National Institute for Health and Care Excellence

Final

Twin and Triplet Pregnancy

[A] Evidence review for ultrasound screening for feto-fetal transfusion syndrome

NICE guideline NG137

Evidence review

September 2019

Final

This evidence review was developed by the National Guideline Alliance which is a part of the Royal College of Obstetricians and Gynaecologists

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Review question

What is the optimal screening programme to identify feto-fetal transfusion syndrome (FFTS) in twin and triplet pregnancy?

Introduction

Approximately 20–25% of twin pregnancies are monochorionic, and about 10–15% of monochorionic twin pregnancies are complicated by FFTS due to unequal placental sharing. This morbid condition may also affect monochorionic and dichorionic triplet pregnancies. FFTS is characterised by progressive growth discordance with decreased blood volume (hypovolaemia), decreased production of urine (oliguria) and lower than average amniotic fluid levels (oligohydramnios) in the donor fetus and volume overload, polyuria, polyhydramnios, high-output cardiac failure and accumulation of fluid (hydrops) in the recipient fetus. Outcomes associated with this chronic condition are very poor, with 60–90% of pregnancies resulting in stillbirth, neonatal death or disability. However, timely diagnosis, staging and fetoscopic laser ablation significantly improve perinatal outcomes, resulting in rates of 70–85% for being able to take at least one baby home with a low incidence of poor neurodevelopmental outcomes.

Summary of the protocols

Feto-fetal transfusion syndrome does not occur in the first trimester of pregnancy and therefore there is a prognostic and a diagnostic component in this evidence review. Table 1 summarises the Population, Prognostic Factor, and Outcome (PPO) characteristics of the prognostic component of this review. This prognostic component is related to screening in the first trimester to predict feto-fetal transfusion syndrome occurring later. Table 2 summarises the Population, Index test, Reference standard and Outcome (PIRO) characteristics of the diagnostic component of this review. This component is included to diagnose the condition once it has occurred.

Table 1: Summary of protocol (Population, Prognostic Factor, and Outcome [PPO]) table

Population	**For twin pregnancies:** • monochorionic diamniotic • monochorionic monoamniotic **For triplet pregnancies:** • dichorionic triamniotic • monochorionic triamniotic • dichorionic, diamniotic (a monochorionic twins set) and monochorionic monoamniotic Setting: Secondary or tertiary care centres
Prognostic factor	**Estimated during ultrasound scan at 11^{+0} to 13^{+6} weeks:** • discrepant crown-rump length • discrepant nuchal translucency • abnormal ductus venosus doppler

	As FFTS occurs after this gestation the prognostic value of first trimester tests to detect FFTS will be prioritised (see appendix A "Review Protocol 1.1"). If no or limited prognostic data is available, then the diagnostic value of first trimester tests 1–3 will be considered. The above tests will be considered in isolation or in combination. Details regarding frequency and duration of testing throughout pregnancy presented in included studies will be recorded
Outcome	**Prognostic value of first trimester tests to predict FFTS according to Quintero criteria:** • odds ratios, relative risks, hazard ratios Estimates derived from multivariate analysis will be prioritised over estimates derived from univariate analysis **Quintero criteria:** • Stage 1: A small amount of amniotic fluid (oligohydramnios - max vertical pocket of <2 cm) is found around the donor twin and a large amount of amniotic fluid (polyhydramnios – max vertical pocket of >8 cm) is found around the recipient twin at 20 weeks. Threshold is >10 cm at over 20 weeks gestational age (US only use >8 cm threshold at any gestational age) • Stage 2: Stage 1 plus the ultrasound is not able to identify the bladder in the donor twin • Stage 3: Stages 1 and 2 plus there is abnormal blood flow in the umbilical cords of the twins with at least one of the following: ○ a) absent end diastolic velocity in the umbilical artery / Reverse end diastolic velocity in the umbilical artery ○ b) reverse flow in the ductus venosus or pulsatile umbilical venous flow • Stage 4: Stages 1–3 plus the recipient twin has swelling under the skin and appears to be experiencing heart failure (fetal hydrops) Stage 5: Stages 1–4 plus one of the twins has died

Table 2: Summary of protocol (Population, Index test, Reference standard and Outcome [PIRO] table)

Population	**For twin pregnancies:** • monochorionic diamniotic • monochorionic monoamniotic **For triplet pregnancies:** • dichorionic triamniotic • monochorionic triamniotic • dichorionic, diamniotic (a monochorionic twins set) and monochorionic monoamniotic Setting: Secondary or tertiary care centres
Index test	**Estimated during ultrasound scan at 11^{+0} to 13^{+6}:** • discrepant crown-rump length • discrepant nuchal translucency • abnormal ductus venosus doppler As FFTS occurs after this gestation the prognostic value of first trimester tests to detect FFTS will be prioritised (see appendix A "Review Protocol 1.2"). If no or limited prognostic data is available, then the diagnostic value of first trimester tests will be considered

	Estimated during ultrasound scan at 14 weeks onwards: • growth discordancy (fetal biometry including head circumference, abdominal circumference), femur length and estimated fetal weight) • amniotic fluid discordancy (amniotic fluid index, amniotic fluid discordance or maximum pool depth) • doppler studies (umbilical artery doppler (3 categories), ductus venosus doppler) • tricuspid regurgitation • absent visualisation of donor bladder • intertwining/infolding of the membrane As FFTS can occur at any point until birth during the second trimester, the diagnostic value of second trimester tests to detect FFTS will be examined The above tests will be considered in isolation or in combination
Reference standard	**Ultrasound diagnosis of FFTS according to Quintero (1999) criteria** • Stage 1: A small amount of amniotic fluid (oligohydramnios - max vertical pocket of <2 cm) is found around the donor twin and a large amount of amniotic fluid (polyhydramnios – maximum vertical pocket of >8 cm) is found around the recipient twin at 20 weeks. Threshold is >10 cm at over 20 weeks gestational age (US only use >8 cm threshold at any gestational age) • Stage 2: Stage 1 plus the ultrasound is not able to identify the bladder in the donor twin • Stage 3: Stages 1 and 2 plus there is abnormal blood flow in the umbilical cords of the twins with at least one of the following: ○ a) absent end diastolic velocity in the umbilical artery / reverse end diastolic velocity in the umbilical artery ○ b) reverse flow in the ductus venosus or pulsatile umbilical venous flow • Stage 4: Stages 1–3 plus the recipient twin has swelling under the skin and appears to be experiencing heart failure (fetal hydrops). • Stage 5: Stages 1–4 plus one of the twins has died
Outcomes	**Diagnostic value of first and second trimester tests** **Critical:** • sensitivity • specificity Sensitivity was regarded as the more important measure for decision making as these are primarily screening diagnostic tests **Important:** • area under the curve (AUC)

See appendix A for the full review protocols.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocols in appendix A and for a full description of methods see supplementary material C.

Declaration of interests were recorded according to NICE's 2014 conflicts of interest policy from March 2017 until March 2018. From April 2018 onwards they were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Interests Register).

Clinical evidence

Included studies

One systematic review (Stagnati 2017) and 7 further cohort studies (Allaf 2014; Allaf 2014a; Maiz 2009; Matias 2010; Memmo 2012; Yamamoto 2013; Zipori 2016) were included in the review.

The systematic review (Stagnati 2017) included 13 studies that examined the accuracy of ultrasound markers that have been carried out in the first- and early second-trimester (prior to 16 weeks' gestation) to predict FFTS in monochorionic twin pregnancies. Seven studies were prospective cohort studies, 4 were retrospective cohort studies, 1 was a prospective case-control study and the study design for 1 study was unclear.

Where the information from the systematic review was insufficient; for example, to assess the risk of bias, relevant data from the original studies were checked and the original study excluded. If studies included in the systematic review reported additional outcomes that were relevant to this review, then these studies were included independently. This resulted in 3 studies being included independently (Maiz 2009; Matias 2010; Memmo 2012).

Four further retrospective cohort studies were identified for inclusion (Allaf 2014; Allaf 2014a; Yamamoto 2013; Zipori 2016). Two (Allaf 2014; Zipori 2016) assessed the value of discordant nuchal translucency and/or crown rump length in predicting adverse outcomes in monochorionic diamniotic twins at 11 to 13^{+6} weeks. Two studies included the same population (Allaf 2014; Allaf 2014a) but the latter assessed the predictive value of discordance in abdominal circumference, head circumference, femur length, and estimated fetal weight in the early second-trimester (16- to 18-weeks' gestation). One study (Yamamoto 2013) assessed the accuracy of amniotic fluid discordance in the early second trimester for the prediction of FFTS in twins.

There were no studies identified that reported on women with triplet pregnancy.

The clinical studies included in this evidence review are summarised in Table 3.

See also the literature search strategy in appendix B, study selection flow chart in appendix C, study evidence tables in appendix D and GRADE profiles in appendix F.

Excluded studies

Studies excluded from this systematic review, with reasons for their exclusion, are listed in appendix K.

Summary of clinical studies included in the evidence review

Table 3 provides a brief summary of the included studies.

Table 3: Summary of included studies for twin pregnancy

Study	Population	Index test	Reference standard	Outcomes	Frequency and duration of screening for each study	Comments
Allaf 2014 Retrospective cohort study USA	N=177 monochorionic diamniotic twin pregnancies	Ultrasound – NT and CRL measured at 11 to 13^{+6} weeks. The intertwin discordances in NT and CRL were calculated as the differences in the measurements between the 2 fetuses, expressed as a percentage of the larger measurement	FFTS defined according to Quintero classification	Diagnostic accuracy of NT and CRL discordance (cut off ≥20%) to predict FFTS (AUC)	All pregnancies included were monitored by serial sonographic evaluations of growth, amniotic fluid volume measurement, and doppler interrogation of the fetal vessels starting at 16 to 18 weeks' gestation and at least every 2 to 4 weeks thereafter until birth	Same study population as Allaf (2014a) The authors stated that they could not demonstrate optimal cut-off point that would be clinically useful in predicting adverse outcomes
Allaf 2014a Retrospective cohort study USA	N=177 monochorionic diamniotic twin pregnancies	Ultrasound (abdominal circumference, femur length, head circumference, estimated fetal weight) measured at 16- to 18-weeks	FFTS defined according to Quintero classification	Diagnostic accuracy of abdominal circumference, head circumference, and femur length discordance (cut-off ≥20%) to predict FFTS (AUC) Diagnostic accuracy of estimated fetal weight discordance to predict FFTS (AUC)	All pregnancies included were monitored by serial ultrasound evaluations of abdominal circumference, femur length, head circumference, and estimated fetal weight measured at 16 to 18 weeks' gestation	Same study population as Allaf 2014

Study	Population	Index test	Reference standard	Outcomes	Frequency and duration of screening for each study	Comments
Maiz 2009 Prospective cohort study UK	N=179 monochorionic twins	Ultrasound – NT, CRL, and DV flow (defined as abnormal when reversed A-wave flow was present) measured at 11 to 13 weeks' gestation	FFTS defined as ultrasound diagnosis of hydramnios in 1 twin and anhydramnios in the other, and absent or reversed end diastolic flow in either the umbilical artery or DV in one or both fetuses	Multiple logistic regression for contribution of reversed DV flow in at least one fetus to severe FFTS	Monochorionic twins were followed up with ultrasound scans at 16-to 18-weeks' gestation and monthly thereafter, unless there was evidence of FFTS, in which case the frequency was increased as necessary	Data from original paper - additional to data reported in Stagnati 2017
Matias 2010 Prospective cohort study Portugal	N=99 monochorionic twins	Ultrasound –NT and CRL intertwin differences, NT and CRL intertwin ratios and abnormal DV blood flow in at least 1 fetus, measured at 11 to 14 weeks' gestation	FFTS defined according to Quintero classification	Diagnostic accuracy (AUC) of NT and CRL intertwin ratios, and relative risk (RR) for abnormal DV blood flow in at least 1 fetus, measured at 11 to 14 weeks' gestation	Measured at 11 to 14 weeks' gestation. After 14 weeks' gestation, twins were assessed every 2 weeks	Data from original paper - additional to data reported in Stagnati 2017
Memmo 2012 Retrospective cohort study UK	N=242 MCDA twin pregnancies	Ultrasound - discrepancies in NT, CRL, and EFW measured at 11- to 14-weeks' gestation	FFTS defined according to Quintero classification	Diagnostic accuracy (AUC) for the prediction of FFTS at 11 to 14 weeks' gestation	All monochorionic pregnancies were followed up with scans every 2 weeks from 16- to 24-weeks, until a diagnosis	Data from original paper - additional to data reported in Stagnati 2017

Study	Population	Index test	Reference standard	Outcomes	Frequency and duration of screening for each study	Comments
					of FFTS was excluded	
Stagnati 2017 Systematic review Multiple countries Includes 13 studies *Retrospective cohort studies:* (Casasbuenas 2008, (South America); Fratelli 2011, (Italy); Linskens 2009, (The Netherlands); Memmo 2012, (UK); *Prospective cohort study:* Kagan 2007, (UK); Lewi 2008, (Belgium, Germany); Maiz 2009, (UK); Matias 2005, (Portugal); Matias 2010,	N=13 studies (8 prospective study designs, 4 retrospective, 1 unclear) N=1,991 monochorionic twin pregnancies	Ultrasound - NT, CRL, and DV flow (defined as abnormal when reversed A-wave flow was present) measured at <16 weeks gestation. The intertwin discordances in NT and CRL were calculated as the differences in the measurements between the 2 fetuses, expressed as a percentage of the larger measurement. Abnormal DV in at least 1 twin	FFTS defined as a discrepancy in DVP of amniotic fluid (>8 cm in recipient twin and <2 cm in donor twin) according to Quintero classification	True positive, false positive, true negative, false negative. Sensitivity and specificity (95% CIs) for: NT (>95th percentile; discrepancy >20%; discrepancy >0.5mm or ≥0.6mm) CRL discrepancy (>10% or 20%; discrepancy ≥10 mm or ≥12 mm); AFD Reversed DV flow Intertwin membrane folding (ultrasound at 15- to 17-weeks' gestation)	Ultrasound follow-up frequency Every 2 weeks El Kateb 2007; Fratelli 2011; Sueters 2006 Every 4 weeks Kagan 2007; Maiz 2009; Matias 2005 At Weeks 16, 20 and 26 Lewi 2008 At Weeks 19, 21 and 23 Sperling 2007 Serial Linskens 2009 Not stated Casasbuenas 2008; Matias 2010; Memmo 2012; Sebire 2000	

Study	Population	Index test	Reference standard	Outcomes	Frequency and duration of screening for each study	Comments
(Portugal); Sperling 2007, (Denmark, Sweden); Sueters 2006, (The Netherlands) El Kateb 2007, prospective case-control (France); Sebire 2000, unclear study design (extended series) (UK);						
Yamamoto 2013 Retrospective cohort study Japan	N=223 women with twin pregnancies; n=20 women with fetuses with FFTS	AFD	Presence of polyhydramnios with an MVP ≥8 cm combined with oligohydramnios with an MVP ≤2 cm	Relationship between AFD (including ≥4 cm and ≥4 cm at <26 weeks' gestation), gestational age, EFW discordant rate >0.25 and development of FFTS	Serial ultrasonographic assessment, including measurement of the MVP of each twin and EFW, was undertaken at intervals of at least 2 weeks after 16 weeks' gestation.	
Zipori 2016 Retrospective cohort study Australia	N=89 MCDA twin pregnancies	Ultrasound – NT and CRL measured at 11 and 13^{+6} weeks. The percentage discrepancy for NT was determined	FFTS defined according to Quintero classification	Diagnostic accuracy (sensitivity, specificity and AUC) of NT discordance (cut-off >31.1%) to predict FFTS	MCDA twins had fortnightly ultrasound assessments until birth, commencing at 16 weeks' gestation, to detect	

Study	Population	Index test	Reference standard	Outcomes	Frequency and duration of screening for each study	Comments
		as the percentage difference relative to the lower value for NT. The percentage discrepancy for CRL was determined as the percentage difference relative to the larger value for CRL		Diagnostic accuracy (sensitivity, specificity and AUC) of CRL discordance (cut-off >3.5%) to predict FFTS	pregnancy complications	

AFD: amniotic fluid discordance; AUC: area under the curve; CI: confidence interval; CRL: crown rump length; DV: ductus venosus; DVP: deepest vertical pocket; EFW: estimated fetal weight; FFTS: feto-fetal transfusion syndrome; MCDA: monochorionic diamniotic; MVP: maximum vertical pocket; NT: nuchal translucency; RR: relative risk

See appendix D for the full evidence tables.

Quality assessment of clinical studies included in the evidence review

The evidence for the prognostic component of this review question is presented in Table 4 (where evidence quality is indicated by the assessment of the risk of bias for the study) and in appendix F (where evidence quality is assessed using a modified GRADE approach for diagnostic test accuracy data). All studies were observational. Quality assessment was performed for each individual study included in Stagnati (2017) and for all additional included studies.

See appendix F for the GRADE tables.

Table 4: Summary clinical evidence profile for screening in first trimester (11^{+0} to 13^{+6} weeks' gestation) to predict subsequent development of FFTS in twin pregnancy

Prognostic factor	No of participants (studies)	Adjusted RR (95% CI)	RoB
NT intertwin ratio	99 (1)	1.20 (0.82 to 1.63)[1]	Very serious[2]
CRL intertwin ratio	99 (1)	1.07 (0.67 to 1.60)[3]	Very serious[2]
Abnormal DV flow in at least 1 fetus	99 (1)	11.99 (3.12 to 58.00)[4]	Very serious[2]

CI: confidence interval; CRL: crown-rump length; DV: ductus venosus; NT: nuchal translucency; RoB: risk of bias; RR: relative risk

1 Adjusted for difference in CRL, NT ratio, CRL ratio, at least one abnormal DV; variable was standardised prior to analysis (by subtraction of the mean and division by the SD)
2 Not reported if women and/or providers were blinded to test results; no description of the study population; not adjusted for any maternal confounding factors
3 adjusted for difference in NT, NT ratio, CRL ratio, at least one abnormal DV; variable was standardised prior to analysis (by subtraction of the mean and division by the SD)
4 Adjusted for difference in NT, difference in CRL, NT ratio, CRL ratio

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

See the appendix B for the economic search strategy and appendix G for the economic evidence selection flow chart for further information.

Excluded studies

No full-text copies of articles were requested for this review and so there is no excluded studies list.

Summary of studies included in the economic evidence review

No economic studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Only sensitivity and specificity values are provided in the evidence statements below. When assessing the diagnostic accuracy of sensitivity and specificity the following thresholds were used: high accuracy: more than 90%; moderate accuracy: 75% to 90%; and, low accuracy: less than 75%.

Area under the curve (AUC) measures are not reported as they are not related to a particular cut-off and are therefore difficult to interpret (AUC up to 70 are described as having 'poor ability to discriminate and AUC of 71 and above would be described as having moderate or good ability to discriminate). Estimates are reported for information in appendix D and appendix F Adjusted risk or odds ratios are also not provided. These are reported in Table 4. For further details see the methods described in supplement document C.

Screening in first trimester (11^{+0} to 13^{+6} weeks' gestation) to predict subsequent development of feto-fetal transfusion syndrome in twin pregnancy

The three measures below related to the prognostic part of the evidence and the quality is assessed using the study's risk of bias (see Table 4).

<u>Nuchal translucency intertwin ratio</u>

One study (N=99) with a very serious risk of bias showed that there was no significant association between nuchal translucency intertwin ratio and the development of feto-fetal transfusion syndrome.

<u>Crown-rump length intertwin ratio</u>

One study (N=99) with a very serious risk of bias showed that there was no significant association between crown-rump length intertwin ratio and the development of feto-fetal transfusion syndrome.

Abnormal ductus venosus flow in at least one fetus

One study (N=99) with a very serious risk of bias showed that there was a significant association between abnormal ductus venosus flow in at least one fetus and the development of feto-fetal transfusion syndrome.

Screening to identify feto-fetal transfusion syndrome in twin pregnancy in first trimester (11^{+0} to 13^{+6} weeks' gestation)

Nuchal translucency >95th percentile

Very low quality evidence from 7 studies (N=689) showed that the pooled sensitivity and specificity for nuchal translucency >95th percentile measured using ultrasound was 23% (9 to 41) and 91% (85 to 96) to detect feto-fetal transfusion syndrome diagnosed using Quintero criteria.

Nuchal translucency discrepancy >31.1%

Very low quality evidence from 1 study (N=89) showed that nuchal translucency discrepancy >31.1% had poor ability to discriminate for the diagnosis of feto-fetal transfusion syndrome using Quintero criteria.

Nuchal translucency discrepancy >20%

Very low quality evidence from 5 studies (N=938) showed that the pooled sensitivity and specificity for nuchal translucency discrepancy >20% was 53% (33 to 72) and 69% (51 to 83) to detect feto-fetal transfusion syndrome diagnosed using Quintero criteria.

Nuchal translucency discrepancy ≥20%

Very low quality evidence from 1 study (N=177) showed that nuchal translucency discrepancy ≥20% had very poor ability to discriminate for the diagnosis of feto-fetal transfusion syndrome using Quintero criteria.

Nuchal translucency discrepancy ≥0.6mm

Low quality evidence from 1 study (N=99) showed that the sensitivity and specificity for NT discrepancy ≥0.6mm was 50% (21 to 79) and 92% (84 to 97) to detect feto-fetal transfusion syndrome diagnosed using Quintero criteria and had good ability to discriminate for the diagnosis of feto-fetal transfusion syndrome.

Nuchal translucency discrepancy ≥0.5mm

Low quality evidence from 1 study (N=50) showed that the sensitivity and specificity for nuchal translucency discrepancy ≥0.5mm was 25% (1 to 81) and 65% (50 to 79) to detect feto-fetal transfusion syndrome diagnosed using Quintero criteria.

Crown-rump length discrepancy ≥20%

Very low quality evidence from 1 study (N=177) showed that crown-rump length discrepancy ≥20% had very poor ability to discriminate for the diagnosis of feto-fetal transfusion syndrome using Quintero criteria.

Crown-rump length discrepancy >10%

Very low quality evidence from 6 studies (N=1082) showed that the pooled sensitivity and specificity for crown-rump length discrepancy >10% was 14% (3 to 33) and 92% (81 to 98) to detect feto-fetal transfusion syndrome diagnosed using Quintero criteria.

Crown-rump length discrepancy >3.5%

Very low quality evidence from 1 study (N=102) showed that crown-rump length discrepancy >3.5% had very poor ability to discriminate for the diagnosis of feto-fetal transfusion syndrome using Quintero criteria.

Crown-rump length discrepancy ≥12mm

Very low quality evidence from 1 study (N=200) showed that the sensitivity and specificity for crown-rump length discrepancy ≥12mm was 56% (31 to 78) and 77% (70 to 83) to detect feto-fetal transfusion syndrome diagnosed using Quintero criteria.

Crown-rump length intertwin ratio

Very low quality evidence from one study (N=99) showed that crown-rump length intertwin ratio had very poor ability to discriminate for the diagnosis of feto-fetal transfusion syndrome (using Quintero criteria).

Amniotic fluid discordance

Low quality evidence from 1 study (N=200) showed that the sensitivity and specificity for amniotic fluid discordance was 22% (9 to 45) and 96% (92 to 98) to detect feto-fetal transfusion syndrome diagnosed using Quintero criteria.

Reverse ductus venosus flow

Low quality evidence from 1 study (N=179) showed that the sensitivity and specificity for reverse ductus venosus flow was 38% (20 to 59) and 85% (78 to 90) to detect feto-fetal transfusion syndrome diagnosed using Quintero criteria. Very low quality evidence from 1 study (N=99) showed that the sensitivity and specificity for reverse ductus venosus flow was 75% (43 to 95) and 92% (84 to 97) to detect feto-fetal transfusion syndrome diagnosed using Quintero criteria.

Intertwin membrane folding (presence or absence)

Low quality evidence from 1 study (N=287) showed that the sensitivity and specificity for intertwin membrane folding was 43% (30 to 57) and 98% (93 to 99) to detect feto-fetal transfusion syndrome diagnosed using Quintero criteria.

Screening to identify feto-fetal transfusion syndrome in twin pregnancy in second trimester

Abdominal circumference discordance ≥20% (16- to 18- weeks' gestation)

Very low quality evidence from 1 study (n=177) showed that abdominal circumference discordance ≥20% had poor ability to discriminate for the diagnosis of feto-fetal transfusion syndrome using Quintero criteria.

Head circumference discordance ≥20% (16- to 18- weeks' gestation)

Very low quality evidence from 1 study (n=177) showed that head circumference discordance ≥20% had poor ability to discriminate for the diagnosis of feto-fetal transfusion syndrome using Quintero criteria.

Femur length discordance ≥20% (16- to 18- weeks' gestation)

Very low quality evidence from 1 study (n=177) showed that femur length discordance ≥20% had poor ability to discriminate for the diagnosis of feto-fetal transfusion syndrome using Quintero criteria.

Estimated fetal weight discordance (16- to 18- weeks' gestation)

Very low quality evidence from 1 study (n=177) showed that estimated fetal weight discordance had poor ability to discriminate for the diagnosis of feto-fetal transfusion syndrome using Quintero criteria.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that prognostic odds ratios would be the critical outcome measures in the first trimester of the twin or triplet pregnancy because the aim of the tests is to predict the condition in the second trimester or later. The committee also prioritised the diagnostic accuracy measure of sensitivity as another critical outcome, because it is important not to miss cases of feto-fetal transfusion syndrome (FFTS).

In the second trimester or thereafter, detection of the presence or absence of FFTS is an important aim of each ultrasound assessment. The committee therefore prioritised both sensitivity and specificity as critical test accuracy measures. Area under the curve was rated as an important rather than critical outcome because it does not provide precise information on the false positive or false negative rates that would have the biggest impact on patient outcomes.

The quality of the evidence

Risk of bias in individual prognostic studies was assessed using the risk of bias items from the QUIPS checklist. The study that reported on predictors, and therefore the most applicable data for first trimester screening of FFTS was rated as having very serious risk of bias. This was mainly due to the uncertainty around the blinding of participants and/or health professionals to the test results, and lack of description of the study population. The committee also noted that the study was quite small and that the results were therefore uncertain.

The quality of the diagnostic accuracy of test results was assessed for the whole evidence base related to each index test using a modified GRADE approach (for a full description of methods see supplementary material C).

For the diagnostic accuracy measures in the first trimester the evidence was rated as very low to low quality. This was mainly due to the risk of bias in the individual studies which often related to lack of clarity about whether the index test results were interpreted without knowledge of the results of the reference standard. In addition, there was often heterogeneity and imprecision in the evidence base with wide confidence intervals which indicated uncertainty about the accuracy measurement.

Benefits and harms

Screening for FFTS in the first trimester

Although there were uncertainties and heterogeneity in the evidence (for instance there was some low quality evidence suggesting good predictive value of DV doppler for FFTS but other tests were neither very sensitive nor specific) the committee concluded that none of the

first trimester screening tests could clearly detect the risk of feto-fetal transfusion syndrome developing later in the pregnancy. This conclusion was also supported by the committee's clinical expertise and their experience of current clinical practice. Therefore the decision was made to retain the 2011 recommendation to not screening for FFTS in the first trimester.

Simultaneous diagnostic monitoring for complications related to monochorionicity (including FFTS)

There are several complications that are restricted to monochorionicity (feto-fetal transfusion syndrome and TAPS) and others, such as fetal growth restriction, are more common in monochorionic babies. All of these are monitored by ultrasound. The committee highlighted that measurements from one ultrasound would be used to monitor for all complications simultaneously (such as feto-fetal transfusion syndrome, intrauterine growth restriction and TAPS) rather than having separate ultrasound scans for each because they are not mutually exclusive conditions. An explanation about the relative likelihood of each complication and when they can occur during her pregnancy should be given to the woman so that she knows the reasons for the different ultrasound measurements that are taken.

Diagnostic monitoring of FFTS in the second and third trimester

There was little evidence relating to accuracy of second or third trimester tests. Only one study reported test findings and the associated accuracy measures were assessed as very low quality evidence. The committee therefore had no confidence in these findings. The committee agreed, based on their expertise that amniotic fluid levels would have sufficiently increased in the second trimester to make it possible to detect differences by ultrasound. They therefore decided that ultrasound monitoring for the development of FFTS should start at 16-weeks gestation so that FFTS can be identified as early as possible. This is consistent with what was recommended in 2011. The committee decided that measures and thresholds should be consistent with stage 1 Quintero criteria (for details see the outcome row of Table 1) because none of the individual measurements used as index tests reached the accuracy of this reference standard. This is also what is used in current practice. The committee decided that ongoing monitoring at 2-weekly intervals (which is current practice based on the previous version of the guideline) until birth would mean that trends in measures could be used to build a clinical picture that may raise concerns. Screening until birth is a change to the previous guideline. This was decided because some of the studies in the current review screened until birth which indicates that detection can take place even in late pregnancy. The committee also discussed that twin or triplet pregnancies involving monochorionic babies would usually have fortnightly screening because the risk of complications is higher, and that this frequency could reduce neonatal mortality and morbidity. The committee agreed that it is best practice to measure the deepest vertical pocket of amniotic fluid with the amniotic membrane visible so that there was no confusion regarding amniotic fluid discrepancy between twins.

Increased monitoring and referral

The committee discussed and agreed, based on their expertise, that where there were concerns regarding discordant fetal growth and discrepant amniotic fluid levels, women would need increased weekly surveillance. The committee agreed that where there was suspicion there should also be umbilical artery doppler assessment to aid diagnosis by measuring the blood flow to each baby. This would detect whether blood is diverted more to one baby than another.

The committee agreed based on their expertise that when the diagnostic thresholds for amniotic fluid depth for FFTS are reached, women with such pregnancies should be referred to a tertiary-level fetal centre for further management.

The committee thought that FFTS warranted immediate referral in the early stages, as the clinical course of FFTS is unpredictable and this allowed time for the diagnosis to be confirmed and timely intervention. The committee agreed that where FFTS was diagnosed, this was best managed in a tertiary centre where therapy for FFTS could be sought. The committee accepted that in the stages prior to development of FFTS (discordant amniotic fluid levels that have not reached the threshold for FFTS diagnosis but raise concerns), these cases could be dealt with by the lead for multiple pregnancy at the woman's local hospital.

Cost effectiveness and resource use

In the absence of any economic evidence or de novo analysis, the committee made a qualitative assessment about the cost effectiveness of first trimester screening and diagnostic monitoring for FFTS.

The committee concluded that currently there is no evidence of cost effectiveness to support the use of first trimester screening for FFTS as there is an absence of evidence demonstrating the usefulness of tests to rule out the risk of FFTS developing later in pregnancy.

The committee acknowledged that there might be some resource impact to the NHS as a result of their recommendation which extends the period of monitoring for FFTS compared to current practice. They considered that any resource impact would not be significant as the scans should be carried out at the same time as the scan to monitor intrauterine growth restriction. They also noted that the size of the population affected by the population is relatively small, with monochorionic twin pregnancies accounting for only approximately 20-25% of all twin pregnancies. The committee concluded that any additional costs of ultrasound from the increased period of monitoring would be cost effective because of substantially improved pregnancy outcomes that would result in women who develop FFTS later in pregnancy.

Other factors the committee took into account

The committee noted that the frequency of these screening recommendations are in agreement with the previous guideline and with guidance from the Royal College of Obstetricians and Gynaecologist (Green top guideline on monochorionic twin pregnancy). However, screening until birth is a change in practice which would lead to better identification of the condition if it occurs late in pregnancy.

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Appendix A – Review protocols

1.1 Review protocol – What is the optimal screening programme to identify feto-fetal transfusion syndrome (FFTS) in twin and triplet pregnancy? Prognostic component for review question

Table 5: Review protocol for feto-fetal (FFTS) transfusion syndrome prediction

ID	Field (based on PRISMA-P)	Content
I	Review question	What is the optimal screening programme to identify feto-fetal transfusion syndrome (FFTS) in twin and triplet pregnancy?
II	Type of review question	Prognostic
III	Objective of the review	To determine what the most accurate screening strategy for FFTS in twin and triplet pregnancies considering the optimum frequency and duration of ultrasound scans throughout pregnancy.
IV	Eligibility criteria – population/disease/condition/issue/domain	**For twin pregnancies:** • monochorionic diamniotic • monochorionic monoamniotic **For triplet pregnancies:** • dichorionic triamniotic • monochorionic triamniotic • dichorionic, diamniotic (a monochorionic twins set) and monochorionic monoamniotic Setting: Secondary or tertiary care centres
V	Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	**Estimated during ultrasound scan at 11^{+0} to 13^{+6} weeks:** • discrepant crown-rump length • discrepant nuchal translucency • abnormal ductus venosus doppler As FFTS occurs after this gestation the prognostic value of first trimester tests to detect FFTS will be prioritised. If no or limited prognostic data is available, then the diagnostic value of first trimester tests will be considered (see Table 2 and appendix A "Review Protocol 1.1"). The above tests will be considered in isolation or in combination. Details regarding frequency and duration of testing throughout pregnancy presented in included studies will be recorded.
VI	Eligibility criteria – comparator(s)/control or reference (gold) standard	**Condition of interest** **Ultrasound diagnosis of FFTS according to Quintero criteria** • Stage 1: A small amount of amniotic fluid (oligohydramnios - max vertical pocket of <2 cm) is found around the donor twin and a large amount of amniotic fluid (polyhydramnios – maximum vertical pocket of >8 cm) is found around the recipient twin at 20 weeks. Threshold is >10 cm at over 20 weeks gestational age (US only use >8 cm threshold at any gestational age) • Stage 2: Stage 1 plus the ultrasound is not able to identify the bladder in the donor twin

ID	Field (based on PRISMA-P)	Content
		• Stage 3: Stages 1 and 2 plus there is abnormal blood flow in the umbilical cords of the twins with at least one of the following: ○ a) absent end diastolic velocity in the umbilical artery / reverse end diastolic velocity in the umbilical artery ○ b) reverse flow in the ductus venosus ○ c) pulsatile umbilical venous flow • Stage 4: Stages 1–3 plus the recipient twin has swelling under the skin and appears to be experiencing heart failure (fetal hydrops) • Stage 5: Stages 1-4 plus one of the twins has died
VII	Outcomes and prioritisation	**Prognostic value of first trimester tests to predict FFTS according to Quintero criteria (as described above):** • odds ratios, relative risks, hazard ratios Estimates derived from multivariate analysis will be prioritised over estimates derived from univariate analysis
VIII	Eligibility criteria – study design	Systematic reviews of studies reporting prognostic value of tests Individual cohort studies reporting prognostic value of tests Prospective cohort studies will be prioritised if: • insufficient data are available from prospective cohort studies, then retrospective cohort studies will be considered. • no prospective or retrospective cohort study data is identified, case control studies may be considered for inclusion. Conference abstracts will not be considered
IX	Other inclusion exclusion criteria	Exclude: • studies that report on quadruplet or higher-order multiple pregnancies as per scope • studies that do not report results specifically for twin and/or triplet pregnancies • studies that include <5 pregnant women • structural or chromosomal anomalies • intra-uterine death at study entry • studies where 95% CIs for point estimates are not presented or where 95% CI for point estimates cannot be calculated
X	Proposed sensitivity/sub-group analysis, or meta-regression	Special consideration will be given to the following groups for which data will be reviewed and analysed separately if available: • twin pregnancies • triplet pregnancies 1. For twin pregnancies: • monochorionic diamniotic • monochorionic monoamniotic 2. For triplet pregnancies: • dichorionic triamniotic • monochorionic triamniotic • dichorionic, diamniotic (a monochorionic twins set) and monochorionic monoamniotic Important confounders for prognostic estimates that should be adjusted for in multivariate analysis:

ID	Field (based on PRISMA-P)	Content
		• age • BMI • parity • intrauterine growth restriction Estimates derived from multivariate analysis that do not adjust for the factors above will be included and the limitation noted
XI	Selection process – duplicate screening/selection/analysis	Formal duplicate screening will not be undertaken for this question although there will be senior supervision of the selection process. Hard copies of retrieved papers will be read by two reviewers and any disputes will be resolved in discussion with the Topic Advisor. Data extraction will be supervised by a senior reviewer. Draft excluded studies and evidence tables will be discussed with the Topic Advisor, prior to circulation to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair
XII	Data management (software)	NGA STAR software will be used for generating bibliographies/citations, study sifting, data extraction and recording quality assessment using checklists
XIII	Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase. Search limits: • limit to English language • limit to human-only studies • no limit on study design • limit year of publication to 2010 (date of previous guideline searches). Supplementary search techniques: no supplementary search techniques will be used
XIV	Identify if an update	This is an update of a review performed in 2011. Question: When and how should screening be used to identify feto-fetal transfusion syndrome in multiple pregnancy? Chapter 6.3 of full guideline Recommendations: **1.3.4 Monitoring for FFTS** 1.3.4.1 Do not monitor for FFTS in the first trimester. 1.3.4.2 Start diagnostic monitoring with ultrasound for FFTS (including to identify membrane folding) from 16 weeks. Repeat monitoring fortnightly until 24 weeks. 1.3.4.3 Carry out weekly monitoring of twin and triplet pregnancies with membrane folding or other possible early signs of FFTS (specifically, pregnancies with intertwin membrane infolding and amniotic fluid discordance) to allow time to intervene if needed. **Research recommendation** RR9 When and how should screening for FFTS be conducted in twin and triplet pregnancies?

ID	Field (based on PRISMA-P)	Content
XV	Author contacts	Developer: National Guideline Alliance https://www.nice.org.uk/guidance/indevelopment/gid-ng10063
XVI	Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014
XVII	Search strategy – for one database	For details please see appendix B.
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix G (clinical evidence tables) or H (economic evidence tables).
XX	Methods for assessing bias at outcome/study level	Quality assessment of individual studies will be performed using the following checklists: • AMSTAR for systematic reviews • QUIPS for cohort studies or case control studies reporting prognostic outcomes For details please see section 6.2 of Developing NICE guidelines: the manual 2014 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ or any adaptation of this will not be used to evaluate risk of bias across all available evidence for each outcome.
XXI	Criteria for quantitative synthesis (where suitable)	For details please see the methods chapter of the guideline and section 6.4 of Developing NICE guidelines: the manual 2014
XXII	Methods for analysis – combining studies and exploring (in)consistency	For a full description of methods see supplementary material C.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see the methods chapter of the in supplementary material C and section 6.2 of Developing NICE guidelines: the manual 2014.
XXIV	Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014.
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review in the guideline.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Anthony Pearson in line with section 3 Developing NICE guidelines: the manual 2014.

ID	Field (based on PRISMA-P)	Content
		Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For a full description of methods see supplementary material C.
XXVII	Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
XXVIII	Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
XXIX	Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England.
XXX	PROSPERO registration number	Not registered with PROSPERO

AMSTAR: Assessing the Methodological Quality of Systematic Reviews; BMI: body mass index; CCTR: Cochrane Central Register for Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; CI: confidence interval; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; QUIPS: Quality In Prognosis Studies tool

1.2 Review protocol – What is the optimal screening programme to identify feto-fetal transfusion syndrome (FFTS) in twin and triplet pregnancy? Diagnostic accuracy component for review question:

Table 6: Review protocol for ultrasound screening for feto-fetal transfusion (FFTS) syndrome

ID	Field (based on PRISMA-P)	Content
I	Review question	What is the optimal screening programme to identify feto-fetal transfusion syndrome (FFTS) in twin and triplet pregnancy?
II	Type of review question	Diagnostic accuracy
III	Objective of the review	To determine what the most accurate screening strategy for FFTS in twin and triplet pregnancies considering the optimum frequency and duration of ultrasound scans throughout pregnancy
IV	Eligibility criteria – population/disease/condition/issue/domain	**For twin pregnancies:** • monochorionic diamniotic • monochorionic monoamniotic **For triplet pregnancies:** • dichorionic triamniotic • monochorionic triamniotic • dichorionic, diamniotic (a monochorionic twins set) and monochorionic monamniotic Setting: Secondary or tertiary care centres
V	Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	**Index tests** **Estimated during ultrasound scan at 11^{+0} to 13^{+6} weeks:** • discrepant crown-rump length

ID	Field (based on PRISMA-P)	Content
		• discrepant nuchal translucency • abnormal ductus venosus doppler As FFTS occurs after this gestation the prognostic value of first trimester tests to detect FFTS will be prioritised (see Table 1 and appendix A "Review Protocol 1.2"). If no or limited prognostic data is available, then the diagnostic value of first trimester tests will be considered **Estimated during ultrasound scan at 14 weeks onwards:** • growth discordancy (fetal biometry including head circumference, abdominal circumference), femur length and estimated fetal weight) • amniotic fluid discordancy (amniotic fluid index, amniotic fluid discordance or maximum pool depth) • doppler studies (umbilical artery doppler (3 categories, ductus venosus doppler) • tricuspid regurgitation • absent visualisation of donor bladder • intertwining/infolding of the membrane As FFTS can occur at any point until birth during the second trimester, the diagnostic value of second trimester tests to detect FFTS will be examined. The above tests will be considered in isolation or in combination. Details regarding frequency and duration of testing throughout pregnancy presented in included studies will be recorded
VI	Eligibility criteria – comparator(s)/control or reference (gold) standard	**Reference standard** **Ultrasound diagnosis according to Quintero criteria:** • Stage I: A small amount of amniotic fluid (oligohydramnios - max vertical pocket of <2 cm) is found around the donor twin and a large amount of amniotic fluid (polyhydramnios – maximum vertical pocket of >8 cm) is found around the recipient twin at 20 weeks. Threshold is >10 cm at over 20 weeks gestational age (US-only use >8 cm threshold at any gestational age) • Stage 2: Stage 1 plus the ultrasound is not able to identify the bladder in the donor twin • Stage 3: Stages 1 and 2 plus there is abnormal blood flow in the umbilical cords of the twins with at least one of the following: ○ a) absent end diastolic velocity in the umbilical artery / reverse end diastolic velocity in the umbilical artery ○ b) reverse flow in the ductus venosus ○ c) pulsatile umbilical venous flow • Stage 4: Stages 1-3 plus the recipient twin has swelling under the skin and appears to be experiencing heart failure (fetal hydrops) • Stage 5: Stages 1-4 plus one of the twins has died
VII	Outcomes and prioritisation	**Diagnostic value of first and second trimester tests** **Critical:** • sensitivity • specificity Sensitivity was regarded as the more important measure for decision making as these are primarily screening diagnostic tests **Important:**

ID	Field (based on PRISMA-P)	Content
		• area under curve (AUC)
VIII	Eligibility criteria – study design	Systematic reviews of diagnostic accuracy studies Individual diagnostic accuracy studies including: • cross-sectional studies • cohort studies Prospective cohort studies will be prioritised. If insufficient data are available from prospective cohort studies, then retrospective cohort studies will be considered Conference abstracts will not be considered. Test and treat trials: CG129 did not include any test and treat trials. Scoping searches and committee advice also confirm that there are no test and treat trials for this topic
IX	Other inclusion exclusion criteria	Exclude: • studies that report on quadruplet or higher-order multiple pregnancies as per scope • studies that do not report results specifically for twin and/or triplet pregnancies • studies that include <5 pregnant women • structural or chromosomal anomalies • intra-uterine death at study entry • studies where 95% CIs for diagnostic accuracy estimates are not presented or where 2 x 2 contingency data are not presented or cannot be calculated
X	Proposed sensitivity/sub-group analysis, or meta-regression	Special consideration will be given to the following groups for which data will be reviewed and analysed separately if available: • twin pregnancies • triplet pregnancies 1. For twin pregnancies: • monochorionic diamniotic • monochorionic monoamniotic 2. For triplet pregnancies: • dichorionic triamniotic • monochorionic triamniotic • dichorionic, diamniotic (a monochorionic twins set) and monochorionic monoamniotic
XI	Selection process – duplicate screening/selection/analysis	Formal duplicate screening will not be undertaken for this question although there will be senior supervision of the selection process. Hard copies of retrieved papers will be read by two reviewers and any disputes will be resolved in discussion with the Topic Advisor. Data extraction will be supervised by a senior reviewer. Draft excluded studies and evidence tables will be discussed with the Topic Advisor, prior to circulation to the Topic Group for their comments. Resolution of disputes will be by discussion between the senior reviewer, Topic Advisor and Chair
XII	Data management (software)	Meta-analyses will be performed using Cochrane Review Manager (RevMan5) and WinBUGS if available data permit.

ID	Field (based on PRISMA-P)	Content
		A modified 'GRADE' method will be used to assess the quality of evidence for each index test. This will be described in the separate methods chapter for the guideline. NGA STAR software will be used for generating bibliographies/citations, study sifting, data extraction and recording quality assessment using checklists
XIII	Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Search limits: • limit to English language • limit to human-only studies • no limit on study design • limit year of publication to 2010 (date of previous guideline searches) Supplementary search techniques: no supplementary search techniques will be used
XIV	Identify if an update	This is an update of a review performed in 2011 Question: When and how should screening be used to identify FFTS in multiple pregnancy? Chapter 6.3 of full guideline Recommendations: **1.3.4 Monitoring for FFTS** 1.3.4.1 Do not monitor for FFTS in the first trimester. 1.3.4.2 Start diagnostic monitoring with ultrasound for FFTS (including to identify membrane folding) from 16 weeks. Repeat monitoring fortnightly until 24 weeks. 1.3.4.3 Carry out weekly monitoring of twin and triplet pregnancies with membrane folding or other possible early signs of FFTS (specifically, pregnancies with intertwin membrane infolding and amniotic fluid discordance) to allow time to intervene if needed. **Research recommendation** RR9 When and how should screening for FFTS be conducted in twin and triplet pregnancies? Main amendments to the protocol from previous protocol in CG129: • Placental anastomoses not included as an index test because this is mainly conducted in a research environment • Upper limited of 26 weeks not applied to capture any evidence of testing performed in the third trimester • Middle cerebral artery doppler maximum systolic velocity (MSV) not added (as suggested by NICE surveillance) as this is more relevant to twin anemia polycythemia sequence (TAPS) and not FFTS • "Subsequent midtrimester loss rate in population" not included as a reference standard as the priority was to diagnose FFTS and this might not relate to FFTS • Area under curve included as important outcome

ID	Field (based on PRISMA-P)	Content
XV	Author contacts	Developer: National Guideline Alliance https://www.nice.org.uk/guidance/indevelopment/gid-ng10063
XVI	Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014
XVII	Search strategy – for one database	For details please see appendix B
XVIII	Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables)
XIX	Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables)
XX	Methods for assessing bias at outcome/study level	Quality assessment of individual studies will be performed using the following checklists: • AMSTAR for systematic reviews • QUADAS-II for cross-sectional or cohort studies reporting diagnostic accuracy outcomes For details please see section 6.2 of Developing NICE guidelines: the manual 2014 The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
XXI	Criteria for quantitative synthesis (where suitable)	For details please see the methods chapter of the guideline and section 6.4 of Developing NICE guidelines: the manual 2014
XXII	Methods for analysis – combining studies and exploring (in)consistency	For a full description of methods see supplementary material C
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see the methods chapter of the guideline and section 6.4 of Developing NICE guidelines: the manual 2014
XXIV	Assessment of confidence in cumulative evidence	For details please see the methods chapter of the guideline and sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review in the guideline
XXVI	Describe contributions of	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and

ID	Field (based on PRISMA-P)	Content
	authors and guarantor	chaired by Anthony Pearson in line with section 3 of Developing NICE guidelines: the manual 2014. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For a full description of methods see supplementary material C
XXVII	Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
XXVIII	Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
XXIX	Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
XXX	PROSPERO registration number	Not registered with PROSPERO

AMSTAR: Assessing the Methodological Quality of Systematic Reviews; CCTR: Cochrane Central Register for Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; CI: confidence interval; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; QUADAS: Quality Assessment of Diagnostic Accuracy Studies

Appendix B – Literature search strategies

Literature search for review question: What is the optimal screening programme to identify feto-fetal transfusion syndrome (FFTS) in twin and triplet pregnancy?

The search cover the prognostic and diagnostic components in one search strategy.

Clinical Searches

Date of initial search: 03/01/2018

Database(s): Embase 1980 to 2018 Week 01, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 06/09/2018

Database(s): Embase 1980 to 2018 Week 36, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	Fetofetal Transfusion/ use ppez
2	newborn anemia/ use emez
3	((fetofetal or foetofoetal) adj2 transfusion syndrome).tw.
4	((feto fetal or foeto foetal) adj2 transfusion syndrome).tw.
5	(twin adj2 twin adj transfusion syndrome).tw.
6	twin-to-twin transfusion syndrome.tw.
7	intertwin transfusion syndrome.tw.
8	inter twin transfusion syndrome.tw.
9	(ttts or ffts).tw.
10	or/1-9
11	limit 10 to (english language and yr="2010 -Current")
12	Letter/ use ppez
13	letter.pt. or letter/ use emez
14	note.pt.
15	editorial.pt.
16	Editorial/ use ppez
17	News/ use ppez
18	exp Historical Article/ use ppez
19	Anecdotes as Topic/ use ppez
20	Comment/ use ppez
21	Case Report/ use ppez
22	case report/ or case study/ use emez
23	(letter or comment*).ti.
24	or/12-23
25	randomized controlled trial/ use ppez
26	randomized controlled trial/ use emez
27	random*.ti,ab.
28	or/25-27
29	24 not 28
30	animals/ not humans/ use ppez
31	animal/ not human/ use emez

#	Searches
32	nonhuman/ use emez
33	exp Animals, Laboratory/ use ppez
34	exp Animal Experimentation/ use ppez
35	exp Animal Experiment/ use emez
36	exp Experimental Animal/ use emez
37	exp Models, Animal/ use ppez
38	animal model/ use emez
39	exp Rodentia/ use ppez
40	exp Rodent/ use emez
41	(rat or rats or mouse or mice).ti.
42	or/29-41
43	11 not 42
44	remove duplicates from 43

Date of initial search: 03/01/2018

Database(s): the Cochrane Library, issue 1 of 12, January 2018

Date of updated search: 06/09/2018

Database(s): the Cochrane Library, issue 9 of 12, September 2018

ID	Search
#1	MeSH descriptor: [Fetofetal Transfusion] this term only
#2	((fetofetal or foetofoetal) near/2 transfusion syndrome)
#3	((feto fetal or foeto foetal) near/2 transfusion syndrome)
#4	(twin near/2 twin next transfusion syndrome)
#5	twin-to-twin transfusion syndrome
#6	intertwin transfusion syndrome
#7	inter twin transfusion syndrome
#8	(ttts or ffts)
#9	{or #1-#8} Publication Year from 2010 to 2018

Health economics

(For the Cochrane Library, see above)

Date of initial search: 03/01/2018

Database(s): Embase 1980 to 2018 Week 01, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date of updated search: 06/09/2018

Database(s): Embase 1980 to 2018 Week 36, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

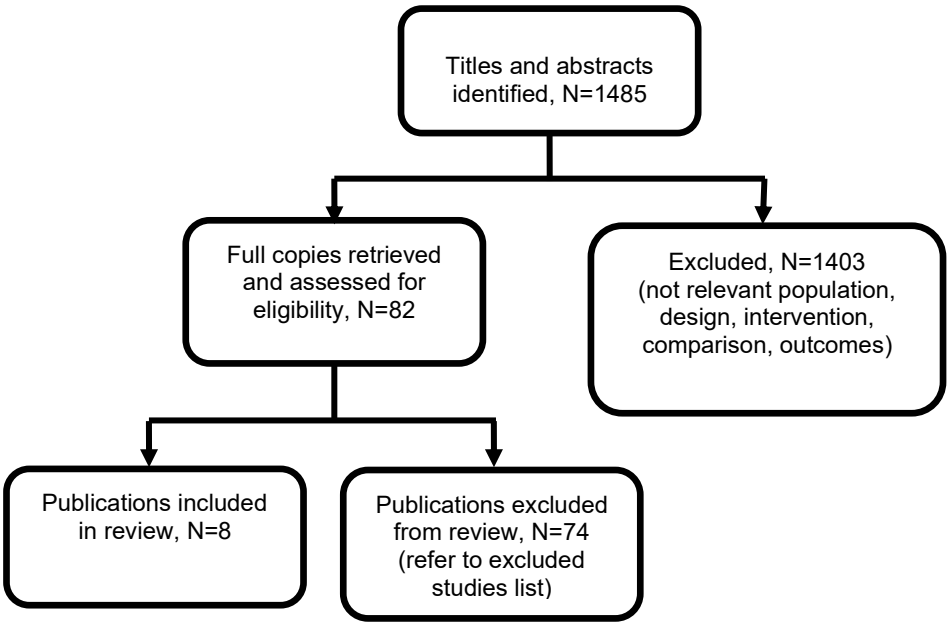
#	Searches
1	Fetofetal Transfusion/ use ppez
2	newborn anemia/ use emez
3	((fetofetal or foetofoetal) adj2 transfusion syndrome).tw.
4	((feto fetal or foeto foetal) adj2 transfusion syndrome).tw.
5	(twin adj2 twin adj transfusion syndrome).tw.
6	twin-to-twin transfusion syndrome.tw.
7	intertwin transfusion syndrome.tw.
8	inter twin transfusion syndrome.tw.
9	(ttts or ffts).tw.
10	or/1-9
11	limit 10 to (english language and yr="2010 -Current")
12	Letter/ use ppez
13	letter.pt. or letter/ use emez
14	note.pt.
15	editorial.pt.
16	Editorial/ use ppez
17	News/ use ppez
18	exp Historical Article/ use ppez
19	Anecdotes as Topic/ use ppez
20	Comment/ use ppez
21	Case Report/ use ppez
22	case report/ or case study/ use emez
23	(letter or comment*).ti.
24	or/12-23
25	randomized controlled trial/ use ppez
26	randomized controlled trial/ use emez
27	random*.ti,ab.
28	or/25-27
29	24 not 28
30	animals/ not humans/ use ppez
31	animal/ not human/ use emez
32	nonhuman/ use emez
33	exp Animals, Laboratory/ use ppez
34	exp Animal Experimentation/ use ppez
35	exp Animal Experiment/ use emez
36	exp Experimental Animal/ use emez

#	Searches
37	exp Models, Animal/ use ppez
38	animal model/ use emez
39	exp Rodentia/ use ppez
40	exp Rodent/ use emez
41	(rat or rats or mouse or mice).ti.
42	or/29-41
43	11 not 42
44	Economics/
45	Value of life/
46	exp "Costs and Cost Analysis"/
47	exp Economics, Hospital/
48	exp Economics, Medical/
49	Economics, Nursing/
50	Economics, Pharmaceutical/
51	exp "Fees and Charges"/
52	exp Budgets/
53	or/44-52 use ppez
54	health economics/
55	exp economic evaluation/
56	exp health care cost/
57	exp fee/
58	budget/
59	funding/
60	or/54-59 use emez
61	budget*.ti,ab.
62	cost*.ti.
63	(economic* or pharmaco?economic*).ti.
64	(price* or pricing*).ti,ab.
65	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
66	(financ* or fee or fees).ti,ab.
67	(value adj2 (money or monetary)).ti,ab.
68	or/61-66
69	53 or 60 or 68
70	43 and 69
71	remove duplicates from 70

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: What is the optimal screening programme to identify feto-fetal transfusion syndrome (FFTS) in twin and triplet pregnancy?

Figure 1: Flow diagram of clinical article selection for the optimal screening programme to identify feto-fetal transfusion syndrome in twin and triplet pregnancy



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is the optimal screening programme to identify feto-fetal transfusion syndrome (FFTS) in twin and triplet pregnancy?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Allaf, M. B., Campbell, W. A., Vintzileos, A. M., Haeri, S., Javadian, P., Ogburn, P., Figueroa, R., Wax, J., Markenson, G., Chavez, M. R., Ravangard, S. F., Ruano, R., Sangi-Haghpeykar, H., Salmanian, B., Meyer, M., Johnson, J., Ozhand, A., Davis, S., Borgida, A., Belfort, M. A., Shamshirsaz, A. A., Does early second-trimester sonography predict adverse perinatal outcomes in monochorionic diamniotic twin pregnancies?, Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine, 33, 1573-1578, 2014	**Sample size** N=177 MCDA twin pregnancies **Characteristics** Maternal age (mean (SD)): 34 (3.9) Gestational age at birth (weeks (SD)): 34.5 (3.9) FFTS: 19 (11%) Growth discordance ≥20%: 14 (8%) Preterm birth ≤28 weeks: 10 (6%) **Inclusion Criteria** 1) MCDA twin pregnancies with two live fetuses at the 16- to 18-week ultrasound scan. 2) Documented first trimester ultrasound scan at 11^{+0} to 13^{+6} weeks. **Exclusion Criteria**	**Tests** **Index test** Ultrasound (abdominal circumference, femur length, head circumference, estimated fetal weight) measured at 16- to 18-weeks. **Reference standard** FFTS defined according to classification of Quintero et al. (1999).	**Methods** This is a multicentre study conducted at 9 regional perinatal centres in the USA. The electronic obstetric ultrasound database of each institution was queried to identify all MCDA twin pregnancies with 2 live fetuses presenting at the 16- to 18 week ultrasound examination who had a documented first trimester ultrasound examination at 11^{+0} to 13^{+6} weeks, between January 2007 and June 2011. All pregnancies included were monitored by serial ultrasound evaluations of abdominal circumference, femur length, head circumference, and estimated fetal weight measured at 16 to 18 weeks' gestation. The intertwin difference between the two fetuses is	**Results** Diagnostic accuracy of abdominal circumference discordance (cut off ≥20%) to predict FFTS: AUC: 0.65 (95% CI 0.46 to 0.75) Diagnostic accuracy of head circumference discordance (cut off ≥20%) to predict FFTS: AUC: 0.61 (95% CI 0.46 to 0.76). Diagnostic accuracy of femur length discordance (cut off ≥20%) to predict FFTS: AUC: 0.62 (95% CI 0.43 to 0.62). Diagnostic accuracy of estimated fetal weight discordance to predict FFTS:	**Limitations** Risk of bias was assessed using QUADAS-II **A. Risk of bias** **Patient sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes (81 neonates excluded from analysis due to incomplete data and 19 because of intrauterine fetal demise) Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** **Patient characteristics and setting** Are there concerns that the included patients and

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 759244 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To assess the value of early second-trimester (16 to 18 weeks) ultrasound examination in predicting adverse outcomes in twin pregnancies. **Study dates** January 2007 to June 2011 **Source of funding** None reported.	1] Pregnancies with known chromosomal abnormality or major congenital malformation. 2] Pregnancies whose initial second-trimester examinations were >18 weeks gestation. 3] Pregnancies that did not have follow-up ultrasound scans.		expressed as a percentage of the larger measurement. Abnormal growth discordance was set at a difference of ≥20% on follow-up ultrasound after 18 weeks. **Power calculation** The available sample sizes for the primary outcomes were 54 for adverse composite obstetric outcomes (31%) and 123 controls (69%). Based on these sample sizes and a minimally acceptable AUC of 0.60, the study had at least 80% power. **Statistical analysis** Sensitivity and specificity for each cut-off value were calculated and displayed on receiver operating curves. Logistic regression and ROC curve analyses were used to estimate the AUC.	AUC: 0.66 (95% CI 0.58 to 0.81).	setting do not match the review question? Unclear concern **Index Test** **A. Risk of bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern **Reference standard** **A. Risk of bias** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or **its**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern **Flow and Timing** **A. Risk of bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? No Could the patient flow have introduced bias? Unclear concern **Other information** Linked to Allaf (2014) - ultrasound (abdominal circumference, femur length, head circumference, estimated fetal weight) measured at 11^{+0} to 13^{+6} weeks.
Full citation Allaf, M. B., Vintzileos, A. M., Chavez, M. R.,	**Sample size** N=177 MCDA twin pregnancies.	**Tests** **Index test**	**Methods** This is a multicenter study conducted at 9 regional	**Results**	**Limitations**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Wax, J. A., Ravangard, S. F., 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, M. A., Ogburn, P., Campbell, W. A., Shamshirsaz, A. A., First-trimester sonographic prediction of obstetric and neonatal outcomes in monochorionic diamniotic twin pregnancies, Journal of Ultrasound in Medicine, 33, 135-40, 2014 **Ref Id** 756483 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study**	**Characteristics** Maternal age (mean (SD)): 34 (3.9) Gestational age at birth (weeks (SD)): 34.5 (3.9) FFTS: 19 (11%) Growth discordance ≥20%: 14 (8%) Preterm birth ≤28 weeks: 10 (6%) **Inclusion Criteria** All monochorionic diamniotic twin pregnancies with two live fetuses presenting at the 11^{+0} to 13^{+6} weeks sonographic examination. **Exclusion Criteria** Cases with known chromosomal abnormalities, major congenital malformations, and single or double IUFD at the time of the first-trimester examination were excluded. Also pregnancies referred at later gestations or with no follow-up	Ultrasound - NT and CRL measured at 11^{+0} to 13^{+6} weeks. The intertwin discordances in NT and CRL were calculated as the differences in the measurements between the two fetuses, expressed as a percentage of the larger measurement. **Reference standard** FFTS defined according to classification of Quintero et al. (1999).	perinatal centers in the USA. The electronic obstetric ultrasound database of each institution was queried to identify all MCDA twin pregnancies with two live fetuses presenting at the 11^{+0} to 13^{+6} weeks sonographic examination between January 2007 and June 2011. All pregnancies included were monitored by serial sonographic evaluations of growth, amniotic fluid volume measurement, and doppler interrogation of the fetal vessels starting at 16 to 18 weeks' gestation and at least every 2 to 4 weeks thereafter until birth. The intertwin discordances in nuchal translucency and CRL were calculated as the differences in the measurements between the two fetuses, expressed as a percentage of the larger measurement. **Statistical analysis** Logistic regression and ROC curve analyses were used to estimate the AUC.	Diagnostic accuracy of NT discordance (cut off ≥20%) to predict FFTS: AUC (area under the curve): 0.52 (95% CI 0.39 to 0.65) Diagnostic accuracy of CRL discordance (cut off ≥20%) to predict FFTS: AUC (area under the curve): 0.57 (95% CI 0.4 to 0.70). Note: the authors stated that they could not demonstrate optimal cut-off point that would be clinically useful in predicting adverse outcomes.	Risk of bias was assessed using QUADAS-II **A. Risk of bias** **Patient sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** **Patient characteristics and setting** Are there concerns that the included patients and setting do not match the review question? Low concern **Index Test** **A. Risk of bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
To test the hypothesis that discordant nuchal translucency, CRL and combined (NT and CRL) measurements in MCDA twins at the time of aneuploidy screening are predictive of adverse obstetric and neonatal outcomes. **Study dates** Between January 2007 and June 2011. **Source of funding** Not reported.	sonographic examinations.				Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern **Reference standard** **A. Risk of bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern **Flow and Timing** **A. Risk of bias**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Other information** None
Full citation Maiz,N., Staboulidou,I., Leal,A.M., Minekawa,R., Nicolaides,K.H., Ductus venosus Doppler at 11 to 13 weeks of gestation in the prediction of outcome in twin pregnancies, Obstetrics and Gynecology, 113, 860-865, 2009 **Ref Id** 3429 **Country/ies where the study was carried out** UK	**Sample size** N=179 monochorionic twin pregnancy (26 with severe FFTS) **Characteristics** Median maternal age - years (IQR) Dichorionic (n=516): 33.5 (29.7-36.7) Monochorionic (n=179): 31.9 (27.7-36.5) Median gestational age - days (IQR) 89 (86-92) **Inclusion Criteria** Diamniotic twin pregnancies with two	**Tests** **Index test** Ultrasound - NT, CRL, and DV flow (defined as abnormal when reversed A-wave flow was present) measured at 11 to 13 weeks' gestation. The intertwin discordances in NT and CRL were calculated as the differences in the measurements between the two fetuses, expressed as a percentage of the larger measurement.	**Methods** Monochorionic twins were followed up with ultrasound scans at 16 to 18 weeks' gestation and monthly thereafter, unless there was evidence of FFTS, in which case the frequency was increased as necessary. **Statistical analysis** Multiple logistic regression analysis was performed to determine the significance of reversed DV flow and intertwin discordance in CRL and NT and maternal characteristics.	**Results** Multiple logistic regression demonstrated a significant contribution to severe FFTS by reversed DV flow in at least 1 fetus* (OR: 5.09, 95% CI 1.94-13.37; p=0.001) *not reported what the analysis was adjusted for	**Limitations** Risk of bias was assessed using QUADAS-II **A. Risk of bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study type Prospective cohort study **Aim of the study** To examine the value of DV flow in predicting adverse outcomes in twin pregnancies at 11 to 13 weeks' gestation. **Study dates** January 2006 to January 2008 **Source of funding** None reported	live fetuses at 11 to 13 weeks. **Exclusion Criteria** Not reported	**Reference standard** FFTS defined as ultrasound diagnosis of hydramnios in one twin and anhydramnios in the other, and absent or reversed end diastolic flow in either the umbilical artery or DV in one or both foetuses.			**Patient characteristics and setting** Are there concerns that the included patients and setting do not match the review question? Low concern **Index Test** **A. Risk of bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern **Reference standard** **A. Risk of bias** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern **Flow and Timing** **A. Risk of bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Other information** Additional data from original paper, to that reported in Stagnati 2017
Full citation	**Sample size**	**Tests** **Index test**	**Methods**	**Results** NT intertwin ratio	**Limitations**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Matias, A., Montenegro, N., Loureiro, T., Cunha, M., Duarte, S., Freitas, D., Severo, M., Screening for twin-twin transfusion syndrome at 11-14 weeks of pregnancy: the key role of ductus venosus blood flow assessment, Ultrasound in Obstetrics & Gynecology, 35, 142-8, 2010 **Ref Id** 756707 **Country/ies where the study was carried out** Portugal **Study type** Prospective cohort study **Aim of the study** To assess the role of ductus venosus blood flow in screening for FFTS in monochorionic twins. **Study dates**	N=99 MCDA twin pregnancies (12 with FFTS) **Characteristics** Median gestational age - weeks (range) 12 (11 to 13+6) CRL (mm) - mean ±SD Total (n=99): 64 (9.6) FFTS (n=12): 61.0 (10.2) Intertwin difference in CRL (mm)- mean ±SD Total: 2.96 (2.41) FFTA: 3.54 (2.90) CRL ratio (mm) - mean ±SD Total: 1.05 (0.04) FFTS: 1.06 (0.06) NT (mm) - mean ±SD Total: 1.6 (0.6) FFTS: 1.9 (0.6) Intertwin difference in NT (mm) - mean ±SD Total: 0.36 (0.58) FFTS: 1.03 (1.12)	Ultrasound - NT and CRL intertwin differences, NT and CRL intertwin ratios and abnormal DV blood flow in at least one fetus, measured at 11 to 14 weeks' gestation. **Reference standard** FFTS defined according to classification of Quintero et al. (1999); severe FFTS was defined by the presence of oligohydramnios and non-visible bladder in the donor, and polyhydramnios and dilated bladder in the recipient, in addition to different stages of doppler deterioration in both the arterial and venous compartments.	After 14 weeks' gestation, twins were assessed every 2 weeks. Laser treatment of placental anastomoses was performed when clinically indicated on diagnosis of FFTS (10 cases). **Statistical analysis** Crude (univariate analysis) and adjusted (multivariate analysis) RR, estimated by Poisson regression model with log link function, and 95% CIs were used to measure the associations between the screening tests and FFTS. The area under the ROC curve and 95% CIs were calculated.	AUC: 0.75 (95% CI: 0.60-0.89) Adjusted NT ratio - RR (95% CI): 1.20 (0.82 to 1.63) CRL intertwin ratio AUC: 0.58 (95% CI 0.42-0.75) Adjusted CRL intertwin ratio - RR (95% CI) 1.07 (0.67 to 1.60) Adjusted abnormal DV flow in at least one fetus - RR (95% CI) 11.99 (3.12 to 58.00)	Risk of bias was assessed using QUADAS-II **A. Risk of bias** **Patient sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** **Patient characteristics and setting** Are there concerns that the included patients and setting do not match the review question? Low concern **Index Test** **A. Risk of bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
December 1997 to October 2008 **Source of funding** None reported	NT ratio (mm) - mean ±SD Total: 1.28 (0.48) FFTS: 1.80 (0.90) DV blood flow (normal flow) - no. (%) Total: 83 (83.8) FFTS: 3 (25.0) DV blood flow (abnormal flow in one fetus) - no. (%) Total: 13 (13.1) FFTS: 6 (50.0) DV blood flow (abnormal flow in two fetuses) - no. (%) Total: 3 (3.0) FFTS: 3 (25.0) **Inclusion Criteria** MCDA twin pregnancies assessed at 11 to 14 weeks' gestation. **Exclusion Criteria** Fetuses with malformations or fetal death.				Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern **Reference standard** **A. Risk of bias** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern **Flow and Timing** **A. Risk of bias**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Limitations assessed with the QUIPS for prognostic factors:** **Participants:** unclear risk of bias (no description of the study population) **Prognostic factor measurement:** unclear risk of bias (not reported if providers and/or women were blinded to test result) **Outcome measurement:** low risk of bias **Confounding:** unclear risk of bias (not adjusted for any maternal confounding factors) **Analysis and reporting:** low risk of bias **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Additional data from original paper, to that reported in Stagnati 2017
Full citation Memmo,A., Dias,T., Mahsud-Dornan,S., Papageorghiou,A.T., Bhide,A., Thilaganathan,B., Prediction of selective fetal growth restriction and twin-to-twin transfusion syndrome in monochorionic twins, BJOG: An International Journal of Obstetrics and Gynaecology, 119, 417-421, 2012 **Ref Id** 272898 **Country/ies where the study was carried out** UK **Study type** Retrospective cohort study **Aim of the study** To assess the ability of discrepancy between CRL and NT in monochorionic twins at 11 to 14 weeks'	**Sample size** N=242 MCDA twin pregnancies (102 with FFTS) **Characteristics** Maternal age (years) - median (IQR) 34 (29-37) Gestation at scan (weeks) - median (IQR) 12.6 (12.1-13.0) Larger twin CRL (mm) - median (IQR) 63.10 (57.50-70.0) Smaller twin CRL (mm) - median (IQR) 61.80 (54.30-67.20) CRL discrepancy (%) 3.83 (1.57-7.54) Larger twin NT (mm) - median (IQR) 1.60 (1.30-2.00) Smaller twin NT (mm) - median (IQR) 1.30 (1.20-1.60)	**Tests** **Index test** Ultrasound - discrepancies in NT, CRL, and EFW measured at 11 to 14 weeks' gestation. The intertwin discordances in CRL and EFW were calculated as the differences in the measurements between the two fetuses, expressed as a percentage of the larger measurement. NT discordance was calculated as a percentage of the smaller twin measurement. **Reference standard** FFTS defined according to classification of Quintero et al. (1999).	**Methods** All monochorionic pregnancies were followed up with scans every 2 weeks from 16 to 24 weeks, until a diagnosis of FFTS was excluded. All twins without the diagnosis of FFTS underwent ultrasound scans every 4 weeks thereafter. **Statistical analysis** ROC curves were used to evaluate the role of inter-twin discrepancies as a marker by comparing TTTS with the control group.	**Results** AUC for the prediction of FFTS (CRL discrepancy): 0.58 (95% CI 0.49-0.66)	**Limitations** Risk of bias was assessed using QUADAS-II **A. Risk of bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes (although includes a control cohort and cohort with sFGR). Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** **Patient characteristics and setting** Are there concerns that the included patients and setting do not match the review question? Low concern **Index Test** **A. Risk of bias**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
gestation to discriminate for the diagnosis of FFTS. **Study dates** January 2000 to March 2010 **Source of funding** None	NT discrepancy (%) 16.65 (7.85-39.60) **Inclusion Criteria** 1] Monochorionic twins complicated with FFTS Quintero stage II or more. 2] Twin pregnancies involving Stage 1 FFTS with worsening amniotic fluid discordance or that progressed to Stage 2 or more were included. **Exclusion Criteria** 1] Monochorionic pregnancies complicated by FFTS of sFGR. 2] Twin pregnancies involving Stage 1 FFTS, managed expectantly, and did not require fetoscopic intervention.				Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? No Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern **Reference standard** **A. Risk of bias** Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern **Flow and Timing** **A. Risk of bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Other information** Additional data from original paper, to that reported in Stagnati 2017
Full citation Stagnati, V., Zanardini, C., Fichera, A., Pagani, G., Quintero, R. A., Bellocco, R., Prefumo, F. Early prediction of twin-to-twin transfusion syndrome: systematic review and meta-analysis, Ultrasound in Obstetrics & Gynecology Ultrasound Obstet	**Sample size** N=13 studies (8 prospective study designs, 4 retrospective, 1 unclear) N=1,991 monochorionic twin pregnancies: Casasbuenas (2008): n=30 (27	**Tests** **Index test** Ultrasound – NT, CRL, and DV flow (defined as abnormal when reversed A-wave flow was present) measured at <16 weeks' gestation. The intertwin discordances in NT and CRL were calculated as the	**Methods** Statistical analysis 2 x 2 contingency tables constructed for each predictive outcome and included study. Sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratios were calculated using	**Results** Ultrasound parameters - % (95% CIs) Casasbuenas (2008) - FFTS (n=6)* NT >95th percentile TP: 1 FP: 4 FN: 5 TN: 20 NT discrepancy >20% TP: 3 FP: 8	**Limitations** **AMSTAR** Did the research questions and inclusion criteria for the review include the components of PICO? Yes Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Gynecol, 49, 573-582, 2017 **Ref Id** 756458 **Country/ies where the study was carried out** Multiple countries **Study type** Systematic review **Aim of the study** To assess the role of first- and early second-trimester markers in the prediction of FFTS in monochorionic twin pregnancies. **Study dates** Search: inception to April 2014 **Includes 13 studies** Casasbuenas,A., Wong,A.E., Sepulveda,W., Nuchal translucency thickness in monochorionic multiple pregnancies: value in predicting pregnancy outcome, Journal of Ultrasound in Medicine, 27, 363-369, 2008	MCDA twin pregnancies; 3 triplet pregnancies with 1 set of monochorionic fetuses) El Kateb (2007): n=103 Fratelli (2011): n=135 Kagan (2007): n=512 Lewi (2008): n=200 Linskens (2009): n=61 Maiz (2009): n=179 Matias (2005): n=50 Matias (2010): n=99 Memmo (2012): n=242 Sebire (2000): n=287 Sperling (2007): n=70 Sueters (2006): n=23	differences in the measurements between the 2 fetuses, expressed as a percentage of the larger measurement. Abnormal DV in at least one twin. **Reference standard** FFTS defined as a discrepancy in DVP of amniotic fluid (>8 cm in recipient twin and <2 cm in donor twin) according to classification of Quintero et al. (1999). **Index test** - by each study NT >95th percentile Sperling (2007); Sueters (2006) NT discrepancy >0.5 mm Matias (2005) NT >95th percentile; intertwin membrane folding Sebire (2000) NT discrepancy (as % of smaller NT); CRL discrepancy >10% Memmo (2012)	DerSimonian-Laird random effects model. Meta-analysis was planned for the following predictive outcomes: 1] Intertwin NT discrepancy; 2] NT >95th percentile in at least one twin (where individual data were available, NT percentile was adjusted for CRL; 3] Intertwin CRL discrepancy as a % of the larger CRL; 4] Abnormal DV flow in at least one twin. Additional data from individual studies El Kateb (2007) Twin pregnancies followed up from 11–14 weeks' gestation onwards and at 2-week intervals up until birth.	FN: 3 TN: 16 CRL discrepancy >10% TP: 0 FP: 3 FN: 5 TN: 21 El Kateb (2007) - FFTS (n=5) NT >95th percentile TP: 1 FP: 4 FN: 4 TN: 94 CRL discrepancy >10% TP: 1 FP: 9 FN: 4 TN: 89 Fratelli (2011) - FFTS (n=16) NT >95th percentile TP: 1 FP: 12 FN: 15 TN: 107 NT discrepancy >20% TP: 6 FP: 46 FN: 10 TN: 73 CRL discrepancy >10% TP: 2 FP: 17 FN: 14	justify any significant deviations from the protocol? Yes (registered on PROSPERO). Did the review authors explain their selection of the study designs for inclusion in the review? No Did the review authors use a comprehensive literature search strategy? Yes Did the review authors perform study selection in duplicate? Yes Did the review authors perform data extraction in duplicate? Yes Did the review authors provide a list of excluded studies and justify the exclusions? Yes Did the review authors describe the included studies in adequate detail? Partial Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review? Yes (QUADAS-II) Did the review authors report on the sources of funding for the studies included in the review? No

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
El Kateb, A., Nasr, B., Nassar, M., Bernard, J. P., Ville, Y., First-trimester ultrasound examination and the outcome of monochorionic twin pregnancies, 27, 922-5, 2007 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 Human Development, 87, 27-30, 2011 Kagan,K.O., Gazzoni,A., Sepulveda-Gonzalez,G., Sotiriadis,A., Nicolaides,K.H., Discordance in nuchal translucency thickness in the prediction of severe twin-to-twin transfusion syndrome, Ultrasound in	**Characteristics** Quintero stage I Excluded: Matias (2005); Memmo (2012) Included: Casasbuenas (2008); El Kateb (2007); Fratelli (2011); Lewi (2008); Linskens (2009); Matias (2010); Sperling (2007); Sueters (2006) Not stated: Kagan (2007); Maiz (2009); Sebire (2000) Ultrasound follow-up frequency Every 2 weeks El Kateb (2007); Fratelli (2011); Sueters (2006) Every 4 weeks Kagan (2007); Maiz (2009); Matias (2005) At Weeks 16, 20 and 26 Lewi (2008) At Weeks 19, 21 and 23 Sperling (2007) Serial Linskens (2009)	NT >95th percentile; CRL discrepancy >10% El Kateb (2007) NT >95th percentile; NT discrepancy >20%; CRL discrepancy >10% Casasbuenas (2008); Fratelli (2011); Kagan (2007); Linskens (2009) NT discrepancy >20%; CRL discrepancy ≥12mm; amniotic fluid discordance; discordant cord insertion; discordant abdominal circumference Lewi (2008) NT ratio; NT discrepancy ≥0.6mm; CRL ratio; CRL discrepancy ≥10mm; reversed DV flow Matias (2010) Reversed DV flow Maiz (2009) **Reference standard** - by each study DVP <2 cm in donor, >8 cm in recipient Casasbuenas (2008); Linskens (2009);		TN: 102 <u>Kagan (2007) - FFTS (n=58)</u> <u>NT discrepancy >20%</u> TP: 33 FP: 105 FN: 25 TN: 349 <u>CRL discrepancy >10%</u> TP: 13 FP: 42 FN: 45 TN: 412 <u>Lewi (2008) - FFTS (n=18)</u> <u>NT discrepancy >20%</u> TP: 10 FP: 79 FN: 8 TN: 103 <u>CRL discrepancy ≥12mm</u> TP: 10 FP: 42 FN: 8 TN: 140 <u>Amniotic fluid</u> Sensitivity: 22.2 (9.0-45.2) Specificity: 95.6 (91.6-97.8)	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? Yes If meta-analysis was performed, did the review authors assess the potential impact of the risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis? No Did the review authors account for the risk of bias in individual studies when interpreting/discussing the results of the review? No Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? Yes If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? No Did the review authors report any potential sources of conflict of interest, including any funding they

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Obstetrics and Gynecology, 29, 527-532, 2007 Lewi, L., Lewi, P., Diemert, A., Jani, J., Gucciardo, L., Van Mieghem, T., Done, E., Gratacos, E., Huber, A., Hecher, K., Deprest, J., The role of ultrasound examination in the first trimester and at 16 weeks' gestation to predict fetal complications in monochorionic diamniotic twin pregnancies, Am J Obstet GynecolAmerican journal of obstetrics and gynecology, 199, 493.e1-7, 2008 Linskens, I. H., de Mooij, Y. M., Twisk, J. W., Kist, W. J., Oepkes, D., van Vugt, J. M., Discordance in nuchal translucency measurements in monochorionic diamniotic twins as predictor of twin-to-twin transfusion syndrome, Twin Res Hum GenetTwin research	Not stated Casasbuenas (2008); Matias (2010); Memmo (2012); Sebire (2000) Casasbuenas (2008)* Maternal age (years) - median (range) 30 (24-43) Gestational age (weeks) - median (range) 12 (11-14) CRL of fetuses (mm) - mean ±SD Larger fetus: 65.1 (9.9) Smaller fetus: 62.4 (10.1) NT (mm) - median (range) Larger fetus: 1.5 (1.0-17.0) Smaller fetus: 1.6 (1.0-4.5) Fratelli (2011)* Gestational age at FFTS diagnosis (range, weeks): 17+2-29+6 NT discordance (range): 0%-37% CRL discordance (range): 1%-24%	Matias (2012); Memmo (2012); Sperling (2007); Sueters (2006) DVP <2 cm in donor, >8 cm before 20 weeks and >10 cm after 20 weeks in recipient El Kateb (2007); Fratelli (2011); Lewi (2008) Not defined Kagan (2007); Maiz (2009) Other Matias (2005); Sebire (2000)		Linskens (2009) - FFTS (n=14) NT >95th percentile TP: 3 FP: 0 FN: 11 TN: 47 NT discrepancy >20% TP: 9 FP: 9 FN: 5 TN: 38 CRL discrepancy >10% TP: 4 FP: 6 FN: 10 TN: 41 Maiz (2009) - FFTS (n=26) Reversed DV flow TP: 10 FP: 23 FN: 16 TN: 130 Matias (2005) - FFTS (n=4) NT discrepancy ≥0.5mm TP: 1 FP: 16 FN: 3 TN: 30 NT >95th percentile TP: 3	received for conducting the review? No **QUADAS-II – individual studies*:** **Casasbuenas (2008)** **A. Risk of bias** **Patient sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** **Patient characteristics and setting** Are there concerns that the included patients and setting do not match the review question? Unclear concern **Index Test** **A. Risk of bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
and human genetics : the official journal of the International Society for Twin Studies, 12, 605-10, 2009 Maiz,N., Staboulidou,I., Leal,A.M., Minekawa,R., Nicolaides,K.H., Ductus venosus Doppler at 11 to 13 weeks of gestation in the prediction of outcome in twin pregnancies, Obstetrics and Gynecology, 113, 860-865, 2009 Matias, A., Ramalho, C., Montenegro, N., Search for hemodynamic compromise at 11-14 weeks in monochorionic twin pregnancy: is abnormal flow in the ductus venosus predictive of twin-twin transfusion syndrome?, Journal of Maternal-Fetal & Neonatal MedicineJ Matern Fetal Neonatal Med, 18, 79-86, 2005	Kagan (2007)* Stage of FFTS: Quintero II: 13 (22.4%) Quintero III: 45 (77.6%) Linskens (2009)* Median maternal age - years (range): FFTS (n=14) 31.8 (20-41) Median CRL discordance - % (range): FFTS (n=14) 6% (0-23%) Median NT discordance - % (range): FFTS (n=14) 28% (0-91%) Median gestational age at birth - weeks (range): FFTS (n=14) 30+6 (17+3-40+2) Stage of FFTS: Quintero II: 2 Quintero III: 12 Matias (2005)* Median maternal age - years (range): 33 (15-44) Median gestational age - weeks (range): 12 (11-13)			FP: 6 FN: 1 TN: 40 Sensitivity: 75.0 (19.0-98.7) Specificity: 87.0 (74.3-94.9) <u>Matias (2010) - FFTS (n=12)</u> <u>NT and CRL ratios (not assessable; NA)</u> <u>Reversed DV flow</u> TP: 9 FP: 7 FN: 3 TN: 80 <u>CRL discrepancy ≥10 mm</u> Sensitivity: 0.8 (NA) Specificity: NA <u>NT discrepancy ≥0.6 mm</u> TP: 6 FP: 7 FN: 6 TN: 80 <u>Memmo (2012) - FFTS (n=102)</u> <u>NT discrepancy (as % of smaller NT) (NA)</u> <u>CRL discrepancy >10%</u> TP: 1 FP: 1 FN: 101 TN: 139	If a threshold was used, was it pre-specified? No (but states that measurements follow recommendations of the UK Fetal Medicine Foundation) Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern **Reference standard** **A. Risk of bias** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Matias, A., Montenegro, N., Loureiro, T., Cunha, M., Duarte, S., Freitas, D., Severo, M., Screening for twin-twin transfusion syndrome at 11-14 weeks of pregnancy: the key role of ductus venosus blood flow assessment, Ultrasound in Obstetrics & Gynecology, 35, 142-8, 2010 Memmo,A., Dias,T., Mahsud-Dornan,S., Papageorghiou,A.T., Bhide,A., Thilaganathan,B., Prediction of selective fetal growth restriction and twin-to-twin transfusion syndrome in monochorionic twins, BJOG: An International Journal of Obstetrics and Gynaecology, 119, 417-421, 2012 Sebire,N.J., Souka,A., Skentou,H., Geerts,L., Nicolaides,K.H., Early prediction of severe	*Data extracted from original paper. **Inclusion Criteria** Studies reporting predictive accuracy of ultrasound scans at <16 weeks' gestation in monochorionic twin pregnancies. Data from primary studies Casasbuenas (2008) Women with live first-trimester monochorionic multiple pregnancies in which fetuses had CRL between 45 and 84mm. **Exclusion Criteria** 1] Prediction of FFTS later than 16 weeks' gestation. 2] Study populations published >1 by the same authors.			Sebire (2000) - FFTS (n=43) NT >95th percentile TP: 12 FP: 25 FN: 31 TN: 219 Intertwin membrane folding - presence or absence (ultrasound at 15–17 weeks gestation Sensitivity: 42.9 (30.0–56.7) Specificity: 98.1 (93.3–99.5) Sperling (2007) - FFTS (n=15) NT >95th percentile (NA) Sueters (2006) - FFTS (n=4) NT >95th percentile TP: 0 FP: 2 FN: 4 TN: 17 * FFTS in twin pregnancies. ** Data extracted from original paper.	Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern **Flow and Timing** **A. Risk of bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **El Kateb (2007)** **A. Risk of bias** **Patient sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? No (136 nonconsecutive monochorionic diamniotic pregnancies used as a control group: 64 developed FFTS and 72 did not) Did the study avoid inappropriate exclusions? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
twin-to-twin transfusion syndrome, Human Reproduction, 15, 2008-2010, 2000 Sperling,L., Kiil,C., Larsen,L.U., Brocks,V., Wojdemann,K.R., Qvist,I., Schwartz,M., Jorgensen,C., Espersen,G., Skajaa,K., Bang,J., Tabor,A., Detection of chromosomal abnormalities, congenital abnormalities and transfusion syndrome in twins, Ultrasound in Obstetrics and Gynecology, 29, 517-526, 2007 Sueters,M., Middeldorp,J.M., Lopriore,E., Oepkes,D., Kanhai,H.H., Vandenbussche,F.P., Timely diagnosis of twin-to-twin transfusion syndrome in monochorionic twin pregnancies by biweekly sonography combined with patient instruction to report onset of symptoms,					Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** **Patient characteristics and setting** Are there concerns that the included patients and setting do not match the review question? Unclear concern **Index Test** **A. Risk of bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern **Reference standard** **A. Risk of bias**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ultrasound in Obstetrics and Gynecology, 28, 659-664, 2006 **Source of funding** None reported.					Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern **Flow and Timing** **A. Risk of bias** Was there an appropriate interval between the index test and the reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Fratelli (2011)**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					A. Risk of bias **Patient sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Unclear (excludes pregnancies referred at a later gestation even if first trimester NT and CRL data available) Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** **Patient characteristics and setting** Are there concerns that the included patients and setting do not match the review question? Unclear concern **Index Test** **A. Risk of bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					(reference values for NT mentioned) Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern **Reference standard** **A. Risk of bias** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Flow and Timing **A. Risk of bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Kagan (2007)** **A. Risk of bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** **Patient characteristics and setting** Are there concerns that the included patients and

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					setting do not match the review question? Low concern **Index Test** **A. Risk of bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? No Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern **Reference standard** **A. Risk of bias** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern **Flow and Timing** **A. Risk of bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Lewi (2008)** **A. Risk of bias** **Patient sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** **Patient characteristics and setting** Are there concerns that the included patients and setting do not match the review question? Low concern **Index Test** **A. Risk of bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? No Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Reference standard **A. Risk of bias** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern **Flow and Timing** **A. Risk of bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Could the patient flow have introduced bias? Low concern **Linskens (2009)** **A. Risk of bias** **Patient sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** **Patient characteristics and setting** Are there concerns that the included patients and setting do not match the review question? Low concern **Index Test** **A. Risk of bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					If a threshold was used, was it pre-specified? No Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern **Reference standard** **A. Risk of bias** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Flow and Timing **A. Risk of bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Matias (2005)** **A. Risk of bias** **Patient sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** **Patient characteristics and setting** Are there concerns that the included patients and

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					setting do not match the review question? Low concern **Index Test** **A. Risk of bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern **Reference standard** **A. Risk of bias** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern **Flow and Timing** **A. Risk of bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same Reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Sebire (2000)** **A. Risk of bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** **Patient characteristics and setting** Are there concerns that the included patients and setting do not match the review question? Low concern **Index Test** **A. Risk of bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? No Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Reference standard **A. Risk of bias** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern **Flow and Timing** **A. Risk of bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Could the patient flow have introduced bias? Low concern **Sperling (2007)** **A. Risk of bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** **Patient characteristics and setting** Are there concerns that the included patients and setting do not match the review question? Low concern **Index Test** **A. Risk of bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					If a threshold was used, was it pre-specified? No Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern **Reference standard** **A. Risk of bias** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Flow and Timing **A. Risk of bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Sueters (2006)** **A. Risk of bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** **Patient characteristics and setting** Are there concerns that the included patients and

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					setting do not match the review question? Low concern **Index Test** **A. Risk of bias** Were the index test results interpreted without knowledge of the results of the Reference standard? Unclear If a threshold was used, was it pre-specified? No Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern **Reference standard** **A. Risk of bias** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern **Flow and Timing** **A. Risk of bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern *Data extracted from original paper. **Other information** Where the same cohort of women were reported in more than one publication, the most comprehensive publication was included to avoid overlapping populations.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Yamamoto, R., Ishii, K., Muto, H., Kawaguchi, H., Murata, M., Hayashi, S., Matsushita, M., Murakoshi, T., Mitsuda, N., The use of amniotic fluid discordance in the early second trimester to predict severe twin-twin transfusion syndrome, Fetal Diagnosis and Therapy, 34, 8-12, 2013 **Ref Id** 744870 **Country/ies where the study was carried out** Japan **Study type** Retrospective cohort study **Aim of the study** To validate the accuracy of amniotic fluid discordance (AFD) in the early second trimester for the prediction of TTTS.	**Sample size** N = 223 women **Characteristics** Maternal age (years) - mean ±SD 30.7 (5.0) Nulliparity - no. (%) 128 (57) Assisted reproductive technology - no. (%) 20 (8.9) Gestational age at the examination (weeks) - median (range) 17 (16-18) Amniotic fluid discordance (cm) - median (range) 0.8 (0-7.3) Estimated fetal weight (g) - median (range) Larger fetus: 175 (79-305) Smaller fetus: 145 (52-275) Discordant rate >0.25: 37 (16) Mean gestational age of FFTS onset 19 weeks (range 17-35). Spontaneous IUFDs	**Tests** **Index test**: AFD. **Reference test:** Presence of polyhydramnios with an MVP ≥8 cm combined with oligohydramnios with an MVP ≤2 cm.	**Methods** Serial ultrasonographic assessment, including measurement of the MVP of each twin and EFW, was undertaken at intervals of at least 2 weeks after 16 weeks' gestation. The AFD was calculated by subtracting the smaller MVP from the larger MVP between 16 and 18 weeks' gestation. The diagnosis of FFTS was made by the presence of polyhydramnios with an MVP ≥8 cm in one twin and oligohydramnios with an MVP ≤2 cm in the second twin. **Statistical analysis** Univariate analysis conducted to assess the relationship between AFD, gestational age at the examination, discordant rate of estimated fetal weight, and the development of FFTS using logistic regression analysis. Multiple logistic regression analysis was performed and discordant rate of EFW was calculated by: (larger EFW	**Results** Relationship between AFD and development of FFTS Multivariate analysis*: OR: 2.34 (95% CI 1.75-3.12); p<0.01 Relationship between gestational age and development of FFTS Univariate analysis: OR: 0.87 (95% CI 0.49-1.54); p=0.63 Relationship between EFW discordant rate >0.25 and development of FFTS Multivariate analysis*: OR: 0.54 (95 %CI 0.12-2.30); p=0.40 *not reported what the analysis was adjusted for AFD cut-off (≥4 cm) for the development of FFTS Sensitivity: 70% Specificity: 97% RR**: 23.6 (95% CI 10.2-54.7) AFD cut-off (≥4 cm) for the development of FFTS <26 weeks Sensitivity: 65% Specificity: 98%	**Limitations** Risk of bias was assessed using QUADAS-II **Patient Selection** **A. Risk of bias** **Patient sampling** Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes (cases excluded due to insufficient amniotic fluid volume data) Could the selection of patients have introduced bias? Low risk **B. Concerns regarding applicability:** **Patient characteristics and setting** Are there concerns that the included patients and setting do not match the review question? Low concern **Index Test** **A. Risk of bias** Were the index test results interpreted without knowledge of the results of

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates October 2008 to March 2012 **Source of funding** None reported.	11 (2.4%); number of cases of demise of both fetuses. **Inclusion Criteria** Monochorionic twin pregnancy. **Exclusion Criteria** 1) Pregnancies with major congenital anomalies, chromosomal abnormalities, IUFD before 15 weeks of gestation, and twin-reversed arterial perfusion 2) Pregnancies that developed FFTS within 7 days from the first visit to hospital.		– smaller EFW)/larger EFW. ROC curves were constructed to assess AFD as a predictor of subsequent FFTS. The optimal cut-off was calculated using the Youden index. All pregnancies were stratified according to an AFD cut-off. Thereafter, maternal characteristics and perinatal outcomes, including FFTS, were compared between groups. Based on the normality of the data assessed by the Shapiro-Wilk W test, continuous variables were evaluated with a Student's t or Mann-Whitney U test. Nominal variables were evaluated with Fisher's exact test.	RR**: 22.5 (95% CI 10.3-48.8) ** not reported whether it is adjusted or not	the reference standard? Unclear If a threshold was used, was it pre-specified? No Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern **Reference standard** **A. Risk of bias** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					does not match the question? Unclear concern **Flow and Timing** **A. Risk of bias** Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Other information** None
Full citation Zipori, Y., Reidy, K., Gilchrist, T., Doyle, L. W., Umstad, M. P., The Outcome of Monochorionic Diamniotic Twins Discordant at 11 to 13+6 Weeks' Gestation, Twin Research & Human Genetics: the Official Journal of the International Society for Twin Studies, 19, 692-696, 2016 **Ref Id**	**Sample size** N=89 MCDA twin pregnancies. **Characteristics** Maternal age (mean (SD)): 31.2 (5.3) Nuchal thickness difference (% (median (IQR))): 15.4 (6.5 - 29.7) CRL difference (% (median (IQR))): 3.6 (1.6, 6.8) Gestational age at birth (weeks, mean (SD)): 34.1 (3.3) FFTS (n): 13 (14%)	**Tests** **Index test** Ultrasound -NT and CRL measured at 11 and 13^{+6} weeks. The percentage discrepancy for NT was determined as the percentage difference relative to the lower value for NT. The percentage discrepancy for CRL was determined as the percentage difference relative to	**Methods** Data were collected from the combined maternal, fetal and neonatal clinical records at the author's hospital. When women gave birth elsewhere, their GP or obstetrician was contacted to collect the clinical details and outcomes. The percentage discrepancy for NT was determined as the percentage difference relative to the lower value for NT.	**Results** <u>Diagnostic accuracy of NT discordance (cut-off >31.1%) to predict FFTS:</u> Sensitivity: 53.8 Specificity: 81.1 AUC (area under the curve): 0.66 (95%CI 0.49 to 0.83) <u>Diagnostic accuracy of CRL discordance (cut-off >3.5%) to predict FFTS:</u> Sensitivity: 69.2 Specificity: 49.35 AUC: 0.60 (95% CI 0.43 to 0.76).	**Limitations** Risk of bias was assessed using QUADAS-II **Patient Selection** **A. Risk of bias** **Patient Sampling** Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes (cases with altered chorionicity findings of

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
756914 **Country/ies where the study was carried out** Australia **Study type** Retrospective cohort study **Aim of the study** To determine the ability of NT and CRL discordances among monochorionic diamniotic twin pregnancies to predict adverse fetal outcomes. **Study dates** Between August 2003 and August 2012. **Source of funding** Not reported.	**Inclusion Criteria** MCDA twins with documented measurements of NT and CRL on ultrasound at 11 to 13^{+6} weeks gestation and known pregnancy outcome. **Exclusion Criteria** **Exclusion Criteria** included known lethal anomalies (including chromosomal abnormalities) at 11–13^{+6} weeks can, loss of one or both twins prior to the 11–13+6 week scan, and altered chorionicity findings on placental histology.	the larger value for CRL. **Reference standard** FFTS defined according to classification of Quintero et al. (1999).	The percentage discrepancy for CRL was determined as the percentage difference relative to the larger value for CRL. Monochorionicity was determined by ultrasound demonstration of a single placental mass with the presence of atypical T-sign and confirmed after birth by placental histology. A routine fetalmorphology scan was performed 18 and 20 weeks' gestation. MCDA twins had fortnightly ultrasound assessments until birth, commencing at 16 weeks of gestation, to detect pregnancy complications. The development of FFTS was defined according to Quintero et al. (1999), EFW discordance of ≥25% on ultrasound at 28 weeks' gestation or a BW discordance of ≥25%. **Statistical analysis** ROC curves were plotted for both NT and CRL discordance to determine the cut-off point that maximised the ability to predict the adverse outcomes. The AUC and	Note: the optimal values for predicting any adverse outcomes derived from the ROC curves for NT were >31.1% and for CRL were >3.5%.	placental histology were excluded) Could the selection of patients have introduced bias? Unclear risk **B. Concerns regarding applicability:** **Patient characteristics and setting** Are there concerns that the included patients and setting do not match the review question? Unclear concern **Index Test** **A. Risk of bias** Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? No (ROC curves plotted for NT and CRL discordance to determine the cut-off point that maximised the ability to predict the adverse outcomes). Could the conduct or interpretation of the index test have introduced bias? Unclear risk **B. Concerns regarding applicability**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			its 95%confidence intervals were used to determine the statistical significance of each of NT and CRL discordance at predicting adverse outcomes. Using the optimal cut-points identified from the ROC curves, sensitivity and specificity were determined for each variable.		Are there concerns that the index test, its conduct, or interpretation differ from the review question? Unclear concern **Reference standard** **A. Risk of bias** Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk **B. Concerns regarding applicability** Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern **Flow and Timing** **A. Risk of bias** Was there an appropriate interval between index test and reference standard? Yes

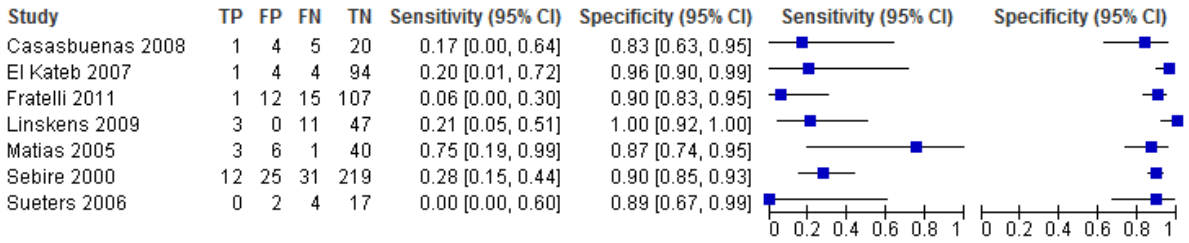
Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Did all patients receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low concern **Other information:** None

AFD: amniotic fluid discordance; AMSTAR: Assessing the Methodological Quality of Systematic Reviews; AUC: area under the curve; BW: birth weight; CRL: crown rump length; DV: ductal venosus; DVP = deepest vertical pocket; EFW: estimated fetal weight; FFTS: feto-fetal transfusion syndrome; IQR: interquartile range; IUFD: intrauterine fetal death; MCDA: monochorionic diamniotic; MVP: maximum vertical pocket; N/A: not applicable; NT: nuchal translucency; OR: odds ratio; PICO: population, intervention, comparator, outcome; QUADAS: Quality Assessment of Diagnostic Accuracy Studies; QUIPS: Quality in Prognosis Studies; ROC: receiver operating characteristic; RR: relative risk; SD: standard deviation; sFGR: selective fetal growth restriction

Appendix E – Forest plots and receiver operating characteristic curves

Forest plots and receiver operating characteristic (ROC) curves for review question: What is the optimal screening programme to identify feto-fetal transfusion syndrome (FFTS) in twin and triplet pregnancy?

Figure 2: Forest plot for nuchal translucency >95th percentile at 11^{+0} to 13^{+6} weeks' gestation



Sensitivity (95% CI): 0.23 (0.09 to 0.41); specificity (95% CI): 0.91 (0.85 to 0.96)

CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive

Figure 3: Receiver operating characteristic curve for nuchal translucency >95th percentile at 11^{+0} to 13^{+6} weeks' gestation

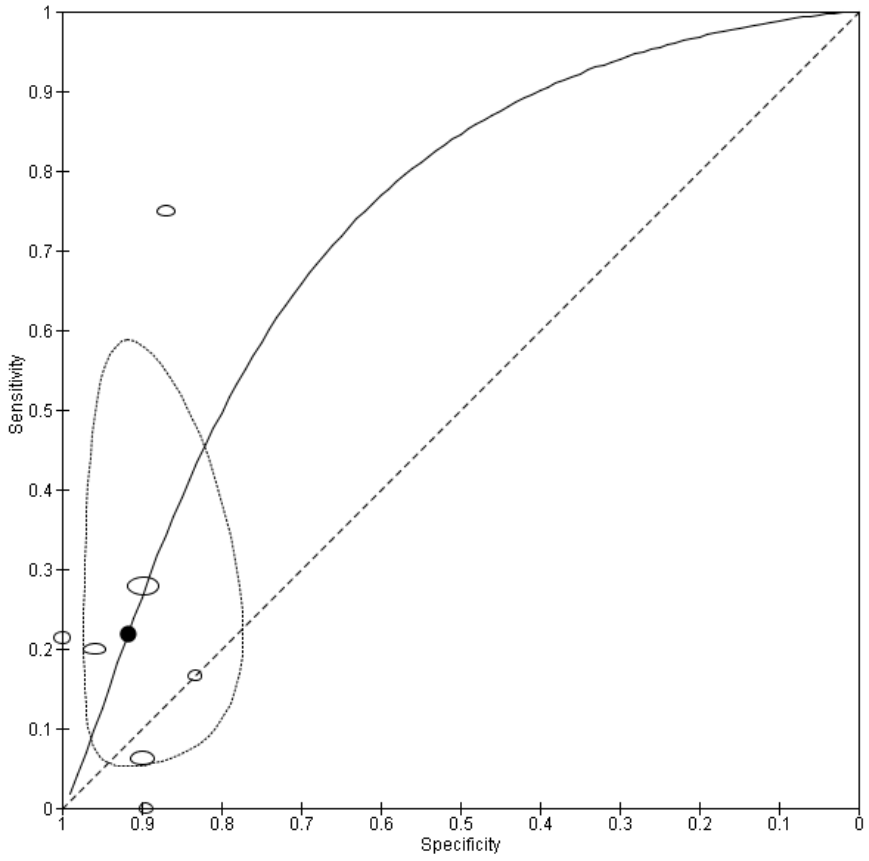
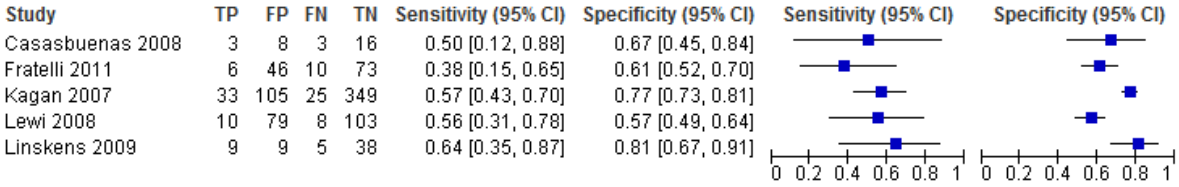


Figure 4: Forest plot for nuchal translucency discrepancy >20% at 11^{+0} to 13^{+6} weeks' gestation



Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Casasbuenas 2008	3	8	3	16	0.50 [0.12, 0.88]	0.67 [0.45, 0.84]
Fratelli 2011	6	46	10	73	0.38 [0.15, 0.65]	0.61 [0.52, 0.70]
Kagan 2007	33	105	25	349	0.57 [0.43, 0.70]	0.77 [0.73, 0.81]
Lewi 2008	10	79	8	103	0.56 [0.31, 0.78]	0.57 [0.49, 0.64]
Linskens 2009	9	9	5	38	0.64 [0.35, 0.87]	0.81 [0.67, 0.91]

Sensitivity (95% CI): 0.53 (0.33 to 0.72); specificity (95% CI): 0.69 (0.51 to 0.83)

CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive

Figure 5: Receiver operating characteristic curve for nuchal translucency discrepancy >20% at 11^{+0} to 13^{+6} weeks' gestation

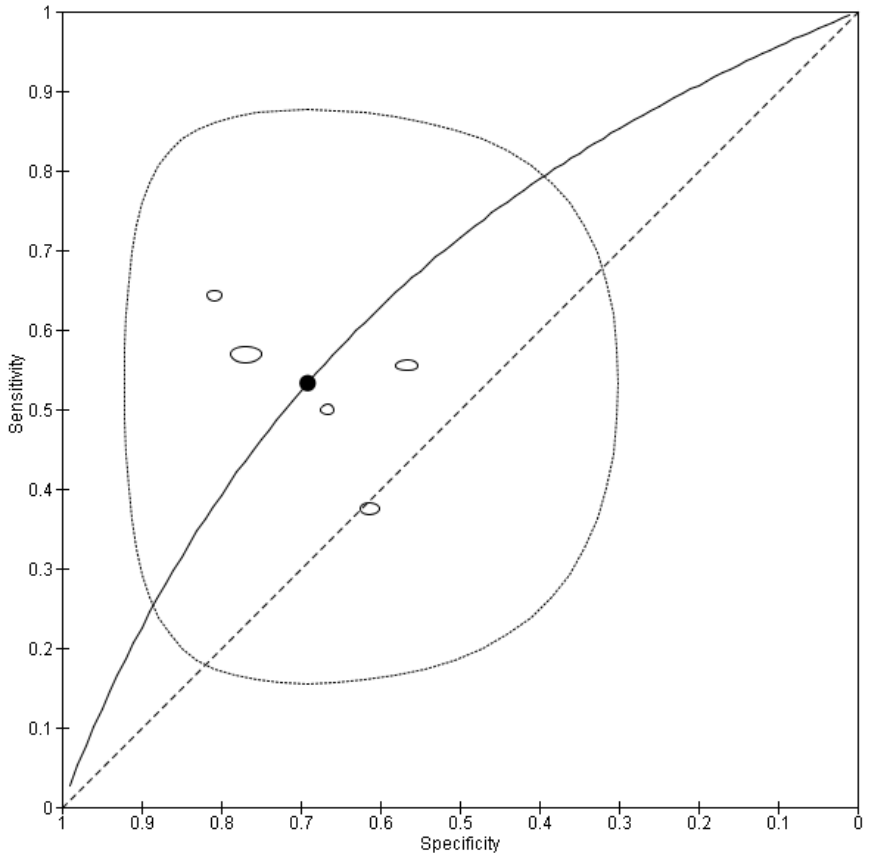
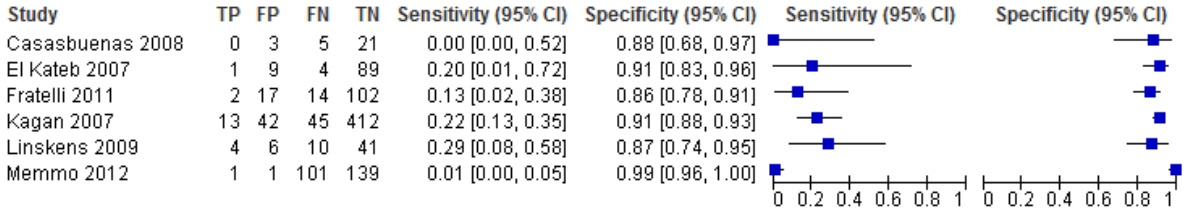


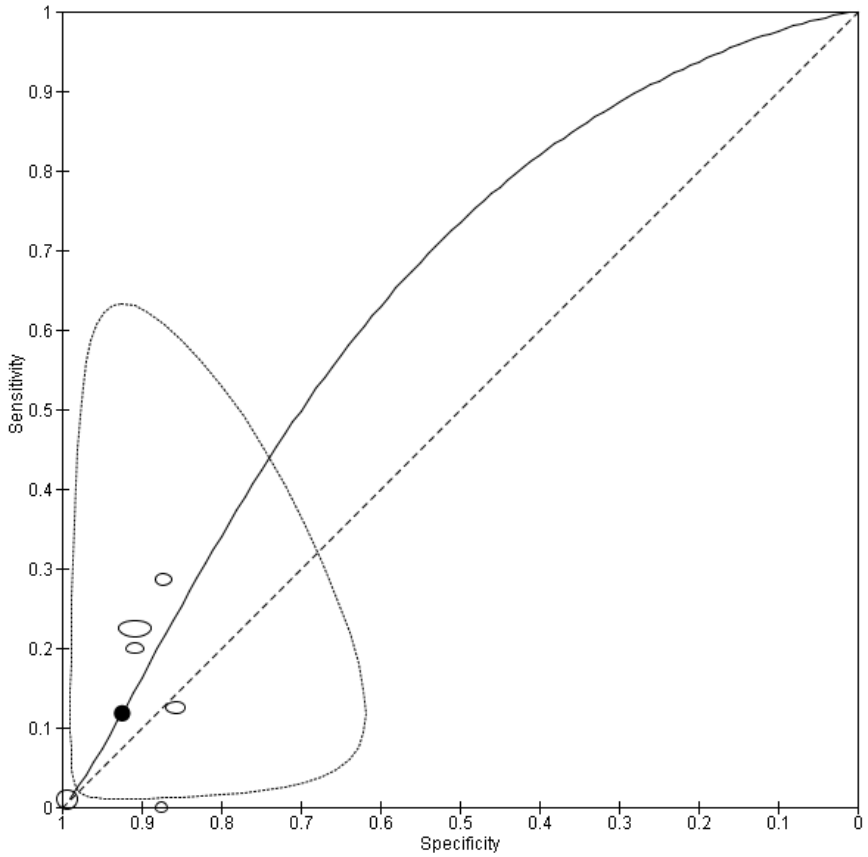
Figure 6: Forest plot for crown-rump length discrepancy >10% at 11^{+0} to 13^{+6} weeks' gestation



Sensitivity (95% CI): 0.14 (0.03 to 0.33); specificity (95% CI): 0.92 (0.81 to 0.98)

CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive

Figure 7: Receiver operating characteristic curve for crown-rump length discrepancy >10% at 11^{+0} to 13^{+6} weeks' gestation



Appendix F – GRADE tables

GRADE profile for review question: What is the optimal screening programme to identify feto-fetal transfusion syndrome (FFTS) in twin and triplet pregnancy?

Table 7: Clinical evidence profile for screening to identify feto-fetal transfusion syndrome in twin pregnancy in first trimester (11^{+0} to 13^{+6} weeks' gestation)

Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	AUC (95%CI)	Quality of the evidence (GRADE)	Importance
NT >95th percentile	7	689	Very serious[1]	Very serious[2]	No serious indirectness	No serious imprecision	0.23 (0.09 to 0.41)	0.91 (0.85 to 0.96)	–	⨁⊖⊖⊖ VERY LOW	CRITICAL
NT discrepancy >31.1%	1	89	Very serious[3]	No serious inconsistency	No serious indirectness	Very serious[4]	–	–	0.66 (0.49 to 0.83)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
NT discrepancy >20%	5	938	Serious[5]	Very serious[2]	No serious indirectness	No serious imprecision	0.53 (0.33 to 0.72)	0.69 (0.51 to 0.83)	–	⨁⊖⊖⊖ VERY LOW	CRITICAL
NT discrepancy ≥20%	1	177	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[7]	–	–	0.52 (0.39 to 0.65)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
NT discrepancy ≥0.6 mm	1	99	Serious[6]	No serious inconsistency	No serious indirectness	Serious[8]	0.5 (0.21 to 0.79)	0.92 (0.84 to 0.97)	–	⨁⨁⊖⊖ LOW	CRITICAL
NT discrepancy ≥0.6 mm	1	99	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[9]	–	–	0.84 (0.70 to 1.00)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
NT discrepancy ≥0.5 mm	1	50	Serious[6]	No serious inconsistency	No serious indirectness	Serious[8]	0.25 (0.01 to 0.81)	0.65 (0.5 to 0.79)	–	⨁⨁⊖⊖ LOW	CRITICAL

Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	AUC (95%CI)	Quality of the evidence (GRADE)	Importance
NT intertwin difference	1	99	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[10]	–	–	0.76 (0.60 to 0.91)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
NT intertwin ratio	1	99	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[11]	–	–	0.75 (0.60 to 0.89)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
CRL discrepancy ≥20%	1	177	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[7]	–	–	0.57 (0.4 to 0.7)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
CRL discrepancy >10%	6	1082	Very serious[13]	Very serious[2]	No serious indirectness	No serious imprecision	0.14 (0.03 to 0.33)	0.92 (0.81 to 0.98)	–	⨁⊖⊖⊖ VERY LOW	CRITICAL
CRL discrepancy >3.5%	1	89	Very serious[3]	No serious inconsistency	No serious indirectness	Very serious[7]	–	–	0.60 (0.43 to 0.76)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
CRL discrepancy ≥12mm	1	200	Very serious[3]	No serious inconsistency	No serious indirectness	Serious[8]	0.56 (0.31 to 0.78)	0.77 (0.70 to 0.83)	–	⨁⊖⊖⊖ VERY LOW	CRITICAL
CRL intertwin difference	1	99	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[13]	–	–	0.57 (0.40 to 0.73)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
CRL intertwin ratio	1	99	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[13]	–	–	0.58 (0.42 to 0.75)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
AF discordance	1	200	Very serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	0.22 (0.09 to 0.45)	0.95 (0.92 to 0.98)	–	⨁⨁⊖⊖ LOW	CRITICAL
Reverse DV flow	1	179	Very serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	0.38 (0.2 to 0.59)	0.85 (0.78 to 0.9)	–	⨁⨁⊖⊖ LOW	CRITICAL
Reverse DV flow	1	99	Very serious[3]	No serious inconsistency	No serious indirectness	Very serious[8]	0.75 (0.43 to 0.95)	0.92 (0.84 to 0.97)	-	⨁⊖⊖⊖ VERY LOW	CRITICAL

Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	AUC (95%CI)	Quality of the evidence (GRADE)	Importance
Reverse DV flow	1	99	Very serious[3]	No serious inconsistency	No serious indirectness	Very serious[14]	-	-	0.84 (0.70 to 1.00)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
Intertwin membrane folding (presence or absence)	1	287	Very serious[3]	No serious inconsistency	No serious indirectness	No serious imprecision	0.43 (0.30 to 0.57)	0.98 (0.93 to 0.99)	-	⨁⨁⊖⊖ LOW	CRITICAL

AF: amniotic fluid; AUC: area under the curve; CI: confidence interval; CRL: crown-rump length; CI: confidence interval; DV: ductus venosus; NT: nuchal translucency; RoB: risk of bias
1 (5 high RoB; 2 very high RoB) Unclear if selection of participants may have introduced bias; Unclear if the index test results were interpreted without knowledge of the results of the reference standard; unclear if the reference standard results were interpreted without knowledge of the results of the index test in 3 studies; Unclear if the index test results were interpreted without knowledge of the results of the reference standard; unclear if the reference standard results were interpreted without knowledge of the results of the index test for 4 studies
2 Inconsistency was assessed by inspection of the sensitivity and specificity forest plots across studies, using the point estimates and confidence intervals.
3 Unclear if a consecutive or random sample of participants was enrolled; unclear if the index test results were interpreted without knowledge of the results of the reference standard; unclear if the reference standard results were interpreted without knowledge of the results of the index test
4 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default cut-offs (0.61 and 0.70)
5 (1 very high RoB; 4 high RoB) Unclear if selection of participants may have introduced bias; Unclear if the index test results were interpreted without knowledge of the results of the reference standard; unclear if the reference standard results were interpreted without knowledge of the results of the index test in 1 study; Unclear if the index test results were interpreted without knowledge of the results of the reference standard; unclear if the reference standard results were interpreted without knowledge of the results of the index test for 4 studies
6 Unclear if the index test results were interpreted without knowledge of the results of the reference standard; unclear if the reference standard results were interpreted without knowledge of the results of the index test
7 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default cut-offs (0.50 and 0.61)
8 The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results are judged to be very seriously imprecise.
9The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 3 default cut-offs (0.71, 0.81 and 0.91)
10 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default cut-offs (0.61, 0.81)
11 The quality of the evidence was downgraded by 2 levels because the 95%CI crosses 3 default cut-offs crosses (0.61, 0.71 and 0.81)
12 (1 very high RoB; 5 high RoB) Unclear if selection of participants may have introduced bias; Unclear if the index test results were interpreted without knowledge of the results of the reference standard; unclear if the reference standard results were interpreted without knowledge of the results of the index test in 1 study; Unclear if the index test results were interpreted without knowledge of the results of the reference standard; unclear if the reference standard results were interpreted without knowledge of the results of the index test for 5 studies
13 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 3 default cut-offs (0.50, 0.61 and 0.71)
14 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 3 default cut-offs (0.71, 0.81 and 0.91)

Table 8: Clinical evidence profile for screening to identify feto-fetal transfusion syndrome in twin pregnancy in second trimester

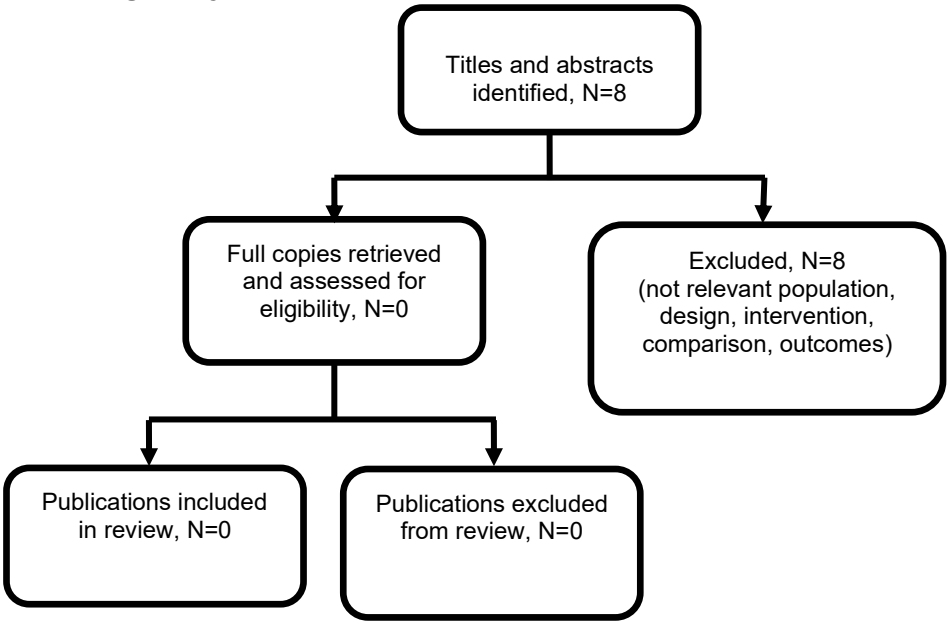
Index test	Number of studies	Number of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	AUC (95%CI)	Quality of the evidence (GRADE)	Importance
AC discordance ≥20% (16- to 18-weeks' gestation)	1	177	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	0.65 (0.46 to 0.75)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
HC discordance ≥20% (16- to 18-weeks' gestation)	1	177	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	0.61 (0.46 to 0.76)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
FL discordance ≥20% (16- to 18-weeks' gestation)	1	177	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[3]	0.62 (0.43 to 0.62)	⨁⊖⊖⊖ VERY LOW	IMPORTANT
EFW discordance[5] (16- to 18-weeks' gestation)	1	177	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[4]	0.66 (0.58 to 0.81)	⨁⊖⊖⊖ VERY LOW	IMPORTANT

AC: abdominal circumference; AUC: area under the curve; AF: amniotic fluid; CI: confidence interval; EFM: estimated fetal weight; FFTS: feto-fetal transfusion syndrome; FM: femur length HC: head circumference
1 Unclear if the study avoided inappropriate exclusions as 81 neonates were excluded from the analysis due to incomplete data and 19 due to intrauterine fetal demise; unclear if the index test results were interpreted without knowledge of the results of the reference standard; unclear if the reference standard results were interpreted without knowledge of the results of the index test
2 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 3 default cut-offs (0.50, 0.61 and 0.71)
3 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default cut-offs (0.50 and 0.61)
4 The quality of the evidence was downgraded by 2 levels because the 95% CI crosses 2 default cut-offs (0.61 and 0.71)
5 Not specified for FFTS, but intrauterine growth restriction defined as EFW below the 10th percentile

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the optimal screening programme to identify feto-fetal transfusion syndrome (FFTS) in twin and triplet pregnancy?

Figure 8: Flow diagram of economic article selection for the optimal screening programme to identify feto-fetal transfusion syndrome in twin and triplet pregnancy



Appendix H – Economic evidence tables

Economic evidence table for review question: What is the optimal screening programme to identify feto-fetal transfusion syndrome (FFTS) in twin and triplet pregnancy?

No economic evidence was identified for this review.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the optimal screening programme to identify feto-fetal transfusion syndrome (FFTS) in twin and triplet pregnancy?

No economic evidence was identified for this review.

Appendix J – Economic analysis

Economic analysis for review question: What is the optimal screening programme to identify feto-fetal transfusion syndrome (FFTS) in twin and triplet pregnancy?

No economic analysis was conducted for this review.

Appendix K – Excluded studies

Excluded studies for review question: What is the optimal screening programme to identify feto-fetal transfusion syndrome (FFTS) in twin and triplet pregnancy?

Clinical studies

Study	Reason for exclusion
Alfirevic, Zarko, Stampalija, Tamara, Dowswell, Therese, Fetal and umbilical Doppler ultrasound in high-risk pregnancies, The Cochrane database of systematic reviews, 6, CD007529, 2017	Population not relevant to protocol – excludes subgroup of multiple pregnancies with FFTS
Antsaklis, A., Pergialiotis, V., Theodora, M., Papazefkos, V., Antsaklis, P., Early prediction of twin-to-twin transfusion syndrome with the use of first trimester ultrasound markers: Is it possible?, Donald School Journal of Ultrasound in Obstetrics and Gynecology, 7, 66-72, 2013	Systematic review - does not present data to calculate 2 x 2 contingency table
Baschat, A., Chmait, R. H., Deprest, J., Gratacos, E., Hecher, K., Kontopoulos, E., Quintero, R., Skupski, D. W., Valsky, D. V., Ville, Y., Twin-to-twin transfusion syndrome (TTTS), Journal of Perinatal Medicine, 39, 107-112, 2011	Study design not relevant to protocol - does not assess prognostic/diagnostic tests
Baud, D., Windrim, R., Van Mieghem, T., Keunen, J., Seaward, G., Ryan, G., Twin-twin transfusion syndrome: a frequently missed diagnosis with important consequences, Ultrasound in Obstetrics & Gynecology, 44, 205-9, 2014	Study examines treatment of FFTS with fetoscopic laser ablation of placental anastomoses
Ben-Ami, I., Molina, F. S., Battino, S., Daniel-Spiegel, E., Melcer, Y., Flock, A., Geipel, A., Odeh, M., Miron, P., Maymon, R., Monochorionic diamniotic in vitro fertilization twins have a decreased incidence of twin-to-twin transfusion syndrome, Fertility & Sterility, 105, 729-33, 2016	Study assesses the distribution of FFTS according to the mode of conception
Blumenfeld, Yj, Momirova, V, Rouse, Dj, Caritis, Sn, Sciscione, A, Peaceman, Am, Reddy, Um, Varner, Mw, Malone, Fd, Iams, Jd, Mercer, Bm, Thorp, Jm, Sorokin, Y, Carpenter, Mw, Lo, J, Ramin, Sm, Harper, M, Accuracy of sonographic chorionicity classification in twin gestations, Journal of ultrasound in medicine, 33, 2187-2192, 2014	Study evaluates the accuracy of sonographic classification of chorionicity, not prognostic/diagnostic evaluation of FFTS
Calvo-Garcia, Ma, Guidelines for scanning twins and triplets with US and MRI, Pediatric Radiology, 46, 155-166, 2016	Guidelines with no systematic review
Carver, A., Haeri, S., Moldenhauer, J., Wolfe, H. M., Goodnight, W., Monochorionic diamniotic twin pregnancy: timing and duration of sonographic surveillance for detection of twin-twin transfusion syndrome, Journal of Ultrasound in Medicine, 30, 297-301, 2011	This study assesses testing frequency
Casasbuenas,A., Wong,A.E., Sepulveda,W., Nuchal translucency thickness in monochorionic multiple pregnancies: value in predicting pregnancy outcome, Journal of Ultrasound in Medicine, 27, 363-369, 2008	Study included in the Stagnati 2016 systematic review. Original publication checked for any additional relevant information and data
Chan, M. P., Hecht, J. L., Kane, S. E., Incidence and clinicopathologic correlation of fetal vessel thrombosis in mono- and dichorionic twin placentas, Journal of PerinatologyJ Perinatol, 30, 660-4, 2010	Study does not examine the accuracy of prognostic/diagnostic tests for FFTS

Study	Reason for exclusion
Chon, A. H., Mamey, M. R., Schrager, S. M., Vanderbilt, D. L., Chmait, R. H., The relationship between preoperative fetal head circumference and 2-year cognitive performance after laser surgery for twin-twin transfusion syndrome, Prenatal Diagnosis, 38, 173-178, 2018	Not a prognostic/diagnostic study - assessing outcomes at 2 years after laser treatment for FFTS
Chon, A., Korst, L., Llanes, A., Miller, D., Ouzounian, J., Chmait, R., Midtrimester isolated polyhydramnios in monochorionic diamniotic multiple gestations, American Journal of Obstetrics and Gynecology, 210, S94-S95, 2014	Study does not examine the accuracy of prognostic/diagnostic tests for FFTS
Couck, I., Mourad Tawfic, N., Deprest, J., De Catte, L., Devlieger, R., Lewi, L., Does the Site of The Cord Insertion increase the risk of Adverse Outcome, Twin-To-Twin Transfusion Syndrome and Discordant Growth in monochorionic twin pregnancies?, Ultrasound in Obstetrics & Gynecology, 11, 11, 2017	Index test not relevant to protocol - cord insertion
D'Antonio, F., Khalil, A., Pagani, G., Papageorghiou, A. T., Bhide, A., Thilaganathan, B., Crown-rump length discordance and adverse perinatal outcome in twin pregnancies: systematic review and meta-analysis, Ultrasound in Obstetrics & GynecologyUltrasound Obstet Gynecol, 44, 138-46, 2014	Study does not examine the accuracy of prognostic/diagnostic tests for FFTS; it examines association between CRL and total fetal and perinatal loss, fetal loss at <24weeks, fetal loss at <24 weeks, BW discordance, preterm birth at <34 weeks and fetal anomalies
D'Antonio, F., Khalil, A., Thilaganathan, B., Southwest Thames Obstetric Research, Collaborative, Second-trimester discordance and adverse perinatal outcome in twins: the STORK multiple pregnancy cohort, BJOG: An International Journal of Obstetrics & Gynaecology, 121, 422-9, 2014	Study does not examine the accuracy of prognostic/diagnostic tests for FFTS - assesses outcomes of stillbirth, neonatal mortality, PTB at <34 weeks of gestation, and BW discordance ≥25%
D'Antonio, F., Odibo, A. O., Prefumo, F., Khalil, A., Buca, D., Flacco, M. E., Liberati, M., Manzoli, L., Acharya, G., Weight discordance and perinatal mortality in twin pregnancy: systematic review and meta-analysis, Ultrasound in Obstetrics & GynecologyUltrasound Obstet Gynecol, 52, 11-23, 2018	The systematic review mainly explores the association between birth weight and perinatal mortality
De Paepe, M. E., Luks, F. I., What-and why-the pathologist should know about twin-to-twin transfusion syndrome, Pediatric & Developmental Pathology, 16, 237-51, 2013	Narrative review
Dekoninck, P., Deprest, J., Lewi, P., Richter, J., Galjaard, S., Van Keirsbilck, J., Van Calsteren, K., Lewi, L., Gestational age-specific reference ranges for amniotic fluid assessment in monochorionic diamniotic twin pregnancies, Ultrasound in Obstetrics & Gynecology, 41, 649-52, 2013	Study does not examine the accuracy of prognostic/diagnostic tests for FFTS
Delabaere, A., Leduc, F., Reboul, Q., Fuchs, F., Wavrant, S., Dube, J., Fouron, J. C., Audibert, F., Factors associated to early intrauterine fetal demise after laser for TTTS by preoperative fetal heart and Doppler ultrasound, Prenatal DiagnosisPrenat Diagn, 38, 523-530, 2018	Not a prognostic/diagnostic study - assessing outcomes (intrauterine fetal demise) in fetuses with FFTS after laser treatment
Divanovic, A., Cnota, J., Ittenbach, R., Tan, X., Border, W., Crombleholme, T., Michelfelder, E., Characterization of diastolic dysfunction in twin-twin transfusion syndrome: association between Doppler findings and ventricular	Study does not examine the accuracy of prognostic/diagnostic tests for FFTS

Study	Reason for exclusion
hypertrophy, Journal of the American Society of Echocardiography, 24, 834-40, 2011	
Duryea, E. L., Happe, S. K., McIntire, D. D., Dashe, J. S., Sonography interval and the diagnosis of twin-twin transfusion syndrome, Journal of Maternal-Fetal & Neonatal Medicine, 30, 640-644, 2017	No relevant comparison. The study examines the relationship between sonographic surveillance interval and the gestational age and Quintero stage at time of FFTS diagnosis
El Kateb, A., Nasr, B., Nassar, M., Bernard, J. P., Ville, Y., First-trimester ultrasound examination and the outcome of monochorionic twin pregnancies, 27, 922-5, 2007	Study included in the Stagnati 2016 systematic review. Original publication checked for any additional relevant information and data
Emery, S. P., Bahtiyar, M. O., Dashe, J. S., Wilkins-Haug, L. E., Johnson, A., Paek, B. W., Moon-Grady, A. J., Skupski, D. W., O'Brien, B. M., Harman, C. R., Simpson, L. L., The North American Fetal Therapy Network Consensus Statement: prenatal management of uncomplicated monochorionic gestations, Obstetrics & GynecologyObstet Gynecol, 125, 1236-43, 2015	Narrative review
Eschbach, S. J., Boons, L. S. T. M., Van Zwet, E., Middeldorp, J. M., Klumper, F. J. C. M., Lopriore, E., Teunissen, A. K. K., Rijlaarsdam, M. E., Oepkes, D., Ten Harkel, A. D. J., Haak, M. C., Right ventricular outflow tract obstruction in complicated monochorionic twin pregnancy, Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology, 49, 737-743, 2017	Outcomes not relevant to protocol - risk prediction model for right ventricular outflow tract obstruction in FFTS cases
Fichera, A., Prefumo, F., Stagnati, V., Marella, D., Valcamonico, A., Frusca, T., Outcome of monochorionic diamniotic twin pregnancies followed at a single center, Prenatal Diagnosis, 35, 1057-64, 2015	Study does not present data on prognostic/diagnostic accuracy tests for FFTS
Fischbein, R., Nicholas, L., Aultman, J., Baughman, K., Falletta, L., Twin-twin transfusion syndrome screening and diagnosis in the United States: A triangulation design of patient experiences, PLoS ONE, 13 (7) (no pagination), 2018	Not relevant to protocol - survey of women with twin pregnancies with FFTS and their experiences
Flock, A., Reinsberg, J., Berg, C., Gembruch, U., Geipel, A., Impact of chorionicity on first-trimester nuchal translucency screening in ART twin pregnancies, Prenatal Diagnosis, 33, 722-5, 2013	Comparator and outcomes not relevant to protocol - rates of FFTS in assisted reproductive technology pregnancies versus spontaneously conceived twins
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 Human Development, 87, 27-30, 2011	Study included in the Stagnati 2016 systematic review. Original publication checked for any additional relevant information and data (confidence intervals around the point estimate are not presented or calculable and better data are available)
Gandhi, M., Papanna, R., Teach, M., Johnson, A., Moise, K. J., Jr., Suspected twin-twin transfusion syndrome: how often is the diagnosis correct and referral timely?, Journal of Ultrasound in Medicine, 31, 941-5, 2012	Data presented do not permit calculation of 2 x 2 contingency tables
Gratacos, E., Ortiz, J. U., Martinez, J. M., A systematic approach to the differential diagnosis and management of the complications of monochorionic twin pregnancies, Fetal Diagnosis & Therapy, 32, 145-55, 2012	Narrative review

Study	Reason for exclusion
Hecher, K., Gardiner, H. M., Diemert, A., Bartmann, P., Long-term outcomes for monochorionic twins after laser therapy in twin-to-twin transfusion syndrome, The Lancet Child and Adolescent Health, 2, 525-535, 2018	Review about long-term neurodevelopmental and cardiovascular outcomes in those who survived laser therapy in FFTS
Hussey, T., Shah, N., Govind, A., MCDA twin pregnancy: is it TTTS or TAPS?, Journal of Obstetrics & Gynaecology, 37, 1091-1092, 2017	Case report
Jahanfar, Shayesteh, Ho, Jacqueline J, Jaafar, Sharifah Halimah, Abraha, Iosief, Nisenblat, Vicki, Ellis, Ursula M, Noura, Mohaddesseh, Ultrasound for diagnosis of birth weight discordance in twin pregnancies, Cochrane Database of Systematic Reviews, 2017	Study protocol
Johansen, M. L., Oldenburg, A., Rosthoj, S., Cohn Maxild, J., Rode, L., Tabor, A., Crown-rump length discordance in the first trimester: a predictor of adverse outcome in twin pregnancies?, Ultrasound in Obstetrics & Gynecology, 43, 277-83, 2014	Outcome not relevant to protocol - assessing CRL discordance as a predictor of fetal loss and pre-term birth before 34 weeks' gestation
Kagan,K.O., Gazzoni,A., Sepulveda-Gonzalez,G., Sotiriadis,A., Nicolaides,K.H., Discordance in nuchal translucency thickness in the prediction of severe twin-to-twin transfusion syndrome, Ultrasound in Obstetrics and Gynecology, 29, 527-532, 2007	Study included in the Stagnati 2016 systematic review. Original publication checked for any additional relevant information and data
Kawamura, H., Ishii, K., Mabuchi, A., Yamamoto, R., Hayashi, S., Mitsuda, N., Perinatal outcome of monochorionic diamniotic twin pregnancies complicated with isolated amniotic fluid volume abnormality of one twin less than 26 weeks of gestation, Journal of Obstetrics and Gynaecology Research, 42, 1657-1665, 2016	No relevant comparison. The study evaluates the incidence of FFTS and the perinatal outcome at 28 days of age
Kontopoulos, E., Chmait, R. H., Quintero, R. A., Twin-to-Twin Transfusion Syndrome: Definition, Staging, and Ultrasound Assessment, Twin Research & Human Genetics: the Official Journal of the International Society for Twin Studies, 19, 175-83, 2016	Narrative review
Lewi, L., Lewi, P., Diemert, A., Jani, J., Gucciardo, L., Van Mieghem, T., Done, E., Gratacos, E., Huber, A., Hecher, K., Deprest, J., The role of ultrasound examination in the first trimester and at 16 weeks' gestation to predict fetal complications in monochorionic diamniotic twin pregnancies, Am J Obstet GynecolAmerican journal of obstetrics and gynecology, 199, 493.e1-7, 2008	Study included in the Stagnati 2016 systematic review. Original publication checked for any additional relevant information and data
Linskens, I. H., de Mooij, Y. M., Twisk, J. W., Kist, W. J., Oepkes, D., van Vugt, J. M., Discordance in nuchal translucency measurements in monochorionic diamniotic twins as predictor of twin-to-twin transfusion syndrome, Twin Res Hum GenetTwin research and human genetics : the official journal of the International Society for Twin Studies, 12, 605-10, 2009	Study included in the Stagnati 2016 systematic review. Original publication checked for any additional relevant information and data (confidence intervals around the point estimate are not presented or calculable and better data are available)
Lopriore, E., Holtkamp, N., Sueters, M., Middeldorp, J. M., Walther, F. J., Oepkes, D., Acute peripartum twin-twin transfusion syndrome: incidence, risk factors, placental characteristics and neonatal outcome, Journal of Obstetrics & Gynaecology ResearchJ Obstet Gynaecol Res, 40, 18-24, 2014	Study does not examine the accuracy of prognostic/diagnostic tests for FFTS
Mackie, F. L., Morris, R. K., Kilby, M. D., The prediction, diagnosis and management of complications in	Study protocol

Study	Reason for exclusion
monochorionic twin pregnancies: the OMMIT (Optimal Management of Monochorionic Twins) study, BMC Pregnancy & ChildbirthBMC Pregnancy Childbirth, 17, 153, 2017	
Maiz, N., Nicolaides, K. H., Ductus venosus in the first trimester: contribution to screening of chromosomal, cardiac defects and monochorionic twin complications, Fetal Diagnosis & Therapy, 28, 65-71, 2010	Narrative review
Matias, A., Ramalho, C., Montenegro, N., Search for hemodynamic compromise at 11-14 weeks in monochorionic twin pregnancy: is abnormal flow in the ductus venosus predictive of twin-twin transfusion syndrome?, Journal of Maternal-Fetal & Neonatal MedicineJ Matern Fetal Neonatal Med, 18, 79-86, 2005	Study included in the Stagnati 2016 systematic review. Original publication checked for any additional relevant information and data
Matias,A., Maiz,N., Montenegro,N., Nicolaides,K., Ductus venosus flow at 11-13 weeks in the prediction of birth weight discordance in monochorionic twins, Journal of Perinatal Medicine, 39, 467-470, 2011	Study does not examine the accuracy of prognostic/diagnostic tests for FFTS - prediction of birth weight discordance
McDonald, R., Hodges, R., Knight, M., Teoh, M., Edwards, A., Neil, P., Wallace, E. M., DeKoninck, P., Optimal Interval between Ultrasound Scans for the Detection of Complications in Monochorionic Twins, Fetal Diagnosis & Therapy, 41, 197-201, 2017	Study does not examine the accuracy of prognostic/diagnostic tests for FFTS
Moon-Grady, A. J., Rand, L., Gallardo, S., Gosnell, K., Lee, H., Feldstein, V. A., Diastolic Cardiac Pathology and Clinical Twin-Twin Transfusion Syndrome in Monochorionic/Diamniotic Twins, American Journal of Obstetrics & Gynecology, 205, 279.e1-279.e11, 2011	Outcome not relevant to protocol - diagnosing diastolic pathology in FFTS and non-FFTS
Morin, L., Lim, K., No. 260-Ultrasound in Twin Pregnancies, Journal of Obstetrics and Gynaecology Canada, 39, e398-e411, 2017	Guideline - does not present data examining the accuracy of prognostic/diagnostic tests for FFTS
Morin,L., Lim,K., Ultrasound in twin pregnancies, Journal of Obstetrics and Gynaecology Canada: JOGC, 33, 643-656, 2011	Guideline - does not present data examining the accuracy of prognostic/diagnostic tests for FFTS
Murakami, M., Iwasa, T., Kiyokawa, M., Takahashi, Y., Morine, M., Investigation of the factors affecting the perinatal outcome of monochorionic diamniotic twins, Archives of Gynecology & Obstetrics, 283, 1239-43, 2011	Study does not examine the accuracy of prognostic/diagnostic tests for FFTS
Murata, M., Ishii, K., Taguchi, T., Mabuchi, A., Kawaguchi, H., Yamamoto, R., Hayashi, S., Mitsuda, N., The prevalence and clinical features of twin-twin transfusion syndrome with onset during the third trimester, Journal of Perinatal Medicine, 42, 93-8, 2014	Study does not examine the accuracy of prognostic/diagnostic tests for FFTS
Nakayama, S., Ishii, K., Kawaguchi, H., Yamamoto, R., Murata, M., Hayashi, S., Mitsuda, N., Perinatal complications of monochorionic diamniotic twin gestations with discordant crown-rump length determined at mid-first trimester, Journal of Obstetrics & Gynaecology Research, 40, 418-23, 2014	Crown-rump length was measured between 8 and 10 weeks of gestation and not at 11–13^{+6} weeks
Neves, A. R., Nunes, F., Branco, M., Almeida, M. D. C., Silva, I. S., The role of ultrasound in the prediction of birth weight discordance in twin pregnancies: Are we there yet?, Journal of Perinatal MedicineJ Perinat Med, 46, 163-168, 2018	Outcomes not relevant to protocol - assessing prediction of birth weight discordance. Cases with FFTS were excluded

Study	Reason for exclusion
Ota, S., Ishii, K., Kawamura, H., Mabuchi, A., Yamamoto, R., Hayashi, S., Kanagawa, T., Mitsuda, N., Transient amniotic fluid leakage after fetoscopic laser photocoagulation for twin-twin transfusion syndrome, Journal of Obstetrics and Gynaecology Research, 44, 223-227, 2018	Not relevant to protocol - not diagnostic/prognostic. Assesses treatment of FFTS with fetoscopic laser photocoagulation
Pan, M., Chen, M., Leung, T. Y., Sahota, D. S., Ting, Y. H., Lau, T. K., Outcome of monochorionic twin pregnancies with abnormal umbilical artery Doppler between 16 and 20 weeks of gestation, Journal of Maternal-Fetal & Neonatal Medicine, 25, 277-80, 2012	Study does not present specific data on the accuracy of prognostic/diagnostic tests for FFTS - diagnostic value of ultrasound for abnormal twin pregnancy more broadly
Persico, N., D'Ambrosi, F., Fabietti, I., Boito, S., Aiello, E., Bulfoni, A., Ciralli, F., Kustermann, A., Mosca, F., Fedele, L., Fetal Doppler changes 1 week after endoscopic equatorial laser for twin-to-twin transfusion syndrome: A longitudinal study, Prenatal DiagnosisPrenat Diagn, 38, 344-348, 2018	Not relevant to protocol - not diagnostic/prognostic. Assesses outcome in FFTS after laser treatment
Pessel, C., Merriam, A., Vani, K., Brubaker, S. G., Zork, N., Zhang, Y., Simpson, L. L., Gyamfi-Bannerman, C., Miller, R., Do Doppler studies enhance surveillance of uncomplicated monochorionic diamniotic twins?, Journal of Ultrasound in Medicine, 34, 569-75, 2015	Study does not examine the accuracy of prognostic/diagnostic tests for FFTS
Sebire,N.J., Souka,A., Skentou,H., Geerts,L., Nicolaides,K.H., Early prediction of severe twin-to-twin transfusion syndrome, Human Reproduction, 15, 2008-2010, 2000	Study included in the Stagnati 2016 systematic review. Original publication checked for any additional relevant information and data
Smith,N.A., Wilkins-Haug,L., Santolaya-Forgas,J., Acker,D., Economy,K.E., Benson,C.B., Robinson,J.N., Contemporary management of monochorionic diamniotic twins: outcomes and delivery recommendations revisited, American Journal of Obstetrics and Gynecology, 203, 133-136, 2010	Study examines outcomes in pregnancies already diagnosed with FFTS
Society for Maternal-Fetal, Medicine, Simpson, L. L., Twin-twin transfusion syndrome.[Erratum appears in Am J Obstet Gynecol. 2013 May;208(5):392], American Journal of Obstetrics & GynecologyAm J Obstet Gynecol, 208, 3-18, 2013	Study does not present data on the accuracy of prognostic/diagnostic tests for FFTS
Sperling,L., Kiil,C., Larsen,L.U., Brocks,V., Wojdemann,K.R., Qvist,I., Schwartz,M., Jorgensen,C., Espersen,G., Skajaa,K., Bang,J., Tabor,A., Detection of chromosomal abnormalities, congenital abnormalities and transfusion syndrome in twins, Ultrasound in Obstetrics and Gynecology, 29, 517-526, 2007	Study included in the Stagnati 2016 systematic review. Original publication checked for any additional relevant information and data
Sueters,M., Middeldorp,J.M., Lopriore,E., Oepkes,D., Kanhai,H.H., Vandenbussche,F.P., Timely diagnosis of twin-to-twin transfusion syndrome in monochorionic twin pregnancies by biweekly sonography combined with patient instruction to report onset of symptoms, Ultrasound in Obstetrics and Gynecology, 28, 659-664, 2006	Study included in the Stagnati 2016 systematic review. Original publication checked for any additional relevant information and data
Suksai, M., Suwanrath, C., Kor-Anantakul, O., Geater, A., Time Interval Measurements of the Ductus Venosus During the Early Second Trimester of Pregnancy: Reference Ranges and Clinical Application, Journal of	A full-text copy of the article could not be obtained

Study	Reason for exclusion
Ultrasound in MedicineJ Ultrasound Med, 37, 745-753, 2018	
Tchirikov,M., Monochorionic twin pregnancy: screening, pathogenesis of complications and management in the era of microinvasive fetal surgery, Journal of Perinatal Medicine, 38, 451-459, 2010	Narrative review
Thorson, H. L., Ramaeker, D. M., Emery, S. P., Optimal interval for ultrasound surveillance in monochorionic twin gestations, Obstetrics & Gynecology, 117, 131-5, 2011	Study does not present data on the accuracy of prognostic/diagnostic tests for FFTS – assesses timing of intervals between ultrasound screening
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 in Obstetrics & Gynecology, 37, 15-21, 2011	Not relevant population as all women had moderately amniotic fluid discordance at the beginning of the study
Vayssiere, C., Benoist, G., Blondel, B., Deruelle, P., Favre, R., Gallot, D., Jabert, P., Lemery, D., Picone, O., Pons, J. C., Puech, F., Quarello, E., Salomon, L., Schmitz, T., Senat, M. V., Sentilhes, L., Simon, A., Stirneman, J., Vendittelli, F., Winer, N., Ville, Y., French College of, Gynaecologists, Obstetricians,, Twin pregnancies: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF), European Journal of Obstetrics, Gynecology, & Reproductive BiologyEur J Obstet Gynecol Reprod Biol, 156, 12-7, 2011	Study does not present data on the accuracy of prognostic/diagnostic tests for FFTS
Wang, Q., Zhou, Y., Xu, H., Qin, G., Diagnosis of abnormal pregnancy and outcomes by color doppler ultrasound, Biomedical Research (India), 28, 3063-3065, 2017	Study does not present specific data on the accuracy of prognostic/diagnostic tests for FFTS – diagnostic value of ultrasound for abnormal twin pregnancy more broadly
Washburn, E. E., Sparks, T. N., Gosnell, K. A., Rand, L., Gonzalez, J. M., Feldstein, V. A., Polyhydramnios Affecting a Recipient-like Twin: Risk of Progression to Twin-Twin Transfusion Syndrome and Outcomes, American Journal of Perinatology, 35, 317-323, 2018	Not a prognostic/ diagnostic study of FFTS – assessing number progressing to FFTS and staging of FFTS
Washburn, E. E., Sparks, T. N., Gosnell, K. A., Rand, L., Gonzalez, J. M., Feldstein, V. A., Polyhydramnios Affecting a Recipient-like Twin: Risk of Progression to Twin-Twin Transfusion Syndrome and Outcomes, American Journal of Perinatology, 29, 29, 2017	Study does not present data on the accuracy of prognostic/diagnostic tests for FFTS
Wohlmuth, C., Boudreaux, D., Moise, K. J., Jr., Johnson, A., Papanna, R., Bebbington, M., Gardiner, H. M., Cardiac pathophysiology in twin-twin transfusion syndrome: New insights into its evolution, Ultrasound in Obstetrics & Gynecology, 31, 31, 2017	Study does not present data on the accuracy of prognostic/diagnostic tests for FFTS
Wohlmuth, C., Osei, F. A., Moise, K. J., Wieser, I., Johnson, A., Papanna, R., Bebbington, M., Gardiner, H. M., Changes in ductus venosus flow profile in twin-twin transfusion syndrome: role in risk stratification, Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology, 48, 744-751, 2016	No relevant comparison. The study examines the changes in the ductus venosus waveforms and timing of events that occur in TTTS

Study	Reason for exclusion
Woolcock, Jane G, Grivell, Rosalie M, Dodd, Jodie M, Regimens of ultrasound surveillance for twin pregnancies for improving outcomes, Cochrane Database of Systematic Reviews, 2017	Study does not present data on the accuracy of prognostic/diagnostic tests for FFTS
Zoppi, M. A., Iuculano, A., Monni, G., Umbilical vein volume flow in monochorionic twin pairs at 11-14 weeks, Journal of Perinatal Medicine, 42, 515-21, 2014	Study does not present data on the accuracy of prognostic/diagnostic tests for FFTS
Zuckerwise, L., Nayeri, U., Abdel-Razeq, S., Copel, J., Bahtiyar, M. O., Doppler abnormalities in monochorionic diamniotic twin pregnancies with discordant growth, Journal of Perinatology, 35, 387-9, 2015	No relevant comparison. The study examines whether abnormal umbilical artery Doppler flow velocity waveforms occur more often in monochorionic diamniotic twin pregnancies

Economic studies

No health economic evidence was identified for this review.

Appendix L – Research recommendations

No research recommendations were made for this review.