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State-of-the-Art Review

Controversies in the management of twin pregnancy

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ABSTRACT

Despite many advances in antenatal care, twin pregnancies still experience more adverse outcomes, in particular perinatal morbidity and mortality. They also pose a multitude of challenges and controversies, as outlined in this Review. Moreover, they are less likely to be included in clinical trials. Many issues on classification and management remain under debate. Efforts at standardizing 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 randomized trials and large well-conducted prospective cohort studies is needed to address these controversies. © 2020 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

The incidence of multiple pregnancy has increased substantially in the last few decades, secondary to the rise in the use of assisted reproductive techniques[1]. However, recent reports from the USA and UK have demonstrated a decline in the twin-birth rate since 2014[2]. These pregnancies not only contribute to a disproportionate number of cases of cerebral palsy[3], stillbirth[4,5] and neonatal morbidity and mortality[6], but also pose an increased risk of maternal complications, such as hypertensive disorders[7], thereby leading to increased healthcare costs, largely due to the high rate of neonatal unit admission[8]. MMBRACE (Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK) published for the first time its report on the Confidential Enquiry into Stillbirth and Neonatal Death in Twin Pregnancies on 14 January 2021 and reported that 'in around 1 in 2 baby deaths, the care was poor, and that if the care had been better it may have prevented the baby from dying'[9]. Despite this, multiple pregnancies are often excluded from research studies, with only 8% of trials on fetal growth restriction (FGR), 17% of those on pre-eclampsia and 2% of those on diabetes including multiple pregnancies over the last 7 years. Furthermore, most of the recommendations in national and international guidelines on the management of multiple pregnancy lack high-quality robust evidence[10]. In this Review, we aim to outline the controversies in the screening, assessment, diagnosis and management of multiple pregnancy.

SCREENING FOR ANEUPLOIDY

First-trimester screening for common aneuploidies in twins can be performed using the combined test (including maternal age, nuchal translucency, serum pregnancy-associated plasma protein-A level and β-human chorionic gonadotropin level), or using maternal age and nuchal-translucency measurement alone[11,12]. A meta-analysis showed that the detection rate (DR) of the combined test for trisomy 21 in twins is similar to that in singletons (86% in dichorionic (DC) and 87% in monochorionic (MC) twins, compared to 89% in singletons), with a false-positive rate (FPR) of 5%[13]. In women who book their pregnancy in the second trimester, only the quadruple test is 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%[12].

Non-invasive prenatal testing (NIPT) is becoming increasingly common and, in singletons, has a DR of > 99%, with a FPR of 0.13%[14]. In twins, aneuploidy is often discordant, and unequal contribution of the fetuses to cell-free DNA (cfDNA) in the maternal blood can lead to a false-negative result in cases in which the normal twin contributes a higher fetal fraction[15,16]. Furthermore, NIPT has a higher failure rate in twin pregnancy, as dichorionicity, conception by *in-vitro* fertilization and higher maternal weight were found to be significant predictors of failure of NIPT, with other predictors being nulliparity and increased maternal age[15,17]. 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% to 9.4%[14–16,18]. For trisomies 18 and 13, the DR was 60% in twins[16], compared to 97.9% and 99%, respectively, in singletons[14], but these results were limited by the small numbers of positive findings. Single-twin demise can also render the results of NIPT unreliable. As these early deaths are more likely to occur in an aneuploid fetus, it can lead to discordant results due to the continued

release of cfDNA of the demised twin into the maternal circulation[19,20].

Screening for aneuploidy in twins therefore offers promising results; however, higher NIPT failure rates and discordance can be seen in twins, and international guidelines have therefore called for further studies with larger numbers of aneuploidy cases. A recent study which recruited more than 1000 twin pregnancies concluded that NIPT using cfDNA testing is the most accurate screening test for trisomy 21 in twin pregnancies, with a DR of 100% and a FPR of 0%[21]. Of note, the failure rate in the study was 0.3%, which is much lower than that reported in other studies[21]. However, the screening performance for trisomies 18 and 13 may be less accurate[21]. An updated meta-analysis on this topic included 137, 50 and 11 twin pregnancies with trisomy 21, 18 and 13, respectively, as well as more than 7500 twin pregnancies not affected by these three common trisomies. The pooled weighted DR and FPR for trisomy 21 were 99.0% and 0.02%, respectively, while those for trisomy 18 were 93% and 0.01%, respectively. The corresponding figures for trisomy 13 were 95% and 0.10%, respectively[22].

Some still argue that the screening performance in twins might be lower than that in singletons. However, the evidence demonstrates that cfDNA screening is more accurate than ultrasound-based or combined screening in twin pregnancies, and it is therefore the most accurate available screening test. Although a recent meta-analysis of 16 studies comparing twin pregnancies undergoing invasive testing and those not undergoing such testing demonstrated no difference in the rate of fetal loss (2.0% *vs* 1.8% for pregnancies undergoing compared with those not undergoing chorionic villus sampling and 2.4% *vs* 2.4% for pregnancies undergoing compared with those not undergoing amniocentesis[23]), women would rather avoid invasive testing during pregnancy. More accurate screening with a lower FPR, as well as earlier diagnosis allowing safer first-trimester selective termination in cases of discordant aneuploidy, supports a policy of primary screening using cfDNA testing in women with twin pregnancy who opt for prenatal trisomy screening. If cfDNA testing is implemented as a first-line screening method, a first-trimester ultrasound examination should still be performed.

ASSESSMENT OF FETAL GROWTH

Twins are known to have lower birth weight than singletons[24], and due to their higher risk of perinatal complications, in particular FGR, more stringent surveillance using ultrasound is required[25,26]. Recent research has found that twins have a different growth trajectory than singletons, with growth being lower from 30 weeks in DC twins compared to singletons, and MC twins being generally smaller than both DC twins and singletons throughout gestation[27,28]. Yet, current practice continues to use singleton growth charts in twins, which can lead to overdiagnosis of FGR and unnecessary iatrogenic preterm delivery. Despite previous evidence which stated that twins diagnosed with FGR according to singleton growth charts still had a higher perinatal mortality rate than singletons, this was only the case in MC twins but not in DC twins[29]. 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 use of these charts does not increase the incidence of stillbirth, but does in fact reduce the number of twins diagnosed as FGR compared to customized singleton charts (7.1% *vs* 12.8%)[30]. Moreover, a recent study which investigated the risk of perinatal mortality, preterm birth, hypertensive disorders of pregnancy and admission to the neonatal unit in twins according to whether classification as small-for-gestational age (SGA) was determined using singleton or twin charts demonstrated that twins classified as SGA according to the singleton charts but not according to the twin charts had similar outcomes to twins classified as appropriate-for-gestational age[31]. The study concluded that the use of singleton charts was associated with misclassification of a large number of twins as at risk of FGR[31]. Therefore, twin-specific charts could reduce unnecessary medical interventions prenatally and postnatally.

It is recommended that DC twins undergo 4-weekly scans for growth surveillance from 24 weeks, and that MC twins undergo 2-weekly scans from 16 weeks[11,26]. 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 and twin anemia–polycythemia sequence (TAPS) and fetal decompensation in twin–twin transfusion syndrome (TTTS) and FGR, and are therefore recommended by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) to be performed at each routine scan[11]. However, other guidelines state that these measurements should be performed only in high-risk pregnancies[26,32].

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 was 18.3% at 20 weeks for DC twins, increasing to 21.9% by 30 weeks, and 22.2% at 20 weeks and 25.4% at 30 weeks for MC twins[33]. Therefore, any discordance within these values is considered part of the normal trajectory. Similarly, D'Antonio *et al.* found that EFW discordance of $\geq$ 25% was associated with a significant increase in the risk of perinatal loss (area under the receiver-operating-characteristics curve, 0.72; 95% CI, 0.65–0.80)[34]. However, a recent meta-analysis showed that the risk of stillbirth was increased in DC twins with weight discordance of $\geq$ 15% (odds ratio (OR), 9.8; 95% CI, 3.9–29.4) and in MC twins with weight discordance of $\geq$ 20% (OR, 2.8; 95% CI, 1.3–5.8), with an increased risk of neonatal death (NND) in MC twins with discordance $\geq$ 25% (OR, 4.66; 95% CI, 1.8–12.4)[35]. 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 + 0 to

30 + 6 weeks, 20% at 31 + 0 to 33 + 6 weeks and 14% at 34 + 0 to 36 + 6 weeks)[36]. Therefore, a decision for delivery should not be based on EFW discordance alone, but on a combination of gestational age, chorionicity, Doppler indices and antenatal complications.

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

MANAGEMENT OF FETAL GROWTH RESTRICTION

Selective FGR (sFGR) is associated with increased perinatal morbidity and mortality, as well as neurological sequelae in both the SGA and the appropriate-for-gestational-age twin[35–37]. Until recently, there have been numerous discrepancies amongst clinicians and researchers with regards to the diagnostic criteria of sFGR. ISUOG guidelines propose that twin pregnancies should be classified as having sFGR if the EFW of one twin is $< 10^{th}$ centile in DC pregnancies, and if the EFW of one twin is $< 10^{th}$ centile and EFW discordance is $> 25\%$ in MC pregnancies[11]. An expert consensus using the Delphi procedure, aimed at unifying the diagnosis of sFGR, has since been developed[38]. It was concluded that, in both MC and DC twins, EFW $< 3^{rd}$ centile in one twin is sufficient to classify the pregnancy as having sFGR. Additionally, DC twins satisfied the diagnosis if two of three contributory parameters were met (EFW $< 10^{th}$ centile, EFW discordance $\geq 25\%$ or UA-PI $> 95^{th}$ centile), and MC twins satisfied the diagnosis if two of four contributory parameters were met (EFW $< 10^{th}$ centile, abdominal circumference $< 10^{th}$ centile, EFW discordance $\geq 25\%$ or UA-PI $> 95^{th}$ centile) (Figure 1 and Table 1)[38]. Research comparing these diagnostic criteria has noted variation in the incidence of sFGR[39], thus supporting the use of the standardized Delphi criteria.

Due to the increased perinatal morbidity and mortality posed by FGR in twins, it is of paramount importance that clinicians are aware of its presentation and that robust guidance is in place to aid its screening and detection[40,41]. Recent updates to the National Institute for Health and Care Excellence (NICE) guidelines have recommended serial growth scans, as described above, together with measurement of the deepest vertical pocket (DVP), calculation of EFW discordance at each scan and UA Dopplers performed together with weekly scans if

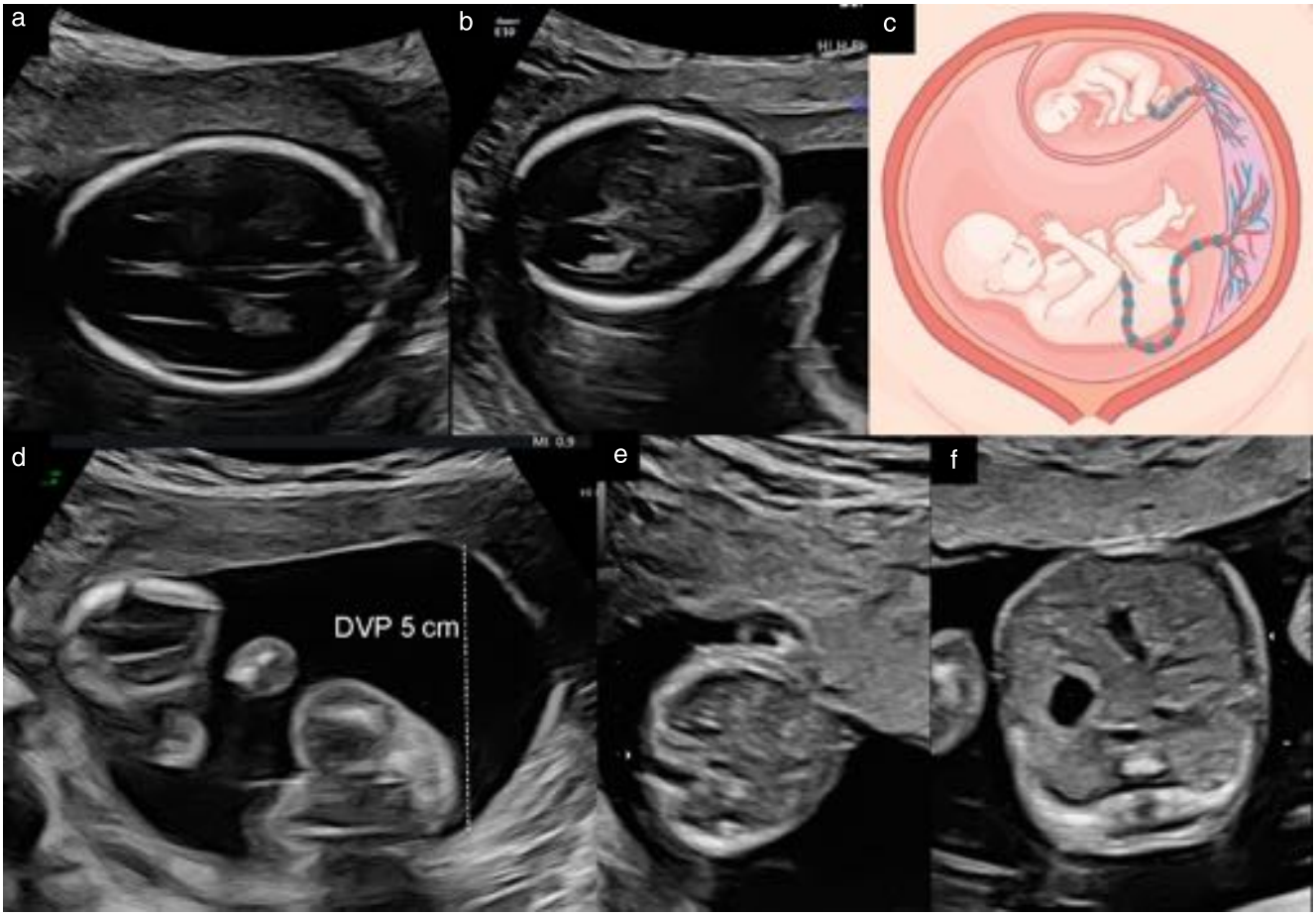

Figure 1 Ultrasound images (a,b,d–f) and schematic diagram (c) of selective fetal growth restriction in a monochorionic twin pregnancy, showing head circumference of the larger (a) and smaller (b) twin, severe oligohydramnios in the smaller twin (left) and normal amniotic fluid volume in the larger twin (right) (d), and abdominal circumference of the smaller (e) and larger (f) twin. DVP, deepest vertical pocket.

Table 1 International consensus diagnostic criteria for selective fetal growth restriction (sFGR) in twin pregnancy[38]

Dichorionic	*Monochorionic*
Solitary	Solitary
EFW < 3rd centile	EFW < 3rd centile
Contributory*	Contributory†
EFW < 10th centile	EFW < 10th centile
EFW discordance ≥ 25%	EFW discordance ≥ 25%
UA-PI > 95th centile	UA-PI > 95th centile
	AC < 10th centile

*At least two out of three contributory parameters are required for diagnosis of sFGR in dichorionic twin pregnancy. †At least two out of four contributory parameters are required for diagnosis of sFGR in monochorionic twin pregnancy. AC, abdominal circumference; EFW; estimated fetal weight; PI, pulsatility index; UA, umbilical artery.

EFW discordance is > 20% or the EFW of one twin is < 10th centile[26]. Further progression to discordance of ≥ 25% should prompt referral to a tertiary fetal medicine unit.

Gratacós *et al.* classified sFGR in MC twins into different types, according to UA Doppler end-diastolic flow (EDF) in the smaller twin, which have different clinical evolution and outcomes[42]. Studies have looked into the progression and overall survival rates of each type in order to aid counseling and management. Type-I sFGR (positive EDF) is associated with a generally good outcome, with a progression rate of up to 26%[43]. Type-II sFGR (persistent absent/reversed EDF) has the least favorable outcome, with progression rates as high as 90%[42]. Type-III sFGR (intermittent absent/reversed EDF) has a lower progression rate but, due to the variable arterioarterial anastomoses, a higher risk of sudden intrauterine demise (IUD) or acute TTTS[42]. Due to the higher risks of preterm delivery (68%), IUD (15%) and neurological sequelae (26%) in the cotwin in the event of demise of the FGR twin if managed conservatively[37], prenatal intervention in the form of selective termination is more likely to be considered in severe cases, especially before 26 weeks[11,44,45]. A recent meta-analysis compared outcome following expectant management, fetoscopic laser photocoagulation and selective termination in twin pregnancies with sFGR, according to the Gratacós classification[46]. In Type-I sFGR, 3.1%, 16.7% and 1.0% of cotwins had IUD following expectant management, laser therapy and selective termination, respectively. In Type-II sFGR, 16.6%, 44.3% and 5.0% of cotwins, respectively, experienced IUD following these treatments, and 89.3%, 100% and 90.6% were free of neurological sequelae. In Type-III sFGR, 13.2%, 32.9% and 0% of cotwins, respectively, had IUD after these treatments, and 61.9%, 100% and 98.8% had intact neurology[46]. This shows that severe cases may benefit from intervention to reduce perinatal morbidity; however, the evidence is based largely on observational studies.

Despite the fact that the Gratacós 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 at diagnosis, the variation in UA Doppler in the smaller twin, especially in early gestation, ductus venosus (DV) Doppler or the coexistence of TTTS or event of IUD of the smaller twin. In a cohort study of MC diamniotic (DA) twin pregnancies followed from the first trimester until birth, in early-onset (< 24 weeks' gestation) cases, the incidence of Type-I, -II and -III sFGR was 81%, 15% and 4%, respectively. In late-onset (≥ 24 weeks) cases, the corresponding figures were 94%, 6% and 0%, respectively. The incidence of superimposed TTTS was 27% in cases affected by early-onset sFGR compared with 6% in those with late-onset sFGR[39]. Therefore, GA at diagnosis influences the incidence, type 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[47,48]. 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[47,48].

A modified classification of sFGR in MC twin pregnancies is proposed in Table 2 and Figure S1. sFGR is classified into early- and late-onset, as well into stages taking into account UA and DV Dopplers, presence of TTTS and IUD of the smaller twin. 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 cases of severe sFGR, in which the risks of stillbirth and cotwin morbidity outweigh the risk of prematurity[44]. In DC twins, however, the risk to the appropriate-for-gestational-age twin is lower following cotwin demise; therefore, conservative management with careful monitoring is preferable. The decision for delivery should be made after thorough

Table 2 Modified classification of selective fetal growth restriction in monochorionic twin pregnancy

Classification	*Criterion*
According to GA at diagnosis	
Early onset	< 24 weeks
Late onset	≥ 24 weeks
According to UA and DV Doppler and coexisting TTTS	
Stage 1	UA Doppler positive EDF in smaller twin
Stage 2	
Stage 2a	UA Doppler persistent AREDF in smaller twin
Stage 2b	UA Doppler intermittent AREDF in smaller twin
Stage 3*	Abnormal DV Doppler in smaller twin
Stage 4*	Superimposed TTTS
Stage 5	Intrauterine demise of smaller twin

*Recommend intervention. AREDF, absent or reversed end-diastolic flow; DV, ductus venosus; EDF, end-diastolic flow; TTTS, twin–twin transfusion syndrome; UA, umbilical artery.

counseling on a case-by-case basis, taking into account the risks *vs* benefits, and is generally not recommended in DC twins before 30 weeks' gestation[11].

The development of standardized 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 the management option with the most favorable outcome.

MANAGEMENT OF TTTS

The diagnosis of TTTS is based on sonographic amniotic fluid discordance in the form of polyhydramnios–oligohydramnios sequence (DVP $\geq$ 10 cm after 20 weeks or $\geq$ 8 cm before 20 weeks in the recipient twin, with DVP $\leq$ 2 cm in the donor twin) (Figure 2)[11]. At the earlier gestational ages (16–18 weeks), however, the normal range for amniotic fluid is lower (DVP 90th centile of 6 cm at 16–17 weeks)[49], possibly due to the fact that fetal urine is not the main constituent of the amniotic fluid at that gestational age. It may therefore be argued that the diagnostic criteria should be modified to lower the threshold for classifying polyhydramnios to 6 cm at earlier gestational ages, in order to avoid misdiagnosis and poor outcome as a result of missed intervention (Table 3)[50].

Various studies have attempted to establish first-trimester ultrasound signs or maternal characteristics predictive of adverse perinatal outcome in MC twins, such as TTTS[51,52]. However, a recent meta-analysis suggested that it is currently not possible to detect these complications at the first-trimester scan[53], limiting the detection and screening for TTTS to 2-weekly scans from 16 weeks[11,26,32]. Amniotic fluid discordance not fulfilling the diagnosis of TTTS generally has a good prognosis, with an overall survival rate of 93%[54], but with an increased risk of developing TTTS, particularly if the discordance is > 3.1 cm before 20 weeks[55]. Therefore, it is recommended that MC twins with amniotic fluid (DVP) discordance of $\geq$ 4 cm should be monitored by ultrasound at least weekly, with the addition of UA Doppler[11,26].

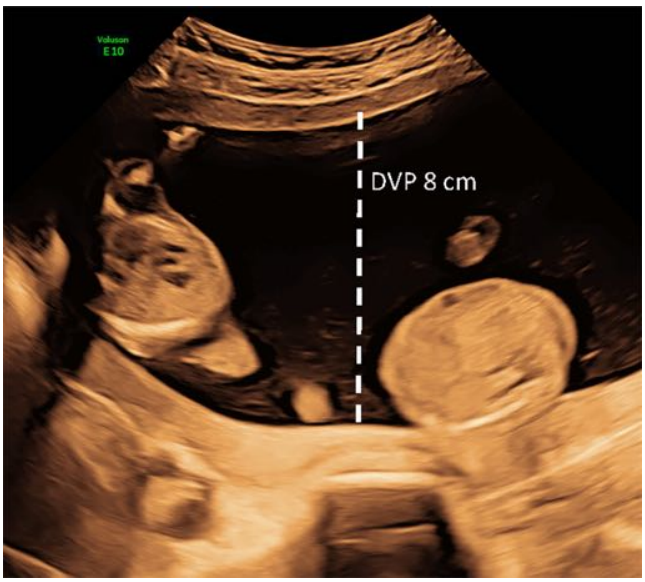

Figure 2 Ultrasound image of a monochorionic diamniotic twin pregnancy at 17 weeks' gestation complicated by twin–twin transfusion syndrome, showing oligohydramnios in the donor twin (stuck twin) (left) and polyhydramnios in the recipient twin (right). DVP, deepest vertical pocket.

Fetoscopic laser photocoagulation is the recommended treatment for pregnancies with Quintero Stage-II or above TTTS before 26 weeks[11], as the long-term neurodevelopmental outcome is superior compared with in those that undergo amniodrainage[56]. Traditionally, laser was avoided before 16 weeks and after 26 weeks due to the lack of fusion between the chorion and amnion at early gestational ages and the poor visibility after 26 weeks. However, Baud *et al.* found that laser treatment performed at these early and late gestational ages yielded similar outcomes to those done at 16–26 weeks, with no added complications[57]. Nevertheless, amniodrainage is a well-recognized treatment option for late TTTS[11] and, when compared with laser, did not yield a higher rate of overall fetal death or NND[56]. Management for Quintero Stage-I TTTS remains controversial. Conservative management with intensive monitoring can be considered in the absence of cervical shortening or maternal discomfort[11], and evidence from a meta-analysis of Stage-I TTTS showed a similar rate of survival of at least one twin in those expectantly managed (87%; 95% CI, 69–98%), in those that underwent amniodrainage (86%; 95% CI, 76–94%) and in those that received laser photocoagulation (81%; 95% CI, 69–90%), with a progression rate of 27% (95% CI, 16–39%)[58]. 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 outcome (OR, 0.12; 95% CI, 0.03–0.44)[59]. A recent multicenter randomized controlled trial (RCT) which included asymptomatic women with Stage-I TTTS at 16–26 weeks' gestation and a long cervix (> 15 mm) investigated whether laser surgery is superior to expectant management. The primary outcome (survival at 6 months without severe neurologic morbidity) was similar in the two study groups. Therefore, laser surgery is unlikely to be of benefit in Stage-I TTTS[60].

Table 3 Modified diagnostic criteria for twin–twin transfusion syndrome in monochorionic diamniotic twin pregnancy[50]

Gestational age	*Criteria*
< 18 weeks	Oligohydramnios (DVP $\leq$ 2 cm) in donor sac Polyhydramnios (DVP $\geq$ 6 cm) in recipient sac
18–20 weeks	Oligohydramnios (DVP $\leq$ 2 cm) in donor sac Polyhydramnios (DVP $\geq$ 8 cm) in recipient sac
> 20 weeks	Oligohydramnios (DVP $\leq$ 2 cm) in donor sac Polyhydramnios (DVP $\geq$ 10 cm) in recipient sac

DVP, deepest vertical pocket.

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[11]. The timing of delivery post laser for TTTS is debatable. It is commonly scheduled for around 34 weeks, due to evidence that the risk for perinatal death or severe brain injury significantly declines if delivered after 34 weeks (35% at 26–28 weeks *vs* 3% at 34–36 weeks)[61], but it may be argued that, in the absence of further pathology, delivery can be postponed until 37 weeks[11].

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-I TTTS, remain controversial.

MANAGEMENT OF TAPS

TAPS, originally described in 2006, remains open to numerous controversies. The standard antenatal diagnostic criteria of MCA-PSV > 1.5 multiples of the median (MoM) in the donor and < 1.0 MoM in the recipient (Figure 3) were found to have a sensitivity of 46% and a specificity of 100%, with positive (PPV) and negative (NPV) predictive values of 100% and 70%, respectively[62]. Recent studies found that recipient twins with MCA-PSV > 1.0 MoM could still be polycythemic at birth, and therefore proposed an alternative diagnostic criterion using delta PSV as opposed to the traditional cut-offs, providing a stronger predictor of hemoglobin discordance at birth[63]. So far, research has proposed delta PSV criteria of > 0.5 MoM[62] and > 0.373 MoM[64], both of which have increased sensitivity (83% and 93%, respectively) and NPV (88% and 99%, respectively) compared to the traditional diagnostic criteria, but the same or lower PPV, which can lead to over diagnosis (Table 4). A Delphi consensus was also carried out to establish unified criteria, in which the experts felt that a MCA-PSV cut-off of ≥ 1.5 MoM in the donor twin and ≤ 0.8 MoM in the recipient twin or a delta MCA-PSV of ≥ 1.0 MoM should be used to achieve an antenatal diagnosis of TAPS (Table 5)[65]. The criteria with the optimal DR and outcome, with the fewest unnecessary interventions, are yet to be established.

ISUOG guidelines recommend 2-weekly screening for TAPS by MCA-PSV measurements in all MC pregnancies[11]. However, due to the controversies and lack of evidence on the management of TAPS, many clinicians felt that it was more appropriate to perform screening in only those with high-risk pregnancy (for example, post laser for TTTS)[26,32]. Apart from discordance in MCA-PSV, other ultrasound features in MCDA pregnancies complicated by TAPS include thin dark placenta and starry-sky appearance of the liver in the polycythemic twin, as well as thick echogenic placenta in the anemic twin (Figure 4). TAPS can develop spontaneously or post laser; however, the natural history and outcome can be

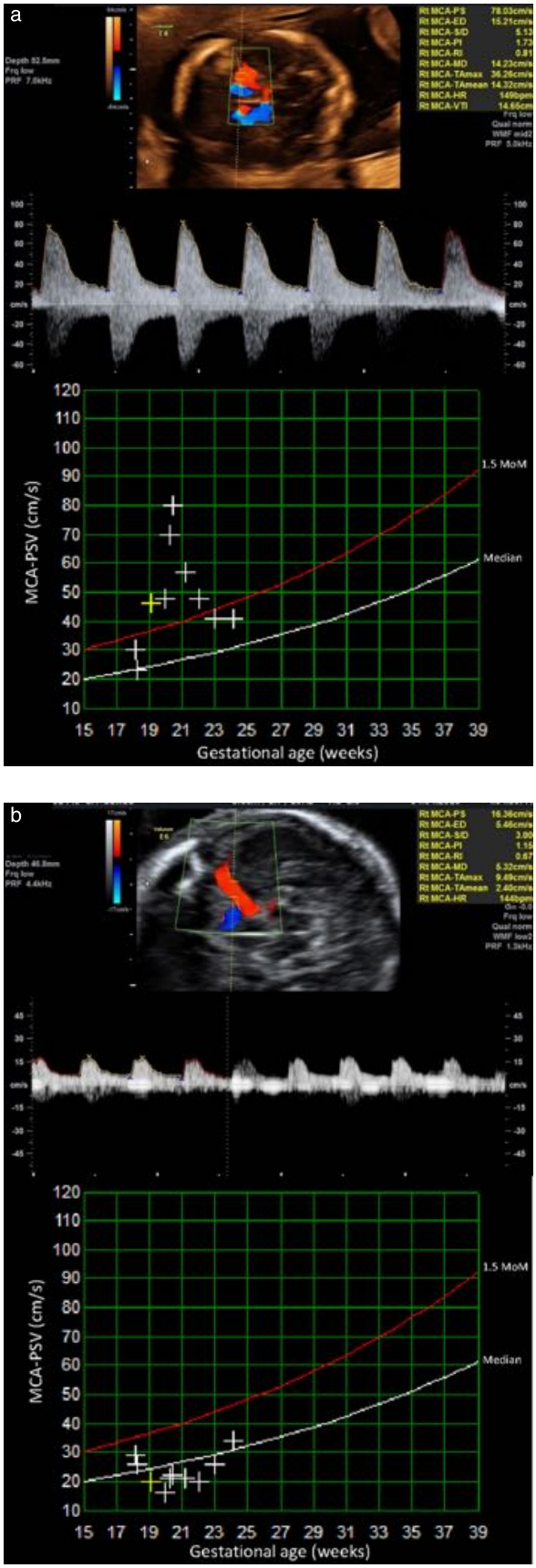

Figure 3 Middle cerebral artery (MCA) Doppler in anemic (a) and polycythemic (b) twins in pregnancies complicated by twin anemia–polycythemia sequence. MCA peak systolic velocity (PSV) reference ranges were obtained from Mari *et al.*[144]. MoM, multiples of the median.

Table 4 Predictive accuracy of various diagnostic criteria reported for twin anemia–polycythemia sequence

Diagnostic criteria	*Sensitivity (%)*	*Specificity (%)*	*PPV (%)*	*NPV (%)*
MCA-PSV > 1.5 MoM (donor) + < 1.0 MoM (recipient)[62]	46	100	100	70
Delta MCA-PSV ≥ 0.5 MoM[62]	83	100	100	88
Delta MCA-PSV ≥ 0.373 MoM[64]	93	96	70	99

MCA, middle cerebral artery; MoM, multiples of the median; NPV, negative predictive value; PPV, positive predictive value; PSV, peak systolic velocity.

Table 5 Consensus diagnostic criteria for twin anemia–polycythemia sequence[65]

Criteria
Antenatal
MCA-PSV ≥ 1.5 MoM in donor twin + ≤ 0.8 MoM in recipient twin
Or MCA-PSV discordance ≥ 1 MoM
Postnatal
Intertwin hemoglobin difference ≥ 8 g/dL + intertwin reticulocyte ratio ≥ 1.7

MCA, middle cerebral artery; MoM, multiples of the median; PSV, peak systolic velocity.

variable, ranging from rapid progression and double IUD to stable/slow progression and the birth of two healthy babies with discordant hemoglobin. Long-term neurodevelopmental outcomes of those babies who developed TAPS post laser have demonstrated neurodevelopmental impairment in 9% of cases and mild–moderate cognitive delay in 17% of cases[66], whereas this delay was proposed to be higher in spontaneous TAPS survivors (26%)[67].

Management options for TAPS include conservative management, intrauterine transfusion/partial exchange transfusion, laser photocoagulation, selective termination or early delivery. Currently, there is no consensus on the superior method of management. The treatment of choice depends on the gestational age at diagnosis, disease progression or severity, access or feasibility of intrauterine intervention, and maternal choice, and should therefore be decided on an individualized basis following thorough counseling[11].

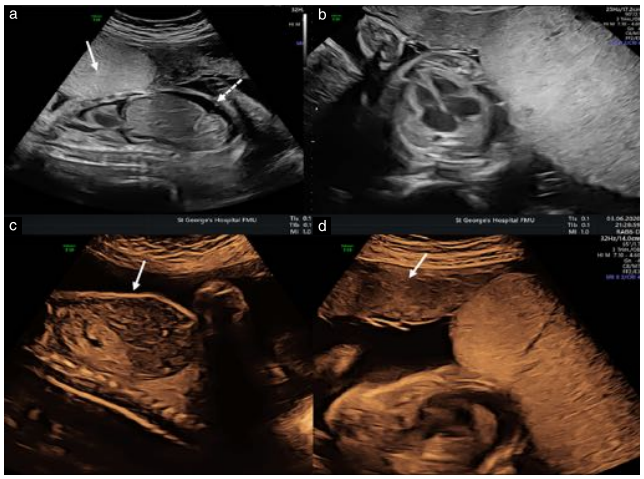

Figure 4 Ultrasound features of twin anemia–polycythemia sequence, including thick echogenic placenta (solid arrow) and ascites (dashed arrow) (a) and cardiomegaly with pericardial effusion (b) in the anemic twin, and starry-sky liver (arrow) (c) and thin dark placenta (arrow) (d) in the polycythemic twin.

MANAGEMENT OF TRAP SEQUENCE

Twin reversed arterial perfusion (TRAP) sequence (Figure 5) can lead to a 33% risk of IUD of the pump twin if managed conservatively before 18 weeks[68], and, following this, the risk of perinatal mortality of the surviving pump twin is stated to be 55%[69]. In an observational study of 26 pregnancies with TRAP sequence, in which two underwent termination of pregnancy, 21% had spontaneous resolution of flow to the acardiac twin and 46% had persistent flow[68]. Treatments include

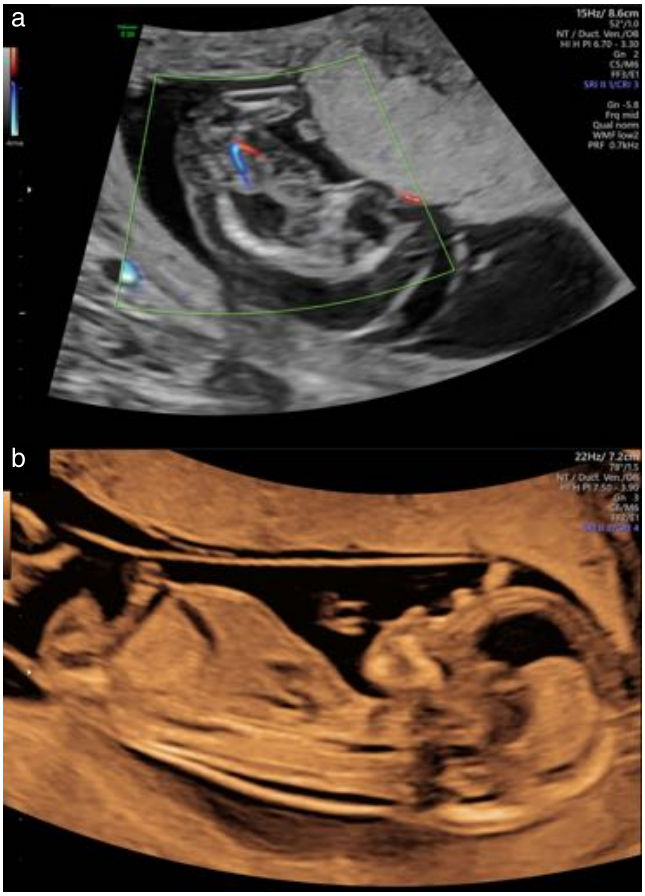

Figure 5 Ultrasound images of the acardiac twin (a) and the pump twin (b) in a monochorionic diamniotic twin pregnancy complicated by twin reversed arterial perfusion sequence.

intrafetal laser or cord coagulation, with intrafetal laser being associated with a later gestational age at delivery (37 *vs* 32 weeks; $P = 0.04$), a higher success rate (77% *vs* 50%; $P = 0.02$) and a lower rate of preterm rupture of membranes or delivery (23% *vs* 58%; $P = 0.003$)[70], with an 80% overall neonatal survival rate of the pump twin following intervention[71]. Traditionally, these procedures were carried out after 16 weeks, due to the separation of the membranes by the exocelomic cavity, particularly if there was evidence of cardiac strain of the pump twin, increased perfusion and growth of the TRAP mass, or polyhydramnios[11]. 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%; $P = 0.003$)[71]. Furthermore, a later meta-analysis revealed that there was an inverse relationship between gestational age at treatment and gestational age at birth[72]. This led to the development of the TRAP Intervention Study (TRAPIST), which is a multicenter RCT aiming to compare whether early intervention (12–14 weeks) improves the outcome of TRAP sequence compared to late intervention (16–18 weeks), and is currently ongoing (https://clinicaltrials.gov/ct2/show/NCT02621645).

In those pregnancies that have a late diagnosis of TRAP sequence or that do not wish to have an intervention, close serial ultrasound monitoring should be carried out 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, the rate of preterm delivery prior to 32 weeks is increased at 10%[71]. There is currently no consensus on the timing of birth in TRAP sequence following expectant or active management; therefore, an individualized approach should be taken based on the success of treatment, fetal Dopplers and cardiac stability of the pump twin.

MANAGEMENT OF MCMA TWIN PREGNANCY

MC monoamniotic (MA) twin pregnancies are at increased risk of perinatal mortality, with rates quoted as high as 50% from the first-trimester ultrasound examination, largely due to congenital anomalies and spontaneous miscarriage[73]. Previously, cord entanglement leading to vascular injury was thought to play a major role in the cause of IUD; however, more recent evidence has shown that not only is cord entanglement present in almost all MCMA twins[74], but it does not contribute to the increased perinatal mortality rate[75].

Antenatal management of MCMA twins has been controversial. Whilst some may suggest that inpatient monitoring with regular fetal monitoring is beneficial, others suggest that this does not influence perinatal outcome[76]. A recent meta-analysis showed that inpatient monitoring was associated with a 3% risk of IUD (95% CI, 1.4–5.2%), while outpatient management had a higher IUD risk of 7.4% (95% CI, 4.4–11.1%)[77]. However, a multicenter cohort study observed no significant difference in perinatal mortality between the inpatient and outpatient management groups of MCMA twins (adjusted OR, 0.21; 95% CI, 0.04–1.17)[78]. Recommendations on timing of delivery in MCMA pregnancies have varied between 32 and 36 weeks. However, recent evidence suggests that early delivery is warranted due to the higher risks than in other twin pregnancies and the fact that the risk of fetal demise from 32 + 4 weeks exceeded the risk of non-respiratory neonatal complications[79]. The aforementioned meta-analysis also found that the highest risk of IUD after 24 weeks was at 24–30 weeks (4.3%; 95% CI, 2.8–6.2%), which reduced to 1% (95% CI, 0.6–1.7%) at 31–32 weeks, and doubled to 2.2% (95% CI, 0.9–3.9%) at 33–34 weeks[77]. Based on these findings, guidelines recommend that MCMA twins should be delivered between 32 and 33 weeks[11,26].

SCREENING AND PREVENTION OF PRE-ECLAMPSIA

Screening and prevention of pre-eclampsia has revolutionized following the publication of the Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial[80]. By using a combination of maternal risk factors, serum biochemistry, mean arterial pressure and uterine artery Doppler, the risk for developing preterm pre-eclampsia was stratified, and those at high risk were randomized to treatment with aspirin or placebo. The DR of preterm pre-eclampsia was 77%, with a reduction of 62% in the incidence in those treated with aspirin[80]. This trial, however, was limited to singleton pregnancies, despite the higher risk of pre-eclampsia in multiple pregnancies. Based on a low-risk population derived from maternal characteristics (Caucasian, height of 164 cm, weight of 69 kg, no family or medical history), the risk of pre-eclampsia < 37 weeks was 0.6% in singletons, 9% in DC twins and 14.2% in MC twins[81]. The application of the same screening tool in twins has since been assessed, and it was concluded that, although this methodology can be applied in twins, a high DR would also require a very high screen-positive rate[82].

Furthermore, aspirin prophylaxis is recommended in the majority of twins if there are any additional risk factors, such as nulliparity[83], but the role of aspirin in pre-eclampsia prevention in multiple pregnancy is yet to be established. Following the finding that aspirin dosage exceeding 100 mg was more beneficial than 75 mg in an individual patient data (IPD) analysis[84], the dose of 150 mg daily began to be used more favorably. A recent study compared the traditional dose of 75 mg with the newly recommended dose of 150 mg in twins, and found that those who took 150 mg daily had a significantly lower rate of pre-eclampsia (1.8% *vs* 11.1%; $P = 0.003$), but the difference in the rate of pre-eclampsia between the 150-mg and no-aspirin groups was not significant[85]. Therefore, the role of pre-eclampsia screening in twins remains controversial, given the insufficient evidence for aspirin in its prevention

and the high screen-positive rate required to achieve a good DR.

MANAGEMENT OF SINGLE INTRAUTERINE DEMISE

The impact on the cotwin following sIUD differs depending on chorionicity. In MC twins, the shared circulation leads to hypovolemic shock in the cotwin, resulting in higher rates of cotwin demise and neurological injury, together with a risk of fetal anemia. This is supported by the findings of a meta-analysis, which demonstrated that the rate of cotwin death following sIUD was 3% in DC twins and 15% in MC twins, that the rate of preterm birth was 54% in DC twins and 68% in MC twins, and that the rate of neurological impairment was 2% in DC twins and 26% in MC twins[37]. Management of the pregnancy following this sIUD is largely dependent on chorionicity and gestational age at the time of fetal demise. Evidence has shown that the gestational age at sIUD is related inversely to the gestational age at delivery[86], and that cotwins 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 gestational age[37].

Immediate delivery is not advisable following sIUD if the death occurs prematurely, as the injury to the cotwin has likely already occurred; it would be reasonable to monitor conservatively the cotwin to minimize the risk of iatrogenic prematurity[11]. Patients should be referred to a fetal medicine center with the relevant expertise for counseling and monitoring. Two-weekly scans should be scheduled together with growth and Doppler assessments for MC twins, in particular MCA-PSV to detect signs of fetal anemia[87], and 4-weekly scans for DC twins[11]. Fetal brain imaging should be performed 4–6 weeks post sIUD, and delivery should be considered at 34–36 weeks following a course of corticosteroids for lung maturity[11]. The recommended gestational age at which to deliver these pregnancies is also controversial, with some clinicians advocating expectant management until term.

MANAGEMENT OF DISCORDANT ANOMALIES

Discordant anomalies can complicate 1–2% of twins[11], with only one twin being affected by an anomaly in 80% of these cases[88]. Whilst genetic discordance is rare in MC twins, heterokaryotypic MC twins with discordant aneuploidies have been reported[89]. Prenatal invasive testing can be offered following diagnosis of these anomalies, for which earlier diagnosis is preferred due to the lower risks of pregnancy loss and preterm delivery when selective termination is performed in the first trimester compared to the second trimester (7% risk of entire pregnancy loss, and 14% risk of preterm delivery)[89]. In DC twins, chorionic villus 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[11].

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

In DC twins, intrathoracic or intracardiac injection of potassium chloride 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 would be preferred[90,91]. 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, and would therefore be a more desirable option than second-trimester selective termination[11]. However, third-trimester selective reduction 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 the procedure in the second trimester, with a reported cotwin survival rate of 83%[92]. A recent cohort study evaluated the outcome of the healthy cotwins in groups of discordant MC twins undergoing expectant management *vs* selective feticide, and found no significant difference in the live-birth rate between the two management groups (88.5% *vs* 82.7%; $P = 0.87$)[93]. Therefore, the management of discordant anomalies remains controversial and requires careful counseling and treatment planning with consideration of patient wishes.

SCREENING, PREVENTION AND MANAGEMENT OF PRETERM BIRTH

Twin pregnancies are at a significantly higher risk of preterm delivery than singletons, with more than half likely to deliver before 37 weeks and 15% prior to 34 weeks[94]. 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[95,96]. The benefits of screening for those at risk of preterm labor remain controversial. Fetal fibronectin assessment has been shown to be of minimal-to-moderate predictive value for preterm birth in twins[97]. 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 in predicting birth < 34 weeks if the cervical length is found to be ≤ 20 mm at 20–24 weeks, and with a positive likelihood ratio of

9.6 in predicting birth < 28 weeks if the cervix is ≤ 25 mm at 20–24 weeks[98,99]. 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[100]. Despite this, it was felt that the benefits of preventative treatment are yet to be ascertained and that the evidence was not robust enough to justify recommendation of ultrasound screening[26]; therefore, the use of routine cervical-length measurements is still under debate.

Cervical cerclage for prevention of preterm birth in twin pregnancy with a short cervix has received conflicting evidence, as it was originally believed to be associated with a significantly increased risk of preterm birth[101]. Some studies have shown a potential benefit of emergency cerclage in twin pregnancy with a short or open cervix, with an increased interval to delivery of 71–92 days[102–104], although these studies were largely observational. Until 2020, the only RCT of cervical cerclage for prevention of preterm birth that included twins, in addition to singletons, involved only seven twin pregnancies[105]. A significantly decreased risk of preterm birth < 34 weeks and a longer interval from diagnosis to delivery (30 days) were found in the cerclage group compared with the bed rest-only group, but these results were reported in the twin and singleton pregnancies combined[105]. This potential benefit of emergency cerclage in twins was further supported by the findings of a recent meta-analysis[106]. However, critics demonstrated that the results derived from the RCTs showed that cerclage was in fact associated with an increased risk of preterm birth and poor perinatal outcome in those with a short cervix[107]. 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 multicenter, open-label RCT, inclusive of twin pregnancies at 16–26 weeks with symptomatic open cervix, randomized to cerclage or conservative management (https://clinicaltrials.gov/ct2/show/NCT03818867). In 2020, a multicenter, parallel group, open-label, RCT of women with twin pregnancy and asymptomatic cervical dilation of 1–5 cm at 16 + 0 to 23 + 6 weeks, found that a combination of physical examination-indicated cerclage, indomethacin and antibiotics reduced the risk of preterm birth (50% reduction in extreme preterm birth < 28 weeks) as well as perinatal mortality (78% reduction)[108]. Despite this promising result, some argued that this trial does not provide a 'screening-and-prevention' approach. Recent evidence from a double-blind placebo-controlled RCT demonstrates that cervical-length assessment at 11–14 weeks' gestation, and administration of vaginal progesterone at a dose of 600 mg per day to those with a short cervix (< 30 mm), may reduce the risk of spontaneous preterm birth < 32 weeks[109]. It is important to highlight that this was a *post-hoc* analysis and universal treatment with vaginal progesterone did not reduce the incidence of spontaneous preterm birth. Therefore, a trial is needed to investigate whether routine cervical-length assessment in the first trimester, combined with administration of vaginal progesterone to those with a short cervix, could reduce the risk of preterm birth in twin pregnancies.

The management of preterm labor in twins poses a further challenge to clinicians. Preterm prelabor rupture of membranes (PPROM) in one twin can predispose to chorioamnionitis, but early delivery could also jeopardize the wellbeing of the other twin, exposing them to iatrogenic preterm delivery. A systematic review of 128 twin pregnancies in which one twin underwent preterm delivery and the second twin was managed conservatively with delayed-interval delivery showed that the rate of mortality of the second twin was significantly lower than that in the first (relative risk, 0.44; 95% CI, 0.34–0.57; $P < 0.001$)[110]. The same review, however, found that 28 out of 90 women developed chorioamnionitis. Outcome can also differ depending on which twin is exposed to PPROM, with a longer latency period (41.3 *vs* 10.1 days from PPROM to delivery; $P < 0.05$) and fewer NNDs (0% *vs* 21.4%; $P = 0.05$) if PPROM occurred in the non-presenting compared with the presenting twin[111]. Therefore, conservative management following preterm delivery of Twin 1 can be considered in a carefully selected population in order to improve the outcome for Twin 2.

Fetal monitoring in labor in preterm twins should be performed in the form of continuous cardiotocography (CTG) from 26 weeks, with an ultrasound scan to locate the separate fetal hearts prior to monitoring[26]. Pregnancies at a lower gestational age may be more difficult to monitor through CTG surveillance; therefore, a discussion should take place between a senior obstetrician and the family regarding the mode and frequency of monitoring[26].

Mode of delivery in preterm twins (24–33 weeks) and their outcome were analyzed by the Canadian Neonatal Network in 3318 sets of twins. Cesarean section (CS) was found to be associated with a lower rate of severe neurological injury (adjusted OR, 0.77; 95% CI, 0.61–0.98), but a higher rate of respiratory distress syndrome (RDS) (adjusted OR, 1.34; 95% CI, 1.15–1.56)[112]. This is also supported by an earlier study of 4428 sets of twins weighing 500 g or more, which found that the rates of neonatal mortality and low Apgar score were lower in babies weighing 500–749 g who were delivered by CS compared with those delivered vaginally ($P < 0.05$), while this protective benefit was not observed in babies weighing > 1000 g[113]. Furthermore, a systematic review found that preterm breech babies had a significantly lower mortality rate if CS, compared with vaginal delivery, was performed (3.8% *vs* 11.5%)[114]. Therefore, it has been recommended that preterm twin pregnancies laboring between 26 and 32 weeks with a non-cephalic presenting twin should be offered CS[26].

TIMING OF BIRTH IN UNCOMPLICATED TWIN PREGNANCY

Twin pregnancies are dated according to the crown–rump length (CRL) measurement in the larger twin at the 11 + 0 to 13 + 6-week scan[11]. Some studies suggested that the CRL of the smaller twin may be more accurate[115] 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[116], in which the IUD risk at 36–37 weeks already equates to that of postmature singletons[117], and significantly increases at 38–39 weeks[118]. According to a recent meta-analysis, if delivered at 36 weeks, the risk of NND was higher than the risk of IUD (3.2:1000 *vs* 1.5:1000), whereas this becomes inversed from 37 weeks, when the risk of IUD overtakes that of NND (3.4:1000 *vs* 2.2:1000)[119], leading to the common practice of delivering DC twins from 37 weeks[26].

In MCDA twins, the risk of IUD is significantly higher than that of DC twins (19.1:1000 *vs* 6.5:1000 after 26 weeks)[120], largely due to MC-specific complications. This risk begins to increase from 32 weeks, and further still from 36 weeks[116], when the risk of composite neonatal morbidity is observed to fall[121]. It was also found that, at 35 weeks, the risk of NND was significantly higher than the risk of IUD (8.1:1000 *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 (9.6:1000 *vs* 3.6:1000)[119]. Therefore, it is commonly recommended that MCDA twins are delivered between 36 and 37 weeks[26]. The timing of birth in MCMA twins is covered in an earlier section of this Review.

ROLE OF CORTICOSTEROIDS

Numerous RCTs in singleton pregnancies have shown that a course of maternal antenatal corticosteroids can reduce the rates of perinatal death, RDS, intraventricular hemorrhage and necrotizing enterocolitis in those with preterm birth before 34 weeks[122], and routine use of corticosteroids is recommended in these cases[123,124]. According a Cochrane database review, previously reported maternal adverse effects, such as chorioamnionitis and endometritis, were not shown to be increased by corticosteroids, and factors such as neurodevelopmental delay and birth weight were also not influenced[122]. However, there remains a risk of maternal hyperglycemia, particularly in those mothers with diabetes, resulting in neonatal hypoglycemia[125].

Twelve studies in the Cochrane review included twins, the findings of which did not suggest a significant difference in the benefit of corticosteroids compared with that in singletons, but only four of these studies reported outcome in twins separately, and all were outdated[122]. Nevertheless, some guidelines recommend the use of corticosteroids in twin pregnancies laboring before 34 weeks, as similar benefits were demonstrated[124,126]. More recent studies have since compared the effects of corticosteroids between twins and singletons, with conflicting findings. A large cohort study found that twins showed a similar reduction in short-term respiratory morbidity, NND and neurological injury compared with singletons when corticosteroids were given 1–7 days before birth, but no reduction in other morbidities[127]. This reduction in respiratory morbidity was supported by the findings of a more recent study[128], but was contradicted by others in which no such improvement in short-term morbidity was observed, but with a possible reduction in neonatal mortality[129,130]. A proposed explanation for the questionable benefit of corticosteroids in twins may be due to the shorter half-life of betamethasone observed in mothers of twins compared with mothers of singletons (7.2 ± 2.4 h *vs* 9.0 ± 2.7 h; $P = 0.017$)[131].

More recently, evidence has also shown that, in singletons, corticosteroids at term (≥ 37 weeks) can reduce the risk of RDS, transient tachypnea of the neonate and neonatal unit admission in those undergoing planned CS[132,133]. Data on the benefit of corticosteroids in twins at this later gestational age, however, are scarce, and the use of corticosteroids at or near term therefore 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 corticosteroids *vs* placebo in twins with late preterm labor at 34 + 0 to 36 + 5 weeks (https://www.clinicaltrials.gov/ct2/show/NCT03547791)[134].

MODE OF DELIVERY

The mode of delivery in twins has been open to numerous controversies in the literature. Whilst older studies did not show any significant association of birth order and mode of delivery with perinatal death, Smith *et al.* demonstrated in a large retrospective cohort study that the second twin is in fact at a significantly higher risk of perinatal death than the first twin when delivered vaginally (OR, 1.16; 95% CI, 1.01–1.35; $P = 0.04$), whereas pregnancies that underwent CS did not have any delivery-related deaths[135]. The same authors went on to analyze the outcomes of a larger cohort of term twins > 36 weeks ($n = 8073$), and found that those delivered by planned CS had a significantly lower rate of death than those delivered by other modes (OR, 0.26; 95% CI, 0.03–1.03; $P = 0.05$)[136]. 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)[136]. The Twin Birth Study randomized 2804 women at 32 + 0 to 38 + 6 weeks with a cephalic presenting twin to vaginal delivery or CS. No significant difference was found in the rate of neonatal mortality or serious morbidity between the planned CS and planned vaginal delivery groups (2.2% *vs* 1.9%; OR, 1.16; 95% CI, 0.77–1.74; $P = 0.49$). They did, however, find that 43.8% of those in whom vaginal delivery was planned went on to deliver by CS[137]. The mode of birth in very preterm twins is covered in an earlier part of this Review.

The findings of the Twin Birth Study led to an update of the NICE guidelines for twin and triplet pregnancies, recommending that women should be informed that both vaginal delivery and CS are safe, provided that they have uncomplicated pregnancy, the presenting twin is cephalic and there are no large size discrepancies or other contraindications for labor[26].

CORE OUTCOMES

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 standardized fashion[138]. 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[139]. 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 in this area. This was performed using a three-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 and fetal, neonatal and maternal outcomes[140]. Similarly, in a systematic review of 39 studies on sFGR, 96 different outcomes were found, and the same group therefore felt that it was important to standardize 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 final set of 11 core outcomes to aid with future research reporting[141].

TWINS AND MULTIPLES PRIORITY SETTING PARTNERSHIP

The numerous controversies and research needs in twin and multiple pregnancies 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 to thereby improve the health and social outcomes for multiples and their families. Following the James Lind Alliance method[142], a steering group of 32 experts from various cultural and professional backgrounds designed an online survey asking participants for their top three unanswered research questions in this field[143]. It 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 five categories, 235 quantitative and 455 qualitative questions remained. Focusing on the quantitative questions, a guideline and literature search was performed, and 89 remained unanswered by robust evidence. It was decided that the qualitative questions would be analyzed at a later stage. A second survey of the 89 unanswered questions was redistributed for the participants to select the top three from each category. The shortlisted questions were taken to the final workshop, consisting of 23 participants (clinicians, researchers and patients), and the top 10 research priorities were chosen (Table S1)[143].

CONCLUSIONS

Twin pregnancies pose a multitude of challenges and controversies, as outlined in this Review. Many issues on classification and management remain under debate. Efforts in standardizing diagnostic criteria and outcome reporting and the development of national and international practice guidelines will help in research effectiveness and clinical practice. The Global Twin and Multiples PSP has 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 is still required to resolve many of these controversies, in order to enable the most optimal care and further improve the outcome of twin pregnancy.

REFERENCES

1. Blondel B, Kaminski M. Trends in the occurrence, determinants, and consequences of multiple births. *Semin Perinatol* 2002; **26**: 239–249.
2. Khalil A. The rate of twin births is declining. *Ultrasound Obstet Gynecol* 2021. DOI: 10.1002/uog.23620.
3. Ortibus E, Lopriore E, Deprest J, Vandenbussche FP, Walther FJ, Diemert A, Hecher K, Lagae L, De Cock P, Lew PJ, Lewi L. The pregnancy and long-term neurodevelopmental outcome of monochorionic diamniotic twin gestations: a multicenter prospective cohort study from the first trimester onward. *Am J Obstet Gynecol* 2009; **200**: 494.e1–8.
4. Russo FM, Pozzi E, Pelizzoni F, Todyrenchuk L, Bernasconi DP, Cozzolino S, Vergani P. Stillbirths in singletons, dichorionic and monochorionic twins: A comparison of risks and causes. *Eur J Obstet Gynecol Reprod Biol* 2013; **170**: 131–136.
5. Danon D, Sekar R, Hack KEA, Fisk NM. Increased stillbirth in uncomplicated monochorionic twin pregnancies: A Systematic Review and Meta-Analysis. *Obstet Gynecol* 2013; **121**: 1318–1326.
6. Peter C, Wenzlaff P, Kruempelmann J, Alzen G, Bueltmann E, Gruessner SE. Perinatal morbidity and early neonatal mortality in twin pregnancies. *Open J Obstet Gynecol* 2013; **3**: 78–89.
7. Luke B, Brown MB. Contemporary risks of maternal morbidity and adverse outcomes with increasing maternal age and plurality. *Fertil Steril* 2007; **88**: 283–293.
8. Elliott JP, Istwan NB, Collins A, Rhea D, Stanziano G. Indicated and non-indicated preterm delivery in twin gestations: Impact on neonatal outcome and cost. *J Perinatol* 2005; **25**: 4–7.
9. Khalil A, Reed K. Confidential Enquiry into Stillbirth and Neonatal Death in Twins: key messages for obstetricians and fetal medicine specialists. *Ultrasound Obstet Gynecol* 2021. DOI: 10.1002/uog.23594.
10. National Collaborating Centre for Women's and Children's Health (UK). Multiple pregnancy. The management of twin and triplet pregnancies in the antenatal period. NICE clinical guideline 129. London: RCOG Press; 2011.
11. Khalil A, Rodgers M, Baschat A, Bhide A, Gratacos E, Hecher K, Kilby MD, Lewi L, Nicolaides KH, Oepkes D, Raine-Fenning N, Reed K, Salomon LJ, Sotiriadis A, Thilaganathan B, Ville Y. ISUOG Practice Guidelines: role of ultrasound in twin pregnancy. *Ultrasound Obstet Gynecol* 2016; **47**: 247–263.
12. Public Health England. NHS Fetal Anomaly Screening Programme: Down's Syndrome, Edwards' Syndrome and Patau's Syndrome Screening Handbook for Laboratories. Public Health England, London, 2018. https://www.gov.uk/government/publications/fetal-anomaly-screening-laboratory-handbook-downs-edwards-and-pataus-syndromes/fetal-anomaly-screening-laboratory-handbook.
13. Prats P, Rodríguez I, Comas C, Puerto B. Systematic review of screening for trisomy 21 in twin pregnancies in first trimester combining nuchal translucency and biochemical markers: A meta-analysis. *Prenat Diagn* 2014; **34**: 1077–1083.
14. Gil MM, Accurti V, Santacruz B, Plana MN, Nicolaides KH. Analysis of cell-free DNA in maternal blood in screening for aneuploidies: updated meta-analysis. *Ultrasound Obstet Gynecol* 2017; **50**: 302–314.
15. Bevilacqua E, Gil MM, Nicolaides KH, Ordonez E, Cirigliano V, Dierickx H, Willems PJ, Jani JC. Performance of screening for aneuploidies by cell-free DNA analysis of maternal blood in twin pregnancies. *Ultrasound Obstet Gynecol* 2015; **45**: 61–66.
16. Sarno L, Revello R, Hanson E, Akolekar R, Nicolaides KH. Prospective first-trimester screening for trisomies by cell-free DNA testing of maternal blood in twin pregnancy. *Ultrasound Obstet Gynecol* 2016; **47**: 705–711.
17. Galeva S, Gil MM, Konstantinidou L, Akolekar R, Nicolaides KH. First-trimester screening for trisomies by cfDNA testing of maternal blood in singleton and twin pregnancies: factors affecting test failure. *Ultrasound Obstet Gynecol* 2019; **53**: 804–809.
18. Le Conte G, Letourneau A, Jani J, Kleinfinger P, Lohmann L, Costa J-M, Benachi A. Cell-free fetal DNA analysis in maternal plasma as screening test for trisomies 21, 18 and 13 in twin pregnancy. *Ultrasound Obstet Gynecol* 2018; **52**: 318–324.
19. Grömminger S, Yagmur E, Erkan S, Nagy S, Schöck U, Bonnet J, Smerdka P, Ehrich M, Wegner RD, Hofmann W, Stumm M. Fetal Aneuploidy Detection by Cell-Free DNA Sequencing for Multiple Pregnancies and Quality Issues with Vanishing Twins. *J Clin Med* 2014; **3**: 679–692.

20. Curnow KJ, Wilkins-Haug L, Ryan A, Kirkizlar E, Stosic M, Hall MP, Sigurjonsson S, Demko Z, Rabinowitz M, Gross SJ. Detection of triploid, molar, and vanishing twin pregnancies by a single-nucleotide polymorphism-based noninvasive prenatal test. *Am J Obstet Gynecol* 2015; **212**: 79.e1–9.
21. Khalil A, Archer R, Hutchinson V, Mousa HA, Johnstone ED, Cameron MJ, Cohen KE, Ioannou C, Kelly B, Reed K, Hulme R, Papageorghiou AT. Non-invasive prenatal screening in twin pregnancies with cell-free DNA using the IONA test: a prospective multicenter study. *Am J Obstet Gynecol* 2021. DOI: 10.1016/j.ajog .2021.01.005.
22. Judah H, Gil M, Syngelaki A, Galeva S, Jani J, Akolekar R, Nicolaides KH. Cell-free DNA testing of maternal blood in screening for trisomies in twin pregnancy: cohort study at 10–14 weeks and updated meta-analysis. *Ultrasound Obstet Gynecol* 2021 DOI: 10.1002/uog.23648.
23. Di Mascio D, Khalil A, Rizzo G, Buca D, Liberati M, Martellucci CA, Flacco ME, Manzoli L, D'Antonio F. Risk of fetal loss following amniocentesis or chorionic villus sampling in twin pregnancy: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2020; **56**: 647–655.
24. Gielen M, Lindsey PJ, Derom C, Loos RJF, Souren NY, Paulussen ADC, Zeegers MP, Derom R, Vlietinck R, Nijhuis JG. Twin-specific intrauterine "growth" charts based on cross-sectional birthweight data. *Twin Res Hum Genet* 2008; **11**: 224–235.
25. Morin L, Lim K, DIAGNOSTIC IMAGING COMMITTEE; SPECIAL CONTRIBUTOR; GENETICS COMMITTEE; MATERNAL FETAL MEDICINE COMMITTEE. Ultrasound in Twin Pregnancies. *J Obstet Gynaecol Canada* 2011; **33**: 643–656.
26. National Guideline Alliance (UK). Twin and triplet pregnancy. NICE clinical guideline 137. London: National Institute for Health and Care Excellence (UK); 2019.
27. Stirrup OT, Khalil A, D'Antonio F, Thilaganathan B. Fetal growth reference ranges in twin pregnancy: analysis of the Southwest Thames Obstetric Research Collaborative (STORK) multiple pregnancy cohort. *Ultrasound Obstet Gynecol* 2015; **45**: 301–307.
28. Briffa C, Stirrup O, Huddy C, Richards J, Shetty S, Reed K, Khalil A. Twin chorionicity-specific population birth-weight charts developed with adjustment for estimated fetal weight. *Ultrasound Obstet Gynecol* 2021. DOI: 10.1002/uog.23606.
29. Hamilton EF, Platt RW, Morin L, Usher R, Kramer M. How small is too small in a twin pregnancy? *Am J Obstet Gynecol* 1998; **179**: 682–685.
30. Kalafat E, Sebghati M, Thilaganathan B, Khalil A; Southwest Thames Obstetric Research Collaborative (STORK). Predictive accuracy of Southwest Thames Obstetric Research Collaborative (STORK) chorionicity-specific twin growth charts for stillbirth: a validation study. *Ultrasound Obstet Gynecol* 2019; **53**: 193–199.
31. Giorgione V, Briffa C, De Fabrizio C, Bhate R, Khalil A. Perinatal Outcomes of Small for Gestational Age in Twin Pregnancies: Twin vs. Singleton Charts. *J Clin Med* 2021; **10**: 643.
32. Royal College of Obstetricians and Gynaecologists. Management of Monochorionic Twin Pregnancy: Green-top Guideline No. 51. *BJOG* 2017; **124**: e1–45.
33. Stirrup OT, Khalil A, D'Antonio F, Thilaganathan B, STORK. Patterns of Second- and Third-Trimester Growth and Discordance in Twin Pregnancy: Analysis of the Southwest Thames Obstetric Research Collaborative (STORK) Multiple Pregnancy Cohort. *Fetal Diagn Ther* 2017; **41**: 100–107.
34. D'Antonio F, Khalil A, Dias T, Thilaganathan B. Weight Discordance And Perinatal Mortality In Twins: The Stork Multiple Pregnancy Cohort. *Ultrasound Obstet Gynecol* 2013; **41**: 643–648.
35. D'Antonio F, Odibo AO, Prefumo F, Khalil A, Buca D, Flacco ME, Liberati M, Manzoli L, Acharya G. Weight discordance and perinatal mortality in twin pregnancy: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2018; **52**: 11–23.
36. D'Antonio F, Khalil A, Morlando M, Thilaganathan B. Accuracy of predicting fetal loss in twin pregnancies using gestational age-dependent weight discordance cut-offs: Analysis of the STORK multiple pregnancy cohort. *Fetal Diagn Ther* 2015; **38**: 22–28.
37. Hillman SC, Morris RK, Kilby MD. Co-twin prognosis after single fetal death: A systematic review and meta-analysis. *Obstet Gynecol* 2011; **118**: 928–940.
38. Khalil A, Beune I, Hecher K, Wynia K, Ganzevoort W, Reed K, Lewi L, Oepkes D, Gratacos E, Thilaganathan B, Gordijn SJ. Consensus definition and essential reporting parameters of selective fetal growth restriction in twin pregnancy: a Delphi procedure. *Ultrasound Obstet Gynecol* 2019; **53**: 47–54.
39. Curado J, Sileo F, Bhide A, Thilaganathan B, Khalil A. Early and late selective fetal growth restriction in monochorionic diamniotic twin pregnancies: natural history and diagnostic criteria. *Ultrasound Obstet Gynecol* 2019; **55**: 661–666.
40. Khalil A, Thilaganathan B. Selective fetal growth restriction in monochorionic twin pregnancy: a dilemma for clinicians and a challenge for researchers. *Ultrasound Obstet Gynecol* 2019; **53**: 23–25.
41. Couck I, Ponnet S, Deprest J, Devlieger R, De Catte L, Lewi L. Outcome of monochorionic twin pregnancy with selective fetal growth restriction at 16, 20 or 30 weeks according to new Delphi consensus definition. *Ultrasound Obstet Gynecol* 2020; **56**: 821–830.
42. Gratacós E, Lewi L, Muñoz B, Acosta-Rojas R, Hernandez-Andrade E, Martinez JM, Carreras E, Deprest J. A classification system for selective intrauterine growth restriction in monochorionic pregnancies according to umbilical artery Doppler flow in the smaller twin. *Ultrasound Obstet Gynecol* 2007; **30**: 28–34.
43. Rustico MA, Consonni D, Lanna M, Faiola S, Schena V, Scelsa B, Introvini P, Righini A, Parazzini C, Lista G, Barretta F, Ferrazzi E. Selective intrauterine growth restriction in monochorionic twins: changing patterns in umbilical artery Doppler flow and outcomes. *Ultrasound Obstet Gynecol* 2017; **49**: 387–393.
44. Townsend R, Khalil A. Twin pregnancy complicated by selective growth restriction. *Curr Opin Obstet Gynecol* 2016; **28**: 485–491.
45. Townsend R, Khalil A. Fetal growth restriction in twins. *Best Pract Res Clin Obstet Gynaecol* 2018; **49**: 79–88.
46. Townsend R, D'Antonio F, Sileo FG, Kumbay H, Thilaganathan B, Khalil A. Perinatal outcome of monochorionic twin pregnancy complicated by selective fetal growth restriction according to management: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2019; **53**: 36–46.
47. Peeva G, Bower S, Orosz L, Chaveeva P, Akolekar R, Nicolaides KH. Endoscopic Placental Laser Coagulation in Monochorionic Diamniotic Twins With Type II Selective Fetal Growth Restriction. *Fetal Diagn Ther* 2015; **38**: 86–93.
48. Monaghan C, Kalafat E, Binder J, Thilaganathan B, Khalil A. Prediction of adverse pregnancy outcome in monochorionic diamniotic twin pregnancy complicated by selective fetal growth restriction. *Ultrasound Obstet Gynecol* 2019; **53**: 200–207.
49. Dekoninck P, Deprest J, Lewi P, Richter J, Galijaard S, Van Keirsbilck J, Van Calsteren K, Lewi L. Gestational age-specific reference ranges for amniotic fluid assessment in monochorionic diamniotic twin pregnancies. *Ultrasound Obstet Gynecol* 2013; **41**: 649–652.
50. Khalil A. Modified diagnostic criteria for twin-to-twin transfusion syndrome prior to 18 weeks' gestation: time to change? *Ultrasound Obstet Gynecol* 2017; **49**: 804–805.
51. Fratelli N, Prefumo F, Fichera A, Valcamonico A, Marella D, Frusca T. Nuchal translucency thickness and crown rump length discordance for the prediction of outcome in monochorionic diamniotic pregnancies. *Early Hum Dev* 2011; **87**: 27–30.
52. Allaf MB, Vintzileos AM, Chavez MR, Wax JA, Ravangard SF, Figueroa R, Borgida A, Shamshirsaz A, Markenson G, Davis S, Habenicht R, Haeri S, Ozhand A, Johnson J, Sangi-Haghpeykar H, Spiel M, Ruano R, Meyer M, Belfort MA, Ogburn P, Campbell WA, Shamshirsaz AA. First-Trimester Sonographic Prediction of Obstetric and Neonatal Outcomes in Monochorionic Diamniotic Twin Pregnancies. *J Ultrasound Med* 2014; **33**: 135–140.
53. Mackie FL, Hall MJ, Morris RK, Kilby MD. Early prognostic factors of outcomes in monochorionic twin pregnancy: systematic review and meta-analysis. *Am J Obstet Gynecol*. 2018; **219**: 436–446.
54. Huber A, Diehl W, Zikulnig L, Bregenzer T, Hackelöer BJ, Hecher K. Perinatal outcome in monochorionic twin pregnancies complicated by amniotic fluid discordance without severe twin–twin transfusion syndrome. *Ultrasound Obstet Gynecol* 2006; **27**: 48–52.
55. Van Mieghem T, Eixarch E, Gucciardo L, Done E, Gonzales I, Van Schoubroeck D, Lewi L, Gratacos E, Deprest J. Outcome prediction in monochorionic diamniotic twin pregnancies with moderately discordant amniotic fluid. *Ultrasound Obstet Gynecol* 2011; **37**: 15–21.
56. Roberts D, Neilson JP, Kilby MD, Gates S. Interventions for the treatment of twin–twin transfusion syndrome. *Cochrane Database Syst Rev* 2014; **1**: CD002073.
57. Baud D, Windrim R, Keunen J, Kelly EN, Shah P, Van Mieghem T, Seaward PGR, Ryan G. Fetoscopic laser therapy for twin–twin transfusion syndrome before 17 and after 26 weeks' gestation. *Am J Obstet Gynecol* 2013; **208**: 197.e1–7.
58. Khalil A, Cooper E, Townsend R, Thilaganathan B. Evolution of Stage 1 Twin-to-Twin Transfusion Syndrome (TTTS): Systematic Review and Meta-Analysis. *Twin Res Hum Genet* 2016; **19**: 207–216.
59. Emery SP, Hasley SK, Catov JM, Miller RS, Moon-Grady AJ, Baschat AA, Johnson A, Lim FY, Gagnon AL, O'Shaughnessy RW, Ozcan T, Luks FI, North American Fetal Therapy Network. North American Fetal Therapy Network: intervention vs expectant management for stage I twin–twin transfusion syndrome. *Am J Obstet Gynecol* 2016; **215**: 346.e1–7.
60. Stirnemann J, Slaghekke F, Khalek N, Winer N, Johnson A, Lewi L, Massoud M, Bussieres L, Aegerter P, Hecher K, Senat MV, Ville Y. Intrauterine fetoscopic laser surgery versus expectant management in stage 1 twin-to-twin transfusion syndrome: an international randomized trial. *Am J Obstet Gynecol* 2020. DOI: 10.1016/j.ajog .2020.11.031.
61. Stirnemann JJ, Quibel T, Essaoui M, Salomon LJ, Bussieres L, Ville Y. Timing of delivery following selective laser photocoagulation for twin-to-twin transfusion syndrome. *Am J Obstet Gynecol* 2012; **207**: 127.e1–6.
62. Tollenaar LSA, Lopriore E, Middeldorp JM, Haak MC, Klumper FJ, Oepkes D, Slaghekke. Improved prediction of twin anemia–polycythemia sequence by delta middle cerebral artery peak systolic velocity: new antenatal classification system. *Ultrasound Obstet Gynecol* 2019; **53**: 788–793.
63. Fishel-Bartal M, Weisz B, Mazaki-Tovi S, Ashwal E, Chayen B, Lipitz S, Yinon Y. Can middle cerebral artery peak systolic velocity predict polycythemia in monochorionic-diamniotic twins? Evidence from a prospective cohort study. *Ultrasound Obstet Gynecol* 2016; **48**: 470–475.
64. Tavares de Sousa M, Fonseca A, Hecher K. Role of fetal intertwin difference in middle cerebral artery peak systolic velocity in predicting neonatal twin anemia–polycythemia sequence. *Ultrasound Obstet Gynecol* 2019; **53**: 794–797.
65. Khalil A, Gordijn S, Ganzevoort W, Thilaganathan B, Johnson A, Baschat A, Hecher K, Reed K, Lewi L, Deprest J, Oepkes D, Lopriore E. Consensus diagnostic criteria and monitoring of twin anemia–polycythemia sequence: a Delphi procedure. *Ultrasound Obstet Gynecol* 2019; **56**: 388–394.
66. Slaghekke F, van Klink JMM, Koopman HM, Middeldorp JM, Oepkes D, Lopriore E. Neurodevelopmental outcome in twin anemia–polycythemia sequence after laser surgery for twin–twin transfusion syndrome. *Ultrasound Obstet Gynecol* 2014; **44**: 316–321.
67. Tollenaar LSA, Lopriore E, Slaghekke F, Oepkes D, Middeldorp JM, Haak MC, Klumper FJCM, Tan RNGB, Rijken M, Van Klink JMM. High risk of long-term neurodevelopmental impairment in donor twins with spontaneous twin anemia–polycythemia sequence. *Ultrasound Obstet Gynecol* 2020; **55**: 39–46.
68. Lewi L, Valencia C, Gonzalez E, Deprest J, Nicolaides KH. The outcome of twin reversed arterial perfusion sequence diagnosed in the first trimester. *Am J Obstet Gynecol* 2010; **203**: 213.e1–4.
69. Moore TR, Gale S, Benirschke K. Perinatal outcome of forty-nine pregnancies complicated by acardiac twinning. *Am J Obstet Gynecol* 1990; **163**: 907–912.
70. Tan TYT, Sepulveda W. Acardiac twin: a systematic review of minimally invasive treatment modalities. *Ultrasound Obstet Gynecol* 2003; **22**: 409–419.
71. Pagani G, D'Antonio F, Khalil A, Papageorghiou A, Bhide A, Thilaganathan B. Intrafetal laser treatment for twin reversed arterial perfusion sequence: cohort study and meta-analysis. *Ultrasound Obstet Gynecol* 2013; **42**: 6–14.

72. Chaveeva P, Poon LC, Sotiriadis A, Kosinski P, Nicolaides KH. Optimal method and timing of intrauterine intervention in twin reversed arterial perfusion sequence: Case study and meta-analysis. *Fetal Diagn Ther* 2014; **35**: 267–279.
73. Prefumo F, Fichera A, Pagani G, Marella D, Valcamonico A, Frusca T. The natural history of monoamniotic twin pregnancies: A case series and systematic review of the literature. *Prenat Diagn* 2015; **35**: 274–280.
74. Dias T, Mahsud-Dornan S, Bhide A, Papageorghiou AT, Thilaganathan B. Cord entanglement and perinatal outcome in monoamniotic twin pregnancies. *Ultrasound Obstet Gynecol* 2010; **35**: 201–204.
75. Rossi AC, Prefumo F. Impact of cord entanglement on perinatal outcome of monoamniotic twins: a systematic review of the literature. *Ultrasound Obstet Gynecol* 2013; **41**: 131–135.
76. Shub A, Walker SP. Planned early delivery versus expectant management for monoamniotic twins. *Cochrane Database Syst Rev* 2015; **4**: CD008820.
77. D'Antonio F, Odibo A, Berghella V, Khalil A, Hack K, Saccone G, Prefumo F, Buca D, Liberati M, Pagani G, Acharya G. Perinatal mortality, timing of delivery and prenatal management of monoamniotic twin pregnancy: systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2019; **53**: 166–174.
78. The MONOMONO Working Group. Inpatient *vs* outpatient management and timing of delivery of uncomplicated monochorionic monoamniotic twin pregnancy: the MONOMONO study. *Ultrasound Obstet Gynecol* 2019; **53**:175–183.
79. Van Mieghem T, De Heus R, Lewi L, Klaritsch P, Kollmann M, Baud D, Vial Y, Shah PS, Ranzini AC, Mason L, Raio L, Lachat R, Barrett J, Khorsand V, Windrim R, Ryan G. Prenatal management of monoamniotic twin pregnancies. *Obstet Gynecol* 2014; **124**: 498–506.
80. Rolnik DL, Wright D, Poon LCY, Syngelaki A, O'Gorman N, de Paco Matallana C, Akolekar R, Cicero S, Janga D, Singh M, Molina FS, Persico N, Jani JC, Plasencia W, Papaioannou G, Tenenbaum-Gavish K, Nicolaides KH. ASPRE trial: performance of screening for preterm pre-eclampsia. *Ultrasound Obstet Gynecol* 2017; **50**: 492–495.
81. Francisco C, Wright D, Benkő Z, Syngelaki A, Nicolaides KH. Competing-risks model in screening for pre-eclampsia in twin pregnancy by maternal characteristics and medical history. *Ultrasound Obstet Gynecol* 2017; **50**: 501–506.
82. Francisco C, Wright D, Benkő Z, Syngelaki A, Nicolaides KH. Competing-risks model in screening for pre-eclampsia in twin pregnancy according to maternal factors and biomarkers at 11–13 weeks' gestation. *Ultrasound Obstet Gynecol* 2017; **50**: 589–595.
83. National Institute for Health and Care Excellence. Hypertension in pregnancy: diagnosis and management. *NICE guideline* **133**, 2019. https://www.nice.org.uk/guidance/ng133.
84. Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. *Lancet* 2007; **369**: 1791–1798.
85. Kalafat E, Shirazi A, Thilaganathan B, Khalil A. The role of aspirin in prevention of preeclampsia in twin pregnancies: Does the dose matter? *Am J Obstet Gynecol* 2020; **223**: 457–458.
86. Cimpoca B, Syngelaki A, Chi Mu A, Savvoulidou E, Nicolaides KH. Twin pregnancy with two live fetuses at 11–13 weeks: effect of one fetal death on pregnancy outcome. *Ultrasound Obstet Gynecol* 2019; **55**: 482–488.
87. Senat MV, Loizeau S, Couderc S, Bernard JP, Ville Y. The value of middle cerebral artery peak systolic velocity in the diagnosis of fetal anemia after intrauterine death of one monochorionic twin. *Am J Obstet Gynecol* 2003; **189**: 1320–1324.
88. Gul A, Cebeci A, Aslan H, Polat I, Sozen I, Ceylan Y. Perinatal outcomes of twin pregnancies discordant for major fetal anomalies. *Fetal Diagn Ther* 2005; **20**: 244–248.
89. Evans MI, Goldberg JD, Horenstein J, Wapner RJ, Ayoub MA, Stone J, Lipitz S, Achiron R, Holzgreve W, Brambati B, Johnson A, Johnson MP, Shalhoub A, Berkowitz RL. Selective termination for structural, chromosomal, and mendelian anomalies: international experience. *Am J Obstet Gynecol* 1999; **181**: 893–897.
90. Rossi AC, D'Addario V. Umbilical cord occlusion for selective feticide in complicated monochorionic twins: a systematic review of literature. *Am J Obstet Gynecol* 2009; **200**: 123–129.
91. Roman A, Papanna R, Johnson A, Hassan SS, Moldenhauer J, Molina S, Moise KJ Jr. Selective reduction in complicated monochorionic pregnancies: radiofrequency ablation *vs* bipolar cord coagulation. *Ultrasound Obstet Gynecol* 2010; **36**: 37–41.
92. Lewi L, Gratacos E, Ortibus E, Van Schoubroeck D, Carreras E, Higueras T, Perapoch J, Deprest J. Pregnancy and infant outcome of 80 consecutive cord coagulations in complicated monochorionic multiple pregnancies. *Am J Obstet Gynecol* 2006; **194**: 782–789.
93. Corroenne R, Al Ibrahim A, Stirnemann J, Hassan Zayed L, Essaoui M, Russell NE, Chalouhi GE, Salomon LJ, Ville Y. Management of monochorionic twins discordant for structural fetal anomalies. *Prenat Diagn* 2020; **40**: 1375–1382.
94. Visintin C, Mugglestone MA, James D, Kilby MD. Antenatal care for twin and triplet pregnancies: Summary of NICE guidance. *BMJ* 2011; **343**: d5714.
95. Roman AS, Saltzman DH, Fox N, Klauser CK, Istwan N, Rhea D, Rebarber A. Prophylactic cerclage in the management of twin pregnancies. *Am J Perinatol* 2013; **30**: 751–754.
96. Norman JE, Mackenzie F, Owen P, Mactier H, Hanretty K, Cooper S, Calder A, Mires G, Danielian P, Sturgiss S, MacLennan G, Tydeman G, Thornton S, Martin B, Thornton JG, Neilson JP, Norrie J. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis. *Lancet* 2009; **373**: 2034–2040.
97. Conde-Agudelo A, Romero R. Cervicovaginal fetal fibronectin for the prediction of spontaneous preterm birth in multiple pregnancies: A systematic review and meta-analysis. *J Matern Neonatal Med* 2010; **23**: 1365–1376.
98. Conde-Agudelo A, Romero R, Hassan SS, Yeo L. Transvaginal sonographic cervical length for the prediction of spontaneous preterm birth in twin pregnancies: A systematic review and metaanalysis. *Am J Obstet Gynecol* 2010; **203**: 128.e1–12.
99. Conde-Agudelo A, Romero R. Prediction of preterm birth in twin gestations using biophysical and biochemical tests. *Am J Obstet Gynecol* 2014; **211**: 583–595.
100. Romero R, Nicolaides K, Conde-Agudelo A, Tabor A, O'Brien JM, Cetingoz E, Da Fonseca E, Creasy GW, Klein K, Rode L, Soma-Pillay P, Fusey S, Cam C, Alfirevic Z, Hassan SS. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: A systematic review and metaanalysis of individual patient data. *Am J Obstet Gynecol* 2012; **206**: 124.e1–19.
101. Berghella V, Odibo AO, To MS, Rust OA, Althuisius SM. Cerclage for short cervix on ultrasonography: Meta-analysis of trials using individual patient-level data. *Obstet Gynecol* 2005; **106**: 181–189.
102. Levin I, Salzer L, Maslovitz S, Avni A, Lessing JB, Groutz A, Almog B. Outcomes of mid-trimester emergency cerclage in twin pregnancies. *Fetal Diagn Ther* 2012; **32**: 246–250.
103. Rebarber A, Bender S, Silverstein M, Saltzman DH, Klauser CK, Fox NS. Outcomes of emergency or physical examination-indicated cerclage in twin pregnancies compared to singleton pregnancies. *Eur J Obstet Gynecol Reprod Biol* 2014; **173**: 43–47.
104. Roman A, Rochelson B, Martinelli P, Saccone G, Harris K, Zork N, Spiel M, O'Brien K, Calluzzo I, Palomares K, Rosen T, Berghella V, Fleischer A. Cerclage in twin pregnancy with dilated cervix between 16 to 24 weeks of gestation: Retrospective cohort study. *Am J Obstet Gynecol* 2016; **215**: 98.e1–11.
105. Althuisius SM, Dekker GA, Hummel P, Van Geijn HP. Cervical incompetence prevention randomized cerclage trial: Emergency cerclage with bed rest versus bed rest alone. *Am J Obstet Gynecol* 2003; **189**: 907–910.
106. Li C, Shen J, Hua K. Cerclage for women with twin pregnancies: a systematic review and metaanalysis. *Am J Obstet Gynecol* 2019; **220**: 543–557.e1.
107. Sanchez-Ramos L. The placement of a cerclage in patients with twin pregnancies and a short cervix is associated with increased risk of preterm birth and adverse perinatal outcome. *Am J Obstet Gynecol* 2020; **222**: 194–196.
108. Roman A, Zork N, Haeri S, Schoen CN, Saccone G, Colihan S, Zelig C, Gimovsky AC, Seligman NS, Zullo F, Berghella V. Physical examination-indicated cerclage in twin pregnancy: a randomized controlled trial. *Am J Obstet Gynecol* 2020; **223**: 902.e1–11.
109. Rehal A, Benkő Z, De Paco Matallana C, Syngelaki A, Janga D, Cicero S, Akolekar R, Singh M, Chaveeva P, Burgos J, Molina FS, Savvidou M, De La Calle M, Persico N, Quezada Rojas MS, Sau A, Greco E, O'Gorman N, Plasencia W, Pereira S, Jani JC, Valino N, Del Mar Gil M, Maclagan K, Wright A, Wright D, Nicolaides KH. Early vaginal progesterone versus placebo in twin pregnancies for the prevention of spontaneous preterm birth: a randomized, double-blind trial. *Am J Obstet Gynecol* 2021; **224**: 86.e1–19.
110. Feys S, Jacquemyn Y. Delayed-interval delivery can save the second twin: evidence from a systematic review. *Facts, views Vis ObGyn* 2016; **8**: 223–231.
111. Mei-Dan E, Hutchison Z, Osmond M, Pakenham S, Ng E, Green J, Nevo O. Preterm Premature Rupture of Membranes in Twins: Comparison of Rupture in the Presenting Versus Non-presenting Sac. *J Obstet Gynaecol Canada* 2020; **42**: 163–168.
112. Hunter T, Shah J, Synnes A, Shivananda S, Ryan G, Shah PS, Murphy KE; on behalf of the Canadian Neonatal Network. Neonatal outcomes of preterm twins according to mode of birth and presentation. *J Matern Neonatal Med* 2018; **31**: 682–688.
113. Zhang J, Bowes WA, Grey TW, McMahon MJ. Twin delivery and neonatal and infant mortality: A population-based study. *Obstet Gynecol* 1996; **88**: 593–598.
114. Bergenhenegouwen LA, Meertens LJE, Schaaf J, Nijhuis JG, Mol BW, Kok M, Scheepers HC. Vaginal delivery versus caesarean section in preterm breech delivery: A systematic review. *Eur J Obstet Gynecol Reprod Biol* 2014; **172**: 1–6.
115. Chaudhuri K, Su LL, Wong PC, Chan YH, Choolani MA, Chia D, Biswas A. Determination of gestational age in twin pregnancy: Which fetal crown–rump length should be used? *J Obstet Gynaecol Res* 2013; **39**: 761–765.
116. Hack KEA, Derks JB, Elias SG, Franx A, Roos EJ, Voerman SK, Bode CL, Koopman-Esseboom C, Visser GHA. Increased perinatal mortality and morbidity in monochorionic versus dichorionic twin pregnancies: Clinical implications of a large Dutch cohort study. *BJOG* 2008; **115**: 58–67.
117. Kalyoncu O, Aygün C, Cetinoğlu E, Küçüködük S. Neonatal morbidity and mortality of late-preterm babies. *J Matern Fetal Neonatal Med* 2010; **23**: 607–612.
118. Kahn B, Lumey LH, Zybert PA, Lorenz JM, Cleary-Goldman J, D'Alton ME, Robinson JN. Prospective risk of fetal death in singleton, twin, and triplet gestations: implications for practice. *Obstet Gynecol* 2003; **102**: 685–692.
119. Cheong-See F, Schuit E, Arroyo-Manzano D, Khalil A, Barrett J, Joseph KS, Asztalos E, Hack K, Lewi L, Lim A, Liem S, Norman JE, Morrison J, Combs CA, Garite TJ, Maurel K, Serra V, Perales A, Rode L, Worda K, Nassar A, Aboulghar M, Rouse D, Thom E, Breathnach F, Nakayama S, Russo FM, Robinson JN, Dodd JM, Newman RB, Bhattacharya S, Tang S, Mol BWJ, Zamora J, Thilaganathan B, Thangaratinam S, Global Obstetrics Network (GONet) Collaboration. Prospective risk of stillbirth and neonatal complications in twin pregnancies: Systematic review and meta-analysis. *BMJ* 2016; **354**: i4353.
120. Southwest Thames Obstetric Research Collaborative (STORK). Prospective risk of late stillbirth in monochorionic twins: a regional cohort study. *Ultrasound Obstet Gynecol* 2012; **39**: 500–504.
121. Hack KEA, Derks JB, Elias SG, Van Mameren FA, Koopman-Esseboom C, Mol BWJ, Lopriore E, Schaap AHP, Arabin B, Duvekot JJ, Go ATJI, Wieselmann E, Eggink AJ, Willekes C, Vandenbussche FPHA, Visser GHA. Perinatal mortality and mode of delivery in monochorionic diamniotic twin pregnancies ≥ 32 weeks of gestation: A multicentre retrospective cohort study. *BJOG* 2011; **118**: 1090–1097.
122. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev* 2017; **3**: CD004454.
123. National Institute for Health and Care Excellence. Preterm labour and birth overview. *NICE guideline 25*, 2015. https://www.nice.org.uk/guidance/ng25.
124. FIGO Working Group on Good Clinical Practice in Maternal-Fetal Medicine. Good clinical practice advice: Antenatal corticosteroids for fetal lung maturation. *Int J Gynecol Obstet* 2019; **144**: 352–355.

125. Haviv HR, Said J, Mol BW. The place of antenatal corticosteroids in late preterm and early term births. *Semin Fetal Neonatal Med* 2019; **24**: 37–42.
126. American College of Obstetricians and Gynecologists' Committee on Obstetric Practice; Society for Maternal-Fetal Medicine. Antenatal Corticosteroid Therapy for Fetal Maturation. *Obstet Gynecol* 2016; **128**: e187–194.
127. Lee SK, Lee SK, Shah PS. The role of antenatal corticosteroids in twin pregnancies complicated by preterm birth. *Am J Obstet Gynecol* 2016; **215**: 482.e1–9.
128. Vaz A, Malheiro MF, Severo M, Rodrigues T, Guimarães H, Montenegro N. Effect of antenatal corticosteroids on morbidity and mortality of preterm singletons and twins. *J Matern Neonatal Med* 2018; **31**: 754–760.
129. Viteri OA, Blackwell SC, Chauhan SP, Refuerzo JS, Pedroza C, Salazar XC, Sibai BM. Antenatal Corticosteroids for the Prevention of Respiratory Distress Syndrome in Premature Twins. *Obstet Gynecol* 2016; **128**: 583–591.
130. Herrera TI, Vaz Ferreira MC, Toso A, Villarroel L, Silvera F, Ceriani-Cernadas JM, Tapia JL; Neocosur Neonatal Network. Neonatal outcomes of antenatal corticosteroids in preterm multiple pregnancies compared to singletons. *Early Hum Dev* 2019; **130**: 44–50.
131. Ballabh P, Lo ES, Kumari J, Cooper TB, Zervoudakis I, Auld PAM, Krauss AN. Pharmacokinetics of betamethasone in twin and singleton pregnancy. *Clin Pharmacol Ther* 2002; **71**: 39–45.
132. Saccone G, Berghella V. Antenatal corticosteroids for maturity of term or near term fetuses: Systematic review and meta-analysis of randomized controlled trials. *BMJ* 2016; **355**: i5044.
133. Sotiriadis A, Makrydimas G, Papatheodorou S, Ioannidis JPA, Mcgoldrick E. Corticosteroids for preventing neonatal respiratory morbidity after elective caesarean section at term. *Cochrane Database Syst Rev* 2018; **8**: CD006614.
134. Hong S, Lee SM, Kwak DW, Lee J, Kim SY, Oh JW, Oh S, Park CW, Park JS, Chung JH, Jun JK. Effects of antenatal corticosteroids in twin neonates with late preterm birth (ACTWIN [Antenatal Corticosteroids in TWIN late preterm neonates] trial): Study protocol for a randomized controlled trial. *BMC Pregnancy Childbirth* 2019; **19**: 114.
135. Smith GCS, Pell JP, Dobbie R. Birth order, gestational age, and risk of delivery related perinatal death in twins: Retrospective cohort study. *Br Med J* 2002; **325**: 1004–1006.
136. Smith GCS, Shah I, White IR, Pell JP, Dobbie R. Mode of delivery and the risk of delivery-related perinatal death among twins at term: A retrospective cohort study of 8073 births. *BJOG* 2005; **112**: 1139–1144.
137. Barrett JFR, Hannah ME, Hutton EK, Willan AR, Allen AC, Armson A, Gafni A, Joseph KS, Mason D, Ohlsson A, Ross S, Sanchez JJ, Asztalos EV; Twin Birth Study Collaborative Group. A Randomized Trial of Planned Cesarean or Vaginal Delivery for Twin Pregnancy. *N Engl J Med* 2013; **369**: 1295–1305.
138. Ioannidis JPA, Greenland S, Hlatky MA, Khoury MJ, Macleod MR, Moher D, Schulz KF, Tibshirani R. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet* 2014; **383**: 166–175.
139. Perry H, Duffy JMN, Umadia O, Khalil A. Outcome reporting across randomized trials and observational studies evaluating treatments for twin-twin transfusion syndrome: systematic review. *Ultrasound Obstet Gynecol* 2018; **52**: 577–585.
140. Perry H, Duffy JMN, Reed K, Baschat A, Deprest J, Hecher K, Lewi L, Lopriore E, Oepkes D, Khalil A, International Collaboration to Harmonise Outcomes for Twin-Twin Transfusion Syndrome (CHOOSE). Core outcome set for research studies evaluating treatments for twin–twin transfusion syndrome. *Ultrasound Obstet Gynecol* 2019; **54**: 255–261.
141. Townsend R, Duffy JMN, Sileo F, Perry H, Ganzevoort W, Reed K, Baschat AA, Deprest J, Gratacos E, Hecher K, Lewi L, Lopriore E, Oepkes D, Papageorghiou A, Gordijn SJ, Khalil A; International Collaboration to Harmonise Outcomes for Selective Fetal Growth Restriction (CHOOSE-FGR). Core outcome set for studies investigating management of selective fetal growth restriction in twins. *Ultrasound Obstet Gynecol* 2019; **55**: 652–660.
142. The James Lind Alliance. http://www.jla.nihr.ac.uk/ [Accessed 9 May 2020].
143. Lam J, Liu B, Bhate R, Fenwick N, Reed K, Duffy JMN, Khalil A GT and MPSPC. Research priorities for the future health of multiples and their families: The Global Twins and Multiples Priority Setting Partnership. *Ultrasound Obstet Gynecol* 2019; **54**: 715–721.
144. Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Moise KJ Jr, Dorman KF, Ludomirsky A, Gonzalez R, Gomez R, Oz U, Detti L, Copel JA, Bahado-Singh R, Berry S, Martinez-Poyer J, Blackwell SC. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. *N Engl J Med* 2000; **342**: 9–14.

SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figure S1 Modified classification of selective fetal growth restriction in monochorionic twin pregnancy.

Table S1 Top 10 research questions according to the Global Twins and Multiples Priority Setting Partnership[143]