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Original Research Article

Clomiphene citrate prevents premature luteinization in stimulated intrauterine insemination cycles

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ABSTRACT

Background: Approximately 13-36% of ovarian stimulation and intrauterine insemination cycles are complicated by premature luteinizing hormone (LH) surge. Gonadotropin releasing hormone (GnRH) agonist or antagonist has been traditionally used to prevent a premature LH surge and premature luteinization in ovarian stimulation cycles. Clomiphene citrate, which competitively inhibits estrogen binding to estrogen receptors, may be used to prevent premature luteinization and premature LH surge in ovarian stimulation with gonadotropins prior to intrauterine insemination (IUI). The objective was to compare the effects of clomiphene citrate with placebo on prevention of premature luteinization in ovarian stimulation with intrauterine insemination cycles.
Methods: This randomized controlled study was conducted from July 2021 to December 2022. A total of 76 participants had ovarian stimulation with tab letrozole and injection r-FSH. Transvaginal ultrasound for folliculometry was done from day 8 onwards as needed. When the leading follicle was at least 14 mm, women were randomly assigned to clomiphene citrate group (n=38) or placebo group (n=38). They were given clomiphene citrate 150 mg or placebo daily up to the day of trigger. Premature LH surge and premature luteinization were assessed on the day of trigger.
Results: Premature luteinization was significantly lower in participants given clomiphene citrate compared to women given placebo (16.7% versus 47.1%, p<0.01). Premature LH surge was also lower in patients given clomiphene citrate but the difference was not statistically significant (47.2% versus 52.9%, p<0.811). Pregnancy rate with clomiphene citrate was higher (11.1% versus 2.9%) than that with placebo.
Conclusions: The addition of clomiphene citrate to gonadotropins in mid to late follicular period decreases the risk of premature luteinization and improves pregnancy rate.

Keywords: Clomiphene citrate, Intrauterine insemination, Premature LH surge, Premature luteinization

INTRODUCTION

Intrauterine insemination (IUI) combined with ovarian stimulation is a cost-effective fertility treatment.[1] Ovarian stimulation is achieved with letrozole, clomiphene citrate and gonadotropins.[2] One frequently occurring problem in gonadotropin induced ovarian stimulation and intrauterine insemination (OS-IUI) is premature luteinization (PL) caused by endogenous LH surge and luteinization of the endometrium before maturation of the follicle. The multifollicular recruitment rapidly increases serum estradiol (E2) level and leads to a luteinizing hormone (LH) surge while follicular growth is still in progress. Approximately 13-36% of IUI cycles are complicated by premature LH surge.[3] Premature luteinization is detrimental to oocyte quality, fertilization, and embryo implantation. There is risk of cycle cancellation and subsequent psychological stress and financial burden for both patients and physicians.[4] To avoid the risk of unexpected premature luteinization, the physician proceeds to IUI as soon as the leading follicle diameter reaches 18 mm, ignoring the number and developmental

status of the other recruited follicles.[5] This results in single pre ovulatory follicle in most of the stimulated cycles. There is reduced chance of pregnancy because at least two mature follicles (≥16 mm) are expected to achieve a satisfactory pregnancy rate in IUI.[6] GnRH agonists (e.g. leuprolide acetate) were initially used to prevent LH surges. GnRH antagonists such as cetrorelix and ganirelix suppress ovulation by competitively blocking GnRH receptors of the pituitary. It induces a rapid suppression of gonadotropin secretion without the flare-up effect of GnRH agonists.[7]

Clomiphene citrate (CC) may be used during ovarian stimulation with gonadotropins to prevent a premature LH surge in intrauterine insemination (IUI). It acts as a selective estrogen receptor modulator and a competitive inhibitor of estrogen binding to estrogen receptors. Previous studies have shown that clomiphene citrate can suppress the LH surge in IVF and IUI cycles.[8,9] Clomiphene is much less expensive, oral administration and easy to store. The anti-estrogenic effect of clomiphene citrate may suppress the premature LH rise while maintaining a positive influence on ovarian follicular development. As data regarding the use of clomiphene citrate for this purpose is limited in the literature, we performed this study to compare the effects of clomiphene citrate with placebo on prevention of premature luteinization in ovarian stimulation and IUI cycles. We hypothesized that clomiphene citrate is effective in preventing premature luteinization in ovarian stimulation with intrauterine insemination.

METHODS

This was a single blind randomized controlled clinical trial carried out in a University Hospital in Dhaka from July 2021 to December 2022. The ethical approval was obtained from the institutional review board of the medical university. The study participants were women aged 18-35 years, with at least one year primary or secondary infertility, selected for ovarian stimulation and intrauterine insemination (indications as unexplained infertility, mild male factor, tubal factor, mild to minimal endometriosis, PCOS etc). The exclusion criteria were bilateral tubal block, diminished ovarian reserve (serum AMH<1 ng/ml, FSH>10 IU/l, antral follicle count <4 in both ovaries), severe male factor (sperm count <5 million/ml), moderate to severe (stage III, stage IV) endometriosis, uterine anomalies and hypogonadotropic hypogonadism. Informed written consent was obtained from the participants after discussing the purpose and procedure of the study with them.

Controlled ovarian stimulation was started after the baseline visit and investigations. Women with normal hormonal profile and baseline endometrial thickness less than 6 mm had ovarian stimulation with tab letrozole (tablet Zoleta, Nuvista Pharmaceuticals Limited, Bangladesh) 2.5 mg 2 tab daily from day 2/3 of menstrual cycle for 5 days and highly purified recombinant FSH injection (injection r-FSH, Popular Pharmaceuticals Limited, Bangladesh) 75 IU subcutaneously on day 5 and day 7 of menstrual cycle. Transvaginal sonography was performed on the day 8/9 of the cycle. Inj. hMG (human menopausal gonadotrophin) (injection HMG, Popular Pharmaceuticals Limited, Bangladesh) 75 IU intramuscularly was given every alternate day till at least two dominant follicles with the size of >18 mm was found. Then, 250 µg of injection r-hCG (injection Ovidrel, Merck Serono, Germany) was injected subcutaneously as trigger.

When the leading follicle was at least 14 mm, the participants were randomized into experimental group given clomiphene citrate or the control group given placebo in place of clomiphene. Clomiphene citrate (tab Ovulet 50 mg, Renata Pharmaceuticals Limited, Bangladesh) was administered in a dose of 150 mg daily until the day of trigger. Those assigned to control group were given placebo in the same manner. Serum LH and estradiol were measured on the day when the lead follicle was at least 14 mm. Premature LH surge and premature luteinization were assessed on the day of trigger by measurement of serum LH and the serum progesterone in the evening, while the trigger was given at night. Measurement of serum estradiol was also done on the day of trigger.

Sperm preparation for intrauterine insemination was done by simple wash and swim up method. IUI was performed once 36 hours after r-hCG administration. Luteal support was given by 400 mg of vaginal micronized progesterone (cap Microgest 400 mg, Renata Pharmaceuticals Limited, Bangladesh) daily for 14 days. serum β-hCG was checked two weeks after IUI. Serum beta hCG >40 mIU/ml was documented as chemical pregnancy. When positive, clinical pregnancy was documented by transvaginal sonography, at 6-7 weeks of gestation.

The main outcome measures were premature luteinization (serum LH≥10 IU/l and serum progesterone ≥1 ng/dl on the day of trigger) and premature LH surge (≥10 mIU/ml on the day of trigger).[7,9] Chemical pregnancy was defined as β serum beta hCG>40 mIU/ml after 14 days of IUI performed. Clinical pregnancy was diagnosed as fetal pole and cardiac activity at sonogram at 6-8 weeks of amenorrhea.

The random sequence generation was done by permuted block randomization with computer generated random numbers by one who was not related to the study. Eligible women were randomized into either clomiphene citrate group or placebo group. Allocation concealment was done using serially numbered closed opaque envelopes. Each envelope was labelled with a serial number and had a card inside noting the intervention type. Allocation was never changed after opening the closed envelopes. Participants were blinded to intervention as placebo was used. Allocation sequence and participants' enrolment were done by one who was not related to the study and principal investigator assigned participants to interventions.

The sample size was estimated for 80% power and 0.5 alpha as 36 for each group, 72 in total. Allowing for 10% drop out, the final sample size was 40. The Statistical Package for Social Science (SPSS) version 23 was used for statistical analysis. Data was analyzed using unpaired t test, chi square test or Fisher's exact test between the groups. P value <0.05 was considered statistically significant. We complied with CONSORT reporting guidelines.[10]

RESULTS

A total of 88 couples were approached. According to eligibility criteria, 76 couples were recruited as study participants. Of them 6 couples started the cycle but discontinued or were cancelled before trigger due to various reasons (Figure 1). Finally, 70 couples, 36 in intervention group and 34 in placebo group were included in analysis.

The sociodemographic variables, clinical presentation and endocrine profiles of study participants are described in Tables 1 and 2. There was no significant difference between the two groups. Most of the participants had monthly income less than 50,000 Taka (532 $). Table 3 shows that the indications of intrauterine insemination were similar in both groups. The majority of cases had male factor infertility.

The endocrine and follliculometry parameters on the day of adding clomiphene citrate were similar in both groups (Table 4).

Table 5 shows that serum estradiol and the number of mature (size >18 mm) follicles on the day of trigger were significantly higher in the women given clomiphene citrate compared to the controls. There was no statistically significant difference between the two groups regarding serum luteinizing hormone, serum progesterone, the total dose and total days of recombinant FSH used and endometrial thickness on the day of hCG administration.

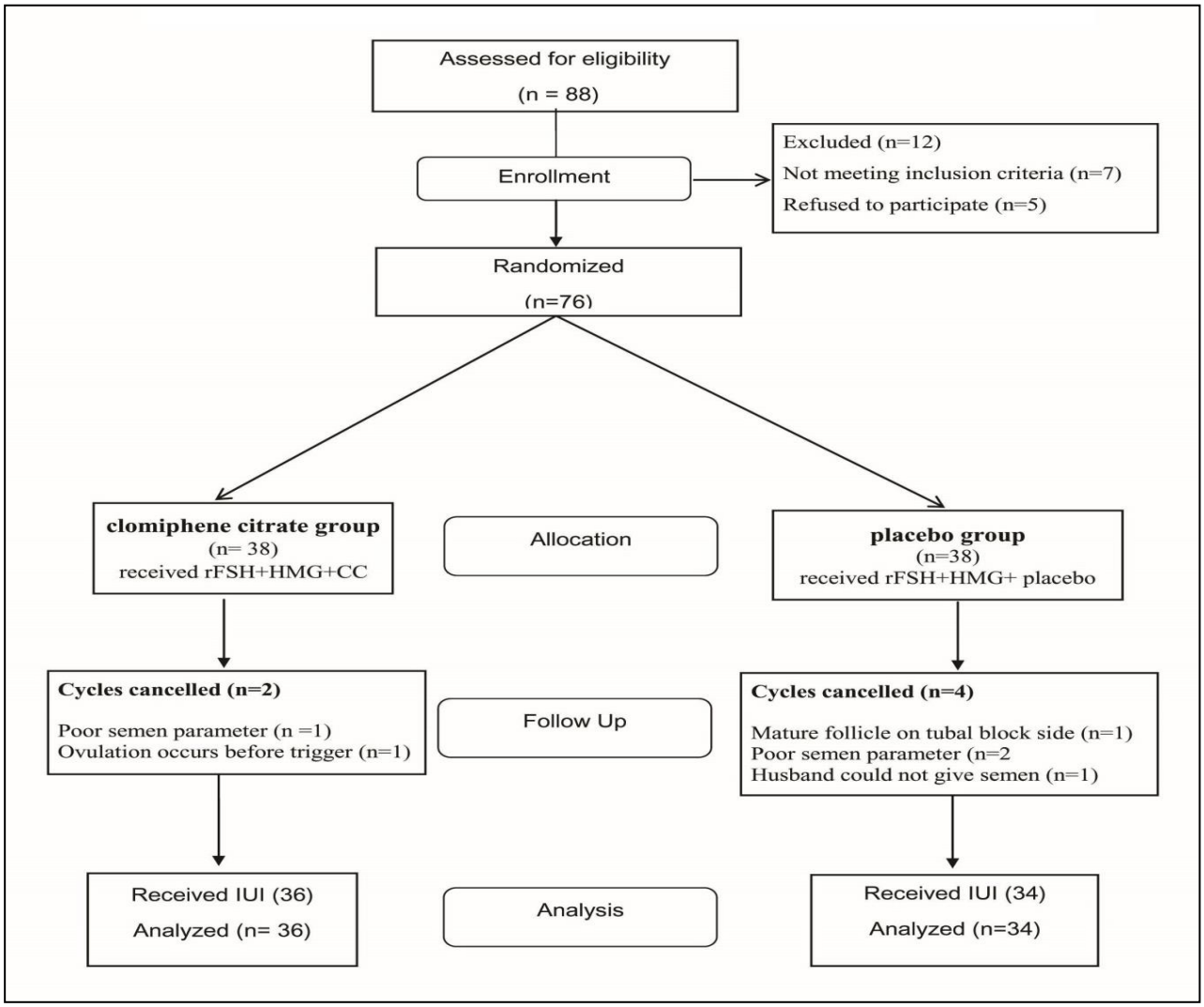

Figure 1: The progress of the two groups of participants.

Table 1: Socio-demographic variables of the study participants.

	CC (n=36)	Placebo (n=34)	P value
Age (years) Mean±SD	30.25±3.524	28.62±3.830	0.068
Residence (%)			
Urban	22 (61.1)	17 (50)	0.471
Rural	14 (38.9)	17 (50)	
Occupation (%)			
Housewife	23 (63.9)	25 (73.5)	0.446
Service	13 (36.1)	9 (26.5)	
Husbands occupation (%)			
Service	24 (66.7)	18 (52.9)	0.482
Business	10 (27.8)	14 (41.2)	
Staying abroad	2 (5.6)	2 (5.9)	
Monthly income			
10,000-20,000 Tk (106-213$)	13 (36.1)	11 (32.4)	0.897
>20,000-50,000 Tk (>213-532$)	17 (47.2)	16 (47.1)	
>50,000 Tk (>532$)	6 (16.7)	7 (20.6)	
Duration of sub fertility (years) Mean±SD	6.08±3.313	6.26±3.612	0.827
Type of sub fertility (%)			
Primary	23 (63.9)	19 (55.9)	0.626
Secondary	13 (36.1)	15 (44.1)	

Table 2: Clinical presentation and endocrine profile of the study participants.

Variables	CC (n=36)	Placebo (n=34)	P value
BMI Kg/m^2 (mean±SD)	24.54±3.02	24.52±2.89	0.974
Tubal patency tests (%)			
Sonohysterography	17 (47.2)	17 (50)	0.963
Hysterosalpingography	16 (44.4)	14 (41.2)	
Laparoscopy and dye test	3 (8.3)	3 (8.8)	
AMH (ng/ml)	3.41±2.50	3.40±2.48	0.985
AFC	14.75±5.69	15.15±6.29	0.783
D2FSH (IU/l)	6.73±1.70	6.26±1.94	0.287
D2 LH (IU/l)	4.16±2.41	5.02±4.08	0.305

Table 3: Causes of infertility of the study participants.

Variables (%)	CC (n=36)	Placebo (n=34)	P value
Unexplained infertility	9 (25)	5 (14.7)	0.131
Male factor	9 (25)	9 (26.2)	
Tubal factor	8 (22.2)	6 (17.6)	
PCOS	5 (13.9)	6 (17.6)	
Endometriosis	4 (11.1)	0 (0)	
Both male and female	0 (0)	3 (8.8)	
Multiple female factor	0 (0)	1 (2.9)	
Others	1 (2.8)	4 (11.8)	

Table 4: Endocrine and folliculometry parameters on the day CC was added.

Variables	CC (n=36)	Placebo (n=34)	P value
Estradiol (pg/ml)	121.66±63.60	97.09±50.09	0.091
Luteinizing hormone (IU/l)	4.45±1.99	4.67±2.86	0.712
Number of growing follicles	3.03±.94	3.16±1.34	0.636
Endometrial thickness (mm)	7.53±1.09	7.25±.93	0.267

Table 5: Endocrine and folliculometry parameters on the day of trigger compared between clomiphene citrate group and placebo group.

Variables	CC (n=36)	Placebo (n=34)	P value
Estradiol (pg/ml)*	367.50 (274.35--679.69)	183 (117.98--293.04)	0.000
Luteinizing hormone* (IU/L)	10.10 (8.03-14.15)	10.31 (5.30--16.23)	0.597
Progesterone*	0.63 (0.42--0.93)	1.20 (.30--1.85)	0.104
Number of mature follicles	2.19±0.920	1.74±0.751	0.026
Endometrial thickness (mm)	8.59±1.64	9.30±1.69	0.078
Endometrium, tri-laminar (%)	86.1	91.2	0.711
Total units of gonadotropins (IU)	320.83±103.94	322.06±127.29	0.965
Total days of gonadotropins injection	4.28±1.39	4.29±1.70	0.965
Total days of clomiphene citrate/placebo used	4.17±1.13	4.73±1.29	0.062

*non-Gaussian distribution and so described as median (interquartile range)

Table 6: Premature luteal surge and premature luteinization compared between clomiphene citrate group and placebo group.

Outcome	CC (n=36)	Placebo (n=34)	P value	Risk ratio	95% CI of risk ratio	
					Lower	Upper
Premature luteal surge (%)	47.2	52.9	0.811	0.892	0.548	1.442
Premature luteinization (%)	16.7	47.1	0.010	0.354	0.330	0.805

Table 7: Pregnancy rate compared between clomiphene citrate group and placebo group.

Outcome	CC (n=36)	Placebo (n=34)	P value	Risk ratio	95% CI of risk ratio	
					Lower	Upper
Biochemical pregnancy (%)	13.9	2.9	0.199	4.793	0.509	18.808
Clinical pregnancy (%)	11.1	2.9	0.358	3.827	0.433	14.983

Table 6 shows that premature luteinization was significantly lower in patients given clomiphene citrate. Premature luteinization was 16.7% in those who received clomiphene citrate compared to 47.1% in those who received placebo ($p<0.01$). Premature LH surge was lower in those given clomiphene citrate than placebo (47.2% versus 52.9%) but the difference was not statistically significant. Weekend free IUI was possible more in the patients having clomiphene citrate (27.78%) compared to those having placebo (17.65%).

Table 7 shows that the pregnancy rate was 3-4 times higher in participants given clomiphene citrate compared to placebo. Two of the 5 pregnancies achieved in clomiphene citrate group resulted in live birth, the remaining included one chemical pregnancy, one anembryonic pregnancy and one spontaneous first trimester abortion. There was no reported side effect in any group.

DISCUSSION

Clomiphene citrate, a selective estrogen receptor modulator that acts as a competitive inhibitor of estrogen binding to estrogen receptor may be used to prevent premature luteinization. Its anti-estrogenic effect may suppress the premature LH rise without hampering ovarian follicular development similar to GnRH antagonists used in stimulation protocols.[9] The primary objective of this study was to compare the efficacy of clomiphene citrate with placebo in preventing premature luteinization during ovarian stimulation for intrauterine insemination. Premature luteinization was significantly lower when clomiphene citrate was added in mid to late follicular phase during controlled ovarian stimulation. Premature LH surge was also lower in patients given clomiphene citrate.

There have been many studies on the use of injectable GnRH antagonists in preventing premature LH surge and premature luteinization. There are three studies exploring a similar effect of clomiphene citrate. There are prospective randomized controlled trials showing that premature LH surge was significantly lower (5.4% and 3% respectively) when clomiphene citrate 150 mg/day was added to gonadotropins during controlled ovarian stimulation.[9,11] Clomiphene was added on day 6 of menstrual cycle or the day 4 of stimulation.[9] The other double blind placebo controlled randomized controlled trial added clomiphene citrate 150 mg/day from day 8 of the cycle and day 6 of stimulation.[11] There was a non-randomized prospective study comparing the effects of clomiphene citrate with injectable GnRH antagonists in preventing premature LH surge during controlled ovarian stimulation (COS) cycles for IVF-ICSI.[12] Premature LH

surge was higher in clomiphene citrate group compared to GnRH antagonist group but the difference was not statistically significant. They added clomiphene citrate or GnRH antagonist when the follicle size was at least 14 mm and continued up to trigger. They concluded that clomiphene citrate administration is associated with significant cost savings when compared to injectable GnRH agonists. Age and BMI of our study participants were comparable to that of their studies. The majority of cases in our study had male factor infertility. The cases were unexplained infertility and male factor infertility in other studies.[9,12] One trial had only women with polycystic ovary syndrome (PCOS) as study participants.[11] The difference of premature LH surge (47.2%) and premature luteinization (16.7%) in our study may be attributed to the different stimulation protocols.

The clinical pregnancy rate in our study was 4 times higher in women having clomiphene citrate than in women having placebo (11.1% versus 2.9%). The clinical pregnancy rate was 10% in women having clomiphene vs. 8.41% in controls in the study by Al-Inany et al.[9] The clinical pregnancy rate was 15.1% in women having clomiphene versus 8.9% in controls in the study by Zarei et al.[11] These results regarding pregnancy rate is comparable to that of our women having clomiphene. The low rate in our controls compared to theirs' may be due to difference in the study population and stimulation protocols. In the study by Shams-Eldeen et al both biochemical pregnancy and clinical pregnancy rate were 36.4% and 31.8%, much higher than ours as their patients had IVF-ICSI instead of IUI.[12]

In our study the number of mature follicles was significantly increased in clomiphene citrate group on the day of trigger. The findings are similar to that of the study by Al-Inany et al and Zarei et al.[9,11]

The serum estradiol (E2) level on day of trigger was significantly higher in clomiphene citrate group than placebo group in our study. The results are similar to that in other studies.[9,11] In the study by Shams-Eldeen et al.[12] serum estradiol was similar in clomiphene citrate and GnRH antagonist groups. They used GnRH antagonist rather than placebo as comparator. They had higher estradiol levels as they used hyper-stimulation protocols for IVF-ICSI.

The endometrial thickness on the day of hCG trigger of women having clomiphene had no significant difference from the controls. The other studies also had no significant difference in endometrial thickness between clomiphene group and controls.[9,11] The study by Shams-Eldeen et al had significantly lower endometrial thickness in clomiphene citrate group compared to GnRH antagonist.[12]

The increased number of mature follicle and significantly higher level of serum estradiol on day of trigger in this study reflect that the anti-estrogenic effect of clomiphene citrate does not counteract the stimulatory properties of gonadotropins. In addition, the similar endometrial thickness of both groups reflects that the anti-estrogenic effects of clomiphene citrate do not adversely affect the endometrium.

There are several studies of GnRH antagonist application in IUI cycles. Premature luteal surge was in the range of 2.9% to 5.5% in those who used injectable antagonists, either cetrorelix or ganirelix. Premature luteinization was in the range of 1.38% to 15.38% in those studies using GnRH antagonist. There was no premature luteinization in studies using antagonists.[13,14] So both the premature luteinization and premature LH surge are much higher with clomiphene compared to GnRH antagonists.

Clinical pregnancy in our study with clomiphene citrate was 11.1%. Regarding the studies with injectable antagonists, clinical pregnancy rate was lower than ours in some studies and higher than ours in other studies. The systematic review and meta-analysis by Vitagliano et al found no significant difference in clinical pregnancy rate between women having antagonists in IUI cycles and controls. The pregnancy rate may be affected more by the timing of injection hCG or IUI than the rate of premature luteinization.[15]

The difference in premature luteal surge, premature luteinization, and clinical pregnancy rate may be attributed to the difference in total dose of gonadotropins used, total duration of stimulation and durations of antagonists in the studies, difference in patient population and stimulation protocols. Some studies started antagonists when the follicle size was 16 mm.[13] The total dose and duration of gonadotropin use was much lower in the women receiving clomiphene citrate compared to those having GnRH antagonist for prevention of premature luteinization.

In our study there was significant difference in the number of mature follicles between clomiphene citrate group and placebo group on the day of trigger. The studies using GnRH antagosists also found statistically significant rise in the number of mature follicles in the women having antagonist compared to the controls.[6,14,15] The increasing pregnancy rate in antagonist group may be related to the number of mature follicles. One study using antagonist found no significant difference in the number of mature follicles between the two groups on the day of trigger in study by.[16]

The serum estradiol level on day of triggering was significantly higher in clomiphene citrate group compared to placebo group in our study though the estradiol level was similar on the day when clomiphene citrate was added. But the meta-analysis and systematic review by Vitagliano et al showed no significant differences in estradiol level between antagonist and control groups.[17]

The endometrial thickness on the day of hCG trigger in the clomiphene citrate group and the controls had no significant difference. Studies also had no significant

difference in endometrial thicknesses of the intervention and control groups. The study conducted by Karthik et al had increased endometrial thickness in GnRH antagonist group in fixed and flexible protocol compared to the controls.[18] The study used hMG in higher doses.

All the studies applying GnRH antagonists in IUI cycles showed that the incidence of premature LH surge and premature luteinization (PL) was significantly higher in control group compared to antagonist group, a finding similar to our study.

Gobernado et al and Matorras et al applied GnRH antagonist in IUI cycles to have weekend free IUI.[16,19] There was no significant difference in clinical and ongoing pregnancy rate between weekend free IUI group and standard IUI group. The mid cycle use of GnRH antagonist in ovarian stimulation with gonadotropins may allow the flexibility of timing of hCG injection and IUI and lower the risk of cycle cancellation.[20] Similar to GnRH antagonists clomiphene citrate can be utilized to have week end free IUI.

Our study has many limitations: a small sample size, study population recruited form one selected center, a short study period and observation of only one cycle of IUI.

Clomiphene citrate may be a safe and cost-effective alternative to GnRH antagonist to prevent premature luteal surge and premature luteinization in ovarian hyper stimulation. It remains to be seen whether changing the dose or time of administration of clomiphene citrate has a more favourable effect on the pregnancy rate.

CONCLUSION

The addition of clomiphene citrate to gonadotropins in mid to late follicular period decreases the risk of premature luteinization and improves pregnancy rate.

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