USE OF ROSIGLITAZONE FOR CLOMIPHENE RESISTANT POLYCYSTIC OVARY SYNDROME (PCOS): A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a condition with an imbalance in the milieu of the sex hormones. This might lead to menstrual disturbances, anovulation and infertility in women.

Methods: This two-treatment parallel-design study included a triple blind, randomized controlled trial with low dose (2mg) Rosiglitazone, which was conducted over two years at an infertility clinic of a reputed private hospital in India. Forty patients with PCOS, who failed to ovulate with Clomiphene citrate 100mg, were randomly selected and treated with two different doses of Rosiglitazone for two cycles. The Intervention Group received 2mg while the Control Group received 4mg of Rosiglitazone. Comparisons were done by non-parametric Mc Nemar’s test and p <0.05 was considered as statistically significant.

Results: In this study, 12(42.9%) participants receiving 2mg of Rosiglitazone ovulated at the end of second cycle as compared to 16(57.1%) in the group receiving 4mg. The cumulative ovulation rate for both the groups was high (70.0%) after the second cycle. It was seen that 3(60.0%) participants receiving 2mg of Rosiglitazone became pregnant at the end of second cycle as compared to 2(40.0%) in the group receiving 4mg. The cumulative pregnancy rate was 12.5%. The insulin resistance got corrected in 10(40.0%) participants receiving 2mg of Rosiglitazone at the end of second cycle as compared to 15(60.0%) by the group receiving 4mg. This suggested that insulin resistance correction was dose dependent. Abnormal testosterone levels got corrected in 15(48.4%) participants in the group receiving 2mg of Rosiglitazone as compared to 16(51.6%) by the group receiving 4mg at the end of the second cycle.

Conclusion: Low dose (2mg) Rosiglitazone had improved the ovulation rate in the Clomiphene citrate resistant PCOS women. However, the cumulative pregnancy rate was not so encouraging as
compared to good ovulation rate. These findings were equivalent to the 4mg of Rosiglitazone regimen. There was no significant adverse effect seen amongst the participants.

**Keywords:** Rosiglitazone, Clomiphene, Polycystic, Ovary.

1. **INTRODUCTION**

Polycystic Ovary Syndrome (PCOS) is complicated by the complexity of the pathophysiologic interaction and heterogeneity of the clinical expression. The exact etiology of PCOS still remains unclear (Dunaif et al., 1992) & (Dunaif, 1995). However, there is well established association between PCOS, insulin resistance and hyperandrogenism (Goldstein, 1999).

Many researchers have attempted to explain the possible molecular and genetic pathogenesis of insulin resistance in PCOS. Dunaif et al. (1992) suggested that the major cellular lesion associated with insulin action in PCOS is due to post binding defect in the insulin receptor or a defect in receptor signal transduction with a less substantial but significant decrease in glucose transport. In effort to characterize the defect, Dunaif (1995) found that increasing insulin receptor serine phosphorylation decreases its protein kinase activity, which represents one of the mechanisms for terminating insulin signaling in PCOS. Hence, improving the action of insulin had become the principle of therapy of PCOS and various insulin sensitizers have been used to improve insulin sensitivity and to reduce the circulating insulin in PCOS women (Dunaif, 1995).

Rosiglitazone is a second generation thiazolidinediones, which is used for pharmacologic treatment of insulin resistance. It acts as ligands for Peroxisome Proliferated Activated Receptor gamma (PPAR-γ), which is directly involved in the regulation of genes controlling glucose homeostasis and lipid metabolism (Goldstein, 1999). It also controls transcription of genes involved in the central mechanisms (Barbieri, 2000). Rosiglitazone also has 99% bioavailability and is unaltered by pH altering drugs (Miller et al., 2002).

Ghazeeri et al. (2003) studied the effect of maximum dose of Rosiglitazone (8mg) on Clomiphene citrate resistant PCOS women and showed the ovulation rate of 33% and 77% at the end of first and second cycle respectively.

With this background, a triple blind, randomized controlled trial was conducted to study the efficacy of a lower dose of Rosiglitazone (2mg) in the treatment of anovulation resistant to Clomiphene citrate. The researchers also wanted to study its effect on insulin resistance and hyperandrogenemia. This pilot study was undertaken to plan for a large scale multi-centric project in future.

2. **OBJECTIVES**

**Primary objective:** To study the efficacy of a lower dose of Rosiglitazone (2mg) in the treatment of Clomiphene citrate resistant PCOS.

**Secondary objectives:** To study its effects on insulin resistance and hyperandrogenemia.

3. **MATERIALS AND METHODS**

A triple blind, randomized controlled trial with two lower doses of Rosiglitazone was conducted over two years (January 2001 to December 2003) at an infertility clinic of a reputed
private hospital in India. This was a two-treatment parallel-design study. Forty patients with PCOS, who failed to ovulate with Clomiphene citrate 100mg, were randomly selected and treated with two different doses of Rosiglitazone for two cycles. They were divided into Intervention Group that received 2mg of Rosiglitazone and Control Group that received 4mg of Rosiglitazone.

3.1. Selection Criteria

Clomiphene citrate resistance was considered as failure of ovulation after two cycles of Clomiphene citrate 100mg for 5 days (D2 to D6) regimen.

3.2. Inclusion Criteria

All women who visited the designated fertility clinic during the study period and fulfilled the criteria for Clomiphene resistance PCOS were eligible to participate in this study.

3.3. Exclusion Criteria

Women with hyperprolactinemia, thyroid disorders and having a previous history of hepatitis or any liver disorders were excluded from the study.

4. STUDY POPULATION

The probability sample size calculation revealed that a total of 20 patients were required to enter this two-treatment parallel-design study. The probability was 84 percent that the study would detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments was 1.405 times the standard deviation. The provided parameters were: significance level (adjusted for sidedness) = 0.025, power = 0.8 and location of mean in one group as a percentile of the other group = 0.92.

4.1. Sampling Method

Block randomization technique was adopted to ensure equal number of participants in each group at the end of study period. Hence, forty women with PCOS, who were resistant to Clomiphene citrate, were included in this study with 20 in each group.

4.2. Ethical Considerations

Approval for the present study was obtained from the research and ethical committees of the designated private hospital in India. The information obtained during the data collection was strictly kept confidential. In order to maintain anonymity, a random code number was issued to each participant of this study while responding to the pre-test and post-test assessments. Informed written consent was obtained from every participant prior to the inception of this study.

4.3. Definition of Intervention Group

The randomly selected participants who received 2mg of Rosiglitazone during the follow-up period constituted the intervention group.
4.4. Definition of Intervention
During the first cycle, 2mg of Rosiglitazone was administered once daily with follicular imaging from D11 of her cycle, with intrauterine insemination (if ovulation occurs). During the second cycle, 2mg of Rosiglitazone was administered once daily along with Clomiphene citrate 100mg daily for 5 days (D2 to D6) with follicular imaging with intrauterine insemination (if ovulation occurs).

4.5. Definition of Control Group
The randomly selected participants who received 4mg of Rosiglitazone during the follow-up period formed the control group.

4.6. Definition of Control
During the first cycle, 4mg of Rosiglitazone was administered once daily with follicular imaging from D11 of her cycle, with intrauterine insemination (if ovulation occurs). During the second cycle, 4mg of Rosiglitazone was administered once daily along with Clomiphene citrate 100mg daily for 5 days (D2 to D6) with follicular imaging with intrauterine insemination (if ovulation occurs).

4.7. Method of Randomization
After obtaining informed written consent from every potential participant of this study, a computer-generated lottery was conducted using their registration numbers to randomly allocate each participant into the intervention and control groups. Block randomization technique was adopted.

4.8. Method of Allocation Concealment
The detailed list of random allocation of the participants into intervention and control groups was kept strictly confidential with the chief investigator and was not shared with other members of the research team in order to avoid bias in this study.

4.9. Method of Blinding
Triple blind method was adopted to minimize bias in this study. The participants were blinded and they were unaware of which group they belonged to (intervention or control). The staffs who conducted the evaluations were blinded and they were unaware of the group allocation of each participant. Finally, the persons who did laboratory analysis of various biochemical parameters and those conducted the statistical analysis was also kept blinded about the individual identity of the participants.

4.10. Study Instruments
A pre-designed and pre-tested proforma was used for the collection of personal details, socio-demographic and biochemical parameters.
5. DATA COLLECTION PROCEDURE

Successful ovulation was determined by presence of $\geq 18$mm follicle with subsequent reduction in size, presence of fluid in pouch of Douglas as seen by Transvaginal Sonography (TVS). The various biochemical and blood parameters like fasting insulin (FI), fasting blood glucose (FBS), insulin resistance (FBS/FI $< 4.5$), ALT, serum testosterone and hemoglobin levels were measured before and after the 2 cycles of Rosiglitazone therapy. ALT and hemoglobin were measured mainly to monitor the patients for any adverse hepatic or hematological effects.

6. OUTCOME ASSESSMENT

The primary outcomes included the ovulation rates at the end of 1 st and 2 nd cycle and the subsequent pregnancy rates for both the groups. Abnormal biochemical parameters of insulin resistance and testosterone levels were measured before and after the two cycles as secondary outcomes to evaluate and compare the efficacy of the two different doses of Rosiglitazone.

7. DATA ANALYSIS

The data collected were tabulated and analyzed by using the Epi info 2000 version 6 and Statistical Package for Social Sciences (SPSS) version 18.0. Results were expressed in terms of Proportions. Comparisons were done by non-parametric Mc Nemar’s test. The Post- test results were compared to estimate the effectiveness of the interventions and were expressed in terms of Relative Risks and their 95% Confidence Intervals (CI). In this study, p $< 0.05$ was considered as statistically significant.

8. RESULTS

All the participants in this study were married women who belonged to the age group of (24 – 42) years. The mean age was 29 years and standard deviation was ($\pm 3.6$) years. There was no significant change in the BMI of the participants during the study period. No adverse effects like anemia and hepatic dysfunction were observed during the study period. Indications for intrauterine insemination (IUI) were mainly cervical factor, endometriosis and male factor infertility.

Table 1 revealed that 8(66.7%) participants receiving 2mg of Rosiglitazone ovulated at the end of first cycle as compared to 4(33.3%) in the control group receiving 4mg of Rosiglitazone. However, this difference was not found to be statistically significant. The cumulative ovulation rate for both the groups was 30.0% after the first cycle. It also showed that 12(42.9%) participants receiving 2mg of Rosiglitazone ovulated at the end of second cycle as compared to 16(57.1%) in the control group. However, this difference was also not found to be statistically significant. The cumulative ovulation rate for both the groups was 70.0% after the second cycle.

Table 2 showed that 1(50.0%) participant receiving 2mg of Rosiglitazone became pregnant at the end of first cycle as compared to 1(50.0%) in the control group receiving 4mg of Rosiglitazone. However, this difference was not found to be statistically significant. The cumulative pregnancy rate for both the groups was 5.0% at the end of the first cycle. It also showed that 3(60.0%) participants receiving 2mg of Rosiglitazone became pregnant at the end of second cycle as compared to 2(40.0%) in the control group. However, this difference was not found to be statistically significant. The pregnancy rate was comparable for both the groups after two
cycles. The cumulative pregnancy rate was considered to be low (12.5%) as compared to a high ovulation rate of 70% which was achieved earlier in both these groups.

The biochemical parameters were categorized into Insulin resistance (fasting blood glucose: fasting insulin <4.5) and Hyperandrogenism (Testosterone levels >1ng/dL). Table 3 indicated that the intervention group receiving 2mg of Rosiglitazone had 6(66.7%) of the insulin resistance cases corrected at the end of first cycle as compared to 3(33.3%) by the control group receiving 4mg of Rosiglitazone. However, this difference was not found to be statistically significant. It also indicated that the intervention group receiving 2mg of Rosiglitazone had only 10(40.0%) of the insulin resistance cases corrected at the end of second cycle as compared to 15(60.0%) by the control group. Though this difference was also not found to be statistically significant, but it suggested that insulin resistance correction was dose dependent.

However, the findings related to correction of abnormal testosterone levels in both cycles were found to be different from correction of insulin resistance. Table 4 revealed that the intervention group receiving 2mg of Rosiglitazone had 9(52.9%) of the abnormal Testosterone level cases corrected at the end of first cycle as compared to 8(47.1%) by the control group receiving 4mg of Rosiglitazone. However, this difference was not found to be statistically significant. The overall correction of abnormal Testosterone levels in both the groups after the first cycle was found to be 42.5%. It also revealed that the intervention group receiving 2mg of Rosiglitazone had 15(48.4%) of the abnormal Testosterone level cases corrected at the end of second cycle as compared to 16(51.6%) by the control group. However, this difference was also not found to be statistically significant. The overall correction of abnormal Testosterone levels in both the groups after the second cycle was found to be 77.5%. These findings suggested that abnormal Testosterone level correction was not dose dependent with Rosiglitazone.

Since, all the participants were followed up till the end of this study period, there was no requirement to conduct the intention to treat analysis. However, due to small sample size, the non-inferiority trial analysis could not be conducted for this study.

9. DISCUSSION

Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder in women of reproductive age group affecting 5-10% of premenopausal women exhibiting the full blown syndrome of hyperandrogenism, chronic anovulation and polycystic ovaries (Sozen and Arici, 2000). It is known that approximately 75% of anovulatory women and 20-25% of women with normal ovulation demonstrate ultrasound findings consistent with polycystic ovaries (Polson et al., 1988). The incidence of insulin resistance as determined by fasting glucose to fasting insulin ratio < 4.5 is between 30-50% of all cases of PCOS (Fox et al., 1991). Similarly 60% women with PCOS exhibit an increased testosterone level >1 but <2.5ng/dL (Fox et al., 1991).

There mechanisms of insulin resistance are not completely defined however Dunaf et al. suggested that the major cellular lesion in insulin action in PCOS is a post-binding defect in the insulin receptor. There has been lots of controversy in the past about whether hyperinsulinemia causes hyperandrogenism or vice versa. Shoupe and Lobo (1984) showed that androgen antagonist spironolactone decreases insulin resistance and fasting insulin levels in patients with PCOS.
cordant with a decline in testosterone levels. Nagamani et al. (1986) observed that bilateral oophorectomy eliminated hyperandrogenism but did not reduce the severity of hyperinsulinism thereby exemplifying that hyperandrogenism does not cause hyperinsulinism. Despite the contrary reports, (Ehrmann et al., 1997a) mentioned that the beneficial effects of Metformin, an insulin sensitizer, on hyperandrogenism could not be demonstrated. In our study Rosiglitazone, second generation insulin sensitizer, has shown to improve both insulin resistance and hyperandrogenism.

The improvement of insulin resistance was more with a higher dose thereby pointing a possibility of dose dependent action which leaves a scope for further research.

Kim et al. (2000) suggested a step by step approach to ovulation induction in women with PCOS where insulin sensitizers and Clomiphene combination comes in the third step, weight loss and only Clomiphene being first and second step respectively. Metformin is used as blood glucose lowering agent in patients with NIDDM is also well known in the use for women with PCOS as an insulin sensitizers (Bailey and Turner, 1996). Introduction of Thiazolidinediones (TZD) was made to treat insulin resistance and be used as a therapeutic agent for Type 2 diabetes (Saltiel and Olefsky, 1996). (Ehrmann et al., 1997b) showed that the first TZD, Troglitazone, improved the insulin sensitivity in PCOS women (Fonseca et al., 1998) & (Olefsky, 2000). However, its image got tarnished by reports of hepatotoxicity and rare cases of liver failure (Neuschwander-Tetri et al., 1998).

Rosiglitazone is the next potent member of the TZD class and was approved for clinical use. Studies have shown that it does not share the same hepatotoxic profile as its predecessor, Troglitazone, but still monitoring of hepatic function was advised (Pasquali et al., 1991). The maximum daily dose of Rosiglitazone is 8mg and it has 99% bioavailability (Miller et al., 2002). Ghazeeri et al. (2003) did a prospective study done with Rosiglitazone where the author used the maximum dose of Rosiglitazone on Clomiphene citrate resistant PCOS women and demonstrated an ovulation rate of 77% at the end of two cycles.

In this study we have used half and one quarter of the maximum dose and have achieved an ovulation rate of 60% with 2mg and 80% with 4mg at the end of two cycles. This reflects that the effect of Rosiglitazone on ovulation rate could be dose related but plateaus after the dosage of 4mg. From our study we can also safely comment that a lower dose of Rosiglitazone will not have any adverse effects like hepatic dysfunction or anemia.

However, in comparison to the good ovulation rate the pregnancy rates were low. This could have discouraged the researchers in studying of this drug as evident from the scarcity of the prospective studies on this drug. Women with PCOS come with an expectation of achieving a pregnancy and not merely to ovulate. Hence, Rosiglitazone may not be able to fulfill these women’s expectation optimally. However, there is a need to conduct a large scale multi-centric randomized controlled trial to confirm the results.

10. CONCLUSION

This triple blind, randomized controlled trial had revealed that 2mg of Rosiglitazone had improved the ovulation rate in women with Clomiphene citrate resistant Polycystic Ovary Syndrome (PCOS). However, the cumulative pregnancy rate was not so encouraging as compared
to good ovulation rate. These findings were comparable with the 4mg of Rosiglitazone regimen. Though low dose (2mg) Rosiglitazone had reduced insulin resistance and testosterone levels in these women, but the higher reduction in insulin resistance by 4mg as compared to 2mg was suggestive of a dose dependant correction. Here, the abnormal Testosterone level correction was not found to be dose dependent with Rosiglitazone. This pilot study would encourage the researchers to plan for a large scale multi-centric project in future to confirm the results.

11. CONSENT STATEMENT

Approval for the present study was obtained from the research and ethical committees of the designated private hospital in India. The information obtained during the data collection was strictly kept confidential. In order to maintain anonymity, a random code number was issued to each participant of this study while responding to the pre-test and post-test assessments. Informed written consent was obtained from every participant prior to the inception of this study.

12. ACKNOWLEDGEMENT

I would like to express my gratitude to the nurses and staff of the reproductive medicine unit who helped me with data collection, information of patient follow up and collection of lab data.

Table-1. Comparison of Ovulation rates with Rosiglitazone

<table>
<thead>
<tr>
<th>End of FIRST Cycle</th>
<th>Intervention n1(%)</th>
<th>Control n2(%)</th>
<th>Total N (%)</th>
<th>RR (95%CI)</th>
<th>P-value from Mc Nemar’s Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation Present</td>
<td>8 (66.7)</td>
<td>4 (33.3)</td>
<td>12 (30.0)</td>
<td>2.00 (0.72-5.59)</td>
<td>0.166</td>
</tr>
<tr>
<td>Ovulation Absent</td>
<td>12 (42.9)</td>
<td>16 (57.1)</td>
<td>28 (70.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20 (50.0)</td>
<td>20 (50.0)</td>
<td>40 (100.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of SECOND Cycle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovulation Present</td>
<td>12 (42.9)</td>
<td>16 (57.1)</td>
<td>28 (70.0)</td>
<td>0.75 (0.49-1.14)</td>
<td>0.301</td>
</tr>
<tr>
<td>Ovulation Absent</td>
<td>8 (66.7)</td>
<td>4 (33.3)</td>
<td>12 (30.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20 (50.0)</td>
<td>20 (50.0)</td>
<td>40 (100.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Here, p <0.05 was considered as statistically significant.

Table-2. Comparison of Cumulative Pregnancy rates with Rosiglitazone

<table>
<thead>
<tr>
<th>End of FIRST Cycle</th>
<th>Intervention n1(%)</th>
<th>Control n2(%)</th>
<th>Total N (%)</th>
<th>RR (95%CI)</th>
<th>P-value from McNemar’s Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Present</td>
<td>1 (50.0)</td>
<td>1 (50.0)</td>
<td>2 (5.0)</td>
<td>1.00 (0.07-14.90)</td>
<td>0.468</td>
</tr>
<tr>
<td>Pregnancy Absent</td>
<td>19 (50.0)</td>
<td>19 (50.0)</td>
<td>38 (95.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20 (50.0)</td>
<td>20 (50.0)</td>
<td>40 (100.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End of SECOND Cycle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Present</td>
<td>3 (60.0)</td>
<td>2 (40.0)</td>
<td>5 (12.5)</td>
<td>1.50 (0.28-8.04)</td>
<td>0.632</td>
</tr>
<tr>
<td>Pregnancy Absent</td>
<td>17 (48.6)</td>
<td>18 (51.4)</td>
<td>35 (87.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20 (50.0)</td>
<td>20 (50.0)</td>
<td>40 (100.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Here, p <0.05 was considered as statistically significant.
Table-3. Comparison of Correction of Insulin Resistance with Rosiglitazone

<table>
<thead>
<tr>
<th>End of FIRST Cycle</th>
<th>Intervention n₁ (%)</th>
<th>Control n₂ (%)</th>
<th>Total N (%)</th>
<th>RR (95% CI)</th>
<th>P-value from McNemar’s Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Resistance Present</td>
<td>14 (45.2)</td>
<td>17 (54.8)</td>
<td>31 (77.5)</td>
<td>0.82</td>
<td>(0.59-1.16) 0.451</td>
</tr>
<tr>
<td>Insulin Resistance Absent</td>
<td>6 (66.7)</td>
<td>3 (33.3)</td>
<td>9 (22.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20 (50.0)</td>
<td>20 (50.0)</td>
<td>40 (100.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

End of SECOND Cycle

| Insulin Resistance Present         | 10 (66.7)           | 5 (33.3)       | 15 (37.5)   | 2.00        | (0.83-4.81) 0.191           |
| Insulin Resistance Absent          | 10 (40.0)           | 15 (60.0)      | 25 (62.5)   |             |                            |
| Total                              | 20 (50.0)           | 20 (50.0)      | 40 (100.0)  |             |                            |

* Here, p <0.05 was considered as statistically significant.

Table-4. Comparison of Correction of Abnormal Testosterone levels with Rosiglitazone

<table>
<thead>
<tr>
<th>End of FIRST Cycle</th>
<th>Intervention n₁ (%)</th>
<th>Control n₂ (%)</th>
<th>Total N (%)</th>
<th>RR (95% CI)</th>
<th>P-value from McNemar’s Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal level Present</td>
<td>Testosterone</td>
<td>11 (47.8)</td>
<td>12 (52.8)</td>
<td>23 (57.5)</td>
<td>0.92</td>
</tr>
<tr>
<td>Abnormal level Absent</td>
<td>Testosterone</td>
<td>9 (52.9)</td>
<td>8 (47.1)</td>
<td>17 (42.5)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>20 (50.0)</td>
<td>20 (50.0)</td>
<td>40 (100.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

End of SECOND Cycle

| Abnormal level Present             | Testosterone        | 5 (55.6)       | 4 (44.4)    | 9 (22.5)    | 1.25                     | (0.39-3.99) 0.705           |
| Abnormal level Absent              | Testosterone        | 15 (48.4)      | 16 (51.6)   | 31 (77.5)   |                           |                            |
| Total                              | 20 (50.0)           | 20 (50.0)      | 40 (100.0)  |             |                            |

* Here, p <0.05 was considered as statistically significant.

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secretion, ovarian steroidogenesis, and fibrinolysis in women with polycystic ovary syndrome. J Clin Endocrinol Metab, 82(7): 2108-2116.


