



Willingness of Women with Endometriosis Planning to Undergo IVF to Participate in a Randomized Clinical Trial and the Effects of the COVID-19 Pandemic on Potential Participation

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Abstract

The Pre-IVF Treatment with a GnRH Antagonist in Women with Endometriosis (PREGnant) Trial (clinicaltrials.gov no. NCT04173169) was designed to test the hypothesis that 60-day pre-treatment with an oral GnRH antagonist in women with documented endometriosis and planning an IVF cycle will result in a superior live birth rate to placebo. Eight hundred fourteen women are required from 4 national sites. To determine the feasibility of using an electronic medical record (EMR)-based strategy to recruit 204 participants at the Colorado site, we conducted a survey of women within the UHealth system. Eligible women, identified using relevant ICD-10 codes, were invited to complete a 6-question survey to assess planned utilization of IVF, potential interest in participation, and whether delays in treatment due to COVID-19 would influence their decision to participate. Of 6354 age-eligible women with an endometriosis diagnosis, 421 had a concurrent infertility diagnosis. After eliminating duplicates, 212 were emailed a survey; 76 (36%) responded, 6 of whom reported no endometriosis diagnosis. Of the remaining 70, 29 (41%) were planning fertility treatment; only 19 planned IVF. All 19 expressed interest in participation. COVID-19 delays in treatment were not considered as a factor affecting participation by 8/19; the remaining 11 felt that it would “somewhat” affect their decision. None reported that they would not consider participation because of COVID-19. EMR-based recruitment for an endometriosis clinical trial is feasible although the overall yield of participants is low. Delays in treatment due to COVID-19 did not appear to overly influence potential recruitment.

Keywords GnRH antagonist · Endometriosis · Infertility · In vitro fertilization

Introduction

Endometriosis is a common gynecological condition, estimated to be present in 2–10% of women [1, 2], and is associated with reduced fecundity. Assisted reproductive technology improves the prognosis for eligible women with endometriosis, but higher cancelation rates [3] have been observed by some. The invasive nature of ovarian endometriosis [4] and the association of the disease with repeated surgery [5] also lead to a greater likelihood of diminished ovarian reserve. In addition to its effects upon the ovary, endometriosis is believed to result in deficient endometrial receptivity [6]. This relative infertility is attributed to abnormal development of the uterus (eutopic endometrium) and has been proposed to be treatable with estrogen deprivation therapy, using agents such as leuprolide acetate [7].

The “Pre-IVF treatment with a GnRH antagonist in women with endometriosis” randomized clinical trial (PREGnant)

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was devised to test the usefulness of elagolix, an orally active GnRH antagonist approved for the treatment of endometriosis-related pain [8], in the treatment of women with endometriosis prior to a planned cycle of in vitro fertilization (IVF). In order to recruit successfully for this trial, women with surgically diagnosed endometriosis or ultrasound-documented endometriomas need to be willing to be randomized to 60 days of treatment with elagolix or placebo prior to the onset of IVF cycle stimulation. Prior studies randomizing women with endometriosis to endocrine ablative therapy did not have access to an orally active GnRH antagonist, which is far more convenient to administer than previously used monthly or 3-monthly GnRH agonist regimens. A recent meta-analysis of GnRH-agonist trials totaled only 640 women and was inconclusive for a live birth outcome [9]. Importantly, in this meta-analysis, GnRH agonist use was required to be long term (at least 3 months). The PREGnant trial plans to randomize 814 participants from 4 national sites and will have superior power to detect a live birth outcome; moreover, duration of ovarian suppression will be shorter and it is therefore less likely to cause problems with ovarian response to IVF stimulation. In order to facilitate timely trial recruitment, it is important to determine both the prevalence and the willingness of potential participants to enroll into the trial.

The global pandemic of COVID-19 has further increased the urgency of effective recruitment into the PREGnant study, because initial IRB approval and study procedures were anticipated to have already been underway. However, the pandemic has led to several months' suspension of activity in most national IVF centers, including ours, as well as the suspension of clinical research. The pandemic-related shutdown led to a prolonged wait for patients intending to conceive via IVF and it was unclear if patients would be willing to wait the further 60 days required by the study protocol.

This study was planned to determine the willingness of women with endometriosis and concurrent infertility to participate in the PREGnant clinical trial. We identified women with the appropriate diagnoses encompassing both endometriosis and infertility and conducted a survey to determine which portion of these women intended to undergo IVF in the near future to conceive a pregnancy. We further surveyed women to determine whether or not the delay imposed on their fertility plans by COVID would have a negative impact on their enthusiasm for participating in the randomized PREGnant trial.

Methods

Parent Trial Details

PREGnant is a phase 3, NICHD-sponsored double-blind, placebo-controlled, randomized clinical trial (clinicaltrials.

gov no. NCT04173169) designed to test the hypothesis that a 60-day pre-treatment with an oral GnRH antagonist (elagolix 200 mg bid prior to initiation of stimulation and/or embryo transfer) in women with well documented endometriosis who are planning an IVF fertility cycle will result in a superior live birth rate to placebo. Participants are required to be aged 18–38, to have surgical or ultrasound diagnosed endometriosis (ultrasound diagnoses will be made locally and confirmed by central review by the protocol PI), and to have a normal uterine cavity assessment. In addition, participants are required to have a BMI of 18–38 kg/m² and adequate ovarian reserve as determined by AMH of 0.8 ng/ml or greater (based on the Bologna criteria for diminished ovarian reserve) [10]. Exclusions include 3 or more prior IVF attempts, presence of hydrosalpinx or untreated endometrial polyps or adhesions, untreated abnormal prolactin or TSH (based on local laboratory normal ranges or screening laboratory normal range at the University of Colorado, which is 0.45–5.33 uU/ml), history of malignancy within 5 years prior to enrollment, or planned surgical treatment of endometriosis within the expected duration of the trial. Exclusionary medications include GnRH agonists or antagonists within 6 months of study start, depot medroxyprogesterone acetate or etonogestrel birth control implants within 10 months of study start, or aromatase inhibitors, danocrine or hormonal contraceptives within 1 month of study start.

Upon enrollment, participants will be randomized 1:1 to either elagolix 200 mg or placebo bid for 2 months prior to IVF. Participants will undergo IVF and embryo transfer as per the usual protocols determined clinically at each of the 4 study sites, all of which are closely aligned in their protocols. Participants will receive FSH stimulation with GnRH antagonist mid-stimulation. All participants will receive some LH activity at the start and throughout the stimulation, since half of the participants will have been on GnRH antagonist and expected to have suppressed LH. Embryo transfers will follow the American Society for Reproductive Medicine guidelines [11]. Women who do not conceive in the initial IVF cycle or who are freezing all embryos for clinical reasons (e.g., undergoing preimplantation genetic testing for aneuploidy) will be offered a second course of elagolix prior to their transfer. Up to 2 embryo transfers preceded by study medication (either elagolix or placebo) will be allowed per participant.

Procedures

This study was reviewed by the Colorado Multiple IRB (20–1127) and considered exempt. We emailed a brief questionnaire to women in the appropriate demographic group within the University of Colorado healthcare system, who carried a diagnosis of endometriosis, based on ICD-10 codes. Using the SlicerDicer feature of the EPIC

electronic medical record (EMR), a list was generated of appropriately aged women with a diagnosis of any type of endometriosis (fallopian tube, lung, ovary, pelvic peritoneum, pelvis) as well as a diagnosis of infertility (female infertility of other origin, female infertility of tubal origin, female infertility, female infertility unspecified), who had been seen in UHealth facilities within the past 2 years. The initial search returned 6,354 patients with any endometriosis diagnosis and 421 women with a concurrent infertility diagnosis. Of the 421 women, 201 were eliminated as being duplicates, 1 was deceased, 1 had left the country, and 6 did not have an email address on record. This gave us a potential total sample size of 212 women (Table 1).

The following questions were included in the questionnaire:

1. Through our electronic medical records, you have been identified as an Ob/Gyn patient in the UHealth system who has both the condition of endometriosis and infertility. Is this correct?
2. Are you currently planning fertility treatment?
3. Does the fertility treatment you are pursuing include in vitro fertilization (IVF)?
4. If there were a study available that could help us improve the chances of IVF pregnancy in women with endometriosis that would take an extra 8 weeks of time prior to your IVF treatment, would you be willing to participate?
5. Most well-designed research studies include using an active treatment (the experimental treatment) and a placebo treatment (inactive substance that is formulated to look like the active, experimental treatment). Would you be willing to be in such a study, which includes the chance that you would be given an inactive treatment?
6. Has the delay of IVF treatments that occurred because of the COVID-19 crisis influenced your decision to consider a treatment that might take an extra 8 weeks prior to your IVF cycle?
 - a. Not at all
 - b. Somewhat
 - c. Very much

Table 1 EPIC electronic medical record review results using SlicerDicer tool

Women with endometriosis and one of four diagnoses of infertility	421
Eliminated as duplicate	201
Out of country	1
Deceased	1
No email address in medical record	6
Total number available for survey completion	212

The questionnaire was designed to end at the first instance the participant answered “no” for any question up to and including question 4. Questionnaires were emailed to women via the CU Denver version of REDCap [12] and responses were recorded directly into the REDCap database by the participants. The surveys were initially sent out in batches over 3 days, beginning 5/26/2020. Reminders were automatically sent once a week for 3 weeks. One final reminder was sent to all non-respondents on 6/25/2020. The study coordinator completed a form in REDCap indicating whether the participant was willing to participate in the proposed study or not. If the participant was interested in participating in the study, the coordinator recorded name, email address, and phone number in REDCap for recruitment purposes. The study coordinator further compiled the reasons participants gave if they were not interested in participating in the study.

Results (Fig. 1)

Questionnaires were emailed to 212 women; 76 questionnaires (36%) were completed in REDCap. Of those completed, 6 women (8%) reported an incorrect diagnosis recorded in the medical records, which left 70 possible study patients. Of those 70, 29 women (41%) were currently planning fertility treatment. Among the women planning to undergo fertility treatment, 19 (66%) indicated IVF was included in their fertility treatment plan. Of our possible 19 patients, all 19 (100%) said they would be willing to participate in a study that could help us improve the chances of IVF pregnancy in women with endometriosis even though it may take an extra 8 weeks of time prior to the IVF treatment. After it was further explained that a placebo would be involved and the participants may either receive the drug or placebo, 18 women (95%) were still interested in participating. This meant that of the original 76 responses, our maximal potential enrollment would be 18 women or 24% of those who responded.

As the women navigated through the questionnaire, if they answered “no” to any question up to and including question 4, the questionnaire automatically ended. We were able to determine a reason for non-participation based on how the questionnaire was answered. The number of women who would not or could not participate was 58 (Fig. 2). The reasons for non-participation were as follows: 6 women reported an incorrect diagnosis in the medical record; 42 women reported they were not currently pursuing fertility treatment; 9 women reported they were pursuing fertility treatment but not IVF; and 1 woman was unwilling to participate in a placebo controlled trial.

The final question asked, “Has the delay of IVF treatments that has occurred because of the COVID-19 crisis influenced your decision to consider a treatment that might

Fig. 1 Flow diagram of the survey

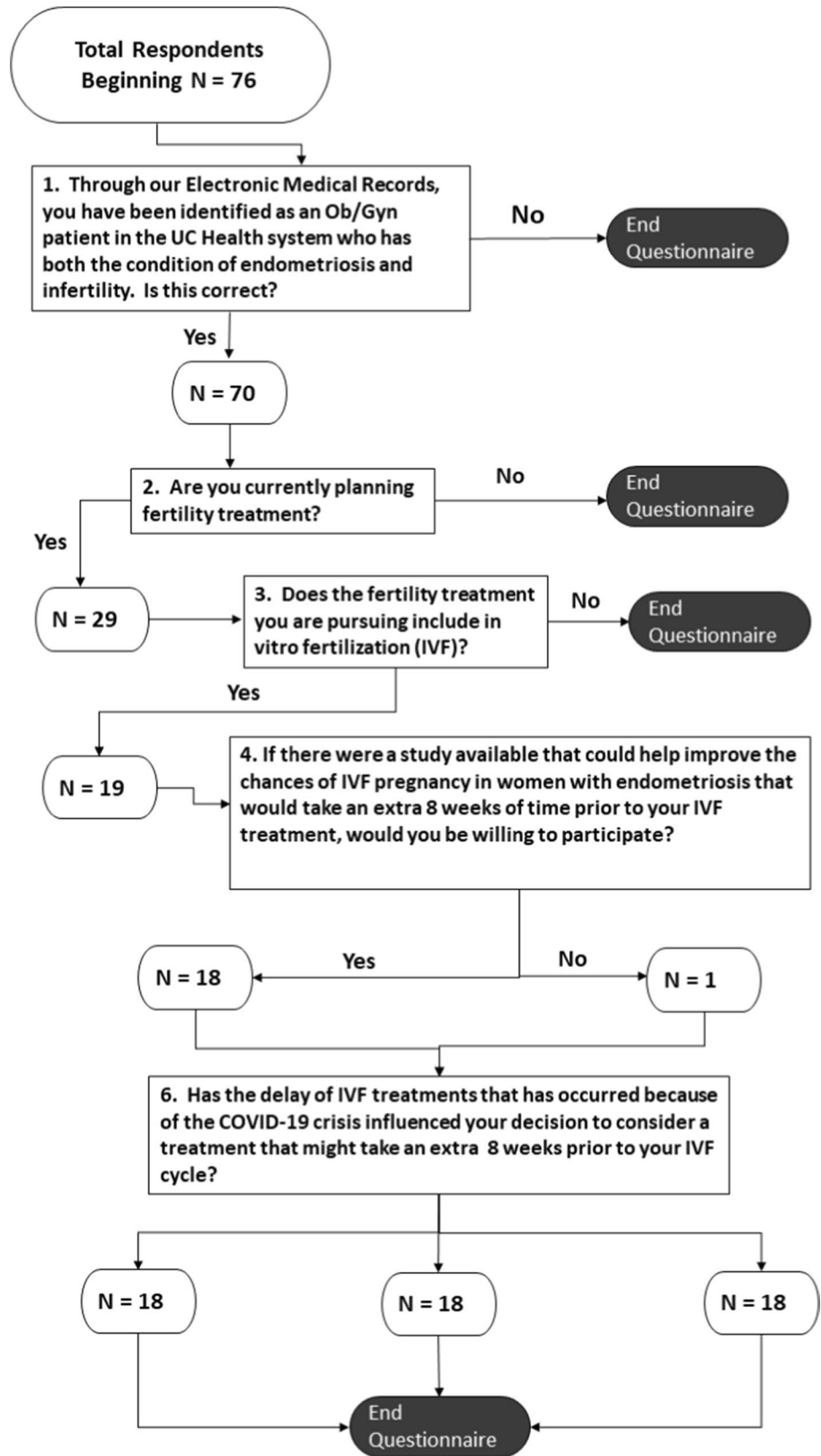


Fig. 2 Table of the survey questions

Question #	Question text
1	Through our Electronic Medical Records, you have been identified as an Ob/Gyn patient in the UC Health system who has both the condition of endometriosis and infertility. Is this correct? Y/N
2	Are you currently planning fertility treatment? Y/N
3	Does the fertility treatment you are pursuing include in vitro fertilization (IVF)? Y/N
4	If there were a study available that could help us improve the chances of IVF pregnancy in women with endometriosis that would take an extra 8 weeks of time prior to your IVF treatment, would you be willing to participate? Y/N
5	Most well-designed research studies include using an active treatment (the experimental treatment) and a placebo treatment (inactive substance that is formulated to look like the active, experimental treatment). Would you be willing to be in such a study, which includes the chance that you would be given an inactive treatment? Y/N
6	Has the delay of IVF treatments that has occurred because of the COVID-19 crisis influenced your decision to consider a treatment that might take an extra 8 weeks prior to your IVF cycle? a. Not at all b. Somewhat c. Very much

take an extra 8 weeks prior to your IVF cycle?." Of the 19 women who responded to this question, 8 (42%) indicated that COVID-19 did not influence their decision to consider study participation and 11 (58%) indicated that COVID-19 somewhat influenced their decision to consider participation.

Discussion

Herein we demonstrate the recruitment potential of women with endometriosis into a randomized clinical trial involving up to 60-day delay in IVF onset in order to accommodate the GnRH antagonist pre-treatment. Our findings indicate that the EPIC EMR is able to assist the clinical investigator in identifying appropriate patients, and that among the 19 women who were planning to undergo IVF and met the basic eligibility criteria, all reported willingness to consider participation. The COVID-19 pandemic appears to have exerted a somewhat negative effect on recruitment as 11/19 women reported that the pandemic would somewhat influence their decision to participate.

Our findings underscore the value and the limitations of using an EMR for recruitment purposes. On the one hand, the use of administrative data allows the clinical investigator to "cast a wide net" and capture as many potential cases as possible. One clinical trial that involved the recruitment of participants with type 2 diabetes mellitus was able to recruit 61.5% of their ultimate sample of 260 using the EMR [13]. These authors felt that EMR use was a far more efficient method than community-based screening but was less efficient than direct referral. On the other hand, an EMR cannot determine the plans of a patient or her willingness to pursue IVF in the near future. By using the survey, we were able to determine that, among respondents with endometriosis who

were planning IVF, all would consider participation. This is encouraging and suggests that use of the EMR may provide a valuable contribution to the recruitment totals needed for the study. However, given the overall low number of women available to participate among the large overall sample of age-eligible women, additional recruitment methods will likely be necessary to attain the total sample required from our site (204 women).

Interestingly, about half of the potentially eligible women indicated that the COVID-19 pandemic might pose a problem for their participation because the additional delay required by study treatment might make participation unacceptable. It will be of interest to understand better, over the coming months of recruitment, how and whether the global pandemic impacts clinical research more broadly or if this effect is confined only to certain geographic areas.

The COVID-19 pandemic has and will continue to impose substantial adversity on research and has limited clinical care for many gynecologic and fertility procedures [14]. Some suggestions specific to the IVF population have been made for alternative, low-cost treatments that may be protective against COVID infection [15]. COVID has already resulted in significant delays in clinical research recruitment [16]. The pandemic has delayed recruitment for this study by more than 1 year and therefore will compress our recruitment into a shorter time frame than anticipated. This means that any and all methods of recruitment need to be considered, and particularly low-cost methods, such as an EMR search described herein, may be especially valuable.

There are several strengths and limitations of this study. Among the strengths are the use of our internal healthcare system that has good population penetration within the Denver metro area (estimated at approximately 25%). Among the respondents, only 8% appear to have been incorrectly

classified as having endometriosis, indicating that ICD-10 coding was a relatively efficient way to identify potential participants. Our overall response rate was 36%, which is consistent with recent survey literature [17] and is substantially better than some internet survey response rates, including physicians [18]. Consistent with best practices, we supplied potential participants with several reminders and kept our survey as brief as possible to facilitate completion. Limitations include a lack of applicability beyond Colorado, as the data have not been compared to those in other regions or other sites. Additionally, we lack insight into why women did not respond. It is possible that they were not planning to pursue IVF and therefore found the survey not of interest, but their reasons for non-participation are not knowable. It is also possible that the positive response we saw in respondents may not reflect our true ability to recruit participants based on the more detailed risk versus benefit of participation discussion that will occur during screening. However, overall tolerance of elagolix appears to be very high [8]. In the pivotal elagolix trials, women with endometriosis noted improved pain after only 1 month and only 3% discontinued medication due to menopausal symptoms in the higher dose elagolix group (200 mg bid), which is the dose to be administered in the PREGnant trial.

Our findings indicate that an initial screen of participants will yield only a fraction of the total participants needed for completion of this trial. This is helpful information for a number of reasons. First, participants who are eligible and eager to participate, even if only 10% of the total needed, can be obtained very efficiently using our healthcare system's EMR. This decreases staff time commitment needed for screening and advertising costs. Once we are actively recruiting, we plan to utilize more traditional methods of recruitment: public service announcements, clinicaltrials.gov registration, advertising in local newspapers, radio and social media, and "snowball" recruitment (asking participants to identify friends or acquaintances with endometriosis through their social networks and support groups). We will also involve ancillary recruitment sites for this study in order to assure that we accrue participants as rapidly as possible.

In summary, we have demonstrated the ability of the EMR to serve as a source for participant recruitment for clinical trials in women with endometriosis. Our detection rate of endometriosis of 212/6354 age-eligible women in our healthcare system yielded a 3.3% prevalence of endometriosis concurrent with infertility, which is consistent with epidemiological data on the prevalence of both conditions [1, 19]. However, it is not possible to extract information from the EMR regarding a patient's intent to pursue IVF as a means to conceive within the time frame of recruitment needed for the PREGnant trial. The effect of COVID-19 on recruitment appears to be modest, but it remains to be seen whether participation will suffer from

the impact of this global pandemic and the associated time lag in couples being able to pursue assisted reproductive technology treatment.

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Availability of Data and Material Relevant data available upon request to the corresponding author.

Code Availability All code used is commercially available.

Declarations

Ethics Approval Exempt approval status was verified by the Colorado Multiple IRB (COMIRB).

Consent to Participate Participants voluntarily provided consent by completing the survey.

Consent for Publication All authors consent to publication of this manuscript.

Conflict of Interest SP, KK, LP, AP, JR, HZ, and NS report no relevant conflicts of interest. SY has served as a consultant to AbbVie. HST has received grant support to his institution from AbbVie.

References

1. Eisenberg VH, et al. Epidemiology of endometriosis: a large population-based database study from a healthcare provider with 2 million members. *BJOG*. 2018;125(1):55–62.
2. Morassutto C, et al. Incidence and estimated prevalence of endometriosis and adenomyosis in northeast Italy: a data linkage study. *PLoS ONE*. 2016;11(4):e0154227.
3. Kuroda K, et al. The impact of endometriosis, endometrioma and ovarian cystectomy on assisted reproductive technology. *Reprod Med Biol*. 2009;8(3):113–8.
4. Sanchez AM, et al. The distinguishing cellular and molecular features of the endometriotic ovarian cyst: from pathophysiology to the potential endometrioma-mediated damage to the ovary. *Hum Reprod Update*. 2014;20(2):217–30.
5. Shah DK. Diminished ovarian reserve and endometriosis: insult upon injury. *Semin Reprod Med*. 2013;31(2):144–9.
6. Lessey BA, Kim JJ. Endometrial receptivity in the eutopic endometrium of women with endometriosis: it is affected, and let me show you why. *Fertil Steril*. 2017;108(1):19–27.
7. Surrey ES, 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(4):699–704.
8. Taylor HS, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. *N Engl J Med*. 2017;377(1):28–40.
9. Georgiou EX, 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(11).

10. Younis JS, Ben-Ami M, Ben-Shlomo I. The Bologna criteria for poor ovarian response: a contemporary critical appraisal. *J Ovarian Res.* 2015;8:76.
11. Practice Committee of the American Society for Reproductive Medicine. Electronic address Aao, et al. ASRM standard embryo transfer protocol template: a committee opinion. *Fertil Steril.* 2017;107(4):897–900.
12. Harris PA, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377–81.
13. Effoe VS, et al. The use of electronic medical records for recruitment in clinical trials: findings from the Lifestyle Intervention for Treatment of Diabetes trial. *Trials.* 2016;17(1):496.
14. Carugno J, et al. COVID-19 pandemic. Impact on hysteroscopic procedures: a consensus statement from the Global Congress of Hysteroscopy Scientific Committee. *J Minim Invasive Gynecol.* 2020;27(5):988–92.
15. BezerraEspinola MS, et al. Inositol and vitamin D may naturally protect human reproduction and women undergoing assisted reproduction from Covid-19 risk. *J Reprod Immunol.* 2021;144:103271.
16. Sathian B, et al. Impact of COVID-19 on clinical trials and clinical research: a systematic review. *Nepal J Epidemiol.* 2020;10(3):878–87.
17. Harrison S, et al. Methods to increase response rates to a population-based maternity survey: a comparison of two pilot studies. *BMC Med Res Methodol.* 2019;19(1):65.
18. Cook DA, et al. Incentive and reminder strategies to improve response rate for internet-based physician surveys: a randomized experiment. *J Med Internet Res.* 2016;18(9):e244.
19. Ozkan S, Murk W, Arici A. Endometriosis and infertility: epidemiology and evidence-based treatments. *Ann N Y Acad Sci.* 2008;1127:92–100.