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Fetal Brain Injury in Survivors of Twin Pregnancies Complicated by Demise of One Twin: A Review

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Perinatal mortality is increased considerably in multiple pregnancies compared to singleton pregnancies, with single intrauterine fetal demise (sIUFD) presenting a rare but unique perinatal problem. Monochorionic pregnancies are at particular risk of sIUFD due to bidirectional inter-twin placental vascular anastomoses. The resulting inter-twin blood flow can become unbalanced, causing acute and chronic inter-twin transfusion and profound anemia secondary to fetal exsanguination into the low-pressure circulation of the dead fetus. If the sIUFD occurs after 14 weeks' gestation it is believed to have the most significant effect on the continuing pregnancy as the co-twin is at increased risk of preterm delivery, long-term neurological complications, and death. This article will focus on fetal brain injury in the surviving co-twin in the case of sIUFD, as it is the most common kind of injury in sIUFD, and one which concerns parents and may be the basis for terminating the pregnancy. We will outline how these brain injuries are thought to occur and describe potential pathophysiological mechanisms. We will discuss risk factors for brain injury in cases of sIUFD, including: chorionicity, cause of the sIUFD (spontaneous or secondary to an underlying pathological process such as twin-to-twin transfusion syndrome), gestation of delivery and how to prevent brain injury in the co-twin. We also review modes of imaging, discuss the difficulties in predicting the long-term outcome for co-twin survivors, and highlight the dearth of research in this area.

■ **Keywords:** single intrauterine fetal demise, fetal death, twin, brain injury

Perinatal mortality is increased considerably in multiple pregnancies compared to singleton pregnancies, with single intrauterine fetal demise (sIUFD) presenting a rare but unique perinatal problem. A recent prospective study by two centers in Belgium as part of the Eurotwin2twin project noted this risk to be higher in monochorionic (MC) twins (7.5%) compared to dichorionic (DC) twins (3%; Lewi et al., 2010). MC pregnancies are at particular risk due to inter-twin placental vascular connections. Although fetal loss (in both MC and DC twins) is more common in the first trimester of pregnancy (known as vanishing twin syndrome), if the sIUFD occurs after 14 weeks' gestation it is believed to have the most significant effect on the continuing pregnancy (Hillman et al., 2010). The incidence of sIUFD after 14 weeks is estimated at 2.6% to 6.2% of all twin pregnancies (varying in the international literature; Pharoah & Adi 2000). With the increasing use of assisted reproductive technology (ART), and consequent increase in multiple pregnancies, the number of pregnancies complicated by sIUFD is likely to continue rising. The occurrence of sIUFD may result in a poor outcome for MC and DC surviving co-twins, with consequences to the surviving fetus being reported as more profound in MC twin pregnancies (Pharoah and Adi 2000). MC, monozygotic twins (30% of total twins) are particularly at risk of sIUFD, as they may develop twin-to-twin transfusion syndrome (TTTS), and also have an increased risk of growth discrepancy and discordant congenital anomalies (Hillman et al., 2010).

Significant effects that sIUFD can have on the surviving co-twin comprise: preterm delivery (whether by the onset of spontaneous labor or iatrogenic intervention) and the associated comorbidities of prematurity such as pulmonary

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hypoplasia, necrotizing enterocolitis, long-term neurological complications, or neonatal death. Another possible outcome is death of the surviving co-twin in utero (following the demise of the first twin); or for survivors, the risk of long-term neurodevelopmental morbidity even if delivered at term (Hillman et al. 2011). In addition, there are increased risks to the mother, with higher than background rates of pre-eclampsia, coagulopathy, and sepsis (Kilby et al., 1994, Santema et al., 1995). This article will focus on fetal brain injury in the surviving co-twin, in the case of sIUFD, as it is the most common kind of injury, and one which concerns parents and may be the basis for terminating the pregnancy. We will outline how these brain injuries are thought to occur, how we can predict which co-twin survivors will acquire a brain injury, and how it is diagnosed and managed.

Pathophysiology of Brain Injury in Co-Twin Survivor

MC pregnancies are at higher risk than DC pregnancies, including risk of brain injury in the surviving co-twin following sIUFD. Hillman et al. (2011) found that surviving MC twins were more likely to have an abnormal cranial ultrasound postnatally than DC twins (34% [95%CI 28.8–46.1] vs. 16% [95%CI 7.8–23.5] respectively) and MC twins were also more likely to have neurodevelopmental morbidity than DC twins (26% [95%CI 46.5–34.6] vs. 2% [95%CI 1.6–4.9] respectively). This is thought to be due to bidirectional inter-twin vascular anastomoses that form in MC placentation. The resulting inter-twin blood flow can become unbalanced, causing acute and chronic inter-twin transfusion and profound anemia, which are seen in conditions such as TTTS, twin-anemia-polycythaemia sequence (TAPS) and twin-oligo-polyhydramnios sequence (TOPS). These conditions may be associated with multi-organ injury, including, most significantly, hypoperfusion caused by acute fetal exsanguination into the low-pressure circulation of the dead fetus, leading to hypoxic–ischaemic injury to the central nervous system of the surviving twin and subsequent brain injury, or intrauterine death (Kilby et al. 1994).

Thromboplastic emboli are also thought to provide a potential mechanism for brain injury in the co-twin, although this is disputed (O'Donoghue et al., 2009, Shek et al., 2014). One study found arteriolar occlusion from disseminating intravascular coagulation (DIC) in the 'surviving' twin at autopsy, thought to be secondary to the presence of emboli; however, there were doubts whether there was sufficient time for DIC to develop, in keeping with the time of the appearance of abnormal ultrasound findings (Murphy, 1995). It is also not clear whether the emboli originated from the dead fetus, or arose in the surviving fetus. Consequently, the thromboplastic emboli theory is not favored (Shek et al., 2014).

The mechanism in DC twins is not as clear, but is thought to be most likely a consequence of prematurity as opposed to a pathology specific to twins.

Different Types of Fetal Brain Injury

One way to divide fetal brain injuries is into antenatal and postnatal; however, it is beyond the scope of this article to describe postnatal brain injuries, therefore we will focus on antenatal injuries. Murphy (1995) describe three types of brain lesions:

1. Hypoxic ischemic injury to the white matter, which most often affects the area supplied by the middle cerebral artery (MCA) causing multicystic encephalomalacia, porencephaly, microcephaly, and hydranencephaly. Hypoxic–ischemic injuries are the most common type of injuries in sIUFD (van Klink et al., 2015).
2. Hemorrhagic lesions, either in isolation or with concomitant ischemic lesions.
3. Anomalies thought to be secondary to vascular disturbance, including neural tube defects, optic nerve hypoplasia, and limb reduction anomalies.

The type of brain injury differs depending on gestation of sIUFD. If the sIUFD occurred prior to 28 weeks' gestation, parenchymal hemorrhage or multicystic encephalomalacia affecting the cerebral white matter were more likely to develop, the white matter consisting mainly of myelinated axons and glial cells (O'Donoghue et al., 2009). After 28 weeks' gestation, the grey matter was more likely to be affected, containing the neuronal cell bodies, synapses, and capillaries. The commonest lesions reported by Van Klink et al. (2015) in the surviving co-twin in sIUFD were: cystic periventricular leukomalacia, MCA infarction or injury to the basal ganglia, thalamus, and/or cortex.

Predicting Brain Injury in Co-Twin Survivor in sIUFD

Gestation at sIUFD

At present, we are unable to predict which co-twins will develop a brain injury following sIUFD, or indeed, what effect the injury will have in the long term, which makes it very difficult to counsel parents. One prognostic factor for brain injury is the gestation at which the sIUFD occurred. If the sIUFD occurred after 28 weeks, it is more likely to be associated with a brain injury compared to before 28 weeks (4/20 [20%] vs. 4/111 [3.6%] respectively; $p = .02$; O'Donoghue et al., 2009). This is supported by another study that also showed that the later the gestation of sIUFD, the greater the association with brain injury (*OR* 1.14 for each week [95% CI 1.01–1.29] $p = .01$; van Klink et al., 2015). This is thought to be because the placental anastomoses grow larger as the pregnancy progresses and therefore the impact of the exsanguination will be greater.

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Chorionicity

As mentioned previously, chorionicity is a known prognostic factor for brain injury, and the difference in risk between chorionicities is more pronounced if the sIUFD occurs later in gestation: between 28–33 weeks MC co-twins have a 7.57 times higher chance of neurodevelopmental comorbidity than DC twins at the same gestation (Hillman et al., 2011); whereas if the demise occurred after 34 weeks, the difference between the chorionicities was smaller: *OR* 1.48 [95% CI 0.13–17.5] when comparing MC to DC twins.

Cause of sIUFD

Whether the cause of the initial twin's IUFD (i.e., spontaneous, secondary to the pathology of TTTS, secondary to the treatment for TTTS, or iatrogenic in the case of selective reduction) is a prognostic factor for brain injury in the surviving co-twin is not clear. Griffiths et al. (2015) compared antenatal fetal brain MRI in MC co-twins complicated by a spontaneous sIUFD ($n = 41$) with those who had a sIUFD following fetoscopic laser ablation (FLA) for TTTS ($n = 27$). They found a similar rate of abnormal fetal brain MRIs in each group: 14.8% versus 12.2% respectively. Unfortunately, these fetuses were not followed up postnatally, and importantly, not all neurological problems detected radiologically in the antenatal period translate into neurodevelopmental problems postnatally, as we will discuss below. Van Klink et al. (2015) did find a difference in pregnancies complicated with TTTS whereby the sIUFD had occurred in cases of TTTS. They divided their MC singleton demise cohort into co-twin survivors with a brain injury ($n = 13$) and co-twin survivors with no brain injury ($n = 37$) and found that a significantly larger proportion of the brain injury group had TTTS (8/13, 62%) than those that had no brain injury but did have TTTS (9/37, 24%; $p = .02$), therefore suggesting that TTTS is a risk factor for brain injury in the surviving co-twin. It is difficult to separate the effect of FLA from the disease process of TTTS. Given the success rate of FLA, it would not be possible to perform a randomized control trial to compare the effects of FLA and the pathophysiological process of TTTS. In an ideal study one would perform fetal MRI before FLA, and after FLA, but given the rapidly evolving course with which TTTS progresses, this is rarely feasible. However, studies that have compared FLA with amniodrainage for TTTS have demonstrated that 2/29 (7%) co-twin survivors treated by FLA had neurological complications at 6 months' postnatal compared to 7/20 (35%) co-twin survivors treated by amniodrainage (RR 0.20, [95% CI 0.05–0.85], $p = .02$), thus supporting that the modality of treatment for TTTS does affect neurological outcome (Senat et al., 2004). A systematic review conducted in 2011 supports that FLA is protective against brain injury in sIUFD as they found no difference in the rates of postnatal neurological impairment in pregnancies with one survivor, and those with two survivors after FLA for TTTS (*OR* 0.67, 95% CI 0.18–2.49; Rossi et al. 2011).

Gestation of Delivery

Of course, one factor that may add to the risk of neurodevelopmental problems following sIUFD is the gestation of delivery, with those who deliver preterm having a higher rate of long-term problems (O'Donoghue et al., 2009). Whether this is a consequence of the underlying pathology or prematurity alone is difficult to decipher, but it is likely to be a combination. Van Klink et al. (2015) reported a decreased risk of brain injury with increasing gestation of delivery (*OR* 0.83 for each week [95% CI 0.69–0.99] $p = .05$; van Klink et al., 2015). There is little other research regarding the effect of gestation of delivery in the case of sIUFD, but two studies (Merhar et al., 2013; Spruijt et al., 2012) examining the effect of gestation of delivery on brain injury in TTTS reported contradictory findings, although it is important to note that in Merhar et al. (2013) there was only one case of sIUFD, and in Spruijt et al. (2012) there was no mention of sIUFD. Merhar et al. compared antenatal fetal brain MRIs with postnatal brain MRIs in twins with TTTS born prematurely and found a higher rate of brain injury postnatally of 68% (15/22) versus antenatally of 23% (5/22). However, they found that the only variable that significantly correlated with the total brain injury score was the Quintero stage; gestation at delivery was not correlated, nor was birth weight, although as the authors highlight they may not have had a sufficient number of cases to demonstrate statistical significance, as the trend towards an increase in the number of abnormal brain MRIs postnatally would suggest that gestation does have an effect. Spruijt et al. (2012) did demonstrate a significant relationship between gestational age at birth and risk of brain injury in pregnancies treated by FLA for TTTS, with an increasing risk for severe brain injury on postnatal ultrasound as gestation of delivery became earlier (*OR* 1.35 [95% CI 1.14–1.59] for each week less $p < .01$. However, the following variables were not significantly associated with risk of brain injury: Quintero staging, failure of FLA, whether the twin was the donor or recipient, the year in which the treatment was performed.

Preventing Brain Injury in Co-Twin Survivor in sIUFD

Spontaneous sIUFD often occurs suddenly, as part of an acute event, with very little warning; therefore, there is little opportunity to prevent brain injury in the co-twin. When the sIUFD is due to a condition where there are signs of evolving pathology such as TTTS, selective intrauterine growth restriction (sIUGR) or discordant congenital anomalies, there is the potential to decrease the risk of brain injury in the co-twin. This could be by treating the underlying condition, for example with FLA, to stop any further inter-twin transfusion; or by performing selective termination to 'save' the healthier co-twin by protecting it from massive acute exsanguination, which may occur if the

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sicker co-twin dies, and lead to brain injury in the co-twin if the condition is allowed to progress. It is thought that the success of FLA depends on the ablation of all the arterio-ovenous anastomoses, and bipolar cord occlusion (BCO) or intrafetal ablation with interstitial laser (IL) depends on ensuring complete cessation of blood flow in the sicker twin. Therefore, the success of the procedure and subsequent risk of brain injury is in part related to operator experience to some degree.

When evaluating whether FLA prevents brain injury in TTTS, Spruijt et al. (2012) found no difference in the incidence of severe cerebral lesions on postnatal ultrasound in the FLA-treated TTTS group compared to normal dichorionic diamniotic (DCDA) pregnancies matched for gestational age at delivery (8.6% [23/267] vs. 6.7% [18/267] $p <$ .44), therefore suggesting that FLA is an effective method to prevent brain injury, although this study did not include sIUFD pregnancies. O'Donoghue et al. (2009) reported a large difference in the rate of brain injuries in co-twin survivors between those who underwent BCO or IL, compared to spontaneous sIUFD. They found a higher rate of abnormal postnatal brain MRIs in spontaneous sIUFD compared to the BCO/IL intervention group (22.2% [6/27 fetuses] vs. 3.2% [2/63 fetuses] respectively). These infants were followed up for 2 years, and 4/8 infants with an abnormal postnatal brain MRI had neurodevelopmental disability.

Another preventative measure is delivery, although this is dependent on gestation. In 1984, a team in Italy investigated immediate delivery as a preventative measure against brain injury in the co-twin and reported on 15 cases of sIUFD, including two sets of triplets (D'Alton et al., 1984). Two of the infants had brain damage, one as the result of prematurity, and the authors advised that a conservative approach is preferable prior to 34 weeks gestation as it is thought likely that ischemic brain injury will occur during the sIUFD or immediately after, and therefore by performing delivery as soon as the sIUFD is diagnosed there is the added complication/risk of prematurity (Lewi & Deprest, 2005; O'Donoghue et al., 2009).

Diagnosis and Management of Brain Injury in Co-Twin Survivor in sIUFD

There is no guidance at present for managing twin pregnancies complicated by sIUFD. The diagnosis and management of these pregnancies is challenging as a myriad of controversies exist, for example: the most appropriate investigations to determine cerebral impairment, the timing and frequency of antenatal surveillance, monitoring any maternal complications such as coagulopathy, or the optimal time or mode of delivery. We will now examine the issues related to imaging brain injuries in the co-twin in more detail.

Antenatal Mode of Imaging

Ultrasound and MRI, although not perfect, are considered acceptable methods for assessing brain injury in sIUFD. The benefits of antenatal ultrasound over MRI are that it is readily available, acceptable to most pregnant women, and does not have the same contra-indications as MRI. MRI is able to detect lesions earlier than ultrasound (Hoffmann et al., 2013; Righini et al., 2004) and is better at demonstrating focal brain injuries, the extent of ischemic pathology and cortical development than ultrasound, whereas ultrasound is able to detect gross abnormalities (de Laveaucoupet et al., 2001; Kline-Fath et al., 2007). Consequently, ultrasound may be used as a triage tool, and those with an abnormal ultrasound will then be offered a fetal MRI. However, Griffiths et al. (2015) found that 6/9 cases of brain injury in co-twin survivors of sIUFD diagnosed on fetal MRI were missed on antenatal ultrasound and subsequently recommend antenatal MRI in all cases of sIUFD, which is now routine practice by many fetal medicine units, irrespective of the cause of the sIUFD. Doppler studies may also provide additional information as they can detect fetal anemia, especially the MCA peak systolic velocity. If anemia is not detected, then significant exsanguination is unlikely and the risk of brain injury is lower (Senat et al., 2003).

However, MRI and ultrasound can be technically difficult to perform in women with a raised body mass index (BMI), and the quality of the images can be significantly affected by fetal movement and position, particularly in MRI. The other contra-indications to MRI in non-pregnant patients still apply in pregnancy: the presence of metallic foreign objects in the body and severe claustrophobia. Even if it is possible to obtain a high-quality fetal MRI, the radiological abnormalities detected do not necessarily equate to clinical neurodevelopmental signs, which is a particular problem in the case of non-progressive ventriculomegaly (Griffiths et al., 2015). Consequently, there are concerns that the use of fetal MRI may result in over diagnosis of neurological comorbidity.

Timing of Imaging

There is debate regarding the optimum time for conducting investigations as although evidence of a brain lesion may present 1–2 weeks after sIUFD, it is thought that brain injuries can take 4 weeks to evolve (Simonazzi et al., 2006). Timely investigation is particularly important if the parents are considering terminating the pregnancy. The generalized consensus is to perform a fetal brain MRI no early than 3 weeks following the sIUFD to allow for cavitation lesions to develop, and brain atrophy to occur (Ong et al., 2006). Regular ultrasound assessments of the brain should also be performed. In a study that performed fetal MRI at 3–4 weeks post-sIUFD, antenatal fetal MRI diagnosed 5/6 babies as having brain injuries (O'Donoghue et al., 2009). In the case that was missed, the lesions were believed to have occurred postnatally, not as a result of the sIUFD, because

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the lesions were noted to be evolving on serial postnatal cranial ultrasound scans and the delivery was preterm.

Timing and Mode of Delivery of a Co-Twin in sIUFD

The presence of a brain injury on imaging should not prompt a decision for preterm delivery. Magnesium sulphate for fetal neuroprotection should be given to women 24–29^{+6} weeks gestation, and considered in women 30–33^{+6} weeks, in established preterm labor or who are very likely to deliver in the next 24 hours (NICE, 2015). Corticosteroid prophylaxis is recommended for fetal lung maturity if delivery is planned for <35 weeks vaginally or <39 weeks for cesarean section (Roberts, 2010). In DC pregnancies with a sIUFD, early delivery is not indicated before 38 weeks' gestation, unless there are other obstetric complications. In MC pregnancies, there is debate regarding the timing of delivery, with some advocating delivery at 32–34 weeks due to the 18% rate of third-trimester loss of the co-twin, and others up to 38 weeks. One study found that in order to prevent one case of subsequent co-twin IUFD, 23 sIUFD pregnancies would have to be delivered at 32 weeks, and 30 pregnancies at 34 weeks, although delivery at these early gestations will increase the surviving co-twin's risk of long-term neurodevelopmental problems as a result of prematurity (Barigye et al., 2005). Mode of delivery should be decided on an individual patient basis. There are no contraindications to vaginal delivery, although patients should be informed of the risk of acute TAPS.

Postnatal Investigations

The placenta should be sent for examination to confirm the chorionicity, and injection studies may provide a reason for the brain injury, as long as the sIUFD occurred 2 weeks prior to delivery, otherwise the placenta is too macerated to assess. It is thought that the presence of large bidirectional anastomoses may explain the presence of brain injury in the surviving co-twin, and if only a few small anastomoses are identified, then this is more favorable for the surviving co-twin's outcome (Lewi et al., 2013).

The option of post-mortem of the demised twin should be discussed with parents. The surviving co-twin should have a thorough neonatal examination, including a neurological examination, and should be followed up to assess for any neurodevelopmental problems. Cranial ultrasound and MRI scans should be performed if there is a suspicion of brain injury, which may confirm the findings of antenatal imaging or indicate new lesions. Postnatal ultrasound has a low sensitivity and specificity for detecting non-hemorrhagic brain injuries in neonates, although it is quick and readily available (Merhar et al., 2013). Postnatal MRI results are better correlated with long-term neurodevelopmental outcomes than postnatal ultrasound (Merhar et al., 2013).

Psychological Burden

The psychological burden on the parents and their families should not be underestimated. sIUFD is a unique scenario, with women reporting paroxysmal feelings of joy that one baby has survived, but grief that one has died. These feelings can be compounded by guilt that she cannot grieve for her demised twin properly because she is focused on caring for her surviving twin, or guilt that she is not able to care for her surviving twin sufficiently because of grieving for the demised twin. The additional concern that the surviving twin may have long-term neurodevelopmental problems that may present in later life is another factor to consider. As alluded to previously, it is difficult to counsel these parents, particularly with regards to long-term prognosis for the co-twin, irrespective of what antenatal imaging may demonstrate. Therefore, it is vital to be vigilant for signs of depression and provide sufficient emotional support for the woman and her family.

Conclusion

MC co-twin survivors are at increased risk of brain injury in the case of sIUFD, as are those where the sIUFD occurred later in pregnancy, or delivered preterm. There is a dearth of knowledge surrounding the prognosis of the surviving co-twin, particularly with regards to brain injury, which makes it very difficult to counsel parents. More research is required in this area, but as the problem is rare in individual units, this will necessitate a multicenter national study, which will decrease the risk of heterogeneity observed in meta-analysis. The subject of sIUFD is thus to be assessed as part of the UKOSS system in 2016.

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