


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

Hugh Taylor,<sup>1</sup> Howard J Li <sup>1</sup>, Sandra Carson,<sup>1</sup> Valerie Flores,<sup>1</sup> Lubna Pal,<sup>1</sup> Jared Robbins,<sup>2</sup> Nanette F Santoro,<sup>3</sup> James H Segars,<sup>4</sup> David Seifer,<sup>1</sup> Hao Huang,<sup>5</sup> Steven Young,<sup>6</sup> Heping Zhang<sup>5</sup>

**To cite:** Taylor H, Li HJ, Carson S, *et al.* Pre-IVF treatment with a GnRH antagonist in women with endometriosis (PREGNANT): study protocol for a prospective, double-blind, placebo-controlled trial. *BMJ Open* 2022;**12**:e052043. doi:10.1136/bmjopen-2021-052043

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-052043>).

Received 20 April 2021  
Accepted 01 June 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

**Correspondence to**  
Dr Hugh Taylor;  
[hugh.taylor@yale.edu](mailto:hugh.taylor@yale.edu)

## ABSTRACT

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

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

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

**Trial registration number** NCT04173169.

## INTRODUCTION

Endometriosis is a disease of ectopic endometrial glands outside the uterus, commonly involving the adnexa and pelvic peritoneum. In addition to being a common cause of chronic pelvic pain, endometriosis is also associated with poorer reproductive outcomes.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Limited evidence suggests that pretreatment with gonadotropin releasing hormone (GnRH) agonists may improve in vitro fertilisation (IVF) outcomes in patients with endometriosis; however, the recently available oral GnRH antagonist has not yet been studied for this purpose.
- ⇒ This study is a multicentre, prospective, randomised, double-blind, placebo-controlled study, randomising 814 patients with endometriosis undergoing fertility treatment 1:1 to elagolix 200 mg two times per day or placebo for 8 weeks prior to undergoing IVF.
- ⇒ This study uses a selective inclusion criteria requiring a documented diagnosis of endometriosis via direct surgical visualisation or standardised sonographical evidence.
- ⇒ Participants will undergo routine IVF protocols at each study site, improving the generalisability of results.
- ⇒ Participants will not be stratified by endometriosis severity or treatment history, and both fresh and frozen embryo transfers will be included in this study, which is not powered to detect differences in effect within these clinical subgroups.

While endometriosis affects 10%–15% of reproductive aged women,<sup>1 2</sup> it is present in 25%–50% of women with infertility and conversely, 30%–50% of women with endometriosis struggle with infertility.<sup>3</sup> The fecundity of normal reproductive age couples without infertility is estimated to be around 15%–20% per month, while the fecundity of women with untreated endometriosis is estimated at 2%–10%.<sup>4 5</sup> Women with mild endometriosis have a significantly lower probability of pregnancy over 3 years compared with women with unexplained fertility (36% vs 55%, respectively).<sup>6</sup> Endometriosis is also associated with

obstetrical complications, including obstetrical haemorrhage, caesarean delivery, pre-eclampsia and pregnancy-induced hypertension, and preterm birth.<sup>7–12</sup> While the mechanism remains controversial and unclear, endometriosis is thought to contribute to reduced fertility via adnexal scarring and poor endometrial receptivity, though studies also suggest with women with advanced endometriosis also have poor ovarian reserve, low oocyte and embryo quality, and poor implantation.<sup>113–15</sup>

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

There is some evidence that endometriosis is also associated with poorer IVF outcomes, though this is controversial. One meta-analysis from 2002 including 22 non-randomised trials reported that the chances of achieving pregnancy with IVF in women with endometriosis was almost half that of those with tubal infertility (OR 0.56, 95% CI 0.44 to 0.7) and women with severe disease had about half the pregnancy rate of those with mild disease.<sup>18</sup> A more recent study published in 2018 showed via retrospective comparison of 531 women with endometriosis and 737 women with unexplained subfertility found that women with endometriosis still have a 24% lower likelihood of live birth after IVF than women with unexplained infertility.<sup>19</sup> However, a larger retrospective study in 2017 comparing 3583 women with endometriosis and 18833 women without endometriosis found that endometriosis was associated with fewer oocytes retrieved, but no significant difference in live birth rates.<sup>20</sup> Similarly, a meta-analysis of 33 studies published in 2015 examined the effect of endometrioma on IVF/ intracytoplasmic sperm injection (ICSI) outcomes and also found that women with endometrioma had fewer oocytes retrieved, but similar live birth rates.<sup>21</sup> A large meta-analysis of 78 studies published in 2014 also found a difference in number of oocytes retrieved but no significant difference in live birth rates between women with and without endometriosis.<sup>22</sup> It is important to note, however, that the effect of endometriosis on IVF outcomes may be underestimated, especially in more recent studies, due to a likely underdiagnosis of endometriosis in the IVF population as laparoscopy is no longer a routine practice in infertility evaluations.<sup>4</sup> As endometriosis commonly presents in conjunction with other infertility diagnoses (eg, male factor, tubal factor, diminished ovarian reserve), it has been suggested that endometriosis, when associated with other barriers to fertility, contributes to poorer IVF outcomes in the general IVF population, even if this effect is not seen with endometriosis in isolation.<sup>23</sup> This

finding may be due to a primary effect of endometriosis on reproductive biology, but may also be secondary to epidemiological or iatrogenic factors associated with an endometriosis diagnosis: greater exposure to prior gynaecological surgery resulting in ovarian injury, diminished reserve, or impaired folliculogenesis),<sup>24–26</sup> or an effect of subsequent adhesive disease on the technical difficulty of oocyte retrievals. These factors, however, have not been well studied as potential mechanisms by which endometriosis may compromise IVF outcomes.

As the association between endometriosis and poorer IVF outcomes remains biologically plausible despite mixed clinical evidence,<sup>113–15 23</sup> pretreatment with gonadotropin releasing hormone (GnRH) agonist therapy has been investigated as a method to improve IVF outcomes, though with mixed evidence. As a hormone-dependent disorder, medical management of symptomatic endometriosis has targeted ovarian oestrogen production, including combined oral contraceptives, progestins, danazol and GnRH agonists or antagonist.<sup>27</sup> While these therapies have been helpful in managing endometriosis-associated pelvic pain, they have not been shown to treat endometriosis-associated infertility in the absence of IVF.<sup>5</sup> In the IVF setting, prolonged GnRH agonist treatment prior to IVF has been shown by several studies to improve fertility rates in women with advanced endometriosis,<sup>28–30</sup> though a recent Cochrane review of 8 randomised controlled trials (RCTs) was unable to determine whether prolonged GnRH agonist treatment improved subsequent IVF outcomes, partly due to low quality of available evidence.<sup>31</sup>

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

## METHODS AND ANALYSIS

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

### Participants

Participants will be recruited based on the following inclusion criteria:

- ▶ Women aged 18–38.

- ▶ Planning to undergo a cycle of IVF for treatment of infertility.
- ▶ Surgical or sonographical diagnosis of endometriosis.
- ▶ Body mass index (BMI) 18–38 kg/m<sup>2</sup> (inclusive) at time of screening.
- ▶ Anti-Mullerian hormone (AMH) >0.8 ng/mL within 6 months of planned IVF cycle start.
- ▶ Uterine cavity assessment by sonohysterogram or hysteroscopy within 6 months indicating adequacy for embryo transfer (ET).
- ▶ Presence of at least one ovary with no clinically significant abnormalities (other than endometrioma).
- ▶ Negative urine or cervical swab for gonorrhoea and chlamydia within 12 months of recruitment.
- ▶ Willingness and ability to comply with trial procedures, including reporting of obstetrical outcomes after delivery.

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

Women will be excluded from the study if there was:

- ▶ Use of GnRH agonists or antagonists within 6 months of study start, except for antagonist use as part of an IVF cycle.
- ▶ Use of depot medroxyprogesterone acetate (MPA) or subdermal contraceptive implant (eg, Implanon or Nexplanon) within 10 months of study start.
- ▶ Continuous use of oral progestins (MPA, norethindrone acetate) within 3 months of study start.
- ▶ Use of aromatase inhibitors, danazol or hormonal contraceptives (including combined contraceptive pill, progestin-only pill, transdermal patch or contraceptive ring) within 1 month of study start.
- ▶ Pregnancy greater than 8 weeks in length within the last 6 months.
- ▶ History of three or more prior IVF/ICSI attempts.
- ▶ Presence of hydrosalpinx >2 cm on ultrasound, untreated endometrial polyps, submucosal uterine leiomyomata or intrauterine adhesions.
- ▶ Abnormal cervical cytology other than low grade within last year.
- ▶ History of malignancy within 5 years of the start of screening, except for adequately managed basal cell carcinoma and squamous cell carcinoma of the skin.
- ▶ History of suicide attempt within the last year of recruitment.
- ▶ Hypersensitivity to study drugs.

- ▶ Planned surgical treatment of endometriosis or planned surgery in the abdominal-pelvic area within the duration of the trial.
- ▶ Untreated abnormal prolactin or thyroid stimulating hormone (TSH).
- ▶ Presence of any condition for which pregnancy is precluded.

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

## Intervention

### GnRH antagonist pretreatment

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

### IVF treatment

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

The standard IVF treatment for the study will be a GnRH antagonist protocol (cetrotide or ganirelix). Gonadotrophin stimulation with recombinant human follicle stimulating hormone and menotropin (supplying 75 IU FSH and 75 IU LH activity per vial) will be started at a daily dose ranging 150–375 IU depending on patient characteristics including age, early follicular phase FSH, AMH, antral follicle count and BMI. Each patient will receive at least 75 IU of LH activity daily as part of the initial stimulation protocol to counteract the LH suppression by the GnRH antagonist. The oral GnRH antagonist will be discontinued at the start of stimulation; addition



of subcutaneous injections of GnRH antagonist will be based on each sites' standard IVF protocol. When at least two leading follicles measuring  $\geq 18$  mm are seen on ultrasound, the trigger injection of u-human chorionic gonadotrophin (hCG) (10 000 IU) or r-hCG (250 mcg) is administered, followed by oocyte retrieval 37 hours later. Depending on sperm parameters following preparation on the day of oocyte retrieval, fertilisation will be achieved either by conventional IVF or ICSI.<sup>34</sup>

### Embryo culture and transfer

ET is performed between days 3 and 5 of development depending on morphological assessment and the woman's age, following American Society for Reproductive Medicine (ASRM) guidelines allowing for transfer of up to two embryos, with an elective single ET preferred.<sup>35 36</sup> Preimplantation Genetic Testing for aneuploidy will be allowed. Frozen ETs are included in this study but must be preceded by the same pre-treatment with GnRH antagonist or placebo for 8 weeks, repeating the same treatment as initially assigned at randomisation. No more than two ETs will be performed under this protocol, limiting administration of study drug to a maximum of three 8 week courses (one prior to IVF and one prior to each ET).

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

### Randomisation

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

- ▶ Elagolix 200 mg two times per day daily for 8 weeks prior to undergoing IVF.
- ▶ Placebo, two times per day daily for 8 weeks prior to undergoing IVF.

A computer-generated randomisation list will be created by staff at the PREGnant Data Coordinating Centre (DCC) and randomisation will be performed prior to the first dose of elagolix or placebo. Randomisation will have random sizes (2, 4 or 6) of blocks, stratified by site and age group ( $< 35$  vs  $\geq 35$  years). Randomisation sequences within each study site and age stratum will be generated randomly and independently. The randomisation list will not be available to any person involved in the conduct and evaluation of the trial until the trial is complete and database is declared clean and is released by the DCC. Randomisation and treatment allocation will be initiated by study staff according to the randomisation list

following enrolment and prior to the first dose of elagolix or placebo, but participants, investigators, trial staff and central laboratory personnel will be blinded to the treatment assignment during the trial duration (except for serious safety concerns). The assigned treatment (GnRH antagonist vs placebo) applied during the fresh cycle will also be used for subsequent frozen ETs resulting from the initial 'fresh' egg retrieval cycle. Most women using elagolix menstruate in the first 2 months with only a 50% amenorrhoea rate after 1 year in the phase III clinical trial, enabling blinding to remain intact.

### Outcome measures

The primary outcome measure will be live birth rate per cycle start, defined as live birth at  $\geq 24$  weeks of gestation. As a secondary outcome measure, we will also analyse the live birth rate per ET.

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

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

Finally, quality of life will be assessed using the FertiQOL, a validated questionnaire that contains Emotional, Mind/Body, Relational and Social domains.<sup>37</sup>

### Statistical analysis

#### Sample size and power calculations

The average live birth rate for women with endometriosis undergoing IVF is estimated to be 39%, based on 2016 SART data showing a live birth rate of 44.7% per cycle in women with endometriosis under the age of 35% and 34.0% in women ages 35–37. Using 386 participants per arm ( $n=772$ ) would provide an alpha of 0.05 and power of 80% to detect an effect of 10% absolute improvement in live birth rate to 49% in the GnRH antagonist arm. This effect is conservatively estimated from prior randomised trials using GnRH agonists,<sup>28–30</sup> and what investigators deemed to be sufficient to recommend the routine use of GnRH antagonists in IVF protocols for this population. However, we acknowledge that the study may be underpowered to detect smaller but still relevant

effects (5%–10% improvement). We will aim to enrol and randomise 814 participants (407 per treatment group), to account for an estimated drop-out rate of 5%.

### Analysis of outcome measures

An intention-to-treat analysis will be performed on primary and secondary outcome measures. The primary outcome, cumulative live birth rate, will be compared between the two intervention arms using Pearson's  $\chi^2$  test of independence. Baseline patient characteristics and secondary outcome measures will also be analysed with Pearson's  $\chi^2$  test and logistic regression as needed.

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

### Safety and adverse events monitoring

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

### Patient and public involvement

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

### Ethics and dissemination

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

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

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

The trial is conducted in accordance with relevant regulations and standard operating procedures, including data protection. Each subject is assigned a unique code for deidentification. Data will be collected electronically and

abstracted from the electronic medical record in a deidentified manner. Any medical information that is obtained in connection with this programme that could identify a subject will remain confidential and will be disclosed only as required by law. All persons responsible for the quality control of the data take all necessary precautions to ensure the confidentiality of information regarding trial participants and in particular the identity of the participants and the results obtained. The final trial dataset will be available to study investigators and Research Ethic Boards at all participating sites. Results of the trial will be published in peer-reviewed journals. We will submit data and samples collected by the trial to the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Data and Specimen Hub (DASH). The informed consent will include permission to bank these samples. The processes included initial data and documentation preparation (eg, codebooks, protocols, informed consent for data sharing), data quality control and submission.

### Trial status and registration

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

### Author affiliations

<sup>1</sup>Obstetrics, Gynecology & Reproductive Sciences, Yale School of Medicine, New Haven, Connecticut, USA

<sup>2</sup>Obstetrics and Gynecology, Northwestern University, Evanston, Chicago, USA

<sup>3</sup>Obstetrics and Gynecology, University of Colorado, Denver, Colorado, USA

<sup>4</sup>Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

<sup>5</sup>BioStatistics, Yale University School of Public Health, New Haven, Connecticut, USA

<sup>6</sup>Obstetrics and Gynecology, The University of North Carolina, Chapel Hill, North Carolina, USA

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

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

**Competing interests** None declared.

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

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible

for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iD

Howard J Li <http://orcid.org/0000-0002-1256-8723>

#### REFERENCES

- Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. *Obstet Gynecol Clin North Am* 2012;39:535–49.
- Taylor HS, Kotlyar AM, Flores VA. Endometriosis is a chronic systemic disease: clinical challenges and novel innovations. *Lancet* 2021;397:839–52.
- Verkauf BS, Incidence VBS. Incidence, symptoms, and signs of endometriosis in fertile and infertile women. *J Fla Med Assoc* 1987;74:671–5.
- Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility: a Committee opinion. *Fertil Steril* 2012;98:591–8.
- Hughes EG, Fedorkow DM, Collins JA. A quantitative overview of controlled trials in endometriosis-associated infertility. *Fertil Steril* 1993;59:963–70.
- Akande VA, Hunt LP, Cahill DJ, et al. Differences in time to natural conception between women with unexplained infertility and infertile women with minor endometriosis. *Hum Reprod* 2004;19:96–103.
- Healy DL, Breheny S, Halliday J, et al. Prevalence and risk factors for obstetric haemorrhage in 6730 singleton births after assisted reproductive technology in Victoria Australia. *Hum Reprod* 2010;25:265–74.
- Takemura Y, Osuga Y, Fujimoto A, et al. Increased risk of placenta previa is associated with endometriosis and tubal factor infertility in assisted reproductive technology pregnancy. *Gynecol Endocrinol* 2013;29:113–5.
- Vercellini P, Parazzini F, Pietropaolo G, et al. Pregnancy outcome in women with peritoneal, ovarian and rectovaginal endometriosis: a retrospective cohort study. *BJOG* 2012;119:1538–43.
- Conti N, Cevenini G, Vannuccini S, et al. Women with endometriosis at first pregnancy have an increased risk of adverse obstetric outcome. *J Matern Fetal Neonatal Med* 2015;28:1795–8.
- Fernando S, Breheny S, Jaques AM, et al. Preterm birth, ovarian endometriomata, and assisted reproduction technologies. *Fertil Steril* 2009;91:325–30.
- Stephansson O, Kieler H, Granath F, et al. Endometriosis, assisted reproduction technology, and risk of adverse pregnancy outcome. *Hum Reprod* 2009;24:2341–7.
- Mataliotakis IM, Cakmak H, Mahutte N, et al. Women with advanced-stage endometriosis and previous surgery respond less well to gonadotropin stimulation, but have similar IVF implantation and delivery rates compared with women with tubal factor infertility. *Fertil Steril* 2007;88:1568–72.
- Brosens I. Endometriosis and the outcome of in vitro fertilization. *Fertil Steril* 2004;81:1198–200.
- Olivennes F. [Results of IVF in women with endometriosis]. *J Gynecol Obstet Biol Reprod* 2003;32:S45–7.
- Terzic M, Aimagambetova G, Garzon S, et al. Ovulation induction in infertile women with endometriotic ovarian cysts: current evidence and potential pitfalls. *Minerva Med* 2020;111:50–61.
- Šalamun V, Verdenik I, Laganà AS, et al. Should we consider integrated approach for endometriosis-associated infertility as gold standard management? rationale and results from a large cohort analysis. *Arch Gynecol Obstet* 2018;297:613–21.
- Barnhart K, Dunsmoor-Su R, Coutifaris C. Effect of endometriosis on in vitro fertilization. *Fertil Steril* 2002;77:1148–55.
- Muteshi CM, Ohuma EO, Child T, et al. The effect of endometriosis on live birth rate and other reproductive outcomes in art cycles: a cohort study. *Hum Reprod Open* 2018;2018:hoy016.
- González-Comadran M, Schwarze JE, Zegers-Hochschild F, et al. The impact of endometriosis on the outcome of assisted reproductive technology. *Reprod Biol Endocrinol* 2017;15:8.
- Hamdan M, Dunselman G, Li TC, et al. The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis. *Hum Reprod Update* 2015;21:809–25.
- Barbosa MAP, Teixeira DM, Navarro PAAS, et al. Impact of endometriosis and its staging on assisted reproduction outcome: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2014;44:261–78.
- Senapati S, Sammel MD, Morse C, et al. Impact of endometriosis on in vitro fertilization outcomes: an evaluation of the Society for Assisted Reproductive Technologies Database. *Fertil Steril* 2016;106:164–71.
- Legendre G, Catala L, Morinière C, et al. Relationship between ovarian cysts and infertility: what surgery and when? *Fertil Steril* 2014;101:608–14.
- Alammari R, Lightfoot M, Hur H-C. Impact of cystectomy on ovarian reserve: review of the literature. *J Minim Invasive Gynecol* 2017;24:247–57.
- Diamond MP, Pellicer A, Boyers SP, et al. The effect of periovarian adhesions on follicular development in patients undergoing ovarian stimulation for in vitro fertilization-embryo transfer. *Fertil Steril* 1988;49:100–3.
- Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis: a Committee opinion. *Fertil Steril* 2014;101:927–35.
- Surrey ES, Silverberg KM, Surrey MW, et al. Effect of prolonged gonadotropin-releasing hormone agonist therapy on the outcome of in vitro fertilization-embryo transfer in patients with endometriosis. *Fertil Steril* 2002;78:699–704.
- Ozkan S, Arici A. Advances in treatment options of endometriosis. *Gynecol Obstet Invest* 2009;67:81–91.
- Guo Y-hong, Lu N, Zhang Y, et al. Comparative study on the pregnancy outcomes of in vitro fertilization-embryo transfer between long-acting gonadotropin-releasing hormone agonist combined with transvaginal ultrasound-guided cyst aspiration and long-acting gonadotropin-releasing hormone agonist alone. *Contemp Clin Trials* 2012;33:1206–10.
- Georgiou EX, Melo P, Baker PE, et al. Long-Term GnRH agonist therapy before in vitro fertilisation (IVF) for improving fertility outcomes in women with endometriosis. *Cochrane Database Syst Rev* 2019;2019. doi:10.1002/14651858.CD013240.pub2. [Epub ahead of print: 20 Nov 2019].
- Taylor HS, Giudice LC, Lessey BA, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. *N Engl J Med* 2017;377:28–40.
- Sallam HN, Garcia-Velasco JA, Dias S, et al. Long-Term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis. *Cochrane Database Syst Rev* 2006:CD004635.
- Practice Committees of the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology. *Intracytoplasmic sperm injection (ICSI) for non-male factor indications: a Committee opinion*. Birmingham, Alabama: American Society for Reproductive Medicine, 2020: 114. 239–45.
- Practice Committee of Society for Assisted Reproductive Technology, Practice Committee of American Society for Reproductive Medicine. Elective single-embryo transfer. *Fertil Steril* 2012;97:835–42.
- Practice Committee of the American Society for Reproductive Medicine. Electronic address: ASRM@asrm.org, Practice Committee of the Society for Assisted Reproductive Technology. Guidance on the limits to the number of embryos to transfer: a committee opinion. *Fertil Steril* 2017;107:901–3.
- Boivin J, Takefman J, Braverman A. The fertility quality of life (FertiQoL) tool: development and general psychometric properties. *Fertil Steril* 2011;96:409–15.