

Comparison of clomiphene citrate, metformin, or the combination of both for first-line ovulation induction, achievement of pregnancy, and live birth in Asian women with polycystic ovary syndrome: a randomized controlled trial

Murizah Mohd Zain, M.D., M.Med. (O&G),^{a,c} Ridzuan Jamaluddin, M.D.,^b Adibah Ibrahim, M.D., M.Med. (O&G),^b and Robert J. Norman, M.D., F.R.A.N.Z.C.O.G., F.R.C.O.G., F.R.C.P.A.^c

^a Department of Obstetric and Gynaecology, Alor Setar Hospital, Kedah, and ^b Department of Obstetric and Gynaecology, Science University Hospital, Kelantan, Malaysia; and ^c Research Centre of Reproductive Health, School of Paediatrics and Reproductive Health, University of Adelaide, South Australia, Australia

Objective: To determine the first-line medication to be used in anovulatory patients with polycystic ovary syndrome (PCOS) for ovulation induction and pregnancy achievement.

Design: Randomized controlled trial.

Setting: Infertility unit of a public hospital.

Patient(s): One hundred fifteen newly diagnosed patients with PCOS based on ESHRE/ASRM criteria.

Intervention(s): These patients were assigned to three groups: group 1 (38 patients) received 500 mg of metformin three times a day; group 2 (39 patients) received clomiphene citrate (CC) at an incremental dose; group 3 (38 patients) received both medications.

Main Outcome Measure(s): Rates of ovulation, pregnancy (PR), and live birth.

Result(s): The ovulation rate was 23.7% in the metformin group, 59% in the CC group, and 68.4% in the combination treatment group. This was translated into a similar PR and live birth rate, which were higher in the CC and combination groups compared to the metformin group (PR: 7.9%, 15.4%, and 21.1%; live birth rate: 7.9%, 15.4%, and 18.4% in metformin, CC, and combination treatment groups, respectively), although statistically the differences were not significant. There were no multiple pregnancies and the rate of spontaneous first trimester loss was similar to the general population.

Conclusion(s): Clomiphene citrate should be the first-line treatment for ovulation induction in anovulatory patients with PCOS. (*Fertil Steril*® 2009;91:514–21. ©2009 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome, infertility, clomiphene citrate, metformin

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies affecting 5%–10% of reproductive age women (1). It was originally described as a triad consisting of obesity, hirsutism, and oligoamenorrhea/infertility (2). This condition is a potential health hazard with long-term sequelae, notably type 2 diabetes, cardiovascular disease, and hyperlipidemia (3). An internationally accepted definition was been adopted in 2003 by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine, known as the ESHRE/ASRM Rotterdam consensus (4). It required the presence of two of the following three diagnostic criteria: [1] oligoamenorrhea or anovulation; [2] clinical or biochemical evidence of hyperandrogenism; and [3] the presence of polycystic ovarian morphology.

Women suffering from PCOS have low fecundity with anovulation (5) and, to an extent, early pregnancy loss (6)

and pregnancy complications (7). Induction of ovulation would restore ovulation and pregnancy. For many years clomiphene citrate (CC) has been the standard treatment for ovulation induction for these patients. Women who fail to ovulate or get pregnant with CC usually were recommended for ovarian diathermy surgery, gonadotropin treatment, or even IVF. However, these treatments are expensive and associated with side effects (8). Because hyperinsulinemia may contribute to hyperandrogenism and infertility in women with PCOS, agents that can ameliorate insulin resistance and reduce circulating insulin level can be used (9, 10). The most extensively studied insulin-lowering agent in the treatment of PCOS was metformin.

A meta-analysis of 13 randomized trials (11–13), comparing metformin with placebo, metformin plus CC, or CC alone in women with PCOS, concluded that metformin increased the ovulation rate by a factor of approximately four. Of note is that the pregnancy rate (PR) did not differ significantly between the metformin and placebo groups, but the PRs for metformin plus CC were significantly higher than for CC alone. In a multicenter randomized trial involving 20 Dutch hospitals and 228 patients, Moll et al. (14) concluded that

Received October 5, 2007; revised and accepted December 7, 2007.
Reprint requests: Murizah Mohd Zain, M.D., University of Adelaide, School of Pediatric and Reproductive Health, 6th floor, Medical School North, Adelaide, South Australia 5005 Australia (FAX: 618-83036100; E-mail: murizahz@hotmail.com).

metformin is not an effective addition to CC as the primary method of inducing ovulation in women with PCOS. The ovulation rate in the metformin/CC group was 64% compared to 72% in the CC/placebo group, a nonsignificant difference. A significant proportion of women in the metformin group discontinued treatment because of side effects. In a larger study (15) involving 626 infertile women with PCOS assigned to either CC, metformin, or combination therapy, it was noted that although ovulation rate in the combination therapy group was significantly higher than that in the other two groups, the increase did not translate into a higher live birth rate. They concluded that CC was superior to metformin in achieving live births in infertile women with PCOS, although multiple pregnancies was a complication.

The ethnic background of women with PCOS may affect the clinical, hormonal, and metabolic characteristics of this condition. In a study conducted among Chinese women who were CC resistant (16), there was no improvement in the ovulation rate despite significant reduction of body mass index (BMI), serum T, and fasting leptin concentrations in the metformin group.

On the basis of these observations, the present study was designed in 2005 to look at our experience with these treatments in an Asian population, particularly in a community where the majority ethnic group was Malay. Our goal was to evaluate the most effective treatment in inducing ovulation and pregnancy.

MATERIALS AND METHODS

Study Design and Participants

This was an unblinded prospective, randomized, control trial conducted at Alor Setar hospital from September 2005 to December 2006. All patients referred to the infertility clinic, Alor Setar Hospital, were screened for PCOS. The patients who were newly diagnosed with PCOS and aged less than 40 years old were included in the study. The diagnosis of PCOS was based on ESHRE/ASRM (4) criteria, which included at least two of three criteria of the following: [1] chronic anovulation; [2] clinical or biochemical signs of hyperandrogenism; and [3] polycystic ovary (PCO) morphology, shown on ultrasound scan, defined as the presence of 12 or more follicles (with one ovary being sufficient for diagnosis) measuring 2–9 mm in diameter or increase in ovarian volume of more than 10 mL. The pelvic ultrasound examinations were done by same investigators using a vaginal endoprobe.

Patients were excluded from the study if they were known to be diabetic or had underlying liver, renal, or heart disease and also those whose partner's sperm quality indicated male factor infertility on at least two occasions (sperm count <20 million/mL, motility <50%, morphology <30% [normal: World Health Organization criteria]). Tubal patency was not tested before induction of ovulation. All patients gave informed and written consent. The study was approved by the medical ethics committee at Alor Setar hospital.

The BMI and waist-to-hip ratio were also measured before entry into the study. All patients were given general advice on the importance of diet and exercise. Appropriate patients were referred for dietary advice. After 3 months on study medication, BMI and waist-to-hip ratio were measured again.

Women who were eligible and consented were randomly allocated to three groups consisting of metformin, CC, or the combination of metformin and CC. Randomizations were done by picking an envelope labeled A, B, or C assigned to metformin, CC, or combination. Equal numbers of envelope were labeled A, B, or C. The randomization was done centrally by an assigned nurse who was naïve to the treatment and who then communicated with the investigator. The envelope that was picked was not returned for further randomization.

The investigators and patients were not blinded to the treatment. We had difficulty in preparing a placebo tablet for CC and metformin. All patients continued to take the study medication until they had a positive pregnancy test, six ovulatory cycles, or developed CC resistance, whichever came first. In the metformin group, if ovulation was not documented, medication was given for a maximum of 6 months. Anovulatory patients had a withdrawal bleed induced with medroxyprogesterone acetate (MPA) before the initiation of the study medication.

Patients randomized to the metformin arm were given the tablets at the initial dose of 500 mg and increased in a stepwise fashion during the first 3 weeks to accommodate the side effects until patients were taking a total dose of 1,500 mg/day. The patients were then asked to make a telephone call once they had a menstrual period and a transvaginal ultrasound (TVS) and follicular tracking was done to document evidence of follicular growth and ovulation on days 2, 8, 12, and 16. A menstrual calendar chart recorded menses cycles monthly.

Patients randomized to the CC only arm were given CC at a dose of 50 mg on days 2–6. The TVS and follicular tracking were done to document follicular growth and ovulation on days 2, 8, 12, and 16. If there was absence of ovulation, the CC dose was increased stepwise on a treatment cycle basis after a P withdrawal bleed to a maximum of 200 mg. If there was evidence of ovulation but the patient did not get pregnant, the same dosage was continued for a maximum of six cycles.

In the combination treatment group, metformin was given in a similar manner to the metformin only group. Clomiphene was given at a dose of 50 mg on days 2–6. The TVS and follicular tracking were done to document evidence of follicular growth and ovulation on days 2, 8, 12, and 16. If there was absence of ovulation, the CC dose was increased stepwise on a treatment cycle basis after a P withdrawal bleed to a maximum of 200 mg. If there was evidence of ovulation but patient did not get pregnant, a similar dosage was continued for a maximum of six cycles.

In all groups a urine pregnancy test was done 3 weeks after documented ovulation and the patient remained amenorrheic.

All study medications were discontinued when there was a positive pregnancy test. Pregnant patients were then followed up until an ultrasound could document the viability of pregnancy. Copies of patients' obstetric records, including delivery records, were reviewed by the investigators to obtain birth outcomes.

Hormone Assays

A complete clinical and laboratory evaluation was performed including renal profile, liver function test, thyroid function test, PRL, serum T, and FSH/LH levels at the initial visit before commencing on study medications and after 3 months on study medications. Other forms of androgen, such as DHEA, DHEAS, and androstenedione (A), were not measured. All blood samples were sent to the same laboratory; however, the analyses were not done at one time point. The LH, FSH, PRL, and TSH levels were measured by chemiluminescence on an automated AD-VIA Centaur (Bayer Diagnostics, Tarrytown, NY) analyzer. The intra-assay coefficient of variation (CV) was less than 10% for all steroid hormone assays. Testosterone was measured using the RIA (DSL Inc., Webster, TX) with intra-assay and interassay CV of 8.1% and 9.1%.

Statistical Analysis

The primary outcome measure was the ovulation rate, which is defined as number of women who ovulated as judged by ultrasound monitoring of the ovaries. The secondary outcome measures were ongoing pregnancy and live birth rate. For numerical data, analysis of variance (ANOVA) was used to compare the homogeneity of the subject between and within the groups. A Pearson χ^2 test was used for testing differences among the three study groups for categorical variables.

With an expected rate of ovulation of 40% in the metformin arm and 60% in the CC group, 96 women was needed to show an absolute increase of 15% in ovulation rate, with a power of at least 80% using a two-sided χ^2 test with a 5% significance level. Taking a possibility of a dropout rate of about 20%, at least 115 women were needed in this study. The data on the dropouts were not included in the analysis. An intent-to-treat analysis was not done.

RESULTS

There were no significant differences in baseline variables in the study groups (Table 1). The most of the participants in the study groups were of the Malay race and this reflects the demographic of the study location where more than 94% of inhabitants of Alor Setar were Malay. There were no differences with regard to age, BMI, and waist-to-hip ratio among the three groups. The mean age was 28.9 years and the mean BMI and waist-to-hip ratio were 33.3 and 0.77, respectively. All groups had comparable proportions of primary or secondary infertility and also duration of infertility was not significantly different among the three study populations.

There was also no significant difference with regard to biochemical parameters, like FSH and LH, within the study

groups (Table 2). The T level was significantly higher in the combination treatment group; however, there was no reason for this observation. All of the patients studied had morphological features of PCOs on TVS. All the patients studied also had abnormal menstruation presenting as amenorrhea, which is defined as absent menstruation for more than 6 months, or oligomenorrhea, which is defined as intermenstrual intervals of more than 35 days. In this study it was noted that hirsutism was not a main feature of patients diagnosed with PCOS, as it is only present in a minority of patients.

Metformin at incremental doses was well tolerated and there were no dropouts because of metformin intolerance in this study group. Three patients complained of nausea, dizziness, and headache, but despite these side effects they continued through the study period. The dropouts, illustrated in Figure 1, had uncontrollable reasons (e.g., moving interstate, living far and having difficulty to come to the hospital for monitoring, particularly for transvaginal monitoring). Two patients, one from the CC arm and one from the metformin arm, had a spontaneous pregnancy after randomization but before commencement of the study medication. These patients were not included in the analysis and intention-to-treat analysis was not done.

The ovulation rate in women taking CC alone and combination of metformin and CC treatment was 59% and 66.6%, respectively. Both were statistically significant when compared to the 24% ovulation rate in the metformin arm (odds ratio [95% confidence interval] for CC and combination were 4.63 [1.73–12.37] and 6.98 [2.53–19.32], respectively). Adding metformin to CC improved the ovulation rate, although statistically the increment is not as significant when compared to the CC only treatment ($P=.74$) (Table 3).

The PR was highest in the combination group (21.1%) compared to the CC (15.4%) and metformin (7.9%) groups, although statistically the difference was not significant. The live birth per cycle in which ovulation occurred was higher in the CC (15.4%) and in the combination therapy groups (18.4%) than in the metformin group (7.9%), although the difference again was not significant. There were no multiple pregnancies documented in any of the three groups. There was only one case of first trimester loss and this was in the combination treatment group. The number was very small to make any statistical inference.

It was noted that metformin did not have a significant effect on body weight or waist-to-hip ratio measurement at 3 and 6 months of treatment, although the regularity of the menstrual cycle increased significantly after 3 and 6 months of metformin treatment. Metformin treatment also did not have any significant effect on biochemical parameters, particularly FSH, LH, and T after 3 months of treatment (Table 4).

DISCUSSION

Clomiphene citrate is a partially selective estrogen (E) receptor modulator with its antiestrogenic effect at the

TABLE 1**Baseline characteristic of women with polycystic ovary syndrome.**

Characteristics	Metformin group (n = 38)	CC group (n = 39)	Combination group (n = 38)	
Age, mean (SD)	27.8 (3.6)	29.6 (4.35)	29.3 (4.95)	
WHR, mean (SD)	0.78 (0.1)	0.76 (0.45)	0.77 (0.14)	
BMI, mean (SD)	33.9 (3.6)	32.9 (4.2)	33.0 (4.1)	
Primary infertility, n (%)	29 (76.3)	28 (71.8)	34 (89.5)	
Length of infertility (y), mean (SD)	3.1 (0.26)	2.9 (0.15)	3.3 (0.14)	
Race				
Malay n (%)	33 (86.8)	35 (89.7)	33 (86.8)	
Morphology feature of PCO on U/S, n (%)	38 (100)	39 (100)	38 (100)	NS
Oligomenorrhea, n (%)	28 (73.7)	30 (76.9)	30 (78.9)	NS
Amenorrhea, n (%)	10 (26.3)	9 (23.1)	8 (21.1)	
Significant hirsutism (Ferriman-Gallway >16)	1 (2.6)	2 (5.1)	1 (2.6)	

Note: P=not significant.
CC = clomiphene citrate; BMI = body mass index; WHR = waist-to-hip ratio; U/S = ultrasound.

Zain. Clomiphene, metformin, or both for infertility. Fertil Steril 2009.

hypothalamus, inducing a change in the GnRH pulse frequency. This causes an increase in the FSH level and results in follicular development and E₂ production. Ovulation is restored in 75%–80% of these patients and pregnancy is achieved in about 35%–40% (17). The discrepancy between ovulation and pregnancy is probably related to the antiestrogenic effect of CC on the cervix and the endometrium, which causes a thickening of the cervical mucus, rendering a hostile environment for sperm transport and thinning of endometrium, which creates an unsuitable site for implantation (18). Clomiphene also has a drawback—it is associated with multiple pregnancies in 5%–10% of the population (19) and side effects such as hot flashes and visual disturbance. In addition, CC does not address the underlying abnormalities in PCOS, including hyperinsulinemia and hyperandrogenism.

Metformin is a biguanide oral antihyperglycemic agent, which has been extensively used in the treatment of type 2 diabetes mellitus. It lowers blood glucose levels mainly by

inhibiting hepatic glucose production and increases in the peripheral glucose uptake (20). Several other actions may contribute, such as increased intestinal use of glucose and decreased fatty acid oxidation (10). Therefore, metformin can reduce peripheral insulin concentrations and improve glucose tolerance and metabolism. There are also preliminary in vitro data indicating that metformin may directly decrease ovarian androgen production (21).

Most studies have demonstrated the efficacy of metformin in inducing ovulation (22–24), whereas other reports disagree with these findings (16, 25, 26). However, at present sample size of the studies were relatively small. In addition, there has been variations in populations, treatments, and outcomes. Some studies also included patients who had failed other treatments to induce ovulation. Our study had the advantage of having 116 patients who were newly diagnosed with PCOS, based on the latest ESHRM/ASRM criteria, naïve to fertility treatment, and almost all of them were of the Malay race. Our patients also were randomly allocated to the study

TABLE 2**Baseline biochemical characteristics.**

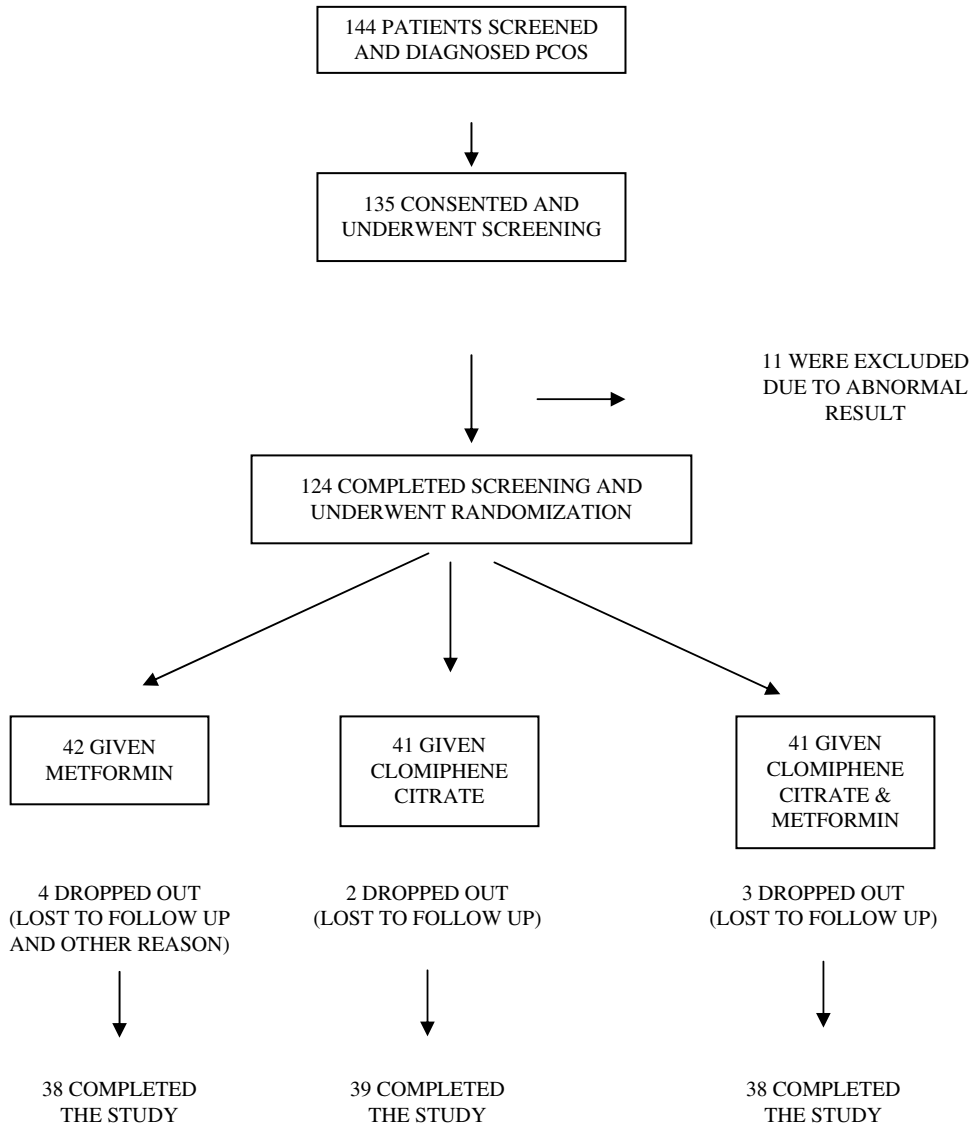
	Metformin group (n = 38)	CC group (n = 39)	Combination group (n = 38)	P value
T, mean (SD)	0.57 (0.10)	0.41 (0.45)	0.77 (0.14)*	.005 (nmol/L)
FSH(IU/L)	4.2 (1.74)	4.5 (1.95)	4.9 (1.75)	NS mean (SD)
LH(IU/L)	11.9 (5.38)	11.3 (5.41)	12.2 (2.95)	NS mean (SD)

Note: NS = not significant.
* T significantly higher in combination group.

Zain. Clomiphene, metformin, or both for infertility. Fertil Steril 2009.

FIGURE 1

Flow chart of the study.



Zain. *Clomiphene, metformin, or both for infertility. Fertil Steril* 2009.

medications and were followed up for at least 6 months. The other advantage of this study was that we did not look into just ovulation but also into PR and live birth rate, which were more definite outcomes. Other studies have mainly looked at the ovulation rate. This was because PRs were harder to interpret and in the meta-analysis no trial had a live birth rate as a defined outcome measure. In the meta-analysis where metformin was used as a sole agent, ovulation was achieved in 46% of recipients compared with 24% in the placebo arm. When metformin and CC were used in combination, 76% of recipients ovulated compared with 42% receiving CC alone (11).

Our findings regarding the effect of combination of metformin and CC were consistent with those of another

large, multicenter, randomized trial reported by Legro et al. (15). Among 626 subjects with PCOS who were randomly assigned to either metformin, CC, or a combination of the two drugs, there were no significant differences in ovulation rates or PRs between the combination therapy group and the group that received CC alone, with an ovulation rate and PR of 60.4% and 38.3% in the combination group compared to 49% and 29.7% in the CC group. The ovulation, PR, and live birth rates were lowest in the metformin group. The study demonstrated that CC was superior to metformin in achieving live births in infertile women with PCOS. It was also noted that there were no significant benefit of combination therapy with CC and metformin versus CC alone with respect to the live birth rate. Another randomized trial from 20 Dutch hospitals (14) involving 228 women with PCOS assigned to

TABLE 3**Rates of ovulation, pregnancy, pregnancy loss, and live birth.**

	Metformin (n = 38)	CC (n = 39)	Combination (n = 38)	CC vs. Metformin		Combination vs. Metformin		CC vs. Combination	
				P & OR (CI)	P & OR (CI)	P & OR (CI)	P & OR (CI)		
Ovulation	9/38 (23.7%)	23/39 (59%)*	26/38 (68.4%)*	.002*	.001*	.742			
Pregnancy	3/38 (7.9%)	6/39 (15.4%)	8/38 (21.1%)	4.63 (1.7-12.7)	6.98 (2.5-19.3)	.416			
First trimester loss	0	0	1/8 (12.5)	.306	.103				
Ectopic	0	0	0	2.12 (0.5-9.2)	3.11 (2.5-19.3)				
Second trimester loss	0	0	0						
Multiple gestation	0	0	0						
Live birth	3/38 (7.9%)	6/39 (15.4%)	7/38 (18.4%)	.306	.175	.126			
			2.12 (0.5-9.2)	2.64 (0.3-11)					

Note: OR = odds ratio; CI = confidence interval.

* Ovulation rate significantly higher in CC vs. metformin and combination vs. metformin.

Zain. Clomiphene, metformin, or both for infertility. Fertil Steril 2009.

either CC or a combination of CC and metformin also demonstrated that metformin offers no superiority to CC. Our study used normally acting metformin, not the long-acting drug, and yet achieved the same results as in the study by Legro et al. (15).

Our results demonstrated that ovulation was significantly more likely to occur after treatment with CC alone or combination therapy than with metformin alone. This differs from the study by Palomba et al. (27), the first clinical trial that directly compares metformin and CC for first-line ovulation induction. In that study, which only includes lean young women with PCOS and normal glucose tolerance, the ovulation rate obtained with both medications was similar but the live birth rate was 52% after 6 months on metformin compared with 18% on CC. Neveu et al. (28), in their observational comparative study involving 154 women with PCOS, noted that metformin was better than CC for ovulation induction and equivalent for pregnancy achievement. It was also noted that there was no additional benefit to the combination of drugs for ovulation induction and pregnancy achievement compared with taking metformin alone. However, the study was limited by lack of standardization and randomization. The decision for choosing the initial medication was not based on randomization but patients' choice, with the more obese patients tending to choose metformin. In our study, the PR and live birth rate were also higher in the CC and combination groups compared to the metformin group, although this was not statistically significant.

The PR and live birth rate were slightly lower in this study and these may be explained by some of the limitations of this study. This study included patients who were slightly obese, had longer duration of infertility, shorter duration of exposure to study medications (6 months), and tubal status not known (hysterosalpingography [HSG] or laparoscopy were not done before prescribing the study medications). We also did not exclude patients who were at risk for tubal disease (e.g., past history of pelvic operation to the ovaries or tubes, appendectomy, or pelvic inflammatory disease). Another limitation of the study: it was not blinded and hence may be subjected to bias. It was not blinded because we had difficulty preparing placebo tablets for CC and metformin. We also had limited laboratory resources, hence we were not able to measure other blood parameters that would have been useful in the evaluation of PCOS such as DHEA, DHEAS, sex hormone-binding globulin (SHBG), and fasting insulin.

This study illustrated that race and ethnicity influence the phenotype manifestation of PCOS. This is a first study on Asian women and it confirms to a certain extent what has been published recently in women from Europe and North America (14, 15). Published research articles on PCOS among Asians women were few and these women may be under-represented. However, our study demonstrated that despite the phenotypic difference, the response to an ovulation induction drug, such as CC, was similar. In our study, significant hirsutism was manifested in less than 5% of the study population. This is consistent with other studies

TABLE 4**Biochemical parameters at entry and after 3 months.**

	LH (IU/L)		FSH (IU/L)		T (nmol/L)	
	Initial	3 months	Initial	3 months	Initial	3 months
Metformin	11.9 (5.38)	12.1(4.95)	4.2 (1.74)	4.4 (2.12)	0.57 (0.1)	0.6 (0.1)
CC	11.3 (5.41)	11.7 (5.10)	4.5 (1.95)	4.3 (2.0)	0.41 (0.2)	0.4 (0.19)
Combination	12.2 (2.95)	11.2 (3.45)	4.9 (1.75)	5.0 (1.9)	0.77 (0.14)	0.59 (0.21)
P value ^a	.710		.710		.069	

^a Use an epsilon correction (Greenhouse-Geisser).

Zain. Clomiphene, metformin, or both for infertility. *Fertil Steril* 2009.

noting that hirsutism is less in Asian patients, particularly from East Asia (29). Hirsutism has a low prevalence in Taiwanese Chinese women and Hsu et al. (30) reported a prevalence of about 28%, whereas Takeshi et al. (31), from Japan, noted a prevalence of 8%. On the other hand, Aruna et al. (32) described a prevalence of 66% of hirsutism in Indian populations. Although clinical and biochemical hyperandrogenism is less in Japanese women, hypersecretion of LH is more prominent (31), making it one of the criteria to diagnose PCOS using the Japanese Society of Obstetric and Gynaecology 1993 (33) criteria. However, hypersecretion of LH was not a prominent finding in our patients. All of our patients had morphological features of PCO on ultrasound. Hsu et al. (30) noted a prevalence of PCO in 91% of the patients with PCOS. We tried to reduce the intraobserver bias by assigning only two doctors to do the TVS for the diagnosis of PCO. Metformin also failed to reduce weight, waist-to-hip ratio, and does not have an effect on the biochemical parameters of FSH, LH, or T. This differs from some studies showing that metformin reduces the effect of LH and T and causes an elevation in serum FSH (9, 33) and agreed with studies showing that metformin has no effect on hormonal parameters (16, 34, 35).

In summary, our study demonstrated that CC is superior to metformin in inducing ovulation in anovulatory women with PCOS. Addition of metformin to CC does not significantly increase the ovulation, PR and live birth rate, although there was a slight increase in the three parameters when compared to the CC only treatment. Clomiphene should be the first-line treatment for ovulation induction in anovulatory patients with PCOS.

REFERENCES

- Frank S. Polycystic ovary syndrome. *N Engl J Med* 1995;333:833–61.
- Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. *Am J Obstet Gynecol* 1934;29:181–91.
- Wild RA. Long-term health consequences of PCOS. *Hum Reprod Update* 2002;8:231–41.
- The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Hum Reprod* 2004;19:41–7.
- Hull MG. Epidemiology of infertility and polycystic ovarian disease: endocrinological and demographic studies. *Gynecol Endocrinol* 1987;1:235–45.
- Homburg R, Armar NA, Eshel A, Adams J, Jacobs HS. Influence of serum luteinising hormone concentrations on ovulation, conception and early pregnancy loss in polycystic ovary syndrome. *BMJ* 1988;297:1024–6.
- Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Hum Reprod Update* 2006;12:673–83.
- Kim H, Taylor AE, Barbieri RL. Insulin sensitizers and polycystic ovary syndrome: can a diabetes medication treat infertility? *Fertil Steril* 2000;73:1097–8.
- Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. *Metabolism* 1994;43:647–54.
- Bailey CS, Turner RC. Metformin drug therapy. *N Engl J Med* 1996;334:574–9.
- Lord JM, Flight IHK, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ* 2003;327:951–3.
- Lord JM, Flight IHK, Norman RJ. Insulin sensitizing drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovarian syndrome [Review]. *Cochrane Database Syst Rev* 2003;3:CD003053.
- Norman RJ. Metformin—comparison with other therapies in ovulation induction in polycystic ovary syndrome [Editorial]. *J Clin Endocrinol Metab* 2004;89:4797–800.
- Moll E, Bossuyt PM, Korevaar JC, Lambalk CB, van der Veen F. Effect of clomiphene citrate plus metformin and clomiphene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomized double blind clinical trial. *BMJ* 2006;332:1485–9.
- Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Sandra AC, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med* 2007;356:551–66.
- Ng EHY, Wat WMS, Ho PC. Effects of metformin on ovulation rate, hormonal and metabolic profiles in women with clomide resistant polycystic ovaries, a randomized, double blinded placebo-controlled trial. *Hum Reprod* 2001;16:1625–31.
- Hugues E, Collins J, Vandekerckhove P, Lilford R. Clomiphene citrate for ovulation induction in women with oligo-amenorrhea. *Cochrane Database Syst Rev* 2000;(2):CD000056.
- Gonen Y, Casper RF. Sonographic determination of a possible adverse effect of clomiphene citrate on endometrial growth. *Hum Reprod* 1990;5:670–4.
- Asch RH, Greenblatt RB. Update on the safety and efficacy of clomiphene citrate as a therapeutic agent. *J Reprod Med* 1976;17:175–80.
- DeFronzo RA, Barzilai N, Simonson DC. Mechanism of metformin action in obese and lean noninsulin-dependent diabetic subjects. *J Clin Endocrinol Metab* 1991;73:1294–301.
- Attia GR, Rainey WE, Carr BR. Metformin directly inhibits androgen production in human theca cells. *Fertil Steril* 2001;76:517–24.

22. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene induced ovulation in the polycystic ovary syndrome. *N Engl J Med* 1998;338:1876–80.
23. Velazquez EM, Acosta A, Mendoza SG. Menstrual cyclicality after metformin therapy in polycystic ovary syndrome. *Obstet Gynecol* 1997;90:392–5.
24. Moghetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, et al. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6 month trial, followed by open, long-term clinical evaluation. *J Clin Endocrinol Metab* 2000;85:139–46.
25. Ehrmann DA, Cavaghan MK, Imperial J, Sturis J, Rosenfield RL, Polonsky KS. Effects of metformin on insulin secretion, insulin action, and ovarian steroidogenesis in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 1997;82:524–30.
26. Yilmaz S, Unal Y, Fahrettin K, Ercan A. The effects of metformin on insulin resistance, clomiphene-induced ovulation and pregnancy rates in women with polycystic ovary syndrome. *J Obstet Gynecol Reprod Biol* 2004;113:214–20.
27. Palomba S, Orio F Jr, Falbo A, Manguso F, Russo T, Cascella T, et al. Prospective parallel randomized, double blind, double-dummy controlled clinical trial comparing clomiphene citrate and metformin as the first line treatment for ovulation induction in nonobese anovulatory women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2005;90:4068–74.
28. Neveu N, Granger L, St-Michel P, Lavoie HB. Comparison of clomiphene citrate, metformin, or the combination of both for first line ovulation induction and achievement of pregnancy in 154 women with polycystic ovary syndrome. *Fertil Steril* 2007;87:113–20.
29. Legro RS, Myers ER, Barnhart HX, Carr BR, Diamond MP, Sandra AC, et al. The pregnancy in polycystic ovary syndrome: baseline characteristics of the randomized cohort including racial effects. *Fertil Steril* 2006;86:914–32.
30. Ming-I Hsu, Tsan-Hon Liou, Szu-Yuan Chou, Chuan-Yaw Chang, Chun-Sen Hsu. Diagnostic criteria for polycystic ovary syndrome in Taiwanese Chinese women: comparison between Rotterdam 2003 and NIH 1990. *Fertil Steril* 2007;88:727–9.
31. Takashi I, Toshiya M, Masahiro M, Naoko T, Fumi S, Yahko H, et al. Diagnostic performance of serum total testosterone for Japanese patients with polycystic ovary syndrome. *Endocrine J* 2007;54:233–8.
32. Aruna J, Mittal S, Kumar S, Misra R, Dadhwal V, Vimala N, et al. Metformin therapy in women with polycystic ovary syndrome. *Inter J Obst Gynaecol* 2004;87:237–41.
33. Sugimoto O, Aono. The Committee for Reproductive and Endocrine in Japan Society of Obstetrics and Gynaecology. Annual Report (1991–1992) for the determination of diagnostic criteria for PCOS. *Acta Obstet Gynaecol Jpn* 1993;45:1359–67.
34. Nestler JE, Jakubowicz DJ. Decreases in ovarian cytochrome P450c17 alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. *N Engl J Med* 1996;335:617–23.
35. Fleming R, Hopkinson ZE, Wallace AM, Greer IA, Sattar N. Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial. *J Clin Endocrinol Metab* 2002;87:569–74.