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Original Research

At-Home IVF Kit: application during the COVID-19 pandemic

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Summary

The guidelines, at the time of writing this manuscript, recommend withholding fertility treatments due to fear of the COVID-19. However, many fertility doctors and many patients, especially those with diminished ovarian reserve (DOR), strongly suggest that their fertility treatment including oocyte and/or embryo freezing is a time-sensitive matter due to fear of losing all their ovarian reserve. This report presents a novel approach for ovarian stimulation at home in women with DOR for oocyte/embryo cryopreservation using At-HOME IVF kit mailed to the patients' home, and without the need for blood hormones and transvaginal ultrasounds monitoring. In this study, women (n = 22) diagnosed with DOR who underwent either oocyte (n = 6) or embryo freezing (n = 16) were included. Each patient took the medications included in the kit without the frequent visits to the office for monitoring and presented only once to the fertility clinic on the day of the oocyte retrieval. Upon presentation on the day of oocyte retrieval, none of the patients had ovulated. All patients underwent oocyte retrieval with 21 out of 22 patients having had at least one or more oocytes collected, with the number of mature oocytes retrieved ranging from 1 to 7. Eight out of 16 patients (50%) who underwent IVF, had embryos cryopreserved at either the cleavage-stage or blastocyst stage. This report suggests that, during the COVID-19 pandemic, At-HOME IVF kit presents a novel solution for women with DOR, or in situations where time is of essence, limiting office visits and thus minimizing the risk of coronavirus infection.

Key words: IVF; Home; Coronavirus; COVID-19; Oocyte freezing; Pandemic.

Introduction

The coronavirus disease 2019 (COVID-19), also called the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), is rapidly spreading all over the world causing a serious global public health issue [1]. During this pandemic, access to fertility has been difficult due to fear of transmission of the virus from patient to patient or from patient to clinic staff members (or vice versa).

On March 17, 2020, the American Society for Reproductive Medicine (ASRM) released new clinical recommendations [2] stating that clinics: 1) do not initiate new treatment cycles — including ovulation induction, intrauterine insemination (IUI), in-vitro fertilization (IVF) (both oocyte retrievals and frozen embryo transfers), and non-urgent oocyte or embryo freezing, 2) strongly consider canceling all embryo transfers (fresh or frozen), 3) continue caring for people who are "in-cycle," or have urgent needs for stimulation or cryopreservation (oocyte or embryo freezing), 4) postpone elective surgeries and any non-urgent diagnostic procedures, and 5) prioritize telehealth over in-person contact. Additionally, the society for assisted reproductive technology (SART) recommended that anyone who is actively pursuing assisted reproductive technology (ART) and meets the diagnostic criteria for the COVID-19 infection consider freezing all oocytes or embryos and waiting until patients are disease-free to do an embryo transfer [3].

On March 19, 2020, the European Society of Human Reproduction and Embryology (ESHRE) recommended a precautionary approach and advised all infertility patients considering or planning treatment to avoid becoming pregnant at this time and they further suggested consideration of deferred pregnancy with oocyte or embryo cryopreservation [4]. Despite these recommendations and other experts' commentaries [5, 6], many fertility doctors and many patients (especially those older than 38 years old and those with diminished ovarian reserve [DOR]) strongly believe and expressed that their fertility treatment (i.e., oocyte and/or embryo freezing) is time-sensitive, even though it is not considered urgent care.

Given this challenging situation and in order to minimize the repeated office visits for monitoring during an IVF cycle, we aimed to test a new modality for IVF treatment using a kit called At-HOME IVF kit. This kit that contains all the necessary medications (oral pills, vaginal pills, and nasal spray) needed for ovarian stimulation, ovulation suppression, and oocyte maturation trigger. During the treatment cycle using the kit, patients did not do any monitoring for frequent blood hormone levels or any transvaginal ultrasounds for follicular measurement. Each patient needed to go to the office only once on the day of the oocyte retrieval procedure.

Methods

This is a retrospective case series study that assessed the response and outcome using the At-HOME IVF kit in

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Table 1. — *Description of the dose and mode of administration of the medications used in the HOME IVF kit based on the day of the menstrual cycle of the patient.*

CYCLE DAY	ORAL MEDICATIONS		NASAL SPRAY	VAGINAL SUPPOSITORIES	URINE OVULATION TEST
3	2 Clomiphene citrate tablets	2 Letrozole tablets			
4	2 Clomiphene citrate tablets	2 Letrozole tablets			
5	2 Clomiphene citrate tablets	2 Letrozole tablets			
6	2 Clomiphene citrate tablets	2 Letrozole tablets			
7	2 Clomiphene citrate tablets	2 Letrozole tablets			
8	2 Clomiphene citrate tablets				
9	2 Clomiphene citrate tablets			1/4 of Elagolix tablet	
10	2 Clomiphene citrate tablets				
11	2 Clomiphene citrate tablets			1/4 Elagolix tablet	Urine test (AM and PM)*
12			Leuprorelin (see Table 3 for details of use)		Urine test (AM and PM)*
13			Leuprorelin (see Table 3 for details of use)		Urine test (AM and PM)*

** The result of the urine ovulation test (ovulation predictor kit) should be "negative" on day 11 of the menstrual cycle but "positive" after administration of the Leuprorelin nasal spray.*

Table 2. — *Instructions on the use of the nasal spray trigger for oocyte maturation in the evening of cycle day 12 of the menstrual cycle.*

LEUPRORELIN NASAL SPRAY INSTRUCTIONS	
STEP 1	Administer 3 puffs per nostril
STEP 2	Wait 10 minutes
STEP 3	Administer 3 puffs per nostril

patients who have DOR (n = 22) based on previous history of poor ovarian response either at our center or at another fertility center, previously documented low serum anti-Mullerian hormone (AMH; < 1 ng/mL), previously documented elevated day 3 follicle-stimulating hormone (FSH; > 10 mIU/mL), or previously documented low antral follicle count by transvaginal ultrasound (AFC; < 8). Telemedicine was used for consultation, instead of an in-office visit, in order to reduce the total waiting time for seeking fertility treatment and in order to minimize exposure of patients to potentially infected individuals [7]. Each patient had a video details call with the physician in order to discuss her medical history, gynecologic/obstetric history, previous surgical history, medication intake, allergies, previous fertility treatment history, allergies, and social history. Exclusion criteria included irregular menstrual cycle or history of any medical conditions that prevent the intake of fertility drugs included in the kit. All patients underwent their fertility treatments at New Hope Fertility Center, New York from September 2019 until April 2020. The main outcome included the number of oocytes and embryos (cleavage-stage or blastocyst-stage depending on the patient's preference) cryopreserved. Because of the COVID-19 pandemic, embryo transfer was not currently recommended. Approval for the study was obtained from New England Institutional Review Board (NEIRB# 16-130). All

Table 3. — *Serum LH hormone level before and after the intake of the conventional Ganirelex/Cetrotide injectable medication versus the vaginal elagolix pi.*

	Serum LH level (mIU/mL) BEFORE medication intake	Serum LH level (mIU/mL) AFTER medication intake	% Drop in blood LH hormone level
Conventional Ganielex/Cetrotide injectables			
Patient 1	4.3	2	53.5%
Patient 2	12.0	6.3	47.5%
Patient 3	12.0	4.9	59.2%
Patient 4	18.0	16	11.1%
Patient 5	14.6	14.1	3.4%
Vaginal Elagolix pill			
Patient 1	7.0	1.0	85.7%
Patient 2	16.7	5.7	65.9%
Patient 3	10.2	3.2	68.6%
Patient 4	8.2	1.7	79.3%
Patient 5	7.0	0.8	88.6%

patients used the At-HOME IVF kit and did not do any monitoring for blood hormone levels or transvaginal ultrasounds for follicular measurement until the day of the oocyte retrieval.

Description of the At-HOME IVF kit

Table 1 describes the medications included in the kit and displays an exemplary medication schedule for at-home controlled ovarian stimulation method. The physician discussed (over the phone or over a video call) all the medication schedule included in the kit and then mailed the kit comprising all the needed medications to the patient's home.

Upon receiving the kit, on the start date (day 3 of the menstrual cycle), the patient was directed to orally take 100 mg of clomiphene citrate (Clomid®) and 5 mg of letrozole (Femara®), instead of the conventional daily injectable gonadotropins. The patient was then directed to take the same oral dosages of clomiphene citrate and letrozole daily on each of days 4-7 of the menstrual cycle. On day 8 of the menstrual cycle, the patient was directed to orally take only 100 mg of clomiphene citrate, and to stop the letrozole.

On day 9 of the menstrual cycle, the patient was directed to orally take 100 mg of clomiphene citrate and to insert vaginally the gonadotropin-releasing hormone (GnRH) antagonist elagolix (ORILISSA®). Elagolix has been used for treatment of endometriosis symptoms [8, 9] and recently used to suppress ovulation [10, 11], instead of the injectable ganirelix acetate (GANIRELEX®) or cetrorelix acetate (CETROTIDE®) used routinely in conventional practices. A dose of 50 mg ($1/4^{th}$ of a 200 mg pill) of Elagolix was used. On day 10 of the menstrual cycle, the patient was directed to orally take only 100 mg of clomiphene citrate.

On day 11 of the cycle, the patient was directed to orally take 100 mg of clomiphene citrate and to insert vaginally Elagolix tablet (50 mg) as a suppository. Also, on day 11, the patient was directed to take a home urine ovulation test (included in the kit) in the morning (9 am) and in the evening (9 pm) to ensure that there was no signs of early ovulation. The results of the urine ovulation tests on day 11 should both be negative. A negative urine ovulation test indicates that Elagolix was properly suppressing the luteinizing hormone (LH) surge from occurring. However, if the results of either ovulation test on day 11 was positive, indicating the patient is having an LH surge, then the patient was advised to contact the physician in order to schedule the oocyte retrieval on the following day.

On days 12 of the menstrual cycle, the patient was directed to take doses of leuprorelin (LUPRON®) dissolved in saline water as a nasal spray (1 : 20 to 1 : 40 dilution in saline, which is a total of 30 Units) prepared by a licensed pharmacist [12]. Leuprorelin is available as a leuprolide acetate injection bottle containing 14 mg/2.8 mL. A 0.3 mL (30 Units) of the leuprolide acetate is added to 5.7 mL of sterile saline to a sterile nasal spray pump device to produce a 6 mL solution that produces 120 sprays. Thus, each spray contain 0.05 mL (6 mL/120 puffs) or 0.25 Units of leuprolide acetate. Conventionally, leuprorelin is administered as an injection to the muscle or under the skin of the patient. However, in the kit, leuprorelin was taken nasally by the patient [12]. Table 2 shows the details on the nasal spray use: 3 puffs (first step) of the nasal spray are self-administered by the patient per nostril, after 10 minutes of waiting (second step), the patient then self-administers 3 more puffs of the nasal spray per nostril (third step). Twelve hours later, the patient repeats steps 1 to 3.

On day 12 of the menstrual cycle, the patient was again

Table 4. — *The clinical outcome of women who underwent oocyte or embryo freezing using the At-HOME IVF kit.*

Patient number	Age	Treatment cycle	Number of large follicles (between 14-22 mm on the day of oocyte retrieval)	Number of total oocytes retrieved (GV, MI, and MII)	Number of immature oocytes (GV or MI) retrieved	Oocytes/embryos cryopreserved
1	43	Embryo freezing	8	7	1	2 blastocysts
2	34	Embryo freezing	4	2	0	1 blastocyst
3	44	Oocyte freezing	2	1	0	1 oocyte
4	34	Embryo freezing	4	4	2	no blastocyst formed
5	41	Oocyte freezing	4	2	0	2 oocytes
6	30	Embryo freezing	1	1	0	no blastocyst formed
7	43	Embryo freezing	1	1	0	no blastocyst formed
8	41	Embryo freezing	2	1	0	no blastocyst formed
9	43	Embryo freezing	4	4	0	1 cleavage-stage embryo
10	34	Embryo freezing	4	4	1	1 blastocyst
11	43	Oocyte freezing	5	2	1	1 oocyte
12	38	Embryo freezing	3	3	0	2 cleavage-stage embryos
13	46	Embryo freezing	3	3	0	no blastocyst formed
14	38	Embryo freezing	3	3	0	1 blastocyt
15	41	Embryo freezing	2	2	1	no blastocyst formed
16	45	Embryo freezing	2	1	0	no blastocyst formed
17	44	Oocyte freezing	1	0	0	none
18	37	Embryo freezing	3	1	0	1 blastocyst
19	43	Embryo freezing	5	4	0	2 cleavage-stage embryos
20	36	Embryo freezing	5	1	0	Oocyte discarded due to poor quality
21	42	Oocyte freezing	2	1	0	1 oocyte
22	38	Oocyte freezing	4	4	0	4 oocytes

directed to take a home urine ovulation test in the morning (9:00 am) and in the evening (9:00 pm). Both urine ovulation tests should be done before the nasal spray intake and both ovulation test results should be negative (for

the same reason as mentioned earlier on cycle day 11 of the menstrual cycle). The self-administration of the leuprorelin nasal spray should be done after 9:00 pm on that day.

On day 13 of the menstrual cycle, the patient is directed to take again a home urine ovulation test in the morning (9:00 am) and in the evening (9:00 pm). The results of the ovulation tests for the patient should be positive for both ovulation tests, indicating proper intake of the nasal spray as reflected usually by an LH surge, which is responsible for turning the urine ovulation test positive. If ovulation is not confirmed on day 13 (i.e., results of ovulation tests on day 13 are negative, which are most likely due to improper intake of the nasal spray), then the patient needs to contact the physician immediately, who will ask the patient to retake properly the nasal spray. If ovulation is confirmed on day 13 (i.e., results of the ovulation tests are positive), then on day 14 the patient presents to the clinic for the oocyte retrieval procedure.

Elagolix for prevention of ovulation

By blocking the GnRH receptor, Elagolix suppresses LH release by the pituitary gland and thus prevents LH surge [10, 11]. Elagolix is generally an oral medication (oral tablet), however in the present kit, it is taken mainly as a vaginal suppository but may be taken orally based on the patient's preference. In order to compare the efficacy of Elagolix on LH suppression, we compared the LH in 5 patients before (cycle day 9 on average) and after (cycle day 10 on average) the intake of Elagolix and in 5 women before and after the intake of the injectable ganirelix acetate (GANIRELEX®) or cetrorelix acetate (CETROTIDE®).

Results

Table 3 provides a comparison of the efficacy of conventional Ganirelex/Cetrotide injectables treatment for IVF in the 5 representative patients versus the Elagolix used in the kit described herein in the 5 representative patients. The results demonstrated that Elagolix showed excellent suppression of serum LH blood hormone levels.

Table 4 shows the age and the clinical outcome of women who underwent oocyte/embryo freezing using the At-HOME IVF kit. On the day of the oocyte retrieval, all patients had transvaginal ultrasound before the procedure and all follicles between 14-22 mm were considered "large" enough for puncture and collection. In all the participants, the number of large follicles that grew in response to the ovarian stimulation ranged from 1 to 8. According to the ultrasound results, none of the patients ovulated on the day of presentation for the oocyte retrieval. As seen in Table 4, all patients underwent oocyte retrieval with 21 out of 22 patients (95.45%) had at least one or more oocytes collected with the number of oocytes ranging from 1 to 7; one participant did not have any oocytes collected. Details on the number of immature oocytes including GV (germinal vesicle) and MI (metaphase I) are shown in Table 4. Eight out of 16 patients (50%) who underwent IVF had embryos cryopreserved at either the cleavage or blastocyst stage.

Discussion

This pilot study showed that the At-HOME IVF kit for oocyte/embryo freezing provides patients with the ability to limit the number of office visits during fertility treatment with an acceptable outcome. Further, because the oocyte/embryo freezing medications are administered in formulations that are not injectables (i.e., oral tablets, vaginal suppositories, and nasal sprays), patients can avoid the uncomfortable and painful injections used in traditional oocyte/embryo freezing medication regimens. Accordingly, the present kit provides a convenient, cost-effective, and pain-free medication regimen for patients seeking oocyte/embryo freezing during the COVID-19 pandemic or when time is of essence.

It has been recently suggested that, during the COVID-19 pandemic, the use of mild stimulation, GnRH antagonist control of the LH surge, GnRH agonist triggering, and single embryo transfer or freeze-all, are the first choice in this period for women entering IVF [6]; all of which are provided by the At-HOME IVF kit presented herein. For mild ovarian stimulation, the kit uses a combination of clomiphene citrate and letrozole; each of which works via a different mechanism to increase endogenous pituitary FSH hormone release. Indeed, recent data have shown that the combination of these two medications can yield great results with ovarian stimulation [13, 14]. For ovulation suppression, the kit uses the vaginal/oral GnRH antagonist pill Elagolix which showed in a pilot of 5 participants that it was able to suppress the LH serum level by up to approximately 88% (Table 3). Interestingly, vaginal Elagolix suppressed ovulation in 100% of the patients in our pilot, and the percentage of LH drop following vaginal Elagolix pill seems much higher than that observed with the traditional Ganirelex/Cetrotide injectable (Table 3). Larger scale studies are needed to compare the effectiveness of Elagolix pill to the traditional Ganirelex/Cetrotide injectable in the prevention of premature LH surge in IVF cycles. To our knowledge, only one study assessed the effect of Elagolix on ovulation suppression [10],however that study used a 28-day dose interval of Elagolix orally in order to mimic the intake the medication in women with endometriosis. Some studies have shown that medroxyprogesterone acetate (MPA) is effective as an oral treatment for the prevention of premature LH surge in IVF treatments [15-17]; however, we chose Elagolix over MPA for several reasons. First, the treatment protocols that uses MPA for the prevention of premature LH surge almost always require the use of injectable gonadotropins for ovarian stimulation [15-17] because MPA acts by inhibiting the hypothalamic-pituitary-ovarian (HPO) axis. Since the At-Home IVF kit relies on an intact HPO axis because it uses clomiphene citrate and letrozole for ovarian stimulation and because the kit does not contain the injectable gonadotropins, MPA was not a viable option for our kit. Second, most protocols that included MPA for the prevention of premature LH surge, have used HCG injection as a trigger for oocyte maturation due to

the fear that the GnRH agonist (such as Leuprorelin) might not work properly due to pituitary suppression by the MPA [15-17]. The At-Home IVF kit herein did not include any injections such HCG that does not come as nasal spray such as GnRH agonist. Third, MPA is taken for much many more days than Elagolix making it less patient friendly. MPA (1 pill daily for up to 12 days) is usually started with start of stimulation because the pituitary suppression needs continuous progesterone exposure [15-17]; while Elagolix in the kit herein is taken only twice (once on cycle day 9 and once on cycle day 11) which makes Elagolix potentially more patient friendly.

In the protocol included in the kit, it uniformly induces oocyte maturation using the leuprorelin nasal spray on the evening of cycle day 12 of the menstrual cycle because the majority of the participants had regular menstrual cycle averaging between 28 and 30 days, and because most women ovulates after cycle day 12 of their menstrual cycle. If oocyte maturation trigger was to occur beyond cycle day 12, this could constitute a risk of ovulation and the loss of the treatment cycle. Even though this protocol is not ideal for all patients undergoing IVF, the kit was standardized in this pilot study for ease of use by patients and for less confusion among the staff managing the patients. However, larger studies using more individualized protocols; i.e., different number of days of ovarian stimulation, different doses of clomiphene citrate (for example 1 or 3 pills daily instead of 2 pills) and letrozole (for example 1 or 3 pills daily instead of 2 pills) based on ovarian reserve, and different cycle day of oocyte maturation trigger, are needed in order to optimize outcome in different patient population such as women with good ovarian reserve, women with short/large menstrual cycles, women with PCOS, and women who need oocyte in vitro maturation.

Strength of our study included the convenience of proceeding with oocyte/embryo freezing in a global environment where “stay at home” is recommended in order to avoid virus transmission. The kit also offers a cost-effective treatment because it does not contain the expensive gonadotropin injectables such as Follistim, Gonal-F, or Menopur. For patients who are fearful of injections and repeated blood draws, the kit provides a great obvious advantage. Limitations of the study include the small sample size of patients, the lack of women with good ovarian reserve, and the lack of information on pregnancy rates. Additionally, the use of oral medications, rather than the injectable gonadotropins, could have yielded lower number of oocytes collected even though some studies showed that the use of gonadotropins does not necessarily improve the final outcome of IVF [18].

In summary, during a global health emergency and pandemic due to an infectious organism, oocyte and embryo cryopreservation can be performed without monitoring and without injectable medications using At-HOME IVF kit. This will allow patients with DOR the possibility of proceeding with fertility treatments with minimum exposure to office visits.

Author Contribution

Z.M. and J.Z. contributed to the literature search, drafting and revising the manuscript, and final approval of the submitted version.

List of Abbreviations

IVF, in vitro fertilization; DOR, diminished ovarian reserve; ASRM, American Society for Reproductive Medicine; IUI, intrauterine insemination; SART, society for assisted reproductive technology; AMH, anti-Müllerian hormone; ICSI, intracytoplasmic sperm injection; AFC, antral follicle count; FSH, follicle-stimulating hormone.

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Conflict of Interest

All authors have nothing to disclose.

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