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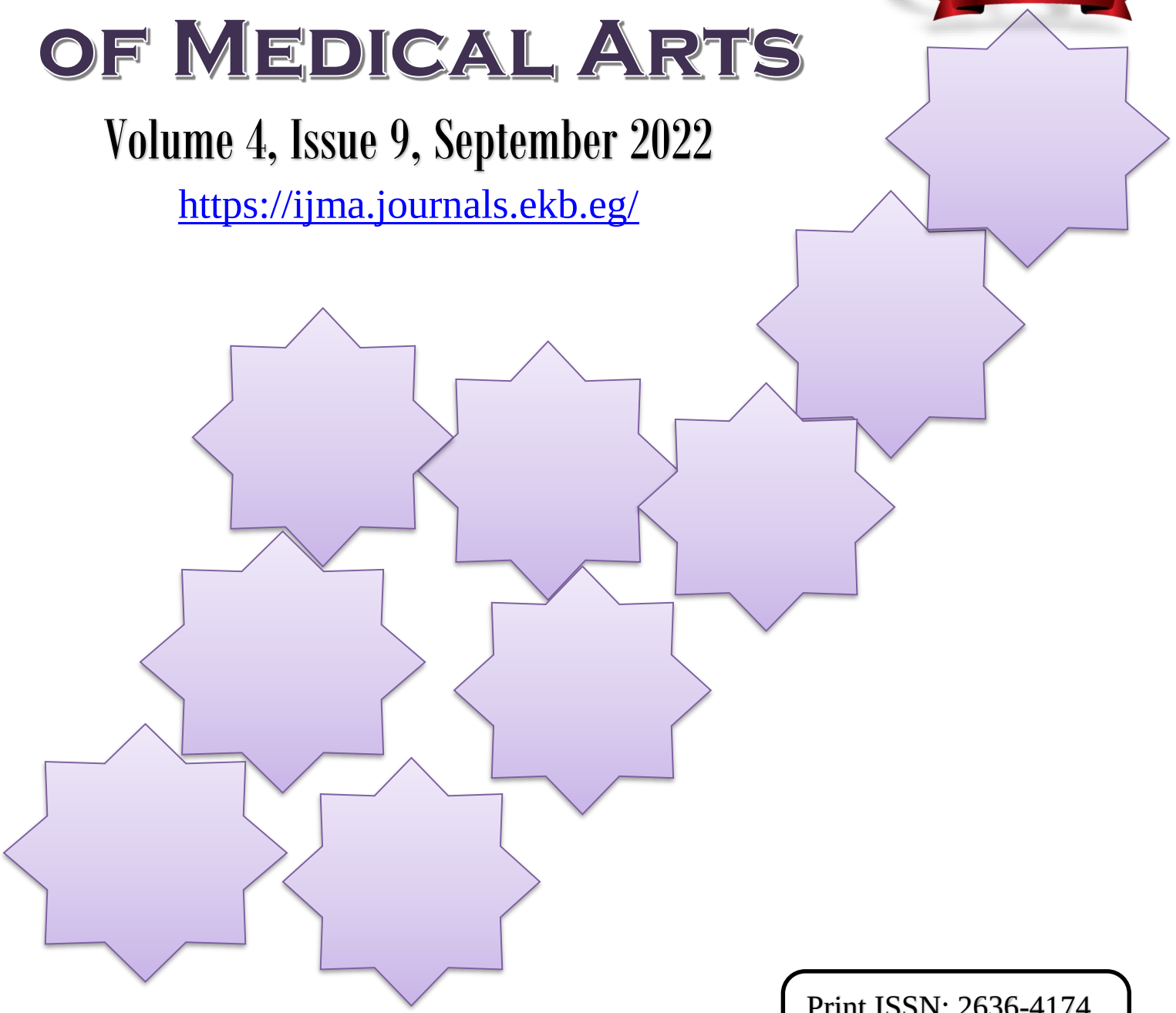

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Original Article

Effect of Low Dose Aspirin on Luteal Phase Uterine Artery Doppler Indices in Women with Recurrent Pregnancy Loss

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ABSTRACT

Background: The obstetrical difficulties associated with repeated miscarriages persist. It's associated with poor uterine blood flow, and vasodilators seem to stop miscarriages from happening again.

Aim of the work: During the luteal phase, Doppler indices of the uterine artery were measured to see whether low-dose aspirin had any effect on recurrent miscarriage.

Patients and methods: Patients experiencing recurrent pregnancy loss [RPL] were randomly assigned to one of two treatment groups in a randomized controlled trial [RCT]; Group A [Case Group]: subjects were those who had a history of two or more recurrent miscarriages and who were administered a modest dosage of Aspirin Group B [Control Group]: Subjects with a history of two or more consecutive miscarriages were not administered Aspirin. Studied Doppler indices included Systolic-to-diastolic ratios [S/D], resistance index [RI] and pulsatility indices [PI]

Results: RI, PI, and S/D were significantly lower among group A group compared to group B group after treatment with aspirin in group A. Individuals who had had one or two prior miscarriages had the lowest uterine index values, although this difference was not statistically significant.

Conclusion: Uterine blood flow was reduced during the luteal phase in those who had had repeated miscarriages. Aspirin, even at modest doses, increased uterine blood flow, and this effect was reversible, suggesting its potential therapeutic use.

Keywords: Aspirin; Recurrent pregnancy loss; Uterine artery blood flow.

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INTRODUCTION

Recurrent pregnancy loss is defined as two or more miscarriages in a row before 20 weeks of pregnancy. This common but stressful pregnancy issue affects anywhere from 1% to 5% of reproductive-age women worldwide. For about half of these people, the cause of this disease is still unknown [1]. It is well accepted that an unsupportive endometrium, which causes improper implantation, is a major contributor to repeated miscarriages. The midluteal phase, which corresponds with the implantation window in time, is when the resistance to blood flow in the uterine arteries is at its lowest [2].

With the advent of Doppler technologies in clinical practice, assessing uterine blood flow has become a promising new tool for assessing endometrial functional capability during the implantation window. Therefore, uterine blood flow is thought to be a controllable element in uterine receptivity, which affects implantation success [3].

Recent research suggests that blood flow through the uterine arteries controls how receptive the uterine lining is to embryo implantation. This suggests that improper blood flow through the uterus may be a contributing factor in spontaneous miscarriages and, more likely, in implantation failure [4]. Many researched recommend more studies for the purpose of better understanding the vascular alterations that accompany recurrent miscarriage and pinpointing the causes of uterine perfusion problems in these women [5].

Decreased uterine blood flow and increased vascular resistance have been hypothesized as reasons for recurrent miscarriage in high-risk pregnancies [6].

Reduced blood flow to the mid-luteal region of the uterus has been linked to a higher risk of miscarriage and preterm birth. Midway through the second trimester, when most pregnancies are lost, an increase in the resistance to blood flow in the uterine arteries has been associated with recurrent pregnancy loss. There is evidence from prior research suggesting that the common anticoagulant, low-dose aspirin, may have a vasodilatory effect [7].

Supplemental low-dose aspirin has been observed to increase uterine blood flow and pregnancy outcomes in women with poor uterine vascularization who have undergone assisted reproductive technology [8].

Antiplatelet aggregation and prostaglandin synthase inhibition are two irreversible effects of aspirin's nonsteroidal anti-inflammatory drug classification. Low-dose aspirin [LDA] has been found in several studies to increase blood flow to the uterus and decrease the risk of miscarriage in women who have had repeated miscarriages [9].

With unexplained RPL, women who took aspirin had a considerably greater live birth rate compared to those who took a placebo or received no treatment. Another study found that taking aspirin with calheparin or prednisone increased the risk of first-trimester pregnancy. But just how LDA consumption might improve the outcome of pregnancy in unexplained RPL patients is unclear [10].

This study aims to ascertain whether low-dose aspirin influences uterine artery function during the luteal phase. Recurrent miscarriage and abnormal Doppler indices in women

PATIENTS AND METHODS

In the Obstetrics and Gynecology Department of Al-Hussein University Hospital, 50 non-pregnant women participated in a prospective, interventional randomized controlled trial [RCT]. The study was conducted after approval was obtained from the ethical committee.

Individuals who are not pregnant, the female participants ranged in age from 18 to 45, and all of them had had a history of at least one miscarriage. Patients who had had hormone therapy during the last three months before admission into the trial, patients who obtain chronic continuing therapies, and immune-compromised pregnant women were not eligible to participate.

Fifty patients were subdivided into two groups using the sealed envelope system used for randomization:

Group [A] [Case Group]: Twenty-five people who had had two or more consecutive miscarriages were given low-dose aspirin before they were evaluated.

Group [B] [Control Group]: Twenty-five patients who presented with a history of two or more recurrent miscarriages were not given aspirin.

All patients had a thorough history taken, a physical examination, an abdominal exam, a check of any suspicious areas, standard laboratory tests, and a transvaginal sonogram. After the bladder was emptied, a vaginal probe was placed under direct observation. The bladder, the presenting organ, and any abnormalities were identified. Once the cervix's midline sagittal plane was found, the probe was retracted until a clear picture of the cervical canal could be seen under the slightest pressure, with the internal os fixed in the image's upper third.

After adjusting the probe's position slightly, the optimal longitudinal cervix axis could be captured. Transvaginal Doppler sonography was performed using a transvaginal micro-convex transducer [6.5 MHz], and a standard anatomical landmark was the presenting fetal part, the urinary bladder, the internal os, the external os, and the cervical canal. All TVS scans were conducted by a sonographer who was unaware of the patient's medical history.

The LH surge was picked up in a home test using an LH ovulation prediction kit because of the elevated levels of LH in the urine. The LH ovulation prediction kit is based on the enzyme immunoassay of LH monoclonal antibodies in urine and has a sensitivity of 30 mlU/ml. It was requested that participants monitor their LH levels in their urine twice daily [in the morning and the evening] and keep a record of the findings.

Midluteal stage, unstimulated cycle, transvaginal convex 7.5 MHz probe measurement of uterine artery blood flow. Transvaginally, on the side of the cervix, we found the right and left uterine arteries and took diameter measurements in the parasagittal plane.

The blood vessel was inserted within the Doppler gate, which measured the wave's velocity. The Doppler beam was always aimed directly at the ship being monitored. Systolic-to-diastolic ratios [S/D] and pulsatility indices [PI] were calculated for both the left and right arteries. Patients were re-examined at the same point in the cycle after 6 months of low-dose aspirin medication.

For the next six months, following a sonographic diagnosis of poor uterine blood flow, the patient was given 75 milligrams of aspirin daily. Any unwanted reactions to the therapy were documented. All information was recorded, examined, and compared.

The impact of low-dose aspirin on Doppler indices of the uterine arteries during the luteal phase of pregnancy in women with recurrent miscarriage was the primary outcome.

The identification of a healthy pregnancy, the absence of miscarriage, and the number of women who are unable to charge or give birth were considered secondary outcomes.

Statistical Analysis

The data was analyzed using SPSS 25. [IBM Corporation, Armonk, NY]. Mean values of the blood flow index were compared between the control and study groups using the Student t-test and Chi square. When analyzing the data, a P value of 0.05 was required as a minimum level of statistical significance.

RESULTS

Table [1] shows there is no significant difference between the groups regarding demographic data.

Table [2] shows there is no significant difference between the groups regarding uterine artery Doppler indices before intervention. We found that RI, PI, and S/D were significantly lower among group A group compared to group B group after treatment with aspirin in group A.

Table [3] shows that lowest uterine indices values were found among patients with previous one pregnancy loss and patients with previous two pregnancy losses, however there is no significant difference found between the groups.

Table [4] shows no significant difference between the two groups regarding outcome.

Table [5] shows that the most common side effects among cases group was gastrointestinal discomfort [68%] followed by abnormal bleeding [36%].

Table [1]: Demographic characteristics among the studied groups

	Group A [n=25]	Group B [n=25]	t	P
Age [years] [Mean ± SD]	29.56 ± 4.73	30.11 ± 4.12	.438	0.663
Weight [kg] [Mean ± SD]	75.13 ± 6.33	72.54 ± 6.82	1.39	0.170
Height [m] [Mean ± SD]	1.62 ± 0.153	1.59 ± 0.117	0.779	0.440
BMI [kg/m^2] [Mean ± SD]	26.34 ± 2.39	27.12 ± 2.64	1.1	0.279
Number of pregnancy losses [Mean ± SD]	3.16 ± 0.711	2.85 ± 1.05	2.32	0.341

Table [2]: Uterine artery Doppler indices between the studied groups

	Group A [n=25]	Group B [n=25]	t	P
Before the intervention				
Resistance index [Mean ± SD]	0.826 ± 0.049	0.813 ± 0.042	1.01	0.319
Pulsatility index [Mean ± SD]	2.65 ± 0.328	2.61 ± 0.356	.413	0.681
S/D [Mean ± SD]	5.62 ± 0.592	5.49 ± 0.523	.822	0.415
After the intervention				
Resistance index [Mean ± SD]	0.714 ± 0.073	0.807 ± 0.045	5.42	**0.000**
Pulsatility index [Mean ± SD]	2.24 ± 0.238	2.6 ± 0.371	4.08	**0.000**
S/D [Mean ± SD]	4.82 ± 0.415	5.51 ± 0.543	5.05	**0.034**

Table [3]: Relation between uterine artery Doppler indices and number of pregnancy losses after intervention among group A

	Resistance index Mean ± SD	Pulsatility index Mean ± SD	S/D Mean ± SD
1 [n=4]	0.693 ± 0.026	2.14 ± 0.172	4.58 ± 0.481
2 [n=7]	0.708 ± 0.024	2.18 ± 0.153	4.77 ± 0.501
3 [n=6]	0.711 ± 0.019	2.23 ± 0.170	4.81 ± 0.485
4 [n=5]	0.716 ± 0.025	2.27 ± 0.185	5.02 ± 0.515
≥ 5 [n=3]	0.724 ± 0.057	2.34 ± 0.201	5.17 ± 0.581
P	0.663	0.475	0.551

Table [4]: Outcome distribution between the studied groups

	Group A [n=25]	Group B [n=25]	χ^2	P
Positive pregnancy	18 [72%]	16 [64%]	.368	.544
Pregnancy loss	3 [12%]	4 [16%]	.166	.684
Gestational HTN	0 [0%]	1 [4%]	1.02	.315
GDM	1 [4%]	2 [8%]	.355	.552
Preeclampsia	1 [4%]	1 [4%]	--	1
Preterm birth	3 [12%]	4 [16%]	.166	.684
Low birth weight	4 [16%]	6 [24%]	.500	.480

Table [5]: Side effects among cases group

Side effect	Group A [n=25]
Gastrointestinal discomfort	17 [68%]
Abnormal bleeding	9 [36%]
Rashes	2 [8%]
Swelling	3 [12%]

DISCUSSION

Recurrent miscarriage refers to the occurrence of two or more miscarriages, whether they occur immediately after each other or at different times. Recurrent pregnancy loss [RPL] is defined as having two or more consecutive spontaneous miscarriages with the same sexual partner. RPL affects up to five percent of reproductive-aged women and causes

great physical, psychological, and social misery for affected couples. Repeated spontaneous miscarriages are common. About a third to a half of cases have a mysterious origin. However, miscarriage repeatability is linked to persistently elevated uterine artery resistance [11].

Repeated miscarriages often include the use of aspirin, a non-steroidal anti-inflammatory medicine. It was recently shown that infant mortality, IUGR, preterm birth, and preeclampsia rates all dropped significantly in pregnancies when the mothers took low-dose aspirin before the 16th week of pregnancy [12].

This study aimed to determine whether low-dose aspirin affected luteal phase Doppler indices of uterine arteries in women with a history of recurrent miscarriage.

According to the data reported in this thesis, there were no significant differences between the groups with regard to age, weight, height, body mass index, or the number of pregnancy losses [p-values = 0.663, 0.170, 0.440, 0.279, and 0.341, respectively].

In agreement was a recent study by **Nori et al.** [13] who found that there was no statistically significant difference between the study and control groups with respect to age, gravidity, or body mass index [BMI; 25.95.9 years, 2.20.9 and 24.12.8 kg/m2, respectively; 25.74.8 years, 2.00.8 and 23.32.3 kg/m2, respectively; p> 0.05]]. The study group received aspirin 75 mg for 3 months.

Our findings demonstrated no statistically significant difference in baseline Doppler indices for the uterine artery across the groups. While aspirin therapy substantially reduced RI, PI, and S/D in group [A] compared to group [B].

In agreement, **Kang et al.** [14] found that a total of 115 women who had had several miscarriages were chosen at random to receive low-dose aspirin therapy. Both PI and S/D in the uterine arteries were significantly reduced after 2 months of therapy with low-dose aspirin. We also analyzed the mean indices of the uterine arteries and found that women who had had many miscarriages had considerably higher PI values than the control group. S/D values also went up, although not by as much. There was a statistically insignificant rise in the mean RI for repeat miscarriages.

In the same line, **Nori et al.** [13] reported that uterine predictors of successful implantation were assessed by transvaginal ultrasonography after 3 months of therapy with low-dose aspirin; they included endometrial thickness, uterine artery PI, and RI. The Doppler indices reveal a notable drop in PI and RI. After taking aspirin, the average PI and RI were 20% and 18.2%, respectively, and the ET increased by 8.5%. Because aspirin inhibits the production of thromboxane A2, the chemical responsible for platelet aggregation and vasoconstriction, this phenomenon makes sense.

Also, **Mesdaghinia et al.** [11] noted that, while there were no significant variations in baseline PI values across groups, aspirin [100 mg/day] dramatically improved uterine artery blood flow, as measured by considerably lower PI values after therapy compared to baseline.

Wang et al. [9] showed that patients with unexplained RPL had substantially higher mean endometrial PI, RI, and S/D values and mean uterine artery PI, RI, and S/D values than controls [P<0.001].

On the other hand, **Rubinstein et al.** [15] showed that, with regards to PI in the uterine arteries, the aspirin group significantly outperformed the control group [p < 0.05]. Comparing the aspirin group to the control group, the PI in the uterine artery was 1.2 vs. 1.9.

Wallenburg et al. [16] reported that recurrent pregnancy loss in non-pregnant people has been linked to a low-dose aspirin regimen, which has been shown to significantly reduce the resistance to blood flow in the uterine arteries, as measured by a drop in PI and S/D values.

Lazzarin et al. [17] reported that repeated miscarriage is associated with higher PI in the uterine arteries in women.

Another study by **Tamura et al.** [18] showed that the RI of the uterine artery was considerably greater in the second part of the menstrual cycle in individuals with recurrent pregnancy loss compared to a control group.

Patients with a history of one pregnancy loss had lower uterine index values than those with a

history of two pregnancy losses, but the difference was not statistically significant.

A previous study done by **Kang et al.** [14] showed that, when individuals with recurrent pregnancy loss were categorized by the number of miscarriages they had, there was no significant difference in PI or S/D [P > 0.05]. Patients with a losing streak of four games or more showed substantially different PI and SD ratios.

Lazzarin et al. [17] reported that women with a history of miscarriage had increased PI and RI in their uterine arteries compared to fertile women during the mid-luteal phase of the menstrual cycle, suggesting that this aberrant uterine perfusion may be a critical component in determining the fate of the pregnancy.

Garhy et al. [19] discovered a positive correlation between uterine PI and RPL and progesterone levels; however, they did not examine the impact of aspirin on these variables. They also report that there is no link between endometrial thickness and RPL.

Different types of literature have addressed the use of aspirin as a therapy during pregnancy, with varying doses or measurements with a Doppler for variations in its indices as the woman's reproductive system develops and evolves. To learn if an increase in uterine blood flow might translate into greater clinical pregnancy and live birth rates, further research is required to find the appropriate values for Doppler indices in the uterus for patients with RPL. At the end, we want to see couples able to have the families they've always dreamed of having.

Conclusions: Our results suggest that low-dose aspirin may be helpful in promoting endometrial receptivity and pregnancy outcomes by acting as a blood flow-enhancing medication. It is a viable treatment option for restoring normal uterine blood flow. It's also looked at as a therapeutic option that's both effective and safe for preventing several pregnancy problems.

Conflict of interest and Financial Disclosure: None

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