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Original paper

A comparison of the use of clomiphene citrate and letrozole in patients undergoing IVF with the objective of producing only one or two embryos

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Abstract

***Aim*: The objective of this study was to compare the use of clomiphene citrate and letrozole in an IVF setting in which the objective was to produce only one or two embryos. Either clomiphene citrate or letrozole was used in conjunction with gonadotropins without the use of GnRH antagonists.**
***Methods*: Sixty-two patients received either clomiphene citrate or letrozole with low dose gonadotropins in 128 non-randomized treatment cycles. HCG was given when one follicle was at least 17 mm. Oocyte retrieval was done 34 hours later and fertilization was performed using ICSI.**
***Results*: There were no statistically significant differences in the number of large follicles produced, oocytes fertilized, endometrial thickness, clinical pregnancy rates, or delivery rates in patients taking letrozole compared to clomiphene citrate. More mature oocytes were retrieved after clomiphene citrate, but a subset analysis of patients undergoing both treatments did not support this difference. The only statistically different finding in both analyses was the peak estradiol levels during treatment, which averaged 516 pg/ml with letrozole and 797 pg/ml with clomiphene citrate (p = 0.005).**
Overall, the cancellation rate due to a premature LH surge was 5%. An average of 2.8 mature oocytes were recovered, 2.1 oocytes fertilized and 1.6 embryos were transferred. The overall clinical pregnancy rate per transfer was 25% (95% confidence interval 17.7% to 33.3%) and the overall live birth rate per transfer was 19.2% (95% confidence interval of 11.6% to 26.8%).
***Conclusions*: Other than peak estradiol levels, there were no clinically significant differences when letrozole or clomiphene citrate was used for mild ovarian stimulation for IVF. There were only rare cancellations because of premature LH surges.**

***Key words:* clomiphene citrate, IVF, mini-IVF, minimal stimulation IVF, natural cycle IVF, letrozole.**

Introduction

Approaches to IVF which use lower doses of gonadotropins than conventional IVF are becoming increasingly popular. In part, this is a reaction to the tactic in conventional IVF of creating as many mature oocytes as safely possible (Edwards, 1996). Maximizing the number of embryos to select for transfer has been highly effective, with reported pregnancy rates per cycle steadily increasing over the years (CDC, 2014). Recent adjuncts to the conventional IVF process include aneuploidy testing using microarray analysis, vitrification of excess embryos with transfer in an artificial cycle and the use of a time-lapse monitoring system for assessment of embryo growth patterns. These may continue to enhance the effectiveness of conventional IVF. However, they do so at a cost of increased complexity with its associated expense and increased challenges for the patient. On the

other hand, not all patients require nor desire the technologically leading edge highest pregnancy rate per cycle. Many would choose an easier, less expensive and more natural feeling approach if it is provided with a "reasonable" pregnancy success rate (Nargund et al., 2001).

Natural cycle IVF in which the power of IVF to retrieve oocytes, create embryos and transfer them back without modifying a woman's natural menstrual cycle has been an understandable response to this concern about the use of too much technology when only some aspects of IVF tools appear to be needed. Natural cycle IVF has been studied for many years, but the primary problem with its clinical application has been its high cycle cancellation rate often due to a premature LH surge (Pelinck et al., 2002).

Many programs have introduced modified approaches to the natural cycle by using either clomiphene citrate, low doses of gonadotropins or GnRH antagonists, resulting in some reduction of the cycle cancellation rate (Vogel et al., 2003). IVF performed without the aim of maximizing the number of embryos results in improved embryo quality (Baart et al., 2007). Minimal stimulation IVF has the objective of producing between 2 and 8 oocytes (Nargund et al., 2007, Zarek and Muasher, 2011). Most approaches to minimal stimulation IVF utilize GnRH antagonists to suppress the LH surge and enable more small follicles to mature in patients with adequate antral follicle (AF) counts (Verberg et al., 2009; Fauser et al., 2010). The combination of clomiphene citrate with low doses of gonadotropins has been studied in intrauterine insemination [IUI] programs (Houmard et al., 2002; Al-Inany et al., 2010). Cycle cancellation due to premature LH surges was uncommon and generally one to two mature follicles were produced (Rose, 1992; Houmard et al., 2002). This suggests that such an ovarian stimulation protocol applied to IVF might produce pregnancy outcomes between modified natural cycle IVF and minimal stimulation IVF using GnRH antagonists. The term "mini-IVF" was used for this strategy to differentiate the application of this protocol targeted to produce one or two embryos as opposed to minimal stimulation IVF and modified natural cycle IVF.

Perhaps more troublesome than premature LH surges is the problem of performing a retrieval in which no oocytes are obtained. This is an intervention without benefit to the patient that was performed at a significant financial cost. Informed by experience with in vitro maturation (IVM) IVF cycles this problem may be minimized by carefully aspirating smaller follicles than those typically thought to contain mature oocytes. Follicles with diameters as small as 12 mm may contain a mature oocyte in the setting where both gonadotropins and hCG have been used (Fadini et al., 2009; Rose, 2014a). Follicle flushing in the context in which there are only a few available follicles may also be beneficial (Rose, 2014b).

Clomiphene citrate for ovarian stimulation has been used for a very long period (Ecochard et al., 2000; Reindollar et al., 2009; Goldman et al., 2014). It works by blocking estrogen receptors in the pituitary and preventing or reducing the normal decline in FSH production as follicles in the ovary begin to produce estrogen. Letrozole also delays this decrease in FSH production in the pituitary by inhibiting estrogen production in the ovaries. In spite of its widespread use, clomiphene citrate has side effects that are worrisome in the context of advanced fertility treatment. Clomiphene citrate binds to estrogen receptors throughout the body, including the endometrium. It reduces growth of the endometrium compared to the natural cycle (Gonen and Casper, 1990; Young et al., 1999; Cortinez et al., 2005). Gene expression in endometrial cells after the use of letrozole is much closer to gene expression in the natural cycle when compared to clomiphene citrate (Wallace, 2011). Clomiphene citrate may also increase the miscarriage rate, perhaps by elevating LH levels (Saunders et al., 1992). Letrozole may improve endometrial receptivity in women whose endometrial linings are integrin negative (Miller et al., 2012). One may hypothesize that the use of letrozole may be less likely than clomiphene citrate to negatively influence the quality of the endometrium.

The primary aim of this paper was to compare the use of letrozole with clomiphene citrate in an IVF setting in which the objective was to produce one or two mature oocytes. A secondary objective was to evaluate the effectiveness of using a mild IVF ovarian stimulation protocol with oral agents and low dose gonadotropins without the use of GnRH antagonists.

Methods

Table I summarizes the mini-IVF ovarian stimulation protocol used in this study. All patients qualifying for IVF in the three-year period between July 2011 and June 2014 were potential candidates for this therapy. Patients were offered the opportunity to undertake this therapy, conventional IVF or IVF using in vitro maturation [IVM]. They were told that conventional IVF was the standard recommended therapy, was the most studied therapy and had the highest expected pregnancy rate per cycle. The advantages highlighted for mini-IVF were its

Table I. — Summary of our ovarian stimulation protocol (OC – oral contraceptives, US – ultrasound)

-3	2 or 3	3	4	5	6	7	8	9	10 to 14	hCG +0	hCG +2	hCG +5
Last day OC	Baseline US	2.5 mg Letrozole or 25 mg Clomiphene	2.5 mg Letrozole or 25 mg Clomiphene	2.5 mg Letrozole or 25 mg Clomiphene	2.5 mg Letrozole or 25 mg Clomiphene	2.5 mg Letrozole or 25 mg Clomiphene			SerialUS if needed	10,000 Units	Oocyte retrieval	Transfer
				hMG 75-150 IU	hMG 75-150 IU	hMG 75-150 IU	hMG 75-150 IU	hMG 75-150 IU	hMG 75-150 IU if needed			

lower cost and its patient-centered approach (fewer injections, fewer visits and less medication used). Patients with decreased ovarian reserve [DOR] were encouraged to undertake mini-IVF. Patients with total antral follicle [AF] counts ≥ 20 or anti-Mullerian hormone [AMH] levels ≥ 2 IU/ml were not included in the study population since these patients were offered the option of IVM if they wished a gentle form of IVF or conventional IVF using a relatively low dose of gonadotropins.

Patients were treated with continuous low dose oral contraceptives for cycle timing. On day 6 after stopping oral contraceptives, a baseline ultrasound was performed to exclude patients with follicle cysts greater than 12 mm in average diameter and to obtain a baseline LH level. Patients were given 25 mg of clomiphene citrate or 2.5 mg of letrozole for 5 days. Patients were also treated with 75 to 150 IU of hMG from day 8 after stopping oral contraceptives. After 5 days of gonadotropins, patients underwent another ultrasound evaluation and blood tests for LH and estradiol. Patients were given 10,000 IU hCG once there was a single follicle with an average diameter of at least 17 mm. Daily gonadotropins were given until the day of hCG and patients were seen daily or every other day until hCG was given or the cycle was cancelled due to inadequate response. Oocyte retrieval was performed 34 hours after hCG. Oocyte recovery employed an 18-gauge single lumen needle (Wallace needle, ONS1833LL-500, Smiths Medical, Kent, UK) using an aspiration pressure of 100 mm Hg. All follicles with a diameter of more than 12 mm were aspirated. An embryologist provided immediate feedback on oocyte recovery and if an oocyte was not recovered from a follicle 14 mm or greater, the follicle was flushed until an oocyte was recovered. Flushing was done using a hand held syringe for back flushing the bung of the needle set (Rose, 2014b).

All embryo transfers were performed on the third day after oocyte retrieval. Assisted hatching was performed on all patients greater than age 38 and in patients with an increased thickness of the zona pellucida. Androgen therapy was used in patients with decreased ovarian reserve for its theoretical benefit on primordial follicles (Vendola, 1998; Balasch et al., 2006; Barad and Gleicher, 2006;). Most patients with DOR also received hCG luteal support. These interventions were routine in our IVF program.

If a patient had a significant rise in her LH level from baseline, she was given hCG as soon as the LH level was available from the laboratory and the retrieval was performed the next morning following a routine aspiration schedule.

High quality embryos were embryos with 7 or 8 cells on day 3 with at most 10% fragmentation and without nuclear or cytoplasmic dimorphisms noted at any oocyte or embryo evaluation.

Statistics

The statistical tests used were the paired and unpaired t-test and the Fisher exact test. For the primary variables of live birth and clinical pregnancy rate, a p-value less than 0.05 was viewed as significant. For secondary variables, because of multiple comparisons, a p-value less than 0.01 was viewed as significant. Standard deviations were used to describe statistical variance.

Results

One hundred and twenty-eight cases were reviewed involving 62 patients. Demographic data on cases using letrozole and clomiphene citrate were not statistically different between both groups although the data suggested a trend of the clomiphene group being younger and having better ovarian reserve

Table II. — Demographic information of each group before starting therapy (AFC = antral follicular count, AMH = Anti-Mullerian Hormone)

	Letrozole (SD or %)	**Clomiphene** (SD or %)	**p value**[1]
Cases (number)	82	46	
Age (years)	38.3 (4.4)	36.2 (4.3)	0.010
BMI	27.6 (5.7)	29.2 (6.0)	0.138
Male factor	25 (34.1%)	18 (39.1%)	0.336
Endometriosis	21 (25.6%)	16 (34.8%)	0.312
AMH (IU/ml)	0.5 (0.4)	0.7 (0.5)	0.021
AFC	6.0 (3.7)	7.2 (3.9)	0.087

[1]Unpaired t-test or Fisher's exact test

Table III. — Use of letrozole compared to clomiphene citrate in cases with transfers

	Letrozole (% or SD)	**Clomiphene citrate** (% or SD)	**p value**[1]
Cases	62	42	
Age	38 (4.3)	36.3 (4.3)	0.050
AMH (IU/ml)	0.5 (0.4)	0.7 (0.5)	0.037
AFC	6.8 (3.8)	7.5 (4.0)	0.369
Gonadotropins used (IU)	831 (396)	829 (299)	0.978
Peak estradiol (ng/ml)	516 (430)	797 (577)	0.005
LH on day of hCG (IU/L)	2.8 (3.1)	3.0 (2.5)	0.728
Number of follicles ≥ 16 mm	1.9 (1.1)	1.7 (1.1)	0.365
Number of follicles ≥ 12 mm	3.1 (1.7)	3.5 (1.8)	0.253
Number of mature oocytes	2.4 (1.2)	3.3 (2.1)	0.007
Number of fertilized oocytes	1.9 (1.1)	2.5 (1.6)	0.025
Number of high quality embryos	0.9 (0.8)	1.3 (0.9)	0.019
Number of embryos transferred	1.5 (0.7)	2.5 (1.6)	0.001
Cases with a single embryo transferred	46 (74.2%)	18 (42.8%)	0.002
Endometrial thickness at hCG (mm)	7.5 (2.4)	7.9 (2.3)	0.398
Endometrial thickness at transfer (mm)	9.8 (2.1)	10.1 (2.1)	0.476
Clinical pregnancies	16 (25.8%)	10 (23.8%)	1.0
Live births	11 (17.7%)	9 (21.4%)	0.8

[1]Two sided unpaired t-test or Fisher's exact test

(Table II). Five cases were cancelled due to a premature LH surge prior to retrieval and seven cases were cancelled for failure to produce a follicle of at least 17 mm in diameter. An additional 11 cases were cancelled after retrieval, primarily for fertilization failure. Only two cases were cancelled for failure to retrieve mature oocytes and both of these were also associated with a premature LH surge. A total of seven cases (5%) were cancelled for having a premature LH surge (two after retrieval without mature oocytes) and an additional 4 cases had early retrievals for presumed LH surges with successful oocyte recovery. The total number of cases with presumed LH surges (retrieval within 24 hours, cancelled prior to retrieval, or cancelled after attempted retrieval) was 11 (8.6%).

Table III compares the results of treatment with letrozole or clomiphene citrate.

The peak estradiol level with letrozole was significantly lower compared to clomiphene citrate (516 pg/ml compared to 797 pg/ml; $p = 0.005$). The clomiphene citrate group also produced more mature oocytes ($p = 0.007$), which resulted in the transfer of more embryos ($p = 0.001$). However,

Table IV. — Use of clomiphene citrate compared to letrozole in 17 patients having both therapies (38 cycles)

	Letrozole	Clomiphene citrate	p value[1]
Age during cycle	36.6 (4.5)	37.1 (4.3)	0.593
Peak estradiol (ng/ml)	360 (212)	916 (673)	0.002
Number of follicles ≥ 16 mm	1.9 (0.8)	1.5 (1.2)	0.134
Number of mature oocytes	2.4 (1.4)	3.1 (1.9)	0.194
Number of fertilized oocytes	1.7 (1.2)	2.5 (1.8)	0.127
Number of high quality embryos	1.0 (1.0)	1.2 (0.9)	0.617
Number of embryos transferred	1.4 (0.7)	1.9 (0.9)	0.333
Cases with a single embryo transferred	10 (58.8%)	8 (47.1%)	0.732
Endometrial thickness at hCG (mm)	7.1 (2.2)	7.6 (2.2)	0.501
Endometrial thickness at transfer (mm)	10.2 (1.8)	9.9 (2.2)	0.635
Clinical pregnancies	3 (15.8%)	3 (15.8%)	1.0
Live births	2 (13.3%)	3 (15.8%)	1.0

[1]Two sided paired t test (pairing of cycles completed in time period closest to each other) and Fisher's exact test

this larger number of embryos transferred did not result in higher pregnancy rates. There was no difference in the endometrial thickness between the letrozole and clomiphene citrate groups either on the day of hCG or on the day of transfer.

There were 17 patients who were treated with both oral agents (some more than once). Those cycles in which treatments occurred temporally closest to each other were compared in Table IV. This comparison, which avoids the potential bias of patient selection for treatments, showed that except for estradiol levels, the treatments did not result in statistically different numbers of mature oocytes nor different embryo transfer numbers.

Combining the treatments (Table V), the average case with a transfer had 2.8 mature oocytes retrieved with 2.1 oocytes fertilized. An average of 1.7 embryos were transferred, but 51.9% had a single embryo transferred (two were transferred in 33.7%, three were transferred in 13.5%, and four were transferred in 1%). The average number of high quality embryos was 1.1. No embryos were cryopreserved. None of our patients experienced ovarian hyperstimulation syndrome.

The average case had 1.8 follicles greater than or equal to 16 mm and 3.2 follicles greater than or equal to 12 mm. The overall clinical pregnancy rate per transfer was 25% with a 95% confidence interval of 16.7% to 33.3%. The live birth rate per transfer was 20% with a 95% confidence interval of 11.6% to 26.8%. There was one set of twins (4.3%) (Table V).

Table V. — Summary for combined Mini-IVF approaches

	Number or mean (SD or percentage)
Cases with retrievals	114 (89.1%)
Cases with no oocytes retrieved after harvest	2 (1.7%)
Cases with failed fertilization after ICSI	9 (7.8%)
Cases with failed cleavage	1 (0.9%)
Cases requiring early retrievals	4 (3.1%)
Cases with embryo transfers	104 (81.3%)
Number of follicles ≥ 16 mm	1.8 (1.1)
Number of follicles ≥ 12 mm	3.2 (1.8)
LH on day of hCG (mIU/ml)	3.1 (3.1)
Endometrial thickness on day of hCG (mm)	7.7 (2.4)
Number of mature oocytes	2.8 (1.7)
Number of fertilized oocytes	2.1 (1.4)
Number of high quality embryos	1.1 (0.9)
Number of embryos transferred	1.6 (0.8)
Cases with single embryo transfer	54 (51.9%)
Implantation rate per embryo	35/190 (18.4%)
Clinical pregnancies per transfer	26 (25%)
Live births per transfer	20 (19.2%)
Multiple gestations (twins)	1 (4.3%)

Discussion

Overall, the use of either letrozole or clomiphene citrate produced similar results using the mini-IVF protocol described in Table I. Our choice of which oral agent to use for a given patient may have had a bias toward letrozole as the theoretically best agent (Young et al., 1999; Cortinez et al., 2005; Miller, 2012) and letrozole could have been preferentially

used in the poorer prognosis patients. Patients treated with letrozole were slightly older and had a lower AMH level than those treated with clomiphene (Table III). This can explain the increased number of mature oocytes, fertilized oocytes and embryos transferred in the clomiphene citrate treated group. However, this bias was eliminated in the subset analysis in which patients treated with both agents served as their own controls. The program had no control of the timing of treatments in patients who required multiple cycles and cycles closest to one another in time were chosen for the comparison. Results of this subset analysis did not suggest that even a very large randomized trial would produce a clinically and statistically significant advantage for the use of either agent. The only observation that was different in the subset analysis was the peak estradiol level. These findings were consistent with prior published comparisons of clomiphene and letrozole for use with IUI (Barroso et al., 2006; Bedaiwy et al., 2009).

Our mini-IVF cycles had pregnancy rates that were inferior to conventional IVF (CDC, 2014) and thus, in terms of pregnancy achievement alone, mini-IVF would be an inadequate replacement for conventional IVF. However, as an intermediate therapy between oral agents with IUI and conventional IVF, these pregnancy rates with mini-IVF are reasonable. Patients with unexplained infertility who fail to achieve pregnancy after use of clomiphene citrate and IUI are often advanced to treatment with gonadotropins with IUI. However, pregnancy rates with this treatment might be significantly lower than pregnancy rates with mini-IVF (Reindollar et al., 2009; Goldman et al., 2014). A randomized clinical trial would be required to demonstrate this hypothesis.

The protocol in this paper differs from the most common approaches to minimal stimulation IVF by using an oral agent, starting gonadotropins earlier and by avoiding the use of GnRH antagonists (Baart et al., 2007, Fauser et al., 2010; Zarek and Muasher, 2011). Our population had a large subset of patients with DOR (average AMH: 0.6 IU/ml).

The patient friendliness of this protocol largely speaks for itself. The average amount of gonadotropins used was 822 U and peak estradiol levels were 624 pg/ml. Once the cycle had started only 3.1 office visits, 3.0 blood samples and 7.0 subcutaneous injections were required. The lower and more predictable cost of this protocol compared to conventional IVF increases the pool of patients who may utilize IVF services (Smith et al., 2011). Patients may also appreciate the low rate of multiple births, avoiding the creation of many excess embryos and the need for cryopreservation.

The primary cost savings of this protocol was due to a decrease in the use of gonadotropins compared to conventional IVF. This was especially apparent in patients with decreased ovarian reserve who were numerous in the population studied. The laboratory work required was also decreased compared to conventional IVF since fewer eggs and embryos were involved. A reasonable estimate of the cost of a mini-IVF cycle was one-third to one-half of a conventional IVF cycle depending on the patient's gonadotropin requirement.

Both letrozole and clomiphene citrate had few cycle cancellations due to premature LH surges. Most cycle cancellations were associated with patients having severe DOR. Measurements of LH levels on the day of hCG were helpful in determining presumed LH surges.

Very few cycles were cancelled because of a failure to retrieve a mature oocyte even though in 55 cycles (48.2%) there was only one follicle with a diameter greater than 15 mm at the time of hCG. We attribute this both to aspirating all follicles with diameters ≥ 12 mm and to the use of flushing. Flushing was done in follicles ≥ 14 mm until an oocyte was recovered, flushing became impossible or flushing returned fluid with very limited number of granulosa cells. There are no randomized studies comparing successful retrieval with and without flushing in the setting of a very low number of follicles. However, theoretical considerations suggest that flushing should be efficacious in this setting (Rose, 2014b).

In 1997, Robert G. Edwards lamented in an editorial about the state and direction of ovulation induction for IVF. He made a number of suggestions, emphasizing "…the use of relatively minor modifications of the natural cycle, or mild forms, of priming follicles…" (Edwards, 1997). He was concerned both about what we were asking women to go through: "Can we avoid the complexities and costs… Are patients placed under needless stress by these prolonged protocols?" Additionally, he was concerned about theoretical and hard to discern risks associated with high doses of gonadotropins: "… suspect there could be as yet unrecognized factors in these complex and powerful endocrine treatments" (Edwards, 1997). More recently, some physician leaders have suggested that IVF technology has advanced to the point that a focus of research ought to be on the challenges of increasing global access to advanced infertility care (Johnson et al., 2014; Ombelet, 2014). This will require the development of simpler and less expensive applications of IVF technology (Van Blerkom et al., 2014). The use and further study of protocols such as the one presented here contribute both to

alleviating Dr. Edwards' concerns and developing protocols which can be used to help patients with limited resources.

Conclusion

This study demonstrates that the use of letrozole is not inferior to clomiphene citrate in low cost ovarian stimulation protocols for IVF. Other than peak estradiol levels, there appear to be minimal differences in how patients will respond to low dose stimulation using either clomiphene citrate or letrozole. With either oral medication there is only minimal risk of a premature LH surge requiring cancellation of the cycle. On average about three mature oocytes can be expected to be harvested and about two oocytes fertilized.

This study can be viewed as a proof of concept that gentle and inexpensive ovarian stimulation using letrozole or clomiphene citrate can be used in IVF programs with reasonable success rates. In our study the intention of producing one or two embryos was achieved and cycle cancellation for an LH surge was lower than for natural cycle or modified natural cycle IVF. The next step would be to organize a randomized prospective study to compare our mini-IVF strategy with gonadotropin-IUI therapy.

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