ARTICLE

Increased Prevalence of Fetal Thrombi in Monochorionic-Twin Placentas

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ABSTRACT

OBJECTIVE. Fetal vessel thrombosis has been related to pregnancy complications and adverse neonatal outcomes in singleton pregnancies, but the clinical and pathologic characteristics of fetal thrombosis in twin pregnancy are still ill defined.

METHODS. To clarify the characteristics of fetal thrombosis in twins, we reviewed the histology slides and medical records of live-born infants of twin pregnancies involving the live birth of at least 1 fetus (monochorionic: 389 cases; dichorionic: 780 cases) and singleton pregnancies (1162 cases).

RESULTS. The incidence of fetal thrombosis in monochorionic-twin pregnancies was significantly higher than that of dichorionic-twin and singleton pregnancies (5.1% vs 3.0% and 2.8%, respectively). The incidence of velamentous umbilical cord insertion in monochorionic- and dichorionic-twin placentas was also higher than in singleton placentas (12% and 7% vs 2%, respectively). Fetal thrombosis in twin placentas was associated with intrauterine growth restriction. In monochorionic twins, fetal thrombosis was associated with co-twin fetal death, but in dichorionic twins no correlation was identified. Microscopically, fetal vessel thrombosis in twin placentas was associated with vascular cushions (fibrous hyperplasia of fetal vessel), as is the case occasionally in singletons.

CONCLUSIONS. The incidence of fetal vessel thrombosis in monochorionic placentas was higher than that seen in dichorionic-twin placentas and singleton gestations. Fetal vessel thrombosis in twin pregnancies showed a correlation with intrauterine growth restriction, peripheral cord insertions, and major vascular cushions.

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Key Words
placenta, thrombosis, twins

Abbreviations
SGA—small for gestational age
PIH—pregnancy-induced hypertension
DM—diabetes mellitus

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FETAL VESSEL THROMBI in singleton placentas occur frequently in the superficial placental vessels and villous stem vessels and are associated with intrauterine small for gestational age (SGA), intrauterine demise, and occasionally neonatal coagulation disorders.[1–5] The clinical and pathologic features of fetal vessel thrombosis in twins, however, are not clear.

Unequal size of fetuses and/or SGA, both of which are frequent complications of multifetal gestations, is associated with increased perinatal mortality and morbidity. Victoria et al[6] and Hanley et al[7] reported that severe discordance occurred significantly more often in monochorionic than in dichorionic twins and was significantly associated with velamentous cord insertions. Redline et al[8] demonstrated that peripheral insertion of the umbilical cord and avascular villi were associated with abnormal growth in twins. However, the incidence in twins, mechanism of disease, and perinatal outcomes of dichorionic and monochorionic twins with fetal thrombosis are not known. Therefore, we reviewed the histology slides and clinical records of all monochorionic and dichorionic live-born twins over a 10-year period and correlated to maternal factors, perinatal outcomes, and placental pathology to fetal vessel thrombosis in twins.

MATERIALS AND METHODS

Study Population

Twin and singleton placentas referred for study were obtained from the department of pathology between 1990 and 2000 at the University of California, San Diego Medical Center. A retrospective review of maternal and infant pair charts was conducted. Authors blinded to the clinical records reviewed the placental reports and histology. Each twin placenta was considered as a single specimen. Cases with 2 stillborn infants and conjoined twins were excluded. Of these referrals, 1169 twin placentas were from live-born infants. Singleton placentas from live-born infants were selected randomly (n = 2662). Maternal factors of interest were age and history of pregnancy-induced hypertension (PIH) and diabetes mellitus (DM). Neonatal factors of interest were respiratory distress syndrome, fetal distress, twin-twin transfusion syndrome, intrauterine growth retardation, discordancy, and co-twin fetal death. SGA was defined as birth weight <10th percentile.[9,10] Discordancy was defined by >15% difference in birth weight relative to the larger twin.[11]

Classification of Placental Findings

Gross findings were recorded from the original pathology reports in all cases. Twins were assigned to their placentas by clamps placed around the umbilical cord by the obstetrician at the time of delivery. Chorionicity was determined by gross examination of the dividing membrane. The number of monochorionic-twin placentas was 389 and that of dichorionic-twin placentas was 780. In monochorionic cases, serial injection of chorionic arteries was performed to evaluate for twin-twin anastomoses. Sections were taken for histology according to criteria developed by the College of American Pathologists.[12] In all cases, ≥4 microscopic slides were available from each twin for review: 2 umbilical cord sections, fetal membrane sections, dividing membrane sections, and villous tissue sections. The umbilical cord was not used for the neonatal determination of gases in any case. Fetal vessel thrombi were defined by agglutinated platelets covered by a leukocyte-containing layer of condensed fibrin. Major vascular cushions were defined as fibrous hyperplasia of the surface or stem vessel walls. Avascular villi were defined by ≥15 affected terminal villi per section.[13] Chorangiosis was defined by 10 villi with ≥10 vascular channels.[14] Tenney-Parker change (excessive syncytial knotting) was defined by ≥30% of the tertiary villi with syncytial buds.[15] We also evaluated each placenta for acute inflammation and atherosis.

Statistical Analysis

Differences between cases and controls for all categorized numerical variables were analyzed for significance by using the χ^2 or Fisher's test. Maternal and gestational age were compared by using the 2-tailed Student's t test. Values of $P < .05$ were considered significant.

RESULTS

There was no significant difference in maternal age, gestational age, and the presence of DM between twin and singleton gestations although, on average, singletons were nearly 4 weeks older (Table 1). PIH was present more often in twins than in singleton gestations.

The incidence of fetal vessel thrombosis in monochorionic placentas was higher than that of dichorionic placentas and that of singleton gestations (5.1% vs 3.0% and 2.8%, respectively) (Table 2). Thrombus formation in both fetuses' placentas was observed in 4 pairs of the 176 monochorionic twins (2.2%) and 3 pairs of the 379 dichorionic twins (0.8%). No significant difference was found between those in monochorionic pairs and those in dichorionic pairs (P = .15). To explore the role of peripheral cord insertion, we compared the incidence of peripheral cord insertion in monochorionic-twin, dicho-

TABLE 1 **Maternal Factors**

	Monochorionic (n = 389)	Dichorionic (n = 780)	Singleton (n = 2662)
Maternal age, y, mean ± SD	29.8 ± 5.9	29.5 ± 6.7	27.3 ± 6.5
Gestational age, wk, mean ± SD	31.9 ± 4.5	32.0 ± 4.8	35.6 ± 4.7
PIH, n (%)	15 (3.8)[a]	29 (3.7)[a]	50 (1.9)
DM, n (%)	4 (1)	4 (0.5)	102 (3.8)

[a] Values have significance at the $P < .05$ level, comparing values with singletons.

TABLE 2 **Incidence of Fetal Vessel Thrombosis and Peripheral Cord Insertion**

	Monochorionic ($n = 389$), *n* (%)	Dichorionic ($n = 780$), *n* (%)	Singleton ($n = 2662$), *n* (%)
Fetal vessel thrombosis	20 (5.1)[a]	24 (3.0)	75 (2.8)
Marginal insertion	88 (23)	133 (17)	271 (10)
Velamentous insertion	45 (12)[a]	57 (7.3)[a]	60 (2.2)

[a] Values have significance at the $P < .05$ level, comparing values with singletons.

rionic-twin, and singleton placentas. The incidence of velamentous insertion was higher in monochorionic and dichorionic placentas than that in singleton placentas (12% and 7.3% vs 2.2%, respectively) (Table 2). The incidence of velamentous cord insertion was also higher in monochorionic twins than in dichorionic twins ($P = .015$).

In monochorionic or dichorionic twins and singleton gestations, fetal vessel thrombosis was associated with SGA (Table 3). In monochorionic twins, fetal vessel thrombosis was also associated with size discordance and fetal death of 1 twin. In dichorionic twins, there was no correlation between fetal thrombosis and fetal death of 1 twin.

Microscopically, fetal vessel thrombosis was associated with major vascular cushions with overlying fibrin in monochorionic, dichorionic, and singleton placentas (Fig 1; Table 4). In dichorionic or singleton placentas, fetal thrombosis was significantly correlated with avascular villi, infarction, chorangiosis, and Tenney-Parker changes. No significant correlation with chorioamnionitis, atherosis, or vascular anastomosis was seen.

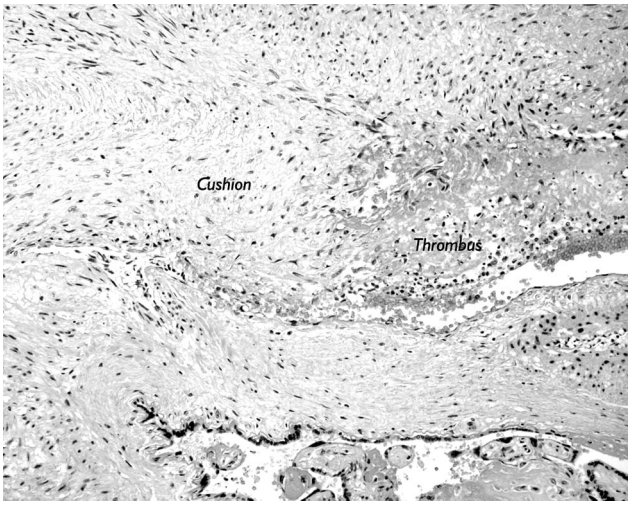

FIGURE 1
Vascular cushion with thrombosis of placental fetal vessel. The stem vessel shows vascular cushion (myxoid fibromuscular hyperplasia) and mural thrombus.

DISCUSSION

To our knowledge, this is first report of the incidence of fetal vessel thrombosis in twin pregnancies. We found that the incidence of fetal thrombosis was higher in monochorionic twins than in dichorionic twins and singleton gestations. Fetal thrombosis was associated with SGA, confirming the work of others.[6,7] Redline et al[8] reported that avascular villi with occlusion of fetal vessels in the placenta was associated with intrauterine growth retardation and discordant growth in monochorionic-twin placentas. Fetal vessel thrombosis is common in the placentas of SGA infants. Our study is consistent with other studies that show a poorer pregnancy outcome in monochorionic twins compared with dichorionic twins.

Antepartum death of a single fetus is associated with a significant morbidity and mortality in the surviving co-twin. Bajoria et al[16] reported that intracranial lesions were greater in monochorionic than in dichorionic twins after a single intrauterine fetal death. A single fetal death in monochorionic twins is associated with brain, digestive organ, kidney, and skin disorders in the live-born infant.[17–19] Margono et al[20] reported foot necrosis in a surviving fetus and observed multiple thrombi of the placental vessels of the surviving fetus. In our study, we found many fetal vessel thrombi in the placentas of live-born infants of monochorionic twins after a single fetal death. In dichorionic twins, there was no statistical correlation between fetal vessel thrombosis and co-twin death; however, additional studies are needed to clarify this point. In theory, the dead fetus in monochorionic twins could cause disseminated intravascular coagula-

TABLE 3 **Relationship of Fetal Vessel Thrombosis and Neonatal Factors**

	Monochorionic Case (T^+) ($n = 20$), *n* (%)	Control (T^-) ($n = 369$), *n* (%)	Dichorionic Case (T^+) ($n = 24$), *n* (%)	Control (T^-) ($n = 756$), *n* (%)	Singleton Case (T^+) ($n = 75$), *n* (%)	Control (T^-) ($n = 2587$), *n* (%)
IUGR	6 (30)[a]	35 (9)	3 (13)[a]	21 (2.7)	15 (20)[a]	138 (5)
RDS	2 (10)	17 (4.6)	1 (4)	37 (4.9)	10 (13)	297 (11)
Fetal distress	0 (0)	13 (3.5)	1 (4)	15 (2)	5 (7)[a]	2 (0.07)
Size discordance	6 (30)[a]	17 (4.6)	2 (8)	22 (3)		
Co-twin demise	5 (25)[a]	14 (3.7)	1 (4)	21 (2.7)		
TTTS	1 (5)	8 (2.1)				

T indicates fetal vessel thrombosis; IUGR, intrauterine growth restriction; RDS, respiratory distress syndrome; TTTS, twin-twin transfusion syndrome.
[a] Values have significance at the $P < .05$ level, comparing control cases with twins.

TABLE 4 **Relationship of Fetal Vessel Thrombosis and Other Pathologic Changes**

	Monochorionic Case (T^+) ($n = 20$), *n* (%)	Control (T^-) ($n = 171$), *n* (%)	Dichorionic Case (T^+) ($n = 24$), *n* (%)	Control (T^-) ($n = 197$), *n* (%)	Singleton Case (T^+) ($n = 75$), *n* (%)	Control (T^-) ($n = 590$), *n* (%)
Vascular cushions	9 (45)[a]	16 (9)	15 (62)[a]	17 (9)	37 (49)[a]	51 (9)
Avascular villi	1 (5)	1 (0.5)	3 (13)[a]	0 (0)	9 (12)[a]	3 (0.5)
Infarction	3 (15)	13 (8)	4 (17)	14 (7)	23 (31)[a]	116 (20)
Chorangiosis	1 (5)	2 (1)	4 (17)[a]	7 (4)	4 (5)[a]	14 (2)
T-P changes	2 (5)	4 (2)	3 (13)[a]	1 (0.5)	12 (16)[a]	42 (7)
Chorioamnionitis	2 (10)	4 (2)	1 (4)	32 (16)	11 (15)	102 (17)
Atherosis	0 (0)	6 (4)	0 (0)	5 (3)	0 (0)	16 (3)
Anastomosis	11 (55)	105 (61)				

T indicates fetal vessel thrombosis; T-P changes, Tenney-Parker changes.

[a] Values have significance at the $P < .05$ level, comparing control cases with twins.

tion or local hypotension via vascular anastomosis and could cause multiple organ disorders in the surviving infants, but direct evidence is lacking.

The frequency of velamentous cord insertion is generally increased in twin placentas.[21] In our study, it was much more common in monochorionic than dichorionic placentas (12% vs 7.3%). Hanley et al[7] reported that the presence of a velamentous cord insertion increases the risk of birth weight discordancy in monochorionic twins. Redline et al[8] also demonstrated an association between peripheral cord insertion and avascular villi, indicating occlusion of fetal vessels in the placenta. Fetal vessel thrombi frequently occurred in placentas with velamentous cords.[22] The membranous vessels are unprotected by Wharton's jelly, and they may be prone to injury from compression.

The relationship between fetal vessel thrombosis and maternal factors (PIH and DM) is controversial. Fox[23] reported that fetal stem vessel lesions were common in diabetes and hypertension. Several studies have identified twin gestations to be at risk for hypertensive disorders,[24] but Maxwell et al[25] demonstrated that there was no difference in the rate of hypertensive disease between monozygotic and dizygotic gestations. Our study showed a higher incidence of PIH in twin pregnancies; however, only monochorionic-twin placentas showed a high incidence of fetal vessel thrombosis, not dichorionic-twin gestations. In our study, although fetal vessel thrombi were more frequently present in pregnancies with PIH than in pregnancies without PIH, there was no significant difference between pregnancies with and without PIH (data not shown). Also, in our study there was no correlation between fetal thrombosis and maternal history of DM. Evers et al[26] and Makhseed et al[27] also reported no difference in the rate of fetal thrombosis between diabetic and control placentas. A larger, more careful study is needed to provide a definitive answer.

Histologically, fetal vessel thrombosis is clearly associated with major vascular cushions. de Sa[28] first described localized, protuberant mural lesions composed of proliferating fibroblasts in the walls of large placental veins, but the precise etiology is not known. It may be that cushions reflect old mural thrombosis, because they often have overlying recent mural thrombi. Our study supports this hypothesis.

REFERENCES

1. Benirschke K, Kaufmann P. *Pathology of the Human Placenta*. 4th ed. New York, NY: Springer; 1999:379
2. Redline RW, Pappin A. Fetal thrombotic vasculopathy: the clinical significance of extensive avascular villi. *Hum Pathol.* 1995;26:80–85
3. Kraus FT. Cerebral palsy and thrombi in placental vessels of the fetus: insights from litigation. *Hum Pathol.* 1997;28:246–248
4. Kraus FT, Acheen VI. Fetal thrombotic vasculopathy in the placenta: cerebral thrombi and infarcts, coagulopathies, and cerebral palsy. *Hum Pathol.* 1999;30:759–769
5. Leistra-Leistra MJ, Timmer A, van Spronsen FJ, Geven WB, van der Meer J, Erwich JJHM. Fetal thrombotic vasculopathy in the placenta: a thrombophilic connection between pregnancy complications and neonatal thrombosis? *Placenta*. 2004; 25(suppl A):S102–S105
6. Victoria A, Mora G, Arias F. Perinatal outcome, placental pathology, and severity of discordance in monochorionic and dichorionic twins. *Obstet Gynecol.* 2001;97:310–315
7. Hanley ML, Ananth CV, Shen-Schwarz S, Smulian JC, Lai YL, Vintzileos AM. Placental cord insertion and birth weight discordancy in twin gestations. *Obstet Gynecol.* 2002;99:477–482
8. Redline RW, Shah D, Sakar H, Schluchter M, Salvator A. Placental lesions associated with abnormal growth in twins. *Pediatr Dev Pathol.* 2001;4:473–481
9. Zhang J, Bowes WA Jr. Birth-weight-for-gestational-age patterns by race, sex, and parity in the United States population. *Obstet Gynecol.* 1995;86:200–208
10. Ananth CV, Vintzileos AM, Shen-Schwarz S, Smulian JC, Lai YL. Standards of birth weight in twin gestations stratified by placental chorionicity. *Obstet Gynecol.* 1998;91:917–924
11. Blickstein I, Manor M, Levi R, Goldchmit R, Weissman A. The intrauterine ponderal index in relation to birth weight discordance in twin gestations. *Int J Gynaecol Obstet.* 1995;50:253–255
12. Altshuler G, Deppisch LM. College of American Pathologists Conference XIX on the Examination of the Placenta: report of the Working Group on Indications for Placental Examination. *Arch Pathol Lab Med.* 1991;115:701–703
13. Redline RW, Ariel I, Baergen RN, et al. Fetal vascular obstruc-

tive lesions: nosology and reproducibility of placental reaction patterns. *Pediatr Dev Pathol.* 2004;7:443–452
14. Altshuler G. Chorangiosis: an important placental sign of neonatal morbidity and mortality. *Arch Pathol Lab Med.* 1984;108: 71–74
15. Benirschke K, Kaufmann P. *Pathology of the Human Placenta*. 4th ed. New York, NY: Springer; 1999:557
16. Bajoria R, Wee LY, Anwar S, Ward S. Outcome of twin pregnancies complicated by single intrauterine death in relation to vascular anatomy of the monochorionic placenta. *Hum Reprod.* 1999;14:2124–2130
17. Liu S, Benirschke K, Scioscia AL, Mannino FL. Intrauterine death in multiple gestation. *Acta Genet Med Gemellol (Roma).* 1992;41:5–26
18. Wagner DS, Klein RL, Robinson HB, Novak RW. Placental emboli from fetus papyraceous. *J Pediatr Surg.* 1990;25: 538–542
19. Fusi L, McParland P, Fisk N, Nicolini U, Wigglesworth J. Acute twin-twin transfusion: a possible mechanism for brain-damaged survivors after intrauterine death of a monochorionic twin. *Obstet Gynecol.* 1991;78:517–520
20. Margono F, Feinkind L, Minkoff HL. Foot necrosis in a surviving fetus associated with twin-twin transfusion syndrome and monochorionic placenta. *Obstet Gynecol.* 1992;79:867–869
21. Benirschke K, Kaufmann P. *Pathology of the Human Placenta*. 4th ed. New York. NY: Springer; 1999:353
22. Redline RW. Clinical and pathological umbilical cord abnormalities in fetal thrombotic vasculopathy. *Hum Pathol.* 2004; 35:1494–1498
23. Fox H. Abnormalities of the foetal stem arteries in the human placenta. *J Obstet Gynaecol Br Commonw.* 1967;74:734–738
24. Sibai BM, Hauth J, Caritis S, et al. Hypertensive disorders in twin versus singleton gestations. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. *Am J Obstet Gynecol.* 2000;182:938–942
25. Maxwell CV, Lieberman E, Norton M, Cohen A, Seely EW, Lee-Parritz A. Relationship of twin zygosity and risk of preeclampsia. *Am J Obstet Gynecol.* 2001;185:819–821
26. Evers IM, Nikkels PGJ, Sikkema JM, Visser GHA. Placental pathology in women with type 1 diabetes and in a control group with normal and large-for-gestational-age infants. *Placenta.* 2003;24:819–825
27. Makhseed M, Musini VM, Ahmed MA, Al-Harmi J. Placental pathology in relation to the White's classification of diabetes mellitus. *Arch Gynecol Obstet.* 2002;266:136–140
28. de Sa DJ. Intimal cushions in foetal placental veins. *J Pathol.* 1973;110:347–352

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