ESP IJAST
ESP International Journal of Advancements in Science & Technology
ISSN: 2583-9233 / Volume 3 Issue 1 January 2025 / Page No: 51–67
Paper Id: IJAST-V3I1P101 / Doi: 10.56472/25839233/IJAST-V3I1P101

Research Article

Assessment of Effectiveness and Outcome of Letrozole Therapy Among Infertile Women at a Secondary Care Hospital: A Retrospective Study

Dawn VJ[1*], Irene V R[2], Anitta Shaji[3], Sreelakshmi N P[3], Sumaya S[3], Elsa Maria John[4], Megha O. O [4]

[1]*Associate Professor, Department of Pharmacy Practice, Sanjo College of Pharmaceutical Studies, Vellapara, Chithali P.O. Kuzhalmannam, Palakkad-678702, Kerala, India.*

[2]*Assistant Professor, Department of Pharmacy Practice, Sanjo College of Pharmaceutical Studies, Vellapara, Chithali P.O. Kuzhalmannam, Palakkad-678702, Kerala, India.*

[3]*8th Semester B Pharm, Sanjo College of Pharmaceutical Studies, Vellapara, Chithali P.O. Kuzhalmannam, Palakkad-678702, Kerala, India.*
[4]*1st Semester M. Pharm, Department of Pharmacy Practice, Sanjo College of Pharmaceutical Studies, Vellapara, Chithali P.O. Kuzhalmannam, Palakkad-678702, Kerala, India.*

Received Date: 10 February 2025 Revised Date: 20 February 2025 Accepted Date: 03 March 2025

Abstract: *The initiative seeks to investigate the efficacy of Letrozole therapy in women undergoing infertility treatment. The goal is to characterize the types of infertility histories among women getting infertility treatment and to estimate the prevalence of Letrozole use during pregnancy. This is a retrospective observational study conducted at the Gynaecology Department of Paalana Institute of Medical Science, Palakkad, Kerala. A self developed data collection form was used to collect the data. Inclusion criteria were women above the age of 20, all women having ovulation induction therapy, and infertile women getting Letrozole medication. Women who did not continue to take Letrozole were excluded. Prior to data collection, the Institution Ethics committee gave their consent. The gathered data was examined and documented. Letrozole's efficacy was statistically examined using the Chi square approach. At end of Treatment Status out of the 49 patients, 26 became pregnant, whereas the remaining 23 did not respond to treatment, meaning they did not become pregnant. This findings shows, Letrozole is an effective method of ovulation induction, particularly for individuals with anovulatory infertility.*

Keywords*: Aromatase inhibitors, Infertility, Letrozole, Reproductive system, , Ovulation induction*

I. INTRODUCTION

Anovulation is the nonappearance of ovulation, or the discharge of an ovum from a female's ovaries. The cause of infertility is frequently chronic anovulation. Ovulation inducement remains among the most crucial treatments for ladies with ovulation dysfunction infertility [(1)].

Clomiphene citrate, a widely used ovulation inducer, may hinder pregnancy due to its anti-estrogenic effects on the endometrium and cervical mucus. Exogenous gonadotropins, a second-line option, pose risks of multifetal pregnancy and ovarian hyperstimulation syndrome, necessitating close monitoring. Letrozole, an aromatase inhibitor initially developed for breast cancer, was identified in 2001 as an effective ovulation inducer without these complications [(2)].

II. REPRODUCTIVE SYSTEM

The combination of organs that make up the female reproductive system are in charge of the human regenerative system [3].Ovaries, oviduct, fallopian tubules, uterus, cervix, uteri, vagina, and external genetalia are among its constituents [3,4].

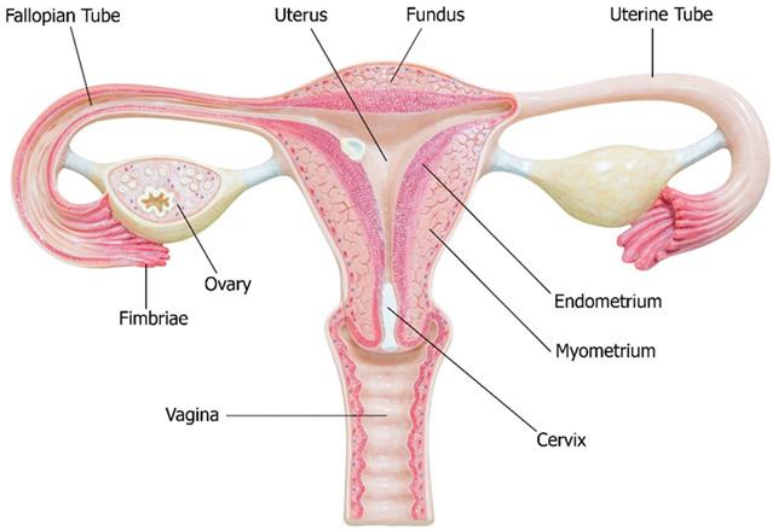

Figure 1: Female reproductive system [5]

III. PHYSIOLOGY OF REPRODUCTIVE SYSTEM

In normal physiology, hypothalamic GnRH regulates the release of FSH and LH, stimulating ovarian follicle development. Although 30–40 follicles start growing each cycle, only one releases a mature egg. The dominant follicle produces rising estrogen levels, triggering an LH surge that induces ovulation [6].

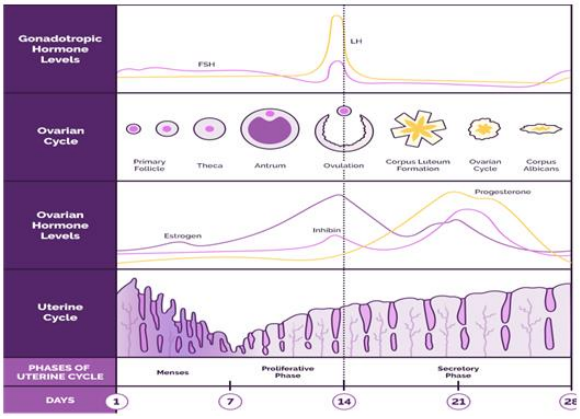

Figure 2: Female reproductive cycle [7]

IV. INFERTILITY

Infertility is the lack of pregnancy after 1 year of frequent, insecure contact. It is properly acknowledged, yet, that many couples are able to become pregnant without treatment within a year or more[8].The existence or absence of a previous pregnancy determines whether infertility is classified as primary or secondary[9].

Table 1: Primary and secondary infertility [6]

PRIMARY INFERTILITY	SECONDARY INFERTILITY
It occurs if a pair has not had any previous pregnancies.	It happens while a couple has earlier conceived though the pregnancy was unsuccessful due to miscarriage or an ectopic pregnancy.

Both female and male factors contribute to infertility. In women, menstrual and ovulation irregularities, along with uterine issues, are common causes. Male infertility often results from reduced sperm production, abnormal morphology, and impaired motility [9].

Unexplained infertility refers to couples with infertility who have had routine examinations, such as semen analysis, ovulation tests, and tubal patency, and found no significant abnormalities [10].

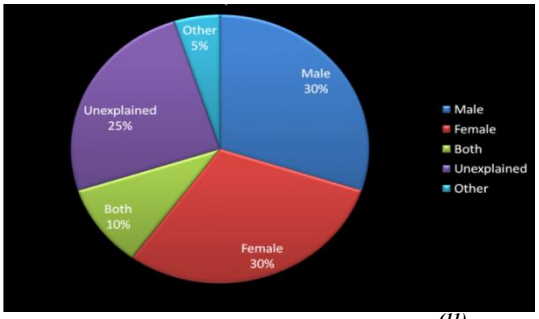

Figure 3: Infertility causes [11]

V. FEMALE INFERTILITY

Key causes of female infertility include:

(a) *Ovarian issues* (e.g., PCOS): PCOS is a hormonal imbalance that leads to irregular periods and problems conceiving. Most women with PCOS have many tiny cysts on their ovaries, hence the name [13].

(b) *Tubal blockages*: The fallopian tube is necessary for natural conception because it facilitates sperm attachment and fertilization. Tubal obstruction is a frequent disease and a leading cause of infertility [14].

(c) *Pelvic inflammatory disease*: Tubal patency can be compromised by pelvic infections, adhesions, previous surgeries, endometriosis, polyps, tubal spasms, or congenital abnormalities. Adhesions, altered motility, and fimbrial obstructions are all examples of peritoneal factors [14].

(d) *Age-related factors*: Fertility declines with age due to ovarian aneuploidy, reducing embryo quality and increasing miscarriage risk. Older parental age also raises the risk of offspring illnesses [15].

(e) *Uterine abnormalities*: Ovarian dysfunction-related infertility can be caused by ovarian obstruction, ovarian dystrophy (damage or cysts), luteinized unruptured follicle syndrome (LUFS), in which the follicle fails to release the matured egg, resulting in anovulation, or a lack of eggs[16].

(f) *Previous tubal ligation*: Tubal ligation is a common contraceptive procedure, yet there is inconsistent evidence linking it to menstrual abnormalities [17].

(g) *Endometriosis*: Endometriosis is a progressive condition in which uterine lining tissue spreads beyond the uterus and affects the ovaries, fallopian tubes, and other abdominal organs [13].

VI. EVALUATION OF INFERTILITY

Physical Examination:

A physical examination can help identify factors contributing to a couple's infertility. For women, a focused assessment includes:

1. *General*: Evaluate height, weight (obesity/anorexia linked to hormone issues), and pulse (thyroid abnormalities may cause tachycardia or bradycardia) [18].
2. *Head and Neck***:** It includes a thyroid examination to check the size and existence of lumps [19].
3. *Breasts:* Assess development (Tanner stage), masses, skin changes, and galactorrhea [18].
4. *Abdomen*: Check for tenderness, masses, or surgical scars [18].
5. *Pelvis*: Pelvic examination often reveals normal external genitalia and vaginal surface. Digital examination may detect a retroverted, immobile, or tender uterus. Endometriomas can present as fixed adnexal masses. Tender nodules or fibrosis may be felt in the vaginal apex, peritoneal pouch, rectovaginal septum, with local discomfort correlating towards endometriosis severity [20].
6. *Skin*: Look for hirsutism and acanthosis nigricans [21].

Findings can guide the infertility workup. For instance, obesity, hirsutism, and acanthosis nigricans may suggest PCOS, while dysmenorrhea and a tender adnexal mass might indicate endometriosis [18].

Investigation:

The investigation of infertility or subfertility should be systematic and guided by clinical features rather than indiscriminate testing. Key considerations include:

- *Mid-luteal progesterone*: Used to assess ovulation. If levels are low, the test may need repeating since ovulation doesn't occur every cycle. The test is done 1 week prior to expected menstrual cycle [22].

- *FSH and LH levels***:** Particularly important if menstrual irregularities exist. High FSH suggests poor ovarian function, in case of increased LH/FSH rate [(22)].FSH is the main gonadotropin in women, promoting ovarian follicle development and dominant follicle selection during the ovulation cycle [(23)].

- *Thyroid function tests (TFTs)*: In both spontaneous and ART-assisted pregnancies, thyroid dysfunction negatively impacts maternal and fetal outcomes and is frequently associated with female infertility(24).Only warranted if clinical suspicion exists, as infertile women do not have a higher risk of thyroid disease compared to the general population[(22)].
- *Prolactin (PRL)*: Should only be measured when clinically indicated [(22)].

- *Chlamydia screening*: Essential, as it can cause infertility and subsequent procedures may increase the risk of pelvic inflammatory disease (PID)[(22)].Although the sexually transmitted disease Chlamydia trachomatis is a global concern to reproductive health, it is unknown how it contributes to infertility, particularly in asymptomatic patients[(25)].

VII. OVULATION INDUCTION

Ovulation induction and superovulation are the two primary methods of treating infertility. While superovulation increases the number of follicles in other forms of infertility, ovulation induction seeks to generate one follicle in anovulatory women [(26)].

Ovulation induction aims to develop a single pre-ovulatory follicle while maintaining optimal endometrial thickness and estradiol (E2) levels. The lowest effective FSH dose is used to prevent multiple follicles, with monitoring via ultrasounds and E2 testing. It primarily treats anovulatory infertility in WHO group I (hypogonadotropic hypogonadism) and group II (PCOS) patients, excluding those with hyperprolactinemia [(27)].

Table 2: Classification of ovulation induction drugs [(28)]

I.	SELECTIVE ESTROGEN RECEPTOR MODIFIER
	Clomiphene Citrate
II.	AROMATASE INHIBITORS
	Letrozole
III.	HUMAN CHORIONIC GONADOTROPIN (hCG)
	Recombinant hCG
	Urinary hCG

VIII. AROMATASE INHIBITORS

Aromatase inhibitors and inactivators suppress the aromatase enzyme, reducing estrogen synthesis from androgens. In premenopausal women, ovarian aromatase, regulated by LH, is the primary estrogen source. Postmenopause, estrogen mainly

originates from fat and muscle aromatase, while tissue-specific aromatase in the breast, uterus, and brain provides local estrogen through autocrine signaling [29].

Table 3: Drugs under Aromatase Inhibitors [29]

DRUG
I. FIRST GENERATION
Aminoglutethimide
II. SECOND GENERATION
Fadrozole
Vorozole
III. THIRD GENERATION
Letrozole
Anastrozole
Exemestane

A. LETROZOLE THERAPY

It is a selective, nonsteroidal aromatase inhibitor that is delivered orally once daily and has mostly been utilized in postmenopausal females with mammary carcinoma.

Letrozole has been recently used in non-fertile premenopausal ladies due to its potential to increase FSH formation and induce egg release [30].

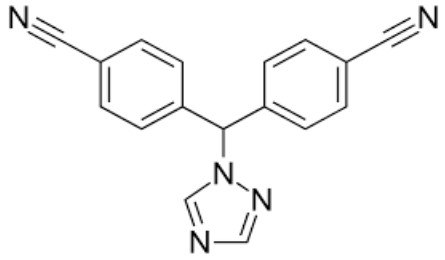

Figure 4: Chemical Structure of Letrozole [31]

B. MECHANISM OF ACTION

Letrozole inhibits aromatase, lowering oestrogen synthesis by 97% to 99%. Its ovarian induction method involves central oestrogen decrease, which eliminates negative feedback on the HPO axis, as well as peripheral suppression of androgen-to-estrogen conversion. This causes androgen buildup in the ovary, which stimulates FSH receptor expression and IGF-1 activity, hence boosting folliculogenesis([32].

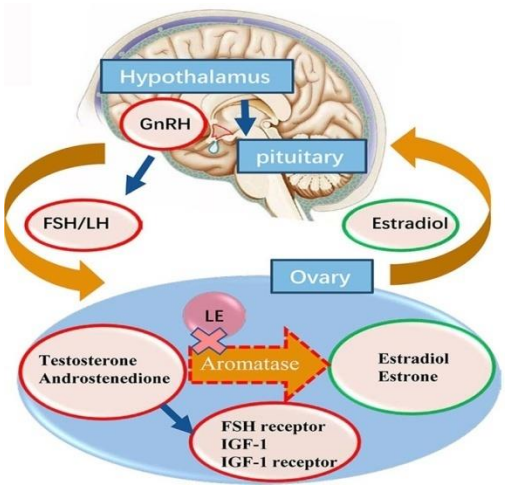

Figure 5: Mechanism of Action of Letrozole [33]

C. DOSE AND FREQUENCY

A daily dose of 2.5 or 5 mg of Letrozole is connected to larger egg sacs also a greater gestation ratio. It suggests that a daily dose of 5mg Letrozole is optimal for superovulation [34], Taken daily from days 3-7 of menstruation for a 5-day regimen [32].

D. PHARMACOKINETICS

- *Absorption*: Letrozole is rapidly absorbed orally, with 99.9% bioavailability. A 2.5 mg dose reaches peak plasma levels of 115 nmol/L within one hour in postmenopausal women [35], Bioavailability is 99.9% [36].
- *Distribution:* It has high systemic bioavailability and is widely disseminated in tissues, with an apparent volume of distribution of 1.87 L per kg [35].
- *Metabolism*: When Letrozole is provided with food, the rate of absorption decreases, but not the extent. After 2 to 6 weeks, plasma concentrations reach steady-state levels [35].
- *Elimination*: Letrozole is eliminated by metabolism by CYP2A6 and CYP3A4 into an inactive carbinol metabolite. It has slow clearance (2.21 L/h), a long half-life, and is primarily excreted via the kidneys [35].Half- life is 45 hours [36].

E. PHARMACODYNAMICS

Letrozole effectively inhibits aromatase activity in postmenopausal women and breast cancer patients. Doses of 0.5–2.5 mg/day reduce aromatization by over 98%, while 0.1–5 mg/day suppresses blood and urinary estrogens by >95% within two weeks. It also inhibits intra- tumoral aromatase in vitro and in vivo [35].

a. Uses

i. Safety of AIs in ovulation induction
ii. Combination of Letrozole and gonadotrophins for intrauterine insemination
iii. Letrozole for in vitro fertilization
iv. Fertility protection with Letrozole during cancer treatment

v. Letrozole treatment for PCOS [37]

b. Adverse Effects

Letrozole is generally well tolerated

- Headache
- Peripheral edema
- Bone and back pain
- Rash [37]
- Nausea
- Fatigue
- Hot flushes
- Hair thinning [37,38]

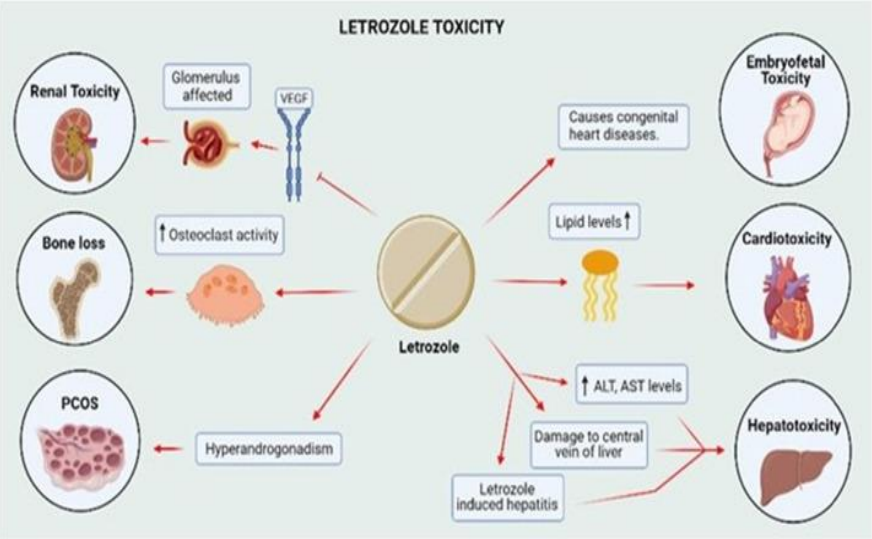

Figure 6: Letrozole Toxicity [39]

F. CLOMIPHENE CITRATE

Clomiphene citrate is a selective estrogen receptor modulator (SERM)(40).Clomiphene citrate inhibits hypothalamic estrogen receptors, boosting GnRH release, which stimulates FSH and LH synthesis, promoting follicular maturation and ovulation[41].The typical therapy is a dosage of 50 mg/d for 5 days, beginning from day 2 to 5 of the periods(40).Multiple pregnancies, missed abortions, ovarian hyperstimulation syndrome, vision problems, hot flashes, nausea, breast soreness, and the possibility of developing ovarian cancer are among the side effects[42].

G. HUMAN CHORIONIC GONADOTROPINS (hCG)

Exogenous hCG is often used to stimulate egg maturation and ovulation, however it raises the risk of OHSS and early LH spike in assisted reproductive cycles. GnRH agonists provide a safer option, generating LH and FSH surges with equivalent efficacy while lowering OHSS risk in IVF [(43)].

H. LETROZOLE WITH METFORMIN

Metformin enhances ovarian steroid synthesis and reduces androgens in PCOS, while Letrozole induces ovulation by inhibiting androgen-to-estrogen conversion, supporting endometrial development and implantation. Prolonged use may affect physical and mental well-being, but personalized nursing care addresses these challenges. Combining Letrozole and metformin, along with tailored patient care, optimizes endometrial receptivity, ovarian function, and metabolic balance, making it an effective PCOS infertility treatment [(44)].

I. LETROZOLE WITH GONADOTROPINS

Adding Letrozole to gonadotropins during ovulation stimulation reduces hormone requirements, particularly in unexplained or male-factor infertility, likely due to varying ovarian sensitivity. Letrozole lowers E2 and estrone levels, slightly reducing endometrial thickness without affecting conception rates. Despite increasing preovulatory follicles, pregnancy and multiple pregnancy rates remain stable [(45)].

IX. METHODOLOGY

The study is a retrospective observational study conducted in the Gynaecology Department at Paalana Institute of Medical Sciences, Kannadi-1, Palakkad, Kerala, over a period of three months. A convenient sampling method will be used, and data will be collected using a self-developed data collection form. The study population includes women undergoing infertility treatment at the institution. Women aged above 20 years, undergoing ovulation induction therapy, and receiving Letrozole treatment for infertility will be included, while those who do not follow up on their Letrozole treatment will be excluded. Ethical approval from the Institutional Ethics Committee was obtained before data collection. A pre-designed data collection form was used to gather patient demographics, fertility history, hormonal profiles, Letrozole treatment details, outcome measures, side effects, adverse events, and follow-up data. The collected data was analyzed and recorded, and the effectiveness of Letrozole was evaluated using the Chi-square test.

X. RESULT

Table 4: Categorization of study population based on age group

AGE	NUMBER OF PATIENTS (N=49)	PERCENTAGE (%)	MEAN =27.102 MEDIAN= 26 STANDARD DEVIATION =4.088
20-24	13	26.53	
25-29	21	42.85	
30-34	13	26.53	
35-39	2	4.09	

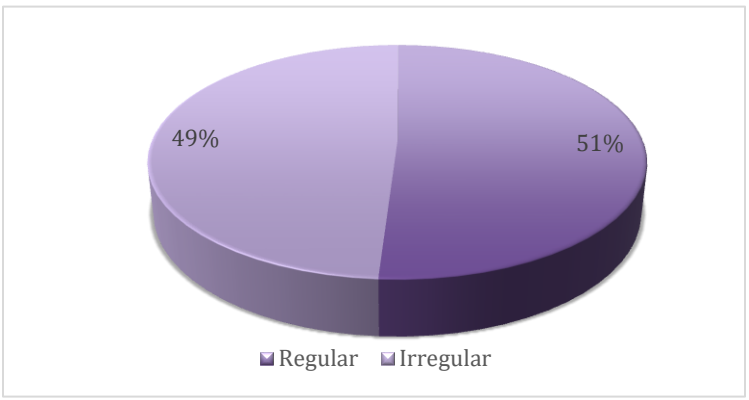

Figure 8: Categorization of study population based on menstrual history of patient

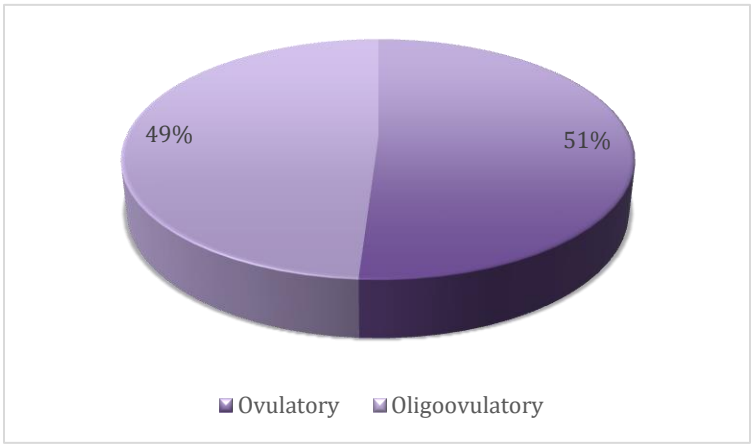

Figure 9: Categorisation of study population based on ovulation status

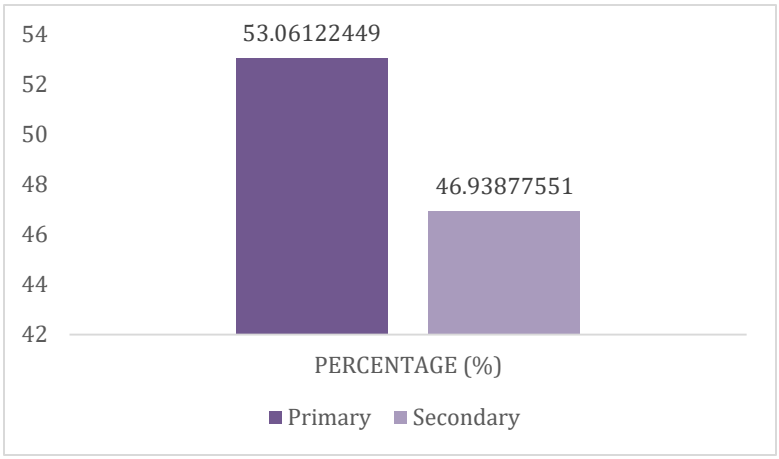

Figure 10: Categorization of study population based on type of infertility

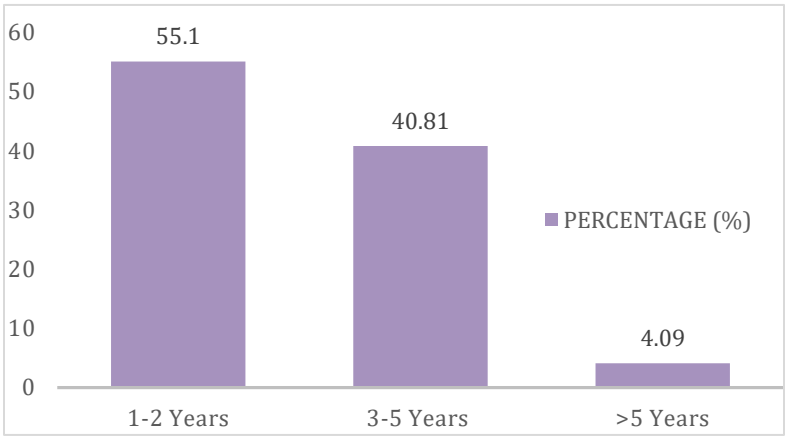

Figure 11: Categorisation of study population based on duration of infertility

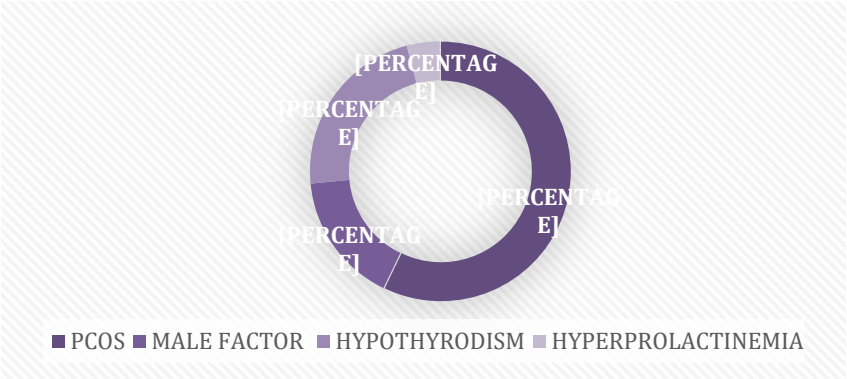

Figure 12: Categorisation of study population based on causes of infertility

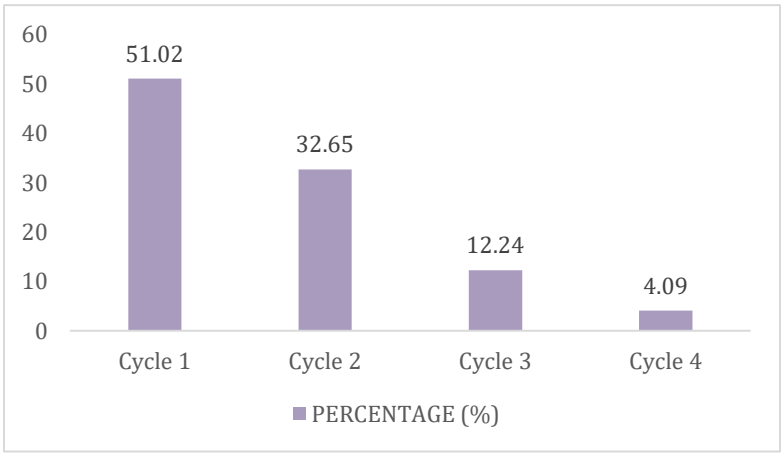

Figure 13: Categorization of study population based on number of Letrozole treatment

Table No. 11: Categorisation of study population based on ovulation status after Letrozole therapy

OVULATION STATUS AFTER LETROZOLE THERAPY	NUMBER OF PATIENTS (N=49)	PERCENTAGE (%)	
Ovulation	34	69.38	P value =1.0000
Anovulation	15	30.62	

Table No. 12: Categorisation of study population based on pregnancy outcome

PREGNANCY OUTCOME	NUMBER OF PATIENTS (N=49)	PERCENTAGE (%)	
Pregnant	26	53.07	P value = 1.0000
Non pregnant	23	46.93	

Table No. 13: Categorisation of study population based on end of treatment status

END OF TREATMENT STATUS	NUMBER OF PATIENTS (N=49)	PERCENTAGE (%)	
Achieved pregnancy	26	53.07	P value =1.0000
Lack of response	23	47.93	

XI. DISCUSSION

The purpose of the study was to investigate how Letrozole therapy is evaluated for effectiveness in treating infertility in women. 49 individuals in all were included in this retrospective observational analysis, and they were grouped according to their reproductive history, Letrozole treatment details, and other demographic characteristics. This conversation describes the results and demonstrates how they aid in our comprehension of Letrozole's efficacy and effects.

The mean age of 49 patients in a secondary care hospital was 27.1 years (±4.088), with a median age of 26 years. The biggest proportion of patients (42.8%) were in the 25–29 age range, followed by the 20–24 (26.53%) and 30-34 (26.53%) age groups, with only 4.09% of patients falling into the 35–39 age range. This is consistent with earlier research published in the Journal of Medical Science and Clinical Research by Dr. Farendra Bharadwaj et al. (2019) titled "Effect of Letrozole in Primary and Secondary Infertile patients: A Prospective study"[(46)]. This finding implies that women in their mid-to-late twenties, a crucial window for fertility treatment, are the ones who receive Letrozole prescriptions the most frequently.

Out of 49 individuals, 25 (51.02%) had regular cycles, and 24 (48.98%) had irregular cycles, according to the classification based on menstrual history. Ovulatory dysfunction is frequently indicated by irregular cycles, which might point to hormonal problems that can lead to infertility, such as PCOS, thyroid issues, or hyperprolactinemia. Depending on these menstrual cycles, Letrozole's ability to induce ovulation may differ.

Letrozole's ovulation induction is evident from patient classification by ovulation state, with 24 (48.98%) being oligo-ovulatory and 25 (51.02%) ovulatory. This variation in response is influenced by factors like PCOS, hormonal imbalances, and infertility duration, making classification essential for evaluating treatment effectiveness.Infertility type classification further aids assessment, with 23 (46.93%) cases of secondary infertility and 26 (53.07%) of primary infertility. While primary infertility often stems from hormonal or ovulatory issues, secondary infertility may involve endometriosis, male factors, or previous pregnancy complications. Analyzing both groups helps determine Letrozole's impact on different infertility types.

Classifying patients by infertility duration provides insight into treatment timelines. Among 49 women on Letrozole, 27 (55.10%) had infertility for 1–2 years, 20 (40.81%) for 3–5 years, and 2 (4.09%) for over five years. Since shorter infertility durations often correlate with better ovulation induction responses, early treatment may enhance outcomes. Evaluating Letrozole's effectiveness across different infertility durations helps assess its impact, particularly in early-stage cases.

Classifying infertility causes in women receiving Letrozole highlights key contributing factors. Among 49 patients, PCOS was the most common (57.14%) due to its link with ovulatory dysfunction. Hypothyroidism (22.44%) affected fertility by disrupting hormonal balance, while male factor infertility (16.32%) played a role in some cases. Hyperprolactinemia (4.1%) also impaired ovulation. Understanding these underlying causes is essential for evaluating Letrozole's effectiveness in infertility treatment.

Treatment success can be assessed by classifying patients based on the number of Letrozole cycles required for pregnancy. Among 49 patients, 25 (51.02%) conceived after the first cycle, 16 (32.65%) after two cycles, 6 (12.24%) after three cycles, and 2 (4.09%) after four cycles. This suggests Letrozole is most effective within the first two cycles. Variations in response may be influenced by factors such as PCOS, hypothyroidism, hormonal balance, and ovulatory function restoration. Clinical judgments regarding the ideal number of cycles for success are aided by the lower success in subsequent cycles, which suggests that non-responders may require extra treatments.

This study's classification of ovulation status following Letrozole medication assesses how well infertile women respond to treatment: Letrozole successfully induced ovulation in the majority of cases, as evidenced by the fact that 34 out of 49 patients (69.38%) were able to achieve ovulation. This shows that Letrozole is a powerful ovulation inducer, particularly for women who have anovulatory infertility, including those with PCOS.Of the 49 individuals, 15 (30.62%) remained anovulatory, implying that Letrozole treatment had no effect on them. Obesity, hormone abnormalities, or ovarian resistance may be the cause of non-reaction. This is similar to the study published in the journal Pak J Med Sci in 2024 by Tayyiba Wasim, Sonia Irshad, et al., titled "Efficacy of Letrozole vs. Clomiphene Citrate for induction of ovulation in women with polycystic ovarian syndrome"[(47).] According to this study, aromatase inhibitors selectively modulate the estrogen receptor, increase the endometrium's physiological hormonal stimulation, and reduce the rate of multiple pregnancies by recruiting only one follicle. Monofollicular formation was extremely statistically significant when Letrozole was used. Only the Letrozole therapy example is examined here.

The study's End of Treatment Status classifies individuals according to how Letrozole therapy for infertility ultimately turns out. Of the 49 patients, 26 (53.07%) became pregnant, whereas the other 23 (47.93%) had a lack of response, which means that they did not become pregnant even after receiving treatment. This is consistent with the study conducted by Li-Juan Chen et al. (2024), which was published in the journal Frontiers in Endocrinology under the title "Sequential 2.5 mg Letrozole/FSH therapy is more effective for promoting pregnancy in infertile women with PCOS: a pragmatic randomized controlled trial"[(48)]. The study found that the cumulative pregnancy rate was significantly higher in the sequential Letrozole 2.5 mg/FSH treatment group than in the Letrozole 5 mg/FSH treatment group. There were no statistically significant changes in ovulation rates or adverse effects since the Letrozole 2.5 mg/FSH group had a significantly greater clinical pregnancy rate than the Letrozole 5 mg/FSH group.

XII. CONCLUSION

The efficacy and results of Letrozole therapy among infertile women in a secondary care hospital were evaluated in this retrospective analysis. The results show that Letrozole is a good way to induce ovulation, especially in those who have anovulatory infertility, such PCOS. Letrozole's great effectiveness in triggering ovulation and obtaining pregnancy was demonstrated by the study's findings that most patients responded favorably to the medication over the first two treatment cycles.

Treatment response was significantly influenced by menstrual history, ovulation status, the type and duration of infertility, and underlying factors such hypothyroidism and PCOS. Although some individuals were able to ovulate, others remained anovulatory, which may indicate resistance brought on by ovarian malfunction, obesity, or hormonal imbalances. Letrozole's importance in treating infertility is further supported by the study's finding that the majority of patients became pregnant. For improved results, non-responders could need combo therapy or further treatments. Overall, this study highlights the necessity for tailored treatment plans to maximize success rates in managing infertility and supports Letrozole as a useful first-line medication for ovulation induction, particularly in women with PCOS.

XIII. AKNOWLEDGEMENT

We sincerely express our gratitude to God Almighty for his blessings and guidance throughout this project. Our heartfelt thanks to Rev. Fr. Dr. Sanil Jose Kuttipuzhakkaran, Rev. Fr. Thomas Kulampallil and Rev. Fr. Renny Kanjirathinkal of Sanjo College of Pharmaceutical Studies for their support. We extend our deep appreciation to our principal, Dr. Vinod K R, for his invaluable guidance and facilities. Special thanks to our guide, Mr. Dawn V J, and HOD, Dr. Purushothama Reddy K, for their mentorship. We also acknowledge our librarians, family, staff, and classmates for their encouragement and assistance.

XIV. CONFLITS OF INTEREST

There are no disclosed conflicts of interest for the authors. The manuscript’s contents have been reviewed by all co- authors, who concur with its contents and have no financial interests to disclose. We confirm that the submission is our original work and isn’t being considered for publication by another journal.

FUNDS: self funding

XV. REFERENCE

1. Polyzos NP, Tzioras S, Badawy AM, Valachis A, Dritsas C, Mauri D. Aromatase inhibitors for female infertility: a systematic review of the literature. Reproductive BioMedicine Online [Internet]. 2009 Oct 1 [cited 2020 Nov 21];19(4):456–71.
2. He D, Jiang F. Meta-analysis of Letrozole versus clomiphene citrate in polycystic ovary syndrome. Reproductive BioMedicine Online. 2011 Jul;23(1):91–6.
3. Soni Deol P. Anatomy and physiology of female reproductive system. Blue rose publishers. 2023;
4. Anatomy of female reproduction. Reproduction of farm animals. 2000;13–29.
5. https://images.app.goo.gl/1SAQpjEn3aqEP8SN6
6. Anwar S, Anwar A. Infertility: A Review on Causes, Treatment and Management. Women's Health & Gynecology. 2016;2(6).
7. https://images.app.goo.gl/KVcosWQM1wN2nwPJ6
8. Larsen U. Research on infertility: Which definition should we use? Fertility and Sterility. 2005 Apr;83(4):846–52.
9. Moridi A, Roozbeh N, Yaghoobi H, Soltani S, Dashti S, Shahrahmani N, et al. Etiology and Risk Factors Associated with Infertility. International Journal of Women's Health and Reproduction Sciences. 2019 Mar 10;7(3):346–53.
10. Bhattacharya S, Johnson N. Female infertility. Clinical evidence. 2010;0819.
11. https://www.indoreinfertilityclinic.com/causes-of-infertility/
12. Mustafa M, Sharifa. Male and female infertility: Causes and Management. IOSR Journal of Dental and Medical Sciences. 2019;18(9):27–32.
13. Anjali C, George M. PCOD in female reproductive age: A review. World Journal of Pharmaceutical Research. 2020;9(1):677–84.
14. Ambildhuke K, Pajai S. A Review of tubal factors affecting fertility and its management. Cereus. 2022;14(11).
15. Liu L, Lu Y. The risk of advanced maternal age: Causes and overview. Journal of gynecological research and obstetrics. 2020;6(2).
16. Olooto, Eniola W. A review of female infertility: important etiological factors and management. Journal of Microbiology and Biotechnology Research. 2012;2(3):379–85.
17. JahanianSadatmahalleh S, Ziaei S. Menstrual Pttern following Tubal Ligation: A Historical Cohort Study. International Journal of Fertility & Sterility. 2015;9(4):477–82.
18. Autor: G Wright Bates. Medical and surgical management of common fertility issues. Editorial: Philadelphia, Pa.; London: Saunders; 2013.
19. Thable A, Duff E, Dika C. Infertility management in primary care. The Nurse Practitioner [Internet]. 2020 May 1;45(5):48–54.
20. Z. Spaczyski R, Duleba AJ. Diagnosis of endometriosis. Seminars in Reproductive Medicine. 2003;21(2):193–208.
21. Carcio HA, Secor RM. Advanced health assessment of women: Clinical skills and procedures. 3rd ed. Springer publishing company;
22. Akhter N, Jebunnaher S. Evaluation of female infertility. Journal of medicine. 2012;13(2):200.

23. Prasad B, Parmar D, Sharma N. A study on serum FSH, LH and Prolactin Levels Among infertile women. International Journal of Medical Research & Health Sciences. 2015;4(4):876.
24. Mazzilli R, Medenica S, Di Tommaso AM, Fabozzi G, Zamponi V, Cimadomo D, et al. The role of thyroid function in female and male infertility: a narrative review. Journal of Endocrinological Investigation. 2022 Aug 9;46(1).
25. Ahmadi MH, Mirsalehian A, Bahador A. Association of Chlamydia trachomatis with infertility and clinical manifestations: a systematic review and meta-analysis of case-control studies. Infectious Diseases. 2016 Apr 11;48(7):517–23.
26. Holzer H, Casper R, Tulandi T. A new era in ovulation induction. Fertility and Sterility. 2006 Feb;85(2):277–84.
27. Messinis IE. Ovulation induction: a mini review. Human Reproduction [Internet]. 2005 Jul 8 [cited 2020 Apr 8];20(10):2688–97. Available from: https://academic.oup.com/humrep/article/20/10/2688/603349
28. Ann Carson S, N Kallen A. Diagnosis and Management of Infertility. Journal of American Medical Association. 2021;326(1):65–76.
29. Fabian CJ. The what, why and how of aromatase inhibitors: hormonal agents for treatment and prevention of breast cancer. International Journal of Clinical Practice [Internet]. 2007 Sep 24;61(12):2051–63.
30. Rose BI. A review of the physiology behind Letrozole applications in infertility: are current protocols optimal? 2020 July 26;37:2093–2104
31. https://en.m.wikipedia.org/wiki/Letrozole
32. Yang AM, Cui N, Sun YF, Hao GM. Letrozole for Female Infertility. Frontiers in Endocrinology. 2021 Jun 16;12.
33. https://www.frontiersin.org/journals/endocrinology/articles/10.3389/fendo.2021.676133/full
34. Al-Fadhli R, Sylvestre C, Buckett W, Tan SL, Tulandi T. A randomized trial of superovulation with two different doses of Letrozole. Fertility and Sterility. 2006 Jan;85(1):161–4.
35. Lamb HM. A Review of its Use in Postmenopausal Women with Advanced Breast Cancer. 2012 Sep 19;56(1998):1125–40.
36. Pajai S, Potdar J. A Review on the Use of Letrozole in Female and Male Infertility. Cureus. 2022;14(11).
37. Requena A, Herrero J, Landeras J, Navarro E, Neyro JL, Salvador C, et al. Use of Letrozole in assisted reproduction: a systematic review and meta-analysis. Human Reproduction Update. 2008 Sep 23;14(6):571–82.
38. Simpson D, P Curran M. Letrozole: A Review of its use in postmenopausal women with breast cancer. Adis Drug evaluation. 2004;64(11):1213–30.
39. https://images.app.goo.gl/fMbBga73V96hveoLA
40. Cunha, MD A. Infertility management in women with polycystic ovary syndrome: a review. Porto Biomedical Journal. 2021;6(1).
41. Patel Sukhpreet, Shah Duru. Controversies in Obstetrics, Gynecology and Infertility. 1/e ed. 2006.
42. Sovino H, Sir-Petermann T. Clomiphene citrate and ovulation induction. Reproductive biomedicine online. 2002;4(3):303–10.
43. Le M, Zolton JR, Thanh C, Nguyen V, Truong VQ, Nguyen ND, et al. GnRH agonist versus HCG trigger in ovulation induction with intrauterine insemination: a randomized controlled trial. Fertility and Sterility. 2017 Sep;108(3): 231–2.

44. Shuai Jiang, Ting Tang. The Effects of Letrozole and Metformin Combined with Targeted Nursing Care on Ovarian Function, LH, and FSH in Infertile Patients with Polycystic Ovary Syndrome. Journal of Healthcare Engineering. 2022 Mar 23;2022(1).
45. Healey S, Tan SL, Tulandi T, Biljan MM. Effects of Letrozole on superovulation with gonadotropins in women undergoing intrauterine insemination. Fertility and Sterility. 2003 Dec;80(6):1325–9.
46. Bharadwaj DF, Nahata DVS. Effect of Letrozole in primary and secondary infertile patients: A prospective study. Journal of medical science and clinical research. 2019;7(7):445–51.
47. Wasim T, Nasrin T. Efficacy of Letrozole vs Clomiphene Citrate for induction of ovulation in women with polycystic ovarian syndrome. Pakistan Journal of Medical Science. 2024;40(1):78–83.
48. Chen L - J, Liu Y. Sequential 2.5mg Letrozole/FSH therapy is more effective for promoting pregnancy in infertile women with PCOS: a pragmatic randomized controlled trail. Frontiers in endocrinology. 2024;1–10.