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Gestational trajectories of the lectin-pathway protein Ficolin-2 in pregnancies complicated by early- and late-onset preeclampsia: evidence from five maternal cohorts

Trond Melbye Michelsen [a,b,c,*], Hilde Bastøe Sellevoll [a,b], Ane C. Westerberg [a,d], Maren-Helene Langeland Degnes [a], Manuela Zucknick [e,f], Tove Lekva [g], Annika Elisabet Michelsen [b,g], Thor Ueland [b,g], Gaurav Bhatti [h], Roberto Romero [i,j,k], Lina Bergman [l,m,n,o], Marie Cecilie Paasche Roland [p], Adi L. Tarca [q,r], Ina J. Andresen [a,**]

[a] Department of Obstetrics, Division of Obstetrics and Gynecology, Oslo University Hospital Rikshospitalet, Oslo, Norway
[b] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
[c] Research Unit, Sørlandet Hospital, Arendal, Norway
[d] School of Health Sciences, Kristiania University College, Oslo, Norway
[e] Oslo Centre for Biostatistics and Epidemiology, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, Oslo, Norway
[f] Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway
[g] Research Institute of Internal Medicine, Oslo University Hospital, Rikshospitalet, Oslo, Norway
[h] Center for Molecular Medicine and Genetics, Wayne State University, Detroit, MI, USA
[i] Pregnancy Research Branch, Division of Obstetrics and Maternal-Fetal Medicine, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, United States Department of Health and Human Services, Bethesda, MD, USA
[j] Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI, USA
[k] Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI, USA
[l] Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[m] Department of Obstetrics and Gynaecology, Sahlgrenska University Hospital, Gothenburg, Region Västra Götaland, Sweden
[n] Department of Obstetrics and Gynecology, Stellenbosch University, Stellenbosch, South Africa
[o] Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden
[p] Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway
[q] Center for Molecular Medicine and Genetics, Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI, USA
[r] Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI, USA

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ABSTRACT

Background: Preeclampsia comprises biologically distinct placental disorders with divergent timing and pathology. Complement activation is implicated in its pathogenesis, but gestational changes in complement-related proteins remain incompletely characterised. We investigated trajectories of ficolin-2 (FCN2), an initiator of the lectin complement pathway, in early- and late-onset preeclampsia and explored relationships with angiogenic biomarkers.

Methods: We studied three prospective pregnancy cohorts with nested case-control analyses and two diagnostic cohorts. FCN2, soluble fms-like tyrosine kinase-1, and placental growth factor were measured using SomaScan proteomics or enzyme immunoassay. We assessed group differences, longitudinal trajectories, and associations with mean arterial pressure. Cross-validated logistic regression and receiver operating characteristic analyses evaluated prediction before diagnosis and classification of established preeclampsia.

Results: FCN2 trajectories differed from healthy controls at distinct gestational stages. In early-onset preeclampsia, FCN2 diverged during early pregnancy and remained reduced, ranging from 17% lower in early gestation to approximately 50% lower at 25–34 weeks. In late-onset disease, divergence emerged during the third trimester, with concentrations approximately 10–20% lower than in controls. Diagnostic cohorts confirmed reductions of approximately 50–80% in established disease ($p < 0.001$). FCN2 correlated negatively with mean

* Corresponding author. Department of Obstetrics, Division of Obstetrics and Gynecology, Oslo University Hospital Rikshospitalet, Oslo, Norway.
** Corresponding author.
E-mail addresses: trmi1@ous-hf.no (T.M. Michelsen), injand@ous-hf.no (I.J. Andresen).

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arterial pressure in mid-to-late gestation. Predictive performance was modest for late-onset disease (cross-validated AUC 0.62–0.68) and acceptable for early-onset disease from the second trimester (AUC 0.70–0.87). Classification performance in diagnostic cohorts was high (AUC 0.93–0.96).
Conclusions: The earlier, persistent FCN2 reduction in early-onset preeclampsia and later reduction in late-onset disease support biological heterogeneity.

1. Background

Preeclampsia remains a major cause of maternal and perinatal morbidity worldwide, yet its definition has been debated for decades. Current evidence indicates that preeclampsia is not a single disorder and may be conceptualized as predominantly placentogenic or maternogenic, reflecting the relative contributions of impaired spiral artery remodeling and maternal cardiovascular and metabolic susceptibility [1–3]. However, the most widely used classification of preeclampsia distinguishes early-from late-onset disease, reflecting some of these differences in the pathophysiology and clinical presentation [4,5]. Early-onset preeclampsia is conventionally defined as disease presenting before 34 weeks of gestation [6] and is primarily initiated by poor placentation and strongly associated with fetal growth restriction. Late-onset preeclampsia, the more prevalent subtype [7], often emerges in the context of maternal metabolic stressors such as diabetes, chronic hypertension and obesity, although these factors may also contribute to early-onset disease [5,8].

Placental dysfunction is central to the pathogenesis of preeclampsia and leads to increased placental release of sFlt-1 and lower circulating PlGF, reflecting specific aspects of the disease biology [9,10]. These markers are now incorporated into various prediction algorithms that estimate an individual's risk of developing preeclampsia by combining maternal characteristics, biophysical measurements such as blood pressure and uterine artery Doppler indices, and biochemical markers. The sFlt-1/PlGF ratio is also increasingly used to assess patients with suspected or established preeclampsia [11,12]. However, the performance of these angiogenic biomarkers varies across populations, and as the biological heterogeneity of preeclampsia becomes increasingly apparent, other biomarkers may provide insights beyond those offered by the widely used angiogenic biomarkers [8,13].

Placental malperfusion and syncytiotrophoblast stress are potent triggers of innate immune activation. Increasing evidence indicates that dysregulated complement activation is implicated in the placental dysfunction of preeclampsia and an important contributor to endothelial injury, fetal growth restriction, and adverse pregnancy outcomes [14–16]. Studies of circulating complement activation products have demonstrated increased activation of the classical, lectin and terminal complement pathways in women with preeclampsia [17,18]. Furthermore, dysregulated complement activation has been proposed as a common pathway of injury underlying preeclampsia and other placenta-mediated pregnancy complications [18]. Experimental and clinical evidence further supports a role for excessive complement activation in placental dysfunction, maternal hypertension, proteinuria, endothelial dysfunction, and angiogenic imbalance [19]. Previous studies have shown that apoptotic syncytiotrophoblast material can activate the lectin pathway of complement through binding of Ficolin-2 (FCN2), providing a mechanistic link between placental injury and maternal innate immune activation [1,16,20–22]. Previous studies have demonstrated FCN2 binding in areas of trophoblast injury and reduced FCN2 concentrations in the maternal circulation [21,23]. We therefore hypothesize that FCN2, a lectin-pathway protein of the complement system, may offer new insight into the pathophysiology of preeclampsia and its biological heterogeneity.

The primary objective of this study was to characterize maternal FCN2 trajectories in early- and late-onset preeclampsia, with each group compared separately with healthy controls. Secondary objectives were to compare the performance of FCN2 with that of established angiogenic biomarkers and to evaluate associations between FCN2 and maternal blood pressure.

2. Methods

This study includes data from five distinct study cohorts without participant overlap. Three prospective pregnancy cohorts with repeated sampling prior to clinical diagnosis (Oslo 1 prospective cohort, Detroit 1 prospective cohort and Detroit 2 prospective cohort) were used to characterize gestational FCN2 trajectories and assess predictive performance. Two diagnostic cohorts (Oslo 2 diagnostic cohort and Gothenburg diagnostic cohort) were used to evaluate FCN2 concentrations in clinically established disease compared to healthy controls. Although the cohorts differed in recruitment period, sampling schedules and original study objectives, analyses were harmonized using consistent gestational age cutoffs and standardized statistical approaches. In all five cohorts, preeclampsia was defined asnew-onset hypertension after 20 weeks of gestation accompanied by proteinuria [24–26]. For all analyses, early-onset preeclampsia was defined as delivery before 34 + 0 weeks of gestation, and late-onset preeclampsia as delivery at or after 34 + 0 weeks. Thus, the operational classification was based on gestational age at delivery rather than the documented timing of disease onset. Each preeclampsia group was compared separately with healthy controls because of established differences in pathophysiology, placental pathology and clinical presentation [2,8]. Detailed information on participant numbers, recruitment procedures, inclusion and exclusion criteria, and blood sampling schedules for each cohort is provided in Supplementary File S1 and Supplementary Table S1. Because protein measurements were available for selected cases and controls rather than complete source cohorts, the present analyses used nested case-control designs.

3. Ethical approval

All studies were conducted in accordance with the Declaration of Helsinki and approved by the relevant institutional review boards or regional ethics committees. Written informed consent was obtained from all participants prior to inclusion.

The Oslo 1 prospective cohort was approved by the Regional Committee for Medical and Health Research Ethics South-East Norway (S-2014/224-0119a). The Oslo 2 diagnostic cohort was approved by the Regional Committee for Medical and Health Research Ethics South-East Norway (S-07174, 2419/2011 and 13885).

The Detroit 1 and Detroit 2 prospective cohorts were approved by the Institutional Review Board of Wayne State University (IRB #110605MP2F and #061217MP2P) and by the Institutional Review Boards of Wayne State University and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH (OH97-CH-N067).

The Gothenburg diagnostic cohort was approved by the Swedish Ethical Review Authority (2023-02271-02) and the Norwegian Regional Ethics Committee (551842).

3.1. Oslo 1 prospective cohort

The Oslo 1 prospective cohort [27,28] recruited healthy women with uncomplicated singleton pregnancies during the first trimester at Oslo University Hospital, Rikshospitalet, Norway, between 2002 and 2008.

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Blood samples were collected at three scheduled antenatal visits corresponding to gestational weeks 12-19, 20-26, and 28-34, and blood pressure was recorded at each visit. The present study includes all 35 women who developed late-onset preeclampsia, along with a randomly selected group of 70 healthy controls from the same prospective cohort. Controls were not individually matched to cases. Three women who developed early-onset preeclampsia were excluded because the number of available cases was insufficient for reliable subtype-specific analyses.

3.2. Detroit 1 and Detroit 2 prospective cohorts

The Detroit prospective cohorts, referred to as Detroit 1 prospective cohort [29] and Detroit 2 prospective cohort [30,31], recruited pregnant women at the Center for Advanced Obstetrical Care and Research of the Pregnancy Research Branch (formerly Perinatology Research Branch), the Detroit Medical Center, in collaboration with Wayne State University, USA. Blood samples were collected throughout pregnancy, and at least two samples were profiled from each participant. Blood samples obtained at or after the diagnosis of preeclampsia were excluded to ensure that predictive analyses were based exclusively on samples collected before clinical diagnosis. A detailed description of recruitment is provided in Supplementary File S1.

The Detroit 1 prospective cohort included 71 women who developed late-onset preeclampsia and 84 pregnant healthy controls, recruited between 2006 and 2010. The Detroit 2 prospective cohort included 33 women who developed early-onset preeclampsia, 76 women who developed late-onset preeclampsia and 90 pregnant healthy controls, recruited between 2007 and 2013. Blood samples were grouped into four gestational-age intervals: weeks 8-15, 15-25, 25-34, and 34-42. Only one sample per individual was included within each gestational-age interval, and the sample closest to the mean gestational week of the respective interval was selected. Controls were not individually matched to cases. Longitudinal FCN2 trajectories were estimated using linear mixed-effects models incorporating data from all profiled samples.

3.3. Oslo 2 diagnostic cohort

The Oslo 2 diagnostic cohort [32] recruited healthy pregnant women and women with a confirmed diagnosis of preeclampsia who were scheduled for cesarean delivery at Oslo University Hospital, Rikshospitalet, Norway, between 2012 and 2019. The present analysis was based on a subset of 104 participants, including 16 women with early-onset preeclampsia (delivery before 34 + 0 weeks of gestation), 18 women with late-onset preeclampsia (delivery at or after 34 + 0 weeks of gestation), and a randomly selected subgroup of 70 healthy term controls (delivery at or after 37 + 0 weeks of gestation). Controls were randomly selected and were not individually matched to cases. Blood samples were collected during the cesarean section and blood pressure recordings from the first trimester were retrieved retrospectively.

3.4. Gothenburg diagnostic cohort

The Gothenburg diagnostic cohort, part of the ongoing Gothenburg Preeclampsia Adverse Event (GoPROVE) Biobank and Database [33], included pregnant women aged ≥18 years who presented with preeclampsia at Sahlgrenska University Hospital, Gothenburg, Sweden, between 2019 and 2023. The present study included 48 women diagnosed with early-onset preeclampsia and 40 healthy controls matched for gestational age at sampling, as well as 97 women with late-onset preeclampsia and 38 gestationally matched healthy controls. Unlike the other four cohorts, in which protein quantification was derived from previously generated proteomic datasets, protein measurements in the Gothenburg diagnostic cohort were generated specifically for the present study, allowing evaluation of FCN2 using an absolute concentration scale.

3.5. Clinical characteristics

Clinical characteristics were summarized as mean (and standard deviation, SD) for continuous variables and as number (and percentage) for categorical variables.

3.6. Proteomic quantification by SomaLogic

FCN2 was selected as the protein of interest based on previously published proteome-wide analyses of the respective cohorts [27,30,31,34], in which correction for multiple testing was applied by controlling the false discovery rate (FDR). The present study was a focused secondary analysis of FCN2 rather than a new proteome-wide screening analysis. Protein quantification for the Oslo 1 prospective cohort, Detroit 1 prospective cohort, Detroit 2 prospective cohort and the Oslo 2 diagnostic cohort was conducted using the SomaScan® assay by SomaLogic, Inc. (Boulder, CO, USA). Assay version 1.1 was used for the Detroit 2 prospective cohort, version 4.0 for the Oslo 1 prospective cohort and the Oslo 2 diagnostic cohort, and version 4.1 for the Detroit 1 prospective cohort. Plasma was mixed with single-stranded DNA aptamers (SOMAmers), which selectively bind to target proteins. Unbound SOMAmers were removed, leaving only those bound to proteins. The proteins were further cleaved off and washed away, and the remaining SOMAmers were quantified using a one-channel microarray. Protein abundances were reported in relative fluorescence units (RFU). SomaLogic performed data preprocessing, including calibration and adaptive normalization by maximum likelihood (ANML). A comprehensive description of the technology can be found elsewhere [35,36]. RFU values were $\log_2$-transformed to approximate normality for statistical analyses. FCN2 was measured by aptamer SeqId 13717-15/SomaId SL006542 (Entrez Gene ID: 2220 and UniProt ID: Q15485), which binds to FCN2 on amino acids 26-275 and had an intra-plate coefficient of variation (CV) of 0.039 and inter-plate CV of 0.031 in plasma [37]. PlGF was measured by aptamer SeqId 3078-1/SomaId SL002640 (Entrez Gene ID: 5228 and UniProt ID: P49763), which had an intra-plate CV of 0.051 and an inter-plate CV of 0.037 in plasma. sFlt-1 (VEGF sR1) was measured by aptamer SeqId 16315-105/SomaId SL003321 (Entrez Gene ID: 2321 and UniProt ID: P17948), with an intra-plate CV of 0.068 and an inter-plate CV of 0.062 in plasma. sFlt-1 was not included in SomaScan Assay version 1.1 employed for the Detroit 2 prospective cohort and was therefore unavailable for analyses in this cohort.

3.7. Protein quantification by enzyme immunoassay (Gothenburg diagnostic cohort)

Plasma levels of sFlt-1 (catalog# DY321B) and PlGF (catalog# DY264) were measured by enzyme immunoassay with antibodies obtained from R&D Systems (Minneapolis, MN) while plasma FCN2 was determined by enzyme immunoassay as previously described [38]. Briefly, microtiter plates were coated with a monoclonal anti-ficolin-2 antibody (FCN216, Santa Cruz Biotechnology, Dallas, TX) in phosphate buffered saline (PBS) overnight at 4°C. Samples were diluted 1 : 20 in sample buffer (PBS-T with 0.5% BSA) while parallel diluted plasma (1:2-1:128) was used as standard and incubated overnight. Washed wells were incubated for 20 min with HRP-conjugated streptavidin. Plates were developed for 15 min with TMB and stopped by adding 1M H_2SO_4. The optical density was measured at 490 nm with correction at 540 nm, and FCN2 concentrations were expressed as arbitrary units. A serum pool with known concentration was used as the assay standard. Inter- and intra-assay CVs were <5%.

3.8. Comparison of FCN2 between the preeclampsia groups and healthy controls

Wilcoxon rank-sum tests were used to assess differences in FCN2 between preeclampsia and healthy controls. Two-sided p-values <0.05

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were considered statistically significant. The results were visualized using the *ggplot2* (v. 3.5.1) package [39] in R. To calculate the percentage differences in FCN2 between groups, we first computed the fold change (FC) as the ratio of the raw group means (not $\log_2$-transformed) using the *gtools* (v. 3.9.5) package [40] in R, and further applied the formula (FC-1) × 100%.

3.9. Longitudinal modelling of FCN2 in the Oslo 1 prospective cohort, Detroit 1 prospective cohort and Detroit 2 prospective cohort

To characterize gestational FCN2 trajectories, each preeclampsia group was compared separately with healthy controls using longitudinal mixed-effects spline models with gestational age as a continuous predictor. Models were fitted using natural cubic splines and included an interaction term between gestational age and disease group using the *lme4* (v. 1.1-36) [41] and *splines* (v. 4.4.2) packages in R. For the models comparing late-onset preeclampsia to healthy controls, four degrees of freedom (with three internal knots) were applied, whereas three degrees of freedom (with two internal knots) were used for models comparing early-onset preeclampsia to healthy controls. A random intercept for each participant was included to account for repeated measurements. Estimated marginal means across a range of gestational weeks were derived using the *emmeans* (v. 2.0.0) R package [42]. Pairwise contrasts were computed using t-tests to compare late-onset preeclampsia to healthy controls and early-onset preeclampsia to healthy controls for each gestational week, with p-values adjusted for multiple testing by controlling FDR using the Benjamini-Hochberg method. Adjusted two-sided p-values (q-values) <0.05 were considered statistically significant.

3.10. Correlations between FCN2 and blood pressure

Spearman correlation analyses between FCN2 and mean arterial pressure were performed using the *ggpubr* (v. 0.6.2) package [43] in R. The mean arterial pressure was calculated based on the recorded systolic and diastolic blood pressure by (2 × diastolic blood pressure + systolic blood pressure)/3. Antihypertensive treatment was not accounted for because treatment data were unavailable in some cohorts and incompletely recorded in others.

3.11. Predictive performance and classification performance of FCN2

Binary outcome models were developed to evaluate predictive performance in the prospective cohorts and classification performance between established preeclampsia and healthy controls in the Gothenburg diagnostic cohort. These models were implemented using the *glmnet* (v. 4.1-8) [44] and *caret* (7.0-1) [45] packages in R, with internal validation via 5-fold cross-validation to reduce overfitting. Cross-validation was performed separately within each cohort. Receiver operating characteristic (ROC) curves, illustrating sensitivity (true positive rate) and 1 – specificity (false positive rate), were generated using the *pROC* (v. 1.18.5) package [46] in R. A cross-validated area under the curve (AUC) of 0.70 to <0.80 was interpreted as moderate discrimination performance and an AUC ≥ 0.80 as strong discrimination [47]. Additional models incorporating clinical characteristics (maternal body mass index (BMI), age, and nulliparity) were constructed to evaluate their combined discriminative performance with FCN2. Models of sFlt-1, PlGF and the sFlt-1/PlGF ratio were also constructed to compare the performance of FCN2 with established biomarkers of preeclampsia. DeLong's statistical tests were used to compare the cross-validated AUCs between models, with two-sided p-values <0.05 indicating statistical significance. For the Gothenburg diagnostic cohort, a tentative optimal classification threshold was identified using the Youden index.

4. Results

4.1. Clinical characteristics

Clinical characteristics are summarized in Table 1. Across cohorts, women who developed preeclampsia generally had higher BMI, were more often nulliparous, and delivered at earlier gestational ages than healthy controls.

4.2. Longitudinal modelling of FCN2 in the Oslo 1 prospective cohort, Detroit 1 prospective cohort and Detroit 2 prospective cohort

Longitudinal mixed-effects spline models revealed different patterns of deviation from healthy controls in early- and late-onset preeclampsia. In the separate comparisons with healthy controls, FCN2 concentrations were lower from early pregnancy in women who subsequently developed early-onset preeclampsia, whereas significant differences in late-onset preeclampsia emerged from approximately gestational week 29 (Fig. 2). Findings from the diagnostic cohorts were consistent with the lower FCN2 concentrations observed in pregnancies complicated by preeclampsia (Supplementary Fig. S1).

4.3. Reduced circulating FCN2 in preeclampsia

Circulating FCN2 was consistently lower in women who developed preeclampsia than in healthy controls across all five cohorts (Fig. 1 and Supplementary Tables S2–3). In the prospective cohorts, the reductions before diagnosis were approximately 10-20% for late-onset preeclampsia and up to approximately 50% for early-onset preeclampsia. In the diagnostic cohorts, FCN2 concentrations were approximately 50-80% lower in women with established preeclampsia than in healthy controls.

4.4. Correlation between FCN2 and mean arterial pressure

A significant negative correlation between FCN2 and mean arterial pressure was observed in late gestation, with weak to moderate negative correlation coefficients (Spearman's ρ approximately −0.6 to −0.2) across cohorts (Fig. 3). Because blood pressure measurements were obtained at different gestational ages across cohorts and antihypertensive treatment was not accounted for, direct comparison of correlation estimates should be interpreted cautiously.

4.4.1. Predictive performance of FCN2

FCN2 demonstrated generally increasing predictive performance for late-onset preeclampsia with advancing gestational age across cohorts (AUC = 0.40-0.54 in early gestation), improving to AUC = 0.62-0.68 in late pregnancy (Fig. 4A–C). Overall, predictive performance remained modest for late-onset disease across cohorts. Maternal clinical characteristics (age, BMI, and nulliparity) alone demonstrated higher predictive performance than FCN2 in early to mid-gestation (AUC = 0.60-0.74), whereas their performance was comparable to or lower than that of FCN2 after gestational week 34 (AUC = 0.40-0.62, Fig. 4A–C and Supplementary Table S4).

For prediction of early-onset preeclampsia, FCN2 demonstrated moderate-to-good predictive performance from gestational week 15 onward (AUC = 0.70-0.87), with higher AUCs than models based on maternal clinical characteristics alone (AUC = 0.43-0.50) (Fig. 4D and Supplementary Table S4).

FCN2 generally demonstrated predictive performance within the range of established biomarkers across cohorts (Supplementary Fig. S2 and Supplementary Table S5). However, PlGF showed higher prediction performance than FCN2 for predicting late-onset preeclampsia at weeks 15-25 and weeks 25-34 in the Detroit 1 prospective cohort (DeLong tests, $p = 0.037$ and $p < 0.001$ respectively). At gestational weeks 8-15, FCN2 demonstrated higher predictive performance than PlGF for early-onset preeclampsia in the Detroit 2 prospective cohort, with AUCs of

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Table 1
Clinical characteristics of each cohort.

Oslo 1 prospective cohort

	Late-onset preeclampsia (N = 35)	Controls (N = 70)
Age in years[a]	29.8 (3.8)	32.1 (3.6)
BMI (kg/m2)[a]	27.0 (4.7)	24.1 (2.9)
Birth GW[a]	39.1 (1.8)	40.3 (1.2)
Sex (M), N (%)	18 (51%)	40 (57%)
Nulliparous, N (%)	24 (69%)	35 (50%)
MAP (mmHg)[a], Weeks 12-19	87 (8.4); missing n = 2	81 (7.5)
MAP (mmHg)[a], Weeks 20-27	86 (9.1); missing n = 1	80 (7.5)
MAP (mmHg)[a], Weeks 28-34	90 (10); missing n = 4	82 (8.0)

Detroit 1 prospective cohort

	Late-onset preeclampsia (N = 71)	Controls (N = 84)
Age in years[a]	24.0 (6.1)	23.8 (5.1)
BMI (kg/m2)[a]	29.9 (8.2)	26.5 (5.6)
Birth GW[a]	38.0 (1.7)	39.6 (1.25)
Sex (M), N (%)	40 (56%)	46 (55%)
Nulliparous, N (%)	41 (58%)	29 (35%)
MAP (mmHg)[a], Weeks 15-25	86 (11); missing n = 24	82 (8.5)
MAP (mmHg)[a], Weeks 25-34	91 (9.2); missing n = 24	83 (8.8); missing n = 2
MAP (mmHg)[a], Weeks 34-42	100 (9.2); missing n = 49	86 (9.0); missing n = 18

Detroit 2 prospective cohort

	Early-onset preeclampsia (N = 33)	Late-onset preeclampsia (N = 76)	Controls (N = 90)
Age in years[a]	23.2 (4.8)	24.5 (6.2)	24.3 (4.4)
BMI (kg/m2)[a]	28.0 (9.2)	31.0 (8.4)	28.3 (7.0)
Birth GW[a]	31.3 (2.5)	38.7 (1.1)	39.6 (1.2)
Sex (M), N (%)	15 (45%)	44 (58%); missing n = 1	45 (50%)
Nulliparous, N (%)	16 (48%)	32 (42%)	26 (29%)

Oslo 2 diagnostic cohort

	Early-onset preeclampsia (N = 16)	Late-onset preeclampsia (N = 18)	Controls (N = 70)
Age in years[a]	33.8 (4.5)	34.4 (6.1)	36.1 (3.8)
BMI (kg/m2)[a]	26.6 (5.5)	23.3 (3.7)	23.5 (3.9)
Birth GW[a]	28.9 (2.7)	37.4 (2.0)	39.2 (0.50)
Sex (M), N (%)	10 (59%)[b]	10 (42%)[c]	39 (56%)
Nulliparous, N (%)	7 (44%)	12 (67%)	16 (23%)
MAP (mmHg)[a], 1st trimester	96 (8.8)	86 (6.3); missing n = 2	82 (8.1); missing n = 3

Gothenburg diagnostic cohort

	Early-onset preeclampsia (N = 48)	Controls for early-onset preeclampsia (N = 40)	Late-onset preeclampsia (N = 97)	Controls for late-onset preeclampsia (N = 38)
Age in years[a]	31.7 (4.8)	31.1 (3.9)	31.3 (5.3)	33.4 (3.9)
BMI (kg/m2)[a]	26.4 (5.0)	24.9 (4.4)	26.7 (6.0)	24.3 (4.1)
Birth GW[a]	32.3 (3.4)	38.6 (3.8)	38.0 (1.6)	39.8 (1.4)
GW at sampling[a]	31.1 (3.3)	27.6 (3.8)	37.7 (1.8)	37.5 (2.1)
Sex (M), N (%)	29 (59%)[b]	16 (39%)[b]	47 (48%)[#]	20 (53%)
Nulliparous, N (%)	36 (75%)	20 (50%)	86 (89%)	20 (53%)
MAP (mmHg)[a]	109 (8.2)	88 (7.1)	107 (8.5)	90 (7.5)

GW = Gestational weeks.
MAP = Mean arterial pressure.
[a] Mean (SD).
[b] One set of twins.
[c] Six sets of twins.

0.64 and 0.47, respectively (p = 0.047). These results indicate that the relative predictive performance of FCN2 and PlGF varied according to gestational age and preeclampsia group.

4.5. Classification performance of FCN2 for established preeclampsia versus healthy controls

FCN2 alone demonstrated very high classification performance between established preeclampsia and healthy controls in the Gothenburg diagnostic case-control cohort for both early-onset preeclampsia (AUC = 0.96) and late-onset preeclampsia (AUC = 0.93) (Fig. 5A and B). Exploratory optimal classification thresholds identified using the Youden index were 41.3 ng/mL for early-onset preeclampsia and 29.8 ng/mL for late-onset preeclampsia. The corresponding sensitivity and specificity were 96% and 98% for early-onset preeclampsia and 84% and 89% for late-onset preeclampsia, respectively (Fig. 5C). These results should be interpreted within the context of a diagnostic case-control design and require validation in independent and clinically representative cohorts.

5. Discussion

The principal finding of this study is that FCN2 deviated from healthy controls at different gestational stages in early- and late-onset preeclampsia. In the separate comparisons with healthy controls, lower circulating FCN2 concentrations were observed from early pregnancy in women who subsequently developed early-onset preeclampsia, whereas differences in late-onset preeclampsia were mainly observed during the third trimester. These findings support the growing evidence that preeclampsia comprises biologically heterogeneous disease processes rather than a single disorder [2,3,8]. FCN2 also showed gestational patterns that differed from those of the established angiogenic biomarkers evaluated in this study.

To our knowledge, this is among the first multi-cohort studies to characterize gestational FCN2 trajectories separately in early- and late-onset preeclampsia across both prospective and diagnostic settings.

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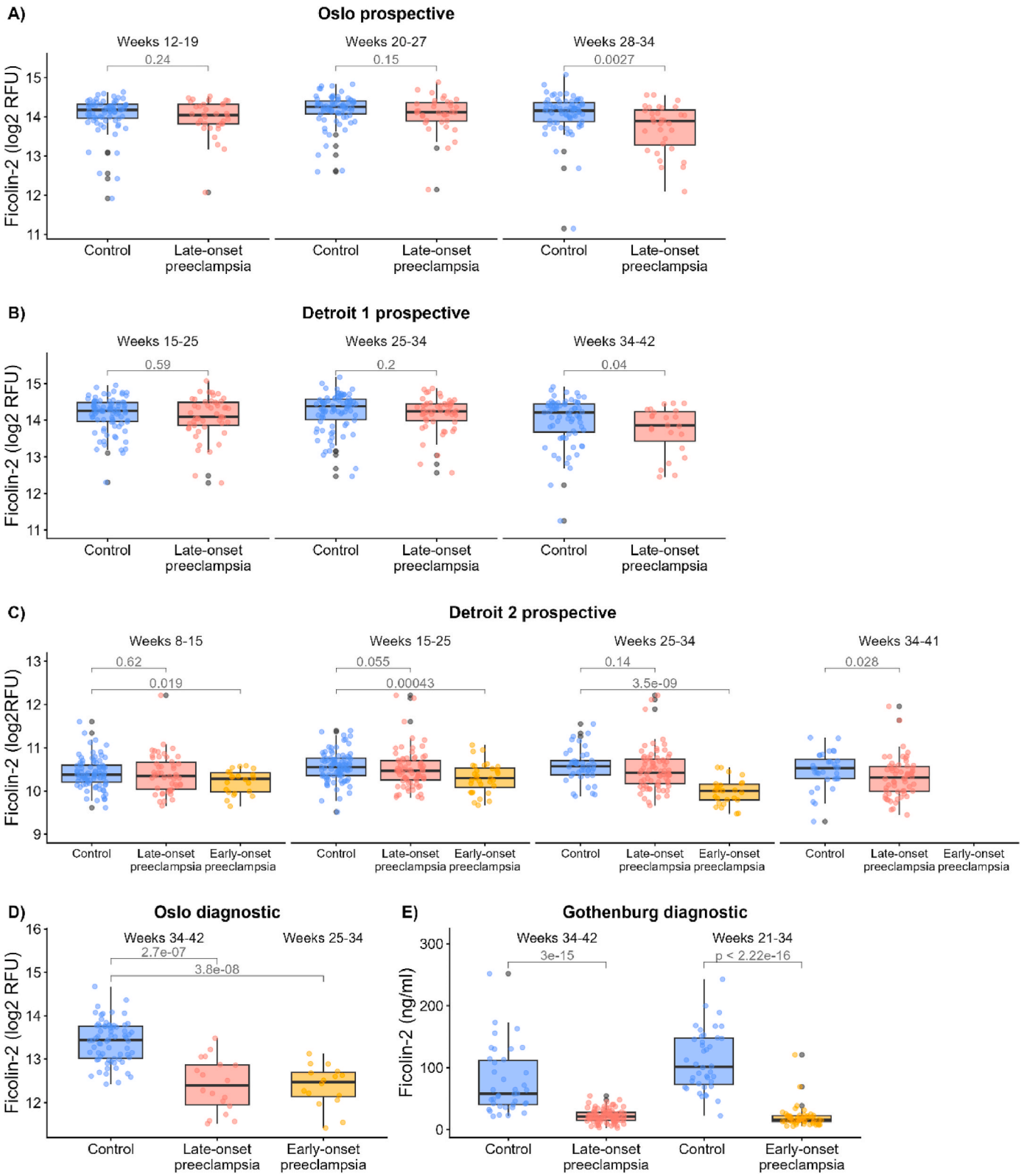

Fig. 1. Ficolin-2 in early-onset preeclampsia and late-onset preeclampsia compared to healthy controls, p-values were calculated using Wilcoxon rank-sum tests in the **A**) Oslo 1 prospective cohort, **B**) Detroit 1 prospective cohort, **C**) Detroit 2 prospective cohort, **D**) Oslo 2 diagnostic cohort, and **E**) Gothenburg diagnostic cohort.

Earlier studies have shown that circulating FCN2 concentrations are lower during pregnancy than in nonpregnant women and are further reduced in pregnancies complicated by preeclampsia [23,29,34,48]. In addition, ficolin binding has been demonstrated in apoptotic placental tissue, suggesting a mechanistic link between trophoblast injury, lectin pathway activation, and placental complement dysregulation [21]. Belmonte et al. [49] reported placental deposition of Ficolin-3 in preeclampsia, whereas Ficolin-2 was practically undetectable, indicating that individual ficolins may differ in their distribution and roles at the maternal-fetal interface. Reduced circulating FCN2 in preeclampsia is

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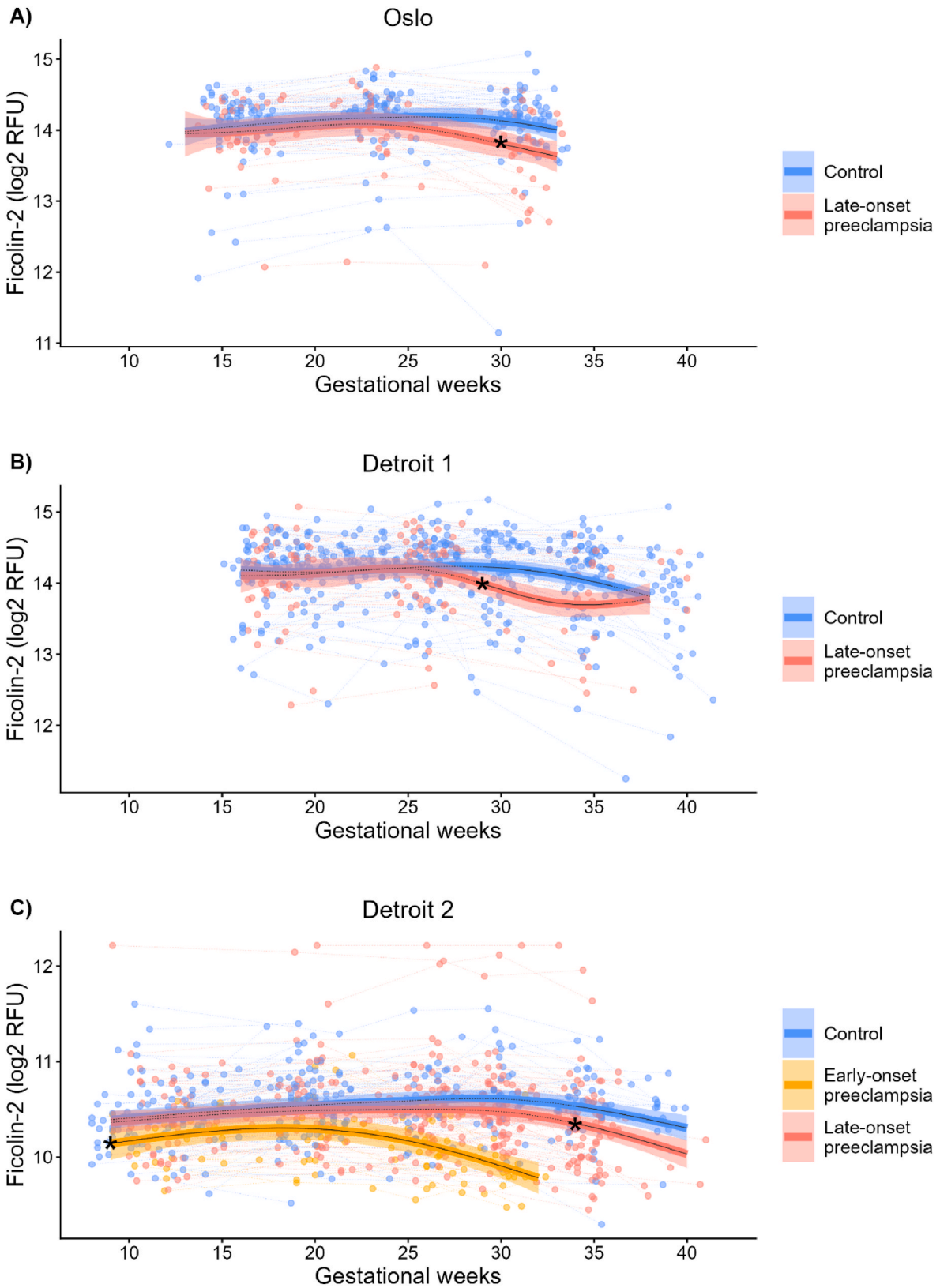

Fig. 2. Longitudinal mixed models of Ficolin-2 in late-onset preeclampsia, early-onset preeclampsia and healthy controls in the three longitudinal cohorts; **A)** Oslo 1 prospective cohort, **B)** Detroit 1 prospective cohort, and **C)** Detroit 2 prospective cohort. Lines represent model-estimated mean trajectories and shaded areas indicate 95% confidence intervals. Solid black lines and asterisks mark the timing of significantly different trajectories between preeclampsia and controls.

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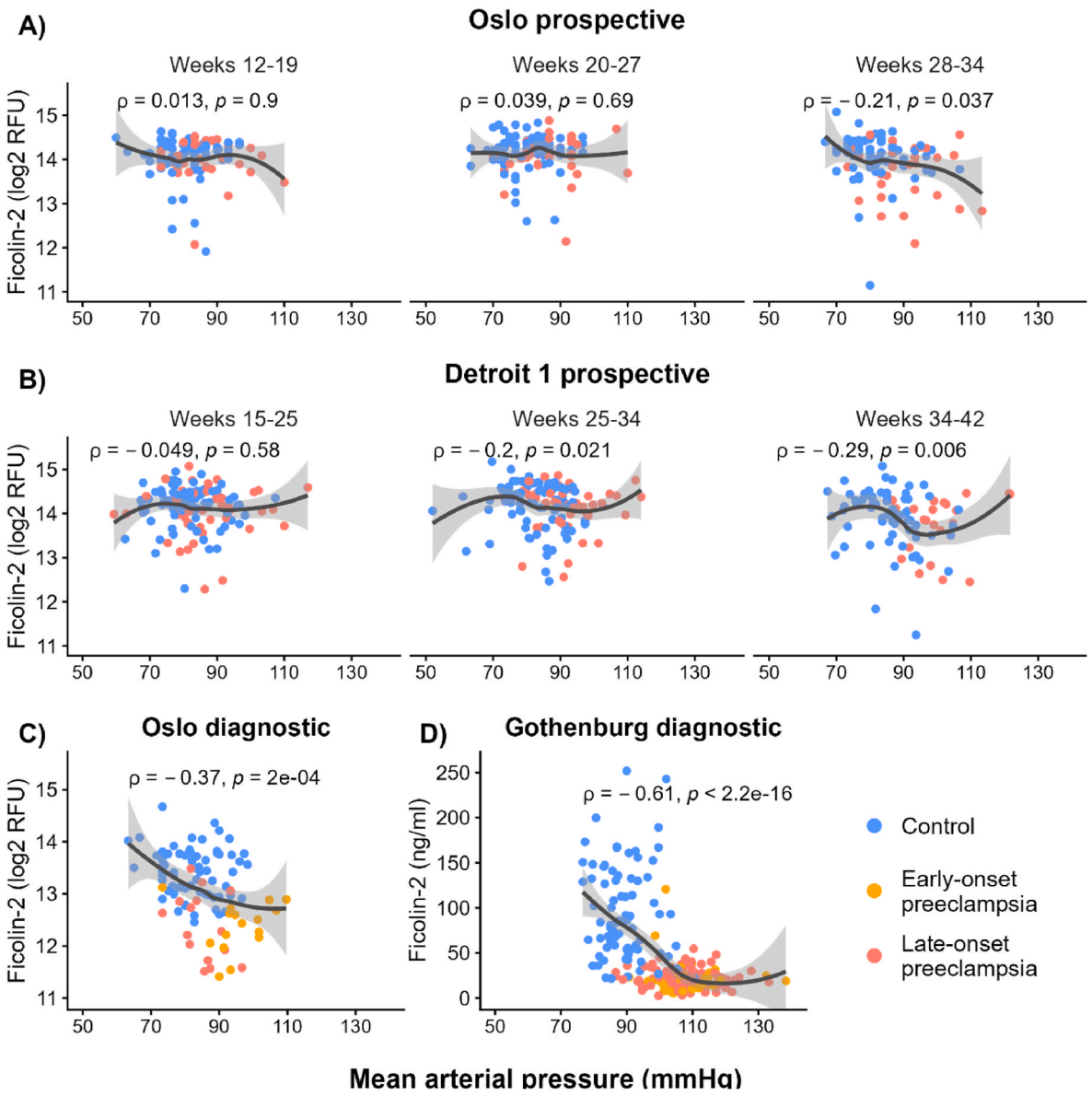

Fig. 3. Spearman correlations between Ficolin-2 and mean arterial pressure in the **A**) Oslo 1 prospective cohort, **B**) Detroit 1 prospective cohort, C) Oslo 2 diagnostic cohort, and D) Gothenburg diagnostic cohort.

compatible with, but does not establish, increased consumption during complement activation [16,50]. Elevated levels of the terminal complement complex C5b-9 have been reported in preeclampsia, although these findings do not establish the mechanism underlying lower FCN2 in the present study [14].

Our longitudinal analyses confirm and extend previous findings by demonstrating that lower circulating FCN2 concentrations were observed at different gestational stages when early- and late-onset preeclampsia were separately compared with healthy controls. These temporal patterns are consistent with biological heterogeneity in preeclampsia and with contemporary models emphasizing varying contributions from placentogenic and maternogenic factors to its pathophysiology. These temporal relationships are also consistent with the concept that FCN2 may reflect dynamic immunological changes at the maternal-fetal interface, rather than serving as a static correlate [2,3]. Early-onset preeclampsia is characterized by defective spiral artery remodeling, early placental ischemia, and increased syncytiotrophoblast stress and apoptosis, processes known to activate the lectin pathway of complement [51–55]. This provides a possible biological context for the lower circulating FCN2 concentrations observed from early gestation in this group, but does not establish complement activation as the underlying mechanism [20,21]. In contrast, late-onset preeclampsia is more closely associated with maternal metabolic factors and accelerated placental ageing, with comparatively preserved early placentation and later development of placental dysfunction [5,51–53]. These differences may provide a biological context for the later reduction in FCN2, although the present study cannot determine the mechanisms underlying either temporal pattern. In particular, we cannot establish whether reduced circulating FCN2 reflects increased consumption, reduced hepatic synthesis, or other processes. FCN2 is primarily liver-derived and has been associated with impaired hepatic function in other disease states [56,57]. Dedicated experimental studies assessing FCN2 in placental tissue alongside maternal circulating concentrations and direct measures of complement activation are needed to clarify the source of FCN2 and the mechanisms underlying its reduction in preeclampsia. Overall, the longitudinal patterns support biological heterogeneity in preeclampsia without establishing distinct FCN2-related mechanisms in early- and late-onset disease.

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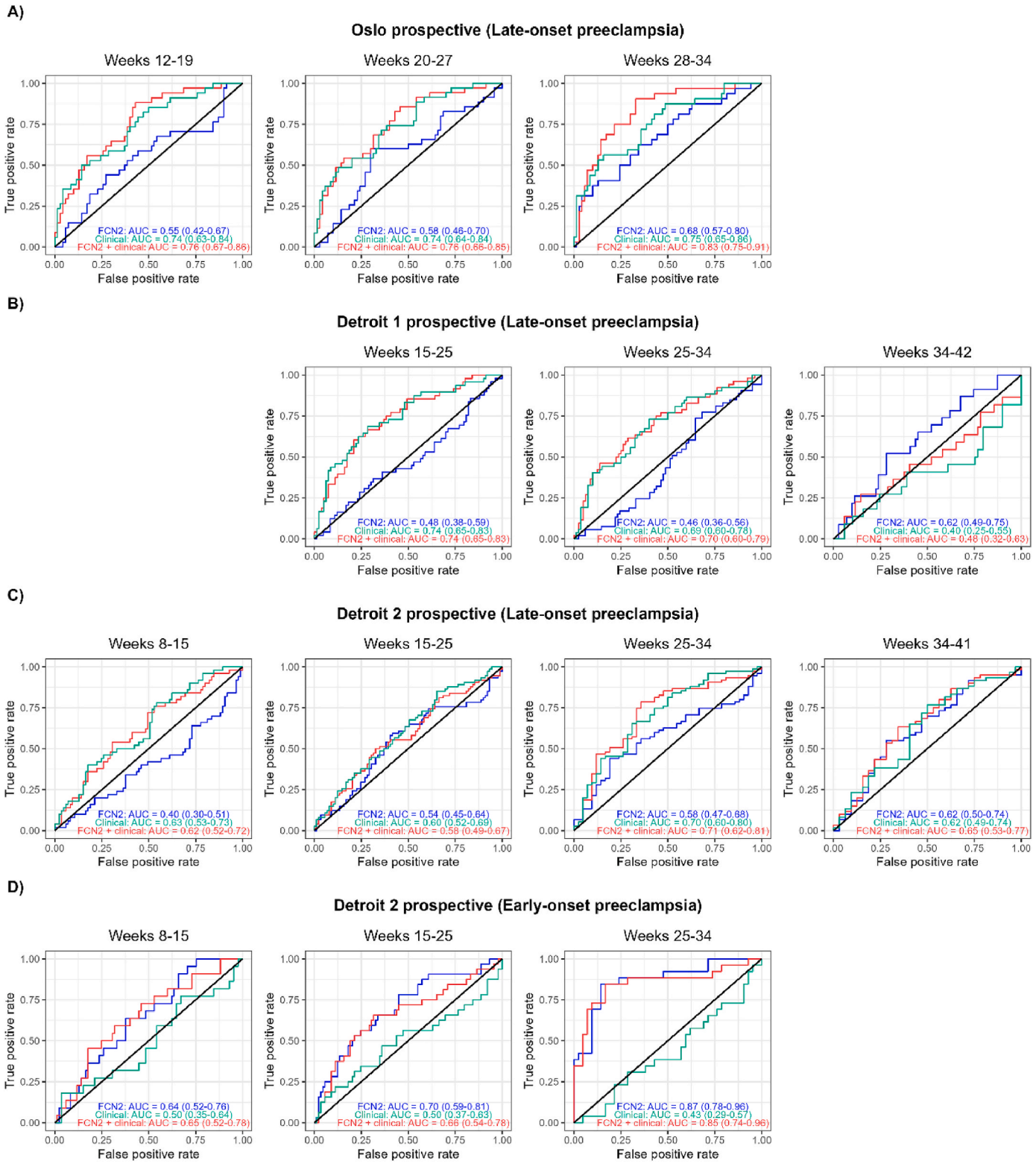

Fig. 4. Receiver Operating Characteristic (ROC) curves for predictive models using Ficolin-2 alone (orange), Ficolin-2 and clinical characteristics combined (green) and clinical characteristics alone (blue) in **A**) The Oslo 1 prospective cohort (late-onset preeclampsia), **B**) The Detroit 1 prospective cohort (late-onset preeclampsia), **C**) The Detroit 2 prospective cohort (late-onset preeclampsia), and **D**) The Detroit 2 prospective cohort (early-onset preeclampsia).

Although the primary value of FCN2 may be biological characterization rather than standalone clinical prediction, FCN2 demonstrated moderate to good predictive performance for early-onset preeclampsia and very high classification performance between established preeclampsia and healthy controls in the Gothenburg diagnostic cohort. Reduced circulating FCN2 has also recently been associated with fetal death among pregnancies complicated by preeclampsia [58], further supporting its relevance to adverse obstetric outcomes. Nevertheless, our nested case-control analyses do not permit direct estimation of absolute risk, predictive values, or population-level clinical utility. The

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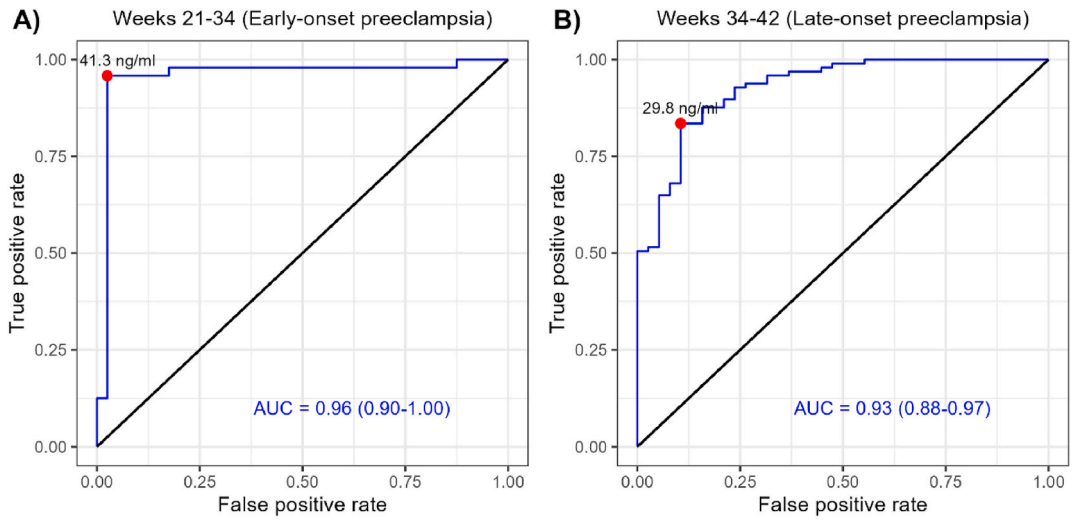

C)

	Specificity	Sensitivity	Youden Index	Ficolin-2 (ng/ml)
Early-onset preeclampsia	0.98	0.96	0.93	41.3
Late-onset preeclampsia	0.89	0.84	0.73	29.8

Fig. 5. Receiver Operating Characteristic (ROC) showing classification performance of Ficolin-2 in established **A**) early-onset preeclampsia and **B**) late-onset preeclampsia in the Gothenburg diagnostic cohort. Ficolin-2 concentration cutoff values based on Youden Index are marked at the respective false positive rate (1 – specificity) and true positive rate (sensitivity). **C**) Ficolin-2 concentration cutoffs at which optimal classification performance was achieved and the corresponding specificity and sensitivity.

classification findings and exploratory optimal classification thresholds reported here require validation in prospective clinical cohorts before any conclusions regarding clinical implementation can be drawn.

A potential value of FCN2 is that its gestational pattern may differ from those of established angiogenic biomarkers. In the present study, the relative predictive performance of FCN2 and PlGF varied according to gestational age and preeclampsia group. However, we did not formally assess whether FCN2 provided incremental predictive value beyond angiogenic biomarkers. The observed correlations between FCN2, sFlt-1, and PlGF indicate associations between FCN2 and angiogenic biomarkers but do not establish the underlying biological mechanism (Supplementary Figs. S3 and S4). In the original analysis of the Detroit 2 prospective cohort, FCN2 was significantly reduced in early-onset preeclampsia, whereas no significant change was observed for PlGF [31].

Collectively, the different patterns of deviation from healthy controls observed in the separate analyses of early- and late-onset preeclampsia support biological heterogeneity in preeclampsia. Whether FCN2 provides information beyond established angiogenic biomarkers requires further evaluation.

5.1. Strengths and limitations

A major strength of this study is the inclusion of five independent cohorts, enabling both robust characterization of FCN2 trajectories prior to clinically established disease and evaluation of FCN2 in established disease. Furthermore, the inclusion of both early-onset and late-onset preeclampsia allowed FCN2 patterns to be characterized separately in the two groups. Future studies using clinical or molecular definitions of predominantly placentogenic and maternogenic preeclampsia may provide a more biologically precise evaluation of FCN2. The early- and late-onset classification used in the present study is clinically established but may not fully capture this biological heterogeneity.

The use of two independent analytical platforms (SomaScan and enzyme immunoassay) strengthens the robustness of the findings across assay platforms.

However, several limitations should be considered when interpreting our findings. First, differences in recruitment strategies, sampling schedules, and cohort composition may have contributed to inter-cohort variability. Second, recruitment occurred across different time periods and healthcare settings. Since recruitment to these study cohorts, the diagnostic criteria for preeclampsia have been revised, and now include hypertension after 20 weeks of gestation in combination with proteinuria and/or maternal organ dysfunction. These differences may have influenced case ascertainment and, despite harmonization of the analyses, should be considered when interpreting the findings [24–26]. In addition, early- and late-onset preeclampsia were operationally classified according to gestational age at delivery because the timing of clinical disease onset was not consistently available. Some participants classified as having late-onset preeclampsia may therefore have developed signs or symptoms before 34 weeks of gestation. The early- and late-onset groups were evaluated separately against healthy controls, and the study was not designed to provide a direct statistical comparison of FCN2 trajectories between the two preeclampsia groups. Third, our predictive models were derived from nested case-control samples with oversampling of preeclampsia cases rather than the complete source cohorts. The analyses therefore cannot directly establish absolute risk, predictive values, or population-level clinical utility. In particular, the very high classification performance observed in the Gothenburg diagnostic cohort should be interpreted in the context of a selected case-control population with established disease and should not be assumed to represent performance in prospective screening populations. Information on antihypertensive treatment was unavailable in some cohorts and incomplete in others, preventing consistent adjustment for treatment in the analyses of FCN2 and mean arterial pressure.

FCN2 should therefore be considered an exploratory marker. Future prospective studies should assess whether FCN2 provides information beyond established clinical factors and angiogenic biomarkers and should validate clinically relevant thresholds in representative populations. FCN2 assays are not yet standardized for routine clinical use, and absolute concentrations could not be compared directly across all cohorts because different assay platforms were used.

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6. Conclusion

This multi-cohort study demonstrates that circulating FCN2 deviates from healthy controls at different gestational stages in early- and late-onset preeclampsia. Lower FCN2 concentrations were observed from early pregnancy in pregnancies that developed early-onset preeclampsia, whereas differences in late-onset preeclampsia emerged mainly during the third trimester. These findings support biological heterogeneity in preeclampsia and provide a basis for further evaluation of FCN2 alongside established angiogenic biomarkers.

CRediT authorship contribution statement

Trond Melbye Michelsen: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Hilde Bastøe Sellevoll:** Writing – review & editing, Visualization, Investigation, Formal analysis, Conceptualization. **Ane C. Westerberg:** Writing – review & editing, Supervision, Data curation. **Maren-Helene Langeland Degnes:** Writing – review & editing, Formal analysis. **Manuela Zucknick:** Writing – review & editing, Validation, Formal analysis. **Tove Lekva:** Writing – review & editing, Investigation. **Annika Elisabet Michelsen:** Writing – review & editing, Investigation. **Thor Ueland:** Writing – review & editing, Validation, Investigation. **Gaurav Bhatti:** Writing – review & editing. **Roberto Romero:** Writing – review & editing, Investigation. **Lina Bergman:** Writing – review & editing, Investigation, Data curation. **Marie Cecilie Paasche Roland:** Writing – review & editing, Data curation. **Adi L. Tarca:** Writing – review & editing, Validation, Investigation, Formal analysis. **Ina J. Andresen:** Writing – review & editing, Visualization, Supervision, Formal analysis, Conceptualization.

Ethics declaration

Written informed consent to take part in the study and to publish the article has been obtained from all participants or their legal representatives. The privacy rights of participants have been observed.

This study includes human biological material and consent was obtained by donors for use in this study and for publication of the article. The samples used in this research were not sourced from executed prisoners or prisoners of conscience.

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place. The Oslo 1 prospective cohort was approved by the Regional Committee for Medical and Health Research Ethics South-East Norway (S-2014/224-0119a). The Oslo 2 diagnostic cohort was approved by the Regional Committee for Medical and Health Research Ethics South-East Norway (S-07174, 2419/2011 and 13885). The Detroit 1 and Detroit 2 prospective cohorts were approved by the Institutional Review Board of Wayne State University (IRB #110605MP2F and #061217MP2P) and by the Institutional Review Boards of Wayne State University and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH (OH97-CH-N067). The Gothenburg diagnostic cohort was approved by the Swedish Ethical Review Authority (2023-02271-02) and the Norwegian Regional Ethics Committee (551842). (Approval No. The Oslo 1 prospective cohort was approved by the Regional Committee for Medical and Health Research Ethics South-East Norway (S-2014/224-0119a). The Oslo 2 diagnostic cohort was approved by the Regional Committee for Medical and Health Research Ethics South-East Norway (S-07174, 2419/2011 and 13885). The Detroit 1 and Detroit 2 prospective cohorts were approved by the Institutional Review Board of Wayne State University (IRB #110605MP2F and #061217MP2P) and by the Institutional Review Boards of Wayne State University and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH (OH97-CH-N067). The Gothenburg diagnostic cohort was approved by the Swedish Ethical Review Authority (2023-02271-02) and the Norwegian Regional Ethics Committee (551842).)

Availability of data and materials

The datasets analyzed during the current study are not publicly available because they contain potentially identifiable participant information and are subject to ethical and institutional restrictions. Data are available from the corresponding author upon reasonable request and subject to the necessary approvals from the participating institutions and ethics committees.

Consent for publication

Not applicable.

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Declaration of competing interest

LB has received reagents for PlGF and sFlt-1 from Roche, PerkinElmer and Thermo Fisher and has received drugs and placebo for a preeclampsia intervention trial from Merck Darmstadt. LB has served as a consultant for DiaMedica and Arraka Therapeutics, companies involved in developing new treatments for preeclampsia. ALT and RR are listed as co-inventors on a patent involving blood FCN2 for prediction of preeclampsia. All other authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.placenta.2026.11.009.

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