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https://doi.org/10.31925/farmacia.2026.4.20 **ORIGINAL ARTICLE**

LOW-DOSE ASPIRIN PROPHYLAXIS IN PREGNANCIES AT INCREASED RISK OF PREECLAMPSIA: LONGITUDINAL BLOOD-PRESSURE TRAJECTORIES AND FIRST-TRIMESTER PLGF ASSOCIATIONS IN A REAL-WORLD COHORT

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Abstract

Preeclampsia remains a major cause of maternal and perinatal morbidity, and low-dose acetylsalicylic acid is the best-established pharmacological preventive intervention in high-risk pregnancies. This retrospective real-world cohort study evaluated evening aspirin 150 mg, blood-pressure trajectories, timing of preeclampsia, fetal growth restriction (FGR), and first-trimester placental growth factor (PlGF) in 42 pregnancies without chronic hypertension. Fourteen women (33.3%) received aspirin at 8 - 11 weeks. Preeclampsia occurred in 5/42 pregnancies (11.9%) and FGR in 14/42 (33.3%). Longitudinal models showed significant preeclampsia-status-by-time interactions for systolic and diastolic blood pressure, with divergence from 24 - 28 weeks onward. All preeclampsia cases occurred in women with first-trimester PlGF < 150 pg/mL (5/19), versus none with PlGF ≥ 150 pg/mL (p = 0.0137). Among documented cases, median gestational age at diagnosis was 28.5 weeks, suggesting delayed clinical expression. Findings support early, risk-stratified aspirin prophylaxis combined with longitudinal haemodynamic and placental-risk surveillance in routine clinical practice, using individualized first-trimester clinical and obstetric risk assessment.

Rezumat

Preeclampsia reprezintă o cauză majoră de morbiditate maternă și perinatală, iar acidul acetilsalicilic în doză mică este intervenția farmacologică preventivă cu cea mai solidă bază de dovezi la gravidele cu risc crescut. Acest studiu retrospectiv observațional a evaluat administrarea profilactică a 150 mg acid acetilsalicilic seara, traiectoriile tensiunii arteriale, preeclampsia, restricția de creștere fetală (FGR) și factorul de creștere placentară (PlGF) în primul trimestru, la 42 de sarcini fără hipertensiune cronică. Paisprezece paciente (33,3%) au primit tratament între 8 - 11 săptămâni. Preeclampsia a apărut la 5/42 paciente (11,9%), iar FGR la 14/42 (33,3%). Modelele longitudinale au evidențiat interacțiuni semnificative între statusul de preeclampsie și timpul gestațional pentru tensiunea sistolică și diastolică, cu divergență după 24 - 28 săptămâni. Toate cazurile de preeclampsie au prezentat PlGF <150 pg/mL, comparativ cu niciun caz la PlGF ≥ 150 pg/mL (p = 0,0137). Rezultatele susțin profilaxia precoce, stratificată după risc, asociată monitorizării hemodinamice și placentare longitudinale în practica clinică curentă.

Keywords: low-dose aspirin, acetylsalicylic acid, preeclampsia, blood pressure trajectory, fetal growth restriction, placental growth factor

Introduction

Preeclampsia is a multisystem hypertensive disorder of pregnancy that develops after 20 weeks of gestation and is characterised by new-onset hyper-tension associated with proteinuria and/or maternal organ or uteroplacental dysfunction (1, 2). Abnormal placentation, impaired spiral-artery remodelling, placental hypoperfusion, angiogenic imbalance and maternal endothelial dysfunction are central to its pathophysiology (3-5). The clinical consequences include medically indicated preterm birth, fetal growth restriction, maternal end-organ injury and increased long-term cardiovascular risk. Clinically, the distinction between early-onset and late-onset pre-eclampsia is relevant because these phenotypes differ in placental contribution, maternal - fetal risk and preventive responsiveness. A commonly used threshold is 34 + 0 weeks: early-onset preeclampsia refers to disease developing before 34 weeks, whereas late-onset preeclampsia (often termed late preeclampsia in clinical literature) refers to disease developing from 34 weeks onward. FIGO additionally classifies PE according to gestational age at delivery, defining early-onset PE as delivery < 34 + 0 weeks and late-onset PE as delivery ≥ 34 + 0 weeks; therefore, the exact terminology should always be interpreted according to the classification framework used (1, 22).

Low-dose acetylsalicylic acid is the best-established pharmacological intervention for prevention of pre-eclampsia in women at increased risk. Its principal mechanism is irreversible cyclooxygenase-1 inhibition with reduced thromboxane A2 synthesis, shifting the thromboxane-prostacyclin balance towards a less proaggregatory and more vasodilatory state. Additional effects on inflammation, trophoblast function and uteroplacental haemodynamics may also contribute (3, 6). The strongest randomised evidence for a 150 mg regimen comes from the ASPRE trial, in which aspirin 150 mg daily from 11 - 14 to 36 weeks reduced preterm preeclampsia from 4.3% to 1.6% (odds ratio 0.38, 95% CI 0.20 - 0.74) in screen-positive high-risk singleton pregnancies (6). Meta-analytic evidence further suggests that the preventive effect is concentrated in preterm disease when aspirin is started at or before 16 weeks and at doses of at least 100 mg/day (7,8). NICE recommends 75 - 150 mg/day from 12 weeks in women at high risk, whereas ACOG/SMFM and USPSTF recommend low-dose aspirin in high-risk pregnancies, optimally started before 16 weeks (9 - 11).

The selection of a 150 mg/day regimen is supported by dose- and timing-dependent evidence from randomised trials and meta-analyses. Earlier antiplatelet studies predominantly evaluated doses of 60 - 100 mg/day, whereas subsequent analyses indicated a greater reduction in preterm preeclampsia when aspirin was initiated at or before 16 weeks and at daily doses of at least 100 mg (7, 8). In the ASPRE trial, aspirin 150 mg administered nightly from 11 - 14 to 36 weeks reduced preterm preeclampsia from 4.3% to 1.6% (OR 0.38, 95% CI 0.20 - 0.74) (6). Guideline recommendations vary according to screening strategy and healthcare setting: ISSHP and FIGO support approximately 150 mg nightly in pregnancies classified as high risk through first-trimester screening, NICE recommends 75 - 150 mg/day from 12 weeks, and ACOG/SMFM and USPSTF recommend 81 mg/day (1, 9-11, 22). Accordingly, the 150 mg evening regimen used in the present study should be interpreted as an evidence-based prophylactic strategy for appropriately selected high-risk pregnancies within specific screening frameworks, rather than as a universally mandated dose.

Eligibility for aspirin prophylaxis should be established from a structured preeclampsia-risk assessment rather than from a single isolated marker. Across major guidelines, high-risk indications include a history of preeclampsia or hypertensive disease in a previous pregnancy, chronic hypertension, pregestational type 1 or type 2 diabetes, chronic kidney disease, autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome, and multifetal gestation (9-11). Aspirin is also considered when several moderate-risk factors coexist, including nulliparity, maternal age $\geq$ 35 - 40 years depending on the guideline, obesity, family history of preeclampsia, a long interpregnancy interval, previous adverse pregnancy outcome, and conception by *in vitro* fertilisation (9-11). In screening-based strategies, clinical characteristics are combined with biophysical and biochemical markers. The FIGO/Fetal Medicine Foundation approach and the ASPRE screening algorithm integrate maternal factors with mean arterial pressure, uterine artery Doppler pulsatility index (UtA-PI) and placental growth factor (PlGF), thereby identifying women whose estimated risk of preterm preeclampsia is sufficiently high to justify prophylaxis (6, 22). An increased mean UtA-PI reflects increased uteroplacental vascular resistance and impaired spiral-artery remodelling and is therefore relevant as part of a multimarker placental-risk assessment, although it should not be interpreted as a universal standalone indication for aspirin.

Blood pressure is not only a diagnostic component of preeclampsia but also a dynamic longitudinal phenotype. Contemporary cohort studies show that pregnancy blood-pressure trajectories contain clinically relevant information beyond a single measurement and may improve identification of women at risk of hypertensive disorders (12, 13). In a clinically selected population receiving risk-oriented preventive pharmacotherapy, repeated blood-pressure me-asurements may therefore provide a useful framework for interpreting when the hypertensive phenotype begins to diverge despite prophylaxis.

The present study was designed as a pharmacologically oriented evaluation of low-dose aspirin pro-phylaxis in a clinically selected population at increased risk of preeclampsia. The primary objectives were to characterise aspirin exposure and treatment selection, quantify the occurrence and gestational timing of preeclampsia, and compare longitudinal systolic and diastolic blood-pressure trajectories according to subsequent preeclampsia status. FGR and neonatal outcomes were assessed as secondary placental outcomes. In the same cohort, first-trimester PlGF was evaluated as a complementary biomarker of placental dysfunction and subsequent preeclampsia risk, with particular attention to the distribution of PE events across prespecified PlGF concentration categories.

Materials and Methods

Study design and population

This retrospective observational cohort study was based on anonymised clinical records from pregnant women evaluated at the Clinical Hospital "Dr. Ion Cantacuzino", Bucharest, Romania. The final analytical cohort comprised 42 pregnancies with longitudinal obstetric follow-up through delivery. The cohort was clinically selected rather than population-based and included women referred for first-trimester risk assessment, placental-function

evaluation, adverse obstetric history, or clinical concern regarding preeclampsia and/or FGR.

For the present blood-pressure-centred analysis, no participant had chronic hypertension at baseline (0/42). Preeclampsia, FGR, gestational age at diagnosis, gestational age at delivery, neonatal birthweight, previous PE/FGR, aspirin exposure and serial blood-pressure measurements were abstracted from the available records.

Ethics

The analysis used anonymised retrospective clinical data. The study was conducted in accordance with the Declaration of Helsinki and the institutional approval reported for the source cohort (Clinical Hospital "Dr. Ion Cantacuzino", protocol 23913, 02 December 2023).

Aspirin prophylaxis

Acetylsalicylic acid 150 mg once, daily in the evening was administered to 14 of 42 women (33.3%). Treatment was initiated between 8 and 11 weeks of gestation (mean 9.7 ± 1.1 weeks; median 10 weeks) following integrated assessment of maternal, obstetric and placental risk. The indication incorporated recognised determinants of increased preeclampsia risk, including previous preeclampsia, previous FGR or another placental-mediated adverse pregnancy outcome, advanced maternal age, elevated body mass index, a concerning blood-pressure/mean arterial pressure profile and/or increased uterine artery pulsatility index on first-trimester Doppler examination. Other clinically relevant maternal risk factors, when present, were incorporated into the same risk-stratification process. Accordingly, aspirin exposure represented clinically indicated prophylaxis in a risk-enriched subgroup rather than allocation based on an isolated biomarker. 6 of the 14 treated women had initiated aspirin before the recorded first-trimester PlGF measurement; PlGF was therefore not used as a stand-alone criterion for treatment. The intended regimen was continued until 36 weeks unless clinical circumstances required modification. Two treated women had documented epistaxis, without treatment discontinuation.

The prescribing strategy was aligned with contemporary guideline-based prevention principles. Previous preeclampsia constitutes a high-risk indication in NICE, ACOG/SMFM and USPSTF recommendations (9-11), whereas combinations of moderate-risk characteristics may further increase eligibility for prophylaxis. In patients undergoing first-trimester placental screening, increased mean UtA-PI was interpreted in conjunction with maternal characteristics and haemodynamic parameters, consistent with the multivariable risk-assessment approach used in FIGO and ASPRE (6, 22). Previous FGR was considered evidence of prior placental dysfunction and contributed to overall obstetric risk assessment, but was not treated as an isolated universal indication for aspirin in the absence of additional preeclampsia risk factors.

Blood-pressure assessment and clinical outcomes

Serial systolic (SBP) and diastolic blood pressure (DBP) values were organised into 6 prespecified gestational windows: baseline/start of aspirin, 16 - 20, 20 - 24, 24 - 28, 28 - 32 and 32 - 36 weeks. Baseline and 16 - 20-week values were available in 31/42 women; 20 - 24, 24 - 28 and 28 - 32-week values were available in all 42 women; and 32 - 36-week values were available in 41/42. For women who developed preeclampsia, blood pressure at diagnosis and maximum documented values were additionally recorded when available.

Antihypertensive treatment was introduced when clinically indicated after the development of gestational hypertension or preeclampsia. Methyldopa was used as part of routine management to control sustained blood-pressure elevation. Accordingly, serial measurements obtained after treatment initiation represent treated haemodynamic values rather than the untreated natural history of preeclampsia. Diagnostic and maximum recorded values were retained separately when available. This distinction is relevant to interpretation of longitudinal trajectories because pharmacological blood-pressure control may attenuate subsequent systolic and diastolic elevations without altering the diagnosis of preeclampsia itself. Preeclampsia was defined according to contemporary international criteria as new-onset hypertension after 20 weeks of gestation accompanied by proteinuria and/or maternal organ or uteroplacental dysfunction (1, 2). FGR was recorded when documented by fetal biometry and Doppler-based clinical assessment. The primary clinical outcome was preeclampsia. Secondary outcomes included FGR, gestational age at preeclampsia diagnosis, gestational age at delivery and neonatal birthweight. For phenotype description, gestational timing was reported explicitly. When referring to onset by diagnosis, preeclampsia diagnosed before 34 + 0 weeks was considered early-onset and preeclampsia diagnosed at or after 34 + 0 weeks late-onset; when citing FIGO literature, the delivery-based definition (<3 4 + 0 versus ≥ 34 + 0 weeks at delivery) was preserved to avoid mixing classification systems (22).

First-trimester PlGF analysis

First-trimester PlGF was measured at 10 - 13 weeks using the DELFIA Xpress platform in the same analytical cohort. Absolute PlGF concentrations were classified as < 50, 50 - 149 and ≥ 150 pg/mL according to the analytical framework used for this cohort. These categories were examined in relation to subsequent preeclampsia, with the principal categorical comparison contrasting PlGF < 150 pg/mL with ≥ 150 pg/mL. The PlGF component was used as a complementary assessment of placental function and

subsequent preeclampsia risk alongside the clinical and haemodynamic evaluation.

Statistical analysis

Continuous variables were summarised as mean ± standard deviation and median (interquartile range) where informative. Categorical variables were presented as n (%). Exact Clopper - Pearson 95% confidence intervals were calculated for the overall incidence of PE and FGR. Given the small, unbalanced groups and limited number of events, continuous between-group comparisons used the two-sided Mann - Whitney U test and categorical comparisons used Fisher's exact test. For the PlGF analysis, the occurrence of subsequent PE among women with PlGF < 150 pg/mL versus ≥ 150 pg/mL was compared using a two-sided Fisher's exact test to assess the association between first-trimester PlGF concentration and subsequent PE within the study cohort. Longitudinal SBP and DBP were analysed separately using generalized estimating equations (GEE) with Gaussian family, identity link, exchangeable working correlation and robust sandwich standard errors, with repeated measurements clustered by patient. Gestational interval was modelled as a categorical factor. Models included PE status, gestational interval and the PE-status-by-time interaction; the joint interaction term tested whether blood-pressure trajectories differed between women who did and did not subsequently develop PE. Prespecified pointwise PE versus non-PE comparisons at each gestational interval were performed with the Mann - Whitney U test and adjusted for 6 comparisons using the Holm procedure. A multivariable treatment-effect model for aspirin efficacy was not fitted because only 5 PE events occurred and treatment allocation was strongly risk-directed, with all PE events arising in the aspirin-treated subgroup. Accordingly, aspirin-exposure comparisons were interpreted in the context of baseline-risk enrichment rather than as a randomized efficacy contrast. Statistical analyses were performed with Python 3.13.5, SciPy 1.17.0 and statsmodels 0.14.6. Two-sided $p < 0.05$ was considered statistically significant.

Results and Discussion

Cohort characteristics and treatment selection

The cohort comprised 42 pregnancies. 14 women (33.3%) received aspirin 150 mg/day and 28 (66.7%) did not. The treated subgroup was substantially enriched for baseline obstetric risk. Aspirin-treated women were older (median 37.0 *vs*. 30.0 years; $p < 0.001$) and had higher BMI (median 30.0 *vs*. 27.5 kg/m²; $p = 0.003$). All 5 women with a history of PE and all 5 with a history of FGR were in the aspirin group (both Fisher $p = 0.002$). This imbalance confirms clinically driven treatment allocation and strong confounding by indication.

Table I

Maternal characteristics and pregnancy outcomes according to aspirin exposure

Variable	Aspirin 150 mg (n = 14)	No aspirin (n = 28)	p value
Maternal age, years	37.0 (33.5 - 39.8)	30.0 (27.0 - 33.0)	< 0.001
BMI, kg/m²	30.0 (29.0 - 30.8)	27.5 (27.0 - 28.3)	0.003
Parity	2.0 (1.0 - 2.8)	1.0 (1.0 - 2.0)	0.1
Previous preeclampsia	5/14 (35.7%)	0/28 (0%)	0.002
Previous FGR	5/14 (35.7%)	0/28 (0%)	0.002
Chronic hypertension at baseline	0/14 (0%)	0/28 (0%)	-
Preeclampsia in current pregnancy	5/14 (35.7%)	0/28 (0%)	0.002*
FGR in current pregnancy	12/14 (85.7%)	2/28 (7.1%)	< 0.001*
Gestational age at delivery, weeks	36.0 (36.0 - 37.0)	39.0 (39.0 - 39.3)	< 0.001*
Neonatal birthweight, g	2425 (2130 - 2697)	3780 (3648 - 3890)	< 0.001*

*Outcome comparisons are descriptive only and must not be interpreted as treatment effects because aspirin allocation was risk-based and non-randomised

Preeclampsia and fetal growth restriction

Preeclampsia occurred in 5/42 women (11.9%; exact 95% CI 4.0 - 25.6%) and FGR in 14/42 (33.3%; exact 95% CI 19.6 - 49.5%). All 5 PE cases were in the aspirin-treated subgroup, in which risk factors were concentrated. 9 of 14 aspirin-treated women (64.3%) remained free of PE. Among the 5 women with previous PE, 3 (60.0%) did not experience recurrent PE in the current pregnancy; this observation is descriptive and cannot establish a preventive treatment effect without an untreated comparable high-risk group. Gestational age at PE diagnosis was available for 4 of the 5 cases: 27, 28, 29 and 34 weeks, giving a mean of 29.5 weeks and a median of 28.5 weeks (IQR 27.8 - 30.3). The corresponding intervals from aspirin initiation to PE diagnosis were 18, 19, 19 and 26 weeks (median 19 weeks). These intervals quantify PE-free follow-up after prophylaxis initiation and, although they cannot establish a causal treatment-associated delay in this observational cohort, they are clinically relevant in the context of randomised evidence suggesting that low-dose aspirin may shift preeclampsia or hypertensive-disease expression toward later gestational ages (25, 26). 3 of the 5 PE pregnancies delivered before 37 weeks (35, 36 and 35 weeks), whereas 2 reached 37 and 39 weeks. Using gestational age at clinical diagnosis as the onset marker, 3 of the 4 classifiable cases represented

early-onset PE (27, 28 and 29 weeks), while 1 was diagnosed at 34 weeks. Because 1 case lacked gestational age at diagnosis, its onset phenotype could not be assigned. Using the FIGO delivery-based subclassification, none of the 5 PE pregnancies delivered before 34 weeks; all therefore fell within the FIGO late-onset category by delivery timing, although 3 remained preterm PE because delivery occurred before 37 weeks. This distinction precludes interchangeability of diagnosis-based early/late-onset terminology with delivery-based preterm/term classification.

Table II

Timing and blood-pressure characteristics of the 5 preeclampsia cases

ID	GA aspirin start	GA PE diagnosis	Aspirin→PE interval, weeks	GA delivery	FGR	BP at PE diagnosis, mmHg	Maximum BP, mmHg
P01	9	27	18	35	Yes	150/100	160/110
P03	9	28	19	36	Yes	160/100	160/110
P05	10	29	19	35	Yes	160/90	160/90
P11	8	34	26	37	Yes	152/98	Not recorded
P14	8	Not recorded	-	39	No	Not recorded	Not recorded

Longitudinal blood-pressure trajectories

At baseline, SBP did not differ between women who later developed PE and those who did not (118.0 ± 5.8 *vs*. 119.8 ± 7.2 mmHg; unadjusted p = 0.570). The longitudinal GEE model showed a highly significant PE-status-by-time interaction for SBP (Wald χ^2 = 27.63, 5 df; p < 0.001), demonstrating that systolic trajectories diverged over gestation. For DBP, the PE-status-by-time interaction was even stronger (Wald χ^2 = 58.68, 5 df; p < 0.001).

After Holm correction, SBP was significantly higher in the PE group from 24 - 28 weeks onward: 145.0 ± 13.7 *vs*. 125.4 ± 8.1 mmHg at 24 - 28 weeks (adjusted p = 0.021), 144.8 ± 14.4 *vs*. 126.7 ± 6.9 mmHg at 28 - 32 weeks (adjusted p = 0.021), and 143.2 ± 8.1 *vs*. 127.5 ± 5.4 mmHg at 32 - 36 weeks (adjusted p = 0.005). DBP separation was significant at 16 - 20 weeks and again from 24 - 28 weeks onward. At 24 - 28 weeks, DBP was 91.8 ± 11.3 *vs*. 68.5 ± 7.7 mmHg (adjusted p = 0.006); at 32 - 36 weeks it was 92.4 ± 9.9 *vs*. 71.4 ± 6.7 mmHg (adjusted p = 0.0069).

Table III

Serial systolic and diastolic blood pressure according to subsequent preeclampsia status

Gestational interval	n PE / no PE	SBP PE	SBP no PE	Holm P	DBP PE	DBP no PE	Holm P
Baseline	5 / 26	118.0 ± 5.8	119.8 ± 7.2	1.000	67.8 ± 8.7	71.0 ± 8.6	0.741
16 - 20 weeks	5 / 26	120.2 ± 9.3	123.2 ± 6.8	1.000	79.8 ± 6.1	71.6 ± 5.4	0.0359
20 - 24 weeks	5 / 37	119.8 ± 8.3	124.9 ± 6.8	0.402	72.8 ± 7.6	69.1 ± 9.0	0.741
24 - 28 weeks	5 / 37	145.0 ± 13.7	125.4 ± 8.1	0.0212	91.8 ± 11.3	68.5 ± 7.7	0.00688
28 - 32 weeks	5 / 37	144.8 ± 14.4	126.7 ± 6.9	0.0212	86.0 ± 12.9	67.7 ± 9.4	0.0242
32 - 36 weeks	5 / 36	143.2 ± 8.1	127.5 ± 5.4	0.00506	92.4 ± 9.9	71.4 ± 6.7	0.00688

Values are mean ± SD. Pointwise P values are two-sided Mann - Whitney U tests adjusted by the Holm method. The primary longitudinal inference is the GEE time-by-PE interaction

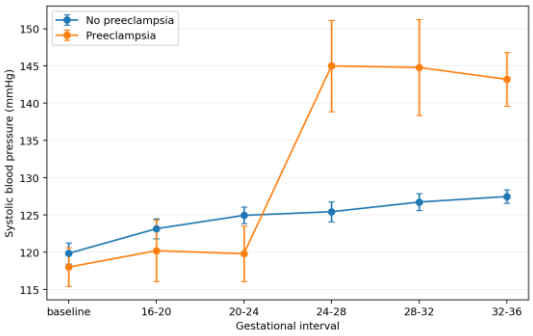

Figure 1.

Longitudinal systolic blood-pressure trajectory by preeclampsia status. Error bars represent standard error of the mean

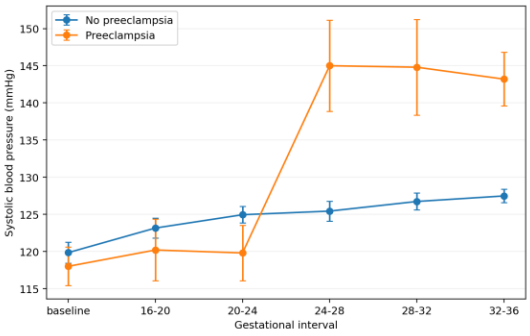

Figure2.

Longitudinal diastolic blood-pressure trajectory by preeclampsia status. Error bars represent standard error of the mean

First-trimester PlGF and subsequent preeclampsia

First-trimester PlGF in the 42-patient cohort had a median concentration of 160.5 pg/mL (IQR 86.3 - 253.4; range 9.3 - 1448.2). 6 women (14.3%) had PlGF <50 pg/mL, 13 (31.0%) had 50 - 149 pg/mL and 23 (54.7%) had ≥ 150 pg/mL. All 5 subsequent

PE cases occurred among the 19 women with PlGF < 150 pg/mL (5/19, 26.3%; exact 95% CI 9.1 - 51.2%), whereas no PE occurred among the 23 women with PlGF ≥ 150 pg/mL (0/23; exact 95% CI 0 - 14.8%); the two-sided Fisher's exact p = 0.013. This distribution demonstrates a statistically significant association between lower first-trimester PlGF concentrations and subsequent PE in the present cohort and supports the contribution of PlGF to early placental-risk stratification.

Table IV

Complementary first-trimester PlGF distribution and subsequent preeclampsia

PlGF category	Patients, n (%)	Preeclampsia, n (%)
< 50 pg/mL	6 (14.3%)	3 (50.0%)
50 - 149 pg/mL	13 (31.0%)	2 (15.4%)
≥ 150 pg/mL	23 (54.7%)	0 (0%)
Total	42	5 (11.9%)

The present real-world cohort yielded three principal observations. First, aspirin prophylaxis was preferentially prescribed to women with a substantially higher baseline obstetric-risk profile, confirming non-random treatment allocation and substantial confounding by indication. Second, serial blood-pressure assessment identified a distinct longitudinal haemodynamic pattern among women who subsequently developed preeclampsia, with the most consistent systolic and diastolic divergence from 24 - 28 weeks onward. Third, lower first-trimester PlGF concentrations were significantly associated with subsequent preeclampsia, providing complementary biomarker information on placental risk. Collectively, these findings support an integrated prevention and surveillance framework in which guideline-based aspirin prophylaxis is complemented by longitudinal haemodynamic assessment and first-trimester placental-risk stratification.

Direct comparison of aspirin-exposed and unexposed women is not appropriate for estimation of treatment efficacy in this cohort. Aspirin was preferentially prescribed to women with a higher baseline probability of placental disease: treated women were older, had higher BMI, and included all patients with previous preeclampsia or previous FGR. All 5 incident preeclampsia cases occurred within this risk-enriched subgroup, a distribution attributable to treatment selection and confounding by indication rather than evidence of an adverse treatment effect or pharmacological failure. In women who clearly fulfil established high-risk criteria for aspirin prophylaxis, prospective assignment to an untreated comparator would raise substantial ethical concerns because it could require withholding a guideline-recommended preventive intervention in the absence of genuine clinical equipoise. The limited number of preeclampsia events and complete separation by treatment exposure further precluded stable multivariable treatment-effect modelling. Consequently, between-group outcome differences are descriptive and cannot be interpreted as causal estimates of aspirin efficacy. Although the present cohort cannot quantify an independent treatment effect, the external evidence supporting low-dose aspirin prophylaxis is robust. In ASPRE, aspirin 150 mg/day from 11 - 14 until 36 weeks reduced preterm preeclampsia from 4.3% to 1.6% (OR 0.38) (6). Meta-analytic data indicate that the reduction in preterm preeclampsia is greatest when aspirin is initiated at or before 16 weeks and at doses of at least 100 mg/day (7, 8). The USPSTF evidence review similarly found low-dose aspirin to be associated with reductions in preeclampsia, preterm birth, perinatal mortality and fetal growth restriction without a significant increase in major bleeding outcomes (10,14). The 150 mg evening regimen used in this cohort should therefore be interpreted within this established evidence base, while recognising that the observational design of the present study does not permit replication of a randomised treatment-effect estimate.

From low-dose aspirin to the 150 mg regimen: evidence and guideline context

The dose of aspirin used for preeclampsia prevention has evolved as evidence accumulated regarding dose, timing and biological responsiveness. Initial trials used a wide range of low doses, commonly 60 - 100 mg/day, based on the concept that preferential inhibition of platelet cyclooxygenase-1 and thromboxane A2 could improve the prostacyclin - thromboxane imbalance implicated in abnormal placentation. However, pooled analyses subsequently suggested that the preventive effect is not uniform across regimens. The benefit for preterm preeclampsia appears greatest when aspirin is started no later than 16 weeks and at doses of at least 100 mg/day (7, 8). These findings provided the pharmacological and clinical rationale for evaluating a higher low-dose regimen.

The pivotal ASPRE trial operationalised this concept by using aspirin 150 mg/day in women identified as high risk through a first-trimester algorithm integrating maternal characteristics, mean arterial pressure, uterine artery Doppler indices and biochemical markers including PlGF. Aspirin was started at 11 - 14 weeks, administered at night and continued to 36 weeks. Preterm preeclampsia occurred in 1.6% of the aspirin group compared with 4.3% of the placebo group (OR 0.38, 95% CI 0.20 - 0.74; p = 0.004) (6). The ASPRE investigators selected 150 mg on the

basis of prior evidence suggesting a dose-dependent benefit and concern that lower doses may produce incomplete platelet inhibition in a proportion of pregnant women. The night-time schedule was also supported by chronotherapy data suggesting greater efficacy when aspirin is taken in the evening or at bedtime (19).

Current guideline recommendations differ with respect to aspirin dose, principally because of variation in screening methodology, available tablet formulations and the evidence framework adopted by individual organisations. ISSHP recommends bedtime administration, preferably initiated before 16 weeks and discontinued by 36 weeks; after multivariable first-trimester screening, 150 mg nightly is recommended, whereas 100 - 162 mg/day is recommended when selection is based on clinical risk factors and blood pressure (1). FIGO recommends approximately 150 mg nightly from 11 - 14 + 6 weeks in women classified as high risk by first-trimester screening (22). NICE recommends 75 - 150 mg/day from 12 weeks until birth for women with one high-risk factor or more than one moderate-risk factor (9). ACOG/SMFM and USPSTF recommend 81 mg/day after 12 weeks, optimally before 16 weeks, for women at increased risk (10, 11). Thus, the 150 mg evening regimen used in the present cohort is concordant with ISSHP and FIGO screening-based strategies and lies within the NICE-recommended dose range, while differing from the standard 81 mg regimen used in United States guidance.

This heterogeneity should be interpreted in the context of the underlying risk-assessment strategy rather than as evidence for a single universally applicable dose. Across major recommendations, the consistent principles are identification of women at increased risk, initiation of prophylaxis early in pregnancy, preferably before 16 weeks and maintenance of daily adherence. Dose-response meta-analysis has demonstrated greater reductions in preeclampsia, severe preeclampsia and FGR when aspirin is initiated at ≤ 16 weeks, with increasing benefit across higher low-dose regimens (7). A separate meta-analysis reported that prevention of preterm preeclampsia was concentrated in trials using ≥ 100 mg/day and initiation at ≤ 16 weeks (8). More recent analyses have also suggested greater efficacy with 150 - 162 mg compared with 75 - 81 mg for prevention of preterm preeclampsia, although the number of direct dose-comparison trials remains limited (23, 24). Accordingly, 150 mg nightly is best regarded as an evidence-supported regimen for selected high-risk populations rather than a universal dose recommendation.

Timing is also relevant. Aspirin was initiated at 8 - 11 weeks in this cohort (median 10 weeks), with 6 women starting before the available PlGF measurement. Although early biological effects on platelet thromboxane signalling and uteroplacental adaptation are plausible, major contemporary recommendations generally initiate prophylaxis from approximately 11 - 12 weeks, with treatment optimally established before 16 weeks (6, 9-11, 22). Accordingly, the earlier starts observed in this retrospective cohort should be regarded as real-world prescribing practice and not as evidence that initiation before the guideline-supported window confers additional benefit.

The longitudinal blood-pressure analysis constitutes an important component of the present study. Baseline systolic blood pressure was comparable between women who did and did not subsequently develop preeclampsia; however, their trajectories diverged during later gestation. The significant PE-status-by-time interactions for both SBP and DBP indicate that temporal haemodynamic evolution, rather than a single early blood-pressure measurement, differentiated pregnancies that subsequently developed preeclampsia. This finding is consistent with contemporary cohort data demonstrating that gestational blood-pressure trajectories contain prognostic information beyond isolated measurements (12, 13). In a high-risk population receiving prophylactic treatment, these results further support serial blood-pressure surveillance as complementary to, rather than replaced by, aspirin prophylaxis.

The observed blood-pressure trajectories should also be interpreted in the context of antihypertensive co-treatment. In women who developed preeclampsia, methyldopa was administered when hypertension required pharmacological control, with the aim of preventing sustained or severe-range blood-pressure elevations and maintaining blood pressure within recommended treatment targets. Consequently, later gestational measurements reflect both disease evolution and the effect of active antihypertensive management. This makes the persistence of a significant PE-status-by-time interaction despite treatment clinically relevant: even under blood-pressure-lowering therapy, women who developed preeclampsia retained a distinct haemodynamic trajectory. At the same time, these data should not be used to quantify an independent antihypertensive effect of methyldopa because treatment was clinically triggered and not protocol-randomised.

The distinction between early-onset and late-onset preeclampsia is particularly important when interpreting aspirin prevention. Early-onset and preterm PE are more strongly associated with placental dysfunction and are the phenotypes for which first-trimester screening and aspirin prophylaxis have shown the clearest preventive benefit. FIGO defines early-onset PE as delivery before 34 + 0 weeks and late-onset PE as delivery at or after 34 + 0 weeks, while also distinguishing preterm PE (< 37 + 0 weeks) from term PE (≥ 37 + 0 weeks) (22). In

routine clinical usage, 'late preeclampsia' is often used as a shorthand for late-onset preeclampsia, but 'late-onset preeclampsia' is the more precise manuscript term. The ASPRE strategy was designed primarily to prevent preterm PE, and its strongest effect was observed in this phenotype (6). This matters for the present cohort: although several women developed PE before 34 weeks by diagnosis timing, none delivered before 34 weeks. Thus, the data are compatible with a clinically meaningful prolongation of pregnancy after diagnosis in some cases, but they cannot establish that aspirin caused conversion from an early-onset to a late-onset phenotype or independently delayed delivery.

The isolated DBP difference observed at 16 - 20 weeks should be interpreted with caution because it is based on 5 preeclampsia cases and 26 controls with available measurements. Greater interpretative weight should be assigned to the sustained and concordant systolic and diastolic separation observed after 24 weeks and to the highly significant overall time-by-preeclampsia interactions. The present dataset therefore supports characterisation of longitudinal blood-pressure trajectories but is not sufficiently powered to define a predictive blood-pressure threshold.

The interval between aspirin initiation and preeclampsia diagnosis was interpreted as a clinically relevant temporal outcome. Among the 4 cases with documented timing, the median aspirin-to-diagnosis interval was 19 weeks and the median gestational age at diagnosis was 28.5 weeks. This observation is concordant with the delay hypothesis described in secondary analyses of randomized trials. In an analysis of ASPRE, aspirin was associated with a modelled shift toward later gestational age at delivery with preeclampsia, with the estimated effect being greatest for disease otherwise expected to result in very early delivery (25). A secondary analysis of the ASPIRIN trial similarly reported fewer hypertensive disorders associated with delivery before 34 and 37 weeks and later delivery among affected pregnancies receiving aspirin (26). These data provide external support for the interpretation that low-dose aspirin may postpone the clinical expression of preeclampsia or disease-associated delivery in a proportion of pregnancies. Within the present cohort, the 19-week median interval is therefore consistent with this biologically and clinically plausible treatment effect, while its magnitude remains dependent on the underlying baseline risk and individual disease trajectory.

The PlGF findings provide a complementary placental-biomarker perspective. All 5 PE cases occurred among women with first-trimester PlGF < 150 pg/mL, whereas no cases occurred in the ≥ 150 pg/mL category (Fisher's exact $p = 0.013$). This distribution demonstrates a statistically significant association between lower first-trimester PlGF concentrations and subsequent preeclampsia in the present cohort and is consistent with the established relationship between impaired placental angiogenic signalling and preeclampsia (5, 15-17). The finding also accords with first-trimester screening strategies in which PlGF is integrated with maternal characteristics, mean arterial pressure and uterine artery Doppler indices to refine risk estimation (6, 22). In this context, PlGF contributed complementary information regarding placental dysfunction and the subsequent development of preeclampsia alongside clinical and haemodynamic risk assessment.

Treatment tolerability was favourable in the available records: 2 of 14 aspirin-treated women had documented epistaxis and neither discontinued treatment. Randomised evidence and meta-analytic data have not demonstrated a significant increase in placental abruption or antepartum haemorrhage with low-dose aspirin used for preeclampsia prevention (10, 14, 20). Observational data nevertheless indicate that bleeding outcomes should remain part of individual clinical risk assessment (21). These safety considerations are relevant to the pharmacological focus of Farmacia, in which aspirin-based interventions and placental haemodynamics in pregnancy have also been addressed (18).

Overall, the aspirin findings are most appropriately interpreted within a clinically selected, risk-enriched prevention cohort. The development of preeclampsia during prophylaxis does not, by itself, indicate absence of treatment benefit, as low-dose aspirin reduces residual disease risk without eliminating it and the treated women in this cohort had the highest baseline probability of placental dysfunction. The median 19-week aspirin-to-diagnosis interval is concordant with the treatment-delay hypothesis described in randomized secondary analyses (25, 26), in which aspirin was associated with later clinical expression of hypertensive disease or later preeclampsia-associated delivery. These observations provide a clinically relevant framework for interpreting PE events occurring despite prophylaxis. Efficacy remains supported by randomized evidence: ASPRE demonstrated a reduction in preterm preeclampsia with aspirin 150 mg initiated at 11 - 14 weeks (6), while meta-analyses support greater preventive benefit when treatment is initiated by 16 weeks and at doses of at least 100 mg/day (7, 8, 23, 24-26).

Strengths and limitations

The principal strengths of this study include patient-level longitudinal blood-pressure measurements across predefined gestational intervals, complete follow-up to delivery, a clearly defined aspirin regimen of 150 mg administered in the evening, and integration of maternal, obstetric and complementary PlGF data within the same cohort. The repeated-measures design provides greater temporal resolution than a

cross-sectional analysis, while the GEE approach appropriately accounts for within-patient correlation. The principal haemodynamic finding was internally consistent: early systolic values were comparable according to subsequent preeclampsia status, whereas both systolic and diastolic trajectories diverged later in gestation, most prominently after 24 weeks. This temporal pattern is compatible with the clinical evolution of preeclampsia and supports the relevance of longitudinal blood-pressure assessment despite the limited sample size.

The study should be regarded as an observational, hypothesis-generating cohort focused on real-world aspirin prophylaxis, longitudinal haemodynamic evolution and complementary first-trimester PlGF assessment in pregnancies at increased risk of preeclampsia. Within this design, the exposure, outcomes and repeated blood-pressure measurements are clinically relevant, and the statistical approach is appropriate for the longitudinal structure of the data. The PlGF analysis provides a biologically coherent and statistically significant association with subsequent PE, complementing the haemodynamic findings and supporting the value of integrated placental-risk assessment. The principal contribution of the study is therefore the combined characterization of pharmacological prophylaxis, blood-pressure trajectories and first-trimester placental biomarker profile in a clinically selected high-risk population.

The principal limitations are the small sample size, retrospective design and clinically selected population, with 5 PE events. Aspirin prescribing was based on baseline clinical risk, resulting in marked differences in the a priori risk profile between treated and untreated participants. Adherence was not objectively measured. Blood-pressure values were obtained during routine care rather than under a research-standardised measurement protocol, and baseline/16 - 20-week data were unavailable for 11 women. Gestational age at PE diagnosis was missing in 1 case. PlGF was analysed as an absolute first-trimester concentration. The limited number of PE events restricts the precision of treatment-effect estimation and multivariable modelling; nevertheless, the longitudinal GEE findings, the statistically significant PlGF association and the consistency of the aspirin regimen with randomized evidence and international prevention frameworks provide complementary and clinically relevant evidence within the scope of this real-world cohort.

Conclusions

In this clinically selected cohort of 42 pregnancies at increased risk of preeclampsia and placental dysfunction, prophylactic acetylsalicylic acid 150 mg administered in the evening represented the main pharmacological strategy for preeclampsia prevention. Aspirin was prescribed according to baseline obstetric risk, resulting in intentional enrichment of the treated subgroup with women at higher *a priori* risk; consequently, the occurrence of preeclampsia during prophylaxis is best interpreted in the context of residual disease risk rather than as evidence of treatment failure. Longitudinal analysis demonstrated significant divergence of systolic and diastolic blood-pressure trajectories in pregnancies that developed preeclampsia, most consistently from 24 - 28 weeks onward, supporting continued haemodynamic surveillance throughout prophylaxis. First-trimester PlGF was also associated with subsequent disease, reinforcing the complementary role of placental biomarkers in risk stratification. Among the 4 PE cases with documented timing, the median aspirin-to-diagnosis interval was 19 weeks; this temporal pattern is concordant with randomised secondary analyses indicating that low-dose aspirin may delay the clinical expression of hypertensive disease and shift preeclampsia-associated delivery toward later gestational ages.

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Availability of data and materials

The anonymised data supporting the findings are available from the corresponding author on reasonable request, subject to institutional and ethical requirements.

Ethics approval and consent to participate

The analysis used anonymised retrospective clinical data. The study was conducted in accordance with the Declaration of Helsinki and the institutional approval reported for the source cohort (Clinical Hospital "Dr. Ion Cantacuzino", protocol 23913, 02 December 2023).

AI use disclosure

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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