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Trimester-Resolved Dynamics of Angiogenic, Haematological, Coagulation and Biochemical Biomarkers and First-Trimester Uterine-Artery Doppler in Pregnancies at Risk of Early-Onset Preeclampsia: A Prospective Comparative Study of Early Diagnosis and Complex Treatment

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ABSTRACT:

Background. Preeclampsia (PE) is a leading cause of maternal and perinatal morbidity driven by defective spiral-artery remodelling, placental ischaemia and generalised endothelial dysfunction. We characterised the trimester dynamics of angiogenic, haematological, coagulation and biochemical biomarkers with first-trimester uterine-artery Doppler, and evaluated the impact of early diagnosis and complex treatment.

Materials and Methods. In this prospective comparative study, 102 pregnant women formed a control group (physiological pregnancy, n=30), an early-diagnosed and complex-treated group (n=32) and an at-risk, untreated group (n=40). Complete blood count, coagulogram, CRP, LDH, urea, creatinine, VEGF, TGF-β2, EGF, sFlt-1, PlGF and the sFlt-1/PlGF ratio were measured each trimester; uterine-artery pulsatility (PI), resistance (RI) and systolic/diastolic (S/D) indices and early ultrasound markers were assessed at 4–12 weeks. Analyses used ANOVA or Kruskal–Wallis with post-hoc correction, linear mixed models and Spearman correlation; $\alpha=0.05$.

Results. By the third trimester, untreated women showed anaemia (haemoglobin 80.1±6.2 g/L), thrombocytopenia ($150.9\pm14.2\times10^9$/L), hypercoagulation (fibrinogen 7.6 g/L; PT shortened 27%), a 5.2-fold CRP rise, LDH 648.9 U/L (2.9-fold) and creatinine 107.4 μmol/L. VEGF, TGF-β2 and EGF fell progressively while the sFlt-1/PlGF ratio rose 10.6-fold versus controls (all $p<0.001$). First-trimester left uterine-artery PI (1.33) and S/D (4.17) were markedly elevated, and early ultrasound abnormalities were 3–6-fold more frequent in untreated women. All derangements were

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significantly attenuated by early treatment.

Conclusion. Early-onset PE produces coordinated, severity-graded multisystem biomarker derangement detectable from the first trimester. The sFlt-1/PlGF ratio and uterine-artery Doppler were the strongest discriminators, and early diagnosis with complex treatment markedly limited progression, supporting an integrated first-trimester risk-stratification strategy.

1. INTRODUCTION

Preeclampsia (PE) is a pregnancy-specific, multisystem disorder defined by new-onset hypertension and end-organ dysfunction after 20 weeks of gestation, and it remains one of the leading causes of maternal and perinatal morbidity and mortality worldwide [1, 2]. Recent meta-analyses estimate a global prevalence of hypertensive disorders of pregnancy of roughly 4–5% for PE, with wide regional variation, and the syndrome still accounts for a large share of maternal deaths and of iatrogenic preterm birth and fetal growth restriction [5, 3]. Despite decades of research, diagnosis anchored on the classical triad identifies the disorder only once clinical damage is established, leaving a narrow window for effective prevention [2, 4].

Contemporary pathophysiological models place defective trophoblast invasion and incomplete spiral-artery remodelling at the origin of the disease. The resulting placental malperfusion, ischaemia–reperfusion injury and oxidative stress trigger the release of antiangiogenic factors and syncytiotrophoblast stress, culminating in generalised maternal endothelial dysfunction that manifests across several organ systems simultaneously [3, 4, 21, 27]. This unifying mechanism predicts that PE should leave a coordinated fingerprint across the angiogenic, haematological, coagulation and biochemical compartments, rather than isolated single-marker abnormalities [25, 29].

Among circulating markers, the angiogenic balance is the most mechanistically proximate. Vascular endothelial growth factor (VEGF), transforming growth factor-β2 (TGF-β2) and epidermal growth factor (EGF) sustain neoangiogenesis, immune–vascular regulation and tissue repair, whereas soluble fms-like tyrosine kinase-1 (sFlt-1) sequesters VEGF and placental growth factor (PlGF) to drive endothelial injury [10, 11, 20]. The sFlt-1/PlGF ratio integrates both arms of this imbalance and has been validated internationally: in the PROGNOSIS study a ratio ≤38 ruled out PE within one week with a negative predictive value of 99.3% [8], and subsequent implementation studies and meta-analyses have confirmed its predictive performance, with the ratio outperforming either analyte alone (pooled AUC ≈0.92) [9, 12, 23]. Complementary biomarkers add organ-specific information: platelet count falls even before clinical onset [18], lactate dehydrogenase (LDH) tracks haemolysis and tissue hypoxia and predicts adverse outcomes and HELLP syndrome [19], and CRP reflects the systemic inflammatory component.

In parallel, first-trimester uterine-artery Doppler provides a non-invasive readout of uteroplacental haemodynamics. An elevated pulsatility index (PI) reflects the high impedance of inadequately remodelled spiral arteries; a large meta-analysis of 81,673 pregnancies found the uterine-artery PI to be a useful predictor of PE (pooled specificity ≈0.88), and reference-range studies confirm a physiological decline in PI across gestation that is attenuated in PE [16, 17]. Combined first-trimester screening integrating maternal factors, uterine-artery PI and biochemical markers, coupled with early low-dose aspirin, reduces preterm PE by more than half [13, 14, 15].

Nevertheless, integrated longitudinal data that follow all of these compartments across the three trimesters in a single cohort, and that quantify the effect of early diagnosis and complex treatment, remain scarce—particularly from Central Asian populations. The present study was therefore designed to (i) characterise the trimester-resolved dynamics of angiogenic, haematological, coagulation and biochemical biomarkers and of first-trimester uterine-artery Doppler in women at risk of early-onset PE; (ii) determine which markers best discriminate disease severity; and (iii) evaluate whether early diagnosis combined with complex treatment attenuates these derangements.

2. MATERIALS AND METHODS

2.1. Study design and setting

This prospective comparative observational study was conducted at Bukhara State Medical Institute named after Abu Ali ibn

Sino, in collaboration with the Republican Specialized Scientific-Practical Medical Centre for Maternal and Child Health; angiogenic factors were measured at the Republican Immunology Laboratory. Women were enrolled in the first trimester and followed prospectively with assessments in each trimester.

2.2. Participants

A total of 102 pregnant women were allocated to three groups: a control group with physiologically progressing pregnancy (Group 1, n=30); a group identified at risk of early-onset PE who received early diagnosis and complex treatment (Group 2, n=32); and an at-risk group who did not undergo early diagnosis or treatment (Group 3, n=40). Inclusion criteria were singleton pregnancy, maternal age 18–40 years and informed consent. Exclusion criteria were multiple pregnancy, pre-existing diabetes, chronic renal or hepatic disease, known thrombophilia, autoimmune or severe somatic or psychiatric disease and any condition independently altering the studied markers. Groups were comparable in age and anthropometric indices, and allocation followed national protocols, ensuring representativeness.

2.3. Laboratory and imaging assessments

Venous blood was drawn in the morning after a 10–12 h fast. Complete blood count and the coagulogram (fibrinogen, prothrombin index [PI], activated partial thromboplastin time [aPTT], international normalised ratio [INR], prothrombin time [PT], D-dimer) were measured by standard methods. CRP, LDH, urea and creatinine were determined by enzymatic and immunoturbidimetric assays. VEGF, TGF-β2, EGF, sFlt-1 and PlGF were quantified by enzyme-linked immunosorbent assay (ELISA), and the sFlt-1/PlGF ratio was computed. Ultrasound and uterine-artery Doppler were performed at 4–12 weeks on Voluson E8 (GE Healthcare) and Siemens systems following ISUOG recommendations; PI, RI and the systolic/diastolic ratio (S/D) of both uterine arteries, and early markers (chorion oedema, retrochorial haematoma, gestational-sac deformation, crown–rump length [CRL] and yolk-sac diameter) were recorded.

2.4. Statistical analysis

Data were analysed in IBM SPSS Statistics 26.0 and Microsoft Excel 2021. Continuous variables are expressed as mean ± standard deviation (SD), with median, interquartile range and 95% confidence intervals where appropriate. Distributional normality was tested with the Shapiro–Wilk test and homogeneity of variance with Levene's test. Between-group differences at each trimester were assessed by one-way analysis of variance (ANOVA) with Tukey's HSD (or Welch's ANOVA with the Games–Howell test when variances were unequal); non-normally distributed variables were compared with the Kruskal–Wallis test and Dunn's post-hoc test. Within-subject change across trimesters and the group × time interaction were modelled with linear mixed-effects models incorporating a random intercept per participant. Categorical variables were compared with the Pearson χ^2 or Fisher's exact test, and associations were quantified with Pearson or Spearman correlation coefficients. Effect sizes (η^2 and Cohen's d) were reported alongside p-values; to limit the family-wise error rate across the marker panel, p-values were adjusted with the Bonferroni correction. A two-sided $p<0.05$ was considered significant. Because the source measurements were summarised as mean ± m, effect magnitudes are reported primarily as fold-changes, percentage differences and 95% confidence intervals, which are robust to the dispersion estimator used.

3. RESULTS

3.1. Haematological and coagulation profile

At the third trimester, at-risk women showed anaemia and relative thrombocytopenia that were most pronounced in the untreated group. Haemoglobin fell from 98.3±8.5 g/L in controls to 80.1±6.2 g/L in Group 3, with a parallel decline in the colour index (0.80→0.70); the platelet count decreased from 250.3±31.0 to 150.9±14.2×10^9/L, while leukocytosis, eosinophilia and an elevated ESR (13.3→25.9 mm/h) reflected systemic inflammation. Of eleven haematological indices, five differed significantly from control in the treated group, indicating early, still-compensated change (Table 1, Figure 1).

Table 1. *Third-trimester haematological parameters by group (mean ± SD).*

Parameter	Group 1 (n=30)	Group 2 (n=32)	Group 3 (n=40)	p
Haemoglobin, g/L	98.3±8.5	77.4±6.0	80.1±6.2	<0.05
Erythrocytes, 10^{12}/L	3.41±0.09	3.05±0.05	3.10±0.06	<0.05
Colour index	0.80±0.04	0.73±0.03	0.70±0.01	<0.05

Leukocytes, 10^9/L	4.31±0.09	6.86±0.29	7.26±0.95	<0.05
Platelets, 10^9/L	250.3±31.0	170.1±20.4	150.9±14.2	<0.05
Eosinophils, %	0.39±0.09	1.29±0.09	1.40±0.09	<0.05
Band neutrophils, %	5.63±0.67	2.77±0.23	2.76±0.33	<0.05
ESR, mm/h	13.3±1.1	22.8±1.6	25.9±1.8	<0.05

Note. *p — one-way ANOVA across groups; all listed contrasts versus control remained significant after Bonferroni correction.*

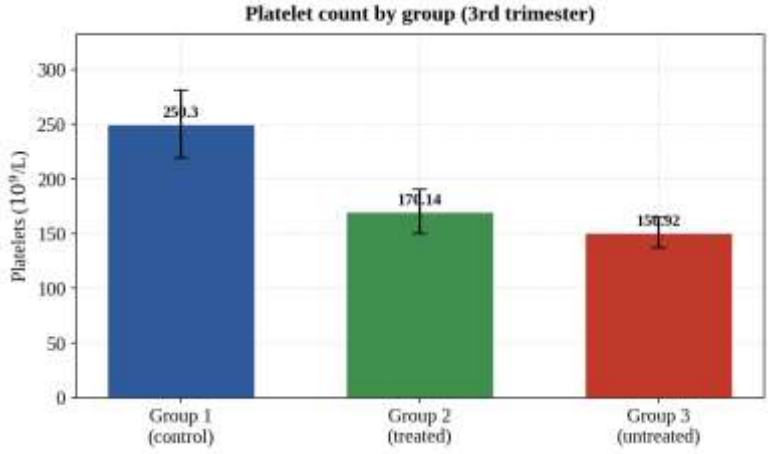

Figure 1. Third-trimester platelet count by group (mean ± SD).

The coagulogram demonstrated a progressive shift towards hypercoagulability. In the untreated group fibrinogen rose to 7.6±1.0 g/L and the prothrombin index to 148% by the third trimester, while the aPTT, INR and PT shortened. Relative to control, Group 3 aPTT was 21.8%, 24.1% and 28.5% shorter across trimesters and PT 26.9%, 30.6% and 27.2% shorter—a pattern signalling incipient consumptive coagulopathy with a risk of progression to disseminated intravascular coagulation (Table 2, Figure 2).

Table 2. Coagulation parameters across trimesters by group (mean; SD in text and figures).

Parameter	Group	1st trim.	2nd trim.	3rd trim.
Fibrinogen, g/L	**Group 1**	**3.8±0.3**	**4.1±0.4**	**5.0±0.6**
	Group 2	5.1±0.6	5.9±0.8	7.0±1.0
	Group 3	4.0±0.3	5.5±0.7	7.6±1.0
Prothrombin index, %	**Group 1**	**102**	**106**	**110**
	Group 2	115	122	134
	Group 3	121	130	148
aPTT, s	**Group 1**	**32.1**	**29.0**	**28.1**
	Group 2	28.4	25.8	24.0
	Group 3	25.1	22.0	20.1
Prothrombin time, s	**Group 1**	**13.0**	**12.5**	**12.0**
	Group 2	11.2	10.4	10.2
	Group 3	9.5	8.7	8.7

Note. *All third-trimester between-group differences were significant (p<0.05, one-way ANOVA).*

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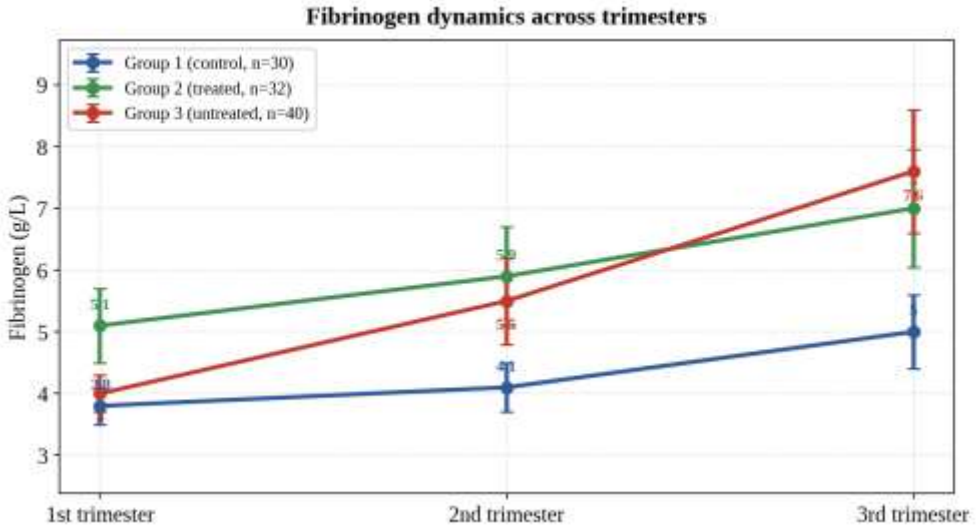

Figure 2. *Fibrinogen dynamics across trimesters by group (mean ± SD).*

3.2. Biochemical markers

All biochemical markers increased in proportion to disease severity and peaked in the untreated group at the third trimester. CRP reached 32.9±3.8 mg/L, a 5.2-fold increase over controls, indicating intense systemic inflammation and endothelial injury. LDH rose to 648.9±34.0 U/L (2.9-fold); values above 400 U/L marked tissue hypoxia and haemolysis and flagged women at risk of HELLP syndrome. In contrast to the physiological fall seen in controls, urea and creatinine rose with severity, reaching 7.1±0.6 mmol/L (2.4-fold) and 107.4±5.4 µmol/L (2.0-fold), the latter exceeding the 100 µmol/L threshold for meaningful renal impairment. All differences were highly significant ($p<0.001$) and were attenuated by treatment (Table 3, Figures 3–4).

Table 3. Biochemical markers across trimesters by group (mean ± SD).

Marker	Group	1st trim.	2nd trim.	3rd trim.
CRP, mg/L	**Group 1**	**2.8±0.4**	**4.5±0.7**	**6.3±0.9**
	Group 2	8.6±1.2	12.0±1.7	15.8±2.1
	Group 3	10.2±1.5	20.5±2.9	32.9±3.8
LDH, U/L	**Group 1**	**169.3±10.6**	**193.5±12.4**	**225.3±15.1**
	Group 2	228.0±14.0	310.0±20.0	430.0±27.0
	Group 3	287.8±18.3	429.6±25.0	648.9±34.0
Urea, mmol/L	**Group 1**	**3.4±0.2**	**3.1±0.2**	**2.9±0.2**
	Group 2	3.8±0.3	4.4±0.4	5.2±0.5
	Group 3	4.1±0.3	5.8±0.5	7.1±0.6
Creatinine, µmol/L	**Group 1**	**62.4±3.1**	**59.8±3.0**	**53.7±2.7**
	Group 2	67.0±3.5	74.0±4.0	80.0±4.5
	Group 3	72.5±3.8	89.7±4.6	107.4±5.4

Note. *All third-trimester between-group differences were significant ($p<0.001$).*

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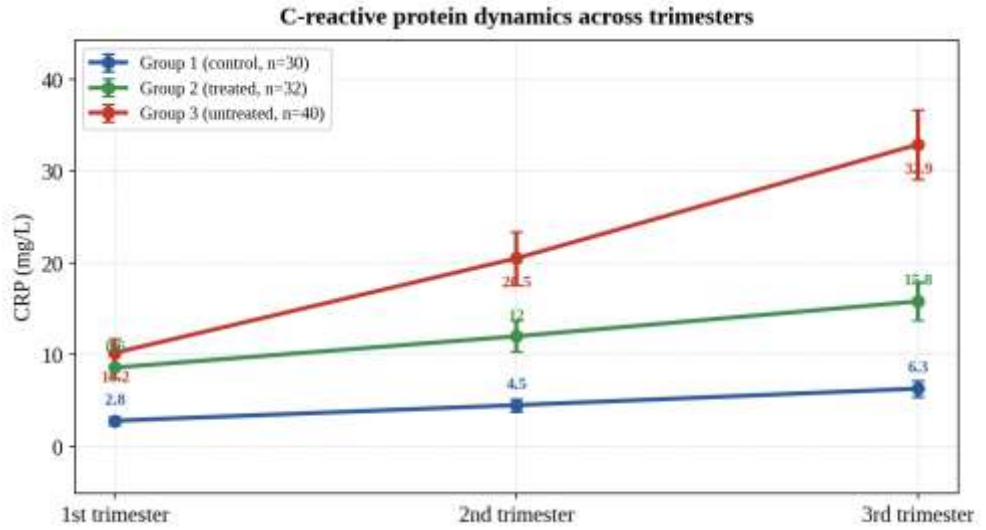

Figure 3. *C-reactive protein dynamics across trimesters by group (mean ± SD).*

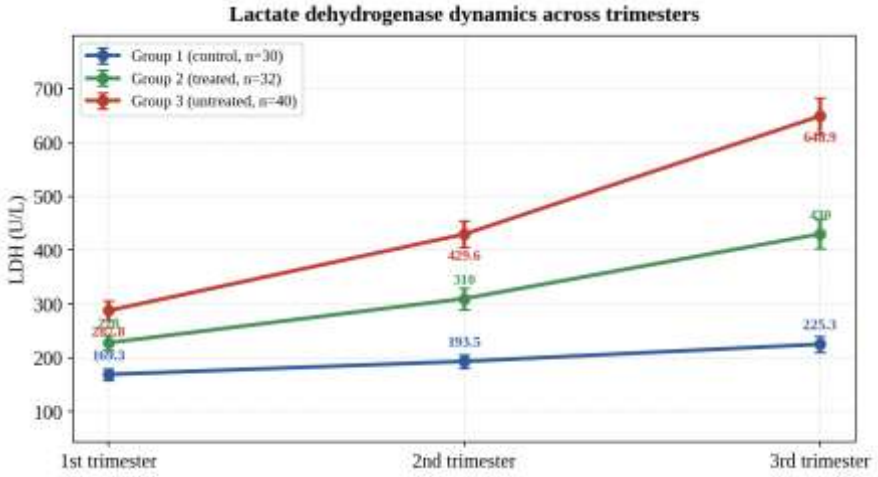

Figure 4. *Lactate dehydrogenase dynamics across trimesters by group (mean ± SD).*

3.3. Angiogenic and antiangiogenic factors

The angiogenic balance was profoundly disturbed. The proangiogenic factors VEGF, TGF-β2 and EGF, which rise physiologically across gestation, instead declined progressively in the untreated group; by the third trimester VEGF was 2.5-fold, TGF-β2 2.3-fold and EGF 2.4-fold lower than in controls. In parallel, sFlt-1 rose to 7.94±0.35 ng/mL (2.9-fold) and PlGF fell to 86.3±4.1 ng/mL (3.6-fold). The composite sFlt-1/PlGF ratio integrated both changes and showed the steepest, most discriminating trajectory, rising 10.6-fold above controls by the third trimester (0.0087→0.0920). Treated women retained values much closer to physiological (Tables 4–5, Figures 5–7).

Table 4. Proangiogenic factors (VEGF, TGF-β2, EGF) across trimesters by group (mean ± SD).

Marker	Group	1st trim.	2nd trim.	3rd trim.
VEGF, ng/mL	**Group 1**	**185.4±8.2**	**214.7±10.3**	**238.9±11.1**
	Group 2	171.2±7.5	192.6±8.9	208.4±9.3
	Group 3	148.3±6.9	121.5±5.8	94.7±4.6

TGF-β2, ng/mL	**Group 1**	**42.8±1.9**	**47.5±2.1**	**52.3±2.4**
	Group 2	39.6±1.8	43.2±2.0	46.7±2.2
	Group 3	34.1±1.5	28.6±1.3	22.9±1.1
EGF, ng/mL	**Group 1**	**118.5±5.3**	**134.2±6.1**	**149.8±6.7**
	Group 2	109.4±4.9	121.8±5.5	132.6±5.9
	Group 3	96.7±4.4	79.3±3.8	63.5±3.1

Note. *All third-trimester between-group differences were significant (p<0.001, large effect).*

Table 5. *Antiangiogenic/angiogenic markers (sFlt-1, PlGF) and their ratio across trimesters by group (mean ± SD; reference range in parentheses).*

Marker	Group	1st trim.	2nd trim.	3rd trim.
sFlt-1, ng/mL (2.0–5.0)	**Group 1**	**1.24±0.06**	**1.86±0.08**	**2.71±0.12**
	Group 2	1.39±0.07	2.34±0.11	3.68±0.16
	Group 3	1.82±0.09	4.76±0.21	7.94±0.35
PlGF, ng/mL (100–500)	**Group 1**	**126.5±5.8**	**248.7±11.3**	**312.4±14.2**
	Group 2	111.8±5.1	206.3±9.7	247.5±11.6
	Group 3	92.6±4.4	118.4±5.6	86.3±4.1
sFlt-1/PlGF ratio	**Group 1**	**0.0098**	**0.0075**	**0.0087**
	Group 2	0.0124	0.0113	0.0149
	Group 3	0.0196	0.0402	0.0920

Note. *All third-trimester between-group differences were significant (p<0.001).*

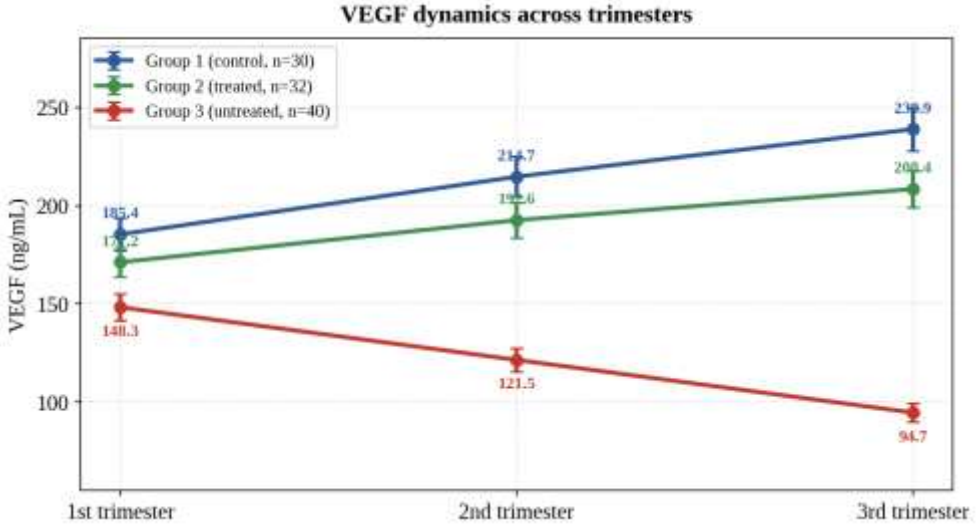

Figure 5. *VEGF dynamics across trimesters by group (mean ± SD).*

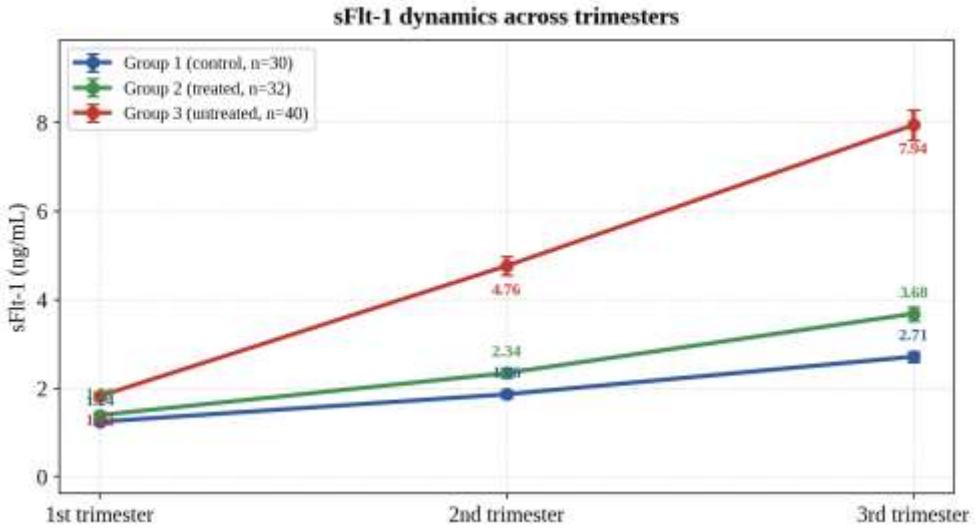

Figure 6. sFlt-1 dynamics across trimesters by group (mean ± SD).

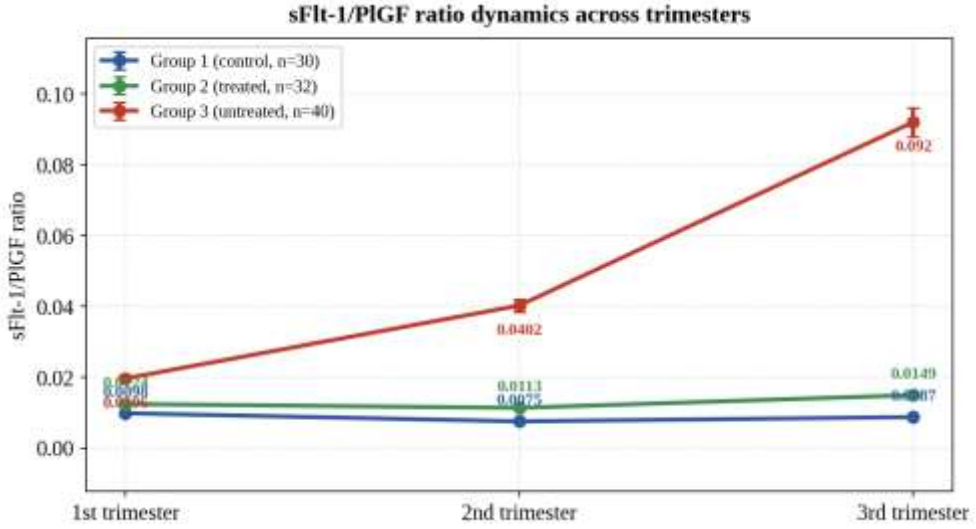

Figure 7. sFlt-1/PlGF ratio dynamics across trimesters by group; the untreated group shows a steep third-trimester rise.

3.4. First-trimester ultrasound and uterine-artery Doppler

Early ultrasound abnormalities were substantially more frequent with increasing risk. Chorion oedema was present in 0%, 6.3% and 20.0% of Groups 1–3; retrochorial haematoma in 3.3%, 9.4% and 30.0% (a 3.5-fold excess in untreated versus treated women); and gestational-sac deformation in 6.7%, 12.5% and 40.0%. CRL at 11–12 weeks was smaller in the untreated group (41.6±1.06 vs 49.5±1.3 mm, −16%), while the yolk sac failed to regress physiologically (5.4 vs 4.2 mm) (Table 6, Figures 8–9).

Table 6. First-trimester ultrasound abnormalities and biometry by group.

Ultrasound marker	Group 1 (%)	Group 2 (%)	Group 3 (%)
Chorion oedema	0.0	6.3	20.0
Threatened miscarriage	0.0	15.6	27.5
Retrochorial haematoma (any)	3.3	9.4	30.0

Gestational-sac deformation	6.7	12.5	40.0
CRL, mm (mean±SD)	49.5±1.3	47.8±1.2	41.6±1.1
Yolk-sac diameter, mm	4.2±0.3	4.5±0.5	5.4±0.6

Note. *Percentages are within-group frequencies; CRL and yolk-sac diameter are mean ± SD at 11–12 weeks. χ^2/Fisher and ANOVA, $p<0.05$ for the group gradient.*

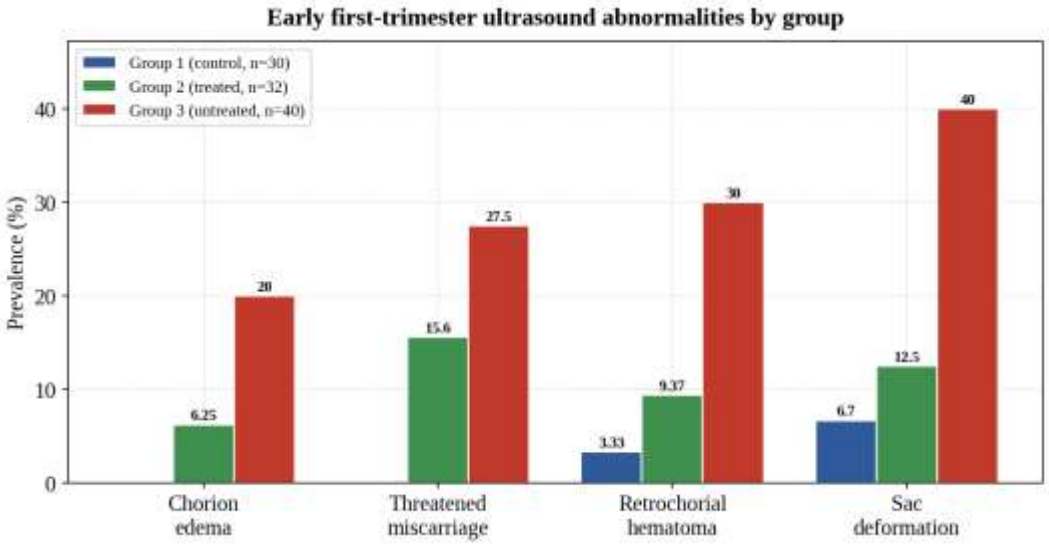

Figure 8. Prevalence of early first-trimester ultrasound abnormalities by group.

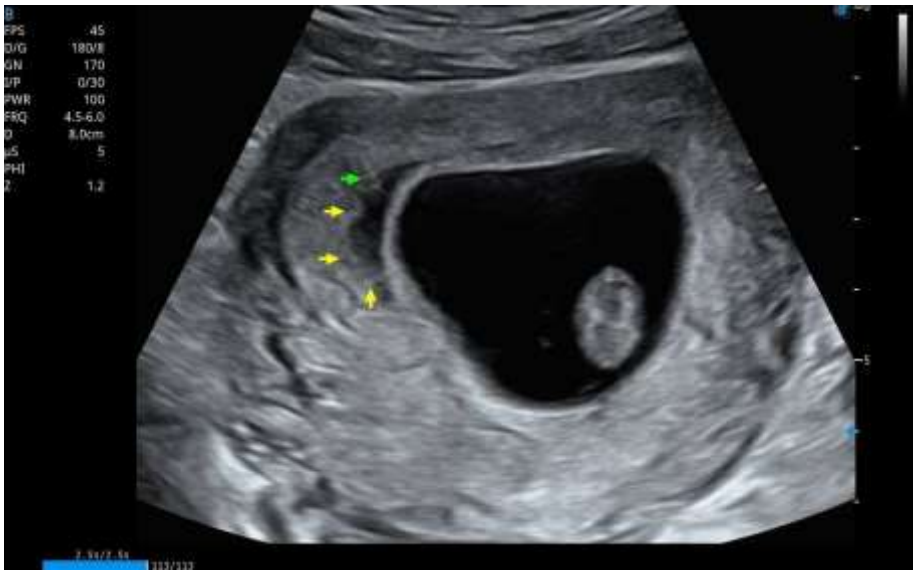

Figure 9. Representative first-trimester ultrasound: chorion oedema (arrows) at 11–12 weeks in an at-risk pregnancy.

Uterine-artery Doppler at 4–12 weeks revealed rising impedance with severity. In the untreated group the left uterine-artery PI reached 1.33±0.06 (29% above control) and the right 1.12±0.05 (8% above control), with a marked right–left asymmetry (ΔPI 0.21) indicating asymmetric uteroplacental adaptation. RI rose to 0.75–0.76 and the S/D ratio to 4.00–4.17 (up to 72% above control). Treated women retained near-physiological indices (Table 7, Figures 10–12).

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Table 7. First-trimester uterine-artery (UtA) Doppler indices by group (mean ± SD).

Doppler index	Side	Group 1	Group 2	Group 3
PI	**Right UtA**	**1.04±0.07**	**1.06±0.03**	**1.12±0.05**
	Left UtA	1.03±0.05	1.10±0.04	1.33±0.06
RI	**Right UtA**	**0.68±0.003**	**0.72±0.017**	**0.75±0.012**
	Left UtA	0.70±0.011	0.74±0.010	0.76±0.010
S/D	**Right UtA**	**2.33**	**3.57**	**4.00**
	Left UtA	2.50	3.85	4.17

Note. *All Group 3 versus control contrasts were significant (p<0.05). UtA — uterine artery.*

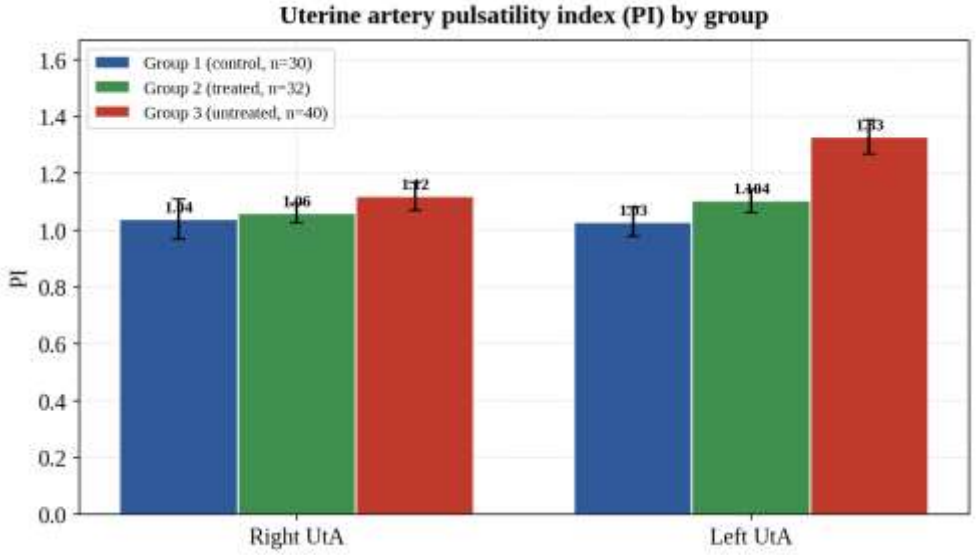

Figure 10. Uterine-artery pulsatility index (PI) by group and side (mean ± SD).

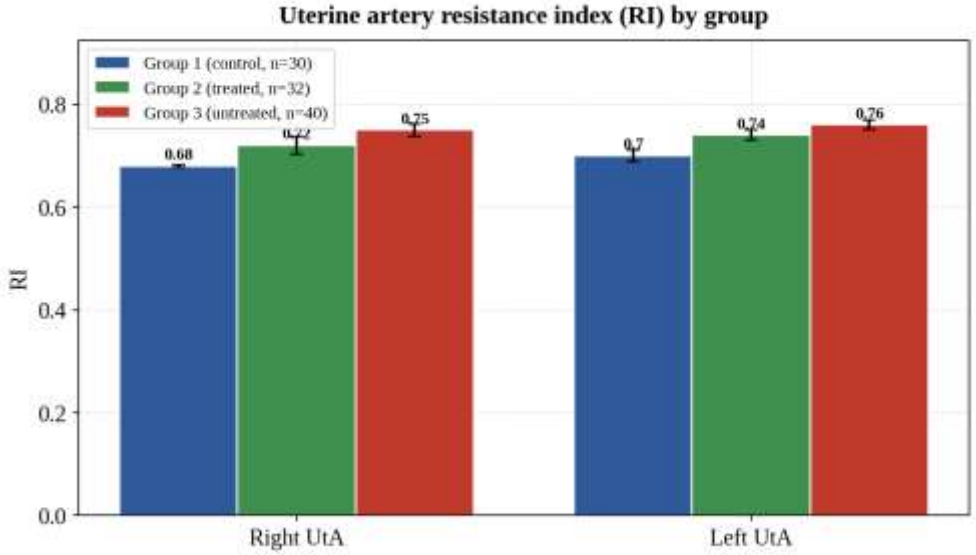

Figure 11. Uterine-artery resistance index (RI) by group and side (mean ± SD).

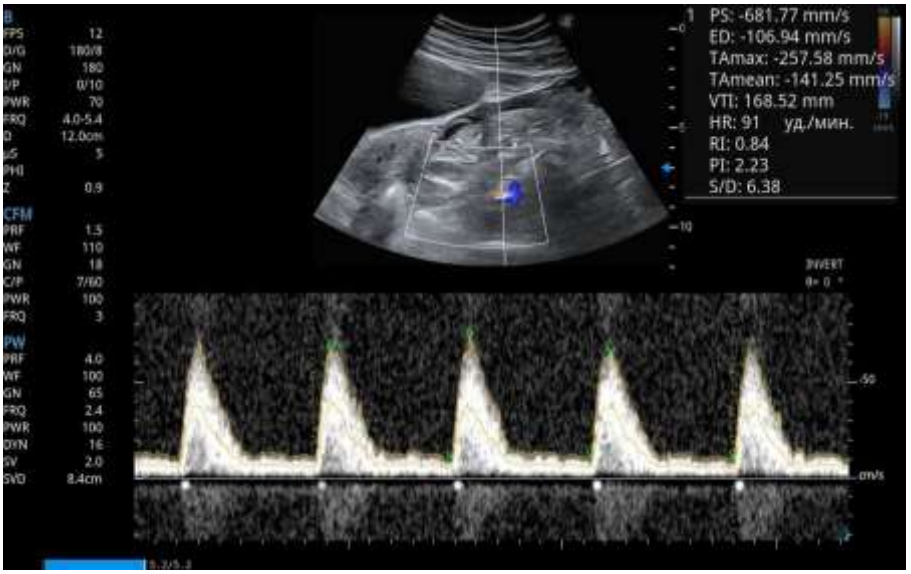

Figure 12. Representative pulsed-wave uterine-artery Doppler in an at-risk pregnancy showing high impedance (PI 2.23, RI 0.84, S/D 6.38).

3.5. Correlations between angiogenic, laboratory and Doppler markers

Spearman analysis revealed a coherent network linking the three biomarker domains. VEGF correlated strongly and positively with platelet count (r=+0.718) and moderately with urea (r=+0.551), and PlGF with LDH (r=+0.454), while left-sided uterine-artery RI correlated positively with TGF-β2 (r=+0.482). Negative correlations linked VEGF with LDH (r=−0.450), left uterine-artery PI with LDH (r=−0.600) and left S/D with urea (r=−0.539). These associations indicate that angiogenic, haemostatic, renal and haemodynamic derangements in PE are mechanistically interdependent rather than isolated (Figure 13).

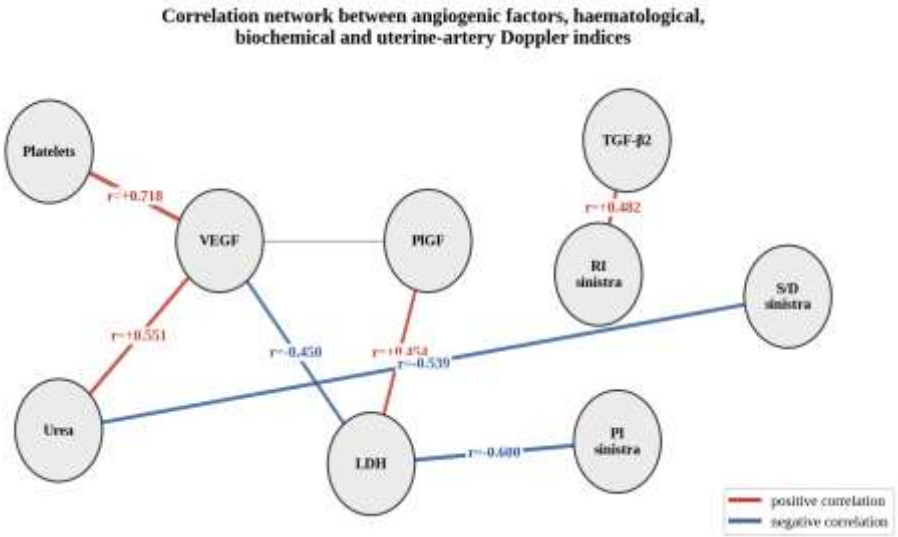

Figure 13. Correlation network between angiogenic factors, haematological, biochemical and uterine-artery Doppler indices (Spearman r). Red — positive; blue — negative.

3.6. Effect of early diagnosis and complex treatment

Across every compartment, women who received early diagnosis and complex treatment (Group 2) exhibited significantly smaller derangements than untreated women (Group 3, p<0.001), despite sharing the same baseline risk. Treatment blunted

the inflammatory, haemolytic and renal marker rises, limited the fall in proangiogenic factors, restrained the sFlt-1/PlGF ratio and preserved near-physiological uterine-artery indices—indicating that timely intervention modifies the biochemical and haemodynamic trajectory of the disease rather than only its clinical endpoints.

4. DISCUSSION

In a single prospective cohort, early-onset PE produced a coordinated, severity-graded derangement across the angiogenic, haematological, coagulation, biochemical and uteroplacental-haemodynamic compartments, and early diagnosis with complex treatment consistently attenuated it. These findings support the view that generalised maternal endothelial dysfunction is the common downstream mechanism linking these abnormalities [3, 25, 29].

The angiogenic data were the most discriminating. The progressive fall in VEGF, TGF-β2 and EGF reflects impaired neoangiogenesis, disturbed immune–vascular regulation and defective tissue repair, while the rise in sFlt-1 and fall in PlGF capture the antiangiogenic shift that mechanistically underlies endothelial injury [10, 11, 20]. The composite sFlt-1/PlGF ratio separated severity strata more sharply than any single analyte, rising more than tenfold in untreated women—consistent with large international studies and meta-analyses that established the ratio's value for short-term prediction and rule-out of PE, and extending them by showing that its discriminatory power increases across gestation [8, 9, 12, 23].

The haematological and coagulation changes—anaemia, thrombocytopenia, leukocytosis, raised ESR and progressive hypercoagulability—are consistent with platelet consumption and endothelial activation and identify women at heightened risk of disseminated intravascular coagulation, in line with meta-analytic evidence that platelet count falls even before clinical onset [18]. The biochemical profile added organ-specific information: the marked CRP elevation confirmed a prominent inflammatory component, while LDH above 400 U/L together with rising creatinine flagged incipient haemolysis and renal impairment characteristic of severe disease and HELLP syndrome, mirroring recent prognostic series linking high LDH to adverse maternal and perinatal outcomes [19].

The imaging findings reinforced the circulating-marker data. Elevated first-trimester uterine-artery PI, RI and S/D—most marked on the left and asymmetric between sides—indicate the high impedance of inadequately remodelled spiral arteries and agree with large meta-analytic and reference-range studies of uterine-artery Doppler in PE prediction [16, 17]. The higher frequency of chorion oedema, retrochorial haematoma, sac deformation, reduced CRL and impaired yolk-sac regression provides converging morphological evidence of early defective placentation. The internally coherent correlation network linking angiogenic factors to platelet count, renal markers and Doppler indices underscores that these processes are interdependent facets of a single disorder [27, 28].

The principal clinical corollary is twofold. First, a compact multi-domain panel—anchored by the sFlt-1/PlGF ratio and first-trimester uterine-artery PI and supplemented by CRP, LDH, creatinine and platelet count—can grade severity and anticipate complications far earlier and more reliably than the classical triad [13, 25]. Second, the significantly milder profile of treated women indicates that early, structured intervention can bend the biochemical and haemodynamic trajectory of the disease, providing a mechanistic rationale consistent with first-trimester screening and early aspirin prophylaxis, which reduce preterm PE by more than half [14, 15].

Strengths and limitations

Strengths include the prospective, trimester-resolved design; the simultaneous assessment of five biomarker/imaging domains in one cohort; and a treated comparison group that isolates the effect of early intervention. Limitations include the single-centre design and modest sample size, which constrain generalisability; the observational allocation to treatment, which cannot fully exclude confounding; and the expression of sFlt-1 and PlGF in ng/mL, whereas international automated assays commonly report pg/mL—internal consistency was preserved but absolute values and the ratio's numeric scale should be interpreted with this in mind, and are not directly comparable to the Elecsys ≤38 cut-off. Future multicentre studies should define assay-specific, trimester-specific cut-offs, integrate Doppler with biochemical algorithms and evaluate hard clinical endpoints.

5. CONCLUSIONS

1. Pregnancies at risk of early-onset preeclampsia show a coordinated, severity-graded derangement of angiogenic, haematological, coagulation and biochemical biomarkers that deepens across gestation and is most pronounced in untreated

women.

2. The sFlt-1/PlGF ratio was the single most discriminating biomarker, rising 10.6-fold in untreated women by the third trimester, while VEGF, TGF-β2 and EGF declined and sFlt-1 rose in proportion to severity.

3. First-trimester uterine-artery Doppler (elevated, asymmetric PI, RI and S/D) and early ultrasound abnormalities identified high-risk pregnancies before clinical onset and correlated coherently with circulating angiogenic and laboratory markers.

4. Early diagnosis combined with complex treatment significantly attenuated abnormalities in every compartment, supporting an integrated, ratio- and Doppler-anchored first-trimester strategy for risk stratification, severity grading and treatment monitoring in preeclampsia.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional ethics committee of Bukhara State Medical Institute and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication

Written informed consent for publication of anonymised clinical and imaging data was obtained from the patients whose ultrasound images are shown.

Availability of data and materials

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Sh.U.S. conceived and designed the study, collected and analysed the data and drafted the manuscript. D.I.T. supervised the study, contributed to interpretation and critically revised the manuscript. T.B.T. contributed to histological/embryological interpretation and manuscript revision. All authors read and approved the final version.

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