Research Article

Role of Lifestyle Modification through Dietary Changes to Endometrial Receptivity on Infertility Women and Obesity with Polycystic Ovary Syndrome

Peran Perubahan Gaya Hidup melalui Perubahan Pola Diet terhadap Reseptivitas Endometrium Perempuan Infertil dan Obesitas dengan Sindrom Ovarium Polikistik

Julianto Witjaksono[1], Fiastuti Witjaksono[2], Andhika A. Perdana[1]

[1]Department of Obstetrics and Gynecology
[2]Department of Clinical Nutrition
Faculty of Medicine Universitas Indonesia
Dr. Cipto Mangunkusumo General Hospital Indonesia
Jakarta

Abstract

Objective: To investigate the effect of lifestyle modification on endometrial receptivity of obese women with polycystic ovary syndrome using ultrasonography.

Methods: This observational study was conducted at Dr. Cipto Mangunkusumo General Hospital Jakarta from August 2019 to May 2020. A total of 14 subjects were participated in this study. The subjects were advised to get nutrition counseling by nutritionist and then followed up the endometrial profiles for 6 months by ultrasonography.

Results: A total 19 subjects were received nutrition counseling by Clinical nutritionist, but then, only 14 subjects were evaluated the endometrial study by Ultrasonography. There were several significant result between before and after treatment some subjects such as calories, body weight, body mass index, waist circumference ($p<0.05$) and type of the endometrial vascular zone, endometrium volume, and vascular flow index by ultrasonography ($p<0.05$). In this study, no significant results have been found on the correlation between dietary changes and changes in endometrial receptivity profiles.

Conclusions: No significant correlation was observed between changes in anthropometrics and daily calorie intake with changes in endometrial vascular zones.

Keywords: endometrial receptivity, obese, polycystic ovary syndrome, ultrasonography.

Abstrak

Tujuan: *Untuk mengetahui pengaruh modifikasi gaya hidup pada reseptivitas endometrium perempuan obesitas dengan sindrom ovarium polikistik menggunakan ultrasonografi.*

Metode: *Penelitian observasional ini dilakukan di Rumah Sakit Umum Cipto Mangunkusumo Jakarta dari Agustus 2019 hingga Mei 2020. Sebanyak 14 subjek berpartisipasi dalam penelitian ini. Semua subyek disarankan untuk mendapatkan konseling gizi oleh ahli gizi dan dilakukan observasi profil endometrium selama 6 bulan dengan ultrasonografi.*

Hasil: *Sebanyak 19 subjek menerima konseling gizi oleh ahli gizi klinis, tetapi kemudian, hanya 14 subjek yang dievaluasi profil endometrium dengan Ultrasonografi. Ada beberapa hasil yang signifikan antara sebelum dan sesudah perawatan beberapa subjek seperti kalori, berat badan, indeks massa tubuh, lingkar pinggang ($p<0,05$) dan tipe zona vaskular endometrium, volume endometrium, dan indeks aliran vaskular dengan ultrasonografi ($p <0,05$). Dalam penelitian ini, tidak ditemukan hasil yang signifikan pada korelasi antara perubahan pola makan dan perubahan dalam profil reseptivitas endometrium.*

Kesimpulan: *Tidak ada korelasi yang signifikan antara perubahan antropometrik dan asupan kalori harian dengan perubahan zona vaskular endometrium.*

Kata kunci: *endometrium, obesitas, reseptivitas, sindrom ovarium polikistik, ultrasonografi.*

Correspondence author. Andhika A. Perdana. doctordhika@gmail.com

Received: July 24 2020. Accepted: December 31, 2020. Published: January 2021

INTRODUCTION

Polycystic Ovary Syndrome was the most (85%) form of ovulation disorders that causes type II infertility according to World Health Organization and being one of the most common endocrinopathies and affects 5% to 10% of childbearing age women.[1, 2] Obesity exacerbates the condition due to increased androgen levels so responsible to occur the symptom of polycystic ovary syndrome such as chronic anovulation.[3] At Dr. Cipto Mangunkusumo General Hospital, about 73% of obesity has been observed among polycystic ovary syndrome women.[4]

Obesity and Polycystic Ovary Syndrome (PCOS) have an impact on the capacity of the endometrium to accept the results of conception.[5] Therefore, nowadays endometrial receptivity is being considered as one determinate factor responsible for infertility treatment. A study conducted in 2010 concluded that pregnancy rates for clomiphene citrate users were only 12.2%, but lifestyle modification, succeed to increase the pregnancy rate of PCOS patients up to 20%.[6]

Examination of endometrial receptivity by the biopsy endometrial dating method done by Noyes since 1950 until now has a weakness, due to it's traumatic clinical procedures carried out during period of embryo implantation. So that this procedure does not become a standard of endometrial receptivity examination.[7, 8] Then ultrasonography has replaced as an important role in the evaluation and treatment of endometrial receptivity in infertility patients because it is expected to be more efficient, cost-effective and a traumatic clinical proceeding procedures.[9]

treatment on endometrial receptivity using ultrasonography. Therefore this study emphasizes the effect of lifestyle modification trough dietary changes on endometrial receptivity of obese women with PCOS using ultrasonography.

METHODS

This was a prospective longitudinal observational study that investigated at the effect of diet controlled by clinical nutritionist in infertile women with PCOS on changes in endometrial vascular zone. This study was conducted at Yasmin Clinic Dr. Cipto Mangunkusumo General Hospital Jakarta from August 2019 to May 2020. Women in reproductive age (20–35 years) women with PCOS, suffered of primer or secondary infertility, obesity according to Asia Pacific WHO criteria we included in this study.

The subject received clinical nutrition interventions by clinical nutritionist once a week in first control, and then once every two weeks until once a month. Every subject that has given intervention also did clinical anthropometrics and daily intake measurement. The subjects also performed ultrasound examination at the first control and then evaluated again in the third month and/or in the sixth month in between 19 to 21 day of menstrual cycle after check the progesterone level. The subjects that become pregnant were considered as intension to treat subject and still included in the study results. This study was approved by ethical committee of Faculty of Medicine, Universitas Indonesia number 596/UN2.F1/ETIK/PPM.00.02/2019.

RESULTS

A total 32 subjects who were willing to participate and meet the inclusion and exclusion criteria were recruited. After the initial ultrasound examination process, subjects were immediately educated about the importance of changing lifestyles in the form of diets and direct physical activity by nutritionist. But, at the end of study there were only 14 subjects that completed the study and 18 subjects were drop out. Baseline characteristics of 14 subjects that had been completed the study can be seen on Table 1.

Table 1. Baseline Characteristics of Subjects

Variable	N (%)	Mean ± SD
Age (year)		30 ± 2.75
Domicile		
Bogor	5 (35.7)	
Bekasi	3 (21.4)	
Tangerang	1 (7.1)	
Cikarang	1 (7.1)	
Jakarta	4 (28.6)	
Education		
High School	2 (14.3)	
University degree	12 (85.7)	
Infertility		
Primer	10 (72)	
Secondary	4 (28)	
Length of Married (years)		4.86 ± 2.21
History of menstrual cycle		
Irreguler	2 (14.3)	
Oligomenorhea	10 (71.4)	
Secondary amenorrhea	2 (14.3)	
Occupation		
Housewife	4 (28.6)	
General employees	6 (42.9)	
State employees	1 (7.1)	
Business woman	3 (21.4)	
Body mass index (kg/m2)		30.0 ± 3.4
Body weight (kg)		75.2 ±11.9
Height (cm)		156.5 ±3.5
Waist size (cm)		98.5 ± 10.0

In all subjects both in the ovulatory and anovulatory cycles group, a significant ratio (p = 0.001) was obtained between the daily calorie intake before and after receiving medical therapy by a clinical nutrition specialist. All subjects were able to decrease by an average of 374.6 calories until the end of the study. Overall, there was also a significant comparison (p = 0.008) in body weight before and after receiving medical therapy by a clinical nutrition specialist, although it did not show statistical significance in each group. The mean weight loss in the group that had an ovulatory cycle was greater than the anovulatory one which was 4 kg compared to 1.8 kg.

Overall there was also a significant difference (p = 0.036) on the Body Mass Index before and after receiving medical therapy by a clinical nutrition specialist, although it did not show statistical significance in each group. In the group of subjects who experienced ovulatory cycles, the mean decrease in waist size was 6.7 cm until completed the study compared to the average decrease in waist size in the group of subjects who experienced anovulatory cycle, the mean decrease in waist size was 5 cm. As can be seen on table 2.

Table 2. Calorie Intake and Clinical Anthropometry, According to Clinical Nutrition Intervention in 14 Subjects

		Ovulatory Cycle (n=6)			Anovulatory Cycle (n=8)			Comparison between the ovulation and anovulation Cycle			Total (n=14)		
	Unit	**Pre**	**Post**	***P-value***	**Pre**	**Post**	***P-value***	**Ovulatory**	**Anovulatory**	***P-value***	**Pre**	**Post**	***P-value***
Calorie*	Calorie	1755.7 (±353.8)	1409.6 (±479.6)	0.014	1494.7 (±278.1)	1099 (±225.7)	0.029	346.1	395.7	0,391	1606.6 (±328.2)	1232 (±375.9)	0.001
Weight*	Kg	70.9 (±10.9)	66.9 (±9.1)	0.050	78.5 (±12.35)	76.7 (±10.9)	0.100	4.04	1.83	0,050	75.2 (±11.9)	72.5 ± 11.0	0.008
BMI*	Kg/m^2	28.5 (±1.5)	27.1 (±1.6)	0.073	31.2 (±4.0)	30.9 (±3.6)	0.392	1.34	0.33	0,016	30.0 (±3.4)	29.3 (±3.4)	0.036
Waist Size*	cm	95.7 (±10.8)	89.0 (±12.3)	0.036	100.7 (± 9.4)	95.7 (±9.3)	0.069	6.62	5.00	0,872	98.5 (±10.0)	92.8 (±10.8)	0.004

*Note. Normal Distribution, ** Abnormal Distribution*

In the ultrasound profile of endometrial vascular zone type, groups experiencing ovulatory cycles found significant differences (p = 0.026) from vascular zones 1 to 3 compared to groups undergoing anovulatory cycles. In all subjects both in the ovulatory cycle group and the anovulatory cycle group there was an increase in endometrial volume and an increase in the Vascular Flow Index which were all statistically significant (p <0.05). There has not been a statistically significant increase in the flow index of subjects who have received medical therapy by a clinical nutrition specialist. As can be seen on table 3.

Table 3. Ultrasound Picture of Endometrial Receptivity after Clinical Nutrition Intervention in 14 Subjects.

		Ovulatory Cycle (n=6)			Anovulatory Cycle (n=8)			Total (n=14)**		
	Unit	**Pre**	**Post**	***P-value***	**Pre**	**Post**	***P-value***	**Pre**	**Post**	***P-value***
Type ZV**		1 (1-3)	3 (1-4)	0.026	1 (1-2)	2 (1-4)	0.066	1 (1-3)	3 (1-3)	0.005
VE*	cm^3	1.67 (±1.03)	3.44 (±1.34)	0.025	1.80 (±1.23)	3.82 (±2.01)	0.039	0.033 (0 – 1.88)	0.747 (0 – 10.94)	0.002
FI*	%	1.67 (±1.03)	3.44 (±1.34)	0.173	19.75 (±13.47)	16.90 (±11.16)	0.199	21.7 (0 – 34.17)	21.2 (0 – 31.12)	0.695
VFI**	%	0.02 (0 – 1.88)	2.87 (0 – 5.33)	0.028	0.067 (0 – 0.91)	0.694 (0 – 10.94)	0.028	0.033 (0 – 1.88)	0.747 (0 – 10.94)	0.002

*Note. Normal Distribution, ** Abnormal Distribution*

In this study, the Spearmans method obtained a positive correlation (r >1) between changes in body weight, body mass index and waist circumference of 14 subjects who received medical therapy by a clinical nutrition specialist with changes in endometrial vascular zones, although not statistically significant (although not statistically significant (p >0.05). While the correlation between changes in calories with changes in endometrial Vascular Zone in this study is negatively correlated (r <1). As can be seen on table 4 and figure 1.

Table 4. Effects of Lifestyle Changes on Endometrial Vascular Zone in 14 Subjects

Variable Factor	VZ		EV		FI		VFI	
	P-value	r	*P-value*	r	*P-value*	r	*P-value*	r
Weight	0.774	0.084	0.982	-0.007	0.325	-0.284	0.313	0.291
BMI	0.646	0,135	0.875	0.046	0.343	-0.274	0.166	0.392
Waist Size	0.191	0.372	0.731	0.101	0.940	-0.022	0.413	0.238
Calories	0.768	-0.087	0.281	-0.310	0.736	-0.099	0.994	0.002

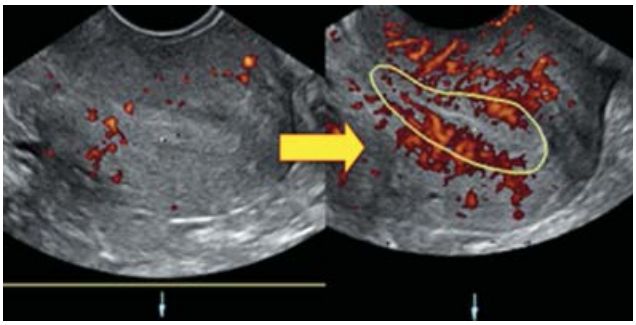

Figure 1. Example of Vascular Zone before and after receive clinical nutrition interventions

DISCUSSION

According to our analysis this is due to the difficulty of changing patients perceptions that lifestyle changes in the form of diet and exercise are first-line management of PCOS treatment, most subjects want to get drugs or actions immediately without any lifestyle changes. This opinion has been refuted in a study that the pregnancy rate of Clomiphene citrate users was only 12.2% while another case with lifestyle changes from the study can increase the pregnancy rate of PCOS patients to 20%.[6]

Seventy one point four percent of the subjects were workers / self-employed so that it became an obstacle to arrange the time to come to the RSCM. Likewise, in 28.6% of the subjects who, although they were a housewife, still found it difficult to regulate their diet and exercise because they were not used to it in their daily lives, especially during this covid-19 era that demanded for people stay at home more and not have activities outside the house. This is correlate with a study revealed that the incidence of obesity is closely related to various physical activities that can be done, the fatter a woman will be lazy to move and do physical activities.[10] Other studies revealed that with increasing time to watch television the physical activity will be reduced will further increase the occurrence of obesity.[11] Another study conducted in Mexico states that the lack of relaxing time to regular exercise is the key to increasing rates of obesity among career women.[12]

All subjects in this study also did physical activity in the form of footsteps that were monitored through a mobile phone application and regular light exercise weekly and managed to achieve a pregnancy rate of 21.4% (3 subjects). This is in line with research who have concluded that by reducing the diet 500 Calories / day consisting of 50-60% carbohydrates, 25-30% fat, 15-20% protein accompanied by risk-free activities such as climbing stairs, relaxing walks, for at least 30 minutes 3 to 5 times a week for 6 months can increase pregnancy rates by 20%.[6]

The coefficient (r) is the closest to 1 in the correlation between decreasing waist size and increasing endometrial vascular zone. This is consistent with statement from WHO that the increasing waist circumference is associated with higher visceral obesity which can increase the occurrence of metabolic syndromes such as insulin resistance.[13] In accordance with a review conducted by Schulte about insulin resistance which is wrong one cause of worsening in endometrial receptivity in PCOS obese patients due to the effects of accumulation of free fatty acids (FFA) resulting from visceral fat.[5]

There has not been found any significant correlation between changes in body weight, body mass index and waist circumference and daily calorie intake with changes in endometrial vascular zones due to high loss to follow-up rates and uncontrolled daily caloric intake for each subject, even in some subjects there are actually increased daily calorie intake because of this. However, in general there were significant differences in the endometrial receptivity of

subjects who had received medical therapy by clinical nutrition specialists as evidenced by the p value <0.05 on the vascular zone type, endometrial volume and Vascular Flow Index values for all subjects. An increase in median vascular zone type 1 to 3 according to Sonal research can increase pregnancy rates from 8.3% to 33.8%. Increasing endometrial volume in a group of subjects undergoing an ovulation cycle from 1.67 to 3.44 cm3 can increase pregnancy rates to 47%. The increase in the percentage of Vascular Flow Index from 0.02 to 2.87% in the group of subjects with ovulation cycle also according in the same year was able to increase the pregnancy rate to 41.4%.[14]

A total 14 subjects at the beginning of the study had obtained clomiphene citrate as standard management of PCOS. However, in this study until the end of the study of 14 patients only 3 subjects were assessed for their endometrial receptivity because of the value of progesterone >10 ng / ml, the remaining 3 more patients were confirmed pregnant so that a total of 6 patients were considered to be ovulating according, regarding progesterone levels ≥ 10 ng / ml in the middle luteal phase can be a marker of ovulation in normal women.[15] The review said that 75 - 80% of patients with PCOS will ovulate after the use of Klomifen citrate, but in this study the percentage of ovulation was 42%.[16] Possible causes of clomiphene citrate failure are obesity, insulin resistance and hyperandrogen which besides requiring clomiphene citrate must also lose weight by 5-10% in the form of lifestyle changes. The possibility in these subjects that the progesterone value is still low is because it is still in the late proliferation phase or early ovulation phase so there has not been an increase in progesterone levels. Therefore, in the future these subjects still have to wait for ovulation if they want to assess their endometrial receptivity, even if we look at the current ultrasound picture of endometrium, we can also see improvements in the endometrium.

The limitation of this study is the still high loss to follow up rate (56%) which is probably due to the difficulty of changing lifestyles without a strong desire from the subjects involved in the study. Another possibility is the lack of the process of taking research subjects where the patients taken in this study were not purely patients who went to RSCM but were invited patients through social media that are located far away from the RSCM so that it becomes an obstacle to follow the control process by the clinical nutrition department. In addition, this study is still observational in nature, so there is no uniformity in the level of obesity or metabolic syndrome in each subject, as well as the amount of daily calorie intake and the type of daily physical activity on each subject so as to make different results on each subject of research.

CONCLUSION

No significant correlation was found between changes in body weight, body mass index and waist circumference and daily calorie intake with changes in endometrial vascular zones due to high loss to follow-up rates and uncontrolled daily caloric intake for each subject. However, in general there were significant differences in the endometrial receptivity of subjects who had received medical therapy by clinical nutrition specialists.

ACKNOWLEDGEMENT

The author thanks Department of Obstetrics and Gynecologic Universitas Indonesia, Dr. Cipto Mangunkusumo National General Hospital for support of this publication.

AVAILABILITY of DATA and MATERIAL

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT of INTERESTS

None to declare.

FUNDING

None.

REFERENCES

1. Roe, A. H.; Dokras, A., The diagnosis of polycystic ovary syndrome in adolescents. Rev Obstet Gynecol. 2011;4 (2): 45-51.
2. In Fertility: Assessment and Treatment for People with Fertility Problems, London. 2013.
3. Domecq, J. P.; Prutsky, G.; Mullan, R. J.; Hazem, A.; Sundaresh, V.; Elamin, M. B.; et al,. Lifestyle modification programs in polycystic ovary syndrome: systematic review and meta-analysis. J Clin Endocrinol Metabol. 2013; 98 (12): 4655-63.

4. A, H., Current updates on Policystic Ovary Syndrome Endometriosis Adenomyosis. Sagung Seto. 2014.
5. Schulte, M. M. B.; Tsai, J.-h.; Moley, K. H., Obesity and PCOS. Reprod Sci. 2014; 22 (1): 6-14.
6. Karimzadeh, M. A.; Javedani, M., An assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate-metformin in patients with polycystic ovary syndrome. Fertil Steril. 2010; 94 (1): 216-20.
7. Noyes, R. W.; Hertig, A. T.; Rock, J., Dating the endometrial biopsy. AJOG. 1975; 122 (2): 262-3.
8. Sterzik, K.; Abt, M.; Grab, D.; Schneider, V.; Strehler, E., Predicting the histologic dating of an endometrial biopsy specimen with the use of doppler ultrasonography and hormone measurements in patients undergoing spontaneous ovulatory cycles. Fertil Steril. 2000; 73 (1): 94-8.
9. Ivanovski, M., The Role of Ultrasound in the Evaluation of Endometrial Receptivity Following Assisted Reproductive Treatments. In In Vitro Fertilization - Innov Clin Lab Aspects. 2012. doi: 10.5772/38592
10. O' Brien, W.; Belton, S.; Issartel, J., The relationship between adolescents' physical activity, fundamental movement skills and weight status. J Sports Sci. 2016; 34 (12): 1159-67.
11. Christofaro, D. G.; De Andrade, S. M.; Mesas, A. E.; Fernandes, R. A.; Farias Júnior, J. C., Higher screen time is associated with overweight, poor dietary habits and physical inactivity in Brazilian adolescents, mainly among girls. Eur J Sport Sci. 2016; 16 (4): 498-506.
12. Coll, J. L.; Bibiloni, M. e. M.; Salas, R.; Pons, A.; Tur, J. A., Prevalence and Related Risk Factors of Overweight and Obesity among the Adult Population in the Balearic Islands, a Mediterranean Region. Obes Facts. 2015; 8 (3): 220-33.
13. WHO, Waist Circumference and Waist–Hip Ratio: Report of a WHO Expert Consultation. WHO. Ed. Geneva. 2011: 19.
14. Chaitanya, P. S. N., Role of 3D and 3D Power Doppler to Assess Endometrial Receptivity in IUI Cycles. Int J Infertil Fetal Med. 2010; 1 (1): 19-24.
15. Leiva, R.; Bouchard, T.; Boehringer, H.; Abulla, S.; Ecochard, R., Random serum progesterone threshold to confirm ovulation. Steroids. 2015; 101: 125-9.
16. Homburg, R., Clomiphene citrate-end of an era? A mini-review. Hum Reprod. 2005. 20; (8): 2043-51.