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Surveillance decision

We will plan an update of the following sections of the guideline:

- **Fetal complications**.

An extension to the scope will be needed to incorporate intrapartum care.

We will amend the guideline in the following clinical area:

- **Fetal complications**
  - When and how should screening be used to identify chromosomal abnormalities in multiple pregnancy?

The proposed amendment is to cross refer to National Screening Committee (NSC) recommendations on cfDNA screening.

**Reason for the decision**

We found 122 new studies through surveillance of this guideline. New evidence that could affect recommendations was identified. Topic experts, including those who helped to develop the guideline, advised us about whether the following sections of the guideline should be updated and any new sections added:

**Fetal complications**

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

Topic experts advised that the update of this question needs to be considered with the review question: What is the optimal screening programme to detect intrauterine growth restriction in multiple pregnancies?

Topic experts recommended that this question should be updated to consider monitoring for FFTS beyond the 24 weeks recommended by NICE guideline CG129 in monochorionic pregnancies. NICE guideline CG129 differs from the RCOG Green Top Guideline 51 (2016) 'Management of monochorionic twin pregnancy' which recommends ultrasound surveillance from 16 weeks until delivery at two weekly intervals.
Further expert advice indicated that detection of twin anaemia polycythemia sequence (TAPS) is too specialised for inclusion in the scope of this guideline and should not be covered in the update.

**Decision:** This question should be updated.

- What is the optimal screening programme to detect intrauterine growth restriction in multiple pregnancies?

Topic experts advised that the update of this question needs to be considered with the review question:

- When and how should screening be used to identify FFTS in multiple pregnancy?

Topic experts advised a review of the recommended threshold of estimated fetal weight (EFW) discordance. In the updated RCOG Green Top Guideline a new EFW discordance threshold of 20% has been advised for monochorionic pregnancies. There is therefore a potential impact on NICE guideline CG129, to review the currently recommended threshold of 25%.

Topic expert feedback and new evidence indicated the need to review the recommended frequency of ultrasound surveillance for growth restriction. NICE guideline CG129 recommends aiming to undertake ultrasound scans at intervals of less than 28 days to estimate fetal weight discordance. It was considered possible to split out recommendations to the different types of multiple pregnancies (monochorionic, dichorionic and trichorionic) for ultrasound surveillance.

Topic experts also indicated that there is insufficient evidence to include the use of growth charts for twins in the guideline, and it was agreed that these should be excluded from the current update.

**Decision:** This question should be updated.

**Preterm birth**

- Predicting the risk of preterm birth: What is the optimal screening programme to predict the risks of spontaneous preterm delivery?

Topic experts advised that abdominal circumference will not predict spontaneous preterm birth. The evidence on measuring abdominal circumference is therefore unlikely to impact on the review question for spontaneous preterm delivery.

**Decision:** This question should not be updated.
Intrapartum care

- Intrapartum care

NICE guideline CG129 does not include recommendations on intrapartum care because this area was not included in the original guideline scope.

Topic experts advised that a significant proportion of multiple pregnancy losses occur intrapartum and cited evidence that the risk of adverse perinatal outcomes is greater than in singleton pregnancies. Therefore this area was recommended for inclusion in an update of the guideline.

Although new guidance is being developed by NICE on high risk intrapartum care, it was decided during scoping for this guideline that this will not cover multiple pregnancy. It was proposed that intrapartum care should be incorporated into the scope of NICE guideline CG129 at its next update. This is potentially a large piece of work, and a scoping exercise will be needed to establish:

- areas of intrapartum care specific to multiple pregnancies
- recommendations from related guidelines to be considered in the update for potential cross referral or incorporation in NICE guideline CG129.

Decision: This area should be included.

Treatment for feto-fetal transfusion syndrome

- Interventions for FFTS

Topic experts advised that interventions for FFTS and TAPS are specialist areas with little variation in the small number of centres that provide treatment. Topic experts did not feel it was necessary to extend the scope to include interventions for FFTS in an update of NICE guideline CG129.

Decision: This review question should not be included.

Other clinical areas

We also found new evidence that was not thought to have an effect on current recommendations. This evidence related to determining gestational age and chorionicity, general care, maternal complications, indications for referral to a tertiary level fetal medicine centre, and timing of birth.
Equalities

No equalities issues were identified during the surveillance process.

Overall decision

After considering all the new evidence and views of topic experts, we decided that a partial update with modified scope is necessary for this guideline.

See how we made the decision for further information.
Commentary on selected new evidence

With advice from topic experts we selected 3 studies for further commentary.

**Fetal complications - Monitoring for intrauterine growth restriction**

We selected the study by Stirrup et al. (2015) for a full commentary because the secondary analysis was performed using a very large dataset of observations obtained in an unselected sample from clinical practice, managed according to NICE guidelines. The study was also highlighted by topic expert feedback as being an important study in this area.

We also selected the study by Corcoran et al. (2015) for a full commentary in this area because of the limited evidence base in dichorionic twin ultrasound surveillance, and because existing recommendations are based on expert opinion. It was also recommended for commentary by topic expert feedback.

**What the guideline recommends**

NICE guideline CG129 recommends aiming to undertake ultrasound scans at intervals of less than 28 days to estimate fetal weight discordance. Scans should start at 20 weeks and use two or more biometric parameters at each scan. It also recommends considering a 25% or greater difference in size between twins or triplets as a clinically important indicator of intrauterine growth restriction (IUGR) and to offer referral to a tertiary level fetal medicine centre. However, NICE guideline CG129 does not make recommendations on the use of growth charts, and concluded that no evidence-based growth charts specific to twin and triplet pregnancies are available for use in the diagnosis of IUGR.

**Methods**

**Growth charts**

Stirrup et al. (2015) conducted a secondary analysis of the STORK (Southwest Thames Obstetric Research Collaborative) multiple pregnancy cohort study.

The aim of the secondary analysis by Stirrup et al. (2015) was to develop and compare reference charts for expected fetal growth in dichorionic diamniotic (DCDA) and monochorionic diamniotic (MCDA) twin pregnancies with those from singleton pregnancies. The study included data from 9 hospitals over a period of 10 years. The following biometric measurements were taken from serial
ultrasound examinations of twin pregnancies in the second and third trimesters, from 14 weeks' gestation to term:

- head circumference
- biparietal diameter
- abdominal circumference
- femur length.

The following pregnancies were excluded from the analysis:

- Where chorionicity and amnionicity were uncertain or inconsistent in the recorded examinations.
- Where the first recorded ultrasound examination was after 14 weeks' gestation. This was to ensure the accuracy of gestational age measurement for included cases.
- Where there were no examinations in the dataset with measurements recorded for both fetuses beyond 14 weeks.
- Monochorionic monoamniotic pregnancies.

**Results**

In total, 1,802 DCDA and 323 MCDA twin pregnancies were included. The biometric variables measured at ultrasound examination showed lower mean values in twin pregnancies than in singletons, particularly for abdominal and head circumference beyond 30 weeks' gestation. The mean values across gestation differed between MCDA and DCDA twin pregnancies.

Ultrasound biometry showed:

- For each variable the mean value for DCDA twins was close to the reported value in singletons at 20–30 weeks and showed a decrease relative to singletons beyond 30 weeks.
- The differences relative to singleton pregnancies were greater in MCDA than in DCDA twins due to lower mean values for MCDA twin pregnancies for all biometric variables across the gestational age range from 14 weeks.
- The equivalent percentile differences in DCDA twins relative to singletons were:
- Abdominal circumference 39th percentile at 25 weeks and 31st percentile at 35 weeks.
- Head circumference 35th percentile at 25 weeks and 29th percentile at 35 weeks.
- Biparietal diameter 45th percentile at 25 weeks and 39th percentile at 35 weeks.
- Femur length 46th percentile at 25 weeks and 40th percentile at 35 weeks.

- The equivalent percentile differences in MCDA twins relative to singletons were:
  - Abdominal circumference 30th percentile at 25 weeks and 25th percentile at 35 weeks.
  - Head circumference 20th percentile at 25 weeks and 26th percentile at 35 weeks.
  - Biparietal diameter 32nd percentile at 25 weeks and 39th percentile at 35 weeks.
  - Femur length 35th percentile at 25 weeks and 29th percentile at 35 weeks.

It should be noted that the authors recommended further prospective studies that also account for pathological complications and their treatment to further inform this area.

**Strengths and limitations**

**Strengths**

- There were a large number of participants in an unselected sample from clinical practice, managed according to NICE guidelines. It therefore minimised the risk of selection bias.

- There were no exclusions relating to pregnancy outcome or pathology, which further strengthened the representativeness of the sample.

- The study addressed a research gap by generating growth charts for twins for comparison with existing growth charts for singleton pregnancies.

**Limitations**

- There was potential confounding due to the retrospective nature of the study. It was therefore not possible to account for the occurrence of pregnancy complications in the evaluation of fetal growth. Prospective studies would be required to verify the findings.

- The analysed dataset was unbalanced, with both the number and timing of observations differing between pregnancies. Outlier observations from higher risk pregnancies may have
biased the results. However, this was partly addressed by the use of a multilevel modelling strategy, to take the structure of the data into account.

• Topic expert feedback indicates that the definition of selective growth restriction most strongly matched to perinatal mortality is percentage difference in estimated fetal weight between twins. It was felt that the ‘threshold’ of difference in estimated fetal weight is a more clinically important indicator of IUGR than growth rate relative to singleton pregnancies. This limits the applicability of the results to the guideline.

• The growth charts are not directly applicable to triplets.

Methods

*Estimated fetal weight discordance*

Corcoran et al. (2015) conducted a secondary analysis of the ESPRiT cohort study (n=789 dichorionic twin pregnancies). The original study was a large multi-centre prospective cohort study that aimed to establish a degree of intertwin size discordance, for both MCDA and DCDA twin pregnancies, that is independently associated with adverse perinatal outcome. The results indicated a birth-weight discordance of 18% to be the best cut-off to predict perinatal loss. This differs from the STORK cohort study, which proposed a greater than 25% difference as the optimal threshold to identify growth-discordant twins at risk for adverse outcomes.

The secondary analysis of the ESPRiT cohort aimed to determine how 2-weekly or 4-weekly ultrasound scanning in DCDA twins may impact the prenatal detection of fetal growth restriction (FGR) and ultimately influence timing of delivery. From 24 weeks’ gestation until delivery, fetal growth was determined by ultrasound. Umbilical and middle cerebral artery Doppler scans were performed every 2 weeks. For comparison with the 2 weekly schedule, the authors simulated a 4-week ultrasound schedule and a schedule that comprised scans every 4 weeks up to 32 weeks’ gestation and every 2 weeks thereafter. The simulation was based on detection probabilities that were defined as the proportion of pregnancies with FGR, abnormal umbilical artery (UA) Doppler, or oligohydramnios that was detected on ultrasound scanning. Differences in mean detection probabilities were compared between the 2 weekly and 4 weekly schedules of assessments.

The outcomes were detection of FGR (defined as estimated fetal weight below 10th percentile), abnormal UA and oligohydramnios (defined as a maximal vertical pocket less than 2 cm). An abnormal UA Doppler scan was classified as a pulsatility index above 95th percentile or absent or reversed end diastolic flow. Complete delivery and perinatal outcome data were also recorded for all pregnancies, including mode of delivery, gestational age, birthweight, and perinatal morbidity.
Twin pregnancies were enrolled before 22 weeks' gestation, with both twins alive at the time of enrolment with intact membranes. Exclusion criteria were confirmed or suspected major fetal structural abnormality or fetal aneuploidy.

Results

There were 789 dichorionic twin pregnancies included in the analysis. The main results were:

- A significant (p=0.006) reduction in the detection of FGR from 88% to 69% with 4-weekly ultrasound surveillance.
- A significant (p=0.011) reduction in the detection of abnormal UA Doppler from 82% to 62% with 4-weekly ultrasound surveillance.
- A non-significant reduction in the recording of oligohydramnios with 4-weekly ultrasound surveillance.
- A non-significant reduction in the detection of FGR, abnormal UA Doppler or oligohydramnios with a programme of 4-week examinations between 24 and 32 weeks' gestation and scans every 2 weeks thereafter.
- Complete delivery and perinatal outcome data were recorded for all pregnancies, with 365 (46%) admissions to neonatal intensive care, 4 (less than 1%) neonatal deaths and 148 (19%) composite outcomes (comprising death, hypoxic ischemic encephalopathy, periventricular leukomalacia, necrotizing enterocolitis, respiratory distress, or sepsis).

Strengths and limitations

Strengths

- The study data were obtained from a prospective cohort study.
- Complete delivery and perinatal outcome data were recorded for all pregnancies reported.
- The study addressed a gap in the evidence base for dichorionic twin ultrasound surveillance because the optimal ultrasound schedule for uncomplicated dichorionic twins has been unclear.

Limitations

- The methods of the original cohort study were not reported in the secondary analysis, and have not been considered in this commentary.
The main outcome measures in the secondary analysis were not clearly described, particularly in terms of the probabilities calculated for the 4-weekly simulated surveillance.

Results were based on a simulated ultrasound schedule for 4-weekly surveillance. Therefore instances in which sonographic findings prompted other clinical actions such as hospital admission and daily cardiotocograph monitoring could not be directly examined.

The definition of FGR was estimated fetal weight below 10th percentile, presumed to be based on a singleton chart, although this was not reported. This was different to the definition used for IUGR in NICE guideline CG129. This may impact on the applicability of the study to the guideline.

**Impact on guideline**

**Growth charts**

The new evidence reports on customised reference charts that have been developed specifically for monitoring fetal growth in twin pregnancies. These appear to be more effective at monitoring fetal growth risk for intrauterine fetal death than those derived using singleton birth data. However, topic experts advised that there is insufficient evidence from prospective studies to include the use of growth charts for twins in the guideline at this time, and it was agreed that these should be excluded from the current update.

**EFW discordance**

The 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 FGR. This has a potential impact on NICE guideline CG129, which advises aiming to undertake scans at intervals of less than 28 days.

Topic expert feedback highlighted the need to establish the optimal threshold of EFW discordance for the prediction of stillbirth and neonatal mortality. New evidence indicates EFW discordance of greater than 25% could represent the optimal cut-off, 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 NICE guideline CG129, which recommends a 25% or greater difference in size between twins or triplets as a clinically important indicator of IUGR. However, existing evidence from the ESPRIT study suggests that an optimal cut-off is 18% EFW discordance. The updated RCOG Green Top Guideline 51 (2016) advises a new threshold of 20%, based on expert opinion and observational study evidence. There
is therefore a potential impact on NICE guideline CG129 to establish the optimal threshold in EFW discordance.

Intrapartum care

We selected the Cochrane review by Hofmeyr et al. (2015) for a full commentary because of its Cochrane systematic review methodology and it was felt the results of the review could inform the new area of intrapartum care. The largest included study in the review was highlighted by topic expert feedback as being particularly important.

What the guideline recommends

NICE guideline CG129 does not include recommendations on intrapartum care because this area was not included in the original scope.

However, NICE guideline CG129 does make recommendations for the timing of birth, including discussing with women with twin and triplet pregnancies the timing of birth and possible modes of delivery early in the third trimester.

It also advises offering women with uncomplicated:

- monochorionic twin pregnancies elective birth from 36 weeks 0 days, after a course of antenatal corticosteroids has been offered.
- dichorionic twin pregnancies elective birth from 37 weeks 0 days.
- triplet pregnancies elective birth from 35 weeks 0 days, after a course of antenatal corticosteroids has been offered.

Methods

The aim of the Cochrane review was to determine the short- and long-term effects of planned caesarean section (CS) for twin pregnancy, on mothers and their babies.

The inclusion criteria were:

- Randomised controlled trials, quasi-randomised trials and cluster-randomised trials.
- Women with a viable twin pregnancy considered suitable for vaginal birth.
- Planned CS compared with planned vaginal birth for women either at, or before term, in accordance with a management protocol.

The exclusion criteria were cross-over trials, non-randomised trials and studies of women with known serious fetal anomaly.

The primary outcomes, measured before 28 days postpartum, were:

- serious neonatal morbidity, including
  - severe birth asphyxia
  - seizures
  - neonatal encephalopathy
  - serious birth trauma
  - severe respiratory distress syndrome
  - prolonged neonatal intensive care unit admission
- perinatal or neonatal death (excluding fatal anomalies)
- perinatal or infant death (excluding fatal anomalies)
- disability in childhood
- serious maternal morbidity, including:
  - admission to intensive care unit
  - septicaemia
  - organ failure
  - uterine rupture
  - hysterectomy
  - major surgical complication
  - life threatening event
  - long-term disability
• maternal death.

Two trials, including 60 and 2,804 women respectively, were included comparing planned caesarean versus planned vaginal birth for twin pregnancies. The smaller trial included women with cephalic or non-cephalic twin pregnancies in labour at 35 or more weeks' gestation. The larger, multi-centre trial was conducted across 25 countries, and included women with a twin pregnancy between 32 weeks' and 38 weeks six days gestation. Inclusion criteria were that the first twin was cephalic, both twins alive and with weight estimated between 1500 g and 4000 g.

Results

Risk of bias was considered to be low for most categories in both included studies. However, the risk of performance bias was considered to be high, due to the lack of blinding, and outcome assessment bias was considered to be unclear.

Primary outcomes

There was no clear evidence of differences between women randomised to planned CS or planned vaginal birth for the following primary outcomes:

• Serious maternal morbidity or maternal death (risk ratio [RR] 0.86, 95% confidence interval [CI] 0.67 to 1.11).

• Perinatal or neonatal death or serious neonatal morbidity (RR 1.15, 95% CI 0.80 to 1.67).

• Neither study reported results for the outcome of disability in childhood.

Strengths and limitations

Strengths

• The study was a systematic review carried out according to Cochrane methodology.

• A large multi-centre randomised controlled trial was included in the analysis with a low risk of bias in most areas.

• The review addressed an evidence gap because previous studies were based on lower quality evidence or did not cover multiple pregnancies.

• The results of the review are consistent with previously published non-randomised research in this area.
Limitations

- The results were based on only two studies and were mainly informed by the largest study.
- The risk of performance bias was considered to be high, due to lack of blinding, although this would not have been feasible in either included study.
- There were no data on long-term infant outcomes, including childhood disability.
- Triplet pregnancies were not included in the scope of the review.
- The included evidence was graded as moderate quality due to the imprecision of effect estimates.

Impact on guideline

NICE guideline CG129 does not include recommendations on intrapartum care because this area was not included in the original scope. Existing NICE guidelines intrapartum care for healthy women and babies, inducing labour and preterm birth 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 incorporated into a new section on intrapartum care in CG129.

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 NICE guideline CG129 at its next update.

Topic expert feedback and the new evidence identified through surveillance indicates that this area should be considered for inclusion in an update of the guideline.

Topic expert feedback also indicated that the review by Hofmeyr et al. supports the view that there is no clear evidence of a difference in outcome between babies delivered vaginally or delivered by CS.
How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 4 years after the publication of multiple pregnancy (2011) NICE guideline CG129.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual'.

Previous surveillance update decisions for the guideline are on our website.

New evidence

We found 111 new studies in a search for systematic reviews, randomised controlled trials and observational studies published between 6 November 2012 and 18 December 2015.

Evidence identified in previous surveillance 2 years after publication of the guideline was also considered. This included 11 studies identified by search.

From all sources, 122 studies were considered to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review of the guideline.

See appendix A: decision matrix and references for all new evidence considered.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline. This included a meeting with experts to discuss potential areas for update.

Views of stakeholders

Stakeholders are consulted only if we decide not to update the guideline following checks at 4 and 8 years after publication. Because this was a 4-year surveillance review, and the decision was to update, we did not consult on the decision.

See ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual' for more details on our consultation processes.
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