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Case Report

Reversion of Fetal Subcutaneous Edema in the First Trimester After Optimization of Anticoagulation in a Pregnant Woman with Thrombophilia: A Case Report

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Received: January 26, 2026; **Published:** March 20, 2026

Abstract

Context: Generalized fetal subcutaneous edema detected in the first trimester of pregnancy represents an ultrasonographic finding of uncertain prognostic significance, traditionally associated with aneuploidies and congenital infections. The literature lacks descriptions of its occurrence in the context of maternal thrombophilia and, especially, the possibility of its reversion through therapeutic intervention.

Objective: To report a case of generalized fetal edema in a pregnant woman with mixed thrombophilia that showed complete regression after adjustment of the enoxaparin dose.

Case Report: A 33-year-old secundigravida, with a history of intrauterine fetal death at 33 weeks and a diagnosis of gestational antiphospholipid syndrome associated with PAI-1 (4G/4G) and MTHFR (C677T heterozygote) gene polymorphisms, started enoxaparin 80 mg/day in the current pregnancy. At 10 weeks and 4 days, ultrasound revealed diffuse fetal subcutaneous edema and tachycardia (185 bpm). Serologies for congenital infections were negative. The enoxaparin dose was increased to 140 mg/day. Ultrasound control after 14 days showed complete disappearance of the edema and normalization of the fetal heart rate (152 bpm).

Conclusion: The case suggests that early fetal edema in thrombophilic pregnant women may be a manifestation of placental hypoperfusion due to insufficient anticoagulation, being potentially reversible with therapeutic optimization.

Keywords: *Thrombophilia; Fetal Edema; Double Contour; Enoxaparin; Low Molecular Weight Heparin; Placental Insufficiency; High-Risk Pregnancy; Antiphospholipid Syndrome*

Introduction

The first trimester of pregnancy is a critical period for embryonic development and the establishment of the uteroplacental circulation. In this phase, the identification of fetal morphological changes by ultrasound plays a fundamental role in screening for anomalies and defining the gestational prognosis.

Fetal subcutaneous edema, characterized by the accumulation of fluid in the subcutaneous cellular tissue and often described as a "double contour" on ultrasound, is a finding that raises immediate concern. When generalized, it is classically associated with conditions of high morbidity, including chromosomal abnormalities-notably trisomies 21, 18, and 13-structural heart malformations, genetic syndromes, and TORCH complex infections (toxoplasmosis, rubella, cytomegalovirus, herpes, and others) [1,2].

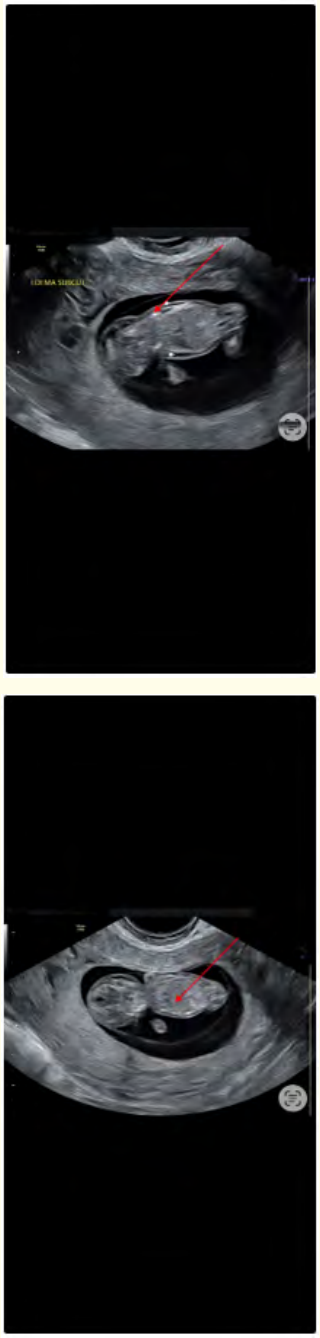

Figure Illustrative 1: *Schematic representation of fetal subcutaneous edema ("double contour"), a warning sign for placental insufficiency.*

Jenewein and colleagues, in a retrospective study published in 2013, evaluated 237 fetuses with increased nuchal translucency in the first trimester and identified generalized cutaneous edema in 17.3% of cases. The presence of this finding strongly correlated with aneuploidy (61% versus 10.2% in fetuses without edema) and with structural malformations in euploid fetuses (43.8% versus 9.1%) [1]. These data consolidated the perception of early fetal edema as a marker of guarded prognosis.

However, the etiology of edema does not always fit into the traditional categories. In a portion of cases, genetic and infectious investigations are negative, leaving the clinician facing a diagnostic dilemma. It is in this context that maternal thrombophilia emerges as a possible etiological factor, although little explored in the literature.

Thrombophilia's-hereditary or acquired-constitute hypercoagulable states that predispose to thrombus formation. During pregnancy, a naturally prothrombotic period due to physiological changes in hemostasis, the presence of thrombophilia amplifies the risk of adverse events [3]. The deposition of fibrin and the formation of microthrombi in the placental villous vessels compromise uteroplacental perfusion, which can result in a spectrum of complications including recurrent miscarriage, fetal growth restriction, pre-eclampsia, placental abruption, and fetal death [4,5].

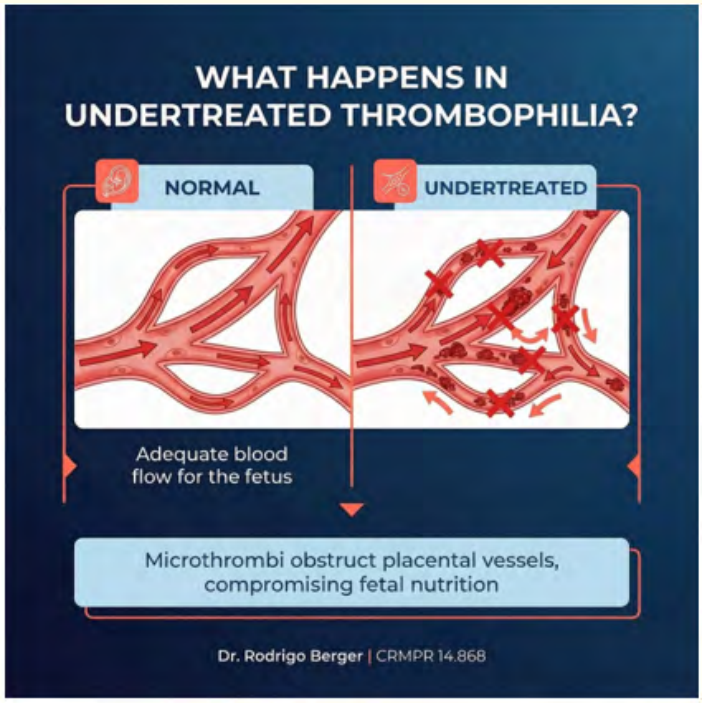

Figure Illustrative 2: *Comparison between normal placental circulation and circulation compromised by microthrombi in undertreated thrombophilia. Microthrombi obstruct placental vessels, compromising fetal nutrition.*

Antiphospholipid Syndrome (APS) deserves particular mention. Characterized by the presence of antiphospholipid antibodies-lupus anticoagulant, anticardiolipin, and anti-beta2-glycoprotein I-associated with thrombotic events or gestational morbidity, APS is among the most important treatable causes of recurrent pregnancy loss [6]. The pathophysiological mechanisms involve not only thrombosis but also direct effects of the antibodies on the trophoblast, interfering with placental invasion and angiogenesis [7].

Genetic polymorphisms associated with thrombophilia, such as variants of the PAI-1 gene (plasminogen activator inhibitor type 1) and the MTHFR enzyme (methylenetetrahydrofolate reductase), further contribute to the prothrombotic state. The 4G/4G genotype of PAI-1 is associated with elevated inhibitor levels, resulting in hypofibrinolysis [8]. The C677T variant of MTHFR, in turn, is related to hyperhomocysteinemia, an independent risk factor for thrombosis [9].

The treatment of pregnant women with thrombophilia is fundamentally based on anticoagulation with low molecular weight heparin (LMWH), with enoxaparin being the most commonly used agent. The definition of the appropriate dose-prophylactic, intermediate, or therapeutic-remains controversial and must consider the patient's individual risk profile [10]. Underdosing exposes the pregnant woman and the fetus to the risks of placental thrombosis; overdosing, to hemorrhagic risks.

Although the literature widely documents the late adverse outcomes of gestational thrombophilia, there is a scarcity of reports on early manifestations of thrombotic placental dysfunction and, especially, on its potential reversibility. We present a case in which generalized fetal edema, detected in the first trimester, completely regressed after adjustment of the enoxaparin dose, suggesting a causal relationship between insufficient anticoagulation and the ultrasonographic finding.

Case Report

History and background

This is a 33-year-old female patient, secundigravida, with a body mass index in the overweight range (weight of 96 kg), referred to our service for specialized prenatal care due to an adverse obstetric history and a diagnosis of thrombophilia.

In the previous pregnancy, the patient had progressed without apparent complications until the third trimester, when, at 33 weeks of gestation, intrauterine fetal death was confirmed. The subsequent etiological investigation, including placental anatomopathological study and a laboratory panel for thrombophilia's, revealed findings compatible with mixed thrombophilia.

The patient's thrombophilic profile was characterized by:

Alteration	Classification	Clinical Significance
Elevated IgM anticardiolipin antibodies	Acquired	Gestational Antiphospholipid Syndrome
PAI-1 4G/4G Polymorphism	Hereditary	Hypofibrinolysis, increased thrombotic risk
MTHFR C677T heterozygote Polymorphism	Hereditary	Risk of hyperhomocysteinemia

Table 1

The combination of acquired thrombophilia (gestational APS) and hereditary thrombophilia (genetic polymorphisms), associated with the history of late fetal loss, configured an extremely high-risk profile for the subsequent pregnancy.

Current pregnancy - Initial management

In the index pregnancy, antithrombotic prophylaxis was started early, as soon as embryonic viability was confirmed. The initial therapeutic regimen consisted of:

- Enoxaparin: 80 mg subcutaneously, once daily.
- Acetylsalicylic acid: 100 mg orally, once daily.
- Folic acid: 5 mg orally, once daily.

The enoxaparin dose corresponded to approximately 0.83 mg/kg/day, placing it in the high prophylactic or intermediate range, according to the different classifications found in the literature.

Ultrasound finding - 10 weeks and 4 days

The obstetric ultrasound performed at 10 weeks and 4 days of gestation, via transvaginal and abdominal routes, revealed unexpected findings that motivated a reevaluation of the therapeutic management.

The examination showed the presence of generalized subcutaneous cellular tissue edema, predominantly affecting the cephalic pole and the fetal trunk. The ultrasonographic appearance was characteristic of the so-called "double contour," with a hyperechoic line corresponding to the fetal skin separated from the underlying tissues by a hypoechoic band representing the interstitial fluid accumulation.

Concomitantly, fetal tachycardia was observed, with a heart rate of 185 beats per minute-above the upper limit of normality for the gestational age. Fetal biometry, represented by the crown-rump length (CRL) of 43.5 mm, was compatible with the gestational age calculated by the last menstrual period.

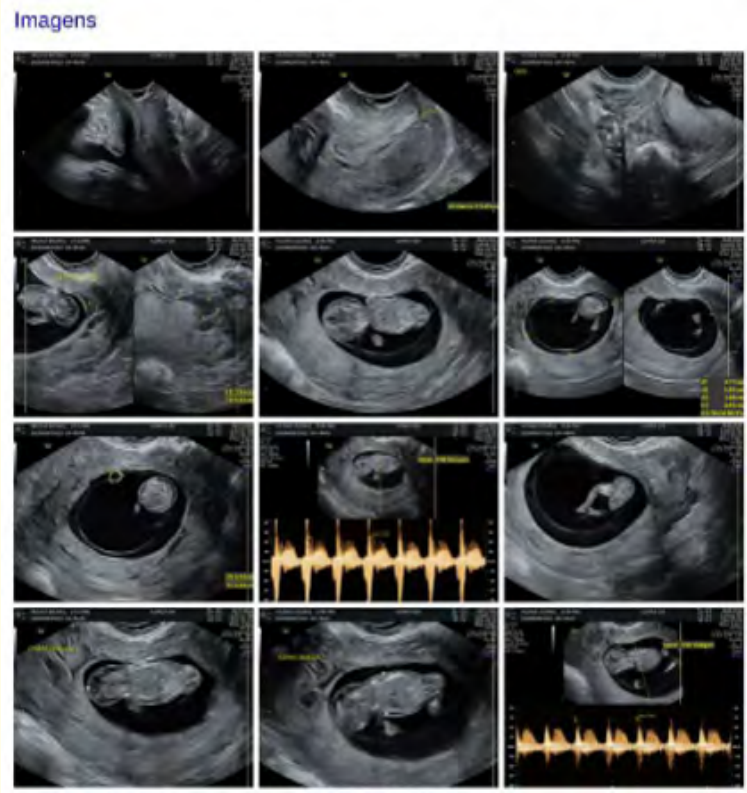

Figure 1A: *Obstetric ultrasound demonstrating generalized fetal subcutaneous edema ("double contour"). The markings indicate fluid accumulation in the subcutaneous cellular tissue. Fetal heart rate of 185 bpm. Examination performed while on enoxaparin 80 mg/day (10 weeks and 4 days).*

Complementary evaluation

Parameter	Value	Interpretation
CRL	43.5 mm	Adequate (83rd percentile)
Parameter	Value	Interpretation
FHR	185 bpm	Mild Tachycardia
Mean uterine artery PI	1.41	Borderline
Yolk sac	4.9 mm	Normal
Cervical length	34 mm	Normal

Table 2

Additionally, an image suggestive of a small subchorionic hematoma was identified, measuring approximately 19 x 8 mm, covering less than 10% of the gestational sac surface.

Diagnostic investigation

Given the finding of generalized fetal edema, a systematic investigation of the most frequent etiologies was performed.

Serological screening for congenital infections:

Examination	Result	Interpretation
Toxoplasmosis IgG	0.2 IU/mL	Non-reactive
Toxoplasmosis IgM	0.04	Non-reactive
Rubella IgG	19.8 IU/mL	Reactive (previous immunity)
Rubella IgM	0.04	Non-reactive
Hepatitis B (HBsAg)	0.49	Non-reactive
Epstein-Barr virus IgG	23.77 S/CO	Reactive (past infection)

Table 3

The results ruled out the possibility of acute infection as the cause of the fetal edema. The patient had immunity to rubella and evidence of previous contact with the Epstein-Barr virus, both without pathological significance in the current context.

Excluding infectious causes and considering the patient's high-risk thrombophilic profile, the hypothesis was raised that the edema resulted from early compromise of the placental circulation due to insufficient anticoagulation.

Therapeutic intervention

It was decided to escalate the anticoagulation to a full therapeutic dose. The new dosage regimen consisted of: Enoxaparin: 80 mg in the morning + 60 mg at night (total: 140 mg/day).

This dose corresponded to approximately 1.46 mg/kg/day, within the therapeutic range recommended for the treatment of thromboembolic events (1.0 to 1.5 mg/kg every 12 hours or 1.5 mg/kg once daily).

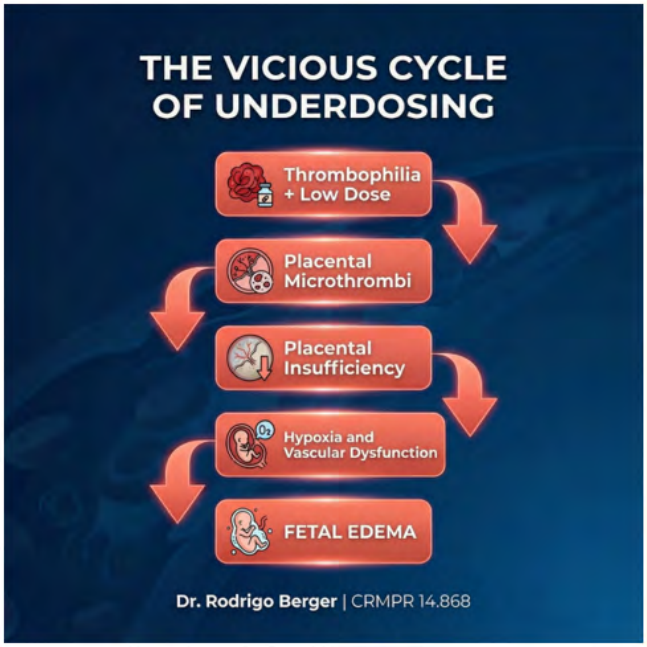

Figure Illustrative 3: *The vicious cycle of anticoagulant underdosing in gestational thrombophilia. Insufficient dose allows the formation of placental microthrombi, leading to placental insufficiency, fetal hypoxia, and consequently, edema.*

The decision was based on the reasoning that the patient, who had gestational APS with multiple associated polymorphisms, would require more intense anticoagulation to maintain placental vascular patency. The history of late fetal death reinforced the need for a more aggressive approach.

Figure Illustrative 4: *Schematic representation of fetal edema reversion after enoxaparin dose adjustment. Increased anticoagulation can reverse the placental insufficiency.*

Evolution - Ultrasound control at 12 weeks and 4 days

The control examination was performed 14 days after the dosage adjustment, at 12 weeks and 4 days of gestation. The findings were remarkable.

The fetal subcutaneous edema had completely disappeared. The subcutaneous cellular tissue had a normal thickness, with no evidence of interstitial fluid accumulation. The "double contour" appearance was no longer identifiable.

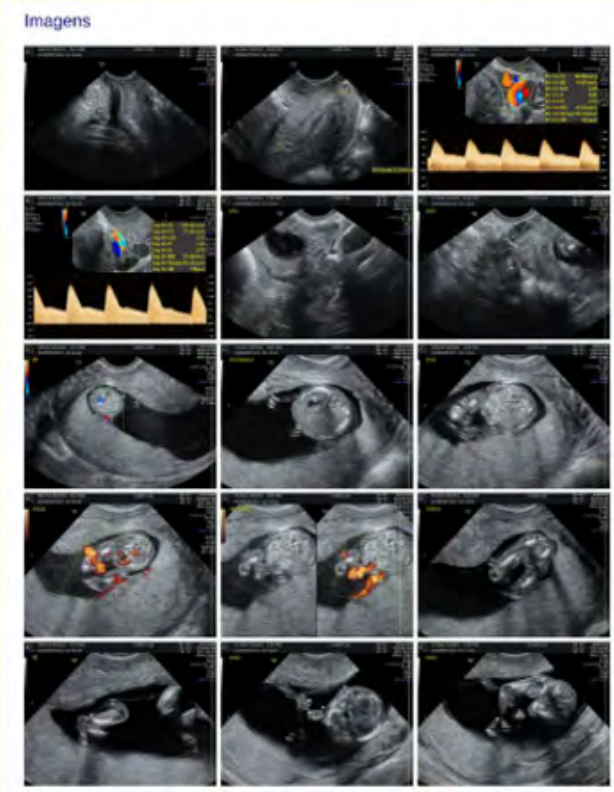

Figure 1B: *Ultrasound control 14 days after increasing the enoxaparin dose to 140 mg/day.*

Complete absence of subcutaneous edema is observed, with normal thickness of the subcutaneous cellular tissue. Fetal heart rate normalized (152 bpm). First-trimester morphological assessment without changes (12 weeks and 4 days).

Normalization of fetal parameters

The fetal heart rate had normalized to 152 beats per minute, within the expected range for the second trimester. The mean pulsatility index of the uterine arteries showed a reduction, placing it at the 10th percentile-suggestive of adequate placentation.

The fetal morphology assessed in the first-trimester screening showed no changes. Nuchal translucency measured 1.4 mm (31st percentile), the nasal bone was present, and tricuspid flow was normal. The risk calculations for aneuploidies, according to the Fetal Medicine Foundation algorithm, were low.

Parameter	Before (10w4d)	After (12w4d)	Evolution
Subcutaneous Edema	Present (generalized)	Absent	Complete Resolution
FHR	185 bpm	152 bpm	Normalization
Mean uterine artery PI	1.41	1.19	Improvement
NT	—	1.4 mm (p31)	Normal
Cervical length	34 mm	36 mm	Stable

Table 4

The pregnancy proceeded without additional complications, with the patient maintaining the therapeutic dose anticoagulation regimen. Serial ultrasound monitoring confirmed adequate fetal growth and normal Doppler throughout the pregnancy.

Discussion

Temporal correlation and biological plausibility

The temporal correlation between the anticoagulation adjustment and the regression of fetal edema in this case is remarkable and difficult to attribute to chance. The interval of only two weeks between the therapeutic intervention and the complete resolution of the finding strongly suggests a cause-and-effect relationship.

The biological plausibility of this association is based on current knowledge about the pathophysiology of gestational thrombophilia. The formation of microthrombi in the placental villous vessels compromises the perfusion of the intervillous space, reducing the supply of oxygen and nutrients to the fetus. The resulting tissue hypoxia triggers a cascade of events that includes endothelial dysfunction, release of inflammatory mediators, and increased capillary permeability [11].

The generalized edema observed can be interpreted as a manifestation of this systemic endothelial dysfunction in the fetus. The extravasation of fluid into the interstitium, particularly evident in the loose subcutaneous cellular tissue, results in the characteristic ultrasonographic appearance. The concomitant tachycardia probably represents a compensatory mechanism in the face of reduced oxygen supply-the fetal heart increases its rate in an attempt to maintain cardiac output and tissue perfusion.

Enoxaparin underdosing: An underestimated problem?

The initial enoxaparin dose in this case-80 mg/day for a 96 kg patient-corresponded to 0.83 mg/kg/day. Although this dose is frequently used in clinical practice and appears in several protocols as "high-risk prophylaxis," it may be insufficient for patients with a high thrombophilic burden.

The literature shows that the pharmacokinetics of enoxaparin undergo significant changes during pregnancy. The increase in distribution volume, glomerular filtration rate, and coagulation factor activity results in a reduction in plasma levels of the drug and its anti-Xa activity [12]. These phenomena are particularly pronounced in obese patients, where drug distribution is even more unpredictable.

Barbour and colleagues demonstrated that pregnant women receiving fixed doses of enoxaparin often do not reach therapeutic anti-Xa levels, especially in the third trimester [13]. Although our case refers to the first trimester, it is reasonable to assume that the patient, with her high-risk profile and high weight, needed more robust doses from the beginning.

The increase to 140 mg/day (1.46 mg/kg/day), divided into two applications, placed the patient within the full therapeutic range. The clinical response-resolution of edema and normalization of fetal parameters-corroborates the hypothesis that the previous dose was, in fact, insufficient.

Figure Illustrative 5: *How the adequate enoxaparin dose restores fetal health: antithrombotic action (Factor Xa inhibition), improved placental perfusion, resolution of fetal hypoxia, and vascular normalization with reabsorption of edema.*

Proposed mechanism for edema reversion

Based on the findings of this case and the available pathophysiological knowledge, we propose the following mechanism to explain the reversion of fetal edema:

1. Baseline state: Patient with high-risk mixed thrombophilia, using enoxaparin at a subtherapeutic dose.
2. Microthrombi formation: Insufficient anticoagulation allows the deposition of fibrin and the formation of small thrombi in the placental villous vessels.
3. Placental hypoperfusion: Microthrombi partially obstruct blood flow in the intervillous space, compromising maternal-fetal exchange.
4. Fetal hypoxia: The reduction in oxygen supply to the fetus triggers an adaptive response, including compensatory tachycardia.
5. Endothelial dysfunction: Hypoxia induces endothelial injury and the release of inflammatory mediators, increasing capillary permeability.
6. Generalized edema: The extravasation of fluid into the interstitium manifests as subcutaneous cellular tissue edema.
7. Intervention: Increase in the enoxaparin dose to therapeutic levels.
8. Restoration of vascular patency: Effective anticoagulation prevents the formation of new thrombi and may facilitate the lysis of existing ones.

9. Normalization of perfusion: The reestablishment of normal placental blood flow normalizes the oxygen supply to the fetus.
10. Resolution of edema: With the correction of hypoxia and endothelial dysfunction, the interstitial fluid is reabsorbed, and the edema regresses.

Parallels in the literature

Although we have not identified previous reports of fetal edema reversion specifically attributed to anticoagulation adjustment, there are parallels in the literature that corroborate our hypothesis.

Magriples and colleagues, in a study published in 2006, evaluated the effect of anticoagulation on ultrasound findings in pregnant women with thrombophilia. The authors demonstrated that heparin treatment was associated with a lower rate of ultrasound changes, including growth restriction, oligohydramnios, and Doppler abnormalities [14]. Although the study did not specifically evaluate early fetal edema, the results suggest that adequate anticoagulation exerts a protective effect on the fetoplacental unit.

Garcia-Manau and colleagues described, in 2020, two cases of transient fetal edema in pregnant women with COVID-19 [15]. The authors attributed the finding to the systemic inflammatory response and endothelial dysfunction associated with the viral infection. Interestingly, the edema regressed spontaneously with maternal clinical improvement, suggesting that reversion is possible when the underlying insult is controlled.

Ramkrishna and colleagues, in a 2021 study, evaluated the outcomes of fetuses with edema detected early in pregnancy. The authors observed that the edema resolved spontaneously in 81.9% of cases that reached the 11-13 week ultrasound, and that these cases had significantly better outcomes than those with persistently increased nuchal translucency [2].

Clinical implications

This case has relevant practical implications for the management of pregnant women with thrombophilia:

1. First: Fetal edema in the first trimester, in the absence of aneuploidy or infection, should raise the consideration of placental insufficiency due to incipient thrombosis, especially in patients with a known thrombophilic profile.
2. Second: The anticoagulation dose must be individualized, taking into account not only body weight but also the patient's thrombophilic burden and obstetric history.
3. Third: In the face of ultrasonographic findings suggestive of placental compromise, the dosage adjustment of enoxaparin should be considered, even in the absence of clinically evident thromboembolic events.
4. Fourth: Serial ultrasound surveillance allows for the evaluation of the response to treatment and guides subsequent therapeutic adjustments.

Limitations of the Study

The present report has limitations inherent to the single-case design. The absence of laboratory monitoring with anti-Xa dosage prevents objective confirmation that the initial dose was, in fact, subtherapeutic and that the adjusted dose reached adequate levels. It is not possible to completely exclude the possibility that the edema would have regressed spontaneously, regardless of the intervention. However, the close temporal correlation and the biological plausibility of the proposed mechanism make this hypothesis less likely.

Figure Illustrative 6: *The importance of individualized monitoring in the management of gestational thrombophilia. The dosage should be adjusted based on clinical and laboratory markers, including Anti-Xa when available.*

Final Considerations

This report documents a case of generalized fetal subcutaneous edema in the first trimester that completely regressed after the optimization of the enoxaparin dose in a pregnant woman with high-risk mixed thrombophilia. The finding suggests that, at least in some cases, early fetal edema may represent a manifestation of placental hypoperfusion due to insufficient anticoagulation, being potentially reversible with adequate therapeutic intervention.

We recommend that, in the face of fetal edema in thrombophilic patients with negative genetic and infectious investigation, the clinician consider the possibility of anticoagulant underdosing and proceed with individualized dosage adjustment. Serial ultrasound surveillance will allow for the evaluation of the response to treatment and guide subsequent management.

Prospective studies are necessary to confirm these observations and establish evidence-based protocols for the management of this specific clinical situation.

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Volume 15 Issue 3 March 2026