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ORIGINAL ARTICLE

Evaluation of the Effect of Low Dose Aspirin on Cervical Length as an Indicator of Preterm Labor in Nulliparous Women

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KEYWORDS

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ABSTRACT: Preterm labor is one of the most common midwifery problems in developing and even advanced countries imposing a huge cost on people and the health system. One of the most important causes of preterm labor is short cervical length. Periodic monitoring of cervical length is an important factor in predicting incidence of preterm labor. The purpose of this study was to determine the effect of low dose aspirin on cervical length in nulliparous women. In a double-blind randomized clinical trial, nulliparous pregnant women with gestational age of less than 13 weeks and 6 days were enrolled in the study and randomly divided into intervention and control groups. Demographic, clinical and Para clinical data were recorded. The intervention group received 80 mg daily aspirin, while the control group received placebo. Cervical length and maternal and fetal outcomes were recorded and analyzed. The results have shown a decrease in cervical length at 12, 18 and 30 weeks of gestation in the control group and an increase in the intervention group, indicating the effect of aspirin administration on prevention of preterm labor ($P < 0.05$). Maternal complications were not significantly different between the two groups. Cervical length with cut-off point of 30 at 30 weeks' gestation had a positive predictive value of 64% and a negative predictive value of 94% in predicting preterm labor. Our study has shown that low-dose aspirin administration may prevent cervical length reduction and preterm labor, although it has had no effect on reducing maternal complications such as preeclampsia, vaginal bleeding, low birth weight, and spontaneous abortion. Moreover, measurement of cervical length (with cut-off point of 30 mm) in the third trimester of pregnancy is a good indicator in predicting preterm labor.

INTRODUCTION

Preterm labor refers to childbirth between gestation age of 20 weeks and the end of 37 weeks of pregnancy and it is one of the major causes of neonatal morbidity and mortality and one of the most common midwifery problems worldwide; especially, in developing countries [1, 2]. Even in developed countries like the United States, despite significant research and clinical efforts, the prevalence of preterm labor in 2006 was about 12.6% and in 2012, about 11.5%, which is relatively significant [3, 4]. There are many factors causing preterm labor, which can be due to intrauterine infections, cervical diseases, excessive uterine dilatation, and placental ischemia caused by preeclampsia and intrauterine growth restriction [5]. Studies have shown that infants' mortality with preterm births before 37 weeks and 32 weeks' gestation were 15 and 75 times more than infants who have term births respectively, respectively. The complications of preterm labor are not limited to a specified time and they may cause problems throughout the

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life [6, 7]. Despite the improved perinatal care for preterm infants, preterm birth still leads to neonatal mortality [8, 9]; therefore, prevention of preterm birth is a major concern of the health system and its staff all over the world, and interventions to reduce the prevalence of preterm labor are strongly recommended [10-13]. Cervical length examination is one of the useful and effective tools in predicting preterm labor [14-16].

Cervical length is considered a reliable factor in predicting preterm delivery [17, 18]. More precise diagnosis of preterm labor is obtained by measuring cervical length with trans-vaginal ultrasound, avoiding unnecessary actions and interventions, especially in cases of cervical length equal to or greater than 30 mm [19]. Periodic cervical length assessment, especially in cases of short cervical length or in the first delivery, may be a useful and appropriate tool in predicting preterm delivery [19-21]. Aspirin has been studied limited in the prevention of preterm labor recently. Aspirin, as an inhibitor of cyclooxygenase, inhibits thromboxane A2, thereby inhibiting vascular contraction, and platelet aggregation [22] .

Administration of aspirin during pregnancy is thought to improve the penetration of uterine spiral arterioles into trophoblasts, leading to optimal fetal blood supply [23, 24]. Aspirin has been described as a cheap, affordable, safe, and potentially effective drug for preventing preterm labor [25, 26]. Studies have shown that low-dose aspirin is safe for the fetus from the age of 8 to 16 weeks of pregnancies [27, 28]. Reduced preeclampsia, low birth weight, and placental insufficiency can be mentioned among the benefits of aspirin in pregnancy, thereby reducing drug-induced preterm delivery [25, 29]. Despite these findings and hypotheses, there is still controversy in various studies regarding the effects of aspirin on reducing the incidence of preterm labor [30].

Therefore, it is necessary to conduct more clinical trials in different societies and with different methods in this field and to pay attention to the sensitivity and high specificity of cervical length measurement in predicting preterm delivery in the third trimester of pregnancy. Furthermore, whether periodic cervical lengthening, especially in cases of short cervical length or in cases of first childbirth, it can be an appropriate and useful tool in predicting preterm delivery [17, 18]. The aim of this study was to determine the effect of low dose aspirin on cervical length of nulliparous women referring to gynecology clinic of Amir al-Momenin Hospital in Semnan, Iran, in 2018-2019, as a predictive tool in preterm delivery of pregnant mothers.

MATERIALA AND METHODS

In a randomized, double-blind clinical trial (patients and the persons who were prescribed drug and placebo and the imaging specialist who performed the sonography were unaware of the type of drug used for each individual). Nulliparous women with gestational age of less than 13 weeks and 6 days referring to gynecology clinics in 2018 and 2019 were studied.

Samples were selected by convenience sampling and with a minimum sample size of 61 people (intervention group 30 persons and control group 31 persons). Inclusion criteria were age between 18 to 40 years old, nulliparous, single-pregnancy between 12 and 13 weeks of gestation with sonography confirmation, having less than two abortions in the first trimester of previous pregnancies.

Exclusion criteria included history of abortion in the second trimester, contraindication of aspirin, cigarette and drug use, polygamy, fetal abnormality in sonography, hematocrit less than 7 mg/deciliter, history of systemic diseases such as lupus, diabetes, hypertension before pregnancy, cyclic anemia, short cervical length below 25 mm, and uterine anomaly.

Primary information in a checklist containing patient demographic information, history, clinical and paraclinical examination, including age, gestational age, BMI, systolic and diastolic blood pressure, maternal outcomes (eclampsia, preeclampsia, hypertension, blood Vaginal delivery during pregnancy, and changes in maternal hematocrit), fetal outcomes (low birth weight, prenatal mortality, spontaneous miscarriage or stillbirth), cervical length sonography results and side effects of drugs were collected and recorded. Then, based on randomized allocation method using Block Stratified Randomization, they were divided into two groups A and B; group A (intervention group) 80 mg daily aspirin plus folic acid +

iron tablets from the second trimester of pregnancy and group B (control group) received daily folic acid plus placebo + iron tablets from the second trimester of gestation until week 32 of gestation (based on the early pregnancy sonography). These patients were periodically examined by a gynecologist with the help of a history and clinical examination. Cervical length measurement (using transvaginal sonography) was performed at the age of 12, 18 and 30 weeks of gestation based on sonography calculation and blood hematocrit level (using Complete Blood Counter) in two times, once per 13 weeks and again at 30 weeks of gestation. During the periodic checkups, the primary and secondary outcomes of the patients were weekly evaluated until the end of pregnancy and delivery and recorded in the relevant forms. After collecting data, the database was created and the data were entered and analyzed. Kolmogorov-Smirnov test was used to check the normality of data distribution. T-test and chi-square test were used for analysis. A value of less than 0.05 was considered significant. SPSS 21 software was used for data analysis.

RESULTS

In this study, 61 patients in two groups (n = 30, intervention) and (n = 31, control) were studied to determine the relationship between low dose aspirin on cervical length and outcomes and side effects (maternal and fetal) of aspirin use. The mean age of mothers was 25.77 ± 5.38 years in the control group and 26.66 ± 5.57 years in the intervention group. Age distribution was normal in both groups (Z = 0.735, P = 0.653). Moreover, the distribution of patients was normal in terms of body mass index, systolic and diastolic blood pressure. Mean of first-time hematocrit in patients was 36.92 ±2.7 (in intervention group: 36.84 ±2.8, in control group: 37.00 ± 2.5) that was not significant (P = 0.817). The mean of second time hematocrit in the patients was 31.95 ± 3.1 (in intervention group: 31.41 ±3.0, in control group: 32.48 ± 3.2) that was not significant (P = 0.191). The minimum fetal age at baseline was 12 weeks and its maximum was 13 weeks and six days. The mean fetal age at baseline was 12.33 ± 0.7 weeks (in intervention group: 12.22 ± ۰.۷ weeks, in control group: 12.43 ± 0.8 weeks) and the difference was not significant (P = 0.411). Twenty-one patients in the intervention group and 21 in the control group had normal delivery. There was no significant difference between the two groups regarding delivery method (P = 0.534). The mean gestational age at birth was 37.83 ± 2.6 weeks (in the intervention group: 38.39۲.۱± weeks, in the control group: 37.30 ± 3.0 weeks). The difference was not significant (P = 0.114). Five persons in the intervention group (16.7%) and nine persons in the control group (29.0%) had preterm labor. There was no significant difference between the two groups in terms of delivery (P = 0.200).

Cervical length was measured three times (at 12, 18, and 30 week's gestation age). The mean cervical length of the groups is presented in Table 1. The mean cervical length in the intervention and control groups was significantly different at all three times (Table 2). At the beginning of the study period (week 12), the mean cervical length in the intervention group was 36.50 ± 3.2 and in the control group was 39.00 ± 3.7, significantly higher in the control group. The mean cervical length in week 18 was 37.67 0 0.3 in the intervention group and 35.29 ± 3.8 in the control group and in week 30, the mean cervical length in the intervention group was 36.60 ± 4.5 and 29.30 ± 6.6 in the control group. In both cases, the mean cervical length intervention group was more than the control group. At week 30, the mean cervical length in both groups decreased compared to week 12, showing a more significant decrease in the control group.

The mean of cervical length at 12 and 18 weeks of gestation in the intervention group was not statistically significant in terms of gestational age at delivery. The mean cervical length at week 30 of gestation in the intervention group and in mothers giving birth between 34 and 37 weeks was 29.75 ± 3.1 mm and in mothers who gave birth after 37 weeks 37.83 ± 0.6. There was a significant difference between two groups (P = 0.001). There was no significant difference between the mean cervical length at week 30 of gestation in the intervention group and in mothers giving birth before week 34 of gestation and with mothers giving birth after week 37 of pregnancy (P = 0.349); moreover, there was no significant difference in mothers giving birth

before week 34 and the mean in mothers delivering between the ages of 34 and 37 weeks of gestation (P = 0.284) (Table 3).

The mean of cervical length at 12 weeks of gestation in the control group was not statistically significant in terms of gestational age at delivery (P >0.05). There was a significant difference in the mean of mothers giving birth after week 37 of pregnancy (P = 0.035). Furthermore, the mean cervical length at week 18 of gestation in mothers giving birth at weeks 34 to 37 of gestation was significantly different from those giving birth after week 37 (P = 0.046) (Table 4).

The mean cervical length at week 30 of gestation in the control group and in mothers giving birth before 34 weeks of gestation was 19.40 ± 4.5, in mothers who had delivered between 34 and 37 weeks 24.50 ± 5.8 mm and in mothers giving birth after week 37 of gestation was 32.09 ± 4.2 mm. The mean cervical length at week 30 of gestation in the control group and mothers giving birth before 34 weeks of gestation was not significantly different from those giving birth between 34 and 37 weeks of gestation (P = 0. 180). However, there was a significant difference between the mean cervical length at week 30 of gestation in the control group and in mothers giving birth after week 37 of gestation with mothers giving birth between 34 and 37 weeks of gestation and in mothers who giving before 34 weeks of gestation with those giving birth after week 37 of gestation (P = 0.004 and P = 0.001, respectively) (Table 4).

There were no cases of eclampsia, stillbirth, and maternal death. There were complications in both groups including preeclampsia, hypertension, vaginal bleeding, low birth weight, and spontaneous abortion. The incidence of complications was not significantly different between the intervention and control groups (Table 5).

Seven patients in the intervention group had drug-induced complications. The most reported complication was nausea. In the intervention group, in those with a cervical length less than 30 mm in the 30th week of gestation, two had term labor and three had preterm labor. In this group, no preterm delivery was seen in any of the cervical lengths above 30 mm. The positive predictive value of preterm delivery based on cut-off point 30 for cervical length at week 30 of gestation was 60% in the intervention group and negative predictive value was 92%.

In the control group, six persons had term delivery and eight had preterm delivery in those with cervical length of less than 30 mm in gestation 30 weeks. In this group, one person with a cervical length of 30 or more had preterm labor, cervical length at 30 weeks of gestation in this person who had a preterm birth was 30 mm. Positive predictive value based on cut-off point 30 for cervical length at the 30th week of pregnancy in the control group was 57% and negative predictive value was 94%. In all mothers who had cervical length less than 30 mm, six had term delivery and eleven had preterm labor. Moreover, of those who had a cervical length above 30 mm, three had preterm labor. The positive predictive value based on cut-off point 30 for cervical length at week 30 of gestation was 64% and negative predictive value was 93%.

Table 1. Mean, standard deviation, and quadratic interval cervical length in the three study periods

CL	Number	Time	Mean	Standard deviation	Minimum	Maximum	P
week 12	30	Intervention group	36.50	3.2	32	50	0.007
		Control group	39.00	3.7	34	50	
		Total	37.77	3.7	32	50	
week 18	31	Intervention group	37.67	3.0	30	48	0.010
		Control group	35.29	3.8	26	43	
		Total	36.46	3.6	26	48	
week 30	61	Intervention group	36.60	4.5	26	49	□0.001
		Control group	29.30	6.5	13	37	
		Total	32.95	6.7	13	49	

Table 2. Comparison of mean cervical length at week 12, 18, and 30 gestation

Group	Period check	Mean difference	Standard deviation	95% CI		P
				Minimum	Maximum	
Intervention	Week 12, 18	1.167	2.79	0.124	2.209	0.030
	Week 12, 30	0.10	4.66	-1.641	1.841	0.907
	Week 18, 30	-1.067	2.87	-2.141	0.007	0.051
Control	Week 12, 18	-3.710	2.57	-4.653	-2.766	□0.001
	Week 12, 30	-9.867	5.84	-12.048	-7.686	□0.001
	Week 18, 30	-6.300	5.44	-8.331	-4.269	□0.001
Total	Week 12, 18	-1.311	3.62	-6.759	-3.008	0.006
	Week 12, 30	-4.883	7.26	-6.759	-3.008	□0.001
	Week 18, 30	-3.683	5.05	-2.377	-5.642	□0.001

Table 3. Comparison of mean cervical length at 12, 18 and 30 weeks of pregnancy term subtypes in intervention group

CL	Pregnancy term (week)	Number	Mean	Standard deviation	Compare subgroups (P value)		
					Subgroup 1 with 3	Subgroup 2 with 3	Subgroup 1 with 2
week 12	Less than 34	2	36.50	0.7	0.961	0.634	0.492
	34-37	4	37.25	0.6			
	More than 37	24	36.38	0.7			
week 18	Less than 34	2	35.50	0.5	0.202	0.106	1.00
	34-37	4	35.50	1.9			
	More than 37	24	38.21	0.5			
Week 30	Less than 34	2	35.50	0.5	0.349	0.001	0.284
	34-37	4	29.75	3.1			
	More than 37	24	37.83	0.6			

Subgroup 1: less than 34 weeks, subgroup 2: 34.34 weeks, subgroup 3 more than 37 weeks

Table 4. Comparison of mean cervical length at 12, 18, and 30 weeks of pregnancy term subtypes in control group

CL	Pregnancy term (week)	Number	Mean	Standard deviation	Compare subgroups (P value)		
					Subgroup 1 with 3	Subgroup 2 with 3	Subgroup 1 with 2
week 12	Less than 34	5	36.40	1.9	0.075	0.270	0.470
	34-37	4	37.50	2.3			
	More than 37	22	39.86	4.0			
week 18	Less than 34	5	32.40	3.9	0.035	0.046	0.964
	34-37	4	32.50	1.7			
	More than 37	22	36.45	3.6			
Week 30	Less than 34	5	19.40	4.5	0.001	0.004	0.180
	34-37	4	24.50	5.8			
	More than 37	22	32.09	4.2			

Subgroup 1: less than 34 weeks, subgroup 2: 34.34 weeks, subgroup 3 more than 37 weeks

Table 5. Frequency of maternal and fetal complications in subjects

Group	Number	Complication	Preeclampsia	Eclampsia	HTN	Vaginal bleeding	Low birth weight	Spontaneous abortion	Stillbirth	Mother's death
Intervention	30	Positive	2	0	2	2	2	1	0	0
		Negative	28	30	28	28	28	29	30	30
Control	31	Positive	4	0	0	5	2	2	0	0
		Negative	27	31	31	26	29	29	31	31
		P	0.414	-	0.144	0.246	0.973	0.573	-	-
Total	61	Positive	6	0	2	7	4	3	0	0
		Negative	55	61	59	54	57	58	61	61

DISCUSSION

This study was aimed at investigating the effect of low dose aspirin on cervical length as an index of preterm labor in nulliparous women and maternal and fetal complications. The results have shown a significant difference in cervical length from 12 to 30 weeks of gestation in the control group (not receiving aspirin) compared to the intervention

group, indicating the effect of aspirin administration on preterm labor (P <0.05). Maternal complications were not significantly different between the two groups.

The results of the present study have revealed a reduction in cervical length of less than 30 mm in the third trimester of pregnancy with a positive predictive value of 64% and a negative predictive value of 93% in predicting preterm labor, so that in 93% of those whose cervical length in the third trimester pregnancy is greater than 30 mm, preterm labor is not seen, which is consistent with the results of the study other [32].

In a clinical trial study [4], the persons were randomly divided into two groups. Intervention group received daily 80 mg aspirin and folic acid and control group received folic acid alone. Although its difference from our study was that people who had a history of miscarriage were examined and if they were pregnant, follow-up during pregnancy were done.

Preterm labor occurred in 27.3% of the aspirin-consuming group and 38.7% of the placebo-consuming group. It can be concluded that low-dose aspirin before pregnancy did not significantly reduce the prevalence of preterm labor, requiring further studies. In our study, the prevalence of preterm labor was 16.7% in the aspirin consuming group and 29% in the control group, which was not significant (P = 0.200). In Silver's study, cervical length was not evaluated; however, in our study the administration of low dose aspirin on cervical length was evaluated, resulting in a slight decrease in cervical length from week 12 to week 30 of pregnancy compared to the control group (P = 0.030). Therefore, aspirin can be effective in preventing preterm labor [4].

In a clinical trial study [33], the effect of low-dose aspirin did not prevent the occurrence of preeclampsia and preterm delivery [33]. This was in line with the results of our study.

In a study [34], there was a significant relationship between short cervical length and gestational age at delivery based on gestational week (P = 0.027). Moreover, cervical length was significantly associated with delivery before 34 weeks (P = 0.045); while less than 37 weeks (P = 0.046) and cervical length at the third trimester pregnancy had high predictive value in determining the age of childbirth and it could be used as a useful and high-precision tool [34], very similar to the results of our study.

In a study other [35], the predictive value of cervical length measurement with transvaginal sonography in the third trimester was evaluated between weeks 24 and 30 of gestation; cervical length in women giving birth before 34 weeks (30 to 34 weeks of gestation) was significantly lower than those giving birth after 34 weeks (P = 0.001). Besides, cervical length in women giving birth before week 37 (34 to 37 weeks of gestation) was significantly lower than those giving birth after week 37 (P = 0.001). The shorter the length of a person's cervix, the greater the likelihood of preterm labor; thus, measuring cervical length in the third trimester of pregnancy, as a useful and high-precision tool, has high predictive value in determining childbirth [35]. This is very similar to the present study despite the small sample size.

In the present study, aspirin was administered during sleeping at a dose of 80 mg in the first trimester of pregnancy (12 to 13 weeks and six days) and continued until the end of pregnancy. In the study by Ayala [36], the group consuming aspirin 8 hours after waking up and during sleep had significantly less preterm labor than the placebo group and the group consuming aspirin in when they were awake. The results of this study were similar to the Ayala study and showed a positive effect of low dose aspirin in preventing reduction of cervical length and preterm labor. However, in our study, there was no significant difference between the two groups in preterm delivery, which may be due to the difference in aspirin dose.

In a systematic review study [31], reviewed articles on aspirin use and the prevalence of preterm labor. The results showed that low doses of aspirin before 16 weeks of gestation compared to placebo had a significant improvement in preterm labor control, although this drug had no significant effect on preeclampsia; the study suggested further studies to clarify the subject. The results of this study are very similar to ours. In our study, low-dose aspirin administered from the first trimester of pregnancy, between 12 and 13 weeks and six days of gestation, had a significant effect on preventing reduction of cervical length

and preterm labor. Comparison of cervical length at weeks 18 and 30 of pregnancy showed a very slight decrease, which was not significant (P = 0.051). In our study, similar to the Roberge study, low-dose aspirin had no effect on the prevalence of preeclampsia (P = 0.414).

The results of a study [37] showed that aspirin administration could not prevent preeclampsia in these women. Furthermore, low-dose aspirin cannot significantly reduce the prevalence of preterm labor. In our study, daily aspirin administration at a dose of had no effect on reducing the incidence of 80-mg preeclampsia (P = 0.414), which is similar to a study [37]. In terms of the effect on cervical length and preterm labor, our study, unlike a study other [37], showed that low-dose aspirin administration had the effect of preventing reduction of cervical length and preterm labor by comparing the cervical length from week 18 to 30 with a very slight decreasing trend that difference was not significant (P = 0.051).

The results of a randomized clinical trial study [38] showed that low-dose aspirin did not significantly decrease the incidence of preeclampsia and the occurrence of spontaneous preterm labor. Moreover, our study showed that aspirin use had no effect on decreasing the incidence of preeclampsia (P = 0.414). Our study was similar to a study other [38], but on the other hand, ours showed that aspirin administration was effective in preventing reduction of cervical length and it could prevent preterm labor and therefore had a conflicting result with a study [38].

CONCLUSIONS

As this study was conducted in a limited population, larger studies with larger sample size are recommended. Larger studies are also recommended, comparing different doses of aspirin in different weeks of pregnancy, in high-risk and low-risk groups so that all individuals can be compared to reach a more definitive and robust conclusion.

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ETHICAL CONSIDERATION

The study project had approved by the research ethics committee of Semnan University of Medical Sciences (approval ID: IR.SEMUMS.REC.1396.9).

Conflict of Interest

The authors declare not having any personal or financial support or involvement with organizations with financial interest in the subject matter or any actual or potential conflict of interest.

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