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Early and Severe Intrauterine Growth Restriction Due to Enterovirus Infection: A Case Report

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ABSTRACT

Maternal enterovirus infections during pregnancy are increasingly recognized for their potential to cause severe fetal complications. However, early-onset severe fetal growth restriction (FGR) as the primary manifestation remains rarely reported.

We report the case of a 31-year-old gravida 2 para 1 woman with an initially uncomplicated pregnancy. At 22 weeks of gestation, ultrasound revealed severe early-onset FGR (<1st percentile) with abnormal Doppler findings and oligohydramnios. Extensive investigations were negative except for the detection of enterovirus RNA in the amniotic fluid by RT-PCR. Follow-up showed persistent severe growth restriction, abnormal placental morphology with cystic changes, and fetal cardiomegaly. Due to poor prognosis, termination of pregnancy was performed at 30+4 weeks. Placental examination demonstrated cystic lesions and histological features of fetal vascular malperfusion, while fetal autopsy confirmed severe FGR without structural anomalies.

Experimental data suggest that enterovirus may contribute to placental dysfunction through inflammatory mechanisms and trophoblast damage. These processes may contribute to the severe early-onset FGR observed in this case. Currently, no specific guidelines or in utero treatments exist for enterovirus infection during pregnancy, and management relies on fetal prognosis and progression.

This case adds to the limited evidence suggesting that enterovirus infection may be associated with severe early-onset FGR and may warrant consideration in the diagnostic assessment of otherwise unexplained cases.

Keywords: *Enterovirus, Congenital Infection, Intrauterine Fetal Growth Restriction, Pregnancy*

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Introduction

Maternal enterovirus infections are common and often asymptomatic or associated with non-specific flu-like, gastrointestinal, or febrile symptoms. During pregnancy, their true prevalence remains difficult to estimate, and vertical transmission is probably underdiagnosed. When fetal or neonatal infection occurs, variable outcomes are possible, ranging from asymptomatic infection to severe complications such as myocarditis, encephalitis, fetal hydrops, prematurity, and intrauterine fetal demise (Belov *et al*., 2021; Khediri *et al*., 2018; Bonnin *et al*., 2014; Longo *et al*., 2024).

While enterovirus is increasingly recognized as an underestimated cause of obstetric complications, fetal growth restriction (FGR) as a primary manifestation of congenital enterovirus infection remains poorly documented in the literature (Khediri *et al*., 2018; Auriti *et al*., 2021), with only isolated case reports describing this association (Bonnin *et al*., 2014; Tassin *et al*., 2014). Most published cases focus on stillbirth or acute fetal complications rather than early-onset severe FGR (Bonnin *et al*., 2014; Tassin *et al*., 2014). This is clinically relevant because unexplained early-onset FGR usually prompts investigations for chromosomal abnormalities, placental dysfunction, pre-eclampsia, and common congenital infections, whereas enterovirus testing is not routinely included in the diagnostic workup (Nardozza *et al*., 2017).

This case report describes a pregnancy complicated by early-onset severe FGR in which amniotic fluid analysis revealed enterovirus RNA as the only identifiable etiology. We present the diagnostic workup, clinical management, and outcome of this case to highlight enterovirus as a potential viral etiology to consider in the diagnostic workup of unexplained severe early-onset FGR and to contribute to the limited evidence on this rare but potentially important association.

Case Presentation

A 31-year-old gravida 2 para 1 woman presented to our maternal-fetal medicine center after the diagnosis of an intrauterine pregnancy at 6 weeks of gestation (WG). This patient has no specific medical history apart from an umbilical hernia repair. She delivered two years before this second pregnancy a 3650 g healthy baby at 40+4 weeks of gestation (WG).

At the beginning of the current pregnancy, maternal serologies were positive for rubeola, negative for toxoplasma, cytomegalovirus, hepatitis viruses, syphilis and HIV. Her vaginal smear was negative for gonorrhea and chlamydia.

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The first-trimester ultrasound examination at 12 WG +1 was normal. A non-invasive prenatal test (NIPT) performed the same day was able to rule out the presence of 3 types of aneuploidies (13, 18 and 21) and confirm the female sex of the fetus.

At 22 WG, during the second trimester ultrasound, though the fetal morphology was normal, its weight estimation was at 250 g, below the1st percentile (-4.7 SD for gestational age), accompanied by an abnormal doppler tracing including an absent diastolic flow and intermittent reverse flow in the umbilical cord, a bilateral elevation of the resistance index in the uterine arteries with a notch perceived on the left side and oligohydramnios. These findings were suggestive of an early onset (< 32 WG) and severe (< 3rd percentile) stage II fetal growth restriction (absence of diastolic flow in the umbilical cord).

After discussions between the medical staff and the patient, the decision to perform an amniocentesis, a week later at 23 WG + 2, was made in hopes of identifying the cause of the FGR.

PCR analysis of the amniotic fluid was negative for toxoplasma gondii, cytomegalovirus (CMV), and parvovirus B19. However, enterovirus RNA was detected in the amniotic fluid by reverse transcription PCR (RT-PCR) [Cycle threshold (Ct) value 13.39, very high viral load]. The patient did not report any gastrointestinal or respiratory symptoms in the weeks preceding the diagnosis.

Genetic analysis performed on the amniotic fluid by QF-PCR confirmed the absence of aneuploidy, CGH was negative and exome sequencing was discontinued following the identification of enterovirus infection in the sample.

The patient also underwent a pre-eclampsia workup. Blood pressure was within normal limits; urine dipstick was negative for proteinuria and liver enzymes were within normal limits which meant that a vascular etiology for FGR was considered unlikely.

At first, the decision to pursue the pregnancy with a weekly ultrasound to monitor the fetus' growth was made. At 25 WG + 3, the doppler tracing was similar, weight estimation at 357 g, still under 1st percentile (-6.6 SD for gestational age), a cardiomegaly with a cardiothoracic ratio of 62% was observed and an abnormal irregular placenta with multiple hypoechogenic areas were noted (Fig. 1).

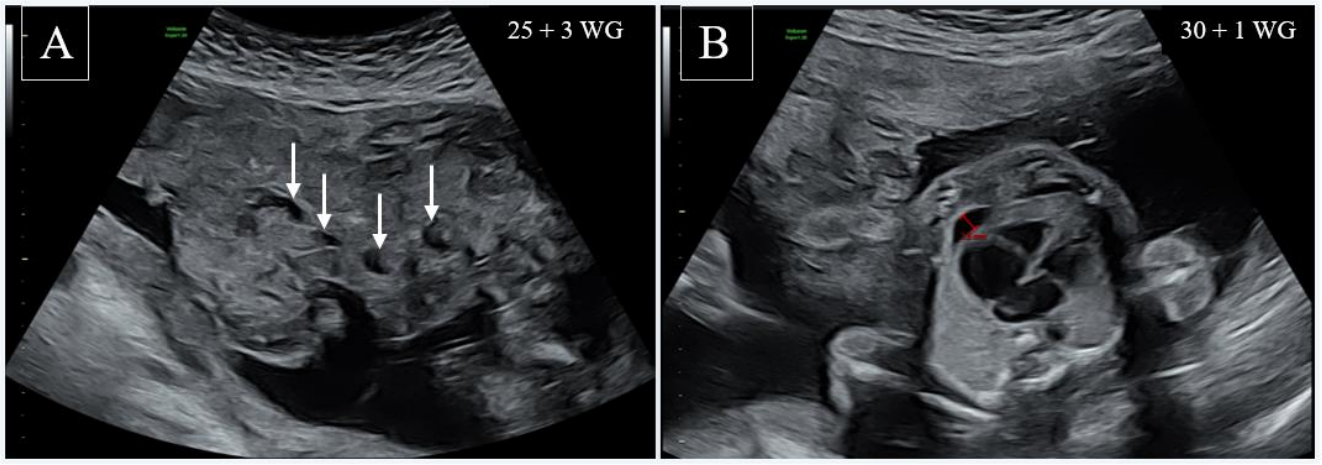

Figure 1: Prenatal ultrasound findings. (A) Two-dimensional ultrasound showing heterogeneous placental parenchyma with multiple cystic hypoechogenic lesions (white arrows) at 25+3 weeks of gestation. (B) Axial fetal thoracic view demonstrating cardiomegaly with minimal pericardial effusion, measured at 3.8 mm (red calipers), at 30+1 weeks of gestation.

After discussion with the medical staff in fetal medicine and neonatology and considering the bad prognosis of the fetus, the couple decided to terminate the pregnancy.

At 30+4 WG, the patient received 200 mg of mifepristone orally. Three days later, in maternal intensive care unit, after vaginal administration of 400 µg of misoprostol and placement of an epidural catheter, she delivered a 750 g baby (female infant) under 1st percentile with a spontaneous expulsion of the placenta five minutes later. The placenta was submitted for pathological examination. Macroscopic examination revealed multiple cystic lesions, a centrally inserted umbilical cord, multiple deposits of blood and fibrin on the basal plate, and heterogeneously hemorrhagic parenchyma with cystic transformation. Microscopic examination showed a large hemorrhagic area adjacent to preserved chorionic villi. Extensive fibrin deposition had replaced the normal villous architecture with infarcted placental tissue. Ghost chorionic villi were identified within the infarcted area, consistent with chronic ischemic placental injury. Overall, these findings were consistent with fetal vascular malperfusion and compatible with severe fetal growth restriction (Fig. 2).

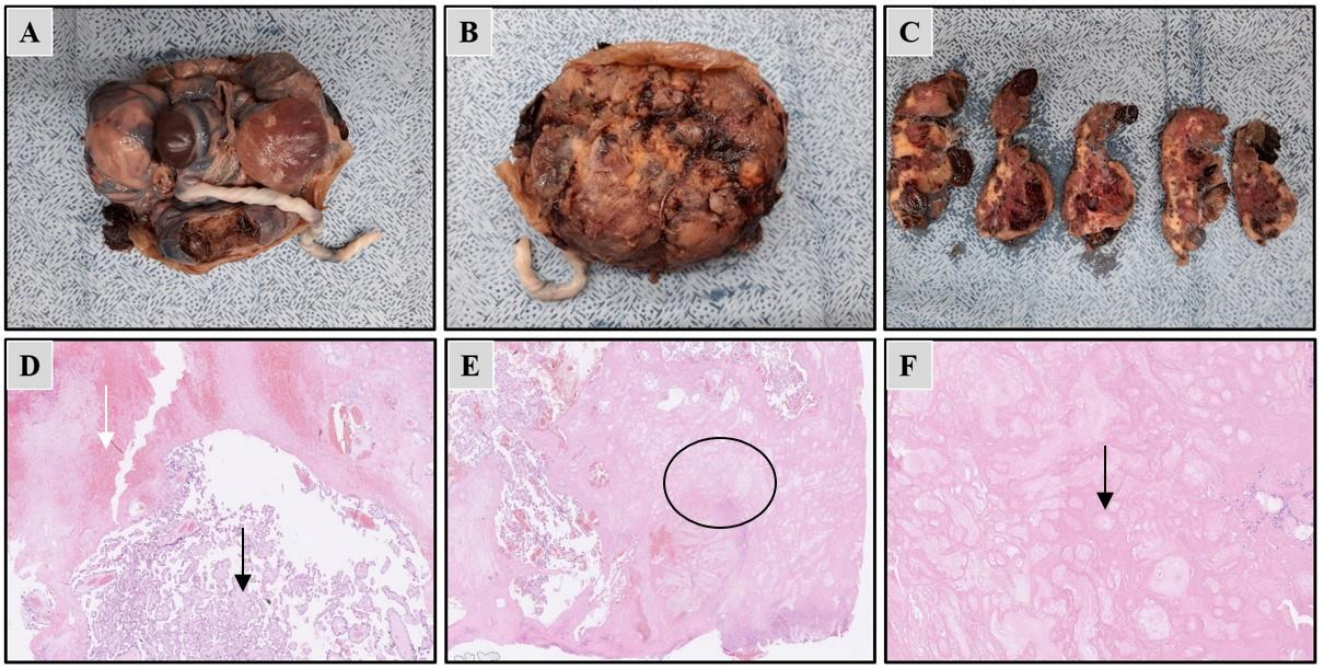

Figure 2: Placental pathological findings. Macroscopic examination: (A) chorionic plate (fetal surface) with multiple cystic lesions and a centrally inserted umbilical cord. (B) basal plate (maternal surface) with blood and fibrin depositions. (C) serial sagittal placental sections showing heterogeneous hemorrhagic parenchyma with cystic transformation. Microscopic examination of H&E-stained sections showed: (D) large hemorrhagic area (white arrow) adjacent to preserved chorionic villi (black arrow). (E) extensive fibrin deposition with replacement of the normal villous architecture by infarcted placental tissue (circled zone). (F) ghost chorionic villi within the infarcted area (black arrow).

Following the acquisition of parents' consent, fetal autopsy was performed. It demonstrated no structural malformations; findings were consistent with severe intrauterine growth restriction of infectious origin.

Discussion

This case is notable because severe early-onset FGR was the predominant clinical manifestation in an otherwise asymptomatic pregnant woman, with enterovirus RNA detected in amniotic fluid after exclusion of the main genetic, infectious, and maternal vascular causes. In contrast to the previously reported cases summarized in the introduction, which mainly describe acute fetal or neonatal complications, this pregnancy was characterized by progressive severe FGR, abnormal Doppler findings, placental abnormalities, and subsequent fetal cardiomegaly.

The temporal association between enterovirus RNA detection in amniotic fluid and the subsequent progression of severe FGR, together with the abnormal placental morphology and histopathological

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vascular lesions, supports a possible contribution of enterovirus infection to the clinical presentation (Khediri *et al*., 2018; Longo *et al*., 2024).

A biologically plausible explanation for the placental abnormalities observed in this case may involve enterovirus-mediated placental injury. Coxsackievirus B (CVB) uses coxsackievirus–adenovirus receptor (CAR) and decay-accelerating factor (DAF/CD55) as key receptors for attachment, entry and dissemination. Hwang, *et al*. (2014) has shown expression of these receptors in multiple embryonic organs, which may explain the cardiac, neurological and other manifestations reported in congenital enterovirus infections, such as myocarditis and meningitis. CAR is also expressed in endometrial epithelium and uterine glands, suggesting a potential mechanism for pregnancy loss in early congenital CVB infection (Hwang *et al*., 2014; Wang *et al*., 2022; Hafenstein *et al*., 2007).

In the placenta, CAR expression has been demonstrated in both villous and extravillous trophoblasts in the first trimester, and adenovirus studies have suggested that this may confer strong susceptibility to viral infection at this stage (Koi *et al*., 2001). In adenovirus-infected trophoblasts, inflammatory responses with lymphocytic infiltration, apoptosis of extravillous trophoblast and accelerated placental ageing have been described, leading to impaired placental function (Auriti *et al*., 2021). Although direct evidence is lacking, it is biologically plausible that similar CAR mediated mechanisms could operate in CVB/enterovirus infections of the placenta, contributing to severe early-onset fetal growth restriction (Longo *et al*., 2024; Wang *et al*., 2022; Hafenstein *et al*., 2007; Hafenstein *et al*., 2007).

There are currently no specific guidelines for the management of enterovirus induced FGR, and decisions are driven by the severity and progression of FGR and its expected neurological prognosis, rather than by viral status alone (Koi *et al*., 2001). No established in utero therapy exists for congenital enterovirus infection; available experimental treatments such as IVIG, interferons or pleconaril have only been used in severely ill neonates, and no studies have evaluated their safety or efficacy in utero (Longo *et al*., 2024). In this case, management was further limited by the asymptomatic maternal presentation, the relatively late virological diagnosis, and ultrasound findings (weight estimation and doppler abnormalities) suggesting that significant brain injury and placental damage were already present when the infection was identified.

The irregular, cystic appearance of the placenta in this case is compatible with infectious FGR, possibly reflecting a markedly inflammatory intra placental environment. Histologic patterns such as fetal vascular malperfusion are well known to be associated with intrauterine growth restriction and adverse perinatal outcomes, including CNS injury and stillbirth. These mechanisms are similar to those described

in other viral placentitides, including SARS CoV 2 and CMV, where villous infarction, fibrin deposition, and vascular thrombosis have been linked to fetal compromise or demise (Nardozza *et al*., 2017; Meler *et al*., 2020; Martins *et al*., 2020).

A substantial number of early-onset FGR cases remain unexplained despite extensive investigation, even when placental maldevelopment is evident (Burton and Jauniaux, 2018; Redline and Ravishankar, 2018; Redline *et al*., 2021). This case has important limitations: it was analyzed retrospectively; the amniotic fluid sample degraded despite cryopreservation, preventing enterovirus typing or additional cytology; extended genetic testing (exome sequencing) was discontinued after detection of enterovirus RNA; and specific placental virological studies, to assess enterovirus invasion, were not performed, partly because robust immunomarkers for enterovirus in placental tissue are not yet established, unlike for CMV, parvovirus B19 or SARS CoV2 (Di Girolamo *et al*., 2021; Pena-Burgos *et al*., 2025).

Therefore, the combination of early severe FGR, abnormal placental morphology, exclusion of other causes, and detection of enterovirus RNA in amniotic fluid supports a potential link between enterovirus infection and the observed clinical presentation. However, given the retrospective nature of this case and the absence of placental virological confirmation, these findings should be interpreted cautiously as a chance association cannot be fully excluded.

Conclusion

This case highlights a possible association between enterovirus infection and severe early-onset FGR. Although a chance association cannot be fully excluded, it supports considering enterovirus testing as part of the workup for selected cases of unexplained severe early-onset FGR and contributes to the limited literature on this rare association.

Declaration of Conflicting Interests: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval: This study was approved by the institutional ethics committee of HUB (n°2026/124). Given the retrospective design, the requirement for informed consent was waived by the ethics committee.

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