sGR is encountered in approximately 10–15% of all monochorionic multiple pregnancies. The pathophysiology and natural history of this condition is different to growth discordance in dichorionic multiple pregnancy. The prospective diagnosis initially may be difficult as there may be diagnostic 'overlap' between mild TTTS and sGR. Amniotic liquor volumes (DVP) in TTTS may differ between the fetuses because of polyhydramnios in one of the amniotic sacs and oligohydramnios in the other amniotic sac (but sGR may also be present). However, in isolated sGR this will differ as there is commonly oligohydramnios in one of the amniotic sacs and normal liquor in the other amniotic sac.[53,57]

Evidence level 3

Poor in utero growth of both twins may reflect multifactorial causes, such as maternal factors resulting in global uteroplacental dysfunction, whereas discordant twin growth may be attributed to differences in genetic potential between co-twins, placental dysfunction confined to one placenta only or one placental territory within a shared placenta.[53] In addition, TTTS represents a distinct entity of which discordant growth is a common feature.[53,57]

Evidence level 2+

Discordant growth is recognised as an independent risk factor for adverse perinatal outcome in monochorionic twins and is associated with a substantial increase in perinatal mortality and morbidity for both twins.[53,58] Clinical evolution depends on the combination of the effects of placental insufficiency in the growth-restricted twin with inter-twin blood transfer through placental anastomoses.[53,57]

It appears that a calculated difference in EFW is a sensitive method of defining sGR and appears to be linked with adverse outcome when this is significantly different (see below). The ultrasonic methods used to estimate fetal weight appear to be equally accurate, but one study favoured formulas that include a combination of head, abdomen and femur measurements.[47,54,55]

A prospective study from Ireland noted that perinatal mortality, individual morbidity and composite perinatal morbidity are all seen to increase with birthweight discordance exceeding 18% for monochorionic twins without TTTS (hazard ratio 2.6, 95% CI 1.6–4.3; $P < 0.001$); a minimum two-fold increase in risk of perinatal morbidity exists even when both twin birthweights are appropriate for gestational age.[56] However, others have studied monochorionic and dichorionic twins and noted that prenatal risk does not increase until the difference in EFW is greater than 25%.[1,54]

Evidence level 2+

A 2013 review, performed by leading international researchers in this area, has advocated a compromise 'cut-off' of a difference in EFW of greater than 20% for monochorionic twins.[19] This is the pragmatic definition used by this guideline (recognising data of increasing perinatal loss at a percentage EFW difference of 18% from the Irish Consortium).

Evidence level 2++

Umbilical artery waveforms in monochorionic twins with sGR may reflect adverse prognosis for the pregnancy.[45,59] For this reason, the guideline recommends that umbilical artery Doppler pulsatility index measurements are taken from 20 weeks of gestation and plotted on gestational nomogram charts (with umbilical artery Doppler velocities noted to have positive or AREDV from 16 weeks). Doppler

Evidence level 2+

waveforms may demonstrate positive diastolic velocities (type I), AREDV (type II) or cyclical diastolic waveforms (type III), with an attendant worsening of prognosis for perinatal mortality and morbidity. iAREDV on umbilical artery Doppler velocity assessment are more common in MCDA sGR (45%) than uncomplicated (5%) pregnancies or those complicated by severe TTTS (2%).[57,59] This condition appears to result from large artery–artery anastomoses.

Evidence level 2+

sGR type I (Table 1) is associated with a relatively good outcome (more than 90% perinatal survival). Type II sGR is associated with a high risk (up to 29%) of intrauterine demise of the growth-restricted twin and/or preterm delivery. Type III sGR is associated with a 10–20% risk of unexpected fetal demise of the smaller twin (even if stable ultrasound features and/or normal computerised cardiotocography [CTG] hours or days before) and a 10–20% risk of neurological injury in the larger twin.[53,57,59]

7. Management of complex pathologies associated with a monochorionic twin pregnancy

7.1 The management of TTTS

7.1.1 How useful are grading systems for severity of TTTS in establishing prognosis?

At diagnosis, TTTS should be staged using the Quintero system. In addition, measurement of umbilical artery Doppler velocities, MCA PSV and ductus venosus Doppler studies should be performed and documented.

D

The Quintero system of staging TTTS (Table 1) has some prognostic value, but the course of the condition is unpredictable and may involve improvement or rapid deterioration within a short time span.[60–62]

In a series of 173 pregnancies complicated by TTTS from three centres in the USA and Australia, where treatment was either by amnioreduction or selective laser ablation, the outcome of at least one neonatal survivor was 91% (stage I), 88% (stage II), 67% (stage III) and 50% (stage IV).[50,60] Similar findings were reported from Germany in a series of 200 TTTS pregnancies treated by laser ablation: at least one neonatal survivor in 93% (stage I), 83% (stage II), 83% (stage III) and 70% (stage IV).[63]

Many reports of TTTS are difficult to interpret because of referral bias. A study from western Australia is valuable because it is population based, coming from the sole perinatal tertiary service in this Australian state.[60] A prospective cohort of 71 women with TTTS was treated with amnioreduction or septostomy. There was a relationship between Quintero stage at diagnosis and mean gestational age at delivery and perinatal survival: stage I, 32 weeks of gestation, 77% survival; stage II, 31 weeks of gestation, 70% survival; stage III, 28 weeks of gestation, 54% survival; and stage IV, 27 weeks of gestation, 44% survival. However, disease progression was often unpredictable, with 28% of pregnancies improving, 35% worsening and 37% remaining in the same grade throughout gestation. Pregnancies appeared, for example, to progress from stage I to stage III without obviously passing through stage II. Very similar findings came from a smaller cohort study in the USA (n = 18).[61] There were similar rates of regression and progression. Another study found a change of stage with time to be of greater prognostic significance than the stage itself[62] and others in a research setting have found recipient cardiac diastolic function to be important in long-term prognosis.[64,65]

Evidence level 2+

Amniotic fluid discordance, without fulfilling the 8 cm/2 cm criteria (i.e. within the 'normal range'), together with normal umbilical artery Doppler velocimetry is associated with good outcome (93% overall survival) and low risks of progression to severe TTTS (14%).[48,66]

There is controversy about the Quintero staging of TTTS, since stage I disease may not necessarily be associated with the best outcome and indeed recipient twins within stage I TTTS may have evidence of cardiac dysfunction.[67]

To emphasise this, a cross-sectional study from a single centre in the USA has indicated that monochorionic twin pregnancies complicated by TTTS as mild as Quintero stages I and II have a significant proportion of recipient twins with ventricular hypertrophy (17/28; 61%), atrioventricular valve regurgitation (6/28; 21%) and objective abnormalities in either right (12/24; 50%) or left (14/24; 58%) ventricular function[64] at fetal echocardiography. The suggestion that structural and/or functional assessment of the fetal heart (especially in the recipient) by echocardiography of monochorionic pregnancies at risk of or with TTTS may be useful in defining the prognostic risk of severe TTTS and treatment modalities, such as fetoscopic laser ablation,[64,65] are of interest.

Evidence level 2+

7.1.2 What is (are) the optimal treatment(s) of TTTS and their outcomes?

TTTS should be managed in conjunction with fetal medicine centres with recourse to specialist expertise and treatment in supraregional centres. ✓

TTTS presenting before 26 weeks of gestation should be treated by fetoscopic laser ablation rather than amnioreduction or septostomy. There is evidence that the fetoscopic laser ablative method should be the Solomon technique. A

Centres performing fetoscopic laser ablation should perform at least 15 procedures per year (rolling 3-year average). ✓

Weekly ultrasound assessment (including examination of the fetal brain, heart and limbs) and serial measurements of UAPI, MCA PSV and ductus venosus Doppler velocities should be performed. After 2 weeks post treatment, the ultrasound interval can be increased to every 2 weeks (noting UAPI, MCA PSV and DVP) with documentation of adequate fetal growth (by calculating EFW). ✓

In treated TTTS pregnancies, ultrasound examination of the fetal heart should be performed by the fetal medicine specialist to exclude functional heart anomalies. ✓

TTTS is a morbid complication of monochorionic twin pregnancies.[4] Once there is a suspicion of the disease or the diagnosis has been prospectively made using ultrasound, the pregnancy should be managed in conjunction with a fetal medicine centre, with specialists that perform treatment of the condition, including fetoscopic laser ablation. This is in concordance with the national commissioning guidance for the management of this condition in England.[68]

There are supraregional centres in the UK that will offer fetoscopic laser ablation for TTTS. Each case should be managed on an individual basis, but commonly, this treatment is for Quintero stage II or more and many will treat this condition if there is Quintero stage I with significant polyhydramnios (8 cm or more) or cervical shortening (less than 25 mm).[4]

Evidence level 4

The Eurofetus consortium trial randomised women with TTTS to either laser ablation or amnioreduction.[69] The planned sample size of 172 women aimed to demonstrate a 15% difference in survival. The large majority of women had Quintero stage II or III TTTS. Three women in the laser group did not undergo the procedure. Two women in the amnioreduction group did not undergo the procedure and seven underwent laser ablation, six following amnioreduction. As compared with the amnioreduction group, the laser group had a significantly higher likelihood of the survival of at least one twin to 28 days of age and 6 months of age. Infants in the laser group also had a lower incidence of cystic periventricular leukomalacia and were more likely to be free of neurological complications at 6 months of age. The authors' conclusion was that fetoscopic laser coagulation of anastomoses is a more effective first-line treatment than serial amnioreduction for severe TTTS diagnosed before 26 weeks of gestation.

Another randomised trial compared amnioreduction with septostomy (the deliberate creation of a hole in the dividing septum with the intention of improving amniotic fluid volume in the donor sac).[70] The trial included 73 women with TTTS (of all stages). The primary outcome was at least one infant surviving until hospital discharge. The trial was stopped after an interim analysis because no significant differences were seen in the primary outcome.

The results of a third study, the National Institute of Child Health and Human Development trial of amnioreduction versus laser ablation,[71] have been added to the Cochrane review on the topic.[72] In this randomised controlled trial, pregnancies with severe TTTS were only entered into the study after a 'test' amnioreduction. This may have produced bias in the study. This trial noted that there was no statistically significant difference in 30-day postnatal survival between laser ablation and amnioreduction treatment for donors at 55% (11/20) versus 55% (11/20) (P = 1.0; OR 1, 95% CI 0.242–4.14) or recipients at 30% (6/20) versus 45% (9/20) (P = 0.51; OR 1.88, 95% CI 0.44–8.64). There was no difference in 30-day survival of one or both twins on a per pregnancy basis between amnioreduction at 75% (15/20) and laser ablation at 65% (13/20) (P = 0.73; OR 1.62, 95% CI 0.34–8.09). Overall survival (newborns divided by the number of fetuses treated) was not statistically significant for amnioreduction at 60% (24/40) versus laser ablation at 45% (18/40) (P = 0.18; OR 2.01, 95% CI 0.76–5.44). There was a statistically significant increase in fetal recipient mortality in the laser ablation arm at 70% (14/20) versus the amnioreduction arm at 35% (7/20) (P = 0.25; OR 5.31, 95% CI 1.19–27.6). This was offset by an increased recipient neonatal mortality of 30% (6/20) in the amnioreduction arm.

Evidence level 1+

The results of the three studies have been reanalysed in a Cochrane review, adjusting where possible for clustering, recognising the nonindependence of twin fetuses within a pair.[72]

The conclusion of the Cochrane review was that endoscopic laser coagulation of anastomotic vessels should continue to be considered in the treatment of all stages of TTTS to improve neurodevelopmental outcomes in the child. When compared with amnioreduction, treatment with laser coagulation does not appear to increase or reduce the risk of overall death (stillbirth, neonatal and postneonatal) in this condition, but it appears to result in more children being alive without neurological abnormality.[72]

Amnioreduction can be retained as a treatment option for those situations where the expertise for laser coagulation is not available, pending transfer to a unit where such treatment can be obtained or when the condition is diagnosed after 26 weeks of pregnancy. However, this may complicate future treatment if associated with inadvertent septostomy.[72]

Randomised evaluation of interventions, such as septostomy, serial amniocentesis and placental laser ablation, with regard to their respective effect on relatively mild forms of TTTS (Quintero stage I) and more severe forms (Quintero stage IV) are required.[72] However, there is some evidence that fetoscopic laser ablation is the best treatment of TTTS in early-onset (less than 17 weeks) and late-onset (after 26 weeks) disease.[73,74]

Evidence level 3

Anastomoses may be missed at fetoscopic laser ablation and this is the most common cause of recurrence and morbidity.[9,15] Recurrent TTTS can occur in up to 14% of pregnancies treated with fetoscopic laser ablation and be associated with or without TAPS.[15,51] Such outcomes are associated with a worsening of neonatal morbidity. There is randomised controlled trial evidence that modification of the primary fetoscopic laser technique by 'equatorial laser dichorionization' (or the Solomon technique) significantly reduces these complications of recurrent TTTS and TAPS.[15]

Evidence level 1+

Fetoscopic laser ablation can be performed in monochorionic and dichorionic (triamniotic) triplet pregnancies, but the placental angioarchitecture is usually more complex and the perinatal outcomes are in general poorer than in the treatment of twins.[75,76]

Evidence level 3

Some women request termination of pregnancy when severe TTTS is diagnosed and this should be discussed as an option. Another option is to offer selective termination of pregnancy using bipolar diathermy of one of the umbilical cords or using radiofrequency ablation, with inevitable sacrifice of that baby.[77,78] This may be appropriate, for example, if there is evidence of cerebral damage in either twin.[79]

There are few data to inform how frequently ultrasound surveillance is required after fetoscopic laser ablation (or amnioreduction). Following laser treatment, the recurrence rate is up to 14%, which is likely to be secondary to missed anastomoses at the time of initial laser treatment.[15] However, most experts advocate that ultrasound examination (with brain imaging, fetal measurement and Doppler assessment, especially of the MCA PSV) should be performed every week for the first 2 weeks and then every other week following clinical resolution. TAPS may complicate post fetoscopic laser ablation in up to 13% of cases (the most common complication after fetal demise). Therefore, at these ultrasound examinations, MCA PSV should be performed and the result recorded.

Evidence level 2+

However, some have indicated that functional cardiac studies may add to the prognosis of MCDA twins complicated by TTTS.[64,65,67] In a case series of 89 survivors from 73 pregnancies treated by laser ablation for severe TTTS, 11% of fetuses had secondary, structural heart disease, primarily right-sided cardiac lesions, predominantly pulmonary stenosis.[63]

Evidence level 2–

7.1.3 When should the delivery of monochorionic twin pregnancies complicated by TTTS take place?

Delivery of monochorionic twin pregnancies previously complicated by TTTS and treated should be between 34^{+0} and 36^{+6} weeks of gestation.

D

International expert opinion has indicated that, even after successful treatment, regular ultrasound surveillance should be routine and good practice.[19,80] Consideration should be given to delivery of the surviving twin(s) between 34^{+0} and 36^{+6} weeks,[4,80,81] or earlier if there are concerns. As with previous RCOG and NICE guidance, prophylactic maternal steroids should be given if possible prior to delivery. Mode of delivery can be individualised, but often this is by caesarean section.[82]

Evidence level 2–

