Comparison of the Effectiveness and Side Effects of Metformin XR and Metformin IR in the Management of Clomiphene Citrate Resistant PCOS

Perbandingan Efektifitas dan Efek Samping Metformin XR dan Metformin IR dalam Pengobatan PCOS yang Resisten terhadap Clomiphene Citrate

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Abstract

Objective : To assess the effectiveness and side effects of metformin XR once daily and metformin IR three times daily in the management of clomiphene citrate resistant (CC-resistant) PCOS.

Method : This is a prospective randomized controlled study conducted at Halim Fertility Centre Medan. Fifty nine CC-resistant PCOS women who met the inclusion criterias were randomly allotted into metformin XR and metformin IR groups. Twenty nine women in the metformin XR group were given 500 mg metformin XR once a day and 30 women in the metformin IR group were given 500 mg metformin IR once a day for the first week, twice a day for the second week and three times a day after the second week. All women in both group were given 10 days of 10 mg norethisterone for withdrawal bleeding and 150 mg clomiphene citrate on day 2 to day 6 of withdrawal bleeding for ovulation induction. TVS were carried out to determine the growth of follicles, ovulation and pregnancy. All women were enquired regarding the side effects of treatment at the end of the week.

Results : The baseline characteristics were not significantly different between the two groups with $p$ value of 0.999 and 0.554 for the age and BMI respectively. Statistically,
side effects of the treatment in the first week were also not significantly different between the two groups with all the p value > 0.05. However there was significant difference statistically between the two groups regarding side effects of the treatment in the second and after the second week with the average p value < 0.05 which favoured the metformin XR group. There were 2 patients dropped out from the study because of the side effects. Each in the second and after the second week. Both of them were from metformin IR group, however there weren’t statistically significant difference with the p value of 1.

The ovulation rate (65.5% vs 53.6%) and pregnancy rate (24.1% vs 17.9%) for metformin XR group vs metformin IR group respectively. Even though there were higher achievements in the ovulation and pregnancy rate for metformin XR group, there weren’t significant differences after analyzed by statistic between the two groups with the p value of 0.358 and 0.561 respectively for ovulation and pregnancy rate.

**Conclusion** : Metformin XR has better side effect profile and achieved higher ovulation and pregnancy rate as compared to metformin IR in the management of CC-resistance PCOS patients. More over metformin XR can be given once daily which can improve patients compliance with the treatment.

**Keywords** : Clomiphene citrate resistance PCOS, metformin XR, metformin IR

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**Abstrak**

**Tujuan** : Untuk membandingkan efektifitas dan efek samping metformin XR sekali sehari dan metformin IR 3 kali sehari dalam pengobatan PCOS yang resisten terhadap clomiphene citrate.

**Metode** : Penelitian prospektif acak terkendali yang dilakukan di Halim Fertility Centre Medan. Lima puluh sembilan wanita PCOS yang resisten terhadap clomiphene citrate yang memenuhi kriteria inklusi di kelompok secara acak ke dalam kelompok metformin XR dan metformin IR. Dua puluh Sembilan wanita pada kelompok metformin XR diberikan metformin XR 500 mg sekali sehari dan 30 wanita pada kelompok metformin IR diberikan metformin IR 500 mg sekali sehari pada minggu pertama, dua kali sehari...
pada minggu ke dua dan tiga kali sehari setelah minggu ke dua. Semua wanita pada kedua kelompok diberikan norethisterone 10 mg selama 10 hari untuk withdrawal bleeding dan clomiphene citrate 150 mg pada hari ke dua sampai hari ke enam withdrawal bleeding untuk induksi ovulasi. TVS dilakukan untuk memantau pertumbuhan folikel, ovulasi dan kehamilan. Semua wanita tersebut di tanyakan tentang efek samping pengobatan pada akhir minggu pengobatan.

**Hasil :** Tidak dijumpai perbedaan yang bermakna dalam karakteristik dasar antara kedua kelompok dengan nilai p = 0,999 untuk umur dan 0,554 untuk BMI. Secara statistik, tidak dijumpai perbedaan bermakna dalam efek samping pengobatan pada minggu pertama antara kedua kelompok dengan semua nilai p > 0,05. Akan tetapi dijumpai perbedaan yang bermakna secara statistik antara kedua kelompok dalam efek samping pengobatan pada minggu kedua dan setelah minggu kedua dengan rerata nilai p < 0,05 yang lebih baik pada kelompok metformin XR. Terdapat 2 wanita yang drop out dari penelitian ini yang disebabkan oleh efek samping pengobatan. Satu wanita pada minggu kedua dan 1 wanita setelah minggu kedua. Keduanya berasal dari kelompok metformin IR, akan tetapi secara statistik tidak dijumpai perbedaan bermakna dengan nilai p = 1. Rerata ovulasi adalah 65,5% dan kehamilan adalah 24,1% untuk kelompok metformin XR. Rerata ovulasi adalah 53,6% dan kehamilan adalah 17,9% untuk kelompok metformin IR. Walaupun terdapat rerata ovulasi dan kehamilan yang lebih tinggi pada kelompok metformin XR, setelah di analisa secara statistik tidak dijumpai perbedaan yang bermakna dengan nilai p = 0,358 untuk ovulasi dan 0,561 untuk kehamilan.

**Kesimpulan :** Metformin XR mempunyai efek samping yang lebih baik dan mencapai rerata ovulasi dan kehamilan yang lebih tinggi dibandingkan metformin IR dalam pengobatan wanita PCOS yang resisten terhadap clomiphene citrate. Lagi pula metformin XR dapat diberikan hanya satu kali sehari sehingga dapat meningkatan kepatuhan pasien dalam pengobatannya.

**Kata kunci :** PCOS yang resisten terhadap clomiphene citrate, metformin XR, metformin IR
Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies affecting 5%–10% of reproductive age women. This syndrome consist of combination between clinical, ultrasonographic and laboratory features such as oligo/amenorrhoea, oligo/anovulation, hirsutism, hyperandrogenaemia, specific ovarian morphology, hyperinsulinaemia and insulin resistance. 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. 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.

The exact aetiology of PCOS is unknown. However, insulin resistance with compensatory hyperinsulinemia is a prominent feature of the syndrome and appears to have a pathophysiologic role in the hyperandrogenism of the disorder, especially in those with CC resistance. Both lean and obese women with PCOS show evidence of decreased insulin sensitivity, but insulin resistance, accompanied by compensatory hyperinsulinemia, is most marked when there is an interaction between obesity and the syndrome. There is ample evidence that hyperinsulinemia results in increased ovarian androgen biosynthesis in vivo and in vitro and decreased sex hormone–binding globulin (SHBG) synthesis from the liver, leading to increased bioavailability of free androgens. This excess in local ovarian androgen production augmented by hyperinsulinemia causes premature follicular atresia and anovulation. Although this idea remains controversial, hyperinsulinemia may have a direct effect on the hypothalamus and/or pituitary to increase serum luteinizing hormone (LH) concentrations and therefore indirectly increase LH-dependent ovarian androgen biosynthesis, possibly resulting in abnormal LH and follicle-stimulating hormone (FSH) release and subsequent oligoamenorrhea. Hyperinsulinemia may also directly affect folliculogenesis and may arrest growth of antral follicles after they have reached a diameter between 5 and 8 mm.
Given the importance of hyperinsulinemia in the development of hyperandrogenism and disrupted folliculogenesis, it seems likely that medications that act as insulin-sensitizing agents may be useful in restoration of normal endocrinologic and clinical parameters of this condition. Therapeutic measures directed at lowering insulin secretion in women with PCOS should theoretically ameliorate their hyperandrogenism and restore normal follicular growth, thus facilitating ovulation\textsuperscript{11}. The most extensively studied insulin-sensitizing drug in the treatment of PCOS is metformin\textsuperscript{12,13}. Metformin (dimethylbiguanide) is an orally administered drug used to lower blood glucose concentrations in patients with noninsulin-dependent diabetes mellitus (NIDDM)\textsuperscript{14}. It is antihyperglycemic in action and does not cause hypoglycemia. Metformin enhances insulin sensitivity in both the liver, where it inhibits hepatic glucose production, and the peripheral tissue, where it increases glucose uptake and utilization in muscle tissue. By increasing insulin sensitivity, metformin reduces insulin resistance, insulin secretion, and hyperinsulinemia. Hence, metformin seems to be a perfect drug to treat patients with PCOS, including those with CC resistance\textsuperscript{12,13}. It was reported that metformin treatment for patients with PCOS improves a patient’s menstrual cycle and increases the sensitivity for the ovulation induction drug reaction, especially in women with CC-resistant PCOS\textsuperscript{11,12,13}.

Even though the use of metformin in PCOS patients so popular, until recently there was no consensus regarding the doses, when and how long the drug should been given. Many studies has been done, however the regimens been use were very wide in variety. The conventional metformin used in many studies was metformin IR, this tandard metformin suffers from the limitations of having to be administered two or three times a day and with the attendant risk of triggering gastrointestinal symptoms such as nausea, vomit, bloated, epigastric pain and diarrhea. This event making dose optimization problematic and reduced patients compliances. Some studies showed the dropout rate in the metformin group was 30\% owing to side effects\textsuperscript{15}.

To overcome the side effects and improved patients compliances of metformin treatments, the joint consensus statement from the American Diabetes Association
(ADA) and the European Society for the study of Diabetes (EASD) give advice on how to minimize poor compliance with standard metformin. In the 5 point plan for introducing metformin, the ADA/EASD draw attention to the recently introduced extended release metformin\textsuperscript{16}. Many studies showed this extended release metformin had similar efficacies, lower side effects as compared to standard immediate release metformin. It also improved patients compliances due to the simple once daily dosing\textsuperscript{17-20}.

This study aimed to assessed the effectiveness and side effects of metformin XR once daily and metformin IR three times daily in the management of CC-resistant PCOS.

**Method**

This is a prospective randomized, controlled study conducted at Halim Fertility Centre Medan. The study protocol was approved by Health Research Ethical Committee of North Sumatera c/o Medical School, Universitas Sumatera Utara. A total of 59 women with CC-resistant PCOS were recruited. The diagnosis of PCOS was based on ESHRE/ASRM 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. Clomiphene resistance was defined as failure of follicular development after CC treatment up to 150 mg daily for 5 days for two cycles. Informed consent was obtained and all baseline evaluations were carried out before entry to study. The body mass index (BMI, weight in kilograms/the square of the height in meters) was calculated. Women who were eligible and consented were randomly allotted to the metformin XR group (A) or metformin IR group (B). Randomizations were done by picking an envelope labeled AB or BA. If the AB labeled envelope was picked out, the first woman was assigned to group A and the second woman was assigned to group B. Vice versa was apply if the BA labeled envelope was picked out. The investigators and patients were not blinded to the treatment.
Women in group A were given 500 mg metformin XR once a day and women in the group B were given 500 mg metformin IR once a day for the first week, twice a day for the second week and three times a day after the second week. All women in both groups were given 10 days of 10 mg norethisterone for withdrawal bleeding and 150 mg clomiphene citrate on day 2 to day 6 of withdrawal bleeding for ovulation induction. At the end of the week, all women will be enquired regarding the side effects of the treatment. A transvaginal ultrasound (TVS) were carried out to determine the growth of follicles on day 8, 12 and 16 of withdrawal bleeding. If there was follicle with diameter ≥ 18 mm (dominant follicle), TVS was carried out daily to determined ovulation. Women were asked to have sexual intercourse after 34-36 hours every 2 day for 5 consecutive times. If there was no dominant follicle, the treatment was considered failed. Urinary pregnancy test was carried out after a week of missing period, and TVS was carried out to confirmed pregnancy. Pregnancy was defined as the presence of a gestational sac seen on TVS. All the side effects will be recorded and if the women were unable to tolerate the treatment, they will be discharged from the study.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software version 17.0 for Windows. Comparisons of baseline values, side effects, ovulation rates and pregnancy rates in the two groups were made by using the chi-square test and t-test. A p value of less than 0.05 was considered statistically significant.

Results
A total of 59 women with CC-resistant PCOS were randomized with 29 women in group A and 30 women in group B. The baseline characteristics were not significantly different between the two groups with p value of 0.999 and 0.554 for the age and BMI respectively (Table 1). We did not analyzed the baseline characteristic of parity as all the women in our study were nulliparous.
Statistically, side effects of the treatment in the first week were also not significantly different between the two groups with all the \textit{p value} > 0.05. However there was significant difference statistically between the two groups regarding side effects of the treatment in the second and after the second week with the average \textit{p value} < 0.05 which favored group A. There were 2 patients dropped out from the study because of the side effects. Each in the second and after the second week. Both of them were from group B, however there weren’t statistically significant difference with the \textit{p value} of 1 (Table 2).
Bloated 0 11 (36.7%) 0.000  
Epigastric pain 1 (3.4%) 11 (36.7%) 0.002  
Diarrhea 1 (3.4%) 7 (23.3%) 0.064  
Drop Out 0 1 (3.3%) 1.000  

After second week:  
Nausea 2 (6.9%) 14 (48.3%) 0.000  
Vomit 0 10 (34.5%) 0.001  
Bloated 1 (3.4%) 14 (48.3%) 0.000  
Epigastric pain 0 9 (31.0%) 0.004  
Diarrhea 0 9 (31.0%) 0.004  
Drop Out 0 1 (3.3%) 1.000  

\( p = \text{chi Square} \)

The ovulation rate (65.5% vs 53.6%) and pregnancy rate (24.1% vs 17.9%) for group A vs group B respectively. Even though there were higher achievements in the ovulation and pregnancy rate for group A, there weren’t significant differences after analyzed by statistic between the two groups with the \( p \) value of 0.358 and 0.561 respectively for ovulation and pregnancy rate (Table 3).

**Table 3. Ovulation and Pregnancy Rate**

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>( P )</th>
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<tbody>
<tr>
<td></td>
<td>( n = 29 )</td>
<td>( n = 28 )</td>
<td></td>
</tr>
<tr>
<td>Ovulation</td>
<td>19 (65.5%)</td>
<td>15 (53.6%)</td>
<td>0.358</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>7 (24.1%)</td>
<td>5 (17.9%)</td>
<td>0.561</td>
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</tbody>
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\( p = \text{chi Square} \)
Discussion
The beneficial effects of metformin in the management of PCOS are now well established, particular in patients with CC-resistance. One of the limiting factors, however, in the use of metformin has been its side effects, which have led to large dropout rates in many studies. These side effects were well known not only in the PCOS patients, many of NIDDM patients whose were on metformin treatment also suffered from these side effects and led to reduction in the compliance with the treatment. To overcome the side effects and improved patients compliances of metformin treatments, the joint consensus statement from the American Diabetes Association (ADA) and the European Society for the study of Diabetes (EASD) give advice on how to minimize poor compliance with standard metformin. In the 5 point plan for introducing metformin, the ADA/EASD draw attention to the recently introduced extended release metformin. Many studies showed this extended release metformin had similar efficacies, lower side effects as compared to standard immediate release metformin. It also improved patients compliances due to the simple once daily dosing.

Our study showed that simple once daily dosing of 500 mg metformin XR achieved higher ovulation and pregnancy rates as compared to 3 times daily of 500 mg metformin IR (65.5% & 24.1% VS 53.6% & 17.9% respectively) even though after analyzed did not showed any statistically significant with $p$ value of 0.358 & 0.561 for ovulation and pregnancy rate respectively. This findings are consistent with previous studies done by Hwu et al\textsuperscript{21} and Khorram et al\textsuperscript{22}. In contrast to ovulation and pregnancy rates, the side effects of the treatment showed significantly differences between the two groups which favored metformin XR group.

The primary outcome of our study is to see the effectiveness and side effects of low dose simple once daily dosing metformin XR in the management of CC-resistance PCOS patients as until recently there was no consensus regarding the used of this medication in such patients. Our study showed it had the benefits as compared to standard dosing of metformin IR.
Even though this is a simple study, only based on the clinical outcomes without any laboratories support to determine the effects of the treatment, hence it showed the benefits. To further proved the beneficial of this simple metformin XR dosing, its required more larger study with clinical and laboratories support to evaluate the effects of this treatment.

Conclusion
Metformin XR has better side effect profile and achieved higher ovulation and pregnancy rate as compared to metformin IR in the management of CC-resistance PCOS patients. More over metformin XR can be given once daily which can improve patients compliance with the treatment.

References


