Virchows Arch (2016) 468:723–732
DOI 10.1007/s00428-016-1921-1

ORIGINAL ARTICLE

Association of coexisting morphological umbilical cord abnormality and clinical cord compromise with hypoxic and thrombotic placental histology

Jerzy Stanek[1]

Received: 1 October 2015 / Revised: 7 February 2016 / Accepted: 25 February 2016 / Published online: 16 March 2016

Abstract To assess the usefulness and limitations of placental histology when morphological umbilical cord (UC) abnormality coexists with clinical UC compromise, 5634 consecutive placentas were divided into four groups and statistically compared: group 1—182 placentas from pregnancies with clinical features of UC compromise (variable decelerations, UC entanglement, prolapse, or true knot at delivery); group 2—1355 placentas with abnormal UC morphology or insertion; group 3—152 placentas with at least one phenotype from group 1 and one from group 2; group 4—3945 placentas with no clinical or morphological UC-related phenotypes (control group).Differences were analyzed by ANOVA or χ^2. Of 68 phenotypes studied, 13 clinical and 18 placental phenotypes were statistically significant. In group 1, 2 phenotypes were most common (oligohydramnios and abnormal fetal heart rate tracing). In group 2, 6 phenotypes were most common, including 4 clinical (abnormal umbilical artery Dopplers, nonmacerated stillbirth, multiple pregnancy, and fetal growth restriction) and 2 placental. In group 3, 23 phenotypes were most common, including 7 clinical (gestational hypertension, polyhydramnios, induction of labor, cesarean section, macerated stillbirth, congenital malformations, and abnormal 3rd stage of labor) and 16 placental. The existence of clinical signs of UC compromise alone was associated with the absence of pathomorphological placental abnormalities. However, the coexistence of clinical and abnormal morphological UC phenotypes was statistically significantly associated with placental histological signs of decreased fetal blood flow, hypoxia (acute and chronic post uterine), shallow placental implantation, and/or amnion nodosum. Thus, confirmation of clinical UC compromise should not be expected on placental examination if no morphological UC abnormality or abnormal UC insertion has been found.

Keywords Umbilical cord · Placenta · Hypoxia · Stasis-induced fetal thrombotic vasculopathy

Introduction

Acute and chronic/occult clinical umbilical cord (UC) compromise (compression, true knot, prolapse) are common obstetric complications contributing to perinatal morbidity [1]. Less frequently, they can be life-threatening to the fetus [2]. In fact, UC complications may be the second most common cause of stillbirth after placental insufficiency, particularly around term [3–6]. However, most fetal deaths are caused by a variety of placental pathologies, including UC compromise [7, 8].

Pathomorphologic confirmation of clinical UC compromise on post-mortem or placental examination can be elusive, especially in cases of entanglements and prolapse [9]. In rare cases, a clinically unsuspected cord encirclement can be retrospectively diagnosed on perinatal autopsy and placental examination [10]. Gross UC abnormalities may also be associated with stillbirth, abnormal perinatal outcome, fetal growth restriction, nonreassuring fetal heart rate tracings (particularly atypical variable decelerations

Presented at the Congress of European Society of Pathology, 5–9 September 2015, Belgrade, Serbia

✉ Jerzy Stanek
jerzy.stanek@cchmc.org

[1] Division of Pathology and Laboratory Medicine, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, MLC 1035, 3333 Burnet Avenue, Cincinnati, OH 45229-3026, USA

in the first stage of labor), meconium-stained amniotic fluid, increased rate of labor induction, and emergency cesarean section [11–18]. Most authors relate clinical risk factors and placental pathomorphological features only to selected UC abnormalities [19] such as abnormal UC length [20, 21] or diameter [4, 13], abnormal coiling [4, 12, 14, 16, 22–28], prolapse [29, 30], entanglement [21, 25], edema [31], abnormal insertion [3, 4, 32], true knots [33], stricture [34, 35], ulcer [10, 19], varix, aneurysms, and pseudocysts [3].

The impact of acute and chronic UC compromise or abnormal morphology (such as abnormal insertion or morphological lesions) on clinical outcome and other placental pathology is largely unknown or misunderstood. Although it is known that obstructive cord lesions are associated with fetal thrombotic vasculopathy (FTV) [18, 36], little is known about the results of comprehensive placental examination in cases of UC complications. This analysis assesses the usefulness and limitations of diagnosing placental villous sequelae associated with UC compromise and gross morphological UC abnormalities.

Material and methods

The author examined 5634 consecutive placentas from pregnancies with a gestational age at birth ≥21 weeks. These examinations were performed during the period 1994–2013 in four tertiary care centers: Department of Pathology, University of Cincinnati Medical Center, Cincinnati, Ohio; Department of Pathology, Sheffield Children's NHS Trust, Sheffield, Great Britain; Department of Anatomical Pathology, Canterbury Health Laboratories, Christchurch, New Zealand; and Division of Pathology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio. Placentas were submitted for

Table 1 Definitions of morphological lesions of the umbilical cord

	Definition	References
Battledore placenta	Insertion of the umbilical cord at the placental edge	[38]
Hypercoiling	Umbilical cord index ≥0.3 coils/cm	[22]
Velamentous insertion	Insertion into membranes with membranous vessels	[38]
Hypocoiled	Umbilical cord index ≤0.1 coil/cm	[22]
Chorda (amniotic web)	An amniotic fold extending from the fetal surface to the umbilical cord.	[35]
Hematoma	Large extravasation of blood into Wharton jelly not related to instrumentation	[41]
Stricture/torsion	Substantial thinning of umbilical cord, usually at fetal end, associated with stasis-related secondary changes	[35, 38]
Necrosis of media of umbilical vessels	Coagulative necrosis of the outer media, usually seen in the umbilical arteries, sometimes only on complement 9 immunostaining	[42]
Edema	Increased cord diameter for gestational age, with dissociation (pseudomicrocysts) of the Wharton jelly microscopically	[19, 41]
Thin	Decreased cord diameter for gestational age, with patent umbilical vessels	[19]
Amniotic cyst	Cysts lined by amniotic epithelium	[1]
Candida funisitis	Yellow surface nodules of the umbilical cord	[38]
Aneurysm/varix	Segmental dilatation of umbilical artery/vein	[19, 59]
Short	Umbilical cord length below normal for the gestational age (if total available for measurement)	[19]
Long	Umbilical cord length above normal for the gestational age	[19]
Hypoplastic umbilical artery	Significant reduction in diameter due to attenuation of media of an umbilical artery	[35]
Subacute necrotizing funisitis (barber pole funisitis)	Rigid cord with yellow-white discoloration of vessels and rings of degeneration/necrosis with chronic inflammatory cells microscopically	[1, 41]
Hemangioma	Clusters of capillary vessels in the Wharton jelly, negative for Glut-1 by immunohistochemistry	[19, 38]
Vessel unprotected by Wharton jelly	Segmental absence of Wharton jelly around an umbilical vessel	[43]
Furcate insertion	Umbilical vessels branch and run without the Wharton jelly protection at placental end	[41]
Amniotic band	Amnion-lined fibrous band constricting the umbilical cord	[41]
Single umbilical artery	One vitelline umbilical artery	[19]
Dysplastic right umbilical vein/remnant	Two umbilical veins with one or two umbilical arteries)	[19]
Focal fusion of umbilical arteries	Focal presence of only one umbilical artery	[41]
Ulcer	Linear, spiral of focal, depending on pathogenesis	[10]

examination at the discretion of obstetricians for the following reasons: abnormal gross placental features at delivery, high-risk pregnancy, operative delivery, poor obstetric outcome, and poor condition of the neonate. Placental examinations were performed according to generally accepted criteria [1, 37, 38]. The definitions of placental lesions have been given previously [39, 40], particularly of those that are not yet in general use. Definitions of some UC lesions are listed in Table 1.

Four groups of placentas were compared retrospectively (Table 2):

Group 1. —182 placentas from pregnancies with only clinical features of UC compromise

Group 2. —1355 placentas with only morphological UC abnormalities (UC itself or its abnormal insertion) (Fig. 1)

Group 3. —152 placentas with at least one phenotype from group 1 and one from group 2

Group 4. —3945 remaining placentas with no clinical or pathological UC-related phenotypes (control group)

Differences among the groups were analyzed by ANOVA or χ^2 with 3 degrees of freedom and 0.0007353 Bonferroni adjustment for 68 clinical and placental phenotypes analyzed.

Table 2 Composition of four studied groups

Phenotypes (in hierarchical order)	Number
Group 1. Clinical features of umbilical cord compromise	182
Umbilical cord prolapse	23
True knot at delivery (loose or tight)	27
Umbilical cord entanglement/encirclement (loose or tight, around neck or body parts)	96
Variable decelerations	36
Group 2. Morphological umbilical cord abnormalities (cord itself or its placental insertion) (Fig. 1)	1355
Battledore placenta (marginal insertion)	452
Hypercoiled umbilical cord	313
Velamentous insertion	151
Two-vessel umbilical cord (single umbilical artery)	142
Hypocoiled umbilical cord	120
Chorda (amniotic web)	67
Hematoma	35
Long umbilical cord	41
Stricture	29
Necrosis of media of umbilical vessels	28
Edema	24
Thin umbilical cord	18
Amniotic cyst	16
Candida funisitis	11
Aneurysm or varix	10
Short umbilical cord	10
Hypoplastic umbilical artery	7
Subacute necrotizing funisitis (barber pole funisitis)	7
Hemangioma	6
Umbilical vessels unprotected by the Wharton jelly	5
Furcate insertion	5
Amniotic band	4
Dysplastic vein/remnant	4
Focal fusion of umbilical arteries	3
Ulcer	1
Group 3. At least 1 phenotype from group 1 and at least 1 phenotype from group 2	152
Group 4 (control). No clinical or pathological umbilical cord-related phenotypes	3945

Fig. 1 Morphological abnormalities of umbilical cord (group 2). *A*. Battledore placenta (marginal insertion). *B*. Velamentous insertion. *C*. Furcate insertion. *D*. Chordae (amniotic webs). *E*. Massive edema. *F*. Thin. *G*. Uncoiled *H*. Hypercoiled. *I*. Long. *J*. Absent. *K*. Periumbilical stricture. *L*. Torsion. *M*. Ulcers. *N*. Amniotic band. *O*. Hypoplastic artery. *P*. Fusion of umbilical arteries. *Q*. Remnant of second umbilical vein. *R*. Single umbilical artery. *S*. Varix of umbilical vein. *T*. Vessel unprotected by Wharton jelly. *U*. Aneurysm of umbilical artery. *V*. *W*. Hematoma. Amniotic cyst. *X*. Hemangioma. *Y*. Necrotic media of umbilical vein. *Z*. Candida funisitis. *AA*. Necrotizing subacute (barber pole) funisitis

Results

Statistically significant differences existed in 31 phenotypes: 13 clinical (Table 3) and 18 placental (Table 4). The most common phenotypes in the first three groups of placentas were as follows:

Group 1. —2 clinical phenotypes (oligohydramnios and abnormal fetal heart rate tracing) and 0 placental phenotypes

Group 2. —4 clinical phenotypes (abnormal umbilical artery Dopplers, nonmacerated stillbirth, multiple pregnancy, and fetal growth restriction) and 2 placental phenotypes (clusters of maternal floor multinucleate giant cells and amnion nodosum)

Group 3. —7 clinical phenotypes (gestational hypertension, polyhydramnios, induction of labor, cesarean section, macerated stillbirth, congenital malformations, and abnormal third stage of labor) and 16 placental phenotypes

Therefore, the frequencies of the most common abnormalities were as follows: group 3 > group 2 > group 1. In the three groups, frequencies for clinical phenotypes were 7, 4, and 2 (respectively) and frequencies for histopathological placental phenotypes were 16, 2, and 0 (respectively).

Table 3 Statistically significant clinical differences among groups 1–4

	Group 1. Clinical	Group 2. Pathological	Group 3. Mixed	Group 4. Control	Chi-square 3 df
Number of cases	182	1355	152	3945	
Gestational hypertension	5 2.7	33 2.4	7 4.6	42 1.1	20.757
Oligohydramnios	20 11.0	108 8.0	12 7.9	207 5.2	20.14
Polyhydramnios	3 1.6	56 4.1	15 9.9	34 0.9	104.29
Abnormal fetal heart rate tracing[a]	69 37.9	212 15.6	41 27.0	610 15.4	74.197
Abnormal umbilical artery Dopplers	3 1.6	52 3.8	5 3.3	42 1.1	43.441
Induction of labor	24 13.2	147 10.8	29 19.1	270 6.8	49.029
Cesarean section	74 40.7	584 43.1	67 44.1	1391 35.2	30.055
Nonmacerated stillbirth	15 8.2	158 11.7	8 5.3	120 3.0	149.61
Macerated stillbirth	17 9.3	50 3.7	46 30.3	168 4.2	215.73
Multiple pregnancy	15 8.2	224 16.5	13 8.5	325 8.2	76.00
Fetal growth restriction[b]	15 8.2	185 13.6	16 10.5	336 8.5	30.177
Congenital malformation	4 2.2	164 12.1	21 13.8	229 5.8	72.353
Abnormal third stage of labor (prolonged, hemorrhage)	9 4.9	65 4.8	15 9.9	133 3.4	18.599

Numbers and percentages are given. Only statistically significant differences with p Bonferroni <0.0007353 by Yates chi-square with 3 degrees of freedom (df) are included

[a] Abnormal nonstress test and/or abnormal contraction stress test and/or abnormal intrapartum cardiotocography (prolonged bradycardia and/or prolonged tachycardia and or decrease of fetal heart rate variability and /or late decelerations)

[b] Birth weight <10 centile

Group 4 (the control group) contained the least frequent statistically significant variables as follows:

- 10 of the 13 least frequent abnormal clinical variables (gestational hypertension, oligohydramnios, polyhydramnios, abnormal antepartum fetal heart rate tracing, abnormal Dopplers, induction of labor, cesarean section, nonmacerated stillbirth, and multiple pregnancy), and
- 11 of the 18 least frequent placental variables (normoblastemia of fetal blood, deep (decidual) meconium penetration, post uterine chronic hypoxic placental injury, chorionic microcysts of the chorionic disk, excessive number of extravillous trophoblasts, choriodecidual hemosiderosis, luminal vascular abnormalities of chorionic villi, diffuse villous fibrosis, fetal vascular thrombi, clusters of avascular chorionic villi, periarterial stem edema, and dilatation of fetal veins (umbilical, chorionic disk, and stem villi)).

In the remaining 37 variables analyzed (clinical or placental), no statistically significant differences existed after Bonferroni correction (not included in Tables 3 or 4).

Discussion

Frequencies of abnormal clinical phenotypes occurred mostly in single digits in group 1, except for abnormal fetal heart rate, induction of labor, and cesarean section. Fetal heart rate abnormalities are common in cord complications, particularly in cases of prolonged pregnancy [44]. However, gestational age did not differ among the groups studied. Also, induction of labor was reported to be associated with cord prolapse [30]. Therefore, it is not only possible but likely that the abnormal results of fetal heart monitoring affected the rates of labor induction and cesarean section [15, 32]. However, the clinical signs of UC compromise were not associated with increased pathomorphological placental abnormalities in group 1. Other authors have also reported that clinical UC complications are unlikely to be associated with abnormal villous lesions [45]. Our previous analysis showed that the full-term placentas were more likely to suffer from acute in utero hypoxia manifesting clinically with fetal distress (abnormal fetal heart rate tracings and thick meconium, possibly resulting from unrecognized UC compromise) and deep meconium penetration [6].

Table 4 Statistically significant placental differences among groups 1–4

	Group 1. Clinical	Group 2. Pathological	Group 3. Mixed	Group 4. Control	Chi-square 3 df
Number of cases	182	1355	152	3945	
A. Hypoxia-related lesions					
Fetal					
Normoblastemia of fetal blood	11 6.0	131 9.7	36 23.7	188 4.7	112.678
Deep (decidual) meconium penetration	14 7.7	98 7.2	23 15.1	245 6.2	18.087
Maternal					
Laminar necrosis of membranes[a]	21 11.5	255 18.8	41 27.0	516 13.0	44.794
Diffuse post uterine pattern of chronic hypoxic placental injury	7 3.8	49 3.6	17 11.2	109 2.8	31.598
Chorionic disk microscopic chorionic pseudocysts[b]	7 3.8	110 8.1	24 15.8	136 3.4	83.685
Maternal floor multinucleate trophoblastic giant cells	11 6.0	165 12.2	7 4.6	292 7.4	33.127
Excessive amount of extravillous trophoblasts in chorionic disk	12 6.6	105 7.7	25 16.4	165 4.2	59.657
Intervillous thrombus	17 9.3	174 12.8	30 19.7	393 9.9	20.387
Choriodecidual hemosiderosis	8 4.4	63 4.6	12 7.9	61 1.5	56.095
B. Lesions related to decreased/absent fetal blood flow					
Luminal vascular abnormalities of chorionic villi	14 7.7	150 11.1	33 21.7	306 7.7	43.376
Diffuse villous fibrosis	13 7.1	165 12.2	36 23.7	249 6.3	93.184
Fetal vascular thrombi	19 10.4	158 11.7	33 21.7	171 4.3	142.129
Cluster(s) of at least three avascular chorionic villi	14 7.7	119 8.8	19 12.5	199 5.0	33.841
Intimal cushions in stem/chorionic veins	5 2.7	61 4.5	15 9.9	109 2.8	27.227
Villous hemosiderosis in lobular distribution	2 1.1	59 4.3	10 6.6	61 1.5	44.762
Perivascular stem edema	9 4.9	68 5.0	40 26.3	52 1.3	334.576
Dilatation of fetal veins (umbilical, chorionic, or stem)	6 3.3	76 5.6	19 12.5	44 1.1	137.847
C. Other					
Amnion nodosum/chorion nodosum	6 3.3	70 5.2	2 1.3	73 1.8	42.153

Numbers and percentages are given. Only statistically significant differences with p Bonferroni <0.0007353 by Yates chi-square with 3 degrees of freedom (df) are included

[a] At least 10% of membrane roll

[b] At least three pseudocysts per section of grossly unremarkable chorionic disk

By comparison, the coexistence of abnormal clinical and morphological placental phenotypes (group 3) was often statistically significantly associated with the following:

- Placental histological signs of decreased fetal blood flow (stasis-induced FTV) (Fig. 2),
- Placental hypoxic lesions and patterns, and features of shallow placental implantation (Fig. 3).

Pathophysiologically, fetal vascular obstructive lesions result from the Virchow's triad: (1) stasis (UC compromise), (2) hypercoagulability (poorly controlled diabetes mellitus, autoimmune conditions, maternal or fetal thrombophilias), and (3) vascular damage within the fetal circulation of the placenta (inflammation, meconium toxicity, hemorrhagic endovasculitis) [46]. FTV is associated with potentially obstructive lesions of the cord and with oligohydramnios (the latter is not in our material) [47].

Our results thus strengthen the evidence that the coexistence of clinical and placental UC abnormalities may indeed play a part in perinatal morbidity and, particularly, in the rate of macerated stillbirth [5, 7, 48, 49]. Of these stillbirths, a proportion shows features of FTV, which are more likely to be seen in unexplained stillbirths [50]. Various UC abnormalities and placental clusters of sclerotic/hemosiderotic chorionic villi were most common in macerated stillbirths [40]. Also, several histological features of prolonged umbilical cord compromise [51] were encountered among the statistically significant pathomorphological findings in group 3. However, in addition to thrombotic lesions (Fig. 2), several hypoxic lesions (Fig. 3) were also common in this group. This finding agrees with the results of those authors who claim that mixed placental pathologies are frequently seen in third trimester stillbirths [11, 36, 52]. We have also found recently that placental hypoxic overlap lesions associated

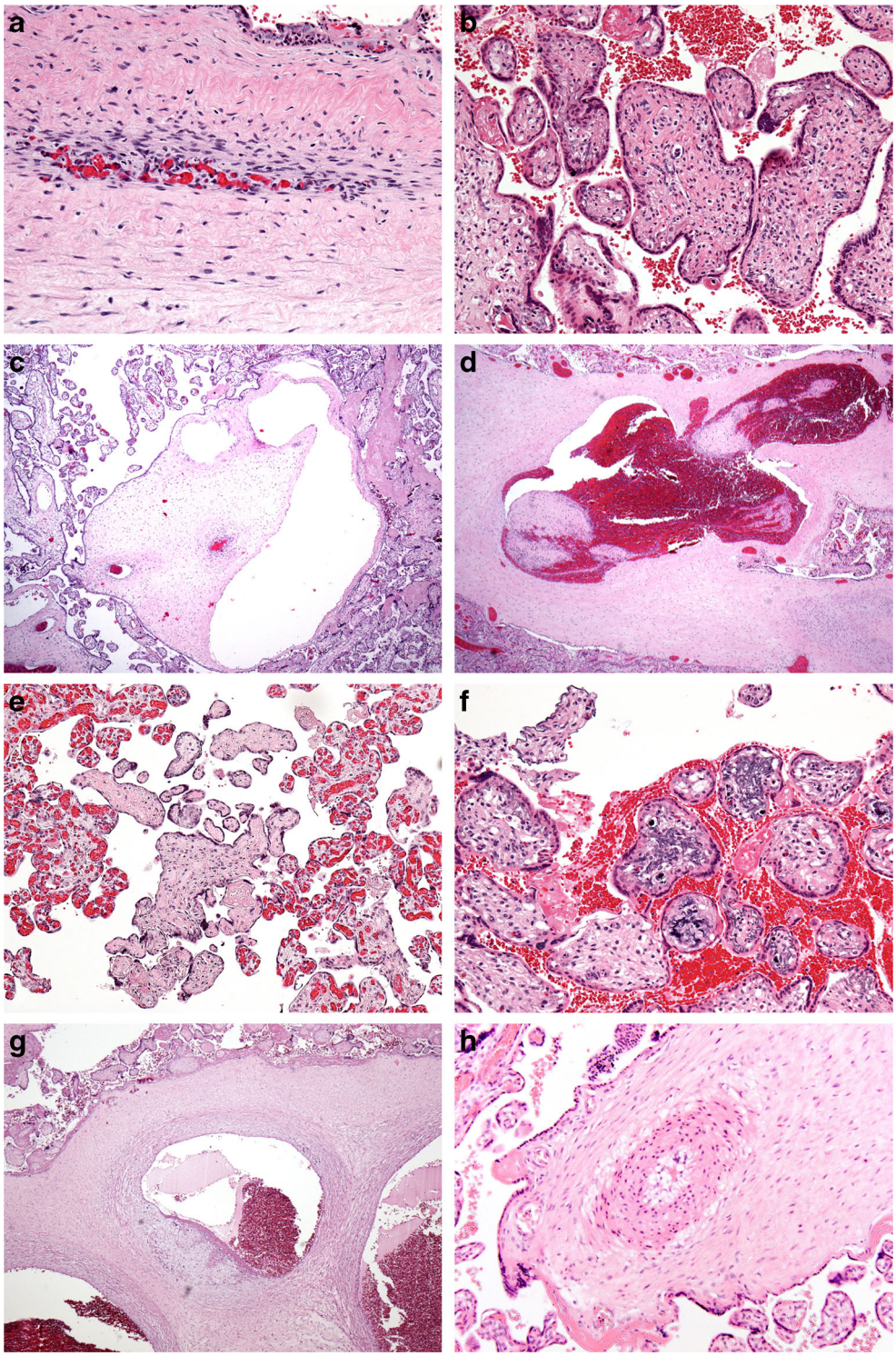

Fig. 2 Statistically significant patterns and lesions related to decreased or absent fetal blood flow (objective magnifications). **a** Luminal vascular abnormalities of stem villi (×20). **b** Increased extracellular matrix of chorionic villi, stillbirth, 23 weeks of pregnancy (×20). **c** Dilatation of stem vein (×4). **d** Thrombi in a stem vessel (×20). **e** Cluster of avascular chorionic villi (×10). **f** Villous hemosiderosis in lobular distribution with calcified microthrombi (×20). G. Intimal cushion in stem vein (×10). **h** Stem perivascular edema and obliterative endarteritis (×20)

with clinical complications of pregnancy predispose to thrombotic lesions, some of which are most likely stasis-induced [53].

Abnormal pathomorphological UC features without clinical signs of UC compromise (group 2) were associated at a moderate frequency with abnormal clinical and placental findings—except at the highest congenital malformation rate or in the presence of clusters of maternal floor multinucleate giant cells. Therefore, the macroscopic morphological features of the UC alone cannot reliably predict the presence or absence of histological placental lesions [54].

The problem of UC-related complications and associated placental pathology is also important because of its medicolegal aspect. Although infrequent, litigation may occur

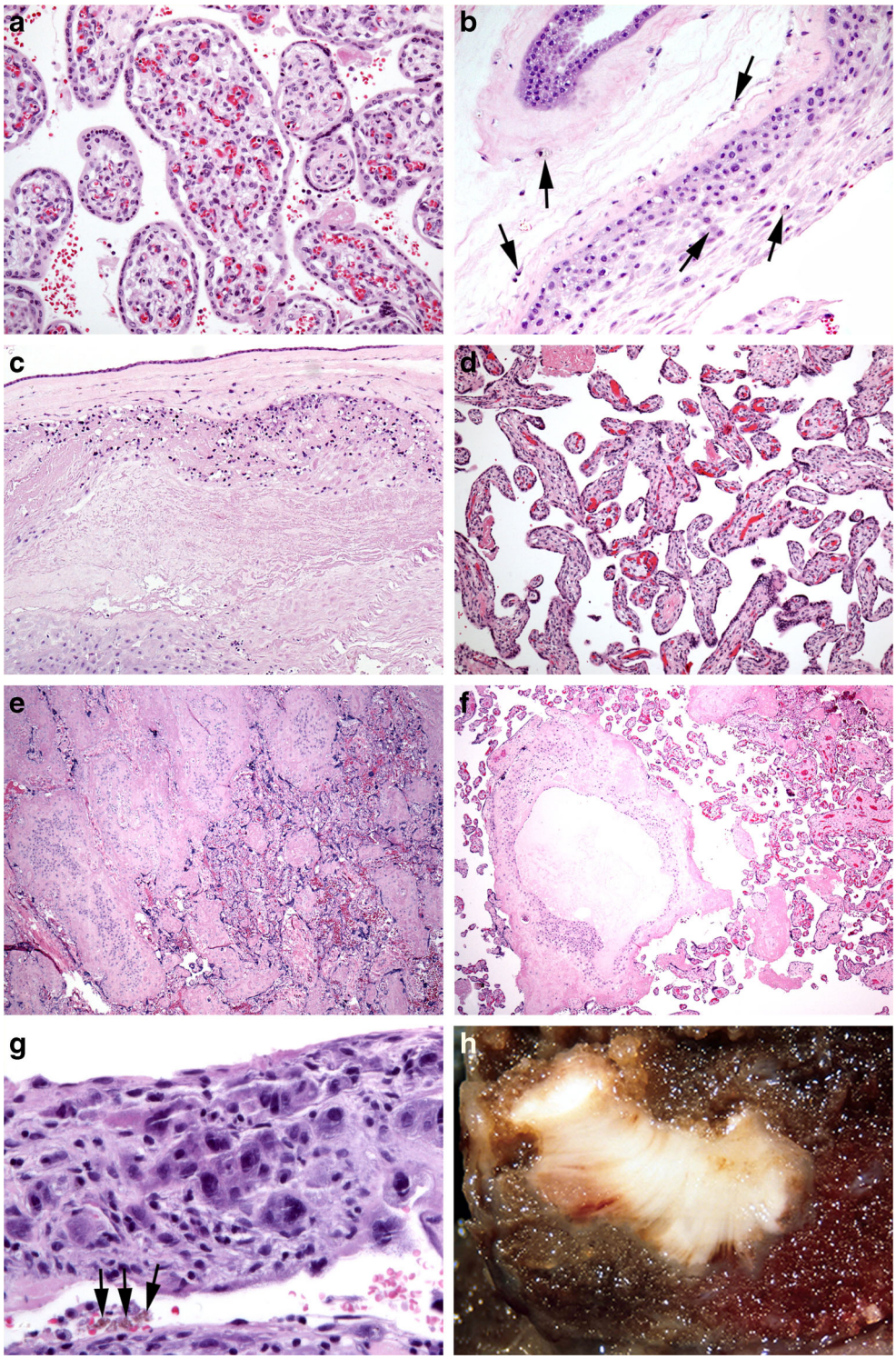

Fig. 3 Statistically significant hypoxic placental lesions and patterns (objective magnifications). **a** Normoblasts in fetal blood (×40). **b** Meconium macrophages in amniotic mesenchyme and decidua (*arrows*) (×20). **c** Laminar decidual necrosis of membranes (×10). **d** Diffuse post uterine pattern of chronic hypoxic placental injury (22 weeks) (×10). **e** Excessive amount of extravillous trophoblasts in chorionic disk (×4). **f** Microscopic chorionic pseudocyst of a cell island (×4). **g** Clusters of maternal floor multinucleate trophoblastic giant cells and decidual hemosiderosis (*arrows*) (×20). **h** Intervillous thrombus (dissecting microscopy ×2)

following the poor outcome associated with UC accidents [5]. Of 158 cases subjected to litigation because of cerebral palsy, 63 % showed clinical and/or pathologic evidence of UC obstruction [55]. In only a portion of these cases could the litigation have been averted by prenatal screening for certain important UC lesions [5, 12, 19, 56]. Litigation might also be avoided by screening for fetal heart rate abnormalities to identify fetuses that might suffer in utero hypoxia and postnatal acidosis. All efforts at prenatal visualization of UC and/or placental lesions are thus warranted, since fetal thrombophilia alone is not usually associated with fetal vascular lesions of the placenta (although it may be an underlying risk factor) [46,

57]. Also, oligohydramnios predisposing to UC compression can be relieved by amnioinfusion [45].

Finally, comparing our results with those of other reports may be difficult because various authors may use different diagnostic criteria for placental lesions, particularly in groups labeled "other placental abnormalities." Some authors exclude FTV as a cause of death if UC blood flow restriction is present [7]. But others take an opposite view and stress that the placental histology provides useful information about fetal acidemia with low-risk term pregnancy in clinically undetectable cases [58]. Previous studies that linked abnormal UC coiling with clinical outcome are generally too small and/or selective to allow meaningful conclusions or to apply to low-risk populations [59].

In conclusion, the clinical signs of UC compromise alone cannot and do not predict the presence or absence of histological placental lesions because they usually occur acutely and too close to delivery for the histological features of FTV to develop. Although UC compromise is an important factor in perinatal morbidity and mortality, confirmation of clinical UC compromise should not be expected on placental examination if no morphological UC abnormality or abnormal UC insertion has been found. However, when clinical UC compromise and morphological UC abnormality or abnormal UC insertion do coexist, they significantly strengthen the case that UC compromise indeed plays a role in perinatal morbidity and mortality.

Compliance with ethical standards

Funding No funding was presented in the study.

Conflict of interest The author declares that he has no conflict of interest.

References

1. Fox H, Sebire NJ (2007) Pathology of the placenta. Saunders, London
2. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Gilstrap LC III, Wenstrom KD (2005) Williams obstetrics, 22nd edn. McGraw-Hill, New York
3. Pásztor N, Keresztúri A, Kozinszky Z, Pál A (2014) Identification of causes of stillbirth through autopsy and placental examination reports. Fetal Pediatr Pathol 33:49–54
4. Parast MM, Crum CP, Boyd TK (2008) Placental histologic criteria for umbilical blood flow restriction in unexpected stillbirth. Hum Pathol 39:948–953
5. Collins JH (2002) Umbilical cord accidents: human studies. Semin Perinatal 26:79–82
6. Stanek J (2014) Comparison of placental pathology in preterm, late-preterm, near-term, and term births. Am J Obstet Gynecol 210(234):e1–e6
7. Korteweg FJ, Erwich JJHM, Holm JP, Ravisé JM, van der Meer J, Veeger NJGM, Timmer A (2009) Diverse placental pathologies as the main causes of fetal death. Obstet Gynecol 114:809–817
8. de Laat MWM, van der Meu JJC, Visser GHA, Franx A, Nikkels PGJ (2007a) Hypercoiling of the umbilical cord and placental maturation defect: associated pathology? Pediatr Dev Pathol 10:293–299
9. Baergen RN (2007) Cord abnormalities, structural lesions, and cord "accidents". Sem Diagn Pathol 24:23–32
10. Wang G, Bove KE, Stanek J (1998) Pathological evidence of prolonged umbilical cord encirclement as a cause of fetal death. Am J Perinatol 15:585–588
11. Chan JSY, Baergen RN (2012) Gross umbilical cord complications are associated with placental lesions of circulatory stasis and fetal hypoxia. Pediatr Dev Pathol 15:487–494
12. Nishio J, Nakai Y, Mine M, Imanaka M, Ogita S (1999) Characteristics of blood flow in intrauterine growth-restricted fetuses with hypercoiled cord. Ultrasound Obstet Gynecol 13:171–175
13. Peyter AC, Delhaes F, Baud D, Vial Y, Diaceri G, Menétrey S, Hohlfeld P, Tolsa JF (2014) Intrauterine growth restriction is associated with structural alterations in human umbilical cord and decreased nitric oxide-induced relaxation of umbilical vein. Placenta 35:891–899
14. Rana J, Ebert GA, Kappy KA (1995) Adverse perinatal outcome in patients with an abnormal umbilical coiling index. Obstet Gynecol 85:573–577
15. Stanek J (1987) Induction of labor: necessity, convenience, or... uncertainty? Ginekol Pol 58:232–239
16. Kashanian M, Akbarian A, Kouhpayehzadeh J (2006) The umbilical coiling index and adverse perinatal outcome. Int J Gynaecol Obstet 95:8–13
17. Tantbirojn P, Saleemuddin A, Sirois K, Crum CP, Boyd TK, Tworoger S, Parast MM (2009) Gross abnormalities of the umbilical cord: related placental histology and clinical significance. Placenta 30:1083–1088
18. Hasegawa J, Matsuoka R, Ischizuka K, Kotani M, Nakamura M, Mikoshiba T, Sekizawa A, Okai T (2009) Atypical variable deceleration in the first stage of labor is a characteristic fetal heart-rate pattern for velamentous cord insertion and hypercoiled cord. J Obstet Gynaecol Res 35:35–39
19. Blackburn W (2006) Umbilical cord. In:Stevenson RE, Hall JG (eds) Human malformations and related anomalies, 2nd edition. Oxford University Press, Oxford, New York: 1413–1472
20. Baergen RN, Malicki D, Behling C, Benirschke K (2001) Morbidity, mortality, and placental pathology in excessively long umbilical cords: retrospective study. Pediatr Dev Pathol 4:144–153
21. Rogers MS, Ip YW, Qin Y, Rogers SM, Sahota D (2003) Relationship between umbilical cord morphology and nuchal cord entanglement. Acta Obstet Gynecol Scand 82:32–37
22. Strong TH, Jarles DL, Vega JS, Feldman DB (1994) The umbilical coiling index. Am J Obstet Gynecol 170:29–32
23. de Laat MW, van Alderen ED, Franx A, Visser GH, Bots ML, Nikkels PG (2007b) The umbilical coiling index in complicated pregnancy. Eur J Obstet Gynecol Reprod Biol 130:66–72
24. Ernst LM, Minturn L, Huang MH, Curry E, Su EJ (2013) Gross pattern of umbilical cord coiling: correlations with placental histology and stillbirth. Placenta 34:583–588
25. Gambhir PS, Gupte S, Kamat AD, Patankar A, Kulkarni VD, Phadke MA (2011) Chronic umbilical entanglements causing intrauterine fetal demise in the second trimester. Pediatr Dev Pathol 14:252–254
26. Georgiou HM, Rice GE, Walker SP, Wein P, Gude NM, Permezel M (2001) The effect of vascular coiling on venous perfusion during experimental umbilical cord encirclement. Am J Obstet Gynecol 184:673–678
27. Machin GA, Ackerman J, Gilbert-Barness E (2000) Abnormal umbilical cord coiling is associated with adverse perinatal outcome. Pediatr Dev Pathol 3:462–471

28. Stanek J (2013a) Periarterial stem villous edema is associated with hypercoiled umbilical cord and stem obliterative endarteritis. OJOG 3(9 A):9–14
29. Furman B, Erez O, Senior L, Shoham-Vardi I, Bar-David J, Maymon E, Mazor M (2000) Hydramnios and small for gestational age: prevalence and clinical significance. Acta Obstet Gynecol Scand 79:31–36
30. Boyle JJ, Katz VL (2005) Umbilical cord prolapse in current obstetric practice. J Reprod Med 50:303–306
31. Coulter JB, Scott JM, Jordab MM (1975) Oedema of the umbilical cord and respiratory distress in the newborn. Br J Obstet Gynaecol 82:453–459
32. Hasegawa J, Matsuoka R, Ichizuka K, Sekizawa A, Farina A, Okai T (2006) Velamentous cord insertion into the lower third of the uterus is associated with intrapartum fetal heart rate abnormalities. Ultrasound Obstet Gynecol 27:425–429
33. Hershkovitz R, Silberstwin T, Sheiner E, Shoham-Vardi I, Holcberg G, Katz M, Mazor M (2001) Risk factors associated with true knots of the umbilical cord. Eur J Obstet Gynecol Reprod Biol 98:36–39
34. Peng HQ, Smith-Levitin M, Rochelson B, Kahn E (2006) Umbilical cord stricture and overcoiling are common causes of fetal demise. Pediatr Dev Pathol 9:14–19
35. Joshi V (1994) Handbook of placental pathology. Igaku-Shoin, New York, Tokyo
36. Lepais L, Gaillot-Durand L, Boutitie F, Lebreton F, Buffin R, Huissoud C, Massardier J, Guibaud L, Devouassoux-Shisheboran M, Allias F (2014) 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 35:611–617
37. Kraus FT, Redline RW, Gersell DJ, Nelson DM, Dicke JM (2004) Placental pathology. American Registry of Pathology, Washington, DC
38. Baergen RN (2005) Manual of Benirschke and Kaufmann's Pathology of the Human Placenta. Springer, New York, NY
39. Stanek J (2013b) Hypoxic patterns of placental injury: a review. Arch Pathol Lab Med 137:706–720
40. Stanek J, Biesiada J (2014) Relation of placental diagnosis in stillbirth to fetal maceration and gestational age at delivery. J Perinat Med 42:457–471
41. Benirschke K, Kaufmann P, Baergen RN (2006) Pathology of the human placenta. Springer, New York
42. Altshuler G (1996) Role of the placenta in perinatal pathology (revisited). Pediatr Pathol Lab Med 16:207–233
43. Kulkarni ML, Prakash S, Matadh S, Ashok C, Pradeep N, Avinash T, Kulkarni AM (2007) Absence of Wharton's jelly around the umbilical arteries. Indian J Pediatr 74:787–789
44. Silver RK, Dooley SL, MacGregor SN, Depp R (1998) Fetal acidosis in prolonged pregnancy cannot be attributed to cord compression alone. Am J Obstet Gynecol 159:666–669
45. Sarno AP, Polzin WJ, Feinstein SJ, Maslow A (1995) Transabdominal amnioinfusion in preterm pregnancies complicated by fetal growth restriction, oligohydramnios and umbilical cord compression. Fetal Diagn Ther 10:408–414
46. Chang KTE (2009) Pathological examination of the placenta: *Raison d'être*, clinical relevance and medicolegal utility. Singap Med J 50:1123–1133
47. Saleemuddin A, Tantbirojn P, Sirois K, Crum CP, Boyd TK, Tworoger S, Parast MM (2010) Obstetric and perinatal complications in placentas with fetal thrombotic vasculopathy. Pediatr Dev Pathol 13:459–464
48. Carey JC, Rayburn WF (2000) Nuchal cord encirclements and risk of stillbirth. Int J Gynecol Obstet 69:173–174
49. Kidron D, Bernheim J, Aviram R (2009) Placental findings contributing to fetal death, a study of 120 stillbirths between 23 and 40 weeks gestation. Placenta 30:700–704
50. Ptacek I, Sebire NJ, Man JA, Brownbill P, Heazell AEP (2014) Systematic review of placental pathology reported in association with stillbirth. Placenta 35:552–562
51. Ryan WD, Trivedi N, Benirschke K, LaCoursiere DY, Parast MM (2012) Placental histologic criteria for diagnosis of cord accident: sensitivity and specificity. Pediatr Dev Pathol 15:275–280
52. Chang KTE, Keating S, Costa S, Machin G, Kingdom J, Shannon P (2011) Third trimester stillbirths: correlative neuropathology and placental pathology. Pediatr Dev Pathol 14:345–352
53. Stanek J (2015) Placental hypoxic overlap lesions: a clinicopathologic correlation. J Obstet Gynecol Res 41:358–369
54. Pathak S, Lees CC, Hackett G, Jessop F, Sebire NJ (2011) Frequency and clinical significance of placental histological lesions in an unselected population at or near term. Virchows Arch 459: 565–572
55. Redline RW (2008) Cerebral palsy in term infants: a clinicopathologic analysis of 158 medicolegal case reviews. Pediatr Dev Pathol 11:456–464
56. Bianchi DW, Crombleholme TM, D'Alton ME, Malone FD (2010) Fetology. Diagnosis and management of the fetal patient. 2nd edition. McGraw Hill Medical, New York:741–745.
57. Ariel I, Anteby E, Hamani Y, Redline RW (2004) Placental pathology in fetal thrombophilia. Hum Pathol 35:729–733
58. Avagliano L, Locatelli A, Danti L, Felis S, Mecacci F, Bulfamante GP (2015) Placental histology in clinically unexpected severe acidemia at term. Early Hum Dev 91:339–343
59. Jessop FA, Lees CC, Pathak S, Hook CE, Sebire NJ (2014) Umbilical cord coiling: clinical outcomes in an unselected population and systematic review. Virchows Arch 464:105–112