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Evaluation and Treatment Strategies for Infertile Patients with Diagnosed Polycystic Ovary Syndrome (PCOS)

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Abstract

Background: PCOS is the most common endocrine disorder in women that can lead to a variety of ailments associated with chronic anovulation and hyperandrogenism, it is also still a common cause of infertility in women. It is the most frequent endocrine and metabolic disorder among reproductive-aged women. PCOS (polycystic ovarian syndrome) is the most frequent cause of anovulatory infertility, accounting for more than 75% of all cases. This widespread problem affects around one in every six marriages and has a variety of causes across countries and social groups. ***Aims and Objective:*** The objective of this study was to evaluate the treatment strategies for infertile patients with diagnosed Polycystic Ovary Syndrome (PCOS). ***Material and Methods:*** This study looked at 80 cases of infertility caused by polycystic ovarian syndrome. From August 2021 to July 2022, this study evaluated 80 cases of infertility with PCOS at a tertiary medical college. The diagnosis was made using a hormone assay, ultrasound, and laparoscopy. Treatment options included clomiphene citrate, letrozole, and laparoscopic ovarian drilling. ***Results:*** In our study, the majority (50%) were between the ages of 26 and 30 years old, and 100% of patients complained of infertility, with 66.25% being of the primary type. Menstrual abnormalities affected 73.75% of women. The LH: FSH ratio was greater than 1.6 in approximately 85% of responders, and 77.5% of women had enlarged polycystic ovaries. Clomiphene citrate had a conception rate of 24%, Letrozole 31% had a rate of 20%, and laparoscopic ovarian drilling followed by Letrozole had a rate of 60%. ***Conclusion:*** Polycystic ovarian syndrome is a complex illness that necessitates a variety of treatment techniques based on the reason a patient seeks treatment. Aside from diet and fitness improvements, most patients with good conception rates require lifestyle modification treatment such as C/C and laparoscopic ovarian drilling.

Keywords: Polycystic Ovarian Syndrome (PCOS), Infertile Patients, Clomiphene Citrate, Letrozole, Laparoscopic Ovarian Drilling.

INTRODUCTION

Infertility, the inability of a couple to conceive after a year of frequent unprotected intercourse, can significantly impact affected individuals' emotional well-being and psychological harmony. Approximately 10 to 15 percent of couples experience childlessness, with some facing primary infertility (no previous pregnancy) and others dealing with secondary infertility (after a prior conception). While primary infertility is often associated with male factors, female factors play a role in secondary infertility.

This widespread issue affects about one in six couples and has diverse causes across countries and social groups. Infertility can result from issues with one partner or both, and a diagnosis can be established in about 80% of cases, with a relatively even distribution of male and female factors, sometimes both in combination.

Male-factor infertility accounts for approximately 25% of cases, while female-factor infertility is primarily attributed to ovulatory dysfunction, tubal, and peritoneal factors. In some cases, a diagnosis of unexplained infertility is made when the cause cannot be identified.

Among the various underlying causes of female infertility, Polycystic Ovarian Syndrome (PCOS) stands out as a complex and heterogeneous syndrome. It is characterized by ovarian abnormalities in morphology and endocrine profiles, often associated with clinical disorders like hyperinsulinemia, diabetes, hypertension, and adverse lipid profiles. PCOS is a common cause of anovulation and infertility in women, as it disrupts regular ovulation, leading to irregular menstrual cycles and the presence of multiple small cystic structures in the ovaries, giving them a characteristic "polycystic" appearance [1-5].

For patients with irregular ovulation, clomiphene citrate (CC) has been the first-line therapy. It has anti-estrogenic properties and inhibits estradiol receptors in the hypothalamus, causing a change in the pulse frequency of gonadotropin-releasing hormone (GnRH), the release of follicle-stimulating hormone (FSH) from the anterior pituitary, and subsequent follicular development [6]. Metformin has been shown in meta-analyses to reduce circulating androgens, possibly through direct ovarian actions, and to enhance ovulation rates over the last 20 years [7, 8]. Laparoscopic Ovarian Drilling (LOD) may also be indicated for patients who persistently oversecrete LH, either naturally or in response to CC because it has been shown to diminish LH secretion [9].

Crucially, this study underscores the importance of individualized care and a collaborative approach in managing PCOS-related infertility. Recognizing that each patient's medical history, reproductive goals, and response to treatment can vary significantly, healthcare providers must tailor interventions to suit their specific needs. The aim of the study was to assess evaluation and treatment strategies for infertile patients with diagnosed Polycystic Ovary Syndrome (PCOS).

MATERIALS AND METHODS

The study was conducted at a tertiary medical institution on 80 individuals with infertility and PCOS who presented with menstrual irregularities between August 2018 and July 2019.

Patients were given a full history as well as a general vaginal examination. Suspected PCOS cases are sent for ultrasonography and other tests such as LH, FSH, and Prolactin. Laparoscopy is not required for diagnosis, although it was used in patients who were resistant to medical treatment and to rule out alternative causes of infertility.

PCOS patients diagnosed by the Rotterdam 2003 Consensus Workshop were eligible for inclusion [10] which was Anovulation and/or Oligomenorrhoea Clinical manifestations of hyperandrogenaemia (acne, hirsutism, etc.) or biochemical manifestations (2nd day of menstruation) -Serum LH, FSH, LH/FSH ratio, Prolactin, and ultrasound evidence of ovarian stromal hypertrophy and many (12), tiny (2-9 mm) follicles arranged peripheral [11].

Patients with congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome, and women over 40 but under 20 years old were excluded.

Clomiphene Citrate, Letrozole, and Laparoscopic Ovarian Drilling are recent PCOS therapy options that have been examined. The HSF examination was performed regularly to rule out any associated male factor issues.

Clomiphene Citrate was given at a starting dose of 25 mg/day rather than 50 mg/day from day 2 to day 6 or day 5 to day 9 after the commencement of menstruation in PCOS patients [12] TVS was used to record ovulation. Ovulation is normally predicted 5-10 days following the last day of treatment. Follicular rupture is treated with a 5,000 IU intramuscular HCG injection.

Letrozole 2.5 to 5mg from d_2/d_3 for 5days with or without adjustment therapy live metformin (500mg) or cabergoline

The dose was then increased to 500 mg with breakfast and 1000 mg with dinner for four days. Following that, up to 1000 mg twice a day with breakfast and dinner. It may take up to two months of treatment before spontaneous ovulation occurs [13, 14].

Laparoscopic ovarian drilling: A three-puncture laparoscopy was used in the majority of patients. A monopolar coagulating current with a power setting of 40 W was applied, and each penetration lasted 5 seconds. Depending on the size of the ovary, three to ten punctures were made, each measuring 4 mm in diameter and 7-8 mm in depth. At the completion of the surgery, the ovarian surface is lavaged with large volumes of normal saline. Post-operative adhesion can be reduced by hydro flotation with 500ml ringer lactate.

RESULTS

The majority of respondents (50%) were between the ages of 26 and 30 (Table 1). All patients in this trial had infertility as their primary complaint, and 73.75% had monthly irregularities (Table 2).

Table 1: Age Distribution of PCOS Cases (n=80)

Age of Patients (Years)	Frequency	Percentage (%)
21-25	26	32.5
26-30	40	50
31-35	12	15
36-40	2	2.5

Table 2: Frequency of Complaints (n=80)

Chief Complaints	Frequency	Percentage (%)
Infertility	80	100
Menstrual irregularities	59	73.75
Acne, Hirsutism	11	13.75
Obesity	10	12.5

Regarding menstrual history, of most patients, 35% have Oligomenorrhea while 32.5 % have normal menses. Normal LH: FSH ratio is around 2.5% in the early follicular phase (Table 3).

Table 3: Menstrual Patterns and LH: FSH Ratio (n=80)

Characteristics		Frequency	Percentage (%)
Menstrual History	Normal Menses	26	32.5
	Oligomenorrhea	28	35
	Irregular Cycle	24	30
	Amenorrhea	2	2.5
LH: FSH Ratio	<1	2	2.5
	1-1.5	10	12.5
	1.6-2	28	35
	>2	40	50

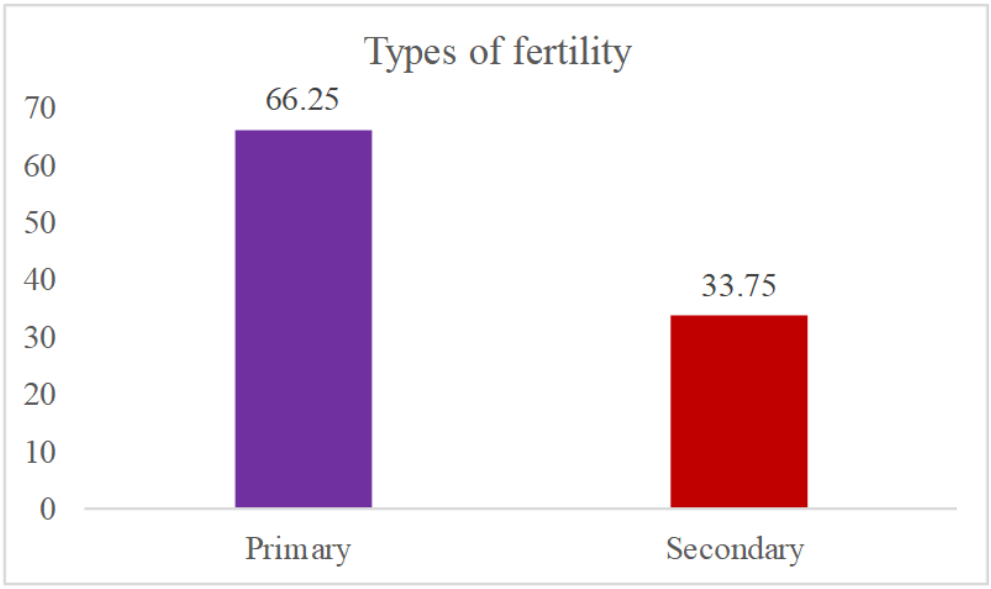

Figure 1: Type of Infertility in PCOS (n=80)

The vast majority of patients (66.25%) suffer from primary infertility. This indicates that the prevalence of primary infertility is significant in PCOS patients (Figure 1).

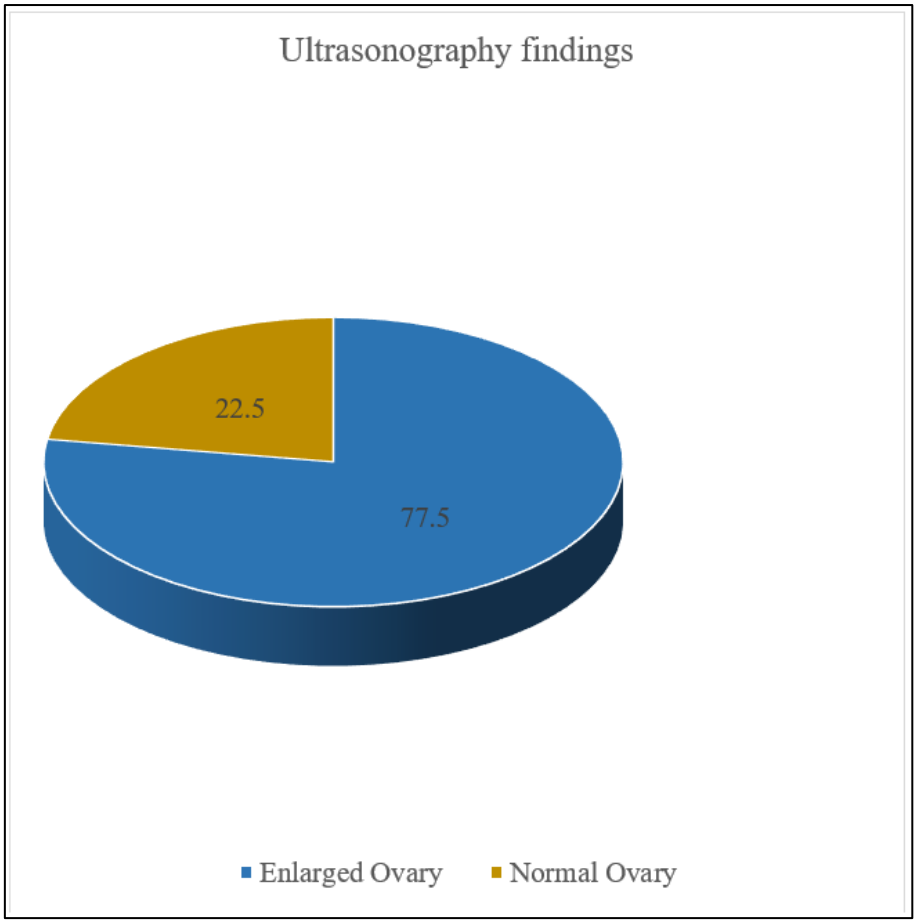

Figure 2: Ultrasonography for PCOS (n=80)

Typical polycystic ovaries (77.5%) look enlarged on TVS, but many women have normal ovaries (22.5%), therefore ultrasonography findings should have been combined with clinical manifestation and other laboratory data (Figure 2).

A total of 25 patients were randomly selected and treated with Clomiphene Citrate as the first mode of therapy; 15 of them reacted by ovulation (60%), with a conception rate of 24% during a 6-month period. Letrozole was given to 25 individuals at random as the first line of treatment; 17 of them reacted by ovulation (68%), with a conception rate of 24% during a 6-month period. Laparoscopic Ovarian Drilling was performed on 30 patients, resulting in a greater ovulatory rate (76.67%) and conception rate (60%) (Table 4).

Table 4: Outcome in Different Modality of Treatment (n=80)

Modality of Treatment	Ovulatory Rate (%)	Conception Rate (%)	Abortion Rate (%)	Total (%)
Clomiphene Citrate	17 (60)	6 (24)	2 (8)	25 (100)
Letrozole	17 (68)	6 (24)	1 (4)	25 (100)
Laparoscopic Ovarian Drilling	23 (76.67)	18 (60)	2 (6.67)	30 (100)

DISCUSSION

PCOS is a complicated disorder characterized by high testosterone levels, irregular menstruation, and/or tiny cysts on one or both ovaries [15]. Women seeking medical attention for concerns such as obesity, acne, amenorrhea, excessive hair growth, and infertility are frequently diagnosed with PCOS [16]. Elevated luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH) levels are clinical indicators of PCOS, although follicular-stimulating hormone (FSH) levels are low or stable. As GnRH levels rise, the ovarian thecal cells are stimulated, resulting in the production of more androgens [17]. Polycystic ovarian syndrome (PCOS) affects 6% to 20% of women. It is the most frequent endocrine and metabolic disorder among reproductive-age women [18].

In this study, all women are infertile with 66.25% of women having primary infertility and 33.75% of women having secondary infertility.A study showed 57% had primary and 30% had secondary infertility.5 Infertility is more common in symptomatic women. Obesity and oligomenorrhea were more frequently related with lower fecundability. In our study, 32.5% of patients had normal menstrual cycles, while 73.75% had

menstrual irregularities, whereas other investigations, such as Stephen Frank's, Vaclav Insler's, and Rajan's, found 80%, 50%, and 51% menstrual irregularities, respectively. Women with oligomenorrhea or amenorrhea have a 90% likelihood of having PCOS, and up to 95% of affected adults have oligomenorrhea or amenorrhea [19]. Furthermore, hirsutism, acne, and alopecia are all linked to high androgen levels, and the prevalence of polycystic ovaries on pelvic ultrasonography approaches 70% in PCOS patients [20].

The definition used to diagnose PCOS influences the proportion of women who have monthly irregularities [21]. When compared to women who present with oligomenorrhea or regular menstrual cycles, amenorrheic women with PCOS typically have the most severe hyperandrogenism and greater antral follicle numbers. Obese patients with PCOS benefit from lifestyle adjustments such as diet, exercise, and behavioral modification, which improve their metabolic and reproductive problems [22].

In our study, 77.5% of PCOS patients had enlarged ovaries, while 22.5% had normal-sized ovaries. The presence of 10 or more follicles (82% and 69% in the left and right ovary, respectively) and a peripheral distribution of follicles (81.8% and 71.9% in the left and right ovary) were the most sensitive features in prospective research. In 86.4% of cases, combining all of the criteria properly predicted a PCOS diagnosis or control. This study demonstrates that the accepted US criteria for polycystic ovaries are still useful in the diagnosis of PCOS [11].

Since its introduction in the early 1960s, clomiphene citrate (CC) has been the medicine of choice for treating anovulation [23]. CC is an estrogen receptor modulator with both agonist and antagonist characteristics [24]. In practical practice, however, clomiphene acts solely as an estrogen antagonist. If ovulation does not occur, the patient is classified as CC-resistant. In general, CC causes ovulation in 75-80% of individuals [25]. The prescription is inexpensive, the oral mode of administration is convenient for patients, there are few side effects, little ovarian response monitoring is necessary, and there is a wealth of clinical data available on the drug's safety.

In our study, the ovulatory rate with Clomiphene Citrate is 60%, the conception rate is 24%, and the abortion rate is 8%. In women ovulating on CC, a life table analysis of the most reputable research revealed a conception rate of up to 22% every cycle [26].

A comprehensive review and meta-analysis that included three RCTs that compared CC to placebo discovered that CC enhances ovulation rate and pregnancy rate, however, no trial on the live birth rate was reported [27]. Following the addition of hCG, the ovulation rate, clinical pregnancy rate, and miscarriage rate did not improve or decrease in a meta-analysis of 305 participants from two RCTs [28].

Approximately 75% of CC pregnancies develop within the first three treatment cycles; a course of 3-6 ovulatory cycles is usually sufficient to assess whether pregnancy occurs using CC before proceeding with further treatment. If the patient ovulates following treatment, factors like as age impact the likelihood of conception. More than 73% of women ovulated, 36% became pregnant, and 29% gave birth in the six months following CC treatment [29].

Two well-designed, industry-sponsored, multicenter, phase 2 studies, both of which were randomized, double-blind, dose-finding, noninferiority studies, compared anastrozole with clomiphene (the latter at a daily dose of 50 mg) in women with oligo-ovulation (most of whom had the polycystic ovary syndrome), with ovulation as the primary outcome [30, 31]. Both studies concluded that treatment with anastrozole was less effective than a 5-day course of clomiphene.

Letrozole, an aromatase inhibitor, is employed as a therapeutic intervention for individuals diagnosed with polycystic ovary syndrome (PCOS) who are experiencing infertility. Its mechanism of action involves the reduction of estrogen production. Additionally, this medication is employed for the treatment of specific types of breast cancer and to enhance fertility in those with ovulation-related complications [32].

In our study, the ovulatory rate is 68%, the conception rate is 24%, and the abortion rate is 4% when Letrozole is used to induce ovulation. Letrozole may be the most effective ovulation induction therapy. A multicenter research in Finland found that adding metformin after three months boosted the conception rate, with the obese PCOS subgroup benefiting the most [33]. Moll *et al.,* studied the efficacy of CC with metformin versus CC plus placebo in 228 women with PCOS. They discovered that the metformin group had a 64% ovulation rate compared to 72% in the placebo group (not significant), and there were no significant changes in either ongoing pregnancy or spontaneous miscarriage rate [34].

The primary reason for Laparoscopic ovarian drilling (LOD) in women with anovulatory PCOS is CC resistance.6 In our study, we attained an ovulatory rate of 76.67%, a conception rate of 60%, and an abortion rate of 6.67%. A large multicenter RCT conducted in the Netherlands comprised 168 patients with CC resistance who were randomly assigned to the LOD group or the FSH group for ovulation induction. The researchers discovered that after six months, the cumulative conception rate for individuals receiving LOD was 34% against 67% for those taking FSH [35].

In another study, LOD was compared to continuing CC for up to six more cycles in 176 infertile PCOS patients who had previously successfully induced ovulation with CC. Both groups had comparable clinical pregnancy rates and cumulative pregnancy rates after six cycles (39 vs 33.7% and 47 vs 39.2%, respectively). In both groups, the rates of miscarriage and live birth were comparable [36]. These trials show that LOD has no advantage over CC as first-line treatment or in CC failure. LOD may be a viable option in CC-resistant PCOS.

CONCLUSION

Infertility has a sad impact on the family lives of many couples. The causes of infertility differ between countries and social groupings. The current PCOS diagnostic criteria (as presented herein) appear to contain a wide range of disease entities that may share some clinical features but differ greatly in terms of causation. Polycystic ovarian syndrome is a complex illness that necessitates a variety of treatment techniques based on the reason a patient seeks treatment.

Ovulation induction therapy can result in acceptable cumulative pregnancy rates and low multiple birth rates, but follicle levels must be closely controlled. There are several ovulation treatment options available for women with PCOS. CC was once the recommended first-line therapy. Metformin has also been advocated as a major therapy for restoring menstrual regularity in teenagers with PCOS. Patients who had Laparoscopic Ovarian Drilling had a 67% ovulation rate and a 60% conception rate. The most important management technique is to tailor treatment to each patient's unique needs. The hunt for the ideal PCOS medication that reduces hyperandrogenism, improves cycle regularity, restores ovulation, and lowers cardiometabolic risks continues.

REFERENCES

1. Kumar, P., & Malhotra, N. (2008). Jeffcoate's principles of gynecology, 7th edition, 699.
2. Edmonds, K. (2007). Dewhurst's Textbook of Obstetrics and Gynaecology, 7th edition, 440.
3. Dechurney, A. H., Nathan, L., Goodwin, M., & Laufer, N. (2001). Current Diagnosis and Treatment of Obstetrics and Gynaecology, 10th edition, 917.
4. Hudson, C. N., & Setchell, M. E. (2001). Shaw's textbook of operative gynecology, 6th edition, 44.
5. Campo, R., & Molinas, C. R. (2008). Modern endoscopic-based exploration of the female reproductive tract: a model for developing countries?. *Human reproduction*, *2008*(1), 54-59.
6. Li, M., Ruan, X., & Mueck, A. O. (2022). Management strategy of infertility in polycystic ovary syndrome. *Global Health Journal*, *6*(2), 70-74.
7. Nestler, J. E., & Jakubowicz, D. J. (1996). Decreases in ovarian cytochrome P450c17 alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. *N Engl J Med*, *335*(9), 617-623.
8. Nestler, J. E., Jakubowicz, D. J., Evans, W. S., & Pasquali, R. (1998). Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *New England Journal of Medicine*, *338*(26), 1876-1880.
9. Poujade, O., Gervaise, A., Faivre, E., Deffieux, X., & Fernandez, H. (2011). Surgical management of infertility due to polycystic ovarian syndrome after failure of medical management. *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *158*(2), 242-247.
10. Azziz, R. (2005). Diagnostic criteria for polycystic ovary syndrome: a reappraisal. *Fertility and sterility*, *83*(5), 1343-1346.
11. Atiomo, W. U., Pearson, S., Shaw, S., & Dubbins, P. (2000). Ultrasound criteria in the diagnosis of PCOS. *Ultrasound Med Biol*, *19*, 41-47.
12. Eijkemans, M. J., Imani, B., Mulders, A. G., Habbema, J. D. F., & Fauser, B. C. (2003). High singleton live birth rate following classical ovulation induction in normogonadotrophic anovulatory infertility (WHO 2). *Human Reproduction*, *18*(11), 2357-2362.
13. Thatcher, S. S., & Jackson, E. M. (2006). Pregnancy outcome in infertile patients with polycystic ovary syndrome who were treated with metformin. *Fertility and sterility*, *85*(4), 1002-1009.
14. Barbieri, R. L. (2003). Metformin for the treatment of polycystic ovary syndrome. *Obstetrics & Gynecology*, *101*(4), 785-793.
15. Umland, E. M., Weinstein, L. C., & Buchanan, E. M. (2011). Menstruation-relateddisorders. In: DiPiro, J. T., Talbert, R. L., Yee, G. C. Pharmacotherapy: A Pathophysiologic Approach, 8th ed. New York: McGraw-Hill, 1393.
16. Ndefo, U. A., Eaton, A., & Green, M. R. (2013). Polycystic ovary syndrome: a review of treatment options with a focus on pharmacological approaches. *Pharmacy and therapeutics*, *38*(6), 336.
17. Urbanek, M. (2007). The genetics of polycystic ovary syndrome. *Natl Clin Pract Endocrinol Metab*, 3, 103–111.
18. Escobar-Morreale, H. F. (2018). Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. *Nature Reviews Endocrinology*, *14*(5), 270-284.
19. Panidis, D., Tziomalos, K., Chatzis, P., Papadakis, E., Delkos, D., Tsourdi, E. A., ... & Katsikis, I. (2013). Association between menstrual cycle irregularities and endocrine and metabolic characteristics of the polycystic ovary syndrome. *European journal of endocrinology*, *168*(2), 145-152.
20. Aziz, R., Carmina, E., Dewailly, D., Diamanti-Kandarakis, E., Escobar-Morreale, H. F., & Futterweit, W. (2006). Position statement: criteria

for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an androgen excess society guideline. *J Clin Endocrinol Metab*, *91*, 4237-4245.

21. Oh, J. Y., Sung, Y. A., & Lee, H. J. (2013). Clinical implications of menstrual cycle length in oligomenorrhoeic young woman. *Clin Endocrinol*, 11, 44-48.
22. Panidis, D., Tziomalos, K., Papadakis, E., Vosnakis, C., & Chatzis, P. (2013). Lifestyle intervention and anti-obesity therapies in the polycystic ovary syndrome: impact on metabolism and fertility. *Endocri*, 10, 22-25.
23. Dickey, R. P., Taylor, S. N., Rye, P. H., & Lu, P. Y. (1998). Future use of clomiphene in ovarian stimulation. A role for clomiphene in the 21st century?. *Human reproduction (Oxford, England)*, *13*(9), 2361-2362.
24. Clark, J. H., & Markaverich, B. M. (1983). The agonistic and antagonistic effects of short acting estrogens: a review. *Pharmacology & therapeutics*, *21*(3), 429-453.
25. Messinis, I. E. (2005). Ovulation induction: a mini review. *Human reproduction*, *20*(10), 2688-2697.
26. Tarlatzis, B., Fauser, B., & Legro, R. (2008). Thessaloniki ESHRE/ASRM-Sponsored PCOS consensus workshop group (2008), consensus on infertility treatment related to polycystic ovary syndrome. *Hum Reprod*, *23*, 462-77.
27. Brown, J., Farquhar, C., Beck, J., Boothroyd, C., & Hughes, E. (2009). Clomiphene and anti-oestrogens for ovulation induction in PCOS. *Cochrane Database of Systematic Reviews*, 7(4).
28. George, K., Kamath, M. S., Nair, R., & Tharyan, P. (2014). Ovulation triggers in anovulatory women undergoing ovulation induction. *Cochrane Database of Systematic Reviews*, 31(1).
29. Homburg, R. (2005). Clomiphene citrate–end of an era? A mini-review. *Hum Reprod*, *20*(8), 2043-2051.
30. Tredway, D., Schertz, J. C., Bock, D., Hemsey, G., & Diamond, M. P. (2011). Anastrozole single-dose protocol in women with oligo-or anovulatory infertility: results of a randomized phase II dose–response study. *Fertility and sterility*, *95*(5), 1725-1729.
31. Tredway, D., Schertz, J. C., Bock, D., Hemsey, G., & Diamond, M. P. (2011). Anastrozole vs. clomiphene citrate in infertile women with ovulatory dysfunction: a phase II, randomized, dose-finding study. *Fertility and sterility*, *95*(5), 1720-1724.
32. HealthMatch Pty Ltd. Letrozole for PCOS: How does it work? [Internet]. HealthMatch. [cited 2023 Oct 7]. Available from: https://healthmatch.io/pcos/letrozole-pcos
33. Morin-Papunen, L., Rantala, A. S., Unkila-Kallio, L., Tiitinen, A., Hippeläinen, M., Perheentupa, A., ... & Tapanainen, J. S. (2012). Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial. *The Journal of Clinical Endocrinology*, *97*(5), 1492-1500.
34. Moll, E., Bossuyt, P. M., Korevaar, J. C., Lambalk, C. B., & van der Veen, F. (2006). Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. *Bmj*, *332*(7556), 1485.
35. Bayram, N., Van Wely, M., Kaaijk, E. M., Bossuyt, P. M., & van der Veen, F. (2004). Using an electrocautery strategy or recombinant follicle stimulating hormone to induce ovulation in polycystic ovary syndrome: randomised controlled trial. *Bmj*, *328*(7433), 192.
36. Abu Hashim, H., Foda, O., Ghayaty, E., & Elawa, A. (2011). Laparoscopic ovarian diathermy after clomiphene failure in polycystic ovary syndrome: is it worthwhile? A randomized controlled trial. *Archives of gynecology and obstetrics*, *284*, 1303-1309.