Effect of Metformin and Clomiphene Citrate in Improving Fertility in Subfertile Women with Polycystic Ovary Syndrome: A Randomized Controlled Trial

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Abstract:
Objective: The main aim of this study was to compare the effect of metformin and clomiphene citrate on ovulation and conception rate in PCOS patients.

Methodology: This randomized controlled trial was undertaken in the infertility outpatient department in Institute of Child and Maternal Health (ICMH), Dhaka during the period from January 2012 to December 2012. Total 71 PCOS women based on Rotterdam criteria were selected after randomization. They were divided into two groups - Group I (n=35) received metformin 500mg per oral thrice daily and Group II (n= 36) received clomiphene citrate 100mg orally per day from D2 for five days up-to six months.

Results: Baseline characteristics of both sample groups were almost similar. Ovulation was confirmed by measuring D21 serum progesterone. Cumulative ovulation rate over six months period was not statistically different (57.14 % and 61.11%); (P=0.115), and pregnancy rate was (34.28 % and 42.85%); (P=0.521) respectively.

Conclusion: Metformin has been found to be as effective as clomiphene citrate in terms of ovulation (57.14 % and 61.11%); and pregnancy rate (34.28 % and 42.85%) respectively.

Introduction:
Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathy¹, affecting 5-10% of women of reproductive age². It is a common cause of anovulatory infertility³. The 2004 Rotterdam criteria for the diagnosis of PCOS required two of the following characteristics: Oligo and/or anovulation, hyperandrogenism (clinical or biochemical), polycystic ovaries with exclusion of other causes of androgen excess.

Insulin resistance with compensatory hyperinsulinemia and chronic anovulation are the pivotal features of PCOS⁴. According to Polson Prevalence of PCOS is approximately 20-33% in general population⁵. Highest prevalence of PCOS has been found (52%) among South Asian women⁶. Chowdhury and Nargis in their study (1998) at Bangladesh found 28.81% of infertile women diagnosed as cases of PCOS⁷. Clomiphene citrate is the first agent used for ovulation induction in anovulatory PCOS women for many years⁸. More recently metformin, an oral biguanide used for type-II diabetes mellitus has been shown to assist ovulatory cycles in anovulatory PCOS⁹. It increases peripheral glucose uptake and utilization and thereby reduces insulin resistance.
Reproductive endocrinologists are increasingly adopting metformin for the treatment of infertility in PCOS. Homburg presents a clear and cogent argument for the use of metformin in the treatment of PCOS\textsuperscript{10}. As Homburg points out, individual studies have shown that metformin alone can restore regular menstrual cycles and reinstate ovulation in 25-95\% cases\textsuperscript{11}. Recent evidence suggests that metformin is effective as first-line therapy for improving ovulation in PCOS women\textsuperscript{9,12}, improves fertility\textsuperscript{13,14} and may even decrease the high rate of early pregnancy loss\textsuperscript{15,16} and incidence of gestational diabetes\textsuperscript{15,17,18}.

So aim of this study was to evaluate and compare the effect of metformin with clomiphene citrate on ovulation and conception rate in PCOS patients.

Materials and methods:
This randomized controlled trial was undertaken in the infertility outpatient department in ICMH, Dhaka during the period from January 12 to December 12. Total 71 PCOS women based on Rotterdam criteria were selected after randomization. During study period out of total 817 subfertile women, 105 PCOS women were enrolled (12.85\%). Thirty four patients were excluded because they did not meet the inclusion criteria and refused to participate in the study. Inclusion criteria were subfertile women with PCOS between 20-35 yrs of ages and diagnosis of PCOS according to Rotterdam criteria. Exclusion criteria were: Age >35yrs; Hypo or hyperthyroidism, hyper-prolactinaemia, diabetes mellitus and male factor infertility.

Randomization was done upon 71 participants by picking equal number of envelope labeled A, B assigned to metformin and clomiphene citrate. Finally 35 women in Group I (Metformin) and 36 women in Group II (Clomiphene citrate) were included for analysis.

Before entry into the study, height, weight, BMI and Waist-to-hip ratio (WHR) of all participants were measured. Serum FSH, LH level, thyroid function test and serum prolactin was performed at initial visit before commencement of study medications. Patients were instructed to take the study medications at least 6 months and follow their usual diet and physical activity.

Metformin given at a dose of 500mg thrice daily (Group I). The patients were instructed to take the tablets with their meals. Clomiphene citrate was given at a dose of 100mg daily for five days started from second day of menstruation following spontaneous or after progesterone withdrawal bleeding. Patients were asked to make a telephone call once they had a menstrual period. Patients were advised for intercourse during the fertile period. Ovulation was confirmed by measuring D\textsubscript{21} serum progesterone level. A value 5ng/ml was considered that ovulation took place. In both groups urine was tested for pregnancy 7 days after missed period. If pregnancy test was positive drug were discontinued. Otherwise treatment was continued as per previous schedule. In both regimen treatment was continued for 6 months. All other necessary information was noted in data collection sheet.

Prior to commencement of this study, the research protocol was approved by ethical clearance committee of ICMH. The procedure and benefits of this study was explained to the patients in easily understandable way by local language. Informed consent was taken from each patient. Confidentiality of data was strictly maintained.

The Statistical Package for Social Science (SPSS 20.0) was used for statistical analysis. Data was expressed as mean ±SD and statistical analysis for ovulation and pregnancy outcomes were performed by $\chi^2$ (chi square) test. Patient characteristics were analyzed with ‘t’ test. A P value of $< 0.05$ was considered as significant.

Results:
Table-I shows baseline characteristics regarding age, BMI, waist-to-hip ratio, type of infertility and duration of infertility, which were similar in both groups. Baseline hormone like serum FSH, LH, prolactin, TSH and biochemical parameter like blood sugar within the study groups shown in Table-II. These were similar in both the groups. Table-III shows, cumulative ovulation rate in women taking metformin was 57.14\% and in CC was 61.11\%, the difference was not statistically significant (P=0.115) and cumulative pregnancy rate was also similar in both groups (34.28\% vs 42.85\% in metformin and CC group respectively (P= 0.521).
Discussion:

Present study was undertaken to find out the efficacy of metformin and clomiphene citrate for ovulation and pregnancy achievement in subfertile PCOS women. For this purpose a randomized clinical trial was designed for the period of one year. Seventy one PCOS women diagnosed by Rotterdam criteria, among them in Group I 35 women received metformin and in Group II, 36 women received clomiphene citrate.

The cumulative ovulation rate over the six months period was not statistically different between the treatment groups [57.14% and 61.11% in metformin and CC group respectively, (P=0.115)]. Other
comparative study between metformin and clomiphene citrate also found similar result\textsuperscript{19}. They found that the cumulative ovulation rate per ovulatory cycle was not statistically different [62.9\% vs. 67.0\% in metformin and CC group respectively; P=0.38]. Another two study done by Velazquez and Fleming have reported an ovulation rate of 86.7\% (13 of 15) and 82\% (37 out of 45) following treatment with metformin in PCOS subfertile women\textsuperscript{20,21}. None used hCG for triggering ovulation, which was also similar to the present study.

In contrast to this Legro in his study supports the use of clomiphene citrate alone as first line therapy for subfertile PCOS women\textsuperscript{3}. They concluded that clomiphene citrate alone is better than metformin alone or combination of both clomiphene citrate and metformin. Though ovulation, pregnancy and live birth rate were higher in combination of metformin and CC group than metformin and CC alone, it was not significant. Legro, had a large sample size, observed for longer duration (more than two years), and subjects of their study received extended-release metformin which may be less efficacious in women with PCOS than immediate release metformin. They gradually increased the dose of two drugs according to the response. Present study was done in a fixed dose in both groups.

Insulin resistance has a key role in the pathogenesis of PCOS associated infertility\textsuperscript{22}. This emphasizes the use of insulin sensitizers as pharmacotherapy for PCOS. Metformin by reducing hyperinsulinemia promotes proper growth of the follicle in contrast to clomiphene citrate, which has no effect on it. Most studies have demonstrated the efficacy of metformin in inducing ovulation\textsuperscript{20,23,24}, whereas others disagreed with these findings\textsuperscript{25,26,27}. The advantage of the present study was, all were newly diagnosed cases of PCOS, based on the latest Rotterdam criteria, no one received any fertility treatment earlier. Patients were randomly allocated to the study medications and each patient were followed up for 6 months during the intervention period to observe ovulation and pregnancy. Above mentioned studies mainly looked at the ovulation rate.

In the present study, a significant difference was found in cumulative pregnancy rate between metformin and clomiphene group 60\% versus 33.3\%; P = 0.02 which goes in accordance with Palomba\textsuperscript{19}. Their study showed that, over six months of treatment a significant difference was observed in the cumulative pregnancy rate (68.9\% vs 34\% in metformin and CC group respectively; P<0.001). In contrast Legro, found that pregnancy was approximately twice in clomiphene group compared to metformin group (29.7\% vs. 12.0\%)\textsuperscript{3}. They described multiple follicular recruitment with clomiphene may have an increased opportunity for fertilization and successful implantation. But several studies showed the discrepancy between ovulation and pregnancy rate in PCOS subfertile women treated with clomiphene citrate\textsuperscript{10,28,29}. The discrepancy is due to its antiestrogenic effect 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. An observational comparative study involving 154 women with PCOS noted that metformin was better than CC for ovulation induction and equivalent for pregnancy achievement\textsuperscript{30}.

Metformin has been found more effective than clomiphene citrate in treating the anovulatory subfertile PCOS women; with ovulation rate of 80\% and 61.1\% and conception rate of 60\% and 33.3\% respectively. As treatment of infertility is very expensive and cumbersome and many of our patients are from low socio-economic group, we can achieve better result with a less expensive and available drug like metformin, which might be helpful in context of our population. Further multicenter randomized controlled trials with large sample size, good laboratory facilities and provision for longer period of follow up may be conducted to establish the efficacy of metformin for the treatment of subfertile PCOS patients.

References:


30. Neveu N, Granger L, St-Michel P, Lavoie HB. Comparison of clomiphene, metformin or the combination of both for first - line ovulation induction and achievement of pregnancy in 154 women with PCOS. *Fertil Steril* 2007;87:113-120.