281 The study was conceived and designed in 2019. Recruitment is expected to begin in April 2021.
4

5 282 This study is registered on ClinicalTrials.gov Identifier NCT04173169. This manuscript
6

7 283 describes the latest version, last updated Dec 10, 2020.
8

9 284

11 285 **Ethics and Dissemination**

13 286 The PREGnant trial is undergoing Institutional Review Board approval at Johns Hopkins
14

15 287 University, pending a minor modification, with reliance agreements at all participating sites.
16

17 288 Protocol modifications will be reviewed by the IRB and reported to the funder.
18

19 289 Participating investigators, providers, and study staff will be informed of protocol changes via
20

21 290 email. Significant protocol modifications will also be noted on ClinicalTrials.gov.
22

23 291 Elagolix has had increasing use in treating endometriosis-related pain, and the findings
24

25 292 of this trial can be easily adopted into the IVF setting. The results of this trial may reveal a new
26

27 293 way to optimize outcomes for women with endometriosis seeking fertility treatment.
28

29 294

31 295 **Safety and adverse events monitoring**

32 296 The safety of the intervention medication elagolix has been previously investigated and
33

34 297 found to be tolerable [24]. All adverse events are collected regardless of their grade of severity
35

36 298 and reported based on established criteria. Data Safety Monitoring Board (DSMB) will receive
37

38 299 unblinded data and advise on potential safety issues. The choice of continuing therapy or trial
39

40 300 participation based on adverse events is at the discretion of the investigator and DSMB
41

42 301 determinations.
43

44 302

45 303 **Data management and sharing**

46 304 The trial is conducted in accordance with relevant regulations and standard operating
47

48 305 procedures, including data protection. Each subject is assigned a unique code for de-
49

50 306 identification. Data will be collected electronically and abstracted from the electronic medical
51

1
2
3 307 record in a de-identified manner. Any medical information that is obtained in connection with this
4
5 308 program that could identify a subject will remain confidential and will be disclosed only as
6
7 309 required by law. All persons responsible for the quality control of the data take all necessary
8
9 310 precautions to ensure the confidentiality of information regarding trial participants and in
10
11 311 particular the identity of the participants and the results obtained. The final trial dataset will be
12
13 312 available to study investigators and Research Ethic Boards at all participating sites. Results of
14
15 313 the trial will be published in peer-reviewed journals.
16
17
18 314

315 **Author Contributions**

316 HST, HJL, SC, VF, LP, JR, NS, JS, DS, HH, SY, HZ each made substantial
317 contributions to the conception or design of the study protocol, design of the study intervention,
318 study outcomes, study procedures, and/or revised the protocol critically for important intellectual
319 content and approved the final version to be published. HZ made substantial contributions to the
320 conception or design of the study protocol and wrote the first draft of the protocol. HJL wrote the
321 first draft of this manuscript. All authors approved the final version to be published.
322

323 **Funding Statement**

324 This study was funded by a grant titled "Pre-IVF treatment with a GnRH antagonist in women
325 with endometriosis - A prospective double blind placebo controlled trial (PREGnant)" from the
326 Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD),
327 1R01HD100336.
328

329 **Competing Interests**

330 The authors have no competing interests to report.
331

332 **References**

- 1
2
3 333 1. Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and
4
5 334 treatment of endometriosis-associated infertility. *Obstet Gynecol Clin North Am.* 2012;39:535–
6
7 335 49.
- 8
9 336 2. Taylor HS, Kotlyar AM, Flores VA. Endometriosis is a chronic systemic disease: clinical
10
11 337 challenges and novel innovations. *Lancet.* 2021;397:839-852.
- 12
13 338 3. Verkauf BS. Incidence, symptoms, and signs of endometriosis in fertile and infertile women. *J*
14
15 339 *Fla Med Assoc.* 1987;74:671–5.
- 16
17 340 4. Practice Committee of the American Society for Reproductive Medicine. Endometriosis and
18
19 341 infertility: a committee opinion. *Fertil Steril.* 2012;98:591–8.
- 20
21 342 5. Hughes EG, Fedorkow DM, Collins JA. A quantitative overview of controlled trials in
22
23 343 endometriosis-associated infertility. *Fertil Steril.* 1993;59:963–70.
- 24
25 344 6. Akande VA, Hunt LP, Cahill DJ, Jenkins JM. Differences in time to natural conception
26
27 345 between women with unexplained infertility and infertile women with minor endometriosis. *Hum*
28
29 346 *Reprod.* 2004;19:96–103.
- 30
31 347 7. Healy DL, Breheny S, Halliday J, Jaques A, Rushford D, Garrett C, et al. Prevalence and risk
32
33 348 factors for obstetric haemorrhage in 6730 singleton births after assisted reproductive technology
34
35 349 in Victoria Australia. *Hum Reprod.* 2010;25:265–74.
- 36
37 350 8. Takemura Y, Osuga Y, Fujimoto A, Oi N, Tsutsumi R, Koizumi M, et al. Increased risk of
38
39 351 placenta previa is associated with endometriosis and tubal factor infertility in assisted
40
41 352 reproductive technology pregnancy. *Gynecol Endocrinol.* 2013;29:113–5.
- 42
43 353 9. Vercellini P, Parazzini F, Pietropaolo G, Cipriani S, Frattaruolo MP, Fedele L. Pregnancy
44
45 354 outcome in women with peritoneal, ovarian and rectovaginal endometriosis: a retrospective
46
47 355 cohort study. *BJOG.* 2012;119:1538–43.
- 48
49 356 10. Conti N, Cevenini G, Vannuccini S, Orlandini C, Valensise H, Gervasi MT, et al. Women
50
51 357 with endometriosis at first pregnancy have an increased risk of adverse obstetric outcome. *J*
52
53 358 *Matern Fetal Neonatal Med.* 2015;28:1795–8.

- 1
2
3 359 11. Fernando S, Breheny S, Jaques AM, Halliday JL, Baker G, Healy D. Preterm birth, ovarian
4 360 endometriomata, and assisted reproduction technologies. *Fertil Steril*. 2009;91:325–30.
5
6 361 12. Stephansson O, Kieler H, Granath F, Falconer H. Endometriosis, assisted reproduction
7 362 technology, and risk of adverse pregnancy outcome. *Hum Reprod*. 2009;24:2341–7.
8
9 363 13. Matalliotakis IM, Cakmak H, Mahutte N, Fragouli Y, Arici A, Sakkas D. Women with
10 364 advanced-stage endometriosis and previous surgery respond less well to gonadotropin
11 365 stimulation, but have similar IVF implantation and delivery rates compared with women with
12 366 tubal factor infertility. *Fertil Steril*. 2007;88:1568–72.
13
14 367 14. Brosens I. Endometriosis and the outcome of in vitro fertilization. *Fertil Steril*. 2004;81:1198–
15 368 200.
16
17 369 15. Olivennes F. [Results of IVF in women with endometriosis]. *J Gynecol Obstet Biol Reprod*
18 370 (Paris). 2003;32:S45-47.
19
20 371 16. Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization.
21 372 *Fertil Steril*. 2002;77:1148–55.
22
23 373 17. Muteshi CM, Ohuma EO, Child T, Becker CM. The effect of endometriosis on live birth rate
24 374 and other reproductive outcomes in ART cycles: a cohort study. *Hum Reprod Open*.
25 375 2018;2018:hoy016.
26
27 376 18. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic
28 377 pain associated with endometriosis: a committee opinion. *Fertil Steril*. 2014;101:927–35.
29
30 378 19. Hughes E, Brown J, Collins JJ, Farquhar C, Fedorkow DM, Vandekerckhove P. Ovulation
31 379 suppression for endometriosis. *Cochrane Database Syst Rev*. 2007;CD000155.
32
33 380 20. Surrey ES, Silverberg KM, Surrey MW, Schoolcraft WB. Effect of prolonged gonadotropin-
34 381 releasing hormone agonist therapy on the outcome of in vitro fertilization-embryo transfer in
35 382 patients with endometriosis. *Fertil Steril*. 2002;78:699–704.
36
37 383 21. Ozkan S, Arici A. Advances in treatment options of endometriosis. *Gynecol Obstet Invest*.
38 384 2009;67:81–91.

- 1
2
3 385 22. Guo Y, Lu N, Zhang Y, Su Y, Wang Y, Zhang Y, et al. Comparative study on the pregnancy
4
5 386 outcomes of in vitro fertilization-embryo transfer between long-acting gonadotropin-releasing
6
7 387 hormone agonist combined with transvaginal ultrasound-guided cyst aspiration and long-acting
8
9 388 gonadotropin-releasing hormone agonist alone. *Contemp Clin Trials*. 2012;33:1206–10.
- 11 389 23. Sallam HN, Garcia-Velasco JA, Dias S, Arici A. Long-term pituitary down-regulation before
12
13 390 in vitro fertilization (IVF) for women with endometriosis. *Cochrane Database Syst Rev*.
14
15 391 2006;CD004635.
- 17 392 24. Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, et al. Treatment of
18
19 393 Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. *N Engl J Med*.
20
21 394 2017;377:28–40.
- 23 395 25. Practice Committees of the American Society for Reproductive Medicine and the Society for
24
25 396 Assisted Reproductive Technology. Intracytoplasmic sperm injection (ICSI) for non-male factor
26
27 397 indications: a committee opinion. *Fertil Steril*. 2020;114:239–45.
- 29 398 26. Practice Committee of Society for Assisted Reproductive Technology, Practice Committee
30
31 399 of American Society for Reproductive Medicine. Elective single-embryo transfer. *Fertil Steril*.
32
33 400 2012;97:835–42.
- 35 401 27. Practice Committee of the American Society for Reproductive Medicine. Practice Committee
36
37 402 of the Society for Assisted Reproductive Technology. Guidance on the limits to the number of
38
39 403 embryos to transfer: a committee opinion. *Fertil Steril*. 2017;107:901–3.
- 41 404 28. Boivin J, Takefman J, Braverman A. The Fertility Quality of Life (FertiQoL) tool: development
42
43 405 and general psychometric properties. *Fertil Steril*. 2011;96:409-415.e3.
- 44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1 Introduction

2			
3	Background and	#6a	Description of research question and justification for undertaking
4	rationale		the trial, including summary of relevant studies (published and
5			unpublished) examining benefits and harms for each intervention
6			
7			
8	Background and	#6b	Explanation for choice of comparators
9	rationale: choice of		
10	comparators		
11			
12			
13	Objectives	#7	Specific objectives or hypotheses
14			
15			
16	Trial design	#8	Description of trial design including type of trial (eg, parallel
17			group, crossover, factorial, single group), allocation ratio, and
18			framework (eg, superiority, equivalence, non-inferiority,
19			exploratory)
20			
21			
22			
23	Methods:		
24	Participants,		
25	interventions, and		
26	outcomes		
27			
28			
29			
30	Study setting	#9	Description of study settings (eg, community clinic, academic
31			hospital) and list of countries where data will be collected.
32			Reference to where list of study sites can be obtained
33			
34			
35	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,
36			eligibility criteria for study centres and individuals who will
37			perform the interventions (eg, surgeons, psychotherapists)
38			
39			
40	Interventions:	#11a	Interventions for each group with sufficient detail to allow
41	description		replication, including how and when they will be administered
42			
43			
44	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a
45	modifications		given trial participant (eg, drug dose change in response to harms,
46			participant request, or improving / worsening disease)
47			
48			
49	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any
50	adherence		procedures for monitoring adherence (eg, drug tablet return;
51			laboratory tests)
52			
53			
54			
55	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or
56	concomitant care		prohibited during the trial
57			
58			
59			
60			

1	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
2				
3				
4				
5				
6				
7				
8				
9				
10				
11	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
12				
13				
14				
15				
16	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
17				
18				
19				
20				
21	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
22				
23				
24				
25	Methods: Assignment			
26	of interventions (for			
27	controlled trials)			
28				
29				
30	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
31				
32				
33				
34				
35				
36				
37				
38				
39				
40	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
41				
42				
43				
44				
45				
46				
47	Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
48				
49				
50				
51	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
52				
53				
54				
55				
56	Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention	9-10
57				
58				
59				
60				

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	
1			
2			
3	Harms	#22 Plans for collecting, assessing, reporting, and managing solicited	12
4		and spontaneously reported adverse events and other unintended	
5		effects of trial interventions or trial conduct	
6			
7			
8	Auditing	#23 Frequency and procedures for auditing trial conduct, if any, and	12
9		whether the process will be independent from investigators and the	
10		sponsor	
11			
12			
13	Ethics and		
14	dissemination		
15			
16			
17	Research ethics	#24 Plans for seeking research ethics committee / institutional review	12
18	approval	board (REC / IRB) approval	
19			
20			
21	Protocol amendments	#25 Plans for communicating important protocol modifications (eg,	12
22		changes to eligibility criteria, outcomes, analyses) to relevant	
23		parties (eg, investigators, REC / IRBs, trial participants, trial	
24		registries, journals, regulators)	
25			
26			
27	Consent or assent	#26a Who will obtain informed consent or assent from potential trial	7
28		participants or authorised surrogates, and how (see Item 32)	
29			
30			
31	Consent or assent:	#26b Additional consent provisions for collection and use of participant	7, 9
32	ancillary studies	data and biological specimens in ancillary studies, if applicable	
33			
34			
35	Confidentiality	#27 How personal information about potential and enrolled participants	13
36		will be collected, shared, and maintained in order to protect	
37		confidentiality before, during, and after the trial	
38			
39			
40	Declaration of interests	#28 Financial and other competing interests for principal investigators	13
41		for the overall trial and each study site	
42			
43			
44	Data access	#29 Statement of who will have access to the final trial dataset, and	13
45		disclosure of contractual agreements that limit such access for	
46		investigators	
47			
48			
49	Ancillary and post trial	#30 Provisions, if any, for ancillary and post-trial care, and for	n/a
50	care	compensation to those who suffer harm from trial participation	
51			
52			
53	Dissemination policy:	#31a Plans for investigators and sponsor to communicate trial results to	13
54	trial results	participants, healthcare professionals, the public, and other relevant	
55		groups (eg, via publication, reporting in results databases, or other	
56		data sharing arrangements), including any publication restrictions	
57			
58			
59			
60			

1	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	12
2	authorship		professional writers	
3				
4	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	n/a
5	reproducible research		participant-level dataset, and statistical code	
6				
7				

8 Appendices

10	Informed consent	#32	Model consent form and other related documentation given to	n/a
11	materials		participants and authorised surrogates	
12				
13	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
14			biological specimens for genetic or molecular analysis in the	
15			current trial and for future use in ancillary studies, if applicable	
16				
17				
18				
19				
20				
21				

22 The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons
 23 Attribution License CC-BY-NC. This checklist can be completed online using <https://www.goodreports.org/>, a
 24 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
 25
 26
 27
 28
 29
 30
 31
 32
 33
 34
 35
 36
 37
 38
 39
 40
 41
 42
 43
 44
 45
 46
 47
 48
 49
 50
 51
 52
 53
 54
 55
 56
 57
 58
 59
 60

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-052043.R1
Article Type:	Protocol
Date Submitted by the Author:	20-Dec-2021
Complete List of Authors:	Taylor, Hugh; Yale School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Li, Howard; Yale School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Carson, Sandra; Yale School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Flores, Valerie; Yale School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Pal, Lubna; Yale University School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Robbins, Jared; Northwestern University, Obstetrics and Gynecology Santoro, Nanette F. ; University of Colorado, Obstetrics and Gynecology Segars, James H. ; Johns Hopkins University School of Medicine, Gynecology and Obstetrics Seifer, David; Yale School of Medicine, Obstetrics, Gynecology, and Reproductive Sciences Huang, H; Yale University School of Public Health Young, Steven; The University of North Carolina at Chapel Hill, Obstetrics and Gynecology Zhang, Heping; Yale University School of Public Health
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Reproductive medicine
Keywords:	Sex steroids & HRT < DIABETES & ENDOCRINOLOGY, Subfertility < GYNAECOLOGY, Reproductive medicine < GYNAECOLOGY, Clinical trials < THERAPEUTICS

SCHOLARONE™
Manuscripts

1
2
3 1 **Pre-IVF treatment with a GnRH antagonist in women with endometriosis (PREGNANT):**

4
5 2 **Study protocol for a prospective, double-blind, placebo-controlled trial**

6
7 3
8
9 4 Hugh S. Taylor¹, Howard J. Li¹, Sandra Carson¹, Valerie Flores¹, Lubna Pal¹, Jared Robbins²,
10
11 5 Nanette Santoro³, James Segars⁴, David Seifer¹, Hao Huang⁵, Steven Young⁶, and Heping
12
13 6 Zhang⁵

14
15
16 7
17
18 8 1. Yale School of Medicine, New Haven, CT

19
20 9 2. Northwestern University, Chicago, IL

21
22 10 3. University of Colorado, Aurora, CO

23
24 11 4. Johns Hopkins University, Baltimore, MD

25
26 12 5. Yale School of Public Health, New Haven CT

27
28 13 6. University of North Carolina, Chapel Hill, NC

29
30
31 14

32
33 15 **Correspondence:**

34
35 16 Hugh S. Taylor

36
37 17 Department of Obstetrics, Gynecology and Reproductive Sciences

38
39 18 Yale School of Medicine

40
41 19 333 Cedar Street

42
43 20 New Haven CT 06520 Phone: 203-785-4001

44
45 21 Email: hugh.taylor@yale.edu

46
47 22

48
49 23 **Word count:** 2926 words

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

50 **Strengths and Limitations of this Study**

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

65 **Introduction**

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

1
2
3 75 55%, respectively) [6]. Endometriosis is also associated with obstetrical complications, including
4
5 76 obstetrical hemorrhage, cesarean delivery, pre-eclampsia and pregnancy-induced hypertension,
6
7 77 and preterm birth [7–12]. While the mechanism remains controversial and unclear,
8
9 78 endometriosis is thought to contribute to reduced fertility via adnexal scarring and poor
10
11 79 endometrial receptivity, though studies also suggest with women with advanced endometriosis
12
13 80 also have poor ovarian reserve, low oocyte and embryo quality, and poor implantation [1,13–
14
15 81 15].

16
17
18 82 Multiple effective treatments exist for the management of endometriosis-associated
19
20 83 infertility, including laparoscopic destruction of endometriotic disease, ovulation induction, and
21
22 84 intrauterine insemination [1,16,17]. While some studies show that conservative treatment alone
23
24 85 may be effective in improving fertility for women with endometriosis and potentially helps avoid
25
26 86 obstetrical complications associated with IVF [17], IVF remains the most direct and effective
27
28 87 treatment for endometriosis-associated infertility, especially in patients who have failed
29
30 88 conservative interventions.

31
32
33 89 There is some evidence that endometriosis is also associated with poorer IVF outcomes,
34
35 90 though this is controversial. One meta-analysis from 2002 including 22 non-randomized trials
36
37 91 reported that the chances of achieving pregnancy with IVF in women with endometriosis was
38
39 92 almost half that of those with tubal infertility (odds ratio [OR] = 0.56, 95% confidence intervals
40
41 93 [CI] = 0.44–0.7) and women with severe disease had about half the pregnancy rate of those with
42
43 94 mild disease [18]. A more recent study published in 2018 showed via retrospective comparison
44
45 95 of 531 women with endometriosis and 737 women with unexplained subfertility found that
46
47 96 women with endometriosis still have a 24% lower likelihood of live birth after IVF than women
48
49 97 with unexplained infertility [19]. However, a larger retrospective study in 2017 comparing 3583
50
51 98 women with endometriosis and 18,833 women without endometriosis found that endometriosis
52
53 99 was associated with fewer oocytes retrieved, but no significant difference in live birth rates [20].
54
55
56 100 Similarly, a metanalysis of 33 studies published in 2015 examined the effect of endometrioma

1
2
3 101 on IVF/ICSI outcomes and also found that women with endometrioma had fewer oocytes
4
5 102 retrieved, but similar live birth rates [21]. A large metanalysis of 78 studies published in 2014
6
7 103 also found a difference in number of oocytes retrieved but no significant difference in live birth
8
9 104 rates between women with and without endometriosis [22]. It is important to note, however, that
10
11 105 the effect of endometriosis on IVF outcomes may be underestimated, especially in more recent
12
13 106 studies, due to a likely underdiagnosis of endometriosis in the IVF population as laparoscopy is
14
15 107 no longer a routine practice in infertility evaluations [4]. As endometriosis commonly presents in
16
17 108 conjunction with other infertility diagnoses (e.g. male factor, tubal factor, diminished ovarian
18
19 109 reserve), it has been suggested that endometriosis, when associated with other barriers to
20
21 110 fertility, contributes to poorer IVF outcomes in the general IVF population, even if this effect is
22
23 111 not seen with endometriosis in isolation [23].
24
25

26 112 As the association between endometriosis and poorer IVF outcomes remains biologically
27
28 113 plausible despite mixed clinical evidence [1,13–15,23], pre-treatment with GnRH agonist
29
30 114 therapy has been investigated as a method to improve IVF outcomes, though with mixed
31
32 115 evidence. As a hormone-dependent disorder, medical management of symptomatic
33
34 116 endometriosis has targeted ovarian estrogen production, including combined oral
35
36 117 contraceptives, progestins, danazol and gonadotropin-releasing hormone (GnRH) agonists or
37
38 118 antagonist [24]. While these therapies have been helpful in managing endometriosis-associated
39
40 119 pelvic pain, they have not been shown to treat endometriosis-associated infertility in the
41
42 120 absence of IVF [5]. In the IVF setting, prolonged GnRH agonist treatment prior to IVF has been
43
44 121 shown by several studies to improve fertility rates in women with advanced endometriosis [25–
45
46 122 27], though a recent Cochrane review of 8 RCTs was unable to determine whether prolonged
47
48 123 GnRH agonist treatment improved subsequent IVF outcomes, partly due to low quality of
49
50 124 available evidence [28].
51
52

53 125 Since then, the GnRH antagonist elagolix has recently become available for use, with a
54
55 126 number of advantages over GnRH agonists: the convenience of oral rather than parenteral
56
57
58
59
60

1
2
3 127 administration, improved tolerability and reduced severity of vasomotor symptoms, rapid onset
4
5 128 of action with suppression of endogenous estradiol levels within 24 hours, and lack of initial
6
7 129 gonadotropin stimulation (“flare” effect) seen with GnRH agonists [29]. However, elagolix has
8
9 130 not yet been studied as an adjunctive treatment prior to IVF for women with endometriosis.
10
11 131 Based on limited evidence from GnRH agonist trials, we hypothesize that GnRH antagonist
12
13 132 therapy may potentially benefit women with endometriosis undergoing IVF treatment, possibly
14
15 133 with a shorter course of treatment compared to what has been studied with GnRH agonists (3-6
16
17 134 months) [28,30].
18
19
20
21

22 136 **Methods and Analysis**

23
24 137 This is a multicenter, prospective, randomized controlled trial to study the effect of GnRH
25
26 138 antagonist pre-treatment for women with endometriosis who are undergoing IVF.
27
28
29

30 140 **Participants**

31
32 141 Participants will be recruited based on the following inclusion criteria:

- 33 142 • Women aged 18-38
- 34 143 • Planning to undergo a cycle of IVF for treatment of infertility
- 35 144 • Surgical or sonographic diagnosis of endometriosis
- 36 145 • Body Mass Index (BMI) 18-38 kg/m² (inclusive) at time of screening
- 37 146 • Anti-Mullerian hormone (AMH) > 0.8 ng/ml within 6 months of planned IVF cycle
38 147 start
- 39 148 • Uterine cavity assessment by sonohysterogram or hysteroscopy within 6 months
40 149 indicating adequacy for embryo transfer
- 41 150 • Presence of at least one ovary with no clinically significant abnormalities (other
42 151 than endometrioma)

- 1
2
3 152 • Negative urine or cervical swab for gonorrhoea and chlamydia within 12 months of
4
5 153 recruitment
6
7 154 • Willingness and ability to comply with trial procedures, including reporting of
8
9 155 obstetrical outcomes after delivery
10

11 156 A diagnosis of endometriosis must be confirmed by surgical visualization of
12
13 157 endometriosis (at the time of laparoscopy or laparotomy) within the last 10 years of initial trial
14
15 158 visit, or by sonographic documentation of an ovarian endometrioma >2 cm, or two or more
16
17 159 smaller endometriomas that total >2 cm in diameter. If a diagnosis of endometriosis was made
18
19 160 sonographically, serial transvaginal ultrasounds must have documented the same unambiguous
20
21 161 endometrioma on two separate occasions in more than one menstrual cycle. Images will be
22
23 162 read centrally by the same investigator to assure uniform diagnostic criteria are applied.
24
25

26 163 Women will be excluded from the study if there was:
27

- 28 164 • Use of GnRH agonists or antagonists within 6 months of study start, except for
29
30 165 antagonist use as part of an IVF cycle
31
32 166 • Use of depot medroxyprogesterone acetate (MPA) or subdermal contraceptive
33
34 167 implant (e.g. Implanon® or Nexplanon®) within 10 months of study start
35
36 168 • Continuous use of oral progestins (MPA, NETA) within 3 months of study start
37
38 169 • Use of aromatase inhibitors, danazol or hormonal contraceptives (including
39
40 170 combined oral contraceptive pill, progestin-only pill, transdermal patch or
41
42 171 contraceptive ring) within 1 month of study start
43
44 172 • Pregnancy greater than 8 weeks in length within the last 6 months
45
46 173 • History of three or more prior IVF/ICSI attempts
47
48 174 • Presence of hydrosalpinx >2cm on ultrasound, untreated endometrial polyps,
49
50 175 submucosal uterine leiomyomata, or intrauterine adhesions
51
52 176 • Abnormal cervical cytology other than low-grade within last year
53
54
55
56
57
58
59
60

- 1
2
3 177 • History of malignancy within 5 years of the start of screening, except for
4
5 178 adequately managed basal cell carcinoma and squamous cell carcinoma of the
6
7 179 skin
8
9 180 • History of suicide attempt within the last year of recruitment
10
11 181 • Hypersensitivity to study drugs
12
13 182 • Planned surgical treatment of endometriosis or planned surgery in the
14
15 183 abdominal-pelvic area within the duration of the trial
16
17 184 • Untreated abnormal prolactin or TSH
18
19 185 • Presence of any condition for which pregnancy is precluded
20
21

22 186 Participants will be recruited from the population of patients already committed to
23
24 187 pursuing IVF at one of the five participating clinical centers in the trial (Yale University,
25
26 188 University of Colorado - Denver, Northwestern University, Johns Hopkins and University of
27
28 189 North Carolina). Additional clinical centers may be added for enrollment if needed. All
29
30 190 participants will provide written, informed consent for their participation in this study. This study
31
32 191 was approved by a central Institutional Review Boards (IRB) as well as local IRBs at all five
33
34 192 participating centers. In addition, the Food and Drug Administration gave permission for the
35
36 193 study to proceed using elagolix as an Investigational New Drug (IND 152645) for this indication.
37
38
39 194

41 195 **Intervention**

43 196 *GnRH antagonist pre-treatment*

45 197 Participants will be randomized 1:1 into one of two treatment groups: GnRH antagonist
46
47 198 (elagolix 200 mg bid) or placebo for 8 weeks, prior to undergoing IVF. While using GnRH
48
49 199 antagonists, hot flashes and other vasomotor symptoms may occur. If indicated, use of
50
51 200 paroxetine mesylate will be allowed. No sex steroids or other hormone modifying treatments are
52
53 201 permitted. The GnRH antagonist will be administered during the routine evaluation conducted
54
55 202 prior to the IVF cycle.
56
57
58
59
60

203

204 *IVF treatment*

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

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

223

224 *Embryo culture and transfer*

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

1
2
3 229 study but must be preceded by the same pre-treatment with GnRH antagonist or placebo for 8
4
5 230 weeks, repeating the same treatment as initially assigned at randomization. No more than two
6
7 231 embryo transfers will be performed under this protocol, limiting administration of study drug to a
8
9 232 maximum of three 8-week courses (one prior to IVF, and one prior to each embryo transfer).

11 233 Luteal support will be initiated 1 day after oocyte retrieval with intramuscular or vaginal
12
13 234 micronized progesterone and continued for 14 days, when a urine pregnancy test is performed.
14
15 235 If pregnant, luteal support is continued until 10 weeks of pregnancy. A transvaginal ultrasound
16
17 236 scan is scheduled to confirm a viable intrauterine pregnancy and determine number of
18
19 237 gestations. Women are then discharged from the care of the IVF unit to their obstetrician for
20
21 238 further prenatal care and delivery. Participants will have been consented for access to
22
23 239 comprehensive pregnancy outcome and birth data at the time of enrollment.
24
25
26
27

28 241 **Randomization**

30 242 Eligible women will be randomized in a 1:1 fashion to one of two treatments:

- 32 243 • Elagolix 200 mg BID daily for 8 weeks prior to undergoing IVF.
- 34 244 • Placebo, BID daily for 8 weeks prior to undergoing IVF.

36 245 A computer-generated randomization list will be created by staff at the PREGnant Data
37
38 246 Coordinating Center (DCC) and randomization will be performed prior to the first dose of
39
40 247 elagolix or placebo. Randomization will have random sizes (2,4, or 6) of blocks, stratified by site
41
42 248 and age group (<35 versus ≥35 years). Both participants and investigators will be blinded to the
43
44 249 treatment assignment during the trial duration (except for serious safety concerns). Treatment
45
46 250 allocation information will not be accessible to investigators (except for serious safety concerns),
47
48 251 trial staff at the site or central laboratory personnel during the trial. The assigned treatment
49
50 252 (GnRH antagonist vs. placebo) applied during the fresh cycle will also be used for subsequent
51
52 253 frozen embryo transfers resulting from the initial 'fresh' egg retrieval cycle. Most women using
53
54
55
56
57
58
59

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

256

257 **Outcome measures**

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

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

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

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

276

277 **Statistical Analysis**

278 *Sample size and power calculations*

1
2
3 279 The average live birth rate for women with endometriosis undergoing IVF is estimated to
4
5 280 be 39%, based on 2016 SART data showing a live birth rate of 44.7% per cycle in women with
6
7 281 endometriosis under the age of 35 and 34.0% in women ages 35-37. We conservatively estimate
8
9 282 an effect of 10% absolute improvement in live birth rate to 49% in the GnRH antagonist arm,
10
11 283 based on prior randomized trials using GnRH agonists. Thus, using 386 participants per arm
12
13 284 (N=772) would provide an alpha of 0.05 and power of 80%. We will aim to enroll and randomize
14
15 285 814 participants (407 per treatment group), to account for an estimated drop-out rate of 5%.
16
17
18 286

19 20 287 *Analysis of outcome measures*

21
22 288 An intention-to-treat analysis will be performed on primary and secondary outcome
23
24 289 measures. The primary outcome, cumulative live birth rate, will be compared between the two
25
26 290 intervention arms using Pearson's chi-square test of independence. Baseline patient
27
28 291 characteristics and secondary outcome measures will also be analyzed with Pearson's chi-square
29
30 292 test and logistic regression as needed.
31

32
33 293 Based on prior experience, we expect a data completion rate of at least 99.5% and we do
34
35 294 not expect missing data to significantly affect trial analysis or results. In the unlikely event of
36
37 295 unexpectedly high rates of missing data, the potential mechanisms for missing data (missing
38
39 296 completely at random, missing at random, or missing not at random) will be examined. We will
40
41 297 compare the available characteristics of those with missing data to those with complete data. If
42
43 298 necessary, imputation techniques may be used.
44

45 299

46 47 300 **Trial status and registration**

48
49 301 The study was conceived and designed in 2019. Recruitment is expected to begin in December
50
51 302 2021. This study is registered on ClinicalTrials.gov Identifier NCT04173169. This manuscript
52
53 303 describes the latest version, last updated November 29, 2021.
54
55

56 304

305 **Ethics and Dissemination**

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

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

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

315

316 **Safety and adverse events monitoring**

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

323

324 **Data management and sharing**

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

1
2
3 331 precautions to ensure the confidentiality of information regarding trial participants and in
4
5 332 particular the identity of the participants and the results obtained. The final trial dataset will be
6
7 333 available to study investigators and Research Ethic Boards at all participating sites. Results of
8
9 334 the trial will be published in peer-reviewed journals. We will submit data and samples collected
10
11 335 by the trial to NICHD DASH. The informed consent will include permission to bank these
12
13 336 samples. The processes included initial data and documentation preparation (e.g., codebooks,
14
15 337 protocols, informed consent for data sharing), data quality control, and submission.
16
17
18 338

339 **Patient and public involvement**

21
22 340 Patients and the public were not involved in the design, or conduct, or reporting, or
23
24 341 dissemination plans of this research.
25

26 342

28 343 **Author Contributions**

29
30 344 HST, HJL, SC, VF, LP, JR, NS, JS, DS, HH, SY, HZ each made substantial
31
32 345 contributions to the conception or design of the study protocol, design of the study intervention,
33
34 346 study outcomes, study procedures, and/or revised the protocol critically for important intellectual
35
36 347 content and approved the final version to be published. HZ made substantial contributions to the
37
38 348 conception or design of the study protocol and wrote the first draft of the protocol. HJL wrote the
39
40 349 first draft of this manuscript. All authors approved the final version to be published.
41
42

43 350

45 351 **Funding Statement**

46
47 352 This study was funded by a grant titled "Pre-IVF treatment with a GnRH antagonist in women
48
49 353 with endometriosis - A prospective double blind placebo controlled trial (PREGnant)" from the
50
51 354 Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD),
52
53 355 1R01HD100336.
54

55 356
56
57
58
59
60

1
2
3 357 **Competing Interests**

4
5 358 The authors have no competing interests to report.

6
7 359

8
9 360 **References**

- 10
11 361 1 Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and
12 362 treatment of endometriosis-associated infertility. *Obstet Gynecol Clin North Am*
13 363 2012;**39**:535–49. doi:10.1016/j.ogc.2012.10.002
- 14
15 364 2 Taylor HS, Kotlyar AM, Flores VA. Endometriosis is a chronic systemic disease: clinical
16 365 challenges and novel innovations. *Lancet* 2021;**397**:839–52. doi:10.1016/S0140-
17 366 6736(21)00389-5
- 18
19 367 3 Verkauf BS. Incidence, symptoms, and signs of endometriosis in fertile and infertile women.
20 368 *J Fla Med Assoc* 1987;**74**:671–5.
- 21
22 369 4 Practice Committee of the American Society for Reproductive Medicine. Endometriosis and
23 370 infertility: a committee opinion. *Fertil Steril* 2012;**98**:591–8.
24 371 doi:10.1016/j.fertnstert.2012.05.031
- 25
26 372 5 Hughes EG, Fedorkow DM, Collins JA. A quantitative overview of controlled trials in
27 373 endometriosis-associated infertility. *Fertil Steril* 1993;**59**:963–70.
- 28
29 374 6 Akande VA, Hunt LP, Cahill DJ, *et al.* Differences in time to natural conception between
30 375 women with unexplained infertility and infertile women with minor endometriosis. *Hum*
31 376 *Reprod* 2004;**19**:96–103. doi:10.1093/humrep/deh045
- 32
33 377 7 Healy DL, Breheny S, Halliday J, *et al.* Prevalence and risk factors for obstetric
34 378 haemorrhage in 6730 singleton births after assisted reproductive technology in Victoria
35 379 Australia. *Hum Reprod* 2010;**25**:265–74. doi:10.1093/humrep/dep376
- 36
37 380 8 Takemura Y, Osuga Y, Fujimoto A, *et al.* Increased risk of placenta previa is associated with
38 381 endometriosis and tubal factor infertility in assisted reproductive technology pregnancy.
39 382 *Gynecol Endocrinol* 2013;**29**:113–5. doi:10.3109/09513590.2012.706669
- 40
41 383 9 Vercellini P, Parazzini F, Pietropaolo G, *et al.* Pregnancy outcome in women with peritoneal,
42 384 ovarian and rectovaginal endometriosis: a retrospective cohort study. *BJOG*
43 385 2012;**119**:1538–43. doi:10.1111/j.1471-0528.2012.03466.x
- 44
45 386 10 Conti N, Cevenini G, Vannuccini S, *et al.* Women with endometriosis at first pregnancy have
46 387 an increased risk of adverse obstetric outcome. *J Matern Fetal Neonatal Med*
47 388 2015;**28**:1795–8. doi:10.3109/14767058.2014.968843
- 48
49 389 11 Fernando S, Breheny S, Jaques AM, *et al.* Preterm birth, ovarian endometriomata, and
50 390 assisted reproduction technologies. *Fertil Steril* 2009;**91**:325–30.
51 391 doi:10.1016/j.fertnstert.2008.01.096
- 52
53
54
55
56
57
58
59

- 1
2
3 392 12 Stephansson O, Kieler H, Granath F, *et al.* Endometriosis, assisted reproduction
4 393 technology, and risk of adverse pregnancy outcome. *Hum Reprod* 2009;**24**:2341–7.
5 394 doi:10.1093/humrep/dep186
6
7 395 13 Matalliotakis IM, Cakmak H, Mahutte N, *et al.* Women with advanced-stage endometriosis
8 396 and previous surgery respond less well to gonadotropin stimulation, but have similar IVF
9 397 implantation and delivery rates compared with women with tubal factor infertility. *Fertil Steril*
10 398 2007;**88**:1568–72. doi:10.1016/j.fertnstert.2007.01.037
11
12 399 14 Brosens I. Endometriosis and the outcome of in vitro fertilization. *Fertil Steril* 2004;**81**:1198–
13 400 200. doi:10.1016/j.fertnstert.2003.09.071
14
15 401 15 Olivennes F. [Results of IVF in women with endometriosis]. *J Gynecol Obstet Biol Reprod*
16 402 (*Paris*) 2003;**32**:S45-47.
17
18 403 16 Terzic M, Aimagambetova G, Garzon S, *et al.* Ovulation induction in infertile women with
19 404 endometriotic ovarian cysts: current evidence and potential pitfalls. *Minerva Med*
20 405 2020;**111**:50–61. doi:10.23736/S0026-4806.19.06346-8
21
22 406 17 Šalamun V, Verdenik I, Laganà AS, *et al.* Should we consider integrated approach for
23 407 endometriosis-associated infertility as gold standard management? Rationale and results
24 408 from a large cohort analysis. *Arch Gynecol Obstet* 2018;**297**:613–21. doi:10.1007/s00404-
25 409 017-4633-0
26
27 410 18 Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization.
28 411 *Fertil Steril* 2002;**77**:1148–55. doi:10.1016/s0015-0282(02)03112-6
29
30 412 19 Muteshi CM, Ohuma EO, Child T, *et al.* The effect of endometriosis on live birth rate and
31 413 other reproductive outcomes in ART cycles: a cohort study. *Hum Reprod Open*
32 414 2018;**2018**:hoy016. doi:10.1093/hropen/hoy016
33
34 415 20 González-Comadran M, Schwarze JE, Zegers-Hochschild F, *et al.* The impact of
35 416 endometriosis on the outcome of Assisted Reproductive Technology. *Reprod Biol*
36 417 *Endocrinol* 2017;**15**:8. doi:10.1186/s12958-016-0217-2
37
38 418 21 Hamdan M, Dunselman G, Li TC, *et al.* The impact of endometrioma on IVF/ICSI outcomes:
39 419 a systematic review and meta-analysis. *Hum Reprod Update* 2015;**21**:809–25.
40 420 doi:10.1093/humupd/dmv035
41
42 421 22 Barbosa M a. P, Teixeira DM, Navarro P a. a. S, *et al.* Impact of endometriosis and its
43 422 staging on assisted reproduction outcome: systematic review and meta-analysis. *Ultrasound*
44 423 *Obstet Gynecol* 2014;**44**:261–78. doi:10.1002/uog.13366
45
46 424 23 Senapati S, Sammel MD, Morse C, *et al.* Impact of endometriosis on in vitro fertilization
47 425 outcomes: an evaluation of the Society for Assisted Reproductive Technologies Database.
48 426 *Fertil Steril* 2016;**106**:164-171.e1. doi:10.1016/j.fertnstert.2016.03.037
49
50 427 24 Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic
51 428 pain associated with endometriosis: a committee opinion. *Fertil Steril* 2014;**101**:927–35.
52 429 doi:10.1016/j.fertnstert.2014.02.012
53
54
55
56
57
58
59
60

- 1
2
3 430 25 Surrey ES, Silverberg KM, Surrey MW, *et al.* Effect of prolonged gonadotropin-releasing
4 431 hormone agonist therapy on the outcome of in vitro fertilization-embryo transfer in patients
5 432 with endometriosis. *Fertil Steril* 2002;**78**:699–704. doi:10.1016/s0015-0282(02)03373-3
6
7 433 26 Ozkan S, Arici A. Advances in treatment options of endometriosis. *Gynecol Obstet Invest*
8 434 2009;**67**:81–91. doi:10.1159/000163071
9
10 435 27 Guo Y, Lu N, Zhang Y, *et al.* Comparative study on the pregnancy outcomes of in vitro
11 436 fertilization-embryo transfer between long-acting gonadotropin-releasing hormone agonist
12 437 combined with transvaginal ultrasound-guided cyst aspiration and long-acting gonadotropin-
13 438 releasing hormone agonist alone. *Contemp Clin Trials* 2012;**33**:1206–10.
14 439 doi:10.1016/j.cct.2012.07.009
15
16 440 28 Georgiou EX, Melo P, Baker PE, *et al.* Long-term GnRH agonist therapy before in vitro
17 441 fertilisation (IVF) for improving fertility outcomes in women with endometriosis. *Cochrane*
18 442 *Database Syst Rev* 2019;**2019**. doi:10.1002/14651858.CD013240.pub2
19
20 443 29 Taylor HS, Giudice LC, Lessey BA, *et al.* Treatment of Endometriosis-Associated Pain with
21 444 Elagolix, an Oral GnRH Antagonist. *N Engl J Med* 2017;**377**:28–40.
22 445 doi:10.1056/NEJMoa1700089
23
24 446 30 Sallam HN, Garcia-Velasco JA, Dias S, *et al.* Long-term pituitary down-regulation before in
25 447 vitro fertilization (IVF) for women with endometriosis. *Cochrane Database Syst Rev*
26 448 2006;:CD004635. doi:10.1002/14651858.CD004635.pub2
27
28 449 31 Practice Committees of the American Society for Reproductive Medicine and the Society for
29 450 Assisted Reproductive Technology. Electronic address: asrm@asrm.org. Intracytoplasmic
30 451 sperm injection (ICSI) for non-male factor indications: a committee opinion. *Fertil Steril*
31 452 2020;**114**:239–45. doi:10.1016/j.fertnstert.2020.05.032
32
33 453 32 Practice Committee of Society for Assisted Reproductive Technology, Practice Committee
34 454 of American Society for Reproductive Medicine. Elective single-embryo transfer. *Fertil Steril*
35 455 2012;**97**:835–42. doi:10.1016/j.fertnstert.2011.11.050
36
37 456 33 Practice Committee of the American Society for Reproductive Medicine. Electronic address:
38 457 ASRM@asrm.org, Practice Committee of the Society for Assisted Reproductive
39 458 Technology. Guidance on the limits to the number of embryos to transfer: a committee
40 459 opinion. *Fertil Steril* 2017;**107**:901–3. doi:10.1016/j.fertnstert.2017.02.107
41
42 460 34 Boivin J, Takefman J, Braverman A. The Fertility Quality of Life (FertiQoL) tool:
43 461 development and general psychometric properties. *Fertil Steril* 2011;**96**:409-415.e3.
44 462 doi:10.1016/j.fertnstert.2011.02.046
45
46 463
47
48
49
50
51
52
53
54
55
56
57
58
59

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

1 Introduction

2			
3	Background and	#6a	Description of research question and justification for undertaking
4	rationale		the trial, including summary of relevant studies (published and
5			unpublished) examining benefits and harms for each intervention
6			
7			
8	Background and	#6b	Explanation for choice of comparators
9	rationale: choice of		
10	comparators		
11			
12			
13	Objectives	#7	Specific objectives or hypotheses
14			
15			
16	Trial design	#8	Description of trial design including type of trial (eg, parallel
17			group, crossover, factorial, single group), allocation ratio, and
18			framework (eg, superiority, equivalence, non-inferiority,
19			exploratory)
20			
21			
22			
23	Methods:		
24	Participants,		
25	interventions, and		
26	outcomes		
27			
28			
29			
30	Study setting	#9	Description of study settings (eg, community clinic, academic
31			hospital) and list of countries where data will be collected.
32			Reference to where list of study sites can be obtained
33			
34			
35	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,
36			eligibility criteria for study centres and individuals who will
37			perform the interventions (eg, surgeons, psychotherapists)
38			
39			
40	Interventions:	#11a	Interventions for each group with sufficient detail to allow
41	description		replication, including how and when they will be administered
42			
43			
44	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a
45	modifications		given trial participant (eg, drug dose change in response to harms,
46			participant request, or improving / worsening disease)
47			
48			
49	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any
50	adherence		procedures for monitoring adherence (eg, drug tablet return;
51			laboratory tests)
52			
53			
54			
55	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or
56	concomitant care		prohibited during the trial
57			
58			
59			
60			

1	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
2				
3				
4				
5				
6				
7				
8				
9				
10				
11	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
12				
13				
14				
15				
16	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
17				
18				
19				
20				
21	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
22				
23				
24				
25	Methods: Assignment			
26	of interventions (for			
27	controlled trials)			
28				
29				
30	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
31				
32				
33				
34				
35				
36				
37				
38				
39				
40	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
41				
42				
43				
44				
45				
46				
47	Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
48				
49				
50				
51	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
52				
53				
54				
55				
56	Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention	9-10
57				
58				
59				
60				

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	
1			
2	Harms	#22 Plans for collecting, assessing, reporting, and managing solicited	12
3		and spontaneously reported adverse events and other unintended	
4		effects of trial interventions or trial conduct	
5			
6			
7			
8	Auditing	#23 Frequency and procedures for auditing trial conduct, if any, and	12
9		whether the process will be independent from investigators and the	
10		sponsor	
11			
12			
13	Ethics and		
14	dissemination		
15			
16			
17	Research ethics	#24 Plans for seeking research ethics committee / institutional review	12
18	approval	board (REC / IRB) approval	
19			
20			
21	Protocol amendments	#25 Plans for communicating important protocol modifications (eg,	12
22		changes to eligibility criteria, outcomes, analyses) to relevant	
23		parties (eg, investigators, REC / IRBs, trial participants, trial	
24		registries, journals, regulators)	
25			
26			
27	Consent or assent	#26a Who will obtain informed consent or assent from potential trial	7
28		participants or authorised surrogates, and how (see Item 32)	
29			
30			
31	Consent or assent:	#26b Additional consent provisions for collection and use of participant	7, 9
32	ancillary studies	data and biological specimens in ancillary studies, if applicable	
33			
34			
35	Confidentiality	#27 How personal information about potential and enrolled participants	13
36		will be collected, shared, and maintained in order to protect	
37		confidentiality before, during, and after the trial	
38			
39			
40	Declaration of interests	#28 Financial and other competing interests for principal investigators	13
41		for the overall trial and each study site	
42			
43			
44	Data access	#29 Statement of who will have access to the final trial dataset, and	13
45		disclosure of contractual agreements that limit such access for	
46		investigators	
47			
48			
49	Ancillary and post trial	#30 Provisions, if any, for ancillary and post-trial care, and for	n/a
50	care	compensation to those who suffer harm from trial participation	
51			
52			
53	Dissemination policy:	#31a Plans for investigators and sponsor to communicate trial results to	13
54	trial results	participants, healthcare professionals, the public, and other relevant	
55		groups (eg, via publication, reporting in results databases, or other	
56		data sharing arrangements), including any publication restrictions	
57			
58			
59			
60			

1	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	12
2	authorship		professional writers	
3				
4	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	n/a
5	reproducible research		participant-level dataset, and statistical code	
6				
7				
8	Appendices			
9				
10	Informed consent	#32	Model consent form and other related documentation given to	n/a
11	materials		participants and authorised surrogates	
12				
13	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
14			biological specimens for genetic or molecular analysis in the	
15			current trial and for future use in ancillary studies, if applicable	
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				
29				
30				
31				
32				
33				
34				
35				
36				
37				
38				
39				
40				
41				
42				
43				
44				
45				
46				
47				
48				
49				
50				
51				
52				
53				
54				
55				
56				
57				
58				
59				
60				

The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist can be completed online using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-052043.R2
Article Type:	Protocol
Date Submitted by the Author:	02-Mar-2022
Complete List of Authors:	Taylor, Hugh; Yale School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Li, Howard; Yale School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Carson, Sandra; Yale School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Flores, Valerie; Yale School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Pal, Lubna; Yale University School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Robbins, Jared; Northwestern University, Obstetrics and Gynecology Santoro, Nanette F. ; University of Colorado, Obstetrics and Gynecology Segars, James H. ; Johns Hopkins University School of Medicine, Gynecology and Obstetrics Seifer, David; Yale School of Medicine, Obstetrics, Gynecology, and Reproductive Sciences Huang, H; Yale University School of Public Health Young, Steven; The University of North Carolina at Chapel Hill, Obstetrics and Gynecology Zhang, Heping; Yale University School of Public Health
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Reproductive medicine
Keywords:	Sex steroids & HRT < DIABETES & ENDOCRINOLOGY, Subfertility < GYNAECOLOGY, Reproductive medicine < GYNAECOLOGY, Clinical trials < THERAPEUTICS

SCHOLARONE™
Manuscripts

1
2
3 1 **Pre-IVF treatment with a GnRH antagonist in women with endometriosis (PREGNANT):**

4
5 2 **Study protocol for a prospective, double-blind, placebo-controlled trial**

6
7 3
8
9 4 Hugh S. Taylor¹, Howard J. Li¹, Sandra Carson¹, Valerie Flores¹, Lubna Pal¹, Jared Robbins²,
10 5 Nanette Santoro³, James Segars⁴, David Seifer¹, Hao Huang⁵, Steven Young⁶, and Heping
11 6 Zhang⁵

12 7
13 8 1. Yale School of Medicine, New Haven, CT

14 9 2. Northwestern University, Chicago, IL

15 10 3. University of Colorado, Aurora, CO

16 11 4. Johns Hopkins University, Baltimore, MD

17 12 5. Yale School of Public Health, New Haven CT

18 13 6. University of North Carolina, Chapel Hill, NC

19 14
20 15 **Correspondence:**

21 16 Hugh S. Taylor

22 17 Department of Obstetrics, Gynecology and Reproductive Sciences

23 18 Yale School of Medicine

24 19 333 Cedar Street

25 20 New Haven CT 06520 Phone: 203-785-4001

26 21 Email: hugh.taylor@yale.edu

27 22
28 23 **Word count:** 2926 words

1
2
3 **24 Abstract**
4

5 *25 Introduction:* Infertility is a common complication of endometriosis. While in vitro fertilization-
6 embryo transfer (IVF-ET) successfully treats endometriosis-associated infertility, there is some
7 *26* evidence that pregnancy rates may be diminished in women seeking fertility treatment for
8 *27* endometriosis-associated infertility compared to other etiologies of infertility. The use of
9 *28* gonadotropin releasing hormone (GnRH) agonist prior to IVF has been suggested to improve
10 *29* success, however studies have been small and rarely reported live birth rates. Recent approval
11 *30* of an oral GnRH antagonist for endometriosis provides a novel option for women with
12 *31* endometriosis who are undergoing IVF. There have been no studies on the efficacy of GnRH
13 *32* antagonists for the treatment of endometriosis-related infertility.
14 *33*

15 *34 Methods and analysis:* This study is a multi-center, prospective, randomized, double-blind,
16 *35* placebo-controlled trial to study the efficacy of GnRH antagonist pre-treatment for women with
17 *36* endometriosis who are undergoing IVF. A total of 814 patients with endometriosis undergoing
18 *37* fertility treatment will be enrolled and randomized 1:1 into two groups: elagolix 200 mg bid or
19 *38* placebo for 8 weeks, prior to undergoing IVF. All participants will then undergo IVF treatment
20 *39* per local protocols. The primary outcome is live birth. Secondary outcomes include oocyte
21 *40* number, fertilization rate, embryo morphology, and implantation rates, as well as rates of known
22 *41* endometriosis-related obstetrical outcomes (pregnancy-induced hypertension, antepartum
23 *42* hemorrhage, cesarean delivery, and preterm birth).
24 *43*

25 *44 Ethics and dissemination:* The PREGnant trial was approved by the Institutional Review Board
26 *45* at Johns Hopkins University. Results will be published in a peer-reviewed journal.
27 *46*

28 *47 Trial Registration:* ClinicalTrials.gov Identifier NCT04173169
29 *48*

30 *49 FDA IND:* 152645
31

32 *47 Key words:* endometriosis; in vitro fertilization; IVF; gonadotropin releasing hormone; GnRH;
33 *48* elagolix; GnRH antagonist; Live birth
34 *49*

50 **Strengths and Limitations of this Study**

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

65 **Introduction**

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

1
2
3 75 55%, respectively) [6]. Endometriosis is also associated with obstetrical complications, including
4
5 76 obstetrical hemorrhage, cesarean delivery, pre-eclampsia and pregnancy-induced hypertension,
6
7 77 and preterm birth [7–12]. While the mechanism remains controversial and unclear,
8
9 78 endometriosis is thought to contribute to reduced fertility via adnexal scarring and poor
10
11 79 endometrial receptivity, though studies also suggest with women with advanced endometriosis
12
13 80 also have poor ovarian reserve, low oocyte and embryo quality, and poor implantation [1,13–
14
15 81 15].

16
17
18 82 Multiple effective treatments exist for the management of endometriosis-associated
19
20 83 infertility, including laparoscopic destruction of endometriotic disease, ovulation induction, and
21
22 84 intrauterine insemination [1,16,17]. While some studies show that conservative treatment alone
23
24 85 may be effective in improving fertility for women with endometriosis and potentially helps avoid
25
26 86 obstetrical complications associated with IVF [17], IVF remains the most direct and effective
27
28 87 treatment for endometriosis-associated infertility, especially in patients who have failed
29
30 88 conservative interventions.

31
32
33 89 There is some evidence that endometriosis is also associated with poorer IVF outcomes,
34
35 90 though this is controversial. One meta-analysis from 2002 including 22 non-randomized trials
36
37 91 reported that the chances of achieving pregnancy with IVF in women with endometriosis was
38
39 92 almost half that of those with tubal infertility (odds ratio [OR] = 0.56, 95% confidence intervals
40
41 93 [CI] = 0.44–0.7) and women with severe disease had about half the pregnancy rate of those with
42
43 94 mild disease [18]. A more recent study published in 2018 showed via retrospective comparison
44
45 95 of 531 women with endometriosis and 737 women with unexplained subfertility found that
46
47 96 women with endometriosis still have a 24% lower likelihood of live birth after IVF than women
48
49 97 with unexplained infertility [19]. However, a larger retrospective study in 2017 comparing 3583
50
51 98 women with endometriosis and 18,833 women without endometriosis found that endometriosis
52
53 99 was associated with fewer oocytes retrieved, but no significant difference in live birth rates [20].
54
55
56 100 Similarly, a metanalysis of 33 studies published in 2015 examined the effect of endometrioma

1
2
3 101 on IVF/ICSI outcomes and also found that women with endometrioma had fewer oocytes
4
5 102 retrieved, but similar live birth rates [21]. A large metanalysis of 78 studies published in 2014
6
7 103 also found a difference in number of oocytes retrieved but no significant difference in live birth
8
9 104 rates between women with and without endometriosis [22]. It is important to note, however, that
10
11 105 the effect of endometriosis on IVF outcomes may be underestimated, especially in more recent
12
13 106 studies, due to a likely underdiagnosis of endometriosis in the IVF population as laparoscopy is
14
15 107 no longer a routine practice in infertility evaluations [4]. As endometriosis commonly presents in
16
17 108 conjunction with other infertility diagnoses (e.g. male factor, tubal factor, diminished ovarian
18
19 109 reserve), it has been suggested that endometriosis, when associated with other barriers to
20
21 110 fertility, contributes to poorer IVF outcomes in the general IVF population, even if this effect is
22
23 111 not seen with endometriosis in isolation [23]. This finding may be due to a primary effect of
24
25 112 endometriosis on reproductive biology, but may also be secondary to epidemiologic or
26
27 113 iatrogenic factors associated with an endometriosis diagnosis: greater exposure to prior
28
29 114 gynecologic surgery resulting in ovarian injury, diminished reserve, or impaired folliculogenesis)
30
31 115 [24–26], or an effect of subsequent adhesive disease on the technical difficulty of oocyte
32
33 116 retrievals. These factors, however, have not been well studied as potential mechanisms by
34
35 117 which endometriosis may compromise IVF outcomes.
36
37
38

39 118 As the association between endometriosis and poorer IVF outcomes remains biologically
40
41 119 plausible despite mixed clinical evidence [1,13–15,23], pre-treatment with GnRH agonist
42
43 120 therapy has been investigated as a method to improve IVF outcomes, though with mixed
44
45 121 evidence. As a hormone-dependent disorder, medical management of symptomatic
46
47 122 endometriosis has targeted ovarian estrogen production, including combined oral
48
49 123 contraceptives, progestins, danazol and gonadotropin-releasing hormone (GnRH) agonists or
50
51 124 antagonist [27]. While these therapies have been helpful in managing endometriosis-associated
52
53 125 pelvic pain, they have not been shown to treat endometriosis-associated infertility in the
54
55 126 absence of IVF [5]. In the IVF setting, prolonged GnRH agonist treatment prior to IVF has been
56
57
58
59
60

1
2
3 127 shown by several studies to improve fertility rates in women with advanced endometriosis [28–
4 128 30], though a recent Cochrane review of 8 RCTs was unable to determine whether prolonged
5 129 GnRH agonist treatment improved subsequent IVF outcomes, partly due to low quality of
6 130 available evidence [31].

7
8
9
10
11 131 Since then, the GnRH antagonist elagolix has recently become available for use, with a
12 132 number of advantages over GnRH agonists: the convenience of oral rather than parenteral
13 133 administration, improved tolerability and reduced severity of vasomotor symptoms, rapid onset
14 134 of action with suppression of endogenous estradiol levels within 24 hours, and lack of initial
15 135 gonadotropin stimulation (“flare” effect) seen with GnRH agonists [32]. However, elagolix has
16 136 not yet been studied as an adjunctive treatment prior to IVF for women with endometriosis.
17
18 137 Based on limited evidence from GnRH agonist trials, we hypothesize that GnRH antagonist
19 138 therapy may potentially benefit women with endometriosis undergoing IVF treatment, possibly
20 139 with a shorter course of treatment compared to what has been studied with GnRH agonists (3-6
21 140 months) [31,33].
22
23
24
25
26
27
28
29
30
31
32
33
34

35 142 **Methods and Analysis**

36
37 143 This is a multicenter, prospective, randomized controlled trial to study the effect of GnRH
38 144 antagonist pre-treatment for women with endometriosis who are undergoing IVF.
39
40
41
42

43 146 **Participants**

44
45 147 Participants will be recruited based on the following inclusion criteria:

- 46
47 148 • Women aged 18-38
48
49 149 • Planning to undergo a cycle of IVF for treatment of infertility
50
51 150 • Surgical or sonographic diagnosis of endometriosis
52
53 151 • Body Mass Index (BMI) 18-38 kg/m² (inclusive) at time of screening
54
55
56
57
58
59
60

- 1
2
3 152 • Anti-Mullerian hormone (AMH) > 0.8 ng/ml within 6 months of planned IVF cycle
- 4
5 153 start
- 6
7 154 • Uterine cavity assessment by sonohysterogram or hysteroscopy within 6 months
- 8
9 155 indicating adequacy for embryo transfer
- 10
11 156 • Presence of at least one ovary with no clinically significant abnormalities (other
- 12
13 157 than endometrioma)
- 14
15 158 • Negative urine or cervical swab for gonorrhoea and chlamydia within 12 months of
- 16
17 159 recruitment
- 18
19 160 • Willingness and ability to comply with trial procedures, including reporting of
- 20
21 161 obstetrical outcomes after delivery

22
23
24 162 A diagnosis of endometriosis must be confirmed by surgical visualization of
25
26 163 endometriosis (at the time of laparoscopy or laparotomy) within the last 10 years of initial trial
27
28 164 visit, or by sonographic documentation of an ovarian endometrioma >2 cm, or two or more
29
30 165 smaller endometriomas that total >2 cm in diameter. If a diagnosis of endometriosis was made
31
32 166 sonographically, serial transvaginal ultrasounds must have documented the same unambiguous
33
34 167 endometrioma on two separate occasions in more than one menstrual cycle. Images will be
35
36 168 read centrally by the same investigator to assure uniform diagnostic criteria are applied.

37
38
39 169 Women will be excluded from the study if there was:

- 40
41 170 • Use of GnRH agonists or antagonists within 6 months of study start, except for
- 42
43 171 antagonist use as part of an IVF cycle
- 44
45 172 • Use of depot medroxyprogesterone acetate (MPA) or subdermal contraceptive
- 46
47 173 implant (e.g. Implanon® or Nexplanon®) within 10 months of study start
- 48
49 174 • Continuous use of oral progestins (MPA, NETA) within 3 months of study start
- 50
51 175 • Use of aromatase inhibitors, danazol or hormonal contraceptives (including
- 52
53 176 combined oral contraceptive pill, progestin-only pill, transdermal patch or
- 54
55 177 contraceptive ring) within 1 month of study start

- 1
2
3 178 • Pregnancy greater than 8 weeks in length within the last 6 months
4
5 179 • History of three or more prior IVF/ICSI attempts
6
7 180 • Presence of hydrosalpinx >2cm on ultrasound, untreated endometrial polyps,
8
9 181 submucosal uterine leiomyomata, or intrauterine adhesions
10
11 182 • Abnormal cervical cytology other than low-grade within last year
12
13 183 • History of malignancy within 5 years of the start of screening, except for
14
15 184 adequately managed basal cell carcinoma and squamous cell carcinoma of the
16
17 185 skin
18
19 186 • History of suicide attempt within the last year of recruitment
20
21 187 • Hypersensitivity to study drugs
22
23 188 • Planned surgical treatment of endometriosis or planned surgery in the
24
25 189 abdominal-pelvic area within the duration of the trial
26
27 190 • Untreated abnormal prolactin or TSH
28
29 191 • Presence of any condition for which pregnancy is precluded
30
31

32 Participants will be recruited from the population of patients already committed to
33
34 pursuing IVF at one of the five participating clinical centers in the trial (Yale University,
35
36 University of Colorado - Denver, Northwestern University, Johns Hopkins and University of
37
38 North Carolina). Additional clinical centers may be added for enrollment if needed. All
39
40 participants will provide written, informed consent for their participation in this study. This study
41
42 was approved by a central Institutional Review Boards (IRB) as well as local IRBs at all five
43
44 participating centers. In addition, the Food and Drug Administration gave permission for the
45
46 study to proceed using elagolix as an Investigational New Drug (IND 152645) for this indication.
47
48
49

50 200

51 201 ***Intervention***

52 202 *GnRH antagonist pre-treatment*

1
2
3 203 Participants will be randomized 1:1 into one of two treatment groups: GnRH antagonist
4
5 204 (elagolix 200 mg bid) or placebo for 8 weeks, prior to undergoing IVF. While using GnRH
6
7 205 antagonists, hot flashes and other vasomotor symptoms may occur. If indicated, use of
8
9 206 paroxetine mesylate will be allowed. No sex steroids or other hormone modifying treatments are
10
11 207 permitted. The GnRH antagonist will be administered during the routine evaluation conducted
12
13 208 prior to the IVF cycle.
14

15 209

16 210 *IVF treatment*

17
18 211 All participants will then undergo IVF treatment per local protocols, with agreed upon
19
20 212 standards. All sites will use standard FSH stimulation and GnRH antagonist in each cycle with
21
22 213 the exception that additional LH activity will always be supplied at the outset of stimulation,
23
24 214 since half of the participants will have been on GnRH antagonist pre-treatment and will be
25
26 215 expected to have suppressed LH. Non-conventional IVF therapies outside of those following
27
28 216 standard protocols at each site will not be performed.
29
30

31
32 217 The standard IVF treatment for the study will be a GnRH antagonist protocol (cetrotide
33
34 218 or ganirelix). Gonadotrophin stimulation with recombinant human follicle stimulating hormone
35
36 219 and menotropin (supplying 75IU FSH and 75 IU LH activity per vial) will be started at a daily
37
38 220 dose ranging 150-375 IU depending on patient characteristics including age, early follicular
39
40 221 phase FSH, AMH, antral follicle count and BMI. Each patient will receive at least 75 IU of LH
41
42 222 activity daily as part of the initial stimulation protocol to counteract the LH suppression by the
43
44 223 GnRH antagonist. The oral GnRH antagonist will be discontinued at the start of stimulation;
45
46 224 addition of subcutaneous injections of GnRH antagonist will be based on each sites' standard
47
48 225 IVF protocol. When at least two leading follicles measuring ≥ 18 mm are seen on ultrasound, the
49
50 226 trigger injection of u-hCG (10,000 IU) or r-hCG (250 mcg) is administered, followed by oocyte
51
52 227 retrieval 37h later. Depending on sperm parameters following preparation on the day of oocyte
53
54 228 retrieval, fertilization will be achieved either by conventional IVF or ICSI [34].
55
56
57
58
59
60

1
2
3 2294
5 230 *Embryo culture and transfer*

6
7 231 ET is performed between Days 3 and 5 of development depending on morphological
8
9 232 assessment and the woman's age, following ASRM guidelines allowing for transfer of up to two
10
11 233 embryos, with an elective single embryo transfer preferred [35,36]. Pre-implantation Genetic
12
13 234 Testing for aneuploidy (PGT-A) will be allowed. Frozen embryo transfers are included in this
14
15 235 study but must be preceded by the same pre-treatment with GnRH antagonist or placebo for 8
16
17 236 weeks, repeating the same treatment as initially assigned at randomization. No more than two
18
19 237 embryo transfers will be performed under this protocol, limiting administration of study drug to a
20
21 238 maximum of three 8-week courses (one prior to IVF, and one prior to each embryo transfer).

22
23 239 Luteal support will be initiated 1 day after oocyte retrieval with intramuscular or vaginal
24
25 240 micronized progesterone and continued for 14 days, when a urine pregnancy test is performed.
26
27 241 If pregnant, luteal support is continued until 10 weeks of pregnancy. A transvaginal ultrasound
28
29 242 scan is scheduled to confirm a viable intrauterine pregnancy and determine number of
30
31 243 gestations. Women are then discharged from the care of the IVF unit to their obstetrician for
32
33 244 further prenatal care and delivery. Participants will have been consented for access to
34
35 245 comprehensive pregnancy outcome and birth data at the time of enrollment.
36
37 246

38
39 247 **Randomization**

40
41 248 Eligible women will be randomized in a 1:1 fashion to one of two treatments:

- 42
43 249 • Elagolix 200 mg BID daily for 8 weeks prior to undergoing IVF.
44
45 250 • Placebo, BID daily for 8 weeks prior to undergoing IVF.
46
47

48
49 251 A computer-generated randomization list will be created by staff at the PREGnant Data
50
51 252 Coordinating Center (DCC) and randomization will be performed prior to the first dose of
52
53 253 elagolix or placebo. Randomization will have random sizes (2,4, or 6) of blocks, stratified by site
54
55 254 and age group (<35 versus ≥35 years). The randomization list will not be available to any
56
57
58
59
60

1
2
3 255 person involved in the conduct and evaluation of the trial until the trial is complete and database
4
5 256 is declared clean and is released by the DCC. Randomization and treatment allocation will be
6
7 257 initiated by study staff according to the randomization list following enrollment and prior to the
8
9 258 first dose of elagolix or placebo, but participants, investigators, trial staff, and central laboratory
10
11 259 personnel will be blinded to the treatment assignment during the trial duration (except for
12
13 260 serious safety concerns). The assigned treatment (GnRH antagonist vs. placebo) applied during
14
15 261 the fresh cycle will also be used for subsequent frozen embryo transfers resulting from the initial
16
17 262 'fresh' egg retrieval cycle. Most women using elagolix menstruate in the first 2 months with only
18
19 263 a 50% amenorrhea rate after 1 year in the Phase III clinical trial, enabling blinding to remain
20
21 264 intact.
22
23
24 265

26 266 **Outcome measures**

27
28 267 The primary outcome measure will be live birth rate per cycle start, defined as live birth
29
30 268 at ≥ 24 weeks of gestation. As a secondary outcome measure, we will also analyze the live birth
31
32 269 rate per embryo transfer.
33

34
35 270 For exploratory analysis, we will examine a number of IVF cycle parameters: 1. Estradiol
36
37 271 (E2) level on the day of human chorionic gonadotrophin (hCG) administration; 2. Progesterone
38
39 272 (P) level on the day of hCG administration; 3. The number of oocytes retrieved; 4.
40
41 273 Gonadotropin dosage and duration; 5. Number and percent of mature metaphase II (MII)
42
43 274 oocytes; 6. Fertilization (2PN) rate; 7. Blastocyst rate; 8. Incidence of moderate-to-severe
44
45 275 ovarian hyperstimulation syndrome (OHSS); 9. Implantation rate; 10. Clinical pregnancy rate;
46
47 276 11. Miscarriage rate (defined as pregnancy loss prior to viability scan and including those
48
49 277 confirmed on ultrasound scan up to $\leq 23w6d$ gestation); 12. Rate of ectopic pregnancy or
50
51 278 pregnancy of unknown location; 13. Ongoing pregnancy rate; 14. Multiple pregnancy rate.
52

53
54 279 We will also measure pregnancy-related parameters to determine the effect of pre-
55
56 280 treatment with GnRH antagonist on pregnancy related complications associated with
57
58
59
60

1
2
3 281 endometriosis: pre-eclampsia and pregnancy-induced hypertension, preterm birth, intrauterine
4
5 282 growth restriction, cesarean delivery, and obstetric hemorrhage.
6

7 283 Finally, quality of life will be assessed using the FertiQOL, a validated questionnaire that
8
9 284 contains Emotional, Mind/Body, Relational and Social domains [37].
10

11 285

13 286 **Statistical Analysis**

15 287 *Sample size and power calculations*

17 288 The average live birth rate for women with endometriosis undergoing IVF is estimated to
18
19 289 be 39%, based on 2016 SART data showing a live birth rate of 44.7% per cycle in women with
20
21 290 endometriosis under the age of 35 and 34.0% in women ages 35-37. Using 386 participants per
22
23 291 arm (N=772) would provide an alpha of 0.05 and power of 80% to detect an effect of 10% absolute
24
25 292 improvement in live birth rate to 49% in the GnRH antagonist arm. This effect is conservatively
26
27 293 estimated from prior randomized trials using GnRH agonists [28–30], and what investigators
28
29 294 deemed to be sufficient to recommend the routine use of GnRH antagonists in IVF protocols for
30
31 295 this population. However, we acknowledge that the study may be underpowered to detect smaller
32
33 296 but still relevant effects (5-10% improvement). We will aim to enroll and randomize 814
34
35 297 participants (407 per treatment group), to account for an estimated drop-out rate of 5%.
36
37
38

39 298

41 299 *Analysis of outcome measures*

43 300 An intention-to-treat analysis will be performed on primary and secondary outcome
44
45 301 measures. The primary outcome, cumulative live birth rate, will be compared between the two
46
47 302 intervention arms using Pearson's chi-square test of independence. Baseline patient
48
49 303 characteristics and secondary outcome measures will also be analyzed with Pearson's chi-square
50
51 304 test and logistic regression as needed.
52

53 305 Based on prior experience, we expect a data completion rate of at least 99.5% and we do not
54
55 306 expect missing data to significantly affect trial analysis or results. In the unlikely event of
56
57
58

1
2
3 307 unexpectedly high rates of missing data, the potential mechanisms for missing data (missing
4
5 308 completely at random, missing at random, or missing not at random) will be examined. We will
6
7 309 compare the available characteristics of those with missing data to those with complete data. If
8
9 310 necessary, imputation techniques may be used.
10

11 311

12 312 ***Safety and adverse events monitoring***

13
14
15 313 The safety of the intervention medication elagolix has been previously investigated and
16
17 314 found to be tolerable [24]. All adverse events are collected regardless of their grade of severity
18
19 315 and reported based on established criteria. Data Safety Monitoring Board (DSMB) will receive
20
21 316 unblinded data and advise on potential safety issues. The choice of continuing therapy or trial
22
23 317 participation based on adverse events is at the discretion of the investigator and DSMB
24
25 318 determinations.
26
27

28 319

29 320 ***Patient and public involvement***

30
31 321 Patients and the public were not involved in the design, or conduct, or reporting, or
32
33 322 dissemination plans of this research.
34
35

36 323

37 324 ***Ethics and Dissemination***

38
39
40 325 The PREGnant trial was approved by the Institutional Review Board at Johns Hopkins
41
42 326 University School of Medicine (JHM IRB) on August 12, 2021, application #IRB00236742, with
43
44 327 reliance agreements at all participating sites.
45
46

47 328 Protocol modifications will be reviewed by the IRB and reported to the funder.
48
49 329 Participating investigators, providers, and study staff will be informed of protocol changes via
50
51 330 email. Significant protocol modifications will also be noted on ClinicalTrials.gov.
52
53
54
55
56
57
58

1
2
3 331 Elagolix has had increasing use in treating endometriosis-related pain, and the findings
4
5 332 of this trial can be easily adopted into the IVF setting. The results of this trial may reveal a new
6
7 333 way to optimize outcomes for women with endometriosis seeking fertility treatment.
8

9 334 The trial is conducted in accordance with relevant regulations and standard operating
10
11 335 procedures, including data protection. Each subject is assigned a unique code for de-
12
13 336 identification. Data will be collected electronically and abstracted from the electronic medical
14
15 337 record in a de-identified manner. Any medical information that is obtained in connection with this
16
17 338 program that could identify a subject will remain confidential and will be disclosed only as
18
19 339 required by law. All persons responsible for the quality control of the data take all necessary
20
21 340 precautions to ensure the confidentiality of information regarding trial participants and in
22
23 341 particular the identity of the participants and the results obtained. The final trial dataset will be
24
25 342 available to study investigators and Research Ethic Boards at all participating sites. Results of
26
27 343 the trial will be published in peer-reviewed journals. We will submit data and samples collected
28
29 344 by the trial to NICHD DASH. The informed consent will include permission to bank these
30
31 345 samples. The processes included initial data and documentation preparation (e.g., codebooks,
32
33 346 protocols, informed consent for data sharing), data quality control, and submission.
34
35
36
37
38

39 348 **Trial status and registration**

40
41 349 The study was conceived and designed in 2019. Recruitment is expected to begin in December
42
43 350 2021. This study is registered on ClinicalTrials.gov Identifier NCT04173169. This manuscript
44
45 351 describes the latest version, last updated November 29, 2021.
46
47
48

49 353 **Author Contributions**

50
51 354 HST, HJL, SC, VF, LP, JR, NS, JS, DS, HH, SY, HZ each made substantial
52
53 355 contributions to the conception or design of the study protocol, design of the study intervention,
54
55 356 study outcomes, study procedures, and/or revised the protocol critically for important intellectual
56
57
58

1
2
3 357 content and approved the final version to be published. HZ made substantial contributions to the
4
5 358 conception or design of the study protocol and wrote the first draft of the protocol. HJL wrote the
6
7 359 first draft of this manuscript. All authors approved the final version to be published.
8
9
10 360

11 361 **Funding Statement**

12
13 362 This study was funded by a grant titled “Pre-IVF treatment with a GnRH antagonist in women
14
15 363 with endometriosis - A prospective double blind placebo controlled trial (PREGnant)” from the
16
17 364 Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD),
18
19 365 1R01HD100336.
20
21

22 366

23 367 **Competing Interests**

24
25 368 The authors have no competing interests to report.
26
27
28 369

29 370 **References**

- 30
31
32 371 1 Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and
33 372 treatment of endometriosis-associated infertility. *Obstet Gynecol Clin North Am*
34 373 2012;**39**:535–49. doi:10.1016/j.ogc.2012.10.002
35
36
37 374 2 Taylor HS, Kotlyar AM, Flores VA. Endometriosis is a chronic systemic disease: clinical
38 375 challenges and novel innovations. *Lancet* 2021;**397**:839–52. doi:10.1016/S0140-
39 376 6736(21)00389-5
40
41 377 3 Verkauf BS. Incidence, symptoms, and signs of endometriosis in fertile and infertile women.
42 378 *J Fla Med Assoc* 1987;**74**:671–5.
43
44 379 4 Practice Committee of the American Society for Reproductive Medicine. Endometriosis and
45 380 infertility: a committee opinion. *Fertil Steril* 2012;**98**:591–8.
46 381 doi:10.1016/j.fertnstert.2012.05.031
47
48 382 5 Hughes EG, Fedorkow DM, Collins JA. A quantitative overview of controlled trials in
49 383 endometriosis-associated infertility. *Fertil Steril* 1993;**59**:963–70.
50
51 384 6 Akande VA, Hunt LP, Cahill DJ, *et al*. Differences in time to natural conception between
52 385 women with unexplained infertility and infertile women with minor endometriosis. *Hum*
53 386 *Reprod* 2004;**19**:96–103. doi:10.1093/humrep/deh045
54
55
56
57
58
59

- 1
2
3 387 7 Healy DL, Breheny S, Halliday J, *et al.* Prevalence and risk factors for obstetric
4 388 haemorrhage in 6730 singleton births after assisted reproductive technology in Victoria
5 389 Australia. *Hum Reprod* 2010;**25**:265–74. doi:10.1093/humrep/dep376
6
7 390 8 Takemura Y, Osuga Y, Fujimoto A, *et al.* Increased risk of placenta previa is associated with
8 391 endometriosis and tubal factor infertility in assisted reproductive technology pregnancy.
9 392 *Gynecol Endocrinol* 2013;**29**:113–5. doi:10.3109/09513590.2012.706669
10
11 393 9 Vercellini P, Parazzini F, Pietropaolo G, *et al.* Pregnancy outcome in women with peritoneal,
12 394 ovarian and rectovaginal endometriosis: a retrospective cohort study. *BJOG*
13 395 2012;**119**:1538–43. doi:10.1111/j.1471-0528.2012.03466.x
14
15 396 10 Conti N, Cevenini G, Vannuccini S, *et al.* Women with endometriosis at first pregnancy have
16 397 an increased risk of adverse obstetric outcome. *J Matern Fetal Neonatal Med*
17 398 2015;**28**:1795–8. doi:10.3109/14767058.2014.968843
18
19 399 11 Fernando S, Breheny S, Jaques AM, *et al.* Preterm birth, ovarian endometriomata, and
20 400 assisted reproduction technologies. *Fertil Steril* 2009;**91**:325–30.
21 401 doi:10.1016/j.fertnstert.2008.01.096
22
23 402 12 Stephansson O, Kieler H, Granath F, *et al.* Endometriosis, assisted reproduction
24 403 technology, and risk of adverse pregnancy outcome. *Hum Reprod* 2009;**24**:2341–7.
25 404 doi:10.1093/humrep/dep186
26
27 405 13 Matalliotakis IM, Cakmak H, Mahutte N, *et al.* Women with advanced-stage endometriosis
28 406 and previous surgery respond less well to gonadotropin stimulation, but have similar IVF
29 407 implantation and delivery rates compared with women with tubal factor infertility. *Fertil Steril*
30 408 2007;**88**:1568–72. doi:10.1016/j.fertnstert.2007.01.037
31
32 409 14 Brosens I. Endometriosis and the outcome of in vitro fertilization. *Fertil Steril* 2004;**81**:1198–
33 410 200. doi:10.1016/j.fertnstert.2003.09.071
34
35 411 15 Olivennes F. [Results of IVF in women with endometriosis]. *J Gynecol Obstet Biol Reprod*
36 412 (*Paris*) 2003;**32**:S45-47.
37
38 413 16 Terzic M, Aimagambetova G, Garzon S, *et al.* Ovulation induction in infertile women with
39 414 endometriotic ovarian cysts: current evidence and potential pitfalls. *Minerva Med*
40 415 2020;**111**:50–61. doi:10.23736/S0026-4806.19.06346-8
41
42 416 17 Šalamun V, Verdenik I, Laganà AS, *et al.* Should we consider integrated approach for
43 417 endometriosis-associated infertility as gold standard management? Rationale and results
44 418 from a large cohort analysis. *Arch Gynecol Obstet* 2018;**297**:613–21. doi:10.1007/s00404-
45 419 017-4633-0
46
47 420 18 Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization.
48 421 *Fertil Steril* 2002;**77**:1148–55. doi:10.1016/s0015-0282(02)03112-6
49
50 422 19 Muteshi CM, Ohuma EO, Child T, *et al.* The effect of endometriosis on live birth rate and
51 423 other reproductive outcomes in ART cycles: a cohort study. *Hum Reprod Open*
52 424 2018;**2018**:hoy016. doi:10.1093/hropen/hoy016
53
54
55
56
57
58
59
60

- 1
2
3 425 20 González-Comadran M, Schwarze JE, Zegers-Hochschild F, *et al*. The impact of
4 426 endometriosis on the outcome of Assisted Reproductive Technology. *Reprod Biol*
5 427 *Endocrinol* 2017;**15**:8. doi:10.1186/s12958-016-0217-2
6
7 428 21 Hamdan M, Dunselman G, Li TC, *et al*. The impact of endometrioma on IVF/ICSI outcomes:
8 429 a systematic review and meta-analysis. *Hum Reprod Update* 2015;**21**:809–25.
9 430 doi:10.1093/humupd/dmv035
10
11 431 22 Barbosa M a. P, Teixeira DM, Navarro P a. a. S, *et al*. Impact of endometriosis and its
12 432 staging on assisted reproduction outcome: systematic review and meta-analysis. *Ultrasound*
13 433 *Obstet Gynecol* 2014;**44**:261–78. doi:10.1002/uog.13366
14
15 434 23 Senapati S, Sammel MD, Morse C, *et al*. Impact of endometriosis on in vitro fertilization
16 435 outcomes: an evaluation of the Society for Assisted Reproductive Technologies Database.
17 436 *Fertil Steril* 2016;**106**:164-171.e1. doi:10.1016/j.fertnstert.2016.03.037
18
19 437 24 Legendre G, Catala L, Morinière C, *et al*. Relationship between ovarian cysts and infertility:
20 438 what surgery and when? *Fertil Steril* 2014;**101**:608–14. doi:10.1016/j.fertnstert.2014.01.021
21
22 439 25 Alammari R, Lightfoot M, Hur H-C. Impact of Cystectomy on Ovarian Reserve: Review of
23 440 the Literature. *J Minim Invasive Gynecol* 2017;**24**:247–57. doi:10.1016/j.jmig.2016.12.010
24
25 441 26 Diamond MP, Pellicer A, Boyers SP, *et al*. The effect of periovarian adhesions on follicular
26 442 development in patients undergoing ovarian stimulation for in vitro fertilization-embryo
27 443 transfer. *Fertil Steril* 1988;**49**:100–3. doi:10.1016/s0015-0282(16)59657-5
28
29 444 27 Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic
30 445 pain associated with endometriosis: a committee opinion. *Fertil Steril* 2014;**101**:927–35.
31 446 doi:10.1016/j.fertnstert.2014.02.012
32
33 447 28 Surrey ES, Silverberg KM, Surrey MW, *et al*. Effect of prolonged gonadotropin-releasing
34 448 hormone agonist therapy on the outcome of in vitro fertilization-embryo transfer in patients
35 449 with endometriosis. *Fertil Steril* 2002;**78**:699–704. doi:10.1016/s0015-0282(02)03373-3
36
37 450 29 Ozkan S, Arici A. Advances in treatment options of endometriosis. *Gynecol Obstet Invest*
38 451 2009;**67**:81–91. doi:10.1159/000163071
39
40 452 30 Guo Y, Lu N, Zhang Y, *et al*. Comparative study on the pregnancy outcomes of in vitro
41 453 fertilization-embryo transfer between long-acting gonadotropin-releasing hormone agonist
42 454 combined with transvaginal ultrasound-guided cyst aspiration and long-acting gonadotropin-
43 455 releasing hormone agonist alone. *Contemp Clin Trials* 2012;**33**:1206–10.
44 456 doi:10.1016/j.cct.2012.07.009
45
46 457 31 Georgiou EX, Melo P, Baker PE, *et al*. Long-term GnRH agonist therapy before in vitro
47 458 fertilisation (IVF) for improving fertility outcomes in women with endometriosis. *Cochrane*
48 459 *Database Syst Rev* 2019;**2019**. doi:10.1002/14651858.CD013240.pub2
49
50 460 32 Taylor HS, Giudice LC, Lessey BA, *et al*. Treatment of Endometriosis-Associated Pain with
51 461 Elagolix, an Oral GnRH Antagonist. *N Engl J Med* 2017;**377**:28–40.
52 462 doi:10.1056/NEJMoa1700089
53
54
55
56
57
58
59
60

- 1
2
3 463 33 Sallam HN, Garcia-Velasco JA, Dias S, *et al.* Long-term pituitary down-regulation before in
4 464 vitro fertilization (IVF) for women with endometriosis. *Cochrane Database Syst Rev*
5 465 2006;:CD004635. doi:10.1002/14651858.CD004635.pub2
6
7 466 34 Practice Committees of the American Society for Reproductive Medicine and the Society for
8 467 Assisted Reproductive Technology. Electronic address: asrm@asrm.org. Intracytoplasmic
9 468 sperm injection (ICSI) for non-male factor indications: a committee opinion. *Fertil Steril*
10 469 2020;**114**:239–45. doi:10.1016/j.fertnstert.2020.05.032
11
12 470 35 Practice Committee of Society for Assisted Reproductive Technology, Practice Committee
13 471 of American Society for Reproductive Medicine. Elective single-embryo transfer. *Fertil Steril*
14 472 2012;**97**:835–42. doi:10.1016/j.fertnstert.2011.11.050
15
16 473 36 Practice Committee of the American Society for Reproductive Medicine. Electronic address:
17 474 ASRM@asrm.org, Practice Committee of the Society for Assisted Reproductive
18 475 Technology. Guidance on the limits to the number of embryos to transfer: a committee
19 476 opinion. *Fertil Steril* 2017;**107**:901–3. doi:10.1016/j.fertnstert.2017.02.107
20
21 477 37 Boivin J, Takefman J, Braverman A. The Fertility Quality of Life (FertiQoL) tool:
22 478 development and general psychometric properties. *Fertil Steril* 2011;**96**:409-415.e3.
23 479 doi:10.1016/j.fertnstert.2011.02.046
24
25
26 480
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1 Introduction

2			
3	Background and	#6a	Description of research question and justification for undertaking
4	rationale		the trial, including summary of relevant studies (published and
5			unpublished) examining benefits and harms for each intervention
6			
7			
8	Background and	#6b	Explanation for choice of comparators
9	rationale: choice of		
10	comparators		
11			
12			
13	Objectives	#7	Specific objectives or hypotheses
14			
15			
16	Trial design	#8	Description of trial design including type of trial (eg, parallel
17			group, crossover, factorial, single group), allocation ratio, and
18			framework (eg, superiority, equivalence, non-inferiority,
19			exploratory)
20			
21			
22			
23	Methods:		
24	Participants,		
25	interventions, and		
26	outcomes		
27			
28			
29	Study setting	#9	Description of study settings (eg, community clinic, academic
30			hospital) and list of countries where data will be collected.
31			Reference to where list of study sites can be obtained
32			
33	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,
34			eligibility criteria for study centres and individuals who will
35			perform the interventions (eg, surgeons, psychotherapists)
36			
37			
38	Interventions:	#11a	Interventions for each group with sufficient detail to allow
39	description		replication, including how and when they will be administered
40			
41	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a
42	modifications		given trial participant (eg, drug dose change in response to harms,
43			participant request, or improving / worsening disease)
44			
45	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any
46	adherence		procedures for monitoring adherence (eg, drug tablet return;
47			laboratory tests)
48			
49	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or
50	concomitant care		prohibited during the trial
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			

1	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
2				
3				
4				
5				
6				
7				
8				
9				
10				
11	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
12				
13				
14				
15				
16	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
17				
18				
19				
20				
21	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
22				
23				
24				
25	Methods: Assignment			
26	of interventions (for			
27	controlled trials)			
28				
29				
30	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
31				
32				
33				
34				
35				
36				
37				
38				
39				
40	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
41				
42				
43				
44				
45				
46				
47	Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
48				
49				
50				
51	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
52				
53				
54				
55				
56	Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention	9-10
57				
58				
59				
60				

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	
1			
2			
3	Harms	#22 Plans for collecting, assessing, reporting, and managing solicited	12
4		and spontaneously reported adverse events and other unintended	
5		effects of trial interventions or trial conduct	
6			
7			
8	Auditing	#23 Frequency and procedures for auditing trial conduct, if any, and	12
9		whether the process will be independent from investigators and the	
10		sponsor	
11			
12			
13	Ethics and		
14	dissemination		
15			
16			
17	Research ethics	#24 Plans for seeking research ethics committee / institutional review	12
18	approval	board (REC / IRB) approval	
19			
20			
21	Protocol amendments	#25 Plans for communicating important protocol modifications (eg,	12
22		changes to eligibility criteria, outcomes, analyses) to relevant	
23		parties (eg, investigators, REC / IRBs, trial participants, trial	
24		registries, journals, regulators)	
25			
26			
27	Consent or assent	#26a Who will obtain informed consent or assent from potential trial	7
28		participants or authorised surrogates, and how (see Item 32)	
29			
30			
31	Consent or assent:	#26b Additional consent provisions for collection and use of participant	7, 9
32	ancillary studies	data and biological specimens in ancillary studies, if applicable	
33			
34			
35	Confidentiality	#27 How personal information about potential and enrolled participants	13
36		will be collected, shared, and maintained in order to protect	
37		confidentiality before, during, and after the trial	
38			
39			
40	Declaration of interests	#28 Financial and other competing interests for principal investigators	13
41		for the overall trial and each study site	
42			
43			
44	Data access	#29 Statement of who will have access to the final trial dataset, and	13
45		disclosure of contractual agreements that limit such access for	
46		investigators	
47			
48			
49	Ancillary and post trial	#30 Provisions, if any, for ancillary and post-trial care, and for	n/a
50	care	compensation to those who suffer harm from trial participation	
51			
52			
53	Dissemination policy:	#31a Plans for investigators and sponsor to communicate trial results to	13
54	trial results	participants, healthcare professionals, the public, and other relevant	
55		groups (eg, via publication, reporting in results databases, or other	
56		data sharing arrangements), including any publication restrictions	
57			
58			
59			
60			

1	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	12
2	authorship		professional writers	
3				
4	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	n/a
5	reproducible research		participant-level dataset, and statistical code	
6				
7				

8 Appendices

10	Informed consent	#32	Model consent form and other related documentation given to	n/a
11	materials		participants and authorised surrogates	
12				
13	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
14			biological specimens for genetic or molecular analysis in the	
15			current trial and for future use in ancillary studies, if applicable	
16				
17				
18				
19				
20				
21				

22 The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons
 23 Attribution License CC-BY-NC. This checklist can be completed online using <https://www.goodreports.org/>, a
 24 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
 25
 26
 27
 28
 29
 30
 31
 32
 33
 34
 35
 36
 37
 38
 39
 40
 41
 42
 43
 44
 45
 46
 47
 48
 49
 50
 51
 52
 53
 54
 55
 56
 57
 58
 59
 60

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-052043.R3
Article Type:	Protocol
Date Submitted by the Author:	05-Apr-2022
Complete List of Authors:	Taylor, Hugh; Yale School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Li, Howard; Yale School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Carson, Sandra; Yale School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Flores, Valerie; Yale School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Pal, Lubna; Yale University School of Medicine, Obstetrics, Gynecology & Reproductive Sciences Robbins, Jared; Northwestern University, Obstetrics and Gynecology Santoro, Nanette F. ; University of Colorado, Obstetrics and Gynecology Segars, James H. ; Johns Hopkins University School of Medicine, Gynecology and Obstetrics Seifer, David; Yale School of Medicine, Obstetrics, Gynecology, and Reproductive Sciences Huang, H; Yale University School of Public Health Young, Steven; The University of North Carolina at Chapel Hill, Obstetrics and Gynecology Zhang, Heping; Yale University School of Public Health
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Reproductive medicine
Keywords:	Sex steroids & HRT < DIABETES & ENDOCRINOLOGY, Subfertility < GYNAECOLOGY, Reproductive medicine < GYNAECOLOGY, Clinical trials < THERAPEUTICS

SCHOLARONE™
Manuscripts

1
2
3 1 **Pre-IVF treatment with a GnRH antagonist in women with endometriosis (PREGNANT):**
4
5 2 **Study protocol for a prospective, double-blind, placebo-controlled trial**
6

7
8
9
10 4 Hugh S. Taylor¹, Howard J. Li¹, Sandra Carson¹, Valerie Flores¹, Lubna Pal¹, Jared Robbins²,
11 5 Nanette Santoro³, James Segars⁴, David Seifer¹, Hao Huang⁵, Steven Young⁶, and Heping
12 6 Zhang⁵
13
14
15

16 7
17
18 8 1. Yale School of Medicine, New Haven, CT

19
20 9 2. Northwestern University, Chicago, IL

21
22 10 3. University of Colorado, Aurora, CO

23
24 11 4. Johns Hopkins University, Baltimore, MD

25
26 12 5. Yale School of Public Health, New Haven CT

27
28 13 6. University of North Carolina, Chapel Hill, NC
29
30
31
32

33 15 **Correspondence:**

34
35 16 Hugh S. Taylor

36
37 17 Department of Obstetrics, Gynecology and Reproductive Sciences

38
39 18 Yale School of Medicine

40
41 19 333 Cedar Street

42
43 20 New Haven CT 06520 Phone: 203-785-4001

44
45 21 Email: hugh.taylor@yale.edu
46
47
48
49

50 23 **Word count:** 2926 words
51
52
53
54
55
56
57
58
59
60

1
2
3 **24 Abstract**
4

5 *25 Introduction:* Infertility is a common complication of endometriosis. While in vitro fertilization-
6 embryo transfer (IVF-ET) successfully treats endometriosis-associated infertility, there is some
7 *26* evidence that pregnancy rates may be diminished in women seeking fertility treatment for
8 *27* endometriosis-associated infertility compared to other etiologies of infertility. The use of
9 *28* gonadotropin releasing hormone (GnRH) agonist prior to IVF has been suggested to improve
10 *29* success, however studies have been small and rarely reported live birth rates. Recent approval
11 *30* of an oral GnRH antagonist for endometriosis provides a novel option for women with
12 *31* endometriosis who are undergoing IVF. There have been no studies on the efficacy of GnRH
13 *32* antagonists for the treatment of endometriosis-related infertility.
14 *33*

15 *34 Methods and analysis:* This study is a multi-center, prospective, randomized, double-blind,
16 *35* placebo-controlled trial to study the efficacy of GnRH antagonist pre-treatment for women with
17 *36* endometriosis who are undergoing IVF. A total of 814 patients with endometriosis undergoing
18 *37* fertility treatment will be enrolled and randomized 1:1 into two groups: elagolix 200 mg bid or
19 *38* placebo for 8 weeks, prior to undergoing IVF. All participants will then undergo IVF treatment
20 *39* per local protocols. The primary outcome is live birth. Secondary outcomes include oocyte
21 *40* number, fertilization rate, embryo morphology, and implantation rates, as well as rates of known
22 *41* endometriosis-related obstetrical outcomes (pregnancy-induced hypertension, antepartum
23 *42* hemorrhage, cesarean delivery, and preterm birth).
24 *43*

25 *44 Ethics and dissemination:* The PREGnant trial was approved by the Institutional Review Board
26 *45* at Johns Hopkins University. Results will be published in a peer-reviewed journal.
27 *46*

28 *47 Trial Registration:* ClinicalTrials.gov Identifier NCT04173169
29 *48*

30 *49 FDA IND:* 152645
31

32 *47 Key words:* endometriosis; in vitro fertilization; IVF; gonadotropin releasing hormone; GnRH;
33 *48* elagolix; GnRH antagonist; Live birth
34 *49*

50 **Strengths and Limitations of this Study**

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

65 **Introduction**

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

1
2
3 75 55%, respectively) [6]. Endometriosis is also associated with obstetrical complications, including
4
5 76 obstetrical hemorrhage, cesarean delivery, pre-eclampsia and pregnancy-induced hypertension,
6
7 77 and preterm birth [7–12]. While the mechanism remains controversial and unclear,
8
9 78 endometriosis is thought to contribute to reduced fertility via adnexal scarring and poor
10
11 79 endometrial receptivity, though studies also suggest with women with advanced endometriosis
12
13 80 also have poor ovarian reserve, low oocyte and embryo quality, and poor implantation [1,13–
14
15 81 15].

16
17
18 82 Multiple effective treatments exist for the management of endometriosis-associated
19
20 83 infertility, including laparoscopic destruction of endometriotic disease, ovulation induction, and
21
22 84 intrauterine insemination [1,16,17]. While some studies show that conservative treatment alone
23
24 85 may be effective in improving fertility for women with endometriosis and potentially helps avoid
25
26 86 obstetrical complications associated with IVF [17], IVF remains the most direct and effective
27
28 87 treatment for endometriosis-associated infertility, especially in patients who have failed
29
30 88 conservative interventions.

31
32
33 89 There is some evidence that endometriosis is also associated with poorer IVF outcomes,
34
35 90 though this is controversial. One meta-analysis from 2002 including 22 non-randomized trials
36
37 91 reported that the chances of achieving pregnancy with IVF in women with endometriosis was
38
39 92 almost half that of those with tubal infertility (odds ratio [OR] = 0.56, 95% confidence intervals
40
41 93 [CI] = 0.44–0.7) and women with severe disease had about half the pregnancy rate of those with
42
43 94 mild disease [18]. A more recent study published in 2018 showed via retrospective comparison
44
45 95 of 531 women with endometriosis and 737 women with unexplained subfertility found that
46
47 96 women with endometriosis still have a 24% lower likelihood of live birth after IVF than women
48
49 97 with unexplained infertility [19]. However, a larger retrospective study in 2017 comparing 3583
50
51 98 women with endometriosis and 18,833 women without endometriosis found that endometriosis
52
53 99 was associated with fewer oocytes retrieved, but no significant difference in live birth rates [20].
54
55
56 100 Similarly, a metanalysis of 33 studies published in 2015 examined the effect of endometrioma

1
2
3 101 on IVF/ICSI outcomes and also found that women with endometrioma had fewer oocytes
4
5 102 retrieved, but similar live birth rates [21]. A large metanalysis of 78 studies published in 2014
6
7 103 also found a difference in number of oocytes retrieved but no significant difference in live birth
8
9 104 rates between women with and without endometriosis [22]. It is important to note, however, that
10
11 105 the effect of endometriosis on IVF outcomes may be underestimated, especially in more recent
12
13 106 studies, due to a likely underdiagnosis of endometriosis in the IVF population as laparoscopy is
14
15 107 no longer a routine practice in infertility evaluations [4]. As endometriosis commonly presents in
16
17 108 conjunction with other infertility diagnoses (e.g. male factor, tubal factor, diminished ovarian
18
19 109 reserve), it has been suggested that endometriosis, when associated with other barriers to
20
21 110 fertility, contributes to poorer IVF outcomes in the general IVF population, even if this effect is
22
23 111 not seen with endometriosis in isolation [23]. This finding may be due to a primary effect of
24
25 112 endometriosis on reproductive biology, but may also be secondary to epidemiologic or
26
27 113 iatrogenic factors associated with an endometriosis diagnosis: greater exposure to prior
28
29 114 gynecologic surgery resulting in ovarian injury, diminished reserve, or impaired folliculogenesis)
30
31 115 [24–26], or an effect of subsequent adhesive disease on the technical difficulty of oocyte
32
33 116 retrievals. These factors, however, have not been well studied as potential mechanisms by
34
35 117 which endometriosis may compromise IVF outcomes.
36
37
38

39 118 As the association between endometriosis and poorer IVF outcomes remains biologically
40
41 119 plausible despite mixed clinical evidence [1,13–15,23], pre-treatment with GnRH agonist
42
43 120 therapy has been investigated as a method to improve IVF outcomes, though with mixed
44
45 121 evidence. As a hormone-dependent disorder, medical management of symptomatic
46
47 122 endometriosis has targeted ovarian estrogen production, including combined oral
48
49 123 contraceptives, progestins, danazol and gonadotropin-releasing hormone (GnRH) agonists or
50
51 124 antagonist [27]. While these therapies have been helpful in managing endometriosis-associated
52
53 125 pelvic pain, they have not been shown to treat endometriosis-associated infertility in the
54
55 126 absence of IVF [5]. In the IVF setting, prolonged GnRH agonist treatment prior to IVF has been
56
57
58
59
60

1
2
3 127 shown by several studies to improve fertility rates in women with advanced endometriosis [28–
4 128 30], though a recent Cochrane review of 8 RCTs was unable to determine whether prolonged
5 129 GnRH agonist treatment improved subsequent IVF outcomes, partly due to low quality of
6 130 available evidence [31].

7
8
9
10
11 131 Since then, the GnRH antagonist elagolix has recently become available for use, with a
12 132 number of advantages over GnRH agonists: the convenience of oral rather than parenteral
13 133 administration, improved tolerability and reduced severity of vasomotor symptoms, rapid onset
14 134 of action with suppression of endogenous estradiol levels within 24 hours, and lack of initial
15 135 gonadotropin stimulation (“flare” effect) seen with GnRH agonists [32]. However, elagolix has
16 136 not yet been studied as an adjunctive treatment prior to IVF for women with endometriosis.
17
18 137 Based on limited evidence from GnRH agonist trials, we hypothesize that GnRH antagonist
19 138 therapy may potentially benefit women with endometriosis undergoing IVF treatment, possibly
20 139 with a shorter course of treatment compared to what has been studied with GnRH agonists (3-6
21 140 months) [31,33].
22
23
24
25
26
27
28
29
30
31

32 141

33 142 **Methods and Analysis**

34
35
36
37 143 This is a multicenter, prospective, randomized controlled trial to study the effect of GnRH
38 144 antagonist pre-treatment for women with endometriosis who are undergoing IVF.
39
40

41 145

42 146 **Participants**

43
44
45 147 Participants will be recruited based on the following inclusion criteria:

- 46
47 148 • Women aged 18-38
48
49 149 • Planning to undergo a cycle of IVF for treatment of infertility
50
51 150 • Surgical or sonographic diagnosis of endometriosis
52
53 151 • Body Mass Index (BMI) 18-38 kg/m² (inclusive) at time of screening
54
55
56
57
58
59
60

- 1
2
3 152 • Anti-Mullerian hormone (AMH) > 0.8 ng/ml within 6 months of planned IVF cycle
4
5 153 start
6
7 154 • Uterine cavity assessment by sonohysterogram or hysteroscopy within 6 months
8
9 155 indicating adequacy for embryo transfer
10
11 156 • Presence of at least one ovary with no clinically significant abnormalities (other
12
13 157 than endometrioma)
14
15 158 • Negative urine or cervical swab for gonorrhoea and chlamydia within 12 months of
16
17 159 recruitment
18
19 160 • Willingness and ability to comply with trial procedures, including reporting of
20
21 161 obstetrical outcomes after delivery
22
23

24 162 A diagnosis of endometriosis must be confirmed by surgical visualization of
25
26 163 endometriosis (at the time of laparoscopy or laparotomy) within the last 10 years of initial trial
27
28 164 visit, or by sonographic documentation of an ovarian endometrioma >2 cm, or two or more
29
30 165 smaller endometriomas that total >2 cm in diameter. If a diagnosis of endometriosis was made
31
32 166 sonographically, serial transvaginal ultrasounds must have documented the same unambiguous
33
34 167 endometrioma on two separate occasions in more than one menstrual cycle. Images will be
35
36 168 read centrally by the same investigator to assure uniform diagnostic criteria are applied.
37
38

39 169 Women will be excluded from the study if there was:
40

- 41 170 • Use of GnRH agonists or antagonists within 6 months of study start, except for
42
43 171 antagonist use as part of an IVF cycle
44
45 172 • Use of depot medroxyprogesterone acetate (MPA) or subdermal contraceptive
46
47 173 implant (e.g. Implanon® or Nexplanon®) within 10 months of study start
48
49 174 • Continuous use of oral progestins (MPA, NETA) within 3 months of study start
50
51 175 • Use of aromatase inhibitors, danazol or hormonal contraceptives (including
52
53 176 combined oral contraceptive pill, progestin-only pill, transdermal patch or
54
55 177 contraceptive ring) within 1 month of study start
56
57
58
59
60

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

192 Participants will be recruited from the population of patients already committed to
193 pursuing IVF at one of the five participating clinical centers in the trial (Yale University,
194 University of Colorado - Denver, Northwestern University, Johns Hopkins and University of
195 North Carolina). Additional clinical centers may be added for enrollment if needed. All
196 participants will provide written, informed consent for their participation in this study (see
197 Supplementary File). This study was approved by a central Institutional Review Boards (IRB) as
198 well as local IRBs at all five participating centers. In addition, the Food and Drug Administration
199 gave permission for the study to proceed using elagolix as an Investigational New Drug (IND
200 152645) for this indication.

201

202 ***Intervention***

203 ***GnRH antagonist pre-treatment***

1
2
3 204 Participants will be randomized 1:1 into one of two treatment groups: GnRH antagonist
4
5 205 (elagolix 200 mg bid) or placebo for 8 weeks, prior to undergoing IVF. While using GnRH
6
7 206 antagonists, hot flashes and other vasomotor symptoms may occur. If indicated, use of
8
9 207 paroxetine mesylate will be allowed. No sex steroids or other hormone modifying treatments are
10
11 208 permitted. The GnRH antagonist will be administered during the routine evaluation conducted
12
13 209 prior to the IVF cycle.
14
15

16 210

17
18 211 *IVF treatment*

19
20 212 All participants will then undergo IVF treatment per local protocols, with agreed upon
21
22 213 standards. All sites will use standard FSH stimulation and GnRH antagonist in each cycle with
23
24 214 the exception that additional LH activity will always be supplied at the outset of stimulation,
25
26 215 since half of the participants will have been on GnRH antagonist pre-treatment and will be
27
28 216 expected to have suppressed LH. Non-conventional IVF therapies outside of those following
29
30 217 standard protocols at each site will not be performed.
31

32
33 218 The standard IVF treatment for the study will be a GnRH antagonist protocol (cetrotide
34
35 219 or ganirelix). Gonadotrophin stimulation with recombinant human follicle stimulating hormone
36
37 220 and menotropin (supplying 75IU FSH and 75 IU LH activity per vial) will be started at a daily
38
39 221 dose ranging 150-375 IU depending on patient characteristics including age, early follicular
40
41 222 phase FSH, AMH, antral follicle count and BMI. Each patient will receive at least 75 IU of LH
42
43 223 activity daily as part of the initial stimulation protocol to counteract the LH suppression by the
44
45 224 GnRH antagonist. The oral GnRH antagonist will be discontinued at the start of stimulation;
46
47 225 addition of subcutaneous injections of GnRH antagonist will be based on each sites' standard
48
49 226 IVF protocol. When at least two leading follicles measuring ≥ 18 mm are seen on ultrasound, the
50
51 227 trigger injection of u-hCG (10,000 IU) or r-hCG (250 mcg) is administered, followed by oocyte
52
53 228 retrieval 37h later. Depending on sperm parameters following preparation on the day of oocyte
54
55 229 retrieval, fertilization will be achieved either by conventional IVF or ICSI [34].
56
57
58
59
60

1
2
3 2304
5 231 *Embryo culture and transfer*

6
7 232 ET is performed between Days 3 and 5 of development depending on morphological
8
9 233 assessment and the woman's age, following ASRM guidelines allowing for transfer of up to two
10
11 234 embryos, with an elective single embryo transfer preferred [35,36]. Pre-implantation Genetic
12
13 235 Testing for aneuploidy (PGT-A) will be allowed. Frozen embryo transfers are included in this
14
15 236 study but must be preceded by the same pre-treatment with GnRH antagonist or placebo for 8
16
17 237 weeks, repeating the same treatment as initially assigned at randomization. No more than two
18
19 238 embryo transfers will be performed under this protocol, limiting administration of study drug to a
20
21 239 maximum of three 8-week courses (one prior to IVF, and one prior to each embryo transfer).

22
23
24 240 Luteal support will be initiated 1 day after oocyte retrieval with intramuscular or vaginal
25
26 241 micronized progesterone and continued for 14 days, when a urine pregnancy test is performed.
27
28 242 If pregnant, luteal support is continued until 10 weeks of pregnancy. A transvaginal ultrasound
29
30 243 scan is scheduled to confirm a viable intrauterine pregnancy and determine number of
31
32 244 gestations. Women are then discharged from the care of the IVF unit to their obstetrician for
33
34 245 further prenatal care and delivery. Participants will have been consented for access to
35
36 246 comprehensive pregnancy outcome and birth data at the time of enrollment.

37
38
39 24740
41 248 **Randomization**

42
43 249 Eligible women will be randomized in a 1:1 fashion to one of two treatments:

- 44
45 250 • Elagolix 200 mg BID daily for 8 weeks prior to undergoing IVF.
46
47 251 • Placebo, BID daily for 8 weeks prior to undergoing IVF.
48

49 252 A computer-generated randomization list will be created by staff at the PREGnant Data
50
51 253 Coordinating Center (DCC) and randomization will be performed prior to the first dose of
52
53 254 elagolix or placebo. Randomization will have random sizes (2,4, or 6) of blocks, stratified by site
54
55 255 and age group (<35 versus ≥35 years). Randomization sequences within each study site and
56
57
58
59
60

1
2
3 256 age stratum will be generated randomly and independently. The randomization list will not be
4
5 257 available to any person involved in the conduct and evaluation of the trial until the trial is
6
7 258 complete and database is declared clean and is released by the DCC. Randomization and
8
9 259 treatment allocation will be initiated by study staff according to the randomization list following
10
11 260 enrollment and prior to the first dose of elagolix or placebo, but participants, investigators, trial
12
13 261 staff, and central laboratory personnel will be blinded to the treatment assignment during the
14
15 262 trial duration (except for serious safety concerns). The assigned treatment (GnRH antagonist vs.
16
17 263 placebo) applied during the fresh cycle will also be used for subsequent frozen embryo transfers
18
19 264 resulting from the initial 'fresh' egg retrieval cycle. Most women using elagolix menstruate in the
20
21 265 first 2 months with only a 50% amenorrhea rate after 1 year in the Phase III clinical trial,
22
23 266 enabling blinding to remain intact.
24
25
26
27

267

268 **Outcome measures**

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

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

1
2
3 281 We will also measure pregnancy-related parameters to determine the effect of pre-
4
5 282 treatment with GnRH antagonist on pregnancy related complications associated with
6
7 283 endometriosis: pre-eclampsia and pregnancy-induced hypertension, preterm birth, intrauterine
8
9 284 growth restriction, cesarean delivery, and obstetric hemorrhage.

11 285 Finally, quality of life will be assessed using the FertiQOL, a validated questionnaire that
12
13 286 contains Emotional, Mind/Body, Relational and Social domains [37].
14
15

16 287

18 288 **Statistical Analysis**

20 289 *Sample size and power calculations*

22 290 The average live birth rate for women with endometriosis undergoing IVF is estimated to
23
24 291 be 39%, based on 2016 SART data showing a live birth rate of 44.7% per cycle in women with
25
26 292 endometriosis under the age of 35 and 34.0% in women ages 35-37. Using 386 participants per
27
28 293 arm (N=772) would provide an alpha of 0.05 and power of 80% to detect an effect of 10% absolute
29
30 294 improvement in live birth rate to 49% in the GnRH antagonist arm. This effect is conservatively
31
32 295 estimated from prior randomized trials using GnRH agonists [28–30], and what investigators
33
34 296 deemed to be sufficient to recommend the routine use of GnRH antagonists in IVF protocols for
35
36 297 this population. However, we acknowledge that the study may be underpowered to detect smaller
37
38 298 but still relevant effects (5-10% improvement). We will aim to enroll and randomize 814
39
40 299 participants (407 per treatment group), to account for an estimated drop-out rate of 5%.

43 300

45 301 *Analysis of outcome measures*

47 302 An intention-to-treat analysis will be performed on primary and secondary outcome
48
49 303 measures. The primary outcome, cumulative live birth rate, will be compared between the two
50
51 304 intervention arms using Pearson's chi-square test of independence. Baseline patient
52
53 305 characteristics and secondary outcome measures will also be analyzed with Pearson's chi-square
54
55 306 test and logistic regression as needed.

1
2
3 307 Based on prior experience, we expect a data completion rate of at least 99.5% and we do not
4
5 308 expect missing data to significantly affect trial analysis or results. In the unlikely event of
6
7 309 unexpectedly high rates of missing data, the potential mechanisms for missing data (missing
8
9 310 completely at random, missing at random, or missing not at random) will be examined. We will
10
11 311 compare the available characteristics of those with missing data to those with complete data. If
12
13 312 necessary, imputation techniques may be used.
14
15
16 313

17 18 314 ***Safety and adverse events monitoring***

19
20 315 The safety of the intervention medication elagolix has been previously investigated and
21
22 316 found to be tolerable [24]. All adverse events are collected regardless of their grade of severity
23
24 317 and reported based on established criteria. Data Safety Monitoring Board (DSMB) will receive
25
26 318 unblinded data and advise on potential safety issues. The choice of continuing therapy or trial
27
28 319 participation based on adverse events is at the discretion of the investigator and DSMB
29
30 320 determinations.
31
32
33 321

34 35 322 ***Patient and public involvement***

36
37 323 Patients and the public were not involved in the design, or conduct, or reporting, or
38
39 324 dissemination plans of this research.
40
41 325

42 43 326 ***Ethics and Dissemination***

44
45 327 The PREGnant trial was approved by the Institutional Review Board at Johns Hopkins
46
47 328 University School of Medicine (JHM IRB) on August 12, 2021, application #IRB00236742, with
48
49 329 reliance agreements at all participating sites.
50

51 330 Protocol modifications will be reviewed by the IRB and reported to the funder.
52
53 331 Participating investigators, providers, and study staff will be informed of protocol changes via
54
55 332 email. Significant protocol modifications will also be noted on ClinicalTrials.gov.
56
57
58
59
60

1
2
3 333 Elagolix has had increasing use in treating endometriosis-related pain, and the findings
4
5 334 of this trial can be easily adopted into the IVF setting. The results of this trial may reveal a new
6
7 335 way to optimize outcomes for women with endometriosis seeking fertility treatment.
8

9 336 The trial is conducted in accordance with relevant regulations and standard operating
10
11 337 procedures, including data protection. Each subject is assigned a unique code for de-
12
13 338 identification. Data will be collected electronically and abstracted from the electronic medical
14
15 339 record in a de-identified manner. Any medical information that is obtained in connection with this
16
17 340 program that could identify a subject will remain confidential and will be disclosed only as
18
19 341 required by law. All persons responsible for the quality control of the data take all necessary
20
21 342 precautions to ensure the confidentiality of information regarding trial participants and in
22
23 343 particular the identity of the participants and the results obtained. The final trial dataset will be
24
25 344 available to study investigators and Research Ethic Boards at all participating sites. Results of
26
27 345 the trial will be published in peer-reviewed journals. We will submit data and samples collected
28
29 346 by the trial to NICHD DASH. The informed consent will include permission to bank these
30
31 347 samples. The processes included initial data and documentation preparation (e.g., codebooks,
32
33 348 protocols, informed consent for data sharing), data quality control, and submission.
34
35
36
37
38

39 350 **Trial status and registration**

40
41 351 The study was conceived and designed in 2019. Recruitment is expected to begin in December
42
43 352 2021. This study is registered on ClinicalTrials.gov Identifier NCT04173169. This manuscript
44
45 353 describes the latest version, last updated November 29, 2021.
46
47
48

49 355 **Author Contributions**

50
51 356 HST, HJL, SC, VF, LP, JR, NS, JS, DS, HH, SY, HZ each made substantial
52
53 357 contributions to the conception or design of the study protocol, design of the study intervention,
54
55 358 study outcomes, study procedures, and/or revised the protocol critically for important intellectual
56
57
58

1
2
3 359 content and approved the final version to be published. HZ made substantial contributions to the
4
5 360 conception or design of the study protocol and wrote the first draft of the protocol. HJL wrote the
6
7 361 first draft of this manuscript. All authors approved the final version to be published.
8
9
10 362

11 363 **Funding Statement**

12
13 364 This study was funded by a grant titled “Pre-IVF treatment with a GnRH antagonist in women
14
15 365 with endometriosis - A prospective double blind placebo controlled trial (PREGnant)” from the
16
17 366 Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD),
18
19 367 1R01HD100336.
20
21
22 368

23 369 **Competing Interests**

24
25 370 The authors have no competing interests to report.
26
27
28 371

29 372 **References**

- 30
31
32 373 1 Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and
33 374 treatment of endometriosis-associated infertility. *Obstet Gynecol Clin North Am*
34 375 2012;**39**:535–49. doi:10.1016/j.ogc.2012.10.002
35
36
37 376 2 Taylor HS, Kotlyar AM, Flores VA. Endometriosis is a chronic systemic disease: clinical
38 377 challenges and novel innovations. *Lancet* 2021;**397**:839–52. doi:10.1016/S0140-
39 378 6736(21)00389-5
40
41 379 3 Verkauf BS. Incidence, symptoms, and signs of endometriosis in fertile and infertile women.
42 380 *J Fla Med Assoc* 1987;**74**:671–5.
43
44 381 4 Practice Committee of the American Society for Reproductive Medicine. Endometriosis and
45 382 infertility: a committee opinion. *Fertil Steril* 2012;**98**:591–8.
46 383 doi:10.1016/j.fertnstert.2012.05.031
47
48 384 5 Hughes EG, Fedorkow DM, Collins JA. A quantitative overview of controlled trials in
49 385 endometriosis-associated infertility. *Fertil Steril* 1993;**59**:963–70.
50
51 386 6 Akande VA, Hunt LP, Cahill DJ, *et al*. Differences in time to natural conception between
52 387 women with unexplained infertility and infertile women with minor endometriosis. *Hum*
53 388 *Reprod* 2004;**19**:96–103. doi:10.1093/humrep/deh045
54
55
56
57
58
59
60

- 1
2
3 389 7 Healy DL, Breheny S, Halliday J, *et al*. Prevalence and risk factors for obstetric
4 390 haemorrhage in 6730 singleton births after assisted reproductive technology in Victoria
5 391 Australia. *Hum Reprod* 2010;**25**:265–74. doi:10.1093/humrep/dep376
6
7 392 8 Takemura Y, Osuga Y, Fujimoto A, *et al*. Increased risk of placenta previa is associated with
8 393 endometriosis and tubal factor infertility in assisted reproductive technology pregnancy.
9 394 *Gynecol Endocrinol* 2013;**29**:113–5. doi:10.3109/09513590.2012.706669
10
11 395 9 Vercellini P, Parazzini F, Pietropaolo G, *et al*. Pregnancy outcome in women with peritoneal,
12 396 ovarian and rectovaginal endometriosis: a retrospective cohort study. *BJOG*
13 397 2012;**119**:1538–43. doi:10.1111/j.1471-0528.2012.03466.x
14
15 398 10 Conti N, Cevenini G, Vannuccini S, *et al*. Women with endometriosis at first pregnancy have
16 399 an increased risk of adverse obstetric outcome. *J Matern Fetal Neonatal Med*
18 400 2015;**28**:1795–8. doi:10.3109/14767058.2014.968843
19
20 401 11 Fernando S, Breheny S, Jaques AM, *et al*. Preterm birth, ovarian endometriomata, and
21 402 assisted reproduction technologies. *Fertil Steril* 2009;**91**:325–30.
22 403 doi:10.1016/j.fertnstert.2008.01.096
23
24 404 12 Stephansson O, Kieler H, Granath F, *et al*. Endometriosis, assisted reproduction
25 405 technology, and risk of adverse pregnancy outcome. *Hum Reprod* 2009;**24**:2341–7.
26 406 doi:10.1093/humrep/dep186
27
28 407 13 Matalliotakis IM, Cakmak H, Mahutte N, *et al*. Women with advanced-stage endometriosis
29 408 and previous surgery respond less well to gonadotropin stimulation, but have similar IVF
30 409 implantation and delivery rates compared with women with tubal factor infertility. *Fertil Steril*
31 410 2007;**88**:1568–72. doi:10.1016/j.fertnstert.2007.01.037
32
33 411 14 Brosens I. Endometriosis and the outcome of in vitro fertilization. *Fertil Steril* 2004;**81**:1198–
34 412 200. doi:10.1016/j.fertnstert.2003.09.071
35
36 413 15 Olivennes F. [Results of IVF in women with endometriosis]. *J Gynecol Obstet Biol Reprod*
37 414 (*Paris*) 2003;**32**:S45-47.
38
39 415 16 Terzic M, Aimagambetova G, Garzon S, *et al*. Ovulation induction in infertile women with
40 416 endometriotic ovarian cysts: current evidence and potential pitfalls. *Minerva Med*
41 417 2020;**111**:50–61. doi:10.23736/S0026-4806.19.06346-8
42
43 418 17 Šalamun V, Verdenik I, Laganà AS, *et al*. Should we consider integrated approach for
44 419 endometriosis-associated infertility as gold standard management? Rationale and results
45 420 from a large cohort analysis. *Arch Gynecol Obstet* 2018;**297**:613–21. doi:10.1007/s00404-
46 421 017-4633-0
47
48 422 18 Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization.
49 423 *Fertil Steril* 2002;**77**:1148–55. doi:10.1016/s0015-0282(02)03112-6
50
51 424 19 Muteshi CM, Ohuma EO, Child T, *et al*. The effect of endometriosis on live birth rate and
52 425 other reproductive outcomes in ART cycles: a cohort study. *Hum Reprod Open*
53 426 2018;**2018**:hoy016. doi:10.1093/hropen/hoy016
54
55
56
57
58
59
60

- 1
2
3 427 20 González-Comadran M, Schwarze JE, Zegers-Hochschild F, *et al.* The impact of
4 428 endometriosis on the outcome of Assisted Reproductive Technology. *Reprod Biol*
5 429 *Endocrinol* 2017;**15**:8. doi:10.1186/s12958-016-0217-2
6
7 430 21 Hamdan M, Dunselman G, Li TC, *et al.* The impact of endometrioma on IVF/ICSI outcomes:
8 431 a systematic review and meta-analysis. *Hum Reprod Update* 2015;**21**:809–25.
9 432 doi:10.1093/humupd/dmv035
10
11 433 22 Barbosa M a. P, Teixeira DM, Navarro P a. a. S, *et al.* Impact of endometriosis and its
12 434 staging on assisted reproduction outcome: systematic review and meta-analysis. *Ultrasound*
13 435 *Obstet Gynecol* 2014;**44**:261–78. doi:10.1002/uog.13366
14
15 436 23 Senapati S, Sammel MD, Morse C, *et al.* Impact of endometriosis on in vitro fertilization
16 437 outcomes: an evaluation of the Society for Assisted Reproductive Technologies Database.
17 438 *Fertil Steril* 2016;**106**:164-171.e1. doi:10.1016/j.fertnstert.2016.03.037
18
19 439 24 Legendre G, Catala L, Morinière C, *et al.* Relationship between ovarian cysts and infertility:
20 440 what surgery and when? *Fertil Steril* 2014;**101**:608–14. doi:10.1016/j.fertnstert.2014.01.021
21
22 441 25 Alammari R, Lightfoot M, Hur H-C. Impact of Cystectomy on Ovarian Reserve: Review of
23 442 the Literature. *J Minim Invasive Gynecol* 2017;**24**:247–57. doi:10.1016/j.jmig.2016.12.010
24
25 443 26 Diamond MP, Pellicer A, Boyers SP, *et al.* The effect of periovarian adhesions on follicular
26 444 development in patients undergoing ovarian stimulation for in vitro fertilization-embryo
27 445 transfer. *Fertil Steril* 1988;**49**:100–3. doi:10.1016/s0015-0282(16)59657-5
28
29 446 27 Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic
30 447 pain associated with endometriosis: a committee opinion. *Fertil Steril* 2014;**101**:927–35.
31 448 doi:10.1016/j.fertnstert.2014.02.012
32
33 449 28 Surrey ES, Silverberg KM, Surrey MW, *et al.* Effect of prolonged gonadotropin-releasing
34 450 hormone agonist therapy on the outcome of in vitro fertilization-embryo transfer in patients
35 451 with endometriosis. *Fertil Steril* 2002;**78**:699–704. doi:10.1016/s0015-0282(02)03373-3
36
37 452 29 Ozkan S, Arici A. Advances in treatment options of endometriosis. *Gynecol Obstet Invest*
38 453 2009;**67**:81–91. doi:10.1159/000163071
39
40 454 30 Guo Y, Lu N, Zhang Y, *et al.* Comparative study on the pregnancy outcomes of in vitro
41 455 fertilization-embryo transfer between long-acting gonadotropin-releasing hormone agonist
42 456 combined with transvaginal ultrasound-guided cyst aspiration and long-acting gonadotropin-
43 457 releasing hormone agonist alone. *Contemp Clin Trials* 2012;**33**:1206–10.
44 458 doi:10.1016/j.cct.2012.07.009
45
46 459 31 Georgiou EX, Melo P, Baker PE, *et al.* Long-term GnRH agonist therapy before in vitro
47 460 fertilisation (IVF) for improving fertility outcomes in women with endometriosis. *Cochrane*
48 461 *Database Syst Rev* 2019;**2019**. doi:10.1002/14651858.CD013240.pub2
49
50 462 32 Taylor HS, Giudice LC, Lessey BA, *et al.* Treatment of Endometriosis-Associated Pain with
51 463 Elagolix, an Oral GnRH Antagonist. *N Engl J Med* 2017;**377**:28–40.
52 464 doi:10.1056/NEJMoa1700089
53
54
55
56
57
58
59
60

- 1
2
3 465 33 Sallam HN, Garcia-Velasco JA, Dias S, *et al*. Long-term pituitary down-regulation before in
4 466 vitro fertilization (IVF) for women with endometriosis. *Cochrane Database Syst Rev*
5 467 2006;:CD004635. doi:10.1002/14651858.CD004635.pub2
6
7 468 34 Practice Committees of the American Society for Reproductive Medicine and the Society for
8 469 Assisted Reproductive Technology. Electronic address: asrm@asrm.org. Intracytoplasmic
9 470 sperm injection (ICSI) for non-male factor indications: a committee opinion. *Fertil Steril*
10 471 2020;**114**:239–45. doi:10.1016/j.fertnstert.2020.05.032
11
12 472 35 Practice Committee of Society for Assisted Reproductive Technology, Practice Committee
13 473 of American Society for Reproductive Medicine. Elective single-embryo transfer. *Fertil Steril*
14 474 2012;**97**:835–42. doi:10.1016/j.fertnstert.2011.11.050
15
16 475 36 Practice Committee of the American Society for Reproductive Medicine. Electronic address:
17 476 ASRM@asrm.org, Practice Committee of the Society for Assisted Reproductive
18 477 Technology. Guidance on the limits to the number of embryos to transfer: a committee
19 478 opinion. *Fertil Steril* 2017;**107**:901–3. doi:10.1016/j.fertnstert.2017.02.107
20
21 479 37 Boivin J, Takefman J, Braverman A. The Fertility Quality of Life (FertiQoL) tool:
22 480 development and general psychometric properties. *Fertil Steril* 2011;**96**:409-415.e3.
23 481 doi:10.1016/j.fertnstert.2011.02.046
24
25
26 482
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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)

Principal Investigator: Dr. Hugh Taylor
 Yale School of Medicine
 310 Cedar Street FMB 3rd Fl Rm #302
 New Haven CT, 06510
 Tel. 203-785-4001
 Email: hugh.taylor@yale.edu

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?

ORLISSA™ (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

1
2
3 drug. Randomization means whichever study regimen you receive it will be determined purely by
4 chance, like a flip of a coin. You will have an equal chance to receive either elagolix or placebo. Neither
5 you nor your physician will be able to decide to which group you are assigned. Neither you nor your
6 study team will know which study drug (elagolix or placebo) you will receive but this information can
7 be made available in case of an emergency. Half of study participants are expected to receive placebo.
8
9

10 In addition to dispensing 30 days of study drug and giving instructions on how to take it, the study
11 doctor or study staff will do the following:
12

- 13 • You will have about 2 teaspoons of blood drawn. The purpose of the blood collection is to store the
14 serum in our biorepository so that we can look at biomarkers in your blood in hopes that we can
15 determine which women with endometriosis will benefit from GnRH antagonist pre-treatment.
- 16 • A urine pregnancy test will be performed.
- 17
- 18 • You will be asked about any medication changes you may have made since the Screening Visit.
19
20
21

22 **Study Visit 2**

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

- 25 • A qualified member of the research team will collect and count any remaining study drug.
- 26 • An additional 30 days of study drug will be dispensed.
- 27 • You will be asked about any adverse events or any medication changes
28
29

30 **Study Visit 3**

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

- 33 • A qualified member of the research team will collect and count any remaining study drug.
- 34 • You will be asked about any adverse events or any medication changes.
- 35 • You will be given two questionnaires to complete, one concerns your infertility, the other asks
36 about your endometriosis symptoms.
- 37 • Blood will be collected. About 2 teaspoons of blood will be drawn for safety labs (CMP) and
38 remaining serum will be stored as in Visit 1.
- 39 • A urine pregnancy test will be performed.
- 40 • A transvaginal ultrasound which involves inserting an ultrasound probe into your vagina to
41 visualize your ovaries and uterus. Measurements and ultrasound pictures will be recorded of your
42 ovaries and uterus.
43
44
45
46

47 **IVF Cycle**

48 You will then undergo your IVF cycle which is standard of care and not a part of the study. We will
49 record information about your IVF cycle and if you are having the embryos transferred within a week of
50 retrieval, (a Fresh Embryo Transfer cycle), we will record the information about your embryo transfer.
51 If you become pregnant, we will record information about your pregnancy.
52
53

54 **Study Visit 4**

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

- 57 • If you had a Fresh Embryo Transfer and did not become pregnant or had a pregnancy loss prior to
58 10 weeks, and have frozen embryos banked and are returning for a Frozen Embryo Transfer.
59
60

- 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.

1
2
3 Ask any member of the research team if you have questions about the signs or symptoms of any side
4 effects that you read about in this consent form. Please tell the study doctor or a member of the research
5 team right away if you have any side effects. Please tell them if you have any other problems with your
6 health or the way you feel during the study, whether you think these problems are related to the study
7 or not.
8
9

Risks of taking ORILISSA™ (elagolix)

10
11
12 The very common side effects of elagolix observed in women include:

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

Mood Change:

16
17
18 During the endometriosis and uterine fibroids clinical trials, some subjects experienced mood changes,
19 including mood swing, depression, depressed mood and anxiety during elagolix administration. In the
20 endometriosis elagolix studies, depression was reported in 1.9% (about 2 in 100) subjects and depressed
21 mood was reported in 0.8% (about 1 in 100) subjects. A number of subjects who reported depression
22 had a history of depression. In the endometriosis program, four cases of suicidal thought, and one case
23 with a history of depression reported suicidal thoughts while on elagolix . One case of depression with
24 suicidal thought was reported while on placebo. There was one case of completed suicide which was
25 considered by the study doctor not related to study drug but rather related to potential life stress. There
26 was one case of suicidal ideation in the uterine fibroids program in a woman who received placebo.
27
28
29

30
31 If you have history of depression, other psychiatric related conditions or taking an anti-depressant,
32 please let your study doctor know. If you have any of the above symptoms, please contact your study
33 doctor immediately.
34

Effects on Menstrual Bleeding:

35
36 While you are taking elagolix you may experience changes in your menstrual cycle and bleeding
37 pattern. Your menstrual bleeding may be more or less, or occur for fewer days or no days. The time
38 between each period may also be shorter or longer and your periods may not be predictable. At higher
39 doses, elagolix may completely suppress your periods. This effect is reversible after stopping elagolix.
40
41

Bone Mineral Density and the Risk of Fractures:

42
43 Similar to other medications that reduce female hormone levels in the body, particularly estrogen levels,
44 elagolix has been shown to reduce bone mineral density and affect laboratory values that measure bone
45 health and strength. The data suggest that higher doses and longer exposure to elagolix result in greater
46 bone loss. Bone loss can place a woman at risk for osteoporosis (softening of the bones) and fractures
47 (broken bones). Inform the study doctor if you or family members have been diagnosed with
48 osteoporosis, if your mother had a hip fracture, if you are a smoker, if you have used or are now using
49 drugs such as corticosteroids or drugs to treat epilepsy (convulsions or seizures), and if you have ever
50 had any fractures.
51
52

53
54 Because the risk of fractures depends on many factors (including your age, overall health status, overall
55 bone strength), you should discuss the possible risk of fractures specific to you with your study doctor.
56 There is evidence that the bone loss associated with the use of elagolix is reversible.
57
58
59

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.

1
2
3
4 **8. What are your options if you do not want to be in the study?**

5 You do not have to participate in this study to receive treatment for your endometriosis-related infertility.
6 Choosing not to participate will not have any effect on your clinical care.
7

8
9 You do not have to join this study. If you do not join, your care at any of the study clinics (Northwestern
10 University, University of Colorado, Yale University, University of North Carolina, and Johns Hopkins
11 University) will not be affected.
12

13
14 **9. Will you be paid if you join this study?**

15 No, you will not receive any payment or compensation if you join this study
16

17 **10. Can you leave the study early?**

- 18
- 19 • You can agree to be in the study now and change your mind later.
 - 20 • If you wish to stop, please tell us right away.
 - 21 • Leaving this study early will not stop you from getting regular medical care.
- 22

23 If you drop out of the study early, the study team (at Northwestern University, University of Colorado,
24 Yale University, University of North Carolina, or Johns Hopkins University) may use your health
25 information that it has already collected if the information is needed for this study or any follow-up
26 activities.
27

28
29 **11. Will the study require any of your other health care providers to share your health**
30 **information with the researchers of this study?**

31 As a part of this study, the researchers may ask to see your health care records from your other healthcare
32 providers.
33
34

35 **12. What is a Certificate of Confidentiality?**

36 Your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in
37 some cases, to refuse to give out your information even if requested using legal means.
38
39

40 It does not protect information that we have to report by law, such as child abuse or some infectious
41 diseases. The Certificate does not prevent us from disclosing your information if we learn of possible
42 harm to yourself or others, or if you need medical help.
43

44 Disclosures that you consent to in this document are not protected. This includes putting research data in
45 the medical record or sharing research data for this study or future research. Disclosures that you make
46 yourself are also not protected.
47
48

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

50 During the study, we will tell you if we learn any new information that might affect whether you wish to
51 continue to participate.
52

53 A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S.
54 Law. This Web site will not include information that can identify you. At most, the Web site will
55 include a summary of the results. You can search this Web site at any time. If you would like to review
56 the information for this study, or a summary of the results, ask the study team doctor for the
57



Approved April 20, 2021

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).

For peer review only

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.



Approved April 20, 2021

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."

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).

For peer review only

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

1	Introduction		
2			
3	Background and	#6a	Description of research question and justification for undertaking
4	rationale		the trial, including summary of relevant studies (published and
5			unpublished) examining benefits and harms for each intervention
6			
7			
8	Background and	#6b	Explanation for choice of comparators
9	rationale: choice of		
10	comparators		
11			
12			
13	Objectives	#7	Specific objectives or hypotheses
14			
15			
16	Trial design	#8	Description of trial design including type of trial (eg, parallel
17			group, crossover, factorial, single group), allocation ratio, and
18			framework (eg, superiority, equivalence, non-inferiority,
19			exploratory)
20			
21			
22			
23	Methods:		
24	Participants,		
25	interventions, and		
26	outcomes		
27			
28			
29			
30	Study setting	#9	Description of study settings (eg, community clinic, academic
31			hospital) and list of countries where data will be collected.
32			Reference to where list of study sites can be obtained
33			
34			
35	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,
36			eligibility criteria for study centres and individuals who will
37			perform the interventions (eg, surgeons, psychotherapists)
38			
39			
40	Interventions:	#11a	Interventions for each group with sufficient detail to allow
41	description		replication, including how and when they will be administered
42			
43			
44	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a
45	modifications		given trial participant (eg, drug dose change in response to harms,
46			participant request, or improving / worsening disease)
47			
48			
49	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any
50	adherence		procedures for monitoring adherence (eg, drug tablet return;
51			laboratory tests)
52			
53			
54			
55	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or
56	concomitant care		prohibited during the trial
57			
58			
59			
60			

1	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
2				
3				
4				
5				
6				
7				
8				
9				
10				
11	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
12				
13				
14				
15				
16	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
17				
18				
19				
20				
21	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	7
22				
23				
24				
25	Methods: Assignment			
26	of interventions (for			
27	controlled trials)			
28				
29				
30	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
31				
32				
33				
34				
35				
36				
37				
38				
39				
40	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
41				
42				
43				
44				
45				
46				
47	Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9-10
48				
49				
50				
51	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
52				
53				
54				
55				
56	Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention	9-10
57				
58				
59				
60				

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	
1			
2			
3	Harms	#22 Plans for collecting, assessing, reporting, and managing solicited	12
4		and spontaneously reported adverse events and other unintended	
5		effects of trial interventions or trial conduct	
6			
7			
8	Auditing	#23 Frequency and procedures for auditing trial conduct, if any, and	12
9		whether the process will be independent from investigators and the	
10		sponsor	
11			
12			
13	Ethics and		
14	dissemination		
15			
16			
17	Research ethics	#24 Plans for seeking research ethics committee / institutional review	12
18	approval	board (REC / IRB) approval	
19			
20			
21	Protocol amendments	#25 Plans for communicating important protocol modifications (eg,	12
22		changes to eligibility criteria, outcomes, analyses) to relevant	
23		parties (eg, investigators, REC / IRBs, trial participants, trial	
24		registries, journals, regulators)	
25			
26			
27	Consent or assent	#26a Who will obtain informed consent or assent from potential trial	7
28		participants or authorised surrogates, and how (see Item 32)	
29			
30			
31	Consent or assent:	#26b Additional consent provisions for collection and use of participant	7, 9
32	ancillary studies	data and biological specimens in ancillary studies, if applicable	
33			
34			
35	Confidentiality	#27 How personal information about potential and enrolled participants	13
36		will be collected, shared, and maintained in order to protect	
37		confidentiality before, during, and after the trial	
38			
39			
40	Declaration of interests	#28 Financial and other competing interests for principal investigators	13
41		for the overall trial and each study site	
42			
43			
44	Data access	#29 Statement of who will have access to the final trial dataset, and	13
45		disclosure of contractual agreements that limit such access for	
46		investigators	
47			
48			
49	Ancillary and post trial	#30 Provisions, if any, for ancillary and post-trial care, and for	n/a
50	care	compensation to those who suffer harm from trial participation	
51			
52			
53	Dissemination policy:	#31a Plans for investigators and sponsor to communicate trial results to	13
54	trial results	participants, healthcare professionals, the public, and other relevant	
55		groups (eg, via publication, reporting in results databases, or other	
56		data sharing arrangements), including any publication restrictions	
57			
58			
59			
60			

1	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	12
2	authorship		professional writers	
3				
4	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	n/a
5	reproducible research		participant-level dataset, and statistical code	
6				
7				
8	Appendices			
9				
10	Informed consent	#32	Model consent form and other related documentation given to	n/a
11	materials		participants and authorised surrogates	
12				
13	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
14			biological specimens for genetic or molecular analysis in the	
15			current trial and for future use in ancillary studies, if applicable	
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				
29				
30				
31				
32				
33				
34				
35				
36				
37				
38				
39				
40				
41				
42				
43				
44				
45				
46				
47				
48				
49				
50				
51				
52				
53				
54				
55				
56				
57				
58				
59				
60				

The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist can be completed online using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)