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Original Research Article

Elagolix as GnRH antagonist in controlled ovarian stimulation for intrauterine insemination

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ABSTRACT

Background: Controlled ovarian stimulation with gonadotropins may be complicated by premature luteinizing hormone surge and premature luteinization. Premature LH surge and premature luteinization can be inhibited by GnRH antagonists so that gonadotropin stimulation can be extended, enabling the appropriate development of more than one follicle. Elagolix is an oral GnRH antagonist used in treatment of endometriosis. Elagolix, like injectable GnRH antagonists, may be applied for preventing premature luteinization. Objective was to compare the effects of elagolix with no elagolix on preventing premature luteinization in ovarian stimulation with intrauterine insemination, on the day of trigger.

Methods: This quasi-experimental study was conducted on a total of 60 infertile women selected for ovarian stimulation and intrauterine insemination. The women were given ovarian stimulation with tab letrozole and injectable gonadotropins. Transvaginal ultrasound for folliculometry was done from day 8 onwards. When the leading follicle was at least 14 mm, the women were assigned into two groups. Elagolix 150 mg once daily was added and continued to the day of trigger in the intervention group. Patients in the control group did not receive elagolix as described above. Premature LH surge (serum LH≥10) and premature luteinization (serum LH≥10 IU/l and serum progesterone ≥1 ng/ml) were assessed on the day of trigger.

Results: Twenty-six women in the elagolix group and 26 in the control arm completed the study. There was total absence of premature LH surge and premature luteinization in the elagolix group as compared to the 30.8% and 23.1% respectively in the control group. There was no statistically significant difference in clinical pregnancy rates.

Conclusions: Elagolix, an oral GnRH antagonist, when applied to controlled ovarian stimulation for intrauterine insemination, eliminate premature luteal surge and premature luteinization. But there is no improvement in clinical pregnancy rate.

Keywords: Elagolix, GnRH antagonists, Intrauterine insemination, Ovarian hyperstimulation

INTRODUCTION

Ovarian stimulation for multifollicular development and intrauterine insemination (IUI) is a commonly practiced method of assisted reproduction. In combination with the controlled ovarian stimulation (COS), IUI has been proved to be a cost-effective line of treatment for many forms of infertility.[1] The application of mild ovarian hyper stimulation for IUI is associated with an increased risk of premature luteinization.[2] Multifollicular recruitment allowed by controlled ovarian stimulations rapidly increases the serum estradiol levels and leads to a luteinizing hormone surge while follicular growth is still in progress. Premature luteinizing hormone surge is

responsible for luteinization and disruption of normal follicle and oocyte development.[3] In order to avoid the risk of unexpected premature follicular luteinization, the physician proceeds to ovulation induction with trigger as soon as the leading follicle reaches 18 mm in diameter, regardless of the number and developmental status of the other recruited follicles.[4] Thus most of the stimulated cycles would be monofollicular. This would reduce the chances of pregnancy because at least two mature follicles >16 mm is needed to achieve a satisfactory pregnancy rate in IUI.[5]

GnRH antagonists have been proposed to prevent the premature LH surges during IVF cycles and COS-IUI treatments.[6] GnRH antagonists successfully protect follicular development against unexpected luteinization in IVF (in vitro fertilization) cycles by preventing untimely LH release.[7] Pituitary gonadotropin secretion is suppressed immediately after the start of therapy. Since GnRH antagonist postpone ovulation, they allow gonadotropin stimulation to be extended, enabling the appropriate development of more than one follicle. In fact, several authors have reported that a significant increase in pregnancy rates is linked to a parallel increase in the number of mature follicles on the day of human chorionic gonadotropin (HCG) administration.[8] GnRH antagonists are easy to incorporate in an IUI cycles without compromising the luteal phase.[9]

Elagolix is a novel, non-peptide short acting competitive gonadotropin releasing hormone (GnRH) receptor antagonist approved for the management of moderate to severe pain associated with endometriosis.[10] Elagolix suppresses gonadotropin hormones.[11] Elagolix, also a GnRH antagonist can be taken orally and it is less expensive compared to injectable GnRH antagonists. We in our institution do IUI for patients who cannot afford injectable antagonists. We wanted to see if oral antagonist could work and have better outcome than no antagonist at all. The study was undertaken to explore the effects of elagolix in preventing premature luteinization in ovarian stimulation with intrauterine insemination.

METHODS

This quasi-experimental (non-randomized prospective controlled) study was carried out in a University Hospital in Dhaka from July 2021 to December 2022. The ethical clearance was obtained from the institutional review board of the Medical University. The study participants were infertile women aged 18-35 years with indications for ovarian stimulation and intrauterine insemination. The women with BMI<18 or >29 kg/m^2, bilateral tubal block, diminished ovarian reserve (serum AMH<1 ng/ml, FSH>10 IU/l or antral follicle count <4 in both ovaries), severe male factor (sperm count <5 million/ml), advanced (stage III, stage IV) endometriosis, uterine anomalies and hypogonadotropic hypogonadism were excluded. Informed consent was obtained from the participants.

Women with normal hormonal profile and baseline endometrial thickness more than 6 mm started ovarian stimulation with tab letrozole (tablet Zoleta, Nuvista Pharmaceuticals Limited, Bangladesh) 2.5 mg 2 tablet daily from day 2/3 of menstrual cycle for 5 days and recombinant FSH (injection r-FSH, Popular Pharmaceuticals Limited, Bangladesh) 75 IU subcutaneous on day 5 and day 7 of stimulation. Transvaginal sonography was performed on the day 8/9 of the cycle and was repeated according to the size and number of stimulated follicles. Human menopausal gonadotropin or hMG (injection HMG, Popular Pharmaceuticals Limited, Bangladesh) intramuscular every day starting from day 9 onwards till at least two dominant follicles with the size of >18 mm were found. When the leading follicle was at least 14 mm, the women were assigned to receive elagolix or not. Tablet elagolix (tab Elagox 150 mg, Nuvista Pharmaceuticals Limited, Bangladesh) was continued once daily up to the day of trigger. Injection hMG was continued daily as long as the patient received tablet elagolix. The control group continued stimulation with injection HMG but did not have elagolix. When the size of the follicle was 18 mm, 250 µg of recombinant human chorionic gonadotropin, (Injection Ovidrel, Merck Serono, Germany) was injected subcutaneously for triggering ovulation. Luteal support was given by 400 mcg of micronized progesterone (capsule Microgest, Renata Pharmaceuticals Limited, Bangladesh) daily per vagina. Pregnancy was diagnosed by serum beta hCG 14 days after IUI and by fetal pole and cardiac activity on sonogram after 6-8 weeks amenorrhea.

A serum estradiol level was performed when the size of the follicle was 14 mm and also on the day of the trigger. Serum LH and serum progesterone was measured on the day of trigger. Premature luteinization was defined when serum LH was ≥10 IU/l and serum progesterone was ≥1 ng/dl on the day of trigger and premature LH surge was defined as serum LH ≥10 mIU/ml on the day of trigger (r-hCG injection). Chemical pregnancy was diagnosed when β serum beta hCG was >40 ng/dl 2 weeks after IUI. Clinical pregnancy was diagnosed when fetal pole and cardiac activity appeared on sonogram after 6 weeks.

The sample size was estimated for 80% power and 0.5 alpha as 30 for each group, 60 in total. Allowing for 10% drop out the final sample size was 35. SPSS (Statistical Package of Social Sciences) version 23 was used for analysis. Socio-demographic and clinical, sonographic characteristics were summarized as frequency for categorical variables, mean±SD or median (interquartile range) as appropriate for continuous variables. Pair wise comparison of outcome variables was done between the treatment arm of elagolix and the control arm of no elagolix. Outcome variables were compared between the groups with chi-square test or Fisher's exact test for categorical variables and independent samples t-test (unpaired t test) for continuous variables. A p value of 0.05 or lower was considered statistically significant.

RESULTS

A total of 68 couples were approached. A total 60 couples fulfilled the eligibility criteria and were recruited as study participants. Eight couples, 4 in each group started the cycle but discontinued or were cancelled before trigger due to various reasons. So finally, 52 couples, 26 in intervention group and 26 in the control group were included in analysis.

The Table 1 and 2 describes that there is no significant difference between the two groups of study participants regarding the socio-demographic variables, clinical presentation and endocrine profiles. Table 3 shows that the causes of infertility were similar in both groups.

Table 1: Socio-demographic variables compared between elagolix and no elagolix group.

	Elagolix (n=26) (%)	No elagolix (n=26) (%)	P value
Age (years) mean±SD	27.00±4.932	29.50±3.766	0.306
Residence (%)			
Urban	13 (50)	17 (64.9)	0.400
Rural	13 (50)	9 (34.6)	
Occupation (%)			
Housewife	22 (84.6)	19 (73.1)	0.499
Service	4 (15.4)	7 (26.9)	
Husband's occupation (%)			
Service	13 (50)	13 (50)	.060
Business	5 (19.2)	12 (46.2)	
Staying abroad	8 (30.8)	1 (3.8)	
Monthly income			
10,000-20,000 Tk (106-213 $)	7 (26.9)	8 (13.8)	1.00
>20,000-50,000 Tk (>213-532$)	17 (65.4)	16 (61.8)	
>50,000 Tk (>532$)	2 (7.7)	2 (7.7)	
Duration of subfertility (years) mean±SD	5.885±3.1283	6.577±3.5713	0.461
Type of subfertility (%)			
Primary	13 (50)	14 (53.8)	0.500
Secondary	13 (50)	12 (46.2)	

Table 2: Clinical presentation and endocrine profile compared between elagolix and no elagolix group.

Variables	Elagolix (n=26)	No elagolix (n=26)	P value
BMI (kg/m^2) (mean ±SD)	25.27±3.18	25.01±3.07	0.763
Tubal patency tests (%)	18 (69.2%)	15 (57.7%)	0.839
Sonohysterography	5 (19.2%)	7 (26.9%)	
Hysterosalpingography	3 (11.6%)	3 (11.5%)	
Laparoscopy and dye test	0	1 (3.8%)	
AMH (ng/ml) median (interquartile range)	3.44 (1.78--5.23)	3.02 (2.25--6.03)	0.475
AFC	14.04±8.04	13.85±6.38	0.924
D2 FSH (mIU/ml) mean±SD	6.24±1.96	5.71±1.90	0.325
D2 LH (mIU/ml) median (interquartile range)	4.42 (2.73--7.61)	4.23 (2.73--7.61)	0.516

*Non Gaussian distribution, so described as median (interquartile range)

Table 3: Causes of infertility compared between elagolix and no elagolix group.

Variables (%)	Elagolix (n=26) (%)	No elagolix (n=26) (%)	P value
Unexplained infertility	4 (15.4)	2 (7.7)	0.749
Male factor	9 (34.6)	8 (30.8)	
Tubal factor	2 (7.7)	3 (11.5)	
PCOS	4 (15.4)	5 (19.2)	

Continued.

Variables (%)	Elagolix (n=26) (%)	No elagolix (n=26) (%)	P value
Endometriosis	3 (11.5)	1 (3.8)	
Both male and female	2 (7.7)	4 (15.4)	
Multiple female factors	0	2 (7.7)	
Others	2 (7.7)	1 (3.8)	

Table 4: Endocrine and folliculometry parameters (on the day elagolix was added) compared between elagolix and no elagolix group.

Variables	Elagolix (n=26)	No elagolix (n=26)	P value
***Estradiol (pg/ml) median (interquartile range)**	103.51 (54.47--146.63)	93.00 (64.90--146.63)	0.913
***Luteinizing hormone (mIU/ml) median (interquartile range)**	4.70 (2.92--7.53)	5.05 (118.12--7.65)	0.855
Number of growing follicles mean±SD	2.23±.99	2.88±1.36	0.054
Endometrial thickness (mm) mean±SD	7.68±1.31	7.21±2.06	0.334

*Non Gaussian distribution, so described as median (interquartile range)

Table 5: Endocrine and folliculometry parameters on the day of trigger compared between elagolix and no elagolix group.

Variables	Elagolix (n=26)	No elagolix (n=26)	P value
***Estradiol (pg/ml) median, (interquartile range)**	99.60 (65.65--185.48)	229.44 (118.12--402.00)	0.006
***Luteinizing hormone (mIU/ml) median, (interquartile range)**	1.30 (.93--3.00)	7.23 (3.98--10.46)	0.000
***Progesterone (ng/ml) median, (interquartile range)**	0.50 (0.25--0.75)	0.79 (0.25--1.59)	0.084
Number of mature follicles	1.58±.75	1.62±0.69	0.850
Endometrial thickness (mm)	9.48±2.66	9.33±2.36	0.838
Endometrium, tri-laminar (%)	22 (84.6)	24 (92.35)	0.668
Total units of gonadotropin	398.08±128.63	360.58±137.50	0.315
Total days of gonadotropin	5.31±1.71	4.73±1.82	0.245

*Non-Guassian distribution, so described as median (interquartile range)

Table 6: Premature luteal surge and premature luteinization compared between elagolix and no elagolix group.

Outcome	Elagolix (n=26)	No elagolix (n=26)	P value
Premature luteal surge (%)	0	8 (30.8)	0.004
Premature luteinization (%)	0	6 (23.1)	0.023

Table 7: Clinical and biochemical pregnancy rate compared between elagolix and no elagolix group.

Outcome	Elagolix (n=26)	No elagolix (n=26)	Risk ratio (RR)	95% CI of RR ratio	
				Lower	Upper
Biochemical pregnancy (%)	1 (3.8)	2 (7.7)	0.49	0.17	0.69
Clinical pregnancy (%)	1 (3.8)	2 (7.7)	0.49	0.17	0.69

Table 4 shows that both groups of participants had similar endocrine and folliculometry parameters on the day of adding elagolix. But on the day of trigger serum estradiol and LH were significantly lower in the women given elagolix (Table 5). Table 5 also shows that there was no statistically significant difference in between the two groups regarding serum progesterone on the day of trigger, the total dose of r-FSH used, total days of treatment with r-FSH, endometrial thickness and pattern on the day of hCG administration and number of mature follicles (with size ≥18 mm).

Premature luteal surge and premature luteinization was totally absent in the women given elagolix. Thirty percent

of the women who were not given elagolix had premature LH surge and 23.1% of them had premature luteinization (Table 6). Pregnancy rate was lower in women given elagolix though the difference was not statistically significant (Table 7).

DISCUSSION

GnRH antagonists are commonly used for pituitary suppression during controlled ovarian stimulation with gonadotropins in assisted reproductive technology cycles to prevent premature luteinization. The addition of GnRH antagonists may obviate the need for intense midcycle monitoring and create more flexibility in the timing of hCG and IUI, which is likely to benefit both patient and physician. Elagolix is a new non peptide, orally bioavailable GnRH antagonist.[12] The primary objective of this study was to compare the effects of elagolix with no elagolix on preventing premature luteinization during ovarian stimulation for intrauterine insemination. Premature luteal surge and premature luteinization were absent in all patients given elagolix. Among patients who did not receive elagolix, premature luteal surge was seen in 30.8% and premature luteinization was present in 23.1%.

There are many published studies on the effect of injectable GnRH antagonists on premature LH surge and premature luteinization. There are few published studies about the similar effect of oral GnRH antagonists. There is only one prospective cohort study of donor oocyte cycles by Boniface et al comparing the effect of Elagolix to ganirelix, an injectable GnRH antagonist.[12] Similar to our study there was no premature ovulation in women having Elagolix. There was significant cost savings when compared to the arm given injectable GnRH agonists. The non randomized prospective study by Komiya et al compared the effects of Relugolix, an oral GnRH antagonist with injectable GnRH antagonists in controlled ovarian stimulation (COS) cycles.[13] Premature ovulation was absent in both groups. Local reactions (redness and pain) at the injection site happened in 1.1% of patients given injectable GnRH antagonist.

The mean age of study participants were similar to those of the study done by Boniface et al but lower than the study done by Komiya et al.[12,13] The participants of the study by Boniface et al had lower mean BMI than that of our participants.[12] The majority of cases in our study had male factor infertility. The majority of cases in the study by Komiya et al had combined factor infertility.[13]

There are many studies on application of injectable GnRH antagonist in IUI cycles. Premature luteal surge was 7.8%, 3%, 2.9%, 5%, 19.4%, and 7% with the use of injectable antagonists, either cetrorelix or ganirelix.[2,9,14-17] The difference may be due to different patient populations e.g. the study by Lee et al excluded PCOS patients.[16] Compared to these studies our study had no premature luteal surge with elagolix.

Premature luteinization in different studies were 1.7%, 1.4%, 1.7%, 1.7% and 1.4%.[2,4,15,17] Compared to these studies with injectable antagonists, there was no premature luteinization in our study with elagolix. Clinical pregnancy in our study with elagolix was 3.8%. Regarding the studies with injectable antagonists, clinical pregnancy rate was 8.8%, 2.8%, 22%, 27.6% and 8.4%.[2,4,8,14,15] The difference in premature luteal surge, premature luteinization, and clinical pregnancy rate may be due to difference in the total dose of gonadotropins used, total duration of stimulation and durations of antagonists between the studies, patient population and stimulation protocols. Some studies started antagonists when the follicle size was 16 mm.[4,8,14,15] The total dose and duration of gonadotropins used was variable according to when the antagonist was added.

In our study there is no significant difference in the number of mature follicles between the two groups on the day of trigger. There are studies which found no statistically significant difference in the number of mature follicles between the group having antagonist and the control group without antagonist.[17,18] The number of mature follicles was higher in the GnRH antagonist group and the increasing pregnancy rate in antagonist group was related to the increased number of mature follicles.[4,19]

The endometrial thickness on the day of hCG trigger had no significant difference. There are studies which had no significant difference in the endometrial thickness of the intervention and control groups.[9,16,17,19] But the study conducted by Checa et al had increased endometrial thickness in GnRH antagonist group compared to the controls.[20] The study used r-FSH in significantly higher doses (1032.8 versus 789.8 IU) and for significantly longer duration (10.34 versus 8.41 days) compared to controls.

All the studies applying GnRH antagonists in IUI cycles reported that the incidence of premature LH surge and premature luteinization was significantly higher in control group compared to antagonist group, a finding similar to our study.[2,4,9,14,16,17,19] In fact all patients having elagolix 150 mg daily had the absence of premature LH surge and premature luteinization.

There was no significant difference in clinical pregnancy rate in women receiving elagolix and the controls. All the above studies except Allegro et al and Gomez-Palomares et al found no significant difference in clinical pregnancy rate between antagonist group and controls, similar to our study.[8,17] Vitagliano et al conducted a systematic review and meta-analysis of fifteen RCTs (3253 IUI cycles, 2345 participants).[17] They also found no significant difference in clinical pregnancy rate between women having antagonists in IUI cycles and controls. The relatively higher clinical pregnancy reported by Gomez-Palomares et al may be due to delayed administration of GnRH antagonist with more days of r-FSH exposure, more follicular recruitment and more mature follicles.[8] The pregnancy rate may be affected more by the timing of trigger or IUI than the rate of premature luteinization.[9]

Compared to injectable antagonists, elagolix is easy to administer orally and less expensive. Tablet elagolix 150 mg administered daily can completely prevent premature luteinization. Since clinical pregnancy rate cannot be improved by the use of the antagonist, application of elagolix should be selective. The candidates may be those with history of premature luteinization during ovarian stimulation or those in need of weekend postponement of IUI. Those who need larger or higher number of mature follicles can also be given antagonist. Adding antagonist when the follicle size is 16 mm may result in higher pregnancy rate.

There are several limitations of the study. Our study was powered to detect a difference only in our primary outcome, the premature luteinization. Proper investigation of the difference in clinical pregnancy rate (CPR), for example, unfortunately required many more subjects than could be enrolled in this time period. This was not a randomized controlled trial, thus rendering our data susceptible to selection bias.

The present study reflects a safe and cost-effective protocol for IUI which can be used in third world countries in IVF cycle in a modified form. Elagolix can be used to allow flexibility in the timing of hCG injection and IUI. Avoiding weekend IUI may be an attractive option. Since clinical pregnancy is lower in this study further studies are needed before recommending elagolix in IUI protocols.

CONCLUSION

Elagolix, an oral GnRH antagonist eliminates premature luteal surge and premature luteinization, when applied to controlled ovarian stimulation for intrauterine insemination, but it does not improve clinical pregnancy rate.

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