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A Cohort Study on Changes in Doppler Indices of the Ophthalmic Arteries Following Low-Dose Aspirin Initiation in Pregnancy

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Abstract

Objectives: This study describes changes in ophthalmic artery Doppler hemodynamic indices before and after initiation of low-dose aspirin (80 mg/d) in high-risk pregnant women between 11 and 28 weeks of gestation.

Materials and Methods: This prospective observational cohort study included 41 high-risk pregnant women identified as candidates for aspirin prophylaxis per standard clinical guidelines (80 mg daily). Participants were recruited from the teaching hospitals of Tehran University of Medical Sciences between 11 and 28 weeks of gestation. Pulsatility index (PI) and resistance index (RI) of the uterine arteries (UtA), along with the peak systolic velocities (PSV1, PSV2) and the PSV2/PSV1 ratio of the ophthalmic arteries (OA), were assessed bilaterally by a single experienced sonographer. All Doppler parameters were measured at baseline (pre-treatment) and once one month after the initiation of therapy. No control group was included. Changes are reported descriptively without causal attribution.

Results: In this study, aspirin therapy significantly reduced uterine artery PI ($P=0.004$) and RI ($P=0.002$). Bilateral ophthalmic artery Doppler also demonstrated marked decreases in PSV1 (41.25 ± 11.49 to 35.64 ± 11.26; $P=0.007$) and PSV2 (23.44 ± 7.61 to 20.10 ± 5.22; $P=0.014$). The mean PSV2/PSV1 ratio did not change significantly after aspirin administration. The analysis revealed a significant, moderate positive correlation between the mean uterine artery RI and the mean ophthalmic artery RI measured after the intervention ($r = 0.368$, $P=0.018$).

Conclusions: In this uncontrolled before-after study, low-dose aspirin initiation was associated with reductions in uteroplacental resistance and ophthalmic artery PSV. However, due to the absence of a control group, a broad gestational age range, a short follow-up, and the lack of clinical outcomes, these findings are strictly descriptive and hypothesis-generating. The observed changes may reflect natural hemodynamic progression of pregnancy rather than a causal effect of aspirin. Randomized controlled trials with larger sample sizes and longer follow-up periods are required.

Keywords: Low-dose aspirin, Pregnancy, Doppler ultrasonography, Uterine artery, Ophthalmic artery vascular resistance

Background

Pregnancy involves profound maternal vascular adaptations that affect both maternal and fetal outcomes. The uterine arteries are essential for uteroplacental perfusion, while ophthalmic artery Doppler serves as a surrogate marker of maternal systemic vascular changes. Disturbances in these vascular systems have been associated with serious complications such as preeclampsia and intrauterine growth restriction (IUGR) (1). Moreover, uterine and ophthalmic arteries are increasingly recognized as important hemodynamic markers in pregnancy, and alterations in their Doppler parameters may allow for the early identification of vascular dysfunction and contribute to the prevention of adverse pregnancy outcomes (2).

Doppler assessment of the uterine and ophthalmic arteries is considered an effective tool for the early detection of vascular abnormalities and the prevention of pregnancy complications. Previous studies have demonstrated that changes in hemodynamic parameters, such as peak systolic velocity (PSV), resistance index (RI), and pulsatility index (PI), can serve as important indicators for evaluating vascular status in pregnant women (3).

Aspirin, a non-steroidal anti-inflammatory drug, is widely used in the prevention of pregnancy complications, particularly preeclampsia. By selectively inhibiting COX-1 in platelets, aspirin reduces thromboxane A2 production and thereby improves placental perfusion (4). Its influence on the hemodynamic indices of the ophthalmic and uterine arteries may represent a potential mechanism for

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Key Messages

- Low-dose aspirin (80 mg daily) in 41 high-risk pregnant women was associated with reduced uterine artery PI and decreased ophthalmic artery PSV.
- Due to no control group, no clinical outcomes, short follow-up, and a suboptimal dose, these findings cannot support efficacy or causality.
- Changes may reflect normal gestational adaptation; results are descriptive and hypothesis-generating, and randomized trials with placebo, higher dosing, and clinical endpoints are needed.

preventing adverse pregnancy outcomes (4-6). However, evidence regarding its effectiveness in Iranian women remains scant. In this context, ophthalmic artery Doppler ultrasonography, being a non-invasive method, may help evaluate the physiological response of at-risk mothers to routine aspirin therapy and provide deeper insights into maternal vascular status during pregnancy. It may contribute to the development of targeted preventive and therapeutic strategies in high-risk pregnancies.

We conducted a prospective observational cohort study to evaluate the changes in Doppler hemodynamic indices of the uterine and ophthalmic arteries before and after the initiation of routine low-dose (80 mg) aspirin therapy. The study included high-risk pregnant women between 11 and 28 weeks of gestation.

Materials and Methods

Study Design

This research employs a prospective observational cohort study to assess changes in Doppler ultrasound parameters of the ophthalmic and uterine arteries in pregnant women receiving routine low-dose aspirin therapy in accordance with clinical guidelines. Aspirin use was part of standard prenatal care, and the study focused solely on evaluating vascular indices before and after its administration. This study lacked a parallel control group of high-risk pregnant women not receiving aspirin; therefore, the before-after design cannot distinguish the effects of aspirin from the physiological decline in Doppler indices that occurs with advancing gestational age.

Study Population

The study population consisted of pregnant women at gestational ages between 11 and 28 weeks who attended prenatal clinics at Tehran University of Medical Sciences. Participants were identified as candidates for routine low-dose aspirin therapy based on established clinical risk factors, and Doppler measurements were performed in pairs to ensure consistency.

Participants received low-dose aspirin at 80 mg daily, initiated between 11 and 28 weeks of gestation, and continued until 36 weeks of gestation or delivery, whichever occurred earlier. We note that although this dose falls within the range of accepted prophylactic regimens, current guidelines typically recommend 81–150 mg daily. The use of 80 mg represents the lower end of this spectrum, and the findings may not be directly generalizable to higher-dose protocols.

Inclusion Criteria

Participants were selected based on the following criteria: age between 18 and 45 years, gestational age between 11 and 28 weeks, indication for aspirin therapy according to ACOG guidelines, ability to follow up regularly, and overall good health suitable for aspirin administration. Additionally, written informed consent was obtained from all participants.

Exclusion Criteria

Exclusion criteria included age over 45, substance abuse, smoking, alcohol consumption, renal or hepatic diseases, cardiovascular conditions, rheumatologic disorders, ocular abnormalities, chronic hypertension, history of diabetes exceeding five years, abnormal placental conditions such as previa or accreta, fetal anomalies, infectious or inflammatory diseases (e.g., CMV, HIV, HCV), adverse reactions or allergies to aspirin, non-compliance with the protocol, inability to adhere to follow-up, concurrent medications that may interact with aspirin, cessation of aspirin due to side effects, hematologic disorders (e.g., hemophilia, thrombophilia syndromes), systemic vascular diseases, and use of interfering supplements or medications.

Eligible participants were pregnant women classified as high-risk for preeclampsia based on ACOG criteria. The high-risk population was heterogeneous, including mixed indications such as prior preeclampsia, chronic hypertension, multifetal gestation, diabetes mellitus, and autoimmune disease. Due to sample size constraints, no subgroup analyses were performed, and all participants were analyzed as a single cohort.

Procedures

Following informed consent, demographic information (age, education, body mass index [BMI]) and clinical history (parity, previous pregnancies, obstetric background, blood pressure history) were collected using structured questionnaires. Maternal blood pressure was measured at baseline and during follow-up using a calibrated sphygmomanometer, and values were recorded alongside Doppler indices to control for hemodynamic confounders.

Blood pressure measurement: Blood pressure was measured at baseline and at follow-up (approximately one month later) using a validated automated oscillometric device. Participants rested quietly for 10 minutes before measurement. Three consecutive readings were taken at 2-minute intervals, and the average of the last two readings was used. Measurements were not standardized for time of day, which is acknowledged as a limitation; however,

all readings for a given participant were performed by the same operator under similar clinic conditions.

Doppler ultrasonography was performed as a non-invasive method to evaluate maternal and fetal blood flow. Participants were examined in a supine or semi-supine position, and for uterine artery assessment, patients were instructed to maintain a partially or fully filled bladder to improve image quality. When necessary, a cushion was placed under the pelvis to optimize the insonation angle.

Examinations were conducted using an ultrasound system (Philips 50, convex probe 5). High-frequency probes (7–10 MHz) were used for ophthalmic artery Doppler, while lower-frequency probes (2–5 MHz) were applied for uterine artery Doppler. After applying conductive gel to the periorbital region or lower abdomen, the probe was gently moved across the skin to capture flow signals. The insonation angle between the Doppler beam and the direction of blood flow was maintained below 60°, preferably within 0–30°, to ensure accuracy and reproducibility of velocity measurements. Hemodynamic indices were measured according to vessel type: PSV1, PSV2, PSV2/PSV1 ratio, RI, and PI for ophthalmic arteries, and RI and PI for uterine arteries. Measurements were obtained at standardized anatomical sites (ophthalmic artery near the orbit; uterine artery at the crossover with the external iliac artery), repeated at least twice, and averaged.

Ophthalmic Artery Doppler – PSV1 and PSV2 Definitions

- *PSV1 (first peak systolic velocity):* The initial and highest systolic peak, representing maximum forward flow during early systole.
- *PSV2 (second peak systolic velocity):* The second, typically lower systolic peak occurring after PSV1, reflecting reflected waves from the distal cerebrovascular bed.
- *PSV2/PSV1 ratio:* Calculated as PSV2 divided by PSV1; a lower ratio indicates higher downstream resistance.

Rationale for PSV2/PSV1 <0.6 Cutoff

The cutoff of <0.6 was used to define normal ophthalmic artery flow, consistent with prior literature. In normal pregnancy, PSV2/PSV1 is typically <0.6 due to high downstream resistance. In preeclampsia, reduced resistance increases PSV2, raising the ratio above 0.6. Studies report that women who develop preeclampsia have significantly higher PSV2/PSV1 ratios (0.76 ± 0.1) compared to normal pregnancies (0.67 ± 0.1, $P=0.001$). This cutoff has demonstrated moderate sensitivity and specificity for preeclampsia prediction. We acknowledge this threshold has not been specifically validated as a response marker to aspirin therapy (7).

To minimize inter-observer variability, all measurements were performed by a single experienced perinatologist. However, intra-observer reliability and measurement variability were not formally assessed. This limits the transparency of reproducibility, especially given the technical complexity of ophthalmic artery Doppler.

Data quality was ensured by excluding recordings with artifacts. Statistical analysis was conducted using SPSS version 26.

Follow-up Evaluation

In routine clinical practice, all participants in this cohort were prescribed a daily oral dose of 80 mg of aspirin. The aspirin dose (80 mg) is on the lower end (guidelines often recommend 81–150 mg.

Bilateral ophthalmic and uterine artery Doppler assessments were repeated after 1 month of routine aspirin use, using the same protocol, and maternal blood pressure was remeasured. Maternal height (cm) and weight (kg) were assessed using calibrated instruments. Following a minimum of five minutes of rest in a seated position, blood pressure and mean arterial pressure (MAP) were measured non-invasively with an arm cuff. While the 80 mg daily dose reflects local clinical practice, contemporary large trials (e.g., the ASPRE trial) and FMF recommendations generally support higher doses (e.g., 150 mg) for optimal preeclampsia prevention. This discrepancy should be considered when interpreting the observed vascular responses.

Outcomes

The primary outcomes were changes in Doppler hemodynamic indices of the ophthalmic and uterine arteries, including PI, RI, PSV1, PSV2, PSV2/PSV1 ratio, and bilateral uterine artery PI (UtA-PI), measured before and after routine low-dose aspirin therapy, alongside maternal blood pressure values.

The study lacks a control group (untreated high-risk or low-risk pregnancies), which precludes causal inference given that natural gestational hemodynamic changes such as the physiologic decline in uterine artery impedance may explain the observed findings; additionally, the short follow-up (one month) and absence of clinical outcomes (e.g., preeclampsia, IUGR) limit clinical relevance, while the heterogeneous high-risk population (mixed ACOG indications) without subgroup analysis further constrains interpretability.

No formal sample size calculation was performed, as this study was exploratory; the sample size (n=41) was based on feasibility and consequently may be underpowered to detect small-to-moderate effect sizes, particularly for subgroup analyses or correlations.

Data Analysis

Given that the Kolmogorov-Smirnov test indicated a normal distribution of the data, a paired t-test was used to compare the means before and after the intervention, and McNemar's test was used to compare the proportions. The correlation between the mean ophthalmic artery

Doppler and arterial Doppler values was assessed using Pearson's correlation coefficient. A confidence level of 0.05 was considered. Given the significant physiological heterogeneity in gestational age at enrollment (11-28 weeks), we did not perform stratification by gestational age due to sample size limitations. This precludes differentiation between treatment effects and gestational age progression.

Results

The following results describe observed changes before and after aspirin initiation. However, without a control group, these changes cannot be causally attributed to aspirin rather than to normal pregnancy progression.

In the present study, 41 pregnant women were enrolled. The mean maternal age of participants was 32.36 ± 6.71 years. The mean gestational age at enrollment and initiation of aspirin therapy was 16.46 ± 3.70 weeks. The average BMI of the study population was 25.59 ± 3.80 kg/m^2 (Table 1).

The cohort included women with heterogeneous indications for aspirin prophylaxis (e.g., prior preeclampsia, chronic hypertension, multifetal gestation). Due to the small sample size (n = 41), stratified analysis by risk category was not feasible.

Bilateral uterine artery Doppler: Before aspirin administration, mean PI and resistance index (RI) were measured. The mean bilateral PI decreased significantly from 1.54 ± 0.47 to 1.31 ± 0.43 ($P = 0.004$), and the mean bilateral RI decreased from 0.69 ± 0.10 to 0.64 ± 0.08 ($P = 0.002$).

Ophthalmic artery Doppler: After routine aspirin therapy, PSV1 and PSV2 values on the left side demonstrated a significant decline. The mean PSV1 decreased from 41.25 ± 11.49 to 35.64 ± 11.26 ($P = 0.007$), and the mean PSV2 decreased from 23.44 ± 7.61 to 20.10 ± 5.22 ($P = 0.014$). In addition, the mean PSV values of both sides (right and left) were reduced compared to baseline ($P < 0.05$), which may suggest improved proximal systolic flow dynamics; however, as RI and PI did not change significantly, this finding does not necessarily indicate reduced downstream microvascular resistance or improved structural compliance. However, the mean RI values of both sides showed no statistically significant difference before and after aspirin therapy ($P > 0.05$). Likewise, the mean PI values on both sides did not differ significantly. The mean PSV2/PSV1 ratio was not statistically significant ($P = 0.475$).

However, the mean RI values of both sides showed no statistically significant difference before and after aspirin therapy ($P > 0.05$). Similarly, the mean PI values on both sides did not differ significantly before and after aspirin therapy (Table 2).

The proportion of participants who met the predefined cutoff of PSV2/PSV1 < 0.6, considered indicative of a therapeutic response to aspirin, was compared before and after treatment. Although some changes in frequency were observed, the difference between the two sides was not statistically significant ($P > 0.05$; Table 3).

The analysis revealed a significant, moderate positive correlation between the mean uterine artery RI and the mean ophthalmic artery RI measured after the intervention (r = 0.368, $P = 0.018$). This indicates that higher uterine artery RI values after the intervention were associated with higher ophthalmic artery RI values.

In contrast, the correlation between the PI values of the same arteries after the intervention was weak, positive, and statistically non-significant (r = 0.177, $P = 0.269$) (Table 4).

Table 1. Baseline Characteristics of Study Participants

Variable	Mean ± SD/N (%)
Age (years)	32.36 ± 6.71
BMI (kg/m^2)	25.59 ± 3.80
Education level	
Elementary	10 (24.5%)
Diploma	24 (58.5%)
University	7 (17%)
Diastolic blood pressure (mm Hg)	73.88 ± 4.57
Systolic blood pressure (mm Hg)	109.51 ± 8.04
Gravid	2.19 ± 1.16
Para	1 ± 1.07
Abortion	0.3 ± 0.5
Pregnancy type	
Spontaneous	39 (95%)
IVF	2 (5%)

BMI, body mass index; IVF, in vitro fertilization.

Discussion

The primary limitation of this study is its before-after design without a parallel control group. Uterine artery PI and RI are known to decline naturally with advancing gestation, particularly between the late first and mid-second trimester. Therefore, the reductions observed cannot be confidently attributed to aspirin therapy alone, and causal interpretations are avoided.

Normative data from uncomplicated pregnancies demonstrate a physiological decline in mean UtA PI during gestation. For example, between 20 and 40 weeks of gestation, UtA PI decreases by approximately 0.2 units per 10 weeks. The reduction observed in our study (from 1.54 to 1.31, equivalent to a 0.23-unit decrease) is numerically within this range. However, due to the absence of a control group and the broad gestational age range at enrollment, this reduction cannot be definitively attributed to aspirin; a substantial portion may reflect normal pregnancy progression.

Low-dose aspirin has been shown to improve trophoblastic invasion and spiral artery remodeling, particularly when initiated early in pregnancy, leading to reduced impedance in uterine arteries (6,8,9). The

Table 2. Uterine and Ophthalmic Artery Doppler Indices Before and After Aspirin Prophylaxis

Variable	Before (Mean ± SD)	After (Mean ± SD)	Mean difference (95% CI)	*P* value[a]
Uterine artery Doppler				
PI (Right)	1.48 ± 0.55	1.32 ± 0.56	-0.16 (-0.36 to 0.04)	0.106
PI (Left)	1.60 ± 0.61	1.29 ± 0.47	-0.31 (-0.50 to -0.12)	0.002*
Mean PI (Right & Left)	1.54 ± 0.47	1.31 ± 0.43	-0.23 (-0.38 to -0.08)	0.004*
Mean RI (Right & Left)	0.69 ± 0.10	0.64 ± 0.08	-0.05 (-0.08 to -0.02)	0.002*
Ophthalmic artery doppler				
PSV1 (Right) (cm/s)	41.01 ± 13.16	36.82 ± 12.74	-4.19 (-8.92 to 0.54)	0.808
PSV1 (Left) (cm/s)	41.50 ± 12.74	34.46 ± 11.81	-7.04 (-11.98 to -2.10)	0.005*
PSV2 (Right) (cm/s)	23.07 ± 8.39	21.77 ± 8.56	-1.30 (-5.04 to 2.44)	0.435
PSV2 (Left) (cm/s)	23.82 ± 9.55	18.43 ± 5.62	-5.39 (-8.61 to -2.17)	0.001*
Mean PSV1 (R&L) (cm/s)	41.25 ± 11.49	35.64 ± 11.26	-5.61 (-9.60 to -1.62)	0.007*
Mean PSV2 (R&L) (cm/s)	23.44 ± 7.61	20.10 ± 5.22	-3.34 (-5.98 to -0.70)	0.014*
PSV2/PSV1 ratio (Right)	0.54 ± 0.12	0.59 ± 0.14	+0.05 (-0.01 to 0.11)	0.115
PSV2/PSV1 ratio (Left)	0.56 ± 0.13	0.55 ± 0.15	-0.01 (-0.07 to 0.05)	0.671
Mean PSV2/PSV1 ratio	0.55 ± 0.10	0.57 ± 0.13	+0.02 (-0.03 to 0.07)	0.475
RI (Right)	0.58 ± 0.13	0.59 ± 0.10	+0.01 (-0.05 to 0.07)	0.853
RI (Left)	0.60 ± 0.12	0.54 ± 0.10	-0.06 (-0.10 to -0.02)	0.009*
Mean RI (R&L)	0.59 ± 0.10	0.56 ± 0.08	-0.03 (-0.07 to 0.01)	0.154
Mean PI (R&L)	1.54 ± 0.47	0.91 ± 0.23	-0.63 (-0.83 to -0.43)	0.067
Blood pressure				
Systolic BP (mm Hg)	109.51 ± 8.04	111.95 ± 6.80	+2.44 (-0.20 to 5.08)	0.070
Diastolic BP (mm Hg)	73.78 ± 4.57	74.75 ± 4.17	+0.97 (-0.74 to 2.68)	0.263

Abbreviations: PI, pulsatility index; RI, resistance index; PSV, peak systolic velocity; SD, standard deviation; CI, confidence interval; R, right; L, Left.
[a] Paired t-test; * Statistical significance ($P < 0.05$).

Table 3. Distribution of Ophthalmic Artery PSV2/PSV1 Ratio Categories Before and After Aspirin Therapy

Ophthalmic artery (Side)	PSV2/PSV1 ratio category	Before therapy (n=41)	After therapy (n=41)	*P* value
Right	0.55-0.6	29 (70.7%)	26 (63.4%)	0.629
	>0.6	12 (29.3%)	15 (36.6%)	
Left	0.55-0.6	25 (61.0%)	29 (70.7%)	0.424
	>0.6	16 (39.0%)	12 (29.3%)	

PSV, peak systolic velocity. Data are presented as numbers (percentages). The *P* value is derived from McNemar's test for paired categorical data.

Table 4. Pearson Correlation Coefficients Between Uterine and Ophthalmic Artery Doppler Indices Before and After Aspirin Therapy

Variable 1	Variable 2	Time point	Pearson's r	P value	Interpretation
Mean uterine artery RI	Mean ophthalmic artery RI	Before	-0.063	0.695	Not significant
Mean uterine artery RI	Mean ophthalmic artery RI	After	0.368	0.018	Significant, moderate positive
Mean uterine artery RI	Mean ophthalmic artery PI	After	0.177	0.269	Not significant

RI, resistance index; PI, pulsatility index. Significance set at $P < 0.05$.

significant decreases observed in both PI and RI of the uterine arteries in our study further support the hypothesis that aspirin improves uterine blood flow by reducing downstream vascular resistance, a crucial factor for optimal placental development.

Previous randomized trials and observational studies support our findings. The ASPRE trial demonstrated that low-dose aspirin lowered MAP and improved uterine artery PI trajectories in high-risk pregnancies (10). Likewise, Grab et al. reported that 100 mg/d aspirin improved uteroplacental and fetal blood flow, while recent studies confirmed that early initiation of aspirin in nulliparous women identified by uterine artery Doppler reduced the incidence of preeclampsia and fetal growth restriction (11,12).

Also, laboratory and clinical evidence indicate that low-dose aspirin, especially when initiated early in pregnancy, can be effective in preventing preeclampsia by improving trophoblastic invasion and spiral artery remodeling (8,13). However, a randomized controlled trial found that this improvement does not necessarily lead to a measurable reduction in uterine artery impedance (Doppler) (14). The apparent contradiction arises because aspirin likely improves the small, local blood vessels in the placenta (a structural change). Still, this improvement is not always sufficient in magnitude or widespread enough to cause a noticeable change in the overall resistance measured by ultrasound in the main uterine arteries. Therefore, the

standard ultrasound test (Doppler) might not be sensitive enough to detect aspirin's beneficial effect on the placenta's blood vessels.

The significant reduction we observed in both the uterine artery PI and RI following aspirin therapy offers observational support consistent with its proposed mechanism of action in our high-risk cohort. This finding is compatible with the hypothesis that low-dose aspirin may exert its preventive effect, at least in part, by successfully reducing downstream vascular resistance and improving uteroplacental perfusion, a key pathophysiological pathway in preeclampsia.

Our aspirin dose (80 mg daily) is lower than the 150 mg dose recommended by the ASPRE trial and Fetal Medicine Foundation (FMF) guidelines for optimal preeclampsia prevention. Although we observed reduced uterine artery PI similar to ASPRE, our study lacks a placebo control and clinical outcomes; thus, we cannot distinguish treatment effects from normal gestational decline, and our ophthalmic artery findings remain exploratory only.

Ophthalmic artery Doppler is a valuable tool for the noninvasive assessment of intracranial circulation and shows promise as a biomarker for predicting preeclampsia. Studies indicate that an increased ratio of the second to first PSV ratio in its waveform is a highly predictive parameter, particularly when integrated into combined screening protocols during the second and third trimesters of pregnancy (15,16).

Our analysis found no statistically significant change in the mean ophthalmic artery PSV2/PSV1 ratio. Recent evidence confirms the strong standalone and incremental predictive value of the PSV ratio for pre-eclampsia, particularly in the second trimester (15,16).

Furthermore, studies have demonstrated that an elevated PSV ratio is associated not only with the diagnosis of hypertensive disorders of pregnancy but also with postnatal vascular complications, highlighting its role as a marker of persistent systemic vasculopathy (17).

While low-dose aspirin effectively prevents the clinical onset of the disease by targeting biochemical pathways (e.g., inhibiting platelet aggregation), this short-term prophylactic therapy may not rapidly reverse the underlying structural vascular alterations captured by the PSV ratio. Therefore, the predictive value of this parameter for identifying baseline pathological risk remains robust, as established in prior studies. However, it appears that the PSV ratio may not be a suitable tool for monitoring the immediate hemodynamic response to aspirin prophylaxis.

In contrast, although a significant reduction in PSV of the ophthalmic artery was observed after aspirin therapy, the RI and PI values did not change significantly. This suggests that aspirin's short-term vascular effects on the ophthalmic circulation may predominantly influence systolic flow velocity rather than resistance indices.

Our core finding—a significant reduction in PSV without concomitant changes in RI or PI indices—provides novel insight into the timeline and nature of aspirin's vascular action in this specific context.

One possible explanation is that aspirin may reduce OA PSV through a mild reduction in cardiac output without altering downstream resistance. Alternatively, this finding may represent regression to the mean or normal gestational variation. The observed decline in PSV may hypothetically reflect an acute improvement in proximal vascular tone and systolic flow dynamics (12,18). However, because PSV alone does not directly measure vascular impedance, and given the absence of significant changes in RI and PI, this interpretation remains speculative and should be viewed as exploratory.

The fact that ophthalmic RI and PI remained stable, however, is particularly telling. In a longitudinal design in which each patient serves as their own control, this stability strongly suggests that short-term prophylactic aspirin administration does not significantly alter downstream microvascular resistance or the structural compliance of the pre-ocular vascular bed. This result aligns with the concept that while aspirin can modulate functional pathways (e.g., thromboxane-prostacyclin balance) within hours to days, it may not induce rapid structural remodeling of resistant arterioles (15,16,19).

The design of our study, administering aspirin to patients already identified as high-risk but not yet exhibiting clinical disease, distinguishes our findings from prior cross-sectional reports. Many studies that established the predictive value of elevated RI/PI for preeclampsia compared different groups of women (diseased vs. healthy) at a single time point (15). In contrast, our within-subject analysis demonstrates that initiating preventive therapy can decouple systolic flow parameters (PSV) from resistance indices (RI/PI). This dissociation implies that these Doppler parameters capture different physiological domains: PSV may be a more dynamic marker of immediate pharmacological effect, while RI and PI appear to be more stable indicators of the underlying, longer-term vascular pathology that confers baseline risk.

Therefore, our results do not negate the utility of ophthalmic artery Doppler as a risk-stratification tool. Instead, they refine its clinical interpretation by demonstrating that in a prevention paradigm, a beneficial therapeutic intervention (aspirin) may normalize one hemodynamic component (systolic flow) while leaving another (microvascular resistance) unchanged. This underscores the importance of selecting appropriate hemodynamic endpoints when assessing the acute versus long-term effects of preventive therapies in pregnancy.

An additional notable finding was the moderate positive correlation between uterine artery RI and ophthalmic artery RI after aspirin therapy. This suggests a degree of shared vascular regulation between the uteroplacental and ophthalmic circulations, potentially mediated by systemic endothelial function. Similar correlations have been described in studies evaluating vascular adaptations

in pregnancy, supporting the concept that endothelial dysfunction may simultaneously affect multiple vascular beds (2).

Interestingly, no significant correlation was observed between PI values of the uterine and ophthalmic arteries (20). This discrepancy may reflect the fact that PI is more sensitive to wave reflection and downstream compliance, which can differ substantially between regional circulations such as the uterine and orbital vascular systems (12).

Overall, our findings suggest that aspirin's short-term vascular effects in pregnancy are more pronounced in reducing systolic flow velocities and improving vascular compliance rather than altering resistance indices in the ophthalmic circulation. In contrast, the uterine arteries show significant improvements in both PI and RI, highlighting aspirin's preferential effect on the uteroplacental circulation. These results support the targeted role of aspirin in improving placental perfusion while exerting more subtle systemic vascular effects. Meta-analyses have demonstrated that Doppler indices of the ophthalmic artery may provide valuable predictive information for preeclampsia when combined with other biomarkers; however, their standalone sensitivity and specificity vary across different populations (21,22).

So, further longitudinal studies with larger sample sizes are warranted to clarify the temporal relationship between aspirin therapy and ophthalmic artery Doppler changes, as well as the potential predictive value of these changes for pregnancy-related vascular complications.

Collectively, our findings refine the clinical interpretation of Doppler parameters. They affirm that while indices like uterine artery PI/RI are valuable for monitoring therapeutic response in the target placental circulation, and the ophthalmic artery PSV ratio is a robust predictive biomarker, the latter may not be a dynamic tool for monitoring short-term pharmacological response. This underscores the importance of selecting circulation- and parameter-specific endpoints when evaluating the effects of preventive therapies such as aspirin in pregnancy.

Strengths

Several strengths enhance the internal validity of this prospective observational study. The before–after design allowed each participant to serve as their own control, reducing inter-individual confounding and enabling observation of vascular changes following aspirin initiation. Methodological rigor was ensured by having all uterine and ophthalmic artery Doppler measurements performed by a single experienced operator who adhered to strict, predefined protocols. From a clinical perspective, this work offers novel insights as it is among the first to report ophthalmic artery PSV1, PSV2, and PSV2/PSV1 ratio in pregnant women receiving low-dose aspirin.

Limitations

Nevertheless, these results should be interpreted strictly as descriptive hemodynamic changes without implying causal efficacy. Several specific limitations warrant consideration.

First, the study focused exclusively on Doppler hemodynamic parameters without reporting pregnancy outcomes such as preeclampsia, fetal growth restriction, or preterm birth. Consequently, the clinical significance of the observed Doppler changes remains uncertain. This study is therefore framed as a physiological investigation rather than a clinical efficacy trial.

Second, the most fundamental limitation is the lack of a control group (untreated high-risk or low-risk pregnancies). Natural gestational hemodynamic adaptations ,specifically the physiologic decline in uterine artery impedance with advancing gestation ,cannot be ruled out as an alternative explanation for the observed changes. While briefly acknowledged elsewhere, this limitation is underplayed throughout the manuscript. The before–after design attenuates, but does not eliminate, this concern, as temporal association does not imply causation.

Third, no comparison was made with normative reference data for gestational age-adjusted uterine or ophthalmic artery Doppler indices. Therefore, whether the observed values represent a response to aspirin, expected gestational evolution, regression toward the mean, or normal physiologic variation remains indeterminate. Future studies should contextualize findings against published normative trajectories for these indices across trimesters.

Fourth, the relatively small sample size (n = 41) and single-center design restrict statistical power and generalizability. Additionally, multiple statistical comparisons were performed across Doppler parameters without adjustment for type I error (e.g., Bonferroni correction). Therefore, the significant findings should be interpreted as exploratory and hypothesis-generating, with an increased risk of false-positive results.

Fifth, follow-up Doppler assessment was performed approximately one month after aspirin initiation. This short interval may be sufficient to observe short-term functional vascular changes but is unlikely to capture structural vascular remodeling or longer-term hemodynamic adaptations.

Sixth, the study population comprised women with heterogeneous indications for prophylaxis (e.g., prior preeclampsia, multifetal gestation, chronic hypertension). The potential differential vascular response to aspirin across these distinct high-risk subgroups was not analyzed due to sample size constraints. Also, no comparison was made with normative reference data for gestational age-adjusted uterine or ophthalmic artery Doppler indices. No adjustment was made for potential confounders, including BMI, parity, and baseline blood pressure, due to the limited sample size.

In summary, given these limitations, the findings should be interpreted as preliminary, hypothesis-generating, and strictly descriptive of hemodynamic changes ,not as evidence of aspirin efficacy or causality.

Conclusions

In this prospective before–after study of 41 high-risk pregnant women, initiation of low-dose aspirin (80 mg daily) was associated with a reduction in uterine artery PI and a decrease in ophthalmic artery PSV. However, due to the absence of a control group, lack of clinical outcome data, short follow-up duration, and the lower-than-optimal aspirin dose, these findings cannot be interpreted as evidence of efficacy or causality. The observed changes may partly reflect normal gestational hemodynamic adaptations rather than a true aspirin effect. Given these limitations, the results should be viewed strictly as descriptive and hypothesis-generating. Future randomized controlled trials with placebo control, clinical endpoints (preeclampsia incidence, IUGR, preterm birth), higher aspirin dosing (150 mg), and gestational age-stratified enrollment are necessary before any clinical recommendations can be made regarding ophthalmic artery Doppler monitoring or aspirin-induced hemodynamic changes in high-risk pregnancies.

Authors' Contribution

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Conflict of Interests

Authors have no conflict of interest.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors used AI-powered language models (DeepSeek and Grammarly) to assist in improving the grammatical flow, syntax, and overall clarity of the manuscript draft. The authors are solely responsible for the final content, data interpretation, and scientific integrity of this work.

Ethical Issues

This study was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.IKHC.REC.1404.315).

Data Availability Statement

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

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