



Gross Abnormalities of the Umbilical Cord: Related Placental Histology and Clinical Significance

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ABSTRACT

Objective: To evaluate umbilical cord abnormalities predisposing to mechanical cord compression and determine their relationship to adverse clinical outcomes and stasis-associated histologic changes in the placenta.

Methods: Placental slides of 224 singleton pregnancies with gross cord abnormality (true knots, long cords, nuchal/body cords, abnormal cord insertion, hypercoiled cords, narrow cords with diminished Wharton's jelly), delivered on or after 28 weeks gestational age, and 317 gestational age-matched controls, were reviewed and specifically evaluated for the following histologic changes: (1) fetal vascular ectasia, (2) fetal vascular thrombosis, (3) and fetal thrombotic vasculopathy/avascular villi. These changes were analyzed in relation to both clinical information and findings at gross pathologic examination.

Results: Gross cord abnormalities were associated with stillbirth, intrauterine growth restriction, non-reassuring fetal tracing, meconium-stained amniotic fluid, and increased rate of emergency Cesarean section. At microscopic evaluation, cases with gross cord abnormalities showed a statistically significant association with both ectasia and thrombosis in the fetal vasculature, as well as changes of fetal thrombotic vasculopathy in the terminal villi. When considering individual gross cord abnormalities, long cord and nuchal cord had the highest rates of thrombosis-related histopathology. Finally, cases with both abnormal cords and histologic thrombosis had significantly higher rates of adverse outcomes, including IUGR and stillbirth.

Conclusion: Gross cord abnormalities predispose the fetus to stasis-induced vascular ectasia and thrombosis, thus leading to vascular obstruction and adverse neonatal outcome, including IUGR and stillbirth. We recommend a thorough histopathologic evaluation of all placentas with gross cord abnormalities predisposing to cord compression.

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1. Introduction

Fatal compromise of umbilical circulation is suspected in at least 20% of stillbirths at autopsy [1]. Any type of force that compresses umbilical cords may lead to diminished blood flow in umbilical vessels and subsequent fetal hypoxia or circulatory compromise. Mechanical cord compression or "cord accident" can be caused by cord entanglements (nuchal/body cords) and cord prolapse; or it may arise from an abnormal configuration of the cord such as true knots, hypercoiling/twisting, abnormally long

cords, abnormal cord insertions, or strictures [2]. These conditions may occur acutely or be present intermittently and cause chronic circulatory obstruction. Many intrapartum complications and adverse perinatal outcomes have been associated with such umbilical cords abnormalities, including stillbirth, intrauterine growth restriction (IUGR), non-reassuring fetal heart tracing (NRFHT), low Apgar scores, and meconium staining, and likely depend on duration and degree of occlusion [4–14]. In addition, late neonatal complications have also been associated with gross cord abnormalities, including pulmonary hypertension and neurologic impairment [15–17]. However, these same cord abnormalities can also be found in unremarkable live births [2], and as such remain controversial as the mechanism behind the above-mentioned peri- and post-natal complications.

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We previously studied umbilical cord pathology and associated histopathologic changes in the fetoplacental circulation in a series of stillbirths, and established highly specific criteria for the histologic diagnosis of non-acute umbilical cord obstruction (“cord accident”) [3]. These changes relate to vascular congestion and stasis, which occur following compression of the umbilical vein, and include ectasia and thrombosis of the large fetal vessels in the placenta as well as avascularity or near-avascularity of terminal chorionic villi [3]. The latter findings, previously labeled as “fetal thrombotic vasculopathy” (FTV), have been found to be highly associated with poor perinatal outcome, including stillbirth and neurologic impairment [4]. While our study showed thrombosis and FTV to be highly specific for cord-related stillbirth, other questions remained: 1) whether these histologic changes occur in placentas of live births with cord abnormalities; and more importantly, 2) whether the presence of thrombosis and FTV could pinpoint the subset of fetuses with umbilical cord abnormalities at risk for adverse outcome. To this end, we set out to compare both perinatal outcome and placental histologic features in all births with and without umbilical cord abnormalities.

2. Materials and methods

After approval by the Internal Review Board, the Pathology Department database at Brigham and Women’s Hospital was searched for cases of singleton placentas with potentially obstructive gross umbilical cord abnormalities, delivered on or after 28 weeks gestational age, received between 1987 and 2007. Cord abnormalities included true knots, excessively long cords, nuchal/body cords, hypercoiled cords (umbilical cord coil index > 0.3 coils per cm) [4], narrow cords due to diminished Wharton’s jelly (maximum cord diameter < 0.8 cm) either focally (“stricture”) or involving a longer segment of cord [18], and abnormal cord insertion (marginal or velamentous). Long umbilical cord was defined as cord length greater than 68th percentile (one standard deviation above the mean) for gestational age [5]. Additional gestational age-matched singleton placenta cases with no gross cord abnormality were selected randomly for the control group. Due to the policy on placental referral for pathologic examination, all placentas used in this study had an associated abnormality either in the fetus (i.e. growth restriction), maternal/obstetric history (i.e. preeclampsia), or in the placenta itself (i.e. true knot in cord). Gross examination and sampling of placentas was consistent over the study period, supervised by one of the authors (K.S.), and included a minimum of one block of umbilical cord and membrane roll and 2 blocks of placental parenchyma. Placental slides were reviewed jointly by two authors (M.M.P. and P.T.), blinded to all clinical and gross information contained in the Surgical Pathology reports. Cases with missing samples of umbilical cord, or containing less than two slides of chorionic plate, were deemed under-sampled for purposes of this study and were thus excluded.

The presence or absence and location of the following microscopic findings were noted: 1) fetal vascular ectasia, 2) fetal vascular thrombosis, 3) avascular villi, and 4) villous stromal karyorrhexis (VSK). Fetal vascular ectasia was defined as vascular distension to at least four times the diameter of an adjacent muscular vessel of similar caliber; for vascular ectasia in the cord, the vessels in one cross-section were compared to an adjacent cord cross-section [3]. Fetal vascular thrombosis included 1) organizing and organized thrombi in muscular vessels, characterized by adherent, fibrin containing thrombi, which are at times calcified [3,15]; 2) early muscular vessel thrombi, identifiable by focal loss of vascular endothelial integrity with erythrocyte fragmentation and mural extravasation (Fig. 1A) [3]; and 3) intimal fibrin cushions

(Fig. 1B) [15]. For both ectasia and thrombosis, the types of muscular fetal vessels involved were documented, including umbilical cord, chorionic plate, and stem villous vessels. In addition, the presence and distribution (focal, regional, or diffuse) of avascular villi or VSK in the terminal chorionic villi were documented. VSK was defined by the presence of fragmented erythrocytes (Fig. 1C) or karyorrhectic debris (Fig. 1D) in terminal villi, while avascular villi represented complete loss of villous vasculature (Fig. 1E) [15]. Fetal thrombotic vasculopathy was defined by the presence of either avascular villi or VSK, the latter being the intermediate lesion with incomplete loss of villous vasculature. Lesions were classified as “focal,” if there were fewer than 15 contiguous terminal villi affected, or as “regional,” if 15 or more contiguous villi were involved [15]. Notation was made if any of the above findings were associated with other placental pathology, such as infarction, abruption, or chronic villitis. Such cases, as well as those with diffuse avascular villi or VSK representing prolonged fetal demise-delivery periods, were subsequently excluded from the study. Histologic findings were then tabulated along with clinical information and gross examination findings obtained from Pathology reports and electronic medical records. The extracted clinical information included maternal age, antepartum and intrapartum complications, as well as birth weight and Apgar scores at 1 min. Intrauterine growth restriction was defined as birth weight less than 10th percentile for gestational age. Not all of the above clinical information was available in every case; hence, the tabulated data includes both the number of cases with the available information, as well as the total number of cases in that category. For example, of control cases without gross cord abnormalities (317 total), data on fetal growth was available in 313, of which 23 showed intrauterine growth restriction (IUGR); hence the percentage with IUGR is shown as 23/313 or 7.3% (Table 1). *P* values were calculated after exclusion of cases with unavailable data.

Statistical analyses were performed with the SPSS for Windows software (version 13; SPSS Inc, Chicago, IL, USA). The statistical significance of differences between the study groups was assessed with the Chi-square or Fisher’s exact tests where appropriate for categorical variables and *t*-test for continuous variables. Multiple logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for adverse outcomes associated with cord abnormalities after adjusting for gestational age.

3. Results

3.1. Clinical information

Of the 224 cases with gross cord abnormality, 68 (30%) had an abnormal insertion, 99 (44%) had nuchal/body cord, 75 (33.5%) had a long cord, 61 (27.2%) had a true knot, and 10 (4.5%) had either a narrow or hypercoiled cord. Also, of the cases, 160 (71.4%) had a single cord abnormality, 53 (23.7%) had two, and 11 (4.9%) had three or more abnormalities. The most common co-incident abnormalities involved long cord, 49% of which also showed other abnormalities, including nuchal cord and true knot.

Comparing the 224 cases with gross cord abnormality and 317 gestational age-matched controls, there was no statistically significant difference in maternal age, gravidity, parity, history of abortion or previous intrauterine fetal demise (Table 1); however, mode of delivery differed with a lower cesarean rate in the cases (40.1%) vs. controls (50.5%) ($P=0.018$). Fetuses with gross cord abnormalities had significantly higher occurrence of non-reassuring tracing and rate of emergency cesarean versus controls, as well as rate of stillbirth (over 10-fold increase) and intrauterine growth restriction (IUGR, 2-fold increase). A clinical history of thick meconium-stained amniotic fluid was four times more common in

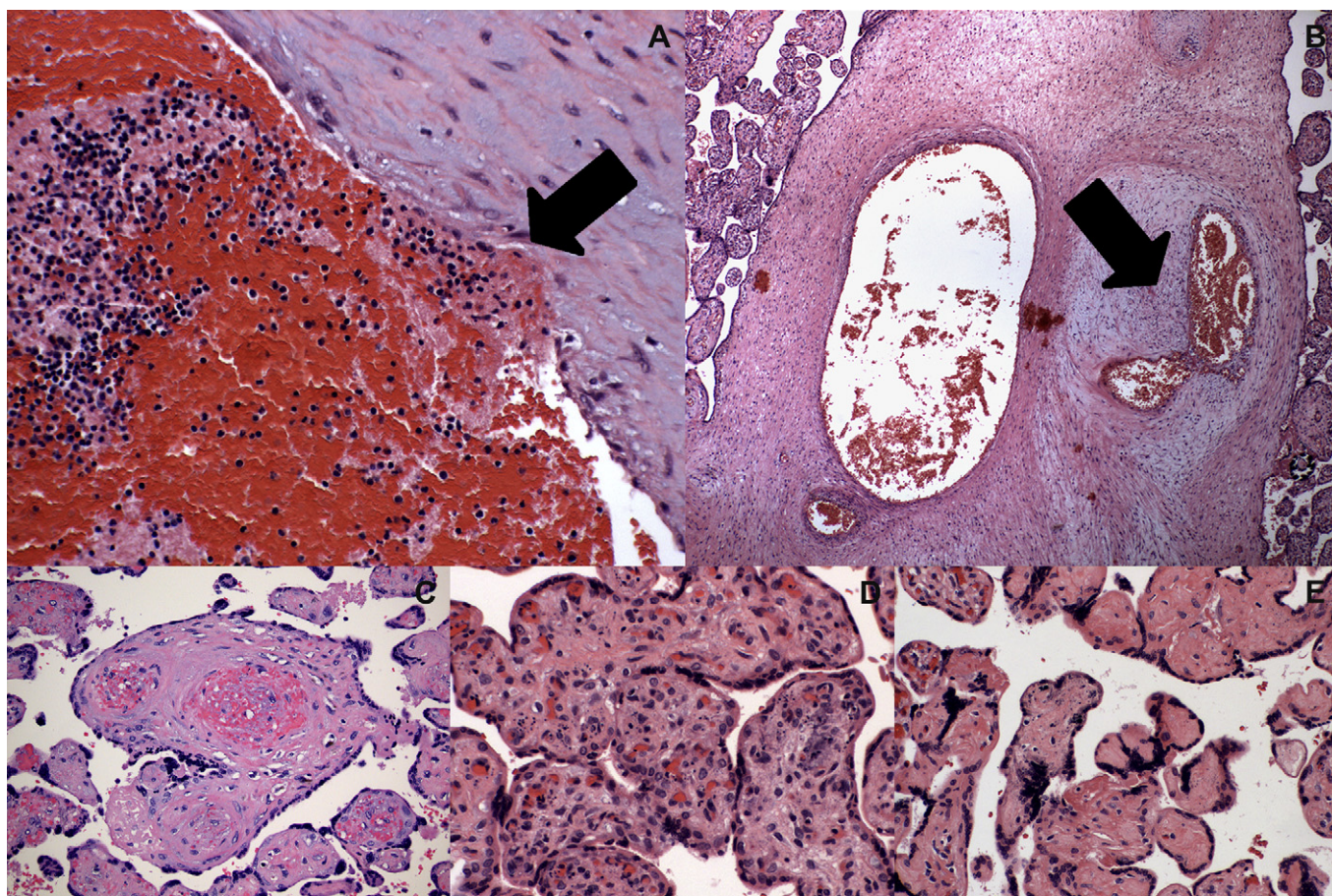


Fig. 1. Histologic changes associated with fetal thrombotic vasculopathy. A) Early organizing thrombus in chorionic plate vessel, identified as fibrin deposit on the vascular wall with focal loss of endothelial lining (H&E, original magnification $\times 200$). B) Organized thrombus in stem villous vessel with intimal thickening on the right, compared to dilated, non-thrombosed vessel on the left (H&E, original magnification $\times 40$). C and D) Villous stromal karyorrhexis (VSK), defined by extravasated red blood cells (C) and karyorrhectic debris (D) in terminal villi (H&E, original magnification $\times 200$). E) Avascular villi with fibrotic stroma and loss of villous vasculature (H&E, original magnification $\times 200$).

cases than controls. Finally, although the delivered infants in the gross cord abnormality group had a higher proportion of low one-minute Apgar scores compared to controls, this difference was not significant.

3.2. Microscopic features

Fetal vascular ectasia, fetal vascular thrombosis, and fetal thrombotic vasculopathy (FTV, defined by avascular villi, villous stromal karyorrhexis or VSK, or a combination thereof) were significantly more common in cases with gross cord abnormalities (Table 2). Vascular ectasia and thrombosis were most common in the chorionic plate and stem villous vessels, but were also more frequently seen in the umbilical cord vessels. Combined histologic findings of ectasia and thrombosis were found 3 times more frequently in abnormal cord cases vs. controls (Table 2); combined histologic findings of ectasia, thrombosis and FTV were over 30 times more frequent in abnormal cord cases (Table 2). In addition, fetal vascular thrombosis and FTV, as well as the combined features, were much more common in cord abnormality cases with adverse fetal outcome, when compared to normal cord controls with similar adverse outcomes (Table 3).

Comparison between subtypes of gross cord abnormalities is summarized in Table 4. This data includes only cases with *single* cord abnormalities. All categories, except for true knots, showed an increased risk of stillbirth. Nuchal cord also showed an increased risk of IUGR, as well as the highest frequencies of non-reassuring

fetal tracing and low Apgar scores. On microscopic examination, fetal vascular ectasia was found at significantly higher frequencies in all categories, except in membranous cord insertions. Thrombosis and FTV were found at significantly higher frequencies in long cords and nuchal cords, although marginal cord insertions also showed a significantly higher frequency of thrombosis in chorionic plate vessels (Table 4). Membranous cord insertions had low prevalence in this study (only 12 cases) and showed only increased frequency of FTV (Table 4). Compared to single abnormalities, the presence of multiple (two or more) gross abnormalities of the umbilical cord was associated with a higher rate of ectasia (2-fold higher) and thrombosis (3–10 fold higher) in the cord and chorionic plate vessels, although the rate and extent of FTV was not further increased. Interestingly, single and multiple cord abnormalities were both associated with a 9–11 fold increase in rate of stillbirth; however, the frequency of IUGR was increased significantly only in the multiple cord abnormalities subgroup (single abnormalities, 11.9% vs. 7.3%, $P=0.12$; multiple abnormalities, 21.7% vs. 7.3%, $P=0.002$).

In addition to gross cord abnormality, the additional presence of thrombosis in the fetal vasculature was associated with both an increased rate of stillbirth and IUGR (Table 5). The rate of stillbirth increased from 1.4% in the control group to 11.7% in abnormal cord cases without thrombosis, but was highest (30.6%) in abnormal cord cases with thrombosis. IUGR was only slightly elevated in abnormal cord cases without thrombosis (10.7% vs. 7.5% in controls), but was significantly elevated in the abnormal cord cases with thrombosis

Table 1
Clinical characteristics of cases with gross cord abnormality vs. controls without gross cord abnormality.

	Control (n = 317)	Abnormal cord (n = 224)	P value ^a
<i>Demographic data</i>			
Maternal age (mean ± SD)	31.3 ± 6.5	31.1 ± 6.2	0.291
Advanced maternal age	112/317 (35.3%)	68/224 (30.4%)	0.23
GA (mean ± SD)	36.7 ± 3.3	37.4 ± 3.3	0.692
<i>Gravidity</i>			
1	119/317 (37.5%)	78/216 (36.2%)	0.33
2	72/317 (22.7%)	61/216 (28.2%)	
>2	126/317 (39.8%)	77/216 (35.6%)	
<i>Parity</i>			
0	152/317 (47.9%)	111/216 (53.4%)	0.85
1	101/317 (31.9%)	66/216 (30.6%)	
2	37/317 (11.7%)	24/216 (11.1%)	
>2	27/317 (8.5%)	15/216 (6.9%)	
Cesarean	160/317 (50.5%)	89/222 (40.1%)	0.018
History of abortion	114/317 (36.0%)	72/216 (33.3%)	0.58
History of IUFD	3/317 (0.9%)	1/216 (0.5%)	0.65
<i>Intrapartum complications</i>			
Non-reassuring fetal heart rate tracing	68/312 (21.8%)	67/170 (39.4%)	<0.001
Emergency cesarean section due to non-reassuring fetal heart rate tracing	63/312 (20.2%)	57/170 (33.5%)	0.002
<i>Early postpartum complications and adverse neonatal outcomes</i>			
Stillbirth	5/317 (1.6%)	36/224 (16.1%)	<0.001
Thick meconium-stained amniotic fluid	9/317 (2.8%)	25/222 (11.3%)	<0.001
Apgar score at 1 min < 4	22/282 (7.8%)	18/159 (11.3%)	0.23
Apgar score at 1 min < 7	56/282 (19.9%)	39/159 (24.5%)	0.28
Intrauterine growth restriction	23/313 (7.3%)	32/219 (14.6%)	0.009

^a Calculated using a *t*-test for continuous variables, or Chi-square test for categorical variables.

(31.0% vs. 7.5% in controls). The presence of thrombosis, in the absence of a gross cord abnormality, was not associated with a significantly increased risk of stillbirth or IUGR (Table 5). After controlling for maternal age and gestational age, the adjusted odds ratio for overall adverse outcome was 2.90 (1.36–6.17, 95% confidence interval) in abnormal cord cases with thrombosis compared to abnormal cord cases without thrombosis. For stillbirth and IUGR, the adjusted odds ratios were 3.34 (1.56–7.13, 95% CI) and 3.73 (1.66–8.37, 95% CI), respectively.

Table 2
Microscopic features in cases (with gross cord abnormalities) and controls (no gross cord abnormality).

	Control (n = 317)	Abnormal cord (n = 224)	P value ^a
<i>Evaluated histologic features</i>			
Vascular ectasia	188/317 (59.3%)	174/224 (77.7%)	<0.001
Umbilical cord	32/317 (10.1%)	48/224 (21.4%)	<0.001
Chorionic plate	82/317 (25.9%)	83/224 (37.1%)	0.006
Stem villi	160/317 (50.5%)	154/224 (68.8%)	<0.001
Thrombosis	21/317 (6.6%)	44/224 (19.6%)	<0.001
Umbilical cord	1/317 (0.3%)	5/224 (2.2%)	0.087
Chorionic plate	7/317 (2.2%)	24/224 (10.7%)	<0.001
Stem villi	13/317 (4.1%)	26/224 (11.6%)	0.001
Fetal thrombotic vasculopathy (FTV = AV or VSK)	17/317 (5.4%)	47/224 (21.0%)	<0.001
Focal	15/317 (4.7%)	33/224 (14.7%)	<0.001
Regional	2/317 (0.6%)	14/224 (6.3%)	<0.001
<i>Combined features</i>			
Ectasia + Thrombosis	21/317 (6.6%)	44/224 (19.6%)	<0.001
Ectasia + Thrombosis + FTV	1/317 (0.3%)	22/224 (9.8%)	<0.001

^a For categorical variables, determined using a Chi-square test or Fisher exact test where appropriate.

Table 3
Microscopic features in gross cord abnormality cases and controls with adverse fetal outcome.^a

Microscopic features	Control with adverse neonatal outcome (n = 84)	Abnormal cord with adverse neonatal outcome (n = 102)	P value ^b
<i>Evaluated histologic features</i>			
Vascular ectasia	55/84 (65.5%)	79/102 (77.5%)	0.074
Thrombosis	6/84 (7.1%)	28/102 (28.4%)	<0.001
Fetal thrombotic vasculopathy (FTV = AV or VSK) ^c	5/84 (6.0%)	29/102 (28.4%)	<0.001
<i>Combined features</i>			
Ectasia + Thrombosis	6/84 (7.1%)	29/102 (28.4%)	<0.001
Ectasia + Thrombosis + FTV	1/84 (1.2%)	16/102 (15.7%)	0.001

^a Stillbirth, low Apgar scores, thick meconium-stained amniotic fluid, intrauterine growth restriction.

^b For categorical variables, determined using a Chi-square test or Fisher exact test where appropriate.

^c AV: avascular villi; VSK: villous stromal karyorrhexis.

Fetuses with abnormal cords and IUGR were 2–3 times more likely to show histologic abnormalities of ectasia, thrombosis and FTV in their placentas, when compared to fetuses with abnormal cord *without* IUGR ($P < 0.05$; data not shown). Interestingly, the rate of stillbirth in this group was actually lower than the fetuses with abnormal cords without IUGR (9.1% vs. 19.1%), although this difference was not statistically significant ($P = 0.22$).

Finally, of the 41 stillbirths present in this study, FTV was present only in cases with grossly abnormal umbilical cords (44.4% vs. 0% of controls). In addition, vascular ectasia and thrombosis (minimal criteria for establishment of cord blood flow obstruction as cause of stillbirth, reference [3]) were present only in 1/5 control stillbirths, while ectasia, thrombosis and FTV (complete criteria for cord-related stillbirth, reference [3]) were present in 0/12 control stillbirths, giving a specificity of 80% and 100% for the respective criteria.

4. Discussion

4.1. Cord abnormalities: adverse perinatal outcome

Several gross umbilical cord lesions are known to obstruct umbilical blood flow. These include true knot, long cord, nuchal/body cord, hypercoiled/hypertwisted cord, narrow/strictured cord with decreased Wharton's jelly, and abnormal cord insertion [1,2]. While many studies of gross cord abnormalities have shown associated adverse neonatal outcome, the presence of a cause–effect relationship remains controversial. The present study confirms previous findings [4–14] of the association between gross cord abnormalities and intrapartum complications (non-reassuring fetal heart rate tracing, thick meconium-stained amniotic fluid), as well as stillbirth and intrauterine growth restriction in singleton pregnancies.

We found a more than two-fold increased risk of stillbirth in cases of abnormal cords *without* IUGR compared to cases of abnormal cords with IUGR, although the difference was not statistically significant. Also, single cord abnormalities did not have a statistically significant increase in frequency of IUGR, despite a more than 9-fold increase in rate of stillbirth. It is likely that the presence of IUGR may trigger patient management procedures, which prevent stillbirth. However, it is also clear from our findings that fetal growth restriction does not often precede, and thus should not be used to screen for, cord-related stillbirth. A prospective study of the relationship between grossly abnormal umbilical cords, IUGR, and stillbirth is warranted, in order to determine prenatally detectable factors, predictive of such adverse perinatal outcome, in fetuses with grossly abnormal umbilical cords.

Table 4

Clinical and microscopic features among different categories of single cord abnormalities, compared to controls without gross cord abnormalities.

	Long cord (n = 31)	Nuchal cord (n = 59)	True knot (n = 33)	Abnormal insertion	
				Marginal insertion (n = 25)	Membranous insertion (n = 12)
<i>Clinical</i>					
Non-reassuring fetal heart rate tracing	5/24 (20.8%)	32/47 (68.1%) ^a	9/25 (36.0%)	5/18 (27.8%)	1/9 (11.1%)
Thick meconium-stained amniotic fluid	2/31 (6.5%)	10/59 (16.9%) ^a	4/32 (12.5%) ^a	0	1/12 (8.3%)
Stillbirth	6/31 (19.4%) ^a	7/59 (11.9%) ^a	2/33 (6.1%)	7/25 (28.0%) ^a	3/12 (25.0%) ^a
Low Apgar scores	1/23 (4.3%)	7/42 (16.7%)	1/23 (4.3%)	1/18 (5.6%)	0
Intrauterine growth restriction	0	13/59 (22.0%) ^a	3/31 (9.7%)	2/25 (8.0%)	1/12 (8.3%)
<i>Microscopic features</i>					
Vascular ectasia	26/31 (83.7%) ^a	44/59 (74.6%) ^a	28/33 (84.8%) ^a	20/25 (80.0%) ^a	7/12 (58.3%)
Thrombosis	6/31 (19.4%) ^a	12/59 (20.3%) ^a	5/33 (15.2%)	4/25 (16.0%)	0
Umbilical cord	0	0	0	1/25 (0.4%)	0
Chorionic plate	2/31 (6.5%)	4/59 (6.8%)	2/33 (6.1%)	3/25 (12.0%) ^a	0
Stem villi	4/31 (12.9%)	11/59 (18.6%) ^a	3/33 (9.1%)	2/25 (8.0%)	0
Fetal thrombotic vasculopathy (AV or VSK)	11/31 (35.5%) ^a	13/59 (22.0%) ^a	4/33 (12.1%)	4/25 (16.0%)	3/12 (25.0%) ^a
Focal	8/31 (25.8%) ^a	10/59 (16.9%) ^a	2/33 (6.1%)	3/25 (12.0%)	2/12 (16.7%)
Regional	3/31 (9.7%) ^a	3/59 (5.1%) ^a	2/33 (6.1%) ^a	1/25 (4.0%)	1/12 (8.3%)

^a *P* < 0.05.

4.2. Cord abnormalities: placental histologic findings

We evaluated placental histologic features in all cord abnormality cases and controls, focusing on fetal vascular changes previously associated with restricted fetal blood flow [3,15]. Each of these parameters (ectasia, thrombosis, and FTV) was found more frequently in cases vs. controls. Overall, similar to our stillbirth study [3], thrombosis and FTV were much more specific than ectasia for umbilical cord abnormalities (93.4% for thrombosis, 94.6% for FTV, vs. 40.7% for ectasia).

We had previously defined minimal histologic criteria for cord compression-related stillbirth as ectasia and thrombosis within the placental fetal vascular tree [3]; complete criteria also included the additional presence of FTV [3]. The current study, which included both stillbirths and live births, also showed high specificity for these criteria. However, as expected, the proportion of cord abnormality cases with these criteria was low, although these numbers increased when measured in the subgroup of cord abnormalities with adverse perinatal outcome. One major limitation may have been inadequate sampling. Both chorionic plate and stem villus vessels need to be properly sampled in order to screen for ectasia and thrombosis. In addition, FTV is by definition a focal or regional finding of avascular or near-vascular villi in the placental parenchyma [15]. This lesion can rarely be seen grossly when it involves a large region of the placenta, in which case it will appear as a discrete, firm area of discoloration [19]. Due to the temporally heterogeneous, and in most cases grossly undetectable, nature of this lesion, proper sampling of the placental parenchyma is also needed. We therefore strongly recommend submission of four sections of placental parenchyma in all such cases; these

sections should include chorionic plate vessels near the cord insertion, as we find this to be the most likely site of muscular vessel thrombosis.

Based on previous stillbirth studies, the presence of completely avascular villi vs. near-vascular villi (or villous stromal karyorrhexis/VSK) likely reflects the time elapsed since occurrence of vascular obstruction, while the distribution (focal or regional) may correlate with severity and frequency of the obstruction [3,15,18,20,21]. Therefore, not only is identification of FTV important for specific confirmation of fetal blood flow obstruction, documentation of the exact nature and distribution of the lesion is also important for establishing the timing and extent of fetal stressors. In our study the majority of abnormal cord cases tended to have focal rather than regional FTV, with a similar overall frequency of avascular villi and VSK (data not shown). However, while long cord and nuchal cord cases showed a mixture of both avascular villi and VSK, true knot and abnormal cord insertion cases tended to only have an increased frequency of VSK (data not shown), suggesting that the former lesions may have caused obstruction over a more prolonged time period. Coincidentally, these cases with long cord and nuchal cord also had a higher frequency of adverse clinical outcome. Future study of large series of FTV cases is needed to better correlate the nature and extent of these histologic findings with cord-related fetal morbidity and mortality.

4.3. Summary of conclusions and limitations

While comprehensive, this study has several limitations. First, as a retrospective study, recording of clinical data was incomplete in some cases, and may have also been biased. Second, as clinical

Table 5

Clinical outcome of abnormal cord cases with thrombosis, vs. various control groups.

	Controls without thrombosis (n = 296)	Controls with thrombosis (n = 21)	Abnormal cord without thrombosis (n = 180)	Abnormal cord with thrombosis (n = 44)	<i>P</i> value ^a
<i>Clinical</i>					
Non-reassuring fetal heart rate tracing	64/292 (21.9%)	4/20 (20.0%)	53/143 (37.1%)	14/27 (51.9%)	<0.001
Thick meconium-stained amniotic fluid	9/296 (3.0%)	0	16/178 (9.0%)	9/44 (20.5%)	<0.001
Stillbirth	4/296 (1.4%)	1/21 (4.8%)	21/180 (11.7%)	15/44 (34.1%)	<0.001
Apgar scores < 4 at 1 min	21/262 (8.0%)	1/20 (5.0%)	15/135 (11.1%)	3/24 (12.5%)	0.619
Apgar scores < 7 at 1 min	52/262 (19.8%)	4/20 (20.0%)	31/135 (23.0%)	8/24 (33.3%)	0.456
Intrauterine growth restriction	22/292 (7.5%)	1/21 (4.8%)	19/177 (10.7%)	13/42 (31.0%)	<0.001

^a Global test: *P* value to test whether any difference exists across groups.

follow-up was limited to NICU notes, only immediate neonatal complications could be recorded and analyzed. Third, clinical conditions that may predispose to cord compression, without gross cord abnormalities, such as oligohydramnios, were not well documented in the charts and therefore could not be analyzed. Finally, since microscopic review was based on limited placental sections (mostly two per case), histologic findings such as focal thrombosis or FTV may have been missed due to inadequate sampling.

In summary, gross cord abnormalities were associated with stillbirth, intrauterine growth restriction, and intrapartum or immediate post-natal complications. Placental microscopic evaluation revealed that stasis-induced changes in the fetal vasculature and chorionic villi were significantly increased in cases with gross cord abnormalities, particularly in those cases with adverse perinatal outcome. We therefore recommend all placentas with gross cord abnormalities, particularly the ones predisposing to vascular obstruction, be sent for pathologic examination; this should include a thorough gross examination as well as adequate sampling of large fetal vessels and placental parenchyma in order to evaluate for the presence of thrombosis and fetal thrombotic vasculopathy.

5. Disclosure/conflicts of interest

There are no conflicts of interest to report.

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