## Decision matrix

### Summary of evidence from previous surveillance

### Summary of new evidence from 4-year surveillance

### Summary of new intelligence from 4-year surveillance

### Impact

#### Determining gestational age and chorionicity

**129 – 01**  
**Gestational age:** What are the optimal ultrasound measurements to determine gestational age in multiple pregnancy? (1.1.1.1)

Are the measurements and charts (crown–rump length, biparietal diameter and head circumference) used for dating singletons equally effective for twins or are there systematic errors introduced from using these charts?

### Surveillance decision

This review question should not be updated.

#### Determination of gestational age  
**2-year Evidence Update (2013)**

No relevant evidence identified.

#### Determination of gestational age

A systematic review (11 trials including 37,505 women) assessed whether routine early pregnancy ultrasound for fetal assessment influences the diagnosis of fetal malformations, multiple pregnancies, the rate of clinical interventions, and the incidence of adverse fetal outcome when compared with the selective use of early pregnancy

None identified relevant to this question.

New evidence is consistent with guideline recommendations.

CG129 recommends (1.1.1.1) that women with twin and triplet pregnancies should be offered a first trimester ultrasound scan when crown–rump length measures from 45 mm to 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days) to estimate gestational age, determine chorionicity and screen for Down's syndrome.
### Summary of evidence from previous surveillance
- Ultrasound. The findings suggested that early ultrasound improves the early detection of multiple pregnancies and improved gestational dating may result in fewer inductions for post maturity. The authors advised caution in interpreting the results in view of the considerable variability in both the timing and the number of scans women received.

### Summary of new evidence from 4-year surveillance
- The new systematic review evidence supports the use of early ultrasound and is therefore consistent with CG129.

### Summary of new intelligence from 4-year surveillance
- Nomenclature of twin fetuses
  - A retrospective study (n=416 twin pregnancies) described a standard method of nomenclature for use in the first trimester of twin pregnancies, and reported the robustness of the method in predicting the presenting twin in subsequent scans and at delivery.
  - The results showed that 90.9% of twin pregnancies were judged to have a lateral and 9.1% a vertical orientation. Although none of the vertically orientated twin pairs changed their presenting order between first scan and the last scan prior to delivery, 8.5% of the laterally orientated twin pairs changed presenting order. There were 108
  - Nomenclature of twin fetuses
    - A retrospective study (n=2103 twin pregnancies) found that antenatal ultrasound labeling did not predict twin birth-order in a significant proportion of twin deliveries.
    - None identified relevant to this question.

### Impact
- New evidence is unlikely to impact on guideline recommendations
  - NICE CG129 recommends assigning nomenclature to babies in twin and triplet pregnancies, with clear documentation in the clinical notes, to ensure consistency throughout pregnancy.
  - New evidence from the evidence update suggests that the antenatal labelling of twins according to lateral (left or right) or vertical (top or bottom) orientation may be more reliable and reproducible than labelling according to proximity to the cervix, although the method cannot be used for monoamniotic twin pregnancies because there is no intertwin membrane.
  - Confusion arising from inconsistent identification of fetuses may result in lack
**Summary of evidence from previous surveillance**

Discordant sex twin pregnancies with ultrasound data available in the third trimester. Of these, 17 (15.7%) changed presentation between final scan and delivery, with the change significantly higher for twins delivered by caesarean section than by vaginal delivery.

This evidence was considered to have a potential impact on NICE CG129 recommendations for assigning nomenclature. However, in 2014 the Centre for Clinical Practice concluded that this evidence was insufficient to warrant an update to the guideline at that time.

**Summary of new evidence from 4-year surveillance**

**Summary of new intelligence from 4-year surveillance**

**Impact**

Of continuity in biometric assessment, and has potentially serious implications where invasive prenatal diagnosis is needed. Consequently, a standardised and reliable method for labelling, such as that described in the new evidence, may be needed. This evidence was considered in the Evidence Update to have a potential impact on NICE CG129 recommendations for assigning nomenclature. However, in 2014 the Centre for Clinical Practice concluded that this evidence was insufficient to warrant an update to the guideline. This was due to concern that nomenclature based on lateral position may not be superior to proximity to the cervix, due to movement of the foetuses. Any change to recommendation 1.1.2.2 was considered to be semantic only and insufficient to justify an update. The new observational study evidence identified at the 4 year surveillance review is unlikely to change this conclusion.

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<thead>
<tr>
<th>129 – 02</th>
<th>Gestational age: Which fetus should be used for estimating gestational age in multiple pregnancies? (1.1.2)</th>
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<tbody>
<tr>
<td><strong>Surveillance decision</strong></td>
<td>This review question should not be updated.</td>
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### Summary of evidence from previous surveillance

#### 2-year Evidence Update (2013)
No relevant evidence identified.

### Summary of new evidence from 4-year surveillance

<table>
<thead>
<tr>
<th>Decision matrix 4-year surveillance</th>
<th>Summary of new evidence from 4-year surveillance</th>
<th>Summary of new intelligence from 4-year surveillance</th>
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<tbody>
<tr>
<td>Determination of gestational age</td>
<td>A retrospective study⁴ (n=52 twin pregnancies) found that the smaller crown rump length (CRL) was more accurate in the estimation of the gestational age for twin pregnancy compared to the larger or mean CRL values.</td>
<td>None identified relevant to this question.</td>
<td>New evidence is unlikely to impact on guideline recommendations. The evidence suggesting that the smaller CRL is more accurate in the estimation of gestational age is insufficient to impact on recommendation 1.1.1.2, which advises using the largest baby to estimate gestational age to avoid the risk of estimating it from a baby with early growth pathology. The Guideline Committee considered it counterintuitive to date the pregnancy by the smallest fetus, which is more likely to be affected by early growth pathology and/or may result in unnecessary early delivery. The Guideline Committee therefore considered it more appropriate to date the pregnancy using the largest fetus. Further research may be needed to impact on this recommendation.</td>
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### Surveillance decision

This review question should not be updated.

<table>
<thead>
<tr>
<th>129 – 03 Chorionicity: What is the optimal method to determine chorionicity in multiple pregnancies? (1.1.2.1-1.1.2.11)</th>
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<tbody>
<tr>
<td>Determination of chorionicity</td>
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<td>Summary of evidence from previous surveillance</td>
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<td>weeks of gestation in twin pregnancies.</td>
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**General care**

129 – 04 Information and emotional support; Is there benefit in giving women with multiple pregnancy additional information and emotional support during the antenatal period? (1.2.1.1)

**Surveillance decision**
This review question should not be updated.

<table>
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<tr>
<th>2-year Evidence Update (2013)</th>
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<tbody>
<tr>
<td>No relevant evidence identified.</td>
<td>No relevant evidence identified.</td>
<td>None identified relevant to this question.</td>
<td>No new evidence was identified that would affect recommendations.</td>
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<td>Summary of evidence from previous surveillance</td>
<td>Summary of new evidence from 4-year surveillance</td>
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<td>129 – 05 Nutritional supplements: What additional (or different) dietary supplements are effective in improving maternal health and wellbeing (for example, reducing the risk of anaemia) in women with multiple pregnancy? (1.2.2.1-1.2.2.3)</td>
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<td>129 – 06 Dietary and lifestyle advice: Is nutritional advice specific to multiple pregnancies effective in improving maternal and fetal health and wellbeing? (1.2.2.1-1.2.2.3)</td>
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<td>129 – 07 Specialist care: Do specialist multiple pregnancy clinics improve outcomes in twin and triplet pregnancies? (1.2.31-1.2.3.9)</td>
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Decision matrix 4-year surveillance 2017 – Multiple pregnancy (2011) NICE guideline CG129
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<tr>
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<tr>
<td>Antenatal clinics compared with 'standard' antenatal care for women with a multiple pregnancy. The findings indicated that, for the only reported primary outcome of perinatal mortality from the 1 included RCT, it was unclear whether specialised antenatal clinics made any difference compared to standard care. Data were not reported in the study on other primary outcomes of small-for-gestational age, very preterm birth (PTB) or maternal death. There were no differences identified between specialised antenatal care and standard care for other secondary outcomes examined. A retrospective cohort study (n=513 twin pregnancies) found that the introduction of a specialised consultant-led, multidisciplinary twins clinic significantly decreased caesarean section rates and late PTB when compared to a general antenatal clinic and to private obstetric care. Length of inpatient stay also decreased significantly with the specialist clinic compared to the general antenatal clinic. Implementation and remaining inequality in the services provided. It was felt that if CG129 is revised this section should certainly be considered for revisions which may strengthen it. In addition there was a suggestion that the way regional services have been organised led by St George’s NHS Trust have reduced still birth rates and improved outcomes. A <a href="#">NICE shared learning case study</a> and a cohort study were cited and are included in evidence summary.</td>
<td>New systematic review evidence was inconclusive as to whether specialised antenatal clinics made any difference to perinatal mortality compared to standard care, and is unlikely to impact on CG129 recommendations. New RCT evidence on a midwife-led intervention was insufficiently powered to establish a definite effect on maternal depression and is therefore unlikely to impact on CG129. New observational study evidence, suggesting that a specialised consultant-led, multidisciplinary twins clinic may decrease caesarean section rates and late PTB, may require further research to verify the findings before any impact on CG129 can be established.</td>
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### Summary of evidence from previous surveillance

**Fetal complications**

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<tr>
<th>Evidence</th>
<th>Question</th>
<th>Recommendation</th>
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<tr>
<td>129 – 08</td>
<td>When and how should screening be used to identify chromosomal abnormalities in multiple pregnancy? (1.3.1.1-1.3.2.6)</td>
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### Summary of new evidence from 4-year surveillance

#### Surveillance decision

This review question should not be updated. A footnote to the recommendations is to be added with reference to National Screening Committee recommendations on cfDNA screening.

#### 2-year Evidence Update (2013)

No relevant evidence identified.

A systematic review\(^1\) (37 studies, number of multiple pregnancy studies not reported) found that screening for trisomy 21 by analysis of cell free DNA in maternal blood was superior to other traditional methods of screening, with higher detection rates and a lower false positive rate. The performance of screening for trisomies 18 and 13 and sex chromosome aneuploidies was not reported for twin pregnancies.

A systematic review and meta-analysis\(^2\) (number of studies not reported) assessed the detection rate and false-positive rate of the combined test for the screening of trisomy 21 in twins. Selected studies included data on maternal age, number of fetuses affected by Down syndrome, test strategy, sensitivity and specificity of the test. The results indicated that the accumulative evidence

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### Summary of new intelligence from 4-year surveillance

A topic expert raised questions around the frequency of ultrasound biometry in:

- Monochorionic twins be continued at 2 weekly intervals beyond 24 weeks until delivery?
- Dichorionic twins be the same frequency as in monochorionic twins to reduce mortality and mortality?

Two references were cited to address those questions and were included in the evidence summary.

### Impact

New evidence identified that may change current recommendations.

New systematic review evidence and clinical feedback indicates that cell free DNA testing may be of value for screening for trisomy 21. This has a potential impact on recommendation 1.3.2.2, which advises using the combined screening test (nuchal translucency, beta-human chorionic gonadotrophin, pregnancy-associated plasma protein-A) for Down's syndrome when crown–rump length measures from 45 mm to 84 mm. CG129 may need to be aligned to National Screening Committee recommendations on cfDNA screening which were published in November 2015 and recommend that this method of screening be tested in practice prior to implementation.

Other new systematic review and observational study evidence confirming the effectiveness of the combined test is
### Summary of evidence from previous surveillance
- on the performance of the combined test in twin pregnancies is good.

A retrospective study\(^\text{13}\) (n=277 twin pregnancies) compared the performance of three different strategies in prenatal screening for Down's syndrome in twins [nuchal translucency, the combined test, the combined test + ductus venosus pulsatility index (DVPI)]. The findings indicated that Down's syndrome screening is feasible in twins and had a low false positive rate. The results were similar to the results achieved in singletons. The combined test appeared to be the most effective. The addition of DVPI did not significantly improve the prenatal screening for trisomy 21.

### Summary of new evidence from 4-year surveillance
- syndrome but also trisomy 13 and 18. The tests are offered privately for twins (for example, SAFE test, Harmony test) and are being used in some NHS services at present. It is confusing for women and their partners as to which tests should be used and the reliability of the predictions as the data on which the evidence is based is from different sources and limited.

Topic expert feedback indicated that it is important that guidance is provided for women and also commissioners. A survey of parents of multiples has been published by Twins and multiple births association (TAMBA) found that only 52% of women with a high risk result said the options and implications had been explained to them indicating a need for more guidance and training for professionals.

### Summary of new intelligence from 4-year surveillance
- consistent with CG129 recommendation 1.3.2.2.

### Impact

#### 129 – 09 When and how should screening be used to identify structural abnormalities in multiple pregnancy? (1.3.3.1-1.3.3.4)

**Surveillance decision**
- This review question should not be updated.

**2-year Evidence Update (2013)**
- No relevant evidence identified.

A diagnostic study\(^\text{14}\) (n=257 twin pregnancies, 514 amniotic fluid samples) assessed the validity of amniotic lamellar body count (LBC) in predicting respiratory disorders in twins. The findings suggested that LBC may have value for

New evidence is unlikely to impact on guideline recommendations.

CG129 recommends (1.3.3.1) offering the same screening for structural abnormalities in twin and triplet pregnancies as in routine
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| predicting respiratory distress syndrome (RDS) and transient tachypnea of the newborn. A cohort study\(^{15}\) (n=1028 twin pregnancies) established reference ranges for the umbilical artery (UA) pulsatility index (PI), UA resistance index (RI), fetal middle cerebral artery (MCA), PI and peak systolic velocity (PSV) and cerebroplacental ratio (CPR). All of the indices appeared to differ from those in singleton pregnancies, suggesting that the derived twin-specific reference ranges may be more appropriate in the surveillance of these high-risk pregnancies. | | | antenatal care, as recommended by ‘Antenatal care’ NICE clinical guideline 62. New observational study evidence was identified in the following areas, but may require further research to confirm the findings:  
- Amniotic LBC in predicting respiratory disorders in twins.  
- Twin-specific reference ranges may be more appropriate in the surveillance of multiple pregnancies, including UA-PI, UA-EI, fetal MCA-PI, PSV and CPR ranges. |

129 – 10  When and how should screening be used to identify feto-fetal transfusion syndrome (FFTS) in multiple pregnancy? (1.3.4.1-1.3.4.3)

**Surveillance decision**  
This review question should be updated.

**2-year Evidence Update (2013)**  
A retrospective cohort study\(^{16}\) investigated the value of intertwin discordance in nuchal translucency (NT) and CRL measured at the first trimester scan, to predict subsequent FFTS. The study also assessed the A cohort study\(^{18}\) (n=43 twin pregnancies) evaluated the diagnostic accuracy of middle cerebral artery peak systolic velocity (MCA-PSV) Doppler measurements in prediction of haemoglobin levels in twin anemia-polycythemia sequence (TAPS). MCA-PSV measurement was found to have Topic expert feedback indicated that there is some evidence from the *International Society of Ultrasound in Obstetrics and Gynecology Clinical Standards Committee* indicating that in monochorionic and dichorionic twins middle cerebral artery Doppler maximum systolic velocity (MSV) and umbilical artery Doppler measurements should New evidence identified that may change current recommendations  
CG129 recommends (1.3.4.1-1.3.4.3) that monitoring for FFTS is not carried out in the first trimester, but should be started using ultrasound (including identifying membrane folding) from 16 weeks and
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<td>high diagnostic accuracy for predicting abnormal fetal haemoglobin levels in fetuses with TAPS. A systematic review(^{19}) (n=28 pregnancies with TAPS) found that diagnosis of TAPS between 15 to 23 weeks’ gestation was associated with more favourable outcomes than later diagnosis. In utero therapy improved neonatal haemoglobin levels but did not change survival rates. Previous twin-to-twin transfusion syndrome did not worsen outcomes. A study(^{20}) (n=223 twin pregnancies) found that inter-twin amniotic fluid discordance (AFD) in the early second trimester found that AFD &gt;4 cm was associated with a significantly increased risk of the development of FFTS suggesting predictive value in screening. A case-control study(^{21}) (n=55 twin pregnancies) investigated whether vector velocity imaging (VVI), a non-Doppler speckle tracking ultrasound technology, is feasible in twin pregnancies and can aid management of FFTS. Right and left ventricular free wall Lagrangian strain was measured from the original coordinates. Within-twin pair ventricular measurements of either discordance was not predicted by first trimester measurements of either discordance in NT nor CRL.</td>
<td>be performed from 16 weeks. The topic expert stated that the evidence base for this guideline is weak and mostly ‘expert view’, however. A topic expert raised the question of whether monochorionic twin pregnancy should be ‘screened’ using MCA-PSV in the second and third trimester in: a) low risk MC twins (background risk ~1-3%) and b) high risk (risk circa 12-15%). The Royal College of Obstetrics and Gynaecology (RCOG) Green Top Guidance (GTG) ‘Management of monochorionic twin pregnancy’ has been revised and published in November 2016. The RCOG GTG reviewed all the recent research relating to monitoring for FFTS but the topic expert felt that CG129 should be reviewed particularly in relation to the recommendation about monitoring. The guideline has been modified to include the recommendation that ultrasound surveillance is performed from 16 weeks until delivery at two weekly intervals. It also states that because TAPS mainly occurs in complicated cases and because there is little evidence to guide management, screening of monochorionic twins for TAPS using serial MCA PSV measurements is not routine and should be confined to complicated monochorionic twin pregnancy where the risk of TAPS is high. New observational study evidence also indicated that in monochorionic and dichorionic twins, middle cerebral artery Doppler maximum systolic velocity (MSV) and umbilical artery Doppler measurements may be advisable from 16 weeks until delivery. The RCOG Green Top Guidance (GTG) ‘Management of monochorionic twin pregnancy’ has been revised. This has potential impact on CG129 recommendation 1.3.4.2, as advised by topic expert feedback in the following aspects of monitoring: • ultrasound surveillance is recommended by GTG to be performed from 16 weeks until delivery at two weekly intervals. • screening of monochorionic twins for TAPS using serial MCA-PSV measurements is not routine and should be confined to complicated monochorionic twin pregnancy where the risk of TAPS is high. New observational study evidence also</td>
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| association between NT and CRL with other adverse outcomes. FFTS occurred in 16 of the 135 pregnancies (12%), with other adverse outcomes occurring in 7 further pregnancies. Median discordance in NT was similar in uncomplicated pregnancies and in those with FFTS or miscarriage before 24 weeks, but was significantly higher in selective intrauterine growth restriction (IUGR). As assessed by the area under the receiver-operating characteristics (ROC) curve, FFTS was not predicted by first trimester measurements of either discordance in NT nor CRL. A retrospective cohort study\(^{17}\) assessed the correlation between NT and CRL in monochorionic twins at 11–14 weeks of gestation, and subsequent development of FFTS and selective IUGR. The analysis included a total of 242 twin pregnancies, with 104 resulting in normal pregnancy, 102 in FFTS and 36 with selective IUGR. |

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<td>association between NT and CRL with other adverse outcomes. FFTS occurred in 16 of the 135 pregnancies (12%), with other adverse outcomes occurring in 7 further pregnancies. Median discordance in NT was similar in uncomplicated pregnancies and in those with FFTS or miscarriage before 24 weeks, but was significantly higher in selective IUGR.</td>
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<td>Summary of evidence from previous surveillance</td>
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<tr>
<td>There was no significant difference in NT discordance between pregnancies that resulted in FFTS, selective IUGR or normal outcome. The discrepancy in CRL was significantly greater in the group with selective IUGR than with FFTS or normal outcome, but there was no significant difference in CRL discrepancy between FFTS and normal pregnancies. Using a CRL discrepancy threshold of 7.12% for the prediction of selective IUGR gave a sensitivity of 92% and a specificity of 76%. Taken together, these studies were considered to show that discordance in NT and CRL at 11–14 weeks does not appear to predict subsequent FFTS, consistent with the recommendations of CG129 not to monitor for this complication in the first trimester. The studies were also considered to show a relationship between CRL discrepancy at 11–14 weeks and subsequent development of selective IUGR. However, this evidence was considered unlikely to have an impact on CG129, which recommends regular serial scans and strain differences were analysed. The results suggested that within-pair strain discordance may distinguish early FFTS from growth discordance and guide timing of and management following treatment. An observational study assessed a myocardial performance index measured by conventional Doppler (MPI) and by tissue Doppler imaging (MPI') at 18 weeks' gestation in monochorionic diamnionic (MCDA) twins for the prediction FFTS. Right ventricle (RV) MPI and left ventricle (LV) MPI and LV-MPI' were found to be predictive indicators in pregnancies that had not yet developed FFTS. The best performing index was LV-MPI'. A cohort study (n=105 twin pregnancies) evaluated the prognostic value of the Children's Hospital Of Philadelphia (CHOP) cardiovascular score and the modified myocardial performance index, in determining the risk of recipient fetal loss in FFTS. CHOP score and myocardial performance index were found to be potential predictors of recipient fetal loss in FFTS and could be should be confined to complicated monochorionic twin pregnancy where the risk of TAPS is high (those with TTTS or SGR). Topic expert feedback indicated that detection of TAPS is too specialised for inclusion in the scope of this guideline and should not be covered in the update. Topic expert feedback indicated that detection of TAPS is too specialised for inclusion in the scope of this guideline and should not be covered in the update. Additional limited observational study evidence was identified in the following areas, but may require further research to confirm any impact on the guideline: • Inter-twin AFD &gt;4 cm in the early second trimester may be associated with a significantly increased risk of the development of FFTS. • The predictive value of left ventricle MPI in predicting FFTS. • The prognostic value of the CHOP cardiovascular score and the modified myocardial performance index, in determining the risk of recipient fetal loss in FFTS. • The role for leptin as a potential biomarker in pregnancies complicated by FFTS, in predicting lower recipient twin birth weight and growth discordance.</td>
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### Summary of evidence from previous surveillance

- Referral to tertiary services if there is growth discordance.

### Summary of new evidence from 4-year surveillance

- Used to supplement Quintero’s classification.
- A retrospective case control study\(^2^4\) (n=44 twin pregnancies) found that recipient twin (RT)-adjusted leptin was significantly higher in cases of FFTS with placental insufficiency compared to FFTS controls. Cases had significantly higher growth discordance and lower RT birth weight compared to controls. The findings suggested a role for leptin in pregnancies complicated by FFTS with placental insufficiency, but further studies were recommended to confirm its mechanism and potential biomarker role.

### Summary of new intelligence from 4-year surveillance

- Impact referral to tertiary services if there is growth discordance.

### Impact

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<tr>
<th>Surveillance decision</th>
<th>Biometry discordance</th>
<th>Impact</th>
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<tbody>
<tr>
<td><strong>2-year Evidence Update (2013)</strong></td>
<td>Growth charts</td>
<td>New evidence identified that may change current recommendations</td>
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<tr>
<td>No relevant evidence identified.</td>
<td>A secondary analysis(^2^5) (n=2125 twin pregnancies, 1802 dichorionic diamnotic and 323 MCDA) of the STORK cohort study established reference charts for fetal growth for twin pregnancies. Ultrasound biometry showed a small but statistically significant reduction in fetal</td>
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<td>A question was raised by a topic expert about the level of difference (18%, 20% or 25%) in estimated fetal weight in twins associated with increased fetal mortality.</td>
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<td>Two cited studies are included in the evidence summary. In addition the topic expert highlighted that in the updated RCOG GTG Management of monochorionic twin</td>
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<td>New evidence identified that may change current recommendations</td>
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Summary of evidence from previous surveillance

- Growth in twin pregnancies relative to that in singletons, particularly in the third trimester, with a more marked difference for MCDA than for DCDA pregnancies. It should be noted that the authors recommended further prospective studies that also account for pathological complications and their treatment.

A retrospective cohort study26 (n=51,150 singleton births, n=1608 pairs of infants) found that customised charts designed specifically for twins were more effective at identifying twin pregnancies at risk for intrauterine fetal death (IUFD) than those derived using singleton birth data.

CRL discordance

- A retrospective analysis of the STORK cohort study27 (n=1356 twin pregnancies) found that in twin pregnancies the predictive accuracy of CRL discordance at 7(+0)-9(+6) weeks for single fetal loss was high. A significant association was also found between the increase in the degree of embryonic discordance and the likelihood of early fetal loss. It should be noted that only a high-risk population was analysed. Therefore, the patients studied were not a representative sample from pregnancy (2016) that a threshold of 20% is recommended.

- A group at St George’s Hospital London led by Professor Thilaganathan has developed growth charts for twins. As this is an important aspect of monitoring in multiple pregnancy and was a recommendation in CG129 it is important to review this new evidence in this area. The related publication25 is included in the evidence summary.

However, additional topic expert feedback highlighted that this study indicates that fetal biometry (especially of MC twins) grows slower than in singleton pregnancy. However, the definition of selective growth restriction most strongly matched to perinatal mortality is % difference in estimated fetal weight. This is likely not to be altered. It was felt that a more important indicator is the ‘threshold’ of difference in estimated fetal weight that may require modification (i.e. % difference of 18% rather than 25% recommended by CG129).

- It was felt that there is some evidence that the cerebroplacental ratio in twins may help prevent neonatal mortality and morbidity42.

- A topic expert also indicated that new data41 on fetal growth and Doppler discordance for the prediction of adverse perinatal outcome is that no evidence-based growth charts specific to twin and triplet pregnancies are available for use in the diagnosis of intrauterine growth restriction.

New evidence identified from the STORK cohort study and subsequent secondary analyses indicates the following:

- Customised reference charts designed specifically for fetal growth in twins appear to be more effective at monitoring fetal growth risk for intrauterine fetal death than those derived using singleton birth data. This has a potential impact on CG129, which does not make recommendations for using growth charts.

- However, topic experts indicated that there is insufficient evidence from prospective studies to include the use of growth charts for twins in the guideline.

EFW discordance

- New evidence identified that may change current recommendations

- New evidence suggests that an ultrasound surveillance programme of every 2 weeks may have predictive value in dichorionic gestations as well as monochorionic twins, as an aid to prenatal detection of fetal growth restriction. This has a potential
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<td>the population of women pregnant with twins.</td>
<td>available which may significantly influence recommendations on timing of birth. This is included in the evidence summary. An ongoing study (Thilaganathan, BMJ in press) was also cited but no further details or expected publication date were provided.</td>
<td>impact on recommendation 1.3.5.2, which advises aiming to undertake scans at intervals of less than 28 days. Topic experts indicated that it would be possible to split out recommendations for the different types of multiple pregnancies (monochorionic, dichorionic and trichorionic) for ultrasound surveillance. Second-trimester EFW and AC discordance appear to have poor predictive value for adverse perinatal outcomes in twin pregnancy. An EFW discordance of greater than 25% could represent the optimal cut-off for the prediction of stillbirth and neonatal mortality, irrespective of chorionicity or individual fetal size. A policy of increased fetal surveillance commencing from 26 weeks’ gestation might be reasonable for pregnancies beyond this cut-off. This is consistent with CG129, which recommends (1.3.5.2) a 25% or greater difference in size between twins or triplets as a clinically important indicator of intrauterine growth restriction. However, In the updated RCOG Green top Guideline a new threshold of 20% has been advised, based on expert opinion and observational study evidence. There is therefore a</td>
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<td>A further retrospective analysis of the STORK cohort study28 (n=2155 twin pregnancies) found that, in the absence of aneuploidy or structural fetal abnormality, CRL discordance was of poor predictive value for adverse perinatal outcome in both MC and DC twin pregnancies. The findings suggested that CRL discordance should not be used routinely to identify twin pregnancies at high risk of adverse perinatal outcome.</td>
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<td>A smaller retrospective cohort study29 (n=126 twin pregnancies) found that discordance of CRL in MCDA twin gestations during the mid-first trimester had predictive value for predicting discordant birthweight.</td>
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<td>A retrospective cohort study30 (177 twin pregnancies) found that NT, CRL, and combined discordances in MCDA twin pregnancies were not predictive of the following adverse composite obstetric and neonatal outcomes: intrauterine growth restriction (IUGR), FFTS, intrauterine fetal death (IUFD), growth</td>
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<td>discordance (&gt; 20%), and PTB before 28 weeks' gestation.</td>
<td>Estimated fetal weight (EFW) The STORK cohort study(^3) (n=2399; 457 monochorionic and 1942 dichorionic) twin pregnancies aimed to determine the association between biometry discordance at the time of the anomaly scan and adverse perinatal outcomes in twin pregnancies. Once structural malformations, chromosomal abnormalities, and twin-to-twin transfusion syndrome had been excluded, second-trimester EFW and abdominal circumference (AC) discordance were found to have poor predictive value for adverse perinatal outcomes in twin pregnancy. Several secondary analyses(^2) of the STORK cohort study were conducted in the following areas: One analysis(^2) (n=2161 twin pregnancies) assessed the performance of intertwin birth weight (BW) and ultrasound EFW discordance in the prediction of perinatal loss in twin pregnancies. The findings indicated that an EFW discordance of &gt;25%</td>
<td>potential impact on CG129 for the recommended threshold to be reviewed. EFW discordance may be independently associated with the occurrence of single fetal loss in twin pregnancies in each gestational age window. Ultrasound estimation of birth weight may be less accurate in twin than in singleton pregnancies. Formulae that include a combination of head, abdomen and femur measurements may perform best in both singleton and twin pregnancies for birth-weight estimation. CRL discordance New evidence is unlikely to impact on guideline recommendations There is conflicting evidence on the predictive accuracy of CRL discordance in twin pregnancies for adverse perinatal outcomes, including single fetal loss. There may be a significant association between the increase in the degree of embryonic discordance and the likelihood of early fetal loss. It is unclear whether CRL discordance should or should not be used routinely to identify twin pregnancies at high risk of adverse perinatal outcome. Additional Parameters</td>
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<td>represented the optimal cut-off for the prediction of stillbirth and neonatal mortality, irrespective of chorionicity or individual fetal size.</td>
<td>A further analysis (n=957 twin pregnancies) found that EFW discordance was independently associated with the occurrence of single fetal loss in twin pregnancies in each gestational age window. The optimal cut-offs of EFW discordance for the prediction of single fetal loss were different in each gestational age window.</td>
<td>Additional observational study evidence, which may require additional research to verify the findings, indicates that:</td>
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<td>Another analysis (n=4280 singleton, n=586 twin fetuses) found that ultrasound estimation of birth weight was less accurate in twin than in singleton pregnancies. Formulae that include a combination of head, abdomen and femur measurements performed best in both singleton and twin pregnancies for birth-weight estimation.</td>
<td>- Umbilical vein doppler parameters could potentially predict acidemia at birth or intrauterine fetal death in monochorionic twins complicated by placental insufficiency.</td>
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<td>A secondary analysis of the ESPRiT cohort study (n=789 dichorionic twin pregnancies) found that an ultrasound surveillance programme of every 2 weeks had predictive value in dichorionic gestations as well as monochorionic</td>
<td>- Reference values for fetal biometric parameters in twin pregnancies appear to be significantly different between monochorionic and dichorionic pregnancies.</td>
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<td>- Estimation of fetal weight using ultrasound in obese women with twin pregnancies appears to be more reliable when performed within 7 days of delivery.</td>
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<td>- The aortic isthmus pulsatility index may have predictive value in predicting growth discordance and birthweight.</td>
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<td>- The combination of EFW discordance and CPR discordance has the potential to identify the majority of twin pregnancies at risk of perinatal loss.</td>
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<td>- Third-trimester CPR has value in predicting stillbirth and perinatal</td>
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### Summary of evidence from previous surveillance

- Twins, as an aid to prenatal detection of fetal growth restriction and ultimately influence timing of delivery.

A retrospective cohort study\(^{38}\) (\(n=1744\) twin pregnancies) found that three sonographic EFW formulas, two derived from singletons and one from twins, performed equally well for estimating birth weight in twin gestations.

A prospective cohort study\(^{37}\) (\(n=18\) monochorionic twin pregnancies) found that umbilical vein doppler parameters could potentially predict acidemia at birth or intrauterine fetal death in monochorionic twins complicated by placental insufficiency.

A retrospective cross sectional study\(^{38}\) (\(n=333\) twin pregnancies, 157 monochorionic and 176 dichorionic) determined reference values for fetal biometric parameters in twin pregnancies and found that these parameters were significantly different between monochorionic and dichorionic pregnancies. Biometric measurements included the biparietal diameter (BPD), AC, femurs length (FL) and EFW.

### Summary of new evidence from 4-year surveillance

- A retrospective cohort study found that three sonographic EFW formulas, two derived from singletons and one from twins, performed equally well for estimating birth weight in twin gestations.

### Summary of new intelligence from 4-year surveillance

- A prospective cohort study found that umbilical vein doppler parameters could potentially predict acidemia at birth or intrauterine fetal death in monochorionic twins complicated by placental insufficiency.

- A retrospective cross sectional study determined reference values for fetal biometric parameters in twin pregnancies and found that these parameters were significantly different between monochorionic and dichorionic pregnancies. Biometric measurements included the biparietal diameter (BPD), AC, femurs length (FL) and EFW.

### Impact

- twins, as an aid to prenatal detection of fetal growth restriction and ultimately influence timing of delivery.

- A retrospective cohort study\(^{38}\) (\(n=1744\) twin pregnancies) found that three sonographic EFW formulas, two derived from singletons and one from twins, performed equally well for estimating birth weight in twin gestations.

- A prospective cohort study\(^{37}\) (\(n=18\) monochorionic twin pregnancies) found that umbilical vein doppler parameters could potentially predict acidemia at birth or intrauterine fetal death in monochorionic twins complicated by placental insufficiency.

- A retrospective cross sectional study\(^{38}\) (\(n=333\) twin pregnancies, 157 monochorionic and 176 dichorionic) determined reference values for fetal biometric parameters in twin pregnancies and found that these parameters were significantly different between monochorionic and dichorionic pregnancies. Biometric measurements included the biparietal diameter (BPD), AC, femurs length (FL) and EFW.

- mortality, but further prospective research may be needed on the role of uterine artery Doppler, CPR.

- NT, CRL, and combined discordances in MCDA twin pregnancies may not be predictive of the composite obstetric and neonatal outcomes, including IUGR, FFTS, IUFD, growth discordance and PTB.
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<td>A retrospective cohort study(^9) (n=300 twin pregnancies) found that estimation of fetal weight using ultrasound in obese women with twin pregnancies appeared to be more reliable when performed within 7 days of delivery.</td>
<td>Additional parameters A prospective cohort study(^40) (n=49 pairs of twin foetuses) found that the aortic isthmus pulsatility index had predictive value in predicting growth discordance and birthweight. A retrospective cohort study(^41) (n=620 [464 dichorionic diamniotic and 156 MCDA]) twin pregnancies) found that EFW discordance and CPR discordance were independent predictors of the risk of perinatal loss in twin pregnancies, suggesting that their combination could identify the majority of twin pregnancies at risk of perinatal loss. A retrospective cohort study(^42) (n=2812) found that third-trimester CPR was an independent predictor of stillbirth and perinatal mortality. Further prospective research was recommended on the role of uterine artery Doppler, CPR and EFW</td>
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<td>in assessing risk of adverse pregnancy outcome.</td>
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**Maternal complications**

**129 – 12 Hypertension: What is the optimal screening programme to detect hypertension in multiple pregnancy in the antenatal period? (1.4.1.1)**

Surveillance decision

This review question should not be updated.

**2-year Evidence Update (2013)**

No relevant evidence identified.

A cross sectional study (n=421 twin pregnancies [384 dichorionic and 37 monochorionic]) found that first-trimester uterine artery assessment had potential value in predicting early pre-eclampsia and small-for-gestational age of either or both foetuses in twin pregnancies.

A study (n=147 twins, 110 singleton pregnancies) evaluated the distribution of mean arterial pressure (MAP) and uterine artery Doppler pulsatility index (PI) in first trimester twins with and without preeclampsia. The findings indicated that for first trimester screening for preeclampsia in twins, a different normal median Doppler PI equation will be needed to that used in singleton pregnancies. It should be noted that the study was underpowered to confidently predict the extent of elevation in these

None identified relevant to this question.

New evidence is unlikely to impact on guideline recommendations

CG129 advises (1.4.1.1) measuring blood pressure and testing urine for proteinuria to screen for hypertensive disorders at each antenatal appointment in twin and triplet pregnancies as in routine antenatal care, as recommended by NICE CG62. CG62 notes multiple pregnancy as a risk factor for pre-eclampsia and recommends more frequent blood pressure measurements. However, it does not refer to the Doppler PI equation or the measurement of protein excretion.

New observational study evidence indicates that the screening programme for preeclampsia in twin pregnancies, as distinct from singleton pregnancies, may need to be reassessed due to:
Decision matrix 4-year surveillance 2017 – Multiple pregnancy (2011) NICE guideline CG129

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<td>markers among affected twins. Hence, the authors acknowledged that the findings need to be confirmed by additional larger studies. A prospective study(^4) (n=99 pregnancies, 50 twin and 49 singleton) found that mean 24-hour urinary protein excretion in twin pregnancies was greater than in singletons, suggesting that the diagnostic criteria for preeclampsia in twin pregnancies may need to be reassessed.</td>
<td>• The potential need for a different normal median Doppler PI equation to that used in singleton pregnancies. • The greater mean 24-hour urinary protein excretion in twin pregnancies than in singletons. Further research may be needed to justify an update to recommendation 1.4.1.1 specifically for multiple pregnancies.</td>
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**Preterm Birth**

129 – 13 Predicting the risk of preterm birth: What is the optimal screening programme to predict the risks of spontaneous preterm delivery? (1.5.1.1-1.5.1.4)

**Surveillance decision**

This review question should not be updated.

**2-year Evidence Update (2013)**

CG129 recommends that cervical length (with or without fetal fibronectin) should not be used routinely to predict the risk of spontaneous PTB in twin or triplet pregnancies.

A meta analysis\(^4\) (21 studies, 16 relating to twin pregnancies, n=2570 women, 5 relating to triplet

**Biometry**

A secondary analysis\(^4\) of the ESPRiT cohort study (n=1028 twin pregnancies) evaluated biometric data, including CRL and AC obtained between 11 and 22 weeks as predictors of a composite of adverse perinatal outcome (mortality, hypoxic ischemic encephalopathy, periventricular leukomalacia, necrotizing enterocolitis, RDS, or sepsis), PTD and Topic experts advised that abdominal circumference will not predict spontaneous pre-term birth.

**Biometry**

New evidence is unlikely to impact on guideline recommendations

New evidence from the ESPRiT cohort study indicates that a difference in AC of over 10% has potential value in predicting a composite of adverse perinatal outcomes, including PTB. The strongest correlation for intertwin differences appears to be between 18 and 22 weeks.
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<td>pregnancies, n=187 women) of cervical length as a predictor of PTB showed a strong association between short cervical length in the second trimester and PTB in multiple pregnancies. The conclusion, that there is currently no place in routine clinical practice for cervical length measurement in this population, was considered to be consistent with the recommendations in NICE CG129.</td>
<td>birthweight discordance greater than 18%. Biometry in the early second trimester was found to have predictive value in identifying twin pregnancies at increased risk. AC between 18 and 22 weeks was found to be the strongest predictor of preterm birth. It should be noted, however, that the lack of early ultrasounds is a limitation of this study as it may have potentially led to inaccurate dating.</td>
<td>A retrospective study46 (n=1993 twin pregnancies) found that CRL discordance in twin pregnancies was associated with, but was not a strong predictor of preterm delivery, birth weight discordance and fetal loss.</td>
<td>This may have a potential impact on CG129, which does not make a recommendation for AC measurement in predicting risk of PTB. However, topic experts advised that abdominal circumference in isolation will not predict spontaneous pre-term birth. The evidence on measuring abdominal circumference is therefore unlikely to impact on the review question for spontaneous preterm delivery. The new evidence indicates that CRL discordance may not be a strong predictor of preterm delivery. This is consistent with CG129, which does not advise using CRL as a predictor for preterm birth.</td>
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<td>Previous PTB</td>
<td>A retrospective cohort study48 (n=576 twin pregnancies) found that PTB in a previous singleton pregnancy was an independent risk factor for PTB in a subsequent twin pregnancy, suggesting the need for close surveillance in this population.</td>
<td>A systematic review50 (13 studies) found that the risk of recurrence of PTB is influenced by the singleton/twin order in</td>
<td><strong>PTB in a previous singleton pregnancy.</strong> New evidence is consistent with guideline recommendations CG129 advises (1.5.1.1) awareness of the risk of spontaneous PTB in women with multiple pregnancy who have had a spontaneous PTB in a previous singleton pregnancy. The new evidence is consistent with this.</td>
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<td>Cervical length measurement</td>
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Decision matrix 4-year surveillance 2017 – Multiple pregnancy (2011) NICE guideline CG129
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<td>both pregnancies, and was highest for twins after a previous preterm singleton.</td>
<td><strong>Cervical length measurement</strong> A systematic review(^{51}) (five studies (n=226)) found limited evidence on the accuracy of cervical length measurement testing the prediction of PTB in symptomatic women with a twin pregnancy. Only one study covered the important outcome of delivery within 7 days. A study(^{52}) ((n=420) twin pregnancies) found that the test of two CL measurements, the first between 20 and 23 weeks gestation and another CL measurement 3-5 weeks later, with a difference of &gt;25%, was a good predictor for PTB in asymptomatic twin pregnancies, even if the CL was &gt;25 mm. A retrospective cohort study(^{53}) ((n=1295)) found that the performance of CL as a test for the prediction of PTD was similar in twin and singleton pregnancies. However, the optimal threshold of CL for the prediction of PTD appeared to be higher in twin pregnancies, mainly owing to the higher baseline risk for PTD in these pregnancies.</td>
<td>New evidence is unlikely to impact on guideline recommendations CG129 advises (1.5.1.4) against using cervical length (with or without fetal fibronectin) routinely to predict the risk of spontaneous PTB in twin or triplet pregnancies. The mixed findings from the new systematic review and observational studies confirm that there is insufficient evidence to recommend routine cervical length measurement for twin or triplet pregnancies at this time.</td>
<td><strong>Fetal fibronectin</strong> New evidence is unlikely to impact on guideline recommendations CG129 advises (1.5.1.2) against using fetal fibronectin testing alone to predict the risk of spontaneous PTB in twin or triplet pregnancies. The new evidence suggesting that fetal fibronectin is superior to cervical length measurement is consistent with recommendation 1.5.1.4, which advises against using cervical length for predicting PTB.</td>
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### Summary of evidence from previous surveillance

A prospective cohort study\(^5^4\) (n=120 asymptomatic twin pregnancies) found that the performance of cervical shortening between 22 and 27 weeks for the prediction of preterm delivery of asymptomatic twins before 34 weeks did not differ from that of CL measurements at 22 or 27 weeks.

A cohort study\(^5^5\) (n=611 twin pregnancies) found that in asymptomatic patients with twin pregnancies, the cervical length, fetal fibronectin (FFN), and gestational age were all significantly associated with spontaneous PTB.

A cohort study\(^5^6\) (n=988 twin pregnancies) found that in twin pregnancies, routine CL and fetal fibronectin screening did not reduce the risk of PTB or spontaneous PTB. However, the routine use of these tests was associated with significantly improved antenatal corticosteroid (ACS) exposure and timing for women who delivered preterm without increasing ACS exposure to women who delivered at term.

Fetal fibronectin (FFN)

### Summary of new evidence from 4-year surveillance

New evidence is consistent with guideline recommendations

New evidence was identified indicating that risk of preterm delivery could be assessed with a multivariable model incorporating cervical length and other predictors, including previous preterm delivery and monochorionicity. However, further research may be required to validate these models before one or more can be recommended in CG129. The potential value of using multiple variables is consistent with CG129, in advising against a single measurement such as fetal fibronectin.

**Other risk factors**

New evidence is unlikely to impact on guideline recommendations

The new evidence identified on the following risk factors may need further research to verify the findings:

- Same-sex pairing, in particular male to male gender.
- Number of abnormalities diagnosed and presence of fetal effusion or hydrops.
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<td>A secondary analysis(^57) (n=412) of an RCT of 17-hydroxyprogesterone caproate (17OHPc) versus placebo in dichorionic-diamniotic twins found that positive FFN was stronger than cervical length less than 25 mm in predicting early PTB in twins, regardless of 17OHPc use. Treatment with 17OHPc did not appear to alter the predictive value of FFN. <strong>Multivariate and risk prediction models</strong> A secondary analysis(^58) (n=507 twin pregnancies) of an RCT found that the risk of preterm delivery could be assessed with a multivariable model incorporating cervical length and other predictors, including previous preterm delivery, monochorionicity, smoking, educational level, and triplet pregnancy. A retrospective observational study(^59) (n=1815 twin births) found that twin pregnancies at significant risk for spontaneous very PTB could be identified in early pregnancy using several risk indicators, including previous preterm delivery, nulliparity, body mass index, hysteroscopic metroplasty, conisation, and monochorionicity.</td>
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<td>• High concentrations of interleukin-8 and matrix metalloproteinases-9 in mid-trimester amniotic fluid in twins.</td>
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<tr>
<td><strong>Other risk factors</strong></td>
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<td>A cross sectional study(^6^0) (n=676 twin pregnancies) found that male-male gender was a risk factor for PTB and very early PTB, in addition to monoamnionicity and history of abortion.</td>
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<td>A retrospective cohort study(^6^1) (n=1,508 twins) found that same-sex pairing was associated with higher mortality/morbidities in very preterm twins admitted to the NICU, and has potential to be used in clinical practice to identify twins at higher risk of adverse neonatal outcomes.</td>
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<td>A cross sectional study(^6^2) (n=197 twin pregnancies) found that, in the second trimester, rapid cervical pH(\text{GFBP-1}) testing in asymptomatic twin pregnancies had a poor performance in predicting spontaneous preterm delivery.</td>
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<td>A retrospective cohort study(^6^3) (n=51 twin pregnancies) found that spontaneous fetal death and/or delivery before 32 weeks in twin pregnancies with one fetus affected by a major structural malformation could be predicted by the number of abnormalities diagnosed and presence of fetal effusion or hydrops.</td>
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## Summary of evidence from previous surveillance

- A retrospective cohort study (n=96 twin pregnancies) found that high concentrations of interleukin-8 and matrix metalloproteinases-9 in mid-trimester amniotic fluid in twins had predictive value in detecting the risk of early PTB.

## Summary of new evidence from 4-year surveillance

- A Cochrane systematic review (six trials n=374 twin pregnancies) found insufficient evidence to support or refute the use of prophylactic oral betamimetics for preventing preterm labour and birth in women with a twin pregnancy.
- A systematic review (36 studies, n=8523 women and 12,515 infants) assessed the benefits and harms of progesterone for the prevention of PTB for women considered to be at increased risk of PTB and their infants. The findings indicated that the use of progesterone significantly reduced:
  - the risk of PTB less than 34 weeks

## Summary of new intelligence from 4-year surveillance

An ongoing study was cited relating to the Arabin pessary: STOPPIT-2: An open randomised trial of the Arabin pessary to prevent PTB in twin pregnancy, with health economics and acceptability estimated completion date 2018.

Topic expert feedback indicated that the Medicines and Healthcare products Regulatory Agency (MHRA) has issued safety advice on short acting beta agonists (2013) with the obstetric indication of inhibition of premature labour.

MHRA recommend that oral short acting beta agonists (SABAs) should not be used in any

## Impact

New evidence is unlikely to impact on guideline recommendations

NICE CG129 recommends (1.5.2.1) that the following interventions (alone or in combination) to prevent spontaneous PTB in twin or triplet pregnancies are not used:

- bed rest at home or in hospital
- intramuscular or vaginal progesterone
- cervical cerclage
- oral tocolytics.

The totality of new systematic review, RCT and observational study evidence on progesterone, prophylactic oral betamimetics, cervical pessary, and
### Summary of evidence from previous surveillance

There was no difference between treatment and control groups in the number of children with adverse neonatal outcomes, assessed using a composite measure. There was also no difference in average gestational age at delivery between pregnancies treated with progesterone and placebo, or the proportion of deliveries before 28 weeks or 32 weeks. There was no significant effect of progesterone treatment in the subgroup of 13 women (2.4%) with cervical length less than 25 mm or the 61 women (11.3%) with cervical length less than 35 mm.

The authors also conducted a meta-analysis of the effect of progesterone (both intramuscular and vaginal), including their findings with another 4 studies (making a total of 2032 participants), and found no impact on delivery before 34 weeks.

A meta-analysis of individual patient data\(^6\) (5 studies, n=775 women [52 twin and 723 singleton pregnancies] and n=827 infants) assessed neonatal morbidity in women with asymptomatic short cervix (defined as ≤25 mm). The risks of adverse infant outcomes were similar for treated and control groups.

### Summary of new evidence from 4-year surveillance

- The risk of adverse infant outcomes following administration in women considered to be at increased risk of PTB due either to a prior PTB or where a short cervix has been identified on ultrasound examination.

However, the role of progesterone in women with a multiple pregnancy was less clear, with no identified differences in the primary outcomes of perinatal death, and PTB less than 34 weeks' gestation.

An RCT\(^8\) (n=84 multiple pregnancies) found that daily treatment with progesterone gel did not prolong multiple pregnancy compared with placebo, and consequently was not effective in preventing PTB.

An RCT\(^7\) (n=813 multiple pregnancies) found that in unselected women with a multiple pregnancy, prophylactic use of a cervical pessary did not reduce poor perinatal outcome.

A systematic review\(^7\) (5 studies, n=310 twin pregnancies) observed no significant difference between cervical cerclage and no cerclage group in the prevention of PTB in twin pregnancies.

### Summary of new intelligence from 4-year surveillance

- Obstetric indication: the benefits do not outweigh the risks in these indications.

The use of parenteral SABAs should be limited to 48 hours maximum and administered under specialist supervision in the authorised indication of inhibition of premature labour.

### Impact

cervical cerclage does support the use of these interventions for multiple pregnancy, and is therefore consistent with CG129, which advises against using these interventions.

Further research may be required, including the ongoing STOPPIT\_2 trial. The progress of this trial will be evaluated at the next surveillance review of the guideline.
25 mm or less on mid-trimester ultrasound).

Although vaginal progesterone was associated with a significant reduction in the risk of PTB (before 33 weeks of gestation) in women with short cervix and a singleton pregnancy, no such association was found for women with short cervix and twin pregnancy.

The findings were considered to be consistent with the recommendation in NICE CG129 not to use intramuscular or vaginal progesterone to prevent PTB in multiple pregnancies. Further research was recommended to assess the efficacy of vaginal progesterone for prevention of PTB in twin gestations in women with short cervix. Further research may also be needed to establish the impact on measures of long-term morbidity of infants.

An RCT\(^{22}\) (n=unreported) found that twice-weekly injections of 17 alpha-hydroxyprogesterone caproate did not prolong pregnancy, and thereby reduce preterm delivery, significantly in asymptomatic women with a twin pregnancy and short cervix.

A systematic review\(^{23}\) (5 studies) assessed the effectiveness of antenatal management based on transvaginal ultrasound of cervical length (TVU CL) screening for preventing PTB. The results provided insufficient evidence to recommend routine screening of asymptomatic or symptomatic pregnant women with TVU CL. It should be noted that only 1 of the included studies covered multiple pregnancy (twins). Further research was recommended.

An RCT\(^{24}\) (n=113) assessed the Arabin cervical pessary in pregnancies with a short cervical length in the second trimester for preventing preterm delivery. For twins the preterm delivery rate was higher in the intervention group before 37 weeks but lower in the intervention group before 34 weeks. It should be noted that

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<td>25 mm or less on mid-trimester ultrasound.</td>
<td>An RCT(^{22}) (n=unreported) found that twice-weekly injections of 17 alpha-hydroxyprogesterone caproate did not prolong pregnancy, and thereby reduce preterm delivery, significantly in asymptomatic women with a twin pregnancy and short cervix. A systematic review(^{23}) (5 studies) assessed the effectiveness of antenatal management based on transvaginal ultrasound of cervical length (TVU CL) screening for preventing PTB. The results provided insufficient evidence to recommend routine screening of asymptomatic or symptomatic pregnant women with TVU CL. It should be noted that only 1 of the included studies covered multiple pregnancy (twins). Further research was recommended. An RCT(^{24}) (n=113) assessed the Arabin cervical pessary in pregnancies with a short cervical length in the second trimester for preventing preterm delivery. For twins the preterm delivery rate was higher in the intervention group before 37 weeks but lower in the intervention group before 34 weeks. It should be noted that</td>
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<td>the proportion of twin pregnancies was only 13% of the sample (n=15). A systematic review(^7) (five trials, n=128 multiple pregnancies) found that for multiple gestations, there was no evidence that cerclage was an effective intervention for preventing PTBs and reducing perinatal deaths or neonatal morbidity. The findings were based on limited data from small trials. In a secondary analysis(^6) (n=525 multiple pregnancies) of an RCT, a tool was developed for identifying the subset of women with multiple pregnancy who could benefit from cervical pessary. The validation analysis showed that the use of the tool could potentially improve selection of patients for pessary insertion and consequently reduce the poor neonatal outcomes in multiple pregnancy. In an economic analysis(^7) (n=808) of the ProTWIN RCT, the cost of cervical pessaries in women with a multiple pregnancy were comparable to those in women without pessary treatment. However, in women with a CL &lt; 38 mm, treatment with a cervical pessary appeared to be highly cost-effective.</td>
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<td>An RCT (n=390 twin pregnancies) found that in nonselected twin pregnancies, vaginal progesterone administration did not prevent preterm delivery and did not reduce neonatal morbidity and death.</td>
<td>A secondary analysis (n=781 children) of the STOPPIT RCT assessed the long-term effects of in utero progesterone exposure in twin children and found no evidence of a detrimental or beneficial impact on health and developmental outcomes at three to six years of age due to in utero exposure to progesterone.</td>
<td>Three observational studies examined ultrasound-indicated cerclage, emergency or physical examination-indicated cerclage in multiple pregnancy. An additional observational study assessed vaginal progesterone for the prevention of PTB in multiple pregnancy. An individual participant data meta-analysis (13 trials n=3768 pregnancies) assessed the effectiveness of progestogen treatment in the prevention of neonatal morbidity or PTB in twin pregnancies. The findings indicated that in unselected women with an</td>
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<td>uncomplicated twin gestation, treatment with progestogens (intramuscular 17Pc or vaginal natural progesterone) did not improve perinatal outcome. In a subgroup analysis, of women with a cervical length of &lt;25 mm, vaginal progesterone reduced adverse perinatal outcome when cervical length was measured at randomisation (15/56 versus 22/60; RR 0.57; 95% CI 0.47-0.70) or before 24 weeks of gestation. An RCT85 (n=284 twin pregnancies) found that Intramuscular 17 alpha-hydroxyprogesterone caproate (17OHPc) therapy did not reduce PTB before 37 weeks of gestation in unselected twin pregnancies. However, 17OHPc significantly reduced neonatal morbidity parameters and increased birthweight. A secondary analysis86 (n=49) found that 17OHPc was not beneficial for women with a prior PTD and current twin gestation in the prevention recurrent PTD.</td>
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### Summary of evidence from previous surveillance

**129 – 15** Untargeted corticosteroids: Is routine/elective antenatal corticosteroid prophylaxis effective in reducing perinatal morbidity, including neonatal respiratory distress syndrome, necrotising colitis and intraventricular haemorrhage, in multiple pregnancy? *(1.5.3.1-1.5.3.2)*

**Surveillance decision**

This review question should not be updated.

### 2-year Evidence Update (2013)

**No relevant evidence identified.**

A retrospective cohort study*87* (*n=468*) in twin pregnancies, found that a single course of antenatal corticosteroid (ACS) treatment was associated with a decreased rate of respiratory distress syndrome only when the ACS-to-delivery interval was between 2 and 7 days.

None identified relevant to this question.

### Impact

New evidence is consistent with guideline recommendations

CG129 advises *(1.5.3.2)* against using single or multiple untargeted (routine) courses of corticosteroids in twin or triplet pregnancies.

The recommendation not to use ACS routinely (as prophylaxis) in twin and triplet pregnancies does not preclude targeted (or rescue) administration when indicated (for example when preterm labour or birth is imminent).

The observational study evidence suggests that ACS treatment may be associated with a decreased rate of RDS only when the ACS-to-delivery interval is between 2 and 7 days. This is consistent with CG129, which does not preclude ACS where birth is imminent.

It remains unclear whether antenatal corticosteroids should be given routinely or
### Summary of evidence from previous surveillance

### Summary of new evidence from 4-year surveillance

### Summary of new intelligence from 4-year surveillance

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<td>targeted indicating the need for further research in this area.</td>
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### Indications for referral to a tertiary level fetal medicine centre

**129 – 16 What are the clinical indications for referral to subspecialist services? (1.6.1.1)**

#### Surveillance decision

This review question should not be updated.

#### 2-year Evidence Update (2013)

**Fetal loss rate in monochorionic monoamniotic (MCMA) twin pregnancies**

A retrospective study\(^6\) (146 monochorionic pregnancies [29 MCMA; 117 MCDA]) (2011c) compared the fetal loss rate of monochorionic twin pregnancies according to their amnionicity.

The overall fetal loss rate was significantly higher for MCMA pregnancies compared with MCDA. Most fetal losses in MCMA pregnancies were due to discordant fetal anomalies, conjoint twins or twin reversed arterial perfusion sequence, all identified in early ultrasound scans. Once these complications identified in early pregnancy were

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A topic expert expressed concern about the implementation of recommendation 1.6.11 as anecdotal information indicates that many women are not seen or do not have an opinion from a fetal medicine specialist as recommended. If the guideline is revised it was suggested that this recommendation should be revisited.

A topic expert raised a query, about the definition of fetal medicine centres and of fetal medicine specialists who do not work in the centres. However this is outside the remit of the NICE guidance.

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<th>New evidence is consistent with guideline recommendations</th>
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NICE CG129 recommends (1.6.1.1) referral for consultant opinion at a tertiary level fetal medicine centre for MCMA twin and triplet pregnancies, (MCDA) and dichorionic diamniotic triplet pregnancies, and multiple pregnancies that are complicated by discordant fetal growth, fetal anomaly, discordant fetal death or FFTS. Women with multiple pregnancies identified by screening as having a high risk of Down’s syndrome should also be referred to a tertiary level fetal medicine centre.

The new observational study evidence confirms the high risks associated with MCMA pregnancies, supporting NICE CG129 guidance that this
### Summary of evidence from previous surveillance

excluded, there was no significant difference in survival of MCMA and MCDA pregnancies or fetuses. The authors acknowledged that the small numbers of MCMA twins could have resulted in the study being underpowered to detect a difference in loss rate associated with amnionicity, once loss due to early abnormalities were excluded. The evidence was considered to support CG129 guidance that this is an indication for referral to a tertiary level fetal medicine centre.

### Timing of birth

**129 – 17** What is the optimal timing of delivery in women with uncomplicated multiple pregnancies? *(1.7.1.1-1.7.1.9)*

### Surveillance decision

This review question should not be updated.

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<tr>
<th>2-year Evidence Update (2013) Uncomplicated monochorionic and dichorionic twin pregnancies</th>
<th>A systematic review(^a) (361 studies) estimated the risk of stillbirth in apparently uncomplicated monochorionic-diamniotic twin pregnancies. Compared with uncomplicated dichorionic pregnancies, the risk of stillbirth at 32, 34, and 36 weeks of gestation was substantially</th>
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<tr>
<td>None identified relevant to this question.</td>
<td>New evidence is consistent with guideline recommendations NICE guideline CG129 recommends informing women with uncomplicated twin pregnancies that elective birth from 36 weeks (monochorionic) or 37 weeks (dichorionic) does not appear to be associated with an increased risk of</td>
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### Impact

is an indication for referral to a tertiary level fetal medicine centre.
### Summary of evidence from previous surveillance

- Evaluated the prospective risk of late stillbirth in a cohort of twin pregnancies in the UK.
- The risk of stillbirth after 26 weeks in monochorionic twins was significantly higher than in dichorionic twins. The risk of stillbirth did not change significantly between 26 and 36 weeks for both monochorionic and dichorionic twins.
- The cohort was managed in line with NICE CG129, with a modal time of delivery of 36 weeks for monochorionic twins and 37 weeks for dichorionic twins, so the study does not provide evidence on the mortality risk after this time.
- Information on morbidity outcomes was not provided by this study.

### Summary of new evidence from 4-year surveillance

- Higher for monochorionic-diamniotic twin pregnancies.
- An updated systematic review (2 RCTs) found that elective early birth at 37 weeks’ gestation compared with ongoing expectant management for women with an uncomplicated twin pregnancy did not appear to be associated with an increased risk of harms.
- A systematic review found that for women with dichorionic pregnancies, delivery at 37 weeks’ gestation reduced the risk of perinatal deaths occurring at or beyond 38 weeks. In monochorionic twins, there was insufficient evidence to recommend routine delivery before 36 weeks. In monochorionic twins, there was a trend towards an increase in stillbirths compared with neonatal deaths after 36 weeks but this was not significant.
- A retrospective study (n=163 twin pregnancies) found that in cases of between 32 and 35+6 weeks’ gestation, the timing of delivery was postponed for 14 days or more from the time of admission, and there were fewer numbers of babies with low Apgar score at birth compared with other groups.

### Summary of new intelligence from 4-year surveillance

- Serious adverse outcomes, and that both monochorionic and dichorionic pregnancies continuing beyond 38 weeks increases the risk of fetal death.
- The new systematic review and observational study evidence identified is consistent with CG129 not to deliver uncomplicated monochorionic twins before 36 weeks. New systematic review evidence indicates that both monochorionic and dichorionic pregnancies continuing beyond 38 weeks increases the risk of fetal death.
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<td>pregnancies. Of the pregnancies that did not have medically indicated deliveries (474 monochorionic, 1978 dichorionic), the risk of serious adverse perinatal events after 31 weeks was similar regardless of chorionicity, and there was no evidence of any low point in prospective risk of adverse perinatal events before 37 weeks. For each gestational week (until 36 completed weeks) MCDA twins had a significantly greater risk of severe adverse perinatal events when compared to MCDA twins delivered in a subsequent week. Practices in the US may differ from the UK, and interpretation of the results is hampered by the inclusion of complicated twin pregnancies in the analysis. Furthermore, there appeared to be few deliveries after 37 weeks, so conclusions about the optimal time of delivery could not be drawn. A retrospective cohort study 91 (465 women and 930 fetuses) of MCDA twin pregnancies assessed perinatal</td>
<td>Important clinical factors during the decision making process of delivery timing in twin pregnancies were the frequency of uterine contraction, presence of premature rupture of membranes, dilatation of cervix, increased white blood cell and high sensitive C-reactive protein levels. A retrospective cohort study 96 (n=17,724 twin births) evaluated the optimal gestational age at delivery for twins. The findings indicated that the balance of risk between neonatal death/intrapartum stillbirth and antepartum stillbirth began to favour delivery at 36 weeks of gestation, particularly in MCDA twins.</td>
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mortality and association with mode of delivery and gestational age.
Overall perinatal mortality was 8 per 1000 infants, with the prospective risk of death after 32 weeks 5 in 1000 and perinatal death at term (≥37 weeks) 7 per 1000. Mode of delivery had no effect on perinatal mortality rate. Neonatal morbidity at 32 and 33 weeks of gestation declined at 34 weeks, and was absent in infants born at 37 weeks of gestation or later.
The evidence from all 3 studies was considered to be consistent with recommendations in CG129 not to deliver uncomplicated monochorionic twins before 36 weeks. However, these studies provide limited information about the risks of continuing gestation beyond 37 weeks.

**Areas not currently covered in the guideline**

**NQ – 01 Intrapartum care**

**Surveillance decision**
This review question should be added.
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| **2-year Evidence Update (2013)** No relevant evidence identified. | **Mode of delivery**  
*Planned delivery*  
A Cochrane review of planned early delivery versus expectant management for monoamniotic twins found no studies. In their absence, reference to historical case series and expert consensus was recommended. The authors also recommended that management plans should take into consideration the availability of high-quality neonatal care if early delivery is chosen. Further recommendations were for women and their families to be involved in the decision making about these high-risk pregnancies, and that ongoing, multicentre audits of maternal and perinatal outcomes for monoamniotic twins are needed.  
An updated systematic review (2 trials, n=2864) aimed to determine the short- and long-term effects on mothers and their babies, of planned caesarean section for twin pregnancy. The findings, based mainly on data from one large, multicentre RCT, showed no clear evidence of benefit from planned caesarean section for term twin pregnancies with leading cephalic presentation. | **Topic expert feedback indicated that the exclusion of mode of delivery is no longer justified.** A significant proportion of multiple pregnancy losses occur intrapartum (NHS Litigation Authority data). The topic experts advised, on that basis, that the guideline scope should be extended to include intrapartum management. The Twin birth trial, was highlighted to support this view and is summarised in the new evidence summary. In addition, during the scoping for the in development NICE guideline on high risk intrapartum care, it was decided that this area should be incorporated into the scope of CG129 at its next update.  
Additional topic expert feedback indicated that the chances of a patient safety incidence and serious harm are significantly increased for mothers or babies from a multiple pregnancy and that many of these relate to problems during the intrapartum period.  
During the scoping for the in development NICE guideline on high risk intrapartum care, it was decided that this area should be incorporated into the scope of CG129 at its next update.  
The Twins and Multiple Births Association provided some information to indicate that the | **New evidence identified that may impact on the guideline**  
CG129 does not include recommendations on intrapartum care because this area was not included in the original scope. However, topic expert feedback and new evidence indicates that this area should be considered for inclusion in an update of the guideline. Existing NICE guidelines *Intrapartum care for healthy women and babies*, and *Inducing labour* do not make specific recommendations for multiple pregnancy. The NICE guideline on *Caesarean section* makes two recommendations relating to multiple pregnancy. It advises that in uncomplicated twin pregnancies at term where the presentation of the first twin is cephalic, the effect of planned CS in improving outcome for the second twin remains uncertain and therefore CS should not routinely be offered outside a research context. It also advises that in twin pregnancies where the first twin is not cephalic the effect of CS in improving outcome is uncertain, but current practice is to offer a planned CS. These recommendations may need to be |
## Summary of evidence from previous surveillance
- Data on long-term infant outcomes are awaited. Women should be informed of possible risks and benefits of labour and vaginal birth pertinent to their specific clinical presentation and the current and long-term effects of caesarean section for both mother and babies. There was insufficient evidence to support the routine use of planned caesarean section for term twin pregnancy with leading cephalic presentation, except in the context of further randomised trials.

## Summary of new evidence from 4-year surveillance
- An RCT\(^\text{100}\) (n=598) found that planned caesarean delivery in twin pregnancy significantly decreased the risk of fetal or neonatal asphyxia morbidity of second fetal, as compared with planned vaginal delivery.

- A retrospective cohort study\(^\text{101}\) (n=40 twin pregnancies) found that a standard protocol of labour induction for singleton gestations was applicable to twins with overall similar favourable intrapartum outcomes.

- A retrospective cohort study\(^\text{102}\) (n=221) found that non-cephalic twin B at admission or following delivery of twin A

## Summary of new intelligence from 4-year surveillance
- One topic expert highlighted that postnatal care for women after a multiple birth is poor as shown by the TAMBA survey and many studies conclude that breast feeding rates are lower. As more babies are admitted to Neonatal Units the psychological support, including when one or more babies die is more complex. For these reasons the topic expert suggested that postnatal care should also be considered for inclusion in the guideline.

## Impact
- The NICE guideline on Neonatal infection: antibiotics for prevention and treatment lists multiple pregnancy as a risk factor for early-onset neonatal infection. If the scope of CG129 is extended to cover intrapartum care, encompassing prevention of neonatal infection, then a cross referral to CG149 may be required from CG129, or from the multiple pregnancy pathway.
- Although new guidance is being developed on high risk intrapartum care, it was decided during scoping that this will not cover multiple pregnancy. It was proposed that intrapartum care should be incorporated into the scope of CG129 at its next update.

### Postnatal care
- Topic expert feedback suggested that postnatal care should also be considered for inclusion in the guideline. However, postnatal care recommendations for all pregnancies, including twins and triplets, are provided by NICE guideline Postnatal care CG37.
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<td>posed a higher risk for combined delivery. Neonatal outcomes of twin B following combined delivery were comparable with those of vaginal delivery. An observational study¹⁰³ (N=283 twin pregnancies) found that active second-stage management of twin pregnancies was associated with neonatal outcomes similar to those with planned caesarean delivery and had a low risk of combined vaginal-caesarean delivery. The fetal outcomes were APGAR score and NICU admission. A secondary analysis¹⁰⁴ (2570 women) of the Twin Birth RCT compared outcomes at 3 months postpartum for women randomised to give birth by planned caesarean section or by planned vaginal birth. The findings showed that outcomes at 3 months postpartum did not differ. The mode of birth was not associated with problematic urinary incontinence or urinary incontinence that affected the quality of life. Breastfeeding at 3 months was not increased with planned vaginal birth.</td>
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<td>A retrospective cohort study(^{105}) (n=214 twin pregnancies, 52 MCDA twins, 172 MCDA twins) found that vaginal delivery appeared to be a good management option in uneventful MCDA twin pregnancies after 34 weeks’ gestation.</td>
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<td>A retrospective cohort study(^{106}) (n=38) found that there were no intrauterine or neonatal deaths at or after 32 weeks of gestation in monoamniotic twin pregnancies. Infants delivered vaginally did not differ significantly from the infants born by caesarean section in terms of umbilical artery pH or 5-min Apgar scores. Continuation of monoamniotic pregnancies beyond 32 weeks of gestation and trial of vaginal delivery were considered reasonable options, with parental consent, and optimal surveillance.</td>
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<td>A retrospective cohort study(^{107}) (n=286 twin pregnancies) found that in patients with twin pregnancies who attempt labour, nulliparity and advanced maternal age were associated independently with caesarean delivery in labour. However, even the patients at highest risk for caesarean delivery had nearly a 50% likelihood of successful vaginal delivery,</td>
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<td>suggesting that vaginal delivery should be allowed if it is desired and not otherwise contraindicated. A secondary analysis of two RCTs(^{108}) (n=311 twin pregnancies) found that in nulliparous women with a twin pregnancy, second-trimester cervical length was not associated with risk of emergency caesarean delivery. A retrospective cohort study(^{109}) (n=193 twin pregnancies) found that vaginal delivery of very low birthweight twins was associated with an increased risk of intraventricular haemorrhage, regardless of presentation. Due to the small sample size and the retrospective cohort design, large prospective randomized studies were recommended by the authors. A retrospective analysis(^{110}) (n=1009 twin pregnancies) found that monochorionic and dichorionic twin pregnancies had similar delivery outcomes. The neonatal outcome for twin 2 was not different between monochorionic and dichorionic pregnancies. The results indicated that vaginal birth could be offered to women with twin pregnancies regardless of chorionicity.</td>
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### Summary of evidence from previous surveillance

A retrospective comparative study\(^{111}\) (n=186 twin pregnancies) found that oral misoprostol and vaginal dinoprostone were similarly effective and safe for the induction of labour in twin gestations. Further trials with larger series were recommended to confirm the results.

A retrospective cohort study\(^{112}\) (n=1282 twin births) found that induction of labour in twin pregnancies increased the risk of caesarean section compared with spontaneous labour onset, especially if Foley catheter or prostaglandins are required. However, approximately 80% of induced labours were delivered vaginally.

### 2-year Evidence Update (2013)

No relevant evidence identified.

A retrospective study\(^{113}\) (n=35) assessed the effectiveness and feasibility of retaining a singleton or twins for multifetal pregnancy reduction (MFPR) in triplet pregnancies that include monochorionic twins. Retaining a singleton rather than twins in MFPR was found to improve pregnancy outcomes. For patients having a triplet pregnancy with monochorionic

### Surveillance decision

This review question should not be added.

### Impact

CG129 does not include recommendations on embryo reduction because this area was not included in the original scope.

Although topic expert feedback indicates that this area should be considered for inclusion in an update of the guideline, the new evidence is unlikely to impact on guideline recommendations.
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<td>twins and strongly desiring to keep twins, MFPR in one monochorionic twin was feasible by aspirating embryonic parts early in gestation (6-8 weeks) with no drug injection. Pregnancy outcomes were similar with twin reduction in trichorionic triplet pregnancy. A cohort study\textsuperscript{114} (5 studies, data from 3 centres, n=331 DCTA triplets) documented the natural history of DCTA triplets and the effect of reduction on the risk of miscarriage and severe preterm delivery, compared with expectant management. Expectant management was found to result in a lower miscarriage rate than either reduction of the monochorionic pair or reduction of the fetus with a separate placenta. Miscarriage rate was found to be similar between expectant management and reduction of one fetus of the monochorionic pair. Fetal reduction was found to result in a lower rate of preterm delivery than expectant management. It should be noted that the statistical significance of the differences was not reported in the abstract. A systematic review\textsuperscript{115} found no RCTs to inform the risks and benefits of</td>
<td>increase in multiple pregnancy. No studies were cited to support this view.</td>
<td>new evidence is inconclusive and further research may be needed to inform an extension to the scope of CG129.</td>
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### Summary of evidence from previous surveillance

Pregnancy reduction procedures for women with a multiple pregnancy. The authors noted that ‘the acceptability of this option, and willingness to undergo randomisation, will depend on the couple’s social background and beliefs, and consequently, recruitment to such a trial may prove exceptionally difficult’.

A meta-analysis (17 studies, n=481 cases of bipolar cord occlusion [BCO], 320 cases of radiofrequency ablation [RFA]) analysed perinatal outcomes after selective reduction in monochorionic pregnancies with the use of either RFA or BCO. The results did not demonstrate clearly the superiority of 1 procedure over the other. The clinical situation and preference of the operator were described as important considerations. Rates of preterm delivery and preterm premature rupture of membranes were substantial for both procedures.

### Summary of new evidence from 4-year surveillance

- Treatment for feto-fetal transfusion syndrome and twin anaemia polycythaemia sequence in multiple pregnancy

### Summary of new intelligence from 4-year surveillance

### Impact

**NQ – 03**  
Treatment for feto-fetal transfusion syndrome and twin anaemia polycythaemia sequence in multiple pregnancy

**Surveillance decision**

This review question should not be added.
### Summary of evidence from previous surveillance

**2-year Evidence Update (2013)**

- No relevant evidence identified.

### Summary of new evidence from 4-year surveillance

An updated systematic review (3 studies n=253 women and 506 babies) evaluated the impact of treatment modalities in FFTS. The results showed that endoscopic laser coagulation of anastomotic vessels improved neurodevelopmental outcomes more than amnioreduction, but there was no difference in overall death between the two interventions.

An RCT (n=274 twin pregnancies) found that fetoscopic laser coagulation of the entire vascular equator (Solomon technique) reduced postoperative fetal morbidity in severe FFTS. The Solomon technique was associated with a reduction in TAPS and recurrence of FFTS. Perinatal mortality and severe neonatal morbidity did not differ significantly between the two groups.

A systematic review including the same RCT and a further 2 cohort studies found a reduction in TAPS and recurrent FFTS and also an increase in twin survival, with no increase in the occurrence of complications or adverse events, when using the Solomon procedure.

### Summary of new intelligence from 4-year surveillance

One topic expert highlighted the modification of management of severe FFTS by a fetoscopic laser ablation technique using the SOLOMON procedure. Two studies (1 RCT and 1 systematic review) were cited. The topic expert stated that this procedure prevents the complications of:
- twin anaemia polycythaemia sequence
- recurrent FFTS and
- neonatal morbidity.

A topic expert highlighted the need to include screening and treatment for TAPS in the guideline. One study was highlighted and is included in the evidence summary.

Overall, topic experts advised that interventions for FFTS and TAPS were specialist areas with little variation in the small number of centres that provide treatment. They did not consider it necessary to extend the scope to include interventions for feto-fetal transfusion syndrome in an update of NICE Guideline CG129.

### Impact

New evidence identified that may impact on the guideline:

- CG129 does not include recommendations on treatment for feto-fetal transfusion syndrome or TAPS because this area was not included in the original scope.

- Treatment of FFTS is partly addressed by the [NICE Multiple pregnancy pathway](https://www.nice.org.uk/guidance/cg129) and by following NICE guidance:
  - [Septostomy with or without amnioreduction for the treatment of twin-to-twin transfusion syndrome](https://www.nice.org.uk/guidance/CG129).

- However, the new evidence supporting the SOLOMON technique may need to be incorporated into the guideline under a new question.

- Further research, including larger studies, may be needed on laser treatment for TAPS to support this intervention.
Summary of evidence from previous surveillance

compared to the selective technique for the treatment of FFTS.

A systematic review\textsuperscript{120} (3 cohort studies n=344) found limited evidence suggesting improved double neonatal survival as well as decreased donor and recipient fetal demise with the use of the sequential laser technique for FFTS, when compared to the standard selective technique. The authors noted the risk of bias and recommended RCT research to confirm the findings.

A cohort study\textsuperscript{121} (n=48, 16 DCTA triplets, 32 MCDA twins) found that DCTA triplet gestations with FFTS had a similar rate of post-laser therapy survival but delivered earlier than MCDA twins treated with laser. A similar post-laser fetal growth pattern in donors and recipients of both groups was noted.

A retrospective cohort study\textsuperscript{122} (n=52) found that laser treatment for TAPS appears to improve perinatal outcome by prolonging pregnancy and reducing RDS.

Summary of new evidence from 4-year surveillance

NICE Priority Research recommendations

RR – 01  Does additional information and emotional support improve outcomes in twin and triplet pregnancies?

Surveillance decision

Overall, topic experts advised that interventions for FFTS and TAPS were specialist areas with little variation in the small number of centres that provide treatment. They did not consider it necessary to extend the scope to include interventions for feto-fetal transfusion syndrome in an update of NICE Guideline CG129.
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<tr>
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<td>This research recommendation should be removed from the NICE version of the guideline and the NICE research recommendations database.</td>
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</tbody>
</table>

**2-year Evidence Update (2013)**  
No relevant evidence identified.

| RR – 02 Does specialist antenatal care for women with twin and triplet pregnancies improve outcomes for women and their babies? |  |
|-------------------------------------------------|-------------------------------------------------|-----------------------------------------------------|--------|
| Surveillance decision  
This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database. |

**2-year Evidence Update (2013)**  
No relevant evidence identified.

| Proposal on retaining the research recommendation  
This was deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation or stand it down.  
No new relevant evidence has been found since the research recommendation was first made. Therefore it is proposed to remove this research recommendation from the NICE research recommendations database. |
| See 129-07 | See 129-07 | Proposal on retaining the research recommendation  
This was deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation or stand it down.  
No new relevant evidence has been found since the research recommendation was first made. Therefore it is proposed to remove this research recommendation from the NICE research recommendations database. |
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<tbody>
<tr>
<td>RR – 03 What is the pattern of fetal growth in healthy twin and triplet pregnancies, and how should intrauterine growth restriction be defined in twin and triplet pregnancies?</td>
<td></td>
<td></td>
<td>New evidence was found that partially answered the research recommendation and it could be useful to wait for additional evidence. Therefore it is proposed to keep this research recommendation.</td>
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</table>

**Surveillance decision**
This research recommendation should be removed from the NICE version of the guideline and the NICE research recommendations database

**2-year Evidence Update (2013)**
No relevant evidence identified.

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<td>This research recommendation should be removed from the NICE version of the guideline and the NICE research recommendations database</td>
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**RR – 04 What interventions are effective in preventing spontaneous PTB in women with twin and triplet pregnancies, especially in those at high risk of PTB?**

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<td>This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database</td>
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</table>

**Proposal on retaining the research recommendation**
This was deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation or stand it down.

New evidence was found and an update to the guideline is proposed. Therefore it is proposed to remove this research recommendation from the NICE research recommendations database and NICE version of the guideline.
### Summary of evidence from previous surveillance

**RR – 05 What is the incidence of monochorionic monoamniotic twin and triplet pregnancies, and what clinical management strategies are most effective in such pregnancies?**

**Surveillance decision**

This research recommendation should be removed from the NICE version of the guideline and the NICE research recommendations database.

<table>
<thead>
<tr>
<th>2-year Evidence Update (2013)</th>
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<tbody>
<tr>
<td>No relevant evidence identified.</td>
<td>See 129-14</td>
<td>See 129-14</td>
<td>Proposal on retaining the research recommendation</td>
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</table>

This was deemed a priority area for research by the GDG, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation or stand it down.

New evidence was found that partially answered the research recommendation and it could be useful to wait for additional evidence. Therefore it is proposed to keep this research recommendation.

**No relevant evidence identified.**

**No new relevant evidence has been found since the research recommendation was first made. Therefore it is proposed to remove this research recommendation.**
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</table>

**RR – 06**  What is the incidence of perinatal and neonatal morbidity and mortality in babies born by elective birth in twin and triplet pregnancies?  

*Surveillance decision*

This research recommendation should be retained in the NICE version of the guideline and the NICE research recommendations database.

**2-year Evidence Update (2013)**  
No relevant evidence identified.

<table>
<thead>
<tr>
<th>2-year Evidence Update (2013)</th>
<th>Surveillance decision</th>
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<tbody>
<tr>
<td>See 129-17</td>
<td>Proposal on retaining the research recommendation</td>
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<tr>
<td>None identified relevant to this question.</td>
<td>This was deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will be taken on whether to retain the recommendation or stand it down. New evidence was found that partially answered the research recommendation and it could be useful to wait for additional evidence in this area. Therefore it is proposed to keep this research recommendation.</td>
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</table>

**NICE Research recommendations**

**RR – 07**  How should gestational age be estimated in twin and triplet pregnancies?  

*Surveillance decision*

This research recommendation will be considered again at the next surveillance point.
### Summary of evidence from previous surveillance

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</table>
| **2-year Evidence Update (2013)**  
No relevant evidence identified. | See 129-01 and 129-02 | See 129-01 and 129-02 | New evidence is unlikely to impact on guideline recommendations.  
This was not deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will not be taken on whether to retain the recommendation or stand it down.  
This research recommendation will be considered again at the next surveillance point. |
| **RR – 08**  
What is the most accurate method of determining chorionicity in twin and triplet pregnancies at different gestational ages, and how does operator experience affect the accuracy of different methods? | No relevant evidence identified. | None identified relevant to this question. | No new evidence was identified that would affect this research recommendation.  
This was not deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will not be taken on whether to retain the recommendation or stand it down. |
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<tr>
<td><strong>RR – 09 Is dietary supplementation with vitamins or minerals, or dietary manipulation in terms of calorie intake, effective in twin and triplet pregnancies?</strong></td>
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<td>This research recommendation will be considered again at the next surveillance point.</td>
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**Surveillance decision**

This research recommendation will be considered again at the next surveillance point.

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<tr>
<th>RR – 10 Is dietary advice specific to twin and triplet pregnancies effective in improving maternal and fetal health and wellbeing?</th>
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**Surveillance decision**

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<tr>
<td>RR – 11 When and how should screening for chromosomal abnormalities be conducted in twin and triplet pregnancies?&lt;br&gt;<strong>Surveillance decision</strong>&lt;br&gt;This research recommendation will be considered again at the next surveillance point.</td>
<td></td>
<td></td>
<td>This was not deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will not be taken on whether to retain the recommendation or stand it down. This research recommendation will be considered again at the next surveillance point.</td>
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<tr>
<td>2-year Evidence Update (2013)&lt;br&gt;No relevant evidence identified.</td>
<td>See 129-08</td>
<td>See 129-08</td>
<td>New evidence identified that may change current recommendations See 129-08</td>
</tr>
<tr>
<td>RR – 12 When and how should screening for structural abnormalities be conducted in twin and triplet pregnancies?&lt;br&gt;<strong>Surveillance decision</strong>&lt;br&gt;This research recommendation will be considered again at the next surveillance point.</td>
<td></td>
<td></td>
<td>New evidence is unlikely to impact on guideline recommendations. This was not deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will not be taken on whether to retain the recommendation or stand it down. This research recommendation will be considered again at the next surveillance point.</td>
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</table>
| **RR – 13**  
When and how should screening for feto-fetal transfusion syndrome be conducted in twin and triplet pregnancies?  
**Surveillance decision**  
This research recommendation will be considered again at the next surveillance point. |

**2-year Evidence Update (2013)**  
No relevant evidence identified.  
See 129-10  
None identified relevant to this question. |

New evidence is consistent with guideline recommendations.  
This was not deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will not be taken on whether to retain the recommendation or stand it down.  
This research recommendation will be considered again at the next surveillance point. |

**RR – 14**  
Which clinical factors, laboratory screening tests, and ultrasound tests are predictive of hypertensive disorders in twin and triplet pregnancies?  
**Surveillance decision**  
This research recommendation will be considered again at the next surveillance point.
| RR – 15 | Which clinical factors or laboratory tests are accurate predictors of spontaneous PTB in twin and triplet pregnancies? |
|-----------------------------------------------|
| **Summary of evidence from previous surveillance** | **Summary of new evidence from 4-year surveillance** | **Summary of new intelligence from 4-year surveillance** | **Impact** |
| 2-year Evidence Update (2013) No relevant evidence identified. | See 129-12 | None identified relevant to this question. | New evidence is unlikely to impact on guideline recommendations. See 129-12. |

**Surveillance decision**
This research recommendation will be considered again at the next surveillance point.

| RR – 16 | What is the clinical and cost effectiveness of referral to tertiary level fetal medicine centres for twin and triplet pregnancies complicated by discordant fetal growth, discordant fetal anomaly or discordant fetal death? |
|-----------------------------------------------|
| **Summary of evidence from previous surveillance** | **Summary of new evidence from 4-year surveillance** | **Summary of new intelligence from 4-year surveillance** | **Impact** |
| 2-year Evidence Update (2013) See 129-14 | No relevant evidence identified. See 129-14 | None identified relevant to this question. | New evidence is consistent with guideline recommendations. See 129-16. |

**Surveillance decision**
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<td>See 129-16</td>
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This was not deemed a priority area for research by the Guideline Committee, therefore at this 4-year surveillance review time point a decision will not be taken on whether to retain the recommendation or stand it down.

This research recommendation will be considered again at the next surveillance point.
References


Decision matrix 4-year surveillance 2017 – Multiple pregnancy (2011) NICE guideline CG129


Decision matrix 4-year surveillance 2017 – Multiple pregnancy (2011) NICE guideline CG129


Decision matrix 4-year surveillance 2017 – Multiple pregnancy (2011) NICE guideline CG129


Decision matrix 4-year surveillance 2017 – Multiple pregnancy (2011) NICE guideline CG129


Decision matrix 4-year surveillance 2017 – Multiple pregnancy (2011) NICE guideline CG129


