Clomiphene citrate plus letrozole versus clomiphene citrate alone for ovulation induction in infertile women with chronic anovulation: A randomized controlled trial

Pattraporn Chera-aree (pattraporn.che@mahidol.ac.th)
Mahidol University Faculty of Medicine Siriraj Hospital https://orcid.org/0000-0001-8373-9537
Sirikul Tanpong
Mahidol University 2 Wanglang Road
Isarin Thanaboonyawat
Mahidol University 2 Wanglang Road
Pitak Laokirkkiat
Mahidol University 2 Wanglang Road

Research Article

Keywords: Letrozole, clomiphene citrate, anovulation, polycystic ovary syndrome, ovulation induction

Posted Date: January 5th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1219372/v1

Abstract

Objective

To compare the efficacy of combination clomiphene citrate (CC) plus letrozole with that of CC alone for ovulation induction in infertile women with chronic anovulation.

Material and methods

This randomized controlled trial was conducted at the Infertility and Reproductive Biology Unit of the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during the August 2020-September 2021 study period. Anovulatory women aged 18-40 years were equally allocated into either the CC 50 mg plus letrozole 2.5 mg once daily group or the CC 50 mg once daily group. The study drugs were administered on days 3-7 of each study patient's menstrual cycle. The primary outcome was the ovulation rate defined by serum progesterone >3 ng/mL at mid-luteal phase. The secondary outcomes were menstrual cycle characteristics, endometrial thickness, conception rate, and adverse events.

Results

One hundred women (50 per group) were enrolled. The mean age and prevalence of polycystic ovary syndrome were non-significantly different between groups. The ovulation rate according to intention-to-treat analysis was 78% and 70% in the combination and CC alone groups, respectively (p>0.05). There was no significant difference between groups for either mean endometrial thickness or number of dominant follicles. No serious adverse events were observed in either group.

Conclusion

There was no significant difference between combination CC plus letrozole and CC alone relative to their ability to induce ovulation in infertile women with chronic anovulation. The small number of live births (1 per group) was too low to be statistically analyzed.

Introduction

Infertility is defined as an inability to achieve pregnancy with regular intercourse without contraception for 12 months, or for 6 months in women above 35 years of age (1). Infertility was reported in 8-12% of women, and in 12% of Thai women (2, 3). The causes of infertility can be female-related, male-related, or both. The most common female-related factor was reported to be anovulation (50%) (4, 5). According to the World Health Organization (WHO), the most common cause of anovulation is hypothalamic-pituitary-

ovarian dysfunction (85%), and polycystic ovary syndrome (PCOS) is the most common cause of ovulatory dysfunction (30-40%) (6).

A mainstay treatment for anovulation, especially among those with PCOS, is to induce ovulation using medical agents. Clomiphene citrate (CC), which is a selective estrogen receptor modulator, continues to be the first-line treatment for this condition (7, 8). It's mechanism of action is competitive attachment to nuclear estrogen receptors. The negative feedback from estrogen causes the release of follicle stimulating hormone (FSH) to increase, which results in follicle growth and maturation. However, CC also exerts antiestrogenic effect on the endometrium and cervical mucous. Previous studies reported thinning of the endometrium and thickening of cervical mucous, which adversely affected the conception rates despite the presence of high ovulation rates (9–12).

Another ovulation induction agent that has been proposed as a first-line treatment is letrozole (13). The mechanism of action of letrozole is different from that of CC. Letrozole is a highly selective aromatase inhibitor (AI) that prevents androgen-to-estrogen conversion at peripheral tissues. The reduced estrogen level increases gonadotropic hormone secretion from the hypothalamus, which encourages follicle growth. Since letrozole does not affect peripheral or central estrogen receptors, there is no thinning of the endometrium that can impair implantation. Moreover and in contrast to CC, letrozole promotes follicular sensitivity to FSH due to the increased amount of androgen within the ovaries, which results in improved follicular growth (14).

Many studies have been conducted to compare CC and letrozole relative to their impact on infertility, especially their effect on ovulation induction. The Pregnancy and Polycystic Ovary Syndrome (PPCOS) II trial reported a significantly higher live birth rate in the letrozole group than in the CC group (27.5% *vs.* 19.1%, p=0.007). That study included only PCOS women, and the primary outcome was the live birth rate. However, the significantly better live birth rate in the letrozole group in that study cannot be conclusively determined to be the result of the use of letrozole. In that study, the ovulation rate was not significantly higher in the letrozole group than in the CC group (15). Another study evaluated the combination of letrozole and CC versus letrozole alone for ovulation induction. The ovulation rates in the combination group were significantly higher than in the letrozole alone group (77% *vs.* 42.9%, respectively; p=0.007). These results suggest that CC enhances the effectiveness of letrozole relative to ovulation induction (9). The aim of the present study was to compare the efficacy of CC plus letrozole with that of CC alone for ovulation induction in infertile women with chronic anovulation.

Material And Methods

Study overview and design

This randomized controlled trial was conducted at the Infertility and Reproductive Biology Unit of the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during the August 2020 to September 2021 study period. Enrolled study women were

allocated into either the CC 50 mg plus letrozole 2.5 mg once daily group or the CC 50 mg once daily group. The study drugs were administered on days 3-7 of each study patient's menstrual cycle. Women meeting all of the following inclusion criteria were eligible for enrollment: infertile Thai women aged 18-40 years with chronic anovulation (cycle length >35 days or diagnosed with PCOS according to modified Rotterdam criteria). Patients having one or more of the following were excluded: 1) spontaneous pregnancy; 2) uncorrected thyroid disease; 3) hyperprolactinemia; 4) allergy or contraindication to letrozole or CC; 5) bilateral tubal occlusion; and/or, 6) having a male partner with a total motile sperm count less than $10x10^6$. Participants unwilling to continue with the study were allowed to withdraw at any time. The protocol for this study was approved by the Siriraj Institutional Review Board (SIRB) (COA no. Si 257/2020), and all patients provided written informed consent to participate in the study. This trial was registered at https://www.thaiclinicaltrials.org (reg. no. TCTR20201108004).

The randomization scheme was generated by computerized randomization using block of four, and the group assignments were concealed in envelopes. Allocated group orders were concealed within the envelopes, and the sonographer was blinded to the group assignments. Participants were randomized to receive letrozole 2.5 mg (letrozole; Frensenius Kabi Oncology Ltd., Calcutta, India) and CC 50 mg daily (Ovamit, Remedica Ltd., Limassol, Cyprus) or CC 50 mg daily at a 1:1 ratio. Both study regimens were taken on days 3 through 7 of the patient's menstrual cycle. Patients with a long cycle length would be prescribed oral progestogen to induce withdrawal bleeding. The following two progestogens were used: medroxyprogesterone acetate (Provera; Pfizer, New York, NY, USA) 10 mg daily or norethisterone acetate (Primolut N, Bayer Thai Co., Ltd. Bangkok, Thailand) 5-10 mg daily for 7-10 days.

On the first day of their menstrual cycle, participants were instructed to contact the investigator and then the ovulation induction schedule was arranged. The allocated treatment medication regimen was taken on days 3 through 7 for one menstrual cycle. Home urinary luteinizing hormone (LH) test was performed in the morning and at night starting on cycle day 12 until positive result or until cycle day 21 if the results continued to be negative. Patients were instructed to send pictures of the urinary LH test result to the researcher to confirm the results. Regular intercourse performed two to three times per week starting on cycle day 12 and on the day of positive surge was recommended. Transvaginal ultrasound was performed by a single operator throughout the project on day 12 to day 14 of the cycle. Follicular growth and endometrial thickness were both recorded. Serum progesterone level was obtained 7 days after a positive urinary LH test or on cycle day 21 or day 22 in cases with negative urinary LH. Urine pregnancy test was performed 7 days after an ovulatory serum progesterone level or on cycle day 35 if no confirmation of ovulation and no menstrual period. Women with a positive urine pregnancy test were appointed for transvaginal ultrasound to confirm pregnancy 2-3 weeks later. A questionnaire was used to elicit information about adverse effects of the study medications during the study.

Outcome measures

The primary outcome was ovulation rate defined as mid-luteal progesterone level >3 ng/mL (16). The secondary outcomes included medical-related side effects; ovulation induction cycle characteristics, including endometrial thickness and number of preovulatory mature follicles defined as follicles with a

diameter greater than 14 mm (17); conception rate diagnosed by positive urine pregnancy test; and, clinical pregnancy rate confirmed by positive fetal heart beat on transvaginal ultrasonography

Sample size calculation and statistical analysis

Meija, *et al*. conducted a randomized controlled trial to investigate the effect of ovulation agents in PCOS women, and they reported a 77% rate of ovulation induction in the letrozole alone group (9). Another study reported an ovulation induction rate of 48% in the CC alone group (15). Using this data, we calculated that 43 subjects per group would be needed to obtain 80% statistical power (β) with a two-sided of significance level (α) of 0.05 to demonstrate a clinically meaningful difference in ovulation rate between our two study groups. We increased the sample size to 50 patients per group to compensate for an estimated dropout rate for any reason of 10%.

The intention-to-treat (ITT) analysis included all randomized participants, and the per-protocol (PP) analysis included only those who took the allocated treatment. For the ITT analysis, the outcome was recorded as “ovulatory” for participants who became pregnant before taking the study medication, and “not ovulatory” for participants whose outcome was unknown. All statistical analyses were performed using PASW Statistics for Windows version 18.0 (SPSS, Inc., Chicago, IL, USA). Categorical outcomes were compared using analysis of variance (ANOVA). Chi-square test or Fisher’s exact test was used to evaluate differences between categorical variables, and those results are shown as number and percentage. Independent Student’s *t*-test and Mann-Whitney U-test were used to compare normally distributed and non-normally distributed continuous variables, respectively. The results of comparisons of continuous data are shown as mean plus/minus standard deviation and median and range for normally distributed and non-normally distributed continuous data, respectively. A *p*-value of less than 0.05 was considered statistically significant for all tests.

Results

A total of 100 women with chronic anovulation were enrolled. They were equally randomized into one of the two following groups: clomiphene citrate 50 mg daily plus letrozole 2.5 mg daily or clomiphene citrate 50 mg daily. Of those, five women were excluded prior to the start of treatment (four due to spontaneous pregnancy, and one decided not to continue with the study). The remaining 95 participants took the allocated treatment (48 in the combination group, and 47 in the CC alone group) (Figure1). Baseline characteristics of study participants are shown in Table 1. The mean ± standard deviation age of participants was comparable between groups (31.8±4.6 years in the combination group versus 32.4±3.8 years in the CC alone group, p=0.54). The mean body mass index was in normal range in both groups (23.5±4.9 and 22.9±3.5 kg/m^2 in the combination group and CC alone groups, respectively). Baseline total motile sperm counts were also comparable between groups (48.7 million and 55.3 million in combination group and CC alone groups, respectively). The median duration of attempting to conceive was 2 years in both groups. The prevalence of polycystic ovarian syndrome (PCOS) according to

modified Rotterdam criteria was not significantly different between groups (48% in the combination group, and 44% in the CC alone group, *p*=0.841).

Table 1
Baseline characteristics compared between the CC + letrozole and CC alone groups

Characteristic	Letrozole + CC group (n=50)	Clomiphene citrate group (n=50)	P-value
Age (years), mean±SD	31.8±4.6	32.4±3.8	0.540
BMI (kg/m^2), mean±SD	23.5±4.9	22.9±3.5	0.456
Fertility history			
Previous live birth, n(%)	5 (10.0%)	2 (4.0%)	0.436
Previous abortion, n(%)	13 (26.0%)	7 (14.0%)	0.211
Duration attempting to conceive (years), median (min, max)	2 (1, 11)	2 (1, 10)	0.554
PCOS	24 (48.0%)	22 (44.0%)	0.841
Coexisting condition, n(%)			
Endometriosis	5 (10.0%)	12 (24.0%)	0.110
Myoma uteri	5 (10.0%)	5 (10.0%)	1.000
Baseline total motile sperm count (millions), median (min, max)	48.7 (10, 418)	55.3 (10, 350)	0.915
- None of the patient in both groups has other coexisting condition (pelvic inflammatory disease, autoimmune disease and recurrent pregnancy loss).			

The reproductive outcomes of study participants are shown in Table 2. The ovulation rate in the combination group was slightly higher than the CC group without statistically significance (ITT: 39 of 50 (78%) versus 35 of 50 (70%), respectively; *p*=0.494; and, PP: 37 of 48 (77%) versus 33 of 47 (70%), respectively; *p*=0.447). Five participants conceived after completing the ovulation induction cycle, three from the combination group and two from CC group. Two pregnancies in the combination group were first trimester pregnancy loss, and one was a clinical pregnancy that continued to live birth. One participant in the CC group was first trimester pregnancy loss, and one continued to live birth.

Table 2
Reproductive outcomes compared between the CC + letrozole and CC alone groups

Outcome	Letrozole + CC	Clomiphene citrate	Absolute difference between group (95% CI)	Rate ratio in combination group (95% CI)	P value
Primary outcome					
Ovulation, n (%)					
Intention to treat analysis[a]	39 (78)	35 (70)	8.0 (-0.09 to 0.25)	1.11 (0.88 to 1.41)	0.494
Per-protocol analysis[b]	37 (77)	33 (70)	6.9 (-0.11 to 0.17)	1.10 (0.86 to 1.40)	0.447
Secondary outcomes					
Pregnancy,n(%)					
Conception	3 (6.3)	2 (4.3)	2.0 (-0.09 to 0.13)	1.47 (0.26 to 8.40)	1.000
Clinical pregnancy	1	2	NA*	NA*	NA*
Live birth	1	1	NA*	NA*	NA*
Pregnancy loss	2	1	NA*	NA*	NA*
Fecundity among those who ovulated					
Conception	3/37	2/33	2.0 (-0.13 to 0.16)	1.34 (0.24 to 7.52)	1.000
Clinical pregnancy	1/37	2/33	NA*	NA*	NA*
Live birth	1//37	1/33	NA*	NA*	NA*
[a] Letrozole + CC, n=50; CC, n=50					
[b] Letrozole + CC, n=48; CC, n=47					
NA* not applicable due to small sample					

Ovulation induction cycle characteristics are shown in Table 3. Progestin-induced withdrawal bleeding in the combination group and in the CC group was 35.4% and 29.8%, respectively (p=0.714). The median day of the menstrual cycle that transvaginal sonography was performed was day 13 in both groups.

Regarding reported urine LH surge, the combination group had non-significantly lower positive results than the CC group (60.4% *vs.* 72%, p=0.311). The median number of women with follicle >14 mm and the median largest follicle size in the combination group and CC group were comparable (64.6% *vs.* 63.8%, p=1.000 and 16.75 mm *vs.* 15.5 mm, p=0.687, respectively). The mean endometrial thickness was 6.85 mm in the combination group, and 7.40 mm in the CC group (p=0.171. Among the participants who ovulated, the median number and size of dominant follicles and endometrial thickness were also comparable between groups.

Table 3
Cycle characteristics compared between the CC + letrozole and CC alone groups

Characteristic	Letrozole + CC group (n=48)	Clomiphene citrate group (n=47)	P value
Progestin withdrawal, n(%)	13 (35.4)	14 (29.8)	0.714
Ultrasound cycle day, median (min, max)	13 (11,15)	13 (12,16)	0.940
Reported urine LH surge, n(%)	29 (60.4)	34 (72)	0.311
Cycle day of LH surge	(n=29)	(n=34)	0.191
median (min, max)	16 (12, 21)	15 (12, 18)	
No. of follicles >10 mm, median (min,max)	1 (0,5)	1 (0,5)	0.815
No. of follicles >14 mm, median (min, max)	1 (0,5)	1 (0,5)	0.919
No. of women with follicle > 14 mm, n(%)	31 (64.6)	30 (63.8)	1.000
Largest follicle size (mm), median (min,max)	16.75 (0,35)	15.50 (5.5,35.5)	0.687
Endometrial lining thickness (mm), median (min,max)	6.85 (3.1,13.5)	7.40 (3.6,12.6)	0.171
Cycle day progesterone level obtained, median (min, max)	22 (19,28)	22 (19,28)	0.768
Progesterone level, ng/ml, median (min, max)	18.40 (0.05,60)	17.90 (0.05,60)	0.387
Cycle characteristics among those who ovulated	**Letrozole + CC group (n=37)**	**Clomiphene citrate group (n=33)**	
Progestin withdrawal, n(%)	10 (27)	9 (27.3)	1.000
Ultrasound cycle day, median (min, max)	13 (11,15)	13 (12,15)	0.197
Reported urine LH surge, n(%)	28 (75.7)	28 (84.8)	0.510
Cycle day of LH surge, median (min, max)	16 (12,21)	15 (12,18)	0.379
No. of follicles >10 mm, median (min, max)	2 (0,5)	2 (0,5)	0.922
No. of follicles >14 mm, median (min, max)	1 (0,5)	1 (0,5)	0.712
No. of women with follicle > 14 mm, n(%)	29 (78.4)	27 (81.8)	0.952
Largest follicle size, mm, median (min, max)	17.6 (0,35)	20.5 (9.5,35.5)	0.572
Endometrial lining thickness, mm, median (min, max)	7 (3.5,13.5)	8 (3.6,12.6)	0.441

Characteristic	Letrozole + CC group (n=48)	Clomiphene citrate group (n=47)	P value
Cycle day progesterone level obtained, median (min, max)	22 (19,28)	22 (19,28)	0.990
Progesterone level, ng/ml, median (min, max)	27.80 (3.5,60)	25.10 (3.28,60)	0.860

Table 4
Drug tolerability and adverse events compared between the CC + letrozole and CC alone groups

Event	Letrozole + CC group (n=48)	Clomiphene citrate group (n=47)	P value
Anaphylaxis, n	0	0	-
Minor side effects, n (%)	24 (50)	22 (46.8)	0.916
Side-effects acceptable	24 (100)	22 (100)	-
Reported side-effects, n (%)			
Headache	3 (12.5)	1 (4.5)	0.609
Dizziness	2 (8.3)	4 (18.2)	0.405
Hot flush	5 (20.8)	1 (4.5)	0.190
Abdominal bloating	7 (29.2)	6 (27.3)	1.000
Abdominal pain including cramping	3 (12.5)	2 (9.1)	1.000
Nausea	2 (8.3)	1 (4.5)	1.000
Mood changes	4 (16.7)	3 (13.6)	1.000
Fatigue	5 (20.8)	3 (13.6)	0.702
Breast discomfort	5 (20.8)	5 (22.7)	1.000
Diarrhea	5 (20.8)	2 (9.1)	0.418
Night sweats	4 (16.7)	1 (4.5)	0.349
Sleep disturbance	3 (12.5)	5 (22.7)	0.451
Adverse events of ongoing pregnancy, n(%)			
Spontaneous complete abortion	1 (2.08)	1 (2.13)	NA*
Early pregnancy loss	1 (2.08)	1 (2.13)	NA*
NA* not applicable due to small sample			

There was no anaphylaxis related to treatment during this study. Among those who reported adverse events, all had minor and tolerable side effects. All participants who reported side effects were willing to continue the allocated medication. The most common side effect was abdominal bloating in both groups. There was no significant difference in the side effects profile between groups.

Discussion

The aim of this study was to compare the efficacy of combination CC plus letrozole versus CC alone for ovulation induction in infertile women with chronic anovulation. A previous randomized controlled trial that compared the ovulation rate between letrozole plus CC versus letrozole alone in PCOS women found a significantly higher ovulation rate in the combination group (9). They hypothesized that the better outcome in the combination group may be due to complementary action between the two agents. However, it is not possible to conclude from their results that CC was the cause of the increased rate of pregnancy. Thus, our study was developed to compare the efficacy of combination letrozole plus CC and CC alone to see if our results could support the hypothesis from that previous study or not. Interestingly, our study found no significant difference in ovulation rate between patients treated with combination therapy and patients treated with CC alone.

Theoretically, the local effect of letrozole and the central effect of CC should have synergistic effect for ovulation induction. Nevertheless, the ovulation rates in our study were comparable between the combination group and the CC alone group. This finding suggests that the main driver of ovulation is CC. Moreover, the dose of CC was the same in both of our study groups, and previous study found a higher ovulation rate in the combination letrozole and CC group compared to the letrozole group alone (9).

Even though many studies have investigated the ovulation rate after letrozole or CC treatment, studies in the combined effect of these two medications remain scarce. Hajishafiha, *et al*. conducted a study of combination letrozole and CC in PCOS patients. They found a follicle development rate of 82.9% in the combination group. However, that study included patients who were refractory to CC and/or letrozole, and the final outcomes were not reported as ovulation rate (10). An open-label randomized controlled trial to compare combination letrozole and CC with letrozole alone for ovulation induction in naive PCOS women found an ovulation rate of 77% in the combination group (9). In that study, it should be noted that there were heterogeneities among the study participants, and the primary outcome was different. They proposed that the combination treatment could be considered as a first-line treatment in infertile PCOS population. Our data show the ovulation rate to be non-significantly different between CC plus letrozole and CC alone, so we suggest the continued use of CC alone as the first-line ovulation induction agent for general chronic anovulation women.

Previous meta-analyses reported significant heterogeneity among included RCTs for the ovulation rate between letrozole and CC in PCOS population, although letrozole significantly increased the ovulation rate compared to CC (18, 19). In contrast, a meta-analysis study in unexplained infertility women that compared the efficacy of letrozole with that of CC found no significant difference in clinical outcomes between the two groups, and there was also significant heterogeneity among the included studies (20). Interestingly, our study showed the ovulation rates in both groups to be higher than the previously reported rates from studies in CC or letrozole alone, but were close to the rate found in the combination group in the Mejia, *et al*. study (9, 21). This could be due to differences in study populations. By way of example, we included both PCOS and chronic anovulation patients, the latter of which could have a better response to the ovulation induction agents, and those participants were naive to ovulation induction.

The side effects between groups in our study were comparable. All adverse effects from medications in both groups were minor and tolerable. The most common side effects in both groups were similar. No congenital anomaly was found in the live births from either group. Taken together, these data suggest very good safety and tolerability of both treatment regimens. Our study is the first to compare the efficacy of ovulation induction between combination letrozole and CC versus CC alone in chronic anovulation women. The major strength of our study is its randomized controlled trial design, which minimizes confounding factors and neutralizes baseline characteristics between groups. The primary outcome was clearly defined by midluteal serum progesterone, and was unaffected by operator and participant biases. Moreover, a single operator who was blinded to the study medications performed all transvaginal ultrasonographic investigations to minimize interobserver variation.

Limitations

This study has some mentionable limitations. First, the pregnancy rate was very low in this study (1 pregnancy per group). Even though we included only participants who were deemed eligible to conceive via timed intercourse, we did not evaluate all possible infertility factors due to the associated costs. Second, although patients were advised regarding the dates of timed intercourse, compliance could not be determined with certainty. Third, the treatment period and follow-up duration were both relatively short. We studied only one cycle of treatment in each patient. Therefore, future study in a longer treatment duration and follow-up is needed to evaluate and compare the cumulative ovulatory rate between these ovulation induction regimens.

Conclusion

There was no significant difference between combination CC plus letrozole and CC alone relative to their ability to induce ovulation in infertile women with chronic anovulation. The small number of live births (1 per group) was too low to be statistically analyzed. Further study is needed to compare the cumulative ovulatory rate and dose-defining efficacy of these ovulation induction regimens.

Declarations

Acknowledgements

The authors gratefully acknowledge the patients that generously agreed to participate in this study, and Dr. Sasima Tongsai for her assistance with statistical analysis.

Conflict of interest declaration

All authors declare no personal or professional conflicts of interest, and no financial support from the companies that produce and/or distribute the drugs, devices, or materials described in this report.

Funding disclosure

This study was funded by a grant from the Siriraj Research Development Fund (Managed by Routine to Research: R2R) of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

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Figures

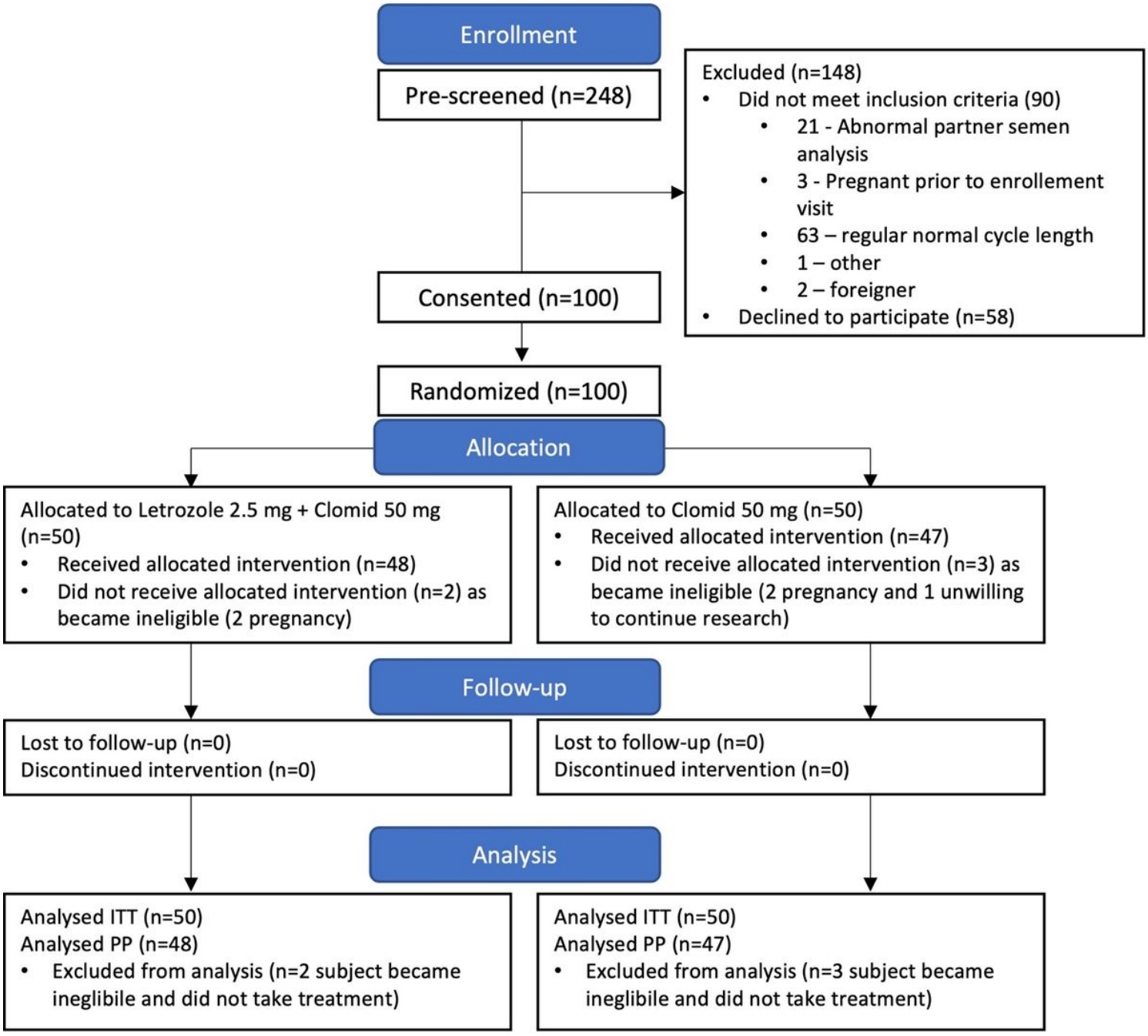

Figure 1

Flow diagram of the study protocol