Ultrasound Obstet Gynecol 2025; **66**: 641–648
Published online 20 September 2025 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.70095.

Role of aspirin therapy in modulating uterine artery resistance and placental growth between first and second trimesters of pregnancy

C. TRILLA[1,2,3], J. PLATERO[1], J. MORA[2,4], M. N. NAN[4], C. MEDINA[1,2,3], O. ALEJOS[1,2], J. PARRA[1,2] and E. LLURBA[1,2,3]

[1]*Department of Obstetrics and Gynecology, Institut d'Investigació Biomèdica Sant Pau - IIB Sant Pau, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;* [2]*Faculty of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain;* [3]*Primary Care Interventions to Prevent Maternal and Child Chronic Diseases of Perinatal and Developmental Origin Network (RICORS, RD21/0012/0001), Instituto de Salud Carlos III, Madrid, Spain;* [4]*Department of Biochemistry, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*

KEYWORDS: first trimester; low-dose aspirin; placental biometry; placental volume; pre-eclampsia; three-dimensional ultrasound; two-dimensional ultrasound; uterine artery Doppler

ABSTRACT

Objective *To evaluate the impact of low-dose aspirin (LDA) on placental size and uterine artery pulsatility index (UtA-PI) by analyzing longitudinal changes between the first and second trimesters in pregnancies at high risk for early-onset pre-eclampsia (PE).*

Methods *This was a prospective observational cohort study of 631 singleton pregnancies. Women at high risk of early-onset PE (delivery ≤ 33 + 6 weeks) were identified using maternal factors or a multivariate screening protocol and were prescribed LDA. Placental size was assessed using two- and three-dimensional ultrasonography, and UtA-PI was measured using transabdominal Doppler, with measurements obtained in the first and second trimesters. Differences in placental measurements and UtA-PI between high-risk women receiving LDA and low-risk untreated women were analyzed.*

Results *Among the 631 participants, 53 (8.4%) women were prescribed LDA for the prevention of early-onset PE. Placental size in the first trimester was significantly smaller in the LDA group compared with the untreated group, as exemplified by placental volume (mean ± SD, 68.46 ± 25.19 cm^3* vs *76.31 ± 23.63 cm^3; P = 0.022), and this trend persisted into the second trimester. However, no significant differences in placental growth from the first to the second trimester were observed between the groups. UtA-PI was significantly higher in the LDA group in both trimesters, but a greater decrease in UtA-PI multiples of the median values between trimesters was noted in these women (mean ± SD, −14.0 ± 0.28%* vs *−4.5 ± 0.31%; P = 0.021). Perinatal outcomes were similar between the groups, with the exception of a higher rate of Cesarean delivery in the LDA group (38.5%* vs *21.1%; P = 0.008).*

Conclusions *Women at high risk for early-onset PE have a smaller placenta and higher UtA-PI in the first and second trimesters. Treatment of high-risk women with LDA did not affect placental growth but was associated with a greater reduction in UtA-PI, suggesting a positive effect of LDA on placental perfusion. These findings provide insight into the mechanism of action of LDA in the prevention of PE.* © *2025 The Author(s). Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Defective placentation is a key mechanism underlying many obstetric disorders[1,2]. Among these, placental insufficiency and its clinical manifestations, including pre-eclampsia (PE) and intrauterine growth restriction (IUGR), are the greatest contributors to maternal and neonatal morbidity and mortality worldwide[3–10]. Understanding their underlying pathophysiology is therefore crucial to mitigating their immediate and long-term impacts.

The extent of trophoblastic invasion determines placental efficiency and fetal viability throughout gestation[2]. PE is believed to result from defective trophoblastic invasion

Correspondence: Dr C. Trilla, Department of Obstetrics and Gynecology, Hospital de la Santa Creu i Sant Pau, Sant Quintí 89, 08025 Barcelona, Spain (e-mail: ctrilla@santpau.cat)

Accepted: 29 July 2025

after embryo implantation[11]. Moreover, spiral artery remodeling is a key element of maternal cardiovascular adaptation to pregnancy[12]. Insufficient arterial transformation leads to placental ischemia, triggering inflammation, oxidative stress and endothelial damage[11,13]. Understanding these processes has made it possible to identify patients at high risk for PE, although this remains challenging in women without known clinical risk factors[14,15].

Placental function can be evaluated using the uterine artery pulsatility index (UtA-PI), a critical tool for PE screening[16,17]. However, some pregnancies with abnormal UtA-PI do not develop complications such as PE or IUGR, suggesting that the placental villous tree has the capacity to adapt to hypoxic situations[18]. This highlights the value of evaluating the placenta directly. Various ultrasound parameters have been proposed for assessing the placenta[19–22], with three-dimensional (3D) placental volume (PV) emerging as a promising predictor of placental insufficiency-related complications[23,24]. Several studies have linked PV with neonatal weight and incidence of PE[25–29]. Additionally, two-dimensional (2D) placental measurements, including placental thickness (PT), basal plate diameter (BP) and chorionic plate diameter (CP), have been associated with adverse outcomes, such as PE and hydrops fetalis[30–32]. However, inconsistent measurements between previous studies have limited their clinical application[26,33–35].

Women at risk for early-onset PE can be identified using multivariate screening methods that integrate maternal, biochemical and biophysical factors[15,36,37], enabling timely initiation of preventive low-dose aspirin (LDA)[38,39]. Consequently, screening programs are being implemented worldwide, and an increasing number of women are being treated with LDA to prevent PE[36,37]. However, the mechanism by which aspirin reduces the incidence of PE remains unclear, and its impact on placental development and growth has yet to be investigated.

This study aimed to assess the impact of LDA on placental size and UtA-PI by evaluating longitudinal changes between the first and second trimesters in pregnancies at high risk for early-onset PE.

METHODS

This was a single-center prospective observational cohort study of women with a singleton pregnancy who underwent routine ultrasound assessment at the Prenatal Diagnosis Unit of Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, between 1 September 2016 and 28 February 2020. Women with a singleton pregnancy and a fetal crown–rump length between 45 mm and 84 mm were invited to participate. Women were withdrawn from the study in the case of pregnancy loss before 20 weeks, fetal chromosomal abnormality, major fetal structural anomaly diagnosed during pregnancy or at birth, congenital infection, SARS-CoV-2 infection during pregnancy or abnormal adherence of the placenta. Women lost to follow-up were also excluded from the analysis. This study was a planned subanalysis of a larger observational study on placental insufficiency that aimed to determine the contribution of placental size to PE and IUGR screening, in combination with other markers. It was approved by the Ethics Committee of the Institutional Review Board at Hospital de la Santa Creu i Sant Pau (IBSP-PLA-2016-31) and was registered with ClinicalTrials.gov (number: NCT02879942). All patients provided written informed consent to participate.

Maternal and pregnancy characteristics

Maternal baseline characteristics were recorded, including age, ethnicity, body mass index (BMI), smoking habit and medical history (chronic hypertension, diabetes mellitus, kidney disease, autoimmune disease, hereditary or acquired thrombophilia and thyroid disorder). Pregnancy characteristics were also registered, including method of conception, parity, aspirin treatment during pregnancy, gestational age (GA) at first-trimester ultrasound assessment, GA at second-trimester ultrasound assessment and site of placental attachment.

First-trimester PE screening

According to our institutional protocol, women at high risk of early-onset PE were identified based on maternal risk factors alone until 2018, including previous PE, chronic kidney disease, autoimmune disease (e.g. systemic lupus erythematosus or antiphospholipid syndrome), Type-1 or -2 diabetes and chronic hypertension[40]. In 2019, a first-trimester multivariate screening protocol was implemented and, from then on, PE risk was calculated using the abovementioned maternal risk factors in addition to placental growth factor (PlGF), pregnancy-associated plasma protein-A (PAPP-A), mean arterial pressure (MAP) and UtA-PI, following published methodology[41].

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured on the day of the first ultrasound scan using a calibrated Tensoval Duo Control device (Hartmann AG, Heidenheim, Germany). Blood pressure was measured once in one arm after a short period of rest and with the woman in a seated position, as per our current clinical practice. MAP was calculated using the formula: $MAP = (SBP + (2 \times DBP))/3$. UtA-PI was measured using transabdominal Doppler in the first and second trimesters according to standardized methodology[42]. The mean of the right and left UtA-PI, and the standardized value in multiples of the median (MoM), were used for analysis. Serum concentrations of PlGF and PAPP-A were determined by fully automated electrochemiluminescence immunoassays, using a Cobas e 601 analyzer (Roche Diagnostics, Basel, Switzerland). MoM values for UtA-PI, PAPP-A and PlGF were calculated from locally derived normal medians using a multivariate Gaussian distribution model validated previously in our population[37]. High risk for PE was defined as a risk of $\geq$ 1:250, and these women were instructed to take 150 mg of aspirin daily at bedtime, starting immediately after risk

assessment (11–14 weeks) until 36 weeks. Compliance with aspirin treatment was verified through individual chart review of all women at high risk for PE.

Placental ultrasonography

In the first trimester, 3D ultrasound datasets were acquired by experienced operators at the Prenatal Diagnosis Unit with specific training in 3D ultrasound. All placental measurements were performed by a single operator (C.T.), prior to the initiation of LDA treatment. PV datasets were acquired transabdominally using commercially available ultrasound systems (iU22 and Epiq7; Philips Healthcare, Best, The Netherlands), equipped with an X6-1 Pure-Wave xMatrix transducer with an extended operating frequency range (1–6 MHz) and a volume of field of view of $90° \times 90°$. The placenta was oriented perpendicularly for image acquisition, with the sweep angle set at 90°. Two or three 3D volume datasets were acquired for each woman to ascertain quality criteria. Volumes were scanned and saved for offline analysis.

The standardized methodology proposed by Schwartz *et al.*[34] was adopted for 2D placental measurements, which were obtained from the acquired datasets. 2D variables included BP, CP and PT. Measurements were performed in two orthogonal planes, as described elsewhere[34,43], with the mean value used for analysis. A curvilinear trace was used for BP and CP, and a linear trace was used for PT. All measurements were performed in the plane with the maximum placental view, independent of the site of cord insertion. Retroplacental veins were carefully excluded for BP and PT measurements.

QLAB GI3DQ software version 10.5 (Philips Healthcare) was used to estimate PV. This software employs a modified multiplanar methodology using a predetermined number of placental sections for volume estimation. The x-plane was selected randomly to draw the placental reference axis, with the 3D dataset adjusted to display the largest view of the placenta. The placental edges were then identified to draw a linear axis (reference axis), from which 15 parallel sections perpendicular to this axis were generated. In each section, the outer contour of the placenta was traced manually, carefully excluding all structures surrounding the placenta. Once tracing of the last section was complete, PV was obtained automatically in cubic centimeters. Figures 1 and 2 illustrate 2D and 3D measurements, respectively. The inter- and intraobserver agreement of these methodologies has been ascertained in a previous study[44].

For placental measurements in the second trimester, 2D variables were measured following the same methodology as described for the first trimester. Placental growth between the first and second trimesters was defined as the percentage change in placental variables (BP, CP and PT) between the two assessments. Changes in placental variables were adjusted for GA. Changes in UtA-PI between the two trimesters were also estimated using this methodology. 3D measurements were not performed in the second trimester.

Pregnancy outcomes

Pregnancy outcomes recorded include GA at delivery, mode of delivery, fetal sex and birth weight. Maternal and fetal complications related to placental insufficiency were also registered, including PE, small-for-gestational age (SGA) and preterm birth. PE was classified into three groups: early-onset PE (delivery $\leq 33+6$ weeks), preterm PE (delivery $\leq 36+6$ weeks) and term PE (delivery $\geq 37+0$ weeks).

Statistical analysis

All placental variables were adjusted for GA by dividing raw values by days of gestation at assessment, yielding placental quotients, as described elsewhere[28].

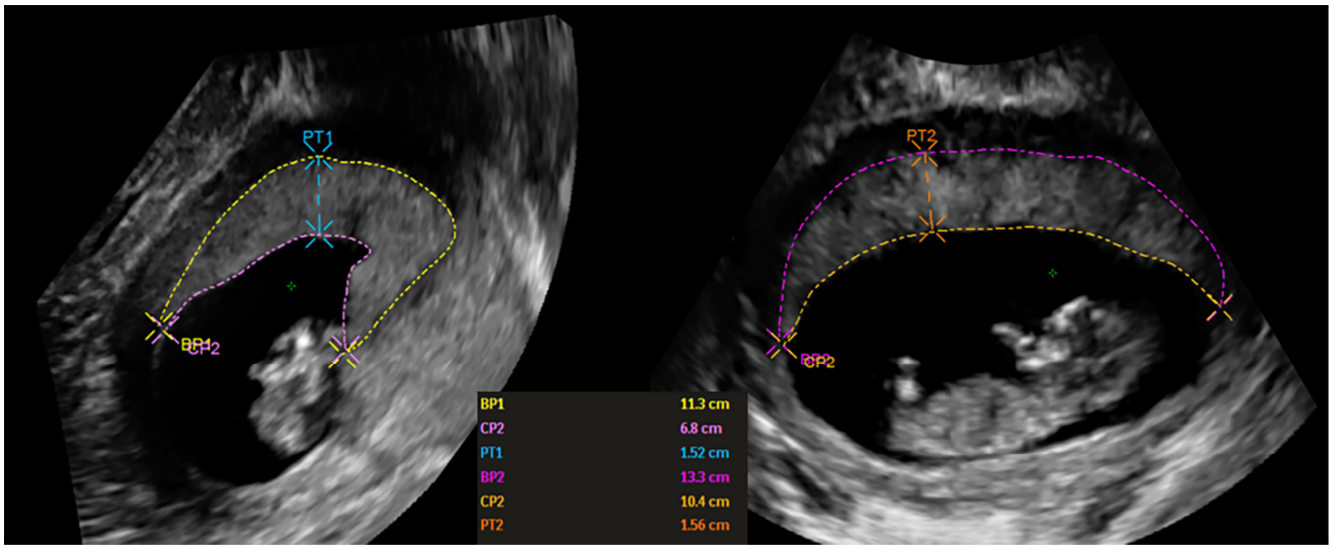

Figure 1 Measurement of placental size using two-dimensional ultrasound. All variables were measured in two orthogonal planes showing largest view of placenta. BP, basal plate diameter (curvilinear); CP, chorionic plate diameter (curvilinear); PT, placental thickness (linear).

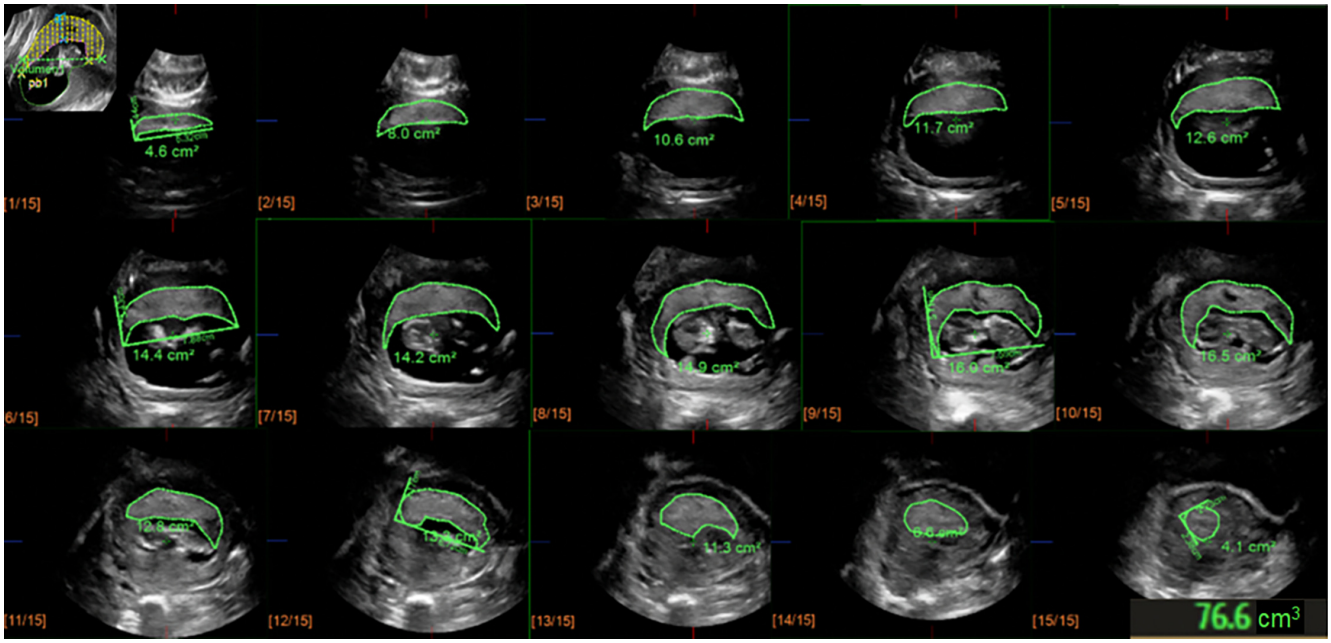

Figure 2 Measurement of placental volume using three-dimensional ultrasound and QLAB GI3DQ software version 10.5 using 15 placental sections. Each frame depicts placental section with manually traced outer contour.

A descriptive analysis was performed using both raw and adjusted measurements of placental biometry, placental growth (expressed as a percentage) and the percentage difference in UtA-PI between the first and second trimesters. The Kolmogorov–Smirnov test was used to assess the normality of distribution for continuous variables. Continuous data are presented as mean ± SD and median (interquartile range) for parametric and non-parametric variables, respectively. Categorical data are presented as *n* (%). Variables were compared between groups using Student's *t*-test, the Mann–Whitney *U*-test or the chi-square test, as appropriate. All *P*-values were two-sided, and unequal variances were assumed. Statistical analysis was performed using SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). $P < 0.05$ was used to define statistical significance.

RESULTS

A total of 1491 women were recruited to the larger observational study, of whom 1340 met the inclusion criteria. Of those, 631 had 2D measurements available in the first and second trimesters so were included in the present analysis. First-trimester screening for PE was by maternal factors alone in 223 (35.3%) women and by a multivariate protocol in 408 (64.7%). A total of 53 (8.4%) women, including eight in the group screened using maternal factors alone and 45 in the group screened using a multivariate protocol, were identified as being at high risk for developing early-onset PE in the first trimester and were prescribed LDA until 36 weeks' gestation. Two high-risk women received a lower dose of aspirin (100 mg) compared with the standard regimen. Good compliance with LDA treatment among the high risk for early-onset PE group was verified by individual chart review. No low-risk women received aspirin.

The placenta was located mostly on the anterior (49.6%) or posterior (45.6%) uterine wall, with fundal and lateral positions accounting for < 5% of cases. Mean ± SD GA at evaluation was 12.6 ± 0.6 weeks in the first trimester and 20.8 ± 0.6 weeks in the second trimester. The Kolmogorov–Smirnov test confirmed a normal distribution for all placental variables.

Table 1 shows the baseline maternal and pregnancy characteristics of women included in the study, according to whether or not they received LDA treatment. Women who received LDA treatment were more likely to be of Black ethnicity, have a higher prepregnancy BMI, exhibit chronic hypertension and/or thrombophilia and to have had a previous pregnancy with obstetric complications related to placental insufficiency. Biochemical and biophysical factors also showed significant differences between the groups.

Women who received LDA treatment had a smaller placenta in the first trimester, with smaller BP (mean ± SD, 11.75 ± 1.64 cm *vs* 12.31 ± 1.77 cm; $P = 0.027$), CP (mean ± SD, 8.74 ± 1.09 cm *vs* 9.15 ± 1.16 cm; $P = 0.013$) and PV (mean ± SD, 68.46 ± 25.19 cm^3 *vs* 76.31 ± 23.63 cm^3; $P = 0.022$) (Table 2). After adjusting for GA, the differences remained statistically significant for CP and PV. The adjusted BP and CP values were also smaller in women treated with LDA in the second trimester, but there were no significant differences in placental growth between trimesters between the two groups. Among the 2D and 3D placental measurements included in the study, only PT showed no significant difference between the groups in either the first or second trimester. Women receiving LDA had significantly higher UtA-PI in the first and second trimesters, and these

Table 1 Maternal and pregnancy characteristics of 631 women according to whether or not they received low-dose aspirin (LDA) during pregnancy for prevention of early-onset pre-eclampsia (PE)

Characteristic	*No LDA (n = 578)*	*LDA (n = 53)*	P
Maternal age (years)	33.3 ± 4.8	33.2 ± 5.4	0.921
Prepregnancy BMI (kg/m^2)	23.8 ± 4.1	26.1 ± 5.4	0.003
Smoker	40 (6.9)	1 (1.9)	0.241
Ethnicity			
White	396 (68.5)	34 (64.2)	0.539
Latin-American	123 (21.3)	10 (18.9)	0.860
Black	7 (1.2)	7 (13.2)	< 0.001
Asian	17 (2.9)	0 (0)	0.385
South-Asian	15 (2.6)	0 (0)	0.628
North-African	20 (3.5)	2 (3.8)	0.706
Medical history			
Chronic hypertension	2 (0.3)	3 (5.7)	0.005
Diabetes mellitus	0 (0)	1 (1.9)	0.084
Kidney disease	0 (0)	1 (1.9)	0.084
Autoimmune disease	7 (1.2)	0 (0)	0.999
Thrombophilia	4 (0.7)	4 (7.5)	0.002
Thyroid disorder	48 (8.3)	7 (13.2)	0.209
Other	7 (1.2)	0 (0)	0.999
Conception by ART	39 (6.7)	6 (11.3)	0.257
Obstetric history			
Nulliparous	346 (59.9)	32 (60.4)	0.999
Parous with previous PE	6 (1.0)	7 (13.2)	< 0.001
Parous with previous SGA fetus	24 (4.2)	6 (11.3)	0.032
Mean arterial pressure (mmHg)	82.8 ± 7.8	88.9 ± 7.5	< 0.001
Biochemical markers			
GA at blood sampling (weeks)	10.5 ± 1.1	10.6 ± 0.9	0.533
PAPP-A MoM	1.07 (0.74–1.50)	0.83 (0.50–1.07)	< 0.001
PlGF MoM*	1.03 (0.80–1.38)	0.61 (0.44–1.08)	< 0.001

Data are given as mean ± SD, *n* (%) or median (interquartile range). *$n = 238$ for no LDA group and $n = 32$ for LDA group. ART, assisted reproductive technology; BMI, body mass index; GA, gestational age; MoM, multiples of the median; PAPP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; SGA, small-for-gestational age.

women exhibited a greater decrease in UtA-PI MoM between trimesters (mean ± SD, −14.00 ± 0.28% *vs* −4.50 ± 0.31%; $P = 0.021$).

Perinatal outcomes are summarized in Table 3. No differences were found in any of the perinatal outcomes considered, with the exception of Cesarean delivery rate, which was higher among women receiving LDA (38.5% *vs* 21.1%; $P = 0.008$).

DISCUSSION

In this study, placental size was significantly smaller in women at high risk for early-onset PE who were receiving LDA compared with low-risk women not receiving LDA in both the first and second trimesters. However, placental growth did not differ between the groups. UtA-PI was higher in LDA-treated high-risk women in both trimesters, even though this group exhibited a greater decrease in UtA-PI between trimesters. To our knowledge, this is the first study to assess placental growth in the context of LDA treatment for the prevention of PE.

LDA is currently recommended in the first trimester for women identified as being at high risk of early-onset PE[39] according to maternal risk factors alone[40] or multivariate screening protocols[15,37]. Consequently, the use of LDA during pregnancy is increasing. Smaller placental size has been associated consistently with placental insufficiency-related complications[28,29,45]. Our findings confirm that BP, CP and PV are smaller in the first trimester in women at high risk of early-onset PE. As expected, these women had different maternal baseline characteristics compared with low-risk women, which is consistent with the use of maternal factors in screening for PE.

Human placentation begins with implantation but continues throughout pregnancy[46]. Thus, differences in placental growth after the first trimester may influence pregnancy outcome. Hafner *et al.*[28] observed distinct placental growth patterns between 12, 16 and 22 weeks' gestation in pregnancies with PE, those with SGA, those with PE plus SGA and uneventful pregnancies. They reported reduced placental size at 12, 16 and 22 weeks in pregnancies with SGA, and restricted placental growth between 16 and 22 weeks in women who developed PE. Our study adds to their findings that LDA treatment does not alter placental size or growth, suggesting that placental size and growth are determined early in pregnancy and remain unaffected by treatment.

Various hypotheses have been proposed for the mechanism by which aspirin may decrease the incidence of PE. During pregnancy, the level of thromboxane A2 (TXA2), a vasoconstrictor produced by activated

Table 2 First- and second-trimester placental biometry and uterine artery pulsatility index (UtA-PI) in 631 women according to whether or not they received low-dose aspirin (LDA) during pregnancy for prevention of early-onset pre-eclampsia

Parameter	*No LDA (n = 578)*	*LDA (n = 53)*	P
First trimester			
UtA-PI	1.70 ± 0.49	2.06 ± 0.49	< 0.001
UtA-PI MoM	1.02 (0.85–1.22)	1.28 (1.04–1.47)	< 0.001
BP (cm)	12.31 ± 1.77	11.75 ± 1.64	0.027
BP quotient*	0.137 ± 0.020	0.132 ± 0.018	0.076
CP (cm)	9.15 ± 1.16	8.74 ± 1.09	0.013
CP quotient*	0.102 ± 0.013	0.098 ± 0.012	0.040
PT (cm)	1.86 ± 0.37	1.83 ± 0.41	0.621
PT quotient*	0.021 ± 0.004	0.020 ± 0.004	0.916
PV (cm^3)	76.31 ± 23.63	68.46 ± 25.19	0.022
PV quotient*	0.84 ± 0.25	0.76 ± 0.004	0.042
Second trimester			
UtA-PI	1.08 ± 0.33	1.22 ± 0.33	0.003
UtA-PI MoM	0.94 (0.78–1.15)	1.11 (0.88–1.32)	0.001
BP (cm)	18.33 ± 2.73	17.48 ± 2.34	0.028
BP quotient*	0.126 ± 0.02	0.120 ± 0.02	0.011
CP (cm)	15.39 ± 1.95	14.93 ± 1.56	0.093
CP quotient*	0.106 ± 0.01	0.103 ± 0.01	0.034
PT (cm)	2.82 ± 0.61	2.83 ± 0.59	0.901
PT quotient*	0.019 ± 0.004	0.019 ± 0.004	0.918
Change between trimesters			
UtA-PI (%)*	−2.93 ± 0.82	−3.26 ± 0.70	0.002
UtA-PI MoM (%)	−4.50 ± 0.31	−14.00 ± 0.28	0.021
BP (%)	51.90 ± 29.11	45.40 ± 26.36	0.314
BP quotient (%)*	10.85 ± 5.33	10.15 ± 6.31	0.317
CP (%)	70.70 ± 25.86	64.60 ± 25.40	0.290
CP quotient (%)*	11.28 ± 3.49	10.78 ± 5.12	0.460
PT (%)	55.50 ± 35.73	52.90 ± 42.02	0.744
PT quotient (%)*	1.72 ± 0.98	1.78 ± 0.97	0.699

Data are given as mean ± SD or median (interquartile range). *Adjusted for gestational age. BP, basal plate diameter; CP, chorionic plate diameter; MoM, multiples of the median; PT, placental thickness; PV, placental volume.

Table 3 Perinatal outcomes in 631 women according to whether or not they received low-dose aspirin (LDA) during pregnancy for prevention of early-onset pre-eclampsia (PE)

Outcome	*No LDA (n = 578)*	*LDA (n = 53)*	P
Male fetal sex	300 (51.9)	33 (62.3)	0.154
Birth weight (g)	3249 ± 484	3148 ± 512	0.146
PE	18 (3.1)	3 (5.7)	0.409
Early-onset PE	2 (0.3)	1 (1.9)	0.232
Preterm PE	6 (1.0)	1 (1.9)	0.461
Term PE	12 (2.1)	2 (3.8)	0.332
SGA	62 (10.7)	6 (11.3)	0.819
SGA without PE	57 (9.9)	4 (7.5)	0.808
Preterm birth	19 (3.3)	1 (1.9)	> 0.999
Cesarean delivery	122 (21.1)	20/52 (38.5)	0.008

Data are given as *n* (%), mean ± SD or *n*/*N* (%). SGA, small-for-gestational age.

platelets, increases physiologically and is counterbalanced by a concurrent increase in prostaglandin I2 (PGI2) levels[47]. In PE, PGI2 levels decrease considerably, favoring the vasoconstrictive action of TXA2[48]. Chorionic villi express cyclo-oxygenase 1 (COX1) and 2 (COX2), which convert arachidonic acid into prostaglandins G2 and H2, which in turn are converted rapidly into TXA2 and PGI2, among other metabolites. Aspirin at doses below 300 mg inactivates COX-1 selectively and irreversibly, thereby suppressing the production of prostaglandins and TXA2, inhibiting inflammation and platelet aggregation and restoring the balance between PGI2 and TXA2[49]. This anti-thrombotic action may underpin the beneficial effect of aspirin in preventing PE.

Another proposed mechanism of action is an improvement in placental development[50]. Our results suggest that women who were identified as being at high risk for early-onset PE and who received LDA have a smaller placenta compared with low-risk untreated women as early as the first trimester, and that their placenta remains smaller in the second trimester, with no significant difference in placental growth. Therefore, our findings do not support the theory of enhanced placental development with LDA administration. However, the limited size of the LDA-treated group precluded a stratified subanalysis by both placental size and treatment. Future studies with larger sample sizes could provide further insight into the effect of LDA on placental growth in women with a small placenta.

UtA-PI decreases physiologically during pregnancy[51]. In our study, this decline was observed in both groups but was significantly greater in women receiving LDA. These findings are consistent with a recently published study that also suggested a positive effect of aspirin on

placental perfusion[52]. However, the lack of a high-risk untreated control group in our study limits our ability to attribute the observed effects solely to aspirin, as all high-risk women were treated in accordance with clinical guidelines. Nevertheless, UtA-PI remained higher in high-risk treated women compared with low-risk untreated women. It has also been suggested that discontinuation of aspirin at 24–28 weeks may be as effective as continuation to 36 weeks for preventing preterm PE[53]. Considering that women at high risk for PE also have a smaller placenta in the second trimester, caution should be applied to their late-pregnancy management. Additional monitoring of fetal growth and placental function may be necessary, especially at term.

The impact of aspirin on trophoblastic invasion, assessed using UtA Doppler, was examined in a randomized study including women with abnormal UtA-PI at 11–14 weeks, who were allocated to LDA or placebo[54]. Follow-up of UtA-PI at 19–22, 23–26 and 28 weeks showed no differences between the groups. However, longitudinal changes throughout gestation were not assessed in this study, and women were included based solely on UtA-PI[55]. In contrast, in our study, women were prescribed LDA if they were identified as high risk for early-onset PE using maternal risk factors and a validated multivariate screening method, resulting in more accurate case selection. Our results indicate that UtA pulsatility is significantly improved in women treated with LDA.

Strengths of our study include its prospective design and the use of a multivariate screening protocol to identify high-risk pregnancies, ensuring clinically relevant findings. Moreover, the use of a standardized protocol with well defined methodology for 2D and 3D ultrasonography ensured that subtle differences in placental growth were captured with a high degree of accuracy. However, there are a number of limitations to acknowledge. First, the small size of the LDA group may limit the generalizability of our findings. Second, although compliance with LDA treatment was reviewed individually, pill counts were not performed, thus partial non-adherence cannot be excluded. Third, the lack of second-trimester PV data warrants further research. Finally, no differences in maternal or neonatal outcomes were observed, with the exception of Cesarean delivery, possibly owing to limited sample size or aspirin prophylaxis. The increased rate of Cesarean delivery in the LDA group remains unexplained beyond pre-existing maternal risk factors. Despite these constraints, our findings provide relevant information regarding the impact of LDA on placental development and UtA-PI in pregnancies at high risk for early-onset PE.

In conclusion, this study evaluated the impact of LDA on placental growth and UtA-PI trajectory between the first and second trimesters. Our findings suggest that, while aspirin does not modify placental growth, it is associated with a greater reduction in UtA-PI, indicating a potential improvement in placental perfusion. This implies that the beneficial effects of LDA on PE prevention are likely mediated through vascular mechanisms rather than enhanced placental development. These findings offer valuable insights into the potential mechanisms and window of action of aspirin in the prevention of PE.

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