Letrozole as an Ovulation Inducing Drug in Anovulatory Patients

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Ovulatory dysfunction or anovulation is one of the most common causes for reproductive difficulty. An anovulatory cycle is a cycle where ovulation does not occur. Generally, women experience anovulatory cycle during menopause. It is more common in perimenopause as well as in adolescence. A Prospective Observational study was carried in the Infertility unit of Bangabandu Sheikh Mujib Medical university (BSMMU), Shahbagh, Dhaka during the period of July 2011 to December 2011. The patients were randomly divided into two groups depending on the inclusion criteria. Group-I: Newly diagnosed cases of sub-fertility studied with letrozole. Group-II: Newly diagnosed cases of sub-fertility studied with clomiphene citrate. The mean number of mature follicles in group I was 1.2± 0.86 in comparison to group II where mean number of developing follicles were 2.4± 0.76. This indicates that in group I treated with Letrozole developed less number of follicles than group II, treated with Clomiphene citrate. The mean endometrial development was 9.2 ± 2.2 in group I and 8.1± 1.9 in group II. The mean endometrial development was higher in group I than group 11 but the difference was not significant. The above table shows that the ovulation rate in group I is 40(72.7%) and 45(80.1%) in group II which significantly high in group II ($p<0.05$). The pregnancy rate was 11(20.0%) in group I treated with Letrozole and 10(18.1%) in group II, treated with Clomiphene citrate which is not significant ($p>0.05$). The induction of ovulation with Letrozole in anovulatory patients is associated with limited number of mature follicles, no adverse effect on endometrium but the number of clinical pregnancies was higher in Letrozole group than in Clomiphene citrate treated group.

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Key words: Letrozole, ovulation

Introduction

Infertility is defined as the inability of a couple to achieve conception after one year of regular unprotected coitus'. Sterility implies an intrinsic inability to achieve pregnancy, whereas infertility implies a disease in the ability to conceive and is synonymous with sub-fertility. Approximately 90% of couples with unprotected intercourse will conceive within 1 year and sterility affects 1- 2% of Couples[2]. Primary sub-fertility is an absolute state of inability to conceive whereas secondary sub-fertility is the same state developing after an initial phase of fertility.[3]

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The number of sub-fertility visits has increased in the last few decades. The reasons for increase in attention given to sub-fertility are multiple. Couples in some cases have voluntarily delayed childbearing in favour of establishing career and many experience an age-related decline in fertility. In some cases choice of prior contraceptive method may have contributed to sub-fertility as with the use of some intrauterine devices (IUDS); having an increased number of sexual partners lead to a great potential for exposure to sexually transmitted disease which may contribute to sub-fertility and now a days Couples less willing to simply accept childlessness and are increasingly aware of available services and option for resolving sub-fertility. The prevalence of sub-fertility ranges from 7-28% depending on the age of the women. Both partners in a relationship contribute to sub-fertility. In any series of infertile marriages the main aetiological factors are found in female about 40% cases, about 35% husbands concerned have some degree of infertility. In 10-20% of cases a combination of factors operates and the rest have unexplained infertility.

A couple is usually referred for investigation of sub-fertility after trying unsuccessfully to conceive for a year. The chance of spontaneous conception during the subsequent year is about 50%. However the chance is reduced if the women have never been pregnant (primary sub-fertility) or aged over 30, or the duration of sub-fertility is longer than three years.[4] The causes of sub-fertility are diverse comprising both male and female factors. Factors relating to female infertility are hypothalamic-pituitary factors, ovarian factors, tubal/peritoneal factors, uterine, cervical and vaginal factors, genetic factor and general factors. Factors relating to male fertility include endocrine disorders, anatomical deformity, abnormal spermatogenesis and sexual dysfunction. The goal of infertility evaluation are to determine the probable cause of infertility, to provide accurate information regarding prognosis, to provide counselling**,** support and education throughout the process of evaluation and also to provide guidance regarding option for treatment. Ovulatory dysfunction or anovulation is one of the most common causes for reproductive difficulty. An anovulatory cycle is a cycle where ovulation does not occur. Generally, women experience anovulatory cycle during menopause. It is more common in perimenopause as well as in adolescence. If anovulation happens before menopause then it plays a role in infertility or difficulty in conception. In general, the most common cause of anovulation is hormonal imbalance. The common causes of anovulation are PCOS, hypothalamic dysfunction, perimenopause, ovulatory dysfunction, thyroid disorder and hyperprolactinaemia. Anovulation may not be easy to diagnose in some women especially those who are having regular periods. In most cases, when a woman does not ovulate she won't menstruate either or have infrequent menstruation. There are so many different potential causes of anovulation that is difficult to make a determination without in depth study of the individual, her history and diagnostic tests. Anovulation is usually associated with some specific symptoms: Amenorrhoea or absence of menstruation, Infrequent/light menstruation. The diagnosis of anovulatory infertility can be established by standard criteria of anovulation, a normal pelvic ultrasonography and bilateral tuba) patency. Anovulation can usually be treated with fertility drugs. It is important to rule out other conditions that could interfere with ovulation. For many years, the first line of

phari-nacologic ovulation induction has involved the use of selective estrogen receptor modulator (SERMS), of which clomiphenes citrate has been most extensively studied. The first trial of CC resulted in successful ovulation induction in approximately 80% of women, and ultimately half were able to achieve pregnancy.[5] The use of CC for superovulation in patient with unexplained infertility[6] has been the mainstay when coupled with intrauterine insemination (IUI). Yet despite the advances in ultrasonographic technique, hormone assay and urinary leutinizing hormone kits success with CC has changed dramatically. Therefore, it is important that we evaluate our option for ovulation or superovulation. However, 20-25% of women are resistant to CC and do not ovulate. In addition clinical data revealed a discrepancy between ovulation and conception rates during treatment and higher incidence of miscarriage in conception cycle.[7]

With the failure of CC, gonadotrophin preparations such as Human Menopausal Gonadotrophin (HMG) or pure Follicle Stimulating Hormone (FSH) have been used as a second line treatment for ovulation induction. In women with Polycystic Ovarian Syndrome (PCOS) because of high sensitivity of ovaries to gonadotrophin stimulation, treatment with HMG or pure FSH induces several ovulatory follicles leading to the risk of multiple pregnancies and ovarian hyper stimulation syndrome (OHSS).[8,9,10]

Letrozole belongs to a new group of very potent, non-steroidal aeromatase inhibitor that is rapidly absorbed from the gastrointestinal tract and excreted by the kidney. The elimination half life of letrozole is about 2 days.[8] In addition, because oestrogen receptor down regulation does not occur, no adverse effects on oestrogen target tissue, as observed in CC cycles would be expected, It is hypothesized that Letrozole mimics the action of CC without depletion of oestrogen receptors by administration of an aeromatase inhibitors.[7,11] This would results the normal central feedback mechanism remain intact. As the dominant follicle grows and estrogen level rises, normal negative feedback occurs centrally, resulting in suppression of FSH and atresia of the smaller growing follicles. A single dominant follicle and mono ovulation should occur in most case.[9]

Methods

A Prospective Observational study was carried in the Infertility unit of Bangabandu Sheikh Mujib Medical university (BSMMU), Shahbagh, Dhaka during the period of July 2011 to December 2011. 110 Women presenting with anovulatory infertility (both primary and secondary) within 20-40 years of age in infertility outpatient unit of BSMMU. The patients were randomly divided into two groups depending on the inclusion criteria. Group-I: Newly diagnosed cases of sub-fertility studied with letrozole. Group-II: Newly diagnosed cases of sub-fertility studied with clomiphene citrate. Patients were followed up for outcome observing TVS on 12^{th} or 13^{th} days of menstruation (spontaneous or progesterone induced) by number and size of developing follicles (≥18 mm), endometrial thickness, day21 serum progesterone level and pregnancy rate. The endometrial thickness was measured in the plane through the central longitudinal axis of the uterus at a point of maximum distance between the echogenic interface of the diameter. A trilaminar diameter of ≥8 mm was considered satisfactory response. Data were collected on a pre-designed questionnaire. Data entry and analysis was

done using computer based software SPSS 23.0 for windows.

Results

This prospective observational study **"Letrozole as an Ovulation Inducing Drug in Anovulatory Patients"** was done in Infertility unit of Obstetrics & Gynaecology in BSMMU from July 2011 to December 2011. Total 110 patients were taken as the study group. The above table shows that women with age between 21-30 years were predominant among the two groups.(Table-1) The above table shows that patients with monthly income 5000-10000 were more among the two groups.(Table-2). The above table shows that patient with BMI between 25 to 29 were common among the two groups.(Table-3) The mean marital age of the patients were 6.5±3.4 in group I and 6.8±4.2 in group II(Table-4) The above table shows 10(18.2%) in group I and 6(10.9%) in group II done S= significant (p=0.05) MR in the study patients. (Table-5) The above table shows 6(10.9%) in group I and 12(21.8%) in group were aborted in this study patients (Table-6). The mean number of mature follicles in group I was 1.2± 0.86 in comparison to group II where mean number of developing follicles were 2.4± 0.76. This indicate that in group I treated with Letrozole developed less number of follicles than group II, treated with Clomiphene citrate. The mean endometrial development was 9.2 ± 2.2 in group I and 8.1± 1.9 in group II. The mean endometrial development was higher in group I than group 11 but the difference was not significant (Table-7). The above table shows that the ovulation rate in group I is 40(72.7%) and 45(80.1%) in group II which significantly high in group II ($p<0.05$).(Table-8) The pregnancy rate was 11(20.0%) in group I treated with Letrozole and 10(18.1%) in group II, treated with Clomiphene citrate which is not significant ($p>0.05$).(Table-9)

Table I: Age distribution of the patients (n=30)

Age in years	Group - I		Group – II		P- Value
	n	%	n	%	
20	1	1.8	7	12.7	
21 –30	32	58.2	29	52.7	0.688^{ns}
31 –40	22	40.0	19	34.5	
Total	55	100	55	100	

ns= not significant

P value reached from Chi square test.

Table II: Socio-economic status of the patients (n=110)

Socio-economic status (monthly income)	Group - I		Group –II	
	n	%	n	%
< 5000	01	1.8	4	7.3
5000-10000	29	52.7	30	54.5
>10000	25	45.5	21	38.2
Total	55	100	55	100

Table III: BMI (Body Mass Index) of the patients (n=110)

BMI (kg/m^2)	Group-I		Group-II	
	n	%	n	%
19-24	17	30.9	20	36.4
25-29	28	50.9	26	47.4
≥30	10	18.2	9	16.4
Total	55	100	55	100

Table IV: Age distribution of the patients (n=110)

Marital age (years)	Group - I		Group - II		p value
	n	%	n	%	
1-5	25	45.5	31	56.4	0.688^{ns}
>5	30	54.5	24	43.6	
Total	55	100	55	100	
Mean±SD	6.5±3.4		6.8±4.2		0.404^{ns}

NS= not significant (p>0.05)
P value reached from chi square test.

Table V: History of MR on the patients (n=110)

MR	Group I		Group II		p
	n	%	n	%	
Yes	10	18.2	6	10.9	0.01^{S}
No	45	81.2	49	89.1	
Total	55	100	55	100	

s=significant
P value reached from chi square test.

Table VI: History of abortion on the patients (n=110)

Abortion	Group I		Group II		p
	n	%	n	%	
Yes	6	10.9	12	21.8	0.406^{ns}
No	49	89.1	43	78.2	
Total	55	100	55	100	

Table VII: Sign of ovulation of the patients (n=110)

Parameters	Group – I Mean±SD	Group – II Mean±SD	P Value
	(Range)	(Range)	GIVs G II
Follicular development by day 12/13(in mm)	20.1 ± 3.6	21.5±3.9	
Number developing follicle (≥18mm) by day 12/13	1.2±0.86	2.4±0.76	0.417 ns
Endometrial development by day 12/13(in mm)	9.2±2.2	3.1 ± 1.9	0.612 ns

Table VIII: Total number of ovulation as measured by day 21 serum progesterone level (n=110)

No of ovulation	Group – I		Group- II		p value
	n	%	n	%	
Yes	40	72.7	45	80.1	$<0.05^{s}$
No	15	27.3	10	19.9	
Total	55	100	55	100	

s=significant
P value reached from Chi square test

Table IX: Pregnancy rate of the patients (n=110)

Pregnancy	Group I		Group II		p
	n	%	n	%	
YES	11	20.0	10	18.1	0.68^{ns}
NO	44	80.0	45	81.9	
Total	55	100	55	100	

ns=not significant
P value reached from Chi square test

Discussion

The observational prospective study was carried out with the objectives to compare the success of Letrozole and Clomiphene citrate for ovulation induction in anovulaory patients. To evaluate the efficacy of Letrozole and clomiphene citrate in ovulation induction and also to discuss the cases of failed ovulation and pregnancy.

This prospective study was done during July 2011 to December 2011in anovulatory patients. Atotal 110 sub-fertile patients were selected and subdivided into two groups. Each group consists of 55 patients. Among them 55 patients of newly diagnosed cases of anovulatory sub-fertility were studied with letrozole considered as group I and 55 cases sub-fertility studied with Clomiphene citrate considered as group II.

In the present study the age range of the patients were 20 -40 years where the age range between 21-30 years were predominant among the two groups. Einashar et al (2004) have shown in their prospective study in 44 sub-fertile patients treated with Clomiphene citrate, the age range was 21-37 years which is similar to the present study[4]. Similarly, Davar et al. (2006) has observed the mean age was 29± 2.9 years in Letrozole group and 25,7± 3.8 years in Clomiphene citrate group which is comparable to the present study.[2]

In the current study it was observed that most of the patients were in the middle income group whose monthly income were TK 5000-10000 in both study groups.

Regarding the type of sub-fertility in this study, it was observed that the majority of the patients were primary sub-fertile in two groups. Duration of sub-fertility of the patients was 1-20 years among the two study groups and a good number of patients were 1-5 years of sub-fertility in two study groups in this study. Davar et al. (2006) has observed the mean duration of sub-fertility was 5.95 ± 2.9 years in Letrozole group and 5.23 ± 2.5 years in Clomiphene citrate group and the difference was not statistically significant which is comparable to the present stud Y2 . Elnashar et al (2004) has observed almost identical period of sub-fertility which was 4.78± 2.86 years.[16]

The mean duration of marital age of the patients was not statistically significant ($p>0.05$) in the present study which were 6.5 ± 3.4 years in group I and 6.8 ± 4.2 years in group II. It was observed that 10 (18.2%) in group I and 6(10.9%) in group II under went MR. In this small series it was observed that a small number of abortion was found which were 6(10.9%) in group I and 12(21.8%) in group II. In the study mean diameter of mature follicle was 20.1± 3.6 mm in group I

newly diagnosed cases of sub-fertility treated with Letrozole) and 21.5± 3.9 ~ in group II (Newly diagnosed cases of sub-fertility treated with Oarimphene citrate). The difference was not statistically significant (p>0.05). These results are in agreement with Elnashar et.al (2004), where they observed the mean diameter of mature follicle was 19.4± 0.96 mm in patients4 rested with Letrozole [4.] Mosammat R. Begum et al. (2005) found the mean diameter of follicle was 12.7 ± 1.0 mm with clomiphene citrate cases and 21.5± 2.66 mm with Letrozole in CC resistant cases.[21] Regarding the number of mature follicle (≥18mm) in the current study it was 12 ± 0.86 mm in group I (treated with Letrozole) and 2.4± 0.76 mm in group I (treated with Clomiphene citrate group. These results are in agreement with the results of Elnashar et al (2004)16. This limited number of follicles (range 1-2) with Letrozole will decrease the risk of multiple pregnancy and ovarian hyper-stimulation syndrome. Therefore Letrozole treatment cycle does not need intensive monitoring compared to CC and Gonadotrophin. In this study endometrial thickness was 9.2± 2.2mm in group I (treated with Letrozole) and 8.1±1.9 mm in group II (treated with Clomiphene citrate). The an endometrial thickness was higher in Letrozole group but not significant. Elnashar et al (2004) has observed the mean endometrial development was 2± 1.13 mm treated with Letrozole which is a little higher than the present study. The ovulation rate in the current study was 72.7 % in Leytrozole treated group J 80.1 % in Clomiphene citrate treated group. Very few studies have reported the effect of Letrozole either alone or in comparison to Clomiphene citrate in ovulation induction. Benha University, Hospital, Egypt, Elnashar et al. (2004) evaluated the efficacy of Letrozole in a dose of 2.5 mg /day from day 3 to day 7 of the menstrual cycle on 44 sub-fertile patients and found ovulation occurred in 24 cases (54.6 %) 4.

In the current study it was observed that pregnancy rate was higher in group I treated with Letrozole in comparison to group II treated with Clomiphene citrate but the difference was not statistically significant (P > 0.05). The Pregnancy rate was 11 (20%) in group I and 10 (18.1 %) in group II which is comparable to Bayar(2006)[17] where pregnancy rate was 19.4% in patient -rested with 100 mg Clomiphene citrate and 21.6% in Letrozole group .

Conclusion

The induction of ovulation with Letrozole in anovulatory patients is associated with limited number of mature follicles, no adverse effect on endometrium but the number of clinical pregnancies was higher in Letrozole group than in Clomiphene citrate treated group. However the Clomikphene citrate treated patients developed multiple follicles, therefore the changes of multiple pregnancy is more. But the other parameters were more or less comparable in both groups. So, the efficacy of both drugs is similar. So in my study, we can demonstrated that Letrozole is as effective as Clomiphene citrate in anovulatory infertility and can be considered as a good alternative to Clomiphene citrate.

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