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Single twin demise: consequence for survivors

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SUMMARY

Multiple pregnancies, the majority of which are twins, are at substantially higher risk of fetal morbidity and mortality when compared with singleton pregnancies. Single fetal demise occurs in up to 6.2% of all twin pregnancies. It may cause considerable risk for the co-twin including increased risk of fetal loss, premature delivery, neurovascular injury and end-organ damage. In this review we seek to summarise the most contemporary literature on the aetiology of single twin demise, the pathophysiology of injury to the surviving twin and the evidence for current management strategies.

1. Introduction

Multiple pregnancies, of which 98% are twins, are associated with a higher risk of perinatal mortality when compared with singleton pregnancies. Single twin demise occurs in up to 6% of twin pregnancies and may occur at any trimester with potentially profound consequences. Not only is fetal mortality increased in the remaining co-twin but so is overall perinatal morbidity, including rates of long term handicap in survivors. One of the key influential factors of twin morbidity and mortality is zygosity. One large retrospective study demonstrated that monozygotic twins had an almost 20 times relative risk (RR) for both twins being stillborn, a 1.63 RR for one twin being a stillborn and 2.26 RR for the live co-twin dying as a neonate when compared to dizygotic pregnancies.[1] However, it is chorionicity rather then zygosity which appears to be of overall importance (mostly because it is clinically definable) when considering perinatal morbidity and mortality rates in twins. Loss rates of up to 30–50% have been associated with monochorionic monoamniotic pregnancies.[2] The importance of chorionicity is related to the placental angioarchitecture of intertwin circulations.

Intrauterine death of one fetus considerably increases the risk of mortality and morbidity to the surviving co-twin. The overall incidence of single twin demise after 20 weeks of pregnancy is estimated at between 2.6% and 6.2% of all twin pregnancies.[3] The exact rate of single intrauterine fetal death (sIUFD) is difficult to define as the loss may occur before the diagnosis of a multiple pregnancy. However, with the introduction of the new National Institute for Health and Clinical Excellence (NICE) guideline in antenatal care in the UK there will be more emphasis on first trimester scanning and the identification and prevalence of sIUFD may rise. sIUFD has implications for both the mother and the surviving co-twin with varying prognosis depending on the gestation at which it occurs.

2. Definitions

2.1. Vanishing twin syndrome

This occurs when a diagnosis of a twin pregnancy is made sonographically (usually in the first trimester), followed by a repeat ultrasound scan weeks later where only one fetus can be identified. The true rate of vanishing twins is difficult to determine but may be as high as 29%.[2] The embryo may become incorporated into the placental membranes and be overlooked at placental examinations.[4] The chorionicity is once again an important factor with the prognosis for monochorionic twins being poor and associated with a high risk of progressing to double intrauterine fetal death.[5] One study has found that there is no developmental delay when comparing surviving twins from a 'vanishing twin' pregnancy to that of singleton pregnancies up to one year of age.[6]

2.2. Antepartum single twin demise >14 weeks of gestation

Here sIUFD occurs in the second or third trimester. Where premature labour of the surviving twin does not supervene, this scenario presents obstetricians with a potential dilemma of delivery of a premature twin or conservative management with the risk of morbidity and mortality to the surviving twin as the pregnancy advances. This period of pregnancy leaves obstetricians with more difficult choices and is the focus of the current review.

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Box 1. Reasons for single intrauterine fetal demise

- Fetal
  - Infection
  - Chromosomal anomaly
  - Structural anomaly
  - Cord anomaly (entanglement, velamentous)
  - Placental (twin–twin transfusion syndrome, selective intrauterine growth retardation)
- Maternal
  - Hypertensive disorders (i.e. pre-eclampsia)
  - Thrombophilia, abruption

3. Aetiology

There are multiple reasons for sIUFD including fetal and maternal factors (Box 1). A structural congenital abnormality of one of the twins (with or without chromosomal differences) may be a contributing factor.[7] Placental abruption or insufficiency and cord anomalies such as velamentous cord insertion have been associated with sIUFD. In monochorionic, monoamniotic twins, cord entanglement has been described. Chorionicity, as previously described, is an important factor in the rate and outcome of sIUFD with monochorionic pregnancies having a much higher rate compared with dichorionic pregnancies.[8] One of the main reasons for this is the presence of a communicating placental circulation and the potential risk of twin–twin transfusion syndrome (TTTS) in monochorionic pregnancies. Here an unbalanced unidirectional arteriovenous shunt results in a net transfer of blood from one twin to another. The donor becomes hypovolaemic which results in a decrease in the donor's cardiac output and an increase in the peripheral vascular resistance. This induces tissue hypoxia, acidosis and a rise in erythropoietin production.[9,10] The recipient twin is hypervolaemic with a significant risk of cardiac dysfunction. Both twins are at high risk of intrauterine death.

The management of TTTS has three main treatment modalities: septostomy, amnioreduction, and endoscopic laser. A recent Cochrane review found no difference in one or both twins surviving when comparing septostomy with amnioreduction. Endoscopic laser surgery, although finding no difference for survival of one twin, found a significant increase in survival of both twins (RR: 0.49; 95% CI: 0.3–0.79) and less perinatal death (0.59; 0.4–0.87) when compared with amnioreduction. More babies were also alive at 6 months without neurological morbidity in the laser group than in the amnioreduction group (1.66; 1.17–2.35).[11]

In addition to TTTS, selective growth restriction can occur in monochorionic twins. There is an overlap between the two conditions and selective intrauterine growth restriction (IUGR) co-exists with TTTS in 50% of cases. In selective IUGR there is unequal placental sharing, leading to an increase in intrauterine death (14% death of at least one twin[12]). Chang et al.[13] concluded that the larger the placental share discordance the greater the risk of neonatal death. When the mean placental share discordance was 15.1% there were no neonatal deaths compared with when the mean placental share discordance was 63.2% and the neonatal death rate rose to 23%.

Maternal factors such as hypertensive disorders in pregnancy and diabetes also have a higher rate of intrauterine death,[3] but may be associated with pregnancies post sIUFD.[7,14]

4. Effect on the co-twin

The surviving co-twin is potentially at risk from the same pathophysiological condition that led to death in the sibling. Other factors of importance to the co-twin's outcome are the timing of fetal demise and the chorionicity.

4.1. Timing

First trimester loss is not known to result in an adverse outcome for the co-twin although this is controversial. However, sIUFD in the second and third trimester theoretically puts the co-twin at substantial risk.[3] Premature delivery is common in both monochorionic and diamniotic pregnancies, resulting in the sequelae of extreme prematurity including neonatal death, pulmonary hypoplasia, and necrotising enterocolitis. A recent systematic review found that the risk of preterm delivery before 34 weeks' gestation is not affected by chorionicity and is 68% (95% CI: 56–78) following sIUFD in monochorionic pregnancies and 57% (34–77) in dichorionic pregnancies. These values included both iatrogenic and spontaneous preterm delivery.[15] The survival of the co-twin is inversely related to the gestation of the sIUFD. Opposite sex twins with a sIUFD at 20–24 weeks are associated with a survival of 12% (8–16%). This rises to 98% (92–100%) after 37 weeks. Same sex twins with a sIUFD at 20–24 weeks have an 8% (6–9%) survival rate, which after 37 weeks rises to 85% (79–89%) (Table 1).[3,16]

4.2. Chorionicity

Monochorionic pregnancies are at greater risk due to their shared placental circulation. A recent systematic review of 19 studies found that following the death of one twin the risk of death in the co-twin was 12% (95% CI 7–18) for monochorionic pregnancies and 4% (2–7) in dichorionic pregnancies. The odds ratio for monochorionic co-twin intrauterine death was six times that of dichorionic twins (6.04; 95% CI: 1.84–19.87).[15] All papers used in this systematic review were retrospective and used cohorts of varying size.

5. Pathophysiology

There appear to be two main theories to explain the risk of morbidity and mortality of the co-twin following sIUFD. These are 'transient' haemodynamic fluctuations between twins and transchorionic embolisation and coagulopathy. However, the former is felt to be more significant in predisposition towards morbidity and mortality for co-twins post sIUFD.

Table 1
Outcome of remaining fetus and the time of single twin demise.[a]

Time of first fetal death (weeks of gestation_	*n*	Outcome of remaining fetus		
		Surviving infant % (95% CI)	Fetal death % (95% CI)	Infant death % (95% CI)
Same sex twins				
20–24	1278	8 (6–9)	69 (66–71)	23 (21–26)
25–28	448	36 (31–40)	49 (44–54)	15 (12–19)
29–32	423	64 (59–68)	31 (27–36)	5 (3–7)
33–36	479	76 (71–79)	21 (18–25)	3 (2–5)
≥37	227	85 (79–89)	15 (11–20)	0 (0–2)
Opposite sex twins				
20–24	351	12 (8–16)	59 (54–65)	29 (24–34)
25–28	70	64 (52–75)	16 (8–26)	20 (11–31)
29–32	96	86 (77–92)	10 (5–18)	4 (1–10)
33–36	135	94 (89–97)	4 (2–9)	2 (0–5)
≥37	92	98 (92–100)	0 (0–4)	2 (0–8)

[a] Adapted with permission from Johnson and Zhang.[16]

Table 2
Results of fetal blood sampling or cord blood at delivery in eight monochorionic twin pregnancies in which twin A died in utero.[a]

Case no.	At referral		<24 h before death of twin A:						<24 h after death of twin A: Twin B				At delivery	
			Twin A			Twin B								
	Gestational age (weeks)	Diagnosis	pH	PO_2 (mmHg)	Hct (%)	pH	PO_2	Hct (%)	pH	PO_2 (mmHg)	Hct (%)		Gestational age (weeks)	Outcome twin B
1	22	TTT	7.11	4	38								40	Alive and well
2	22	TTT	7.29	28	37	7.34	29	39					39	Alive and well
3	22	TTT	7.17	7	33	7.41	42	36					40	Alive and well
4	28	TTT	7.34	24	34	7.35	39	35					28	Intrauterine death
5	22	TTT	7.31	19	39	7.38	35	40	7.08	14	17		22	TOP
6	25	TTT							7.44	34	18		25	TOP
7	34	Cord knot							7.32		29		34	Alive with serious neurological damage
8	27	IUGR							7.31	28	20		27	Neonatal death

PO_2, partial pressure of oxygen; Hct, haematocrit; TTT, twin–twin transfusion; TOP, termination of pregnancy; IUGR, intrauterine growth restriction.
[a] Results reproduced with permission from Nicolini et al.[18]

5.1. Haemodynamic fluctuations

The theory first proposed by Fusi et al. hypothesised that the death of one twin leads to transfer of blood from the surviving fetus to the dead fetus (a 'back-bleed'). This leads to hypoperfusion, hypotension and fetal anaemia in the surviving fetus. This is turn results in tissue hypoxia, acidosis and damage in fetal systems, particularly within the central nervous system (CNS). They derived this theory from a case report describing a surviving twin from sIUFD that sustained cerebral and renal lesions. The twin at delivery had no derangement in coagulation but was anaemic.[17]

To further support this hypothesis Nicolini et al.[18] reported on eight pregnancies with sIUFD that underwent blood sampling either less than 24 h before sIUFD occurred (five cases) or less than 24 h after sIUFD (four cases). Four of the five pregnancies were not anaemic prior to the sIUFD (haematocrit: 33–40%) and neither were their co-twins, but all survivors sampled within 24 h after the death of their co-twin were anaemic (haematocrit: 17–29%) (Table 2). Similarly Okamura et al. obtained fetal blood from five monochorionic twin survivors following sIUFD and found that all five were anaemic, particularly when the IUD had occurred within 24 h of sampling. One twin was sampled before and after death of the co-twin and the haemoglobin concentration decreased from 15 to 10 g/dl. All five surviving fetuses sustained a cerebral injury.[19]

Bajoria et al. determined the outcome of twin pregnancies complicated by sIUFD in relation to vascular anatomy of the monochorionic placenta. They established that in twins without TTTS the presence of superficial arterial–arterial (AA) anastomosis or venous–venous (VV) anastomosis had a higher incidence of intrauterine death, fetal anaemia and neurological handicap. It is hypothesised that these AA/VV anastomoses allow a relatively rapid transfer of blood from the live fetus to the dead fetus, causing neurological damage or fetal demise. This goes against the thromboembolic theory, as the gradient is such that thromboembolic material could not have flowed from the dead fetuses' circulation to the survivor. A favourable outcome was seen with multiple bidirectional arterial–venous (AV) anastomoses. None of these twins had significant anaemia at birth and all had normal neurological development. It is hypothesised that a steady haemodynamic state can be achieved along the AV/VA channels with oppositely directed blood flow.[20]

5.2. Transchorionic embolisation and coagulopathy

Benirschke in 1961 first hypothesised that it was a passage of 'thromboplastic material' from the dead twin to its co-twin via placental vascular anastomoses that in turn induced disseminated intravascular coagulation (DIC) in the co-twin.[2] Thromboembolic material may be seen in surviving co-twins but there is still some doubt as to whether the thrombi have arisen from circulation within the dead twin or as a result of haemodynamic changes within the survivor. The resulting DIC can cause infarcts and cystic changes in the survivor's renal, pulmonary, hepatic, splenic and neurological systems.[21] The resulting arteriolar occlusion causes end organ damage which has been shown both angiographically and from autopsy data.[2] There are questions relating to the speed at which intracranial ultrasound anomalies have been found (as early as 7 days) and as to whether DIC could have arisen this quickly or whether other factors are to blame. For this reason, it is unlikely that such a mechanism is causative.

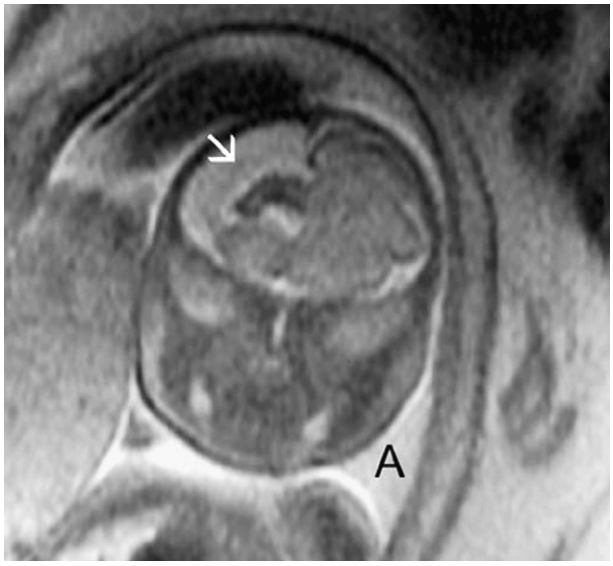

Fig. 1. A 31-year-old woman at 28 weeks' gestation with a monochorionic, diamniotic twin pregnancy. Co-twin demise was confirmed two weeks prior to the magnetic resonance imaging. A large porencephalic defect (arrow), likely secondary to ischaemic injury, is demonstrated in the brain of surviving twin A on a coronal T2-weighted image. Demise of co-twin B, with twin embolic disease, was thought to be the cause of the porencephalic changes. Reproduced with kind permission from springer science and business media: Hu et al.[38]

6. Resulting injury to the survivor

6.1. Central nervous system

Three patterns of brain pathology have been described in surviving twins of sIUFD: [2]

1. Hypoxic ischaemic lesions of white matter. These usually occur in the area supplied by the middle cerebral artery leading to porencephaly, multicystic encephalomalacia, microcephaly and hydrancephaly (Fig. 1).
2. Haemorrhagic lesions either isolated or in combination with ischaemic lesions. They may lead to post-haemorrhagic hydrocephalus (Fig. 2).
3. Anomalies secondary to a vascular disturbance. These include neural tube defects, limb reduction anomalies and optic nerve hypoplasia.

It is suggested that co-twin death in an early gestation is less likely to lead to severe neurological morbidity compared with a late gestation. O'Donoghue et al.[22] found that sIUFD occurring before 28 weeks was less likely to lead to brain abnormality compared with a gestation at more than 28 weeks (3.6% vs 20.0%; $P = 0.02$). If an insult occurs prior to 28 weeks' gestation it is more likely to result in development of multicystic encephalomalacia affecting the cerebral white matter or parenchymal haemorrhage. Closer to term, the grey matter is often also affected.[22] Arterial thrombosis results in softening of the white matter (leukomalacia); then after a phase of glial and macrophage activity the lesion becomes cystic and results in multicystic encephaomalacia.[2]

Monochorionic twins are more susceptible to these described types of CNS damage after death of a co-twin. Adegbite et al.[23] reviewed images taken by neonatal cranial ultrasound of 17 surviving twins of sIUFD pregnancies shortly after birth and one week post delivery. Twelve were from monochorionic and five were from dichorionic twin pregnancies. In the dichorionic twin group none of the five sustained cerebral white matter lesions and one infant had a grade 1 intraventricular haemorrhage. This was in contrast to the 12 monochorionic survivors, of which eight of the infants (67%) sustained white matter lesions, and five of these twins died in infancy.

6.2. Injury to other systems

Many other systems can be affected by sIUFD. Renal cortical necrosis, unilateral damage of a kidney, small bowel atresia, gastroschisis, aplasia cutis and terminal limb infarction have all been described.[24] These are less common than CNS injury.

6.3. Neurological injury and cerebral palsy rates

Many studies have examined the neurological outcome of twin survivors with varying outcomes. It has been recognised that surviving twins are more at risk of cerebral palsy than when both twins survive. Bonellie et al.[25] found that the odds ratio for cerebral palsy was 6.3 (95% CI: 3.1–12.8) for the survivor of a co-twin demise compared with twins that both survived. Similarly Luu and Vohr[26] estimated the probability of cerebral palsy in a twin infant to be 1.8% (1.3–2.4) if both twins survive compared with 9.5% (3.6–19.6%) if one twin dies in utero.

Pharoroah and Adi[27] used epidemiological methods (using registered twin births) to review the rate of cerebral palsy between same and different sex twin pairs. They found that the rate of cerebral palsy in same sex twins that survived to infancy was 106 per 1000. This is compared with different sex twins that had a cerebral palsy rate of 29 per 1000 infant survivors, leading the authors to conclude that cerebral palsy rates were higher in monozygous twins. Similarly Glinianaia et al.[28] used the Northern Perinatal Mortality Survey to review cerebral palsy rates in same and different sex pairs. They found a rate of 114 (95% CI: 51–213) per 1000 infants with cerebral palsy in same sex pairs compared with 45 (1–228) in different sex pairs.

Benirschke[4] retrospectively reviewed 38 twin and three triplet pregnancies with intrauterine death of at least one fetus. Neurological damage occurred in 19 of the 39 (49%) survivors. Fifteen of these (79%) were from monochorionic placentations. When normal infants were compared with those with neurological abnormalities, those with neurological problems had the co-twin die later in gestation (31 vs 16.5 weeks), had a shorter duration between death of the co-twin and delivery (2.5 vs 21 weeks) and were delivered earlier in gestation (36.5 vs 39.5 weeks).

By contrast, Fichera et al. studied neurological follow-up for 18 twins that had survived a co-twin death (10 from monochorionic and eight from dichorionic pregnancies). All 10 monochorionic twins were neurologically normal at 12 months. Among those infants from dichorionic pregnancies, one had major neurological abnormalities thought to be secondary to a suspected perinatal infection.[29]

Ong et al.[15] performed a systematic review using 17 studies including 267 pregnancies to examine rates of neurological abnormality in surviving twins of sIUFD. The rate of neurological abnormality in monochorionic co-twin demise was 18% (95% CI: 11–26) compared with 1% (0–7) in dichorionic survivors. This gave an odds ratio of 4.07 (1.32–12.5) for monochorionic survivors compared with dichorionic survivors.

Nelson and Ellenberg found that in addition to cerebral palsy rates the incidence of non-febrile seizures was also increased in a survivor of co-twin demise (5% in sIUFD vs 0.8% if both twins survive). There was no significant difference in observed IQ in survivors of a co-twin demise compared with when both twins survived.[30] By contrast, Whitfield et al. compared various cognitive measures in survivors of co-twin demise to those where both twins

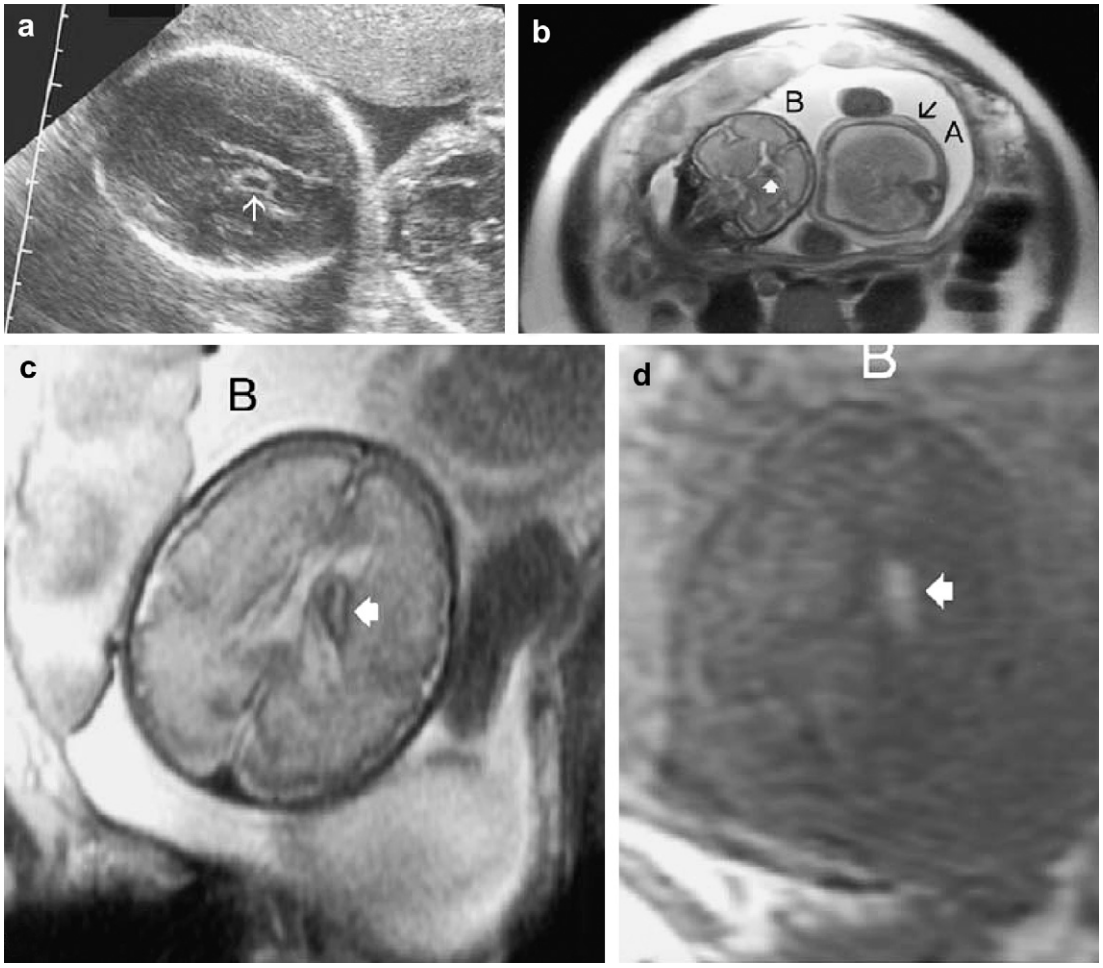

Fig. 2. A 23-year-old woman with a monochorionic diamniotic twin pregnancy with a history of co-twin demise at 28 weeks, 5 days. (a) Prenatal ultrasonographic image at 29 weeks taken in axial plane through the head of the surviving twin shows a 'hypoechoic area' in the periventricular region (arrow) suspicious for haemorrhage. (b) T2-weighted coronal image at 29 weeks, 4 days' gestation through the brain of the surviving twin B shows preservation of sulcal spaces and normal intracranial morphology, with an area of decreased signal in the germinal matrix (white arrow) with abdominal hydrops (black arrow) of the adjacent demised twin A. (c) T2-weighted axial image through the brain of twin B shows the area of decreased signal in the periventricular region without intraventricular involvement (arrow). (d) This corresponds to a focus of increased signal (arrow) on a T1-weighted axial image taken at a similar level. These findings confirm an early subacute Grade I haemorrhage. Reproduced with kind permission from springer science and business media: Hu et al.[38]

survived into adulthood and found a significant reduction in the overall cognitive performance of those that were survivors of co-twin death.[31]

As mentioned above, one of the major risk factors for sIUFD is TTTS. The treatment modality used for the TTTS seems to affect the neurological outcome of monochorionic twins. Numerous studies have shown that compared with serial amniocenteses, fetoscopic laser ablation has a reduced risk of neurological abnormalities. Amnioreduction has a 16–33% risk of minor neurological problems (defined as minor neurological deficiencies with prospect to normalisation) compared with 7.2–11% if laser therapy is used. For major neurological abnormalities (defined as severe neurological abnormalities leading to permanent disability) amnioreduction has a 7–26% risk compared with laser treatment (6–11%).[32] The treatment modality not only affects the overall risk of neurological abnormalities but also of neurological problems in a co-twin if death of one twin does occur. Baneck et al.[33] compared 24 infants born as co-twin survivors with 65 infants born as twins, all following laser treatment for severe TTTS. They found that there was no difference in neurological outcome for those born as twins and those born as singletons ($P = 0.19$). Graef et al.[32] compared 31 survivors of co-twin death with 136 infants born as twins following laser therapy for TTTS and found no significant difference in neurological morbidity ($P = 0.154$). There is in fact evidence that the risk of neurological sequelae in monochorionic twins following laser ablation therapy is greatest if both twins survive as opposed to sIUFD.[34]

O'Donoghue et al.[22] compared pregnancies in which a sIUFD occurred following some form of vascular occlusion (laser therapy for TTTS or feticide) to pregnancies where sIUFD occurred spontaneously. They found that a brain abnormality was detected less often in neonatal survivors where sIUFD had occurred following vascular occlusion treatment (2.6%, 2/77 cases both of which were following cord occlusion for fetocide; neither was following fetoscopic laser ablation for TTTS) than in those where sIUFD had occurred spontaneously (22.2%, 6/27 cases).

Selective intrauterine growth restriction in monochorionic twins with intermittently absent or reversed end-diastolic flow in the umbilical artery has also been treated with fetoscopic placental laser ablation. Gratacos et al.[35] used this technique in 16 monochorionic twins and 31 cases were managed expectantly. They found that placental ablation significantly increased the proportion of sIUFD in the growth-restricted twin (19.4% expectant vs 66.7% laser, $P = 0.001$), although laser treatment was protective of co-twin death in the surviving twin should sIUFD of the growth restricted twin occur (50% vs 0%, $P = 0.02$). However, it was not

found to be significantly protective of neurological morbidity (14.3% expectant group vs 5.9% laser group, $P = 0.63$).

Gratacos et al.[12] also looked at the prevalence of neurological damage in monochorionic twins with selective growth restriction and intermittent absent or reversed end-diastolic umbilical artery flow. These patients did not undergo fetoscopic ablation treatment. Whereas the risk of sIUFD was significantly higher in the smaller twin of the selective IUGR group compared with normal monochorionic/normal dichorionic pregnancies ($P < 0.0001$), the risk of parenchymal brain damage was significantly higher in the larger twin of the selective IUGR group compared with normal pregnancies ($P < 0.005$).

7. Management

Management of a surviving co-twin following sIUFD is dependent on the gestation of the surviving twin and also on the chorionicity of the pregnancy. The sequelae of premature delivery have to be weighed against the risk of morbidity and even mortality for the co-twin.

7.1. Previable

sIUFD in the first trimester is unlikely to have any lasting sequelae for the survivor. Clearly a conservative approach must be instituted at this stage but the lack of predictive investigation for long term problems in the surviving twin means that some patients may wish to terminate the pregnancy.[3]

In dichorionic pregnancy, expectant management with surveillance of the co-twin is implemented and delivery advocated at term (around 38 weeks' gestation).

7.2. Viable

7.2.1. Monochorionic

Risks in survivors of sIUFD in a monochorionic pregnancy are preterm delivery (either due to spontaneous labour or iatrogenic) and intrauterine death or ischaemic brain damage. Delivery immediately following sIUFD was attempted in a case series of 13.[36] Two infants had brain damage, one as a result of prematurity. The authors concluded that a conservative policy where sIUFD occurs before 34 weeks should be implemented. In fact it is thought that ischaemic brain damage in the survivor occurs during or soon after the death of the co-twin and therefore immediate delivery would only serve to add the complications of prematurity.[24] These pregnancies should be referred to a tertiary centre for discussion of management and undergo regular fetal surveillance.

7.2.2. Dichorionic

The main risk with dichorionic pregnancies is preterm delivery. A conservative approach is advocated with regular fetal and maternal surveillance. Delivery is not indicated prior to term unless other obstetric factors supervene. However, regular growth assessment of the surviving twin and maternal surveillance for hypertension, pre-eclampsia and disseminated intravascular coagulation is warranted.

7.3. Fetal surveillance

7.3.1. Ultrasound

Chorionicity, if this has not yet been determined, is essential following sIUFD given the elevated risk in a monochorionic pregnancy and the differences in management strategies. Chorionicity cannot be accurately determined by ultrasound after 20 weeks. After this time the fetal sexing should be performed and if sex is concordant then monochorionicity should be assumed. A thorough ultrasound examination of the surviving twin should be performed for abnormalities and then regular scans for growth and liquor volume on a two-weekly basis are recommended.[2] Doppler studies may be of use, specifically middle cerebral artery peak systolic velocity to examine for fetal anaemia and to determine which fetus may benefit from an intrauterine blood transfusion.[24] This should be performed as close as possible to the 'sentinel event' as anaemia is likely to occur in the first 24 h.[37]

Regular ultrasound of the fetal brain is indicated to look for signs of injury. O'Donoghue et al.[22] performed cranial ultrasound on a weekly basis following sIUFD. From 121 pregnancies, 6 (4.9%) developed abnormal prenatal ultrasound 1–2 weeks after the death of the twin.

7.3.2. Magnetic resonance imaging (MRI)

How soon after sIUFD a neurological insult becomes radiographically visible is controversial. Fichera et al.[29] performed MRI on eight monochorionic twins following sIUFD (median latency period 15 days). All were normal, and went on to have a normal neurological neonatal course. Hu et al.[38] imaged two survivors 6 days and 2 weeks after the death of the co-twin, finding evidence of subacute grade 1 haemorrhage and a porencephalic defect respectively. Glenn et al.[39] suggested that fetal MRI should be performed as early as possible following sIUFD to identify acute injury, and then repeated 2 weeks after the demise to detect subacute/chronic sequelae of intracranial injury in the surviving fetus.

However, in a fetal MRI study Child et al.[40] detected 23% more anomalies that were not apparent on fetal ultrasound scan. The MRI was performed on average 3.42 weeks after the sIUFD. O'Donoghue et al.[22] performed MRI for fetuses following sIUFD 3–4 weeks after the event and an anomaly was detected in 6.6%. Only one case had an abnormal MRI postnatally following a normal antenatal MRI and in this case the lesions seemed to have occurred long after the delivery. This supports other studies which have found that cavitating lesions appear 2 or more weeks after sIUFD and brain atrophy weeks later, therefore some units advocate that an interval of at least 3 weeks should be implemented between sIUFD and MRI of the surviving twin.[3]

7.3.3. Fetal blood sampling and intrauterine transfusion

Following sIUFD, risk to the surviving twin may be secondary to large haemodynamic changes with a net transfusion of blood from the survivor into the dead twin. This leaves the surviving twin anaemic and at risk of hypoxic tissue damage and acidaemia. Fetal blood sampling within 24–48 h after sIUFD would allow clinicians to determine the survivor's haemoglobin in addition to checking the fetal haematocrit and acid–base balance.[2]

Two main studies have looked at the effects of fetal blood sampling in cases of sIUFD. Senat et al.[37] and Tanawattanacharoen et al.[41] studies a total of 22 cases where fetal blood sampling had occurred following sIUFD. Thirteen were found to be anaemic and underwent in-utero blood transfusion. The other nine cases without anaemia had normal outcomes. Six of the transfused fetuses had normal neurological development. In three cases the fetus had an abnormal brain scan and was terminated. Two fetuses died in utero 24 h after transfusion and two had premature deliveries at 34 weeks, developing neurological abnormalities at 1 month of age and delivery at 29 weeks resulting in a neonatal death. The authors concluded that intrauterine blood transfusion may prevent death but is less good at preventing brain injury.

7.4. Gestation of delivery

Administration of a course of betamethasone to promote lung maturation is indicated in fetuses before 34 weeks' gestation. Delivery of dichorionic twins if there are no other obstetrics factors intervening is not advocated before 38 weeks' gestation. In monochorionic twins the gestation of delivery following a sIUFD is still debatable but most would suggest delivery by 38 weeks and some as early as 32–34 weeks.[3] Barigye et al.[42] found that in uncomplicated monochorionic pregnancies there is a high rate of third trimester loss. They calculated that one case of co-twin demise would be saved for every 23 cases delivered at 32 weeks and one case for every 30 pregnancies at 34 weeks.

7.5. Mode of delivery

Vaginal delivery is not contraindicated in cases of sIUFD. However, an obstructed labour can occur if the dead twin is presenting. In monochorionic twins complicated by a sIUFD, caesarean section may avoid the risk of acute TTTS due to vascular anastomoses.

7.6. Post delivery

The couple should be counselled regarding a postmortem for the dead twin, especially if a cause of death has not been found. The placenta should undergo specialist examination using 'injection' studies and for confirmation of chorionicity. A full examination of the surviving neonate should be carried out, especially neurological examinations including the possibility of cranial ultrasound and MRI. This may help to confirm lesions that were seen in the antenatal period and to detect new neurological abnormalities.[22] The surviving twin should also be placed under paediatric follow-up to ensure normal developmental milestones are being met.

7.7. Maternal monitoring

Following sIUFD, rhesus-negative women should have a Kleihauer test and anti-D administered. There is also a theoretical risk of DIC which is reported in women carrying a singleton IUFD. Fusi et al.[43] found that among 16 cases of sIUFD there was just one case of mild coagulation disturbance, and this could have been caused by pre-eclampsia rather than by a retained fetus. One hypothesis as to why rates of DIC appear to be much lower in sIUFD compared with singleton IUFD is that the thromboplastic material may be prevented from reaching the extravascular circulation and that the coagulation disorder is restricted to the shared fetal circulation.[9] Monitoring of the mother's coagulation and platelets is recommended and, if coagulopathy develops, treatment with heparin.[24] Pre-eclampsia and other hypertensive disorders are associated with an increased risk of sIUFD.[7,14] These women need regular blood pressure monitoring and urinalysis for proteinuria. As they are at increased risk of postnatal depression, more surveillance in the postnatal period is warranted and referral for counselling should be made if the parents wish. The family will require psychological support before and after delivery. Often parents of sIUFD have equivalent grief to that of losing a singleton but often do not receive equal sympathy. This is further complicated by the joyous event of a surviving twin's birth and feelings of guilt can ensue.

8. Conclusion

Single twin demise can pose real risks for the surviving co-twin; the prevailing view is that morbidity and mortality in the survivor may be caused by haemodynamic instability. The most important factors when considering risk to the surviving twin are the gestation at which the co-twin died and the chorionicity of the pregnancy. Management should include fortnightly ultrasound scans for growth, peripheral and intracardiac arterial/venous Doppler studies and liquor volume, and an MRI at least 3 weeks after the fetal death to look for changes in the surviving twin's brain. Fetal blood sampling with or without transfusion may be considered in monochorionic pregnancies if there are ultrasound signs of fetal anaemia. With no other obstetric problems, dichorionic pregnancies can be delivered at term. Monochorionic pregnancies are more difficult to manage and often are delivered between 34 and 38 weeks. Parents will often require psychological support for their grief, both during pregnancy and post delivery after losing a twin. The incorporation of fetal and maternal care following sIUFD in multiple pregnancies within the NICE antenatal guideline would help to ensure a consistent level of care throughout the UK.

Practice points

- sIUFD can occur in up to 6.2% of all multiple pregnancies.
- Monochorionic twin survivors are at substantial risk of double intrauterine fetal death following sIUFD [12% (95% CI 7–18)], six times that of dichorionic pregnancies.
- Monochorionic survivors are at substantial risk of neurological abnormality following sIUFD [18% (95% CI: 11–26)], four times higher then dichorionic pregnancies.
- MRI of the surviving twin's brain should be performed at least 3 weeks after the death of a co-twin.
- Fetal blood sampling with or without transfusion could be considered within 24–48 h of sIUFD in a monochorionic pregnancy, if there is evidence of fetal anaemia in the survivor. Although transfusion improves overall survival in co-twins there is no evidence for improvement in morbidity (CNS damage).

Research directions

- Fetal blood sampling with or without transfusion in monochorionic pregnancies following sIUFD, long term follow-up neurological data.
- Assessment of outcome for single surviving fetus in a monochorionic twin set where in-utero therapy has been instigated.
- Markers of cell damage (i.e. cellular RNA) following laser for TTTS and its use as a predictor of sIUFD.
- sIUFD in monochorionic twins and correlation between placental angioarchitecture and fetal morbidity.

Conflict of interest

The authors declare no conflicts of interest.

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