Effect of Low-Dose Aspirin on Mid-Luteal Phase Uterine Artery Blood Flow in Women with Unexplained Recurrent Pregnancy Loss

Original Article

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ABSTRACT

Objectives: As a possible therapy for recurrent pregnancy loss, this study sought to ascertain if low-dose aspirin was effective in increasing uterine artery blood flow.

Study Design: This investigation was structured as a single-arm clinical trial

Patients and Methods: All participants were aged 39 years or younger and had no prior or current indications of abnormal glucose tolerance, thyroid dysfunction, hyperprolactinemia, or Antiphospholipid antibody syndrome. Bilateral assessments of the Systolic/Diastolic (S/D) ratio, Resistive Index (RI), and Pulsatility Index (PI) were conducted in the chosen patients in the mid-luteal phase, before to and following a minimum of two weeks of low-dose aspirin administration.

Results: The results of this investigation showed significant variation in the S/D and PI prior to and following aspirin administration. There was no discernible shift in RI. The analysis revealed a statistically significant reduction in uterine artery PI after aspirin administration (1.92±0.29) compared to the pre-treatment value (2.22±0.27), with a *p-value* of 0.0001. Remarkably, the pulsatility indices of the left and right uterine arteries did not significantly differ from one another.

Conclusion: For women who have a history of miscarriages, low-dose aspirin can be recommended as an adjuvant therapy as it effectively improves uterine artery blood flow in these patients. However, more well-designed research is required to ascertain whether improved pregnancy outcomes are correlated with improved uterine perfusion. The current study supported the aspirin guideline for women with a history of recurrent miscarriages by showing that aspirin treatment resulted in a reduction in uterine artery PI.

Key Words: Low-dose aspirin, recurrent pregnancy loss, uterine artery blood flow.

Received: 14 October 2024, **Accepted:** 26 December 2024

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ISSN: 2090-7265, 2025, Vol. 15

INTRODUCTION

The occurrence of two or more consecutive losses before the end of 20 weeks of gestation is what is known as recurrent pregnancy loss. About 1% to 5% of women worldwide who are of reproductive age suffer with this common and upsetting pregnancy problem[1].

The successful implantation of an embryo is contingent upon the intricate interaction between the blastocyst and a receptive endometrium. Evidence suggests that a conducive endometrial environment is essential for effective implantation[2].

Uterine receptivity is likely influenced by various factors, including uterine perfusion, this is essential to getting a good pregnancy. According to research, endometrial receptivity may be influenced by uterine artery perfusion. Inadequate uterine perfusion may be a factor in inexplicable miscarriages and may also affect implantation[3].

An endometrium that is not supportive, resulting in abnormal implantation, is recognized as a significant factor in recurrent pregnancy loss[4]. Since the introduction of Doppler technology into clinical practice, measuring uterine blood flow has been more crucial in determining the endometrium's functional capability during the implantation window[5].

Doppler ultrasound serves as a valuable instrument for assessing blood supply to the entire endometrium and the

DOI:10.21608/EBWHJ.2024.323829.1369

sub endometrial[6] Colored Doppler is utilized in obstetric ultrasound as an adjunct to grayscale imaging, providing insights into the presence, direction, and velocity of blood flow[7].

High-risk pregnancies have been linked to increased vascular resistance in the uterine arteries and decreased uterine blood flow, both of which may be contributing causes to recurrent pregnancy loss[8].

Ultrasonography can be used to evaluate potential uterine predictors for implantation such as endometrial thickness, volume, pattern, and blood flow in the uterine and sub endometrial arteries[9]. The uterine artery's blood flow is very resistant before conception and frequently shows missing or reversed diastolic flow[10]. It is well known that the uterine artery's pulsatility index gradually declines throughout the luteal phase, which is when implantation occurs[3]. Reduced uterine blood flow has been identified as a contributing factor to recurrent pregnancy loss[11].

Research has shown that low-dose aspirin, a commonly used anticoagulant, can induce a vasodilatory effect[12].

In women undergoing assisted reproductive technologies with insufficient uterine vascularization, taking low-dose aspirin can boost uterine blood flow for enhanced pregnancy outcomes[13].

Assessing the uterine artery's pulsatility index during mid-luteal phases of spontaneous cycles can help diagnose those who experience repeated miscarriages caused by impaired uterine circulation[3].

Lazzarin *et al*[14] found that women with unexplained mid-late follicular phase subfertility exhibit reduced endometrial and sub-endometrial vascularity, as observed through Doppler ultrasound in women who had undergone recurrent pregnancy loss.

Access to prenatal care, timely identification of disorders, diligent monitoring, and appropriate management are essential components in preventing complications related to pregnancy[15].

This study aims to evaluate the impact of low-dose aspirin on uterine artery blood flow, perhaps providing a treatment option for women who repeatedly miscarry before becoming pregnant.

PATIENTS AND METHODS

This investigation was structured as a single-arm clinical trial, took place at the recurrent pregnancy loss clinic within Ain Shams University Maternity Hospital, spanning from January 2018 to February 2019. The Department of Obstetrics and Gynaecology's Ethics Committee is responsible for this faculty. Ain Shams University's Faculty of Medicine authorized the study. After being accepted, the article was added to the journal. All the study participants gave their informed written permission after being fully informed.

A total of seventy participants were enrolled from women visiting the outpatient recurrent pregnancy loss clinic at Ain Shams University Maternity Hospital.

Inclusion Criteria for Participants

- Age between 20 and 40 years.
- A history of three or more unexpected, recurring miscarriages.
- Not currently pregnant.
- Consistent menstrual cycles for the three months before the research.
- No intrauterine devices or hormonal contraceptives are used.

Exclusion Criteria

- Autoimmune disorders that may influence blood vessel function (e.g., systemic lupus erythematosus).
- Systemic conditions that could affect hemodynamic parameters (e.g., thrombocytopenia, thyrotoxicosis, etc.).
- Any identified cause of recurrent pregnancy loss (e.g., genetic abnormalities, anatomical anomalies).
- Thrombophilia identified and/or managed.
- Vascular conditions of any kind, such as coronary artery disease.
- Consanguinity history.
- A family history of chromosomal disorders (such as Turner syndrome, trisomy 21, trisomy 13, etc.).

Contraindications of aspirin

Confirmed peptic ulcer disease has been identified within the last three years. There is also a noted sensitivity to aspirin.

Methodology

1. Participants were recruited from the outpatient clinic by applying specific inclusion and exclusion criteria.

2. Written informed consent was secured, and the study was sanctioned by the hospital's ethics committee.

3. A comprehensive medical history was collected from the women, which included:

    - Personal history: information on age, way of life, and any consanguinity history.

    - Menstrual history: questions concerning the time of the previous menstrual period, frequency, length, and volume of bleeding, as well as the regularity of menstrual cycles.

    - Obstetric history: enquiries about parity, past delivery techniques, when past abortions were performed, if dilation and curettage were performed afterwards, and when the most recent delivery or abortion occurred.

    - Previous medical history: systemic ailments, including hypertension, diabetes mellitus, renal abnormalities, and thyroid problems in the past, should be highlighted.

4. Clinical examination

A clinical examination that comprised pelvic, abdominal, and general exams was performed after the application of inclusion and exclusion criteria and the gathering of medical history.

- General examination: evaluated vital signs (heart, blood pressure, and temperature), general appearance, weight, and height.

- Abdominal examination: performed to rule out any organic abnormalities that can be clinically identified.

5. Six to eight days after ovulation, transvaginal Doppler sonography was performed on each patient to measure the systolic-to-diastolic ratio (S/D), resistive index (RI), and pulsatility index (PI) of the left and right major uterine arteries. Individuals who had previously experienced repeated miscarriages were given low-dose aspirin (Aspocid 70 mg/day) orally for a minimum of two weeks, following which the blood flow indices were assessed.

6. In a subset of patients of recurrent pregnancy loss during the mid-luteal phase, the uterine arteries' pulsatility index, resistive index, and systolic/diastolic ratio were bilaterally evaluated before and after the two-week low-dose aspirin course.

Regarding the medication, low-dose aspirin (Aspocid 75 mg) was prescribed once daily after meals for at least two weeks.

Sonographic assessments were carried out between days 18 and 23 of the menstrual cycle, which is the second phase of the cycle. The participants were told to lie in the lithotomy posture and empty their bladders.

The Samsung WS80A system, which was outfitted with an Elite V5-9 Endo cavity probe transducer, was utilized to conduct ultrasound imaging. The uterus could be seen in mode B when the transvaginal probe was placed in the anterior fornix and pushed into the vagina. After determining the internal and external cervical os, the uterus was carefully examined to rule out any structural abnormalities that could have an impact on pregnancy, such as uterine myomas, bicornuate uterus, or uterine septum. Additionally, any abnormalities in the secretory endometrium were assessed, and all relevant data regarding the uterus and uterine arteries Doppler measurements were collected.

The subsequent figures illustrate the measurements obtained from the women participating in this study. (Figure 1) showing uterus in 2D plane to measure endometrial thickness and exclude any uterine anomaly.

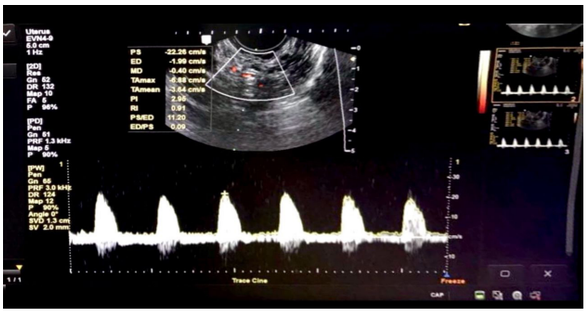

Fig. 1: 2D plane to measure endometrial thickness and exclude any uterine anomaly

Sample Size Justification

PASS® version 11 software was used to calculate the sample size, with a power (1-β) of 0.9 and a type-1 error (α) fixed at 0.05. The uterine artery's mean pulsatility index (PI) and systolic/diastolic (S/D) ratio were 2.19 ± 0.14 and 1.91 ± 0.14, respectively, before and after aspirin treatment, according to earlier study (Kang *et al*., 2016). These numbers were used to determine the required

minimum sample size, which was 70 instances. Reference for Software: Stata Corp. 2001. Statistical Software: Release 7.0. College Station, TX: Stata Corporation.

Statistical analysis

After revision, coding, tabulation, and introduction to a PC, the gathered data was processed with JMP® version 13.2.1 (SAS® Institute Inc., Cary, NC). Data were shown, and appropriate analysis was carried out in accordance with the kind of data found for each parameter. The statistical significance of the difference between the means of the two research groups was evaluated using the Student T Test. Analysis of correlation (using Pearson's method): to evaluate how strongly two quantitative variables are associated. The degree and direction of the linear link between two variables are defined by the correlation coefficient, symbolically represented by "r".

RESULTS

Demographic data were enumerated in this table (Table 1).

Table 1: Demographic characteristics of the study population

Variable	Mean ± SD	Minimum-Maximum
Age (years)	31.4 ± 3.1	24 – 39
BMI (kg/m2)	26.7 ± 2.5	20.7 - 31.6

Mean of age among the group of recurrent pregnancy loss was 31.4 ± 3.1 years old (range: 24 - 39 years old), mean of body mass index was 26.7 ± 2.5 kg/m2 (range: 20.7 - 25.76 kg/m2) (Table 2).

Table 2: Obstetric history of the study population

Variable		n	%
Frequency of previous abortions	Three	31	44.3%
	Four	20	28.6%
	Five	9	12.9%
	Six	5	7.1%
	Seven	4	5.7%
	Eight	1	1.4%
Number of previous live births	Nil	43	61.4%
	One	23	32.9%
	Two	4	5.7%

As regards Pulsatile index (PI), and before aspirin receiving, mean of uterine artery PI in the Right side was (2.21±0.28) and the mean of Left of UA PI was (2.22±0.26). Thus, the average of both sided was (2.22±0.27). Meanwhile, after aspirin intake, mean of uterine artery PI in the Right side was (1.92±0.30) and the mean of Left of UA PI was (1.91±0.28). Thus, the average of both sided was (1.92±0.29) (Table 3).

Resistive Index (RI) does not show statistical difference before and after aspirin. Average value (0.83±0.08) was the same before and after with P value (0.614. RI mean in the left side was (0.83±0.08) the same before and after Aspirin. While in the right UA it was (0.83±0.08) before treatment and (0.83±0.07) after it (Table 4).

As shown in, before aspirin receiving, the mean of Systolic/Diastolic Ratio (S/D) of uterine artery in the Right side was (5.75±0.42) and the mean (S/D) of Left of UA was (5.80±0.63). Thus, the average of both sided was (5.77±0.51). Meanwhile, after aspirin intake, mean (S/D) of uterine artery in the Right side was (5.45±0.42) and the mean of Left of UA (S/D) was (5.49±0.65). Thus, the average of both sided was (5.47±0.53) (Table 5).

Table 3: Comparison of UA PI before and after treatment

Variable	n	Before aspirin		After aspirin		Paired differences			
		Mean	SD	Mean	SD	Mean	SD	95% CI	*P-value**
Right UA PI	70	2.21	0.28	1.92	0.30	-0.30	0.07	-0.31 to -0.28	<0.0001
Left UA PI	70	2.22	0.26	1.91	0.28	-0.31	0.08	-0.33 to -0.29	<0.0001
Average UA PI	70	2.22	0.27	1.92	0.29	-0.30	0.07	-0.32 to -0.28	<0.0001

Data are mean and standard deviation (SD). 95% CI = 95% confidence interval. *Paired-samples Student t-test.

Table 4: Comparison of UA RI before and after treatment

Variable	n	Before aspirin		After aspirin		Paired differences			
		Mean	SD	Mean	SD	Mean	SD	95% CI	*P-value**
Right UA RI	70	0.83	0.08	0.83	0.07	0.00	0.01	-0.004 to 0.003	0.860
Left UA RI	70	0.83	0.08	0.83	0.08	0.00	0.01	-0.002 to 0.005	0.293
Average UA RI	70	0.83	0.08	0.83	0.08	0.00	0.01	-0.002 to 0.004	0.614

Data are mean and standard deviation (SD). 95% CI = 95% confidence interval. *Paired-samples Student T-test

Table 5: Comparison of UA SD before and after treatment

Variable		Before aspirin		After aspirin		Paired differences			
	n	Mean	SD	Mean	SD	Mean	SD	95% CI	*P-value**
Right UA SD	70	5.75	0.40	5.45	0.42	-0.29	0.08	-0.31 to -0.27	<0.0001
Left UA SD	70	5.80	0.63	5.49	0.65	-0.31	0.09	-0.33 to -0.28	<0.0001
Average UA SD	70	5.77	0.51	5.47	0.53	-0.30	0.09	-0.32 to -0.28	<0.0001

Data are mean and standard deviation (SD). 95% CI = 95% confidence interval. *Paired-samples Student t-test.

DISCUSSION

Two or more consecutive pregnancies ending before week 20 are defined as recurrent pregnancy loss. 1-5% of women worldwide during their reproductive years' experience this pregnancy complication[1].

A receptive endometrium is necessary for the blastocyst's implantation to be successful. According to research by Ng *et al*[2], an optimal endometrial environment is crucial for successful implantation.

Doppler assessment of uterine blood flow is crucial for evaluating the endometrium's functional capacity during implantation[5] In the luteal phase, a decrease in the pulsatility index of the uterine artery indicates reduced uterine blood supply, a risk factor for miscarriages[3,11].

Showing vasodilation from low-dose aspirin could diagnose recurrent pregnancy loss due to impaired mid-luteal phase uterine blood flow[3,12].

70 women, who had unexplained recurrent spontaneous abortions, underwent this study to evaluate the effectiveness of low-dose aspirin in improving uterine artery blood flow as a possible therapy for recurrent pregnancy loss.

39-year-old or younger participants had no history or current presence of abnormal glucose tolerance, thyroid dysfunction, hyperprolactinemia, or antiphospholipid antibody syndrome. 31.4-year-old participants had an average BMI of 26.7.

From both uterine arteries, we obtained independent and trustworthy flow velocity waveforms using pulsed wave Doppler during the investigation. The Pulsatility Index, Resistive Index, and Systolic/Diastolic Ratio were obtained from both sides, both before and after a two-week course of aspirin therapy (75 mg once daily with meals).

With a multi-frequency convex probe from a Samsung H60 ultrasound device, trans-vaginal evaluations were performed. Assessments were conducted during the second phase of the menstrual cycle, on the mid-luteal day.

The Systolic/Diastolic Ratio (S/D) and Pulsatility Index (PI) demonstrated significant differences according to the study results. The Resistive Index (RI) showed no significant statistical difference. In this study, using the mean values from both the left and right uterine arteries as an index of uterine artery blood flow impedance makes sense, given that both arteries supply blood to the uterus. On both sides, the Systolic/Diastolic Ratio (S/D), Resistive Index (RI), and Pulsatility Index (PI) were unchanged.

Regarding the Pulsatility Index (PI), prior to aspirin administration, the mean PI for the right uterine artery was (2.21±0.28), while the mean for the left uterine artery was (2.22±0.26), resulting in an average of (2.22±0.27) for both sides. Following aspirin intake, the mean PI for the right uterine artery decreased to (1.92±0.30), and the mean for the left uterine artery was (1.91±0.28), yielding an average of (1.92±0.29) for both sides.

The study demonstrated that the Pulsatility Index (PI) was significantly lower after aspirin administration (1.92±0.29) compared to the pre-administration value (2.22±0.27) with a *p-value* of 0.0001, while no statistically significant difference was found between the pulsatility indices of the right and left uterine arteries.

The Uterine Artery Systolic/Diastolic Ratio (S/D) exhibited a statistically significant increase following the administration of Aspirin, with values recorded at 5.47±0.53 post-treatment compared to 5.77±0.51 prior to intake (p = 0.0001). Notably, the S/D ratios of the left and right uterine arteries did not significantly vary from one another. Before starting aspirin therapy, the right uterine artery's mean S/D ratio was 5.75±0.42, while the left uterine artery's mean S/D ratio was 5.80±0.63, for an overall average of 5.77±0.51, as shown in Table 7. On the other hand, following the aspirin administration, the left uterine artery's mean S/D ratio was 5.49±0.65 and the right uterine artery's mean S/D ratio dropped to 5.45±0.42, for a combined average of 5.47±0.53.

Conversely, the Resistive Index (RI) did not demonstrate any statistically significant variation before and after the administration of Aspirin, maintaining an average value of 0.83±0.08 with a *p-value* of 0.614. According to Table 6, the mean RI for the left uterine artery remained consistent

at 0.83±0.08 both before and after treatment. Similarly, the right uterine artery recorded an RI of 0.83±0.08 prior to treatment and 0.83±0.07 following it.

These findings align with the research conducted by Kang *et al*.[16], which involved a cohort of 353 women with a history of recurrent pregnancy loss (the study group) who were administered a low dose of Aspirin (50 mg/d orally) for a duration of two months, alongside a control group of 85 women without such a history. The study compared the mean indices of uterine arteries 6 to 8 days after ovulation using transvaginal Doppler arteries' S/D ratios and Pulsatility Index (PI) were both noticeably higher during the mid-luteal phase. In addition, the recurrent pregnancy loss group's mean PI was significantly greater than the control groups.

An equivalent rise was seen in the S/D values. In cases of repeated pregnancy loss, there was a little increase in the mean resistance index (RI), however this difference did not become statistically significant. The pulsatility index (PI), RI, and S/D values were determined to be (2.09 ± 0.16), (0.81 ± 0.02), and (5.46 ± 0.50) in the control cohort, respectively. In contrast, the study group exhibited values of (2.17 ± 0.19), (0.82 ± 0.04), and (5.60 ± 0.58)[16].

Lazzarin *et al*.[12] studied the influence of diverse therapeutic measures on uterine artery pulsatility index in a population of sixty women whose RM was unexplained and had impaired uterine circulation. 3 treatment groups were designated for the participants: one group of 20 received 100 mg of daily aspirin (LDA), another group of 20 took 4 mg of daily omega-3 fatty acids, and the last group of 20 took both medications. The study indicated a 27% decrease in uterine artery PIs for the aspirin group, from 3.05 to 2.16. The combination of aspirin and omega-3 fatty acids lowered uterine PIs by 28%, decreasing from 3.02 to 2.15. These results were statistically significant. Conversely, the group receiving only omega-3 fatty acids exhibited a 16% decrease in PIs, with values shifting from 3.09 to 2.47, which was not statistically significant. The findings from this investigation align with our results regarding the impact of aspirin on lowering mean uterine PI[12].

50 women were given Plavix (75 mg daily for three months) and 55 received low-dose aspirin (also 75 mg daily for three months). The study by Abdelaziz *et al*.[17] compared uterine artery perfusion between these two groups of 105 women with recurrent miscarriages. Post-ultrasound measurements were recorded for endometrial pattern, thickness, uterine artery resistance, and pulsatility indices. The PI and RI of the uterine artery showed considerable differences among the groups.

Implantation and pregnancy continuation depend on an adequate blood supply to the uterus and endometrium[18]. Unexplained recurrent miscarriage is linked to heightened uterine artery resistance and decreased endometrial blood supply.

Low-dose aspirin prevents vasoconstriction and platelet aggregation by inhibiting the cyclooxygenase enzyme in platelets, thereby blocking the synthesis of thromboxane. Improved endometrial receptivity for implantation could be achieved through increased uterine blood flow and tissue perfusion[19].

In IVF patients treated with low-dose aspirin, Rubinstein *et al*. (1999) reported an implantation rate of 17.8%, higher than the 9.2% in the control group.

45% of treatment group patients had clinical pregnancies, compared to 28% of control group patients. An indication of Aspirin's beneficial, effective, and safe role in assisted reproductive technologies.

Duvan *et al*.[20] examined the outcomes of short-term aspirin and/or steroid therapy on implantation and pregnancy rates for ICSI cycles without prior patient selection, using a randomized trial design involving 200 patients at the time of embryo transfer. 100 mg/day.

187 patients received either Aspirin (10 mg/day) or Prednisolone (same dose), or both, or a placebo during their initial ICSI attempt. The demographic data of age and BMI did not exhibit statistically significant differences among the groups. In all groups, ovulation induction cycles exhibited similar characteristics. The number of top-quality embryos and embryos transferred was equivalent between study groups. The implantation rates in the Aspirin and control groups were 9.8% and 10.9%, respectively, with no significant difference. The clinical pregnancy rates didn't significantly differ between the Aspirin and control groups, with rates of 27% (11/41) and 35% (14/40) respectively. 29.3% (12/41) of women in the Aspirin group became pregnant, contrasted to 40% (16/40) of those in the control group.

Mesdaghinia *et al*.[21] assessed uterine artery blood flow improvement in women with recurrent miscarriages caused by impaired flow due to vitamin E and aspirin treatment. 99 women with a PI greater than 2.5 and at least two miscarriages took part in this randomized clinical trial. The groups were assigned to receive either aspirin alone, vitamin E alone, or a combination of both. After two months, the groups' uterine PIs were compared. The uterine artery PI values exhibited a significant decrease, signaling enhanced uterine perfusion for all treatment regimens.

The group on both vitamin E and aspirin had the lowest average PI (2.3) compared to the other groups (2.41 and 2.57, $p<0.001$).

In women with recurrent miscarriages, taking low-dose aspirin enhances uterine artery blood flow, as confirmed by an increase in Pulsatile Index and Systolic/Diastolic Ratio, without affecting the Resistive Index

CONCLUSION

For women who have a history of miscarriages, low-dose aspirin can be recommended as an adjuvant therapy as it effectively improves uterine artery blood flow in these patients. However, more well-designed research is required to ascertain whether improved pregnancy outcomes are correlated with improved uterine perfusion. The current study supported the aspirin guideline for women with a history of recurrent miscarriages by showing that aspirin treatment resulted in a reduction in uterine artery PI.

CONFLICT OF INTEREST

There are no conflicts of interest.

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