ATLANTIS PRESS

Advances in Health Sciences Research, volume 26

2nd Bakti Tunas Husada-Health Science International Conference (BTH-HSIC 2019)

Evaluation of Label Drug in the Treatment Polycystic Ovary Syndrome

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***Abstract*—Objectives: Polycystic ovary syndrome (PCOS) is defined as high levels of hyperandrogenism, menstrual irregularities, anovulation and high levels of insulin (hyperinsulinemia secondary to increased insulin resistance).The estimated that> 75% of women with PCOS are insulin resistant, the incidence of PCOS affects 4% -8% of reproductive-aged women. The aims of this study to an evaluation of metformin treatment of PCOS. This research was a cross-sectional study with prospective data collection conducted From January to May 2019. Data from 16 participants were involved in this study, with the criteria inclusion. Data were processed statistically using Paired Sample T-test analysis to determine the effectiveness and side effects of metformin. There was a significant difference between the thickening of the endometrium before and after metformin treatment (P 0.001 <0.005). In observing the side effects, it was found that the use of metformin treatment was seen from random plasma glucose measurements on day 0, 3, 6 and 9 obtained (P 0.009<0.005) there were significant differences between the groups of random plasma glucose measurement days 0, 3, 6 and 9.**

Keywords: off label, ovary, polycystic, syndrome

I. INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common disorder affecting 15–20% of the women in reproductive age worldwide. (PCOS) is a heterogeneous disorder characterized by hyperandrogenism, insulin resistance and chronic anovulation [1]. Several factors are correlated with the development of PCOS, including insulin resistance (found in 50–70% of the patients with PCOS) (2). Clomifene citrate and metformin have been increasingly used off-label for the treatment of polycystic ovary syndrome (PCOS) Clomifene citrate and metformin which are often used to increase insulin sensitivity and reduce insulin resistance, are considered the first-line ovulation-inducing drugs in PCOS either alone or in combination(3). Effectiveness of using metformin and clomifene citrate can be seen from the results of the ultrasound that will endometrial thickness in patients with PCOS, the endometrium normal is 3 mm whereas in patients PCOS has a thick endometrium abnormal and seen from the results of the treatment which will show the respondent can ovulate(4).

II. MATERIAL AND METHOD

Desain Study

In this cross-sectional observational study, 16 subjects were included. which conducted from January to May 2019 The inclusion criteria were women with PCOS, Treatment with metformin, informed consent approved All participants had given written informed consent. The study was approved by ethics committee Universitas Padjajaran Bandung with number 224/UN6.KEP/EC/2019.

A. Adherence

Self-reported medication adherence was measured by the MMAS-8. The scale consists of eight questions, first, seven items having a dichotomous answer (yes/no) that indicates adherent or non-adherent behavior.

B. Adverse Drug Reaction

The Naranjo algorithm scale was used for causality assessment Adverse Drug Reaction in a participant who gets metformin treatment.

C. Analysis

The data were analyzed using the *T*-test and *One Way Anova test* method using SPSS version 24.00.

III. RESULTS

Table 1. Participant Based on Marital Status

Status	∑	Percent (%)
Married	2	12.5
Single	14	87.5

The most of participant in married status, because respondents who are married will pay more attention in the reproductive system, especially to have a child, so it can be said that respondents who are married will pay more attention to the health of the reproductive system than a single participant.

Table 2. Profile of a drug for Therapy PCOS in Participant

Drug	∑	Percent (%)
Metformin	4	28
Metformin+ Ethinyl estradiol, drospirenone	3	18
Metformin+ Ethinyl estradiol, cyproterone acetate	5	32
Metformin+Clomiphen Citrate (CC)	4	25

Base on Table 2, respondents using metformin (25%), a combination of metformin with Ethinyl estradiol, drospirenone there are 3 respondents (18%), metformin with hormone Ethinyl estradiol, cyproterone acetate. Five 5 respondents (32%) and combination metformin with clomiphene citrate there are 4 participants (25%), use of this drug-related to the recommended therapy According to National Health and Medical Research Council (NHMRC) PCOS therapy for the main therapy that is used drugs metformin, then used therapy a combination of metformin with clomiphene citrate and for second therapy is the use of hormones. CC will bind to estrogen in the hypothalamus which will stimulate and accelerate the formation of FSH (follicle stimulating Hormone) (5).

The effectiveness of metformin in PCOS

Based on the results of analysis Paired T-Test statistics obtained P-value 0.001 <0.05. The significant differences between the thickness of the endometrium on day 0 before using metformin thickly endometrium on the 30 days after the use of metformin. Ultrasound results before use of metformin on days 0 and after using metformin on the 30 days.

Table 3. Endometrial thickness before and after therapy

Before treatment (mm)	After treatment (mm)	P< 0.05)
7,8	6	
7,5	4,8	
7	4,5	
7,4	6,7	
6,5	4,7	
13	15	
7,5	4	0,001
8,1	7,3	
6	5,6	
6,1	4,9	
7,1	6,7	
6,8	5,6	
7,3	6,4	
6,6	5	
8,8	8	

No significant relationship between patient compliance with therapeutic success conducted by related PCOS respondents with the use of this drug metformin because this research has a thing limitations in time due to therapy or PCOS treatment has the most therapy short for at least 3 months and will continue to be, results of research shows a change in PCOS respondent endometrial thickness at on the day PCOS was diagnosed and at when the respondent controls after 3-4 weeks treatment, but thickness changes. This endometrium has not been demonstrated therapeutic success until ovulation or a normal menstrual cycle occurs. Can be seen in Table 3 thickness changes endometrium before and after treatment of metformin and adherence scores which shows PCOS patients have scored high adherence.

Table 4. Endometrial thickness and adherence

Before treatment metformin (mm)	After treatment (mm)	MMAS 8 Score	P< 0.05)
7,8	6	9	
7,5	4,8	6	
7	4,5	9	
7,4	6,7	10	
6,5	4,7	9	
13	15	10	
7,5	4	9	
8,1	7,3	8	
6	5,6	11	0.357
6,1	4,9	9	
7,1	6,7	10	
6,8	5,6	9	
7,3	6,4	9	
6,6	5	10	
8,8	8	8	

Adverse Drug Reaction in PCOS therapy

An adverse drug reaction (ADR) is an unwanted, undesirable effect of a medication that occurs during usual clinical use. Results from random plasma glucose measurements are conducted with 4 measurement groups i.e. on day 0, day 3, day 6 and day 9 is processed by One Way statistical test Anova shows normally distributed data and variations inhomogeneous data obtained P-value 0.009 <0.05 this result shows that there are differences significant from intergroup measurements random plasma glucose on day 0, day 3, day 6 and on day 9 showed a decrease in sugar this blood occurs due to the use of drugs the metformin the therapy.

Table 5. Random Plasma Glucose concentration

Random plasma glucose level (mg/dL)				P< 0,05
Day 0	Day 3	Day 6	Day 9	
178	168	153	150	
170	161	147	158	
200	173	170	160	
185	189	179	159	
173	170	180	161	
173	180	161	169	
181	176	179	186	
183	179	181	180	0,009
189	179	175	171	
181	178	177	168	

168	171	169	175
183	173	177	171
182	180	179	181
176	174	179	171
194	189	186	188
188	181	178	175

Naranjo's algorithm is a score of 0 (Doubtful) which means it is not a side effect, 1-4 (Possible) may be a side effect, 5-8 (Probable) most likely to occur side effects from a suspected drug, and ⩾ 9 (Definite) occurs incidence of side effects (6).

Table 6. Adverse drug reaction Naranjo Scale

Naranjo Scale	∑ Participant	Percent (100%)
0 (Doubtful)		
1-4 (Possible)		
5-8 (Probable)	16	100
9 (Definite)		
Total	16	100

This combination is often used to treat ovulation dysfunction in women with PCOS but related to side effects that arise in the short term namely headaches, nausea, changes in atmosphere liver, pimples or breast pain, and deep long term, risk of thromboembolic events or breast cancer (7)

IV. DISCUSSION

WHO showing that in 2010 there were 46.5 million couples worldwide unable to have children, a condition when women have a desire to have children but are unable to do so because there are problems in their endocrine system, one of which is women with involuntary childlessness or PCOS (8)

PCOS is a risk factor endometrial hyperplasia or the thickening of the uterine wall. PCOS has high levels of the hormone estrogen which is not balanced with the hormone progesterone so that it will continue to cause thickening of the uterine wall (7). Combination of metformin with the PCOS hormone has been medically treated with progesterone oral (alone or in combination with estrogen in PCOS. This combination is often used to treat ovulation dysfunction in PCOS this treatment combination provides the benefits of maintaining fertility (7). Which method used to measure adherence using the Morisky Medication questionnaire Adherence Scale (MMAS-8). After scores obtained from the results of the study show scores on a scale > 8 shows the respondent has adherence high by looking at the correlation of results measurement of Adherence as measured by therapeutic success in PCOS respondents by looking at the thickness of the endometrium will be tested using statistical analysis Spearman The results show strength relationship between PCOS participant Adherence with the success of PCOS therapy with value correlation coefficient 1, shows that the correlation is perfect or there is a relationship perfect. The participant has high adherence then it will affect the success of that therapy used in PCOS, where success PCOS therapy can be seen from the shrinking endometrial thickness and ovulation (9).

Adverse drug reactions occur almost daily in health care institutions and can adversely affect a patient's quality of life, often causing considerable morbidity and mortality (10). ADR obtained can be of a decrease in random plasma glucose, are GI disorders such as nausea, dizziness feeling weak abdominal pain, bloating or diarrhea. (11)

The mechanism of metformin which causes vomiting, use metformin has a pharmacological action of activation serotonin selective receptor type 3 (5-HT 3) which causes gastrointestinal disorders like nausea and vomiting. Use metformin can trigger the onset of taste dizzy with the use of metformin is one of the symptoms of hypoglycemia (12). ADR from metformin in PCOS therapy is given combination using hormones, PCOS has medically treated with oral progestogens (alone or combined with estrogen in PCOS).

V. CONCLUSION

The effectiveness of metformin can be seen from the thickness of the endometrium before usage and after use metformin and processed statistically obtained p = 0.001 <0.05 significant between endometrial thickness before the use of metformin and after use of metformin. Side effects of metformin in therapy PCOS include nausea, dizziness, and random plasma glucose concentration reduction. Based on research results p= 0.009 <0.05 shows that there are differences significant from intergroup measurements random plasma glucose concentration on day 0, day 3, day 6 and 9 days, and seen from the Naranjo algorithm which shows the probable meaning the possibility of ADR from a drug be suspected.

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