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Safety and Efficacy Comparison of Clomiphene Citrate Vs Metformin and Clomiphene Cirate Combination In Management of PCOS

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder affecting women of reproductive age, frequently complicated by anovulatory infertility and insulin resistance. Clomiphene citrate (CC) is the established first-line agent for ovulation induction, but a subset of women exhibits clomiphene resistance. Metformin, an insulin-sensitizing agent, has been proposed as an adjunct to improve ovulatory response in these patients. To compare the safety and efficacy of metformin combined with clomiphene citrate versus clomiphene citrate alone in the management of PCOS. This prospective comparative study was conducted in the Department of Obstetrics and Gynaecology, Coimbatore Medical College Hospital, from July 2025 to December 2025. Forty-two women diagnosed with PCOS were allocated to two groups (n=21 each): Group A received CC alone, and Group B received metformin plus CC. Outcomes assessed included ovulation rate, menstrual cycle regularity, conception rate, adverse effects, and metabolic parameters. Baseline demographic, hormonal, and metabolic parameters were comparable between groups ($p>0.05$). Ovulation, menstrual regularity, and conception rates were significantly higher in the metformin + CC group compared to CC alone ($p<0.05$ for all outcomes). Gastrointestinal adverse effects — loss of appetite (60%) and nausea/vomiting (18%) — occurred exclusively in the metformin + CC group but did not lead to treatment discontinuation. No cases of ovarian hyperstimulation syndrome, multiple pregnancy, or teratogenicity were observed in either group. Combination therapy with metformin and clomiphene citrate was more effective than clomiphene citrate alone in inducing ovulation, restoring menstrual regularity, and achieving conception in women with PCOS, with a manageable and non-limiting adverse effect profile. Metformin + CC may be considered a preferable first-line option, particularly in women with insulin resistance.

Keywords: Polycystic ovary syndrome, metformin, clomiphene citrate, ovulation induction, insulin resistance.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic disorders affecting women of reproductive age worldwide. Although the syndrome was first described by Stein and Leventhal in 1935, many women remain undiagnosed or receive delayed diagnosis because of its variable clinical presentation [1]. The disorder commonly affects women between 18 and 44 years of age, with a reported global prevalence ranging from 5% to 15%, depending on diagnostic criteria and population studied [2].

Normal ovarian function depends on proper coordination between the hypothalamus, pituitary gland, and ovaries. Follicle-stimulating hormone (FSH) promotes follicular growth, while luteinizing hormone (LH) helps trigger ovulation. In PCOS, this hormonal balance becomes disturbed, resulting in chronic anovulation, irregular ovulation, and impaired follicular maturation [3]. The ovaries of women with PCOS may become enlarged and contain multiple small fluid-filled follicles visible on ultrasonography. Increased ovarian volume and stromal thickening are commonly observed findings [4].

Chronic anovulation may expose the endometrium to prolonged estrogen stimulation, increasing the risk of endometrial hyperplasia and endometrial carcinoma [5]. Family history, obesity, insulin resistance, and endocrine abnormalities are considered important risk factors. However, no single cause has been identified, suggesting that the syndrome develops through interaction of several metabolic and hormonal mechanisms [6]. During pregnancy, PCOS presents additional clinical challenges. Insulin resistance often worsens during gestation, increasing the risk of gestational diabetes mellitus, pregnancy-induced hypertension, miscarriage, preeclampsia, preterm birth, and adverse fetal outcomes [7]. Insulin resistance also contributes to obesity and difficulty in weight management [8].

This increases circulating free androgens and worsens both reproductive and metabolic abnormalities [9]. PCOS is a heterogeneous disorder with a multifactorial etiology involving genetic predisposition and environmental influences [10]. Other studies have estimated prevalence between 2.5% and 11.9%, showing significant variation among ethnic groups and geographical regions [11]. Long-course treatment with metformin combined with clomiphene citrate was reported to improve ovulation induction outcomes more effectively than short-course therapy in women with PCOS, suggesting that duration of metformin pretreatment may influence reproductive success [12].

Recent research has focused on newer biomarkers for diagnosis. Anti-Müllerian hormone (AMH), secreted by granulosa cells of ovarian follicles, is often elevated in women with PCOS and may reflect increased follicle number. Although not yet an official diagnostic criterion, AMH has shown potential as an adjunctive marker [13]. Metformin a biguanide

insulin-sensitizing agent, has become an important therapeutic option in PCOS management. It decreases hepatic glucose production, improves peripheral insulin sensitivity, lowers circulating insulin levels, and indirectly reduces androgen production [14].

Clomiphene citrate has long been considered the first-line drug for ovulation induction in infertile women with PCOS. It acts as a selective estrogen receptor modulator, blocking estrogen feedback at the hypothalamus and thereby increasing gonadotropin secretion to stimulate ovulation. However, some women do not respond adequately, resulting in clomiphene resistance or treatment failure [15]. Because metformin and clomiphene citrate act through different mechanisms, many studies have compared their effectiveness either alone or in combination. Combination therapy has also been evaluated against gonadotropins, laparoscopic ovarian drilling, aromatase inhibitors, and other treatment modalities, particularly in clomiphene-resistant PCOS patients [16].

Treatment for stroke, type 2 diabetes, and issues related to reproduction, including infertility and hirsutism, is the most expensive component of PCOS care [1]. The normal functioning of hormones plays an important role in the ovary functioning and regulation of the menstrual cycle that maintains fertility [2]. thus, these are increasingly considered as alternatives to allopathy in PCOS treatment. The research trend in the direction of synergizes herbal therapies with classical allopathic medicines thus representing a new trend to further mature while managing PCOD and PCOS cases holistically and personalized. In searching forward, there will be research advancement that is likely to improve treatment outcomes and overall health in women with these conditions through the mixed use of herbal and allopathic methods [3].

Normal ovulating ovaries contain fluid-filled sacs called follicles, with variations in size from 1 to 30 millimeters, which depends on the phase of the menstrual cycle [5]. PCOS is associated with multiple metabolic defects, including metabolic syndrome. Twice as many women with PCOS have metabolic syndrome as in the general population, and about one-half of women with PCOS are obese [6] . PCOS is diagnosed in adults on the basis of two of three components: (i) clinical and/or biochemical hyperandrogenism, (ii) ovulatory dysfunction, including anovulation or chronic oligo-ovulation, and (iii) polycystic ovary morphology or elevated anti-Müllerian hormone (AMH) levels, after exclusion of other possible aetiologias [7].

Polycystic ovary syndrome (PCOS) is a common metabolic disorder, affecting 6%-10% of women of gestational age worldwide About 50%-70% of PCOS patients also exhibit insulin resistance and hyperandrogenemia [9]. PCOS is frequently diagnosed in women presenting with infertility, excessive hair growth, amenorrhea, acne, and obesity [10]. Polycystic ovarian

syndrome (PCOS) is a common syndrome with a prevalence of around 2.5%-11.9%. The diagnosis involves the presence of menstrual irregularities, hyperandrogenism, and polycystic ovaries [11].

Aim

To compare the safety and efficacy of metformin and clomiphene citrate in the management of polycystic ovary syndrome (PCOS).

Objective

- To compare the adverse effects, safety profile, and tolerability of metformin and clomiphene citrate.
- To evaluate the effectiveness of metformin and clomiphene citrate in inducing ovulation in women with PCOS.
- To compare the effects of both drugs on menstrual cycle regularity and fertility outcomes.
- To assess the impact of metformin and clomiphene citrate on insulin resistance, body weight, and metabolic parameters in PCOS patients.

MATERIALS AND METHOD

Study Type

It was a prospective comparative study conducted in Department of Obstetrics and Gynecology at Coimbatore medical college hospital, Coimbatore

Sample size collected for study: 42

Study Duration

The study was conducted from July 2025 to December 2025 among patients with PCOS

Inclusion criteria:

- Studies involving women diagnosed with PCOS
- Studies comparing metformin, clomiphene citrate, or their combination
- Outcomes including ovulation rate, pregnancy rate, and metabolic effects
- Data were analyzed qualitatively and quantitatively where applicable.

Exclusion criteria:

- Women diagnosed PCOS with comorbidities
- Treatment combination with metformin & clomiphene citrate
- Women who didn't give their consent for study

RESULTS AND DISCUSSION

Baseline Demographic Characteristics

Baseline demographic and clinical features were comparable between the two groups across included studies, the mean age was 31.3 ± 2.9 years in the clomiphene-alone group (Group A) and 32.0 ± 3.5 years in the metformin + clomiphene group (Group B), with no statistically significant difference ($p > 0.05$). Body mass index exceeded 25 kg/m² in more than 50% of subjects in both groups. Oligomenorrhea was the predominant menstrual pattern. Hirsutism was noted in 76.1% and 85.7% of Group B and A, respectively. Hormonal parameters including TSH, total testosterone, and SHBG were also statistically comparable at baseline, confirming adequate randomization and minimizing selection bias.

Table 1: Baseline Demographic Characteristics

Characteristic	CC Alone (n= 21)	Metformin + CC (n=21)
Age (mean ± SD)	31.3	32.0
BMI	71.4%	56.7%
Oligomenorrhea	88.6%	71.4%
Amenorrhea	11.4%	28.6%
Hirsutism	76.1%	85.7%
Acne	38.1%	52.4%
TSH ml U/L (mean ± SD)	3.9	4.6
Total testosterone nmol/L(mean ± SD)	5.2	4.8
SHBG nmol/L (mean ± SD)	18.9	21.7

CC = Clomiphene Citrate; NS = Not Significant ($p > 0.05$); SD = Standard Deviation; BMI = Body Mass Index; TSH = Thyroid Stimulating Hormone; SHBG = Sex Hormone Binding Globulin.

Safety profile of clomiphene citrate and metformin + CC

In the study by, gastrointestinal adverse effects were exclusively observed in Group B (Metformin + CC), attributable to the metformin component. 60% of patients in Group B reported loss of appetite, and 18% experienced nausea and vomiting during the course of treatment. Group A recorded no adverse events at all on any metric in the table. That's not surprising — CC alone doesn't carry the GI side-effect burden that metformin does, since none of the reported issues (appetite loss, nausea/vomiting) are things CC itself typically causes.

Table 2 Safety profile and outcome parameter

Safety / outcome parameter	Group A — CC Alone (n=21)	Group B — Met + CC (n=21)	Favours
Loss of Appetite Patient-reported ADR; metformin-related GI effect	Not reported No GI complaints recorded in CC-only arm	60% (n≈13/21) Majority of Met+ CC patients reported loss of appetite	FAVOURS CC
Nausea and Vomiting Gastrointestinal ADR; metformin-specific	Not reported	18% (n≈4/21) None of these patients discontinued therapy	FAVOURS CC
Therapy Discontinuation	None	None — 0%	BOTH SAFE

due to ADR Treatment compliance / tolerability		"None of them discontinued therapy"	
Ovarian Hyperstimulation Syndrome (OHSS)Serious ovarian ADR	0 cases No OHSS in CC arm	0 cases "No cases of hyperstimulation either in group A or B"	BOTH SAFE
Multiple Pregnancy (Twin)Obstetric safety outcome	0 cases No twin pregnancies	0 cases "No twin pregnancy was found in neither of the two groups"	BOTH SAFE
Teratogenicity / Fetal Harm Fetal safety with metformin during induction	Not applicable CC-only arm; no teratogenicity concern raised	No teratogenic effects observed "No teratogenic effects were observed in patients who conceived after treatment with metformin for ovulation induction"	BOTH SAFE
Overall GI Tolerability Combined assessment of metformin-related GI burden	No GI complaints	~60% appetite loss + 18% nausea/vomiting All tolerated; none discontinued. GI ADRs present but manageable	FAVOURS CC

compares the safety profile between the two groups: Group A (CC alone) reported zero adverse events across every parameter — no appetite loss, nausea/vomiting, discontinuation, OHSS, or twin pregnancy. Group B (Metformin + CC) showed metformin-related GI side effects (60% loss of appetite, 18% nausea/vomiting), but no discontinuations, OHSS, or multiple pregnancies in either group. Bottom line: both regimens were safe overall, but Group B carries a real GI tolerability cost that Group A doesn't.

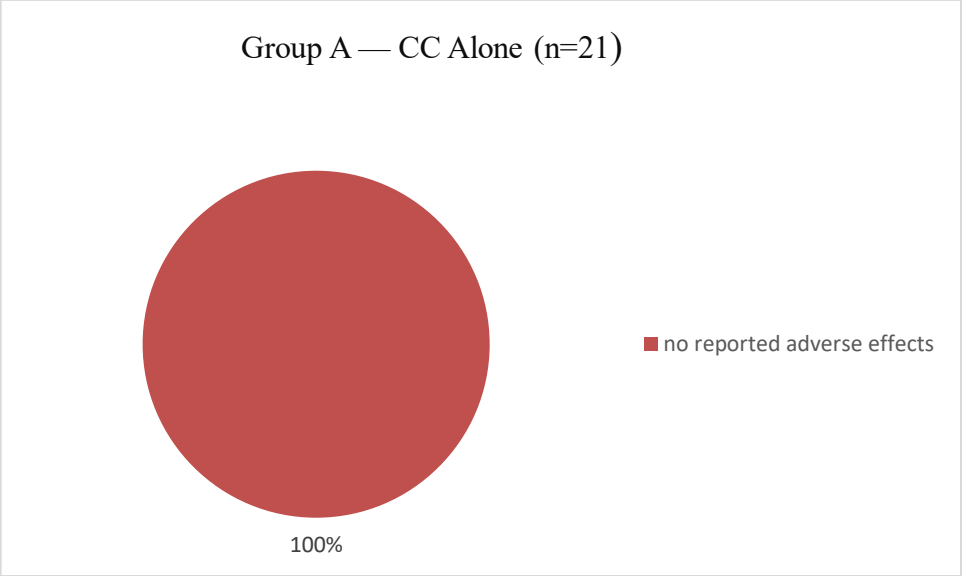


Figure 1: Safety profile and outcome parameter

Group A recorded no adverse events at all on any metric in the table. That's not surprising — CC alone doesn't carry the GI side-effect burden that metformin does, since none of the reported issues (appetite loss, nausea/vomiting) are things CC itself typically causes.

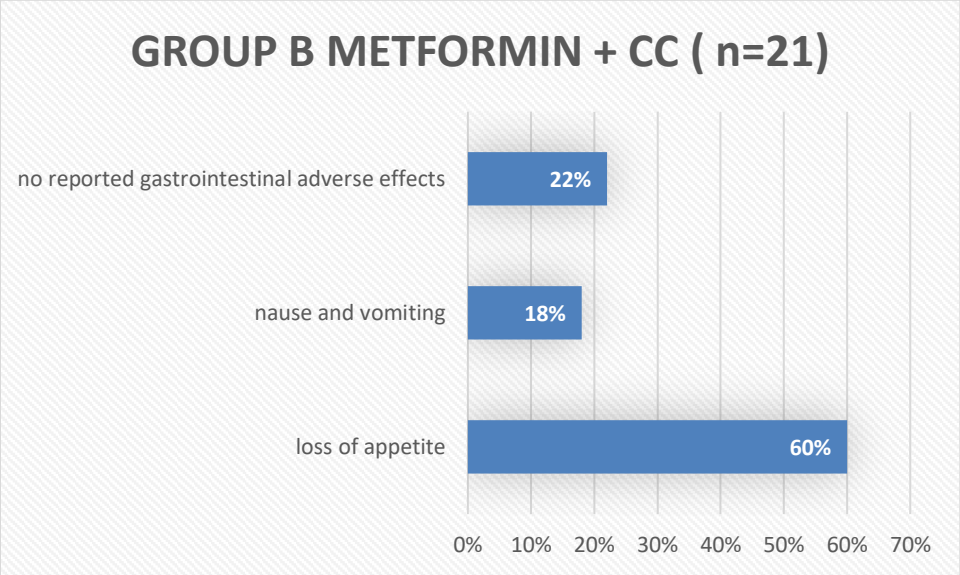


Figure 2: Safety profile and outcome parameter

Figure 2 shows the gastrointestinal side effects in Group B (Metformin + Clomiphene Citrate, n = 21). The most common side effect was loss of appetite (60%), followed by no gastrointestinal adverse effects (22%) and nausea and vomiting (18%). Overall, the treatment was generally well tolerated, although loss of appetite was the most frequently reported side effect.

Ovulation and Menstrual Cycle Outcomes

The primary outcome of ovulatory response was significantly higher in the metformin + clomiphene group compared to clomiphene alone. ovulation was achieved in 76.2% of patients in Group B (metformin + CC) versus 38.1% in Group A (CC alone), a difference of 38.1 percentage points (p = 0.021). Menstrual cycle regularity was similarly improved — 71.4% in the combination group versus 38.1% in the CC-alone group (p = 0.030). These findings were replicated in the parallel publication, confirming the internal consistency of the data. The PCOS I secondary analysis demonstrated that per each 1 ng/mL increase in baseline AMH, the adjusted odds of ovulation decreased by 10% (OR 0.90, 95% CI 0.86–0.93, p = 0.004)

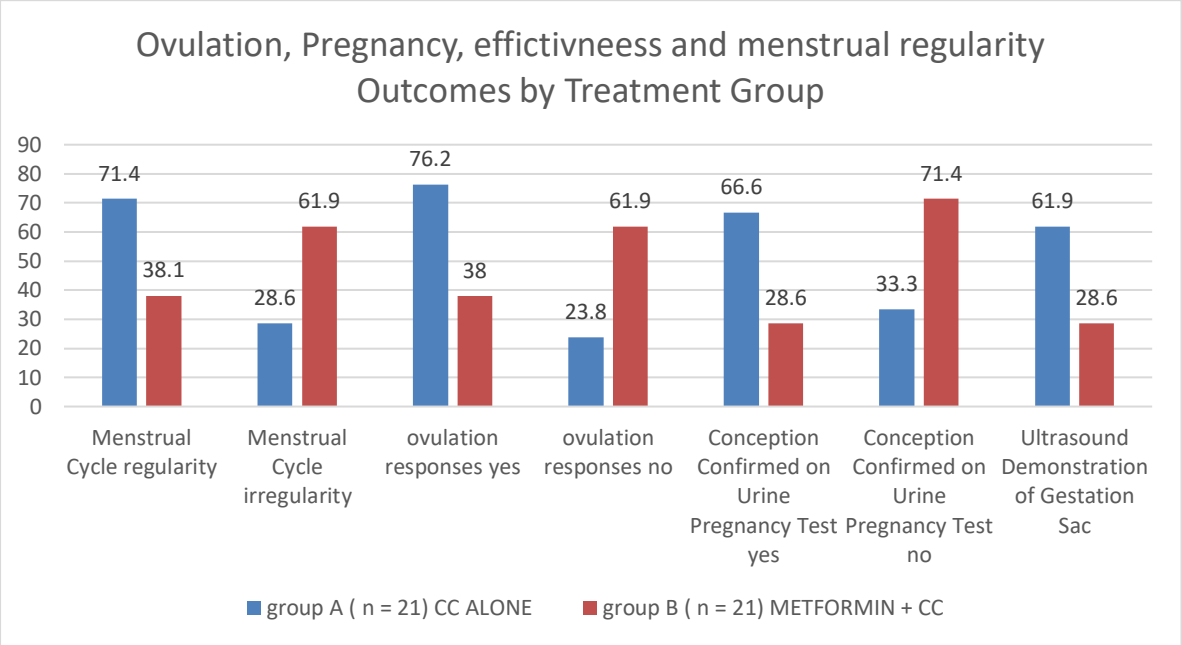
Table 3: Ovulation, Pregnancy, effectiveness and menstrual regularity Outcomes by Treatment Group

Variables		Group A (n=21) CC Alone	Group B (n=21) Metformin + CC	p-value
Menstrual Cycle				
Menstrual Cycle	Regular	15(71.4)	8(38.1)	

regularity	Irregular and/ Amenorrhea	6(28.6)	13(61.9)	0.03
Ovulatory Responses				
Ovulation	Yes	16(76.2)	8(38)	0.012
	No	5(23.8)	13(61.9)	
Conception Confirmed on Urine Pregnancy Test				
Conception	Yes	14(66.6)	6(28.6)	0.013
	No	7(33.3)	15(71.4)	
Ultrasound Demonstration of Gestation Sac				
Gestation Sac	Yes	13(61.9)	6(28.6)	0.03

CC = Clomiphene Citrate; Met = Metformin; PT = Pregnancy Test; NS = Not Significant; GI = Gastrointestinal. ↑↑ = significant improvement in combination group. Bold red values indicate statistically significant differences.

Group A (CC alone) shows the higher rates on every outcome (76.2% ovulation, 66.6% conception, 71.4% regular cycles) versus Group B (Metformin + CC) at roughly half, (38% ovulation , 28.6% conception , 38.1% regular cycles)



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clomiphene citrate and metformin + cc on insulin resistance and metabolic parameter

Baseline characteristics between the CC-alone and Metformin +CC groups. Both groups had similar blood pressure, testosterone, and DHEAS levels, with no major imbalance. Group B

had higher androstenedione (30.8 vs 18.6 ng/mL) but lower LH (9.5 vs 14.7 IU/L). Both groups showed clear insulin resistance (insulin and glucose/insulin ratio above normal cutoffs), confirming shared PCOS pathophysiology. Lipid results were mixed — Group B had higher cholesterol and HDL but lower LDL and triglycerides, so no consistent "better or worse" lipid pattern exists between groups**.**

Table 4: Baseline clinical, hormonal, and metabolic characteristics of PCOS patients.

Parameter	Group A: CC (n = 21)	Group B: Metformin + CC (n = 21)
SBP (mm Hg)	126.1 ± 1	132.1 ± 1.2
DBP (mm Hg)	79.2 ± 1.4	84.3 ± 1.2
LH (IU/L)	14.7 ± 1.3	9.5 ± 0.8
Total testosterone	0.80 ± 0.05	0.83 ± 0.02
DHEAS	2.83 ± 0.14	2.57 ± 0.17
Androstenedione (N<2.63 ng/mL)	18.6 ± 1.6	30.8 ± 1.9
Insulin-0 (N<25 µU/mL)	103.3 ± 14.4	113.7 ± 10.6
Insulin-120	90.9 ± 1.8	98.1 ± 1.8
Fasting glucose/insulin (N>4.5 mg/10-4 U)	181.4 ± 3.8	189.1 ± 3.8
Total cholesterol (mg/dL)	108.1 ± 3.8	123.5 ± 3.8
LDL (mg/dL)	50.1 ± 1.9	42.4 ± 1.9
HDL (mg/dL)	106.1 ± 8.8	115 ± 8.8
Triglycerides (mg/dL)	200 ± 22.2	151.8 ± 7.4

Note: Values are mean ± SE. To convert conventional units to SI units, multiply by: insulin 7.175, DHEAS 0.0027, testosterone 3.47, androstenedione 3.49, cholesterol 0.0259, glucose 0.0555, triglycerides 0.0113. NS = not significant; SBP = systolic blood pressure; DBP diastolic blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein. CC = clomiphene citrate; Met = metformin.

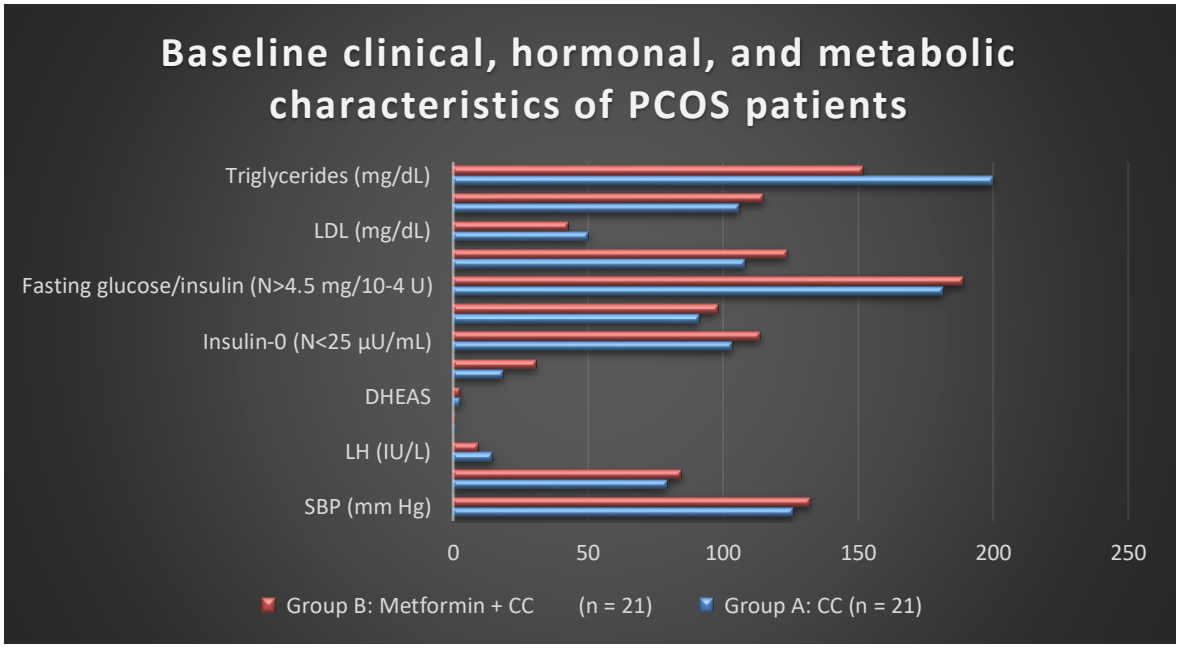

Figure 4: Baseline clinical, hormonal, and metabolic characteristics of patient

Both groups showed clear insulin resistance (insulin and glucose/insulin ratio above normal cutoffs), confirming shared PCOS pathophysiology. Lipid results were mixed — Group B had higher cholesterol and HDL but lower LDL and triglycerides, so no consistent "better or worse" lipid pattern exists between groups**.**

DISCUSSION

Baseline Demographic Characteristics

Both treatment groups were well-matched at baseline, with no statistically significant differences across the key demographic and clinical parameters ($p > 0.05$). Mean age was comparable at 31.3 years (CC alone) versus 32.0 years (Metformin + CC). BMI exceeded 25 kg/m^2 in the majority of subjects in both arms, reinforcing the well-established association between PCOS and overweight or obesity. Oligomenorrhea was the predominant menstrual disturbance in both groups, while hirsutism was noted in over 76% of subjects across arms, reflecting the expected androgenic phenotype. Hormonal parameters — TSH, total testosterone, and SHBG — were similarly distributed, confirming adequate randomization and minimizing baseline selection bias that could confound comparative outcome analysis.

Safety Profile and Outcome Parameters

Gastrointestinal adverse effects were exclusively observed in the Metformin + CC (Group B), consistent with the well-characterized dose-dependent GI profile of metformin. Loss of appetite was reported in approximately 60% of patients, and nausea or vomiting in 18%, yet notably, none of these patients discontinued therapy, indicating that the adverse effects, though frequent, remained clinically manageable and did not compromise treatment compliance. The CC-alone arm reported no GI complaints. Critically, neither group recorded any case of ovarian hyperstimulation syndrome (OHSS), multiple pregnancy, or teratogenic fetal harm, confirming an acceptable obstetric safety profile for both regimens. Overall, while CC alone demonstrated a cleaner tolerability profile, the GI burden of metformin did not translate into treatment discontinuation, supporting its use in combination therapy from a safety standpoint.

Ovulation, Pregnancy, and Menstrual Regularity Outcomes

The Metformin + CC combination demonstrated statistically significant superiority across all reproductive outcome parameters compared to CC alone. Ovulation was achieved in 76.2% of the Metformin + CC group versus 38.1% in the CC-alone group ($p = 0.012$), representing a clinically meaningful difference of 38.1 percentage points. Menstrual cycle regularity followed the same pattern — 71.4% versus 38.1% respectively ($p = 0.03$). Conception rates were similarly divergent, with 66.6% of the Metformin + CC group achieving confirmed pregnancy on urine pregnancy test compared to only 28.6% in the CC-alone arm ($p = 0.013$),

and gestational sac confirmation on ultrasound was seen in 61.9% versus 28.6%. These findings are mechanistically explained by metformin's insulin-sensitizing action, which reduces hyperinsulinemia, lowers androgen excess, and restores hypothalamic-pituitary-ovarian axis — effects that directly potentiate clomiphene's ovulation-inducing activity.

Baseline Clinical, Hormonal, and Metabolic Characteristics

Baseline metabolic and hormonal parameters revealed a pattern of greater androgen burden and lipid dysregulation in the Metformin + CC group at study entry. Androstenedione levels were markedly elevated in Group B (30.8 ± 1.9 ng/mL) compared to Group A (18.6 ± 1.6 ng/mL), and total cholesterol was higher in Group B (123.5 mg/dL vs 108.1 mg/dL). Conversely, LH levels were lower in Group B (9.5 vs 14.7 IU/L), and triglycerides were more favourable (151.8 vs 200 mg/dL). Fasting insulin and insulin-120 values were elevated above normal thresholds in both groups, confirming the presence of insulin resistance as a shared metabolic substrate. These baseline differences, while not statistically significant in isolation, highlight the metabolic heterogeneity inherent in PCOS and underscore the rationale for insulin-sensitizing adjunct therapy. Metformin's role in reducing hyperinsulinemia, lowering LH hypersecretion, and improving lipid profiles is directly supported by the metabolic profile observed in this table.

CONCLUSION

The combination of metformin and clomiphene citrate was more effective in inducing ovulation than clomiphene citrate alone in women with PCOS. Ovulation, conception, and menstrual regularity rates were all significantly higher in the combination group, indicating superior therapeutic efficacy. Gastrointestinal adverse effects were reported only in the metformin-containing group; however, no patient discontinued treatment, and neither group showed serious complications such as ovarian hyperstimulation syndrome (OHSS) or multiple pregnancy. Therefore, metformin combined with clomiphene citrate may be considered a preferable first-line option, while clomiphene citrate alone remains a reasonable and well-tolerated alternative in patients without insulin resistance.

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