Controversies in the management of twin pregnancies

A. Khalil[1,2], B. Liu[1,2]

[1]Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust, Blackshaw Road, London SW17 0QT, UK

[2]Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, Cranmer Terrace, London SW17 0RE, UK.

Corresponding author:

Professor Asma Khalil MRCOG MD MSc (Epi) DFSRH Dip (GUM)
Address:

Fetal Medicine Unit

Department of Obstetrics and Gynaecology

St. George's University Hospitals NHS Foundation Trust

Blackshaw Road

London SW17 0QT

United Kingdom.

Email address: akhalil@sgul.ac.uk

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ABSTRACT

Despite many advances in antenatal care, twin pregnancies still experience more adverse outcomes, in particular higher perinatal mortality and morbidity. They also pose a multitude of challenges and controversies as outlined in this paper. Moreover, they are less likely to be included in clinical trials. Many issues on classification and management remain under debate. Efforts on standardising diagnostic criteria, monitoring protocols, management and outcome reporting are likely to reduce their perinatal risks. The top 10 most important research uncertainties related to multiple pregnancies have been identified by both clinicians and patients. More robust research in the form of randomised trials and large well-conducted prospective cohort studies are needed to address these controversies.

Introduction

The incidence of multiple pregnancies has increased substantially in the last few decades. This increase is most likely to be related to the rise in the use of assisted reproductive techniques[1]. These pregnancies not only contributes to a disproportionate number of cerebral palsy[2], stillbirths[3, 4], and neonatal morbidity and mortality[5], it also poses an increased risk of maternal complications such as hypertensive disorders[6], thereby leading to increased healthcare costs, largely due to the high rate of neonatal unit (NNU) admissions[7]. Despite this, multiple pregnancies are often excluded from research studies, with only 8% of trials into fetal growth restriction (FGR), 17% of pre-eclampsia and 2% of diabetes research that included multiple pregnancies over the last 7 years. Furthermore, most of the recommendations in national and international guidelines on the management of multiple pregnancies lack high quality robust evidence[8].

In this paper, we aim to outline the controversies in the screening, assessment, diagnosis, and management of multiple pregnancies.

Controversies in the screening for aneuploidy in twin pregnancies

First trimester screening for common aneuploidies in twins can take place using the combined test (including maternal age, nuchal translucency (NT), serum PAPP-A and β-hCG levels), or using the maternal age and NT measurements alone[9,10]. A meta-analysis has shown that the detection rate (DR) for trisomy 21 in twins was similar to singletons (86% in dichorionic (DC) and 87% in monochorionic (MC) twins, compared to 89% in singletons), with a false positive rate (FPR) of 5%[11]. In those who book their pregnancy in the second trimester, a quadruple test is only available for the detection of trisomy 21, with a DR of 80% and 40-50% for MC and DC twins respectively, for a standard screen positive rate of 3%[10].

Non-invasive prenatal testing (NIPT) is becoming increasingly common, and in singletons, has a DR of >99%, with a FPR of 0.13%[12]. In twins, aneuploidies are often discordant, and unequal contribution of the fetuses to cell-free DNA (cfDNA) can lead to a false negative result, in cases where the normal twin contributes to a higher fetal fraction[13, 14]. Furthermore, NIPT had a higher failure rate in twin pregnancies as dichorionicity, conception by in-vitro fertilisation (IVF), and higher maternal weight were significant predictors in the failure of NIPT, with other predictors being nulliparity and increased maternal age[13,15]. Few studies have investigated the validity of NIPT in twins. For trisomy 21, the reported DR ranges from 94 to 100%, with a failure rate of 2.9-9.4%[12–14,16]. In trisomy 18 and 13, the DR was 60% in twins[14], compared to 97.9% and 99% in singletons[12], respectively, but these results were limited by the small numbers of positive findings. Single twin demise can also render the results of the NIPT unreliable. As these early deaths are more likely to be aneuploid, it can lead to discordant results, due to the continued release of cfDNA of the demised twin into the maternal circulation[17,18].

Screening for aneuploidies in twins therefore offers promising results, however, higher failure rates and discordance can be seen in twins, and further studies with larger numbers of aneuploidies are required to ascertain the validity of these tests.

Controversies in the assessment of fetal growth in twin pregnancies

Twins are known to have lower birthweight than singletons[19], and due to their higher risk of perinatal complications, in particular FGR, more stringent surveillance using ultrasound is required[20,21]. Recent research have found that twins have a different growth trajectory than singletons, where in DC twins, the growth is lower from 30 weeks compared to singletons, and MC twins are generally smaller than both DC twins and singletons throughout the gestations[22]. Yet, current practice continues to use singleton growth charts, which can lead to an overdiagnosis of FGR in twins, and unnecessary iatrogenic preterm deliveries. Despite previous evidence which stated that twins diagnosed as FGR according to singleton growth charts still had a higher perinatal mortality rate than singletons, this was only the case in MC but not in DC twins[23]. Twin-specific growth charts have now been designed based on their normal reference ranges and are readily available for use. It has been shown that these charts do not increase the incidence of stillbirth, but do in fact reduce the number of twins diagnosed as FGR compared to those diagnosed by customised singleton charts (7.1% vs 12.8%, respectively)[24].

It is recommended that DC twins undergo 4 weekly scans for growth surveillance from 24 weeks, and MC twins 2 weekly from 16 weeks[9,21]. Fetal Doppler measurements such as umbilical artery (UA) and middle cerebral artery (MCA) pulsatility index (PI) as well as MCA peak systolic velocity (PSV) can allow for detection of placental insufficiency, twin-anaemia-polycythaemia sequence (TAPS), and fetal decompensation in twin-twin-transfusion syndrome (TTTS) and FGR, and is therefore recommended by the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) to be performed at each routine scan[9]. However, other guidelines state that these measurements should only be performed in high-risk pregnancies[21,25].

Various thresholds have been used to classify estimated fetal weight (EFW) discordance. The Southwest Thames Obstetric Research Collaborative (STORK) found that the 95th centile of EFW discordance for DC twins was 18.3% at 20 weeks, increasing to 21.9% by 30 weeks, and in MC twins, 22.2% at 20 weeks, and 25.4% at 30 weeks[26]. Therefore, any discordance within these values is considered as a part of the normal trajectory. Similarly, D'Antonio et al found that an EFW discordance of ≥25% was associated with a significant increase in perinatal loss (area under the curve (AUC) 0.72, 95% confidence interval (CI) 0.65-0.80)[27]. However, a recent meta-analysis showed that risk of stillbirth increased from a discordance of ≥15% in DC twins (odds ratio (OR) 9.8, 95% CI 3.9-29.4) and ≥20% in MC twins (OR 2.8, 95% CI 1.3-5.8), with an increased risk of neonatal death (NND) from ≥25% in MC twins (OR 4.66, 95% CI 1.8-12.4)[28]. Moreover, one size does not fit all, as the optimal cut-off for prediction of single intrauterine death (sIUD) differs with increasing gestational age (48% at 28-30+6 weeks, 20% at 31-33+6 weeks, and 14% at 34-36+6 weeks)[29]. Therefore,

a decision for delivery should not be based on EFW discordance alone, but on a combination of gestation, chorionicity, Doppler indices, and antenatal complications.

The controversies in fetal growth assessment are improving through the development of twin-specific growth charts and national guidelines, but can be further unified by standardising twin growth chart utilisation, routine Doppler measurements, classification of EFW discordance, and indications for delivery.

Controversies in the management of fetal growth restriction in twin pregnancies

Selective FGR (sFGR) is associated with an increased perinatal morbidity and mortality, as well as neurological sequelae in both the small for gestational-age (SGA) and appropriate for gestational-age (AGA) twins[28,30]. Until recently, there have been numerous discrepancies amongst clinicians and researchers on the diagnostic criteria of sFGR. ISUOG proposed that DC twins were classified as sFGR if the EFW of one twin was <10th centile, whilst in MC twins, if the EFW of one twin was <10th centile and the EFW discordance was >25%[9]. An expert consensus using the Delphi procedure aimed to unify diagnosis was since developed, where it concluded that in both MC and DC twins, an EFW <3rd centile in one twin would classify as sFGR. Additionally, DC twins satisfied the diagnosis if 2 of the 3 parameters were met: EFW <10th centile, EFW discordance ≥25%, or UA PI >95th centile, and in MC twins, 2 of the 4 parameters: EFW <10th centile, AC <10th centile, EFW discordance ≥25%, or UA PI >95th centile (Figure 1)[31]. Research comparing these diagnostic criteria have noted a variation in incidence, thus supporting the use of the standardised Delphi criteria[32].

Due to the increased perinatal morbidity and mortality posed by FGR in twins, it is paramount that clinicians are aware of its presentation and a robust guidance is in place to aid its screening and detection. Recent updates to the National Institute of Clinical Excellence (NICE) guidelines have recommended serial growth scans as described above, together with deepest vertical pocket measurements (DVP), an EFW discordance to be calculated at each scan, and UA Dopplers to be performed together with weekly scans if an EFW discordance was >20% or the EFW of one twin was <10th centile[21]. Further progression to a discordance ≥25% should prompt a referral to a tertiary fetal medicine unit.

Gratacós et al classified sFGR in MC twins according to UA Doppler end-diastolic-flow (EDF) in the smaller twin, which have different clinical evolution and outcomes[33]. Studies have looked into the progression and overall survival rates of each type in order to aid counselling and management. Type I (positive EDF) is associated with a generally good outcome, with a progression rate of up to 26%[34]. Type II (persistent absent/reversed EDF) has the least favourable outcome, with progression rates as high as 90%[33]. Type III (intermittent absent/reversed EDF) has a lower progression rate, but due to the variable AA anastomoses, has a higher risk of sudden intrauterine demise (IUD) or acute TTTS[33] (Figure 2). Due to the higher risks of preterm delivery (68%), IUD (15%), and neurological sequelae (26%) to the co-twin in the event of demise in the FGR twin if conservatively managed[30], prenatal intervention in the form of selective termination are more likely considered in severe cases, especially before 26 weeks[9,35,36]. A recent meta-analysis compared the outcomes

following expectant management, fetoscopic laser photocoagulation, and selective termination according to Gratacós classification. In type I sFGR, 3%, 16.7%, and 0% (co-twin) suffered an IUD following expectant, laser and selective termination. In type II sFGR, 16.6%, 44.3%, and 5% (co-twin) experienced an IUD following the above treatments respectively, and 89.3%, 100%, and 90.6% were free of neurological sequelae (Figure 3). In type III sFGR, 13.2%, 32.9%, 0% (co-twin) had an IUD after these treatments, and 61.9%, 100%, and 98.8% had intact neurology[37]. This shows that the severe cases may benefit from intervention to reduce perinatal morbidity, however, the evidence is largely based on observational studies.

Despite the fact that Gratacos classification has been used since its publication in 2007, debate exists regarding whether a modification is needed as it does not take into account the gestational age (GA) at diagnosis, the variation in the UA Doppler in the smaller twin especially at early gestation, the ductus venosus (DV) Doppler or the co-existence of TTTS or event of IUD of the smaller twin. In a cohort study of MCDA twin pregnancies followed from the first trimester until birth, in early-onset (<24 weeks' gestation) cases, the incidence of Types I, II and III sFGR were 81%, 15% and 4%, respectively (Figure 4). In late-onset (≥24 weeks) cases, the corresponding figures were 94%, 6% and 0%. The incidence of superimposed TTTS was 27% in cases affected by early-onset sFGR compared with 6% in those with late-onset sFGR[32]. Therefore, GA at diagnosis influences the incidence, types and prognosis of sFGR and should be taken into account. Several studies have reported that DV Doppler is an independent predictor of the risk of demise of the smaller or the larger twin[38,39]. This supports its incorporation in a staging or a classification system of sFGR. Moreover, despite the fact that the presence of TTTS is not an independent predictor of the risk of demise, it does alter management and represents an urgent need for intervention[38,39].

A modified classification of sFGR in MC twin pregnancies is proposed in Box 1 and Figure 5. sFGR is classified into early and late-onset, as well into stages taking into account the UA and DV Dopplers, presence of TTTS, and IUD of the smaller twin (Box 1 and Figure 5). Future studies are required to validate this proposed classification and assess its prognostic value.

After 26 weeks' gestation, early delivery after a course of steroids can be considered in the case of severe sFGR, where the risks of stillbirth and co-twin morbidity outweighs those of prematurity[35]. In DC twins however, the risks to the AGA twin is lower following co-twin demise, therefore, conservative management with careful monitoring is preferable. The decision for delivery should be made after thorough counselling on a case-by-case basis, taking into account the risks versus benefits, and is generally not recommended in DC twin before 30 weeks' gestation[9].

The development of a standardised diagnostic criteria and national guidance on surveillance protocols has the potential to improve the diagnosis and monitoring of sFGR. The optimal antenatal intervention and timing of delivery in sFGR continues to pose a conundrum, therefore more robust research is required to establish a management with the most favourable outcome.

Controversies in the management of TTTS

The diagnosis of TTTS is based on a sonographic amniotic fluid discordance in the form of polyhydramnios oligohydramnios sequence (DVP ≥10cm after 20 weeks or ≥8cm before 20 weeks in the recipient twin, with a DVP ≤2cm in the donor twin)[9]. In the earlier gestations however (16-18 weeks), the normal range for amniotic fluid is lower (90th centile 6cm at 16-17 weeks)[40], possibly due to the fact that fetal urine is not the main constituent of amniotic fluid at that gestation. It may therefore be argued that the diagnostic criteria is modified to lower the threshold for classifying polyhydramnios at the earlier gestations to 6cm, in order to avoid misdiagnoses and poor outcomes as a result of missed intervention (Figure 6)[41].

Various research have attempted to establish first trimester ultrasound signs or maternal characteristics predictive of adverse perinatal outcomes in MC twins, such as TTTS[42,43]. However, recent meta-analysis has suggested that it is currently not possible to detect these complications in the first trimester scan[44], limiting the detection and screening for TTTS to 2 weekly scans from 16 weeks[9,21,25]. Amniotic fluid discordance not fulfilling the diagnosis of TTTS generally have a good prognosis, with an overall survival rate of 93%[45], but is at an increased risk of developing TTTS, particularly if the discordance is >3.1cm before 20 weeks[46]. Therefore, it is recommended that MC twins with an amniotic fluid discordance (DVP) of ≥4cm should be monitored by ultrasound at least weekly, with the addition of UA Dopplers[9,21].

Fetoscopic laser photocoagulation is the recommended treatment for Quintero stage 2 or above, before 26 weeks[9], as the long-term neurodevelopmental outcome is superior to those who underwent amniodrainage[47]. Traditionally, laser was avoided before 16 and after 26 weeks, due to the lack of fusion between the chorion and amnion in the early gestations, and the poor visibility after 26 weeks. However, Baud et al found that laser treatments performed at these early and late gestations yielded similar outcomes to those done at 16-26 weeks, with no added complications[48]. Nevertheless, amniodrainage is a well-recognised treatment option for late TTTS[9], and when compared with laser, did not yield a higher rate of overall fetal or neonatal death[47]. The management for Quintero stage 1 remains controversial. Conservative management with intensive monitoring can be considered, in the absence of cervical shortening or maternal discomfort[9], and evidence from a meta-analysis of stage 1 TTTS has shown a similar rate of survival of at least one twin in those expectantly managed (87%, 95% CI 69-98%), underwent amniodrainage (86%, 95% CI 76-94%), and those who received laser photocoagulation (81%, 95% CI 69-90%), with a progression rate of 27% (95% CI 16-39)[49]. Furthermore, the North American Fetal Therapy Network found that both amniodrainage (OR 0.11, 95% CI 0.02-0.68) and laser photocoagulation (OR 0.07, 95% CI 0.01-0.37) reduced the risk of no survivors, and that laser was in fact protective against poor outcomes (OR 0.12, 95% CI 0.03-0.44)[50].

Post laser, it is common practice to perform weekly scans for the first 2 weeks, and if clinical resolution is evident, 2 weekly scans can be resumed. In cases of sIUD, fetal brain MRI should be considered 4-6 weeks post demise to exclude neurological injury[9]. The timing of delivery post laser for TTTS is debatable. It is commonly scheduled by 34 weeks, due to the evidence that the risk for perinatal death or severe brain injury significantly declines if

delivered after 34 weeks (35% 26-28 weeks vs 3% 34-36 weeks)[51], but it may be argued that in the absence of further pathology, delivery can be postponed until 37 weeks[9].

Although the diagnosis and treatment of TTTS have been supported by robust evidence, the diagnostic criteria for early TTTS, and the management of early and late TTTS, as well as Quintero stage 1 TTTS, remains controversial.

Controversies in the management of TAPS

TAPS, originally described in 2006, remains open to numerous controversies. The standard antenatal diagnostic criteria of MCA PSV >1.5MoM in the donor and <1.0MoM in the recipient was found to have a sensitivity of 46%, specificity of 100%, with positive and negative predictive values (PPV and NPV) of 100% and 70% respectively[52]. Recent studies found that recipient twins with an MCA PSV >1.0MoM could still be polycythaemic at birth, therefore proposed an alternative diagnostic criterion using delta PSV as opposed to the traditional cut offs, providing a stronger predictor of haemoglobin discordance at birth[53]. So far, research has proposed delta PSV criteria of >0.5MoM[52] and >0.373MoM[54], both with increased sensitivity (83% and 93% respectively) and NPV (88% and 99% respectively) compared to the traditional diagnostic criteria, but a lower PPV, which can lead to over diagnosis (Table 1). A Delphi consensus was also carried out to establish unified criteria, where experts felt that an MCA PSV cut off of >1.5MoM and <0.8MoM in the donor and recipient, or a delta PSV of >1.0MoM should be used to achieve an antenatal diagnosis of TAPS (Figure 7)[55]. The criteria with the most optimal detection and outcome with the least unnecessary intervention are yet to be established.

The ISUOG guideline recommends 2 weekly screening for TAPS through MCA PSV measurements in all MC pregnancies[9]. However, due to the controversies and lack of evidence in its management, many clinicians felt that it was more appropriate to only perform this screening in those with high risk pregnancies (e.g. post laser for TTTS)[21,25]. TAPS can develop spontaneously or post laser, however, the natural history and outcomes can be variable, ranging from rapid progression and double IUD to stable/slow progression and the birth of 2 healthy babies with discordant haemoglobin. Long-term neurodevelopmental outcomes of those babies who developed TAPS post laser have suggested a 9% neurodevelopmental impairment, and a 17% mild-moderate cognitive delay[56], whereas this delay was proposed to be higher in spontaneous TAPS survivors (26%)[57].

Management options include conservative management, intrauterine transfusion/partial exchange transfusion, laser photocoagulation, selective termination, or early delivery. Currently, there is no consensus on the most superior method of management. The treatment of choice depends on the gestation at diagnosis, disease progression or severity, access or feasibility of intrauterine intervention, and maternal choice, and therefore should be made on an individualised basis following thorough counselling[9].

Controversies in the management of TRAP sequence

Twin reversed arterial perfusion (TRAP) sequence can lead to a 33% risk of IUD of the pump twin if managed conservatively before 18 weeks[58], and following this, the risk of perinatal mortality of the surviving pump twin is stated to be 55%[59]. In an observational study of 26 pregnancies with TRAP sequence, where 2 underwent termination of pregnancy, 21% had spontaneous resolution of flow to the acardiac twin, and 46% had persistent flow[58]. Treatments include intrafetal laser or cord coagulation, where it was found that the intrafetal techniques were associated with a later gestation at delivery (37 vs 32 weeks, p=0.04), a higher success rate (77% vs 50%, p=0.02), and a lower preterm rupture of membranes or delivery rate (23% vs 58%, p=0.003), with an 80% overall survival of the pump twin following intervention[60]. Traditionally, these procedures were carried out after 16 weeks, due to the separation of the membranes by the exocoelomic cavity, particularly if there was evidence of cardiac strain of the pump twin, or increased perfusion, growth of the TRAP mass, or polyhydramnios[9]. However, it was suggested by more recent evidence that treatment prior to 16 weeks was associated with a significantly lower rate of adverse outcome (19% vs 66%, p=0.003)[61]. Furthermore, a later meta-analysis revealed that there was an inverse relationship between the gestation at treatment and gestation at birth[62]. Therefore, this led to the development of the TRAP Intervention Study (TRAPIST), which is a multi-centre randomised controlled trial aiming to compare whether early intervention (12-14 weeks) improves the outcomes of TRAP sequence compared to late intervention (16-18 weeks), and is currently still ongoing (https://clinicaltrials.gov/ct2/show/NCT02621645).

In those pregnancies that had a late diagnosis of TRAP sequence, or did not wish for intervention, close serial ultrasound monitoring should take place by a fetal medicine specialist, for signs of cardiac decompensation and hydrops in the pump twin. Due to the likely development of polyhydramnios around the TRAP mass, preterm delivery prior to 32 weeks is increased at 10%[61]. There is currently no consensus on the timing of birth in TRAP sequence following expectant or active management, therefore, an individualised approach should be taken based on the success of treatment, fetal Dopplers, and cardiac stability of the pump twin.

Controversies in the management of MCMA twin pregnancies

Monochorionic monoamniotic (MCMA) twin pregnancies are at increased risk of perinatal mortality, with rates quoted as high as 50% from the first trimester ultrasound, largely due to congenital anomalies and spontaneous miscarriage[63]. Previously, cord entanglement leading to vascular injury was thought to play a major role in the cause of IUD, however, more recent evidence have shown that not only is cord entanglement present in almost all MCMA twins[64], but does not contribute to the increased perinatal mortality rate[65].

Antenatal management of MCMA twins have been controversial. Whilst some may suggest inpatient monitoring with regular fetal monitoring is beneficial, others suggest that this does not influence perinatal outcome[66]. A recent meta-analysis showed that inpatient monitoring had a 3% risk of IUD (95% CI 1.4-5.2%), where outpatient management had a higher IUD risk of 7.4% (95% CI 4.4-11.1%)[67]. However, a multicentre cohort study observed no significant difference in perinatal mortality between the inpatient and outpatient managed

groups of MCMA twins (adjusted OR 0.21, 95% CI 0.04-1.17)[68]. Recommendations on timing of birth have varied between 32-36 weeks. However, recent evidence suggests that early delivery is warranted due to the higher risks than other twin pregnancies, and the fact that the risk of fetal demise from 32 weeks and 4 days exceeded the risk of non-respiratory neonatal complications[69]. The fore mentioned meta-analysis also found that the highest risk of IUD after 24 weeks was 24-30 weeks (4.3%, 95% CI 2.8-6.2%), which reduced to 1% at 31-32 weeks (95% CI 0.6-1.7%), and doubled to 2.2% at 33-34 weeks (95% CI 0.9-3.9%)[67]. it was felt that MCMA twins should be delivered between 32-33 weeks[9,21].

Controversies in screening and prevention of preeclampsia in twins

Screening and prevention of preeclampsia has revolutionised following the publication of the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial. By using a combination of maternal risk factors, serum biochemistry, mean arterial pressure (MAP), and uterine artery Doppler, a risk for developing preterm preeclampsia was stratified and those high risk were randomised to treatment with Aspirin or placebo. This screening tool found that the detection rate of preterm preeclampsia was 77%, with a reduction of 62% in those treated with Aspirin[70]. This trial however, was only limited to singleton pregnancies, despite the higher risk of preeclampsia in multiple pregnancies. Based on a low risk population derived from maternal characteristics (Caucasian, height 164cm, weight 69kg, no family or medical history), the risk of preeclampsia <37 weeks was 0.6% in singletons, 9% in DC twins, and 14.2% in MC twins[71]. Studies since have assessed the application of the same screening tool in twins, which concluded that although this methodology can be applied in twins, a high detection rate would also require a very high screen-positive rate (SPR)[72].

Furthermore, the majority of twins are recommended aspirin prophylaxis if there are any additional risk factors such as nulliparity[73], but the role of aspirin in preeclampsia prevention in multiple pregnancies is yet to be established. Following the finding that aspirin dosage exceeding 100mg was more beneficial than 75mg from an individual patient data (IPD) analysis[74], the dose of 150mg daily began to be more favourably used. A recent study compared the traditional dose of 75mg with the newly recommended dose of 150mg in twins, and found that those who took 150mg daily had a significantly lower rate of preeclampsia (1.8% vs 11.1%, p=0.003), but the rate of preeclampsia between the 150mg and no aspirin groups saw no significant difference[75]. Therefore, the role in preeclampsia screening in twins remains controversial, given the insufficient evidence for aspirin in prevention, and the high SPR required achieving a good detection rate.

Controversies in the management of single intrauterine demise in twins

The impact on the co-twin following sIUD differs depending on chorionicity. In MC twins, the shared circulation leads to hypovolaemic shock to the co-twin, resulting in higher rates of co-twin demise and neurological injury, together with a risk of fetal anemia. This is supported by a meta-analysis which demonstrated that co-twin death following sIUD was 3% in DC and

15% in MC twins, preterm birth 54% in DC twins and 68% in MC twins, and neurological impairment 2% in DC twins vs 26% in MC twins[30]. Management of the pregnancy following this event is largely dependent on the chorionicity and gestation at the time of sIUD. Evidence has shown that the gestation at sIUD is inversely related to the gestation at delivery[76], and that co-twins are less likely to suffer neurological morbidity if the sIUD occurred after 34 weeks in MC twins, which may be due to a lower risk of prematurity at that gestation[30].

Immediate delivery is not advisable if the death occurs prematurely, as the injury to the co-twin has likely already occurred, it would be reasonable to conservatively monitor the co-twin to minimise the risk of iatrogenic prematurity[9]. Patients should be referred to a fetal medicine centre with the relevant expertise for counselling and monitoring. Two weekly scans should be scheduled together with growth and Doppler assessments for MC twins, in particular the MCA PSV to detect signs of fetal anaemia[77], and 4 weekly scans for DC twins[9]. Fetal brain imaging should be performed 4-6 weeks post sIUD, and delivery should be considered at 34-36 weeks following a course of steroids for lung maturity[9]. The recommended gestation to deliver these pregnancies is also controversial, with some clinicians advocating expectant management until term.

Controversies in the management of discordant anomalies

Discordant anomalies can complicate 1-2% of twins[9], where only one twin is affected by an anomaly in 80% of cases[78]. Whilst genetic discordance is rare in MC twins, heterokaryotypic MC twins with discordant aneuploidies have been reported[79]. Prenatal invasive testing can be offered following diagnosis of these anomalies, where earlier diagnosis is preferred due to lower risks of pregnancy loss and preterm delivery when selective termination is performed in the first trimester compared to the second trimester (7% entire pregnancy loss, 14% preterm delivery)[80]. In DC twins, CVS sampling of both placentas is recommended, whilst in MC twins, sampling the single placenta may miss rare cases of discordant aneuploidies, therefore, amniocentesis of both sacs should be considered when technically feasible[9].

The decision for expectant management or selective termination can pose a clinical dilemma. The risk of sIUD of the discordant twin can result in serious consequences for the normal twin, particularly in MC pregnancies. Counselling regarding management should involve careful consideration of the nature of the abnormality (lethal or non-lethal), patient choices, gestational age and chorionicity. Women with lethal abnormalities may be counselled regarding the option of palliative care of the abnormal twin after birth, whilst those with non-lethal abnormalities wishing to discontinue the pregnancy may prefer the option of selective termination.

In DC twins, intrathoracic or intracardiac injection of Potassium Chloride (KCl) can be performed, whilst due to the shared circulation in MC twins, this procedure would be contraindicated. Therefore, methods of cord occlusion, intrafetal laser ablation, or radiofrequency ablation (RFA) would be preferred[81, 82]. In cases of diagnosis after the first

trimester, selective termination in the third trimester will only expose the healthy twin to the risk of preterm birth, ameliorating the added risk of a second trimester miscarriage, therefore, would be a more desirable option[9]. However, this may be technically challenging to perform in MC twins due to an increased thickness of the umbilical cord, therefore, some clinicians may prefer to perform these procedures in the second trimester due to technical feasibility, with a reported co-twin survival rate of 83%[79]. A recent cohort study evaluated the outcomes of the healthy co-twins in groups of discordant MC twins undergoing expectant management versus selective fetocide, and found that no significant differences in livebirth rates were seen with either form of management (88.5% expectant management, 82.7% selective fetocide, p=0.87)[83]. Therefore, the management of discordant anomalies remain controversial, and requires careful counselling and treatment planning with consideration of patient wishes.

Controversies in the screening, prevention, and management of preterm birth in twins

Twin pregnancies are at significantly higher risk of preterm delivery than singletons, where more than half is likely to deliver before 37 weeks, and 15% prior to 34 weeks[84]. Despite the proven benefits of progesterone and cerclage placement in preventing preterm delivery in high risk singletons, these treatments have not shown similar effects in twin pregnancies[85, 86]. The benefits of screening for those at risk of preterm labour remain controversial. Fetal fibronectin assessments have been shown to be of minimal to moderate predictive value for preterm birth in twins[87]. Cervical length screening through transvaginal ultrasound measurements is likely to be a good predictor of preterm birth in asymptomatic women, with a positive likelihood ratio of 10.1 in predicting birth <32 weeks and 9.0 <34 weeks if the cervical length is found to be ≤20mm at 20-24 weeks, and a positive likelihood ratio of 9.6 in predicting birth <28 weeks if the cervix was ≤25mm at the same gestation[88,89]. A meta-analysis of IPD showed that vaginal progesterone use in those with a sonographically short cervix can reduce the risk of preterm birth and perinatal morbidity and mortality[90]. Despite this, it was felt that the benefits of preventative treatment are yet to be ascertained and that that the evidence was not robust enough to justify recommendation of ultrasound screening[21], therefore, routine cervical length measurements is still under debate.

Cervical cerclage in twin pregnancies with a short cervix has received conflicting evidence, where it was originally believed to be associated with a significantly increased risk of preterm birth[91]. Some studies have shown a potential benefit of emergency cerclage in twins with a short or open cervix, with an increased interval to delivery of 71-92 days[92-94], but these studies were largely observational. The only RCT included only 7 twins, where they found a significant decreased risk of preterm birth <34 weeks and a longer interval from diagnosis to delivery (30 days) in the cerclage group than bed-rest alone, but these results were reported together with the singleton pregnancies[95]. This potential benefit in emergency cerclage in twins was further supported by a recent meta-analysis[96]. However, critics demonstrated that the results derived from the randomised trials showed that cerclage was in fact associated with increased preterm birth and poor perinatal outcome, but in those with a short cervix[97]. In view of the numerous controversies, the Emergency Cerclage in Twin Pregnancies at

Imminent Risk of Preterm Birth (ENCIRCLE) trial was created. This is a multi-centre, open-label RCT, inclusive of twins 16-26 weeks with symptomatic open cervix, where they are randomised to cerclage or conservative management (https://clinicaltrials.gov/ct2/show/NCT03818867).

The management of preterm labor in twins pose a further challenge to clinicians. Preterm prelabor rupture of membranes (PPROM) in one twin can predispose to chorioamnionitis, but early delivery could also jeopardise the wellbeing of the other twin, exposing them to iatrogenic preterm delivery. A systematic review of 128 twin pregnancies where one twin underwent preterm delivery, and the second twin was conservatively managed with delayed-interval delivery showed that the mortality of the second twin was significantly lower than the first (relative risk (RR) 0.44, 95% CI 0.34-0.57, p<0.001). The same review however found that 28 out of 90 women developed chorioamnionitis[98]. Outcomes can also differ depending on the twin exposed to PPROM, where a longer latency period (41.3 vs 10.1 days from PPROM to delivery, p<0.05) and fewer neonatal deaths (0% vs 21.4%, p=0.05), if PPROM occurred in the non-presenting twin[99]. Therefore, conservative management following preterm delivery of twin 1 can be considered in a carefully selected population in order to improve outcome for twin 2.

Fetal monitoring in labor in preterm twins should be performed in the form of a continuous CTG from 26 weeks, with an ultrasound scan to located the separate fetal hearts prior to monitoring[21]. Lower gestations may be more difficult to monitor through CTG surveillance, therefore a discussion should take place with a senior Obstetrician with the family regarding the mode and frequency of monitoring[21].

Mode of delivery (MOD) in preterm twins (24-33 weeks) and their outcomes were analysed by the Canadian Neonatal Network in 3318 sets of twins. Caesarean section (CS) was found to have a lower rate of severe neurological injury (adjusted OR 0.77, 95% CI 0.61-0.98), but higher rate of respiratory distress syndrome (RDS) (adjusted OR 1.34, 95% CI 1.15-1.56)[100]. This is also supported by an earlier study of 4428 sets of twins weighing 500g or more, which found that neonatal mortality and low Apgar scores were lower in babies weighing 500-749g who underwent a CS (p<0.05), where this protective benefit was not observed in babies weighing >1000g[101]. Furthermore, a systematic review found that preterm breech babies had a significantly lower mortality rate if a CS was performed (3.8% vs 11.5% in vaginal birth)[102]. Therefore, it has been recommended that preterm twins labouring between 26-32 weeks with a non-cephalic presenting twin should be offered a CS[21].

Controversies in the timing of birth in uncomplicated twin pregnancy

Twin pregnancies are dated according to the crown rump length (CRL) measurement of the larger twin at the 11-13+6 week scan[9]. Some studies suggested that the CRL of the smaller twin may be more accurate[103], but as this can give false reassurance that the smaller twin is growing appropriately, leading to a missed diagnosis of aneuploidy or sFGR, this method is not commonly used in practice.

In DC twins, the main cause of late IUD is thought to be due to FGR[104], where the IUD risk at 36-37 already equates to those of post-mature singletons[105], and significantly increases at 38-39 weeks[106]. According to a recent meta-analysis, if delivered at 36 weeks, the risk of neonatal death (NND) was higher than IUD (3.2 vs 1.5:1000), whereas this becomes inversed from 37 weeks, where the risk of IUD overtakes that of NND (3.4 vs 2.2:1000)[107], leading to the common practice of delivering DC twins from 37 weeks[21].

In MCDA twins, the risk of IUD is significantly higher than that of DC twins (19.1 vs 6.5:1000 after 26 weeks)[108], largely due to the MC specific complications. This risk begins to increase from 32 weeks, and further still from 36 weeks[104], when the risk of composite neonatal morbidity is observed to fall[109]. It was also found that at 35 weeks, the risk of NND was significantly higher than IUD (8.1 vs 2.8:1000), which sees a reversal in its relationship from 37 weeks, when the risk of IUD becomes greater than that of NND (9.6 vs 3.6:1000)[107]. Therefore, it is commonly recommended that MCDA twins are delivered between 36-37 weeks[21]. The timing of birth in MCMA twins is covered in an earlier section of this paper.

Role of steroids in twin pregnancy

Numerous RCTs in singleton pregnancies have shown that a course of maternal antenatal corticosteroids can reduce perinatal death, respiratory distress syndrome (RDS), intraventricular haemorrhage (IVH), and necrotising enterocolitis, in those with preterm birth below 34 weeks[110]. Its use is routinely recommended in singletons undergoing preterm birth below 34 weeks[111,112]. According the Cochrane database review, previously reported maternal adverse effects such as chorioamnionitis and endometritis were not shown to be increased by steroids, nor were factors such as neurodevelopmental delay or birthweight influenced[110]. However, there remains a risk of maternal hyperglycaemia, particular in those mothers with diabetes, resulting in neonatal hypogycaemia[113].

Twelve studies included twins in the Cochrane review, which did not suggest a significant difference in its benefit than shown in singletons, but only 4 of these studies reported the outcomes in twins separately, and all were outdated[110]. Nevertheless, some guidelines recommended the use of steroids in twins labouring before 34 weeks as similar benefits were demonstrated[112,114]. More recent studies have since compared the effects of steroids between twins and singletons, with conflicting findings. A large cohort study found that twins showed a similar reduction in short term respiratory morbidity, neonatal death, and neurological injury as singletons when steroids were given 1-7 days before birth, but no reduction in the other morbidities[115]. This reduction in respiratory morbidity was supported by a more recent study[116], but was contradicted by others, where they observed no such improvement in short term morbidities, but possibly a reduction in neonatal mortality[117,118]. A proposed explanation to the questionable benefit of steroids in twins may be due to a shorter half-life of betamethasone observed in mothers of twins (7.2 +/- 2.4 vs 9.0 +/- 2.7 hours, p=0.017)[119].

More recently, evidence have also shown in singletons that steroids at term (at or after 37 weeks) can reduce the risk of RDS, transient tachypnoea of the neonate (TTN), and NNU admissions in those undergoing planned CS[120,121]. Data on the benefit of steroids on twins at this later gestation however, is scarce, therefore the use of steroids at or near team remains under debate. The Effects of antenatal Corticosteroids in Twin neonates with late preterm birth (ACTWIN) trial is an RCT that is currently underway to compare the benefit of steroids vs placebo in twins with late preterm labour at 34-36^{+5} weeks (https://www.clinicaltrials.gov/ct2/show/NCT03547791)[122].

Mode of delivery in twin pregnancy

Mode of delivery in twins have been open to numerous controversies in the literature. Whilst older studies did not show any significant associations between the birth order and mode of delivery with perinatal deaths, Smith et al have demonstrated through a large retrospective cohort study that second twins were in fact at a significantly higher risk of perinatal death than the first twins when delivered vaginally (OR 1.16, 95% CI 1.01-1.35, p=0.04), whereas those who underwent CS did not have any delivery rated deaths[123]. The same authors went on to analyse the outcomes of a larger cohort of term twins over 36 weeks (n=8073), and found that those who had a planned CS had a significantly lower rate of death than other deliveries (OR planned CS 0.26, 95% CI 0.03-1.03, p=0.05). They also found that the second twin had a higher rate of intrapartum anoxia compared to the first twin (OR 21, 95% CI 3.4-868.5), as well as a higher death rate (OR 5.00, 95% CI 2.00-15.7)[124]. The Twin Birth Study randomised 2804 women at 32-38^{+6} weeks with a cephalic presenting twin to vaginal or Caesarean delivery. This RCT found no significant difference in the rate of neonatal mortality or serious morbidities in the planned CS or vaginal delivery groups (2.2% vs 1.9% respectively, OR 1.16, 95% CI 0.77-1.74, p=0.49). They did find however that 43.8% of those who planned a vaginal delivery went on to deliver by CS[125]. The mode of birth in very preterm twins is covered in an earlier part of this paper.

This led to an update in the NICE guidelines in twin and triplet pregnancies, where women should be informed that both vaginal or CS deliveries are safe, provided they have uncomplicated pregnancies, the presenting twin is cephalic, there are no large size discrepancies, or other contraindications for labor[21].

Core outcomes in twins

It has come to the attention of researchers that in order to increase the value of research and to adequately reflect the disease impact and the risks and benefits of treatments, outcomes should be defined and reported in a standardised fashion[126]. It was demonstrated in a systematic review of 100 studies on TTTS that 62 different outcomes were reported, with only a very limited focus on neonatal morbidity[127]. Therefore, the International Collaboration to Harmonise Outcomes for Twin-Twin Transfusion Syndrome (CHOOSE) set out to establish a core outcome set of essential reported outcomes in TTTS, in order to advance the effectiveness of research into this area. This was performed using a 3-round

Delphi survey involving 103 participants from 29 countries, and a final consensus meeting, formed of clinicians, patients and researchers. Twelve final core outcomes were decided which included a combination of antenatal complications, fetal, neonatal, and maternal outcomes[128]. Similarly, in sFGR 96 different outcomes were found from 36 studies in a systematic review, therefore, the same group felt that it was important to standardise outcome reporting in this condition (CHOOSE-FGR). This was also performed using a step-wise approach inclusive of participants from different multidisciplinary perspectives, as well as patients themselves, leading to a concluding set of 11 core outcomes to aid with future research reporting[129].

Twin and Multiples Priority Setting Partnership

The numerous controversies and research needs in twin and multiple pregnancies have led a group of experts and patient representatives to come together to form the Global Twins and Multiples Priority Setting Partnership (PSP), whose common goal was to establish the 10 most important research uncertainties in multiple pregnancies, and thereby improving the health and social outcomes for multiples and their families. Following the James Lind Alliance method[130], a steering group of 32 experts from various cultural and professional backgrounds designed an online survey asking participants for their top 3 unanswered research questions in this field. This received an overwhelming response from 1120 participants from 31 countries, who suggested 2891 research uncertainties. After the removal of duplicates and classification into indicative questions in 5 categories, 235 quantitative and 455 qualitative questions were found. Focusing on the quantitative questions, a guideline and literature search was performed and 89 remained unanswered by robust evidence, and the qualitative questions were decided to be analysed at a later stage. A second round of surveys with the 89 unanswered questions was redistributed for the participants to select the top 3 from each category. The final questions were taken to the final workshop, consisting of 23 participants (clinicians, researchers, patients), and the top 10 research priorities were chosen (Box 2)[131].

Conclusions

Twin pregnancies pose a multitude of challenges and controversies as outlined in this paper. Many issues on classification and management remain under debate. Efforts on standardising diagnostic criteria, outcome reporting, and the development of national and international practice guidelines will help in research effectiveness and clinical practice. The Twin and Multiples PSP have also elicited the top 10 most pressing research uncertainties identified by both clinicians and patients. Nevertheless, more robust research in the form of RCTs or large well-conducted cohort studies are still required to ameliorate many of these controversies, in order to enable the most optimal care and further improve the outcomes in twin pregnancies.

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FIGURE LEGENDS

Figure 1. Diagnostic criteria of selective fetal growth restriction in twin pregnancy: International consensus

Figure 2. The classification of selective fetal growth restriction in monochorionic twin pregnancies. In type I the umbilical artery Doppler waveform has positive end-diastolic flow, while in type II there is absent or reversed end-diastolic flow (AREDF). In type III there is a cyclical/intermittent pattern of AREDF.

Figure 3. Perinatal outcomes (intrauterine demise 3a and intact survival 3b) following expectant management, fetoscopic laser photocoagulation, and selective termination in monochorionic twin pregnancies complicated by selective fetal growth restriction according to Gratacós classification.

Figure 4. Incidence and type of selective fetal growth restriction in monochorionic twin pregnancy according to the gestational age at diagnosis.

Figure 5. Modified classification of selective fetal growth restriction in monochorionic twin pregnancy

Figure 6. Modified diagnostic criteria of twin-to-twin transfusion syndrome

Figure 7. Diagnostic criteria of twin anemia polycythemia sequence: International consensus

Table 1. Predictive accuracy of various diagnostic criteria of twin anemia polycythemia sequence

Diagnostic criteria	Sensitivity	Specificity	Positive predictive value	Negative predictive value
MCA PSV >1.5MoM + <1MoM	46	100	100	70
MCA PSV delta ≥0.5MoM	83	100	100	88
MCA PSV delta ≥0.373MoM	93	96	70	99

All the values are percentages.

MCA: middle cerebral artery; PSV: peak systolic velocity; MoM: multiple of median

Box 1. Modified classification of selective fetal growth restriction in monochorionic twin pregnancy

Selective Fetal Growth Restriction in Monochorionic Twin Pregnancy: New Classification

According to the gestational age at diagnosis:

- Early-onset (<24 weeks)
- Late-onset (≥24 weeks)

According to the umbilical artery, ductus venosus Doppler and co-existing TTTS:

- Stage 1: umbilical artery Doppler positive EDF in the smaller twin
- Stage 2:
  - 2a:umbilical artery Doppler persistent AREDF in smaller twin
  - 2b: umbilical artery Doppler intermittent AREDF in the smaller twin
- Stage 3: abnormal ductus venosus Doppler in the smaller twin
- Stage 3: superimposed twin-to-twin transfusion syndrome
- Stage 5: intrauterine demise of the smaller twin

*Stage 3 and 4: recommend intervention

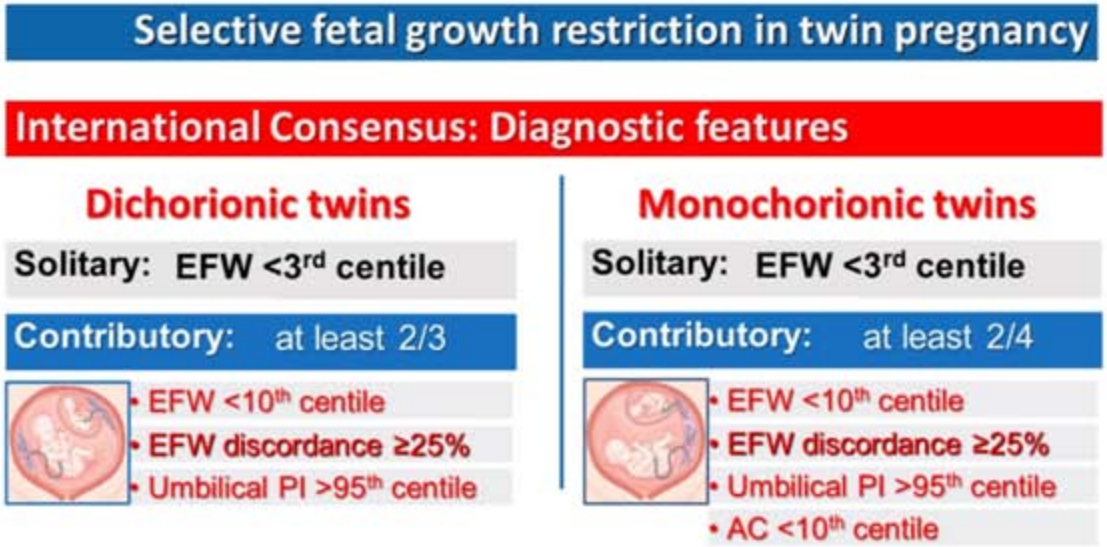


Figure 1

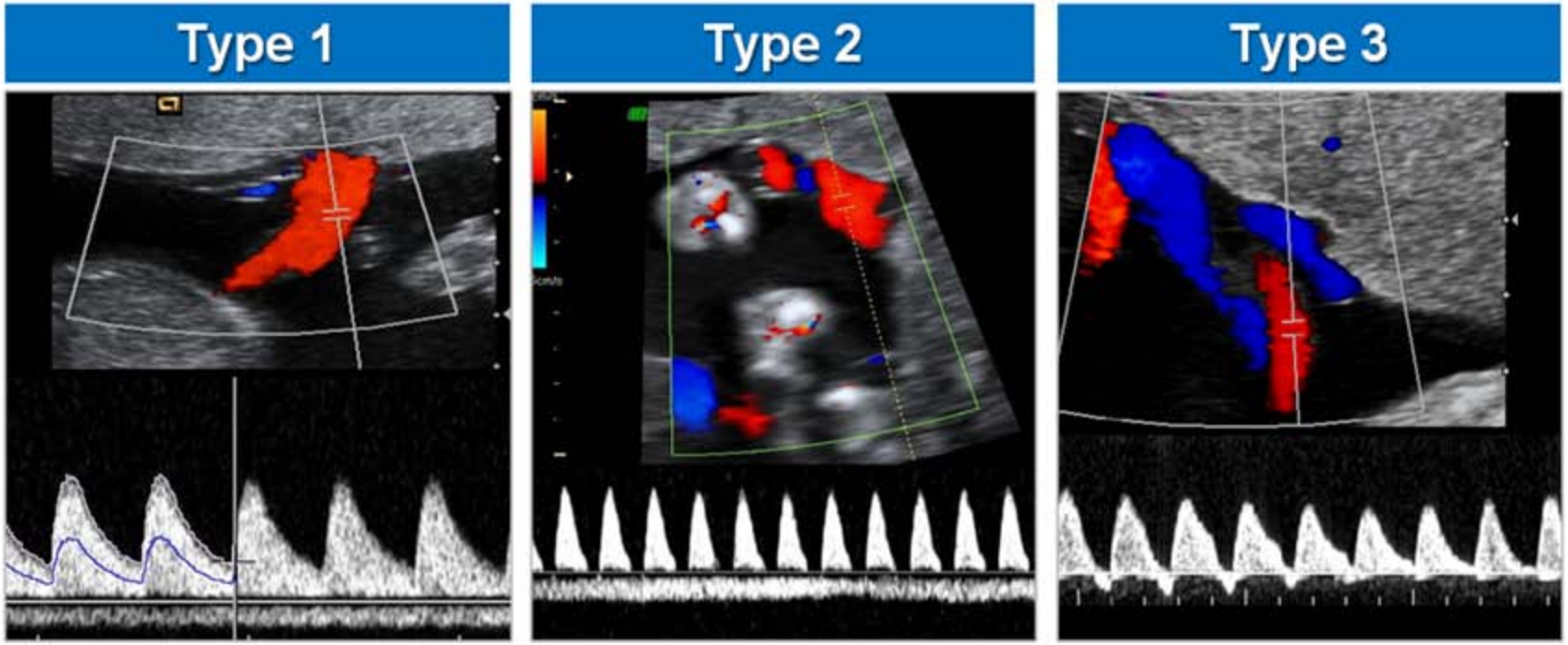


Figure 2

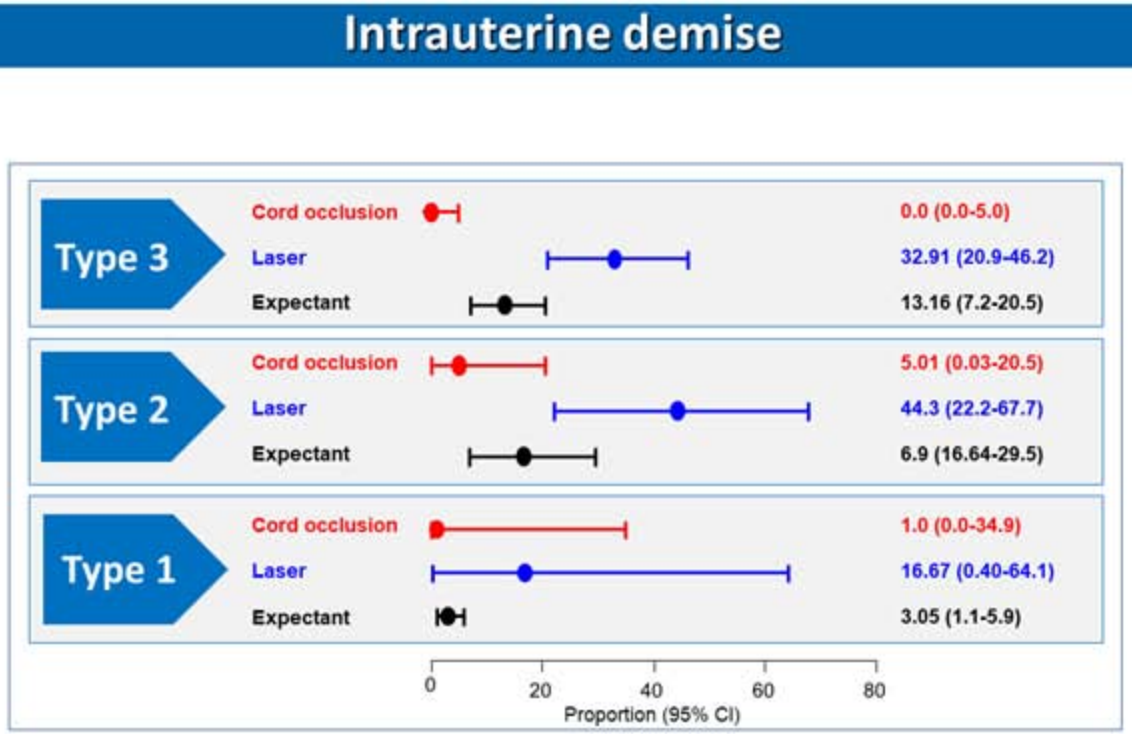


Figure 3a

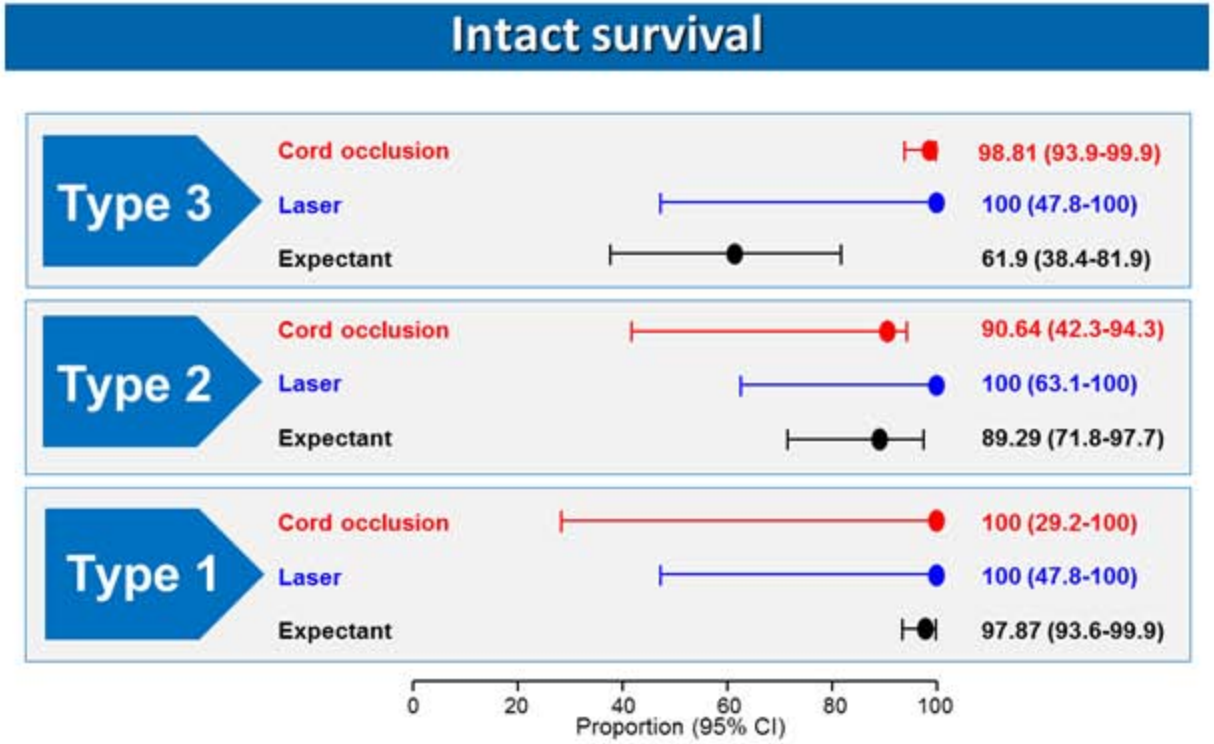


Figure 3b

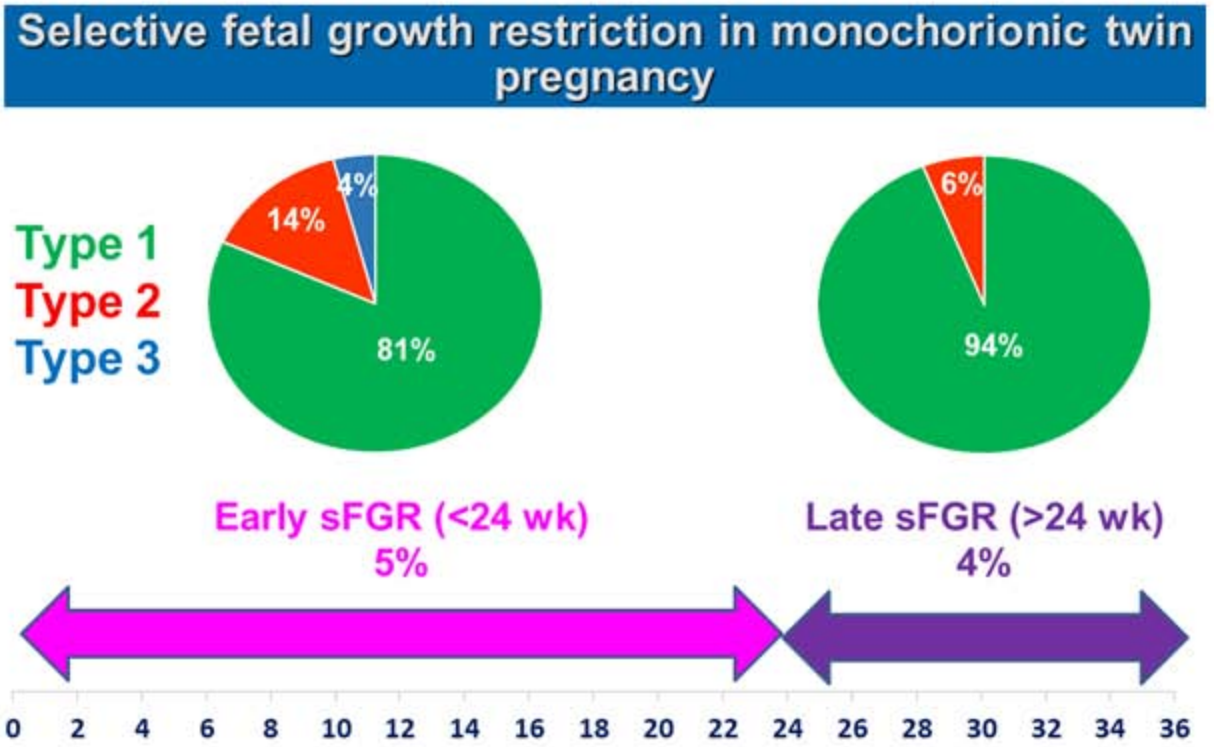
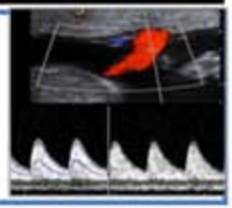


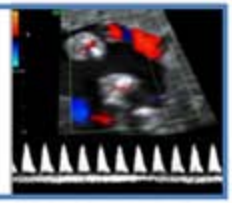
Figure 4

Selective Fetal Growth Restriction in Monochorionic Twin Pregnancy: New Classification

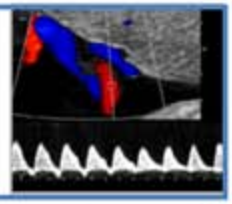
Stage 1
Umbilical artery Doppler positive EDF in the smaller twin



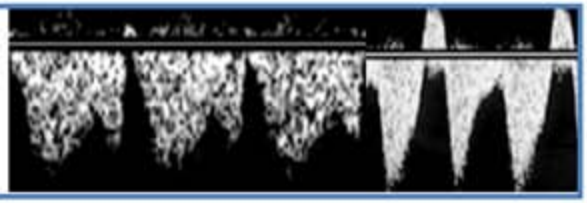
Stage 2a
Umbilical artery Doppler persistent AREDF in the smaller twin



Stage 2b
Umbilical artery Doppler intermittent AREDF in the smaller twin



Stage 3
Abnormal ductus venosus Doppler in the smaller twin



Stage 4
Superimposed twin-to-twin transfusion syndrome

Stage 5
Intrauterine demise of the smaller twin

Figure 5

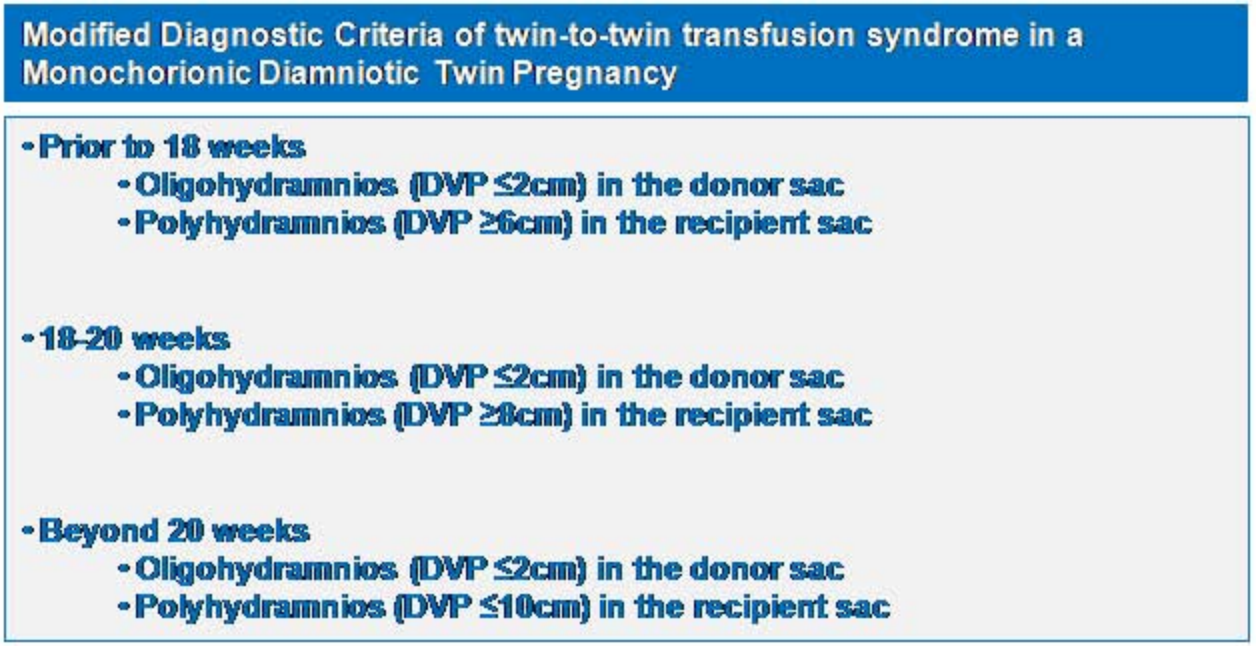


Figure 6

Twin Anemia Polycythemia Sequence

International consensus: Diagnostic criteria

Antenatal

- MCA PSV ≥ 1.5MoM in the donor twin + ≤ 0.8MoM in the recipient twin
  OR
- MCA PSV discordance ≥ 1MoM

Postnatal

- Inter-twin hemoglobin difference ≥ 8g/dL

  +

- Inter-twin reticulocyte ratio ≥ 1.7

Figure 7

Box 2. Top 10 research questions according to the Global Twins and Multiples Priority Setting Partnership (PSP)

1. Would staff with specialist training in multiple pregnancies improve outcomes in these pregnancies?
2. How can we reduce multiples' admission to the neonatal unit? If admitted, how can we reduce multiples' length of stay in the neonatal unit?
3. What interventions prevent and support postnatal mental-health problems in parents of multiples?
4. How can we prevent maternal complications in multiple pregnancies?
5. What are the short- and long-term outcomes in multiple pregnancies? How are these outcomes affected by antenatal events and medical interventions?
6. How are higher-order multiple pregnancies best managed?
7. What are the expected growth patterns of small-for gestational-age multiples? How can we assess the growth of infant multiples and ensure that they follow a satisfactory growth trajectory?
8. What parental interventions can improve the developmental outcomes (i.e. speech, language, education) of multiples?
9. What are the short- and long-term maternal health risks following a multiple pregnancy?
10. What prenatal factors (including changes to lifestyle, health history, personality characteristics) and supports for parents of multiples have the most benefit on birth and ongoing health outcomes for both parents and their children?