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RESEARCH ARTICLE

The predictive value of systemic immune-inflammation index for clinical pregnancy achievement in recurrent implantation failure: A study of euploid frozen-thawed embryo transfer cycles

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Abstract

Introduction: To evaluate the association between the systemic immune-inflammation index (SII) measured on the day of embryo transfer (ET) and clinical pregnancy outcomes in patients with recurrent implantation failure (RIF) undergoing euploid frozen–thawed embryo transfer (FET) cycles.

Methods: This retrospective cohort study included 160 RIF patients who underwent PGT-A-confirmed euploid blastocyst transfer between January 2022 and December 2024. SII was calculated as platelet count × (neutrophil count / lymphocyte count) using blood samples obtained on the morning of ET. Multivariable logistic regression and receiver operating characteristic (ROC) curve analyses were performed to evaluate predictive factors.

Results: Clinical pregnancy was achieved in 29.4% (47/160) of patients. SII levels were lower in patients with clinical pregnancy compared to those without (321.4 ± 115.0 vs. 448.6 ± 166.8; p=0.009). Each 100-unit decrease in SII was independently associated with an increased likelihood of clinical pregnancy (OR: 1.29; 95% CI: 1.03–1.62; p=0.025). ROC analysis identified an optimal cut-off value of 380 (AUC=0.68). Clinical pregnancy rates were higher in the low SII group (<380) compared to the high SII group (40.3% vs. 20.5%; p=0.009).

Conclusion: SII measured on the day of ET is an independent predictor of clinical pregnancy in euploid FET cycles among RIF patients and may serve as a practical, non-invasive marker for risk stratification.

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Introduction

RIF is one of the most challenging clinical problems in ART, characterized by the failure to achieve a clinical pregnancy despite the transfer of genetically normal embryos.[1,2] Although the selection of euploid embryos through PGT has largely eliminated embryo-related factors, the persistence of implantation failure in a subset of patients has highlighted the potential role of endometrial receptivity and immune-inflammatory mechanisms.[3,4] This issue is particularly relevant in PGT-euploid FET cycles, in which embryo-independent mechanisms contributing to implantation failure warrant more detailed investigation.

Implantation is a complex biological process involving a dynamic interaction between the embryo and the endometrium and is critical for the establishment of a successful pregnancy.[5] Traditionally, implantation success has been attributed mainly to local factors such as embryo quality and endometrial receptivity. However, accumulating evidence suggests that implantation is not solely determined by local endometrial factors but is also influenced by the systemic immune and inflammatory milieu.[5,6] In patients undergoing infertility treatment and ART, circulating inflammatory markers have been reported to be associated with pregnancy outcomes; nevertheless, the timing-specific and clinically relevant implications of this association remain incompletely understood.[7]

In this context, biomarkers reflecting systemic inflammatory burden have attracted increasing interest as potential predictors of implantation failure. Several studies have reported associations between infertility or IVF outcomes and composite inflammatory indices, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and the SII.[8,9] In general, higher inflammatory index values have been linked to lower implantation and clinical pregnancy rates.[9] However, most available studies have assessed inflammatory markers during early cycle phases or prior to ovarian stimulation, resulting in limited data that directly reflect the inflammatory milieu at the time of embryo transfer.[10]

The SII is a composite parameter that integrates systemic inflammation and immune response and has been established as a prognostic marker in various systemic diseases.[11] Its prognostic value is based on the combined assessment of increased pro-inflammatory cellular activity, suppression of adaptive immunity, and platelet-mediated microvascular dysfunction.[11] These mechanisms are biologically relevant to immune tolerance, endometrial receptivity, and tissue perfusion, all of which are essential for implantation and early placentation.[6,9] Nevertheless, evidence regarding the role of SII in the context of infertility—particularly in cycles involving euploid embryo transfer and timing-specific assessment at embryo transfer—remains limited.

Therefore, the aim of the present study was to evaluate the association between the SII measured prior to embryo transfer and pregnancy outcomes in patients with recurrent implantation failure undergoing PGT-euploid frozen embryo transfer cycles, and to investigate whether SII serves as an independent predictor of pregnancy after adjustment for clinical and embryological factors. In addition, the discriminatory ability of SII for pregnancy outcomes was assessed using receiver operating characteristic (ROC) curve analysis.

Material and Methods

Study Design and Patient Population

This study was designed as a single-center, retrospective cohort study conducted at the Department of Reproductive Medicine, Memorial Hospital Diyarbakır,Turkey between January 2022 and December 2024, a total of 160 patients who underwent FET within the scope of ART and met the diagnostic criteria for RIF were consecutively enrolled, provided that they fulfilled all inclusion criteria.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows:

- A diagnosis of RIF, defined as failure to achieve a clinical pregnancy despite at least two consecutive embryo transfer attempts using euploid blastocysts under optimal endometrial conditions; this operational definition is consistent with the conceptual framing of recent consensus statements, in which RIF is regarded as a secondary phenomenon of ART characterized by the repeated failure of embryos considered viable to implant. We acknowledge that current ESHRE good-practice recommendations favor an individualized definition based on a cumulative predicted chance of implantation rather than a fixed number of transfer attempts, and that the Lugano workshop has questioned whether RIF, as conventionally defined, represents a distinct biological entity or a statistical artifact.[1,2] By restricting the cohort to repeated failures of PGT-A-confirmed euploid (i.e., known-viab-

le) blastocysts, the present definition is intentionally stringent and aligns with the euploid-specific spirit of these recommendations,

- Transfer of a euploid embryo in the current cycle,
- Endometrial thickness ≥7 mm on the day of ET,
- Availability of complete clinical and laboratory data.

Exclusion criteria included:

- Uterine cavity abnormalities (uterine septum, submucosal fibroid, intrauterine adhesions, or endometrial polyps),
- A history of defined thrombophilia (antiphospholipid syndrome, Factor V Leiden mutation, prothrombin G20210A mutation, protein C, protein S, or antithrombin III deficiency),
- Endocrine disorders, including uncontrolled diabetes mellitus, thyroid dysfunction, hyperprolactinemia, or adrenal/pituitary pathology,
- Active or chronic systemic inflammatory or autoimmune diseases, as well as evidence of active infection,
- Parental karyotype abnormalities.

Study Groups

Patients were divided into two groups according to clinical pregnancy outcome following embryo transfer:

- Clinical pregnancy–positive group (n = 47): presence of an intrauterine gestational sac detected by transvaginal ultrasonography.
- Clinical pregnancy–negative group (n = 113).

Endometrial Preparation and Embryo Transfer

Endometrial preparation was performed using either a natural cycle or a hormone replacement therapy (HRT) protocol, based on the patient's clinical characteristics.

In natural cycles, ovulation was confirmed by either a spontaneous luteinizing hormone (LH) surge or human chorionic gonadotropin (hCG) trigger, and embryo transfer was performed on day 5 or day 6 after ovulation.

In HRT cycles, progesterone supplementation was initiated once endometrial thickness reached ≥7 mm following estrogen administration, and embryo transfer was carried out on the 5th or 6th day of progesterone exposure.

Luteal phase support was standardized across all patients using routine protocols. Embryo transfer was completed by transferring day 5 (D5) or day 6 (D6) frozen–thawed euploid blastocysts, either as single embryo transfer (SET) or double embryo transfer (DET).

Number of Previous Embryo Transfers: The total number of all previous fresh and frozen embryo transfer attempts prior to the current cycle (excluding canceled cycles), recorded as a continuous variable.

SII: Peripheral blood samples for complete blood count analysis were obtained from all patients on the morning of the embryo transfer day, prior to the procedure. SII was calculated using the formula: SII = (platelet count × neutrophil count) / lymphocyte count. A higher SII reflects a relative increase in neutrophil and platelet counts together with a relative reduction in lymphocytes, and therefore indicates a shift toward enhanced innate/pro-inflammatory and platelet-mediated activity accompanied by relative suppression of adaptive (lymphocyte-mediated) immunity; higher values thus correspond to a greater systemic immune-inflammatory burden. To limit the potential effect of circadian variation on inflammatory cell counts, all blood samples were obtained during a standardized morning time window on the day of embryo transfer. All patients were in a fasting state at the time of sampling. For logistic regression analyses, SII values were scaled per 100-unit change to enhance clinical interpretability.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27. The distribution of continuous variables was evaluated using the Shapiro–Wilk test. Normally distributed continuous variables were compared using the independent samples t-test, while non-normally distributed variables were analyzed using the Mann–Whitney U test. The chi-square test was used for categorical variables. Multivariable logistic regression analysis was conducted to assess factors associated with clinical pregnancy.

The optimal cut-off value of SII for predicting clinical pregnancy was determined using receiver operating characteristic (ROC) curve analysis and the Youden index. A p-value below 0.05 was considered statistically significant.

Results

A total of 160 patients diagnosed with RIF who underwent euploid FET were included in the study. During follow-up, clinical pregnancy was achieved in 47 patients (29.4%), whereas 113 patients (70.6%) did not achieve a clinical pregnancy.

Comparisons of demographic, clinical, and cycle characteristics according to clinical pregnancy status are presented in Table 1. There were no statistically significant differences between the clinical pregnancy positive and negative groups with respect to maternal age, body mass index (BMI), active smoking status, endometrial thickness on the day of ET, endometrial preparation protocol (natural cycle vs. hormone replacement therapy [HRT]), embryo transfer type (single vs. double embryo transfer), or blastocyst development day (day 5 vs. day 6) (all $p > 0.05$).

In contrast, passive smoking exposure was significantly more frequent in the clinical pregnancy negative group compared with the pregnancy positive group ($p = 0.048$).

When systemic immune-inflammation index (SII) values measured on the day of embryo transfer were evaluated, SII levels were significantly lower in patients who achieved clinical pregnancy (321.4 ± 115.0 (145–610)) than in those who did not (448.6 ± 166.8 (210–890); $p = 0.009$).

Table 1. Comparison of clinical and cycle characteristics according to clinical pregnancy status in patients with RIF (mean ± SD (min–max))

Variable	Clinical Pregnancy (+) (n = 47)	Clinical Pregnancy (–) (n = 113)	Total (n = 160)	p-value
Age (years)**	32.1 ± 5.9 (21–44)	33.4 ± 6.7 (20–48)	33.0 ± 6.5 (20–48)	0.29
Body mass index (kg/m²)**	24.6 ± 3.8 (18.5–34.1)	25.1 ± 3.9 (18.2–36.5)	24.9 ± 3.8 (18.2–36.5)	0.51
Endometrial thickness (mm)	8.8 ± 1.6 (6.1–12.4)	8.5 ± 1.5 (5.8–12.1)	8.6 ± 1.5 (5.8–12.4)	0.47
SII on ET day	321.4 ± 115.0 (145–610)	448.6 ± 166.8 (210–890)	411.2 ± 161.4 (145–890)	**0.009***
Active smoking, n (%)***	4 (8.5)	13 (11.5)	17 (10.6)	0.58
Passive smoking, n (%)***	9 (19.1)	38 (33.6)	47 (29.4)	**0.048***
Endometrial prep. (HRT / Natural), n (%)***	21 / 26 (44.7 / 55.3)	64 / 49 (56.6 / 43.4)	85 / 75 (53.1 / 46.9)	0.62
ET type (SET / DET), n (%)***	40 / 7 (85.1 / 14.9)	87 / 26 (77.0 / 23.0)	127 / 33 (79.4 / 20.6)	0.23
Blastocyst day (D5 / D6), n (%)***	32 / 15 (68.1 / 31.9)	62 / 51 (54.9 / 45.1)	94 / 66 (58.8 / 41.2)	0.12

* Statistically significant at the 0.05 level. ** Independent-samples t-test; endometrial thickness and SII were compared with the Mann–Whitney U test. *** Chi-square test for categorical variables. SII, systemic immune-inflammation index; ET, embryo transfer; HRT, hormone replacement therapy; SET, single embryo transfer; DET, double embryo transfer.

The results of the multivariable logistic regression analysis performed to identify independent factors associated with clinical pregnancy are summarized in Table 2. In this analysis, each 100-unit decrease in SII measured on the day of embryo transfer was independently associated with a statistically significant increase in the likelihood of clinical pregnancy (OR: 1.29; 95% CI: 1.03–1.62; $p = 0.025$). In addition, the number of previous failed embryo transfer attempts demonstrated an independent inverse association with clinical pregnancy (OR: 0.73; 95% CI: 0.58–0.93; $p = 0.010$).

The effect of passive smoking exposure remained at a borderline level in the multivariable model and did not reach statistical significance (OR: 0.52; 95% CI: 0.26–1.04; $p = 0.064$). Other variables, including age, BMI, endometrial thickness on the day of ET, embryo transfer type, blastocyst development day, and endometrial preparation protocol, were not independently associated with clinical pregnancy outcomes.

Table 2. Multivariable logistic regression analysis of factors associated with clinical pregnancy

Variable	OR	95% CI	p-value
SII (ET day, per 100-unit decrease)	1.29	1.03–1.62	**0.025***
Passive smoking (Yes / No)	0.52	0.26–1.04	0.064
Number of previous ETs (per additional attempt)	0.73	0.58–0.93	**0.010***
Age (years)	0.98	0.92–1.05	0.49
BMI (kg/m²)	0.96	0.90–1.02	0.18
Endometrial thickness on ET day (mm)	1.05	0.81–1.36	0.71
Embryo transfer type (SET vs. DET)	1.08	0.49–2.37	0.85
Blastocyst day (D5 vs. D6)	1.30	0.69–2.44	0.41
Endometrial preparation protocol (HRT vs. natural)	0.62	0.30–1.26	0.19

* Statistically significant at the 0.05 level. OR, odds ratio; CI, confidence interval; SII, systemic immune-inflammation index; ET, embryo transfer; BMI, body mass index; SET, single embryo transfer; DET, double embryo transfer.

Receiver operating characteristic (ROC) curve analysis demonstrated that SII levels measured on the day of embryo transfer had a moderate discriminatory ability for predicting clinical pregnancy (AUC = 0.68, 95% CI: 0.60–0.76). Using the Youden index, an optimal cut-off value of 380 was identified, yielding a sensitivity of 67.2% and a specificity of 65% (Figure 1/Table 3).

Based on this cut-off value, comparative analyses were performed (Table 4). The clinical pregnancy rate was significantly higher in the low SII group (<380) compared with the high SII group (≥380) (40.3% vs. 20.5%, respectively; p = 0.009). No significant differences were observed between SII groups regarding age, BMI, endometrial thickness, number of previous embryo transfers, or blastocyst development day (p > 0.05 for all).

Although passive smoking exposure was numerically more frequent in the high SII group, this difference did not reach statistical significance (p = 0.083).

Table 3. ROC curve analysis of embryo-transfer-day SII for predicting clinical pregnancy

Parameter	Result
Cut-off value	380
Sensitivity	67.2%
Specificity	65.0%
Area under the curve (AUC)	0.68
95% CI	0.60–0.76
p	**0.003***

* Statistically significant at the 0.05 level. The optimal cut-off was determined using the Youden index. AUC, area under the curve; CI, confidence interval; SII, systemic immune-inflammation index.

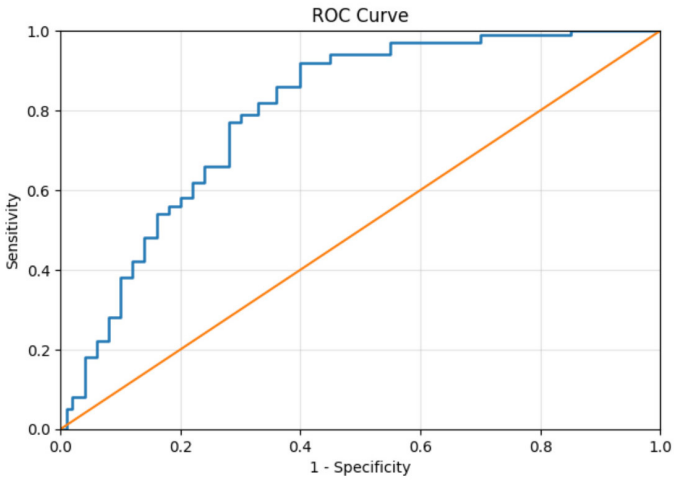

Figure 1. ROC curve of embryo transfer day SII for predicting clinical pregnancy

Table 4. Clinical comparison according to the SII cut-off value (380)

Variable	SII < 380 (n = 72)	SII ≥ 380 (n = 88)	Total (n = 160)	p-value
Age (years)**	32.8 ± 4.1 (24–41)	33.4 ± 4.3 (25–42)	33.1 ± 4.2 (24–42)	0.92
Body mass index (kg/m²)**	24.2 ± 3.3 (19.8–32.7)	25.0 ± 3.7 (20.1–33.9)	24.6 ± 3.5 (19.8–33.9)	0.73
Endometrial thickness (mm)	8.6 ± 1.1 (6.6–11.2)	8.4 ± 1.2 (6.5–11.0)	8.5 ± 1.1 (6.5–11.2)	0.61
Number of previous embryo transfers	2.0 ± 1.0 (0–5)	2.1 ± 1.1 (0–5)	2.1 ± 1.0 (0–5)	0.88
Clinical pregnancy, n (%)***	29 (40.3)	18 (20.5)	47 (29.4)	**0.009***
Blastocyst day (D5 / D6), n***	46 / 26	48 / 40	94 / 66	0.47
Passive smoking exposure, n (%)***	16 (22.2)	31 (35.2)	47 (29.4)	0.083

* Statistically significant at the 0.05 level. ** Independent-samples t-test; other continuous variables were compared with the Mann–Whitney U test. *** Chi-square test for categorical variables. SII, systemic immune-inflammation index; D5, day 5; D6, day 6.

Discussion

In this study, we found that the systemic immune-inflammation index (SII) measured on the day of embryo transfer was associated with clinical pregnancy in patients with recurrent implantation failure undergoing euploid blastocyst transfer. Lower SII levels on the day of embryo transfer were linked to higher clinical pregnancy rates. In addition, a higher number of previous embryo transfer attempts was associated with reduced clinical pregnancy rates. In contrast, clinical and cycle-related variables such as maternal age, body mass index (BMI), endometrial thickness, embryo transfer type, and endometrial preparation protocol were not independently associated with clinical pregnancy in multivariable analyses.

The role of systemic inflammatory markers in implantation and IVF outcomes has received growing attention. Composite indices based on neutrophil, lymphocyte, and platelet counts have been associated with endometrial receptivity and early pregnancy outcomes.[12] Among these, the systemic immune-inflammation index (SII), which integrates these cellular components into a single parameter, has been proposed as a more comprehensive marker; however, its role in reproductive medicine has been investigated in only a limited number of studies to date .[13]

Previous studies conducted in IVF and FET cycles have suggested that higher SII, NLR, or PLR levels may be associated with lower clinical pregnancy and live birth rates.[14] Nevertheless, interpretation of these findings is often complicated by heterogeneous patient populations, the lack of exclusion of embryo aneuploidy, and insufficient control of endometrial factors. In the present study, the inclusion of a highly selected cohort consisting exclusively of patients with RIF undergoing euploid blastocyst transfer and with adequate endometrial thickness on the day of ET allowed the association between SII and clinical pregnancy to be examined within a more homogeneous clinical context.

Implantation is a complex immunological process that primarily occurs within the local endometrial microenvironment, where cytokine balance, natural killer cell activity, and endometrial receptivity play critical roles.[15] Accordingly, the importance of local endometrial factors in implantation failure has long been emphasized. However, it has been proposed that systemic inflammatory burden may indirectly influence the endometrial microenvironment through vascular responses, immune cell migration, and platelet–immune interactions, thereby modulating local receptivity.[16] From this perspective, systemic inflammatory markers may not represent a direct surrogate of local endometrial conditions but rather indicate a broader biological milieu that is less favorable for implantation.

Several diagnostic tools have been developed to assess endometrial receptivity, most notably the endometrial receptivity analysis (ERA), which aims to identify timing discrepancies in the window of implantation and has been incorporated into clinical practice in selected RIF cases.[17] However, ERA primarily focuses on molecular timing and does not directly evaluate the immune or inflammatory status of the endometrial microenvironment.[18] Therefore, local assessment tools such as ERA and systemic inflammatory markers should be considered complementary rather than mutually exclusive, as they reflect different dimensions of implantation biology.

Multivariable logistic regression analysis further demonstrated an inverse association between the number of previous embryo transfer attempts and clinical pregnancy. This finding may reflect the cumulative biological and immunological burden associated with recurrent implantation failure. Previous studies have suggested that repeated failed transfers may be associated with persistent endometrial inflammation, alterations in immune cell distribution, and impaired endometrial tolerance mechanisms.[19] Recurrent implantation failure has also been linked to changes in local cytokine profiles and natural killer cell activity, potentially reducing implantation potential in subsequent cycles.[20]

Although passive smoking exposure did not reach statistical significance in multivariable analysis, it exhibited a borderline negative association with clinical pregnancy. Prior studies have shown that exposure to cigarette smoke may impair endometrial vascularization, increase oxidative stress, and modulate immune responses, thereby adversely affecting implantation.[21–23] It is therefore plausible that the borderline association observed in the present study might reach statistical significance in cohorts with larger sample sizes. Of note, in the present cohort the association with clinical pregnancy appeared more pronounced for passive (secondhand) than for active smoking, which may at first seem counterintuitive. Several factors may account for this observation. First, the number of active smokers was small (n=17), which substantially limited the statistical power to detect an effect of active smoking, whereas passive exposure was more prevalent (n=47). Second, self-reported active smoking is prone to under-reporting and misclassification, which may dilute its apparent association, whereas chronic household secondhand exposure tends to be continuous and may be more reliably reported. Third, experimental and clinical data indicate that environmental tobacco smoke exerts oxidative, vascular, and immunomodulatory effects on the endometrium that are qualitatively similar to those of active smoking.[21–23] These findings should nonetheless be interpreted with caution, as smoking status was self-reported and not biochemically confirmed (e.g., by cotinine measurement), and residual confounding cannot be excluded.

Conversely, the lack of a significant association between clinical pregnancy and variables such as maternal age, BMI, endometrial thickness on the ET day, embryo transfer type, blastocyst development day, and endometrial preparation protocol may be explained by the exclusive inclusion of euploid embryo transfers and the prior optimization of endometrial conditions. Indeed, previous studies have reported that when embryo aneuploidy is excluded and endometrial parameters are standardized, the direct impact of age and BMI on implantation outcomes appears to be attenuated.[24] This homogenous study design reduced the influence of major confounders and enabled the evaluation of more subtle biological factors, such as systemic inflammation, in relation to clinical pregnancy.

With respect to endometrial preparation protocols, multivariable analysis did not demonstrate a statistically significant association between HRT versus natural cycles and clinical pregnancy. However, this finding should not be interpreted as evidence of equivalence between protocols. In routine clinical practice, protocol selection is rarely randomized and is often influenced by patient characteristics and logistical considerations, which may introduce confounding by indication and mask true effects. Moreover, the greater scheduling flexibility offered by HRT protocols may result in more complex cases being preferentially allocated to this group, further complicating causal interpretation.

Importantly, the apparent similarity in clinical pregnancy rates between protocols highlights that clinical decision-making should not be based solely on implantation success but should also consider maternal safety and obstetric outcomes. Several studies have reported higher risks of hypertensive disorders of pregnancy and preeclampsia in programmed/HRT FET cycles compared with natural cycles.[25] Additionally, recent large randomized trials have suggested potential advantages of natural cycles in ovulatory women with respect to live birth rates and certain maternal outcomes.[26] Accordingly, although protocol type was not a significant predictor in the present study, protocol selection remains clinically relevant and should be interpreted as reflecting current practice patterns rather than causal equivalence.[27,28]

ROC curve analysis demonstrated that SII measured on the day of embryo transfer exhibited a moderate discriminatory ability for predicting clinical pregnancy. This finding suggests that SII should not be viewed as a standalone diagnostic tool with high predictive accuracy but rather as an adjunctive risk stratification marker within a broader clinical and biological framework. Given the multifactorial nature of implantation, it is not unexpected that a single biomarker would have limited discriminatory power, and the observed AUC value is consistent with this biological complexity. Accordingly, an AUC of 0.68 should be explicitly acknowledged as reflecting only moderate, and clinically limited, discriminatory performance; SII measured on the day of embryo transfer is therefore best regarded as an adjunctive risk-stratification marker to be integrated with established clinical and embryological parameters, rather than as a standalone predictive or decision-making tool. With respect to the identified cut-off value of 380, it should be interpreted as an exploratory threshold derived from the Youden index in a single-center cohort rather than as a validated clinical decision boundary. In routine practice, such a value should not be used to withhold, defer, or prioritize embryo transfer; at most, it might help identify patients who could benefit from closer counseling or from optimization of modifiable inflammatory contributors (e.g., avoidance of tobacco-smoke exposure) prior to transfer, pending external validation in larger, multicenter cohorts. A particular strength of the present analysis is that SII was measured on the day of embryo transfer, thereby capturing the systemic inflammatory milieu within the peri-implantation window itself, in contrast to most previous studies that assessed inflammatory indices during ovarian stimulation, at the ovulation trigger, or at oocyte retrieval.

In a recently published conference abstract in Human Reproduction,[29] no significant association was observed between SII levels and pregnancy outcomes in euploid FET cycles, with embryonic parameters reported to be more prominent determinants. The discrepancy between these findings and the results of the present study may be attributed to differences in patient populations, heterogeneity in study design, or distinct immunological responses in specific clinical subgroups such as patients with RIF.

Recent studies further support a link between systemic inflammation and reproductive outcomes. In a comprehensive assessment of the maternal immune system on the day of frozen euploid embryo transfer, specific circulating immune and angiogenic mediators differed between cycles resulting in live birth and those that did not, underscoring the relevance of systemic immune status at the time of transfer.[30] Newer

composite hematological indices, such as the systemic immune-response index (SIRI) and the pan-immune-inflammation value (PIV), have likewise been associated with oocyte and embryo development in infertile women,[31] and low-grade systemic inflammation has been negatively associated with live birth following IVF.[32] With regard to environmental exposures, earlier work demonstrated that sidestream (secondhand) smoke exposure can be as detrimental to IVF outcomes as active smoking, which is concordant with the prominent association of passive smoking observed in our cohort.[33] Taken together, these data reinforce the concept that the systemic immune-inflammatory environment—particularly when assessed close to the time of implantation—may modulate the likelihood of clinical pregnancy.

This study has several limitations. First, its retrospective, single-center design may limit the generalizability of the findings and introduces the potential for selection and information bias. Second, although the cohort was relatively homogeneous, the sample size was modest, and the moderate discriminatory performance of SII (AUC = 0.68) indicates limited standalone predictive accuracy. Third, we assessed only the systemic inflammatory milieu and did not directly evaluate local endometrial immune mechanisms—such as uterine natural killer cell activity, endometrial cytokine profiles, or immune-cell populations at the maternal–fetal interface—which are central to implantation; systemic markers can therefore only indirectly reflect the local environment. Fourth, SII was derived from a single time-point measurement, additional acute-phase markers (e.g., C-reactive protein) were not available, and smoking status was self-reported rather than biochemically verified. Finally, the primary outcome was clinical pregnancy; data on live birth and obstetric outcomes were not analyzed. These limitations should be addressed in larger, prospective, multicenter studies that incorporate concurrent assessment of local endometrial immune parameters as well as longer-term outcomes.

Conclusion

In conclusion, within these constraints, SII measured on the day of embryo transfer was independently associated with clinical pregnancy in patients with RIF undergoing euploid FET and may serve as a practical, non-invasive, adjunctive marker for risk stratification rather than as a definitive predictive test.

Ethical Approval:

The study protocol was approved by the Ethics Committee of University of Health Sciences, Gazi Yaşargil Training and Research Hospital (Decision Date: 30 December 2022; Approval Number: 289). All procedures were conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants.

Conflict of Interest:

The authors declare that they have no conflict of interest.

Financial Disclosure:

No financial support has been received for this study.

Author Contributions:

Concept: ZK.FY

Design: ZK, FY

Data Collection and/or Processing: FTC

Analysis and/or Interpretation: FY,FTC

Literature Review: ZK, FY,FTC

Writing: ZK,FY

Critical Review: ZK, FY, FTC

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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CASE REPORT

Progressive Umbilical Vein Varix Enlargement Preceding Fetal Growth Restriction: A Longitudinal Ultrasonographic Case Report

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Abstract

Background: Umbilical vein varix (UVV) is a rare umbilical cord abnormality associated with adverse perinatal outcomes, including fetal growth restriction (FGR), although its clinical significance remains unclear.

Case Presentation A 31-year-old gravida 2 woman was diagnosed with intra-abdominal UVV at 20 weeks of gestation. Serial ultrasonography demonstrated progressive enlargement of the varix from 8.4 mm to 15.3 mm at 26 weeks, followed by stabilization. Fetal growth progressively declined, and FGR was diagnosed at 26 weeks of gestation when the estimated fetal weight fell to the 2nd percentile, despite preserved conventional Doppler findings. Serial evaluation suggested a visual inverse temporal relationship between varix size and fetal growth percentile. The pregnancy was closely monitored, and a healthy female infant weighing 2349 g was delivered at 37 weeks without immediate neonatal complications.

Conclusion: Progressive enlargement of umbilical vein varix may be associated with the subsequent development of fetal growth restriction, even in the presence of preserved conventional Doppler parameters, and could represent a potential early imaging marker requiring close surveillance. These findings underscore the potential value of serial ultrasonographic monitoring of varix size, flow characteristics, and fetal growth for individualized antenatal management in pregnancies complicated by UVV.

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Introduction

Umbilical vein varix (UVV) is a rare vascular abnormality of the umbilical cord, defined as a focal dilatation of the umbilical vein exceeding 9 mm or 50% of the adjacent segment.[1] Its reported incidence ranges from 0.4 to 1.1 per 1,000 pregnancies.[2] Due to its rarity, current knowledge is largely based on case reports and small series.[3,4]

UVV has been associated with adverse perinatal outcomes, including thrombosis, fetal growth restriction (FGR), and intrauterine fetal demise.[5,6,9,10] The underlying mechanism is thought to involve structural vessel wall weakness and abnormal hemodynamics, with turbulent flow predisposing to endothelial injury and thrombus formation.[10,11] Larger varix size and turbulent flow may increase the risk of fetal compromise.[12,13]

Diagnosis is primarily established by ultrasonography with Doppler imaging, although differentiation from other cord abnormalities may be challenging, necessitating serial evaluation.[1,5]

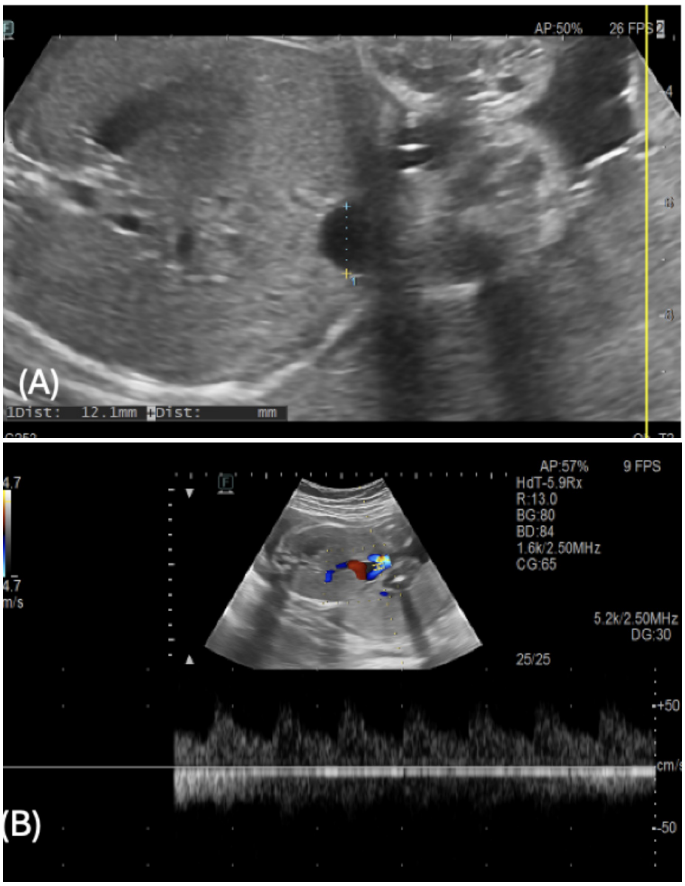
Here, we present a case of UVV with longitudinal ultrasonographic follow-up, highlighting its dynamic progression and potential association with FGR.

Case Presentation

A 31-year-old gravida 2, para 0 woman was referred for routine antenatal follow-up. Based on the last menstrual period, gestational age was 9 weeks and 4 days at initial presentation. First-trimester ultrasonography demonstrated a viable singleton pregnancy with normal fetal anatomy. Crown–rump length was consistent with gestational age, nuchal translucency measured 2.5 mm, and nasal bone was present. Ductus venosus a-wave was positive, and uterine artery Doppler findings were within normal limits.

At 20 weeks of gestation, detailed fetal anatomical evaluation revealed appropriate growth parameters; however, an umbilical vein diameter of 8.4 mm raised suspicion for umbilical vein varix. All ultrasonographic and Doppler evaluations were performed using an ARIETTA 850 ultrasound system with a 3.5-MHz abdominal transducer by an experienced operator. The maximal diameter was measured on grayscale ultrasonography using electronic calipers placed perpendicular to the long axis of the vessel in the transverse (short-axis) plane at the point of maximal dilatation. Color Doppler imaging demonstrated turbulent venous flow within the dilated segment, supporting the diagnosis of umbilical vein varix. Representative ultrasonographic images are shown in Figure 1.

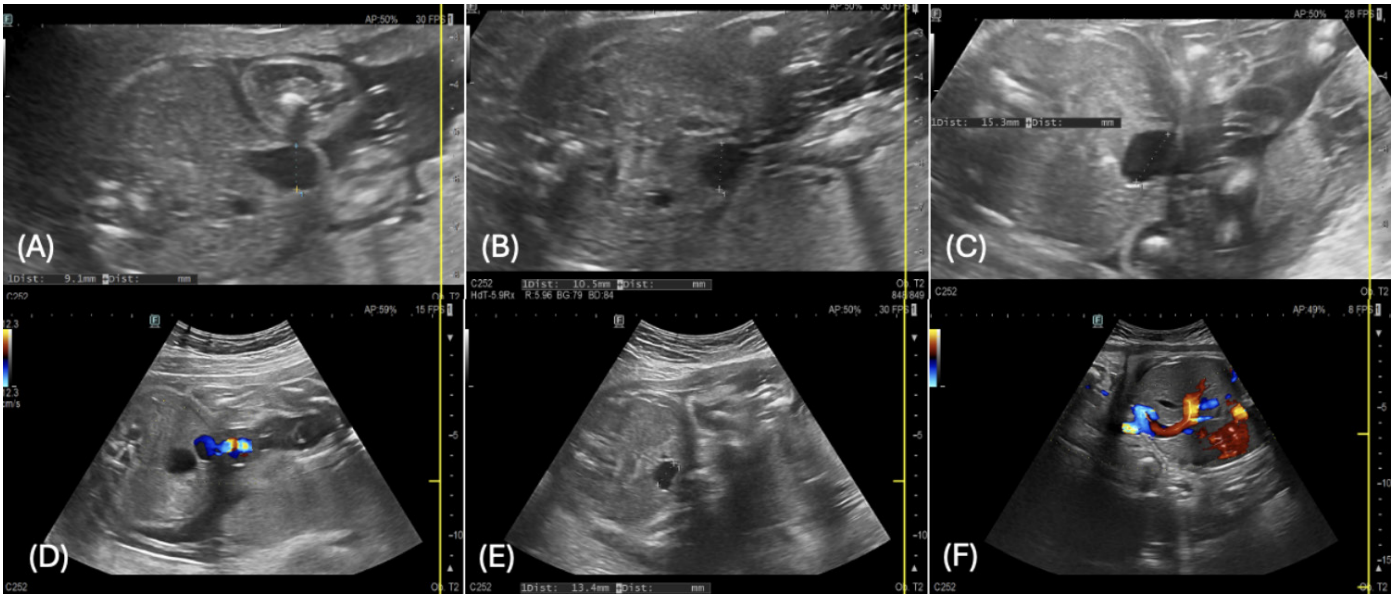
Figure 1. Ultrasonographic evaluation of intra-abdominal umbilical vein varix



(A) Grayscale ultrasonographic image demonstrating intra-abdominal umbilical vein varix. The maximal diameter was measured in the transverse (short-axis) plane using electronic calipers, and the measurement point is indicated. **(B)** Color Doppler ultrasonographic image demonstrating turbulent venous flow within the dilated segment of the umbilical vein. The presence of turbulent flow at the measurement site supported the diagnosis of umbilical vein varix.

Serial follow-up examinations demonstrated progressive enlargement of the umbilical vein varix. The diameter increased from 9.1 mm at 22 weeks to 10.5 mm at 24 weeks, followed by a marked increase to 12.2 mm at 25 weeks and a peak value of 15.3 mm at 26 weeks. After reaching this maximum, the varix diameter remained relatively stable, measuring 15 mm at 28 weeks and gradually decreasing to approximately 12–13 mm in the later weeks of gestation. Representative serial ultrasonographic and Doppler images illustrating this progression are presented in Figure 2.

Figure 2. Serial ultrasonographic and Doppler images demonstrating the progression of umbilical vein varix across gestation



(A) Mild dilatation at 22 weeks (9.1 mm).
(B) Progressive enlargement at 24 weeks (10.5 mm).
(C) Marked dilatation reaching peak size at 26 weeks (15.3 mm).
(D) Color Doppler imaging demonstrating turbulent flow within the dilated segment.
(E) Persistent varix during the period of established fetal growth restriction at 30 weeks (13.4 mm).
(F) Late gestational image demonstrating relative stabilization of varix size with preserved flow characteristics.

Fetal growth parameters were initially within normal limits; however, from 24 weeks onward, a progressive decline in growth percentiles was observed. Estimated fetal weight decreased to the 7th percentile at 24–25 weeks and further declined to below the 5th percentile from 26 weeks onward, reaching the 1st–2nd percentile range during late gestation. Abdominal circumference showed a similar pattern, falling to the 1st–2nd percentile, consistent with fetal growth restriction. Fetal growth restriction was diagnosed based on severely reduced fetal growth percentiles, including estimated fetal weight and/or abdominal circumference below the 3rd percentile during follow-up, consistent with consistent with the Delphi consensus criteria for early-onset fetal growth restriction .[7]

Despite the presence of growth restriction, Doppler parameters remained largely within normal limits throughout follow-up. Umbilical artery pulsatility index values did not indicate increased placental resistance, middle cerebral artery Doppler findings were within expected ranges, and ductus venosus a-wave remained positive in all examinations. No signs of fetal hydrops or cardiac compromise were detected.

The pregnancy was managed with close surveillance, including serial ultrasonographic biometry and Doppler assessments. All longitudinal ultrasonographic and Doppler findings are summarized in Table 1 and further illustrated in Figures 2-4.

At 37 weeks of gestation, a live female infant weighing 2349 g was delivered with an Apgar score of 8 at 1 minute and 10 at 5 minutes. The neonatal period was uneventful, and no immediate complications were observed. Umbilical artery pH was not available. The umbilical cord was macroscopically normal, with two arteries and one vein. No gross placental or cord abnormality requiring further pathological evaluation was noted. Therefore, placental pathological examination was not performed, and placental weight, detailed gross morphology, histopathological findings, and cord insertion characteristics could not be assessed. At 3 months of age, a small umbilical hernia was observed, which resolved spontaneously during follow-up without requiring surgical intervention. No causal relationship between this postnatal finding and umbilical vein varix is known.

Table 1. Longitudinal ultrasonographic, Doppler, and umbilical vein varix measurements during pregnancy

GA (weeks)	BPD (p)	HC (p)	AC (p)	FL (p)	EFW (g, p)	Umbilical Artery PI	MCA PI / PSV	DV a-wave	UVV (mm)
20+0	20p	13p	15p	23p	329 g (21p)	1.19	2.38/ 28	+	8.4
22+0	27p	22p	14p	16p	439 g (24p)	0.69	1.25 / 35	+	9.1
24+0	26p	17p	7p	12p	545 g (7p)	0.80	1.86 / 33	+	10.5
25+0	27p	11p	10p	7p	724 g (7p)	0.90	1.50 / 28	+	12.2
26+0	12p	13p	2p	6p	772 g (2p)	0.96	2.27 / 35.3	+	15.3
28+0	21p	11p	3p	7p	1058 g (4p)	0.55	1.63 / 46.1	+	15
30+0	10p	2p	1p	2p	1116 g (1p)	0.82	1.84 / 41.1	+	13.4
32+0	11p	19p	1p	2p	1421 g (2p)	0.85	1.32/ 29.1	+	12
34+0	49p	4p	2p	5p	1862 g (3p)	0.83	1.52/ 46	+	12
35+0	8p	14p	2p	1p	1938 g (2p)	0.95	1.60/ 38	+	12
36+0	7p	8p	1p	0p	2008 g (1p)	0.68	1.68 / 53.3	+	12
37+0	13p	17p	1p	1p	2349 g (2p)	1.04	1.87/ 52	+	12

GA: gestational age; BPD: biparietal diameter; HC: head circumference; AC: abdominal circumference; FL: femur length; EFW: estimated fetal weight; PI: pulsatility index; MCA: middle cerebral artery; PSV: peak systolic velocity; DV: ductus venosus; UVV: umbilical vein varix. Percentiles are expressed according to gestational age–adjusted reference ranges. (+) indicates a positive ductus venosus a-wave.

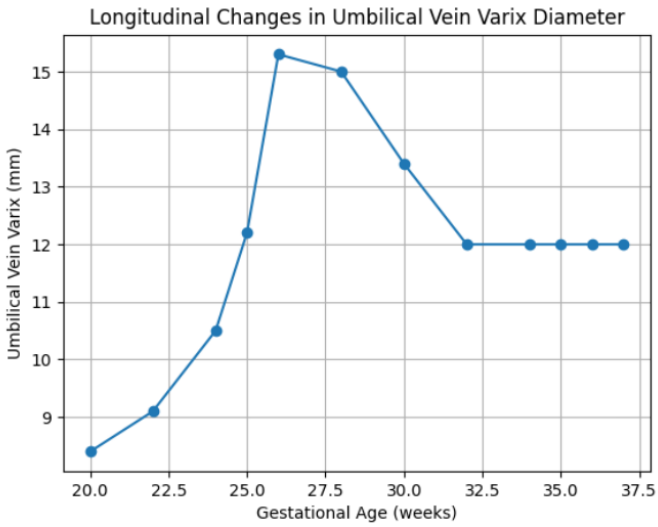


Figure 3: Longitudinal progression of umbilical vein varix (UVV) diameter across gestation and its temporal association with fetal growth restriction.

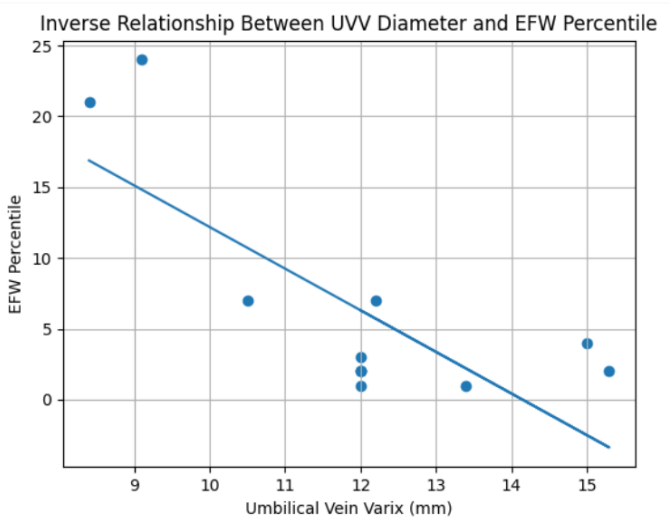


Figure 4. Relationship between umbilical vein varix (UVV) diameter and estimated fetal weight (EFW) percentile.

Longitudinal measurements demonstrate progressive enlargement of the umbilical vein varix, reaching a peak diameter at mid-gestation followed by relative stabilization. The timing of maximal dilation coincides with the onset of fetal growth restriction, suggesting a potential temporal relationship between increasing varix size and impaired fetal growth.

There was a negative association between umbilical vein varix (UVV) diameter and estimated fetal weight (EFW) percentile. As the UVV diameter increased, EFW percentiles showed a progressive decline, particularly beyond 12 mm. Fetuses with larger UVV measurements (≥12 mm) were predominantly below the 5th percentile for EFW, suggesting a potential relationship between progressive venous dilatation and fetal growth restriction. Despite some variability in early gestational weeks, the overall trend indicates an inverse relationship.

Discussion

Umbilical vein varix (UVV) is a rare umbilical cord vascular abnormality that has been associated with adverse perinatal outcomes, including fetal growth restriction (FGR), thrombosis, hydrops fetalis, and intrauterine fetal demise.[1–3] However, due to its low incidence, the natural history, prognostic factors, and optimal management strategies of UVV remain incompletely understood.

In the present case, serial ultrasonographic evaluation demonstrated a distinct temporal relationship between progressive UVV enlargement and the subsequent diagnosis of FGR. The varix diameter increased progressively from 8.4 mm to 15.3 mm, while fetal growth percentiles gradually declined, with FGR diagnosed at 26 weeks of gestation when the estimated fetal weight reached the 2nd percentile. This occurred despite persistently reassuring umbilical artery, middle cerebral artery, and ductus venosus Doppler findings. This observation suggests that progressive venous changes may be associated with fetal growth deterioration even before conventional arterial Doppler abnormalities become evident.[5,6,8]

Several pathophysiological mechanisms may explain this relationship. Progressive venous dilatation and turbulent flow may lead to endothelial injury, altered venous return, and impaired fetoplacental circulation, potentially contributing to chronic placental insufficiency.[8-10] In addition, structural abnormalities of the vessel wall, including alterations in collagen composition and vascular integrity, may predispose affected vessels to progressive dilatation and abnormal venous hemodynamics. Although these mechanisms are biologically plausible, the present case cannot establish a direct mechanistic or causal relationship between UVV progression and FGR.

Recent systematic reviews and meta-analyses evaluating umbilical cord vascular abnormalities have similarly demonstrated increased risks of FGR, preterm delivery, and adverse perinatal outcomes.[8–11] Although evidence specifically focused on UVV remains limited, and most available data are derived from case reports and small series. Therefore, our findings should be interpreted as a hypothesis-generating observation rather than evidence of causality.

Previous studies have suggested that larger varix diameters and rapid interval progression are associated with worse perinatal outcomes, with diameters exceeding 9–10 mm considered potentially high risk.[2,8] In our case, fetal growth decline became more pronounced after the UVV diameter exceeded approximately 12 mm. However, this observation should not be interpreted as a definitive threshold effect. Rather, it highlights the potential clinical value of serial varix measurements during antenatal surveillance.

Despite marked enlargement of the varix and persistent turbulent flow, no acute complications such as thrombosis, hydrops, or fetal compromise occurred. This finding highlights the heterogeneous clinical course of UVV and supports previous reports demonstrating favorable outcomes with close surveillance and individualized management.[12] Importantly, our observations suggest that careful longitudinal monitoring may allow continuation of pregnancy in selected cases when fetal Doppler parameters remain reassuring.

Currently, there is no consensus regarding the optimal timing of delivery in pregnancies complicated by UVV. While some authors advocate early delivery because of the risk of sudden fetal demise, others recommend expectant management with intensive ultrasonographic follow-up in the absence of Doppler deterioration or fetal compromise.[14,15] Our findings support the latter approach and emphasize the importance of serial assessment of varix size, flow characteristics, and fetal growth throughout gestation.

From a clinical perspective, progressive UVV enlargement may be associated with subsequent development of FGR and could represent a potential early imaging marker of fetoplacental dysfunction. However, this interpretation remains speculative in the absence of placental pathological confirmation. Future prospective studies incorporating serial UVV measurements, detailed Doppler evaluation, neonatal outcomes, and placental pathology are needed to determine whether changes in varix diameter have predictive value for adverse fetal outcomes.

This report is limited by its single-case design and the inability to establish causality between UVV progression and fetal growth impairment. In addition, although the umbilical cord was macroscopically normal with two arteries and one vein, placental histopathological evaluation was not performed because no gross placental or cord abnormality requiring further pathological examination was noted. Therefore, placental weight, detailed gross placental morphology, histopathological findings, and cord insertion characteristics could not be assessed, limiting further mechanistic interpretation. Nevertheless, the major

strength of this report lies in its detailed longitudinal ultrasonographic documentation, including serial assessment of UVV progression, Doppler findings, and fetal growth parameters throughout gestation.

Conclusion

In conclusion, progressive enlargement of umbilical vein varix may be associated with the subsequent development of fetal growth restriction and could represent a potential early imaging marker of fetoplacental dysfunction, even in the presence of preserved conventional Doppler findings. Although causality cannot be established from a single case, this observation highlights the potential value of careful serial ultrasonographic surveillance for early recognition of interval changes and individualized antenatal management in pregnancies complicated by UVV.

Contributors

Ecem Okşen contributed to patient follow-up, conception of the case report, acquisition and interpretation of ultrasonographic and Doppler data, literature review, and drafting of the manuscript. Selvi Aydın Şenel contributed to patient management, interpretation of clinical findings, critical revision of the manuscript for important intellectual content, and supervision of the study process. Barış Boza contributed to data collection, image evaluation, and manuscript revision. All authors approved the final submitted version of the manuscript.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying ultrasonographic images.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Declaration of generative AI and AI-assisted technologies in the writing process

No generative artificial intelligence or AI-assisted technologies were used in the preparation, writing, editing, or revision of this manuscript.

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Declaration of competing interest

The authors declare that they have no competing interests related to this publication.

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