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Original article

The invisible killer: fetal vascular malperfusion in stillbirths without macroscopic cord abnormalities

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Summary

Objective. The aim was to evaluate the association between fetal vascular malperfusion (FVM) and the umbilical cord characteristics in stillbirth. FVM is a category of placental lesions consistent with restriction/interruption of fetal blood flow, frequently associated with a "cord accident". In some stillbirths, gross umbilical cord abnormalities unravel at birth, helping to elucidate the cause of death; however, other cases do not show any structural alterations and therefore these cases do not have an obvious cause of death.

Methods. Retrospective histopathological evaluation of singleton antepartum stillbirths affected by of FVM. Clinical and histopathological findings were compared among cases with or without gross umbilical cord abnormalities.

Results. One hundred and three cases were evaluated. Forty-eight cases (48/103; 46.6%) of stillbirth with FVM showed gross umbilical cord abnormalities, whereas 55/103 cases (53.4%) did not show any gross anomalies. Clinical risk factors for stillbirth were equally distributed between cases. Notably, the main histological lesion observed in cases without gross umbilical cord abnormalities was fatal thrombosis of the fetal vessels along the cord-placental vascular tree. This finding implies that the absence of macroscopic cord anomalies is not a sufficient criterion to exclude reduction/interruption of fetal blood flow and cord accidents as a potential cause of stillbirth.

Conclusion. Knowing the cause of fetal death is paramount both for bereaved parents and clinicians, helping in stillbirth acceptance and future prevention strategies. Our findings show the occurrence of FVM in cases without macroscopic umbilical cord anomalies. Therefore, an in-depth placental histopathological examination is mandatory to unravel signs of fetal blood flow obstruction in cases in which umbilical cord looks grossly normal. This knowledge helps parents, and health care providers in the real identification of the pathogenesis of fetal death, as the first step for personalized future actions of stillbirth prevention.

Key words: stillbirth, placenta, umbilical cord, histology, malperfusion, pregnancy

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Introduction

Every year more than 2.5 million babies die in utero worldwide [1]. Knowing the real cause of fetal death is paramount both for bereaved parents and clinicians: the possibility of understanding the cause of stillbirth may help with its acceptance, especially when an obvious cause of death is not uncovered at the diagnosis of stillbirth [2,3].

Sometimes in stillborn cases, gross umbilical cord abnormalities unravel at birth [4], suggesting a fatal unpreventable cord accident. Macroscopic umbilical cord abnormalities encompass structural alterations of umbilical cord anatomy that impair fetal blood flow. Structural alterations of the umbilical cord can be acquired during pregnancy (such as true knots or loops

of the cord around the fetal neck, called nuchal cord) or can be constitutional (such as an abnormal cord insertion, irregular thickness with stricture of the cord, abnormalities of cord length or abnormalities in number of coils of the blood vessels within the cord). Both acquired and constitutional cord abnormalities can lead to acute-sudden or intermittent-chronic fetal circulatory obstruction, both able to determine stillbirth [5,6]. These "cord accidents" can also affect the placental circulation at the microscopic-histological level, causing placental changes related to vascular congestion and stasis [7]. Such placental changes can include multiple lesions such as thrombosis of umbilical vessels and/or placental vessels, stem vessel obliteration, segmental avascular villi, villous stromal-vascular karyorrhexis, vascular intramural fibrin deposition and vascular ectasia [8]. These features are classified in the category of placental lesions called "fetal vascular malperfusion" (FVM) [8]. Indeed, lesions consistent with FVM often can be attributable to obstruction of fetal blood flow [8] and could be used as diagnostic feature for restriction/interruption of umbilical blood flow. Therefore, histological diagnosis of FVM can be used as a tool to suspect a cord accident as a cause of stillbirth [6,7], even in cases without evident gross cord abnormalities. Sometimes, other clinical conditions can cause mechanical obstruction of an otherwise anatomically normal umbilical cord: for example, oligohydramnios can lead to cord compression and blood flow interruption due to insufficient amniotic fluid around the fetus and the cord [9]. Furthermore, acute or intermittent obstruction of umbilical cord blood flow can also be related to fetal movements: the fetus itself can cause traction/compression of the cord vessels thus compromising the blood flow, irrespective of the amniotic fluid volume.

In stillbirths with histological signs of fetal vascular malperfusion, our purpose is to estimate how many cases are related to gross umbilical cord abnormalities and how many are macroscopically beyond suspicion.

Methods

This is a retrospective cohort study carried out on consecutive placentas collected from antepartum stillbirths in singleton pregnancies ≥22 weeks of gestation during a 15-year period (2007-2022) at the University Hospital of Modena, Italy.

The aim of the present study is to evaluate the association between placental lesions consistent with FVM and umbilical cord gross characteristics in stillbirths.

The gross cord abnormalities included were: abnormal (velamentous) cord insertion, true knots, abnormal cord length (both excessively long and short cords: > 90° centile for gestational age or < 10° centile for gestational age respectively) [10], single or multiple nuchal cords, abnormal coils of blood vessels (both hypercoiled or hypocoiled cords defined as > 3 coils per 10 cm or < 1 coil per 10 cm, respectively) [10], segmental stricture of the cord (narrow cords due to diminished Wharton's jelly), abnormal number of vessels in the umbilical cord (single umbilical artery). Examples of gross cord abnormalities are shown in supplementary Figure 1.

According to international criteria [8], FVM was defined in presence of thrombi in large vessels (umbilical cord, chorionic plate and major stem villi) and/or stem vessel obliteration (fibromuscular sclerosis) [9] and/or segmental avascular villi and/or villous stromal-vascular karyorrhexis and/or vascular intramural fibrin deposition (also called intimal fibrin cushion) and/or vascular ectasia (vessels that are four times the luminal diameter of the surrounding vessel).

Two patterns of FVM were also distinguished: segmental complete FVM (with thrombotic occlusion of chorionic or stem villous vessels, or stem vessel obliteration) and global partial FVM (with venous ectasia, intramural fibrin deposition in large vessels, and/ or small foci of avascular or karyorrhectic villi, distributed in multiple foci of the placenta) [8,9]. The onset time of the lesions determines their histological characteristics/appearance. Early thrombus (recent lesion) is diagnosed in presence of reticular or layered organization of fibrin with lyses of the vascular endothelial layer and evidence of erythrocyte fragmentation and extravasation [11]. Conversely, the presence of calcification indicates a remote lesion, associated or not with areas of recanalization [8].

To avoid confounders, exclusion criteria were multiple pregnancy, fetal structural anomalies, and abnormal karyotype. Figure 1 summarizes the study flow-chart.

Placental and umbilical cord slides of 4 µm thick tissue sections, stained with hematoxylin and eosin, were jointly reviewed by two authors, blinded to all clinical information and gross cord appearance. The pathologists that originally collected the placental and umbilical cord samples are not the same that reviewed the slides. The placentas were examined, sampled and processed according to the national guidelines [12]. The procedure includes an extensive analysis of the maternal plate, the fetal plates, the umbilical cord and membranes. As we previously described [13], the samples collection of the umbilical cord includes at least 3 samples (near the placental insertion, near the fetal insertion, and at the center). For each case, at least three full-thickness samples of the placental disc were also analyzed: three samples of grossly unremarkable placental parenchyma must be collected in every

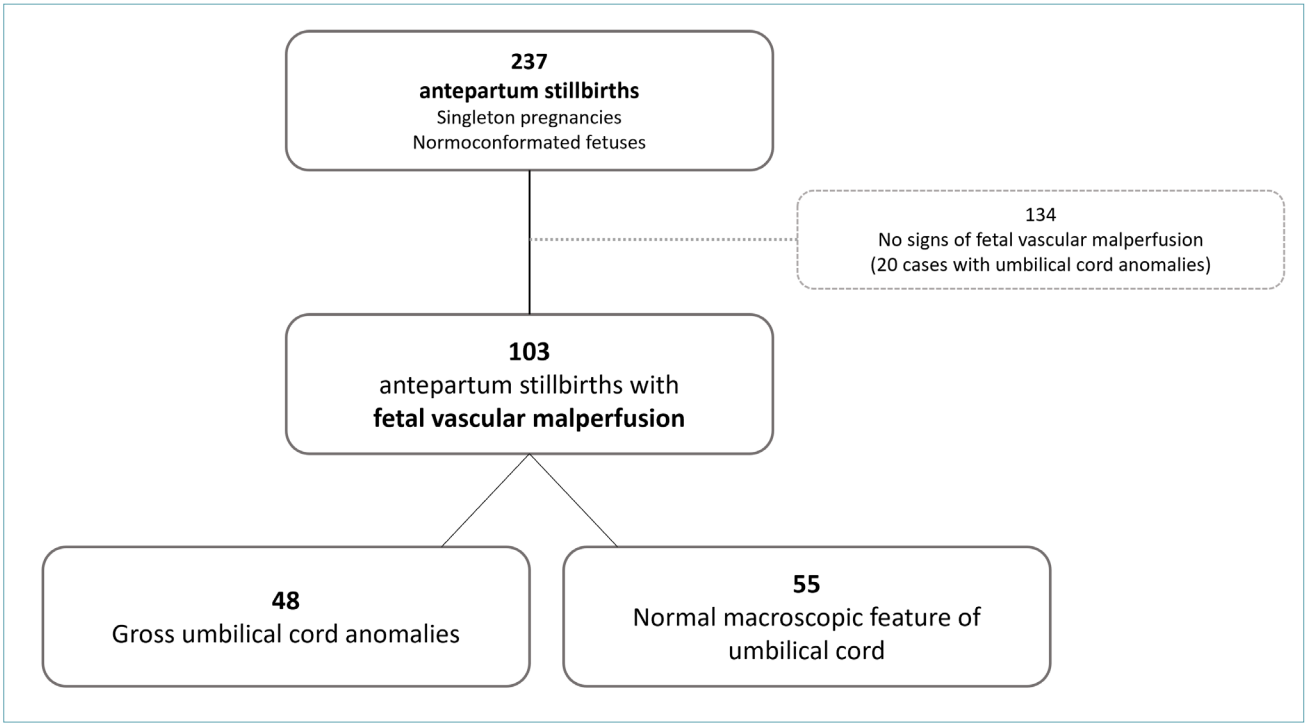


Figure 1. Study flow-chart about antepartum stillbirths in fifteen-years period (2007-2022).

case, and areas of placental macroscopic lesions must be also collected to warrant the histological evaluation and the specific identification of such lesions. Tissue samples were formalin-fixed, paraffin-embedded and processed for conventional histopathological examination by light microscopy.

Ethical approval was obtained from the local Institutional Review Board (#35265; date of approval: November 24, 2021).

The method of the study agrees with the Declaration of Helsinki.

The study was retrospective, and therefore patients' signed release forms were unobtainable. On the other hand, the study was performed in a university hospital, and the data in question were obtained with the patients' understanding that they might be published/re-used for secondary analyses. Moreover, informed consent for diagnostic work-up was not required, because diagnostic investigations are mandatory by law in cases of stillbirth in our Country [14] (legal references D.M. 7/2014 and D.P.C.170/99). Patient and fetus privacy was ensured during all the phases of the study, from data collection to analysis. All data was stored anonymously in a secure database.

Statistical analysis. The rate of placental histological lesions was compared between stillbirths with/without gross umbilical cord abnormalities using Fisher's exact test for categorical variables. $P < 0.05$ was considered statistically significant.

Results

Our population included 103 cases of singleton pregnancies that ended with antepartum stillbirth affected by histological signs of fetal vascular malperfusion. Our population included both cases of stillbirths occurring before the COVID-19 pandemic (n = 67) or during it (n = 36). However, none of the mothers were affected by symptomatic COVID-19 or asymptomatic positive SARS-COV2 swab.

Clinical characteristics of our population are summarized in Table I: several risk factors for stillbirth affected our population, such as coagulation disorders, preeclampsia, gestational diabetes, maternal obesity. Clinical characteristics were comparable between the pandemic and pre-pandemic periods, except for small for gestational age fetuses that occurred more frequently in pre-pandemic period (31.3% during the years 2007-2019; 11.1% during the years 2020-2022; supplementary Table I).

In the overall population, 48 cases (48/103; 46.6%) showed gross umbilical cord abnormalities. Clinical risk factors for stillbirth were equally distributed in

cases with and without umbilical cord abnormalities (Tab. I), as well as placental lesions consistent with maternal vascular malperfusion, ascending infection, and villitis of unknow etiology (Tab. II).

However, more than half of our population (55/103 cases, 53.4%) did not show any gross umbilical cord anomalies. Table IV summarizes the prevalence of histological abnormalities consistent with FVM. Notably,

Table I. Clinical characteristics of stillbirths affected by FMV from singleton pregnancies (N = 103).

Clinical characteristics	Overall results N = 103	Cases with umbilical cord abnormalities N = 48	Cases without umbilical cord abnormalities N = 55	p
Maternal age (years)	34.7 ±5.6	35.7±5.2	33.8±5.6	0.06
Obesity (BMI ≥30 kg/m^2)	10 (9.7)	2 (4.2)	8 (14.5)	0.07
Acquired thrombophilia (Antiphospholipid antibodies)	4 (3.9)	1 (2.1)	3 (5.4)	0.62
Inherited thrombophilia (mutation factor V, factor II, protein S deficiency, hypodysfibrinogenemia)	11 (10.7)	7 (14.6)	4 (7.3)	0.34
Preeclampsia	4 (3.9)	2 (4.2)	2 (3.6)	1.00
Gestational diabetes	13 (12.6)	9 (18.7)	4 (7.3)	0.13
Gestational age at delivery (weeks)	34.5 ±5	35.1±4.6	33.9±5.4	0.24
Birthweight (grams)	2203.4±1006.7	2315.9±939.2	2105.1±1015.1	0.29
SGA at birth (< 10° centile)	25 (24.3)	15	10	0.17

Data are presented as mean ± standard deviation or number (percentage). . SGA = small for gestational age.

Table II. Other categories of placental lesions in stillbirths affected by FMV from singleton pregnancies (N = 103).

Placental lesions	Overall results N = 103	Cases with umbilical cord abnormalities N = 48	Cases without umbilical cord abnormalities N = 55	p
Maternal vascular malperfusion:	53 (51.5)	23 (47.9)	30 (54.5)	0.56
infarcts	15 (14.6)	5 (10.4)	10 (18.2)	0.40
retroplacental hemorrhage	14 (13.6)	4 (8.3)	10 (18.2)	0.16
decidual arteriopathy	26 (25.2)	11 (22.9)	15 (27.3)	0.65
distal villous hypoplasia	3 (2.9)	3 (6.2)	0	0.10
accelerated villous maturation	19 (18.4)	9 (18.7)	10 (18.2)	1.0
Ascending infection (maternal inflammatory response)	21 (20.4)	10 (20.8)	11 (20)	1.00
with fetal inflammatory response	8 (7.8)	4 (8.3)	4 (7.3)	1.00
Villitis of unknown etiology	12 (11.6)	4 (8.3)	8 (14.5)	0.37

Data are presented as number (percentage). Different types of placental lesions are not mutually exclusive, more than one anomaly may coexist in the same case.

As summarized in Table III, the most commonly observed cord anomalies were nuchal cord (12/103 cases; 11.6%) and hypercoiling (10/103; 9.7%), followed by true knots (8/103 cases; 7.8%).

Sometimes, a combination of more than one abnormality affects the umbilical cord, likely increasing the odds of adverse fetal outcome. Various associations were observed in our population. Nuchal cord (n = 12) was associated with velamentous cord insertion (3/12 cases), excessive cord length (2/12 cases), stenosis (2/12 cases) and true knots (1/12 cases). Excessive cord length (n = 5) was associated with nuchal cord (2/5 cases), multiple loops (1/5 cases), true knots (1/5 cases), hypocoiling (1/5 cases) and single umbilical artery (1/5 cases). Velamentous cord insertion (n = 4) was associated with nuchal cord (3/4 cases), stenosis (2/4 cases) and hypercoiling (2/4 cases).

Table III. Details on cord abnormalities in 103 stillbirths with FVM.

Type of macroscopic abnormalities	N (%)
Velamentous cord insertion	4 (3.9)
Furcate insertion	1 (1)
True knots	8 (7.8)
Multiple loops	5 (5.8)
Hypercoiling	10 (9.7)
Hypocoiling	6 (5.8)
Excessive length	5 (5.8)
Short cord	3 (2.9)
Stenosis	5 (5.8)
Single umbilical artery	4 (3.9)
Nuchal cord	12 (11.6)
No cord abnormalities	55 (53.4)

Different types of cord abnormalities are not mutually exclusive, and more than one anomaly may coexist in the same umbilical cord.

Table IV. Histological lesions consistent with FVM in cases with and without macroscopic cord abnormalities.

Histological lesions	Cases with umbilical cord abnormalities N = 48	Cases without umbilical cord abnormalities N = 55	p
Thrombosis	35 (72.9)	33 (60)	0.21
Stem vessel obliteration	12 (25)	23 (41.8)	0.09
Avascular villi	12 (25)	23 (41.8)	0.09
Intramural fibrin deposition	24 (50)	17 (30.9)	0.07
Villous karyorrhexis	5 (10.4)	10 (18.2)	0.40
Vascular ectasia	2 (4.2)	5 (9.1)	0.44
Overall cases of segmental complete fetal vascular malperfusion	33 (68.7)	39 (70.9)	0.83
Overall cases of global partial fetal vascular malperfusion	15 (31.2)	16 (29.1)	0.83

Data are presented as number (percentage). Lesions are not mutually exclusive, more than one anomaly may coexist in the same case.

The main lesion observed in cases without gross cord abnormalities was thrombosis of fetal vessels (33/55; 60%) along the vascular tree, from umbilical vessels to chorionic vessels and stem villi. Example of lesions are shown in Figures 2-5. None of these lesions were more frequent during the pandemic (supplementary Table II).

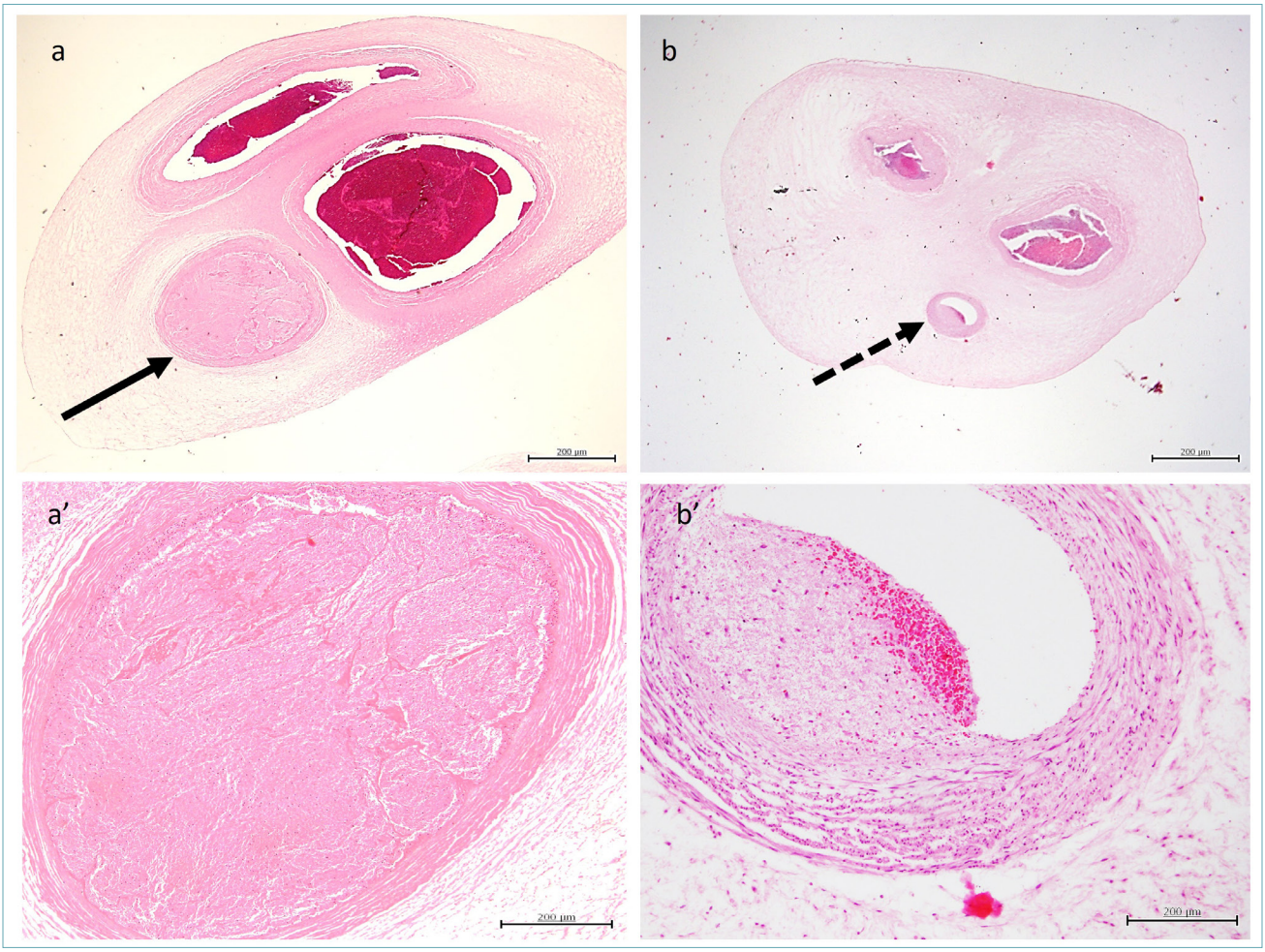


Figure 2. Histological lesions of the umbilical vessels (hematoxylin-eosin). (a): occlusive thrombus of the umbilical artery with complete occlusion of the vessel (arrow); (b): intimal fibrin cushion: note the intraluminal nodularity resulting in bulging/protrusion of entothelium with fibromyxoid material (dashed arrow). The surface of the lesion still shows progressing features. Scale bars = 200 µm

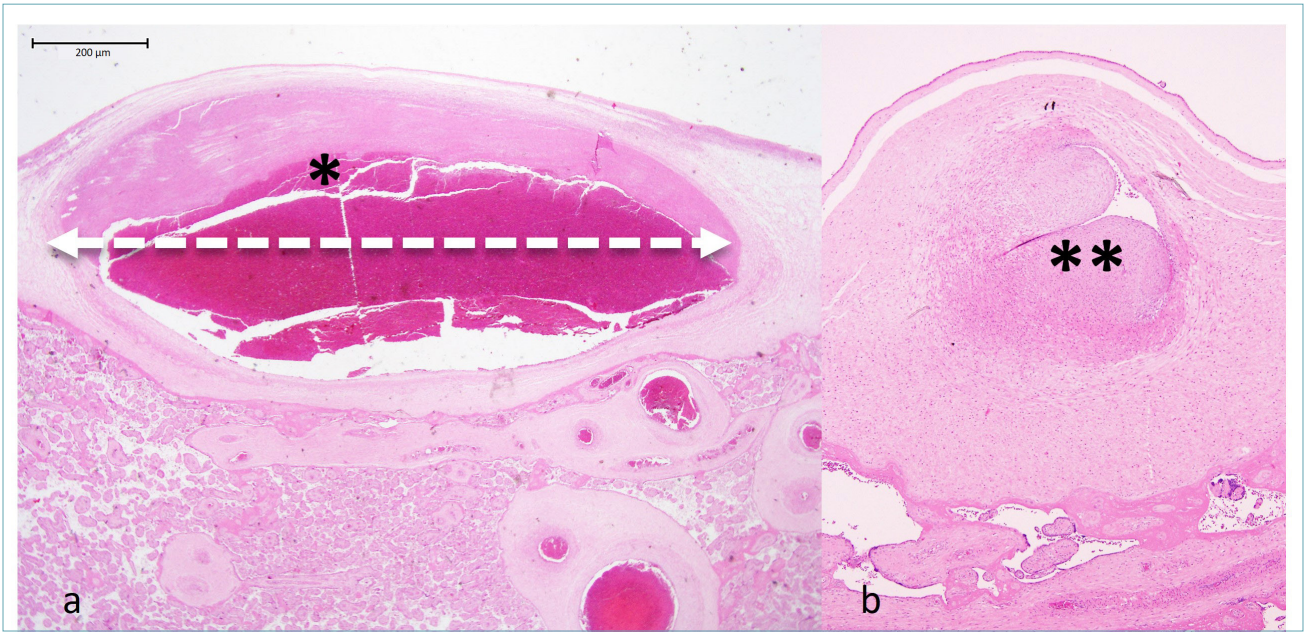


Figure 3. Histological lesions of chorionic vessels (hematoxylin-eosin). (a): vascular ectasia (markedly dilated vessel - white dashed arrow) with fresh thrombus (asterisk); (b): remote intramural fibrin deposition with nodular myxofibromatous endothelial lesion (double asterisks). Scalebar = 200 µm

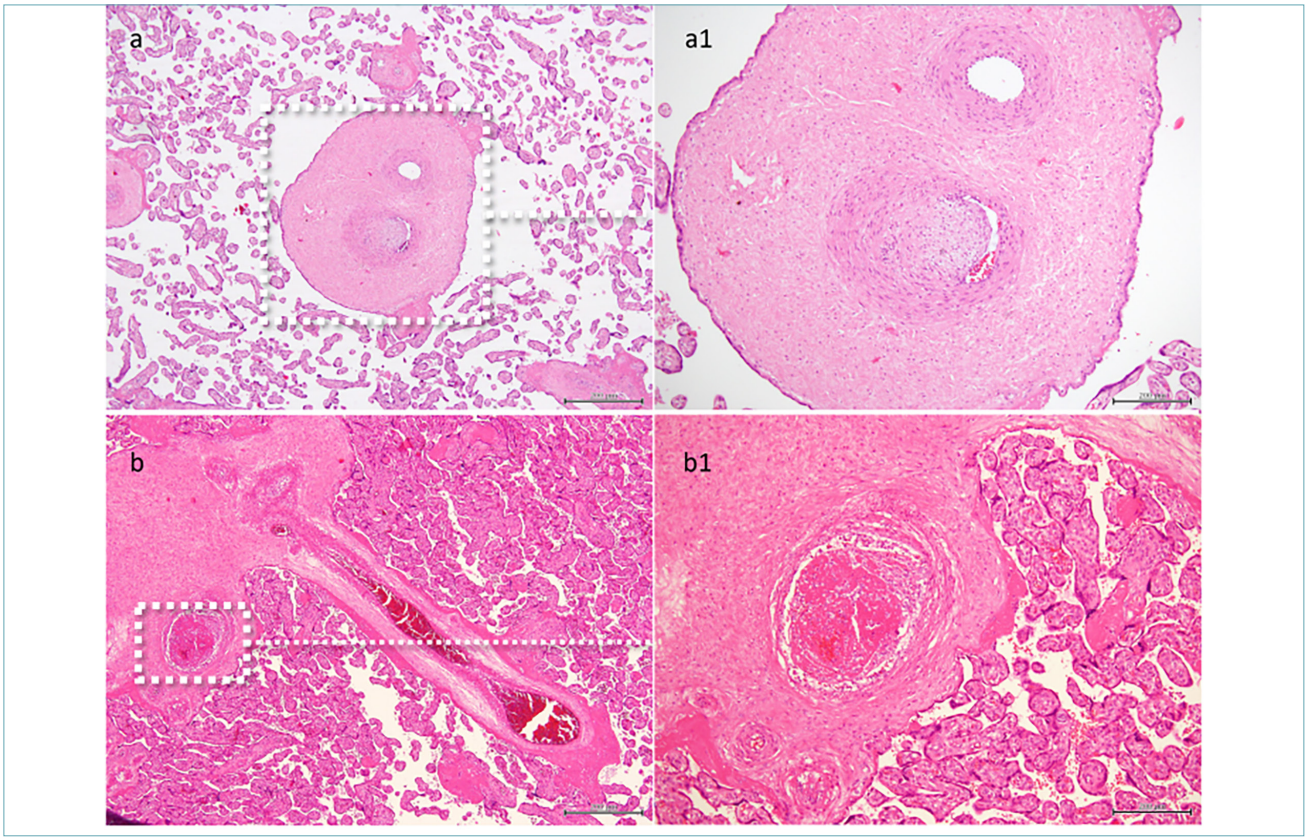


Figure 4. Histological lesions of stem villous vessels (hematoxylin-eosin). (a-a1) nearly occlusive endothelial cushion; (b-b1) occlusive endoluminal thrombosis. Scale bars = 200 µm

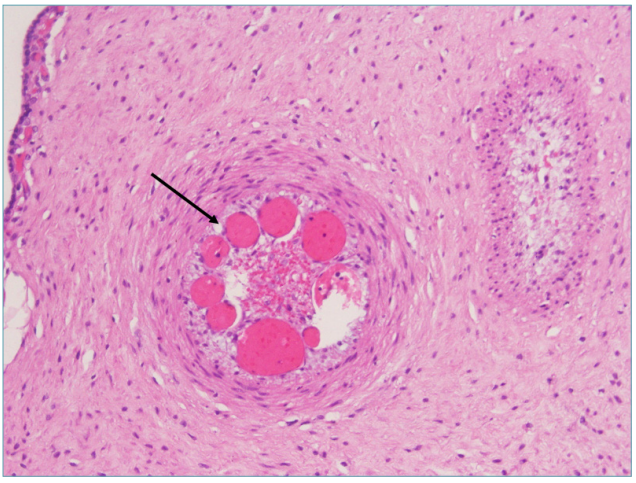


Figure 5. Remote thrombotic lesion with recanalization (arrow) of stem villous vessel (hematoxylin-eosin).

Notably the prevalence of placental histological lesions suggestive for reduction/interruption of fetal blood flow was not significantly different between cases with and without gross umbilical cord abnormalities (Tab. IV). Moreover, the prevalence of both patterns of global and segmental FVM were comparable in cases with or without gross cord abnormalities. These findings imply that the absence of macroscopic cord anomalies is not sufficient criterion to exclude cord accidents as a potential cause of stillbirth.

Discussion

Stillbirth is a devastating adverse pregnancy outcome, and intense trauma and grief overwhelm the bereaved parents. Commonly, parental emotions comprise high levels of anxiety and self-blame [15] with wide ranging consequences, including experience of prolonged grief disorder and post-traumatic stress [16]. The lack of the identification of the cause of death can increase the risk of lifelong grief that is struggling to overcome. Investigating the cause of death, some stillbirths show impressive gross cord abnormalities at birth [17]. Our results are in agreement with those previously reported [5,17,18,19] and show that many FVM are associated with gross cord abnormalities.

However, other stillborn cases (the most challenging ones) do not show any gross cord abnormalities at all at birth. Nevertheless, our study highlights that in stillbirth without gross cord abnormalities, placental histological evaluation can still detect signs of fetal blood flow obstruction. This observation agrees with what has been previously established by other investigations [6,7]. We therefore recommend that all placentas from stillbirths undergo histopathologic examination, irrespective of the presence/absence of gross cord abnormalities. The lack of gross umbilical cord abnormalities is not a sufficient condition to exclude a cord accident as a potential cause of death. Moreover, at gross placenta evaluation, FMV does not alter the macroscopic placental appearance, only infrequently does it appears as a discrete, firm, pale area [5]. Though invisible at the macroscopic placental and cord examination, these events can nonetheless compromise fetal wellbeing. Therefore, an extensive cord and placenta histopathologic examination is needed to identify FVM. The finding of lesions consistent with FVM can hint towards occult events of fetal blood flow reduction/occlusion as a potential mechanism of death.

Our cases were unaffected by the COVID-19 pandemic and showed a number of risk factors both for umbilical cord thrombosis and stillbirth, including inherited thrombophilia and clotting disorders, maternal obesity, diabetes and abnormal fetal growth, in agreement with previous reports [20,21]; this multifactorial predisposition is also in agreement with the "triple risk model" [22]: this model has been proposed in the pathogenesis of fetal death, suggesting that fetal demise results from the interplay of a variety of factors [22]. Stillbirth can be a result of the concurrent action of maternal factors, fetoplacental factors, and stressor conditions [23]. Death occurs when the individual vulnerability of the specific fetus is overwhelmed by the additive effect of stressors and maternal factors [22]. Following this model, risk factors such as reduced placental function due to multiple areas of damaged villi (as occurs in FVM and observed in our cases) may act in combination with maternal factors (such as maternal obesity, diabetes, or maternal thrombophilia) and/or fetal factors (such as fetal growth restriction), lowering the threshold to resistance of stressors (such as transient episodes of hypoxia due to transient cord compression). This model can explain the pathogenesis of stillbirth, both in cases with or without gross cord anomalies. Irrespective of the presence/absence of gross cord abnormalities, FVM increases the risk of fetal death with a nine-fold increase in rate of stillbirth in comparison to pregnancies without FVM [23]. Therefore, regarding the cause-effect relationship, the identification of FVM is more important than the identification of gross umbilical cord abnormalities.

As expected [24], our FVM-stillborn cases showed other additional abnormal placental findings. This is not surprising because the previous medical literature highlighted the worsening of pregnancy outcomes in cases with multiple placental anomalies including FVM [24].

Our study has several limitation; we acknowledge the

characteristics of a retrospective cohort study design, which limits the availability of some clinical data: clinical information about abnormal umbilical blood flow during pregnancy (such as data about umbilical Doppler waveform assessment) as well as data about conditions that may predispose to cord compression (such as oligohydramnios) are not recorded in our hospital medical record, and therefore could not included in our analysis. We attempted to mitigate this limitation by carefully evaluating a high number of umbilical cord sections, blinded for clinical data. Moreover, we recognize that the recording of some gross umbilical cord abnormalities may have been biased: it is important to remember that some gross cord abnormalities observed in the delivery room may no longer be apparent at the time of autopsy, as is the case for nuchal cord or multiple loops around the neck or the fetal body. In these cases, a detailed description of fetal and umbilical cord appearance at birth should be provided in the pathology request forms, facilitating the extent of investigation, the search of histological abnormalities and the placement of the pathologic findings within the proper clinical context. This is an important issue that health care providers should always keep in mind facing stillbirth, allowing pathologists and in turn parents in the reconstruction of the mechanisms that led to fetal death.

We are conscious that the discrimination between signs of in vivo pathological interruption of fetal blood flow and postmortem cessation of fetal circulation can be challenging. In vivo interruption of fetal blood flow in the placenta leads to vascular stasis first, then to thrombosis, and then to a gradual loss/karyorrhexis of fetal blood vessels in a portion of chorionic villi downstream the obstruction, leading to avascular villi [5,8]. The zonal distribution and the temporal heterogeneity of these features warrant the occurrence of the lesions before the fetal death, allowing the distinction between ante-mortem and post-mortem placental histological lesions (Fig. 6), in agreement with the international criteria [24]. Conversely, postmortem placental changes result from total cessation of blood flow through all fetal vessels, with homogenous, diffuse, changes throughout the entire placenta [20,23]. In this context, a strength of our study was the rigorous adoption of standardized diagnostic criteria [7-9] allowing an in-depth identification of the actual cases of FVM and avoiding erroneous interpretation.

In conclusion, when investigating the etiopathogenesis of fetal death, our data suggest that the absence of gross cord abnormalities is not enough to exclude the occurrence of a cord accident. We suggest that placental histology should be always thoroughly investigated, especially when the umbilical cord shows normal gross appearance. Changes consistent with FVM mainly affect cases without gross anomalies and act as an invisible killer. We recognize that most cases of FVM are sporadic and the risk of FVM recurrence in subsequent pregnancies is low [25]; obviously anatomical cord abnormalities are not preventable in future pregnancies but the risk of recurrence of cases of FVM related with maternal clinical conditions (i.e. thrombophilia, obesity, diabetes) are potentially preventable. Future studies need to document preventive

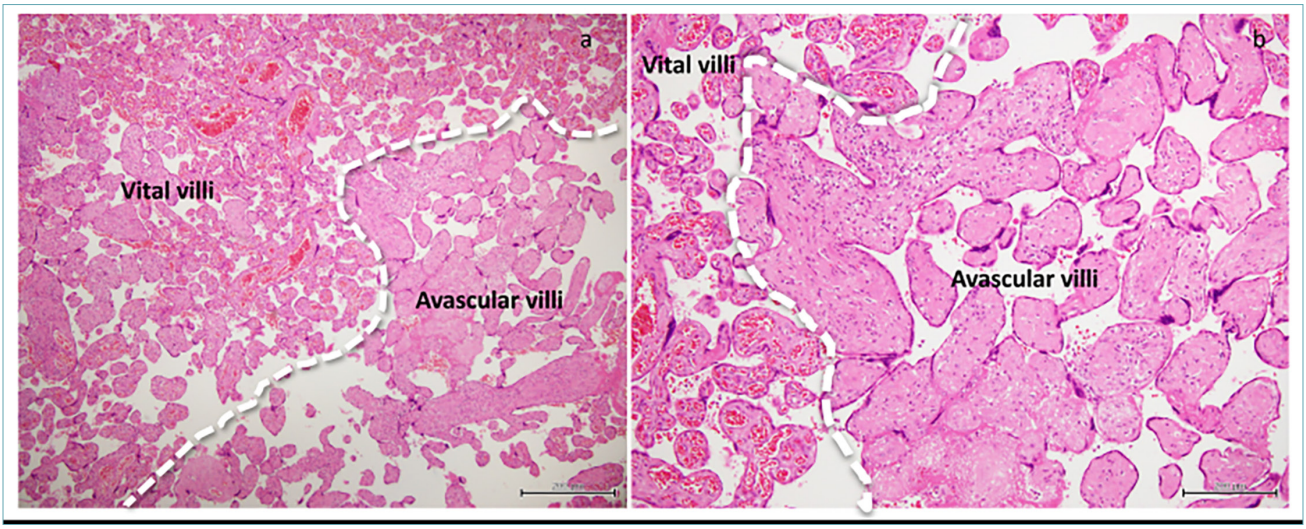


Figure 6. Low (a) and high (b) powered images of avascular villi on the right and normally vascularized villi on the left. The histological picture is an expression of FVM: the co-occurrence of avascular villi in contiguity with vital villi indicates an antemortem lesion rather than a post-mortem involution. Scale bars = 200 µm

strategies about this histological lesion [25]. However, the first mandatory step for future preventive actions is through the understanding of the clinical significance of this histological lesion, helping parents and health care providers in the real identification of the actual cause of fetal death.

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Conflicts of interests statement

The authors declare no conflicts of interest.

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Authors' contributions

LA: conceptualization; investigation; data curation; data analysis; writing original draft.
FM: investigation; data curation; review & editing. BM: data curation; review & editing. FF: supervision; review & editing. GB: supervision; investigation; review & editing.

Ethical considerations

Ethical approval was obtained from the local Institutional Review Board (Ethical committee Area Vasta Emilia Nord, #35265; date of approval: November 24, 2021). The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki. The study was retrospective, and therefore patients' signed release forms were unobtainable. On the other hand, the study was performed in a university hospital, and the data in question were obtained with the patients' understanding that they might be published/re-used for secondary analyses. Moreover, informed consent for diagnostic work-up was not required, because diagnostic investigations, among which histopathologic examination of the placenta, are mandatory by law in cases of stillbirth in our Country (legal references D.M. 7/2014 and D.P.C.170/99).

Availability of data and materials

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

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