RESEARCH REPORTS

Treatment Outcome in Polycystic Ovarian Syndrome-Related Infertility

AMINATH EFA IBRAHIM, AHMED YAZDHAN, FATHIMATH INA SHAREEF, & AHMED SHABIN

School of Medicine, The Maldives National University

ABSTRACT: *The declining fertility rate has been observed in the past few decades in Maldives. One of the most prevalent diseases that cause this complication is polycystic ovarian syndrome (PCOS). PCOS is a hormonal condition that has affected 13% of women in the reproductive age group globally. This is a chronic condition where various treatment options have been used to counter the complication. In this study, we analyze the effectiveness of one of the most common treatment regimens available in Maldives, letrozole, and letrozole combined with gonadotropins, for women with PCOS-related infertility. This quantitative, retrospective study analyzes data from 2019 to 2024. The population consists of women who received treatment for infertility due to PCOS at Indira Gandhi Memorial Hospital and My Clinic Private Limited, between January 1, 2019, and December 31, 2023. Our total study sample was 173 patients. Using the logistic regression model, we observed that, when compared with those who were more than 35 years, patients who were less than 25 years old, had a 9.5 times more likelihood of getting pregnant. After excluding the other variables, the odds ratio for ages less than 25 years increased from 9.5 to 13.3. Furthermore, patients who are 26 to 30 years of age show a significantly higher successful outcome when other variables are adjusted. This study shows that there is a significant relationship between age and treatment outcome of PCOS-related infertility.*

Keywords: Polycystic Ovarian Syndrome, Infertility, Letrozole, Gonadotropin, Treatment outcome

Introduction

Polycystic Ovary Syndrome (PCOS) is a hormonal condition that affects 8 to 13% of women in the reproductive age range, according to WHO (2023). The exact etiology of PCOS is still unknown. However, these patients have excess levels of androgens which are associated with a myriad of symptoms that affect both their physical and emotional well-being. These include acne, hirsutism, male-pattern baldness, weight gain, menstrual irregularities, and even infertility. Women suffering from PCOS also have a higher likelihood of having other comorbidities such as type II diabetes mellitus, hypertension, dyslipidemia, etc (WHO, 2023). Not only this, but they mention that unwanted facial hair and weight gain lead to social stigma and a negative body image, which evidently affects their social and occupational functioning, as well as causing anxiety and depression in some individuals (WHO, 2023).

Although PCOS is a chronic condition, symptomatic treatment is available and

ISSN 2308-5959/20241130

lifestyle modifications with dietary changes and regular exercise have proven to make a significant difference (WHO, 2023). This condition is diagnosed based on the modified Rotterdam criteria, where having any two out of the three proposed criteria is considered diagnostic (Christ & Cedars, 2023).

In the Maldives, not only is PCOS a common disorder, but a declining fertility rate has also been a growing concern for the past few decades (Maldives National Reproductive, Maternal, Newborn, Child, and Adolescent Health, 2021; The World Bank, 2022; UNFPA Maldives, 2024). This is evidenced by the low fertility rate in the year 2023, where the rate was 1.7; which is a marked decline from the fertility rate 10 years back, where the rate was 2.1 (The World Bank, 2022; UNFPA Maldives, 2024). This decline has been steeper and far more significant when compared to the fertility rates 30 or 40 years back with the rates being 5.0 and 7.2 respectively (The World Bank, 2022).

For the treatment of PCOS-related infertility, a hierarchy has been established, with the first line of treatment starting with lifestyle modifications to lose excess weight (Akre et al., 2022; Flickr, 2024; Li et al., 2022). Ovulation induction agents such as clomiphene citrate, aromatase inhibitors, and gonadotropins are next in line; followed by laparoscopic ovarian drilling; and assisted reproductive technology (ART) such as Intrauterine Insemination (IUI), In Vitro fertilization (IVF), and Intracytoplasmic Sperm Injection (ICSI), as the next options in line (Akre et al., 2022; Flickr, 2024; Li et al., 2022).

Unfortunately, even with PCOS being the most common cause of anovulation leading to infertility, research on PCOS in the Maldives is scarce (WHO, 2023; Maldives National Reproductive, Maternal, Newborn, Child and Adolescent Health, 2021). Additionally, the treatment for PCOS was not covered under the governmentɔs universal healthcare insurance scheme, Aasandha, until December of 2023 (The President's Office, 2023). Thus, it is irrefutable that an utmost importance should be given for the research and treatment needed to overcome this worsening dilemma in this country.

Background

Polycystic ovarian syndrome (PCOS) is a complex endocrine disorder, affecting females of reproductive age. This syndrome has a plethora of manifestations, including insulin resistance, obesity, infertility, and cardiovascular consequences. PCOS accounts for 90% of cases of anovulatory infertility and represents the leading cause of female infertility (Eniola et al., 2017). Globally, infertility accounts for 10% of the world's population.

Several diagnostic criteria for PCOS have been used in various studies. The Rotterdam criteria, published in 2003, is one of the most commonly adopted. As per the criteria, diagnosis of PCOS requires the presence of two of the following three criteria: (1) oligo-ovulation or anovulation, (2) hyperandrogenism (clinical evidence of hirsutism, acne, alopecia, and/or biochemical hyperandrogenemia), and (3) polycystic ovaries, as assessed by ultrasound scan with ≥20 follicles, measuring 2-9 mm in diameter and/or an ovarian volume of ≥10 cm3 in at least one ovary Confirmation of diagnosis also requires other related disorders to be ruled out. (The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group,

2004).

Various factors influence the ovarian function in PCOS, including patients being overweight, having hyperandrogenism, and having elevated serum LH. Hyperandrogenism results in an increased number of preovulatory follicles, measuring 2-5mm, which do not respond to the normal concentration of the follicular-stimulating hormone (FSH). In addition, the action of premature luteinizing hormone impairs the formation of the dominant follicle, resulting in anovulatory cycles (Costello et al., 2012).

Furthermore, additional factors influence infertility, including age, weight, frequency of sexual activity, and behaviors, such as smoking. Studies report that patients diagnosed with PCOS gain more weight in comparison to women without PCOS, which further exacerbates androgen and insulin levels, increasing the severity of reproductive features observed in PCOS (Glueck et al., 2005). Although fertility rates are lower among obese patients, there is limited evidence of successful pregnancy outcomes with lifestyle intervention in PCOS (Balen et al., 2016).

As there is no definitive cure for PCOS, the management focuses on a holistic approach to the different manifestations of the disease. Treatment modalities include lifestyle modification, through diet and exercise, pharmacotherapies, such as clomiphene citrate, letrozole, metformin, and gonadotropins, and surgical therapies, such as laparoscopic ovarian surgery. The overall management of PCOS is targeted towards the improvement in the quality of life of the patients.

Two studies were conducted to study the effect of letrozole and clomiphene citrate in ovulation induction. Al-Omari reported 84.4% of patients treated with letrozole to have ovulated, while another study reports 62% successful ovulation among the sample population. As reported by Banerjee, no differences were observed in the efficacy of letrozole and clomiphene citrate. However, letrozole was reported to significantly improve the endometrial thickness, resulting in a higher rate of successful conceptions (Banerjee et al., 2012). As the rate of ovulation and live birth rate observed with letrozole was higher than CC, letrozole is now considered the first line of treatment for ovulation induction (Waldman et al., 2019).

A study conducted comparing letrozole and hMG for ovulation induction observed an ovulation rate of 70%, with multiple births reaching up to 5.7%. A second study comparing FSH and hMG, reported that 75% of women induced with FSH ovulated, while 94% induced with hMG ovulated (Sagle et al., 1991).

Although gonadotropins are more effective, it is also associated with a higher risk of ovarian hyperstimulation syndrome (OHSS) and multiple gestations. OHSS is more commonly observed in young age, low body weight, and high dosage regimen of gonadotropins (Amer, 2007). Studies report that treatment regimens consisting of letrozole combined with gonadotropin increase the number of preovulatory follicles, decrease endometrial thickness, and decrease the gonadotropin requirements (Mitwally et al., 2003). Thus, decreasing the side effects related to gonadotropin.

General Objectives

The goal of this research is to understand the effectiveness of various treatment regimens in cases of infertility due to Polycystic Ovarian Syndrome among women consulting at Indira Gandhi Memorial Hospital and My Clinic Private Limited.

Specific Objectives

1. To study the distribution of women diagnosed with PCOS-related infertility, depending on age group and the type of infertility (primary and secondary) at Indira Gandhi Memorial Hospital and My Clinic Private Limited.
2. To study the association between age and the treatment outcome of treatment regimens (Letrozole, and Letrozole combined with Gonadotropins) for PCOS-related infertility.
3. To study the association between the number of cycles of treatment with the treatment outcome of the treatment regimens (Letrozole, and Letrozole combined with Gonadotropins) for PCOS-related infertility.
4. To study the association between the type of infertility (primary and secondary) and the treatment outcome of treatment regimens (Letrozole, and Letrozole combined with Gonadotropins) in PCOS-related infertility.

Methodology

Research Designs

This is a quantitative, retrospective study, analyzing data from January 1, 2019 to December 31, 2024. It will focus on women with diagnosed PCOS who are consulting at Indira Gandhi Memorial Hospital and My Clinic Private Limited. The variables that were collected included patient age, the type of infertility, and the number of cycles of treatment taken, and these variables were compared to the different treatment regimens.

Sample, population, or subjects

The study population consists of women who received treatment for infertility due to PCOS. Census sampling was done, where all patients who received and completed or terminated PCOS-related infertility treatment at Indira Gandhi Memorial Hospital and My Clinic Private Limited, between January 1, 2019, and December 31, 2023, were collected. The patients who received treatment up until December 31, 2023, were followed via medical records until February 29, 2024. After the application of the inclusion and exclusion criteria, the study sample was 173 patients.

Inclusion criteria:

- Patients who are between 18 to 45 years of age.
- Patients who are diagnosed with PCOS.
- Patients who have taken at least 1 cycle of infertility treatment by taking letrozole therapy alone or letrozole therapy with gonadotropins.
- Patients who have taken infertility treatment between January 1, 2019, and December 31, 2023.

Exclusion criteria:

- Patients with other causes of infertility such as endometriosis, structural disorders, endocrine disorders, and male factors.
- Patients who did not follow up regularly after initiation of treatment.

Instruments and Materialsy

Data was collected from the records kept in Hinai (a computer-based hospital information management system with patient prescriptions, laboratory reports, etc.), as well as the Medical Records Department in Indira Gandhi Memorial Hospital, and patient record files from My Clinic Private Limited. Data relevant to this study was recorded on Google Sheets (attached in Annex 1). Data collection and recording was done using laptops and tablets. The collected data was processed using IBM SPSS software, as well as Microsoft Excel Office 2016.

Data Collection

After ethical approval from the National Health Academy (NHA), the management of My Clinic Private Limited, National Health Research Council (NHRC), and the Research Development Office of the Maldives National University (MNU), data collection was commenced.

Data was taken from the records in Hinai and the Medical Records Department of Indira Gandhi Memorial Hospital, as well as the patient records from My Clinic Private Limited. A list of patients diagnosed with PCOS and being treated for infertility was obtained from both institutions, and all those that meet the criteria were manually chosen after evaluation of their data by the 4 members of the research team.

Once patients were chosen, the relevant information was recorded in a common Google Sheet which was only accessible to the members of the team and supervisors. The information collected includes patient ID, age, type of infertility, comorbidities, type of treatment taken, number of cycles, and whether there was a successful conception. The patients were assigned unique number codes, and the ID numbers were permanently deleted after cross-checking between the two institutions and verifying that patients were not repeated. Data collected by each member of the team was re-checked by the remaining members, in order to verify that the data entered was error-free.

Patient confidentiality was maintained throughout the data collection process, as all ID numbers were permanently deleted after cross-checking to verify no patient data was repeated. Additionally, the devices with access to the patient data were password-protected and any Google sheets with any patient information were exclusively shared between the 4 members of the research team our coordinator, and 2 supervisors. Furthermore, all the remaining data will also be deleted, 6 months after publication.

Data Management and Data Analysis

After data collection, the collected data was cleaned and coded. They were then analyzed using IBM SPSS software version 29.0.2.0, and Microsoft Excel . For descriptive statistics, mean, median, and mode were obtained for continuous

variables, and frequency and percentage were obtained for categorical variables. These are presented in the form of tables, graphs, and charts.

The hypotheses were tested for inferential statistics with a critical value of p=0.05. The data was tested for normality. Logistic regression tests were run to analyze the treatment outcomes based on age, type of infertility, number of cycles, and treatment type.

Results

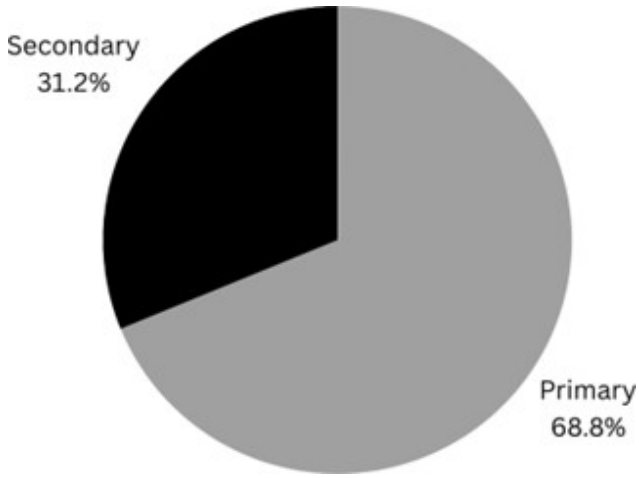
Table 1 shows the demographic data that was collected during this study. For the percentage age distribution of the total study population, the majority of patients (46.2%) were found to be between the ages of 26 to 30 years old. The least number of patients were in the age group above 35 years (11.6%). When looking at the letrozole group and the combined group separately, similar trends were seen.

Table 1
Percentage distribution of age distribution, type of infertility, number of cycles, and treatment outcome among the study group.

	Percentage (%)		
Age-groups	**Overall**	**Letrozole**	**Combined**
< 25	12.1	13.2	9.6
26-30	46.2	48.8	40.4
31-35	30.1	27.3	36.5
> 35	11.6	10.7	13.5
Type of Infertility			
Primary	68.8	67.8	71.2
Secondary	31.2	32.2	28.8
Number of Cycles			
1	58.4	60.3	53.8
2	27.2	23.1	36.5
> 3	14.5	16.5	9.6
Treatment Outcome			
Successful	25.4	27.3	21.2
Unsuccessful	74.6	72.7	78.8

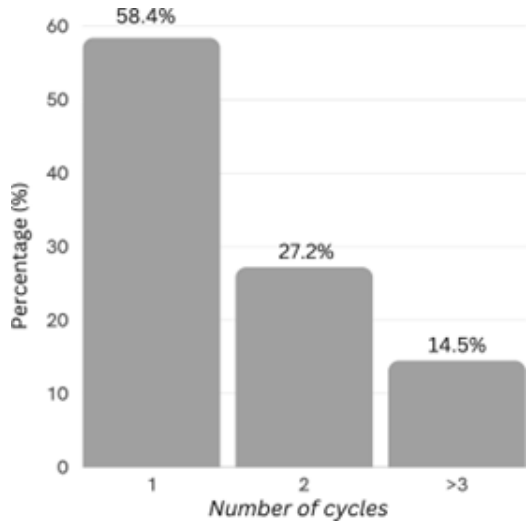
The percentage distribution of types of infertility shows that more than half of the study population had primary infertility at %68.8, and %31.2 had secondary infertility (Figure 1). This trend is similar in both letrozole and combined groups.

Figure 1: Percentage distribution of type of infertility among the total study population.



The percentage distribution of the number of cycles shows that %58.4 of the study population was given only one cycle of treatment (Figure 2). This is similar in both individual groups.

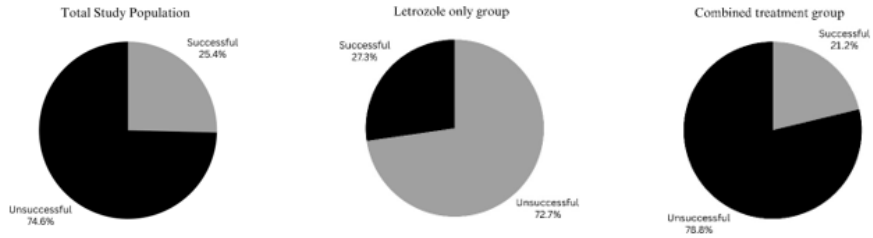
Figure 2: Percentage distribution of the number of cycles among the total study population



The percentage distribution of treatment outcomes for the total study population showed that the greater percentage of treatments were unsuccessful. This is

observed in both letrozole and combined groups individually as well (Figure 3).

Figure 3: Percentage distribution of treatment outcomes among the study population and individual group



To obtain inferential statistics, the logistic regression model was used. Based on our analysis, when compared with those above the age of 35, patients who were less than 25 years old had a nine and a half times higher likelihood of getting pregnant, which was significant. Hence indicating that there is a relationship between age and treatment outcome, thus rejecting our null hypothesis. However, for the ages between 26 to 30 and 31 to 35, the results were not significant.

When analyzing how the number of cycles affected the treatment outcome, the results obtained were not significant. This indicates that the number of cycles does not influence the treatment outcome.

The results for the relationship between type of infertility and treatment outcome were also not significant. This confirms our null hypothesis, which states that there is no relationship between infertility and treatment outcome.

The logistic regression model for the relationship between the type of treatment and the treatment outcome was also not significant, confirming our null hypothesis.

When all four variables are combined, the odds ratio for ages less than 25 years increased from 9.5 to 13.3. This indicates that compared to patients aged more than 35, patients aged less than 25 had a 13 times higher likelihood of getting pregnant when adjusted to other variables. The p-value for the age group 26 to 30 years, was previously not significant. However, when we exclude other variables, it is now significant, suggesting that when adjusted to other variables, this age group is 10 times more likely to get pregnant compared to the age group of more than 35.

Table 2.2
Logistic Regression Model for factors predicting treatment outcome

Variable	Category	n	OR	CL-95%	p-value
Age	<25	21	13.259	1.392-126.302	**0.025**
	26-30	80	10.502	1.271-86.806	**0.029**
	31-35	52	6.941	0.830-58.065	0.074
	>35	20	Reference category		
Number of cycles	1	101	Reference category		
	2	47	1.632	0.716-3.719	0.244
	>3	25	1.205	0.434-3.343	0.721
Type of infertility	Primary	121	Reference category		
	Secondary	52	2.14	0.973-4.705	0.058
Treatment type	Letrozole	119	Reference category		
	Combined	54	0.73	0.322-1.656	0.451

Discussion

In this study, the majority of patients belonged to the 26 - 30 years age group, with a mean age of 30. Similarly, in a study done at Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh assessing the prevalence and characteristics of PCOS in women, 47% of the patients were between 21 and 25 years old. However, this study had a mean age group of 24.3 years (Fatema et al., 2021). In a meta-analysis done to study the prevalence of PCOS among Chinese women, it was shown that the prevalence of PCOS decreases with age - suggesting a relationship between age and PCOS.This may be due to the gradual decline in ovarian endocrine function with advancing age (Wu et al., 2021).Gupta & Deshpande reported that 57.5% of patients had primary infertility in a study done to identify the causes and prevalence of factors causing infertility (Deshpande & Gupta, 2019). In a systematic review where the prevalence of primary and secondary infertility was reviewed, it was found that out of 6400 infertile couples, 3600 (56.25%) reported primary infertility (Jabeen et al., 2022). Similar to the results of these studies, this study also found that the majority of women have primary infertility.

In this study, the majority of women received only one cycle of treatment. A few received more than 3 cycles. However, it was noted that women with PCOS require at least 90 days or about 3 cycles of letrozole therapy for successful conception (Kotlyar & Seifer, 2023). In another study, it was shown that patients receiving letrozole only underwent an average of 4.1 cycles, and those receiving combination therapy underwent an average of 2.9 cycles (Chen et al., 2016). In women undergoing in-vitro fertilization, no significant difference was found for the number of cycles that need to be administered when compared to patients with other causes of infertility (Hwang et al., 2016).

Overall, 25.4% of the patients in this study had successful conception. This

includes 27.3% of the letrozole group and 21.2% of the letrozole + gonadotropin group. When compared to other infertility treatments; - for IUI, out of 1053 cycles, 11% resulted in positive pregnancy tests (Vargas-Tominaga et al., 2019). In women with PCOS aged 33-35 years, the live birth rate was 41.3% with in-vitro fertilization (Hwang et al., 2016). In contrast to our study, in women receiving Letrozole treatment, 52% resulted in clinical pregnancy, with 44% live births (Sakar & Oglak, 2020). Similarly, in another study, those receiving letrozole in combination with gonadotropins had a pregnancy rate of 55.7% which was significantly higher than those receiving letrozole therapy alone (Chen et al., 2016).Analytical results after comparing the different age groups with the treatment outcome showed a statistical significance ($p = 0.045$) in our study, where patients who were 25 years and younger were 9.5 times more likely to conceive, compared to patients who were 35 years or older. In addition, when all four variables of our study were combined, the odds ratio of this age group increased up to 13.3, and the age range between 26 to 30 years also showed a statistical significance ($p = 0.029$); patients aged 26 to 30 years were 10.5 times more likely to have a successful treatment outcome compared to those who were 35 years or older. These findings may be explained by the fact that the peak reproductive age of a woman ranges between late teens and late 20s, (ACOG, 2023) with an 85% chance of conception within 1 year, in those who are younger than 30 years (Delbaere et al., 2020). This likelihood decreases at age 30, with a steeper decline at age 35 with the rates being 75% and 66% respectively (ACOG, 2023; Delbaere et al., 2020). There is also evidence that the other variables (number of cycles, type of infertility, and the treatment type) in the study affect the treatment outcomes in women of different ages. This is evidenced by the change seen in the p-value of the age group 26 to 30 years when the influence of all these other factors was excluded.

The logistic regression model for the number of cycles predicting the treatment outcome was not statistically significant in our study when compared to 1 cycle of the treatment regimen. Similarly, a study done in 2022 comparing the pregnancy outcomes in patients with PCOS-related infertility who underwent IUI with different attempts of previous OI also shows no significant difference in pregnancy rates between the number of cycles of treatment with OI agents (Gao et al., 2022). In our study, 58% of the participants had only one cycle of treatment regimen and 27% had two, with the remaining participants having undergone three or more cycles of treatment. According to a retrospective record review done in 2023 where the pregnancy rates in PCOS patients were compared between letrozole and CC, the average number of cycles to achieve a successful pregnancy in the letrozole group was observed to be 1.8 ± 0.8 cycles (Bahawi et al., 2023).

There was no statistical significance between the type of infertility and treatment outcome according to the results of our study. A study done in Canada showed the cumulative pregnancy rates in secondary infertility at 56% and the rates of primary infertility at 44%, with a significance of $p = 0.001$, indicating a better prognosis in patients with secondary infertility (Collins et al., 1986). The study predicts that the results may be due to a high proportion of participants with ovulation disorders having a short duration of infertility. Our study may have shown no significance relationship due to the small sample size and the fact that only 31% of our sample population consists of those with secondary infertility.

Our study showed no significance when logistic regression was done to predict

the treatment outcome depending on the type of treatment given. Similarly, a study on the effects of letrozole combined with hMG in ovarian stimulation for IUI cycles also showed no significance relationship between pregnancy rates ,letrozole and letrozole combined with hMG (Yu et al., 2019). On the other hand, 2 studies comparing the effects between letrozole and letrozole combined with hMG on ovulation and pregnancy of patients with PCOS-related infertility showed that the pregnancy rates of letrozole combined with hMG were significantly higher than that of the letrozole group (Chen et al., 2016; Dai et al., 2023).

Strengths and Limitations

The strengths of this research are as follows: all the data of women with PCOS-related infertility within the past 5 years were collected from the 2 major health care facilities in Male' that provided infertility treatments at the time of our research. These samples were collected while being vigorously checked for the inclusion and exclusion criteria that have been clearly stated in this article. Furthermore, all these cases were thoroughly discussed in detail with our clinical supervisor before they were enrolled in the study.

The limitations of this study are as follows: due to the loss to follow-up of numerous patients, multiple samples that fit into the inclusion criteria had to be excluded, shrinking the sample size. The final small sample size was a mere 173 participants. Moreover, among the sample population that was tested, other causes of infertility such as lifestyle factors could not be excluded due to lack of data. This could potentially influence the results of the research.

Conclusion

From our study, we have deduced that patients with PCOS-related infertility who are 25 years and younger have a higher likelihood of having a successful conception after receiving Letrozole or Letrozole combined with hMG. Additionally, patients who are in the age range 26 to 30 years, also show a significantly higher chance of having a successful treatment outcome when all other variables (type of infertility, number of cycles and treatment type) are excluded.

Recommendations

The authors thank the supervisors who overlooked this research project: Dr. Hussain Juman Jaleel, Dr. Md Parwez Ahmad, and Dr. Razana Faiz. Our grateful acknowledgments extend to the staff of Indira Gandhi Memorial Hospital and My Clinic Private Limited for their continual support and cooperation.

Funding: none.

Conflict of interest

There is no conflict of interest in this study.

References

Akre, S., Sharma, K., Chakole, S., & Wanjari, M. B. (2022). Recent advances in the management of polycystic ovary syndrome: A review article. *Cureus, 14*(8). https://doi.org/10.7759/cureus.27689

Amer, S. (2007). Gonadotropin induction of ovulation. Obstetrics, *Gynaecology and Reproductive Medicine, 17*(7), 205–210. https://doi.org/10.1016/j.ogrm.2007.06.001.

Mitwally, M. F., & Casper, R. F. (2003). Aromatase inhibition reduces gonadotrophin dose required for controlled ovarian stimulation in women with unexplained infertility. *Human Reproduction, 18*(7), 1588-1597. https://doi.org/10.1093/humrep/deg311.

Bahawi, Y. O., Radwan, E. M., Khouj, M. A., Alotaibi, R. K., Bajuwaiber, N. A., Baghlaf, L. F., AlFaraj, W. F., & Oraif, A. M. (2023). Pregnancy rates in women with polycystic ovary syndrome (PCOS) using letrozole versus clomiphene citrate: *A retrospective record review. Cureus, 15*(7). https://doi.org/10.7759/cureus.42257techfore.2020.119919.

Balen, A. H., Morley, L. C., Misso, M., Franks, S., Legro, R. S., Wijeyaratne, C. N.,Stener-Victorin, E., Fauser, B. C. J. M., Norman, R. J., & Teede, H. (2016). The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. *Human Reproduction Update, 22*(6), 687–708. https://doi.org/10.1093/humupd/dmw025.

Banerjee Ray, P., Ray, A., & Chakraborti, P. S. (2012). Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction in Indian women with polycystic ovarian syndrome. *Archives of Gynecology and Obstetrics, 285*(3), 873–877. https://doi.org/10.1007/s00404-011-2091-7

Chen, Z., Zhang, M., Qiao, Y., & Yang, J. (2016). Effects of letrozole in combination with low-dose intramuscularinjection of human menopausal gonadotropin on ovulation and pregnancy of 156 patients with polycystic ovary syndrome. *Pakistan Journal of Medical Sciences, 32*(6). https://doi.org/10.12669/pjms.326.11391

Christ, J. P., & Cedars, M. I. (2023). Current guidelines for diagnosing PCOS. *Diagnostics (Basel, Switzerland), 13*(6), 1113. https://doi.org/10.3390/diagnostics13061113

Collins, J. A., Rand, C. A., Wilson, E. H., Wrixon, W., & Casper, R. F. (1986). The better prognosis in secondary infertility is associated with a higher proportion of ovulation disorders. *Fertility and Sterility, 45*(5), 611–616. https://doi.org/10.1016/s0015-0282(16)49330-1

Costello, M. F., Misso, M. L., Wong, J., Hart, R., Rombauts, L., Melder, A., Norman, R. J., & Teede, H. J. (2012). The treatment of infertility in polycystic ovary syndrome: a brief update. *The Australian & New Zealand journal of obstetrics & gynecology, 52*(4), 400-403. https://doi.org/10.1111/j.1479-828X.2012.01448.x

Dai, X., Li, J., Fu, T., Long, X., Li, X., Weng, R., Liu, Y., & Zhang, L. (2023). Ovulation induction using sequential letrozole/gonadotropin in infertile women with PCOS: a randomized controlled trial. *Reproductive Biomedicine Online, 46*(2), 352–361. https://doi.org/10.1016/j.rbmo.2022.08.002

Delbaere, I., Verbiest, S., & Tydén, T. (2020). Knowledge about the impact of age on fertility: a brief review. *Upsala Journal of Medical Sciences, 125*(2), 167–174. https://doi.org/10.1080/03009734.2019.1707913

Deshpande, P. S., & Gupta, A. S. (2019). Causes and prevalence of factors causing infertility in a public health facility. *Journal of Human Reproductive Sciences, 12*(4), 287. https://doi.org/10.4103/jhrs.jhrs_140_18

Eniola, O.W., Adetola, A. A., & Abayomi, B. T. (2017). A review of Female Infertility; important etiological factors and management. *Journal of Microbiology and Biotechnology Research,* 2(3), 379-385. https://jmbronline.com/index.php/JMBR/article/view/130

Fatema, K., Das, T. R., Kazal, R. K., Mahamood, S., Pervin, H. H., Noor, F., & Chakma, B. (2021). Prevalence and characteristics of polycystic ovarian syndrome in women attending in outpatient department of obstetrics and gynecology of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology, 10*(3), 830. https://doi.org/10.18203/2320-1770.ijrcog20210469

National Institute of Child Health and Human Development (NICHD). (2024). Treatments for infertility resulting from PCOS. Retrieved May 17, 2024, from https://www.nichd.nih.gov/health/topics/pcos/conditioninfo/treatments/infertility

Flickr, F. us on. (2024). Treatments for infertility resulting from PCOS. Https://www.nichd.nih.gov/. Retrieved May 17, 2024, from https://www.nichd.nih.gov/health/topics/pcos/conditioninfo/treatments/infertility

Gao, Y., Jiang, S., Chen, L., Xi, Q., Li, W., Zhang, S., & Kuang, Y. (2022). The pregnancy outcomes of infertile women with polycystic ovary syndrome undergoing intrauterine insemination with different attempts of previous ovulation induction. *Frontiers in Endocrinology, 13.* https://doi.org/10.3389/fendo.2022.922605

Glueck, C. J., Dharashivkar, S., Wang, P., Zhu, B., Gartside, P. S., Tracy, T., & Sieve, L.(2005). Obesity and extreme obesity, manifest by ages 20-28 years, dramatically increase lifetime risk of polycystic ovary syndrome in white and black women. *Gynecological Endocrinology, 21*(6), 3–5. https://doi.org/10.1080/09513590500371929

American College of Obstetricians and Gynecologists. (2023). Having a baby after age 35: How aging affects fertility and pregnancy. https://www.acog.org/womens-health/faqs/having-a-baby-after-age-35-how-aging-affects-fertility-and-pregnancy

Jabeen, F., Khadija, S., & Daud, S. (2022). Prevalence of Primary and Secondary

Infertility. *Saudi Journal of Medicine, 7*(1), 22–28. https://doi.org/10.36348/sjm.2022.v07i01.004

Kotlyar, A. M., & Seifer, D. B. (2023). Women with PCOS who undergo IVF: a comprehensive review of therapeutic strategies for successful outcomes. *Reproductive Biology and Endocrinology, 2*1(1). https://doi.org/10.1186/s12958-023-01120-7

Li, M., Ruan, X., & Mueck, A. O. (2022). Management strategy of infertility in polycystic ovary syndrome. Global Health Journal (Amsterdam, Netherlands), 6(2), 70–74. https://doi.org/10.1016/j.glohj.2022.03.002

Maldives National Reproductive, Maternal, Newborn, Child and Adolescent Health (RMNCAH). (2021). https://health.gov.mv/storage/uploads/7jqJZrq5/o4bszjk3.pdf

Mitwally, M. F., & Casper, R. F. (2003). Aromatase inhibition reduces gonadotrophin dose required for controlled ovarian stimulation in women with unexplained infertility. *Human Reproduction, 1*8(7), 1588–1597. https://doi.org/10.1093/humrep/deg311

World Bank Open Data. (2022). World Bank Open Data. https://data.worldbank.org/share/widget?indicators=SP.DYN.TFRT.IN&locations=MV

World Health Organization. (2023). Polycystic ovary syndrome. https://www.who.int/news-room/fact-sheets/detail/polycystic-ovary-syndrome

Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. (2004). *Human Reproduction*, *19*(1), 41-47. https://doi.org/10.1093/humrep/deh098Sachdeva

Sagle, M. A., Hamilton-Fairley, D., Kiddy, D. S., & Franks, S. (1991). A comparative, randomized study of low-dose human menopausal gonadotropin and follicle-stimulating hormone in women with polycystic ovarian syndrome. *Fertility and Sterility, 55*(1), 56–60.https://doi.org/10.1016/s0015-0282(16)54059-x

Sakar, M. N., & Ogak, S. C. (2020). Letrozole is superior to clomiphene citrate in ovulation induction in patients with polycystic ovary syndrome. *Pakistan Journal of Medical Sciences, 36*(7). https://doi.org/10.12669/pjms.36.7.3345

The President's Office. (2023). The President decides to offer blanket coverage for "Endometriosis" and "PCOS" treatments under the Aasandha Scheme. https://presidency.gov.mv/Press/Article/29321

UNFPA Maldives. (2024). Uniting for reproductive health equity in the Maldives.

https://maldives.unfpa.org/en/UnitingForRH-OpEd

Vargas-Tominaga, L., Alarcón, F., Vargas, A., Bernal, G., Medina, A., & Polo, Z. (2019). Associated factors to pregnancy in intrauterine insemination. *JBRA Assisted Reproduction, 23*(4), https://doi.org/10.5935/1518-0557.20190060

Waldman, I. N., & Legro, R. S. (2019). Polycystic ovary syndrome. In S. S. Channing & J. A. Simon (Eds.), *The Ovary* (pp. 415–435). Elsevier.

Wu, Q., Gao, J., Bai, D., Yang, Z., & Liao, Q. (2021). The prevalence of polycystic ovarian syndrome in Chinese women: A meta-analysis. *Annals of Palliative Medicine, 10*(1), 74–87. https://doi.org/10.21037/apm-20-1893

Yu, X., Cao, Z., Hou, W., Hu, W., & Yan, G. (2019). Effects of letrozole combined with human menopausal gonadotropin in ovarian stimulation for intrauterine insemination cycles. *Annals of Translational Medicine*, *7*(23), 771–771. https://doi.org/10.21037/atm.2019.11.58