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## Case Report

# Plavix versus Low Dose Aspirin Impact on Blood Flow of the Uterine Artery in Women with Unexplained Recurrent Miscarriage

### Abstract

**Objective:** To evaluate Plavix impact on the perfusion of the uterine artery compared to low dose aspirin in women with unexplained recurrent miscarriage

**Patients and Methods:** It was a prospective case control study that was carried out at Ain Shams University Maternity Hospital and included women who were presented to the outpatient clinic hospital department due to unexplained recurrent miscarriage. This study was performed over a 2-year period, between January 2014 and January 2016. 105 patients were recruited and divided into two arms. Group I (plavix group) included 50 women who had a history of recurrent miscarriage and received plavix (75 mg) for 3 successive months, while group II (low dose aspirin group) included 55 women who had previously early pregnancy loss and received low dose aspirin (75 mg) for 3 successive months. After ultrasound examination had done, endometrial pattern and thickness, uterine artery resistance and pulsatility indices were measured.

**Results:** There was a significant effect of the two drugs in improving the endometrial thickness and pattern (trilaminar) when compared with the previously untreated cycles. Also, there was a significant difference between Plavix and Aspirin effects as regards improvement of endometrial pattern but not thickness. Also, there was a significant difference between the two groups as regards uterine artery PI and RI.

**Conclusions:** Compared to aspirin, plavix treatment resulted in a strikingly better endometrial pattern (trilaminar) and endometrial blood flow with no significant increase in endometrial thickness.

## Introduction

Spontaneous miscarriage is known as the spontaneous termination of gestation before the age of fetal viability (20 weeks of gestation dated from the first day of the last menstrual period) or fetal expulsion with weight of < 500 grams [1]. Lower pregnancy rates were observed in women with bad endometrial pattern or low uterine flow [2-4]. Angiogenesis accounts for an important role in different processes of female reproduction like development of ovarian follicles, corpus luteum, and growth of receptive endometrium and implantation. A sufficient endometrial perfusion is usually needed as a vital prerequisite for implantation [5].

Uterine perfusion is usually assessed by colored Doppler ultrasound and is presented as a downstream impedance to blood flow, however, the evaluation of blood flow volume is not accurate and hard. This is depending on the insonation angle, the accurate measurement of vessels' caliber and tortuosity. Dickey R, 1997 [6], reported that the implantation rate in stimulated cycles was lower when the uterine artery pulsatility index (PI) was  $\geq 3.3-3.5$  and the uterine artery resistance index (RI) was  $\geq 0.95$  at the time of HCG injection.

Low dose aspirin may enhance the pregnancy rates with artificial reproductive technique (ART) [2,4,5]. Kuo et al. [7], showed that

aspirin might improve uterine blood flow. Wada et al. [8], suggested an improved uterine blood flow impedance, pregnancy rate, and lower miscarriage rate in women with low uterine flow after therapy with low dose aspirin.

Plavix is an antagonist to adenosine diphosphate receptor (ADP), a class of oral antiplatelet drugs that block P2Y12 part of adenosine diphosphate receptor thus it blocks platelet activation and aggregation. It possesses a fast and statistically significant action within hours after the first dose and effect is continued during long term therapy [9].

The goal of this study is to assess the plavix impact on uterine artery perfusion compared to low dose aspirin in women with unexplained recurrent miscarriage in order to counsel them about the possible fate of their pregnancies and the most appropriate protocols of management.

## Patients and Methods

This was a prospective case control study that was performed at Ain Shams University Maternity Hospital over a 2-year period, between January 2014 and January 2016 and included 105 women who were presented at the outpatient clinic hospital department for having unexplained recurrent miscarriage. Patients were divided into two groups; group I (plavix group) included 50 women who had a

history of recurrent miscarriage and received plavix (75 mg) for 3 successive months, while group II (low dose aspirin group) included 55 women who had previously early pregnancy loss and received low dose aspirin for 3 successive months.

### Inclusion criteria

1. Pregnant women between the ages of 18 and 35 years.
2. Regular menstruation
3. Women with 2 or more spontaneous miscarriages with normal routine investigations e.g. antiphospholipid antibodies, karyotyping, pelvic sonar and thrombophilia screening.

### Exclusion criteria

1. loss to follow-up or who got pregnant during the 3-month follow-up
2. Any hypersensitivity to Plavix or aspirin
3. Endocrinopathies, anticoagulant use, antiplatelet treatment in the last 3 months

Informed consent was taken from every participant, after they were fully informed about the nature and scope as well as the potential risks of the study. All included women were subjected to revising history and examination sheets with particular emphasis on personal history: age, residence, education level and socioeconomic status, Complaint regarding the recurrent miscarriage, obstetric history including parity and gravidity. Investigations were done to exclude the common causes of miscarriage as lupus anticoagulant, anticardiolipin, prothrombin time, thrombophilia screening and pelvic sonar to exclude local causes as uterine anomalies.

### All patients underwent midluteal sonography and Doppler surveys

Sonographic and Doppler evaluation were done with a 3.5-MHz endovaginal probe of VOLUSON, GENERAL ELECTRIC 7500 USA. The endometrial pattern, thickness, pulsatility index (PI) and resistance index (RI) of the uterine artery were assessed. Endometrial thickness was measured at the largest antero-posterior diameter of under a vertical section or the maximum distance between each myometrial-endometrial interface through the central vertical uterine axis. Two endometrial patterns were seen: trilaminar and nontrilaminar. A trilaminar pattern was known as hypoechoic layer with a central hyperechoic line or an isoechoic layer with a central echogenic line. A nontrilaminar pattern was defined as a single homogeneous layer. For Doppler evaluation, it was focused on the ascending branch of the uterine arteries. Pulsatility and resistance indices were assessed for right and left arteries and an average was calculated and used for comparison.

- **Changes in Uterine Artery Doppler Waveform**

Resistance index (RI): Maximum – minimum velocity/maximum velocity

Pulsatility index (PI): Maximum – minimum velocity/mean velocity

### The hospital ethics committee approved the study. All patients gave their informative consent before entering into the study

**Statistical analysis:** Retrieved data were recorded on an investigative report form. The data were analyzed with SPSS<sup>®</sup> for Windows<sup>®</sup>, version 15.0 (SPSS, Inc, USA). Description of quantitative (numerical) variables was performed in form of mean, standard deviation (SD) and range. Description of qualitative (categorical) data was performed in the form of numbers and percent. Analysis of numerical variables was performed by using student's unpaired t-test (for two groups) or ANOVA (for more than two groups). Analysis of categorical data was performed by using Fischer's exact test and Chi-squared test. Logistic regression analysis was performed to calculate association between variables and their odds ratios. Association between variables was estimated using Pearson's correlation coefficient (for parametric variables) and Spearman's correlation coefficient (for non-parametric variables). Significance level was set at 0.05.

### Results

The current study was conducted on 105 women presented at Ain Shams Maternity University Hospital during the period between Jan 2014 and Jan 2016. The study included 3 groups of women: group I [n=50]; women who had had recurrent miscarriages and treated by plavix, and group II [n=55]; women who suffered from recurrent miscarriage and treated by low dose aspirin while group III [n=35]. Follow up by ultrasound for endometrial thickness and pattern, and Doppler was done to evaluate the PI and RI of uterine artery. Both groups were comparable in terms of age, body mass index, gravidity, level of education ( $\leq$ High school or  $>$ High school), occupation (house wife or employed/business woman) (Table 1).

Table 2 showed that in group I, the endometrial thickness was  $6.2 \pm 0.8$  mm and  $8.4 \pm 1.6$  mm before and after treatment with Plavix respectively and there was a significant difference between the two measures and the same was in group two in whom the endometrial thickness was  $6.7 \pm 0.9$  mm and  $8.3 \pm 1.1$  and this reflects the significant effect of the two drugs in improving the endometrial

**Table 1:** The clinic-demographic differences between group I (plavix) and Group II (low dose aspirin).

	Group I (50)	Group II (55)	P- value
Age	27.1 $\pm$ 3.2	28.2 $\pm$ 2.8	> 0.05
Body mass index (kg/m <sup>2</sup> )	26.1 $\pm$ 3.2	26.3 $\pm$ 2.2	> 0.05
Previous gravidity	4 $\pm$ 0.9	4.1 $\pm$ 1.1	> 0.05
Previous parity	0.5 $\pm$ 0.4	0.6 $\pm$ 0.2	> 0.05
Duration of marriage	8.5 $\pm$ 3.1	8.3 $\pm$ 2.8	> 0.05
Education			
$\leq$ High school	13	17	> 0.05
$>$ High school	37	38	
Occupation			
House wife	35	40	> 0.05
Employed/business Woman	15	15	

\* Analysis using independent student's t-test. NS = non-significant.

**Table 2:** The Comparison of Endometrial Thickness and Patterns and Uterine Artery PI and RI in Plavix and Aspirin Groups.

	Group I	Group II	P value
<b>Endometrial thickness</b>			
Before	6.2 ± 0.8	6.7 ± 0.9	>0.05
After	8.4 ± 1.6	8.3 ± 1.1	>0.05
P value	<0.05*	<0.05*	
<b>Trilaminar pattern</b>			
Before	32%	32.7%	>0.05
After	50%	40%	<0.05
P value	<0.05*	<0.05*	
<b>Uterine artery</b>			
PI	1.7 ± 0.4	2.5 ± 0.3	< 0.05
RI	0.6 ± 0.1	0.9 ± 0.2	<0.05

\* Analysis using independent student's t-test. < 0.05 = significant.

thickness but there was no significant difference between Plavix and Aspirin effect as regards this parameter. Also there was a significant effect of Plavix and aspirin as regards improving the endometrial pattern (trilaminar) before and after treatment. Also, there was a significant difference between the two groups as regards the uterine artery pulsatility and resistance indices.

## Discussion

The aim of the current study was to assess the effect of Plavix and low dose aspirin on improving the endometrial parameters and hence the pregnancy outcome and to compare their effects. Plavix was licensed for usage in different fields; however, it is limited to the cardiology branch. In this study, we assessed endometrial thickness and pattern, uterine artery PI and RI in both groups (Plavix and low dose aspirin respectively). We found a significant effect of the two drugs in improving the endometrial thickness and pattern (trilaminar) when compared to the previously untreated cycles. Also, there was a significant difference between Plavix and Aspirin effects as regards improvement of endometrial pattern but not thickness. Also, there was a significant difference between the two groups as regards uterine artery PI and RI.

Weckstein et al. [10], considered the value of low dose aspirin is through decreasing the impedance of uterine perfusion in the peri-implantation phase by increasing local synthesis of prostacyclins on the expense of thromboxane pathway. In contrast, Check et al. [11], suggested the absence of positive effect of low dose aspirin therapy on implantation rates following frozen embryo transfer.

Some studies had reported that women with a history of recurrent miscarriage had increased uterine artery PI and RI in the mid-luteal stage of the cycle compared to fertile women, so, abnormal uterine perfusion may be a crucial factor in women with recurrent miscarriage and negatively affecting the gestational outcome, independent from other possible factors [12].

In a recent study done by El-Sokkary M. and Hussein A 2016 [5], there was a statistically significant effect of the two regimens in increasing the endometrial thickness and pattern (trilaminar) when compared with the previous untreated cycles but there was no significant difference between Plavix and low dose aspirin effects as regards these parameters. Also, there was no significant difference

between the two groups as regards uterine artery PI and RI, mean diameter of dominant follicle and pregnancy rates.

Also, in disagreement to our results, in a randomized controlled study in women with recurrent miscarriage, 364 patients were divided into 3 groups, group I received low dose aspirin, group II administered low molecular weight heparin and the third group was on placebo. It was shown that neither aspirin nor heparin showed significant improvement in the birth rate [13].

This study involved a prospective case control study, but it is nevertheless limited in some ways. First, the number of participants needs to be more, even though all efforts were done to pick up more patients to be able to get more accurate results. Second, the study didn't involve the intake of placebo and so not double-blinded. Future studies should be a multicenter, double-blinded and include more patients.

## Conclusion and Recommendations

In view of these findings, the goal of the current work was to explore the possible values of Plavix and aspirin in cases of recurrent miscarriage and compare their effects. We found higher than expected improved endometrial thickness and pattern in both groups in comparison with previous cycles. Endometrial thickness and pattern and uterine artery PI and RI were comparable in both groups. Review of these informations led to a change of recurrent miscarriage workup protocols, with the usage of aspirin and Plavix therapy for those women with recurrent miscarriage. We expect to utilize the conclusions of this trial to help design and complete larger clinical studies using other medications for therapy of such clinical dilemma. This may show the way towards increased specification and characterization of this subset of women whose endometrial receptivity is currently insufficient.

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