Clomiphene based ovarian stimulation in a commercial donor program

ABSTRACT

OBJECTIVE: This study was conducted to compare an extended clomiphene-based ovarian stimulation regimen with the conventional antagonist protocol in donor-recipient cycles. MATERIALS AND METHODS: A total of 170 (N) donors were stimulated between January 2013 and December 2013. Conventional antagonist protocol (group I) was employed in (n1 = 31) cycles, and clomiphene was used in (n2 = 139) donor cycles (group II). 50 mg clomiphene was given simultaneously with gonadotropins from day 2 of the cycle until the day of trigger. The analysis was performed retrospectively for oocytes retrieved, fertilization rates, cycle cancelation, blastocyst formation, and pregnancy rates. The dosages, cost, and terminal E2 (estradiol) were also compared between the two groups. RESULTS: The donor age groups were comparable in both the groups. There were no unsuccessful egg retrievals with clomiphene. The pregnancy rate (positive beta human chorionic gonadotropin) was significantly higher in the clomiphene group (odds ratio: 2.453; \( P = 0.02 \)). Similarly, fertilization rate was significantly higher in the clomiphene group (59.5/50.5, \( P = 0.04 \)). Eggs retrieved were similar in both groups, but the terminal E2 was significantly higher in the clomiphene group (\( P = 0.001 \)). Average gonadotropin used was also significantly lower in clomiphene group (\( P < 0.001 \)). CONCLUSION: Clomiphene can effectively prevent luteinizing hormone surge and limit the dose of gonadotropins thus bringing down the costs and its negative impact on the endometrium and oocyte quality.

KEY WORDS: Clomiphene, egg donors, oocyte retrieval

INTRODUCTION

Advanced age and delayed reproductive choices of women have led to increased use of donor oocyte in assisted reproduction. As a result, commercial oocyte donations have come into being. Donor stimulation should be cost effective and have minimal side effects with little risk of ovarian hyperstimulation syndrome (OHSS).

Controlled ovarian hyperstimulation combines the use of gonadotropins with luteinizing hormone (LH) suppressing agents. Gonadotropin-releasing hormone (GnRH) antagonist as compared to GnRH agonist is somewhat effective in cutting cost and reducing the duration of stimulation, this is not without the inconvenience of daily injections or the expense of antagonist itself. In addition, gonadotropins are used in high doses for prolonged durations, leading to increased costs and adverse effect on oocyte quality. [11]

Antagonist protocol, when used with GnRH agonist trigger, does reduce the risk of moderate to severe OHSS. The use of clomiphene seems another attractive alternative for donors as it may reduce the dose of stimulation and at the same time eliminate the need for the antagonist.
Clomiphene used in minimal stimulation protocols has been demonstrated to effectively suppress LH surge alone and with acceptable pregnancy rates in 20,244 cycles.[2] Yet, routine stimulation regimens do not incorporate clomiphene because of its feared negative effect on the endometrium.

In the present retrospective study, we attempt to evaluate clomiphene as compared to conventional injectable GnRH antagonists in donor-recipient cycles.

MATERIALS AND METHODS

A total of 170 donor stimulation cycles between January 2013 and December 2013 were included in this retrospective study. The procedures and analysis were carried out in concomitance with the Institutional Review Committee.

Conventional antagonist protocol was employed in n1 cycles in group I, and clomiphene was used in n2 donor cycles in group II. In group I, stimulation was started from day 2 with recombinant gonadotropins (75–225 IU) and GnRH antagonist was added when leading follicle reached 14 mm in diameter. In group II 50 mg clomiphene was given simultaneously with gonadotropins from day 2 of the cycle until the day of the human chorionic gonadotropin (hCG) trigger [Figure 1]. The starting dose was decided as per age, body mass index, antimullerian hormone (AMH) and previous stimulation history. A less than average starting dose of gonadotropins in group II was dictated by the use of clomiphene from the start of stimulation, as it is known to increase endogenous follicle-stimulating hormone.

Ultrasound was performed after 5 days of stimulation and then after every 2–3 days. Serum LH and E2 were performed on every visit. It was proposed that antagonist would be started if an increase in LH were observed at follicle size 15 or less. Injection leuprolide or alternatively hCG was used for maturation in group I. 10,000 IU of urinary hCG was used in group II. Oocyte pick-up was scheduled 33–35 h after the hCG trigger [Figure 2].

Intracytoplasmic sperm injection (ICSI) was done in selected cycles with a coexisting male factor. The embryos were transferred to recipients of both groups after programing the endometrium with estradiol valerate and progesterone according to the day of transfer. Only 2–3 embryos were transferred per recipient. Single embryo transfer (SET) was done only when Gardner and Schoolcraft’s grade 4 or 5 embryos were available on day 5.[3] Embryos were frozen at both day 3 and day 5; and were subjected to a variable period of post thaw culture to assess viability. Pregnancies from both fresh and frozen embryo transfers were included in the analysis.

The analysis was performed on average oocytes retrieved, fertilization rates, blastocyst transfers, clinical pregnancy rates, and cycle cancelation between the two groups. The dosages, cost, terminal (estradiol on the day of the trigger) E2 was also analyzed and compared among the two groups. The analysis was performed using Chi-square test for qualitative and Student’s t-test or ANOVA for quantitative data.

RESULTS

The average donor age and serum AMH in group II (n2 = 31) and I (n1 = 139) were comparable. The mean age was 25.48. The average usage of gonadotropins in group I was 1336 IU and 978 IU in group II. The average started dose of gonadotropin used for stimulation was also significantly less in group II [Table 1]. No emergency pickups had to be scheduled in any of the two groups based on LH levels done at each clinic visit.[4] In group II, none of the donors, required additional antagonist or failed retrieval of eggs at pick-up. There were 2 donor cycles in group I which resulted in failure to recover oocytes. One donor had a poor response to stimulation with an E2 of 508 after a 9-day stimulation with 300 IU of gonadotropin. The other donor had a normal response (E2 = 1854) but failed to recover oocytes.
The average E2 in group II was significantly higher than in group I (3233 vs. 1941, *P* = 0.001). The number of eggs retrieved was comparable (13.18 and 13.77) in group II and I. Metaphase II oocytes in ICSI cycles were similar in both groups [Table 1]. No admission was required for moderate to severe OHSS in any of the two groups.

The fertilization rate was significantly better in group II (59.5/50.5, *P* = 0.04). There were 25 pregnancies in fresh transfers. The remaining pregnancies were from frozen thawed embryos transferred in recipients. 85% of recipients had two or three embryos transferred while the other 15% had a SET.

The clinical pregnancy rate in the clomiphene group was significantly higher (54.8%/33.1%, *P* = 0.02). In group II recipients had more blastocyst transfers, although it did not reach a significant level. The estimated average expense as expected was much lesser in group II [Table 1].

### DISCUSSION

Clomiphene has been commonly used for ovulation induction in polycystic ovarian syndrome. It has also been used in minimal stimulation protocol. The abundance of experience with clomiphene comes from Kato Ladies clinic, where they routinely practice minimal stimulation, within all age groups and couples with various infertility diagnoses.[2,4,5,10] This includes a dataset of about 20,244 cycles with 78% successful retrievals. The reported overall pregnancy rate was 21.8% and live birth rate of 16.5%. This data include only minimal stimulation, and the average number of oocytes retrieved was 1.54.

It becomes important to review the pharmacology of clomiphene citrate (CC) here, which is a racemic mixture of cis-clomiphene (enclomiphene) and trans-clomiphene (zucloclomiphene). Both these isomers have distinct pharmacokinetics and pharmacodynamics. After oral administration, enclomiphene attains a much lower plasma level, and its elimination is also faster.[6,7] The two isomers accumulate over a period of time on daily dosing. Antagonistic actions of clomiphene are from its cis-isomer.

Enclomiphene suppresses both positive and negative feedback of estrogen at the level of the hypothalamus.[8] It thereby stimulates ovaries, and is capable of preventing LH surge.[9] Its short half-life (24 h) however, necessitates daily dosing.

The present study includes a cohort of favorable outcome patients (donors), which provides the advantage of a homogenous group of subjects and eliminates a suspected negative impact of CC on the endometrium. The cohort of donors had a mean age of 25.48 pmol/L (±3.5) and average AMH of 27.5. Clomiphene was evaluated as a single agent for suppressing LH surge in donor stimulation. In the present study, average oocyte retrieved in group II was 13.77. Here the average terminal E2 was also 3233 pg/ml and yet no untoward failed retrievals were seen in this group. Previous studies have used the extended clomiphene regimen in minimal stimulation where average estradiol was 850 (44,345 cycles) and mean no of oocytes retrieved were 2.2.[4]

There were no unsuccessful retrievals in this study and a pregnancy rate higher than conventional stimulation was achieved with the extended CC regimen. Group I had 9 cycles with no embryos for transfer. It can, therefore, be deemed that an extended CC based regimen is efficient in blocking a premature LH surge. In the study at Kato clinic, there were 2.35% unsuccessful retrievals, which were primarily in the age group 45 years and above.[10]

The extended regimen decreases the total dose of exogenous gonadotropins and also is effective in suppressing LH, even with high terminal E2. The higher terminal E2 in group-II can be explained by the additional endogenous gonadotropin acting synergistically. There were, however, no OHSS reported from these donors besides mild ovarian enlargement and minimal symptoms of bloating and distention. Decreasing the dose of gonadotropins also reduces the adverse effect on oocyte quality.[11,9]

There could be a possible confounding effect of the hCG trigger in the clomiphene arm, this is a limitation of the retrospective nature of the study. Although there is evidence that GnRH agonist trigger is more physiologic, and oocyte maturation is not hampered.[10] There is no hypothetical explanation of GnRH agonist trigger not working with clomiphene although the retrospective nature of the study limited this analysis.

### Table 1: Results

<table>
<thead>
<tr>
<th></th>
<th>Group I (conventional stimulation)</th>
<th>Group II (extended clomiphene group)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>25.68±3.5</td>
<td>24.58±3.5</td>
<td>0.105</td>
</tr>
<tr>
<td>Serum AMH (pmol/L)</td>
<td>26.05</td>
<td>28.99</td>
<td>0.46</td>
</tr>
<tr>
<td>Starting dose of gonadotropin (IU)</td>
<td>184.5±39.28</td>
<td>133±31.87</td>
<td>0.00</td>
</tr>
<tr>
<td>Number of days of stimulation</td>
<td>7.35±1.778</td>
<td>7.26±1.548</td>
<td>0.795</td>
</tr>
<tr>
<td>Terminal E2 (pg/ml)</td>
<td>1941</td>
<td>3233</td>
<td>0.00</td>
</tr>
<tr>
<td>Estimated expense (INR)</td>
<td>31,302</td>
<td>18,268</td>
<td>0.000</td>
</tr>
<tr>
<td>Eggs retrieved</td>
<td>13.18±7.228</td>
<td>13.77±4.931</td>
<td>0.795</td>
</tr>
<tr>
<td>MII oocytes</td>
<td>9.88</td>
<td>9.06</td>
<td>0.579</td>
</tr>
<tr>
<td>Fertilization rate (%)</td>
<td>50.54</td>
<td>59.5</td>
<td>0.04</td>
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<tr>
<td>Blast transfers (%)</td>
<td>10.1</td>
<td>22.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Clinical pregnancy rate</td>
<td>33.1</td>
<td>54.8</td>
<td>0.02</td>
</tr>
</tbody>
</table>

AMH= Antimullerian hormone, MII= Metaphase II


[4] 144
This study is also relevant as more and more data is coming in favor of freeze-thawed embryo transfers.\textsuperscript{[11]} This happens to be a scenario where clomiphene can be used without any apprehension of an unfavorable endometrium.

**CONCLUSION**

Thus, clomiphene seems an inexpensive, safe and effective alternative to GnRH analogs. The study proves the practicability of clomiphene in conventional stimulation. It can in future provide a more flexible and safer alternative to antagonist or agonist cycles. The results are significant; even so a prospective randomized controlled trial is required which could also include cycles with freeze all policy. It may be argued that the endometrial effects are merely hypothetical. It is not reported to be of significant consequence in minimal ovarian stimulation. Thus, clomiphene can find wider application in assisted reproductive technology with adequate randomized studies in this direction.

In countries where commercial oocyte donation is permissible, stress should be laid on making it safe and tolerable. Clomiphene goes a long way in decreasing costs, injections and improving quality.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**REFERENCES**