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ORIGINAL ARTICLE

Outcome of treatment with letrozole versus gonadotrophins stimulated IUI (Intrauterine Insemination) in the management of unexplained infertility.

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ABSTRACT… Objective: To compare the outcome of treatment in patients with primary unexplained infertility with gonadotrophin v/s letrozole stimulated IUI (intrauterine insemination). **Study Design:** Prospective Experimental study. **Setting:** Obstetrics and Gynaecology Department of Al- Shifa Healthcare Group, Al- Shifa Multi Speciality Medical Centers, Sharjah, United Arab Emirates. **Period:** October 2022 till April 2023. **Methods:** 110 patients of primary unexplained infertility were included in this study who were randomly divided into 2 groups and were treated with stimulated IUI. One group was stimulated with Gonadotrophin, Gonal-f, while, the other was treated with letrozole, an oral anti-estrogen. Ovarian response was noted in the form of 2 dominant follicles of 18-22 mm in diameter, in whom, ovulation was triggered with 250 mcg of choriogonadotrophin-alpha. Patients who did not had menstruation on the expected date, were tested for pregnancy 1 week after missing the due date of menstruation. Statistically significant parameters were recorded between the 2 groups (serum AMH value, FSH value, BMI and Age) with and without ovulation and pregnancy. **Results:** In the letrozole treated group; 28 out of 55 patients responded in the form of adequate ovarian response, whereas 27 patients did not attain adequate ovarian response. Among the 28 ovulating patients 12 got pregnant being 21.8 % of total letrozole treated women. Regarding gonadotrophin group, 44 out of 55 patients had an adequate ovarian response, being 80 % and only 11 patients could not attain an adequate ovarian response. Out of ovulating patients, pregnancy was achieved in 27 patients being 49.09%. **Conclusion:** Among the women with unexplained infertility of primary origin, treated with stimulated Intra-Uterine Insemination with gonadotrophins and letrozole, ovulation as well as pregnancy rates were significantly higher among the patients who were treated with gonadotrophins for controlled ovarian stimulation, in terms of ovulation as well as pregnancy rates, as compared to letrozole treated patient. Moreover, regarding the outcomes measured in this study; ovulation as well as pregnancy, both are seen to be higher among the younger ages, high AMH, low FSH, low basal LH and low BMI patients.

Key words: AMH, Dominant Follicle, FSH, Gonal-f, Letrozole, LH, Ovulation Induction, Pregnancy.

INTRODUCTION

Unexplained infertility is defined as inability to conceive, in spite of regular unprotected sexual intercourse for at least 12 months, if age is up to 35 years, and up to 6 months in women of 36 years and above, with no identifiable cause of infertility, with normal semen analysis, normal mid luteal phase serum progesterone and a confirmed tubal patency.[1] Infertility has an identifiable cause in as many as 75% of the cases, but still, in significant number of infertile couples, being almost 25% worldwide[2], no cause can be identified. Though, Unexplained infertility is diagnosed in the absence of any abnormalities of the female and male reproductive systems after 'standard' investigations, still, a consensual standardization of the diagnostic work-up is lacking. Pragmatic treatment options in these couples are directed at trying to improve chances to conceive, with efforts being directed at, intrauterine insemination (IUI) with ovarian stimulation and in vitro fertilization (IVF) as standard clinical practices, while expectant management remains an important alternative.

Various available treatment options have been tried for the management of unexplained infertility, including ovulation induction with anti-estrogens, IUI (Intra-Uterine Insemination) with/without controlled ovarian stimulation and IVF.

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As far as ovulation induction drugs are concerned, it is evident from the previous literature that as compared to expectant management, Clomiphene citrate had no statistically significant difference in shortening the time to pregnancy and live birth rates.[3,4] However, Letrozole is found to be more effective in the management of unexplained infertility as compared to clomiphene citrate[5] and expectant management, and it is recommended as first choice by ACOG in 2018 (committee opinion No.738).[6,7] That's why Letrozole is experimented in this study.

Next to anti-estrogens, is the treatment with Gonadotrophins. Various Gonadotrophin drugs are available currently. The history underpinning the development of gonadotrophins spans over 300 years and provides a splendid example of how basic experimentation and technological advances have progressed to clinical application. Following the discovery of germ cells in 1677 and realizing in 1870 that fertilization involved the merging of two cell nuclei, one from the egg and one from sperm, it took another 40 years to discover the interplay between hypothalamus, pituitary and gonads. The potential roles of gonadotropin regulation were discovered in 1927.[8]

Gonal-f is a gonadotrophin containing Follitropin alpha, which is a recombinant human follicle stimulating hormone. Each vial contains 5.5 mcg of follitropin-alfa, equivalent to 75 IU. It is used in an-ovulation unresponsive to anti-estrogen class of drugs. It is mainly used for multi-follicular development in women undergoing ART.

In low dose protocol, 75 to 150 IU is given daily with an increment of 37.5 to 75 IU at weekly or fortnightly intervals preferably, if adequate ovarian response is not achieved. The maximum daily dose can be increased up to 225 IU. If a patient fails to respond after 4 weeks of treatment with Gonal-f, then this treatment should be abandoned-1.

Although IVF is the definitive treatment for unresolved unexplained infertility of 2 years duration or more, but it is very expensive, time demanding and associated with risks of ovarian hyper-stimulation and multi-fetal pregnancies with their inherent risks of perinatal and postnatal morbidity and mortality, obstetric complications and significant burden on the healthcare system.[9] Hence, IUI with controlled ovarian stimulation was selected as the treatment modality in this study. IUI is a process of introduction of a prepared semen sample into the uterine cavity with the help of a special cannula, which bypasses the cervical factors and ensures the presence of highly motile sperms in the upper genital tract.[10]

METHODS

In this study 110 women with unexplained primary infertility were recruited after fulfilling the criteria of informed patient consent and Ethical Committee approval (1197-1/8/22). Unexplained infertility was diagnosed after confirming normal semen analysis and mid luteal phase serum progesterone level and tubal patency.

Patients with medical disorders, previous cervical surgery, previous treatment with ovulation induction and IVF and usage of hormonal contraceptives were excluded from the study.

Age, BMI and a detailed medical, obstetric, gynecological and contraceptive histories were recorded. Serum FSH, LH, TSH, Prolactin and AMH between D-2nd to D-5th of the menstrual cycle along with metabolic profile was done. TV-USG was done before ovulation induction therapy, for the assessment of antral follicle count, ovarian morphology and pathology. Patients were divided into 2 groups randomly and ovulation induction with letrozole was done in one group and with inj. Gonadotrophin Gonal-f in the other group. 5 mg of Letrozole was used once per day starting from day -3rd to day- 5th of the menstrual cycle for 5 days and ovarian response was monitored with TVS-USG, starting from day-11th of the cycle, every 2 days untill an adequate ovarian response was achieved i.e. 2 DF's of 18-22 mm in diameter.

In Gonadotrophin group; Inj Gonal-f was started at a dose of 75IU s/c every day. Follicle study was done after every 2 days, starting from d-11th of the cycle till an adequate ovarian response was

achieved. Dose of Gonal-f was increased by an increment of 37.5 IU after 1 week in those patients in which previous dose could not lead to follicular development. Maximum number of patients responded to 150 IU dose in 4 weeks time period.

Ovulation was triggered with the help of inj. Choriogonadotrophin-alpha with a dose of 250 micrograms/0.5ml, subcutaneously to all those patients, from both groups, who developed 2 DFs of 18-22 mm in diameter. After 36-hours of ovulation trigger, IUI was performed in an out-patient settings after adopting the strict aseptic measures. Those patients who missed their menstruation at the expected date were tested for pregnancy with serum beta- HCG 1 week after missing the due date. Those who had menstruation same cycle was repeated in both groups.

Development of the DFs and positive pregnancy test were the outcomes measured in this study.

RESULTS

In this study, a total of 110 patients with unexplained infertility were included and categories into 2 groups with 55 patients in each. One group of patients was treated with Gonadotrophin injection, Gonal F for Follicular Development, followed by Induction of ovulation in those who cases who showed adequate ovarian response in the form of at least 2 dominant follicles of 18-22 mm in diameter. Ovulation trigger was followed by (36 hours layer) Intra-Uterine Insemination. Among those cases who were treated with Gonadotrophins, 22/55 got pregnant by this method being 40%, whereas 33/55 could not achieve this outcome.

As far as Letrozole treated group of patients is concerned, 10/55 cases conceived with this treatment method being 18.2%, however, 82.8% could not get pregnant with letrozole stimulated IUI.

Is evident from the literature that, success of Gonadotrophin treated infertility has been higher, as compared to Letrozole, as an ovulation induction drug, for the treatment of infertility and it has been consistent across the studies. Same trend has been observed in this study also.

In this study, number of women got pregnant with Gonadotrophin therapy were 22/55 i.e. 40%, which is more than double, as compared to Letrozole group, being 10/55 i.e 18.2%. Overall pregnancy rate was 29.1% with both infertility treatments.

When we look at the confounders, we can clearly observe that more pregnancies were achieved in younger age group and in those women who were having healthier BMI, whether it was Gonadotrophin or Letrozole, the medication for ovulation induction.

As far as age is concerned, maximum number of pregnancies were seen in the patients between 21 to35 years of age, being 68.8%, whereas teenage group pregnancies were of minimum number of 3/10 being 9.4%. Overall success of ovulation induced IUI treatment has been observed minimum in under-weight I.e less than 20 BMI, being 3.1%, further emphasizing the importance of optimal fat percentage of the body, for spontaneous as well as treated conception.

The association of healthier BMI with successful pregnancy outcome in the treatment of unexpected infertility with ovulation induction medication Has been observed in this study also, with maximum number of conceptions were reported in women with BMI of 21-25, being 59.4% (19/52). It was followed by over-weight women between 26-30 BMI, where success of treatment was 28.1%, whereas those who were having obesity, successful pregnancy outcome was reported only in 9.4% of the cases.

Interestingly, overall treatment success in the form of conception, was almost 1/3rd in over-weight women as compared to healthy-weight patients, again stressing upon importance of maintaining healthy weight for successful pregnancy outcome.

Independent sample t-test is applied for comparison of quantitative variables and chi-square test is applied for comparison of

qualitative variables. No relative risk and odds ratio is calculated as your study is interventional study no case control or cohort study.

DISCUSSION

Infertility is defined as the failure to achieve pregnancy after 12 months of regular unprotected sexual intercourse.[1,2,3]

	N	Minimum	Maximum	Mean	Std. Deviation
Age in years	110	18	40	29.88	5.563
BMI	110	18	34	25.33	4.016
Valid N (list wise)	110				

Table-I. Descriptive statistics

	Group	N	Mean	Std. Deviation	P-Value
Age in years	Gonadotropin	55	30.09	5.529	0.695
	Letrozole	55	29.67	5.641	
BMI	Gonadotropin	55	24.98	3.974	0.369
	Letrozole	55	25.67	4.065	

Table-II. Gonadotrophins and letrozole, distribution according to age and BMI

		Group		Total
		Gonadotropin	Letrozole	
Age distribution	< 20 years	5 (9.1%)	5 (9.1%)	10 (9.1%)
	21-35 years	37 (67.3%)	38 (69.1%)	75 (68.2%)
	> 35 years	13 (23.6%)	12 (21.8%)	25 (22.7%)
Total		55 (100.0%)	55 (100.0%)	110 (100.0%)

Table-III. Distribution in different age groups
p-value = 0.974

		Group		Total
		Gonadotropin	Letrozole	
BMI	< 20	4 (7.3%)	4 (7.3%)	8 (7.3%)
	21-25	26 (47.3%)	26 (47.3%)	52 (47.3%)
	26-30	17 (30.9%)	19 (34.5%)	36 (32.7%)
	> 30	8 (14.5%)	6 (10.9%)	14 (12.7%)
Total		55 (100.0%)	55 (100.0%)	110 (100.0%)

Table-IV. BMI wise distribution in both groups
p-value = 0.941

		Group		Total
		Gonadotropin	Letrozole	
Ethnicity	South Asians	34 (61.8%)	36 (65.5%)	70 (63.6%)
	Arabs	10 (18.2%)	11 (20.0%)	21 (19.1%)
	Western	6 (10.9%)	3 (5.5%)	9 (8.2%)
	Philipines	4 (7.3%)	4 (7.3%)	8 (7.3%)
	Others	1 (1.8%)	1 (1.8%)	2 (1.8%)
Total		55 (100.0%)	55 (100.0%)	110 (100.0%)

Table-V. Ethnicity and infertility
p-value = 0.894

		Group		Total
		Gonadotropin	Letrozole	
Pregnancy	Yes	22 (40.0%)	10 (18.2%)	32 (29.1%)
	No	33 (60.0%)	45 (81.8%)	78 (70.9%)
Total		55 (100.0%)	55 (100.0%)	110 (100.0%)

Table-VI. Outcome (pregnancy) of treatment
p-value = 0.012

		Pregnancy		Total
		Yes	No	
Age distribution	< 20 years	3 (9.4%)	7 (9.0%)	10 (9.1%)
	21-35 years	22 (68.8%)	53 (67.9%)	75 (68.2%)
	> 35 years	7 (21.9%)	18 (23.1%)	25 (22.7%)
Total		32 (100.0%)	78 (100.0%)	110 (100.0%)

Table-VII. Age and infertility treatment success
p-value = 0.99

		Pregnancy		Total
		Yes	No	
BMI	< 20	1 (3.1%)	7 (9.0%)	8 (7.3%)
	21-25	19 (59.4%)	33 (42.3%)	52 (47.3%)
	26-30	9 (28.1%)	27 (34.6%)	36 (32.7%)
	> 30	3 (9.4%)	11 (14.1%)	14 (12.7%)
Total		32 (100.0%)	78 (100.0%)	110 (100.0%)

Table-VIII. Impact of BMI on success of treatment with both drugs
p-value = 0.368

		Pregnancy		Total
		Yes	No	
Ethnicity	South Asians	19 (59.4%)	51 (65.4%)	70 (63.6%)
	Arabs	7 (21.9%)	14 (17.9%)	21 (19.1%)
	Western	3 (9.4%)	6 (7.7%)	9 (8.2%)
	Philipines	1 (3.1%)	7 (9.0%)	8 (7.3%)
	Others	2 (6.2%)	0 (.0%)	2 (1.8%)
Total		32 (100.0%	78 (100.0%)	110 (100.0%)

Table-IX. Ethnicity and outcome of treatment with both drugs
p-value = 0.176

Approximately 75% of infertile couples have an identifiable cause, however, remaining 25% of infertile couples have no identifiable cause, called unexplained infertility.[2,3] Approximately 1 in 8 women aged 15 to 49 years receive infertility services.[2] Although success rates vary by age and accurate diagnosis and effective therapy along with shared decision-making can facilitate achievement of fertility goals in many couples treated for infertility.

This study is focused on ovarian stimulation with 2 different drugs, followed by INTRA-UTERINE INSEMINATION (IUI). Drugs studied are oral as well as injectable and results are compared with each other and with the evidence based guidelines and previous research. Though Results mainly support the evidence based on previous researchers, however, somewhere conflicting evidence also exists.

For couples with unexplained infertility, the American Society for Reproductive Medicine recommends an initial 3 to 4 cycles of ovarian stimulation with intrauterine insemination- 5, But, this study favors the use of Gonadotrophins as the agent of choice, for ovarian stimulation and IUI, as compared to Letrozole stimulated IUI, in terms of more number of ovulations and pregnancies.

When, we look at the mechanism of action of ovulation inducing oral medications, we see that end result is the same, i.e. Increased Pituitary Gonadotrophin Production. Clomiphene citrate, a selective estrogen receptor modifier that blocks the negative feedback effect of circulating estradiol and causes an increased hypothalamic gonadotropin-releasing hormone (GnRH) pulse frequency and subsequent pituitary FSH and luteinizing hormone (LH) production, promoting ovarian follicular growth.

Letrozole blocks aromatase enzyme, reducing serum concentrations of estradiol and stimulating pituitary gonadotropins production. Though end result is the same but outcomes vary widely. Literature supports higher efficacy of Letrozole as compared to Clomiphene citrate.[4]

Both clomiphene citrate and aromatase inhibitors have a multiple pregnancy rate of less than 10%, the majority of which are twin gestations.[6,7,8,9,10,11]

Where natural production of pituitary Gonadotrophins is ineffective in achieving the desirable outcomes in terms of ovulation and conception, Injectable drugs are used, i.e. Gonadotropins. Gonadotrophin therapy is very crucial to infertility treatment. It is evident from the literature that, success of Gonadotrophin treated infertility has been higher, as compared to Letrozole, as an ovulation induction drug, for the treatment of infertility and it has been consistent across the studies. Same trend has been observed in this study also.[12,13]

IUI is accomplished by placing the prepared sperm sample into the uterus 24 to 36 hours after an endogenous LH surge or an exogenous ovulation trigger. IUI is typically first-line therapeutic strategy for mild male sub-fertility, however, it has been recommended as an initial treatment option with controlled ovarian stimulation in clinical practice and research, and is evidence based approach before opting for IVF.[13]

A Cochrane review of 10 RCTs involving 757 patients, in 2016, found no evidence of a difference between IUI and timed intercourse.[14] However, evidence was low quality. In patients with unexplained infertility, IUI should be administered in combination with ovulation stimulation because IUI alone does not increase pregnancy rates in this population.[15]

In this study also, number of women got pregnant with Gonadotrophin therapy were 22/55 i.e. 40%, which is more than double, as compared to Letrozole group, being 10/55 i.e 18.2%. Overall pregnancy rate was 29.1% with both infertility treatments.
On contrary to my study results, The Fast Track and Standard Treatment Trial, which randomized women with unexplained infertility to either 3 cycles of clomiphene-IUI followed by 3 cycles of gonadotropins-IUI prior to IVF or 3 cycles of clomiphene-IUI followed by cycles of IVF, determined that the time to pregnancy was significantly faster (8 vs 11 months), with a cost savings of $2624 per couple, in the clomiphene to IVF group, Thus, did not considering the gonadotropin-IUI cycles superior to oral drugs for ovulation induction therapy for unexplained infertility.[15]

Age is another consideration that should guide decision-making. Success rates for fertility treatment decline with age: the per-cycle pregnancy rates for clomiphene and intrauterine insemination are 8.2% in women aged 35 to 37 years, 6.5% in women aged 38 to 40 years, 3.6% in women aged 41 to 42 years, and 0.8% in women older than 42 years.[17]

One RCT evaluating the treatment strategies for unexplained infertility in women 38 to 42 years old, found higher live birth rates in couples undergoing immediate IVF (31.4% over 2 treatment cycles) as compared with those undergoing ovarian

stimulation–IUI with clomiphene (15.7%) or gonadotropins (13.5%).[18] Thus, immediate IVF may be considered as a first-line treatment strategy in women older than 38 to 40 years.

When we look at the confounders in this study, we can clearly observe that more pregnancies were achieved in younger age group and in those women who were having healthier BMI, whether it was Gonadotrophin or Letrozole, the medication for ovulation induction, further supporting the literature and previous studies.

As far as age is concerned, maximum number of pregnancies were seen in the patients between 21 to35 years of age, being 68.8%, whereas teenage group pregnancies were of minimum number of 3/10 being 9.4%. Overall success of ovulation induced IUI treatment has been observed minimum in under-weight I.e less than 20 BMI, being 3.1%, further emphasizing the importance of optimal fat percentage of the body, for spontaneous as well as treated conception.

Systematic reviews and meta-analyses have shown that female obesity (BMI >30) is negatively associated with live birth rates following fertility treatments.[19] For obese women, delaying conception to achieve weight loss should be strongly considered. In a secondary analysis of 2 RCTs of overweight/obese women with infertility, delayed treatment with ovulation induction therapies, after lifestyle modification and weight loss resulted in improved ovulation and live birth rates when compared with immediate treatment.[20] However, 2 recent RCTs found that for 962 infertile, obese women (BMI, 30–35) undergoing IVF, randomization to weight reduction with a low calorie diet (880 kcal/d for 12 weeks; mean weight reduction, 9.44 kg) did not improve live birth rates in the index cycle.[21] Whether weight loss can reverse the deleterious effect of obesity on oocyte quality is also not clear.[21]

Like above mentioned previous studies, the association of healthier BMI with successful pregnancy outcome in the treatment of unexplained infertility with ovulation induction medication has been observed in this study also, with maximum number of conceptions were reported in women with BMI of 21-25, being 59.4% (19/52). It was followed by over-weight women between 26-30 BMI, where success of treatment was 28.1%, whereas those who were having obesity, successful pregnancy outcome was reported only in 9.4% of the cases. Interestingly, overall treatment success in the form of conception, was almost 1/3rd in the over-weight women as compared to healthy-weight patients, again stressing upon importance of maintaining healthy weight for successful pregnancy outcome.

This study's findings are consistent with the results of previous studies in terms of efficacy of Gonadotrophins, as is evident from a Cochrane review in 2019, which concluded that gonadotropins resulted in a higher live birth rate than continued oral medication, after 6 cycles for women with infertility, it was associated with more side effects like multiple pregnancy rates, being as high as 36% have been reported with the use of gonadotropins[13], and Ovarian hyper-stimulation syndrome with its associated serious complications (1%–5%).[12]

Hence, this study also supports the findings seen in several studies in the past. According to this study, it is clearly evident that Gonadotrophin are the agent of choice, for stimulated Intra-uterine insemination (IUI), as compared to Letrozole as an ovulation induction drug, for the treatment of unexplained infertility, in those subset of patients who do not opt for IVF and for those who don't find IVF as a cost effective therapy.

Second important observation which is consistent across the Studies is importance of healthy weight and younger age for the overall success of unexplained infertility treatment.

CONCLUSION

According to this study, it is clearly evident that Gonadotrophin are the agent of choice, for stimulated Intra-uterine insemination (IUI), as compared to Letrozole as an ovulation induction drug, for the treatment of unexplained infertility, in those subset of patients who do not opt for

IVF and for those who don't find IVF as a cost effective therapy.

Second important observation is importance of healthy weight and younger age, for the overall success of unexplained infertility treatment.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Nadia Sharif:** Manuscript writing, data collection.
2	**Rashid Mahmood:** Study design, data analysis.