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Combined Clomiphene Citrate-Metformin Versus Letrozole-Metformin in Achieving Pregnancy among Women with Polycystic Ovary Syndrome

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ABSTRACT

Background: *Polycystic ovary syndrome is one of the most common causes of anovulatory sub-fertility in women of reproductive age-group. The therapeutic procedure for women with polycystic ovary syndrome wanting to be pregnant is ovulation induction. Different medicines have been used based on individual signs and symptoms as the most effective one is not clearly evident. Clomiphene citrate and letrozole are the most common drugs used alone or in combination with metformin to achieve pregnancy in women with polycystic ovary syndrome. In this study, the efficacy of combined clomiphene citrate-metformin is compared with letrozole-metformin in achieving pregnancy among women with polycystic ovary syndrome.*

Methods: *A retrospective study was performed among women with polycystic ovary syndrome attending Infertility Center, Kathmandu, Nepal from January 2013 to December 2015. Samples were randomly selected from list of the record in the treatment centre within the study duration. Total 146 cases with 73 each in clomiphene citrate-metformin group and letrozole-metformin group were entered into the analysis. Participants had received metformin in combination with either clomiphene citrate (100 mg) or letrozole (2.5 mg) from day 3 to 5 of their menstrual cycle. Odds ratio, with confidence interval set at 95%, was calculated to compare the efficacy between two groups.*

Results: *The pregnancy rate of clomiphene citrate-metformin was 54.79% and letrozole-metformin was 34.25%. Patients treated with clomiphene citrate-metformin were two times more likely to get pregnant [OR: 2.33, 95% CI: 1.19 – 4.54] than those treated with letrozole-metformin. Miscarriage rate was not found to be statistically significant.*

Conclusion: *Clomiphene citrate in combination with metformin is more likely to be effective than letrozole with metformin in achieving pregnancy.*

Keywords

PCOS, Clomiphene citrate, Letrozole, Pregnancy rate, Infertility.

Background

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorder in women of reproductive age-group with a prevalence of 12-18% [1,2]. It affects the ovulatory function of a woman [3] and has significant implications to their reproductive potential like increased risk of anovulatory infertility as well as miscarriage and other pregnancy-related complication [1,3,4]. PCOS is responsible for 70% of anovulatory sub-fertility [5]. But there is no single diagnostic criterion for the clinical diagnosis of PCOS. The Rotterdam 2003 ESHRE/ASRM-sponsored PCOS consensus workshop group has given the revised criteria for the diagnosis of PCOS which requires the presence of at least two of three features: oligo-anovulation, clinical or biochemical evidence of hyperandrogenism and polycystic ovaries on ultrasound examination [6]. However, presence of hyperandrogenism is the requiring diagnostic criteria for PCOS [7]. One of the main therapeutic procedure for women with PCOS wanting to be

pregnant is ovulation induction [8] though most effective treatment therapy for fertility is not clearly evident. Thus, the treatment should be individualized based on the symptoms [2,9].

Clomiphene citrate (CC) is considered to be the first line drug for the induction of ovulation and restoration of fertility in women with PCOS. CC is a selective estrogen-receptor modulator [1,10,11]. Under this medication, the ovulation rate of 50% to 76% was reported while the pregnancy rate varied from 7% to 36% [8,11-13]. It has been considered relatively safe drug with little difference in adverse effects between CC and placebo [10]. However, increased risk of multiple pregnancy is evident by administration of this drug [14].

Letrozole is an aromatase inhibitor which is more sensitive to induction of ovulation for those women who are resistant to CC. Varied ovulation rate from 64.9% to 88% has been observed in various studies [12,15]. It has a lower risk of multiple pregnancy [1,12].

Metformin, a biguanide and insulin-sensitizing drug, appears to be effective in follicular development, improving oocyte quality and in regulating the endocrine balance of PCOS patients [16]. Use of metformin is associated with more controlled and orderly ovulation and fertility induction [8,11,17]. Many studies have been conducted to identify the combined effect of metformin with CC or letrozole [8,11,15,18-23]. Improved results have been observed with combined medication than using CC or letrozole alone. Studies done among women with PCOS showed that ovulation and pregnancy rates were higher with combined medication than using CC or metformin alone [11,19]. However, few studies have been carried out to compare the efficacy of combined CC-metformin therapy with those of letrozole-metformin.

In Nepal, the greater degree of negative consequences of infertility is experienced by women. A study carried out in Jhapa district found that infertile women experienced any or all form of abuse like physical, emotional psychological, societal or marital [24]. In recent years, this syndrome seemed to be increasingly diagnosed and treated. However, to our knowledge, not even a single study has been done in Nepal to assess the efficacy of treatment. Thus, the aim of this study was to compare the efficacy of combined CC-metformin therapy to that of letrozole-metformin therapy for pregnancy among women with PCOS.

Methods

Study design

This is a retrospective study performed among women with PCOS attending Infertility Center, Bijulibazaar, Kathmandu, Nepal from January 2013 to December 2015 for the treatment of infertility. The study was approved by research ethics committee of National Health Research Council of Nepal. Eligible participants were married women of reproductive age with PCOS diagnosed in accord with the revised 2003 Rotterdam criteria. The sample size was calculated considering pregnancy rate of 34.50% for letrozole-metformin therapy, 16.67% for CC-metformin [25], 90% power, and 5% level of significance. Thus 146 cases with 73 in each group (CC-metformin and letrozole-metformin) meeting the eligibility criteria were randomly selected from the larger set of record in the treatment centre within the study duration to avoid the selection bias. Patients who continued the medication for at least 6 months and those who were able to ovulate and get pregnant within 6 months were subjected to the study. But the previous treatment histories in other clinical settings were not considered. Only the patients with patent fallopian tube were included. Patients with a history of cardiovascular disease, diabetes or liver, and kidney failure were excluded. Similarly, patients whose partner's sperm count was less than 20 million/ ml and sperm motility less than 20% were also not included in the study. All the study participants had polycystic ovaries at transvaginal sonography and oligomenorrhea or clinical characteristics of hyperandrogenism. The patients were examined and observed by infertility specialist and gynaecologist. After clinical examination, all the patients had their follicular stimulating hormone (FSH), luteinizing hormone (LH), estradiol, thyroid stimulating hormone (TSH) & prolactin tested on day 2 of the menstrual cycle.

The study participants had received either 100 mg CC or 2.5 mg letrozole orally for 5 days starting from day 3 or day 5 of the menstrual cycle every month. As the dose of letrozole had not yet been determined our study used a dosage of 2.5 mg daily for letrozole based on other studies who used letrozole dose between 2.5 and 7.5 mg [26]. Metformin was given oral 500mg twice daily to both the groups. Follicle monitoring, and endometrial thickness measurement were done with the help of transvaginal sonography serially starting from the 6th day of the drug administration when at least one follicle reached maturity (>18mm). On the same day, serum estradiol was measured. Confirmation of the pregnancy was done through urine test using a pregnancy test kit as well as through transvaginal sonography. After confirmation of pregnancy, these patients were followed up & treated as antenatal cases. Metformin was continued until 28 weeks. In the case of miscarriage, transvaginal ultrasound was done to confirm the loss.

Data were coded and entered into Epi data version 3.1 which was then imported into SPSS version 17.0 for data checking, cleaning, and statistical analysis. The t-test was applied to check any statistical difference in demographic variables and baseline parameters between the groups to be compared. Odds ratio (OR) was calculated to compare the efficacy of treatment therapies. The p-value less than 0.05 was considered to be significant and the confidence interval for odds ratio was set at 95%.

Results

The analysis included 146 women with 73 women in each group – CC-metformin and letrozole-metformin. The mean age of our study participants was 28.60±3.91 years while 96.6% had normal blood pressure level. Similarly, mean duration of marriage was 5.87±3.83 years. The mean body mass index (BMI) was 28.7±1.86kg/m2.

As shown in table 1, when comparing the letrozole-metformin group with CC-metformin group, we found that baseline estradiol

and TSH levels were higher in CC-metformin group than in the letrozole-metformin group. Age, BMI and duration of the marriage, as well as other baseline parameters like FSH, LH, and prolactin, showed no statistical difference between these groups.

Variable	CC-Metformin	Letrozole-metformin
Age of the client	28.90±0.47	28.30±0.45
BMI	28.3±1.72	29.5±1.58
Duration of marriage	6.23±0.49	5.51±0.39
FSH	10.31±1.04	8.03±0.59
LH	9.72±1.37	10.63±1.14
Prolactin	15.93±1.90	16.53±2.01
TSH	4.19±0.32	3.26±0.21
Estradiol	95.25±6.23	76.19±3.62

Table 1: Comparison of baseline parameters and different variables in the CC-metformin group and the letrozole-metformin group based on mean±S.E of mean.

Table 2 shows that the serum estradiol level was higher in CC-metformin group (198.17) than in letrozole metformin group (169.20). However, endometrial thickness was lower in CC-metformin group (10.3 ± 0.3) than in letrozole metformin group (12.5 ± 0.5). Likewise, pregnancy rate was higher in CC-metformin group (54.79%) than letrozole-metformin group (34.25%). Women treated with CC-metformin were twice likely to get pregnant than those treated with letrozole-metformin [OR: 2.33, 95% CI: 1.19 – 4.54]. Miscarriage rate was not statistically significant. Women treated with CC-metformin had only one case of multiple pregnancy, one case of ectopic pregnancy and one case of gestational diabetes mellitus.

Variable	CC Metformin	Letrozole-metformin	Odds Ratio (95% CI)	P-value
Estradiol (pg/mL)	198.17 ± 5.17	169.20 ± 2.51	-	0.006*
Endometrial thickness at hCG (mm)	10.3 ± 0.3	12.5 ± 0.5	-	0.038
No. of mature follicles (>18mm)	3.4 ± 0.3	2.1 ± 0.6	-	.028
Pregnancy	40 (54.79)	25 (34.25)	2.33 (1.19 – 4.54)	0.012#
Miscarriage	04 (10.0)	05 (20.00)	0.44 (0.11 – 1.85)	0.288*

Table 2: Comparison of the prevalence of different variables in CC-metformin group and letrozole-metformin group.

Discussion

Clomiphene citrate has been used as the first line drug to induce ovulation and treat infertility since 1962 [27]. However, studies have shown that pregnancy rate was higher with letrozole [28,29]. Other studies showed that effectiveness of letrozole is similar to other methods of ovulation induction [30,31]. Metformin, an insulin-sensitizing drug, has been found to be effective in regulating menstruation by inducing ovulation [31,32].

Metformin is reported to be effective, single or in combined form, with other drugs in the treatment of infertility and ovulation induction [16]. Thus, in this study, we compared the efficacy of combined CC-metformin with combined letrozole-metformin.

In this study, no significant difference was observed in age or duration of marriage as well as in basal parameters except estradiol and TSH level between CC group and letrozole group. The mean baseline Estradiol and TSH level were within the normal level in both groups. Studies showed that thyroid dysfunction can cause menstrual irregularities and infertility due to ovarian dysfunction [33,34]. The mean duration of infertility was observed longer in women with lower TSH level [34].

We found that the estradiol level was higher in CC-metformin group than letrozole group though not statistically significant, which aligns with the study done by Badawy et.al. where the differences in estradiol level was statistically significant between the two treatment groups [26]. Similarly, we found that PCOS women treated with CC-metformin were twice likely to be pregnant when compared with those treated with letrozole-metformin therapy. The pregnancy rate of the CC-metformin group was 54.79% while it was 34.25% for the letrozole group. Sohrabvand et.al compared CC-metformin with letrozole-metformin in the treatment of PCOS for fertility and found the pregnancy rate of 34.50% from letrozole-metformin medication which is almost similar to our study. However, it was only 16.67% for those treated with CC-metformin, much lower when compared with our study. Unlike our study, the rate was higher in letrozole group than in CC group though no statistical significance was observed [21]. The study done in Iran had low pregnancy rate with both CC-metformin and letrozole-metformin groups and the difference was also not statistically significant [18].

Another study done among moderately obese women showed significantly higher pregnancy rate among the letrozole-metformin group (20.6%) than the CC-metformin group (9.6%) [20]. These higher pregnancy rates among letrozole group in most of the studies might be because letrozole was used among those PCOS women who were resistant to CC. Similarly, we found significantly lower TSH level in letrozole-metformin treatment group which itself is a factor that reduces ovulation induction and pregnancy [33,34]. But, when compared CC alone with letrozole alone, letrozole was found to increase the pregnancy rate. A study by Atay et al. showed statistically significant higher pregnancy rate with letrozole (21.6%) than CC (9.1%) [35]. A meta-analysis also showed a statistically significant increase in the pregnancy rate among those treated with letrozole [29]. However, another meta-analysis by He et al. showed no statistical differences in pregnancy rate between these treatments [30]. The pregnancy rate with letrozole and CC was 28.9% and 17.9% respectively in a study carried out in India but the difference was not statistically significant [36].

Miscarriage rate was seemed to be higher in the letrozole-metformin group than in CC-metformin group but no statistical difference

was observed in our study. In other studies, the miscarriage rate was higher in CC-metformin group than the letrozole-metformin group but the difference was not statistically significant [18,21]. Systematic reviews of the studies to compare CC to letrozole alone in PCOS also showed no statistical difference in the occurrence of miscarriage between these drugs [29,30].

Conclusion

CC-metformin was effective in achieving fertility than letrozole-metformin for PCOS women. Miscarriage rate had no statistical association. With limited sample size, few or no cases of ectopic pregnancy, gestational diabetes mellitus, and multiple pregnancy were found in both groups. Since pregnancy outcomes are the ultimate endpoint of the treatment, further prospective study with larger sample size is recommended.

Ethical Consideration

The study proposal was reviewed and approved by research ethics committee of National Health Research Council, Nepal.

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