



The Effect of Aspirin Administration on Fetal Cardiovascular Function Between 18 to 24 Weeks of Gestation: A New Perspective on ASA Indication in Obstetrics

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Abstract

Background: Low-dose aspirin (ASA) is used in obstetrics for different indications, mainly to prevent preeclampsia. This study investigated the underlying mechanism of ASA's effect on the fetus's cardiovascular functions.

Methods: 42 pregnant women at 18-24 weeks of gestation, identified as high-risk for preeclampsia, received 160 mg of ASA daily. Fetal Doppler ultrasound was performed before and three weeks after ASA treatment, assessing ductus venosus, middle cerebral, umbilical, and uterine arteries pulsatility indices as well as pulmonary, aorta, and superior vena cava (SVC) diameters in the three-vessel view, including pulmonary/aorta and SVC/aorta ratios. All analyses were performed using SPSS software version 27, with a significance threshold set at $p < 0.05$. A paired t-test was used to assess differences in means. The Chi-square and Fisher's exact test analyzed nominal variables.

Results: Post-intervention analysis revealed significant improvements in abnormal uterine artery resistance ($p < 0.001$) and abnormal pulsatility index of the umbilical artery, middle cerebral artery, and ductus venosus ($p < 0.001$ for all). Moreover, 160 mg/day aspirin administration significantly increased mitral E/A (early filling velocity/atrial contraction velocity: 0.397 ± 0.029 ; $p < 0.001$), diameters of aorta (4.390 ± 0.852 ; $p < 0.001$), pulmonary artery (4.895 ± 1.087 ; $p < 0.001$), and SVC (2.511 ± 0.535 ; $p < 0.001$), while significantly decreasing left ventricular myocardial performance index ($p < 0.05$).

Conclusion: Daily administration of 160 mg of aspirin enhances fetal vascular and cardiac function. Evaluating fetal cardiovascular parameters beyond routine uterine artery Doppler, especially in high-risk pregnancies, and initiating ASA therapy in cases of insidious abnormalities, may help delay or prevent fetal complications such as intrauterine growth restriction (IUGR) by improving cardiovascular function.

Keywords: Aspirin, Cardiovascular functions, Ultrasound imaging, Obstetrics.

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Introduction

Aspirin is an analgesic, non-opioid, antiplatelet, and non-steroidal anti-inflammatory drug that reduces the synthesis of thromboxane

A₂, a vasoconstrictor helping in platelet aggregation. This mechanism of action prevents the development of vascular thrombosis. The effect of

low-dose aspirin treatment (150-80 mg) in the second and third trimesters has been well-proven (1).

Aspirin is recommended for preventing preeclampsia according to the guidelines of American College of Obstetricians and Gynecologists, which is often associated with impaired placental perfusion and uteroplacental vascular insufficiency (2). Preeclampsia is linked to increased maternal and fetal morbidity and mortality, and leads to a significant number of preterm births and neonatal complications. Preeclampsia frequently results in uteroplacental dysfunction and fetal growth restriction with increased rates of complications, like pulmonary hypertension, necrotizing enterocolitis, intraventricular hemorrhage, and, often, mortality, due to the combination of prematurity and extremely low birth weight (3). Because of these numerous effects of preeclampsia on pregnancy, ASA finds its crucial role in obstetrical care. An individual patient data meta-analysis has indicated a modest 10% reduction in preeclampsia rates with the use of aspirin. Later meta-analyses of aggregate data have revealed a dose-response effect of aspirin on preeclampsia rates, which is maximized when the medication is initiated before 16 weeks of gestational age. The Aspirin for Evidence-Based Preeclampsia Prevention (ASPREE) trial recently demonstrated that administering 150 mg of aspirin daily, initiated before 16 weeks of gestation and taken at night by women identified as high-risk through combined first-trimester screening, reduced the incidence of preterm preeclampsia by 62% (4). Some studies show that taking 1 to 1.6 mg/kg of aspirin with 225 mg dipyridamole daily significantly reduces the incidence of idiopathic recurrent fetal growth restriction in 16–34-week fetuses (3, 5). Lazzarin et al. reported that taking 100 mg of aspirin with omega-3 daily improves uteroplacental blood flow in cases of asymmetric IUGR (6). In another study, daily administration of 75 mg aspirin initiated at 28-30 weeks of gestation improved abnormal umbilical artery blood flow and led to better fetal weight gain in cases of idiopathic asymmetric IUGR (7). Increased resistance in placental vessels causes a decrease in maternal-fetal gas exchange, resulting in hypoxia and subsequent alterations in cardiac function (8). Consequently, perfusion is preferentially directed toward the brain and other vital organs. Preferential cerebral perfusion is determined by the pulsatility index (PI) of the middle cerebral artery (MCA) and

Cerebroplacental ratio (CPR) on Doppler ultrasound imaging (9). The decrease in the resistance of the fetal cerebral vascular network leads to reductions in MCA, PI, and CPR (9).

A significant increase in ductus venosus pulsatility index (DV PI), along with other abnormalities, may be associated with an increased risk of intrauterine death before 34 weeks of gestation (7).

Although some articles address the effect of ASA on fetal cardiovascular function and show no adverse effects at low doses, there is no specific article demonstrating a positive effect of ASA on improving fetal circulation, which in turn could have a beneficial impact on fetal growth in cases of IUGR. If aspirin administration is shown to improve fetal cardiovascular function, as assessed by specific Doppler indices, then prescribing ASA to correct these abnormalities may enable successful management or prevention of some cases of IUGR caused by impaired fetal circulation, which is the primary focus of this study.

Methods

Study design: This single-center prospective observational study evaluated fetal cardiovascular and placental function before and after aspirin administration in pregnant women at 18-24 weeks of gestation who were prone to preeclampsia and indicated for ASA use according to the American College of Obstetricians and Gynecologists guidelines. Aspirin was not administered at 11–13 weeks of pregnancy, since our goal was to perform fetal echocardiography to ensure that the fetuses did not have structural congenital heart diseases; the minimum gestational age for conducting the echocardiography was 18 weeks. The study protocol was approved by the ethics committee of Tehran University of Medical Science (IR.TUMS.MED-ICINE.REC.1402.283).

The study was conducted in accordance with the principles of the Declaration of Helsinki. The objective and protocol of the study were explained to the patients who met the inclusion criteria in simple language. All patients gave written informed consent before initiation of any study procedure. All the information of the participants in this study was ethically and legally confidential. Participation in this study caused no disorder in diagnostic and therapeutic procedures, and all visits for pregnancy care, Doppler ultrasound imaging, and echocardiography were provided at no additional cost to the patients.

Study population and sample size calculation: According to the prevalence of IUGR as mentioned in Sekielska-Domanowska et al.'s study (2), the required sample size for each group was calculated as 21, for a total of 42 participants.

Between March 2022 and March 2023, 42 eligible pregnant women with gestational ages between 18-24 weeks, who were allocated to daily ingestion of 160 mg of aspirin according to the study protocol, were invited to enroll in the study.

Inclusion and exclusion criteria: The inclusion criteria were: 1) pregnant women aged ≥ 18 years; 2) singleton pregnancy; 3) gestational age between 18 to 24 weeks with a normal anatomical survey (when assessing fetal vascular and cardiac indices indicative of impaired blood flow or function); 4) high risk for preeclampsia and an indication of ASA use according to the American College of Obstetricians and Gynecologists guidelines; and 5) understanding of the study's purpose, risks and benefits, with voluntary participation.

The exclusion criteria were: 1) multiple pregnancies; 2) history of ASA consumption before the study; 3) maternal contraindications to aspirin, including allergies or active vaginal bleeding; 4) any structural and functional abnormality in the fetus; 5) viral infection of the fetus (detected by appropriate diagnostic test); 6) fetal chromosomal abnormalities (detected by invasive fetal testing); 7) threat of abortion; 8) lack of consent to participate; and 9) presence of IUGR.

Intervention: Fetal ultrasound imaging assessment was performed with the Philips Affiniti 70 ultrasound (Philips, USA) and the convex probe 2-MHz 6C2 on patients who met the inclusion criteria (1). Before ASA administration, the PI was measured in the free loop of the fetal umbilical artery. Also, the MCA pulsatility index was calculated in the transverse section of the fetal head at the circle of Willis, using a zero-degree insonation angle. DV PI was also assessed in the sagittal section of the chest and abdomen, where the DV and hepatic vein joined. Then, their diameters were measured in the three-vessel view to analyze the transverse dimensions of the pulmonary artery, aorta, and SVC. The ratios of pulmonary to aorta (Pul/Ao) and SVC to aorta diameter (SVC/Ao) were calculated (pulmonary artery is typically larger in diameter than the aorta and also greater than the SVC). Patients with abnormalities in the assessed parameters were included in the study, defined as umbilical artery PI $>95\%$, MCA

PI $<5\%$, DV-PI $>95\%$, Pul/Ao ratio <1 , and SVC/Ao ratio <0.7 . After this step, echocardiography was performed to rule out cardiac structural and functional abnormalities. The myocardial performance indices (MPI) of the left and right ventricles were evaluated. Additionally, the E/A ratio, defined as the ratio of peak early diastolic filling velocity (E-wave) to peak late diastolic velocity due to atrial contraction (A-wave), was assessed at the tricuspid and mitral valve levels. By completing these steps, a dosage of 160 mg per night was prescribed. The patients were revisited three weeks later to evaluate the fetus's vascular and cardiac function. Lastly, these parameters were compared before and after receiving 160 mg ASA to clarify whether ASA improves fetal cardiovascular function.

Statistical analysis: All analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 27 (IBM, USA), adhering to the intention-to-treat principle, with statistical significance set at $p < 0.05$. Descriptive data was presented as mean $\pm$ SD, and prevalence, frequency, and percentages were presented in the corresponding tables. Paired T-test was applied to evaluate the differences in means. The Chi-square test was used in the analysis of nominal variables. Fisher's exact test was used when the distribution was incompatible with the Chi-square test in the analysis of nominal variables.

Results

General characteristics of study participants: A total of 42 participants were included in the study. Their average age was 32.05 ± 5.63 years, with a mean gestational age of 18.88 ± 1.60 weeks (18–24 weeks). Their average body weight was 67.26 kg (40–82 kg). Among the participants, 17 women (40.5%) had a history of preeclampsia, and 19 women (45.2%) were gravid 2 (Table 1).

The effect of 160 mg/day aspirin on uterine artery resistance in fetuses: The administration of 160 mg of aspirin daily significantly reduced uterine artery resistance. Regarding right uterine artery resistance, the number of abnormal cases decreased from 20 to 3 after aspirin treatment, demonstrating a significant improvement (Table 2, $p < 0.001$). Similarly, the left uterine artery resistance was significantly reduced, with the number of abnormal cases decreasing from 28 to 8 following aspirin administration (Table 2, $p < 0.001$). These findings suggest that 160 mg/day of aspirin consump-

Table 1. Baseline characteristics, uterine artery resistance, pulsatility index, and fetal cardiac parameters of the participants (n=42)

Characteristics		n (%)	Mean (SD)	Range
Age (years old)		-	32.05 (5.63)	21–43
Gestational age (weeks)		-	18.88 (1.60)	18–24
Weight (kg)		-	67.26 (11.26)	40–82
Preeclampsia	Yes	17 (40.5%)	-	-
	No	25 (59.5%)		
Gravidity	1	15 (35.7%)	-	-
	2	19 (45.2%)		
	3	7 (16.7%)		
	4	1 (2.4%)		
Infertility	Negative	30 (71.4%)	-	-
	Positive	9 (21.4%)		
	Positive (IUI)	3 (7.1%)		
Placenta position	Anterior	19 (45.2%)	-	-
	Posterior	17 (40.5%)		
	Anterior-lateral	2 (4.8%)		
	Left-lateral	2 (4.8%)		
	Lateral	2 (4.8%)		

Table 2. Uterine artery resistance, pulsatility index, and fetal cardiac parameters before and after aspirin intake (160 mg/day)

Parameters	Before aspirin intake (N/mean±SD)		After aspirin intake (N/mean±SD)		p-value
Right uterine artery	Normal: 22	Abnormal: 20	Normal: 39	Abnormal: 3	<0.001
Left uterine artery	Normal: 14	Abnormal: 28	Normal: 34	Abnormal: 8	<0.001
Umbilical artery PI	Normal: 32	Abnormal: 10	Normal: 42	Abnormal: 0	N/A
MCA PI	Normal: 38	Abnormal: 4	Normal: 42	Abnormal: 0	N/A
MCA-PSV PI	Normal: 42	Abnormal: 0	Normal: 42	Abnormal: 0	N/A
DV PI	Normal: 18	Abnormal: 24	Normal: 40	Abnormal: 2	<0.001
Mitral E-wave (cm/s)	20.98±3.18		21.74±2.08		0.217
Mitral A-wave (cm/s)	48.21±5.22		54.90±5.12		<0.001
Mitral E/A	0.437±0.057		0.397±0.029		<0.001
Tricuspid E-wave (cm/s)	20.86±3.55		21.88±2.94		0.178
Tricuspid A-wave (cm/s)	50.31±6.53		54.67±5.43		0.005
Tricuspid E/A	0.424±0.112		0.400±0.035		0.209
RV MPI	0.477±0.061		0.475±0.044		0.914
LV MPI	0.458±0.079		0.419±0.072		0.018
Aorta size (cm)	3.436±0.827		4.390±0.852		<0.001
Pulmonary size (cm)	3.093±0.740		4.895±1.087		<0.001
SVC size (cm)	1.944±0.444		2.511±0.535		<0.001
Pul/Ao ratio	0.899±0.065		1.110±0.172		<0.001
SVC/Ao ratio	0.776±0.115		0.574±0.097		<0.001

* RV: Right Ventricle, LV: Left Ventricle, MPI: Myocardial Performance Index, SVC: Superior Vena Cava, Ao: Aorta, Pul: Pulmonary

tion substantially reduces uterine artery resistance in both the right and left uterine arteries.

The effect of aspirin on PI of the umbilical artery, MCA, and DV: Aspirin administration (160 mg/

Table 3. Fetal cardiac biomarkers in participants with normal uterine artery resistance (n=5) before and after aspirin intake (160 mg/day)

Parameters	Mean (SD) before	Mean (SD) after	p-value
DV PI	2.00 (0.00)	1.40 (0.548)	0.083
Umbilical artery PI	1.00 (0.00)	1.00 (0.00)	1.000
MCA PI	1.00 (0.00)	1.00 (0.00)	1.000
Pul/Ao ratio	0.890 (0.078)	1.080 (0.366)	0.345
SVC/Ao ratio	0.728 (0.163)	0.544 (0.121)	0.043
Tricuspid E/A	0.452 (0.039)	0.408 (0.067)	0.288
Mitral E/A	0.424 (0.038)	0.389 (0.030)	0.080

day) significantly affected the PI of several key fetal arteries. Regarding the umbilical artery, the abnormal PI values became normal post-treatment in all 10 participants with abnormal PI before treatment (Table 2, $p < 0.001$). The MCA PI also showed improvement. All four participants with abnormal values before aspirin treatment had reached a normal condition (Table 2). Regarding DV PI, 24 participants had initially abnormal PI values; this number was reduced to two after aspirin administration (Table 2, $p < 0.001$). These results suggest a marked improvement in fetal blood flow indices following aspirin administration.

The effect of aspirin on fetal cardiac parameters: Fetal cardiac function, particularly the A-wave velocity at the mitral and tricuspid valves, was significantly enhanced following 160 mg/day aspirin administration. The mitral valve A-wave velocity increased significantly ($p < 0.001$), and a similar significant increase was observed in the tricuspid valve A-wave velocity ($p < 0.01$) (Table 2). No significant changes were observed in the E-wave velocity at the mitral or tricuspid valves. Additionally, the diameters of aorta, pulmonary artery, and SVC increased significantly after aspirin consumption ($p < 0.001$ for all). The pulmonary artery-to-aorta ratio increased substantially ($p < 0.001$), whereas the SVC-to-aorta showed a marked decrease ($p < 0.001$) after aspirin treatment (Table 2). These findings suggest that aspirin administration contributes to the normalization of fetal pulmonary-to-aortic and SVC-to-aortic dimension ratios. Also, the left ventricular myocardial performance index ($p < 0.05$) significantly decreased at post-treatment assessment (Table 2). Moreover, there was a significant decrease in the ratio of E/A at the mitral valve ($p < 0.001$). These changes indicate that aspirin enhances specific cardiac performance metrics in the fetus.

The effect of aspirin on fetal cardiac biomarkers in participants with normal uterine artery resistance: Aspirin treatment substantially decreased SVC/Ao ratio in women with normal uterine artery resistance (Table 3, $p < 0.05$). At the same time, there were no significant changes in the other cardiac parameters of this group (Table 3, $p > 0.05$). Aspirin may have less effect on fetuses with normal uterine artery resistance.

Discussion

Our results show that 160 mg/day of aspirin can improve cardiovascular parameters in fetuses at 18-24 weeks of gestation. Our findings also reveal aspirin's possible therapeutic or preventive mechanism in improving fetal cardiovascular function, which can be crucial in high-risk pregnancies.

The resistance of both the left and right uterine arteries was considerably reduced with the daily administration of 160 mg of aspirin. These findings indicate that aspirin is an effective intervention for reducing uterine artery resistance, thereby enhancing uteroplacental blood flow and potentially mitigating the adverse consequences of impaired placental perfusion, including preeclampsia and IUGR (10). In a study of pregnancies with abnormal uteroplacental blood flow, the rate of severe preeclampsia and growth restriction was significantly lower in aspirin-treated patients (11) despite contradictory findings reported in the literature (12, 13).

Additionally, aspirin administration significantly impacted the PI of different fetal arteries. The PI of the umbilical artery, MCA, and DV significantly improved after using aspirin for three weeks per day. Notably, all patients with abnormal umbilical artery PI and MCA PI demonstrated normalization, and the number of cases of abnormal DV significantly reduced from 24 to 2. Maintaining appropriate fetal oxygenation and nutrition

depends on appropriate arterial compliance. Increasing resistance of the main arteries can complicate this vital requirement. It has been calculated that an increase in the PI of DV in the second trimester by one unit causes a 38-fold increase in fetal growth restriction (14). It has also been shown that the decrease in atrial contraction wave (A-wave) velocity causes an 11-fold increase in the risk of IUGR (15).

To our knowledge, no study has been conducted on the possible effects of 160 mg/day aspirin on fetal cardiac function. Our study showed that aspirin significantly affected several fetal cardiac measures. Aspirin was assumed to improve cardiac output based on the markedly increased velocity of mitral and tricuspid valves, along with elevated diameter ratios of the pulmonary artery, aorta, and SVC. The idea that aspirin improves fetal cardiac function, possibly by lowering cardiac afterload (after lowering uteroplacental resistance) and improving myocardial function, is further supported by normalizing the pulmonary artery-to-aortic diameter ratio and the SVC-to-aortic diameter ratio following aspirin treatment.

An Australian study examined the relationship between fetoplacental Doppler indices and fetal cardiac function in uncomplicated singleton pregnancies. The findings demonstrated that placental-fetal Doppler parameters, including the cerebroplacental ratio, exhibit a positive correlation with key cardiac performance indicators (8).

In a study in Japan, the ratio of the SVC diameter to the aorta in the three-vessel view in fetuses with fetal growth restriction was compared to fetuses with normal growth. The average diameter of the SVC relative to the diameter of the aorta in the case group was significantly higher than that of the control group. It was shown that the ratio of SVC diameter to the aorta in the three-vessel view can be used as an effective and accurate diagnostic tool for the timely diagnosis of IUGR and subsequent treatment (16). Consistent with these findings, our study also showed that the ratio of SVC to aorta in several fetuses was higher than normal. Administration of aspirin at a daily dose of 160 mg appeared to help normalize this ratio.

Moreover, another study investigated the role of blood flow parameters of the DV in the first and second trimesters of pregnancy to predict the well-being of the fetus and newborn. The findings show that DV is an indirect indicator of intrauterine hypoxia with a moderate predictive value for adverse obstetric outcomes. A significant differ-

ence was observed between fetuses with normal and reduced velocities in terms of birth weight, the incidence of complications such as IUGR and congenital heart disease, and the requirement for neonatal intensive care (2).

A notable finding in our study was that aspirin treatment substantially decreased the SVC to aortic diameter ratio in women with normal uterine artery Doppler indices. Still, there were no significant changes in other cardiac parameters of this group. Aspirin may exert less effect in fetuses with normal uterine artery resistance compared with those exhibiting abnormal uterine artery Doppler findings. This may suggest that aspirin primarily influences vascular resistance in this context, rather than exerting a direct effect on myocardial or other cardiac tissues. Because of small sample size of this study (42 participants), further studies are needed to investigate this hypothesis. Furthermore, the absence of a control group limits the ability to attribute the observed effects solely to aspirin, as other variables may have contributed. The study's brief follow-up period limits assessing long-term impacts on fetal development and postnatal health. Furthermore, the heterogeneity of the study population, which encompassed a range of risk factors such as infertility and preeclampsia, introduced potential confounding variables that were not fully controlled. Lastly, the results might have been impacted by the measurement variability in Doppler ultrasound examinations as well as unmeasured confounding factors such as maternal diet and underlying medical disorders.

Future research should focus on larger, multicenter randomized controlled trials to overcome these limitations and validate the efficacy of 160 mg/day aspirin in various groups.

Conclusion

Our study revealed that the administration of 160 mg/day of aspirin can improve disturbances in fetal cardiovascular function parameters. Therefore, using these indices along with the uterine artery PI is suggested. The administration of aspirin in such vascular disturbances may prevent IUGR or other pregnancy complications. This can be the subject of further studies.

Long-term follow-up studies are also required to assess the long-term effects of aspirin on prenatal and neonatal outcomes, such as growth, neurodevelopment, and cardiovascular health. To improve treatment regimens, investigating the underlying

processes by which aspirin affects fetal cardiac function and uterine artery resistance would be beneficial. The best course of treatment may also be determined by subgroup analysis based on particular maternal risk factors and comparative studies evaluating various dosages and alternative medicines. Refinement of clinical guidelines and fetal and maternal safety will depend on investigating the duration and timing of aspirin treatment and evaluating maternal outcomes.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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