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REVIEW ARTICLE

Fetal Thrombotic Vasculopathy

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Abstract Fetal thrombotic vasculopathy (FTV) is the term used to encompass the histologic findings identified in placentas with fetal thrombotic lesions: occlusive and nonocclusive chorionic vessel thrombi, avascular villi in the distribution of a single villous tree, intramural vascular fibrin, and hemorrhagic endovasculitis. The underlying etiology of FTV is largely unknown though hypercoagulability and circulatory stasis have been the main focuses in the literature to explain the hemostatic abnormalities. This article reviews the literature in both defining and discussing, potential etiologies of FTV, as well as neonatal outcomes.

Keywords Fetal thrombotic vasculopathy · Thrombophilia · Thrombosis · Avascular villi · Cerebral palsy

Introduction

Fetal thrombotic vasculopathy (FTV) is a term that was originally coined by Redline and Pappin in 1995 to encompass the histologic findings identified in placentas with fetal thrombotic lesions: occlusive and nonocclusive chorionic vessel thrombi, avascular villi in the distribution of a single villous tree, intramural vascular fibrin, and hemorrhagic endovasculitis [1]. In 2004, the Fetal Vascular Obstruction Nosology Committee formally defined FTV as the presence of 15 or more avascular villi or villous stromal-vascular karyorrhexis in two or more foci per slide, with or without an identifiable fetal vessel lesion and in the absence of "villitis of unknown etiology with stem villitis and avascular villi" [2]. Using this criteria, the published incidence of FTV varies from 1 to 6.4 %, though the higher percentages may be inflated due to examination of only placentas from high-risk pregnancies and cases of intrauterine fetal demise (IUFD) [1, 3–7].

Gross findings are not necessary for the diagnosis of FTV. While it can be helpful to visualize thrombi in the vessels of the chorionic plate or large stem vessels, often, the occluded vessels are not grossly identifiable [3]. This accounts for the widely variable gross appearance of placentas with FTV. Placentas often have only subtle changes that are easily overlooked. When grossly identifiable, early FTV lesions appear as wedge-shaped areas of parenchymal pallor with the same consistency as the surrounding uninvolved parenchyma [3, 7]. Late lesions become gray-white and firm, which can make them difficult to distinguish from maternal villous infarcts grossly [3].

Microscopically, FTV can be recognized definitively by identifying one or more thrombosed fetal vessel. More frequently, the diagnosis is inferred based on the distribution of avascular villi, which conforms to the vascular distribution of a single villous tree, with adjacent normally vascularized villi and surrounded by an open maternal space. If the occluded vessel is visualized microscopically, the timing of lesions can be estimated by a recognizable evolution of change. Early lesions are fibrin-rich and expand the vessel, resulting in destruction of endothelial cells and extravasation of erythrocytes. As the thrombus organizes, fibroblast-like cells can be seen within the thrombus, imparting a multiluminal appearance that resembles recanalization. In the literature, this is referred to

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as septation [3, 4, 8]. Septation also occurs in large superficial placental vessels and vessels of stem villi as consequence of vascular stasis (Fig. 1). Regional vascular septation and avascular villi are probably the most objective and sensitive markers of fetal vascular stasis in the placenta [1]. Affected villi characteristically show fragmentation of capillary endothelial cell nuclei, erythrocyte extravasation, and stromal karyorrhectic debris. Ultimately, the vessels become completely obliterated leading to fibrotic villous stroma with no capillaries (Figs. 1, 2). In the absence of identifiable thrombi, avascular villi can be classified as FTV if other nonthrombotic causes such as chronic villitis and perivillous fibrin deposition are not present [3].

Similar regressive changes can be seen in placentas from IUFD secondary to ultimate circulatory stasis [3]. The earliest demonstrable change in fetal vessels after demise is karyorrhexis of endothelial cells, which is usually seen within 48 h [9]. Even with some allowance for variation in the evolution or organization, vessel septation and complete obliteration is suspicious for pre-mortem thrombus formation if time of demise is known to be less than 48 h before delivery [4, 8]. Fetuses retained for an unknown amount of time pose a greater diagnostic dilemma. Because of the global vascular stasis that occurs after fetal demise, the regressive vascular changes should occur diffusely throughout the placenta [3, 7]. In contrast, focal clustering of avascular villi interspersed among normally vascularized villi would be more consistent with an isolated vessel thrombus, as would be seen in FTV [7]. Widely-disparate timing in the microscopic appearance of fetal vascular changes also suggests a pre-mortem onset of the thrombotic process.

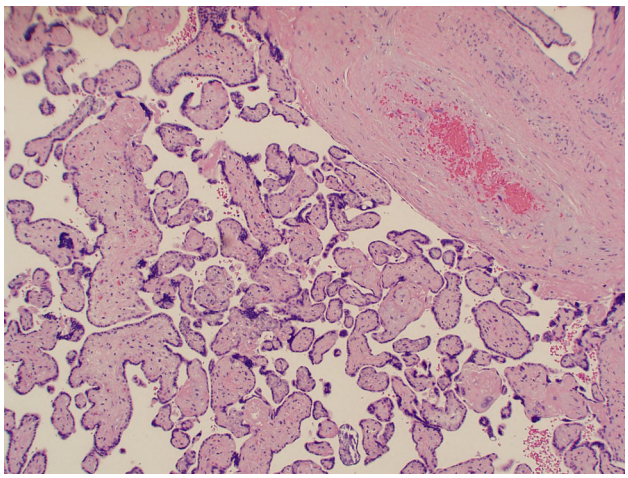

Fig. 1 A stem villus (*upper right*) contains a septated vessel, and is surrounded by villi with extravasated *red cells* and absent capillaries

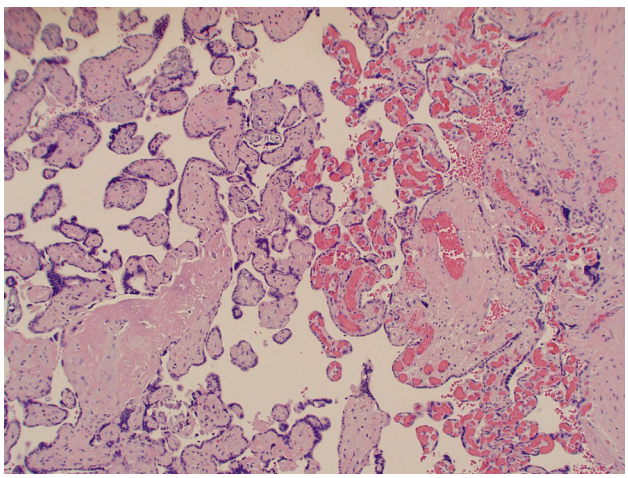

Fig. 2 Avascular villi (*left*) are easily identified next to normal villi (*right*)

Discussion

The underlying etiology of FTV is largely unknown, but the large body of literature covering the subject highlights its significant complexity. The balance between bleeding and clotting is tilted toward the former in normal fetuses and neonates secondary to lower levels of vitamin K-dependent clotting factors and lower reactivity of platelets and endothelium [10]. Because of this, thrombotic lesions in the placenta suggest a significant hemostatic abnormality. Hypercoagulability and circulatory stasis have been the main focuses in the literature to explain those hemostatic abnormalities.

In the realm of hypercoagulability, one hypothesis suggests an association between FTV and an acquired or genetic thrombophilia in the mother, fetus, or both. This is a controversial theory with inconsistent findings among studies. One of the first to suggest the role of hypercoagulability in the development of FTV was Redline and Pappin in 1995 [1]. Among 29 cases of FTV, five mothers had either antiphospholipid (APL) antibodies, antiplatelet antibodies, or recurrent DVT, though it is unclear whether thrombophilia testing was performed on all 29 cases. Numerous studies have been performed to further define this hypothesis. Arias and colleagues [11] evaluated 13 women referred for poor pregnancy outcome and placental thrombotic lesions with comprehensive thrombophilia testing (antithrombin III [ATIII] activity, protein-C activity, protein-S deficiency, activated protein-C resistance [APCR], lupus anticoagulant [LA], anticardiolipin antibodies, antinuclear antibodies [ANA] and factor V Leiden [FVL] mutation). Seven of these women (54 %) had one or more positive test (protein-S deficiency, FVL heterozygosity or ATIII deficiency) leading them to suggest a

relationship between thrombophilia and placental thrombosis. Kraus and Acheen [4] evaluated 84 perinatal autopsies, identifying 16 cases of FTV. Upon chart review, eight cases had received thrombophilia testing, four of which (50 %) had one or more positive test (APCR, protein S deficiency, ATIII deficiency, anticardiolipin antibodies, elevated ANA, or a methylenetetrahydrofolate reductase [MTHFR] mutation). Though testing was not complete, they still felt that there was a strong correlation between FTV and coagulopathy. Vern and colleagues [6] performed genetic testing on fetal DNA for FVL and the prothrombin G20210A. They first, prospectively, analyzed 155 placentas. Five of these cases (3 %) fit their criteria for "fetal side thromboembolic" (FST) events and none had mutations. They then did a retrospective search of their database for FST and were able to successfully amplify 27 cases. No prothrombin mutations were identified but five had heterozygous FVL mutations, which was more than three times that of their control population. Because of a lack of other known risk factors for FST, they felt that FVL, likely, contributed to fetal thrombophilia. Gogia and colleagues [12] evaluated 3600 singleton placentas for placental thrombotic disease and found 11 cases with FTV. Nine of these (82 %) were positive for a thrombophilia (protein-S deficiency, protein-C deficiency, ATIII deficiency, FVL heterozygosity, MTHFR mutation, and anticardiolipin antibodies).

Probably, the most cited article in support of the thrombophilia hypothesis is Khong and Hague's [13] case report of discordant intrauterine growth restriction (IUGR) in dichorionic twins with known polymorphisms in MTHFR. Twin A was of normal weight upon delivery and other than a single umbilical artery had no pathologic placental lesions. Twin B, on the other hand, was below the 3rd percentile in weight and had significant FTV in its placenta. The mother was found to be a compound heterozygote for the C677T and A1298C polymorphisms and the father carried a single A1298C polymorphism. Twin A inherited a single C677T polymorphism but twin B was homozygous for the A1298C polymorphism. This is the first reference to the possibility of FTV secondary to fetal and not just maternal thrombophilia. Since then, MTHFR polymorphisms in cases of FTV have been repeatedly described. Ernst and colleagues [14] presented a case of a woman with a single MTHFR A1298C polymorphism who had three consecutive pregnancies complicated by IUFD in one case and fetal liver disease in the other two. The placenta was only examined in the 1st pregnancy and showed extensive FTV. The only child tested (from the 2nd pregnancy) was positive for the A1298C polymorphism. Though neither the father nor the two other offspring were tested, the authors surmised that there could have been a genetic component causing thrombophilia. Wintermark et al. [15] presented a case of FTV associated with a premature neonate born with persistent thrombocytopenia and disseminated intravascular coagulopathy. The mother was found to be a complex heterozygote with both C677T and A1298C polymorphisms and the baby was positive for the C677T polymorphism. Demirel et al. [16] identified 30 cases of FTV and performed genetic thrombophilic testing on both the mother and liveborn infants (IUFD occurred in two cases and conceptus was not tested). Testing included MTHFR polymorphisms, FVL, prothrombin, factor XIII, B-fibrinogen, plasminogen activator inhibitor, human platelet antigen 1, angiotensin-converting enzyme, Apo A, and Apo E. Seven cases had a positive workup, all of which, had MTHFR polymorphisms (either heterozygous or homozygous) in all infants and six mothers. Though this seemed significant, the prevalence was not greater than the background incidence of this mutation in their general population.

Other studies have contradicted the hypothesis of thrombophilia as a significant cause of FTV. Ariel et al. [10] gathered placentas from 64 pregnancies complicated by either pre-eclampsia, placental abruption, and/or IUGR. Both the mother and neonate were tested for FVL, prothrombin G20210A, and the C677T MTHFR mutations. Nineteen of their cases had mutations but there was no statistical difference in prevalence between placentas with and without fetal vascular lesions. Beeksma et al. [8] first looked at consecutive cases of singleton IUFD with available thrombophilia testing results (protein-S deficiency, FVL, prothrombin, LA, APL antibodies, and MTHFR C677T, and A1298C polymorphisms). Fifty-four of the IUFD cases had FTV and 22 of these (41 %) had positive thrombophilia testing. They then selected 30 random placentas from livebirths with known positive thrombophilia testing results. In this cohort, only five had FTV lesions. After statistical analysis of their results, there was no significant correlation between maternal thrombophilia and FTV.

There are two significant limitations in the studies that have evaluated thrombophilia in cases of FTV. The first is that there are different definitions of FTV between papers. This is especially true in papers published before 2004, when FTV was formally defined [2]. Many papers included the presence of hemorrhagic endovasculitis, intimal fibrous cushions, and/or allowed foci of avascular villi fewer than the 15 considered diagnostic today [1, 5, 6, 8, 10, 11]. The second is the inconsistency of thrombophilia testing among studies. Many of the studies were retrospective and were thus limited to tests that had been chosen by the clinicians at the time [1, 4, 6, 8, 10, 12]. Three studies limited their testing to genetic thrombophilias that could be directly diagnosed by DNA methodology [6, 10, 16]. While it is

convenient and relatively noninvasive to identify thrombophilia mutations by PCR (FVL, prothrombin, MTHFR), the more classic thrombophilias (protein-S deficiency, LA, APL syndrome) cannot be evaluated this way.

It is obvious from the number of FTV cases in these studies, which have no identifiable thrombophilia, that the presence of a thrombophilic disorder is not necessary to produce FTV. Whether or not identifiable thrombophilias play a significant role in the development of FTV, the coagulation abnormalities that have been studied thus far, are at most risk factors that require a 2nd, more common antenatal event to cause thrombosis [17]. When present, thrombophilias, most likely, act in concert with other more potent initiators of thrombosis such as fetal blood flow reduction (umbilical cord obstruction), increased fetal circulatory stasis (cardiac insufficiency, hyperviscosity), or placental tissue damage that activate endothelium, platelets, and the coagulation system (cytokines, meconium, activated complement components) [10, 15, 17–19].

Probably, the most discussed source of circulatory stasis and fetal blood flow obstruction discussed in the literature is umbilical cord abnormality (UCA). The presence of UCA in placentas with FTV is significantly variable among studies, with estimates anywhere from 8 to 79 % [17, 20–22]. Redline was the first to formally study this association when he evaluated the placentas of 125 infants with neonatal encephalopathy (NE) [17]. FTV was identified in 23 placentas, 17 of which had UCA (nuchal/body part cords, true knots, marginal/membranous insertion, decreased Wharton's jelly, abnormal coiling). Tantbirojn et al. [21] performed a retrospective review of 224 singleton placentas with UCA (true knots, long cords, nuchal/body part entanglement, abnormal coiling, and decreased Wharton's jelly) and 317 gestationally-matched controls. The incidence of FTV was four times more common in the group with UCA compared to controls (69 vs. 18 cases). This group published a 2nd article outlining complications associated with FTV and found that in term deliveries, cord abnormalities were statistically increased in cases of FTV compared to controls [23]. Avagliano et al. [20] analyzed 317 perinatal autopsies and found 32 cases with thrombosed umbilical cord vessels. Because specific evaluation of UCA was not the primary purpose of the study, the presence of abnormalities was only addressed in the setting of thrombosed umbilical vessels. In this group, 23 of 32 cases had UCA (entanglement, abnormal coiling, marginal insertion). Ten cases of FTV were also identified in the original 32 cases, of which, 50 % had UCA. Ernst and colleagues [22] limited their evaluation to 314 cases of hypercoiled umbilical cords and significant FTV was identified in 25 cases. Of note, if less severe histology of fetal vascular obstruction is included, the incidence increases to 56 %, which is closer to the incidence reported in the other studies.

This shows that sampling error could be a significant limitation to the studies discussed thus far. In Redline's study, 31 additional placentas had a cord abnormality but no evidence of FTV [17]. He addressed that the cases evaluated were sent to him for consultation and placental sampling was sometimes inadequate for thorough evaluation, increasing the possibility of missing microscopically-significant lesions. Tantbirojn [21] also addressed this limitation given that only two placental sections were examined per case in the study.

While there is no consensus on the cause of FTV, the adverse outcomes found in conjunction with this lesion have been well described. The proposed mechanisms by which FTV is involved in disease include hypoxia secondary to extensive placental damage, or direct organ damage caused by thromboembolic disease. The presence of FTV is thought to reliably predict the presence of thrombi and infarcts in various organs [4] but there is no way to establish whether the thrombi form in situ or first occur in the placenta and embolize into fetal circulation. Unlike in adults where the lung is the main organ involved by thromboembolic disease, shunting of blood through the ductus venosus and foramen ovale in the fetus changes the predominant distribution of thromboemboli, which are more commonly found in the liver, heart, and brain.

Many publications have linked FTV to NE and the development of cerebral palsy (CP) [4, 24–26]. A study comparing 93 term infants with NE to 387 random controls found FTV to be significantly increased in the NE group (13 vs. 3 %) [25]. In a study looking through the medicolegal registry, evaluation of the placentas of 125 infants with NE, CP, or other long-term neurologic impairment found FTV in 18 %, compared to 2 % in a control group of 250 without documented neurologic sequelae [26]. Other studies have found a slightly higher occurrence of neurodevelopmental delay, behavior disorders, motor disorders, and language retardation, though this was not found to be statistically significant when compared to control populations (long-term follow-up was unavailable in many of their cases so long-term neurologic sequelae could not be evaluated) [23, 27]. IUFD is the other adverse outcome that has shown association with FTV. Whether FTV directly results in IUFD or is an element of a more global insult is unknown. In a study that looked at 16 cases of FTV in IUFD, 10 had no other significant finding to explain demise [5]. Saleemuddin and colleagues [23] found that IUFD was significantly more common in cases of FTV compared to their control population (12.4 vs 1.4 %, respectively). Lepais and colleagues [27] found that mortality in cases of FTV was three times that seen in their control population. Other complications that have shown

significant association with FTV include liver injury [14, 28], IUGR [13, 21, 29], intestinal atresia [30], cardiac abnormalities [23], oligohydramnios [23], and major thromboembolic events [1, 4, 25, 27].

Conclusion

It is obvious that FTV is a complicated, multifactorial phenomenon and the literature pertaining to the subject is far from complete. While searching for a single overriding cause is unrealistic, proper identification of significant and potentially-treatable risk factors could guide our clinical colleagues in appropriate maternal and infant or fetal workup. Proper elucidation of this problem will require controlled prospective studies with complete placental examination and comprehensive testing of parents and children for coagulopathies, as well as long-term follow-up of children diagnosed with FTV for sequelae of disease that may not be apparent in the immediate postnatal period.

Compliance with Ethical Standards

Conflict of interest None.

References

1. Redline RW, Pappin A. Fetal thrombotic vasculopathy: the clinical significance of extensive avascular villi. Hum Pathol. 1995;26(1):80–5.
2. Redline RW, Ariel I, Baergen RN, Desa DK, Kraus FT, Roberts DJ, Sander CM. Fetal vascular obstructive lesions: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol. 2004;7(5):443–52.
3. Kraus FT, Redline RW, Gersell DJ, Nelson DM, Dicke JM, editors. Placental pathology atlas of nontumor pathology. Washington DC: Armed Forces Institute of Pathology; 2004.
4. Kraus FT, Acheen VI. Fetal thrombotic vasculopathy in the placenta: cerebral thrombi and infarcts, coagulopathies, and cerebral palsy. Hum Pathol. 1999;30(7):759–69.
5. Leistra-Leistra MJ, Timmer A, van Spronsen FJ, Geven WB, van der Meer J, Erwich JJ. Fetal thrombotic vasculopathy in the placenta: a thrombophilic connection between pregnancy complications and neonatal thrombosis? Placenta. 2004;25(Suppl A):S102–5.
6. Vern TZ, Alles AJ, Kowal-Vern A, Longtine J, Roberts DJ. Frequency of factor V(Leiden) and prothrombin G20210A in placentas and their relationship with placental lesions. Hum Pathol. 2000;31(9):1036–43.
7. Gersell DJ. Selected vascular lesions of the placenta. Clin Lab Med. 1995;15(3):611–29.
8. Beeksma FA, Erwich JJ, Khong Y. Placental fetal vascular thrombosis lesions and maternal thrombophilia. Pathology. 2012;44(1):24–8.
9. Genest DR. Estimating the time of death in stillborn fetuses: II. Histologic evaluation of the placenta; a study of 71 stillborns. Obstet Gynecol. 1992;80(4):585–92.
10. Ariel I, Anteby E, Hamani Y, Redline RW. Placental pathology in fetal thrombophilia. Hum Pathol. 2004;35(6):729–33.
11. Arias F, Romero R, Joist H, Kraus FT. Thrombophilia: a mechanism of disease in women with adverse pregnancy outcome and thrombotic lesions in the placenta. J Matern Fetal Med. 1998;7(6):277–86.
12. Gogia N, Machin GA. Maternal thrombophilias are associated with specific placental lesions. Pediatr Dev Pathol. 2008;11(6):424–9.
13. Khong TY, Hague WM. Biparental contribution to fetal thrombophilia in discordant twin intrauterine growth restriction. Am J Obstet Gynecol. 2001;185(1):244–5.
14. Ernst LM, Grossman AB, Ruchelli ED. Familial perinatal liver disease and fetal thrombotic vasculopathy. Pediatr Dev Pathol. 2008;11(2):160–3.
15. Wintermark P, Boyd T, Parast MM, Van Marter LJ, Warfield SK, Robertson RL, Ringer SA. Fetal placental thrombosis and neonatal implications. Am J Perinatol. 2010;27(3):251–6.
16. Demirel G, Celik IH, Zergeroglu S, Erdeve O, Dilmen U. Neonatal outcome of the pregnancies associated with placental villous thrombosis—thrombophilic status of the mothers and the infants. J Matern Fetal Neonatal Med. 2012;25(11):2225–9.
17. Redline RW. Clinical and pathological umbilical cord abnormalities in fetal thrombotic vasulopathy. Hum Pathol. 2004;35(12):1494–8.
18. Gomez B, Romero R, Ghezzi F, et al. The fetal inflammatory response syndrome. Am J Obstet Gynecol. 1998;179:194–202.
19. Matzinger P. The danger model: a renewed sense of self. Science. 2002;296(5566):301–5.
20. Avagliano L, Marconi AM, Candiani M, Barbera A, Bulfamante G. Thrombosis of the umbilical vessels revisited. An observations study of 317 consecutive autopsies at a single institution. Hum Pathol. 2010;41(7):971–9.
21. Tantbirojn P, Saleemuddin A, Sirois K, Crum CP, Boyd TK, Tworoger S, et al. Gross abnormalities of the umbilical cord: related placental histology and clinical significance. Placenta. 2009;30(12):1083–8.
22. Ernst LM, Minturn L, Huang MH, Curry E, Su EJ. Gross patterns of umbilical cord coiling: correlations with placental histology and stillbirth. Placenta. 2013;34(7):583–8.
23. Saleemuddin A, Tantbirojn P, Sirois K, Crum CP, Boyd TK, Tworoger S, et al. Obstetric and perinatal complications in placentas with fetal thrombotic vasculopathy. Pediatr Dev Pathol. 2010;13(6):459–64.
24. Kraus FT. Cerebral palsy and thrombi in placental vessels of the fetus: insights from litigation. Hum Pathol. 1997;28(2):246–8.
25. McDonald DG, Kelehan P, McMenamin JB, Gorman WA, Madden D, Tobbia IN, et al. Placental fetal thrombotic vasculopathy is associated with neonatal encephalopathy. Hum Pathol. 2004;35(7):875–80.
26. Redline RW. Severe fetal placental vascular lesions in term infants with neurologic impairment. Am J Obstet Gynecol. 2005;192(2):452–7.
27. Lepais L, Gaillot-Durand L, Boutitie F, Lebreton F, Buffin R, Huissoud C, et al. Fetal thrombotic vasculopathy is associated with thromboembolic events and adverse perinatal outcome but not with neurologic complications: a retrospective cohort study of 54 cases with a 3-year follow-up of children. Placenta. 2014;35(8):611–7.
28. Dahms BB, Boyd T, Redline RW. Severe perinatal liver disease associated with fetal thrombotic vasulopathy. Pediatr Dev Pathol. 2002;5(1):80–5.
29. Redline RW, Shah D, Sakar H, Schluchter M, Salvator A. Placental lesions associated with abnormal growth in twins. Pediatr Dev Pathol. 2001;4(5):473–81.
30. Lian DW, Lam JC, Aung AC, Li FX, Change KT. Intestinal atresia occurring in association with placental fetal thrombotic vasculopathy: a case report with literature review. Pediatr Dev Pathol. 2013;16(1):28–31.