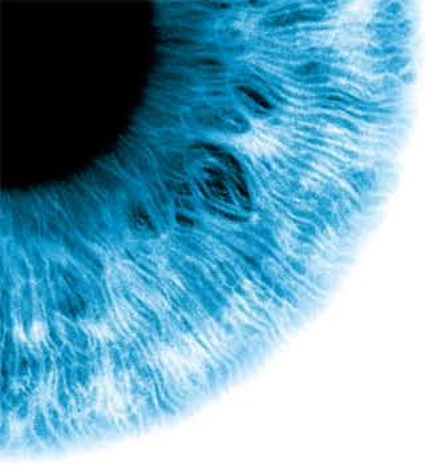

Multiple pregnancy: Evidence Update March 2013

A summary of selected new evidence relevant to NICE clinical guideline 129 'The management of twin and triplet pregnancies in the antenatal period' (2011)

Evidence Update 37

Evidence Updates provide a summary of selected new evidence published since the literature search was last conducted for the accredited guidance they relate to. They reduce the need for individuals, managers and commissioners to search for new evidence. Evidence Updates highlight key points from the new evidence and provide a commentary describing its strengths and weaknesses. They also indicate whether the new evidence may have a potential impact on current guidance. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline available from the NHS Evidence topic page for antenatal care.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care.

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Contents

Introduction

This Evidence Update identifies new evidence that is relevant to, and may have a potential impact on, the following reference guidance:

[1] **Multiple pregnancy. NICE clinical guideline 129 (2011).**

A search was conducted for new evidence from 1 November 2010 to 6 November 2012. A total of 1338 pieces of evidence were initially identified. Following removal of duplicates and a series of automated and manual sifts, 12 items were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprising topic experts, reviewed the prioritised evidence and provided a commentary.

Although the process of updating NICE guidance is distinct from the process of an Evidence Update, the relevant NICE guidance development centres have been made aware of the new evidence, which will be considered when guidance is reviewed.

Other relevant NICE guidance

The focus of the Evidence Update is on the guidance stated above. However, overlap with other NICE guidance has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following guidance:

[1] Diabetes in pregnancy. NICE clinical guideline 63 (2008).

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

[1] NICE-accredited guidance is denoted by the Accreditation Mark

Key points

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key points for this Evidence Update. It also indicates the EUAG's opinion on whether the new evidence may have a potential impact on the current guidance listed in the introduction. For further details of the evidence behind these key points, please see the full commentaries.

The section headings used in the table below are taken from the guidance.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

	Potential impact on guidance	
Key point	**Yes**	**No**
Determining gestational age and chorionicity		
• Ultrasound by trained ultrasonographers shows high sensitivity and specificity (for determining chorionicity in the first trimester).		✓
• The antenatal labelling of twins according to lateral (left or right) or vertical (top or bottom) orientation appears to be more reliable and reproducible than labelling according to proximity to the cervix.	✓*	
Fetal complications		
• Discordance in nuchal translucency or crown rump length (CRL) at 11–14 weeks of gestation does not appear to predict subsequent feto-fetal transfusion syndrome in monochorionic diamniotic (MCDA) twin pregnancies.		✓
• CRL discordance at 11–14 weeks may indicate subsequent development of selective intrauterine growth restriction, but this is unlikely to change current approaches to detecting and managing growth restriction.		✓
Maternal complications		
• Limited evidence suggests that multiple pregnancies may be a risk factor for the development of gestational diabetes.	✓*	
Preterm birth		
• Women with short cervix in the second trimester are at increased risk of preterm birth, but sensitivity associated with this measure is low and there are no effective strategies to prevent preterm birth.		✓
• Although progesterone may have a place in preventing preterm births in singleton pregnancies, there appears to be no such benefit (at least for the regimens investigated) in multiple pregnancies, even in women with short cervix.		✓

* Evidence Updates are intended to increase awareness of new evidence and do not change the recommended practice as set out in current guidance. Decisions on how the new evidence may impact guidance will not be possible until the guidance is reviewed by NICE following its published processes and methods. For further details of this evidence in the context of current guidance, please see the full commentary.

Key point	Potential impact on guidance	
	Yes	No
Indications for referral to a tertiary level fetal medicine centre • Although fetal loss from monochorionic monoamniotic (MCMA) pregnancies is high compared with MCDA pregnancies, this is mainly due to discordant congenital abnormality, conjoint twins or twin reversed arterial perfusion, with loss comparable once these early identifiable problems are excluded.		✓
Timing of birth • Evidence suggests that mortality and morbidity outcomes are optimised with delivery of uncomplicated MCMA and MCDA twin pregnancies from 36 weeks.		✓

1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update. The commentaries focus on the 'key references' (those identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update), which are identified in bold text. Section headings are taken from the guidance.

1.1 Determining gestational age and chorionicity

Determination of chorionicity

NICE clinical guideline 129 (CG129) recommends determining chorionicity at the time of detecting twin and triplet pregnancies by ultrasound using the number of placental masses, the lambda or T-sign, and membrane thickness (and discordant fetal sex if presentation is after 14 weeks). Regular training of ultrasonographers is recommended, and less experienced ultrasonographers should have support from senior colleagues or another healthcare professional if required. Regular clinical audit is also recommended to evaluate the accuracy of determining chorionicity.

Dias et al. (2011a) conducted a retrospective observational study to determine the accuracy of ultrasound in establishing chorionicity at 11–14 weeks of gestation in twin pregnancies. The study included all routine and referred twin pregnancies assessed by transabdominal ultrasound at a tertiary fetal medicine centre in the UK during the period 1999–2010. Ultrasound examinations were carried out by qualified ultrasonographers, trained in first trimester determination of chorionicity, with a second opinion obtained from a fetal medicine specialist if required. Pregnancies were considered monochorionic in the presence of the T-sign and dichorionic in the presence of the lambda sign or when two placental masses were present. At birth, chorionicity was ascertained by discordant sex (dichorionic) or placental histology.

Of the 648 twin pregnancies (524 routine scans, 124 tertiary referrals) eligible for inclusion in the study, chorionicity was identified on ultrasound in 613 pregnancies, of which 467 (76%) were classed as dichorionic and 146 (24%) as monochorionic. Of the 613 pregnancies with sufficient post-birth information to classify chorionicity, 612 were correctly assigned by first trimester ultrasound (sensitivity 100%, 95% confidence interval [CI] 97.5 to 100%; specificity 99.8%, 95% CI 98.9 to 100%). The only misclassification occurred in a pregnancy where there was a small haematoma running along the site of the membrane insertion.

This study conducted in the UK adds to the body of evidence on use of the lambda and T-signs and provides evidence that supports NICE CG129 recommendations for first trimester ultrasound by trained ultrasonographers with appropriate support.

Key reference

Dias T, Arcangeli T, Bhide A et al. (2011a) First-trimester ultrasound determination of chorionicity in twin pregnancy. Ultrasound in Obstetrics & Gynecology 38: 530–2

Nomenclature of twin fetuses

NICE CG129 recommends assigning nomenclature to babies in twin and triplet pregnancies, with clear documentation in the clinical notes, to ensure consistency throughout pregnancy. The method for nomenclature is not specified, though examples of methods are suggested (upper and lower, or left and right).

A retrospective study by **Dias et al. (2011b)** 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 study included all twin pregnancies assessed by ultrasound during weeks 11–14 of gestation at a tertiary fetal medicine centre in the UK during the period 2000–10. At the 11–14 week ultrasound assessment, the fetus in the gestational sac closer to the maternal cervix was designated as Twin 1, and the relative orientation of the fetuses to each other defined as either lateral (left or right) or vertical (top or bottom). The nomenclature was recorded and was visible on computerised records available at all subsequent scans, when the ultrasonographer documented which twin (left or right, or top or bottom) was the presenting twin. The sex and presenting order of all discordant sex twins on the final scan prior to delivery was compared with the sex and birth order at delivery.

The analysis included 416 twin pregnancies, with 378 (90.9%) judged to have a lateral and 38 (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, 32 (8.5%, 95% CI 5.9 to 11.8%) of the laterally orientated twin pairs changed presenting order. There were 108 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 (p=0.0319) for twins delivered by caesarean section (15 of 74, 20.3%) than by vaginal delivery (2 of 34, 5.9%).

The authors noted that the orientation of the gestational sac remains unchanged throughout pregnancy because the base of the intertwin membrane is fixed, although the fetuses in a lateral orientation may move up or down within the sac, thereby changing which fetus is closest to the cervix. Consequently, the authors concluded that the antenatal labelling of twins according to lateral (left or right) or vertical (top or bottom) orientation is more reliable and reproducible than labelling according to proximity to the cervix, although they noted that 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 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 by Dias et al. (2011b), is needed. This evidence may, therefore, have a potential impact on NICE CG129, although the details of any impact are outside the scope the Evidence Update. Decisions on how the new evidence may impact guidance will not be possible until the guidance is reviewed by NICE following its published processes and methods.

Key reference

Dias T, Ladd S, Mahsud-Dornan S et al. (2011b) Systematic labeling of twin pregnancies on ultrasound. Ultrasound in Obstetrics & Gynecology 38: 130–3

1.2 General care

No new key evidence was found for this section.

1.3 Fetal complications

Monitoring for feto-fetal transfusion syndrome (FFTS) and intrauterine growth restriction (IUGR)

NICE CG129 recommends 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 repeated fortnightly until 24 weeks. Fetal weight discordance should be estimated using 2 or more biometric parameters at each ultrasound scan from 20 weeks, with a difference of 25% or more considered a clinically important indicator of IUGR.

A retrospective cohort study by **Fratelli et al. (2011)** investigated the value of intertwin discordance in nuchal translucency (NT) and crown rump length (CRL), measured at the first trimester scan, to predict subsequent FFTS. The study also assessed the association between NT and CRL with other adverse outcomes (miscarriage at less than 24 weeks of gestation; spontaneous death of at least 1 fetus; and selective IUGR, which was defined as estimated fetal weight below the tenth percentile in 1 twin together with abnormal umbilical artery Doppler). The study was conducted at a maternal and fetal medicine unit at a hospital in Italy, and included all monochorionic diamniotic (MCDA) twin pregnancies with ultrasound scans in the first trimester (routinely conducted at 11–13 weeks of gestation) during the period 2001–09. Of the 136 pregnancies identified, 1 case of trisomy 21 in both fetuses was excluded from the analysis.

FFTS occurred in 16 of the 135 pregnancies (12%), with other adverse outcomes occurring in 7 further pregnancies (4 instances of selective IUGR, and 3 miscarriages before 24 weeks). Median discordance in NT was similar in uncomplicated pregnancies (14%, range 0–86%) and in those with FFTS (15%, range 0–37%) or miscarriage before 24 weeks (13%, range 12–19%), but was significantly higher in selective IUGR (47%, range 30–50%, p=0.004). 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 (0.50, 95% CI 0.35 to 0.64) nor CRL (0.52, 95% CI 0.38 to 0.67). The study was limited by the small number of pregnancies affected by adverse outcomes.

Memmo et al. (2012) also reported a retrospective cohort study to assess correlation between NT and CRL in monochorionic twins at 11–14 weeks of gestation, and subsequent development of FFTS and selective IUGR. The study was conducted at a tertiary fetal medicine unit in the UK. All chromosomally and structurally normal MCDA twin pregnancies (routine and referred) with first trimester ultrasound records that prospectively collected NT and CRL measurements during the period 2000–10 were included in the analysis. Pregnancies that resulted in spontaneous loss before 16 weeks were excluded. The analysis included a total of 242 twin pregnancies, with 104 resulting in normal pregnancy, 102 in FFTS and 36 with selective IUGR.

There was no significant difference in NT discordance between pregnancies that resulted in FFTS, selective IUGR or normal outcome (p=0.869). The discrepancy in CRL was significantly greater in the group with selective IUGR (11.9%) than with FFTS (3.8%, p<0.001) or normal outcome (3.5%, p<0.001), but there was no significant difference in CRL discrepancy between FFTS and normal pregnancies (p=0.12). Using a CRL discrepancy threshold of 7.12% for the prediction of selective IUGR gave a sensitivity of 92% (95% CI 78 to 98%) and a specificity of 76% (95% CI 70 to 82%). The authors noted that the high-risk nature of the study population (which included referrals with a high prevalence of FFTS and selective IUGR) precluded estimation of the positive and negative predictive values of CRL discrepancy for selective IUGR.

These studies both show that discordance in NT and CRL at 11–14 weeks does not appear to predict subsequent FFTS, consistent with the recommendations of NICE CG129 not to

monitor for this complication in the first trimester. The studies also show a relationship between CRL discrepancy at 11–14 weeks and subsequent development of selective IUGR. However, this evidence is unlikely to have an impact on NICE CG129, which recommends regular serial scans and referral to tertiary services if there is growth discordance. This approach ensures that selective IUGR will be detected and managed appropriately if it occurs. As prevention is not possible, this approach also avoids the undue anxiety that could result from false positives arising with earlier monitoring.

Key references

Fratelli N, Prefumo F, Fichera A et al. (2011) Nuchal translucency thickness and crown rump length discordance for the prediction of outcome in monochorionic diamniotic pregnancies. Early Human Development 87: 27–30

Memmo A, Dias T, Mahsud-Dornan S et al. (2012) Prediction of selective fetal growth restriction and twin-to-twin transfusion syndrome in monochorionic twins. BJOG: An International Journal of Obstetrics and Gynaecology 119: 417–21

1.4 Maternal complications

Gestational diabetes

NICE CG129 does not make specific recommendations about gestational diabetes. This is addressed in 'Diabetes in pregnancy' (NICE CG63), which recommends offering a diagnostic test for gestational diabetes (glucose tolerance test using 75 g glucose at 24–28 weeks) to pregnant women at high risk (specified as body mass index above 30 kg/m^2, previous macrosomic baby weighing 4.5 kg or above, previous gestational diabetes, family history of diabetes, or family origin with a high prevalence of diabetes). Multiple pregnancy is not identified as a risk factor for the development of gestational diabetes.

A retrospective cohort study by **Samuel and Simhan (2011)** assessed the frequency of abnormal results from glucose tolerance tests conducted in early pregnancy according to the reason for testing. The study included women receiving prenatal care at a US outpatient clinic during the period 2003–06 who underwent an oral glucose tolerance test with 50 g of glucose at less than 24 weeks of gestation. Women without adequate documentation of risk factors or test results, or who were given a different test (for example, 75 g of glucose) were excluded. Analysis was based on the risk factor indicated by the provider as the reason for the test, even in the presence of more than one risk factor.

Of the 305 women included in the analysis, most received early screening for gestational diabetes because of obesity (n=161, 53.8%), with other common reasons being family history (n=45, 14.8%) and personal history of gestational diabetes (n=31, 10.2%). Multiple pregnancy was the fourth most common reason for the test, indicated for 16 (5.3%) of the women in the study. Of all the women tested, 43 showed abnormality, with the frequency of abnormality varying by indication for testing. The highest rate of abnormality was in women with multiple pregnancies (7 of 16 women, 43.8%, 95% CI 19.4 to 68.1%), with lower rates of abnormality in women referred for testing for other reasons, including a personal history of gestational diabetes (29.0%, 95% CI 13.1 to 45.0%) and obesity (13.0%, 95% CI 7.8 to 18.2%).

The authors noted that the evidence was limited by the retrospective nature of the study, reliance on clinical provider documentation and the possible presence of multiple risk factors. Despite these limitations, and the small numbers of women with multiple pregnancies included in the study, the evidence suggests that women with multiple pregnancies may be at increased risk of developing gestational diabetes. This may have a potential impact on NICE CG129 and NICE CG63, although the details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will not be

possible until the guidance is reviewed by NICE following its published processes and methods.

Key reference

Samuel A, Simhan HN (2011) Clinical indications for abnormal early gestational 50 g glucose tolerance testing. American Journal of Perinatology 28: 485–8

1.5 Preterm birth

Predicting the risk of preterm birth

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

Lim et al. (2011a) conducted a systematic review of the literature on cervical length as a predictor of preterm birth in women with multiple pregnancies. Studies were included if they reported on women with multiple pregnancy in whom cervical length was measured by ultrasound during pregnancy and for whom gestational age at birth was known. Of the 21 studies included in the review, 16 related to twin pregnancies (n=2570 women) and 5 to triplet pregnancies (n=187 women), with study sizes ranging from 14 to 383 women.

Meta-analysis using a bivariate model showed a strong association on the summary ROC curve between short cervical length in the second trimester and preterm birth in multiple pregnancies. Sensitivity and specificity for preterm birth before 34 weeks were determined from ROC curves for cervical length 35 mm (78% and 66%, respectively), 30 mm (41% and 87%), 25 mm (36% and 94%) and 20 mm (30% and 94%).

There was no assessment of publication bias of the included studies, although the review included detailed meta-analysis to address heterogeneity in study characteristics. The authors concluded that women with a short cervix are at increased risk of preterm birth, but sensitivity associated with this measure is low, indicating that many women with a multiple pregnancy will deliver prematurely despite a long cervix in the second trimester. Furthermore, as there are no effective preventative strategies, the authors concluded that there is currently no place in routine clinical practice for cervical length measurement in this population, in line with the recommendations in NICE CG129. However, this evidence suggests that studies to evaluate interventions to prevent preterm birth in multiple pregnancies should focus on women with short cervix, who may be at increased risk.

Key reference

Lim AC, Hegeman MA, Huis in 't Veld MA et al. (2011a) Cervical length measurement for the prediction of preterm birth in multiple pregnancies: a systematic review and bivariate meta-analysis. Ultrasound in Obstetrics & Gynecology 38: 10–7

Preventing preterm birth

NICE CG129 recommends that interventions to prevent spontaneous preterm birth in twin or triplet pregnancies are not used, including (alone or in combination), bed rest at home or in hospital, intramuscular or vaginal progesterone, cervical cerclage or oral tocolytics.

A multicentre, double-blind, randomised controlled trial (RCT) by **Lim et al. (2011b)** investigated whether administration of intramuscular progesterone can prevent neonatal morbidity in multiple pregnancies by preventing preterm birth in 55 obstetric clinics in the Netherlands. Women with a multiple pregnancy received weekly injections of 17 alpha-hydroxyprogesterone caproate 250 mg or placebo, starting between 16 and 20 weeks of gestation, and continuing until 36 weeks of gestation. Women with a previous spontaneous preterm birth before 34 weeks or primary cerclage were excluded, as were pregnancies with serious congenital defects, death of 1 or more fetus and those with early signs of FFTS.

Participants were stratified by chorionicity, and cervical length was measured at randomisation or at the next visit.

Although 1865 women met the entry criteria, only 671 women (36%) agreed to participate (653 twin pregnancies, 17 triplet pregnancies, 1 quadruplet pregnancy). There were 1322 live births. There was no difference between treatment and control groups in the number of children with adverse neonatal outcomes (16% vs 12%, relative risk [RR]=1.34, 95% CI 0.95 to 1.89), assessed using a composite measure. There was also no difference in average gestational age at delivery between pregnancies treated with progesterone (35.4 weeks) and placebo (35.7 weeks, p=0.32), or the proportion of deliveries before 28 weeks (6% vs 5%, RR=1.04, 95% CI 0.56 to 1.94) or 32 weeks (14% vs 10%, RR=1.37, 95% CI 0.91 to 2.05). Cervical length was measured in 542 women. 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 (odds ratio [OR]=1.1, 95% CI 0.9 to 1.4).

Romero et al. (2012) considered the impact of vaginal progesterone on preterm delivery and neonatal morbidity in women with asymptomatic short cervix (defined as 25 mm or less on midtrimester ultrasound) in a systematic review and meta-analysis of individual patient data. RCTs comparing vaginal progesterone with placebo or no treatment were included if the primary aim of the study was to prevent preterm birth in women with a short cervix (or to prevent preterm birth in women with other risk factors, as long as outcomes were also reported for women with a short cervix). Studies were excluded if they evaluated women with threatened preterm birth, second trimester bleeding, or premature rupture of membranes, or if they assessed only first trimester use of progesterone to prevent miscarriage, were quasi-randomised or did not report clinical outcomes. A total of 5 trials were identified (n=775 women [52 twin and 723 singleton pregnancies] and n=827 infants), including 2 trials of singleton pregnancies only (489 women), 2 trials of singleton and twin pregnancies (265 women, 296 infants) and 1 trial of twin pregnancies (21 women, 42 infants). The progesterone administration regimen (formulation, dose, gestation week for start of administration, duration of treatment, and gestation week for end of administration) varied between trials.

Although vaginal progesterone was associated with a significant reduction in the risk of preterm birth (before 33 weeks of gestation) in women with short cervix and a singleton pregnancy (RR=0.56, 95% CI 0.40 to 0.80), no such association was found for women with short cervix and twin pregnancy (RR=0.70, 95% CI 0.34 to 1.44). There were also no significant effects of vaginal progesterone on 5 adverse neonatal morbidity outcomes (occurrence of low birthweight, Apgar score, need for mechanical ventilation, admission to neonatal intensive care, or mortality of twin pregnancies), though a composite neonatal morbidity and mortality score reached statistical significance (RR=0.52, 95% CI 0.29 to 0.93).

The studies of both Lim et al. (2011b) and Romero et al. (2012) were limited by the use of composite neonatal outcome measures. The studies may also have been underpowered with respect to women with short cervix in Lim et al. (2011b) and twin pregnancies in Romero et al. (2012). Nevertheless, the evidence suggests that, although progesterone has a place in preventing preterm births in singleton pregnancies, there appears to be no such benefit (at least for the regimens investigated) in multiple pregnancies, even in women with short cervix. These findings are, therefore, consistent with the recommendation of NICE CG129 not to use intramuscular or vaginal progesterone to prevent preterm birth in multiple pregnancies. Romero et al. (2012) concluded that a properly designed RCT was required to assess the

efficacy of vaginal progesterone for prevention of preterm birth in twin gestations in women with short cervix. While there is limited evidence from Romero et al. (2012) that vaginal progesterone may have some beneficial effects on neonatal outcomes, further research is also needed to establish the impact on measures of long-term morbidity of infants.

Key references

Lim AC, Schuit E, Bloemenkamp K et al. (2011b) 17α-hydroxyprogesterone caproate for the prevention of adverse neonatal outcome in multiple pregnancies. Obstetrics & Gynecology 118: 513–20

Romero R, Nicolaides K, Conde-Agudelo A et al. (2012) Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. American Journal of Obstetrics & Gynecology 206: 124.e1–19

1.6 Indications for referral to a tertiary level fetal medicine centre

Fetal loss rate in monochorionic monoamniotic (MCMA) twin pregnancies

NICE CG129 recommends 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.

A retrospective study by **Dias et al. (2011c)** compared the fetal loss rate of monochorionic twin pregnancies according to their amnionicity. A search was conducted for monochorionic pregnancies in the ultrasound database of a tertiary fetal medicine centre in the UK for the period 1997–2008. Twin pregnancies were eligible for inclusion in the study where monochorionicity was identified before 16 weeks and confirmed with histopathology of the placenta. All MCMA pregnancies were included in the analysis. MCDA pregnancies that were booked for delivery in the unit were included but those referred from other hospitals were excluded. Pregnancy outcome was obtained from the database where possible (if it had been entered as part of routine practice), or parents, referring physicians or GPs were contacted where information on outcome was missing. Fetal loss was defined as miscarriage, fetal death, or stillbirth of one or both twins.

The analysis included 183 monochorionic pregnancies (36 MCMA; 147 MCDA), with the outcome available for 147 pregnancies (30 MCMA pregnancies, 52 fetuses; 117 MCDA pregnancies, 233 fetuses). The overall fetal loss rate was significantly higher for MCMA pregnancies (23 of 52, 44.2%) compared with MCDA (28 of 233, 12%, $p<0.001$). 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 excluded, there was no significant difference in survival of MCMA and MCDA pregnancies ($p=0.54$) or fetuses ($p=0.15$).

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. Nevertheless, this evidence confirms the high risks associated with MCMA pregnancies, supporting NICE CG129 guidance that this is an indication for referral to a tertiary level fetal medicine centre.

Key reference

Dias T, Contro E, Thilaganathan B et al. (2011c) Pregnancy outcome of monochorionic twins: does amnionicity matter? Twin Research and Human Genetics 14: 586–92

1.7 Timing of birth

Uncomplicated monochorionic and dichorionic twin pregnancies

NICE 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 serious adverse outcomes, and that both monochorionic and dichorionic pregnancies continuing beyond 38 weeks increases the risk of fetal death.

A retrospective study by **Southwest Thames Obstetric Research Collaboration (STORK, 2012)** evaluated the prospective risk of late stillbirth in a cohort of twin pregnancies in the UK. All women registering for routine antenatal care by 11 weeks of gestation with a confirmed diamniotic twin pregnancy delivered after 26 weeks of gestation in the 9 hospitals within the Southwest Thames region during the period 2000–09 were included in the study. Pregnancies of unknown chorionicity, delivery prior to 26 weeks, termination of pregnancy and stillbirth with a birthweight less than 500 g were excluded. Scan data were obtained from each hospital's obstetric ultrasound computer database, and birth details were obtained from computerised maternity records. A total of 3005 diamniotic twin pregnancies (549 monochorionic, 2456 dichorionic) were included in the analysis.

The risk of stillbirth after 26 weeks in monochorionic twins (19.1 per 1000 fetuses) was significantly higher than in dichorionic twins (6.5 per 1000 fetuses, OR=2.97, 95% CI 1.71 to 5.18). The risk of stillbirth did not change significantly between 26 and 36 weeks for both monochorionic (1.8 vs 3.4 per 1000 fetuses, OR=1.85, 95% CI 0.3 to 13.2) and dichorionic (0.6 vs 2.1 per 1000 fetuses, OR=3.4, 95% CI 0.9 to 13.2) twins.

The authors noted that the retrospective design of the study was a limitation, but this was mitigated by validation of the ultrasound database against the delivery suite and national stillbirth registers. The authors also noted that assumptions made about the gestational age at which intrauterine death was diagnosed may have affected the findings. 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.

Sullivan et al. (2012) reported a retrospective analysis of morbidity and mortality of twin pregnancies in the USA. Records for all women with twin pregnancies attending 18 hospitals during the period 2000–09 were reviewed. Patients with monoamniotic twins and those with unknown chorionicity were excluded. A total of 3799 women (852 monochorionic, 2947 dichorionic) and their 7598 neonates were included in the analysis.

After 28 weeks, the prospective risk of perinatal mortality for each week of gestation did not differ between monochorionic and dichorionic pregnancies (data presented graphically). 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 (data presented graphically). 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.

The authors noted that completeness of data from different centres and the risk of potential complications had delivery been delayed were unknown. 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 cannot be drawn.

Hack et al. (2011) reported a retrospective cohort study of MCDA twin pregnancies in the Netherlands to assess perinatal mortality and association with mode of delivery and gestational age. Records of all monochorionic twin pregnancies delivered during the period 2000–05 at all 10 perinatal referral centres in the Netherlands were reviewed. Pregnancies complicated by FFTS, chromosomal and congenital malformations and delivery before 32 weeks of gestation were excluded. In 7 of the centres, elective delivery was offered around 37 weeks of gestation if no complications occurred, with elective delivery only undertaken in the other 3 centres if there were fetal or maternal complications. A total of 465 women and 930 fetuses were included in the analysis.

After 32 weeks, a total of 19 infants died before, during or after birth. 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 (assessed using a composite measure) at 32 and 33 weeks of gestation (24.3% and 22.9% respectively) declined at 34 weeks (12.5%), reaching 1.7% at week 35 and 36, and was absent in infants born at 37 weeks of gestation or later.

This was not a population study, and the authors also noted the potential for referral bias, with 31% of participating women referred from regional hospitals. The authors noted that prenatal surveillance and care may have differed between centres, with a possible impact on outcomes. Nevertheless, this study provides evidence that is consistent with the studies of STORK (2012) and Sullivan et al. (2012). The evidence from all 3 studies is also consistent with recommendations in NICE 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.

Key references

Hack KEA, Derks JB, Elias SG et al. (2011) Perinatal mortality and mode of delivery in monochorionic diamniotc twin pregnancies ≥32 weeks of gestation: a multicentre retrospective cohort study. BJOG: An International Journal of Obstetrics & Gynaecology 118: 1090–7

Southwest Thames Obstetric Research Collaboration (2012) Prospective risk of late stillbirth in monochorionic twins: a regional cohort study. Ultrasound in Obstetrics & Gynecology 39: 500–4

Sullivan AE, Hopkins PN, Weng H-Y et al. (2012) Delivery of monochorionic twins in the absence of complications: analysis of neonatal outcomes and costs. American Journal of Obstetrics & Gynecology 206: 257.e1–7

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Preterm birth

- Vaginal progesterone for women with an asymptomatic short cervix to prevent neonatal mortality or morbidity in twin pregnancy

Further evidence uncertainties for the management of multiple pregnancies can be found in the UK DUETs database and in the NICE research recommendations database.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Multiple pregnancy. NICE clinical guideline 129 (2011).

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 1 November 2010 (the end of the search period for NICE clinical guideline 129) to 6 November 2012:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- HTA (Health Technology Assessment) database
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- NHS EED (Economic Evaluation Database)

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy used for NICE clinical guideline 129 was adapted to provide a more focused set of results; this was tested to ensure that the comprehensiveness of the results was not compromised.

The search strategy for MEDLINE was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs, systematic reviews, observational studies and diagnostic studies (the search output for the other databases searched was small enough that no study design filters were needed).

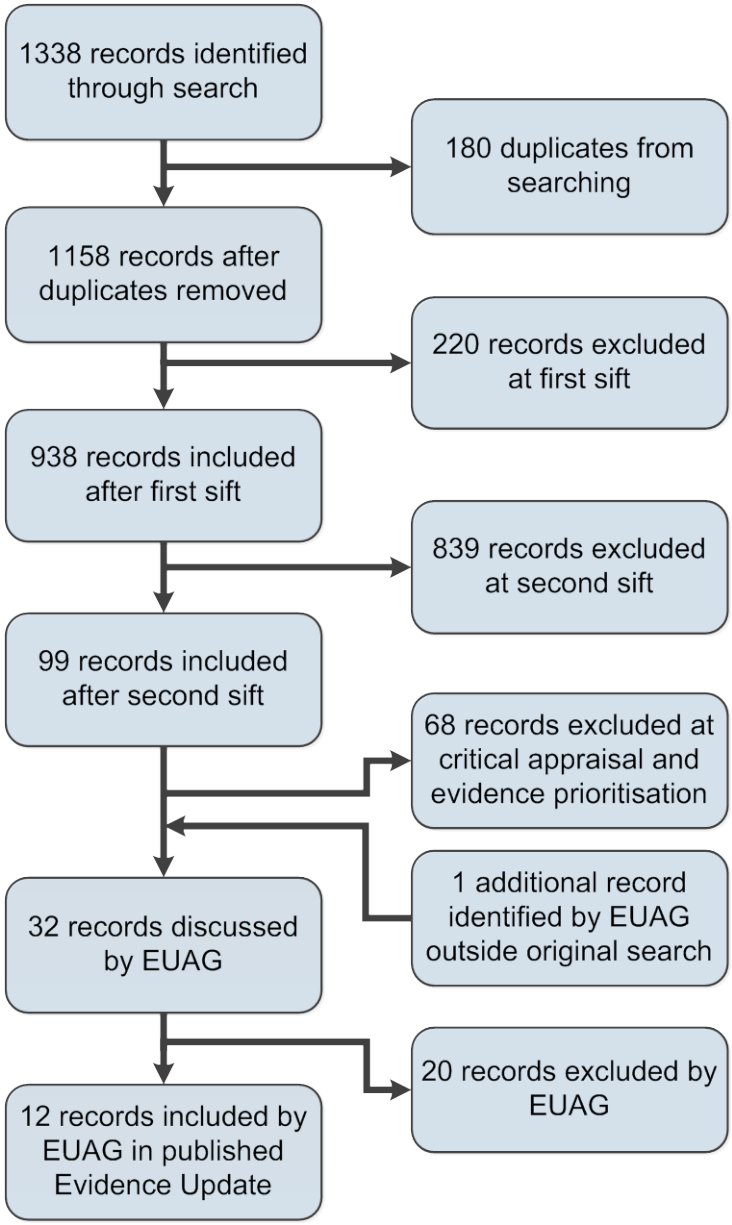
Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

There is more information about how NICE Evidence Updates are developed on the NHS Evidence website.

Table 1 MEDLINE search strategy (adapted for individual databases)

1	exp PREGNANCY, MULTIPLE/
2	((twin$ or triplet$ or multiple) adj5 (pregnan$ or gestation$ or foetus$ or foetal or fetus$ or fetal)).ti,ab.
3	(monochorionic$ or dichorionic$ or trichorionic$).ti,ab.
4	or/1-3

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

Professor Mark Kilby – Chair

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Mrs Sandra Bosman

Midwife for Multiples, The Newcastle-upon-Tyne Hospitals NHS Foundation Trust

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