Effects of Simvastatin Pretreatment on Clomiphene Response in Clomiphene – Resistant Women with Polycystic Ovary Syndrome

Azam Azargoon; M.D.[1], Raheb Ghorbani; Ph.D.[2], Zahra Faraji; M.D.[3]

1 Department of infertility, Semnan University of Medical Sciences, Semnan, Iran
2 Department of Community Medicine, Semnan University of Medical Sciences, Semnan, Iran
3 Department of obestertics & gynecology, Semnan University of Medical Sciences, Semnan, Iran

Received February 2013; Revised & accepted March y2013

Abstract

Objective: The aim of this study is to determine if simvastatin pretreatment would change clomiphene response in clomiphene citrate-resistant (CC-R)women with (PCOS).

Materials and methods: This quasi experimental study included twenty five clomiphene resistant women with PCOS. All patients received cyclic oral contraceptives pills (OCP) (30µg of ethinyl estradiol and 150µg of desogestrol) from the 5th day of their spontaneous or progesterone (P) induced menstrual cycle; in addition, they received simvastatin (20mg/day) from the first day of cycle for two consecutive months. Then, patients were given 100 mg clomiphene citrate (CC) (Iran Hormone, Iran) for five days starting from day three of their menstrual cycles. The primary outcome measures were ovulation and pregnancy rates. The change in body mass index (BMI), the mean number of follicles ≥ 18 mm, the mean of follicular size and endometrial thickness on the day of human chorionic gonadotropin (HCG) administration were secondary outcome measures.

Results: Ovulation occurred in 5 out of 25 (20 %) patients, but none of the patients conceived in this study. No important change in BMI was observed after using simvastatin (0.28+1.13; p=0.228). In all patients with ovulation, the number of follicles ≥ 18mm was one. The mean follicular size and endometrial thickness on the day of HCG administration were 19.67 ± 2.04 and 7.00 ± 1.34, respectively.

Conclusion: In this study, we did not observe the favorable effect on ovulation and pregnancy rates with CC following of simvastatin pretreatment in CC-resistant PCOS women. So, further studies with a larger number of patients, higher doses of CC and more cycles are necessary to make this obvious.

Keywords: Clomiphene-Resistant, Poly Cystic Ovary Syndrome, Simvastatin, Statins

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common causes of anovulatory infertility and affects 6-7% of women of reproductive age (1, 2). The current first line therapy is the weight loss in the obese group of women, and then induction ovulation with clomiphene (1, 3). Since 20-25% percentage of PCOS women show resistance to clomiphene citrate they are unable to ovulate (4). Ovulation induction with gonadotropins is the standard treatment for

Correspondence:
Azam Azargoon, M.D.,Amir-AL-Momenin Hospital, Madar Square, Semnan Postal code 35197-34731, Iran.
Email: azarmona2003@yahoo.com

clomiphene-resistant (CR) women; however, this method is expensive, as well as it has high risks of ovarian hyperstimulation and multiple pregnancies (1,5). Hyperinsulinemia is one of the diagnostic features of PCOS patients with resistance to either endogenous or exogenous insulin (6). It is also known that patients with PCOS and insulin resistance are often resistant to CC (7), so the recommended treatment is insulin sensitizers, such as metformin (8) or troglitazone (9). Recently a new therapeutic approach has been tried for PCOS women and that is the use of statins. Statins works basically by competitively inhibiting 3-hydroxy-3 methylglutaryl-coenzyme A (HMG-COA) reductase, which is the first stage of mevalonate pathway; there for, it causes a decrease in cholestrole synthesis and a compensatory increase in the expression of LDL receptors in the liver (10). Some studies have reported that simvastatin decreases serum androgen levels and normalizes gonadotropin levels in women with PCOS (11-13). Kazerooni et al (2010) showed that with this type of patients, using a combination of metformin and simvastatin results in a much improved reduction of T and LH levels, and this consequently overturns the LH:FSH ratio, lipid profile and insulin resistance(14).

Also, two separate studies by Sathyapalan et al. (2009 and 2010) have shown that atrovastatin improves biochemical hyperandrogenamia, insulin resistance and inflammatory markers in patients with PCOS; furthermore, by augmenting and facilitating the effect of metformin improve the actions of the above factors (15,16). Also, they have illustrated that atrovastatine decreases the levels of dehydroepiandrosterone (DHEAS) and androstendione, which remain effective within three months of metformine therapy (17). Several studies also showed a decrease in insulin resistance with statins (16,18-19). It is possible that the reduction of testosterone level and insulin resistance may be related to increase the likelihood of ovulation. On the other hand, statin therapy is contraindicated in all stages of pregnancy and it is suggested not to continue it when pregnancy is expected to occur. So, according to these findings, this study was undertaken to determine if simvastatin pretreatment would change clomiphene response in CC-resistance patients with PCOS.

Materials and methods

Twenty five women were enrolled in this quasi experimental study at the infertility clinic of the Amir-Al-Momenin Hospital, Semnan University of Medical Sciences, Seman, Iran from June 2009 to December 2011. All patients were informed about the study and the possible complications of the drugs by a specialist; in addition, the signed consents were obtained from them. This study was supervised and approved by the Research Council and Ethical Committee of Semnan University of Medical Sciences.

The inclusion criteria were as follows: 18-40 years of age, a period of infertility more than 1.5 years, normal serum prolactin and thyroid function tests, having documented patent tubes by hysterosalpingography, lack of other infertility factor, and failure in ovulation after using a dose of 150 mg CC per day for five consecutive days from the day 3 of menstrual period. Also, any patient with diabetes mellitus, hypertension, smoking habit, history of cardiovascular disease, hepatic, renal dysfunction, or an ovarian drilling procedure was excluded from the study.

PCOS was defined according to the Rotterdam criteria. Specifically, an eligible patient was presented with at least two of the three following criteria: (i) chronic anovulation, (ii) hyperandrogenism (hirsutism, acne) and/or hyperandrogenemia and (iii) polycystic ovaries (20). Hirsutism was diagnosed when the Ferriman and Gallway score was >8 (21).

A trans-vaginal ultrasound examination using a vaginal transducer 6.5 MHZ (Honda, Japan) was performed to exclude any pelvic pathology before a treatment with simvastatin.

Study design

All women were examined clinically, so their weight, height and body mass index (BMI) were recorded before and after the study. All patients received cyclic oral contraceptives (30µg of ethinyl estradiol and 150µg of desogestrol) from the 5th day of their spontaneous or progesterone (P) induced menstrual cycle; in addition, they received simvastatin (20mg/day) from the first day of cycle for two consecutive months.

The possible teratogenicity of statins was explained to all participants, and they were asked to use oral contraceptive pills (OCP), regularly. Then, patients were given 100 mg clomiphene citrate (CC or Clomid) (Iran Hormone, Iran) for five days starting from day 3 of their menstrual cycles.

Ovarian follicular response was monitored by transvaginal sonography every other day from day 10

of the cycle by a single sonographist. When at least one follicle reached ≥ 18 mm in diameter, 10000 IU of HCG (Pregnyl; N.V. Organon, OSS, Netherlands) was given intramuscularly, and timed intercourse was advised (every other day for one week starting after receiving HCG). Endometrial thickness and the number of mature follicles were determined on the day of HCG administration. If there was no follicle ≥12mm by day 16, the cycle was presumed to be anovulatory and monitoring was discontinued. Clinical pregnancy was determined to have occured when at least one gestational sac was discovered on transvaginal ultrasound examination which started one week after the missed period.

Outcome measures

The primary outcome measures were ovulation and pregnancy rates. Change in BMI after using simvastatin, the mean number of follicles ≥ 18 mm, the mean of follicular size and endometrial thickness on the day of HCG administration were secondary outcome measures.

Statistical analysis

Data are shown as mean ± standard deviation. All data was entered into the SPSS software (Version 11.5.0, © SPSS Inc., USA). Paired t-test was used for analysis of change in BMI. The value of $p<0.05$ was considered significant.

Results

Out of 29 patients, four women refused to participate in the study. Mean age and mean BMI of patients before treatment were 25.2 ± 5.6 and 31.92 ± 6.38, respectively.

Table 1 shows demographic, clinical and hormonal features of all women involving in this study. More than 70% of patients had primary infertility. Mean duration of infertility was approximately three years.

Ovulation occurred in 5 out of 25 patients (20 %), but none of the patients conceived in this study. Before and after using simvastatin, mean values of BMI were 31.92 ± 6.38 and 31.64±6.35, respectively. No significant change in BMI was observed following simvastatin therapy (0.28+1.13; p=0.228).

Most of the patients had high BMI prior to this study. Before using simvastatin, 10 out of 25 women (40%) were overweight (BMI: 25-29.9), while 12 out of 25 women (48%) were obese (BMI:≥30). These numbers after using simvastatin were changed to 11 out of 25 women (44%) in either overweight or obese group. In all patients with ovulation, the number of follicles ≥ 18mm, was one.

Table 1: Main demographic, clinical and hormonal characteristics of the patients

Variables	All patients
Age (years) (Mean± SD)	25.2± 5.6
BMI (kg/m2) (Mean± SD)	31.92± 6.38
Duration of infertility (years) (Mean± SD)	3.77± 4.76
Primary infertility [n (%)]	19 (76)
PCO feature in sonography in both ovaries [n (%)]	23 (92)
Menstrual pattern	
Oligomenorrhea [n (%)]	20 (80)
Amenorrhea [n (%)]	5 (20)
Hirsutism [n (%)]	9 (36)
LH (mIU/ml) (Mean± SD)	7.64± 6.46
FSH (mIU/ml) (Mean± SD)	5.3± 2.64
LH/FSH (Mean± SD)	1.52± 1.1
FBS (mg/dl)	91.6± 16.4
FBS/Ins	13.07± 8.17
HOMA-IR	2.98± 2.76

The mean follicular size and endometrial thickness on the day of HCG administration are shown in Table 2. All patients tolerated the simvastatin, and none of the subjects developed any side effects.

Table 2: Characteristics of treatment cycles with CC and simvastatine on the day of HCG

Mean-number of follicles ≥ 18 mm	1
Size of follicles ≥ 18 mm (Mean± SD)	19.67 ±2.04
Endometrial thickness (mm) (Mean± SD)	7.00 ± 1.34
Ovulation [n (%)]	5/25 (20)
Pregnancy/cycle [n (%)]	0/25 (0)

Discussion

This study presents the effects of simvastatin pretreatment on CC response in CC- resistant PCOS patients. A number of clinical trials have been done to evaluate the impacts of statins on women with PCOS and they have reported remarkable improvement in many clinical, metabolic and endocrine aspects of this disorder. In the first clinical trial by Duleba et al (2006), women with PCOS, defined according to the Rotterdam criteria, were

randomized to be treated with simvastatin plus OCP or OCP alone. In the presence of OCP, simvastatin significantly decreases T levels, as well as lowers LH level and LH/FSH ratio (11). Simvastatin also decreases levels of markers of systemic inflammation and endothelial cells (ECs), like: c-reactive protein (CRP) and soluble vascular cell adhesion molecule-1 (sVCAM-1). A subsequent trial was performed without OCP in order to compare the effects of simvastatin along with metformin, as well as the combination of simvastatin plus metformin (13). They have demonstrated the following results: (i) simvastatin and metformin play a big role in reducing testosterone, clinical hyperandrogenism, BMI, and markers of systemic inflammation and endothelial function, (ii) lipid profile, DHEAS, and insulin sensitivity are remarkably improved by simvastatin alone , and the fact that (iii) the combination of simvastatin and metformin was not in any significant way preferable to simvastatin alone with respect to any of the studied variables. Other studies have also tried to demonstrate the effects of simvastatin and atorvastatin on women with PCOS, defined according to the Rotterdam criteria. Both treatments resulted in significant improvement of lipid profile, while a reduction in CRP, oxidative stress and homocysteine level (19, 22). Recently, Sathyapalan et al (2012) have showed that use of atorvastatin for twelve weeks significantly reduces both DHEAS and androstenedione, contributing to a total reduction of androgen concentrations. This obtained result indicates that the reduction of the hyperandrogenaemia could be partly due to the action of atorvastatin in both the ovary and the adrenal gland (17). Raja-khan et al. (2010) have also demonstrated reduction of DHEAS and androstenedione after six weeks of treatment with atrovastatin (23). The capacity of simvastatin in order to attenuate serum testosterone comes from its mevalonate pathway inhibition,(which alternatively causes a reduction in testosterone level through decreasing its available precursors (10) as well as suppression of the theca interstitial compartment cells (24), which has nothing to do with the availability of cholesterol and works regardless of leukocytes in the ovary (25).

Atorvastatin treatment was considered to have improved insulin sensitivity. These findings were consistent with observations of a placebo-controlled trial evaluating effects of atorvastatin (20 mg/day) over a 12-week period. In that study, atorvastatin improved lipid profile, reduced CRP and improved insulin sensitivity (15). Also, Kaya et al. (2009) in a randomized comparative study between simvastatin and atrovastatin have showed that atrovastatin has more noticeable effects on fasting insulin and insulin sensitivity, but simvastatin has a dominant effect on total T in PCOS (19). In addition, Banaszewska et al. (2009) have illustrated that simvastatin treatment is associated with a reduction in fasting insulin, so it improves insulin sensitivity (13). The fact that statin improved insulin sensitivity, may be a passing phenomenon or may be due to the treated population since in a number of other clinical trials statins had no noticable effect on insulin sensitivity (11, 26).

Recently, in a placebo-controlled trial, administration of atorvastatin (40 mg/day) for six weeks resulted in a significant increase in insulin levels, indicating reduced insulin sensitivity (23). By combining the results from several small studies with meta-analysis, Gao et al. (2012) have showed that patients taking statin have a positive decrease in testosterone compared to placebo. The combined therapy, consisting of statin plus metformin has a much better effect on reducing the testosterone than metformin alone, in addition to lipid profile which exerts cardioprotective properties (27).

Women with PCOS, who need induced ovulation, would benefit greatly from these corrections since a high level of testosterone and the ‘‘inverted’’ LH/FSH proportion are presumed typical of hypothalamic-pituitary-ovary dysfunction which is often seen in PCOS patients.

In this study, we did not observe any improvement on ovulation or pregnancy rates after taking CC following of simvastatin pretreatment in CC-resistant PCOS women. This may be related to the following factors: (i) use the combination OCP and simvastatin (ii) delay in ovulation because of using OCP, and (iii) high BMI in this small population. To the best of our knowledge, there has been no study about statin therapy in CC-R/PCOS patients; however, ovulation and pregnancy rates were assessed in the other studies using letrozole (28-30), letrozole plus metformine (31-32) and CC plus metformine (33) in CC-resistant patients. The results of other studies revealed considerable higher ovulation and pregnancy rates in comparison to the result of this study (ovulation rate:90.57-40.6; pregnancy rate: 25.5-27.27%) (22-26).

Recently, Rashidi et al. (2011) in a clinical randomized trial compared simvastatin with placebo on selected biochemical parameters and reproductive

outcome among patients with PCOS who underwent IVF. Although oocyte maturation, fertilization, and clinical pregnancy rates were higher after using simvastatin, none of these improvements were statistically significant. However, after simvastatin treatment, the reductions in T levels, CRP, and vascular cell protein-1 were significant (26). In this study, we did not observe any important change in BMI after using simvastatin. This was consistent with the findings of two other randomized trials (11,21) and contrary to some studies (13-14). This study has had some limitations. This study evaluated only the effects of a single statin in the presence of concomitant initiation of OCP.Thus, one cannot exclude the possibility that the observed effects were due to synergy between simvastatin and OCP. We decided to use OCP because of potential teratogenic actions of statins. Also, it should be noted that this study included a population with relatively high BMI, while we used only a single dose of CC (100mg) in one cycle.

Conclusions

In this study, we did not observe any favorable effect on ovulation and pregnancy rates with CC following of simvastatin pretreatment in CC-resistant PCOS women. So, re-evaluation of the present findings with larger and diverse populations of patients, higher dose of CC, more cycles, and preferably with placebo group are necessary to make this obvious.

Acknowledgments:

The authors gratefully like to thank all the patients participating in the study and Mrs. Fatemeh Azizi for her assistant throughout this research. There is no conflict of interest in this study. Also, we did not receive any financial support. This is post graduate thesis of Dr Zahra Faraji

References

1. Gardner DK,Weissman A,Howles CM,Shoham Z. Assisted Reproductive Technologies.3rd ed.United Kingdom:Informe health care;2009;721.
2. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004; 89:2745–9.
3. Lidor AL ,Goldenberg M ,Cohen SB, Seidman DS, Mashiach S, Rabinovici J. Management of women with polycystic ovary syndrome who experienced premature luteinization during clomiphene citrate treatment. Fertil Steril 2000; 74:749-52.
4. Polson DW,Kiddy DS,Mason HD, Franks S.Induction ovulation with clomiphene citrate in women with polycystic ovary syndrome:the difference between responders and nonresponders.Fertil Sterli 1989; 51:30-4.
5. George SS, George K, Irwin C, Job V, Selvakumar R, Jeyaseelan V, Seshadri MS. Sequential treatment of metformin and clomiphene citrate in clomiphene-resistant women with polycystic ovary syndrome: a randomized, controlled trial. Hum Reprod 2003; 18:299-304.
6. Ciaraldi TP, el-Roeiy A, Madar Z, Reichart D, Olefsky JM, Yen SS. Cellular mechanisms of insulin resistance in polycystic ovarian syndrome. J Clin Endocrinol Metab 1992; 75:577–83.
7. Murakawa H, Hasegawa I ,Kurabayashi T, Tanaka K. Polycystic ovary syndrome.Insuline resistance and ovulatory response to clomiphene citrate.J Reprod Med1999;44:23-7.
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 .
9. Mitwally M.F, Kuscu N.K,Yalcinkaya TM.High ovulatory rates with use of troglitazone in clomiphene –resistant women with poly cystic ovary syndrome. Hum Repro. 1999; 14:2700-3.
10. Goldstein JL, Brown MS. Regulation of the mevalonate pathway.Nature1990; 343:425–30.
11. Duleba AJ, Bonaszewska B, Spaezynski RZ,Powelczyk L. Simvastatin improve biochemical parameters in women with polycystic ovary syndrome:results of a prospective randomize trial. Fertil Steril 2006; 85:996–1001.
12. Banaszewska B, Pawelczyk L, Spaczynski RZ, Dziura J, Duleba AJ. Effects of simvastatin and oral contraceptive agent on polycystic ovary syndrome: prospective, randomized, crossover trial. J Clin Endocrinol Metab 2007; 92:456-61.
13. Banaszewska B, Pawelczyk L, Spaczynski RZ, Duleba AJ. Comparison of simvastatin and metformin in treatment of polycystic ovary syndrome: prospective randomized trial. J Clin Endocrinol Metab 2009 Dec; 94:4938-45.
14. Kazerooni T, Shojaei-Baghini A, Dehbashi S, Asadi N, Ghaffarpasand F, Kazerooni Y. Effects of metformin plus simvastatin on polycystic ovary syndrome: a prospective, randomized, double-blind, placebo-controlled study. Fertil Steril2010; 94:2208-13.
15. Sathyapalan T, Kilpatrick ES, Coady AM, Atkin SL. The effect of atorvastatin in patients with polycystic ovary syndrome: a randomized double-blind placebo-controlled study. J Clin Endocrinol Metab2009; 94:103–8.
16. Sathyapalan T, Kilpatrick ES, Coady AM, Atkin SL.

Atorvastatin pretreatment augments the effect ofmetformin in patients with polycystic ovary syndrome (PCOS). Clin Endocrinol2010; 72: 566–8.
17. Sathyapalan T,Smith KA, Coady AM, Kilpatrick ES, Atkin SL Atorvastatin therapy decreases androstenedione anddehydroepiandrosterone sulphate concentrations in patientswith polycystic ovary syndrome: randomized controlled study.Ann Clin Biochem2012; 49:80-5.
18. Navali N,Pourabolghasem S,Fouladi RF,Nikpour MA.Theraputic effects of biguanide vs.statin in poly cystic ovary syndrome:a randomized clinical trial.Pak J Biol Sci 2011;14:658-63.
19. KayaC, Cengiz SD, Berker B, Demirtas S, Cesur M, Erdogan G.Comparative effects of atorvastatin and simvastatin onthe plasma total homocysteine levels in women with polycystic ovary syndrome: a prospective randomized study .Fertil Steril 2009; 92:635-42.
20. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised2003consensus on diagnostic criteria and longterm health risks related to polycystic ovary syndrome.The Rotterdam ESHRE\ASRM-sponsored pcos consensus workshop group.Fertil steril 2004; 81:19-25.
21. Speroff L,Fritz MA.Induction ovulation In :Clinical gynecologic endocrinology and infertility. 7th ed. Philadelphi: Lippincott,Williams and Wilkins;2005: 499-530.
22. Kaya C, Pabuccu R, Cengiz SD, Dunder I. Comparison of the effects of atorvastatin and simvastatin in women with polycystic ovary syndrome: A prospective, randomized study. Exp Clin Endocrinol Diabetes 2010; 118:161–6.
23. Raja-Khan N, Kunselman AR, Hogeman CS, Stetter CM, Demers LM, Legro RS. Effects of atorvastatin on vascular function, inflammation, and androgens in women with polycystic ovary syndrome: a double-blind, randomized,placebo-controlled trial. Fertil Steril 2010; 95:1849–52.
24. Izquierdo D, Foyouzi N, Kwintkiewicz J, Duleba AJ. Mevastatin inhibits ovarian theca-interstitial cell proliferation and steroidogenesis. Fertil Steril 2004;82:1193–7.
25. Sokalska A, Piotrowski PC, Rzepczynska IJ, Cress A,Duleba AJ. Statins inhibit growth of human theca-interstitial cells in PCOS and non-PCOS tissues independently of cholesterol availability. J Clin Endocrinol Metab 2010; 95: 5390–4.
26. Rashidi B, Abediasl J, Tehraninejad E, Rahmanpour H, Sills ES. Simvastatin Effects on Androgens, Inflammatory mediators, and endogenous pituitary gonadotropins among patients with PCOS undergoing IVF: Results from a prospective,randomized, placebo-controlled clinical trial.J Investig Med 2011;59:912-6.
27. Gao L,Zhao FL,Li SC. Statin is a Reasonable Treatment Option for Patients with Polycystic Ovary Syndrome: a Meta-analysis of Randomized Controlled Trials. Exp Clin Endocrinol Diabetes 2012; 120: 367–75.
28. Al-Omari WR, Sulaiman WR, Al-Hadithi N. Comparison of two aromatase inhibitors in women with clomiphene-resistant polycystic ovary syndrome. Int J Gynaecol Obstet 2004;85:289-91.
29. Mitwally MF, Casper RF.Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. Fertil Steril 2001; 75:305-9.
30. Elnashar A, Fouad H, Eldosoky M, Abelgafar N. Letrozole induction of ovulation in clomiphene citrate resistant polycystic ovary syndrome: responders and non-responders. Fertil Steril 2006;85:511-3.
31. Sohrabvand F, Ansari Sh, Bagheri M. Efficacy of combined metformin-letrozole in comparison with metformin-clomiphene citrate in clomiphene-resistant infertile women with polycystic ovarian disease. Hum Reprod 2006;21:1432-5.
32. Azargoon A ,Alavy Toussy J, Fakhr Darbanan F. Pregnancies following the use of sequential treatment of metformin and incremental doses of letrozole in clomiphen-resistant women with polycystic ovary syndrome. Iran J Reproduc Med 2012; 10:33-40.
33. Ashrafi M, Zafarani F, Baghestani AR.Effects of metformin on ovulation and pregnancy rate in women with clomiphene resistant poly cystic ovary syndrome. Int J Fertil Steril 2007;1: 39-42.