Estimating the Time of Death in Stillborn Fetuses: II. Histologic Evaluation of the Placenta; a Study of 71 Stillborns

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Objective: **To determine whether placental histologic examination is useful for predicting the approximate time of death in stillborn fetuses.**

Methods: **Hematoxylin and eosin slides of 71 placentas of stillborns with accurately timed deaths were studied retrospectively. Fifty-one placentas (learning set) were used to develop proposed histologic criteria for the timing of fetal death, which were then tested in the remaining 20 placentas (test set).**

Results: **Among 15 histologic variables assessed in the learning set, three features appeared to correlate well with specific death-to-delivery intervals: 1) villous intravascular karyorrhexis (6 or more hours); 2) vascular lumen abnormalities of stem villi, including fibroblast "septation" and total luminal obliteration (multifocal, 2 or more days; extensive, 2 or more weeks); and 3) extensive fibrosis of terminal villi (2 or more weeks). When the placentas in the test set were evaluated using the three histologic criteria, 18 of 20 cases were classified correctly with respect to the approximate time of fetal death.**

Conclusions: **Placental histologic examination seems to be useful for determining the approximate time of death in many stillborn fetuses.** ***(Obstet Gynecol 1992;80:585–92)***

Stillbirth is a major component of perinatal mortality, accounting for approximately half of perinatal deaths.[1,2] Although it has been estimated that 50% of fetal deaths occur within 24 hours of delivery,[3] the exact time of death in individual cases is often unknown. To understand better the causes of stillbirth and to develop strategies for its prevention, it would be useful to devise pathologic methods for retrospectively determining the approximate time of fetal death. Histologic examination of fetal tissues and the placenta is a potential method for estimating the time of intrauterine death.[4,5] Because parental permission is required for an autopsy examination, fetal tissues are not always available for assessment. In contrast, the placenta is nearly always available. In some circumstances, therefore, the placenta is the only tissue from which a pathologic estimate of the timing of fetal death can be made. This study was designed to determine to what extent placental histology alone can be used to determine the time of intrauterine death in stillborn fetuses.

Materials and Methods

We reviewed the medical records of women who delivered stillborn fetuses at Brigham and Women's Hospital from 1980–1991. For 71 stillborns, the time of fetal death was accurately determined by clinical studies (serial ultrasound or Doppler examinations) and placental histologic slides were available for review. The 71 fetuses represented 47% of the 150 stillborns previously described in our accompanying report on autopsy histology (this issue, page 575). An "accurately timed" death was defined as one in which confirmation of fetal cardiac activity by ultrasound or Doppler instrumentation was followed shortly by confirmation of fetal asystole by ultrasound or Doppler. In multiple gestations, only ultrasound was considered sufficiently reliable for evaluating fetal status. Maternal recall of fetal activity was not used. We tabulated the following clinical data and autopsy findings in all cases: gestational age at death, birth weight, and clinical/pathologic evidence of acute or chronic fetal stress (fetal growth retardation, fetal hydrops, maternal preeclampsia, abruptio placentae, prolapsed cord, numerous petechiae, or diffuse interstitial hemorrhage at autopsy).

Each placenta had originally been assessed pathologically according to a protocol developed by Driscoll.[6] Briefly, placentas designated for pathologic

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Table 1. Placental Histology Assessed in the 51 Learning Cases

A. Umbilical cord
1. Vasculitis
2. Loss of nuclear basophilia of stromal cells
3. Loss of nuclear basophilia of vascular smooth-muscle cells
B. Chorionic plate
4. Acute chorioamnionitis
5. Meconium-laden macrophages in chorion
C. Stem villi
6. Vascular luminal abnormalities (multifocal*/extensive†)
D. Terminal villi: stroma
7. Infarction
8. Villous edema
9. Extensive villous fibrosis
10. "Dusty" stromal microcalcification
E. Terminal villi: blood vessels
11. Nucleated red blood cells
12. Intravascular karyorrhexis
F. Terminal villi: trophoblast
13. Increased syncytial knots
14. Trophoblast basement membrane thickening/calcification
15. Increased number of cytotrophoblast cells

* Present in 10–25% of stem villi.
† Present in more than 25% of stem villi.

assessment were kept refrigerated at 5C until they were examined in the fresh state. Following gross assessment of the intact specimen, the umbilical cord and membranes were removed and the disk was weighed. The placental parenchyma was examined by slicing the disk at approximately 1-cm intervals; representative sections of the umbilical cord, membranes, and placental parenchyma (including grossly normal and abnormal areas) were fixed overnight in either Bouin's solution (1980–1989) or 10% buffered formalin (1990–1991). Tissue blocks were embedded in paraffin and histologic slides were prepared with hematoxylin and eosin stain.

Before the histologic slides of the 71 placentas were assessed retrospectively, the cases were randomly divided into a "learning set" (51 placentas) and a "test set" (20 placentas); the initial investigation involved the learning set.

All hematoxylin and eosin-stained placental slides of the learning set were reviewed retrospectively in an unblinded fashion for the presence of the 15 histologic features listed in Table 1. Loss of nuclear basophilia (karyolysis) was defined as absence of hematoxylin (blue) staining in at least 1% of nuclei in the specified tissues. Acute chorioamnionitis included polymorphonuclear leukocytes in the subchorionic fibrin or the chorioamnion; umbilical vasculitis was defined as polymorphonuclear leukocytes in the wall of an umbilical cord vessel. Luminal abnormalities in muscular vessels of the stem villi were defined as either total luminal obliteration of a vessel (with complete loss of the endothelial lining and luminal blood), or fibroblast "septation" of the lumen into several small, irregular spaces containing degenerated blood (resembling recanalization in a thrombus). Such vascular abnormalities were quantified as either "multifocal" (present in 10–25% of stem villi) or "extensive" (present in more than 25% of stem villi). Vascular wall thickness was not assessed when evaluating the blood vessels in stem villi. Villous edema was identified when numerous "swiss cheese-like" spaces containing central macrophages were seen in the villous stroma. Extensive fibrosis of the terminal villi was defined as a completely avascular, hyalinized, and fibrotic appearance of more than 25% of the terminal villi. "Dusty" stromal microcalcification was identified when some villi demonstrated numerous, finely punctate, hematoxylin-stained granules resembling microcalcifications. An increase in nucleated red blood cells was identified when such cells were visualized frequently in fetal vessels. Intravascular karyorrhexis was defined as numerous particles of hematoxylin-stained nuclear debris located within small villous vessels in several different regions. Increased syncytial knots were identified if clusters of hyperchromatic, enlarged syncytiotrophoblastic cells were prominent. Trophoblast basement membrane thickening/calcification was defined as a wavy, linear, basophilic thickening located in the villous stroma subjacent to trophoblast. Increased numbers of cytotrophoblast cells were identified if numerous terminal villi had four or more easily identifiable cytotrophoblast cells per villus.

Histologic findings were compiled and compared with the duration of intrauterine retention following fetal death. To identify histologic features that might be good candidates for determining the time of fetal death, we analyzed each feature as a diagnostic test in terms of its sensitivity, specificity, and positive predictive value for each of the following death-to-delivery times: less than 2 hours, 2 or more hours, 4 or more hours, 6 or more hours, 8 or more hours, 12 or more hours, 18 or more hours, 24 or more hours, 36 or more hours, 48 or more hours, 1 or more weeks, 2 or more weeks, 3 or more weeks, 4 or more weeks, and 8 or more weeks. Histologic features with high sensitivity, specificity, and positive predictive values for specific times were used to evaluate the 20 test cases.

Hematoxylin and eosin-stained placental slides from the 20 test cases were randomly and blindly evaluated using the histologic criteria developed from analysis of the learning cases. Each histologic variable was then assessed as an individual diagnostic test for determining the time of fetal death. Next, all histologic features

Table 2. Learning Cases: Histologic Features With Time-Related Onset

Histologic feature	Time of fetal death before delivery: Cases with histologic feature						
	<6 h (N = 15)	6–24 h (N = 13)	24–48 h (N = 5)	2–7 d (N = 5)	7–14 d (N = 4)	14–28 d (N = 4)	>28 d (N = 5)
Intravascular karyorrhexis	0%	85%	100%	100%	100%	100%	100%
Extensive villous fibrosis	0%	0%	0%	20%	50%	100%	100%
Stem vessel luminal abnormalities							
Multifocal (10–25% of stem villi)	0%	0%	0%	60%	100%	50%	0%
Extensive (>25% of stem villi)	0%	0%	0%	20%	0%	50%	100%
Cord stromal necrosis	7%	31%	0%	60%	75%	67%	100%
Cord vascular necrosis	0%	0%	0%	0%	50%	33%	100%
Stromal "dusty" calcification	7%	0%	20%	40%	75%	75%	40%
Trophoblast basement membrane calcification/thickening	13%	0%	0%	40%	100%	50%	40%

found in each case were assessed collectively to determine their predictive value for the time of fetal death.

To determine the reproducibility of this method of placental assessment, selected histologic features were blindly evaluated in 40 randomly chosen cases; intraobserver agreement values and kappa values[7] were calculated.

In addition to the foregoing retrospective histologic analysis, we prospectively assessed four fresh placentas from live-born infants (20, 32, 35, and 40 weeks' gestation) for "refrigeration artifact." The placentas were immediately refrigerated (5C) after delivery, and widely spaced random samples of the cord and placental parenchyma were removed at each of the following times: 0, 12, 24, and 48 hours, and 7 and 14 days. The samples were fixed in 10% buffered formalin for 24 hours, then embedded in paraffin and stained with hematoxylin and eosin. The histologic findings listed in Table 1 were assessed in each sample.

Results

Among the 71 cases, the mean gestational age at the time of fetal death was 26.7 weeks (range 11–43); the mean value for the learning set (26.5 weeks) was similar to that of the test set (27.1 weeks). Among the 71 fetuses, the mean interval from the last confirmation of cardiac activity until the documentation of death was 58.3 hours (range 0–1008). Among fetuses who died within 24 hours of birth, the mean interval was 3.5 hours (range 0–16); in fetuses who died 1–7 days before birth, the mean interval was 34.4 hours (range 4–144); in those who died more than 7 days before birth, the mean interval was 200 hours (range 0–1008). The median length of time from death to birth was 17 hours for all 71 cases, 17 hours in the 51 learning cases, and 18 hours in the 20 test cases. One-third of the fetuses died within 6 hours of delivery (29% learning set, 30% test set), one-third died between 6–48 hours of delivery (35%, both sets), and one-third died more than 48 hours before birth (36% learning set, 35% test set). The birth weight averaged 1147 g for all 71 cases (range 124–3550); the weights in the 51 learning cases (mean 1163 g; range 180–3550) and the 20 test cases (mean 1110 g; range 124–3350) were similar. Clinicopathologic evidence of acute or chronic stress/hypoxia before fetal death was present in 52% of the 71 cases (51% of learning cases and 55% of test cases). Among all cases, the duration of placental refrigeration before fixation ranged from 1–83 hours and averaged 19.6 hours (18% less than 6 hours, 55% 6–24 hours, 16% 24–48 hours, 9% 48–72 hours, and 2% more than 72 hours). The mean number of slides per case was 4.4 (range two to eight); the average number of slides per case was similar in the learning set (4.3) and the test set (4.6).

We found no apparent correlation with the timing of fetal death for eight of the 15 histologic variables evaluated: meconium-laden macrophages, umbilical vasculitis, acute chorioamnionitis, villous infarction, villous edema, nucleated red blood cells, increased syncytial knots, and increased numbers of cytotrophoblast cells. Among the 51 learning cases, the incidence of acute chorioamnionitis was related to gestational age; it was present in 19 of 37 cases (51.3%) with a gestational age of less than 34 weeks and in one of eight cases (12.5%) with a gestational age greater than 34 weeks. Meconium was present in chorionic macrophages in 58% of cases, but did not correlate with the timing of fetal death or with the mean length of placental refrigeration before fixation.

Seven histologic features developed in a time-related fashion after fetal death (Table 2). Table 3 presents the performance of these features as diagnostic tests for various death-to-delivery intervals. The three features that performed best ("good predictors") had sensitivities, specificities, and positive predictive values greater than 0.750. Among these three predictors, the

Table 3. Learning Cases: Histologic Features as Individual Diagnostic Tests

Histologic feature	Time of fetal death (before birth)	Sensitivity	Specificity	Positive predictive value
Good predictors				
Intravascular karyorrhexis	≥6 h	0.935	1.000	1.000
Stem vessel luminal abnormalities				
Multifocal	≥48 h	0.944	1.000	1.000
Extensive	≥14 d	0.777	0.976	0.875
Extensive villous fibrosis	≥14 d	1.000	0.928	0.750
Poor predictors				
Stromal "dusty" calcification	≥24 h	0.478	0.969	0.916
Wharton jelly necrosis	≥48 h	0.733	0.843	0.688
Trophoblast basement membrane calcification/ thickening	≥48 h	0.333	0.928	0.667
Cord vascular necrosis	≥7 d	0.600	1.000	1.000

first change to develop after fetal death was villous intravascular karyorrhexis; this finding was present in zero of 15 cases in which fetal death preceded delivery by less than 6 hours, but was seen in 29 of 31 cases (94%) with an interval of more than 6 hours. Leukocytes appeared to be the cell of origin of much of the intravascular karyorrhectic debris (Figure 1); the possibility that vascular endothelial cells may also contribute to this finding cannot be excluded. Stem villous vascular lumen abnormalities (Figures 2 and 3) also appeared to correspond well with the timing of death. This change was usually present "multifocally" (involving 10–25% of stem villi) 48 or more hours after fetal death and was seen "extensively" (involving more than 25% of stem villi) in most placentas 14 or more days after fetal death. Extensive villous fibrosis (Figure 4) was present in all cases with death 14 or more days before birth. The four remaining histologic features listed in Table 3 had sensitivities or positive predictive values below 0.750; consequently, these were categorized as poor predictors for the timing of fetal death.

We developed the following hypothesis from analysis of the 51 learning cases: Three placental histologic features (villous intravascular karyorrhexis, stem villous vascular abnormalities, and extensive villous fibrosis) can be used to determine the approximate time of death in stillborns (less than 6 hours before birth, more than 6 but less than 48 hours before birth, more than 48 hours but less than 2 weeks before birth, and more than 2 weeks before birth). To test this hypothesis, the hematoxylin and eosin slides of the 20 unknown cases (test set) were randomly and blindly assessed for the three specified histologic findings. Eighteen of the 20 cases (90%) were correctly classified for the approximate time of fetal death. Most histologic features performed well in predicting the time of death. Villous intravascular karyorrhexis was not present in any of six fetuses who died less than 6 hours before birth, but was identified in all 14 who died more than 6 hours before birth. Similarly, diffuse villous

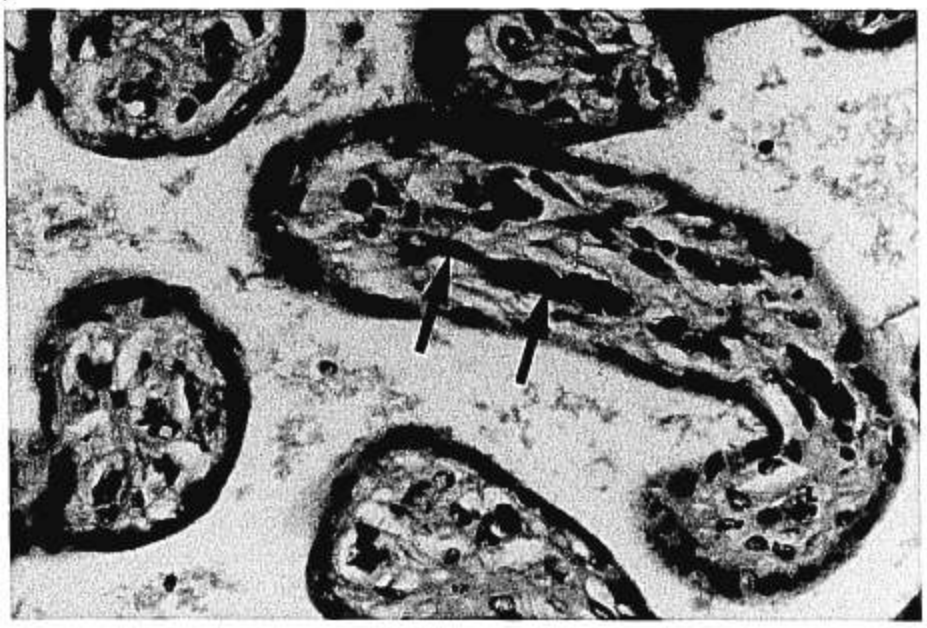

Figure 1. Placenta of 26-week stillborn fetus with hydrocephalus and nonimmune hydrops; fetal death occurred 24–48 hours before birth. Intravascular karyorrhexis is present in a capillary of a terminal villus (*arrows*); the small, irregular, basophilic nuclear fragments appear to be derived from degenerating fetal blood cells (hematoxylin and eosin, × 500).

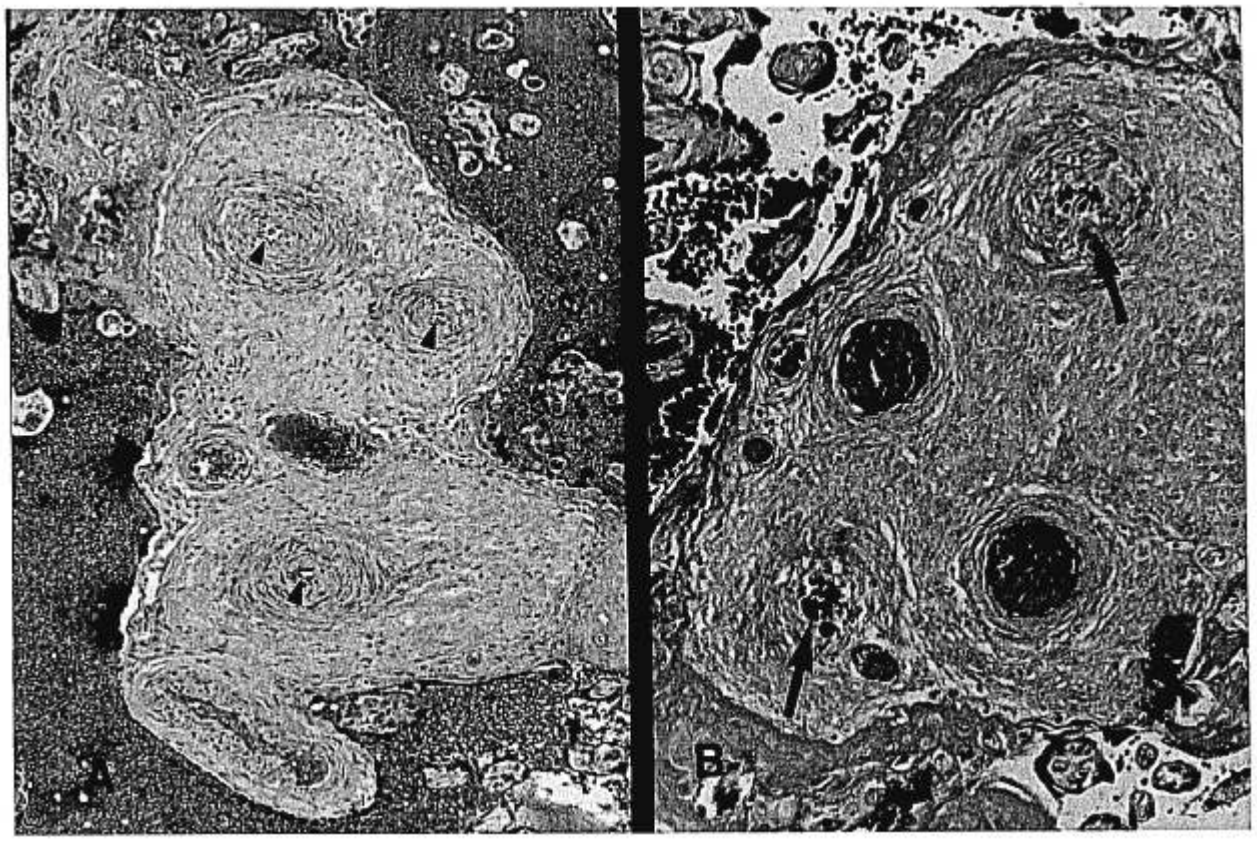

Figure 2. A) Placenta of a stillborn fetus who died 12–24 hours before birth; the 41-week pregnancy was complicated by ruptured membranes, acute chorioamnionitis, and umbilical cord prolapse. Stem vessel lumen abnormalities are not present; although the vessel walls appear thickened with narrowed lumina, each vessel has a single, central lumen (*arrowheads*) (hematoxylin and eosin, × 80). B) Placenta of a growth-retarded stillborn fetus who died at 34 weeks' gestation, 8–12 days before birth. Large-vessel lumen abnormalities were found multifocally in this placenta (ie, present in 10–25% of stem villi). In the stem villus shown, two vessels have abnormal lumens (*arrows*) characterized by multiple irregular blood-containing spaces surrounded by fibroblasts (hematoxylin and eosin, × 100).

fibrosis and extensive large-vessel luminal abnormalities (involving more than 25% of stem villi) were not seen in any of the 18 cases with fetal death less than 14 days before birth, but were present in the two instances in which the fetus died more than 14 days before delivery. Multifocal luminal abnormalities (involving 10–25% of stem villi) correctly predicted the time of death of 18 of 20 cases and incorrectly classified two cases (one false-positive and one false-negative).

To determine intra-observer variability in applying the histologic criteria, 40 randomly selected cases were reevaluated blindly for the three good predictors. The percentage of agreement between the observations ranged from 87–95%; kappa values[7] ranged from 0.539 (for extensive large-vessel lumen abnormalities) to 0.896 (for villous intravascular karyorrhexis).

When the refrigerated placentas of four live-born infants (20, 32, 35, and 40 weeks' gestation) were assessed histologically, none of the 15 features (Table 1) were influenced by the length of placental refrigeration before fixation. One histologic alteration did develop upon refrigeration: After 7–14 days of refrigeration, endothelial cells were frequently found "floating freely" in vascular lumens, individually and as sheets of cells. However, the specific vascular changes that correlated with time of death (intravascular karyorrhexis, large-vessel luminal abnormalities, and villous fibrosis) were not seen in placentas subjected to prolonged refrigeration (up to 14 days).

Discussion

Although many studies have stressed the importance of placental examination in determining an etiology for fetal death in cases of stillbirth,[8–11] relatively little attention has been focused on the placenta as a potential tool for determining retrospectively the time of fetal death. The only previous work that systematically

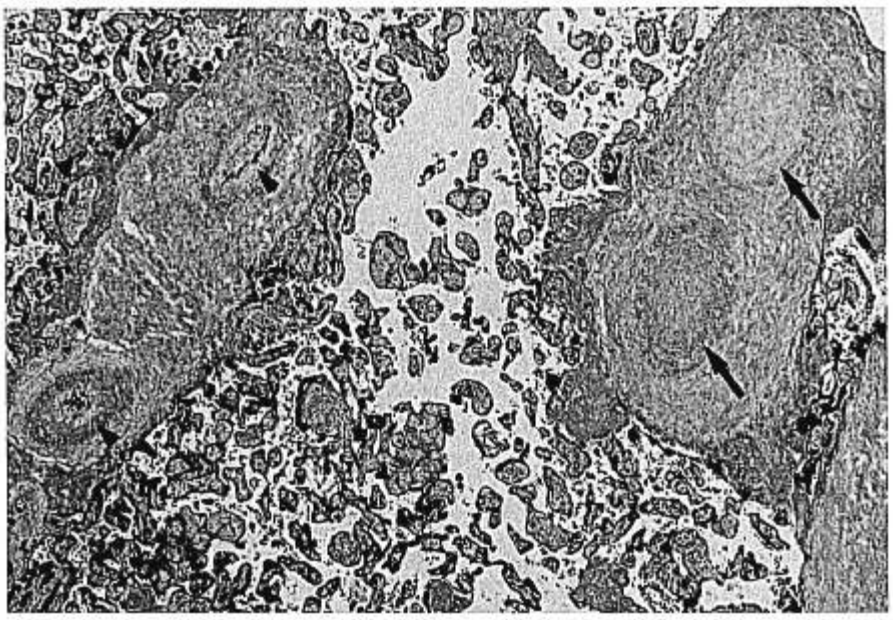

Figure 3. Stem vessel abnormalities in the placenta of a stillborn fetus, a diamniotic, dichorionic twin who died at 33 weeks' gestation and was retained in utero for 4–5 weeks (the co-twin survived). Placental stem vessel luminal abnormalities were extensive (ie, more than 25% of stem villi were involved). Two types of stem vessel abnormalities are illustrated. In the stem villus on the left, fibroblast septation of vessel lumens (*arrowheads*) is characterized by multiple, irregular vascular spaces. In the right stem villus, total obliteration of the stem vessel lumina is present (*arrows*) (hematoxylin and eosin, × 40).

related placental histology to the time of fetal death was the 1968 study of Fox.[5] Although this important work clarified the evolution of many histologic changes with reference to the time of fetal death, it did not directly address the issue of "timing" death from an evaluation of microscopic placental changes. Fox evaluated placentas from 36 stillborns (21 delivered within 24 hours of death, nine delivered 1–7 days after death, and six delivered more than 1 week after death). He used auscultation of the fetal heart or maternal recall of fetal movement to time fetal death. The microscopic finding that correlated best with the time of fetal death was arterial fibromuscular sclerosis in the stem villi, defined by Fox as "marked hyperplasia of the fibrous and muscular tissue of the vessel wall and growth of subintimal fibrous tissue into the vascular lumen."[12] Fibromuscular sclerosis was not found in any of 21 fetuses who died within 24 hours of birth.

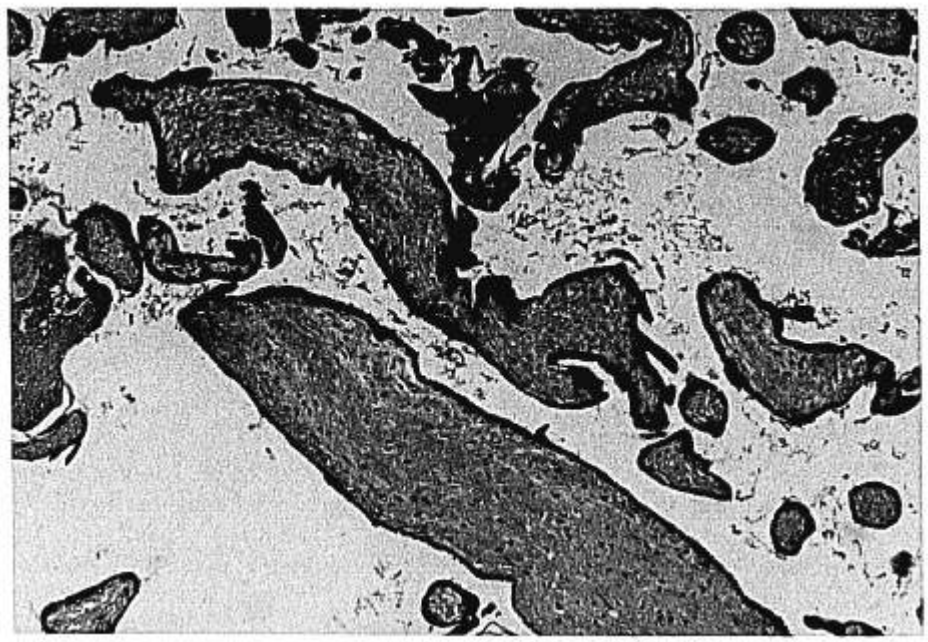

Figure 4. Placenta demonstrating extensive fibrosis of terminal villi. Fetal death occurred in a diamniotic, dichorionic twin at 19 weeks' gestation, followed by 4–8 weeks of intrauterine retention. More than 25% of the terminal villi are totally avascular, characterized by stromal sclerosis with evenly spaced oval fibroblast nuclei (hematoxylin and eosin, × 200).

"Slight" fibromuscular sclerosis ("sufficient to produce only mild or moderate stenosis of the lumen") was found in eight of nine fetuses who died 1–7 days before birth, and "severe" fibromuscular sclerosis (characterized by vessels "almost occluded by the growth of fibrous tissue into the vascular lumen") was found in five of six cases dead more than 7 days before birth.[5] This categorization of fibromuscular sclerosis, based on the degree of luminal stenosis, was not used in the current study because great variability in the diameters of vascular lumina is common in the placenta (Figure 2A). To quantify stem vessel lesions in this study, we estimated the percent of stem villi containing abnormal vessels.

Many findings of this study agree with the results of the earlier work by Fox.[5] In particular, histologic changes relating to cessation of fetal vascular perfusion of the placenta (intravascular karyorrhexis, vascular abnormalities in stem villi, and diffuse fibrosis of villi) were found to correlate well with the time of fetal death. Two additional findings that Fox related to fetal death ("dusty" villous microcalcification and basement membrane thickening) were also loosely associated with the time of fetal death in this study, but were not sufficiently sensitive or specific for use in estimating the time of death. Two other findings that Fox related to the time of fetal death (increased syncytial knots and increased numbers of cytotrophoblast cells) were not found to relate to the time of death in the current study. Because these findings are now considered developmentally related to maternal (not fetal) placental underperfusion,[10] it is not surprising that they do not precisely correlate with the time of fetal death.

Because the common alteration in all placentas following fetal death is the cessation of fetal placental perfusion due to fetal asystole, it is not unexpected that the histologic changes correlating best with the time of fetal death involve the fetal vasculature. To function optimally as markers of fetal death, it would be helpful if such vascular abnormalities were seen exclusively with fetal death. Unfortunately, such changes are not limited to the placentas of stillborns. Similar histologic findings are seen with fetal vascular thrombosis, often localized to a portion of the placental vascular tree that is underperfused because of the thrombus.[13] Fetal vascular thrombosis has been associated with several adverse pregnancy events including maternal diabetes, viral infection, fetal trisomy, long umbilical cord, and amputation necrosis in the fetus.[13] In addition, hemorrhagic endovasculitis, a vascular lesion associated with stillbirth, shares many histologic features of the vascular changes described in this study.[14] Antemortem fetal vascular abnormalities of the placenta that mimic the vascular changes following fetal death appear to occur infrequently; a prospective study of 1938 consecutive third-trimester placentas found fetal vessel thrombosis in 4.4% of cases and hemorrhagic endovasculitis in 0.7%.[15] These antemortem vascular changes often affect the placenta regionally (rather than diffusely, as is characteristic of the vascular changes following fetal death). Therefore, the extent to which they interfere with the estimation of the time of fetal death might not be great; additional studies are necessary to clarify this issue.

Relevant to this discussion is an experimental model described by Silver et al[16] in which short-term placental organ cultures were used to simulate the environment of the placenta retained in utero after fetal death. When chorionic tissues from the placentas of 15 liveborn fetuses were maintained in culture for variable periods and then assessed histologically, most cases demonstrated abnormalities of chorionic blood vessels after 3 days in culture. A vascular abnormality ("hemorrhagic endovasculitis-like lesion") was judged to be present if at least three of the following histologic changes were seen: intravascular karyorrhexis, luminal septation, myointimal proliferation, intravascular fibrin deposition, and transmural dissection of erythrocytes or leukocytes. Although this composite-type definition of a vascular lesion differs from that used in the current study, the conclusion that it takes approximately 3 days before vascular abnormalities become apparent in culture is not greatly different from the 48-hour interval observed in vivo in the current study. Of further interest, among the vascular changes assessed by Silver et al, intravascular erythrocyte/leukocyte fragmentation was generally noted to be the earliest change (M. M. Silver, personal communication); our findings agree.

With what precision can placental histology be used to identify the time of fetal death? Although a high degree of precision is desirable, the current study suggests that in practical terms, the maximum achievable precision involves assigning a fetal death to one of several approximate times: recent (less than 6 hours before birth in this study), short (more than 6 hours but less than 48 hours), intermediate (more than 48 hours but less than 2 weeks), and prolonged (more than 2 weeks).

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