Sequential clomiphene/corifollitrophin alpha as a technique for mild controlled ovarian hyperstimulation in IVF: a proof of concept study

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Abstract

Purpose Mild controlled ovarian hyperstimulation (COH), combined with oocyte retrieval (OR) under local anaesthesia (LA), may provide low-impact IVF. Since a single injection of corifollitrophin alfa (CFA) provides 7 days of COH, we hypothesised that clomiphene-citrate (CC) followed by CFA may provide adequate COH response from one single FSH injection. Therefore, the aim was to assess IVF outcomes after a novel clomiphene citrate/CFA (CC/CFA) protocol, compared to women undergoing standard rFSH COH protocols (good prognosis comparative cohort:GPCC) in a 1:2 matched design.

Materials and methods In this pilot study of 25 patients (ANZCTR id:ACTRN12612000740897, MINIVA:Minimal Stimulation in IVF), we examined the effectiveness of oral clomiphene (100 mg-days 2–6) followed by CFA in a GnRH antagonist protocol producing a single injection COH stimulation regime. All OR were conducted under LA pre-ovarian block. Cycle outcomes were compared to a matched good prognosis comparative cohort (GPCC) undergoing standard rFSH COH.

Results Mild stimulation was achieved with less oocytes being collected compared to the GPCC (6.4 ± 0.7 vs. 10.7 ± 0.9 , $p < 0.001$), resulting in a reduced number of good quality embryos available for transfer/cryopreservation (3.7 ± 0.6 vs. 5.7 ± 0.5 , $p = 0.01$). While embryo quality was similar between the two groups, endometrial thickness was significantly lower in the group receiving CC/CFA. Pregnancy rates were significantly lower in the CC/CFA cohort compared to GPCC (31.8 vs. 57.1%, $p = 0.04$) and 44% of CC/CFA participants required supplemental rFSH in order to achieve the hCG trigger criteria.

Conclusion Sequential clomiphene CFA protocol does not appear to be an optimal regime for low impact IVF treatment as it does not provide adequate COH from a single CFA injection and results in lower fresh embryo transfer pregnancy rates and fewer embryos for cryopreservation.

Keywords Clomiphene · Corifollitrophin alfa · IVF · Controlled ovarian hyperstimulation

Introduction

Recently many providers of IVF services in Australia have commenced offering “low impact/low cost” IVF treatment

characterised by milder Controlled Ovarian Hyperstimulation (COH) as a means of providing a more low-cost “patient friendly” IVF treatment protocol. The use of a lower than usual dosage of FSH during COH produces fewer patient side effects (pain, bloating) and enables the oocyte retrieval to be comfortably performed under local anaesthetic since fewer follicles are punctured, thereby reducing theatre costs. The collection of fewer oocytes also reduces work load for embryology staff, which when combined with reduced theatre costs (no sedation, oocyte retrieval conducted in procedure room) enables clinics to offer significantly reduced fee IVF compared to traditional treatment. This is a significant advantage for many couples who cannot afford traditional IVF.

Low-impact IVF is currently performed by administering daily FSH stimulation at dosages that are typically 25–50% reduced compared to traditional COH protocols [1, 2].

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However, with the advent of corifollitrophin alpha (CFA), a long acting FSH stimulant, a new alternative protocol has become possible. A single dose of CFA is capable of providing adequate COH stimulus for 7 days and therefore potentially holds the promise of providing adequate COH from a single injection, especially if the goal of treatment is only a moderate number of mature oocytes, as is the case in low-impact IVF. Recent large randomised controlled trials have reported that corifollitrophin alpha (CFA) is an effective stimulant for controlled ovarian hyperstimulation in IVF (COH), producing pregnancy rates equivalent to traditional rFSH, but requiring significantly fewer COH stimulant injections [3, 4]. While no RCT study has confirmed a patient preference for once-a-week stimulant over traditional daily rFSH approach, surveys do suggest that women prefer fewer injections provided that this approach does not compromise their IVF outcomes [2].

Previous studies have reported that a single dose of CFA is capable of providing adequate COH stimulus for 30% of good prognosis patients without the need for any additional daily FSH “top up” injections [5]. As our aim was to create a single injection (CFA) mild COH protocol, we decided to investigate if commencing clomiphene citrate stimulation before administration of CFA could result in the majority of patients reaching the criteria for hCG trigger without the need for any daily FSH “top-up” stimulation. Clomiphene citrate has been widely used as an IVF stimulant in the past [6], but is now rarely used as it is incapable of producing a COH response comparable in oocyte number to traditional FSH preparations [7, 8], thereby resulting in reduced pregnancy rates [9]. Conversely, clomiphene does have the advantage of being able to be administered orally, with only minimal side effects and an extremely low risk of OHSS. However, clomiphene cannot be relied upon to produce endogenous FSH stimulation once a GnRH antagonist is commenced since that treatment also blocks endogenous FSH production. Therefore some form of exogenous FSH stimulation such as CFA is optimally required from the point of initiation of GnRH antagonist therapy [7].

It is proposed that a sequential COH protocol consisting of initial clomiphene stimulation (days 2–6), followed by CFA (day 6 onwards) may be capable of providing adequate COH response from a solitary gonadotrophin injection, while also reducing the likelihood of an excessive response. By starting the COH using oral clomiphene, two potential advantages are anticipated. Firstly, the initial 4 days of FSH stimulation are provided by clomiphene, meaning that a single injection of CFA on the night of day 6 is more likely to be able to provide adequate ovarian stimulation without the need for “top up” supplemental daily FSH. Secondly, by delaying the administration of CFA until the sixth day of the IVF cycle, it is hoped that many small follicles will undergo atresia and be

unresponsive to CFA stimulation, thereby reducing the chances of developing an excessive response.

Prior to commencing this study, all oocyte retrievals in our unit were conducted under sedation. As such, a secondary outcome of this study was to investigate how patients undergoing the CC/CFA protocol would tolerate egg retrieval under local anaesthetic. Assessment of patient acceptance of this alternative approach was important as it would allow further cost reduction by minimising anaesthetic and recovery costs.

The primary objective of the MINIVA study (**M**inimal Stimulation **I**VF) was to conduct an initial pilot feasibility study to determine if a single injection COH can be adequately achieved using a sequential clomiphene/CFA approach in at least 80% of patients, while still producing adequate pregnancy rates compared to women undergoing standard COH protocols. The secondary objective was to determine patient acceptability for conducting oocyte retrievals under local anaesthetic using this mild COH approach.

Materials and methods

Good prognosis patients (age < 38 years, AMH between the 25th and 75th percentile for age, first or second cycle of IVF, use of ejaculate sperm only) were recruited for the CC/CFA regime from a private infertility treatment unit in Adelaide, Australia (Repromed), between December 2012 and October 2015. Only first or second cycle patients were included as the literature demonstrates that pregnancy rates significantly decline from the third stimulated cycle, thereby minimising the potential for selection bias [10]. Patients with a diagnosis with PCOS or an antral follicle count greater than 20 (2–10 mm) were also excluded from undergoing CC/CFA protocol as per the manufacturer guidelines for the use of CFA (MSD, Australia). The outcomes of this regime were compared to match women (age and BMI) undergoing standard COH protocols at the same time (good prognosis comparative cohort:GPCC) in a 1:2 matched design.

Patients COH commenced with a daily oral dose of 100 mg clomiphene citrate (Clomid, Sanofi-Aventis, Sydney, Australia) on the morning of days 2 to 6 of their menstrual cycle [11]. Higher doses of clomiphene citrate were not used as these have been linked to reduce endometrial thickness and were therefore avoided [12]. On the evening of day 6, a single dose of 100 mgm (patients < 60 kg) or 150 mgm (patients ≥ 60 kg) of CFA was administered subcutaneously as per the manufacturer’s guidelines (MSD, Sydney, Australia) [13]. Ovulation was suppressed using a daily dose of GnRH antagonist (250 µg Orgalutran, MSD, Sydney, Australia) from day 7 of the cycle (day 6 COH) and a pelvic ultrasound plus endocrine assessment (E2, P4) made on either day 9 or 10 of the cycle. If the criteria for hCG trigger were not met on Day 9/10, a follow-up scan and blood test were performed 2 days

later. Once two or more follicles reached 17 mm or greater, an hCG “trigger” injection (250 µg Ovidrel, Merck Serono, Sydney, Australia) was administered and oocyte retrieval performed 36 h later. If the criteria for triggering was not achieved by the end of the CFA stimulation (day 13), “top up” daily rFSH (Puregon, MSD, Sydney, Australia) was administered at a dose of 150 IU daily until these criteria were achieved.

All oocyte retrievals were performed under pre-ovarian local anaesthetic block with fentanyl analgesia, as previously published [14]. Typically 6 ml of 1% plain lignocaine was infiltrated into the vaginal wall under ultrasound guidance at the point where the oocyte retrieval needle was to later enter the ovary. Patients were given 40 mcg of fentanyl (AstraZeneca, Macquarie Park, Australia) prior to infiltration of lignocaine, followed by 20 mcg intravenous boluses as required to a maximal dose of 100 mcg in total. Pain scores experienced during oocyte retrieval were assessed 20 min after exiting from theatre using a visual analogue score of 0 to 100 (0 = no pain, 30 = mild, 50 = moderate, 70 = severe, 100 = unbearable pain) [15]. GPCC patients underwent OR under sedation using a combination of propofol, midazolam and fentanyl analgesia, and therefore, no pain scores were assessed from this cohort as they were completely sedated during OR.

Fertilisation was conducted by either IVF or ICSI, as dictated by semen quality. Embryos were cultured to day 4 or 5 using sequential culture system (G-1 PLUS/G-2 PLUS: Vitrolife, Goteborg, Sweden) before the best quality embryo was selected for transfer, with the remaining good quality embryos being vitrified (Rapid-I system: Vitrolife). Luteal support was provided using either nightly vaginal progesterone (Crinone 8%, Merck Serono, Sydney, Australia) if nine or more oocytes were collected in order to minimise ovarian hyperstimulation risk, or a single sub-cuticular injection of 1500 IU hCG (Pregnyl, Merck Serono, Sydney, Australia) on the fourth and seventh day of the luteal phase if fewer than nine oocytes were collected [16].

Pregnancy was confirmed with a serum β HCG, 16 days following oocyte retrieval in the absence of menses, and a pregnancy scan conducted between 7 and 8 weeks gestation.

A good prognosis comparator cohort (GPCC) having standard COH IVF in the same week as the CC/CFA cohort was generated by retrospectively matching patient maternal age and BMI in a 2:1 ratio. The purpose of this GPCC was to provide the reader of an indication of typical IVF and pregnancy outcomes in a comparable prognosis group using traditional rFSH COH protocols within our IVF unit. In this GPCC, rFSH was commenced on day 2 of the cycle (Puregon; Merck Sharp and Dohme (MSD) NSW or Gonal F; merck Serono, NSW, Australia), with starting dosage determined by patient age, prior IVF response, antral follicle count and anti-mullerian hormone level. The majority of patients in this GPCC started on 150–250 IU/day of rFSH. On

the sixth stimulation day, a GnRH antagonist was commenced (250 µg Orgalutran, MSD, NSW) which was taken every day until hCG administration. After 7 days of gonadotrophin stimulation, serum oestrodial was measured and a pelvic ultrasound was performed to assess ovarian response and the gonadotrophin dose was adjusted accordingly. The patient was scheduled for a hCH trigger (Ovidrel, Merck Serono, NSW) when at least 2× lead follicles were observed at 17–20 mm in diameter.

As this was a pilot proof of concept study, no formal power analysis was conducted. It was proposed that an initial pilot study examining the outcome of 25 completed cycles of IVF in a good prognosis patient group should be capable of giving some indication if clomiphene/CFA is a useful COH regime. The a priori-defined standards of success were:

- Creation of at least four mature oocytes per cycle. This number was felt to be sufficient to allow the creation of at least one good quality embryo for transfer (assumption 70% fertilisation rate, 40% of embryos good quality by day of transfer).
- Those IVF cycles requiring the administration of supplemental daily FSH stimulation after day 13 (end of CFA stimulation action) would be deemed treatment failures from the perspective of not allowing for single injection COH. We decided that the use of supplemental FSH stimulation in > 20% of participants would suggest this modified COH protocol is not an effective form of single injection COH in the vast majority of patients.

Patient demographics, hormone parameters, day of OPU, blood and scan data as well as embryology parameters were statistically analysed using univariate general linear model where the differences between years were assessed using the least significant difference method via GraphPad Prism Software V 5.02 (GraphPad Software, La Jolla, CA, USA). All other proportion data (such as infertility diagnosis and pregnancy) were assessed using Chi-square (National Science Foundation, Arlington, VA, USA) or Fishers exact test (Graphpad). Statistical significance was set at $p < 0.05$. This project was reviewed and approved by the relevant institutional ethics review board (WCH approval number REC2438/12/14), our internal clinic scientific advisory committee and all participants provided written informed consent. In addition, the trial was registered on ANZCTR with the trial identity being as follows: ACTRN12612000740897.

Results

Patient baseline characteristics are outlined in Table 1 with the only significant difference being that the experimental arm of the study had a slightly longer duration of infertility compared

Table 1 Patient baseline characteristics

	CC/CFA	GPCC	<i>P</i> value
Characteristic	<i>n</i> = 25	<i>N</i> = 50	
Age	31.7 ± 0.8	31.4 ± 0.5	NS
BMI (kg/m ²)	25.4 ± 0.8	25.6 ± 0.6	NS
Duration of infertility	2.3 ± 0.3	1.6 ± 0.2	<i>p</i> < 0.01
Basal antral follicle count	15.5 ± 1.2	19.1 ± 1.3	NS
Gravida	0.5 ± 0.2	0.4 ± 0.1	NS
Parity	0.2 ± 0.1	0.3 ± 0.1	NS
Infertility diagnosis			
Male factor	44% (11)	54% (27)	NS
Endo	4% (1)	4% (2)	NS
Tubal	8% (2)	12% (6)	NS
Anovular	0% (0)	16% (8)	<i>p</i> < 0.05
Other	14% (7)	44.0% (11)	<i>p</i> < 0.01
Hormone concentrations			
Serum FSH (IU/L)	7.0 ± 0.3	7.4 ± 0.3	NS
Serum AMH (pmol/L)	22.3 ± 1.3	27.8 ± 2.0	NS

CC/CFA: MINIVA trial clomiphene citrate/corifollitrophin alpha cohort. GPCC good prognosis comparative cohort. Data is presented as mean ± SEM. *P* value represents statistical analysis between groups; NS no significant difference detected *p* > 0.05

to the good prognosis comparator cohort (GPCC) (2.3 ± 0.3 v 1.6 ± 0.2, *p* < 0.01). There was no significant difference between maternal age, ovarian reserve status (AMH and AFC), maternal BMI or gravida/parity, with most patients being nulliparous. However, the CC/CFA cohort had significantly fewer patients with an ovular infertility diagnosis, an expected finding given that PCOS was an exclusion criterion for this group (Table 1).

By day 9/10 of the cycle (3–4 days post CFA administration), none of the participants on the CC/CFA protocol had reached the criteria for administration of the hCG trigger injection. However, by day 11/12 (5–6 days post CFA administration), the majority of patients had several potentially mature follicles > 14 mm in size, but only 16% had reached the criteria for hCG administration by this stage. On average, the oocyte retrieval was conducted on day 15 ± 0.5 of the cycle, with 44% of participants failing to reach trigger criteria by day 13 and thereby requiring supplemental daily FSH stimulation. Of those patients who did require supplemental daily FSH injections, an average of 1.7 days (range 1–2 days) was used. In comparison GPCC patients had their OR on day 13.7 ± 0.2 (*p* < 0.01) and required significantly less scans. In addition, it should also be noted that patients undergoing the CC/CFA protocol had significantly reduced endometrial thickness at trigger compared to the GPCC (9.2 mm ± 0.4 vs 10.8 mm ± 0.9, *p* = 0.01).

Patient's assessment of the adequacy of analgesia during OPU under local anaesthetic was generally good, with the

average pain score on the VAS being 26/100 (range 0–80), with pain scores over 30 generally considered as clinically significant [15]. The time spent in post-operative recovery for the CC/CFA trial participants was on average 42 min (range: 31–64 min), which is significantly less than the average 97 min (range 70–155 min) spent in recovery by patients undergoing OR under full sedation in our unit.

The IVF outcomes for the study are summarised in Table 2. On average 6.4 ± 0.7 mature oocytes were obtained for the CC/CFA group which was significantly less than women on standard COH (10.7 ± 0.9, *p* < 0.01). Oocyte morphology, fertilisation rates and embryo utilisation rate (% embryos of sufficient quality to transfer or freeze) were not statistically different between the two study arms, although fewer oocytes from the CC/CFA group resulted in a significant reduction in the number of embryos created and significantly less patients had embryos cryopreserved. The majority (81.8%) of women on the CC/CFA protocol were able to generate at least one good quality D4/5 embryo (as defined by a grade 1 or 2) [17, 18] for transfer, with an average embryo grade for transfer also being comparable (1.8 ± 0.2 CC/CFA vs. 1.7 ± 0.2 GPCC).

The biochemical and viable clinical pregnancy rates per embryo transfer for the CC/CFA group were 31.8 and 27.3%, respectively, significantly less than the GPCC group (biochemical pregnancy rate of 57.1% and viable clinical pregnancy rate of 49.0% per transfer (Table 3: *p* < 0.05).

Table 2 Patient cycle characteristics and IVF laboratory outcomes

	CC/CFA	GPCC	<i>P</i> value
Characteristic	<i>n</i> = 25	<i>N</i> = 50	
Day of OPU	15.0 ± 0.5	13.7 ± 0.2	0.01
Average # scans	2.2 ± 0.2	1.6 ± 0.9	0.01
Average # blood tests	2.2 ± 0.2	2.1 ± 0.1	NS
# Follicles on day 8–10 scan	2.7 ± 0.5	9.2 ± 0.7	0.001
Patient requiring FSH top up	11 (44%)	N/A	–
P4 (nmol/L) at trigger	2.4 ± 0.2	2.6 ± 0.2	NS
Endometrial thickness (mm) at trigger	9.2 ± 0.4	10.8 ± 0.6	0.01
# Eggs OPU	6.4 ± 0.7	10.7 ± 0.9	0.01
# Inseminated	5.8 ± 0.7	9.1 ± 0.7	0.01
# Fertilised	4.2 ± 0.6	6.5 ± 0.5	0.01
% Fertilisation	68.1 ± 6.3	72.8 ± 2.4	NS
% Embryo utilisation/2PN	58.8 ± 6.4	56.9 ± 3.7	NS
% patients with freezing	56.0	76.0	0.05
# Supernumerary embryos	3.7 ± 0.6	5.7 ± 0.5	0.01
# Embryos frozen	1.9 ± 0.3	2.9 ± 0.4	NS
% OHSS	0.0	0.0	NS

CC/CFA: MINIVA trial clomiphene citrate/corifollitrophin alpha cohort. GPCC good prognosis comparative cohort. Data is presented as mean ± SEM. *P* value represents statistical analysis between groups; NS no significant difference detected *p* > 0.05

Table 3 Patient pregnancy outcomes

	CC/CFA	GPCC	P value
Patients with an ET	22	49	
% Grade 1 or 2 for ET	81.8% (18/22)	85.7% (42/49)	NS
+ve HcG	31.8% (7/22)	57.1% (28/49)	< 0.05
Clinical pregnancy	31.8% (7/22)	51.0% (25/49)	NS
+ve fetal heart	27.3% (6/22)	49.0% (24/49)	0.07
FET	11	17	
+ve HcG	63.6% (7/11)	41.2% (7/17)	NS
Clinical pregnancy	63.6% (7/11)	29.4% (5/17)	NS
+ve fetal heart	63.6% (7/11)	29.4% (5/17)	NS

CC/CFA: MINIVA trial clomiphene citrate/ corifollitrophin alpha cohort. GPCC good prognosis comparative cohort. Data is presented as mean $\pm$ SEM. Numbers in parenthesis indicate actual patient numbers. *P* value represents statistical analysis between groups; *NS* no significant difference detected $p > 0.05$

There was no significant difference in pregnancy rate between GPCC and CC/CFA cohort that subsequently underwent a frozen embryo transfer after a failed fresh transfer, although we acknowledge that this sub-group analysis is underpowered due to low number of pregnancies (Table 3).

Discussion

The results of this pilot study suggest that the use of a sequential CC/CFA stimulation protocol can result in reasonable fresh embryo transfer clinical pregnancy rates, although significantly lower than a matched patient cohort undertaking a standard stimulation regime. Given that fresh embryo quality and frozen embryo transfer pregnancy rates were similar between the two study groups, the observation of a lower fresh transfer pregnancy rate in the CC/CFA arm suggests the possibility that the CC/CFA protocol may impair endometrial receptivity. Traditional markers of endometrial receptivity such as endometrial thickness and serum progesterone levels on the day of trigger were measured and interestingly while serum progesterone levels were not statistically different, it was noted that the endometrial thickness in patients undergoing the CC/CFA protocol was significantly less than in GPCC patients. Previous studies have confirmed that the oestrogen antagonist effect of clomiphene can alter endometrial development and receptivity which may account for the lower fresh embryo transfer pregnancy rates in the women exposed to clomiphene [19, 20]. Finally, the fact that clinical pregnancy rates from frozen embryo transfers in the CC/CFA cohort were excellent suggests that the reduced pregnancy rates in the fresh transfers are likely related to impaired implantation than diminished embryo quality.

Since only half (56%) of the participants reached the hCG trigger criteria without requiring supplemental daily FSH

injections, the clomiphene/CFA protocol does not appear to hold the answer to patient friendly single injection COH. As all the participants in this study were good prognosis with normal ovarian reserve, it is likely that this outcome is the best case scenario for this type of COH protocol. In the general infertile population containing older and poor ovarian reserve patients, the need for supplemental rFSH injections is likely to be even higher than that observed in this study.

On average, only 3.7 supernumerary embryos were available to assess for cryopreservation (with only 1.9 being suitable) using the CC/CFA protocol, a number that is less than the GPCC cohort who had on average 5.7 supernumerary embryos available with 2.9 cryopreserved. While in the past, a reduction in the number of embryos available for slow freezing and later transfer may have been a reasonable trade-off for a reduced risk of OHSS because of the relatively poor embryo thaw survival and pregnancy rates associated with slow-freezing, this trade-off is no longer acceptable in the setting of the excellent pregnancy rates using embryo vitrification [21] and new effective tools for the prevention of OHSS such as GnRH agonist trigger [22]. As such, the CC/CFA protocol cannot be seen as an efficient form of IVF treatment compared to traditional rFSH COH protocols, especially when considering the cumulative pregnancy rate associated with the use of all fresh and frozen embryos generated from a single cycle of IVF.

While we acknowledge that a sample size of 25 participants is insufficient to make definitive comment regarding the ability of the combined CC/CFA protocol to completely avoid OHSS, the fact that participants made on average only 6.4 mature oocytes, with the maximal number of oocytes being 15, we feel that it is highly unlikely that the this COH protocol would result in severe OHSS. However, none of our study participants had PCOS, a known risk factor for the development of OHSS. Therefore, it is yet to be determined if CC/CFA is either safe or effective in this high-risk group of patients. However, we do not anticipate conducting such a trial as alternative techniques for avoiding OHSS such as tailored starting dose of rFSH using AMH assessment, GnRH agonist triggers are likely to be better treatment alternatives [22].

Patient acceptance of oocyte retrieval under local anaesthetic was excellent in the setting of a mild COH response, and since conducting this study, our clinic has expanded the use of local anaesthetic oocyte retrievals to standard higher dose COH and in general, found it to be an excellent method that is well accepted by the majority. While not a novel observation, the results of this study support the use of local anaesthetic as an effective technique for patient analgesia in oocyte retrievals which has the advantage of accelerating post-operative recovery and reducing costs.

In summary, we can see limited value for this sequential CC/CFA protocol for COH in IVF as it is unable to achieve the stated aim of single injection COH in the vast majority of patients (> 80%) and results in inferior pregnancy rates and

number of embryos available for cryopreservation than traditional CFA or daily FSH stimulation regimes. While we acknowledge that this protocol does result in a mild stimulation outcome with no or negligible risk of OHSS, we believe there are now better alternative therapies to avoiding this serious complication of IVF therapy. Our results do support the use of local anaesthetic as a viable alternative to sedation during oocyte retrieval, with significant benefits in terms of speed of recovery and associated cost savings.

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