Single fetal death in twin gestations

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Abstract
Twin pregnancies are at higher risk for fetal mortality when compared with singleton pregnancies. Single fetal demise occurs in 3.7–6.8% of all twin pregnancies and considerably increases the complication rate in the co-twin including fetal loss, premature delivery, and end-organ damage. In this review, we summarize the current information on the etiology of single twin demise, the pathophysiology of injury to the surviving twin, and the preventive and secondary management strategies.

Keywords: End-organ damage; fetal death; premature delivery; twin gestation.

Introduction
Single intrauterine fetal demise (sIUFD) occurs in roughly 3.7–6.8% of twin pregnancies [8, 12, 32]. Death may occur anytime and increases mortality and morbidity of the survivor twin secondary to the cause of death of the co-twin, to preterm labor, or both. sIUFD in twin pregnancy thus further complicates an already complicated case and has different consequences in terms of fetofetal effects and fetomaternal problems compared with a singleton pregnancy.

The etiology of sIUFD in twin pregnancy could be either similar to that in singletons or unique to the twinning process. sIUFD might be caused by genetic and anatomical anomalies, abruption, placental insufficiency, absolute or relative (discordant) growth restriction, cord abnormalities, infection, and maternal disease, including diabetes and hypertension. In monochorionic (MC) pregnancies, sIUFD may result from the twin-twin transfusion syndrome (TTTS). Monoamniotic twins are at increased risk of cord entanglement and subsequent IUFD. Similar to the situation in singletons, the etiology of IUFD often remains elusive. Chorionicity (related to the placental angioarchitecture of inter-twin circulations), rather than zygosity, is an important determinant of the risk of intrauterine mortality and morbidity, thus the sequelae of sIUFD in a twin pregnancy mainly depends on chorionicity and, evidently, on the gestational age at diagnosis. This paper reviews the current management of sIUFD (Figure 1).

Fetal demise in dichorionic twins
The prevalence of sIUFD among dichorionic (DC) twins is lower than that reported for MC twins. When maternal conditions that are potentially associated with fetal death are excluded, and the well-being of the survivor is established, no immediate intervention should be taken as sIUFD in DC twins is not associated with fetofetal effects, and the risk for the survivor is negligible. It is, however, recommended to follow such cases with weekly assessments of the biophysical profile along with growth assessment of the survivor.

The risk of preterm delivery before 34 weeks’ gestation is increased in DC pregnancies complicated by sIUFD and is reported to be as high as 57% [19]. However, in the absence of spontaneous preterm delivery or other obstetric complications, elective preterm delivery of the survivor is not indicated. For similar reasons, sIUFD in DC twins is not an indication for abdominal delivery.

Unlike the case of IUFD in singletons, maternal disseminated intravascular coagulation (DIC, the so-called dead fetus syndrome) is, for an unclear reason, extremely rare or never exists in multiples [25]. Hence, except for a baseline coagulation profile including fibrinogen level, there is no need to follow these (DC as well as MC) pregnancies with serial coagulation studies. Also, in D-negative women, anti-D prophylaxis should be considered when transfer of D-positive blood might be anticipated. Kleihauer-Betke test in maternal blood may measure the amount of fetal erythrocytes transferred to the maternal circulation and help in establishing the amount of anti-D that should be given to the mother.

Fetal demise in MC twins
Assisted reproduction technology (ART) has markedly increased the number of multiple pregnancies with the vast majority (roughly 95%) being DC. However, ART also increases fivefold the frequency of monozygotic twinning. Monozygotic gestations might be DC or MC, but the MC subset of monozygotic twins notoriously carries an exceptionally increased risk of pregnancy loss, congenital abnormalities, TTTS, selective intrauterine growth restriction, and intrauterine death.

The prevalence of MC twinning among cases of sIUFD in twins is 50–70% [26]. Poor prognosis of the surviving

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co-twin is a well-known complication. A 2006 meta-analysis [19] assessed the risk of co-twin mortality, neurological morbidity, and preterm labor of the surviving co-twins following sIUFD after 14 weeks’ gestation. The risk of MC and DC co-twin death was 12% and 4%, respectively. The odds of MC twin death following sIUFD after 20 weeks of gestation was six times higher compared with that in DC twins. The risk of neurological abnormality in the surviving MC and DC co-twin was 18% and 1%, respectively. These data are concordant with those reported in a recently published meta-analysis by Hillman et al. [10].

The observed disadvantaged survival difference between DC and MC twins has been attributed to placental vascular anastomoses, which are invariably present in MC placentas and (almost) never seen in DC placentas. The reported frequency of vascular connections in MC placentas approaches 98% in placental injection studies [24, 29]. Based on the unique MC vascular architecture, two main theories to explain the increased risk of morbidity and mortality of the surviving co-twin have been proposed. These are known as the “twin embolization syndrome” and “hemodynamic imbalance.”

Historically, poor prognosis had been related to some form of DIC caused by an influx of thromboplastin-like substance from the dead twin to its co-twin via the placental vascular anastomoses. Thromboembolic material may be seen in surviving co-twins, but there is still some doubt as to whether the thrombi have arisen from the circulation within the dead twin or as a result of hemodynamic changes within the survivor.

The resulting DIC was postulated to cause infarcts and cystic changes in the survivor’s renal, pulmonary, hepatic, splenic, and neurological systems [1]. However, fetal blood sampling did not reveal abnormal coagulation status in the surviving fetus [18]. Moreover, intracranial sonographic anomalies appeared too early to support this mechanism. Thus, the embolization theory has been discarded. Currently, it is held that fetofetal hemorrhage is the main mechanism leading to the adverse outcome of the surviving fetus. It is hypothesized that sudden and significant fall in vascular resistance around the time of death of one twin causes shunting of blood from the surviving fetus to the dead fetus. This leads to hypoperfusion, hypotension, and fetal anemia in the survivor and, in turn, results in tissue hypoxia, acidosis, and tissue damage particularly within the central nervous system. This theory was based on the finding that although fetal blood sampling of the surviving fetus did not show coagulation derangements, fetal anemia was clearly documented [17, 18, 27]. Nicolini et al. reported on eight pregnancies with sIUFD that underwent blood sampling either <24 h before or after sIUFD. Four of the five pregnancies were not anemic before the sIUFD (hematocrit: 33–40%) and neither were their co-twins, but all survivors sampled within 24 h after the death of their co-twin were anemic.

Similarly, Okamura et al. [18] obtained fetal blood from five MC twin survivors after sIUFD and found that all five were anemic, particularly when the twin death occurred within 24 h of sampling. Perimortem fetoscopic observation further supports this theory [23].

Of note is the fact that diagnosis of fetal anemia via cordocentesis has been replaced by the reliable and noninvasive sonographic measurement of the middle cerebral artery peak systolic velocity to detect fetal anemia [15, 16, 28]. Bajoria et al. [1] determined outcomes of twin pregnancies complicated by sIUFD in relation to vascular anatomy of the MC placenta. They established that in the absence of TTTS, the presence of superficial arterio-arterial or veno-venous anastomosis increases the incidence of intrauterine death, fetal anemia, and neurological handicap. It is hypothesized that these large bidirectional anastomoses are of low resistance and allow a pretty rapid blood shunting from the live fetus to the dead fetus, in contrast to the relatively steady hemodynamic state achieved along the high-resistance arteriovenous/veno-arterial channels with blood shunt in the opposite direction. This observation also refutes the thromboembolic theory, as the gradient is such that thromboembolic material could not flow from the dead fetus to the circulation of the survivor.

Regardless of the mechanism, no dispute exists about the poor prognosis for the surviving co-twin. The major dilemma in cases of sIUFD is how soon to deliver the survivor. The risks of leaving the surviving twin in a potentially hostile intrauterine environment that may have caused the death of the co-twin must be balanced against the risks of preterm delivery. Hillman et al. [10] recently meta-analyzed the effect of gestational age at the time of demise of one twin on the subsequent odds of death of its co-twin. The odds ratio if death occurred at 13–27 or at 28–34 weeks’ gestation had no effect on the risk of death of the co-twin. This report further justified decision-making based on gestational age.

**First trimester loss (the vanishing twin syndrome)**

The vanishing twin syndrome (or embryonic loss in a multiple pregnancy) is a well-known phenomenon since the early days of ultrasonography. Over the years, it became clear that many more twins are formed than born. This means that many are lost during the first trimester. The reason of embryonic loss, as well as the magnitude of the phenomenon, is unknown. What is known is that embryonic loss in polychorionic multiples...
is probably harmless to the survivor. In fact, some scholars believe that many singletons actually had a co-twin during the first trimester. In MC twins, however, the prognosis for the survivor is unknown because it is unknown if the very early MC placenta has anastomoses, and if present, it is unknown if these anastomoses are functional. Because signs of TTTS are not seen before the second trimester, and because presumable signs, such discordant nuchal translucency, may be seen not earlier than at 10 weeks’ gestation, it is, at present, prudent to deduce that embryonic loss in MC pregnancies before that age is also probably harmless to the survivor. There are some unsupported hypotheses that loss of an MC twin may lead to the so-called twin reversed arterial perfusion sequence. Because this deduction is no more than an educated guess, follow-up of the survivor with ultrasound and possibly with third-trimester magnetic resonance imaging (MRI) to exclude brain and kidney abnormalities is advocated.

**Fetal demise between the first trimester and viability**

The risk of damage to the survivor is significant in this period. Ultrasound scan may provide information concerning end-organ damage of the survivor; however, detection of cerebral injury depends on the time interval from the insult to the scan. Unlike hemorrhagic lesions, ischemic lesions in the early phase may be difficult to visualize.

Patten et al. [20] have demonstrated that a normal initial scan cannot rule out damage and that sonographic evidence of intracranial abnormalities in the surviving twin may manifest as early as 7 days after the death of its co-twin. Structural abnormalities observed in survivors include neural tube defects, optic nerve hypoplasia, hypoxic ischemic lesions of the white matter ( multicystic encephalomalacia), microcephaly (cerebral atrophy), hydranencephaly, porencephaly, hemorrhagic lesions of white matter, post-hemorrhagic hydrocephalus, bilateral renal cortical necrosis, unilateral absence of a kidney, gastrointestinal tract atresia, gastroschisis, hemifacial microsomia, and aplasia cutis of the scalp, trunk, or limbs [11]. Sonographic scan might be complemented with MRI [7]. If time permits, the best timing for MRI is at 32 weeks or later, when white matter is developed and minor (yet clinically important) lesions in the white matter can be visualized. Considering risks and timing, the option of termination of the entire pregnancy should be discussed with the parents. The patient should be informed, however, that despite the ominous prognosis, the chance of a favorable outcome is greater than that of an adverse outcome.

**Fetal demise at the late second and early third trimester**

This scenario presents clinicians with most difficult choices and the potential dilemma of either delivery of a premature twin or conservative management with the risk of morbidity and mortality to the survivor as pregnancy advances. Because premature fetuses are more susceptible to insults leading to neurological and other long-term complications and given that the surviving fetus seems to be intact, most clinicians will not intervene, as the synergic effects of prematurity and low birth weight superimpose upon the potential damage to the co-twin.

Intrauterine transfusion (before or after viability) may save the survivor by replacing the blood lost from the survivor to the dead fetus. Such treatment would be effective, obviously, only if performed at the reversible phase of the hypovolemic insult to the survivor. Clearly, the window for a potentially effective treatment is very narrow.

Senat et al. [27] transfused in utero 6 of 12 surviving albeit anemic fetuses within 24 h after demise of the co-twin. Four of the six had normal neurological development at 1 year of age. A less optimistic observation was reported by Tanawattanacharoen et al. [30] who performed intrauterine rescue transfusion in seven anemic fetuses within 24 h after death of a co-twin due to TTTS. Two severely acidemic fetuses at blood sampling died in utero within 24 h of the procedure, two surviving twins had abnormal sonographic findings of the brain and underwent late termination, two cases continued to an uneventful delivery with good neonatal outcome, and one case was delivered a week after the procedure, at 28 weeks, but died within the first day of life.

Once choosing a conservative management, one should be aware, however, to the natural history of approximately 90% deliveries within 3 weeks from the time of diagnosis of sIUFD [6]. Preterm delivery is therefore common and steroid prophylaxis for lung maturity enhancement should be given. Interestingly, the risk for preterm labor is not affected by chorionicity [19].

**Prompt delivery vs. close surveillance**

When the intrauterine environment is judged to be hostile and potentially responsible to the death of one of the twins, delivery becomes a more realistic option at this period of gestation. D’Alton et al. [6] delivered by cesarean section 14 out of 15 fetuses upon confirmation of sIUFD provided that the second twin was not severely immature. Such an aggressive approach, however, did not prove to have a better outcome [6, 22]. Kilby et al. [12], Prömpeler et al. [21], and others [4] maintained that fetal outcome is mainly gestational age dependent and the goal should be to prolong pregnancy. Once conservative management is chosen, close surveillance of the survivor should be performed including non-stress testing and sonographic biophysical profiles along with growth assessment. As mentioned earlier, sonography, with or without MRI, is used to detect end-organ damage. Unfortunately, normal fetal surveillance is not a guarantee for a good outcome. Neurological damage may occur in the surviving co-twin with normal antenatal ultrasound findings, reactive cardiotocography tracings, and an intact brainstem as detected by postnatal computed tomography [6].
Timing of elective delivery after conservative management for late second trimester sIUFD is a matter of debate in the literature. Cattanach et al. [4] favor conservative management until 37 weeks’ gestation as long as surveillance tests are normal. Santema et al. [26] suggested intravenous tocolytics treatment for impending preterm labor before 34 weeks’ gestation. Others advocate delivery at 32 weeks after documentation of lung maturity, even when the fetus is in no apparent distress [3, 9].

**Fetal demise at term**

In many of these circumstances, especially when the etiology of fetal demise is unknown, the clinician may opt for delivery instead of continued close monitoring of the pregnancy.

The mode of delivery should be tailored to the patient’s condition and to the fetal size and presentation. Vaginal delivery is not contraindicated in cases of single fetal demise; however, an obstructed labor can occur if the dead twin is present.

**Prophylaxis**

Preterm birth is the common denominator of most adverse outcomes related to twinning in general and to MC twins in particular. Therefore, the source of many of the adverse outcomes associated with MC twins might, in fact, be a result of preterm birth. Although the inherent pathology associated with MC twins leads to increased prevalence and a wide range of fetal and placental malformations, not all MC twin pregnancies are a priori complicated [13, 14]. However, even this subset of apparently “uncomplicated” MC twins was found to be at a considerably excess risk (about 4% per pregnancy) of IUFD [2]. In their discussion of the unexpected IUFD rate among these MC twins, Cleary-Goldman and D’Alton [5] suggested that elective preterm delivery (at 34–35 weeks) might be a reasonable policy to avoid unexpected IUFD. Several other hospital-based studies found a much lower risk, but had an important disadvantage of coming from tertiary centers, some with special interest in MC twinning, which do not represent the population at large. A recent population-based study, however, confirmed the excessive risk of unexpected IUFD in apparently uncomplicated MC twins, with a prospective risk of 6.2% (95% CI, 4.2–9.1%) stillbirths per pregnancy after 33 weeks of gestation [31].

The population-based data also suggested that as many as 30% of the stillbirths could have been avoided with elective preterm births at 34 weeks without any neonatal deaths among twins born at 34–35 weeks [31]. This latter observation supports the idea that MC twins may benefit from elective preterm birth [5] or suggests that, perhaps, a strict (and costly) protocol of very close surveillance could make the difference for these high-risk twin gestations. In the absence of randomized studies, as well of corroborative or contradicting data from other populations, one has to acknowledge that the potential benefit from decreased IUFD rates might be offset by increased neonatal morbidity due to iatrogenic prematurity. Hence, although elective preterm delivery of apparently uncomplicated gestations seems to be a new hidden cost of MC twins, this issue is still very controversial.

**Summary**

Single fetal demise poses real risks for the surviving co-twin, especially for MC twins, when morbidity in the survivor is caused by hemodynamic instability. The most important variables in counseling are gestational age and chorionicity. It is clear that all twin pregnancies with a single dead fetus should be managed in a tertiary referral center. In the absence of other obstetrical problems, DC pregnancies can be delivered at term, whereas MC pregnancies are more difficult to manage and often are delivered between 34 and 37 weeks.

**References**


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