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Original article

Effect of Low Dose Aspirin Administration in Idioipathic Alpha-fetoprotein Elevation

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Abstract

Objective: This study aims to evaluate the outcome of low-dose aspirin administration in complicated pregnancies with idiopathic alpha-fetoprotein (AFP) elevation. ***Methods:*** In this randomized controlled trial, 200 participants with singleton pregnancies presenting with idiopathic elevated alpha-fetoprotein (AFP>2 multiples of the median (MoM)) were recruited. Patients in their 16th to 20th week underwent ultrasonography and Doppler imaging as diagnostic tests. Based on the results of the diagnostic tests, patients were divided into two groups. Normal uterine artery Doppler group (N=100) and Abnormal group(N=100). patients divided into two groups in terms of aspirin intake. Primary complications included preterm delivery, fetal death, intrauterine growth restriction (IUGR), preeclampsia and neonatal hospitalization. ***Results:*** From May 2015 through June 2016, 200 women were randomized as follows: 100 to 80 mg ASA tab; 100 to no treatment. Most characteristics were similar across groups. The risk of the IUGR was 2% versus 14% p-value: 0.027, the risk of preterm labor and Neonatal hospitalization were also less, but the risk of IUFD and preeclampsia did not change. ***Conclusion:*** Administration of low dose of aspirin can have prophylactic effects against some adverse outcomes in complicated pregnancies presenting with elevated alpha-fetoprotein levels.

Keywords: ***AFP, alpha-fetoprotein elevation, low-dose aspirin, uterine artery Doppler, pregnancy complications.***

Introduction

The American College of Obstetricians and Gynecologists recommends alpha-fetoprotein (AFP) screening in the second trimester of gestation as a part of serum marker screenings between 15th and 20th weeks of pregnancy [1]. AFP screening has a predictive value of 2-6%, hence abnormal levels need further consultation and diagnostic tests [1,2]. Various factors, including weight, gestational age, race and a history of diabetes contribute to the elevation of maternal serum AFP [2-4].

AFP is important for different stages of both oncogenic and autogenic growth pathways, including proliferation, differentiation, transformation and regeneration [4]. AFP also serves as a marker in research related to cancer, fetal development and fetal pathophysiology. Elevated level of maternal serum AFP can be a consequence of fetal, placental or maternal disorders [2], and can be an indication for various congenital anomalies, low birth weight and placental abruption [5]. Aside from being a standard biomarker for neural tube defects, AFP has also been used as a marker for other prenatal diseases since 1976 [4-9]. If patients with elevated AFP present with placental trauma, there is an excessive transition of AFP from fetus to mother which can result in adverse outcomes [5].

Unexplained levels of maternal serum markers is a term used for abnormal levels of markers after estimation of gestational age with ultrasonography and ruled-out maternal-fetal and placental causes [2]. Uterine artery doppler could be used as a pregnancy outcome anticipator in women with elevated levels of AFP [10-15]. A complication in placental morphology (small, thick or jelly like placenta) can be a determinant of an adverse outcome. Comparatively, women with one or more abnormal placental functions are at a higher risk of adverse pregnancy outcomes [7]. Administration of aspirin from early pregnancy has proven to reduce cases of preeclampsia and other adverse pregnancy outcomes [16-20].

Low dose aspirin acts as an anticoagulant by irreversibly inhibiting platelet cyclooxygenase, which reduces thromboxane A_2, a vasoconstrictor. In previous years, it was prescribed to patients that presented with repeated abortions and a history of phospholipid syndrome [9].

In this study, the outcome of administration of low dose aspirin in complicated pregnancies with idiopathic alpha-fetoprotein elevation will be evaluated.

Materials and Methods

This study was conducted from May 23,2015 to March 5,2016 and study was registered following the actual study start date. This clinical trial was registered in Iranian RCT center with ID number IRCT2014042017365N1.

Pregnant women undergoing second trimester screening with levels of AFP higher than 2 MoM (multiples of the median) who referred to perinatology clinic were assessed in this trial. So, women presenting with increased risk of neural tube defects (NTD) due to elevated levels of alphafeto protein were included in this trial. Patients were evaluated during 16th-20th week of gestation with targeted ultrasonography for fetal anomalies, uterine arteries Doppler test, vaginal ultrasonography for cervical incompetency. ***Consent for acquisition and review of data was obtained from all participants.

Patients with singleton pregnancies and AFP value ≥ 2 MoM were divided into two groups based on the results of uterine arteries Doppler. Abnormal uterine artery Doppler was defined as the presence of one or more of the following aspects: (1) mean PI ≥1.45 MOM, (2) bilateral or (3) unilateral notching.

One group consisted of patients with diastolic notch or increased uterine artery resistance (n=100), and another group with normal uterine arteries (n=100). Using random allocation software, each group was further subdivided into aspirin-treated group (n=50 versus n=50) and control group (n=50 versus n=50). Aspirin was administered to the treated group until the 34th week of pregnancy. Figure 1 shows a schematic of these steps. (**Figure 1**).

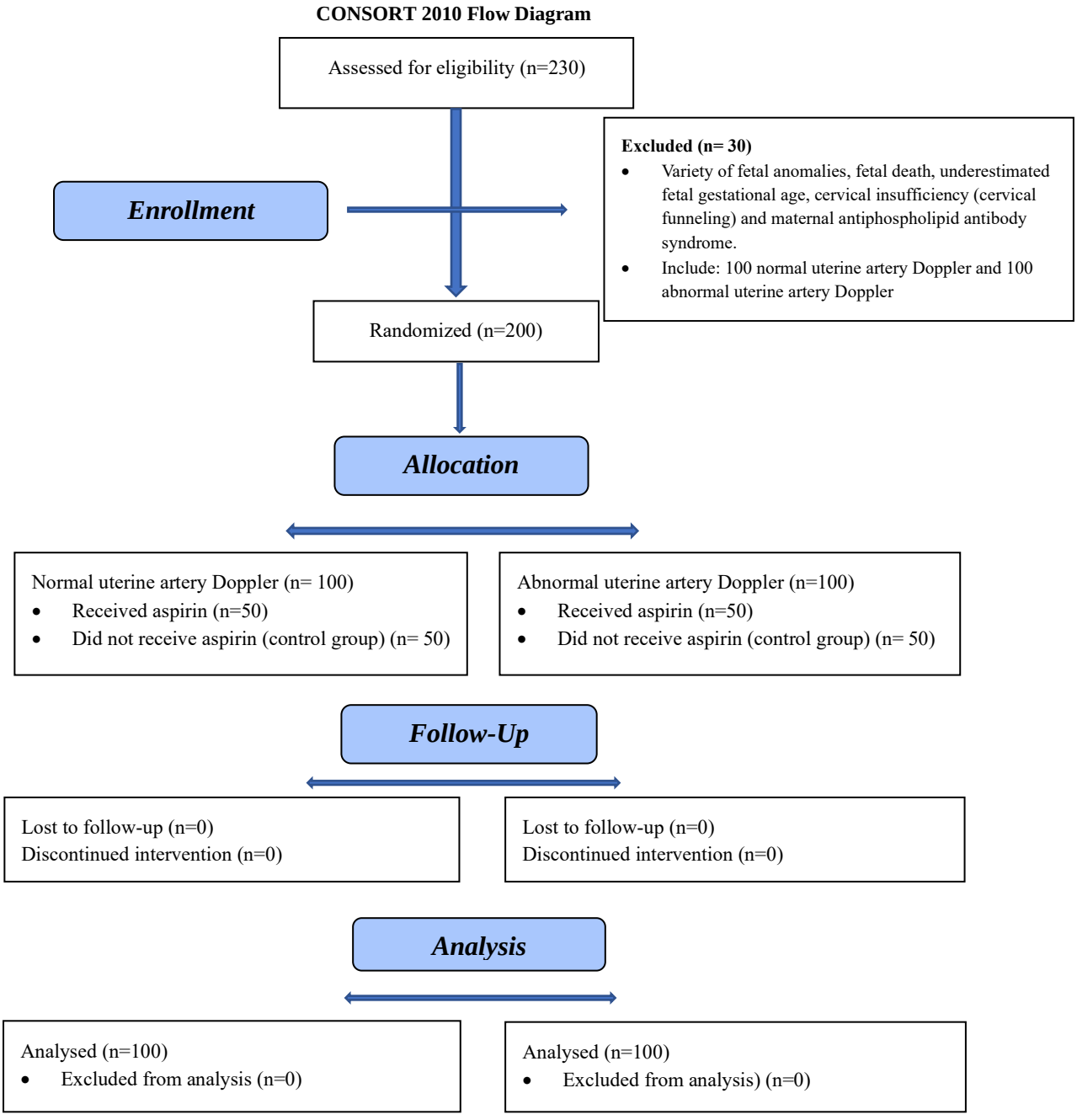

Figure 1. CONSORT 2010 flow diagram

The sample size was calculated using this formula:

$$N = \frac{(Z_{\frac{\alpha}{2}} + Z_{\beta})*2*P*(1-P)}{(P1-P0)\text{^}2}$$

All statistical data were analyzed with SPSS 16 with significant p value<0/05.This randomized clinical trial is registered in the Iranian RCT center with ID number IRCT2014042017365N1 in 05/05/2015.

80 mg aspirin tablet was continued until 34 weeks of pregnancy. Routine prenatal care and delivery were done in our tertiary hospital. The primary outcomes were preterm birth (delivery at less than 37 completed weeks), fetal death (IUFD as fetal death after the beginning of the study), and preeclampsia (blood pressure ≥140/90 mm Hg after 20 weeks of gestation at least 4 hours apart and proteinuria ≥300 mg/24 hours or ≥1+ dipstick). Intra-Uterine growth restriction (IUGR) was used to define a fetus with an estimated weight less than the 10th percentile for the gestational age and an increased Pulsatility index (PI) of umbilical artery in ultrasonography, and neonatal admission at neonatal ward or Neonatal Intensive Care Unit (NICU). Patients with positive thrombophilia, thrombocytopenia, structural or chromosomal anomalies of the fetus, placental hematoma, early severe IUGR, multiple pregnancies, ultrasonographic sign of cervical incompetency, maternal chronic HTN or any use of ASA were excluded from the study. All screened women gave informed consent to data acquisition and review as part of their participation in the study. Gestational age of patients was ascertained by the last menstrual period (LMP) or early ultrasound dating when dating was uncertain. Ultrasonography was performed by an experienced perinatologist (fetomaternal specialist) using AquvixVten Ultrasonography system. All Data collection was done by the resident of obstetrics and gynecology who was not aware of uterine artery Doppler results and the use of ASA. Data were analyzed using SPSS 16 software (Chicago, IL, USA).

In order to compare quantitative variables t- test, One Way Anova and Fisher's extract test were used. Qualitative variables were analyzed using the Chi-square test and Relative Risk (RR) of adverse pregnancy outcome was calculated with confidence interval (CI) 95%. In all tests P<0.05 was considered as significant. NNT (number needed to treat) was calculated using $1/(p_B - p_A)$[24] formula. P_A is the probability of having APO (Adverse Pregnancy Outcoe) (IUGR, IUFD, Preterm labor, Preeclampsia) and neonatal hospitalization after taking the ASA and P_B is the probability of having APO without taking ASA.

Results

In the study period, from pregnant women were referred to the perinatology clinic 200 women with unexplained elevated Alphafeto protein (100 pregnant women with normal uterine artery Doppler and 100 pregnant women with abnormal uterine artery Doppler) were included in study.

Demographic characteristics of the aspirin-treated group and the control group are shown in Table 1. Based on the data in the table, there are no significant differences between groups in terms of receiving or no aspirin.

The mean gestational age at delivery in Abnormal Doppler of uterine artery group was 36.6±2.21 for aspirin-receiving group and 35.1±2.15 for the control group with (*P*=0.272). In patients with Normal uterine arteries Doppler in the aspirin-treated group was 38.9±1.58 and 38.2±1.77 in the group with no aspirin administration (**Table 2**).

In the abnormal uterine arteries group, mean neonatal birth weight in the aspirin group and the control group were 2.09±.33 kg and 2.01±.46 kg respectively. On the other hand, in the normal Doppler group, the mean birth weight in the aspirin and control groups were 3.54±1.46 and 3.98±1.46 kg respectively. There was no significant difference between the *P* values of both groups (*P*=0.392 and *P*=0.397) (**Table 3**).

In the review from the point of IUGR and Preterm delivery as outcomes of complicated pregnancy shows a significant statistical difference between normal and abnormal Doppler in terms of aspirin intake, also reduction in risk (2% versus 14% in Abnormal doppler group (p value =0.027)) and (4% versus 16% in Normal group (p value =0.04)) (**Table 5**). (4% versus 16% (p value =0.044) in Abnormal doppler group and 8% versus 34% (p value=0.001) the Normal doppler group) (**Table 6**).

As shown in Table 7, there is no statistically significant difference between the abnormal and normal Doppler groups in terms of aspirin intake and preeclampsia. However, a reduced risk of developing preeclampsia with aspirin is seen in patients with abnormal Doppler. (14% versus 24% (p value=0.202 Relative Risk =0.516 (0.184,1.443)) in Abnormal doppler group and 10 % versus 2% (p value=0.092) the Normal doppler group (**Table 7**).

There was a significant difference between two groups with receiving aspirin and those who did not in Abnormal uterian artery doppler in Neonatal hospitalization, although reduction in the risk of hospitalization was also seen in the group with receiving aspirin. (4% versus 30% (p value=0.001in Abnormal doppler with intake of aspirin and do not and 4% versus 20% 9 (p-value=0.014) in Normal doppler (**Table 8**).

Except for two cases of intrauterine death and preeclampsia in other outcomes, we have a statistically significant difference in terms of aspirin intake in patients with abnormal Doppler. As shown in Table 4, intrauterine fetal death rate in abnormal doppler group were 1 (2%) versus 4(8%) in the aspirin-treated group and control group. (*P*-value=0.169) same to Normal Doppler of uterine artery with or without ASA use (2% versus 10%) P-value=0.09. However, there is a reduced risk of intrauterine death in both normal and abnormal Doppler and preeclampsia in patients with abnormal Doppler. In all patients, whether abnormal or normal uterine artery Doppler, there is a difference in pregnancy outcome with aspirin use in the such as IUGR, preterm delivery, and neonatal hospitalization (**Table 5,6 & 8**).

Table 1: Demographic characteristics of the study groups.

Parameters	Abnormal Doppler with aspirin (n=50)	Abnormal Doppler without aspirin (n=50)	Normal Doppler with aspirin (n=50)	Normal Doppler without aspirin (n=50)	*P*-value
Mean maternal age	27±5.47	28.5±6.71	29.7±4.51	27±4.98	0.224
Mean number of pregnancies	1.92±0.8	2.18±1.24	2.16±1	2.16±1	0.217
Mean MoM of AFP	3.24±1.08	3.02±0.6	2.86±0.71	2.81±0.6	0.232
Mean risk of NTD	54.1±1.5	63.1±3.1	106.1±1.5	77.1±8.1	0.325

Table 2: Mean gestational age for the aspirin-treated and control groups.

	Mean ± SD	Max	Min	(t-test)
Abnormal Doppler with aspirin (n=50)	36.6±2.21	39	25	0.272
Abnormal Doppler without aspirin (n=50)	35.1±2.15	38	27	
Normal Doppler with aspirin (n=50)	38.9±1.58	42	35	0.101
Normal Doppler without aspirin (n=50)	38.2±1.77	42	32	

Table 3: Mean birth weight for all groups.

	Mean ± SD	Max	Min	(t-test)
Abnormal Doppler with aspirin (n=50)	2.09±.33	2.8	1.4	0.392
Abnormal Doppler without aspirin (n=50)	2.01±.46	2.9	1.3	
Normal Doppler with aspirin (n=30)	3.54±1.46	3.9	2.9	0.397
Normal Doppler without aspirin (n=30)	3.98±1.46	3.4	1.55	

Table 4: Fetal death in both groups

			IUFD		t-test	*P*-value	Relative risk (Confidence interval)
			Yes	NO			
Abnormal Doppler	Yes	Aspirin	1(2%)	49(98%)	1.42	0.309	0.32 (0.31,0.32)
		No aspirin	6%)(3	47(97%)			
	No	Aspirin	1(3.2%)	30(96.8%)	1.01	0.500	1.03 (1.1,0.98)
		No aspirin	0(0%)	31 (100%)			

Table 5: Preterm delivery in aspirin-treated and control groups

			Premature birth		t-test	*P*-value	Relative risk (Confidence interval)
			Yes	NO			
Abnormal Doppler	Yes	Aspirin	2(4%)	48(96%)	5	0.026	0.19 (0.92,0.39)
		No aspirin	9(18%)	41(82%)			
	No	Aspirin	1(3.2%)	30(96.8%)	0.35	0.5	0.48 (5.62,0.04)
		No aspirin	2(6.5%)	29(93.5%)			

Table 6: Neonatal hospitalization in aspirin-treated and control groups

			Hospitalization		t-test	*P*-value	Relative risk (Confidence interval)
			Yes	NO			
Abnormal Doppler	Yes	Aspirin	2(4%)	48(96%)	4	0.046	0.21 (1.08,0.04)
		No aspirin	8(8%)	42(92%)			
	No	Aspirin	1(3.2%)	30(96.8%)	0.35	0.5	0.48 (5.62,0.04)
		No aspirin	2(6.5%)	29(93.5%)			

Table 7: IUGR in aspirin-treated and control groups

			IUGR		t-test	*P*-value	Relative risk (Confidence interval)
			Yes	NO			
Abnormal Doppler	Yes	Aspirin	1(2%)	49(98%)	3.84	0.056	0.15 (1.29,0.01)
		No aspirin	6(12%)	44(88%)			
	No	Aspirin	0(0%)	31(100%)	1.01	0.5	1.03 (1.1,0.96)

Discussion

AFP screening is part of the second trimester maternal serum marker screening test between weeks 15-20. With positive neural tube defect, risk-selective ultrasonography is a standard diagnostic test for other fetal anomalies. Although it can be excluded, the most common cause of idiopathic AFP elevation is maternal stress. There is no standard management for pregnancies with unexplained elevated levels of alpha-fetoprotein, but it is associated with adverse pregnancy outcomes. In this study, vaginal ultrasonography for diagnosis of cervical incompetency was done. In addition, color Doppler for assessment of uterine arteries, diagnosis of early onset intrauterine fetal growth restriction, assessment of placental size and abnormal placental adhesion after detailed fetal anatomy were performed.

It has been reported that elevation of AFP (above 2 MoM) in the second trimester with the absence of any accompanying issue such as fetal anomaly, maternal ovarian tumor and maternal hepatocellular carcinoma, increases the risk of adverse pregnancy outcomes like preterm labor, IUGR, small for gestational age (SGA), and fetal death especially in hypertensive patients [5].

It has also been reported that pregnant women with high serum AFP and abnormal uterine arteries were associated with adverse pregnancy outcomes, especially SGA. However, normal levels do not rule out adverse outcomes [13]. Placenta previa in second and third trimester accompanied with unexplained elevation of maternal serum AFP may result in placenta accreta, increta and percreta [10]. MRI and ultrasonography assessment should be performed to determine placenta-uterus distance.

Knocha et al reported that abnormal uterine artery Doppler in AFP elevated pregnancies results in adverse pregnancy outcomes,

and has a remarkable sensitivity in preeclampsia prediction. They also pointed out that the presence of uterine artery notch is a better predictor of adverse pregnancy outcome compared to elevated maternal serum AFP [14]. Likewise in our study, patients with high AFP and abnormal uterine artery Doppler had more adverse pregnancy outcomes compared to patients with high AFP and normal Doppler.

Francois et al studied low dose aspirin effects in abnormal Doppler pregnant patients on preeclampsia and IUGR incidence. They concluded that uterine artery Doppler screening has no effect on prenatal morbidity, birth weight and preeclampsia incidence, but amends prenatal outcome [15]. Our study also shows that there is no significant difference between the two groups in birth weight.

Our study showed that low dose aspirin can reduce some adverse outcomes of pregnancy such IUGR, and preterm labor. Khazardoost in her study reported that "Low-dose aspirin reduces APO (Adverse Pregnancy Outcome) and delivery before 34 weeks of gestation in pregnant women with unexplained elevated AFP" [16]. They were somehow different from our study and their randomization was not on the basis of uterine artery Doppler. APO in aspirin and control groups in their study were 26.1% versus 44.1% (p-value=0.045).

In current study, in abnormal Doppler and ASA group neonatal Hospitalization was significantly lower than control group (P-value<0.001), Khazardoost et al Similar to our study, showed Preterm delivery was significantly reduced in ASA group [16].

Aspirin reduces the risk of preeclampsia if administered from the start of pregnancy [9]. However, it cannot prevent preeclampsia if administered after 16th week [17,18]. Aspirin can also reduce gestational hypertension and preterm delivery if administered before 16th week. ACOG in 2018 published committee Opinion 743 and recommend use of ASA 81 mg for prevention of preeclampsia in 12-28 weeks of gestational age [19].

Our study showed that low dose aspirin can reduce some adverse outcomes of pregnancies such as IUGR and preterm labor. Reduced neonatal hospitalizations with aspirin administration was also reported in this study, which was not studied in other clinical trials. There are some reports about association of placental abruption with use of aspirin in gestational ages after 1st week, but no such association was found in this study.

Conclusively, it is advised to perform uterine artery Doppler in cases with abnormal screening test results. If the results are not promising, aspirin should then be administered.

Declarations

Ethics approval and consent to participate

All research methods, tests, and procedures performed were approved by the Research Ethics Committee of Urmia University of Medical Sciences. The verification code is included in the first page of the article and all patients are still fully satisfied. This randomized clinical trial is registered in the Iranian RCT center with ID number IRCT2014042017365N1 in 05/05/2015. all methods were performed in accordance with the relevant guidelines and regulations of Research Ethics Committee of Urmia University of Medical Sciences and supported and registered by this committee.

Members of the Research Ethics Committee

1. Dr. Javad Aghazadeh, President of the University
2. Dr. Iraj Mohebbi, Vice President for Research and Technology
3. Dr. Saeed Samadzadeh, a prominent researcher
4. Dr. Firooz Qaderi, a prominent researcher
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9. Dr. Rasoul Qara Aghaji Biostatistics
10. Dr. Nazafarin Ghasemzadeh Biomedical ethics)
11. Mahin Kohankari, a representative of the community

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

Informed consent was obtained from all participants include a brief overview of the study on a level of understanding for the person who will be signing the form.

Conflict of Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information file is attached.

Competing interests

Not applicable

Funding Statement

Research and Technology Committee of Urmia University of Medical Sciences

Authors' contributions

Fatemeh Bahadori as the first author in charge of planning and performing sonography. Yasaman Oliapour and Samira Jahangard were responsible for collecting data and conducting administrative affairs and coordinating patients. Hamid Khalkhali was responsible for statistical analysis and Azam Taghavi was responsible for editing and reviewing.

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Disclosure Statement

The authors report no conflict of interest.

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The clinical trial identification number and the URL of the registration site

Date of registration: 05/05/2015

Clinical trial identification number: IRCT2014042017365N1

URL of the registration site: https://en.irct.ir/trial/15984

Synopsis

In participants with idiopathic elevated AFP, and Abnormal uterian artery doppler, ASA intake reduce complications such as IUGR, preterm labor was less than other group.

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