Research Article ISSN 2639-9342

Gynecology & Reproductive Health

Use of Clomiphene Citrate as an Inhibitor of Ovulation in an Oocyte Cryopreservation Cycle

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Received: 10 Apr 2025; **Accepted:** 06 May 2025; **Published:** 16 May 2025

Citation: Shelby Howard, Elizabeth F Sutton, Briasha Jones, et al. Use of Clomiphene Citrate as an Inhibitor of Ovulation in an Oocyte Cryopreservation Cycle. Gynecol Reprod Health. 2025; 9(2): 1-4.

ABSTRACT

Objective: *To determine if Clomiphene Citrate (CC) is an effective option for inhibiting ovulation during controlled ovarian hyperstimulation for elective oocyte cryopreservation (OC). Design: We conducted a prospective, observational study in eight individuals undergoing ovarian stimulation wherein CC was used to prevent premature ovulation. The study was registered as a clinical trial (Reference ID: NCT05866068)*

Subjects: *Females (n=8) 18-42 years old and undergoing elective OC were eligible to participate. Individuals using tobacco or illicit drugs, with a history of infertility, undergoing cancer treatment, previous failed IVF, drug allergy to CC, hypertension, or history of migraines with aura were excluded.*

Main Outcome Measures: *The primary outcome was incidence of premature ovulation. Secondary outcomes include the number of oocytes retrieved, number of mature oocytes, and study-related adverse events.*

Results: *The average age was 35.75 ± 5.04 (range 26-41). Six participants were Caucasian, and two were Asian. The average body mass index (BMI) was 24.4 ± 4.5kg/m2 (range 20.1-31.3), and the average AMH was 3.78 ± 1.74 ng/mL(range 1.78-6.58). CC was well tolerated with no evidence of early ovulation. The total gonadotropin dose ranged from 1775IU to 4950IU. The peak LH ranged from 7.64 mIU/mL to 28.4 mIU/mL, and the peak progesterone ranged from 0.71 ng/mL to 4.11 ng/mL. The number of oocytes retrieved ranged from 7 to 24 with an average maturity rate of 87%.*

Conclusion: *CC prohibits ovulation during OC; however, transient higher LH levels noted in a few of the cycles may predispose to premature luteinization, or even ovulation, resulting in a canceled cycle.*

Keywords

Clomid, Egg retrieval, Oocyte cryopreservation, Ovulation inhibition.

Introduction

In vitro fertilization (IVF) has been used for over 40 years as an assisted reproduc-tive technology for treating infertility and providing reproductive autonomy. With advancing technology in cryopreservation, it is now possible to stimulate, retrieve, and freeze gametes and embryos for later use. Indeed, in 2012, the American Society for Reproductive Medicine recommended the removal of the experimental label from oo-cyte cryopreservation (OC). This allowed OC cycles to become a standard of care for individuals with conditions that threaten their ovarian reserve and

for those who wish to preserve their fertility electively [1].

Stimulation protocols for superovulation of oocytes for OC involve subcutaneous injections of gonadotropin-releasing hormone (GnRH) agonists or antagonists. This is to inhibit premature ovulation in response to the supraphysiologic recruitment of oocytes [2]. Agonist protocols are efficacious. However, they can require longer stimula-tion with more medication, increasing both cost and risk of ovarian hyperstimulation syndrome (OHSS) [2]. Furthermore, by nature of the downregulation of the GnRH receptor, patients require human chorionic gonadotropin (HCG) trigger. This trigger can increase the risk of OHSS, and at the very least, can result in more postretrieval dis-comfort. Antagonist protocols generally use less medication and allow for the option of a Lupron trigger which eases recovery; however, most formulations are subcutaneous injections and thus can be perceived as more burdensome. Indeed, even the oral an-tagonists that are currently under investigation are costly [3]. More recently, down-regulation with oral progesterone has been shown to be an efficacious and cost-effective option that is easy to administer with minimal side effects [4,5]. Nev-ertheless, due to the progesterone administration in the follicular phase, there is no op-tion for a fresh transfer of an embryo in [5]. Therefore, it is of interest to develop pro-tocols that are both less burdensome for patients and more cost effective.

Clomiphene citrate (CC) is a selective estrogen receptor modulator (SERM) [6]. CC selectively binds to estrogen receptors in the hypothalamus, pituitary, ovary, en-dometrium, and cervix producing estrogenic and anti-estrogenic effects [7]. In the hypothalamus and pituitary specifically, CC has an anti-estrogen effect, generating a stronger negative feedback signal which increases gonadotropin secretion. When given as a short course at the beginning of a menstrual cycle, it has been shown to be a safe and effective option for ovulation induction [7,8]. However, in theory, persistent use of CC would potentially inhibit the ovulatory surge of luteinizing hormone (LH) mid-cycle. To date, there are no studies published on the use of CC as an inhibitor of ovulation in ovarian stimulation despite numerous studies of its safe and effective use in other fertility treatment protocols.

The aim of this observational study is to determine if daily CC is a novel option to inhibit ovulation during a standard stimulation for an egg retrieval in an OC cycle. The primary outcome is the incidence of premature ovulation, defined as elevation of LH or progesterone above baseline , loss of follicles on ultrasound during stimulation, or free fluid in the posterior cul-de-sac on transvaginal ultrasound that would signify premature ovulation. Secondary outcomes include the number of oocytes retrieved, number of mature oocytes, and study-related adverse events. We hypothesized that oral administration of daily CC during ovarian stimulation for OC will inhibit ovula-tion. To test our hypothesis, we conducted a prospective observational study of eight patients undergoing elective OC. Participants underwent ovarian stimulation with continuous CC as the mechanism to prevent ovulation in place of the current standard of care.

Materials and Methods

A prospective observational study was designed to determine if daily CC is a novel option to inhibit premature ovulation during controlled ovarian hyperstimulation. Individuals receiving treatment at a Reproductive Endocrinology & Infertility clinic in southern Louisiana who were 18-42 years old and planning to undergo ovarian stimu-lation for elective OC were offered to participate. Exclusion criteria included use of tobacco or illicit drugs, history of infertility or undergoing cancer treatment, previous-ly failed IVF or OC cycle, drug allergy to CC, hypertension, or history of migraines with aura. Participants in the study received a $500 stipend at the conclusion of the study. The study was approved and monitored by the Woman's Hospital Institutional Review Board, and informed consent was obtained prior to the initiation of study procedures. The study was also registered as a clinical trial with the NIH (Reference ID: NCT05866068).

Participants underwent transvaginal ultrasounds and lab evaluation of estradiol, LH, and progesterone to monitor their stimulation,. Hormone levels were evaluated using a Beckman Coulter hormone assay from blood sampled during the stimulation phase, approximately three to five monitoring visits within a 2-week period, as per standard of care. Post retrieval outcomes were documented. The primary outcome was premature ovulation defined as elevation in LH or progesterone, loss of follicles, or free fluid within the posterior cul-de-sac on transvaginal ultrasound noted at any moni-toring visit prior to retrieval. A predefined limit on the level of LH or progesterone was not set a priori as this was an investigational pilot study; rather, the recording of peak LH and progesterone levels were considered along with the overall oocyte yield and maturity rate to elucidate if premature ovulation were to have occurred. Additional outcomes included the number of oocytes retrieved, the number of mature oocytes, and any observed or self-reported adverse events. Maturation rate was calculated by the number of metaphase II (MII) oocytes divided by the total number of oocytes retrieved.

Patients underwent OC stimulation with mixed dosing of gonadotropins for con-trolled ovarian hyperstimulation with dosing determined by the physician of record. In place of typical medications for ovulation inhibition, participants were prescribed CC 100mg orally daily during the stimulation beginning on stimulation day 1 and ending on day of trigger. 100mg dose is a mid-range dose chosen because it is well studied with a good side effect profile considering an investigational study of this nature [9]. Leuprolide acetate 4mg and approximately 1800IU of hCG were used to trigger ovu-lation. Oocyte retrieval was performed under transvaginal ultrasound guidance. A 17 gauge needle was passed across the wall of the vagina and inserted into each follicle to puncture and to aspirate the follicular fluid which was then passed to the embryology laboratory to locate oocytes contained in the follicular fluid were isolated and ulti-mately cryopreserved. Eight patients enrolled in the study, and their demographics are summarized in Table 1. The mean age was 35.8 ± 5.0 years (range 26-41 years). All the participants had a college degree or higher

level of education completed and had private health insurance. Seventy-five percent of the participants were Caucasian. The average BMI was 24.4 ± 4.5kg/m^2 (range 20.1-31.3) and average AMH was 3.78 ± 1.74 ng/mL (range 1.78-6.58).

Table 1: Demographics of patients included in the study.

	Age	AMH	Race	Degree	Insurance	BMI
1	37	2	Asian	More than a college degree	Yes	22.31
2	32	6.58	Asian	More than a college degree	Yes	20.12
3	41	5.1	Caucasian	College degree	Yes	31.32
4	39	1.78	Caucasian	More than a college degree	Yes	23.11
5	35	4.3	Caucasian	College degree	Yes	23.56
6	41	5.1	Caucasian	College degree	Yes	31.32
7	35	2.5	Caucasian	College degree	Yes	20.42
8	26	2.9	Caucasian	More than a college degree	Yes	22.63

Results

Effect of Clomiphene Citrate on Primary and Secondary Outcomes

The outcomes of the study are summarized in Table 2. One participant had a transient elevation in LH of 28 mIU/mL at one monitoring visit, though the oocyte yield was appropriate for her ovarian reserve with a maturity rate of 100%. Four participants had a progesterone level above 3 ng/mL, however each also had appropriate oocyte yields with acceptable maturity rates. Therefore, it is concluded that there was no evidence of early ovulation among study participants.

CC was used for 9 to 12 days to prevent ovulation. The total gonadotropin dose ranged from 1775 IU to 4950 IU. The peak LH ranged from 7.64 mIU/mL to 28.4 mIU/mL and the peak progesterone ranged from 0.71 ng/mL to 4.11 ng/mL. The number of oocytes retrieved ranged from 7 to 24 with an average maturity rate of 87% with a range of 68% to 100% (Table 2). The medication was well tolerated with no documented adverse effects.

Discussion

Clomiphene Citrate is a well-tolerated and affordable medication that appears to sup-press ovulation when taken throughout controlled ovarian hyperstimulation The yield for oocytes was acceptable with similar maturity rates comparable to outcomes seen in other stimulation protocols. However, there was evidence of , transient elevation in LH noted during some of the stimulation cases that warrants further consideration. LH is the trigger for maturation and ovulation of the oocyte and luteinization of the sup-porting granulosa cells. Therefore, premature exposure to LH at significant levels may predispose the granulosa cells supporting folliculogenesis to shift to a more post-ovulatory profile prior to complete development of the oocyte, thus impairing the full potential of each oocyte resulting in a fertilized embryo and subsequent live birth. The exact threshold of LH levels is not known and likely variable across cycles. As such, threfore it is common practice to monitor LH levels during IVF stimulation with the goal of keeping LH levels quiescent until the point at which ovulation is desired. A prior study found similar results in GnRH antagonist cycles with concurrent use of CC where there were significantly higher LH levels in both follicular and luteal phases when compared to GnRH antagonist cycles without CC [10]. Giles et al. [11] noted low-er LH levels in stimulation using medroxyprogesterone acetate compared with an an-tagonist protocol and postulated lower LH levels could lead to improved oocyte quali-ty. In this regard, it may be that CC may not sufficiently blunt LH pulsatility ,possibly posing a risk of premature luteinization of developing follicles [11]. It is unlikely to be the case that there are clinical factors from the patient side that predispose to prema-ture ovulation in the case of the observed higher LH levels in this cohort of patients. Rather, it is probable that in the setting of hyperstimulation for an IVF cycle, clomi-phene alone may be insufficient to prevent intermittent pulses of LH during the stim-ulation. These intermittent higher ranges of LH would be directly responsible for premature luteinization of the follicles. Further studies to clarify true significance of these levels, and which patients are at risk, would be helpful in steering future directions.

There are several strengths and limitations of this study. One strength is that it is a novel study, and no prior research has been done on this topic. Another strength is that CC was a well-tolerated medication with an acceptable side effect profile. The

Table 2: Stimulation Outcomes.

	Days of Clomid	Total GND (IU)	Peak E2 (pg/mL)	Peak LH (mIU/mL)	Peak P4 (ng/mL)	Oocytes Retrieved	Mature oocytes	Maturity Rate (%)
1	11	4950	1370	8.82	0.71	7	7	100
2	9	1775	9363	15.98	3.12	24	21	87.5
3	9	3375	4297	11.06	2.57	19	19	100
4	11	4500	4698	16.00	2.15	19	13	68.4
5	9	3000	3849	28.40	2.60	20	20	100
6	11	4125	4552	13.16	4.11	19	16	84.2
7	12	4500	2649	7.64	3.22	10	8	80
8	11	4500	1329	1.84	3.44	28	22	78.6

GND: Gonadotropin, E2: Estradiol, LH: Luteinizing Hormone, P4: Progesterone.

most significant limitation of this study is that it was developed with a homogenous pop-ulation of limited numbers of participants and lack of control group. Although, given the exploratory nature of the observational study, this was an appropriately sized co-hort for this investigation. Ultimately, an oral agent that can adequately inhibit ovula-tion without altering the endometrial environment to allow for fresh embryo transfer would allow for improved flexibility of care for patients that may be candidates for a fresh transfer while keeping costs at a minimum. At present, the only oral option is medroxyprogesterone as an ovulation inhibitor which is inexpensive and easy to ad-minister compared to the injectable GnRH agonists and antagonists that have been standard of care for years. However, the use of medroxyprogesterone in the follicular phase precludes the option of fresh embryo transfer, thus requiring a subsequent treatment cycle for a frozen embryo transfer in all cases. CC may represent an option that is still affordable and easy to use, thus retaining excellent patient compliance, without prohibiting the option of fresh transfer.

Conclusions

Clomiphene citrate does inhibit ovulation during oocyte stimulation cycles; how-ever, with the higher levels of transient LH throughout the cycles, premature lutein-ization and potentially overt ovulation may result in a canceled cycle. With further research, alternative dosing strategies, or perhaps other SERMs, could be cost effective alternatives to standard ovulation inhibitors.

Grant Funding

Foundation for Woman's: Pilot and Feasibilty Study Grant.

References

1. Mature oocyte cryopreservation: a guideline. Fertil Steril. 2013; 99: 37-43.
2. Al-Inany HG, Youssef MA, Aboulghar M, et al. Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. In: Al-Inany HG, ed. Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd. 2011.
3. Boniface C, Schnorr JN, Gray J, et al. The role of elagolix in the suppression of ovulation in donor oocyte cycles. FS Rep. 2023; 4: 179-182.
4. La Marca A, Capuzzo M. Use of progestins to inhibit spontaneous ovulation during ovarian stimulation: the beginning of a new era? Reprod Biomed Online. 2019; 39: 321-331.
5. Massin N. New stimulation regimens: endogenous and exogenous progesterone use to block the LH surge during ovarian stimulation for IVF. Hum Reprod Update. 2017; 23: 211-220.
6. Wallach EE, Adashi EY. Clomiphene citrate: mechanism(s) and site(s) of action-a hypothesis revisited. Fertil Steril. 1984; 42: 331-344.
7. Use of clomiphene citrate in infertile women: a committee opinion. Fertil Steril. 2013; 100: 341-348.
8. Hughes E, Brown J, Collins JJ, et al. Clomiphene citrate for unexplained subfertility in women. Cochrane Database Syst Rev. 2010; CD000057.
9. Von Hofe J, Bates GW. Ovulation induction. Obstet Gynecol Clin North Am. 2015; 42: 27-37.
10. Tavaniotou A, Albano C, Smitz J, et al. Effect of clomiphene citrate on follicular and luteal phase luteinizing hormone concentrations in in vitro fertilization cycles stimulated with gonadotropins and gonadotropin-releasing hormone antagonist. Fertil Steril. 2002; 77: 733-737.
11. Giles J, Alama P, Gamiz P, et al. Medroxyprogesterone acetate is a useful alternative to a gonadotropin-releasing hormone antagonist in oocyte donation: a randomized, controlled trial. Fertil Steril. 2021; 116: 404-412.