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Original Article

Effects of enoxaparin sodium combined with magnesium sulfate on coagulation and pregnancy outcomes in early-onset preeclampsia with severe features: a retrospective cohort study

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Abstract: Objectives: To examine whether adding prophylactic-dose enoxaparin to magnesium sulfate is associated with coagulation and pregnancy outcomes in early-onset preeclampsia with severe features (EO-PE-SF) managed expectantly. Methods: Consecutive EO-PE-SF patients hospitalized from January 2021 to December 2023 who were eligible for expectant management with ≥5 days of observation and complete coagulation data were analyzed (n=200; 100 magnesium sulfate monotherapy, 100 combined therapy). Coagulation markers, angiogenic biomarkers, blood pressure, proteinuria, maternal and neonatal outcomes, and adverse events were compared using t-tests, Mann-Whitney U tests, chi-square or Fisher's exact tests, analysis of covariance, multivariable regression, and propensity score matching. Results: Combined therapy was associated with lower post-treatment D-dimer (276.25±91.65 vs. 347.89±80.20 μg/L fibrinogen-equivalent units, P<0.001), more favorable soluble fms-like tyrosine kinase-1/placental growth factor profiles, lower blood pressure and proteinuria, and longer gestation at delivery (33.47±2.36 vs. 32.28±2.25 weeks, P<0.001). Unadjusted neonatal intensive care unit admission was lower in the combined group (51.0% vs. 76.0%, P<0.001) but not after adjustment (odds ratio 1.15, 95% confidence interval 0.45-2.90, P=0.775). Magnesium-related adverse effects did not differ significantly (13.0% vs. 9.0%, P=0.499). Conclusions: In selected EO-PE-SF patients eligible for expectant management, combined prophylactic-dose enoxaparin and magnesium sulfate was associated with more favorable coagulation and angiogenic profiles and longer pregnancy prolongation. Randomized trials are needed before clinical practice changes.

Keywords: Early-onset preeclampsia, severe features, enoxaparin, magnesium sulfate, D-dimer, expectant management

Introduction

Preeclampsia with severe features complicating pregnancy before 34 weeks - often termed early-onset severe preeclampsia (ES-PE) - is linked to placental dysfunction, coagulation activation, and high rates of preterm delivery [1-4].

Magnesium sulfate remains standard for eclampsia prophylaxis, whereas the role of low-molecular-weight heparin (LMWH) after established severe preeclampsia remains off-label and controversial in many guidelines [3, 5-8]. Prior studies suggested that enoxaparin combined with magnesium sulfate may be associated with lower D-dimer and longer gestation [9-13], but most data are from small, non-randomized series.

We performed a retrospective cohort study comparing prophylactic-dose enoxaparin plus magnesium sulfate versus magnesium sulfate alone in EO-PE-SF patients who were clinically selected for expectant management.

Materials and methods

Study design and participants

This single-center retrospective cohort study included consecutive patients hospitalized for

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EO-PE-SF between January 2021 and December 2023. The study was approved by the Hainan General Hospital, Hainan Affiliated Hospital of Hainan Medical University institutional ethics committee (Ethics No. [2025]-365) with waiver of informed consent for de-identified chart review.

EO-PE-SF was defined as preeclampsia with onset before 34 weeks plus severe features per the American College of Obstetricians and Gynecologists (ACOG) criteria (blood pressure ≥160/110 mmHg and/or thrombocytopenia, elevated liver enzymes, renal dysfunction, pulmonary edema, or neurological symptoms) [3]. Because our center applies expectant management only to a subset of such patients, the analyzed cohort represents those eligible for prolonged inpatient observation rather than all EO-PE-SF admissions.

Inclusion criteria: (1) Age 18-40 years; (2) Singleton pregnancy; (3) EO-PE-SF with chart documentation of at least one ACOG severe feature verified during data abstraction; (4) Clinical decision for expectant management with magnesium sulfate for ≥5 days; (5) Complete coagulation data at T0 (within 24 h of admission) and T1 (days 5-7).

Exclusion criteria: chronic hypertension, pregestational diabetes, severe organ failure, primary coagulopathy, autoimmune disease, active bleeding, platelet count $<100\times10^9$/L or other institutional anticoagulation contraindications, heparin allergy or prior anticoagulation, major fetal anomalies, anticipated or actual delivery within 24 h of admission, or incomplete records.

Treatment exposure was defined at admission (T0): enoxaparin was initiated on the day of admission in the combined group, and group assignment was fixed at T0 rather than during follow-up, so that no immortal exposure window existed between admission and treatment initiation. The requirement of at least 5 days of expectant management was applied identically to both groups; patients who delivered or deteriorated within the first 5 days were therefore excluded from both arms.

Treatment protocols

Both groups received standard care including antihypertensive therapy, antenatal corticosteroids when indicated, and fetal surveillance per institutional protocols [14-16].

Magnesium sulfate was administered according to institutional protocols for seizure prophylaxis: an intravenous loading dose of 4-6 g over 20-30 minutes, followed by a continuous maintenance infusion of 1-2 g/h, adjusted by clinical status, renal function, urine output, and deep tendon reflex monitoring. Continuation during labor, cesarean delivery, and up to 24 h postpartum was determined by the treating team rather than a fixed pre-delivery stop rule.

Enoxaparin sodium was prescribed as once-daily prophylactic-dose subcutaneous therapy (4000 anti-factor Xa [anti-Xa] IU if body weight <50 kg; 4000-6000 IU if 50-70 kg; 6000 IU if >70 kg), intended for thromboprophylaxis rather than full therapeutic anticoagulation [9, 10, 17, 18]. During the study period, the decision to add enoxaparin was made by the treating team at admission for patients selected for expectant management who were considered at increased thrombotic risk - typically D-dimer elevation above the institutional pregnancy-specific reference range, anticipated prolonged hospitalization with reduced mobility, or suspected placental insufficiency with fetal growth restriction - provided that no contraindication to anticoagulation was present; the final decision was at the discretion of the attending physician after multidisciplinary evaluation. Enoxaparin was withheld ≥12 h before neuraxial anesthesia and ≥24 h before cesarean delivery per local policy. Anti-Xa monitoring was not routine.

Outcomes

Primary outcome: the change in coagulation parameters from T0 to T1, with the change in D-dimer prespecified as the primary endpoint. D-dimer was measured by immunoturbidimetric assay and reported as fibrinogen-equivalent units (FEU; μg/L).

Secondary outcomes: soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PLGF), and sFlt-1/PLGF ratio (measured on the institutional immunoassay platform with manufacturer reference intervals); blood pressure; 24-h proteinuria; gestational age at delivery; interval from treatment initiation to delivery; pregnancy prolongation ≥7 or ≥14 days; delivery before 34 weeks; delivery mode; pla-

cental weight; postpartum hemorrhage; birth weight; Apgar scores; small-for-gestational age (SGA; <10th percentile for gestational age); neonatal intensive care unit (NICU) admission; composite adverse perinatal outcome; and adverse events. All secondary outcomes were prespecified as exploratory.

NICU admission was defined as neonatal intensive care unit stay ≥24 h for monitoring or treatment, regardless of duration of respiratory support. The composite adverse perinatal outcome was defined as the occurrence of at least one of the following components: fetal distress, NICU admission, low birth weight (<2500 g), small for gestational age (<10th percentile for gestational age), or 5-min Apgar score <7; components were combined as a binary any-component composite. Magnesium-related adverse effects included hyporeflexia, respiratory depression, oliguria, or symptomatic hypermagnesemia prompting dose reduction; this definition was broader than severe magnesium toxicity.

Statistical analysis

All eligible consecutive patients during the study period were included (n=200; 100 per group). Analyses were performed using SPSS 26.0 and Python 3.11. Normality was assessed with the Shapiro-Wilk test. Continuous variables are presented as mean ± SD and compared using independent t-tests or Mann-Whitney U tests; paired within-group comparisons used Wilcoxon signed-rank tests. Categorical variables are presented as n (%) and compared using chi-square or Fisher's exact tests.

ANCOVA evaluated post-treatment D-dimer and fibrinogen adjusting for baseline values, age, body mass index (BMI), blood pressure, proteinuria, and platelet count. Gestational age at delivery was analyzed by multivariable linear regression. Binary outcomes were analyzed by multivariable logistic regression adjusting for age, BMI, gestational age at admission, blood pressure, proteinuria, platelet count, fibrinogen, D-dimer, antenatal corticosteroids, and suspected fetal growth restriction (FGR); NICU models additionally adjusted for gestational age at delivery, birth weight, and cesarean delivery. Preterm birth was not modeled because ES-PE onset before 34 weeks makes this endpoint unstable. One-to-one propensity score matching (PSM; caliper 0.2) was performed as a sensitivity analysis, yielding 95 matched pairs. Two-sided P<0.05 was considered significant. To limit inflation of type I error, formal hypothesis testing was restricted to the prespecified primary endpoint (change in D-dimer from T0 to T1); all other between-group comparisons were designated exploratory. Nominal *P* values are reported without formal multiplicity adjustment, and these results should be interpreted as hypothesis-generating rather than confirmatory.

Results

In this selected cohort of early-onset severe preeclampsia (ES-PE) patients eligible for expectant management, combined enoxaparin plus magnesium sulfate was associated with (1) greater post-treatment reduction in D-dimer (50.0% vs. 36.1% from baseline); (2) more favorable post-treatment soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PLGF) profiles; (3) lower post-treatment blood pressure and proteinuria; (4) longer gestation at delivery (mean difference 1.19 weeks); and (5) higher birth weight and 1-min Apgar scores. Neonatal intensive care unit (NICU) admission was lower in the combined group in unadjusted comparisons (76 (76.0%) vs. 51 (51.0%), P<0.001), but this association was not independent after adjustment for gestational age at delivery, birth weight, and other perinatal factors (adjusted odds ratio [OR] 1.15, 95% confidence interval [CI] 0.45-2.90, P=0.775). Magnesium-related adverse effects did not differ significantly (9 (9.0%) vs. 13 (13.0%), P=0.499); any apparent difference should not be interpreted as a pharmacologic effect of enoxaparin.

Patient flow and baseline characteristics

Of 312 hospitalized patients with early-onset preeclampsia with severe features, 112 were excluded because of emergency delivery within 24 h of admission (n=22), active bleeding or anticoagulation contraindications (n=18), incomplete coagulation records (n=48), chronic comorbidities (n=18), or other protocol violations (n=6). The remaining 200 patients met criteria for expectant management with at least 5 days of inpatient observation and com-

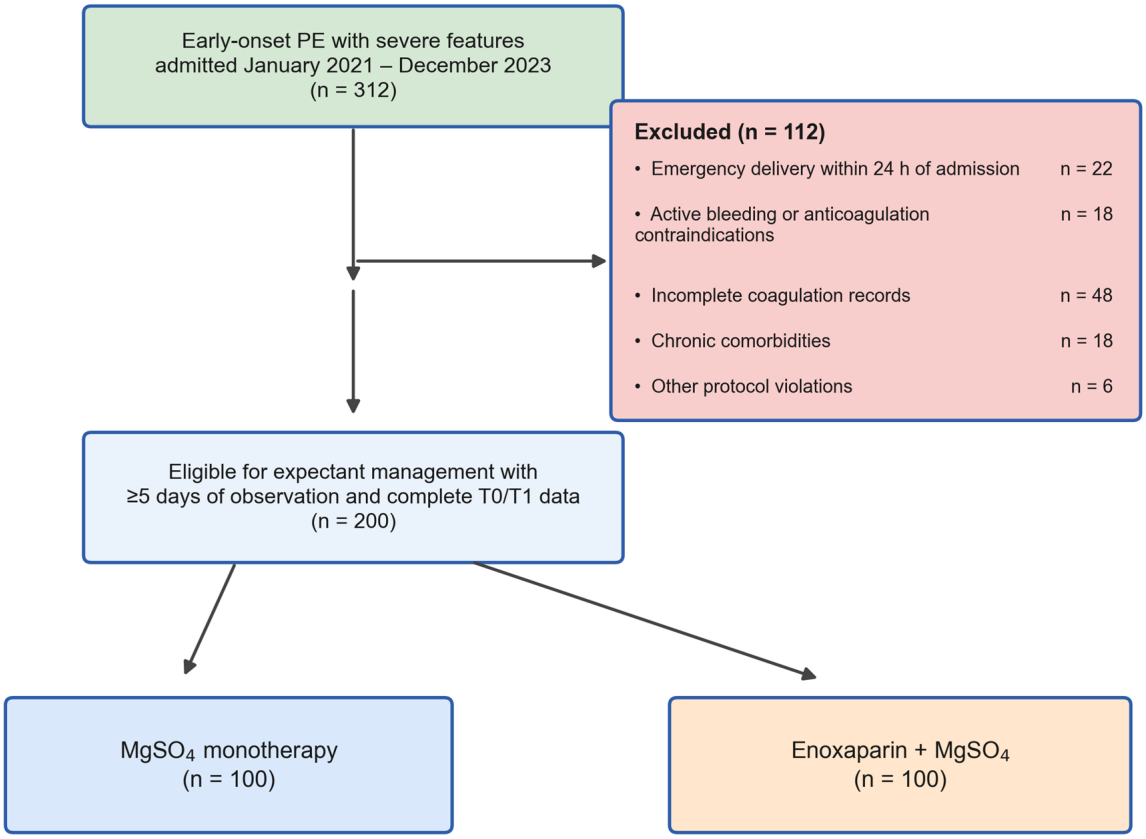


Figure 1. Patient selection flowchart. The exclusion box lists the five categories reported in Section 3.1: emergency delivery within 24 h of admission (n=22), active bleeding or anticoagulation contraindications (n=18), incomplete coagulation records (n=48), chronic comorbidities (n=18), and other protocol violations (n=6). Only patients eligible for expectant management with complete T0 and T1 data were included. T0, baseline within 24 h of admission; T1, days 5-7 of treatment.

plete T0/T1 coagulation data (100 monotherapy, 100 combined therapy; **Figure 1**).

This population therefore represents ES-PE patients selected for prolonged in utero management rather than the entire early-onset severe preeclampsia spectrum, and findings should not be extrapolated to patients requiring immediate delivery.

Baseline characteristics were largely comparable between groups (**Table 1**). Mean age, body mass index (BMI), gestational age at preeclampsia (PE) onset and admission, blood pressure, 24-h proteinuria, D-dimer, platelet count, and creatinine did not differ significantly. Aspartate aminotransferase (AST) at T0 was modestly higher in the monotherapy group (P=0.002); given the small absolute difference and multiple comparisons, this is unlikely to materially affect interpretation. Nulliparity, antenatal corticosteroid use, labetalol use, low-dose aspirin before admission, and suspected fetal growth restriction (FGR) were also balanced. All included patients had chart documentation of at least one American College of Obstetricians and Gynecologists (ACOG) severe feature at enrollment, verified during data abstraction.

Treatment exposure

Treatment exposure differed by design (**Table 2**). Both groups received magnesium sulfate according to institutional protocols, with total exposure duration determined by clinical status and delivery timing rather than a fixed stop point before delivery. The combined group additionally received weight-based prophylactic-dose enoxaparin once daily until held per institutional policy before neuraxial anesthesia or operative delivery.

Table 1. Baseline characteristics before treatment (T0)

Variable	MgSO4 monotherapy (n=100)	Enoxaparin+MgSO4 (n=100)	*P* value
Age (years)	29.15±3.03	29.33±3.00	0.675
Pre-pregnancy BMI (kg/m^2)	25.80±2.93	26.66±3.39	0.056
GA at PE onset (weeks)	30.26±2.01	29.74±1.98	0.063
GA at admission (weeks)	31.13±2.06	30.58±2.09	0.065
SBP at T0 (mmHg)	168.17±9.06	167.50±8.71	0.729
DBP at T0 (mmHg)	107.27±6.40	107.62±6.68	0.703
MAP at T0 (mmHg)	127.57±5.48	127.58±5.37	0.983
24-h proteinuria at T0 (g)	5.58±2.48	5.46±2.31	0.964
D-dimer at T0 (μg/L FEU)	544.82±72.74	552.15±76.50	0.488
PT at T0 (s)	11.21±1.03	11.10±0.84	0.58
APTT at T0 (s)	28.54±3.30	28.64±3.27	0.827
Fibrinogen at T0 (g/L)	5.14±0.73	5.14±0.86	0.993
Platelet count at T0 (×10^9/L)	167.82±35.24	171.18±36.49	0.509
Serum creatinine at T0 (μmol/L)	79.71±17.12	79.91±17.57	0.934
AST at T0 (U/L)	40.66±15.23	34.01±13.13	0.002
Nulliparity [n (%)]	34 (34.0%)	40 (40.0%)	0.464
Antenatal corticosteroids [n (%)]	70 (70.0%)	74 (74.0%)	0.637
Labetalol use at admission [n (%)]	83 (83.0%)	88 (88.0%)	0.422
Low-dose aspirin before admission [n (%)]	8 (8.0%)	8 (8.0%)	1.0
Suspected fetal growth restriction [n (%)]	28 (28.0%)	26 (26.0%)	0.874

Note: Data are mean ± SD or n (%). *P* values from independent-samples t test or Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables. BMI, body mass index; GA, gestational age; PE, preeclampsia; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PT, prothrombin time; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; FEU, fibrinogen-equivalent units.

Table 2. Treatment exposure during hospitalization

Variable	MgSO4 monotherapy (n=100)	Enoxaparin+MgSO4 (n=100)	*P* value
In-hospital expectant management (days)	7.48±1.64	7.43±1.68	0.798
Total magnesium sulfate exposure (days)	9.03±2.04	8.95±2.01	0.832
Enoxaparin treatment days	0.00±0.00	7.43±1.68	<0.001
Enoxaparin prophylactic dose (anti-Xa IU/day) [median (IQR)]	Not applicable	5000 (5000-6000)	-

Note: Data are mean ± SD unless otherwise indicated. IQR, interquartile range; anti-Xa, anti-factor Xa.

Coagulation parameters

Both groups showed significant within-group reductions in D-dimer and fibrinogen after 5-7 days of treatment (**Table 3**; **Figure 2**). Post-treatment D-dimer remained lower in the combined group (347.89±80.20 vs. 276.25± 91.65 μg/L FEU, P<0.001). Analysis of covariance (ANCOVA) adjusting for baseline D-dimer, age, BMI, blood pressure, proteinuria, and platelet count showed an independent group association of -78.3 μg/L FEU (P<0.001, R^2=0.729). A similar adjusted analysis for fibrinogen showed a group coefficient of -0.504 g/L (P<0.001).

Activated partial thromboplastin time (APTT) was modestly longer in the combined group (30.59±3.34 vs. 32.37±3.53 s, P=0.001), whereas prothrombin time (PT) did not differ significantly (11.48±1.05 vs. 11.40±0.87 s, P=0.544). These APTT/PT changes were statistically detectable but remained within normal reference ranges and are not interpreted as clinically meaningful anticoagulation by conventional coagulation tests. D-dimer and fibrin-

Table 3. Coagulation parameters before and after treatment

Marker	Group	Before treatment (T0)	After treatment (T1)	Within-group P	Between-group P at T1
D-dimer (μg/L FEU)	MgSO4 monotherapy	544.82±72.74	347.89±80.20	<0.001	<0.001
D-dimer (μg/L FEU)	Enoxaparin+MgSO4	552.15±76.50	276.25±91.65	<0.001	-
Fibrinogen (g/L)	MgSO4 monotherapy	5.14±0.73	4.57±0.81	<0.001	<0.001
Fibrinogen (g/L)	Enoxaparin+MgSO4	5.14±0.86	4.06±0.98	<0.001	-
APTT (s)	MgSO4 monotherapy	28.54±3.30	30.59±3.34	<0.001	0.001
APTT (s)	Enoxaparin+MgSO4	28.64±3.27	32.37±3.53	<0.001	-
PT (s)	MgSO4 monotherapy	11.21±1.03	11.48±1.05	<0.001	0.544
PT (s)	Enoxaparin+MgSO4	11.10±0.84	11.40±0.87	<0.001	-
TT (s)	MgSO4 monotherapy	16.78±1.51	17.04±1.57	<0.001	0.485
TT (s)	Enoxaparin+MgSO4	16.58±1.26	17.19±1.39	<0.001	-
INR	MgSO4 monotherapy	1.02±0.09	1.04±0.10	<0.001	0.543
INR	Enoxaparin+MgSO4	1.01±0.08	1.04±0.08	<0.001	-
Platelet count (×10^9/L)	MgSO4 monotherapy	167.82±35.24	174.42±35.89	<0.001	0.011
Platelet count (×10^9/L)	Enoxaparin+MgSO4	171.18±36.49	188.06±38.86	<0.001	-

Note: Data are mean ± SD. Within-group *P* values from Wilcoxon signed-rank tests; between-group *P* values at T1 from independent-samples t test or Mann-Whitney U test. D-dimer measured by immunoturbidimetric assay and reported as FEU. APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; INR, international normalized ratio; FEU, fibrinogen-equivalent units; T0, baseline within 24 h of admission; T1, days 5-7 of treatment.

ogen changes are considered the most clinically relevant coagulation findings.

Angiogenic biomarkers

Baseline soluble fms-like tyrosine kinase-1 (sFlt-1) at T0 differed slightly between groups (P=0.047). After treatment, sFlt-1 was lower (1374.76±192.02 vs. 1092.65±200.04 pg/mL, P<0.001), placental growth factor (PLGF) was higher (48.60±5.73 vs. 57.96±7.53 pg/mL, P<0.001), and the sFlt-1/PLGF ratio was lower (28.60±4.85 vs. 19.13±4.09, P<0.001) in the combined group (**Table 4**; **Figure 3**). Assays were performed on the same institutional platform; reference intervals were applied per manufacturer instructions. These biomarker shifts suggest a more favorable angiogenic profile after combined therapy, although causality cannot be inferred in this observational design.

Clinical parameters

After treatment, the combined group had lower systolic blood pressure (SBP; 154.88±10.78 vs. 150.61±9.43 mmHg, P=0.003), lower mean arterial pressure (MAP; 117.59±5.39 vs. 114.97±5.62 mmHg, P<0.001), and lower 24-h proteinuria (4.34±2.01 vs. 3.38±1.61 g/24 h, P<0.001; **Table 5**). Diastolic blood pressure (DBP) showed a similar trend (P=0.092).

Maternal and neonatal outcomes

Gestational age at delivery was higher in the combined group (32.28±2.25 vs. 33.47±2.36 weeks, P<0.001), corresponding to a mean prolongation of 1.19 weeks (8.3 days). Multivariable linear regression adjusting for baseline clinical factors showed an independent group association of +1.72 weeks (P<0.001). Pregnancy prolongation ≥7 days and ≥14 days, and delivery before 34 weeks, were more favorable in the combined group in adjusted models (**Table 8**; **Figure 4**). The distribution of gestational age at delivery showed a rightward shift in the combined group (**Figure 6**).

Birth weight (2012.97±372.58 vs. 2343.48±419.67 g, P<0.001) and the 1-min Apgar score (7.69±0.95 vs. 8.19±1.02; P=0.002) were higher in the combined group; 5-min Apgar scores did not differ significantly (P=0.302). Small-for-gestational-age (SGA; <10th percentile) rates were 26 (26.0%) vs. 26 (26.0%) (P=1.000). Low birth weight (<2500 g) was less common in the combined group (87 (87.0%) vs. 64 (64.0%), P<0.001). Other neonatal outcomes, including fetal distress and

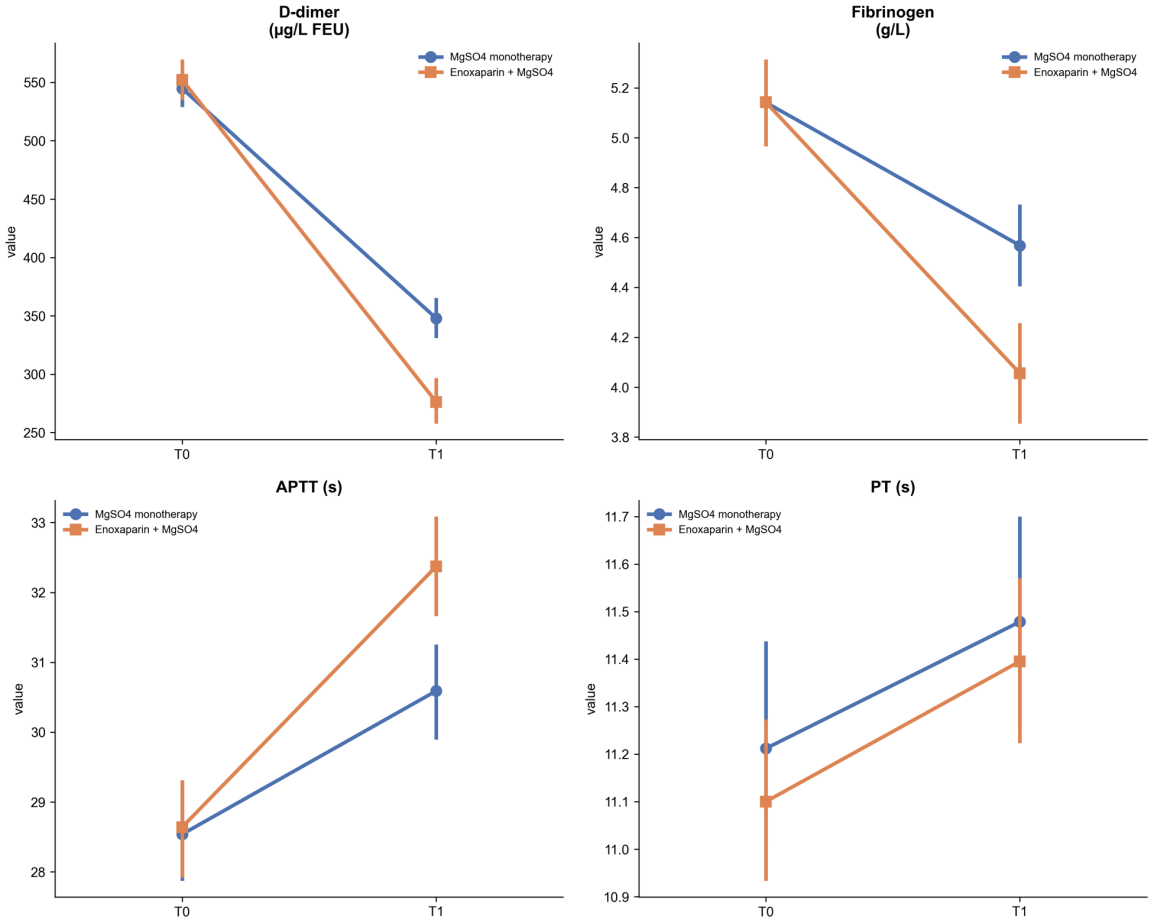


Figure 2. Coagulation parameter changes from T0 to T1. D-dimer reported as μg/L FEU by immunoturbidimetric assay. FEU, fibrinogen-equivalent units; APTT, activated partial thromboplastin time; PT, prothrombin time; T0, baseline; T1, days 5-7 of treatment.

Table 4. Angiogenic biomarkers

Marker	MgSO4 monotherapy	Enoxaparin+MgSO4	*P* value
sFlt-1 at T0 (pg/mL)	1527.68±171.76	1574.50±159.64	0.047
sFlt-1 at T1 (pg/mL)	1374.76±192.02	1092.65±200.04	<0.001
PLGF at T0 (pg/mL)	40.16±4.81	40.47±5.40	0.674
PLGF at T1 (pg/mL)	48.60±5.73	57.96±7.53	<0.001
sFlt-1/PLGF ratio at T0	38.55±6.23	39.54±6.29	0.196
sFlt-1/PLGF ratio at T1	28.60±4.85	19.13±4.09	<0.001

Note: Data are mean ± SD. *P* values from independent-samples t test or Mann-Whitney U test. sFlt-1, soluble fms-like tyrosine kinase-1; PLGF, placental growth factor; T0, baseline within 24 h of admission; T1, days 5-7 of treatment.

the composite adverse perinatal outcome (defined in Section 2.3), are summarized in **Table 7**. The high event rates of this composite (94.0% vs. 78.0%) reflect the inclusion of NICU admission and low birth weight as components in an early-onset severe preeclampsia cohort with predominantly preterm, low-birth-weight neonates.

NICU admission was recorded in 76 (76.0%) vs. 51 (51.0%) (P<0.001). Because NICU use is strongly influenced by gestational age at delivery, birth weight, and institutional admission policy, the adjusted OR was 1.15 (95% CI 0.45-2.90, P=0.775) and this outcome is interpreted descriptively rather than as an independent treatment effect. Placental weight

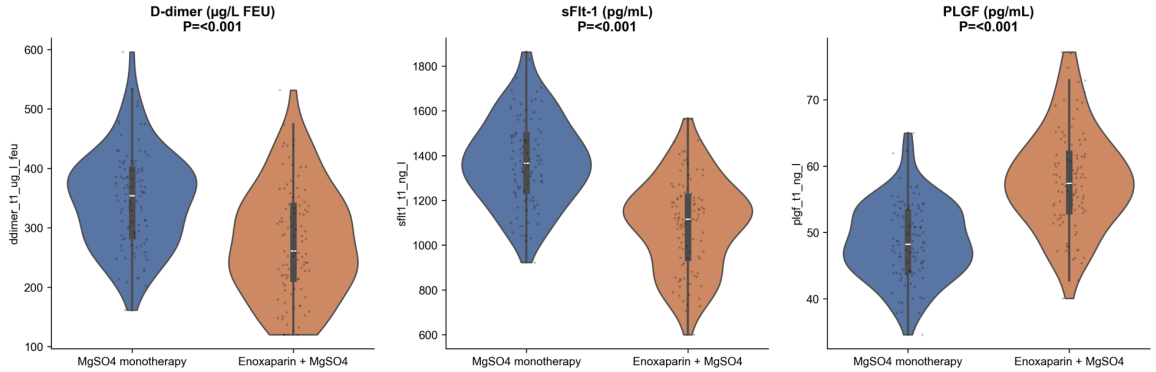


Figure 3. Post-treatment sFlt-1 and PLGF by treatment group. sFlt-1, soluble fms-like tyrosine kinase-1; PLGF, placental growth factor.

Table 5. Clinical parameters after treatment (T1)

Variable	MgSO4 monotherapy	Enoxaparin+MgSO4	*P* value
SBP at T1 (mmHg)	154.88±10.78	150.61±9.43	0.003
DBP at T1 (mmHg)	98.94±5.65	97.15±6.75	0.092
MAP at T1 (mmHg)	117.59±5.39	114.97±5.62	<0.001
24-h proteinuria at T1 (g)	4.34±2.01	3.38±1.61	<0.001
24-h urine output at T1 (mL)	1610.00±266.02	1761.37±283.13	<0.001

Note: Data are mean ± SD. *P* values from independent-samples t test or Mann-Whitney U test. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; T1, days 5-7 of treatment.

Table 6. Maternal outcomes

Variable	MgSO4 monotherapy (n=100)	Enoxaparin+MgSO4 (n=100)	*P* value
Gestational age at delivery (weeks)	32.28±2.25	33.47±2.36	<0.001
Interval from treatment to delivery (days)	8.94±6.06	19.73±7.55	<0.001
Placental weight (g)	389.06±48.03	419.64±53.61	<0.001
Pregnancy prolongation ≥7 days [n (%)]	53 (53.0%)	91 (91.0%)	<0.001
Pregnancy prolongation ≥14 days [n (%)]	22 (22.0%)	79 (79.0%)	<0.001
Delivery before 34 weeks [n (%)]	71 (71.0%)	55 (55.0%)	0.028
Cesarean delivery [n (%)]	88 (88.0%)	81 (81.0%)	0.241
Placental abruption [n (%)]	2 (2.0%)	5 (5.0%)	0.445
Postpartum hemorrhage [n (%)]	7 (7.0%)	4 (4.0%)	0.537

Note: Data are mean ± SD or n (%). *P* values from independent-samples t test or Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables.

was slightly greater in the combined group (389.06±48.03 vs. 419.64±53.61 g, P<0.001), consistent with longer gestation but also with placental insufficiency common in ES-PE. Cesarean delivery, placental abruption, and postpartum hemorrhage are shown in **Table 6**.

Spearman correlation analysis among post-treatment variables showed that D-dimer was inversely associated with gestational age at delivery and birth weight, and positively associated with the sFlt-1/PLGF ratio (**Figure 5**).

Adverse events

Enoxaparin injection-site bruising was recorded only in the combined group (**Table 9**; **Figure 7**). Intravenous (IV) cannulation-site bruising occurred in the monotherapy group. Clinically significant bleeding was infrequent and did

Table 7. Neonatal outcomes

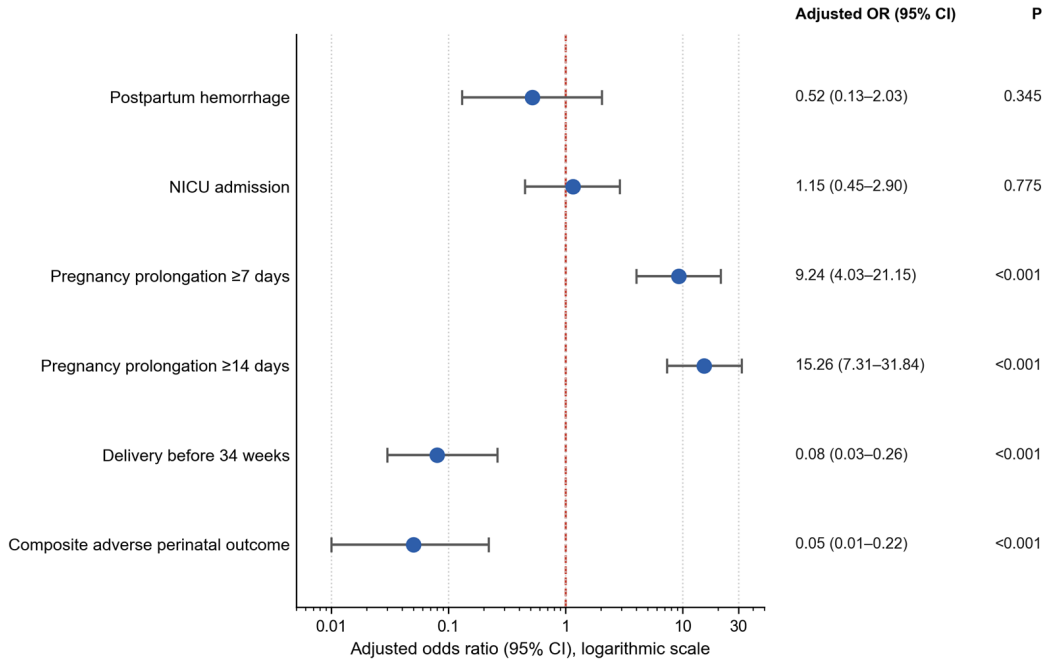
Variable	MgSO4 monotherapy (n=100)	Enoxaparin+MgSO4 (n=100)	*P* value
Birth weight (g)	2012.97±372.58	2343.48±419.67	<0.001
Birth length (cm)	39.98±2.92	41.89±2.90	<0.001
Apgar score at 1 min	7.69±0.95	8.19±1.02	0.002
Apgar score at 5 min	8.66±1.24	8.88±1.02	0.302
Fetal distress [n (%)]	25 (25.0%)	17 (17.0%)	0.224
NICU admission [n (%)]	76 (76.0%)	51 (51.0%)	<0.001
Low birth weight (<2500 g) [n (%)]	87 (87.0%)	64 (64.0%)	<0.001
Small for gestational age (<10th percentile) [n (%)]	26 (26.0%)	26 (26.0%)	1.000
Composite adverse perinatal outcome [n (%)]	94 (94.0%)	78 (78.0%)	0.002

Note: Data are mean ± SD or n (%). *P* values from independent-samples t test or Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables. NICU, neonatal intensive care unit. The composite adverse perinatal outcome was defined as the occurrence of at least one of: fetal distress, NICU admission, low birth weight (<2500 g), small for gestational age (<10th percentile for gestational age), or 5-min Apgar score <7.

Table 8. Multivariable regression models

Outcome	Adjusted OR	95% CI	*P* value	Covariates
Postpartum hemorrhage	0.52	0.13-2.03	0.345	Baseline clinical model
NICU admission	1.15	0.45-2.90	0.775	Extended model
Pregnancy prolongation ≥7 days	9.24	4.03-21.15	<0.001	Baseline clinical model
Pregnancy prolongation ≥14 days	15.26	7.31-31.84	<0.001	Baseline clinical model
Delivery before 34 weeks	0.08	0.03-0.26	<0.001	Baseline clinical model
Composite adverse perinatal outcome	0.05	0.01-0.22	<0.001	Baseline clinical model

Note: OR, odds ratio; CI, confidence interval; NICU, neonatal intensive care unit. The baseline clinical model was adjusted for age, body mass index, gestational age at admission, blood pressure, proteinuria, platelet count, fibrinogen, D-dimer, antenatal corticosteroids, and suspected fetal growth restriction; the extended model additionally adjusted for gestational age at delivery, birth weight, and cesarean delivery. Estimates from multivariable logistic regression.



Dashed line: OR = 1. NICU admission used the extended model (additionally adjusted for gestational age at delivery, birth weight, and cesarean delivery); all other outcomes used the baseline clinical model (Table 8).

Figure 4. Forest plot of all six multivariable models reported in **Table 8**. Point estimates are adjusted odds ratios with 95% confidence intervals on a logarithmic scale; the dashed vertical line indicates OR=1. Numeric estimates and *P* values are shown at right. The NICU model used the extended covariate set; all other models used the baseline clinical model. OR, odds ratio; CI, confidence interval; NICU, neonatal intensive care unit.

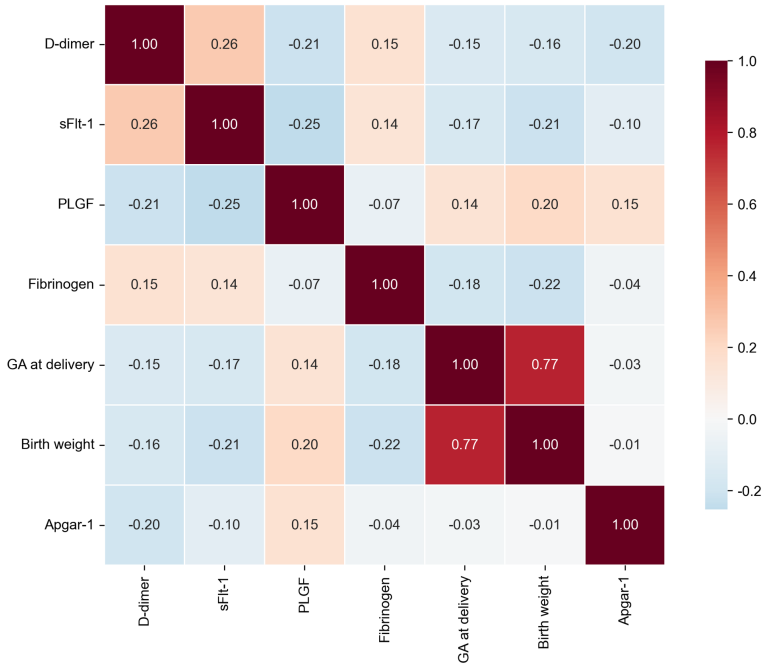


Figure 5. Spearman correlation among post-treatment variables. sFlt-1/PLGF, soluble fms-like tyrosine kinase-1/placental growth factor.

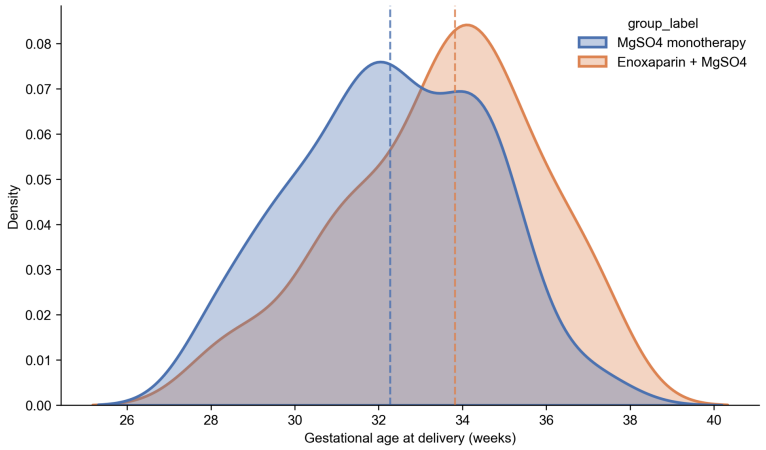


Figure 6. Distribution of gestational age at delivery.

not differ significantly (2 (2.0%) vs. 3 (3.0%), P=1.000); the numerically higher bleeding rate in the anticoagulated group is biologically plausible and warrants continued surveillance.

Magnesium-related adverse effects - defined as hyporeflexia, respiratory depression, oliguria, or symptomatic hypermagnesemia prompting dose reduction - did not differ significantly between groups (9 (9.0%) vs. 13 (13.0%), P= 0.499). Enoxaparin is not expected to modulate magnesium toxicity; any recorded differences likely reflect monitoring intensity, renal function, magnesium exposure, or selection bias.

Sensitivity analysis

After 1:1 propensity score matching (PSM) on baseline age, BMI, gestational age at admission, blood pressure, proteinuria, platelet count, fibrinogen, D-dimer, and suspected FGR, 95 matched pairs were retained (five combined-therapy patients were unmatched). Group differences in post-treatment D-dimer and gestational age at delivery persisted (Supplementary Table 1). Unadjusted NICU rates remained lower in the combined group in the matched sample (72/95 vs. 49/95), but this sensitivity analysis did not include full perinatal covariate adjustment and should not be interpreted as an independent treatment effect on NICU use. Residual confounding by unmeasured clinical judgment cannot be excluded.

Discussion

In this retrospective cohort of 200 EO-PE-SF patients selected for expectant management, the combination of prophylactic-dose enoxaparin and magnesium sulfate was associated with more favorable post-treatment coagulation and angiogenic profiles and with longer gestation at delivery compared with magne-

Table 9. Adverse events

Adverse event	MgSO4 monotherapy	Enoxaparin+MgSO4	*P* value
Enoxaparin injection-site bruising	Not applicable	7 (7.0%)	-
IV cannulation-site bruising	2 (2.0%)	-	-
Clinically significant bleeding	2 (2.0%)	3 (3.0%)	1.000
Thrombocytopenia (PLT <100×10^9/L during treatment)	1 (1.0%)	0 (0.0%)	1.000
Liver dysfunction	11 (11.0%)	6 (6.0%)	0.311
Allergic reaction	1 (1.0%)	0 (0.0%)	1.000
Magnesium-related adverse effects	9 (9.0%)	13 (13.0%)	0.499
Any adverse event	23 (23.0%)	25 (25.0%)	0.869

Note: Data are n (%). *P* values from chi-square or Fisher's exact test. IV, intravenous; PLT, platelet count.

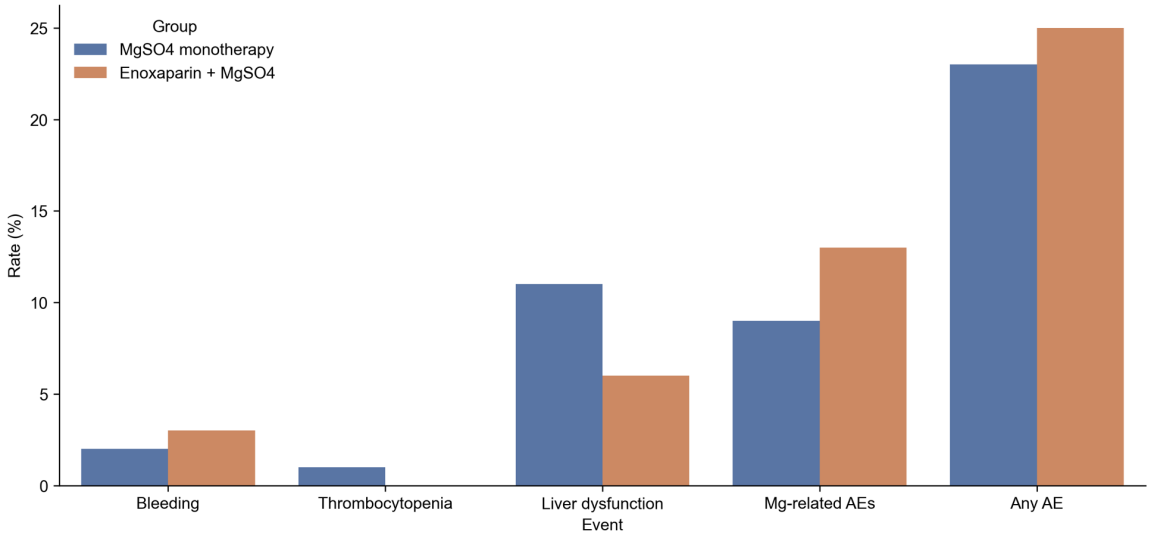


Figure 7. Selected adverse event rates. IV, intravenous.

sium sulfate alone. These observations are hypothesis-generating and consistent with prior non-randomized reports [9-11], but causality cannot be established.

Hypercoagulability is common in severe preeclampsia [17-19]. The greater D-dimer decline in the combined group persisted after ANCOVA (coefficient -78.3 μg/L FEU, P<0.001). APTT and PT changes were statistically detectable but remained within normal ranges; LMWH primarily affects anti-Xa activity, so conventional coagulation tests should not be over-interpreted [20-23].

More favorable sFlt-1/PLGF profiles after combined therapy may reflect an association rather than direct restoration of placental angiogenesis [24, 25]. Improved laboratory markers do not prove improved placental perfusion.

Longer gestation and higher birth weight in the combined group are clinically important but may be partially mediated by successful expectant management rather than drug effect alone. Multivariable analysis suggested an independent association with gestational age at delivery (+1.72 weeks, P<0.001). Placental weights in both groups were within the lower range expected for 32-34 weeks and are consistent with placental insufficiency common in ES-PE, despite modestly higher values in the combined group reflecting longer gestation. NICU admission was lower in unadjusted comparisons (76 (76.0%) vs. 51 (51.0%)), but not after adjustment for delivery gestational age and birth weight (OR 1.15, 95% CI 0.45-2.90). We therefore avoid attributing NICU reduction directly to enoxaparin.

Enoxaparin in established severe preeclampsia remains off-label in many guidelines; our find-

ings should be considered exploratory [5, 6, 26, 27]. Early-onset preeclampsia is associated with a substantially higher burden of adverse maternal and neonatal outcomes than late-onset disease [28], which likely contributes to the high absolute event rates observed in this cohort. Moreover, most of the supportive evidence for low-molecular-weight heparin in preeclampsia derives from prophylaxis combined with low-dose aspirin in at-risk women [29] rather than from treatment of established severe disease. Bleeding was infrequent; the direction of association (slightly higher in the combined group) is pharmacologically plausible and should be monitored in future trials.

Magnesium-related adverse effects did not differ significantly between groups (P=0.499). Enoxaparin is not expected to reduce magnesium toxicity; recorded events may reflect documentation, monitoring, renal function, magnesium exposure, or selection bias and should not be interpreted as a treatment benefit.

Major limitations of this study include single-center retrospective design, non-randomized treatment allocation, confounding by indication (clinicians may preferentially add enoxaparin when prolongation appears feasible), potential immortal time bias related to the ≥5-day inclusion criterion, lack of anti-Xa monitoring, absence of long-term follow-up, and the large number of exploratory comparisons without formal multiplicity adjustment. To mitigate immortal time bias, treatment exposure was classified at admission (T0) and the ≥5-day expectant-management requirement was applied identically to both groups; nevertheless, patients who delivered or deteriorated within the first 5 days were excluded from both arms, so the cohort represents a selected population and residual bias cannot be excluded. The inclusion strategy excludes the sickest patients requiring immediate delivery, limiting generalizability. Propensity score matching attenuated but did not eliminate these concerns.

Conclusions

Among selected EO-PE-SF patients eligible for expectant management, enoxaparin sodium combined with magnesium sulfate was associated with more favorable coagulation and angiogenic profiles and with greater prolongation of pregnancy compared with magnesium sulfate monotherapy. Perinatal associations may be mediated in part by gestational age at delivery. Multicenter randomized trials are required before changing clinical practice.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Propensity score-matched sensitivity analysis (95 pairs)

Outcome	MgSO4 monotherapy (n=95)	Enoxaparin+MgSO4 (n=95)	*P* value
D-dimer at T1 (μg/L FEU)	348.71±81.15	272.92±90.38	<0.001
GA at delivery (weeks)	32.19±2.17	33.40±2.34	<0.001
NICU admission	72/95	49/95	<0.001

Note: Data are mean ± SD or n/N. *P* values from independent-samples t test or Mann-Whitney U test for continuous variables and chi-square test for categorical variables in the propensity score-matched sample. The matched sample comprised 95 pairs (five combined-therapy patients were unmatched at caliper 0.2). D-dimer at T1 and gestational age at delivery were complete in all 95 pairs; NICU admission is therefore reported with denominators of 95 per group. FEU, fibrinogen-equivalent units; GA, gestational age; NICU, neonatal intensive care unit.