Original Article

Effects of aspirin on adverse pregnancy outcome in patients with abnormal aneuploidy screening biochemistry tests: A randomized clinical trial

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Abstract

Background: The aim of the present study was to study the effects of low dose aspirin on preventing any Adverse Pregnancy Outcome (APO) in women with aneuploidy abnormal screening tests in the second quarter and to compare the effects of aspirin on normal and abnormal Doppler.

Methods: The current clinical trial study was performed on pregnant women with abnormal aneuploidy screening tests and normal Karyotype at the gestational age 15-18 week. Participants consisted of 83 individuals in aspirin-receiving group and 84 persons in control group. Doppler ultrasound was simultaneously performed to survey the Doppler results. Any APO was compared between the two groups.

Results: The frequency of APO was 32.8% in aspirin-receiving group and 41.7% in control group (*P*=0.01, RR=0.438). The frequencies of preterm delivery before the 37th week were 8.07% in the group receiving aspirin with normal Doppler and 32.7% (*P*=0.02) in the control group. The frequency of NICU reception with normal Doppler was 5.8% in the aspirin group and 19.7% in control group (*P*=0.01). APO frequency in the group with many abnormal factors was 11.5% in the group receiving aspirin and 53.8% in control group (*P*=0.01). APO frequency in abnormal Doppler group was found to be 46.7% in the group receiving aspirin and 50% in the control group (*P*=0.84, RR=0.112).

Conclusion: Low dose of aspirin reduced APO. It reduced preterm delivery and reference of pregnant women to NICU with abnormal aneuploidy screening tests.

Keywords: Adverse Pregnancy Outcome; Aneuploidy; Doppler; Screening

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Introduction

Today, using maternal serum markers, including alpha-fetoprotein, non-conjugated estriol, inhibin A, and BHCG, is described as aneuploidy screening. The increased levels of these markers reflect placenta function and are related to Adverse Pregnancy Outcome (APO) (1). Doppler ultrasound of umbilical cord is an assessment method of maternal-fetal blood flow. As a predictive

factor in high-risk pregnancies, Doppler is related to reduction of adverse outcomes such as perinatal mortality, hospitalization, caesarean section, fetal distress, and encephalopathy (2, 3). APO is one of the critical problems in the developing countries. The most important APOs are blood pressure disorders, abruption and placenta previa, intrauterine death, intrauterine growth retardation, and preterm delivery (4). It is estimated that annually, 500000 women die due to adverse pregnancy outcomes. Most of these deaths happen in the developing countries (5).

The results of a study about the effects of aspirin on APO indicated a relationship with increased levels of alpha-fetoprotein. Consumption of low-dose aspirin at a gestational age of 15 to 18 weeks reduces APOs in women with increased level of alpha-fetoprotein (6). Prescription of low-dose aspirin in weeks 14 to 16 of pregnancy for pregnant women with a high risk of pre-eclampsia and findings of abnormal uterine Doppler can decrease or modify severe pre-eclampsia (7). For women who are at high risk of pre-eclampsia, considering Doppler analysis, the consumption of low-dose aspirin can reduce the incidence of gestational hypertension especially pre-eclampsia (8).

Most studies have been carried out on patients who have increased levels of alpha-fetoprotein, or patients with abnormal Doppler ultrasound. Therefore, the present clinical trial study was done with the aim of determining the effects of aspirin on adverse pregnancy outcomes in pregnant women with abnormal screening biochemistry tests of Down syndrome with normal Karyotype. Also, the comparison was performed on APO in women with normal and abnormal Doppler ultrasound.

Methods

The present randomized clinical trial study was performed on 170 pregnant women (85 women in the intervention group and 85 in the control group) referring to pre-natal clinic of Afzalipour Hospital in Kerman city, from January 2014 to May 2015. Assuming type 1 error as 0.05, type 2 error as 0.8, the prevalence of pre-eclampsia in the intervention group as 14.1%, and in the control group as 31.8% (6), the sample size was calculated to be 85 in each group.

First, in order to perform the study, we obtained permission from the Ethics Committee of Kerman Medical School. Also, the study was registered at the center for registration of Iran clinical trial studies under the code: IRCT2014120620218N1. The study included all qualified pregnant women referring to this center with abnormal aneuploidy biochemistry tests in the second trimester (15^{th}–18^{th} week). Participants had undergone amniocentesis and, accordingly, had normal Karyotype without any justification of abnormal biochemistry tests. All the participants signed the informed consent as a prerequisite to enter the study. Using block randomization method, the pregnant women were randomly divided into two groups of treatment with aspirin and no treatment. Successive blocks of four patients were determined and unequal allocation combinations were ignored. A blinded midwife distributed colored cards with letters “A” or “B” on them among the participants. Participants were allocated to the intervention (A) and control (B) groups according to the card they received. In each group, patients with multiple pregnancies, old age, gestational diabetes, bleeding at the first half of pregnancy, underlying maternal diseases, congenital anomalies, sensitivity to aspirin, addiction, and heparin consumption were omitted from the study. In the intervention group, aspirin was given from 15-18 to 34 weeks of pregnancy. The aspirin prescription was 80 milligrams per day. All patients were followed up in all routine medical visits till delivery.

Biochemistry factors, such as alpha-fetoprotein, non-conjugated estriol, inhibin A, and βHCG were examined. Alpha-

fetoprotein levels of 2.5 Multiple of Median (MOM) and more, conjugated than or equal to 0.3 MOM, inhibin A more than 2 MOM, and BHCG more than 3 MOM were considered abnormal.

Every uterine artery was specified using color Doppler at uterocervical place and at the intersection with the external iliac artery. The wave was specified using wave pulse and Pl was measured at two sides and the mean was achieved. Two waves were examined considering notch. Pl mean more than 95% or the existence of notch were considered as abnormal Doppler. The plan executor was an obstetrician skilled in doing uterine artery Doppler.

In the first visit, the relevant information was registered in a data gathering researcher-constructed form. In each visit, any new complication was added to the data gathering form and after delivery, patients were followed up by telephone contacts during the postpartum period to add any additional adverse outcomes. Finally, APO was examined in all the patients and registered in the data gathering form. The first APO includes preterm delivery, intrauterine death, infant death, intrauterine growth restriction, pre-eclampsia , and abruption. Preterm delivery is the delivery before week 37^{th}. Weight loss with respect to gestational age is birth weight under the curve of 10% for gestational age. Hypertension during pregnancy includes pre-eclampsia (blood pressure 140/90 mmHg or more, also proteinuria) and hypertension in pregnancy (blood pressure 140/90 mmHg without proteinuria), IUFD is intrauterine fetal death after 20 weeks, and neonatal death is the death at 1 to 28 days after birth. In the cases of abruption, the clinical diagnosis is placental abruption. Finally, the data were inserted in IBM SPSS software (version 20). Descriptive data was obtained in frequency, percent, average, and standard deviation. To analyze quantitative data, independent sample t-test and to analyze qualitative data chi-square and Fisher exact tests were run. The relative risk and estriol less

confidence interval were considered 95% and the significance level 0.05. The value of abnormal Doppler ultrasound diagnosis to determine the risk of APOs was examined by the amounts of sensitivity, property, positive predictive value, and negative predictive value.

Results

A total of 170 pregnant women comprised the first pool of the study. From among these women, 167 were included in the study: they were at the age of 17-41 with abnormal biochemistry tests of aneuploidy screening carried out between weeks 15^{th} to 18^{th} of pregnancy and, following that, had normal Karyotype. Doppler ultrasound was performed for all of these participants. They were then divided into control (N=84) and intervention groups (N=83), the latter receiving aspirin as treatment (Figure 1).

A total of 26.2% of the participants had high alpha-fetoprotein. non-conjugated estriol was reported low in 22.6% of them. Also, 46.4% had high inhibin and 38.1% had high βHCG. Demographic indicators were compared between the two groups (Table 1). There was no meaningful difference between the intervention group and control group considering demographic and clinical variables effective on APOs prior to the study.

Table 2 presents the occurrence of APO during pregnancy or postpartum period, which was found to be significantly different in 23.8% of the group treated with aspirin (N=20) and in 41.7% of the control group (N=35) (P=0.01). The risk of APO in the group under treatment with aspirin was 56% less than that in the control group. Other APOs revealed no meaningful difference between the two groups. But all the adverse outcomes, except for abruption, were lower in the group under treatment with aspirin compared with that of the control group.

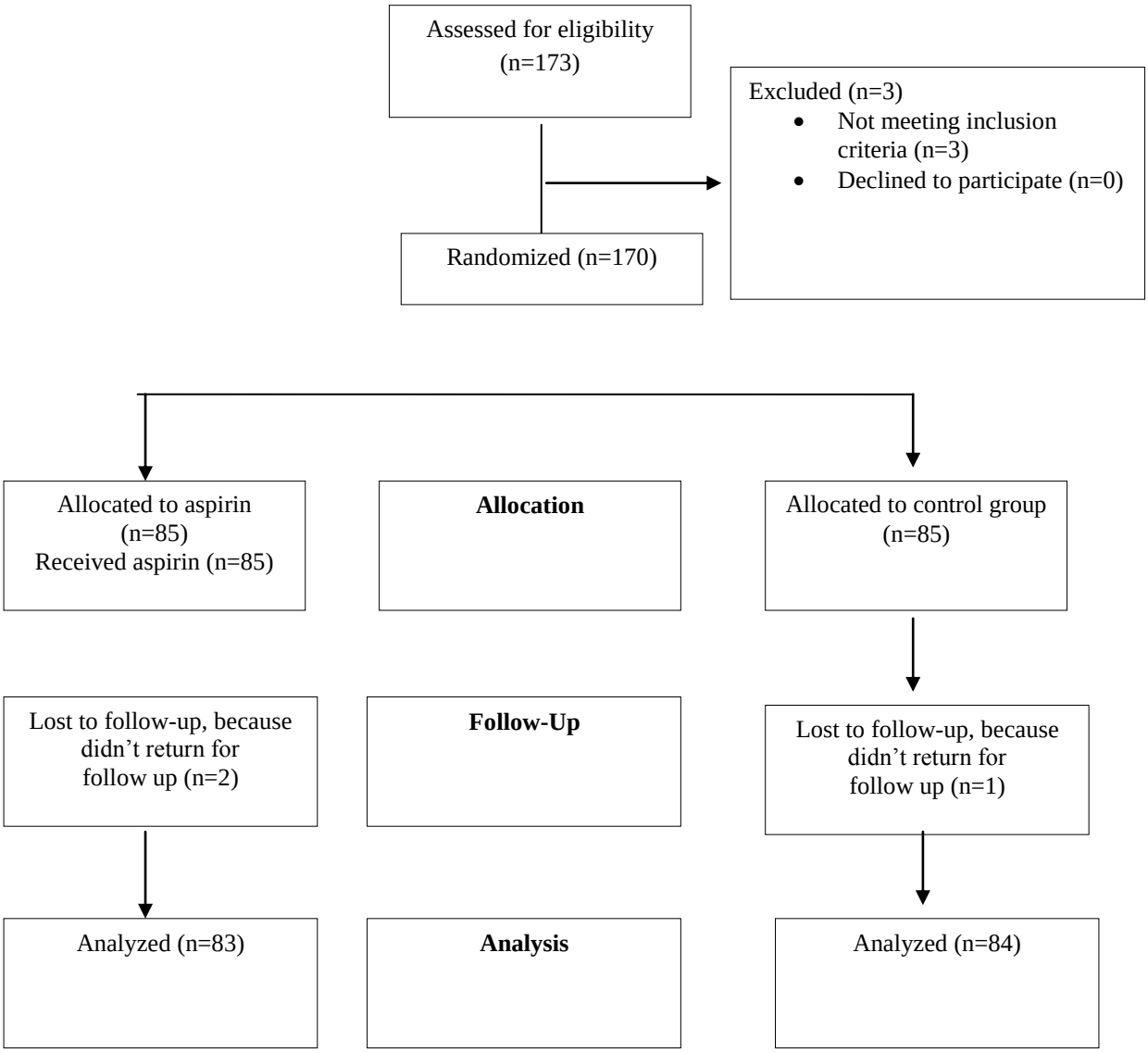

Figure 1. CONSORT flow diagram

Table 1. Comparison of demographic and clinical characteristics of intervention and control groups

Variable	Aspirin	Control	*P*	95% CI
Maternal Age (Year)	30.57±5.1	29.59±5.2	0.22	-2.5-0.5
Gravid	2±1.2	1.8±1.1	0.145	-0.64-0.09
Previous Abortion	0.26±0.4	0.21±0.4	0.472	-0.17-0.08

For all the patients, uterine artery Doppler was performed before receiving aspirin. A total of 80.4% of them had normal Doppler and 19.6% had abnormal Doppler. The two groups were compared considering abnormal Doppler, as well, revealing that 17.9% in intervention group and 21.4% in control group had abnormal Doppler ultrasound results, although no meaningful difference was observed between the two groups (*P*=0.56).

Table 3 presents the comparison of APO between the two groups of intervention and control in the groups of normal and abnormal uterine artery Doppler. The results show that in normal Doppler group, aspirin meaningfully reduced APO risk (*P*=0.008). But, in abnormal Doppler group, despite APO reduction in aspirin-receiving group, there was no meaningful difference between intervention and control groups.

Table 2. Comparison of pregnancy outcome between intervention and control groups

Variable	Aspirin N (%)	Control N (%)	*P*	Odds ratio
SGA	5 (6.3)	10 (11.9)	0.18	0.47
IUFD	1 (1.2)	3 (3.6)	0.62	0.33
Neonatal death	4 (4.8)	10 (11.9)	0.11	0.37
Preterm delivery	12 (14.3)	18 (21.4)	0.22	0.61
Placental Abruption	5 (6)	4 (4.8)	0.99	1.26
pre-eclampsia	5 (6)	10 (11.9)	0.17	0.47
Abnormal Apgar	4 (4.8)	8 (9.5)	0.23	0.48
NICU admission	9 (10.7)	15 (17.9)	0.18	0.55
APOs	20 (23.8)	35 (41.7)	0.01	0.43

Table 3. Comparison of pregnancy outcome between normal and abnormal Doppler patients

	Normal Doppler			Abnormal Doppler		
	Aspirin N (%)	Control N (%)	*P*	Aspirin N (%)	Control N (%)	*P*
APOs	13 (18.8)	26 (39.4)	0.008	7 (46.7)	9 (50)	0.84
Normal outcomes	56 (81.2)	40 (60.6)		8 (53.3)	9 (50)	

According to Table 4, pregnancy outcome was compared between the group under treatment with aspirin and the control group with one abnormal factor. According to the results, APO decreased. The comparison of APO between the intervention group and control group with several abnormal factors indicated that APO decreased significantly in the group under treatment with aspirin (Table 5).

Table 4. Comparison of pregnancy outcome in patients with one abnormal factor in intervention and control groups

Variable	Aspirin N (%)	Control N (%)	*P*	Odds ratio
SGA	3 (5.3)	6 (10.3)	0.49	0.48
IUFD	1 (1.8)	2 (3.4)	0.99	0.50
Neonatal death	3 (5.2)	6 (10.3)	0.49	0.47
Preterm delivery	10 (17.2)	12 (20.7)	0.63	0.79
Placental Abruption	5 (8.6)	3 (5.2)	0.71	1.73
pre-eclampsia	3 (5.2)	7 (12.1)	0.18	0.39
Abnormal Apgar	4 (6.9)	4 (6.9)	0.98	1.0
NICU admission	8 (13.8)	10 (17.2)	0.60	0.77
APOs	17 (29.3)	21 (36.2)	0.42	0.73

Table 5. Comparing pregnancy outcome in patients with more than one abnormal factor in intervention and control group

Variable	Aspirin N (%)	Control N (%)	*P*	Odds ratio
SGA	2(7.7)	4(15.4)	0.66	0.48
IUFD	0(0.0)	1(3.8)	1.000	-
Neonatal death	1(3.8)	4(15.4)	0.35	0.22
Preterm delivery	2(7.7)	6(23.1)	0.24	0.28
Placental Abruption	0(0.0)	1(3.8)	1.000	-
pre-eclampsia	2(7.7)	3(11.5)	1.000	0.64
Abnormal Apgar	0(0.0)	4(15.4)	0.11	-
NICU admission	1(3.8)	5(28)	0.19	0.17
APOs	3(11.5)	14(53.8)	0.001	0.11

When comparing APO occurrence in the two groups of normal Doppler and abnormal Doppler, among individuals who were under aspirin treatment, 46.7% (N=7) with abnormal Doppler had adverse outcomes and 18.7% (N=13) with normal Doppler had adverse outcomes. The difference was found to be meaningful (*P*=0.04).

Also, when comparing APO occurrence in the two groups of normal and abnormal Doppler, among individuals who were not under treatment with aspirin, 50% (N=9) with abnormal Doppler had adverse outcomes and 34.9% (N=26) with normal Doppler had adverse outcomes. No meaningful difference was found between the two groups (*P*=0.41).

The number of IUFD in abnormal Doppler was zero in control and aspirin groups. The number of IUFD, abruption, and abnormal Apgar was zero in the intervention group with several abnormal factors, as well.

In the group under treatment with aspirin, Doppler ultrasound used to diagnose APO had 35% sensitivity, 87% specificity, 46% positive predictive value, and 81% negative predictive value. As for the control group, Doppler ultrasound implemented to diagnose APO had 25% sensitivity, 81% property, 50% positive predictive value, and 61% negative predictive value.

Discussion

The findings of the present study indicated that receiving a low dose of aspirin between week 15^{th}-18^{th} of pregnancy to week 34^{th} for pregnant women with abnormal biochemistry tests of aneuploidy screening and normal Karyotype significantly reduced APO by 50%. The results of another randomized clinical trial study performed on pregnant women during their 15^{th} to 18^{th} weeks of pregnancy and with alpha-fetoprotein level more than 2.5 MOM showed that low dose of aspirin reduces APO and preterm delivery in women with increased level of alpha-fetoprotein (6).

The results of the current study showed that treatment with aspirin slightly reduces infant death, IUFD, preterm labor, SGA, and Apgar lower than 7 five minutes after birth, although it was not significant. Another study reported that low dose of aspirin prescribed at the gestational age less than 16^{th} week had a significant relationship with reduction of prenatal death, pre-eclampsia, IUGR, and preterm labor. The present study showed that taking aspirin before week 16^{th} has more beneficial effects (9). In the current study, we had to wait for the preparation of abnormal screening test results and certainty about normal Karyotype. Therefore, we prescribed aspirin after week 15^{th}.

Our findings demonstrated that aspirin slightly decreases pre-eclampsia and slightly increases abruption, though it was not statistically significant. Likewise, in a meta-analysis, it was shown that giving aspirin to high-risk patients decreases pre-eclampsia and increases abruption (OR: 1.35, 95% CI: 1.5-1.7) (10).

In the current study, aspirin prescription for pregnant women with abnormal Doppler did not bring about a significant effect on decreasing APO. But in pregnant women with normal Doppler, the APO had a meaningful difference between the group under treatment with aspirin and control group. Findings of one study conducted by Khazardoust et al. demonstrated that APO decreased in the group with abnormal Doppler under treatment with aspirin but it was not significant (6). In another study conducted by Flippi E. et al., increased APO in pregnant women with high alpha-fetoprotein and abnormal Doppler was reported (2). In another randomized clinical trial study, the findings indicated beneficial effects of treatment with low dose of aspirin on abnormal alpha-fetoprotein in maternal serum and abnormal uterine Doppler, but the difference was not statistically significant (11). Also, in another clinical trial study carried out on two groups of pregnant women with abnormal Doppler ultrasound of uterine artery, the pre-eclampsia risk decreased significantly in the group under treatment with aspirin. But there was no meaningful difference between the two groups of control and treatment with aspirin considering preterm delivery, Apgar, birth weight and IUGR (12).

In conclusion, in the group under treatment with aspirin and with one abnormal factor, the APO decreased in the group under treatment with aspirin compared with the group receiving no aspirin, but this decrease was not found to be meaningful. With two or more abnormal factors, aspirin can significantly reduce APO. It is possible to conclude that aspirin has more effects on several abnormal factors. The treatment with aspirin at weeks 15-18 of pregnancy for women with abnormal levels of aneuploidy tests can decrease APO. In patients with abnormal aneuploidy screening tests, the treatment with aspirin is effective in preventing APO.

The strengths of the present study include its clinical trial design and performance of Doppler by one person. Considering the time available, administrative limits, and a small number of APO cases that could be a problem for statistical analysis, it is suggested that more studies with larger samples be carried out. Also, it is suggested that the effects of aspirin on abnormal Doppler be studied, as well.

Conflicts of Interest

Authors declare no conflict of interests.

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