Original Article:

Efficacy of Omega-3, -6, and -9 Fatty Acids, Alone or in Combination With Low Dose Aspirin, in Improvement of Uterine Blood Flow in Women With History of Recurrent Miscarriage: A Prospective, Randomized, Clinical Trial

Shahram Ala[1*], Sepideh Payvandi[2], Maryam Barzin[3], Mahdieh Tavajoh[1], Hamidreza Samaei[1]

1. Pharmaceutical Sciences Research Center, Department of Clinical Pharmacy, School of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.
2. Department of Obstetrics and Gynecology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
3. Department of Radiology, Imam Khomeini Hospital, Mazandaran University of Medical sciences, Sari, Iran.

*** Corresponding Author:**
Shahram Ala, PhD.
Address: Pharmaceutical Sciences Research Center, Department of Clinical Pharmacy, School of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.
Phone: +98 (113) 354 3729
E-mail: sh204ala@gmail.com

Copyright© 2020, The Authors.

Article info:
Received: 11 Feb 2021
Accepted: 12 Jun 2021

Keywords:
Recurrent miscarriage, Omega-3, -6, and -9, Aspirin, Uterine blood flow

ABSTRACT

Background: Much evidence suggests that increased uterine blood flow resistance (reduced uterine perfusion) raises the risk of Recurrent Miscarriage (RM).

Objectives: This study aimed at evaluating the efficacy of omega-3, -6, and -9 fatty acids, alone or in combination with aspirin, in reducing uterine blood flow resistance in women with a history of RM.

Methods: A total of 45 women with a history of two or more miscarriages and increased uterine artery blood flow resistance were included in this randomized clinical trial. They were randomly assigned to aspirin (80 mg/d) (group A, n=15), omega-3, -6, and -9 fatty acids (4800 mg/d) (group O, n=15), or combination therapy (group AO, n=15). The patients were visited after two months, and the uterine artery blood flow resistance was measured by Doppler sonography.

Results: The Mean±SD age of participants was 32±3.5 years in group A, 32±3 years in group O, and 32.4±3 years in group AO. There was no significant difference between three groups in age (P=0.7), duration of marriage (P=0.55), duration of infertility (P=0.43) and number of previous miscarriages (P= 0.51). In all three groups, after two months of treatment, the average uterine artery blood flow resistance reduced considerably compared with the beginning of the trial (P=0.0001); however, there was no significant difference between the three groups (P=0.56).

Conclusion: According to the study results, omega-3, -6, and -9 fatty acids can reduce uterine artery blood flow resistance and improve the uterine blood flow in women with RM, with equal efficacy to aspirin. Also, combination therapy offers no advantages over monotherapy.

Citation Ala S, Payvandi S, Barzin M, Tavajoh M, Samaei HR. Efficacy of Omega-3, -6, and -9 Fatty Acids, Alone or in Combination With Low Dose Aspirin, in Improvement of Uterine Blood Flow in Women With History of Recurrent Miscarriage: A Prospective, Randomized, Clinical Trial Pharmaceutical and Biomedical Research. 2022; 8(1):43-52. http://dx.doi.org/10.18502/pbr.v8i1.9387

http://dx.doi.org/10.18502/pbr.v8i1.9387

Introduction

Recurrent Miscarriage (RM) refers to three or more consecutive or non-consecutive spontaneous miscarriages, affecting 2%-5% of couples [1-3]. The causes of RM are genetic, anatomical, endocrinological, immunological, microbiological, and environmental. However, many cases of miscarriages remain with no defined etiology [4, 5]. Although RM has been the subject of several studies, vascular changes associated with RM have not been sufficiently studied. It has been well documented that high blood flow resistance and abnormal uterine perfusion at implantation are associated with reduced conception and increased risk of miscarriage [6-11].

Therefore, it is reasonable that vasoactive substances may benefit patients with impaired uterine perfusion. Low dose aspirin has been reported to improve uterine perfusion and pregnancy outcome [12, 13]. Aspirin, at low doses, inhibits the synthesis of Thromboxane A2 (TxA2) by the platelets and shifts the TxA2/Prostaglandin I2 (PGI_2) ratio toward the dominance of PGI_2, which results in vasodilation [14]. In addition, aspirin is supposed to reduce the excretion of TxA2 from endometrial cells and reduce the TxA2 levels at the site of embryo implantation, which is crucial for a successful pregnancy [12, 15].

Polyunsaturated Fatty Acids (PFAs) have been introduced as a new therapeutic category for the management of RM. PFAs can decrease platelet reactivity, reduce blood pressure and improve vessel wall characteristics and blood rheology, thus having beneficial effects in women with abnormal uterine artery blood flow [16]. Maternal omega-3 supplementation can prevent pregnancy complications, such as preterm delivery, fetal growth restriction, and improve fetal neurological development [17]. It seems that PFAs can act as substrates for the same enzyme system of prostaglandins and competitively inhibit cyclooxygenation, reducing TxA2 production by platelets and vasodilation [18-22]. However, there are very few available data on the efficacy of PFAs in RM [3, 23].

Because of RM undesirable outcomes in women and the availability of omega-3, -6, -9, and aspirin medications, this study was conducted to evaluate the efficacy of omega-3, -6, and -9 fatty acids, alone or in combination with low dose aspirin, in the improvement of uterine blood flow in women with a history of RM due to abnormal uterine artery blood flow.

Materials and Methods

The study was approved by the Research Ethics Committee of Mazandaran University of Medical Sciences and registered at the Iranian Registry of Clinical Trials (registration code: IRCT201103253014N3, the whole trial protocol could be accessed at: www.irct.ir). The trial was conducted according to the Declaration of Helsinki. The written informed consent was obtained from all patients before recruitment.

Trial design

This study was a prospective, randomized clinical trial and was carried out at Imam Khomeini Educational Hospital, Sari City, Mazandaran Province, Iran. The inclusion criteria were women aged 15-35 years, with a history of two or more miscarriages within the first trimester, referring to Imam Khomeini Hospital with a reduction in uterine blood flow (having pulsatility index of 2 or more). The exclusion criteria were women with pathological, anatomical, endocrine, or genetic risk factors, chronic diseases, chronic ongoing drug consumption, and a history of hypersensitivity to aspirin or salicylates. To ascertain the absence of any endocrine or anatomical disorders, we performed a thorough uterine evaluation, endocrine evaluation (measuring thyroid-stimulating hormone, free thyroxin, and progesterone level on day 21 of the menstrual cycle), and hysterosalpingography on all patients before their inclusion in the trial. In addition, both parents of all patients were checked to have normal karyotyping.

Sampling process and randomization

The sample size was determined according to some previous studies on the effect of aspirin and omega fatty acids in preventing recurrent miscarriage. So, a total sample size of 60, with 20 patients in each study arm, was estimated to be sufficient. However, due to the problems in the recruitment procedure (the majority of the screened patients declined to participate in the study), we could only recruit 45 patients (15 in each group). The sampling process of patients is shown in a CONSORT flow diagram (Figure 1). The patients were randomly divided into three groups by simple randomization procedure using a computer-generated list of random numbers.

Treatment

Each group was assigned to a different therapeutic regimen: Group A received 80 mg of aspirin per day, group O received 4800 mg (4 capsules of 1200 mg) Omega-3,

-6, and -9 fatty acids per day, and group AO received a combination of the two regimens. Since the use of a placebo in patients with RM was not permitted by the Research Ethics Committee of Mazandaran University of Medical Sciences, no control group was included in this study. Since the dosage form and package and administered dose were different, the trial could not be double-blinded. The data collectors (the radiologist and the gynecologist) were blinded to the allocation group. Still, the patients and the pharmacist who provided the therapeutic regimens were not blinded.

Primary outcomes and measures

The exact primary outcome of the trial was an improvement of uterine blood flow at the midluteal phase (5-8 days after ovulation), measured by Doppler sonography, first at the beginning of the trial (before receiving any treatments) and then 2 months after therapy (without discontinuing the treatment). The resistance to uterine artery blood flow was demonstrated by the "Pulsatility Index" (PI), which is a function of the maximum velocity and mean velocity of the ultrasound wave. It is obtained according to the following equation:

$$PI = \frac{Maximum\ velocity\ excursion}{Mean\ velocity}$$

The higher the pulsatility index, the higher the resistance, and consequently, the lower the blood flow in the artery. The PI values of the right and left uterine arteries were recorded. The average PI of the bilateral uterine artery was obtained by calculating the statistical mean of the values of PI for the two arteries. The ultrasound examinations were performed using a G-4O S ultrasound instrument (Siemens medical solutions, Germany) with a 7.5 MHz, ECG- 4 vaginal probe. The examinations included transvaginal ultrasound associated with pulsed color Doppler assessment of the blood flow. To avoid the fluctuations in uterine artery blood flow due to the circadian changes in cardiac rhythm, all ultrasound measurements were carried out in the morning. The patients were asked to rest for 30 minutes before the procedure.

Statistical analysis

The statistical analysis was performed by SPSS v.16, and quantitative characteristics are described as the number (percentage); 95% confidence intervals were also calculated, and the results were reported as mean±SD. The paired t test was used to compare values within each group, and the independent sample t test and 1-way Analysis of Variance (ANOVA) were used to compare the values between different groups. P values less than 0.05 were considered statistically significant.

Results

The demographic data of the study patients are presented in Table 1. As seen, most of the participants were more than 25 years old, married for less than 6 years, suffered from infertility for less than 4 years, and had experienced two or three miscarriages. As mentioned in Table 1, there was no significant difference between three groups in age (P=0.7), duration of marriage (P=0.55), duration of infertility (P=0.43), and number of previous miscarriages (P=0.51).

Table 2 presents the values of PI of the right and left uterine artery, which had the highest frequency in each group of patients before and after treatment. The average PI values of the right and left uterine arteries in the three study groups before and after the treatment are depicted in Table 3. In contrast, Table 4 presents the changes to the average PI values of the right and left uterine arteries due to treatment within each study group. At the beginning of the trial, the average PI values of the right, left, and bilateral uterine arteries of patients in group AO were lower than the other two groups (Table 3), but the difference was not statistically significant (P_1=0.4, P_2=0.5, P_3=0.3 respectively). After two months of treatment, although a considerable reduction in the average PI of the right, left, and the bilateral uterine arteries were observed in all three groups, no significant difference between the three groups was found (P_1=0.4, P_2=0.5, P_3=0.3, respectively; Table 3).

The comparison of the average PI values of the right and left arteries before and after the treatment within each group showed a considerable reduction in the average PI both in the right and left uterine artery after treatment in all three groups. At the beginning of the trial, the average PI of the left uterine artery was greater than the right uterine artery in all three groups. However, after two months of treatment, only in the AO group the same condition was saved, while in patients receiving omega-3, -6, and -9, the average PI values of the right and left uterine arteries were equal. In patients receiving aspirin, contrastingly, the right uterine artery showed higher PI than the left artery.

The extent of reduction of PI in the two arteries as a result of treatment in different groups also demonstrated a greater reduction in the PI of the left uterine artery than the right uterine artery for groups A and AO. While in group O, there was no difference in the extent of reduction of PI between the two arteries. Furthermore, com-

Table 1. Demographic characteristics of patients

Characteristics	Mean±SD			P
	Group A (n=15)	Group O (n=15)	Group AO (n=15)	
Age (y)	32.0±3.5	32.0±3.0	32.4±3.0	0.7
Duration of marriage (y)	4.0±0.4	3.5±0.7	4.2±0.5	0.55
Duration of infertility (y)	3.8±1.2	4.5±0.9	3.7±1.5	0.43
Number of previous miscarriages	2.9±0.9	3.0±1.1	3.6±0.8	0.51

Group A: aspirin (80 mg/d); Group O: omega-3, -6, and -9 fatty acids (4800 mg/d); Group AO: combination therapy

PBR

paring the extent of reduction in the average PI of the right uterine artery and the left uterine artery between different groups indicated that for the right artery, the between-group differences were minimal. In contrast, for the left artery, there was a considerably higher reduction in the PI in the aspirin group compared to the latter two (Tables 3 and 4).

The within-group and between-group changes to the average PI of the right, left, and bilateral uterine arteries during the trial could be better visualized by graphs 1, 2, and 3. As evident from these graphs, the extent of reduction in average PI after treatment is greater in the left uterine artery, suggesting that this artery is more responsive to the administered pharmacotherapies compared with the right uterine artery. It could also be observed that the range of between-group variations in the average PI was reduced after treatment (initial range=2.19-2.73, final range=2.06-2.20).

Discussion

RM is a condition that affects 2%-5% of women and is multifactorial. Genetic, anatomical, endocrinological, immunological, microbiological, and environmental factors are all supposed to be possible causes of RM [2-5]. Low doses of aspirin (75-100 mg/d) have been used effectively in the management of RM. More recently, PFAs have been introduced as a new alternative to current pharmacotherapies for the management of RM. According to the study results, omega-3, -6, and -9 fatty acids can reduce uterine artery blood flow resistance and improve blood flow in women with RM.

Rossi and Costa treated 22 patients with Persistent Antiphospholipid Syndrome (PAPS) associated with RM with fish oil, equivalent to 5.1 g Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) at a ratio of 1.5 EPA to DHA over 3 years. All but one patient had a normal pregnancy, and no adverse reactions were observed in any of the patients [3]. In Lazzarin et al.'s study, the efficacy of omega-3 fatty acids and low dose aspirin, alone and in combination, in improving uterine blood flow in women with a history of RM was evaluated [23]. The results showed improvement in the uterine artery blood flow (reduction in the pulsatility index) with all therapeutic regimens; aspirin alone or in combination with omega-3 was found to achieve the greatest improvement of uterine blood flow, while omega-3 supplementation was less effective [23].

In the present study, the efficacy of omega-3, -6, and -9 fatty acids, alone or in combination with low dose aspirin, was evaluated in the improvement of uterine artery blood flow (reduction of uterine artery blood flow resistance) in women with a history of two or more miscar-

Table 2. Mode value and frequency of PI for right and left uterine arteries in different groups before and after the treatment

Time points	Blood Vessel	Mode of PI			Frequency (%)		
		Group A	Group O	Group AO	Group A	Group O	Group AO
Before the treatment	Right artery	2.50	2.50	2.30	26.7	13.3	20
	Left artery	2.35	2.42	2.50	26.7	20	20
After the treatment	Right artery	1.90	1.90	2.15	26.7	20	33.3
	Left artery	2.20	2	2.10	26.7	20	20

Group A: aspirin (80 mg/d); Group O: omega-3, -6, and -9 fatty acids (4800 mg/d); Group AO: combination therapy.

PBR

Table 3. Mean±SD PI of the right and left uterine arteries in the three study groups before and after the treatment

Time points	Blood Vessel	Pulsatility Index (Mean±SD)			P
		Group A	Group O	Group AO	
Before the treatment	Right uterine artery	2.38±0.13	2.36±0.18	2.19±0.11	0.4
	Left uterine artery	2.54±0.21	2.73±0.07	2.39±0.08	0.5
	Bilateral uterine artery	2.41±0.17	2.36±0.12	2.29±0.09	0.3
After the treatment	Right uterine artery	2.17±0.19	2.16±0.18	2.06±0.12	0.6
	Left uterine artery	2.12±0.08	2.16±0.11	2.20±0.12	0.45
	Bilateral uterine artery	2.14±0.13	2.16±0.14	2.13±0.12	0.56
Reduction	Right uterine artery	0.20±0.12 (9%)	0.20±0.11 (9%)	0.12±0.15 (6%)	0.2
	Left uterine artery	0.33±0.24 (14%)	0.21±0.10 (8%)	0.18±0.16 (8%)	0.07
	Bilateral uterine artery	0.27±0.04 (12%)	0.20±0.10 (9%)	0.16±0.15 (7%)	0.04

Group A: aspirin (80 mg/d); Group O: omega-3, -6, and -9 fatty acids (4800 mg/d); Group AO: combination therapy.

riages. Since the use of a placebo in women with RM was not permitted according to the guidelines of the Research Ethics Committee of Mazandaran University of Medical Sciences, there were no placebo groups, and aspirin was used as an active control in this study.

The administered dose of aspirin was reduced from 100 mg/d in the study by Lazzarin et al. to 80 mg/d, and omega-3, -6, and -9 unsaturated fatty acids were used instead of omega-3 fatty acids to evaluate their therapeutic value in the management of RM [23]. The most appropriate administration dose of polyunsaturated fatty acids has not been established, but amounts of 4-5 g/d are effective

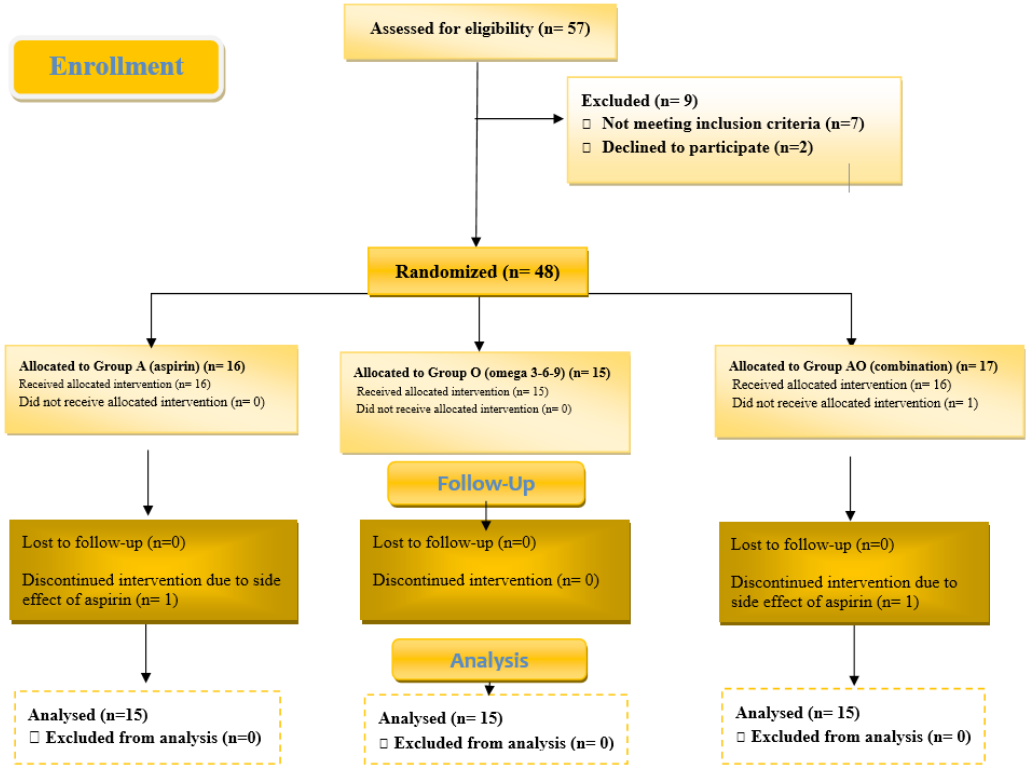


Figure 1. Consort 2010 flow diagram

Table 4. Mean±SD PI of the right and left uterine arteries, at the beginning and end of the trial, within each study group

Study Groups	Blood Vessel	Time Point (Mean±SD)		P
		Before the Treatment	After the Treatment	
Group A	Right uterine artery	2.38±0.13	2.17±0.19	0.0001
	Left uterine artery	2.54±0.21	2.12±0.08	0.0001
Group O	Right uterine artery	2.36±0.18	2.16±0.18	0.0001
	Left uterine artery	2.73±0.07	2.16±0.11	0.0001
Group AO	Right uterine artery	2.19±0.11	2.06±0.12	0.005
	Left uterine artery	2.39±0.08	2.20±0.12	0.001

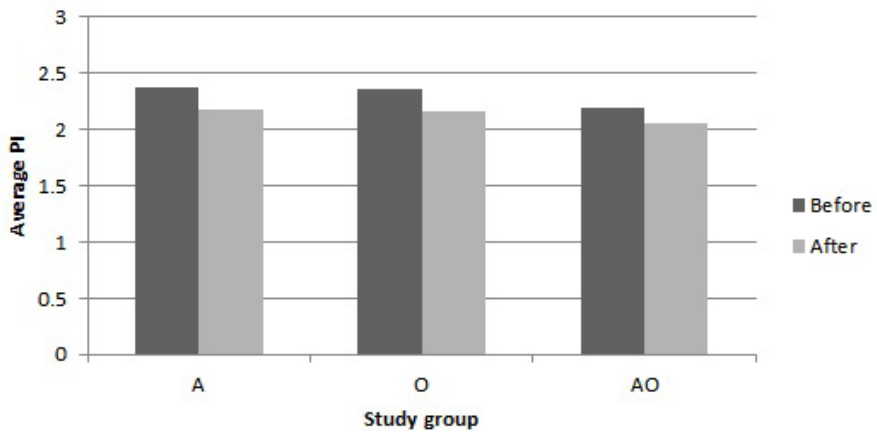
Group A: aspirin (80 mg/d); Group O: omega-3, -6, and -9 fatty acids (4800 mg/d); Group AO: combination therapy.

PBR

without any adverse effects (3, 15-17). Thus, the amount of 4800 mg/d (4.8 g/d) was tried in this study. Unlike the study by Lazzarin et al. in which the average PI of the bilateral uterine artery was reported due to negligible difference in the PI of the right and left branches, in the present study, a considerable difference was observed between the two arteries. Therefore, the PI of the right and left branches of the uterine artery are provided as well as the average PI of the bilateral uterine artery to map the observations better.

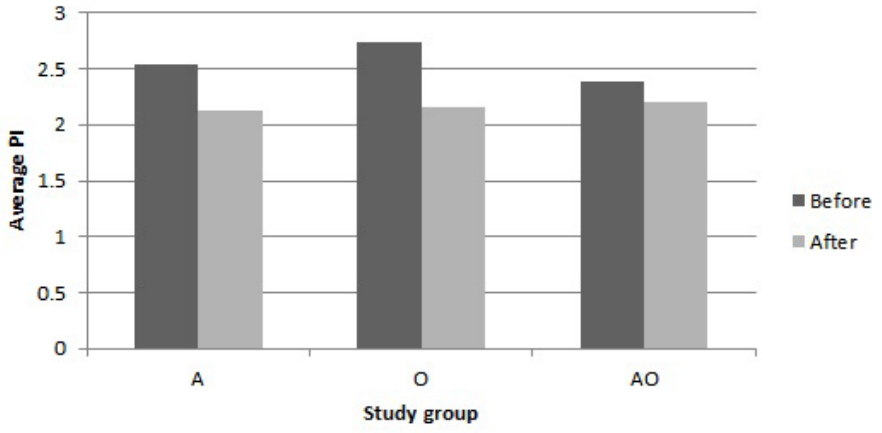
As it could be inferred from Table 3, in all three groups, the PI was markedly reduced after treatment, although the between-group differences were not significant. Therefore, it could be deducted that the uterine perfusion has improved as a result of treatment with all of the three therapeutic regimens, but the extent of this effect did not differ significantly between the groups, suggesting that none of the three therapeutic regimens had superiority to others (Table 3). However, the values of PI at the end of the trial showed less between-group variations than at the beginning of the trial. Thus, it seems that the average PI of the uterine artery had a narrow range of variation, whatever the initial PI.

The amount of reduction in average PI of the bilateral uterine artery due to treatment was highest in patients receiving aspirin. The AO group demonstrated the lowest reduction in the average PI among the three groups (P=0.04). These results further confirm that the combination therapy was not more effective than the monotherapy with either drug. Though the combination therapy (group AO) was expected to be more effective due to the synergistic effect of the two drugs, the results contradicted the preliminary assumption. It seems that omega-3, -6, and -9 and aspirin possess some kind of inhibitory action, which leads to attenuation of the net effect of each one. Since both pharmacotherapies affect the blood vessels



PBR

Figure 2. Average Pulsatility Index (PI) of the right uterine artery in different study groups before and after the treatment
Group A: aspirin (80 mg/d); Group O: omega-3, -6, and -9 fatty acids (4800 mg/d); Group AO: combination therapy.



PBR

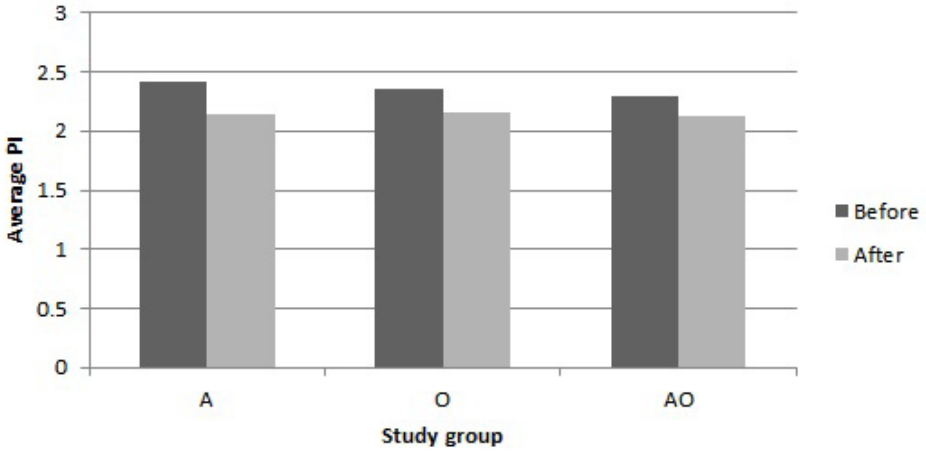
Figure 3. Average Pulsatility Index (PI) of the left uterine artery in different study groups before and after the treatment
Group A: aspirin (80 mg/d); Group O: omega-3, -6, and -9 fatty acids (4800 mg/d); Group AO: combination therapy.

through the inhibition of Cyclooxygenase (COX) and reduction of TxA2 synthesis, one possible explanation for this observation could be the competition between aspirin and omega-3, -6, and -9 fatty acids for the same active site in the COX enzyme. Thus they act as competitive inhibitors for cyclooxygenase. If this assumption is valid, the outcome depends on the concentration of each drug at the site of action and its affinity to the enzyme.

The marked reduction in the average PI in the right and left uterine arteries, which was observed after treatment within all of the three groups, further confirms the efficacy of all of the three therapeutic regimens in lowering the blood flow resistance and improving uterine perfusion (Table 4). Comparing the changes to the average PI of the right and left uterine arteries caused by different therapeutic regimens suggests that the effect of aspirin on the uterine artery's blood flow is more dominant in the left uterine artery. At the same time, omega-3, -6, and -9 seem to affect both the right and left uterine arteries equally. The authors could suggest no explanation for this observation since no background data on the selective effect of aspirin on different blood vessels could be found elsewhere.

Conclusion

According to the present study results, omega-3, -6, and -9 fatty acids can reduce the pulsatility index and improve uterine artery blood flow in pregnant women with impaired uterine perfusion and could therefore be regarded as a possible alternative to aspirin in the management of recurrent miscarriage. However, there is no benefit



PBR

Figure 4. Average Pulsatility Index (PI) of the bilateral uterine artery in different study groups before and after the treatment
Group A: aspirin (80 mg/d); Group O: omega-3, -6, and -9 fatty acids (4800 mg/d); Group AO: combination therapy.

for combination therapy compared with monotherapy. Therefore, we suggest that other clinical trials with a larger sample size be conducted to confirm these results.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Research Ethics Committee of Mazandaran University of Medical Sciences and registered at the Iranian Registry of Clinical Trials (Code: IRCT201103253014N3).

Funding

The paper was extracted from the Pharm.D Thesis of Mahdieh Tavajoh, Department of of Clinical Pharmacy, Faculty of Pharmacy, Mazandaran University of Medical Sciences.

Authors' contributions

Writing the original draft: Shahram Ala, Hamidreza Samaee, and Mahdieh Tavajoh; Data collection: Shahram Ala, Sepideh Payvandi, Maryam Barzin, and Mahdieh Tavajoh.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors acknowledge Dr Zoleykha Atarod and Dr Taraneh Geran for their assistance in patient selection, Dr Ahmadreza Bekhradnia for his assistance in the literature review, Dr Jamshid Yazdani for statistical consultancy, and Dr Roja Hadianamrei for her assistance in literature review and drafting the manuscript.

References

[1] Vinatier D, Dufour P, Cosson M, Houpeau JL. Antiphospholipid syndrome and recurrent miscarriages. Eur J Obstet Gynecol Reprod Biol. 2001; 96(1):37-50. [DOI:10.1016/S0301-2115(00)00404-8]

[2] Costa M, Rossi E. Antiphospholipid antibodies and pregnancy. Ann N Y Acad Sci. 1999; 876:383-6. [DOI:10.1111/j.1749-6632.1999.tb07661.x] [PMID]

[3] Rossi E, Costa M. Fish oil derivatives as a prophylaxis of recurrent miscarriage associated with antiphospholipid antibodies (APL): A pilot study. Lupus. 1993; 2(5):319-23. [DOI:10.1177/096120339300200508] [PMID]

[4] Blétry O, Piette AM. Recurrent fetal loss and antiphospholipid antibodies: Clinical and therapeutic aspects. Infect Dis Obstet Gynecol. 1997; 5:480963. [DOI:10.1155/S1064744997000288] [PMID] [PMCID]

[5] Abdel Wahab H, Salah El-Din D, Zain E, Abdelgany M, Youssef MAFM. Uterine artery Doppler and subendometrial blood flow in patients with unexplained recurrent miscarriage. Middle East Fertil Soc J. 2011; 16(3):209-14. [DOI:10.1016/j.mefs.2011.04.001]

[6] Tohma H, Hasegawa I, Sekizuka N, Tanaka K. Uterine blood flow. Assessment in an intrauterine insemination program for unexplained infertility. J Reprod Med. 1997; 42(8):463-6. [PMID]

[7] Salle B, Bied-Damon V, Benchaib M, Desperes S, Gaucherand P, Rudigoz RC. Preliminary report of ultrasonography and color Doppler uterine score to predict uterine receptivity in an in-vitro fertilization programme. Hum Reprod. 1998; 13(6):1669-73. [DOI:10.1093/humrep/13.6.1669] [PMID]

[8] Ferreira AM, Pires CR, Moron AF, Araujo Júnior E, Trania E, Mattar R. Doppler assessment of uterine blood flow in recurrent pregnancy loss. Int J Gynecol Obstet. 2007; 98(2):115-9. [DOI:10.1016/j.ijgo.2007.05.006] [PMID]

[9] Lazzarin N, Vaquero E, Exacoustos C, Romanini E, Amadio A, Arduini D. Midluteal phase Doppler assessment of uterine artery blood flow in nonpregnant women having a history of recurrent spontaneous abortions: Correlation to different etiologies. Fertil Steril. 2007; 87(6):1383-7. [DOI:10.1016/j.fertnstert.2006.11.049] [PMID]

[10] Chien LW, Lee WS, Au HK, Tzeng CR. Assessment of changes in utero-ovarian arterial impedance during the periimplantation period by Doppler sonography in women undergoing assisted reproduction. Ultrasound Obstet Gynecol. 2004; 23(5):496-500. [DOI:10.1002/uog.975] [PMID]

[11] Bernstein IM, Ziegler WF, Leavitt T, Badger GJ. Uterine artery hemodynamic adaptation through menstrual cycle into early pregnancy. Obstet Gynecol. 2002; 99(4):620-4. [DOI:10.1016/S0029-7844(01)01787-2]

[12] Rubinstein M, Marazzi A, Polak de Fried E. Low-dose aspirin treatment improves ovarian responsiveness, uterine and ovarian blood flow velocity, implantation, and pregnancy rates in patients undergoing in vitro fertilization: A prospective, randomized, double-blind, placebo-controlled assay. Fertil Steril. 1999; 71(5):825-9. [DOI:10.1016/S0015-0282(99)00088-6]

[13] Wada I, Hsu CC, Williams G, Macname MC, Brinsden PR. The benefits of low-dose aspirin therapy in women with impaired uterine perfusion during assisted conception. Hum Reprod. 1994; 9(10):1954-7. [DOI:10.1093/oxfordjournals.humrep.a138366] [PMID]

[14] Patrono C, Coller B, Dallen JE, Fitzgerald GA, Fuster V, Gent M, et al. Platelet-active drugs: The relationships among dose, effectiveness and side effects. Chest. 2001; 119(1 Suppl):39S-63. [DOI:10.1378/chest.119.1_suppl.39S] [PMID]

[15] Battaglia C, Sgrabi L, Salvatori M, Maxia N, Gallinelli A, Volpe A. Increased anticardiolipin antibodies are positively related to uterine artery pulsatility index in unexplained infertility. Hum Reprod. 1998; 13(12):3487-91. [DOI:10.1093/humrep/13.12.3487] [PMID]

[16] Rustan AC, Drevon CA. Fatty acids: Structures and properties [Internet]. 2005 [Updated 2005 September 23]. Available from: [DOI:10.1038/npg.els.0003894]

[17] McGregor JA, Allen KG, Harris MA, Reece M, Wheeler M, French JI, et al. The omega-3 story: Nutritional prevention of preterm birth and other adverse pregnancy outcomes. Obstet Gynecol Surv. 2001; 56(5):S1-13. [DOI:10.1097/00006254-200105001-00001] [PMID]

[18] Saldeen P, Saldeen T. Women and omega-3 Fatty acids. Obstet Gynecol Surv. 2004; 59(10):722-30. [DOI:10.1097/01.ogx.0000140038.70473.96] [PMID]

[19] Wathes DC, Abayasekara DRE, Aitken RJ. Polyunsaturatd fatty acids in male and female reproduction. Biol Reprod. 2007; 77(2):190-201. [DOI:10.1095/biolreprod.107.060558] [PMID]

[20] Jensen CL. Effects of n-3 fatty acids during pregnancy and lactation. Am J Clin Nutr. 2006; 83(6):1452S-7. [DOI:10.1093/ajcn/83.6.1452S] [PMID]

[21] Knapp HR, Reilly IA, Alessandrini P, FitzGerald GA. In vivo indexes of platelet and vascular function during fish-oil administration in patients with atherosclerosis. N Engl J Med. 1986; 314(15):937-42. [DOI:10.1056/NEJM198604103141501] [PMID]

[22] Schiff E, Ben-Baruch G, Barkai G, Peleg E, Rosenthal T, Mashiach Sh. Reduction of thromboxane A2 synthesis in pregnancy by polyunsaturated fatty acid supplements. Am J Obstet Gynecol. 1993; 168(1):122-4. [DOI:10.1016/S0002-9378(12)90898-4]

[23] Lazzarin N, Vaquero E, Exacoustos C, Bertonotti E, Romanini ME, Arduini D. Low-dose aspirin and omega-3 fatty acids improve uterine artery blood flow velocity in women with recurrent miscarriage due to impaired uterine perfusion. Fertil Steril. 2009; 92(1):296-300. [DOI:10.1016/j.fertnstert.2008.05.045] [PMID]

This Page Intentionally Left Blank