Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2022**; 49(2): 039
http://doi.org/10.31083/j.ceog4902039

Original Research

Predicting factors of clomiphene citrate responsiveness in infertile women with normogonadotropic anovulation (WHO group II anovulation)

Theeraporn Areetheerapas[1], Artitaya Singwongsa[2,*], Komsun Suwannarurk[1], Junya Pattaraarchachai[3]

[1]Department of obstetrics and gynecology, Thammasat University Hospital, 12120 Pathum Thani, Thailand
[2]Department of obstetrics and gynecology, Ramathibodi Hospital, Mahidol University, 10400 Bangkok, Thailand
[3]Chulabhorn International College of Medicine, Thammasat University, 12120 Pathum Thani, Thailand
*Correspondence: artitaya.sin@mahidol.ac.th (Artitaya Singwongsa)
Academic Editor: Michael H. Dahan
Submitted: 27 August 2021 Revised: 26 October 2021 Accepted: 4 November 2021 Published: 9 February 2022

Abstract

Background: Clomiphene responsiveness has been varied in WHO group II anovulatory patients. Our study evaluates factors associated with clomiphene citrate responsiveness in this population. Various parameters were studied, including anthropometric, hormonal and transvaginal ultrasonographic measurements. **Methods**: A retrospective case-control study was done over a period of three years. A total of 260 women with WHO group II anovulatory related infertility treated with clomiphene citrate 100 mg/d for five consecutive days were enrolled. 173 women were categorized in clomiphene citrate resonsive group (CCR), defined as patients with at least one dominant follicle $\geq$17 mm or at least 2 dominant follicles $\geq$15 mm. 87 women were categorized in the non-ovulatory group (NCCR), defined as patients who not meet the responsive group criteria. Various clinical, metabolic, hormonal and ultrasound features were compared between two groups. Logistic regression analysis was used to analyze the significant factors. **Results**: Among all participants, the mean age was 32.6 $\pm$ 4.0 years. The mean body mass index in CCR and NCCR group was 23.9 $\pm$ 10.7 kg/m^2 and 24.0 $\pm$ 4.0 kg/m^2, respectively. The mean waist-hip ratio (WHR) of the NCCR group was higher than that of the CCR group, i.e., 0.83 $\pm$ 0.06 vs 0.81 $\pm$ 0.05 ($p = 0.004$). The waist-hip ratio was the most sensitive anthropometric predictor of non-responsiveness to clomiphene: cut-off value of 0.775 (90.8% sensitivity and 20.2% specificity) and cut-off value of 0.805 (73.6% sensitivity and 42.2% specificity). Age, clinical hyperandrogenism, polycystic ovarian morphology, low antral follicle count ($\leq$5 follicles), baseline follicle-stimulating hormones and estradiol levels were not significantly different. **Conclusions**: The waist-hip ratio is a clinically useful parameter in predicting clomiphene responsiveness in normogonadotropic anovulatory women (WHO group II anovulation).

Keywords: Clomiphene response; Anovulatory infertility; Ovulation induction

1. Background

Ovulatory dysfunction, a condition with multifactorial causes, is one of the major causes of female infertility [1], accounting for over 50% of infertile etiologies [2]. In 1973, the World Health Organization (WHO) classified anovulatory patients into three groups based on the levels of gonadotropins and estrogens [3], namely, WHO group I: hypogonadotropic hypogonadal anovulation, WHO group II: normogonadotropic anovulation and WHO group III: hypergonadotropic hypogonadal anovulation. The most problematic and common anovulation is WHO group II which includes women with hypothalamic-pituitary-ovarian dysfunction. Cases diagnosed with polycystic ovarian syndrome (PCOS) are the most prominent in WHO group II [3,4]. The classification has been used widely as a guidance for ovulation induction [3].

Clomiphene citrate (CC), a triphenylethylene derivative has traditionally been used as the first-line ovulation induction therapy for anovulatory women [5–8]. As a selective estrogen-receptor modulator, clomiphene citrate reduces sex steroidal negative feedback at the hypothalamic-pituitary axis, thereby enhancing secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland. This action, which stimulates the growth of the ovarian follicle and selection of dominant follicle and thus initiates ovulation, is initiated within the first five days of menstrual cycle under the theorical basis that physiologic lower levels of FSH permit dominant follicle selection [8]. The starting dose is usually 50 mg per day, as the ovulation rate is generally between 50% and 75% in PCOS cases [9]. Among responders, successful ovulation, singleton and multiple pregnancy was reported at 75%, 15–47% and 8–10%, respectively, within six months of ovulation induction [6,8,10]. Some studies reported a 74% chance of ovulation with a starting dose of CC at 100 mg/day [8]. Evidence suggests that CC was 1.35 to 20 times more likely to trigger ovulation compared to placebo [5].

Responsiveness to CC for each individual depends on numerous factors, including age, body weight and biochem-

ical blood test [11]. In our clinic, CC is the first-line drug prescribed for ovulation induction in anovulatory women in either artificial insemination cycles or timing for sexual intercourse cycles. Overall ovulatory rate was 75–80%. Previous studies demonstrated that younger age, lower BMI, less insulin resistance and less hyperandrogenism were all found to be predictive of ovulation [12–14]. Our study aimed to investigate the predicting factors of responsiveness to CC in infertile women with WHO group II among the Thai population. Accordingly, the enrolled participants were a broader subset than PCOS patients. Secondary outcome included prediction of ovulation success rate and further appropriate treatment planning via CC. Alternative treatment options for the predicted non-responder were also recorded.

2. Methods

A retrospective case control study was performed at Thammasat Fertility Center of Thammasat University Hospital, Thailand. A total of 260 patients meeting the criteria were enrolled between January 2017 and August 2020.

The sample size was calculated from G*power 3.1.9.4 for case control study [15]. The case group was responders to CC, and control group was non-responders, with an allocation ratio of 2:1. The effect size was set to 0.5 based on the study conducted by Sachdeva G *et al*. [13] with power (1-β error) at 0.95. The resulting sample size was 157 in the case group, and 79 in the control group. In order to prevent loss of information along the process, the population was increased by at least 10% in each group.

The CC responsive group (CCR) was defined as patients who were examined by transvaginal ultrasound with at least 1 dominant follicle $\geq$17 mm or at least 1 dominant follicle $\geq$15 mm, provided that the attending physician concluded they should receive ongoing treatment within the cycle. The CC non-responsive group (NCCR) was defined as patients who did not meet the responder group criteria and whose cycles were cancelled, accordingly.

The participants included in this study were all anovulatory women WHO group II, 20–40 years of age who received CC in initial treatment at Thammasat Fertility Center of Thammasat University Hospital. The cases were considered as anovulatory WHO group II if they had baseline FSH between 4–10 mIU/mL on early menstrual days (day 2–3) combined with at least one of the following conditions:

(1) Had a history of irregular menstrual period longer than 35 days, or

(2) Presented with oligomenorrhea, or

(3) Presented with secondary amenorrhea, or

(4) Reported no ovulation with the use of at least three cycles of self LH tests.

Excluded from the study were participants with a body mass index (BMI) lower than 18.5 or higher than 35 kg/m^2, a history of ovarian or fallopian tubal surgery, history of endocrine disorder affecting ovulation (hyperprolactinemia, thyroid, and adrenal gland diseases), prior use of metabolic disease medication (insulin sensitizing drugs, lipid-lowering drugs, anti-obesity drugs, gonadotropin-releasing hormone analogs, oral contraceptive pills, anti-androgenic drugs, ovulation-inducing agent, dopamine agonist drugs), and those with incomplete data. Flow chart of the study is shown in Fig. 1.

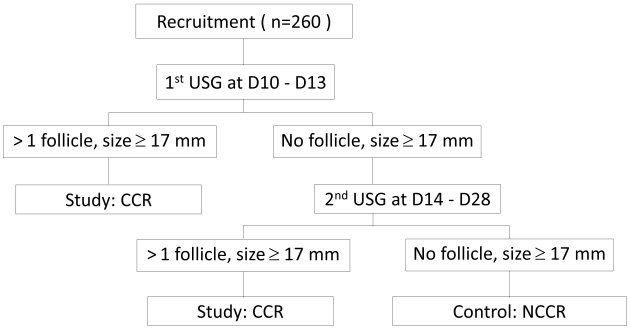

Fig. 1. Flow chart of study. Recruitment: infertile women with WHO group II anovulation who received clomiphene citrate 50 mg 2 tabs oral at day 2–5 of cycle, CCR, CC responsive group; NCCR, non-CC responsive group, study group: patients who were examined by transvaginal ultrasound to record at least 1 dominant follicle $\geq$17 mm; control group: patients who did not meet the study group criteria.

All participants received standard care, including medical history on obstetric-gynecologic history, infertility history, and general physical examination, including body weight, height, waist and hip circumference measurement. The waist circumference was measured midway between the lower rib margin and the iliac crest in the mid-axillary line at the end of normal expiration. The hip circumference was measured at the highest prominence of the buttocks parallel to the floor [16,17]. Patients underwent transvaginal ultrasonography (TVS) for pelvic organ evaluation, measurement of antral follicles in early follicular phase (day 1–5 of cycle) and baseline hormonal measurement, including follicle stimulating hormones, luteinizing hormones, prolactins and estradiol levels. Low antral follicle count was defined as AFC $\leq$5 follicles. Participants who agreed to start the ovulation induction cycles were treated with CC 100 mg/day (2 tablets of CC 50 mg) oral at bedtime, starting within second to fifth day of cycle for 5 consecutive days. Treatment was followed by TVS at day 10–13 of cycle to check for follicular growth. The TVS was performed by five certified reproductive medicine specialists. If dominant ovarian follicular size did not meet the responding criteria, patients were appointed for the next ultrasonographic evaluation in 2–7 days, but not exceeding the 28thday.

Data were collected from the medical records of fertility clinic. The acquired information included age, body weight, height, waist circumference, hip circumference, ob-

stetric data, menstrual cycle, diagnosis of PCOS, lifestyle habit (such as alcohol drinking and smoking), current medication and baseline hormones. Information concerning number of visits as well as follicular growth and size was also recorded.

Statistical analysis was done by SPSS Statistics Version 23 (IBM Corp., Armonk, NY, USA). The continuous parameters were recorded as mean and standard deviation (SD). Normality of quantitative data was calculated by Kolmogorov Smirnov tests. Independent *t*-test or Mann Whitney U test was used for two independent variables based on whether the data was normally distributed. Frequency and percentage were used to represent category parameters. Medium effect size, alpha value (two-sides) and power significant level were set at 0.5, 0.05 and 0.95, respectively. Logistic regression analysis was used for factors associated with the CC responsiveness.

3. Results

A total of 260 infertile women with normogonadotropic anovulation (WHO group II anovulation) who received CC as an ovulation induction were enrolled in this study.

Study (CC responder: CCR) and control (non-CC responder: NCCR) groups consisted of 173 and 87 cases, respectively. Demographic characters among study CCR group and NCCR group were compared as represented in Table 1. The only difference of statical significance was that waist-hip ratio (WHR) of NCCR was greater than that of CCR group.

Regarding anthropometric measures, the average body mass indexes were 23.9 $\pm$ 10.7 and 24.0 $\pm$ 4.0 kg/m^2. There were 77 (44.51%) participants in the responsive group and 48 (55.17%) in non-responsive group who had obesity (BMI $\geq$23 kg/m^2). No significant differences between the groups were detected. Interestingly, WHR were 0.81 $\pm$ 0.05 and 0.83 $\pm$ 0.06, respectively (p = 0.004).

Regarding ovarian reserves, baseline hormonal levels (FSH, LH, prolactin and estradiol) of infertile cases were comparable between both groups as cited in Table 2. These biological hormones were at normal range in early follicular phase of reproductive age. The number of participants who had low antral follicle counts (AFC $\leq$5 follicles) was 30 in CCR (17.34%) and 12 (13.79%) in NCCR group. Hyperandrogenism state among participants was 57.3% (149/260).

Regarding clinical characteristics of PCOS, the patients who presented with at least one of the clinical characteristics of hyperandrogenism, such as hirsutism, oily face skin, and acne were 99 (57.23%) and 50 (57.47%), a difference that was not statistically significant. Participants with PCOM on TVS were 104 (60.12%) and 58 (66.67%), respectively.

Subgroup analysis of ovulatory group is shown in Table 3. A total of 173 participants were divided into two groups, single follicular development and multiple follicular development. The average age of multifollicular developing patients was significantly lower than that of patients with single follicular development, i.e., 31.7 $\pm$ 4.1 and 33.0 $\pm$ 3.8 years, respectively (p = 0.037). Other parameters were not statistically different.

In univariate logistic regression analysis between CCR and NCCR, WHR was the only factor associated with successful ovulation prediction (odds ratio 1.97, p = 0.02). After performing binary logistic regression analysis with the BMI group, the adjusted odds ratio was 1.789 (p = 0.06), a potential predictor of CC-responsiveness.

Receiver operating curve (ROC) was generated to predict the CC responsiveness as shown in Fig. 2. The best cut point value of WHR at 0.775 was chosen to give the appropriate area under curve (AUC). At this cut point, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 90.8, 20.2%, 44.9% and 70.7%, respectively.

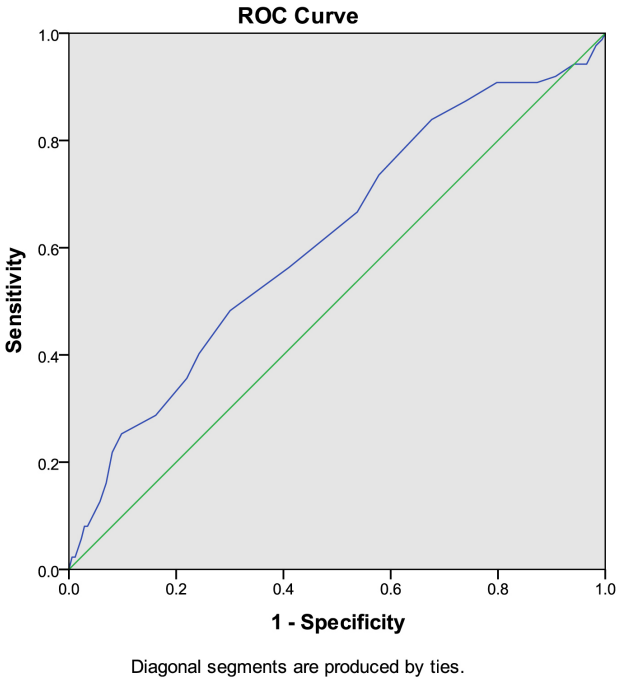

Fig. 2. Receiver operating curve (ROC) of waist-hip ratio for predicting clomiphene responsiveness.

4. Discussion

WHO group II anovulation is the most common anovulatory infertility worldwide. The majority of cases (80%) are polycystic ovary syndrome (PCOS) which is usually associated with underlying metabolic abnormalities. Patients diagnosed with PCOS are often obese and have insulin resistance associated with resistance to ovulation, lower pregnancy rate, live birth rate and obstetric complications [18,19].

Table 1. Demographic data of participants in CCR (n = 173) and NCCR (n = 87) groups.

Demographic data	Total (n = 260)	CCR	NCCR	*p*-value
Age (years)*	32.6 ± 4.0	32.6 ± 3.9	32.5 ± 4.2	0.806
Fertility history				
Duration (years)*	3.3 ± 2.3	3.4 ± 2.3	2.9 ±2.1	0.152
Previous pregnancy**		36 (20.8)	17 (19.5)	0.069
Starting date**				0.363
Day 1	2 (0.8)	1 (0.6)	1 (1.2)	
Day 2	180 (69.2)	118 (68.2)	62 (71.3)	
Day 3	55 (21.2)	39 (22.5)	16 (18.4)	
Day 4	16 (6.2)	9 (5.2)	7 (8.1)	
Day 5	7 (2.7)	6 (3.5)	1 (1.2)	
SBP (mmHg)*	117.7 ± 14.0	117.0 ± 13.7	119.5 ± 14.6	0.150
DBP (mmHg)*	73.5 ± 10.7	72.9 ± 11.1	74.8 ± 9.7	0.196
BMI (kg/m^2)*	23.9 ± 9.0	23.9 ± 10.7	24.0 ± 4.0	0.903
WHR*	0.82 ± 0.55	0.81 ± 0.05	0.83 ± 0.06	0.004
Truncal obesity**	69 (26.5)	38 (21.9)	31 (35.6)	0.019
Obesity**	125 (48.1)	77 (44.5)	48 (55.2)	0.104
PCOS**	207 (79.6)	137 (79.2)	70 (80.4)	0.528

*Mean ± standard deviation (SD), **n (%).

CCR, clomiphene citrate responsive group; NCCR, non- clomiphene citrate responsive group; Duration, duration of infertility; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WHR, waist-hip ratio; truncal obesity, WHR >0.85; obesity, BMI ≥23 kg/m^2.

Table 2. Baseline reproductive endocrinologic characteristics of the study population.

	Total (n = 260)	CCR	NCCR	*p*-value
Hormone at 2nd date				
FSH (mIU/L)*	6.5 ± 2.7	6.4 ± 2.3	6.6 ± 3.1	0.535
LH (mIU/L)*	7.5 ± 4.7	7.1 ± 4.7	8.4 ± 4.7	0.032
Prolactin (ng/mL)*	23.4 ± 61.5	24.8 ± 75.0	20.8 ± 10.8	0.628
Estradiol (pg/mL)*	37.8 ± 24.6	38.5 ± 25.7	36.4 ± 22.2	0.526
Hyperandrogenism**	149 (57.3)	99 (57.2)	50 (57.5)	0.970
Ultrasonographic findings				
PCOM**	162 (62.3)	104 (60.1)	58 (66.7)	0.304
Low AFC**	42 (16.2)	30 (17.3)	12 (13.8)	0.463

*Mean ± standard deviation (SD), **n (%).

Hormonal measurements were done at the second date of menstruation.

CCR, clomiphene citrate responsive group; NCCR, non-clomiphene citrate responsive group; FSH, follicle stimulating hormone; LH, luteinizing hormone; Hyperandrogenism, clinical of hyperandrogenism; PCOM, polycystic ovarian morphology; Low AFC, low antral follicle count (AFC ≤5 follicles).

Clomiphene citrate has been widely accepted as the first line ovulation induction medical treatment [19], regarding its high efficacy, easy to administer, safety profile, and low cost. However, the variation of clomiphene responsiveness has been reported [10–13].

Kuang H. *et al*. [12] validated the predictive model for ovulatory and pregnancy outcome for PCOS patients based on the cumulative study of 1376 women in 2015. The ovulatory drugs in the study compared clomiphene citrate (CC) to metformin or their combination (PPCOS-I) and clomiphene citrate compared to letrozole (PPCOS-II). Younger age, lower BMI, shorter duration of attempting to conceive, less insulin resistance and less hyperandrogenism were all found to be predictive of ovulation, conception, and clinical pregnancy. Nevertheless, there was a minor discrepancy between the PCOS I and II.

Table 3. Demographic data of participants in single follicle ovulation and multiple follicle ovulation groups.

	Single*	Multiple*	*p*-value
Age (years)	33.0 ± 3.8	31.7 ± 4.1	0.037
Duration (years)	3.4 ± 2.5	3.3 ± 2.0	0.700
Starting date	2.4 ± 0.7	2.6 ± 0.9	0.090
SBP (mmHg)	116.6 ± 13.9	117.3 ± 13.3	0.772
DBP (mmHg)	73.2 ±11.1	72.5 ± 11.1	0.692
BMI (kg/m^2)	24.4 ± 12.7	22.8 ± 4.5	0.353
WHR	0.82 ± 0.04	0.81 ± 0.06	0.212
FSH (mIU/L)	6.6 ± 2.4	6.1 ± 2.3	0.247
LH (mIU/L)	7.1 ± 4.4	6.9 ± 5.3	0.875
Prolactin (ng/mL)	27.2 ± 91.8	19.8 ± 9.2	0.538
Estradiol (pg/mL)	36.9 ± 24.3	41.5 ± 28.3	0.274

*Mean ± standard deviation (SD).

Duration, duration of infertility; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WHR, waist-hip ratio; FSH, follicle stimulating hormone; LH, luteinizing hormone.

Our study findings support the evidence that patients with higher WHR, especially those with truncal obesity, are less likely to respond to CC [20]. After performing logistic regression analysis, we found that truncal obesity remained a significant predictor of ovulation.

Sachdeva G. *et al*. [13] conducted a prospective observational study in infertile PCOS women who received incremental doses of clomiphene citrate from 50 mg/d to a maximal dose 150 mg/d. The results demonstrated that BMI and WHR could be used as the anthropometric predictors for clomiphene responsiveness. The study concluded that BMI is the best predictor. Nevertheless, BMI was not significantly different between the two groups in our study. This can be explained by the following reasons, Firstly, the mean BMI among our participants is lower than that in previous reports, and did not reflect the common characteristics in those populations. Secondly, underscoring a difference of interventions, our study recruited only the first cycle of participants to examine the effect of 100 mg clomiphene in a single cycle, since only 11.7–13% of participants who did not respond to CC 50–100 mg per day could ovulate with CC 150 mg per day [14,21]. Therefore, the NCCR group in our study was not comparable to "clomiphene resistance". Consequently, this might limit the power of BMI to detect any significant difference. Lastly, the underlying pathophysiology causing the anovulatory failure in PCOS is well defined. Truncal obesity is more associated with visceral fat distribution, insulin resistance and ovulatory failure than obesity diagnosed by BMI [22,23]. As such, truncal obesity is more sensitive than BMI in predicting clomiphene responsiveness.

As for the clinical feasibility of WHR to predict CC responsiveness, we therefore used the ROC curve. The cut-off value to predict drug responsiveness is 0.775, with 90.8% sensitivity and 20.2% specificity. This value could be used for considering other treatment strategies. There are many proposed strategies for improving ovulatory outcome. The first strategy entails intervention to reduce truncal obesity such as preconception lifestyle modification, including weight loss program [24,25], caloric restriction, behavioral modification and increased physical activity [26]. These can improve both reproductive, metabolic outcome and ovulation with clomiphene citrate [27]. The second strategy involves other ovulation-stimulating agents such as letrozole, clomiphene combined with other agents such as metformin, gonadotropins or letrozole [18,27–29]. Letrozole, the first-line ovarian stimulating agent, was found to be more effective than clomiphene in PCOS patients [11,30]. Letrozole significantly increases ovulation, pregnancy and live birth rate [4,11,19]. The combination of letrozole with clomiphene citrate was also reported in some studies. The WHR cut-off value supports our clinical practice guideline for ovulation induction and can also be used in counseling sessions.

The current study did not include participants who were taking metformin. The data showed that clomiphene citrate combined with metformin resulted in statistically significant higher ovulation rates [4,31]. Hashim *et al*. [32] conducted a meta-analysis in 2015 and found that the ovulatory rate by clomiphene citrate plus metformin was higher than clomiphene alone (odds ratio 1.55, 95% CI 1.02–2.36) in the PCOS population with insulin resistance. Wang R. *et al*. [5] found that the clinical pregnancy rate was greater in clomiphene plus metformin group compared to the clomiphene group alone (8 RCTs, 1039 women, RR 1.18, 95% CI 1.00–1.39).

A limitation of our study is that we recruited the group of normogonadotropic anovulatory women including PCOS who share distinct pathophysiology from the rest of this group. Our study demonstrated that PCOS is not a predictive factor for clomiphene resistance. But we should interpret the data carefully. In our center, not all participants were evaluated by the serum androgen levels. Therefore, the accurate prevalence of PCOS in our participants is still uncertain and may be underestimated. The outcome is only "ovulation" which is the surrogate marker for fertility treatment. Also, the endocrinologic data was limited due to the nature of retrospective review. Further prospective study with androgen and metabolic profile with a focus on pregnancy outcomes or a well-designed, randomized controlled trial with other agents in this population are recommended.

5. Conclusions

Our study demonstrated that waist-hip ratio greater than 0.775 is associated with non-responsiveness to clomiphene citrate in ovulation induction cycle and can be considered as a predictor for clomiphene responsiveness in normogonadotropic, normogonadal anovulatory pa-

tients. Alternative ovulatory drugs or interventions to reduce WHR should be considered in such cases to maximize the ovulatory, and hence fecundity, outcomes.

Abbreviations

AFC, antral follicle count, BMI, body mass index; CC, clomiphene citrate; CCR, Clomiphene responsive group or ovulatory group; NCCR, Clomiphene non-responsive group or anovulatory group; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PCOM, polycystic ovarian morphology; PCOS, polycystic ovarian syndrome; WHO, world health organization; WHR, waist-hip ratio.

Author contributions

TA and AS conceived and designed the study. All authors took parts in data collection and evaluation, drafting and statistical analysis. TA performed data collection, statistical analysis, and interpretation of data under supervision by JP and AS. TA Drafted the manuscript, which was revised by AS and KS. All authors performed editing and finalization of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by Human Research Ethics Committee of Thammasat University No.1 (MTU-EC-OB-1-162/62). This study was designed as a retrospective assessment of data, and therefore, informed consent was not required.

Acknowledgment

The authors would like to express their gratitude to all the doctors, scientists and medical staffs in Thammasat fertility center, department of Obstetrics and Gynecology, Thammasat university hospital.

Funding

This trial was supported by Faculty of Medicine, Thammasat University research fund No.1-08/2563.

Conflict of interest

The authors declare no conflict of interest.

References

[1] Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, *et al*. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Human Reproduction. 2019; 33: 1602–1618.

[2] Talmor A, Dunphy B. Female obesity and infertility. Best Practice & Research. Clinical Obstetrics & Gynaecology. 2016; 29: 498–506.

[3] Dhont M. Who-classification of anovulation, background, evidence and problems. International Congress Series. 2005; 1279: 3–9.

[4] World Health Organization. Waist Circumference and Waist–Hip Ratio, Report of a WHO Expert Consultation. World Health Organization (WHO): Geneva. 2008.

[5] Wang R, Li W, Bordewijk EM, Legro RS, Zhang H, Wu X, *et al*. First-line ovulation induction for polycystic ovary syndrome, an individual participant data meta-analysis. Human Reproduction Update. 2019; 25: 717–732.

[6] Brown J, Farquhar C, Beck J, Boothroyd C, Hughes E. Clomiphene and anti-oestrogens for ovulation induction in PCOS. Cochrane Database of Systematic Reviews. 2009; CD002249.

[7] Baird DT, Balen A, Escobar-Morreale HF, Evers JLH, Fauser BCJM, Franks S, *et al*. Health and fertility in World Health Organization group 2 anovulatory women. Human Reproduction Update. 2013; 18: 586–599.

[8] Pfeifer S, Fritz M, Lobo R, McClure RD, Goldberg J, Thomas M, *et al*. Use of clomiphene citrate in infertile women, a committee opinion. Fertility and Sterility. 2013; 100: 341–348.

[9] Legro RS. Ovulation induction in polycystic ovary syndrome, Current options. Best Practice & Research Clinical Obstetrics & Gynaecology. 2016; 37: 152–159.

[10] Imani B, Eijkemans MJ, te Velde ER, Habbema JD, Fauser BC. Predictors of chances to conceive in ovulatory patients during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. The Journal of Clinical Endocrinology and Metabolism. 1999; 84: 1617–1622.

[11] Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, Casson P, *et al*. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome. The New England Journal of Medicine. 2014; 371: 119–129.

[12] Kuang H, Jin S, Hansen KR, Diamond MP, Coutifaris C, Casson P, *et al*. Identification and replication of prediction models for ovulation, pregnancy and live birth in infertile women with polycystic ovary syndrome. Human Reproduction. 2016; 30: 2222–2233.

[13] Sachdeva G, Gainder S, Suri V, Sachdeva N, Chopra S. Prediction of Responsiveness to Clomiphene Citrate in Infertile Women with PCOS. Journal of Reproduction & Infertility. 2020; 20: 143–150.

[14] Ellakwa HE, Sanad ZF, Hamza HA, Emara MA, Elsayed MA. Predictors of patient responses to ovulation induction with clomiphene citrate in patients with polycystic ovary syndrome experiencing infertility. International Journal of Gynaecology and Obstetrics. 2017; 133: 59–63.

[15] Faul F, Erdfelder E, Lang A, Buchner A. G*Power 3, a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior Research Methods. 2007; 39: 175–191.

[16] Ma W, Yang C, Shih S, Hsieh H, Hung CS, Chiu F, *et al*. Measurement of Waist Circumference, midabdominal or iliac crest? Diabetes Care. 2013; 36: 1660–1666.

[17] Nishida C, Ko GT, Kumanyika S. Body fat distribution and noncommunicable diseases in populations, overview of the 2008 who Expert Consultation on Waist Circumference and Waist–Hip Ratio. European Journal of Clinical Nutrition. 2010; 64: 2–5.

[18] Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, *et al*. The management of anovulatory infertility in women with polycystic ovary syndrome, an analysis of the evidence to support the development of global who guidance. Human Reproduction Update. 2016; 22: 687–708.

[19] Costello M, Garad R, Hart R, Homer H, Johnson L, Jordan C, *et al*. A Review of first Line Infertility Treatments and Supporting Evidence in Women with Polycystic Ovary Syndrome. Medical Sciences. 2019; 7: 95.

[20] Bergh CM, Moore M, Gundell C. Evidence-Based Management of Infertility in Women with Polycystic Ovary Syndrome. Jour-

nal of Obstetric, Gynecologic, and Neonatal Nursing. 2016; 45: 111–122.
[21] Seyam E, Al Gelany S, Abd Al Ghaney A, Mohamed MAA, Youseff AM, Ibrahim EM, *et al*. Evaluation of prolonged use of statins on the clinical and biochemical abnormalities and ovulation dysfunction in single young women with polycystic ovary syndrome. Gynecological Endocrinology, the Official Journal of the International Society of Gynecological Endocrinology. 2018; 34: 589–596.
[22] Khmil M, Khmil S, Marushchak M, Halnykina S, Khmil A. Reproductive hormone metabolism in women with infertility due to polycystic ovary syndrome depending on the constitutional body types. Polski Merkuriusz Lekarski. 2020; 48: 152–156.
[23] Lord JM, Norman R. Obesity, polycystic ovary syndrome, infertility treatment, lifestyle modification is paramount. British Medical Journal. 2006; 332: 609.
[24] Cena H, Chiovato L, Nappi RE. Obesity, Polycystic Ovary Syndrome, and Infertility, a New Avenue for GLP-1 Receptor Agonists. the Journal of Clinical Endocrinology & Metabolism. 2020; 105: e2695–e2709.
[25] Wang R, Kim BV, van Wely M, Johnson NP, Costello MF, Zhang H, *et al*. Treatment strategies for women with who group II anovulation, systematic review and network meta-analysis. British Medical Journal. 2017; 356: j138.
[26] Lord JM, Norman R. Obesity, polycystic ovary syndrome, infertility treatment, lifestyle modification is paramount. British Medical Journal. 2006; 332: 609.
[27] Costello MF, Ledger WL. Evidence-based lifestyle and pharmacological management of infertility in women with polycystic ovary syndrome. Women's Health. 2012; 8: 277–290.
[28] Costello MF, Garad RM, Hart R, Homer H, Johnson L, Jordan C, *et al*. A Review of second- and third-line Infertility Treatments and Supporting Evidence in Women with Polycystic Ovary Syndrome. Medical Sciences. 2020; 7: 75.
[29] Costello MF, Misso ML, Balen A, Boyle J, Devoto L, Garad RM, *et al*. A brief update on the evidence supporting the treatment of infertility in polycystic ovary syndrome. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2019; 59: 867–873.
[30] Kruljac I, Butorac D, Vrkljan M. Letrozole or clomiphene for infertility in the polycystic ovary syndrome. The New England Journal of Medicine. 2014; 371: 1462–1463.
[31] Metformin Therapy for the Management of Infertility in Women with Polycystic Ovary Syndrome, Scientific Impact Paper No. 13. BJOG: An International Journal of Obstetrics & Gynaecology. 2017; 124: e306–e13.
[32] Abu Hashim H, Foda O, Ghayaty E. Combined metformin-clomiphene in clomiphene-resistant polycystic ovary syndrome, a systematic review and meta-analysis of randomized controlled trials. Acta Obstetricia Et Gynecologica Scandinavica. 2015; 94: 921–930.