Ibrahim Card Med J 2024; 14 (2): 17-25

An Evaluation of The Outcome of Stepwise Treatment of Subfertility in Women with Polycystic Ovary Syndrome

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ABSTRACT

Background & objective: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women accounting for approximately 80% of all cases of anovulatory infertility. This prospective study evaluated the fertility outcomes of a stepwise conservative management protocol for women with polycystic ovary syndrome (PCOS) and anovulatory infertility.

Methods: A total of 117 eligible women were initially enrolled, with 104 completing the 2.5-year treatment and follow-up with 13 patients completely lost to follow up. The protocol followed a progressive approach, beginning with lifestyle modifications and advancing to pharmacological ovulation induction with clomiphene citrate and letrozole. In the 1st-line of treatment, there were three steps. The Step-I, 1st-line of treatment consisted of Life-style modification (dietary modification and exercise) with or without Metformin (850 mg in twice daily doses). The Step-II, 1st-line of treatment comprised of Clomiphen citrate, started with 50 mg/day, increased by 50 mg in each cycle up to 250 mg daily for a maximum of 6 cycles. The Step-III, 1st-line of treatment was done with Letrozole (started with 2.5 mg daily increased by 2.5 mg in each cycle up to 6 cycles). In the 2nd line of treatment there were two steps. The Step-I, 2nd-line of treatment was given with combination of clomiphene citrate + FSH + hCG. The Step-II, 2nd-line of treatment was done with Letrozole + FSH started at 37.5–75 IU/day (maintained for 1 week and then increased every week until follicular growth) + hCG. While the main outcome variable was live-birth, occurrence of ovulation, clinical pregnancy and miscarriage were the accessory outcome variables.

Results: The study found a clinical pregnancy rate of 82.7% and a cumulative live birth rate of 63.5% (66/104). Lifestyle modifications alone were effective for a portion of the cohort, leading to a 19.2% clinical pregnancy rate. Subsequent treatment with clomiphene citrate and letrozole further increased pregnancy rates, with letrozole demonstrating a higher live birth rate (31.25%) compared to clomiphene citrate (28.1%). An overall miscarriage rate of 23.3% was observed.

Conclusion: These findings suggest that a stepwise conservative approach is a highly effective management strategy for anovulatory infertility in this specific patient population, and they support the use of letrozole as a first-line pharmacological agent. The study highlights the feasibility and success of this treatment paradigm in a regional context and provides a foundation for future, larger-scale research.

Key words: Evaluation, Outcome, Treatment, Subfertility, Polycystic Ovary Syndrome

ORIGINAL ARTICLE

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ORIGINAL ARTICLE

INTRODUCTION:

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder and a leading cause of anovulatory infertility in women of reproductive age. This condition is characterized by hormonal imbalances, including insulin resistance and high androgen levels, which significantly impact fertility and overall health. While many women with PCOS can conceive naturally, a notable number experience subfertility and require medical intervention.

Polycystic ovary syndrome (PCOS) affects up to 18% of reproductive-aged women.[1,2] The hormonal abnormalities, particularly hyperandrogenism and insulin resistance play a significant role in its pathophysiology.[3] As PCOS presents a diverse range of symptoms, from menstrual irregularities and hyperandrogenism to polycystic ovaries on ultrasound, there is no single diagnostic criterion, leading to the development of the Rotterdam consensus criteria, which require the presence of at least two of the following: oligo- or anovulation, clinical or biochemical signs of hyperandrogenism, or polycystic ovarian morphology on ultrasound.[4]

The management of subfertility in women with PCOS typically follows a stepwise treatment approach aimed at restoring ovulation and improving the chances of a successful pregnancy. This approach begins with non-invasive methods and progresses to more intensive therapies as needed. The management of subfertility in women with PCOS is a stepwise process. The first step involves lifestyle modifications through diet and exercise, which can improve insulin sensitivity and boost ovulation, especially in overweight and obese women.[5] If lifestyle changes are insufficient, the next step involves ovulation induction. The first-line oral agents are clomiphene citrate or letrozole, with recent evidence favoring letrozole for higher live birth rates.[6] Metformin, an insulin-sensitizing drug, can be used as an adjunct to these therapies, particularly in patients with insulin resistance, as it may improve ovulation and pregnancy rates.[6,7] When oral agents fail, gonadotropin therapy is used as a second-line treatment, but requires close monitoring due to the risk of multiple pregnancies and ovarian hyperstimulation syndrome.[8]

Although the stepwise approach is well-established, its effectiveness needs rigorous evaluation within specific populations, such as in Bangladesh, where limited studies exist. This research aims to assess the success of this treatment paradigm in the context Bangladeshi PCOS women with subfertility. While its general objective is to determine the fertility outcomes of the stepwise conservative treatment in women with PCOS, its specific objectives include assessing the proportion of patients who achieve pregnancy and live births after each step-lifestyle modification, metformin, and ovulation induction drugs.

METHODS:

The present prospective study intended to determine the fertility outcome of step-wise treatment (each step was of 6 months duration with a total of 5 steps) of the women with polycystic ovary syndrome (PCOS) with infertility. Based on the predefined enrolment criteria, initially the study included a total of 117 eligible women.

Management of infertility was given in two lines of treatment-1st-line and 2nd-line. In the 1st-line, there were three steps of treatment. The Step-I, 1st-line of treatment consisted of life-style modification (dietary modification and exercise) with or without Metformin (850 mg in twice daily doses). The Step-II, 1st-line of treatment comprised of Clomiphen citrate, started with 50 mg/day, increased by 50 mg in each cycle up to 250 mg daily for a maximum of 6 cycles with the purpose of inducing of ovulation. The Step-III, 1st-line of treatment was done with Letrozole (started with 2.5 mg daily increased by 2.5 mg in each cycle up to 6 cycles) for the same purpose as was done in Step-II treatment. In the 2nd line of treatment there were two steps. The Step-I, 2nd-line of treatment was given with combination of clomiphene citrate + FSH (follicle stimulating hormone) + hCG (human chorionic gonadotropin). The Step-II, 2nd-line of treatment was done with Letrozole + FSH started at 37.5–75 IU/day (maintained for 1 week and then increased

every week until follicular growth) + hCG. During the 2 and a ½ year period of treatment 13 patients completely lost to follow up leaving 104 patients for final analysis. Efficacy was primarily analyzed in terms of live-birth, while occurrence of ovulation, clinical pregnancy and miscarriage were the supporting outcome variables.

Data were processed analyzed using SPSS (Statistical Package for Social Sciences), version 16.0. The test statistics used to analyze the data were descriptive statistics. While the data presented on categorical scale was expressed as frequencies with corresponding percentages, the data presented on continuous scale were expressed as mean ± SD.

RESULTS:

This prospective study investigated the fertility outcomes of a stepwise treatment protocol for subfertile women with polycystic ovary syndrome (PCOS). The protocol, which spanned 2.5 years and consisted of five steps (each lasting six months), was initiated with 117 eligible women. After excluding 13 women lost to follow-up, the final analysis included 104 participants. Of these, 30 patients withdrew or did not respond to treatment and were considered to have failed conservative management.

Patient Demographics & Clinical Characteristics

The study population had a mean age of 26.5 ± 4.9 years, with nearly 70% in their second decade of life. Most participants were from rural areas (65.4%) and worked as housewives (78.8%), with an even split between lower-middle (40%) and middle-class (40%) socioeconomic statuses. Over two-thirds of the women were overweight or obese (69.1%), while 30.8% had a normal BMI and only 1% were underweight (Table I).

The most common presenting PCOS feature was oligomenorrhea (79.8%), followed by hirsutism (47.1%), hyperinsulinemia (18.3%), & amenorrhea (7.7%). Comorbidities such as hypertension, and diabetes mellitus were rare (4.8% & 6.7% respectively) (Fig. 1 & 2). Infertility-related investigations revealed that two-thirds of the women had high serum testosterone levels (>70 ng/dL) (66.3%), and nearly half had an elevated LH:FSH ratio (>2) (54.8%) or elevated serum TSH (>2.5 mIU/L) (47.1%) (Table II).

Fertility Treatment Outcomes

The treatment protocol was divided into a first line with three steps and a second line with two steps.

First-line Treatment:

- **Step I:** This step involved lifestyle modification (diet and exercise) with or without metformin (850 mg twice daily). This resulted in a 19.2% clinical pregnancy rate (20/104), with a live birth rate of 75% (15/20) (Table III).
- **Step II:** The remaining 89 patients received clomiphene citrate (50-250 mg/day). This led to ovulation in 65.1% of women (58/89). Among those who ovulated, 48.2% achieved clinical pregnancy (28/58), with a live birth rate of 89.3% (25/28) (Table IV).
- **Step III:** The 64 patients who did not respond to the previous step were offered letrozole (2.5 mg daily, increased as needed). Of the 48 women who participated, 68.7% (33/48) ovulated. Of these, 63.6% achieved clinical pregnancy (21/33), with a live birth rate of 71.4% (15/21) (Table V).

Second-line Treatment:

- **Step I:** 19 patients received a combination of clomiphene citrate, FSH, and hCG. 57.1% (8/14) achieved clinical pregnancy, with a live birth rate of 62.5% (5/8) (Table VI).
- **Step II:** The remaining 14 patients were treated with letrozole, FSH, and hCG. 83.3% (10/12) of those who ovulated achieved clinical pregnancy, with a live birth rate of 66.7% (6/9) (Table VII).

Overall Treatment Outcome

Out of the 104 patients included in the final analysis, 86(82.7%) achieved clinical pregnancy. The overall live birth rate from the conservative stepwise treatment was 63.5% (66/104). Miscarriage occurred in 23.3% (20/86) of the clinical pregnancies. The study noted that 30 patients withdrew at different stages of the treatment and were considered failed conservative management (Table VIII).

ORIGINAL ARTICLE

Table I. Distribution of patients by their socio-demographic characteristics (n= 104)

Socio-demographic characteristics	Frequency	Percentage
Age* (years)		
≤ 20	13	12.5
21 – 30	72	69.2
> 30	19	18.3
Residence		
Rural	68	65.4
Urban	36	34.6
Occupation		
Business	2	1.9
Service	19	18.3
Labor	1	1.0
Housewife	82	78.8
Socioeconomic status		
Poor	9	8.7
Lower middle class	43	41.3
Middle class	41	39.4
Upper middle class	11	10.6
BMI (kg/m2)		
< 18.5 (Underweight)	1	1.0
18.5 – 25.0 (Normal)	32	30.8
≥ 25.0 (Overweight or obese)	40	38.5

***Mean age** = 26.5 ± 4.9 yrs; **range** = (17 – 38) yrs.

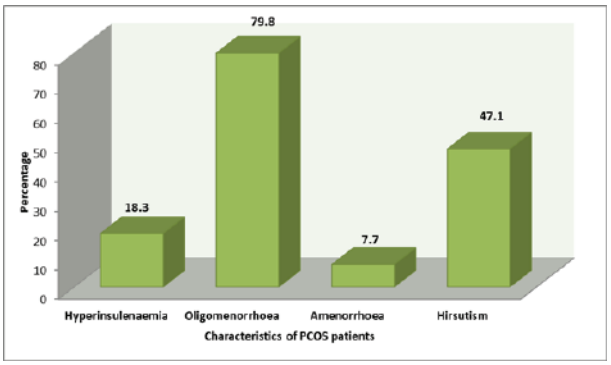

Fig 1: Distribution of patients by their characteristic signs of PCOS (n = 104*)
(*Total will not correspond to 100% for presence of multiple features in the same patient)

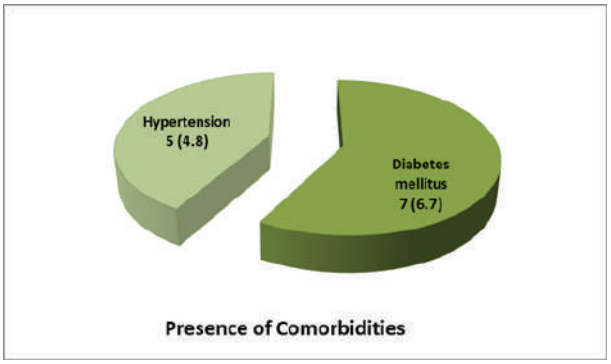

Fig 2: Distribution of patients by their presence of comorbidities (n = 104)

Table II. Distribution of patients by infertility-related lab findings (n = 104)

Investigation findings	Frequency (%)	Mean ± SD	Median (Range)
FBS (mmol/L)			
Raised (≥ 6.5)	8(7.7)	5.6 ± 1.02	5.3(3.9-10.1)
Normal (< 6.5)	96(92.3)		
S. Testosterone (ng/dL)			
High (> 70)	69(66.3)	1.1 ± 0.8	0.9(0.17-4.5)
Normal (15-70)	35(33.7)		
LH/FSH Ratio			
Increased (> 2)	57(54.8)	5.6 ± 2.3	5.3(1.36-11.2)
Normal (≤ 2)	4745.2		
S. TSH (mIU/L)			
Raised (> 2.5)	49(47.1)	4.2 ± 7.3	14.5(0.38-68.3)
Normal (≤ 2.5)	55(52.9)		
S. FT4 (pmols/L)			
Low (< 12)	19(18.3)	14.7 ± 4.2	14.6(3.19-28.1)
Normal (12-30)	85(81.7)		
S. FT3 (pmols/L)			
Low (< 2)	4(3.8)	3.9 ± 1.1	4.0 (0.12-9.2)
Normal (2-7)	100(96.2)		
S. Prolactin (ng/mL)			
High (≥ 25)	12(11.5)	15.2 ± 8.1	13.2(0.98-48.5)
Normal (< 25)	92(88.5)		

Table III. Distribution of patients by outcome of Step I, 1st-line treatment (n = 104*)

Step I, 1st-line treatment	Frequency	Percentage
Treatment provided		
Dietary modification	101	97.1
Exercise	100	96.2
Metformin (850 mg in twice daily doses)	94	90.4
Outcome		
Clinical pregnancy	20	19.2
Outcome of Clinical pregnancy (n = 20*)		
Live-birth	15	75.0
Miscarriage	5	25.0
Multiple pregnancy	1	5.0

*Total will not correspond to 100% for multiple response

Table IV. Distribution of patients by outcome of Step II, 1st-line treatment (n = 89)

Outcome of Step II - 1st line treatment Induction of ovulation: Clomiphen citrate (started with 50 mg/day increased by 50 mg in each cycle up to 250 mg daily up to 6 cycles)	Frequency	Percentage
Ovulation occurred	58	65.1
Clinical pregnancy (n = 58)	28	48.2
Outcome of clinical pregnancy (n = 28*)		
Live-birth	25	89.3
Miscarriage	3	10.7
Multiple pregnancy	1	3.6

*Total will not correspond to 100% for multiple response

Table V. Distribution of patients by outcome of step III, 1st-line treatment (n = 48)

Outcome of Step III - 1st line treatment Letrozole (started with 2.5 mg daily increased by 2.5 mg in each cycle up to 6 cycles)	Frequency	Percentage
Ovulation occurred	33	68.7
Clinical pregnancy (n = 33)	21	63.6
Outcome of clinical pregnancy (n = 21*)		
Live-birth	15	71.4
Miscarriage	6	28.6
Multiple pregnancy	2	9.5

*Total will not correspond to 100% for multiple response

Table VI. Distribution of patients by outcome of step I, 2nd-line treatment (n = 19)

Outcome of Step I, 2nd line treatment (Combination of clomiphene citrate + FSH+ hCG)	Frequency	Percentage
Ovulation occurred	14	73.7
Clinical pregnancy (n = 14)	8	57.1
Clinical pregnancy (n = 8)		
Live-birth	5	62.5
Miscarriage	3	37.5

Table VII. Distribution of patients by outcome of step II, 2nd-line treatment (n=14*)

Outcome of Step II - 2st line treatment [Letrozole + FSH (started at 37. 5-75 IU/day, maintained for 1 week and then increased every 7 days until follicular growth) + hCG]	Frequency	Percentage
Successful ovarian stimulation	12	85.7
Ovulation occurred (n = 12)	10	83.3
Clinical pregnancy (n = 10)	9	90.0
Outcome of clinical pregnancy (n = 9*)		
Live-birth	6	66.7
Miscarriage	3	33.3
Multiple pregnancy	1	11.1

*Total will not correspond to 100% for multiple response

Table VIII. Final outcome of treatment of PCOS women with infertility (n = 117)

Final outcome of treatment	Frequency	Percentage
Completely lost to follow up (n = 117)	13	11.1
Clinical pregnancy (n = 104)	86	82.7
Live-birth	66	76.7
Miscarriage	20	23.3
Withdrawal from conservative treatment (failed conservative treatment)		
After Step-II, 1st-line treatment	16	13.7
After Step-III, 1st-line treatment	14	11.9

DISCUSSION:

Polycystic ovarian syndrome (PCOS), a disorder regularly seen in general practice, can have an untold impact on the quality of life of young women. Changes in lifestyle are frequently the focus of treatment for PCOS women who are infertile. The next phase is pharmacological ovulation induction, during which letrozole, clomiphene citrate, or gonadotropins are advised for use. When these measures do not work, laparoscopic ovarian drilling or assisted reproductive technologies are commonly suggested.[9] The present study, which evaluated a step-wise conservative management protocol for anovulatory infertility in women with polycystic ovarian syndrome (PCOS), achieved a notable overall live birth rate of 63.5%. This high rate, derived from a clinical pregnancy rate of 82.7%, suggests a high degree of efficacy for the protocol within the studied cohort. The findings indicate that a structured approach, commencing with lifestyle modifications and progressing to pharmacological ovulation induction with clomiphene citrate and letrozole, can yield favorable reproductive outcomes.

This finding is consistent with established literature, which shows that women with PCOS have a significantly higher risk of miscarriage, with rates reported to range from 42 to 73% in some studies, compared to a general population rate of 15 to 25%.[10-12] The increased risk of pregnancy loss in PCOS is linked to underlying factors such as hyperandrogenism, obesity, and insulin resistance, all of which were highly prevalent in the study cohort.[10] The high miscarriage rate is a direct consequence of the metabolic and hormonal environment.[10] This observation suggests that successful fertility management in PCOS must extend beyond simply inducing ovulation and conception. A critical focus on optimizing the patient's hormonal and metabolic state is necessary to support a healthy and viable pregnancy.

Patient Demographics and Clinical Characteristics

Our study population was characterized by a mean age of 26.5 ± 4.9 years, with a high prevalence of young women in their second decade of life. A majority of the participants were from rural areas

ORIGINAL ARTICLE

and identified as housewives, with a socioeconomic background predominantly in the lower-middle and middle classes. The most frequent presenting symptom was oligomenorrhea (79.8%), followed by hirsutism (47.1%), with a smaller percentage experiencing hyperinsulinemia and amenorrhea. The overall prevalence of comorbidities like hypertension and diabetes mellitus was low.

A notable finding was the high prevalence of overweight or obesity, reported in nearly 70% of the women. This figure aligns with or exceeds international data, which indicates that 40% to 80% of women with PCOS are overweight or obese,[13] with some studies reporting a prevalence as high as 80% in the United States.[14] Despite the high prevalence of obesity, the rates of associated comorbidities were low, with hypertension observed in only 4.8% and diabetes mellitus in 6.7% of the patients. This apparent paradox can be attributed to the young age of the cohort, as these cardiometabolic complications often manifest over a longer duration.

Endocrine and Metabolic Profile

Elevated serum testosterone was a key finding, present in two-thirds of the women. While testosterone is essential for follicular development, excessive levels, as seen in PCOS, can impair follicle and oocyte quality and disrupt normal ovulatory cycles. The high luteinizing hormone (LH) to follicle-stimulating hormone (FSH) ratio (> 2) observed in a significant portion of the women is a classic feature of PCOS.[15] This elevated LH can prevent the necessary LH surge required for ovulation, leading to irregular or absent periods.

Furthermore, a substantial number of women presented with an elevated thyroid-stimulating hormone (TSH) level (> 2.5 mIU/L), which is a value associated with poorer pregnancy and ovulation rates. Both hyper- and hypothyroidism are known to interfere with menstrual cyclicity and fertility. Although a normal TSH range is important for overall health, a value ≤ 2.5 mIU/L is considered ideal for women trying to conceive.

The study also identified cases of elevated fasting blood sugar, consistent with **insulin resistance**, a core pathological feature of PCOS. Hyperinsulinemia and elevated LH work synergistically to increase ovarian androgen production, which in turn inhibits follicular maturation and contributes to infertility.[16] Additionally, a small percentage of women had elevated prolactin levels, which can also disrupt the menstrual cycle by suppressing estrogen production.

Efficacy of Stepwise Management

The study's primary finding was the high overall success rate of 63.5% for live births using a conservative stepwise approach. Of the 104 women who completed the treatment, 82.7% achieved a clinical pregnancy.

Lifestyle Modifications (Step-I)

Lifestyle modifications, including dietary changes and exercise, are the cornerstone of initial management. The study found that nearly 20% of the women who underwent this step achieved clinical pregnancy. This is in line with previous research suggesting that a modest weight loss of as little as 5% can improve menstrual regularity & enhance the effectiveness of ovulation-inducing medications.[17] It is well known that maintaining a healthy weight and getting enough sleep each night will reduce insulin resistance and hyperandrogenism, as well as improve hormonal imbalance and other metabolic processes. However, there is insufficient evidence that a change in lifestyle alone has any effect on fertility when it comes to the results of conception. Infertile obese or overweight PCOS women who lose weight may experience intermittent ovulation, a favourable response to ovulation induction therapies, and an increase in pregnancy and live birth rates.[18,19] Furthermore, regular physical activity may enhance reproductive outcomes by modulating the hypothalamic-pituitary-gonadal axis.[20]

Ovulation Induction with Clomiphene Citrate (Step-II)

Clomiphene Citrate in Step-II induced ovulation in 65% and pregnancy in 48.2%, with a high live-birth rate (89.3%). Though ovulation occurs in most CC users, pregnancy rates are lower due to anti-estrogenic effects on the endometrium.[21,22] Clomiphene resistance affects about 15% of PCOS patients, with obesity and hyperandrogenism being major risk factors.[23]

Ovulation Induction with Letrozole (Step-III)

For patients who were resistant to or did not conceive with CC, letrozole was used as a second-line option. It induced ovulation in 68.7% of cases, with a 63.6% conception rate and a live birth rate of 71.4%. Letrozole is a non-steroidal aromatase inhibitor that promotes mono-follicular development by transiently suppressing estrogen production, which leads to increased pituitary FSH secretion.[24] Mitwally and Casper published the first study on the use of letrozole for ovulation induction in women who did not well-respond to CC in 2001.[25] Recent evidence suggests that letrozole may be superior to CC in achieving live births, with a lower risk of multiple pregnancies and ovarian hyperstimulation syndrome (OHSS).[26,27] Our findings align with this, showing a lower incidence of multiple pregnancies compared to the CC group, reinforcing its role as a highly effective and safe alternative.

Of the remaining 19 patients who did not conceive with letrozole received a combination of clomiphene citrate, FSH, and hCG. Over half (57.1%) of them achieved clinical pregnancy, with a live birth rate of 62.5%. The remaining 14 patients were treated with letrozole, FSH, and hCG achieving a high clinical pregnancy rate of 83.3% with a live birth rate of 66.7%.

Study Limitations and Strengths

A critical evaluation of the study's design is necessary to appropriately interpret its findings. The primary limitations stem from its design as a single-center, prospective study with a small sample size. A single-center study inherently lacks external validity, meaning its findings may not be generalizable to broader populations, as institutional practices and regional demographics can differ. This is particularly relevant given the study's specific patient cohort of young, predominantly rural and lower-to-middle-class women, as the results may not be applicable to more diverse or urban populations. The small sample size (n=117 at enrollment) further reduces the statistical power and robustness of the findings, making the results susceptible to chance occurrences, such as the anomalous multiple pregnancy rate observed with letrozole. The high dropout rate, with 11.1% of patients leaving the study before treatment, also limits the ability to draw definitive conclusions about the efficacy of the protocol for the entire patient population.

Despite these limitations, the study possesses significant strengths. Its prospective design, which followed patients through a structured, step-wise protocol, provides valuable real-world data on a patient population for which limited research is available. The comprehensive collection of demographic, clinical, and biochemical data adds depth to the findings, confirming the intricate pathophysiology of PCOS within this cohort. The study provides an excellent foundation and a strong impetus for more extensive, large-scale research.

Clinical Implications & Future Research Directions

The high success rate of lifestyle modifications validates its role as the critical first step in treatment, providing empirical evidence for the established clinical consensus.[4] The re-analysis of the pharmacological outcomes further fortifies the modern understanding that letrozole offers a superior live birth rate compared to clomiphene citrate & should be considered the preferred first-line pharmacological agent for ovulation induction in anovulatory women with PCOS.[27]

The study's limitations, however, highlight the critical need for future research. The primary recommendation is for larger, multi-center, randomized controlled trials in similar patient populations. Such studies would overcome the issues of limited generalizability and small sample size, providing more robust and statistically reliable data to confirm the efficacy of the protocol. Additionally, future research should focus on longitudinal studies to follow young PCOS patients to monitor the progression of their cardiometabolic risks over time.

CONCLUSION:

This study provides a comprehensive overview of the clinical characteristics of PCOS patients and the efficacy of a stepwise, conservative treatment approach. The high success rate underscores the importance of a structured treatment protocol

beginning with lifestyle interventions, followed by targeted ovulation induction with CC or letrozole. The findings highlight the significant impact of key metabolic and endocrine markers-including insulin resistance, hyperandrogenism, and thyroid function-on fertility outcomes and emphasize the need for a holistic management strategy. Future research should explore the long-term fertility outcomes and the role of additional treatment modalities in PCOS management.

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