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Intrauterine Death in Multiple Gestation

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Abstract. Intrauterine death of one fetus in a multiple gestation is associated with significant morbidity and mortality in the surviving infant. This study is a retrospective review of 38 twin and 3 triplet gestations involving the intrauterine death of at least one fetus. The obstetrical history, placental pathology, autopsy findings, and neonatal history of the surviving infant are reviewed. Three cases involved the recent stillbirth of both twins, the remaining cases involved a surviving infant. In one case, neonatal death of a surviving twin occurred on day 19. In two sets of triplets, two stillbirths occurred, in the third case two infants were liveborn. The incidence of preterm delivery was 34%, which decreased to 18% if fetal cotwin death had occurred before 20 weeks gestation. Cesarean section was the method of delivery in 16 cases. There was an excess of velamentous cord insertions, which was most pronounced in the stillborn twin. Monochorionic placentation was found in 72%, also an excess.

Neurological damage was known to have occurred in 19 of the 39 surviving infants. Fifteen of these 19 (79%) were associated with monochorionic placentation. The neurologically damaged twin infants, when compared to the normal infants, had the cotwin die later in gestation (31 vs 16.5 weeks), had a shorter duration between the death of the cotwin and delivery (2.5 vs 21 weeks), and delivered earlier in gestation (36.5 vs 39.5 weeks). The probable cause of neurological damage, in our opinion, was either exsanguination into the dead twin fetus, or disseminated intravascular coagulation which occurred in at least 13 cases. The incidence of antepartum death in a multiple gestation, and the potential for neurological damage is probably higher than previously thought. A review of the literature is presented and the clinical implications of this phenomenon are discussed.

Key words: Twins, Fetal Death, CNS damage

INTRODUCTION

Intrauterine death of one fetus in a multiple gestation affects between 0.5% to 6.8% of all twin pregnancies and in an estimated 4.9% of triplet gestations [14,17]. Although the cause of fetal death is often unclear, possible explanations have included the twin-to-twin transfusion syndrome, cord accidents, congenital anomalies, and "placental insufficiency" [12]. When it occurs in early pregnancy, fetal death of one fetus may result in the "vanishing twin phenomenon". A fetus papyraceus results from death occurring in the second trimester [3].

There are numerous reports of significant neurological damage in the surviving infant of such twins [1,4,8,41]. In monochorionic twins, one possible cause of this damage is the transfer of thromboplastin from the dead to the live fetus via placental vascular anastomoses, leading to multiple organ injury from disseminated intravascular coagulation and tissue necrosis. An alternative theory is that exsanguination of the surviving fetus occurs through placental anastomoses into its deceased cotwin in utero, resulting in acute hypotension with cerebral and visceral tissue compromise in the surviving twin [4,16]. In addition, the transfusion syndrome can cause severe anemia or polycythemia with hyperviscosity, also resulting in CNS damage of a survivor.

The incidence of fetal death in multiple gestation (and thus neurological or other damage in the surviving twin) may be more common than was previously believed. Specifically, the increasing use of prenatal ultrasound examination has led to the early diagnosis of twin gestation and apparently frequent documentation of antepartum fetal death. Prenatal and neonatal craniosonography can be used to diagnose brain lesions noninvasively. Moreover, the complications afflicting the survivor have become more apparent as many have become the subject of medicolegal pursuits.

The very comprehensive paper by Enbom [14] gathered 13 reports from the literature and summarized the findings from cases of intrauterine death in multiple gestations. Since then, important publications have come from Szymonowicz et al [41] (6 cases), Cherouny et al [8] (20 cases), and Galea et al [16] (8 cases). The purpose of the present study is to review 41 cases of intrauterine death that occurred in patients with multiple gestation and to examine the possible etiology of neurological and other damage in the surviving infants.

METHODS

We reviewed 41 cases occurring between 1973-1990, which included 38 twin and 3 triplet gestations and which involved the prenatal death of at least one fetus. To enable the reader easier access to the material, Fig. 1 presents a flow sheet of these cases. The cases were identified as follows: (1) 13 cases occurred at UCSD Medical Center, (2) one of the authors (K.B.) had been consulted on 7 cases by local outside sources, and (3) by consultations in 21 litigation cases. The maternal obstetrical and the neonatal histories of the surviving infants, placental pathology, and autopsy reports were reviewed. Long-term follow-up was available for 24 of 39 liveborns. The time of prenatal death was estimated using obstetrical history, crown-heel length, crown-rump length, and weight of the fetus [7,33]. One limitation of this study was the inability to obtain the complete clinical records from some referred cases.

RESULTS

Obstetrical Data

Thirty-eight cases involved twin gestations, and 3 cases were triplets. Three of the cases resulted in the recent stillbirth of both twins, and in another case, the surviving twin died at age 19 days. In two cases of triplets, two of the triplets were stillborn (Fig. 1). Maternal antepartum complications were noted in 21 of 41 mothers; in some, more than one complication was found. Preterm delivery (Table 1) occurred in only 14 cases (34%), although the incidence of prematurity of multiple gestation is usually higher. If the co-twin died in early to mid-gestation ($\leqslant$ 20 weeks) the incidence of preterm delivery was even lower (18%). The range of prematurity was 28 to 37 weeks gestation, with one half being less than 34 weeks, including the two cases where both twins were stillborn. Only one of the liveborn preterm twins was known to have had a normal longterm neurological outcome; two others were neurologically normal in the neonatal period. Premature labor after treatment with ritodrine occurred in one case (2.4%). Hypertension without preeclampsia affected 2 patients (5%), while one patient experienced mild preeclampsia. Disseminated intravascular coagulation (DIC), associated with the diagnosis of the classical twin-twin transfusion syndrome, occurred in one mother with fetal death at 18 weeks gestation. It was successfully treated with heparin until delivery at 35 weeks gestation, without further maternal complications. The infant, thought to be the "reci-

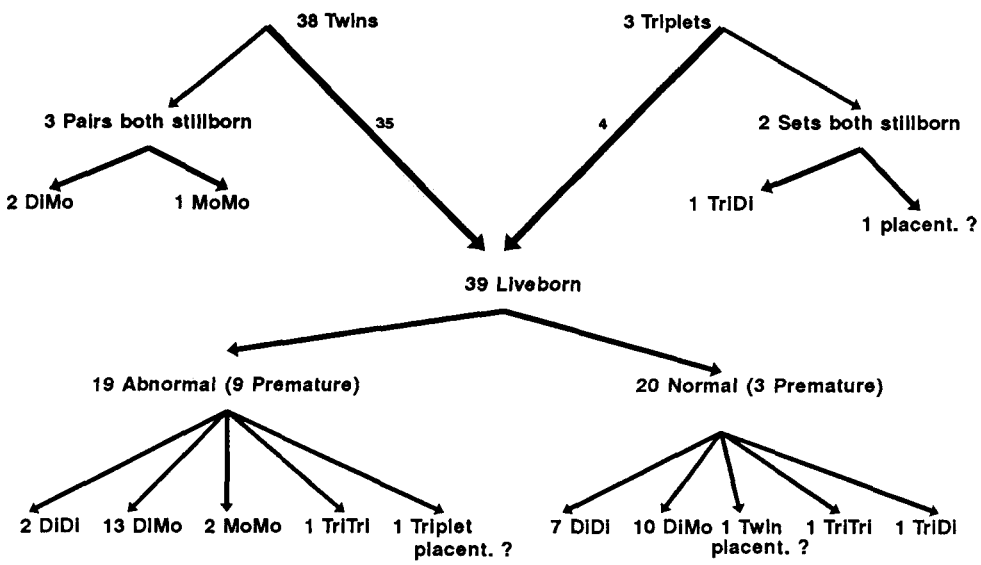

Fig. 1 Flowsheet to explain the origin of various stillborn and liveborn multiples.

Legend: DiMo = Diamnionic monochorionic twin placenta; DiDi = Diamnionic dichorionic twin placenta; MoMo = Monoamnionic monochorionic twin placenta; TriDi = Triamnionic dichorionic triplet placenta; TriTri = Triamnionic trichorionic triplet placenta.

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Table 1 - Preterm delivery and overall outcome

Case no.	Gest. age (wk) at delivery	Delivery history	Longterm outcome of survivor
5	33	spontaneous	intraventricular hemorrhage, developmental and growth delay, hypotonia
7	36	C/S for acute abruptio placentae	well at 15 months
14	35	twin-twin transfusion syndrome, maternal DIC treated successfully at 18 weeks gestation; spontaneous delivery	porencephaly
20	36	C/S for fetal distress	cerebral palsy
21	31	C/S for absence of fetal activity; treated for premature labor at 30 weeks	porencephaly; cerebral atrophy
27	37	spontaneous	cerebral palsy with right hemiplegia, left hemiatrophy, left posterior porencephalic cyst
31	31	C/S for fetal distress; premature labor with unsuccessful treatment	stillbirth of both twins; twin B multiple congenital anomalies, including CNS
32	35	spontaneous	cerebral palsy; diffuse brain damage
33	37	spontaneous	cerebral palsy; evidence of emboli on head CT
34	30	C/S for decreased fetal activity	stillbirth of both twins
35	30	spontaneous; placenta delivered after twin A, stillbirth of twin B with abruptio	respiratory distress syndrome as a neonate; unknown long-term outcome
38	28	C/S for fetal distress	deceased at day 19 of life after removal of ventilator; diffuse cerebral infarctions
40	36	spontaneous; triplets	A: stillborn; B: cerebral palsy; C: fetus papyraceus
41	28	C/S after unsuccessful treatment of premature labor	A: normal head ultrasound and neurological examination at birth (B and C stillborn)

Legend
C/S = Cesarean section
DIC = Disseminated intravascular coagulation
CT = Computed tomography

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pient", was found to have porencephalic cysts. Hydramnios was diagnosed in 2 cases, both with diamnionic, monochorionic (DiMo) placentation One was diagnosed by ultrasound examination at 14 weeks gestation. By 17.5 weeks gestation, fetal death of one twin was affirmed sonographically. Further follow-up revealed the gradual disappearance of hydramnios; the mother had a septate uterus. The other case of hydramnios occurred at 27 weeks gestation with a slight difference in fetal size. Abdominal pain with vaginal bleeding was noted in 4 cases. The diagnosis of intrauterine fetal death was made prior to delivery in 12 patients, with 7 cases detected within a week of delivery. The method and time of diagnosis in relation to the time of delivery are described in Table 2. In all cases, this diagnosis was made by ultrasound study. In the remaining 29 cases, the diagnosis was made at delivery.

Table 2 - Antepartum diagnosis of intrauterine fetal death

Case no.	Gest. age (wk) at diagnosis	Reason for ultrasound examination	Gest. age (wk) at delivery
1	14	advanced maternal age	40
5	10	suspected multiple gestation	33
11	25	unknown	40
14	18	suspected twin-twin transfusion	35
15	17	hydramnios diagnosed; follow-up examination	40
20	36	brown discharge; abdominal discomfort	36
23	40	brown amniotic fluid after spontaneous ruptúre of membranes	40
26	39	decreased fetal activity immediately prior to delivery	39
32	35	spotting, "twinges" in abdomen	35
34	30	decreased fetal activity 36-48 hours prior to delivery	30
38	28	decreased fetal activity x 48 hours	28
41	27.5	cramping pains, vaginal spotting	28

Delivery Data

Of the 41 cases, 16 were delivered by Cesarean section and 25 vaginally. Indications for Cesarean section are summarized in Table 3. Delivery complications occurred in 5 cases. Abruptio placentae, found during delivery of the second twin, a stillbirth, occurred in case 35. In case 35, placental abruption occurred following the delivery of twin A, resulting in the stillbirth of twin B. It was delivered by version extraction. A retained placenta with need for manual removal occurred in 2 cases. Postpartum maternal DIC, associated with hemorrhage, occurred in 2 cases. One of these patients developed an abdominal wall hematoma, which was successfully evacuated one day postpartum.

Table 3 - Indications for cesarean section

Indication	N	Case Number
Fetal distress	8	11, 20, 21, 29, 31, 34, 38, 39
Malpresentation	4	19, 23, 26, 28
Repeat cesarean section	2	15, 25
Acute abruptio placentae	1	7
Premature labor, failed tocolysis, and triplets	1	41

Pathology of Placenta and Umbilical Cord

Of the 38 twin gestations, the placenta was diamnionic, dichorionic (DiDi) in only 9 cases; it was diamnionic monochorionic (DiMo) in 25, and monoamnionic monochorionic (MoMo) in 3, and unknown in one (Fig. 2). One triplet pregnancy was triamnionic, trichorionic and another was dichorionic for "A" and monochorionic for "B" and "C". Although the placentation of the remaining triplet is unknown, the fetus papyraceus was in a separate sac. Thus, 29 cases (71%) had monochorionic placentation. Twenty-three of 41 placentas had some small infarcts. Decidual and amnionic necrosis were seen frequently. Inflammation, such as deciduitis, chorioamnionitis, or

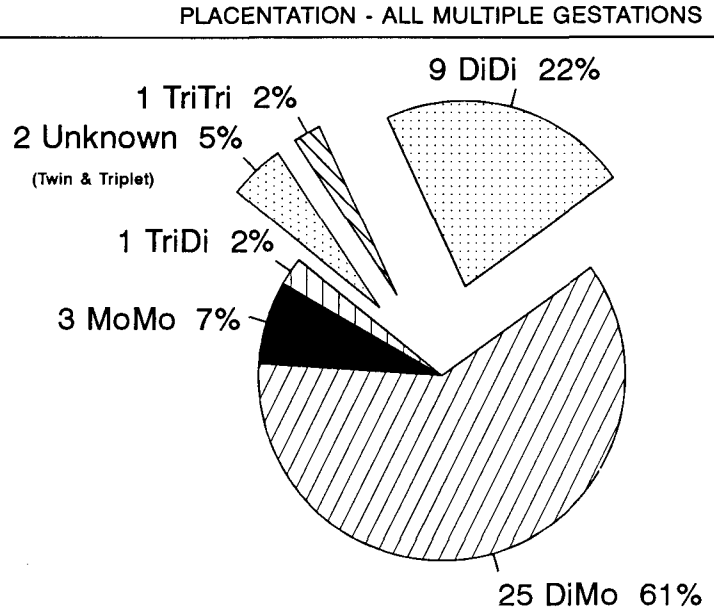

Fig. 2 Graphic representation of types of placentation for all multiple gestations.

Legend: DiMo = Diamnionic monochorionic twin placenta; DiDi = Diamnionic dichorionic twin placenta; MoMo = Monoamnionic monochorionic twin placenta; TriDi = Triamnionic dichorionic triplet placenta; TriTri = Triamnionic trichorionic triplet placenta.

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villitis was present in 9 cases. Meconium staining was found in 9 placentas. Eight reports mention the presence of surface chorionic vascular anastomoses; 2 of these were of the artery-to-artery type (A-A), another was arterio-venous (A-V), and one had A-A and A-V anastomoses. In 4 cases, the nature of the anastomoses was not specified. There were 3 cases with evidence of abruptio placentae. In addition, thrombi were present in 4 placentas.

The site of umbilical cord insertion was reported in 58 of 85 fetuses (Table 4). This was often difficult to determine in dead twins because of the maceration and/or disruption of the placenta. Twenty percent of the stillbirths had velamentous insertion of the umbilical cord (35% if unknown insertions are omitted from analysis). A single umbilical artery (SUA) was present in 5 stillborns, including one of the triplet stillbirths. Only one case of SUA occurred in a liveborn infant which was associated with SUA in its dead cotwin also. Thrombi were seen in the umbilical cord vessels of three stillborns and in one liveborn infant. Cord accidents were the presumed cause of intrauterine fetal death in cases 11, 34, and 38. The stillborn in case 23 had a 2 mm cord stricture.

Table 4 - Cord insertion of twin/triplet gestations

	Liveborn	Stillborn	All
Central	12 (31%)	2 (4%)	14 (16%)
Eccentric	7 (18%)	3 (7%)	10 (12%)
Marginal	11 (28%)	12 (26%)	23 (27%)
Velamentous	2 (5%)	9 (20%)	11 (13%)
Unknown	7 (18%)	20 (44%)	27 (32%)
Total	**39**	**46**	**85**

Outcome of Liveborn Infants

Of the 39 liveborns, 19 (49%) are known to have neurological damage, including one who died at 19 days of age with multiple brain infarctions. Thirteen of the remaining 18 suffer from cerebral palsy, 2 have porencephaly, 1 suffers from unspecified "brain damage", 1 had brain edema and seizures, and 1 is known to have developmental and growth delay and global hypotonia following a left intraventricular hemorrhage. Five liveborn infants had a favorable long-term outcome. In 15 cases, the long-term outcome was not known, although the infants did well in the newborn period.

Figure 3 demonstrates the relationship between placentation and outcome. Of the 19 liveborns with known neurological damage, 2 (11%) were DiDi, 13 (68%) were DiMo, 2 (11%) were MoMo, and 2 (11%) were from triplet placentas (one trichorionic and one unknown placentation). Liveborns who were known to have neurological damage had the cotwin die later in gestation compared to the normal infants (31 vs 16.5 weeks gestation), delivered more prematurely (36.5 vs 39.5 weeks gestation at delivery), and had a shorter duration from the death of the cotwin to delivery (2.5 vs 21 weeks delay). The three twin cases in which both twins were stillborn had a mean gestation of 33 weeks.

The twins had died within one week of each other and within one week or less before delivery. Seven cotwins died at term gestation. All 7 liveborn infants were neurologically damaged. The duration of fetal death to delivery was less than 2 days and all 7 had a monochorionic placentation.

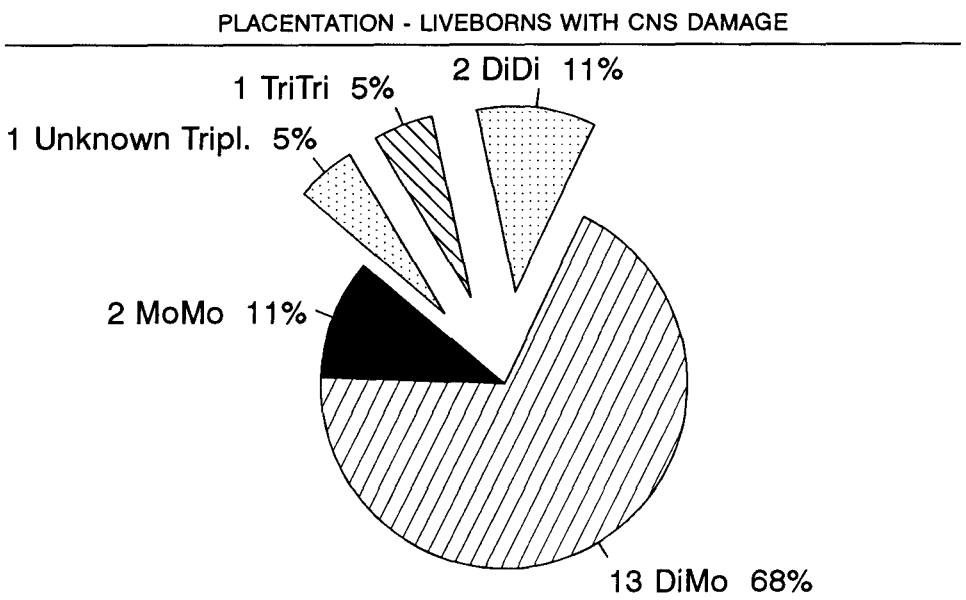

Fig. 3 Graphic representation of types of placentation liveborn infants with neurological damage.

Legend: DiMo = Diamnionic monochorionic twin placenta; DiDi = Diamnionic dichorionic twin placenta; MoMo = Monoamnionic monochorionic twin placenta; TriDi = Triamnionic dichorionic triplet placenta; TriTri = Triamnionic trichorionic triplet placenta.

The locations of cord insertion of the 19 liveborns with neurological damage were central in 6 (32%), eccentric in 1 (5%), marginal in 4 (21%), velamentous in 1 (5%), and unknown in 7 (37%). Of the 20 dead fetuses associated with these 19 cases (including one of the triplet cases associated with 2 stillbirths), there were 1 (5%) central, 1 (5%) eccentric, 7 (35%) marginal, 7 (35%) velamentous, and 4 (20%) had unknown cord insertions. The distribution of the cord insertions was similar to the total group (Table 4).

Table 5 describes the probable cause of poor neurological outcome in these 19 cases, which is to say that, in these cases at least, no other possible cause of the fetal damage could be ascertained. In at least 14 cases, the etiology of fetal CNS damage was presumed to be due to either disseminated intravascular coagulation, possible, hyperviscosity, or acute hypotension from exsanguination into the deceased twin at the time of its death. This is discussed in more detail below. A summary of the maternal history, placental pathology and fetal/neonatal findings for the 41 cases is listed in Table 6. The time of fetal death was determined by using obstetrical history, and/or it was estimated by assessing crown-heel length and weight of the fetus [7,33].

Table 5 - Proposed cause of neurological damage in 19 survivors after intrauterine death of one fetus

Case	Outcome	Proposed Cause	Placentation
5	developmental delay, global hypotonia growth delay, retinopathy; brain atrophy	prematurity and left intraventricular hemorrhage	DiDi
14	porencephalic cysts	transfusion syndrome	DiMo
19	cerebral palsy, mental retardation, blind; CT: infarct, encephalomalacia	DIC/? exsanguination	MoMo
20	cerebral palsy	exsanguination	DiMo
21	porencephaly, cerebral atrophy; anemia, hydropic at birth	exsanguination	DiMo
22	hydranencephaly, cerebral palsy, mental retardation, seizures	bilateral carotid occlusion due to DIC or emboli	DiMo
23	cerebral palsy	chronic placental abnormalities	DiMo
24	cerebral palsy, anomalus facies, anemic at birth	probable exsanguination	DiDi
25	brain damage; abnormal EEG and CT	exsanguination	DiMo
27	cerebral palsy, porencephalic cyst	DIC vs. exsanguination	MoMo
29	cerebral palsy; anemic at birth	probable exsanguination	DiMo
30	cerebral palsy; anemic at birth, cutis marmorata	DIC vs. exsanguination	DiMo
32	cerebral palsy; anemic at birth	probable exsanguination	DiMo
33	cerebral palsy; CT: emboli	probable DIC	DiMo
36	cerebral palsy	probable DIC	DiMo
37	cerebral palsy, blind, seizures	probable DIC	DiMo
38	anemic at birth, died age 19 d.; CT: bilateral cerebral infarction	probable exsanguination	DiMo
39	brain edema, seizures; anemic at birth	possible chronic placental insufficiency	TriTri
40	cerebral palsy, mental retardation	unknown	?Placentation

Legend:
CT = Computed tomography
DIC = Disseminated intravascular coagulation
EEG = Electroencephalogram

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Table 6 - Cases of intrauterine death in a multiple gestation

	Maternal history	Placenta liveborn	Placenta deceased	Cord liveborn	Cord deceased	Outcome liveborn	Outcome deceased
1	38 yr G4P2Ab1 40 wk	DiDi 14x2 cm normal	Complete infarction old clot	50 cm central normal	8 cm	3000 g Apgar 8/9	40 g. death @ 14 wk norm.x-rays
2	34 yr	DiDi 460 g 21x2 cm	12x0.5 cm complete infarction	78 cm eccentric normal	46 cm	Unknown 12 cm CRL	40 g. death @ 16 wk
3	17 yr G1P0 41 wk	DiMo 730 g mec. 19x2 cm	Amnion necrosis	37 cm eccentric	?	3740 g Apgar 7/9	13 cm CRL death @ 17 wk
4	37 yr G1P0 41 wk	DiDi 350 g 20x12x2 cm	30 g complete infarction	37 cm marginal	28 cm	3020 g.mec. Apgar 8/9 ok, 3 yr	50 g. 11 cm CHL death @ 14 wk
5	28 yr G3P1 33 wk	DiDi 330 g 14x2 cm inflamm.	Infarction 11x4 cm plasma cells	45 cm velament. inflamm.	marginal	1540 g Apgar 8/9 IVH, atrophy devel. delay	11 cm CRL death @ 16 wk
6	42 wk unexpect. twins	?Placent. 550 g. mec. 19x3 cm	370 g 17x0.6 cm	50 cm central	65 cm	3180 g Apgar 8/9	580 g death @ 24 wk
7	35 yr 36 wk C/S abruptio	DiDi 500 g 20x2 cm abruptio	Separate abruptio	45 cm central	?	2410 g Apgar 8/9 ok @ 15 mo.	2 cm CHL fet. papyr. death @8 wk
8	37 yr G2P0Ab1 44 wk SROM	Prob.DiMo 510 g 18x2 cm anast.	1/10 of plac. amnion nodosum	30 cm velament	8 cm thin	2610 g aplasia cutis	6 g. 6.5 cm CRL,fet. papyr.death @ 12 wk
9	35 yr G7P5Ab1 40 wk	DiMo 500 g 19x2 cm	Amnion nodosum	Central SUA	SUA	6 toes	5 cm CRL death @ 11 wk
10	26 yr 40 wk	DiMo 550 g 18x2 cm	20% infarct	20 cm marginal	7 cm macerated	2740 g Apgar 8/9	80 g. 14.5 cm CRL, death @ 19 wk
11	G1P0 40 wk C/S distr.	DiMo 530 g 21x2 cm 1 A-A	infarction amnion nodosum	40 cm marginal	48 cm eccentric around leg thin	2610 g Apgar 8/8 well neonate	13 cm CRL death @ 17 wk from cord
12	20 yr 40 wk	DiMo 500 g 19x2.5 cm mec., anast.	Infarction	50 cm marginal	70 cm marginal macerated	Unknown	120 g. 16 cm CRL, death @ 20 wk

Table 6 – *contd*

Maternal history	Placenta liveborn	Placenta deceased	Cord liveborn	Cord deceased	Outcome liveborn	Outcome deceased
13 16 yr G1P0 hypert.	DiMo 380 g 16x2 cm	Atrophy infarcts	20 cm marginal	Thin	2551 g Apgar 8/9 scalp def.	160 g. 17 cm CRL, death @ 10 wk
14 31 yr G2P1 DIC 35 wk	DiMo 650 g 23x15x2 cm T.syndr.	Infarction 16x1.5 cm	50 cm eccentric	34 cm velament. macerated	2410 g Apgar 8/9 porenceph. "recipient"	160 g. 17 cm CRL, death @ 18 wk "donor"
15 27 yr 40 wk C/S, sept. uterus T.syndr.	DiMo 390 g 17x1.5 cm A-V anast.	Infarction	25 cm central	19 cm marginal	Well at birth	10 cm CRL death @ 15 wk
16 20 yr G2P0Ab1 39 wk	DiMo 500 g 19x2 cm	Infarction	25 cm eccentric	Unknown	3370 g Apgar 10/10	Fetus papyraceus
17 G2P1 40 wk DIC	DiDi 500 g 34x11x2 cm	Infarction	34 cm central	?	Apgar 6/7	2 cm CHL fetus papyr. death @ 8 wk
18 30 yr G3P2 39 wk	DiDi 400 g 15x1.5 cm	45 g infarct	40 cm eccentric	SUA	3360 g	25 g. death @ 13 wk
19 38 wk C/S for breech	MoMo 544 g 33x24 cm	—	2.8 cm,thick central	0.6 cm thin velament.	2363 g Apgar 6/9 cereb. palsy	1960 g 42 cm CHL deadx1-2d
20 19 yr G4P3 36 wk C/S distr.	DiMo 670 g 22x19x2 cm anast	25% villi congested	13 cm central	15 cm marginal	1840 g Apgar 1/4 Hcrt.<33% cerebral palsy	1480 g 28 cm CRL death @ 23 wk
21 37 yr G5P2Ab2 31 wk C/S distr. tocolysis	DiMo	—	?	Velament.	1960 g Apgar 2/4/5 hydrops Hgb 6 g. porenceph.	1530 g dead x 30 hr
22 27 yr G1P0 PIH 40 wk ↓ fet.act.	DiMo 995 g 27x24x3 cm anast.	Villitis NRBCs infarcts	40 cm marginal	41 cm marginal	3150 g Apgar 1/3 Hgb. 9 g Plat. 54000 cereb.palsy	2920 g 45 cm dead 2d hydranenc.
23 29 yr G2P1 C/S 40 wk breech	DiMo 780 g 20x18x4 cm meconium	Atrophy infarct villitis	35 cm central NRBCs	12 cm eccentric stricture 0.2 cm	2800 g Apgar 8/9 cerebral palsy	Dead <1 d

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Table 6 – *contd*

Maternal history	Placenta liveborn	Placenta deceased	Cord liveborn	Cord deceased	Outcome liveborn	Outcome deceased
24 33 yr G2P1 40 wk hyperten.	DiDi 980 g 20x19x6 cm	Atrophy	35 cm	28 cm	3060 g Apgar 1/2 ↓ Hcrt. cereb. palsy	1620 g
25 32 yr G2P1 38 wk C/S	DiMo 850 g anastomos. meconlum	—	27 cm	25 cm marginal tortuous	2400 g Apgar 5/7/9 Hcrt. 37% Plat 35000 NRBCs, cereb. palsy	2420 g 34 cm CRL dead 1-2 d urethral obstruction
26 37 yr G1P0 C/S 39 wk ↓ fet. act.x1 d. **both dead**	DiMo 785 g mec. 19x17x3 cm large ana-stomosis inflamm.	inflamm. meconium		A: 36 cm velament. necrotic B: 43 cm marginal		A: 2765 g 36 cm CRL B: 3395 g 37 cm CRL
27 25 yr G2P1 37 wk	MoMo thrombus in vessels	Thrombi	30 cm marginal	30 cm marginal thrombl	2690 g Apgar 7/9 porenceph.	2520 g nuchal cord macerated death @ 35 wk
28 G4P3 40 wk tocolys. Bandl's r.	DiMo 1250 g 25x17x3 cm	Hemorrh.	Marginal	Marginal compress.	3090 g Apgar 8/10 well neon. vag.deliv.	2490 g death @ 35 wk C/S
29 20 yr G1P0 40 wk C/S distr. DIC	DiMo 1200 g 20x22x7 cm	Smaller abruptio	Central	Central thin	2200 g Apgar 1/5 cereb. palsy	1650 g 43 cm CHL deadx<24h big heart IVH
30 29 yr G3P1Ab1 38 wk	DiMo 900 g 20x17x4 cm	Infarct	35 cm central	22 cm velament. SUA macerated	2550 g Apgar 8/9 Hcrt. 30% CT: old inf. 37 NRBCs cereb.palsy	1280 g macerated dead x 1 wk
31 19 yr G2P1 31 wk C/S distr. **both dead**	DiMo 925 g A: 20x10 cm meconium NRBCs	14x7 cm NRBCs		A: velament. 35 cm B: ?		A: 1725 g 40 cm CHL B: 1600 g 22 cm; anomalies
32 35 wk discord. @ 23 wk	DiMo 660 g 20x12 cm meconium infarcts	Thrombosis villitis 10x1 cm	30 cm central	28 cm marginal SUA	2070 g Apgar 7/8 Hcrt.40% 56% NRBCs cereb.palsy	Macerated

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Table 6 – *contd*

Maternal history	Placenta liveborn	Placenta deceased	Cord liveborn	Cord deceased	Outcome liveborn	Outcome deceased
33 30 yr G2P1 37 wk	DiMo 910 g	—	26 cm	39 cm	2345 g Apgar 8/9 cereb. palsy emboli	1515 g 27 cm CRL macerated death @ 32 wk
34 23 yr G4P1Ab2 30 wk C/S ↓ fet. act.x48 hr **both dead**	MoMo 1120 g 21x18x2 cm edema	Infarcts		A: 60 cm B: 60 cm central knotted NRBCs		A: 1620 g cord broke B: 1730 g cords entwined
35 25 yr G5P3Ab1 30 wk bleeding	DiDi abruptio	Abruptio	Eccentric	Eccentric	1500 g Apgar 6/7 RDS	1500 g macerated death @ 30 wk
36 30 yr G3P2 38 wk breech	DiMo 1176 g 24x20x5 cm meconium	Infarct smaller surface	35 cm marginal	35 cm velament.	2500 g Apgar 1/6 Hcrt. 38% plat 86000 cereb.palsy	1790 g 30 cm CRL macerated NRBCs dead x 1 d
37 25 yr 39 wk hydramn. @ 27 wk	DiMo NRBCs meconium	Abruptio infarct	?	Velament. thrombus ruptured membr. art.	2500 g Apgar 1/5 cereb.palsy seizures	2010 g macerated dead x 24 hr
38 34 yr G1P0 28 wk ↓ fet. act.x48 hr C/S distr.	DiMo ruptured 590 g 22x2 cm A-A, V-V	—	30 cm marginal entwined	59 cm marginal entwined nuchal	1520 g Apgar 3/6 Hcrt. 21% CNS infarcts dead @ 19 d	1420 g 27 cm CRL macerated absent kidney
Triplets						
39 27 yr G1P0 38 wk salpingos. C/S distr.	TriTri 1110 g A/B fused C separate A: amn.nod. C: large	B: edema	A: ? C: marginal	B: velament.	A: 2675 g Apgar 3/9 anemia seizures C: 2800 g Apgar 8/9 Hcrt. 56% plat. 56000	B: 2050 g macerated 30 cm CRL ↑ NRBCs
40 25 yr G2P1 36 wk clomid **two dead**	?placent A/B dichor. 1110 g	Infarct C: 9x5 cm	B: 20 cm	A: 20 cm C: 5 cm macerated	B: 2380 g Apgar 6/8 cereb. palsy	A: 2240 g 41 cm CHL macerated NRBCs C: 35g, 9 cm fetus papyraceus

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Table 6 – *contd*

Maternal history	Placenta liveborn	Placenta deceased	Cord liveborn	Cord deceased	Outcome liveborn	Outcome deceased
41 16 yr G1P0 28 wk premature labor C/S **two dead**	TriDi B/C DiMo 410 g 21x1.5 cm A-A in B/C atherosis	B: atherosis C: Inflamm.	A: 24 cm eccentric	B: 32 cm marg/velam C: 42 cm central	A: Apgar 8/8 CNS normal	B: 620 g 31 cm CRL macerated C: 1090 g 28 cm CRL macerated

Legend:

Amn.nod. = Amnion nodosum
Anastomos. = Anastomoses
Bandl's r. = Bandl's ring
Cereb. palsy = Cerebral palsy
CHL = Crown-heel length
CRL = Crown-rump length
C/S = Cesarend section
d = days
DIC = Disseminated intravascula coagulation
DiDi - Diamnionic dichorionic twin placenta
DiMo = Diamnionic monochorionic twin placenta
Def. = Defect
Develop. = Development
Discord. = Discordant
Distr. = Distress (fetal)
Ft. = Fetal
Fet. papyr. = Fetus papyraceus
Hct. = Hematocrit
Hgb. = Hemoglobin
Hydramn. = Hydramnios
Hydranenc. = Hydranencephaly
Hypert. = Hypertension
Imp. = Imperforate
Inflamm. = Inflammation
IVH = Intraventricular hemorrhage
Membr. art. = Membranous artery
Mo = Months
MoMo = Monoamnionic monochorionic twin placenta
Mec. = Meconium
NRBCs = Nucleated red blood cells
PIH = Pregnancy induced hypertension
Plac. = Placenta
Placent. = Placentation
Plat. = Platelets
Porenceph. = Porencephaly
Post p. = Post partum
Prob. = Probable
RDS = Respiratory distress syndrome
Salpingos. = Salpingostomy
SROM = Spontaneous rupture of membranes
Stb. = Stillborn
SUA = Single umbilical artery
T_x. syndr. = Transfusion syndrome
Wk = Weeks
Unexpect. = Unexpected
Velament. = Velamentous insertion of cord

↓ Fet. act. = Decreased fetal activity

DISCUSSION

While prematurity usually occurs in over 50% of otherwise uncomplicated twin gestations, intrauterine death of one fetus in a multiple gestation is uncommon. In a review of cases reported prior to 1985, Enbom found that intrauterine death of one fetus in a multiple gestation occurs in 0.5% to 6.8% of cases [14]. Dudley and D'Alton observed it in 4.6% of their cases and emphasized that 73% were monochorionic twins [12]. In 742 triplet pregnancies collected from the recent literature, Gonen et al [17] found that 4.9% of the triplets were stillbirths, suggesting that one in seven triplet pregnancies may involve the death of at least one fetus. As is the case of most other studies, it is impossible to suggest an incidence from our review because the cases were gathered retrospec-

tively from several sources. Also, because many cases were obtained from cerebral palsy litigation cases, there is an overrepresentation of twins with cerebral palsy in this group of patients. Nevertheless, it is noteworthy that we also observed such a high frequency of monochorionic (monozygotic) twins among multiple gestations with one twin having died prenatally. While not addressing placentation, Russell had earlier reported that cerebral palsy is increased in twins (9%) and that, when only one twin is so afflicted, the other is usually a stillborn fetus [36].

Obstetrical History

Maternal antepartum complications occur more commonly in those pregnancies that are associated with antepartum fetal death of one twin when compared to twin pregnancies overall [28].

Preterm delivery occurred in 14/41 (34%) of our cases, less than the 45% preterm delivery incidence reported by Enbom [14] or that which is commonly observed in multiple gestation. When a twin pregnancy converted into a "singleton" gestation during the first or early second trimester by fetal death of one, then the cases in our series pursued a near normal gestation. This probably explains the relatively low incidence of prematurity in our series. The long-term outcome of the 14 premature infants in our study was unfavorable. A similar observation is especially noteworthy in the material of six cases reported by Szymonowicz et al [41]. Four of their six cases died neonatally and the two survivors had severe CNS handicaps. Two cases of ours resulted in the peripartum death of both twins, and 9 preterm infants (75% of liveborn prematures) had neurological damage, representing 47% of the liveborns with known neurological damage. Durkin et al [13] reviewed 281 children with cerebral palsy and mental retardation. They reported an increased incidence in premature infants and twins, including 8 cases involving the antepartum death of one twin. While prematurity contributed significantly to the poor long-term outcome of infants, it did not account for all of the infants with poor outcomes in our series. All seven infants whose cotwins died at term were abnormal. The group with monochorionic placentation appears to be at highest risk.

Only one episode of antepartum maternal DIC was encountered in a case of twin-twin transfusion syndrome following the death of one twin at 18 weeks. The liveborn twin, who was thought to be the recipient in the transfusion syndrome, was born with porencephalic cysts. Maternal DIC has been reported repeatedly after the death of a singleton fetus [34], but maternal DIC in association with the antepartum death of one fetus in a multiple gestation is apparently rare [35,40]. Skelly et al [40] described a triplet pregnancy with the intrauterine death of 2 fetuses, where the mother was successfully treated with heparin for weeks, resulting in a normal triplet survivor. Romero and his colleagues reported a preterm twin pregnancy that was complicated by the death of one twin and maternal DIC. The maternal complication was successfully treated with heparin from 29 to 36 weeks; the twin was normal, and the mother survived [35]. Our case demonstrates the possibility of poor neonatal outcome despite successful treatment for DIC of the mother.

The diagnosis of fetal death of one twin was made by ultrasound examination in 12 of our cases. In 5, it was made at least three weeks prior to delivery, whereas 7 were detected within a week of delivery. Sonographic diagnosis of a fetus papyraceus is fre-

quently an incidental finding [27]. Several authors have suggested that episodes of vaginal bleeding, acute illness, sudden lower abdominal pain, and the escape of amnionic fluid may be related temporally to fetal death [24,32]. The sudden appearance of preeclampsia has also been suggested as a possible warning sign of intrauterine death [27].

Pathogenesis of Intrauterine Fetal Death

The fetal death rate in twins is approximately three times higher than that of singletons [28] and the time in gestation at which intrauterine death occurs appears to affect the outcome of the surviving fetus. If one twin dies at an early stage of gestation, dissolution of its gestational sac may occur and result in the "vanishing twin phenomenon" [8,25]. This may be detected by serial sonographic studies, as well as with careful gross and microscopic examination of the placenta. In one prospective sonographic study of 1,000 pregnancies, Landy et al [25] found the overall incidence of multiple gestation to be 3.29%, with 21.2% of these demonstrating a vanished twin. The distinction of fetus papyraceus and vanishing twin is not yet well defined, but Landy et al reported sonographic criteria for a vanishing twin in early pregnancy. Three of our cases (No. 7,13 and 17) resulted in small fetus papyracei, with crown-heel lengths ranging from 2 to 5 cm, indicating first trimester losses.

Intrauterine death occurring in the second trimester results in a fetus compressus (fetus papyraceus) if the pregnancy continues [3]. This is estimated to occur in 1 of 184 twin gestations, and in 1 of 12,000 live births [37]. While this diagnosis is usually made at delivery, the fetus papyraceus may be overlooked at birth. Thus, the incidence of both multiple gestation and fetus papyraceus may actually be higher. When death occurs in the third trimester, the dead fetus may not readily compress because of its larger mass and time required for this to occur. Because of its larger size it may pose a higher risk to the viable cotwin in becoming the potential recipient for acute transplacental blood transfer through placental surface vascular connections [44], a suggestion already made by Galea et al [16]. Our data support such a hypothesis.

The cause of the intrauterine twin death is related to a variety of factors. Several authors have noted that fetal death is more often associated with monochorionic placentation rather than dichorionic or trichorionic placentation [2,8,9,12,16,22]. In our obstetric population, one-third of twins are monochorionic [4], while in this study as in others, 71% of the population had monochorionic placentas. The percentage of monochorionic placentation in neurologically damaged liveborns was of a similar magnitude (79%). DiDi placentation was commoner in infants with a normal outcome. The mechanism by which monochorionicity is thought to contribute to a higher perinatal mortality rate is not known with certainty. Three possible explanations are: *1*) It relates to the increased frequency of cord complications (entangling, velamentous insertion); *2*) It is the result of problems with large intertwin vascular anastomoses; *3*) It results from the twin-to-twin transfusion syndrome [9]. The latter was thought to be the cause of death of at least one twin in our series. In this respect it would have been helpful if more attention had been paid to the nature, number, and size of anastomoses at the time of placental examination, but this was not done in many cases. Placental infarction and fetal death from poor maternal blood supply are also more frequent in multiple preg-

nancy [28]. Some degree of placental infarction was noted in 54% of our study. Abruptio placentae was the cause of death in one case.

Velamentous insertion of the umbilical cord is a common feature in twin pregnancies. It is generally found in 1% of singleton placentas and in 7% twin gestations [4]. It is associated with lower birth weight and frequently also with compromised fetal circulation through the membranous vessels [5]. The role of the velamentous insertion of the cord as a cause in the development of a fetus papyraceus was discussed by Ottolenghi-Preti [30]. Enbom's review of cases of twins associated with intrauterine death revealed a 29% incidence of velamentous cord insertion [14]. We found velamentous insertion in 13% of our patients. It was more frequent in the dead than the surviving twin (20% vs 5%) (Table 4). These results may be underestimations because of those cases with unrecorded cord insertions from outside referrals and in fetus papyracei. The high frequency of velamentous cord insertions suggests that it may play pivotal role in antepartum fetal death, as it does in singletons [4]. It is thus interesting to note that two of the DiDi twins who died in the series of 20 fetal deaths after 20 weeks' gestation reported by Cherouny et al [8] had velamentous cord insertions. Cord entanglement occurred in 3 cases and is primarily a problem of MoMo twin gestations. A stricture of the umbilical cord was found in one case. Other possible cord problems correlated with intrauterine fetal death may be the putative focal absence of Wharton's jelly, cord compression, or excessive twisting [4,12]. A single umbilical artery (SUA) was found in 6 births (7%), 5 of which were stillborn and 4 of these fetuses had monochorionic placentas. SUA has also been associated with fetal death, anomalies, growth retardation and twinning [4].

Congenital anomalies can occasionally cause the intrauterine death of one fetus but this is uncommonly reported in the publications of this syndrome. D'Alton et al [9] thus ascribed two fetal deaths to congenital heart disease, and one case of Potter's syndrome in their 15 cases of single twin demise. Lumme and Saarikoski [28] found serious malformations in 4 of 24 stillborns. Our cases No. 22, 25 and 31, showed at autopsy severe malformations in the stillborn; all of these had monochorionic placentas and structurally normal cotwins. Our observations thus support the suggestion by Schinzel et al [38] that the excess of malformations found in twins is most likely related to the monozygotic twinning event.

Outcome of the Surviving Twin

Although the exact incidence of morbidity in survivors after single intrauterine death of a cotwin is unknown, physicians have recognized its potential for serious sequelae. Enbom [14] reported that 46% of the survivors suffered major morbidity or death, although he recognized the shortcomings of his retrospective study, and the report by Szymonowicz et al [41] is even more devastating. Numerous other investigators have reported that significant neurological damage may occur in the surviving twin, and many additional case reports may be found referred to in these publications [2,9,13,20,21,23,38,44,45]. Thus, Hoyme et al [20] outlined structural defects observed in children whose monochorionic cotwin died in utero. Central nervous system defects included cerebral necrosis, hydranencephaly, porencephaly, multicystic encephalomalacia, hydrocephaly, microcephaly, and spinal cord transection. Dudley and D'Alton [12]

reported that CNS damage was as frequent as 20% in the survivors. The theory that the neurologic damage is secondary to vascular accidents is supported by the preponderance of monochorionic placentation and their associated intertwin placental vascular communications. One possible explanation suggests that the disruptive defects are secondary to embolic phenomena or to release of thromboplastin. These are believed to originate in the dead twin and transferred into the survivor through placental anastomoses. They were thus conceived of as causing a disseminated intravascular coagulation event in the survivor before birth [2]. Szymonowicz et al [41] even considered this coagulative phenomenon to extend past delivery in some of their cases. The hypothesis of embolization is also highlighted by the five cases of monochorionic twins with sonographically diagnosed cerebral defects in survivors reported by Patten et al [31]. Among the numerous other cases reported, that of Bulla et al [6] is of interest. They decribed a neonate with cerebral and renal necrosis, associated with a macerated cotwin. This report also illustrated the very large venous connection between these monoamnionic twins, similar to those identified in the initial description of this coagulative phenomenon [2]. The neonate of that report died at two days of age. Bilateral renal cortical necrosis and splenic infarcts were found at autopsy, and numerous vessels were occluded by thrombi; cortical brain necrosis with fibrin deposits was pronounced.

A more likely possibility, it seems to us now, is that a twin may acutely bleed into its dead cotwin in utero through interfetal placental anastomoses, and that acute hypotension results in cerebral and visceral tissue compromise [3,4,16]. Since the most common anastomosis between monochorial twins is of the large artery-to-artery type, it would accommodate rapid transplacental blood exchange [22]. Thus, the death of one twin would lead to an acutely diminished vascular counterpressure in his circulation, with acute exsanguination of the surviving cotwin a possibility. This is envisaged to promote severe and acute hypotension in the survivor with possible cerebral necrosis. Support for this hypothesis has come from sporadic reports as well. Thus, Larroche and her colleagues [26] suggested that in utero damage to the brain may result from acute hypotension. Donnenfeld et al [11] found that, after unsuccessful elective termination of a hydrocephalic twin with potassium chloride injection, the normal twin exsanguinated. Fusi et al [15] illustrated a monochorionic twin with acute exsanguination after fetal death. The cerebral and renal lesions were typical of what is usually seen in DIC, but coagulation parameters were normal; they also made management suggestions for such pregnancies. Finally, structural loss may occur from thrombosis in vessels that may be due to hyperviscosity and plethora in the recipient twin of the twin-to-twin transfusion syndrome. Shah et al [39] examined the results of 48 cases of the "transfusion syndrome" diagnosed between 24 and 28 weeks gestation. Twenty percent of their twin cases suffered from this disease with a 70% mortality. Importantly, when there was no sonographically recognized weight discrepancy, the mortality was 75%. They suggested that the diagnosis of the twin transfusion syndrome will not be made sonographically in 40% of cases and called for a more "innovative approach" for the management.

In our study, 19 liveborns have severe neurological damage, 15 (79%) of which were associated with a monochorionic placentation. This high frequency of monochorionic placentation supports the hypothesis of such a vascular etiology of the neurological damage (Table 5). Structural defects seen in our cases were similar to those outlined above (porencephaly, encephalomalacia, hydranencephaly, cerebral atrophy, edema,

thrombosis and infarction). Seven cases had anemia at birth without significant discordance in fetal weights.

Other investigators have noted that the survivor's morbidity depends upon the time during gestation when the cotwin dies. Thus, Yoshida and Soma [44] reported 21 cases with death of one twin and found that death in the last trimester may lead to premature delivery of the viable twin and that it may induce intravascular thromboses. Yoshida and Matayoshi [43] also recognized a more unfavorable prognosis when the cotwin died in the latter half of pregnancy; they attributed the structural defects of the survivors to arterial embolism and infarction. As an explanation they theorized that the immature dead fetus of early gestation had not yet produced enough coagulative factors to affect the live cotwin. In any event, if fetal twin death occurs in early gestation, vascular thrombosis is less likely to occur, while infarction and resorption may result in the absence or atresia of certain structures [2,20,44]. Fifteen of 18 normal twins were associated with a stillbirth at 20 weeks gestation or less. Conversely, 16 of the 19 infants with neurological damage in our series were associated with a third trimester death. Conversely, all surviving infants with a fetal demise at term were abnormal and all had monochorial placentation.

Mannino et al [29] have described a congenital skin defect known as aplasia cutis, a degenerative sloughing of the skin of the scalp, trunk and thighs, in one of MoMo twins. This is case 8 of the present study. Death of the cotwin was estimated to have occurred in the third or fourth month of gestation. Cutaneous ischemia of the survivor from localized intravascular coagulation or from local hypotension is a possible explanation. In another case (No 13), the liveborn suffered a scalp defect, with death of its cotwin having occurred at about 10 weeks of gestation. Other cases involving intestinal atresia associated with twin death in early gestation have been reported [20]. In a case involving colonic and appendiceal atresia, the cotwin died at 6 weeks gestation [20]. It, therefore, appears that "vascular disruption" in early gestation is less likely to cause central nervous system damage in the survivor, while skin and intestinal systems may then be more susceptible to the insult that results from fetal death of one twin. Finally, it must be considered that the cause of fetal death of one twin may also adversely affect the ultimate survivor. Other than the frequent velamentous insertion of the stillborn twin's umbilical cord, however, no possible causes of the initial fetal death emerged from the study of these records.

Clinical Implications

Early diagnosis of a multiple gestation, the determination of placental chorionicity, and the early recognition of intrauterine death, are key considerations. Antepartum events such as vaginal bleeding, abdominal pain, escape of amniotic fluid, and the sudden appearance of preeclampsia may serve as signs of possible intrauterine fetal death. The high rate of multiple gestations and "vanishing twins" described by Landy et al [25], however, implies that fetal death of one twin may often go unrecognized. Numerous factors contribute to the death of one fetus, including twin-to-twin transfusion, placental insufficiency, velamentous insertion of the cord, and congenital anomalies. Hainline and Nagey [18], and Hanna and Hill [19] have suggested a management for these high-risk patients. It includes serial ultrasound examinations every two to four weeks, to

evaluate fetal growth and integrity in twin gestations. Serial evaluation of maternal coagulation profiles, including fibrinogen, prothrombin time, partial thromboplastin time, platelet counts, and fibrin degradation products, has been recommended by some authors [18,28], despite the apparently rare occurrence of DIC in multiple gestation deaths versus that of singleton pregnancy. Antepartum surveillance of placental function in twin pregnancy starting at 30 to 34 weeks gestation until delivery is considered essential. In cases without evidence of compromise to the living twin, efforts to extend the pregnancy to 37 weeks gestation should be made, although some authors suggested prompt intervention when one fetus dies [41]. It should be noted, however, that several reports indicate that early delivery has not prevented serious brain, renal, or cutaneous damage [19] once one fetus has died. The management of such pregnancies is far from agreed upon. It must be stressed that exsanguination can occur rapidly; thereafter, the blood in the dead twin coagulates and the exchange of blood is stopped. In this consideration a relevant case was reported by Hughes and Miskin [21]. In this case, microcephaly and multicystic encephalomalacia were documented as early as at 30 weeks gestation in utero, with fetal death having been diagnosed at 21 weeks. It is hoped that future ultrasound examination techniques will enhance our understanding of placental perfusion and the mechanism and time sequence of fetal compromise.

The possibility of the development of DIC or exsanguination after the death of one twin in utero may have important implications in the treatment of the twin-to-twin transfusion syndrome or in cases of fetal anomalies by selective feticide of one twin. This has been practiced so as to allow the continuation of pregnancy for the other twin [11,42]. The possibility of serious fetal damage in the survivor as outlined above must be considered. For this reason it may be more prudent to consider intervention at the root of the problem, the anastomoses, by selective laser obliteration of these vessels [10].

When intrauterine fetal death of one twin has occurred, it is imperative to perform a careful pathological examination of the cord and placenta. This must include the type of placentation, a recording of the cord insertion, the delineation of anastomoses, and the presence of possible embryonal remnants of a deceased twin or fetus papyraceus. The detailed examination of the dead fetus is also important for the determination of the time and cause of fetal death. The survivor should be examined immediately for possible renal, circulatory, cutaneous, and central nervous system damage, and hematological abnormalities. It is imperative that the survivor have neonatal sonographic CNS evaluation that may disclose prenatal cystic changes. Newborn follow-up on growth and development will determine if the incidence of cerebral palsy is higher than previously recognized in these pregnancies.

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