Original Article

Role of Aspirin in Secretory Phase in Pre-implantation Pregnancy

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Abstract

Background: The endometrium is a complex multicellular tissue that undergoes dynamic remodelling to establish a microenvironment that is suitable for supporting a pregnancy**.** Low-dose aspirin is thought to increase uterine blood flow thus improving implantation in early pregnancy.

Aim: The current study aimed to estimate the role of low-dose aspirin in increasing fertility among reproductive-age women.

Patients and Methods: A comparative clinical trial was conducted in Salahadeen General Hospital /Gynecology and Obstetrics department and ultrasound private clinic in Baghdad during the period from 1st of January to 30th of June 2022. A convenient sample of 100 women who were at the secretory phase of the uterine cycle and planned to become pregnant in the next cycle was enrolled. The sample was divided into two groups: The intervention group (including 50 women who received low-dose aspirin (100 mg/day) starting on day 3 of the next ovulatory cycle beyond their enrollment in the current study) and the control group (which included 50 women without intervention)

Results: According to the results of the current study, aspirin was associated with a higher percentage of trilaminar endometrial wall. Aspirin was significantly associated with increased endometrial wall thickness in the intervention group. There was a significant decrease in the resistance index after aspirin use in the intervention group, there was no significant association between aspirin use and the pulsatility index. The proportion of women who become pregnant was significantly higher in the intervention group than in the control group. In conclusion, the use of aspirin in the secretory phase in pre-implantation was associated with an increase in endometrial thickness, improvement of the endometrial pattern, decrease in the resistance index of the uterine artery, and increase in the pregnancy rate.

Keywords: Aspirin, Secretory Phase, Pre-implantation, Pregnancy.

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INTRODUCTION

The endometrium is a complex multicellular tissue that creates a microenvironment that is suitable for supporting pregnancy through dynamic remodelling[(1)]. The proliferative phase, secretory phase, and menstruation are the three phases that make up the endometrial cycle. Each phase is characterised by physiological adjustments that are managed by circulating levels of progesterone and oestrogen, which are in turn influenced by the ovary[(2)]. The endometrium remodels, sheds, and regenerates during the menstrual cycle, all of which are triggered by significant changes in gene expression in the underlying cellular hierarchy[(3)]. The receptive endometrium is defined as a healthy uterine milieu containing the transformation of endometrial cells into decidua cells appropriate for implantation of blastocysts, and rapid growth of the placenta[(4)]. The development of a healthy secretory endometrium is essential for implantation and successful development of pregnancy[(5)]. It was established that pregnancy rate was affected negatively by endometrial thickness <7 mm and thin endometrium resulted in significantly lower implantation and pregnancy rates and also correlated with a higher risk of miscarriage. Therefore, the thin endometrium is an extremely poor factor that interferes with an ongoing pregnancy[(6)]. Aspirin, also known as acetylsalicylic acid, is a salicylate drug with analgesic, antipyretic and anti-inflammatory activity[(7)]. The main mechanism of action of aspirin is existing in the irreversible inactivation of cyclooxygenase-1 (COX-1), officially known as prostaglandin-endoperoxide synthase (PTGS1), and the inhibition of COX-2/PTGS2, thus suppressing the production of pro-inflammatory, thrombocyte-aggregating

prostaglandins, and thromboxane. Despite the common use of low-dose aspirin among reproductive-age women, its impact on menstrual cyclicity and hormonal profiles is not known. Aspirin and other nonsteroidal inflammatory drugs have the potential to interfere with ovulation by inhibiting prostaglandin production by cyclooxygenase[8]. Traditionally, low-dose aspirin (LDA) is thought to increase uterine blood flow thus improving implantation in early pregnancy[9]. By improving endometrial receptivity, which is a temporary state in which the endometrium is acceptable for embryo implantation, aspirin has been shown to increase pregnancy rates in patients undergoing in vitro fertilisation. Aspirin is closely associated with embryo implantation rate and pregnancy rates as nearly two-thirds of implantation failures correlate with poor endometrial receptivity[10]. The current study aimed to estimate the role of low-dose aspirin in increasing fertility among reproductive-age women.

PATIENTS AND METHOD

A comparative clinical trial study was done in Salahadeen General Hospital /Gynecology and Obstetrics Department and ultrasound private clinic in Baghdad from 1st of January to 30th of June 2022.

Ethical considerations

The study was proposed and subsequently approved by the scientific committee of the College of the Medicine/University of Tikrit.

Sampling and inclusion criteria

A convenient sample of 100 women who were at the secretory phase of the uterine cycle and planned to become pregnant in the next cycle was enrolled in the current study. The sample was divided into two groups:

Intervention group: Including 50 women who received low-dose aspirin (100 mg/day) starting on day 3 of the next ovulatory cycle beyond their enrollment in the current study.

Control group: Included 50 women without intervention.

Exclusion criteria

- Allergy or any contraindication to using aspirin.
- Loss to follow up.
- Uterine anatomical abnormalities

Data collection

The data were obtained through direct interviews, medical history, examination, and results of the ultrasound examination inquiring for information using a questionnaire formulated by the researcher and then revised by the supervisor. The data collection was obtained through three steps, including:

Step one: History, including age, parity, and abortions.

Step two: Examination, including weight, and height.

Step three: Ultrasound examination (including Doppler ultrasound) at the secretory phase of the menstrual cycle at the beginning of the study and the secretory phase of the next cycle, it included the assessment of endometrial pattern (trilaminar and non-trilaminar), endometrial thickness, and vascular impedance (pulsatility index (PI) and resistance index (RI) of the uterine artery). A transabdominal ultrasound examination was done in Salahadeen General Hospital, while in the private ultrasound clinic in Baghdad the ultrasound examination was transvaginal.

The measurement of the endometrial thickness was done at the greatest anterioposterior dimension of the endometrium under a longitudinal section. There were two patterns of the endometrium: trilaminar and non-trilaminar. A trilaminar pattern was recognized as a hypoechoic layer and a central hyperechoic line or an isoechoic layer and central echogenic line. The non-trilaminar pattern was defined as a single homogeneous layer.

The Doppler ultrasound examination was focused on the ascending branch of the uterine artery.

Definition of variables

The resistance index is defined as the systolic flow velocity minus the diastolic velocity divided by the systolic velocity, and the pulsatility index is defined as the systolic flow velocity minus the diastolic velocity divided by the mean velocity(43).

After measurement of the weight and height, the body mass index (BMI) was calculated according to the formula:

BMI= weight (Kg) / **(**height (m)**)**^{2}[44]

RESULTS

A total of 100 women were enrolled in the current study, there were no significant differences between the study groups regarding age, parity, abortion, and BMI. As shown in table 1.

Table 1: Characteristics of the participants

Participants characteristics		Groups		Total	P-value
		Intervention N (%)	Control N (%)		
Age (years)	<20	7 (14.0)	10 (20.0)	17 (17.0)	0.680
	21-30	23 (46.0)	23 (46.0)	46 (46.0)	
	>30	20 (40.0)	17 (34.0)	37 (37.0)	
Parity	0	1 (2.0)	0 (0.0)	1 91.0)	0.146
	1	8 (16.0)	14 (28.0)	22 (22.0)	
	2	23 (46.0)	27 (54.0)	50 (50.0)	
	3	13 (26.0)	8 (16.0)	21 (21.0)	
	4	5 (10.0)	1 (2.0)	6 96.0)	
Abortion	0	44 (880)	43 (86.0)	87 (87.0)	0.750
	1	2 (4.0)	2 (4.0)	4 (4.0)	
	2	3 (6.0)	2 (4.0)	5 (5.0)	
	3	1 (2.0)	3 (6.0)	4 (4.0)	
Body mass index	Normal	30 (60.0)	33 (66.0)	63 (63.0)	0.829
	Overweight	15 (30.0)	13 (26.0)	28 (28.0)	
	Obese	5 (10.0)	4 (8.0)	9 (9.0)	

Chi-Square test

The was no significant difference between the study groups regarding the endometrial wall pattern at the beginning of the study, while after the intervention, the intervention group had a significantly higher percentage of trilaminar endometrial wall (P-value=0.022). As shown in table 2.

Table 2: Effects of the aspirin on the endometrial wall pattern

Endometrial wall pattern	Groups		P-value
	Intervention N (%)	Control N (%)	
	First menstrual cycle		
Trilaminar	37 (52.9)	33 (47.1)	0.383
Non-trilaminar	13 (43.3)	17 (56.7)	
	Second menstrual cycle		
Trilaminar	45 (55.6)	36 (44.4)	0.022
Non-trilaminar	14 (73.3)	5 (26.3)	

Chi-Square test

Aspirin was significantly associated with increased endometrial wall thickness in the intervention group (P-value==0.001) As shown in table 3.

Table.3: Trend of the endometrial wall thickness after intervention

Groups	Endometrial thickness (mm) Mean (SD)		P-value
	First cycle	**Second cycle**	
Intervention	9.18 (1.6)	13.2 (2.0)	0.001
Control	9.64 (1.7)	9.98 (1.8)	0.120

Chi-Square test

There was a significant decrease in the resistance index after aspirin use in the intervention group, with there was no significant association between aspirin use and the pulsatility index (Table 4).

Table 4: Association between aspirin use and vascular impedance

Groups	Pulsatility index Mean (SD)		P-value
	First cycle	**Second cycle**	
Intervention	2.340 (0.13)	2.33 (0.12)	0.630
Control	0.746 (0.1)	0.694 (0.1)	0.056
	Resistance index Mean (SD)		
	First cycle	**Second cycle**	
Intervention	0.754 (0.10)	0.692 (0.11)	**0.002**
Control	2.320 (0.11)	2.360 (0.13)	0.146

t-test

At enrollment of the participant, the was no significant difference between the study groups regarding the percentage of those with a thin endometrial wall. After the intervention, there was a significant difference between the study groups regarding the percentage of the participants with a thin endometrial wall, the intervention group had a significantly lower percentage of a thin endometrial wall than the control group (Table.5).

Table.5: Effect of aspirin on the abnormal uterine thickness (>8 mm)

Endometrial wall pattern	Groups		P-value
	Intervention N (%)	Control N (%)	
	First menstrual cycle		
Normal thickness	40 (49.4)	41 (50.6)	0.799
Abnormal thickness (<8mm)	10 (52.6)	9 (47.4)	
	Second menstrual cycle		
	Intervention N (%)	Control N (%)	
Normal thickness	48 (53.9)	41 (46.1)	0.025
Abnormal thickness (<8mm)	2 (18.2)	9 (81.8)	

The proportion of women who become pregnant was significantly higher in the intervention group than in the control group (P-value=0.045), as shown in figure 1.

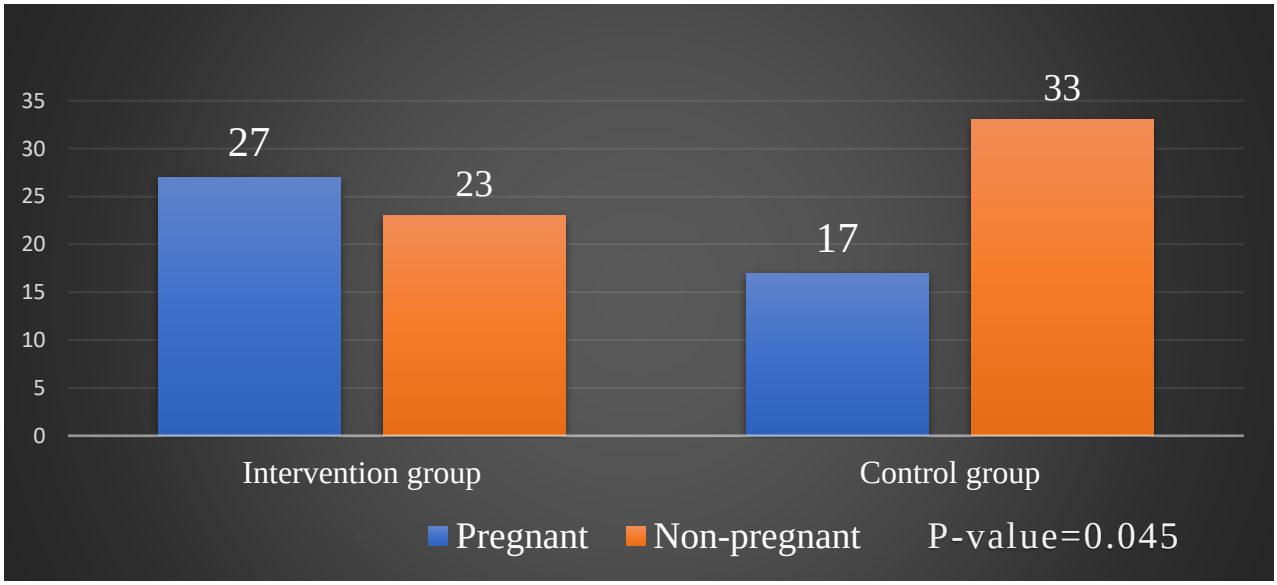

Figure 1: Proportion of conception among the participants

Discussion

Transferred embryo quality and endometrium receptivity are the most important factors influencing the implantation and clinical pregnancy rates following embryo transfer. Aspirin is a non-steroidal anti-inflammatory drug that is commonly used in repeated abortions[11]. This study was one among others that tried to assess the effect of aspirin on the endometrium and pregnancy rate.

The first finding of the current study was a significant increase in the proportion of women with trilaminar endometrium in the intervention group compared to a non significant change in the control group. In agreement, the same results were obtained by another study that was done in China[12]. In Taiwan, revealed that a higher percentage of women had trilaminar endometrium with aspirin use compared to the control group[13].

Aspirin use was associated with a significant increase in the endometrial thickness compared to nin significant change in the control group. In comparison, the same results were obtained in by in Iraq, 2020 and revealed a significant association between aspirin use and improvement in endometrial thickness[14].

In contrast, another study done in China revealed an insignificant association between aspirin use and endometrial thickness[15].

A significant association was obtained between Aspirin use and a decrease in the resistance index of the uterine artery, while non a significant association between aspirin use and pulsatile index. In agreement with the current study, Xiaoxin et al. reported that the low-dose aspirin treatment resulted in a significant decrease in endometrial and uterine arterial blood flow resistance[16].

In Iraq, a study that was done in 2020 revealed that the use of aspirin significantly improve the resistance index and pulsatile index of the uterine artery[11]. Tongfei et al. revealed that aspirin use was significantly associated with decreased

resistance index and pulsatile index[17]. In China, a study was done there revealed an insignificant association between pulsatile index, resistance index and aspirin use[46].

There was a significant improvement in the endometrial thickness among those with abnormal endometrium with aspirin use. The proportion of them was significantly decreased in the second menstrual cycle with aspirin use. The same results were obtained in another that was done in Taiwan and concluded a higher pregnancy rate and better endometrial pattern were attained in patients with thin endometrium after aspirin administration[18].

The current study revealed a significant association between aspirin use and the percentage of conception as more than half of the women were becoming pregnant with aspirin use compared to the control group where about one-third of the women were becoming pregnant. In another study, the percentage of conception was two times more in the intervention group with aspirin use than in the control group[16]. In agreement with these results, Utku et al revealed that the histological alterations in the uterus epithelium revealed that low-dose aspirin had positive contributions in preparing rat endometrium for implantation[19].

Conclusion

The use of aspirin in the secretory phase in pre-implantation is associated with an increase in endometrial thickness, improvement of the endometrial pattern, decrease in the resistance index of the uterine artery, and an increase in the pregnancy rate.

Recommendations

1. Aspirin should be prescribed in the management of women with infertility, and those with abnormal uterine patterns or thickness.
2. Other studies should be carried out during the upcoming period to evaluate the other factors that could impact the uterine ability to receive the fertilized ova and their association with aspirin use.

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