Royal College of Obstetricians and Gynaecologists

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Multiple pregnancy: the management of twin and triplet pregnancies in the antenatal period

September 2011

NICE Clinical Guideline

National Collaborating Centre for Women's and Children's Health

Multiple pregnancy: the management of twin and triplet pregnancies in the antenatal period

National Collaborating Centre for
Women's and Children's Health

Commissioned by the National Institute for
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This guideline has been fully funded by NICE. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient.

Implementation of this guidance is the responsibility of local commissioners and/or providers.

NCC-WCH Editor: Karen Packham

Contents

Appendices E to J (review protocols, search strategies, excluded studies, evidence tables, Forest plots, and GRADE findings, respectively) are presented as separate files

1 Guideline summary

1.1 Guideline development group membership, NCC-WCH staff and acknowledgements

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- Zosia Beckles
- Nicholas Cole
- Sarah Latreille

1.2 Care pathway/algorithm

General care

Information and emotional support

- Explain sensitively the aims and possible outcomes of screening and diagnostic tests to minimise anxiety.
- Offer information and support specific to twin and triplet pregnancies at first contact and provide ongoing opportunities for discussion covering:
    - antenatal and postnatal mental health and wellbeing
    - antenatal nutrition (see below)
    - the risks, symptoms and signs of preterm labour and the potential need for corticosteroids for fetal lung maturation
    - likely timing and possible modes of delivery[†]
    - breastfeeding
    - parenting.

Nutritional supplements and diet and lifestyle advice

- Give the same advice about diet, lifestyle and nutritional supplements as in routine antenatal care.[‡]
- Be aware of the higher incidence of anaemia in women with twin and triplet pregnancies. Perform a full blood count at 20–24 weeks to identify a need for early supplementation with iron or folic acid, and repeat at 28 weeks as in routine antenatal care.[§]

Maternal complications

Hypertension

Also see the NICE guideline on hypertension in pregnancy (www.nice.org.uk/CG107).

- Measure blood pressure and test urine for proteinuria at each appointment, as in routine antenatal care. [‡]
- Advise women to take 75 mg of aspirin[**] daily from 12 weeks until the birth of the babies if they have one or more of the following risk factors for hypertension:
    - first pregnancy
    - age 40 years or older
    - pregnancy interval of more than 10 years
    - BMI of 35 kg/m^2 or more at first visit
    - family history of pre-eclampsia.

[†] Specific recommendations about mode of delivery are outside the scope of this guideline.
[‡] See 'Antenatal care' (NICE clinical guideline 62). Available from www.nice.org.uk/guidance/CG62
[§] This is in addition to the test for anaemia at the routine booking appointment; see 'Antenatal care' (NICE clinical guideline 62)
** This drug did not have UK marketing authorisation for this indication at the time of publication (September 2011). Informed consent should be obtained and documented. [This recommendation is adapted from recommendation 1.1.2.2 in 'Hypertension in pregnancy', NICE clinical guideline 107.]

Determining gestational age and chorionicity

Early scan for confirmed multiple pregnancy

- Aim to determine all of the following in the same first trimester scan when crown–rump length measures from 45 mm to 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days):*
  - gestational age
  - chorionicity (see below) and
  - the risk of Down's syndrome .
- Assign nomenclature to the babies (for example, upper and lower, or left and right) and document.
- Use the largest baby to measure gestational age.

* 'Antenatal care' (NICE clinical guideline 62) recommends determination of gestational age from 10 weeks 0 days. However, the aim in this recommendation is to keep to a minimum the number of scan appointments that women need to attend within a short time, especially if it is already known that a woman has a twin or triplet pregnancy.

Chorionicity

- Determine when multiple pregnancy is detected using:
  - the number of placental masses and/or
  - the lambda or T-sign and/or
  - membrane thickness.
- For women presenting after 14 weeks 0 days, use all of the above features **and** discordant fetal sex.
- Do not use three-dimensional ultrasound scans to determine chorionicity.

Problems determining chorionicity

- If transabdominal views are poor because of a retroverted uterus or high BMI, use transvaginal ultrasound.
- If it is not possible to determine chorionicity when detecting the multiple pregnancy, seek a second opinion from a senior ultrasonographer or refer to a healthcare professional competent in determining chorionicity by ultrasound as soon as possible.
- If it is still difficult after referral, manage as monochorionic until proved otherwise.

Indications for referral

- Seek a consultant opinion from a tertiary level fetal medicine centre for:
  - monochorionic monoamniotic twin pregnancies
  - monochorionic monoamniotic triplet pregnancies
  - monochorionic diamniotic triplet pregnancies
  - dichorionic diamniotic triplet pregnancies.

Schedule of specialist antenatal appointments:

Weeks 6 to 19

<table>
<tr><th>Type of pregnancy</th><th>6</th><th>7</th><th>8</th><th>9</th><th>10</th><th>11</th><th>12</th><th>13</th><th>14</th><th>15</th><th>16</th><th>17</th><th>18</th><th>19</th></tr>
<tr><td></td><td colspan="11"></td><td colspan="2">Anomaly scan (18+0 to 20+6 weeks)**</td></tr>
<tr><td>Monochorionic diamniotic twins</td><td colspan="5" rowspan="4">Booking appt by 10 weeks*</td><td colspan="3" rowspan="4">Appt + early scan (approximately 11+0 to 13+6 weeks)</td><td></td><td></td><td>Appt/ scan FFTS</td><td></td><td>Appt/ scan FFTS</td><td></td></tr>
<tr><td>Dichorionic twins</td><td></td><td></td><td>Appt only (no scan)</td><td></td><td></td><td></td></tr>
<tr><td>Monochorionic & dichorionic triplets (triamniotic)</td><td></td><td></td><td>Appt/ scan FFTS</td><td></td><td>Appt/ scan FFTS</td><td></td></tr>
<tr><td>Trichorionic triamniotic triplets</td><td></td><td></td><td>Appt only (no scan)</td><td></td><td></td><td></td></tr>
</table>

*See ‘Antenatal care’ at www.nice.org.uk/guidance/CG62

**Consider scheduling anomaly scan slightly later if needed.

Key

Appt/scan: Appointment plus scan (note that all women should have at least 2 of their appointments with the specialist obstetrician)

FFTS: Monitor for feto-fetal transfusion syndrome

Weeks 20 to29

Type of pregnancy	20	21	22	23	24	25	26	27	28	29
	Anomaly scan (18^{+0} to 20^{+6} weeks)									
	Screen for IUGR at each scan from 20 weeks									
Monochorionic diamniotic twins	Appt/ scan FFTS		Appt/ scan FFTS		Appt/ Scan FFTS				Appt/ scan	
Dichorionic twins	Appt/ scan				Appt/ scan				Appt/ scan	
Monochorionic triamniotic & dichorionic triamniotic triplets	Appt/ scan FFTS		Appt/ scan FFTS		Appt/ scan FFTS		Appt/ scan		Appt/ scan	
Trichorionic triamniotic triplets	Appt/ scan				Appt/ scan				Appt/ scan	

*See 'Antenatal care' at www.nice.org.uk/guidance/CG62

**Consider scheduling anomaly scan slightly later if needed.

Key

Appt/scan: Appointment plus scan (note that all women should have at least 2 of their appointments with the specialist obstetrician)

FFTS: Monitor for feto-fetal transfusion syndrome

IUGR: Intrauterine growth restriction

Weeks 30 to 37

Type of pregnancy	30	31	32	33	34	35	36	37
	Screen for IUGR at each scan from 20 weeks							
Monochorionic diamniotic twins			Appt/ scan		Appt/ scan		Offer birth If declined: weekly appts + scans	
Dichorionic twins			Appt/ scan		Appt only (no scan)		Appt/scan	Offer birth If declined: weekly appts + scans
Monochorionic triamniotic & dichorionic triamniotic triplets	Appt/ scan		Appt/ scan		Appt/ scan	Offer birth If declined: weekly appts + scans		
Trichorionic triamniotic triplets			Appt/ scan		Appt/ scan	Offer birth If declined: weekly appts + scans		

*See 'Antenatal care' at www.nice.org.uk/guidance/CG62

**Consider scheduling anomaly scan slightly later if needed.

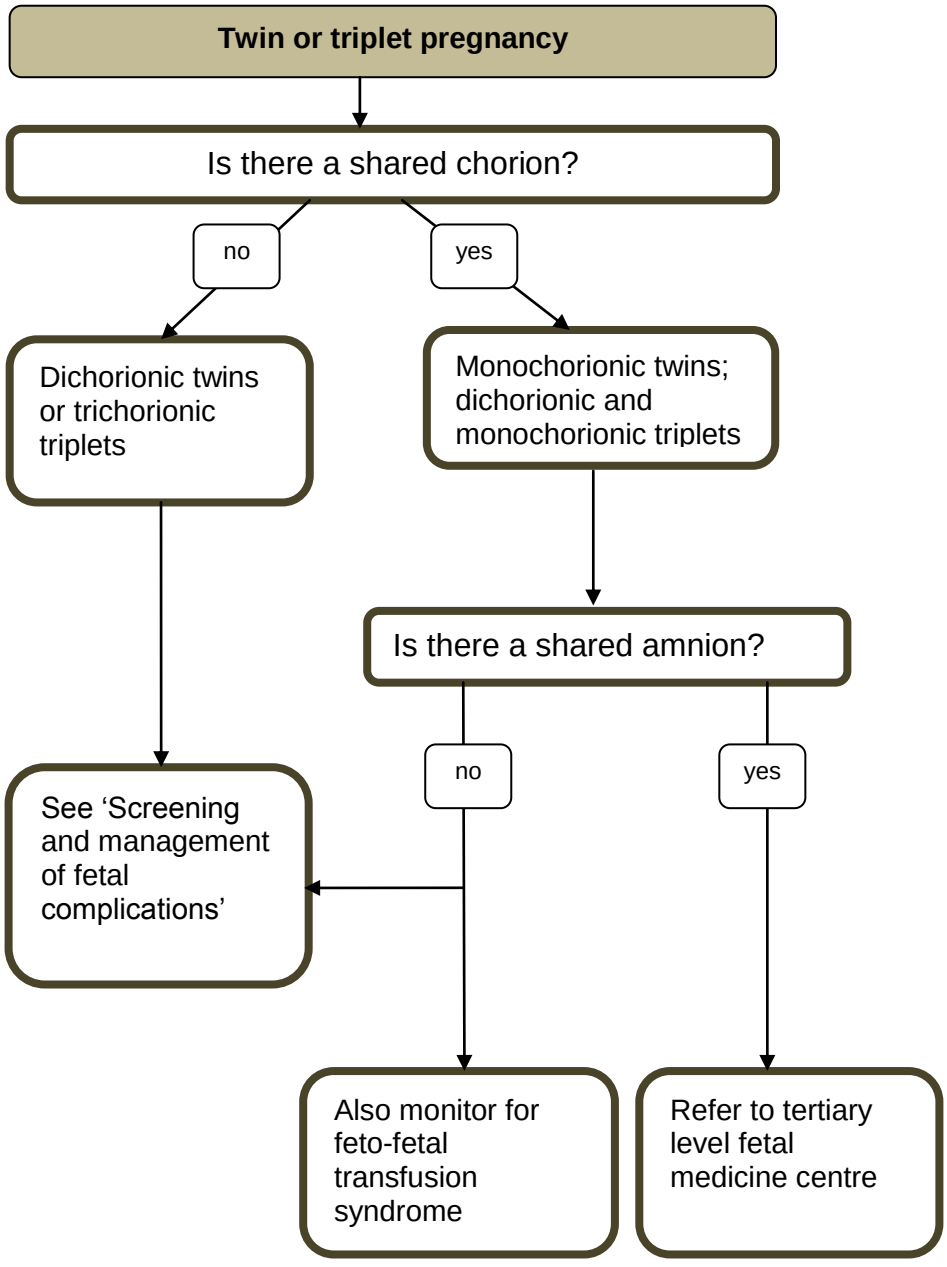
Key

Appt/scan: Appointment plus scan (note that all women should have at least 2 of their appointments with the specialist obstetrician)

FFTS: Monitor for feto-fetal transfusion syndrome

IUGR: Intrauterine growth restriction

Planning care according to chorionicity



Screening and management of fetal complications

Information about screening

- A healthcare professional experienced in twin and triplet pregnancies should offer information and counselling before and after every screening test.
- Inform women about the complexity of decisions they may need to make depending on screening outcomes, including different options according to chorionicity.

Screening for Down's syndrome

- Before screening, inform women about the:
  - greater likelihood of Down's syndrome in twin and triplet pregnancies
  - different options for screening*
  - higher false positive rate of screening tests in twin and triplet pregnancies
  - greater likelihood of being offered invasive testing and of complications occurring from this testing
  - physical and psychological risks related to selective fetal reduction.
- Carry out screening when crown–rump length measures from 45 mm to 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days)
- Map fetal positions
- Calculate risk per pregnancy in monochorionic pregnancies and for each baby in dichorionic and trichorionic pregnancies.

*See 'Antenatal care' (NICE clinical guideline 62). Available from www.nice.org.uk/guidance/CG62

Twin pregnancies

- Use the 'combined test'.
- Consider second trimester serum screening if woman books too late for first trimester screening. Explain the potential problems (particularly the increased likelihood of pregnancy loss associated with double invasive testing because the risk cannot be calculated separately for each baby).

Triplet pregnancies

- Use nuchal translucency and maternal age.
- Do not use second trimester serum screening.

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Indication for referral

Offer women whose risk of Down's syndrome exceeds 1:150 (as defined by the NHs Fetal Anomaly Screening programme [FASP]**) referral to a fetal medicine specialist in a tertiary level fetal medicine centre.

**See http://fetalanomaly.screening.nhs.uk/standardsandpolicies

Structural abnormalities (such as cardiac abnormalities)

- Offer screening as in routine antenatal care.* Consider scheduling scans slightly later and be aware that they will take longer. Allow 45 minutes for the anomaly scan (as recommended by FASP**) and 30 minutes for growth scans.

* See 'Antenatal care' (NICE clinical guideline 62) and also FASP at http://fetalanomaly.screening.nhs.uk/standardsandpolicies
** See http://fetalanomaly.screening.nhs.uk/standardsandpolicies

Intrauterine growth restriction

- Estimate fetal weight discordance using two or more biometric parameters at each scan from 20 weeks. Do not scan more than 28 days apart. Consider a ≥ 25% difference in size as clinically important and refer woman to a tertiary level fetal medicine centre.
- Do not use:
  - abdominal palpation or symphysis–fundal height measurements to predict intrauterine growth restriction
  - umbilical artery Doppler ultrasound to monitor for intrauterine growth restriction or birthweight differences.

Feto-fetal transfusion syndrome (monochorionic pregnancies only)

- Do not monitor for feto-fetal transfusion syndrome (FFTS) in the first trimester.
- Monitor with ultrasound (including to identify membrane folding) from 16 weeks. Repeat fortnightly until 24 weeks.
- If membrane folding or other possible signs (pregnancies with intertwin membrane infolding and amniotic fluid discordance) are found, monitor weekly to allow time to intervene if needed.

Preterm birth

Predicting the risk of preterm birth

- Be aware that women with twin pregnancies have a higher risk of spontaneous preterm birth if they have had a spontaneous preterm birth in a previous single pregnancy.
- Do not use cervical length (with or without fetal fibronectin) routinely to predict the risk of preterm birth
- Do not use the following to predict the risk of preterm birth:
    - fetal fibronectin testing alone
    - home uterine activity monitoring.

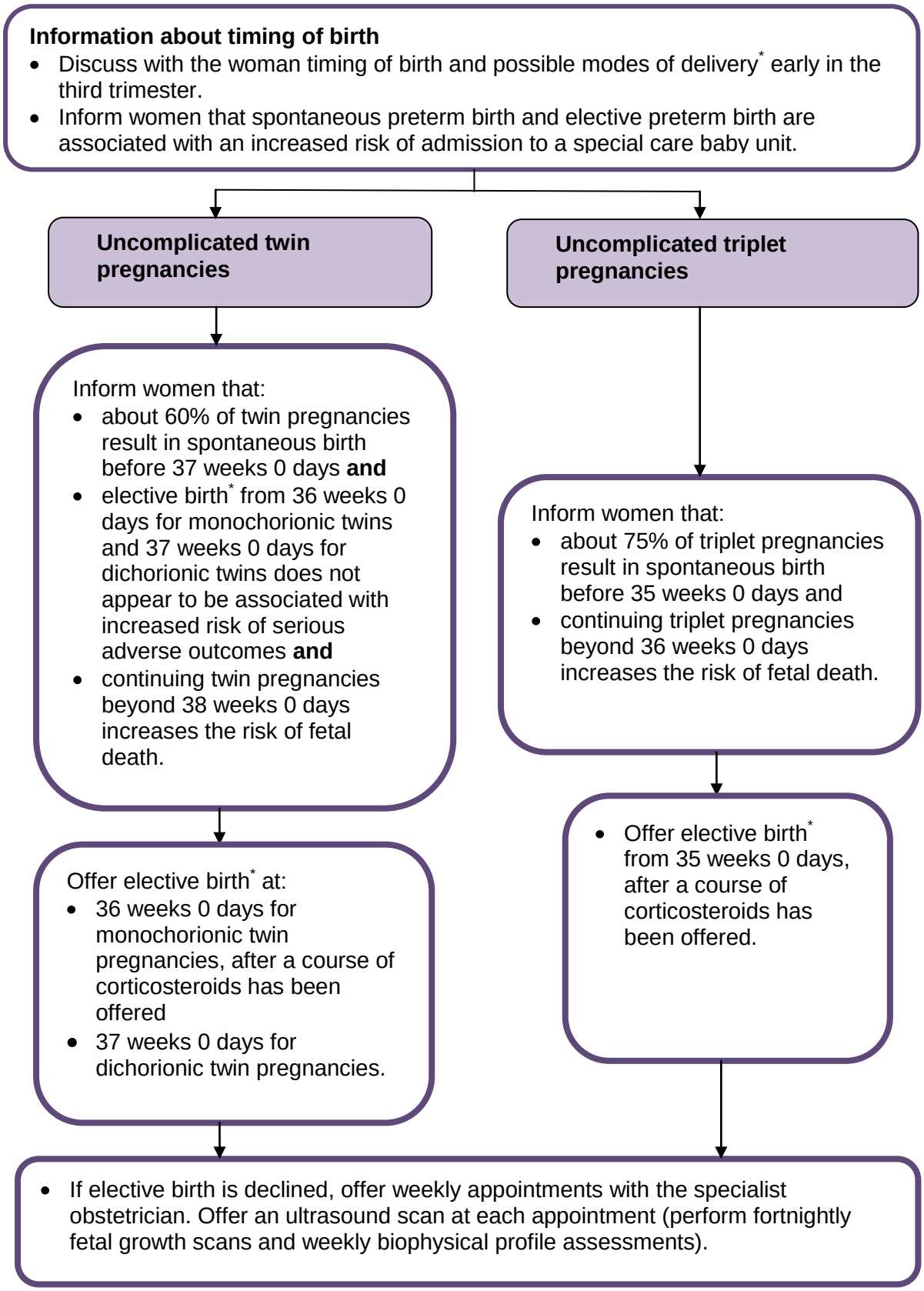
Preventing preterm birth

- Do not use the following (alone or in combination) routinely to prevent spontaneous preterm birth:
    - bed rest at home or in hospital
    - intramuscular or vaginal progesterone
    - cervical cerclage
    - oral tocolytics.

Untargeted corticosteroids

- Inform women:
    - of their increased risk of preterm birth
    - about the benefits of targeted corticosteroids
    - that there is no benefit in using untargeted administration of corticosteroids.
- Do not use single or multiple untargeted (routine) courses of corticosteroids.

Timing of birth



*Specific recommendations about mode of delivery are outside the scope of this guideline

1.3 Key priorities for implementation

Number	Recommendation	See section
	Determining gestational age and chorionicity	4
1	Offer women with twin and triplet pregnancies 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 (ideally, these should all be performed at the same scan).[††]	4.1
3	Determine 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.	4.2
4	Assign nomenclature to babies (for example, upper and lower, or left and right) in twin and triplet pregnancies and document this clearly in the woman's notes to ensure consistency throughout pregnancy.	4.2
13	Networks should agree care pathways for managing all twin and triplet pregnancies to ensure that each woman has a care plan in place that is appropriate for the chorionicity of her pregnancy.	4.2
	Specialist care	5
18	Clinical care for women with twin and triplet pregnancies should be provided by a nominated multidisciplinary team consisting of: • a core team of named specialist obstetricians, specialist midwives and ultrasonographers, all of whom have experience and knowledge of managing twin and triplet pregnancies • an enhanced team for referrals, which should include: – a perinatal mental health professional – a women's health physiotherapist – an infant feeding specialist – a dietitian. Members of the enhanced team should have experience and knowledge relevant to twin and triplet pregnancies.	5.4
20	Coordinate clinical care for women with twin and triplet pregnancies to: • minimise the number of hospital visits • provide care as close to the woman's home as possible • provide continuity of care within and between hospitals and the community.	5.4
21	The core team should offer information and emotional support specific to twin and triplet pregnancies at their first contact with the woman and provide ongoing opportunities for further discussion and advice including: • antenatal and postnatal mental health and wellbeing	5.4

[††] 'Antenatal care' (NICE clinical guideline 62) recommends determination of gestational age from 10 weeks 0 days. However, the aim in this recommendation is to keep to a minimum the number of scan appointments that women need to attend within a short time, especially if it is already known that a woman has a twin or triplet pregnancy.

- antenatal nutrition
- the risks, symptoms and signs of preterm labour and the potential need for corticosteroids for fetal lung maturation
- likely timing and possible modes of delivery‡‡
- breastfeeding
- parenting.

Monitoring for intrauterine growth restriction

6

43 Estimate fetal weight discordance using two or more biometric parameters at each ultrasound scan from 20 weeks. Aim to undertake scans at intervals of less than 28 days. Consider a 25% or greater difference in size between twins or triplets as a clinically important indicator of intrauterine growth restriction and offer referral to a tertiary level fetal medicine centre. 6.4

Indications for referral to a tertiary level fetal medicine centre

9

54 Seek a consultant opinion from a tertiary level fetal medicine centre for: 9

- monochorionic monoamniotic twin pregnancies
- monochorionic monoamniotic triplet pregnancies
- monochorionic diamniotic triplet pregnancies
- dichorionic diamniotic triplet pregnancies
- pregnancies complicated by any of the following:
  - discordant fetal growth
  - fetal anomaly
  - discordant fetal death
  - feto-fetal transfusion syndrome.

Timing of birth

10

62 Offer women with uncomplicated: 10

- 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.

1.4 Recommendations

The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

This guideline should be read in conjunction with 'Antenatal care' NICE clinical guideline 62 (www.nice.org.uk/guidance/CG62). This guideline specifies the care that women with twin and triplet pregnancies should receive that is additional or different from routine antenatal care for women with singleton pregnancies. Table 5.8 shows a comparison of the schedule of appointments for women with singleton pregnancies and women with multiple pregnancies.

Note that for many women the twin or triplet pregnancy will be detected only after their routine booking appointment.

‡‡ Specific recommendations about mode of delivery are outside the scope of this guideline.

The following terms are used in the recommendations.

- Dichorionic twin pregnancies: each baby has a separate placenta.
- Monochorionic diamniotic twin pregnancies: both babies share a placenta but have separate amniotic sacs.
- Monochorionic monoamniotic twin pregnancies: both babies share a placenta and amniotic sac.
- Trichorionic triplet pregnancies: each baby has a separate placenta and amniotic sac.
- Dichorionic triamniotic triplet pregnancies: one baby has a separate placenta and two of the babies share a placenta; all three babies have separate amniotic sacs.
- Dichorionic diamniotic triplet pregnancies: one baby has a separate placenta and amniotic sac and two of the babies share a placenta and amniotic sac.
- Monochorionic triamniotic triplet pregnancies: all three babies share one placenta but each has its own amniotic sac.
- Monochorionic diamniotic triplet pregnancies: all three babies share one placenta; one baby has a separate amniotic sac and two babies share one sac.
- Monochorionic monoamniotic triplet pregnancies: all three babies share a placenta and amniotic sac.

Number	Recommendation	See section
	Determining gestational age and chorionicity	4
	Gestational age	4.1
1	Offer women with twin and triplet pregnancies 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 (ideally, these should all be performed at the same scan; see 3 and 4).[§§]	4.1
2	Use the largest baby to estimate gestational age in twin and triplet pregnancies to avoid the risk of estimating it from a baby with early growth pathology.	4.1
	Chorionicity	4.2
3	Determine 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.	4.2
4	Assign nomenclature to babies (for example, upper and lower, or left and right) in twin and triplet pregnancies and document this clearly in the woman's notes to ensure consistency throughout pregnancy.	4.2
5	If a woman with a twin or triplet pregnancy presents after 14 weeks 0 days, determine chorionicity at the earliest opportunity by ultrasound using all of the following: • the number of placental masses	4.2

[§§] 'Antenatal care' (NICE clinical guideline 62) recommends determination of gestational age from 10 weeks 0 days. However, the aim in this recommendation is to keep to a minimum the number of scan appointments that women need to attend within a short time, especially if it is already known that a woman has a twin or triplet pregnancy.

- the lambda or T-sign
- membrane thickness
- discordant fetal sex.

6	If it is not possible to determine chorionicity by ultrasound at the time of detecting the twin or triplet pregnancy, seek a second opinion from a senior ultrasonographer or offer the woman referral to a healthcare professional who is competent in determining chorionicity by ultrasound scan as soon as possible.	4.2
7	If it is difficult to determine chorionicity, even after referral (for example, because the woman has booked late in pregnancy), manage the pregnancy as monochorionic until proved otherwise.	4.2
8	Provide regular training so that ultrasonographers can identify the lambda or T-sign accurately and confidently. Less experienced ultrasonographers should have support from senior colleagues.	4.2
9	Training should cover ultrasound scan measurements needed for women who book after 14 weeks 0 days and should emphasise that the risks associated with twin and triplet pregnancies are determined by chorionicity and not zygosity.	4.2
10	Conduct regular clinical audits to evaluate the accuracy of determining chorionicity.	4.2
11	If transabdominal ultrasound scan views are poor because of a retroverted uterus or a high body mass index (BMI), use a transvaginal ultrasound scan to determine chorionicity.	4.2
12	Do not use three-dimensional ultrasound scans to determine chorionicity.	4.2
13	Networks should agree care pathways for managing all twin and triplet pregnancies to ensure that each woman has a care plan in place that is appropriate for the chorionicity of her pregnancy.	4.2
	General care	5
	Information and emotional support	5.1
14	Explain sensitively the aims and possible outcomes of all screening and diagnostic tests to women with twin and triplet pregnancies to minimise their anxiety.	5.1
	Diet, lifestyle and nutritional supplements	5.2
15	Give women with twin and triplet pregnancies the same advice about diet, lifestyle and nutritional supplements as in routine antenatal care.[***]	5.2
16	Be aware of the higher incidence of anaemia in women with twin and triplet pregnancies compared with women with singleton pregnancies.	5.2
17	Perform a full blood count at 20–24 weeks to identify women with twin and triplet pregnancies who need early supplementation with iron or folic acid, and repeat at 28 weeks as in routine antenatal care.[†††]	5.2

[***] See 'Antenatal care' (NICE clinical guideline 62). Available from www.nice.org.uk/guidance/CG62

[†††] This is in addition to the test for anaemia at the routine booking appointment; see 'Antenatal care' (NICE clinical guideline 62). Available from www.nice.org.uk/guidance/CG62

Specialist care

5.4

18 Clinical care for women with twin and triplet pregnancies should be provided by a nominated multidisciplinary team consisting of: 5.4

- a core team of named specialist obstetricians, specialist midwives and ultrasonographers, all of whom have experience and knowledge of managing twin and triplet pregnancies
- an enhanced team for referrals, which should include:
  - a perinatal mental health professional
  - a women's health physiotherapist
  - an infant feeding specialist
  - a dietitian.

Members of the enhanced team should have experience and knowledge relevant to twin and triplet pregnancies.

19 Referrals to the enhanced team should not be made routinely for women with twin and triplet pregnancies but should be based on each woman's needs. 5.4

20 Coordinate clinical care for women with twin and triplet pregnancies to: 5.4

- minimise the number of hospital visits
- provide care as close to the woman's home as possible
- provide continuity of care within and between hospitals and the community.

21 The core team should offer information and emotional support specific to twin and triplet pregnancies at their first contact with the woman and provide ongoing opportunities for further discussion and advice including: 5.4

- antenatal and postnatal mental health and wellbeing
- antenatal nutrition (see 15)
- the risks, symptoms and signs of preterm labour and the potential need for corticosteroids for fetal lung maturation
- likely timing and possible modes of delivery[‡‡‡]
- breastfeeding
- parenting.

22 Offer women with uncomplicated monochorionic diamniotic twin pregnancies at least nine antenatal appointments with a healthcare professional from the core team. At least two of these appointments should be with the specialist obstetrician. 5.4

- Combine appointments with scans when crown–rump length measures from 45 mm to 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days) and then at estimated gestations of 16, 18, 20, 22, 24, 28, 32 and 34 weeks (see 55).

23 Offer women with uncomplicated dichorionic twin pregnancies at least eight antenatal appointments with a healthcare professional from the core team. At least two of these appointments should be with the specialist obstetrician. 5.4

- Combine appointments with scans when crown–rump length measures from 45 mm to 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days) and then at

[‡‡‡] Specific recommendations about mode of delivery are outside the scope of this guideline.

estimated gestations of 20, 24, 28, 32 and 36 weeks (see 55).
- Offer additional appointments without scans at 16 and 34 weeks.

24 Offer women with uncomplicated monochorionic triamniotic and dichorionic triamniotic triplet pregnancies at least 11 antenatal appointments with a healthcare professional from the core team. At least two of these appointments should be with the specialist obstetrician. 5.4

- Combine appointments with scans when crown–rump length measures from 45 mm to 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days) and then at estimated gestations of 16, 18, 20, 22, 24, 26, 28, 30, 32 and 34 weeks (see 55).

25 Offer women with uncomplicated trichorionic triamniotic triplet pregnancies at least seven antenatal appointments with a healthcare professional from the core team. At least two of these appointments should be with the specialist obstetrician. 5.4

- Combine appointments with scans when crown–rump length measures from 45 mm to 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days) and then at estimated gestations of 20, 24, 28, 32 and 34 weeks (see 55).
- Offer an additional appointment without a scan at 16 weeks.

26 Women with twin and triplet pregnancies involving a shared amnion should be offered individualised care from a consultant in a tertiary level fetal medicine centre (see 54). 5.4

Fetal complications 6

Information about screening 6.1

27 A healthcare professional with experience of caring for women with twin and triplet pregnancies should offer information and counselling to women before and after every screening test. 6.1

28 Inform women with twin and triplet pregnancies about the complexity of decisions they may need to make depending on the outcomes of screening, including different options according to the chorionicity of the pregnancy. 6.1

Screening for Down's syndrome 6.1

29 Before screening for Down's syndrome offer women with twin and triplet pregnancies information about: 6.1

- the greater likelihood of Down's syndrome in twin and triplet pregnancies
- the different options for screening[§§§]
- the false positive rate of screening tests, which is higher in twin and triplet pregnancies
- the likelihood of being offered invasive testing, which is higher in twin and triplet pregnancies
- the greater likelihood of complications of invasive testing
- the physical risks and psychological implications in the

[§§§] See 'Antenatal care' (NICE clinical guideline 62). Available from www.nice.org.uk/guidance/CG62

short and long term relating to selective fetal reduction.

30 Healthcare professionals who screen for Down's syndrome in twin pregnancies should: 6.1

- map the fetal positions
- use 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 (at approximately 11 weeks 0 days to 13 weeks 6 days; see 1)
- calculate the risk of Down's syndrome per pregnancy in monochorionic twin pregnancies
- calculate the risk of Down's syndrome for each baby in dichorionic twin pregnancies.

31 Healthcare professionals who screen for Down's syndrome in triplet pregnancies should: 6.1

- map the fetal positions
- use nuchal translucency and maternal age to screen for Down's syndrome when crown–rump length measures from 45 mm to 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days; see 1)
- calculate the risk of Down's syndrome per pregnancy in monochorionic triplet pregnancies
- calculate the risk of Down's syndrome for each baby in dichorionic and trichorionic triplet pregnancies.

32 Where first trimester screening for Down's syndrome cannot be offered to a woman with a twin pregnancy (for example, if the woman books too late in pregnancy) consider second trimester serum screening and explain to the woman the potential problems of such screening. These include the increased likelihood of pregnancy loss associated with double invasive testing because the risk of Down's syndrome cannot be calculated separately for each baby. 6.1

33 Do not use second trimester serum screening for Down's syndrome in triplet pregnancies. 6.1

34 Offer women with twin and triplet pregnancies who have a high risk of Down's syndrome (use a threshold of 1:150 as defined by the NHS Fetal Anomaly Screening Programme [FASP])[****] referral to a fetal medicine specialist in a tertiary level fetal medicine centre. 6.1

Screening for structural abnormalities 6.2

35 Offer screening for structural abnormalities (such as cardiac abnormalities) in twin and triplet pregnancies as in routine antenatal care.[††††] 6.2

36 Consider scheduling ultrasound scans in twin and triplet pregnancies at a slightly later gestational age than in singleton pregnancies and be aware that the scans will take longer to perform. 6.2

37 Allow 45 minutes for the anomaly scan in twin and triplet pregnancies (as recommended by FASP).**** 6.2

[****] See http://fetalanomaly.screening.nhs.uk/standardsandpolicies
[††††] See 'Antenatal care' (NICE clinical guideline 62) and also FASP at http://fetalanomaly.screening.nhs.uk/standardsandpolicies

38	Allow 30 minutes for growth scans in twin and triplet pregnancies.	6.2
	### Monitoring for feto-fetal transfusion syndrome	6.3
39	Do not monitoring for feto-fetal transfusion syndrome in the first trimester.	6.3
40	Start diagnostic monitoring with ultrasound for feto-fetal transfusion syndrome (including to identify membrane folding) from 16 weeks. Repeat monitoring fortnightly until 24 weeks.	6.3
41	Carry out weekly monitoring of twin and triplet pregnancies with membrane folding or other possible early signs of feto-fetal transfusion syndrome (specifically, pregnancies with intertwin membrane infolding and amniotic fluid discordance) to allow time to intervene if needed.	6.3
	### Monitoring for intrauterine growth restriction	6.4
42	Do not use abdominal palpation or symphysis–fundal height measurements to predict intrauterine growth restriction in twin or triplet pregnancies.	6.4
43	Estimate fetal weight discordance using two or more biometric parameters at each ultrasound scan from 20 weeks. Aim to undertake scans at intervals of less than 28 days. Consider a 25% or greater difference in size between twins or triplets as a clinically important indicator of intrauterine growth restriction and offer referral to a tertiary level fetal medicine centre.	6.4
44	Do not use umbilical artery Doppler ultrasound to monitor for intrauterine growth restriction or birthweight differences in twin or triplet pregnancies.	6.4
	## Maternal complications	7
	### Hypertension	7.1
45	Measure blood pressure and test urine for proteinuria to screen for hypertensive disorders at each antenatal appointment in twin and triplet pregnancies as in routine antenatal care.[‡‡‡‡]	7.1
46	Advise women with twin and triplet pregnancies that they should take 75 mg of aspirin[§§§§] daily from 12 weeks until the birth of the babies if they have one or more of the following risk factors for hypertension: • first pregnancy • age 40 years or older • pregnancy interval of more than 10 years • BMI of 35 kg/m^2 or more at first visit • family history of pre-eclampsia.	7.1
	## Preterm birth	8
	### Predicting the risk of preterm birth	8.1
47	Be aware that women with twin pregnancies have a higher risk of spontaneous preterm birth if they have had a spontaneous preterm birth in a previous singleton pregnancy.	8.1

[‡‡‡‡] See 'Antenatal care' (NICE clinical guideline 62). Available from www.nice.org.uk/guidance/CG62

[§§§§] At the time of publication (September 2011) this drug did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented. [This recommendation is adapted from recommendation 1.1.2.2 in 'Hypertension in Pregnancy' NICE clinical guideline 107.]

48 Do not use fetal fibronectin testing alone to predict the risk of spontaneous preterm birth in twin or triplet pregnancies. 8.1

49 Do not use home uterine activity monitoring to predict the risk of spontaneous preterm birth in twin or triplet pregnancies. 8.1

50 Do not use cervical length (with or without fetal fibronectin) routinely to predict the risk of spontaneous preterm birth in twin or triplet pregnancies. 8.1

Preventing preterm birth 8.2

51 Do not use the following interventions (alone or in combination) routinely to prevent spontaneous preterm birth in twin or triplet pregnancies: 8.2

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

Untargeted corticosteroids 8.3

52 Inform women with twin and triplet pregnancies of their increased risk of preterm birth and about the benefits of targeted corticosteroids. 8.3

53 Do not use single or multiple untargeted (routine) courses of corticosteroids in twin or triplet pregnancies. Inform women that there is no benefit in using untargeted administration of corticosteroids. 8.3

Indications for referral to a tertiary level fetal medicine centre 9

54 Seek a consultant opinion from a tertiary level fetal medicine centre for: 9

- monochorionic monoamniotic twin pregnancies
- monochorionic monoamniotic triplet pregnancies
- monochorionic diamniotic triplet pregnancies
- dichorionic diamniotic triplet pregnancies
- pregnancies complicated by any of the following:
  - discordant fetal growth
  - fetal anomaly
  - discordant fetal death
  - feto-fetal transfusion syndrome.

Timing of birth 10

55 Discuss with women with twin and triplet pregnancies the timing of birth and possible modes of delivery* early in the third trimester. 10

56 Inform women with twin pregnancies that about 60% of twin pregnancies result in spontaneous birth before 37 weeks 0 days. 10

57 Inform women with triplet pregnancies that about 75% of triplet pregnancies result in spontaneous birth before 35 weeks 0 days. 10

58 Inform women with twin and triplet pregnancies that spontaneous preterm birth and elective preterm birth are associated with an increased risk of admission to a special care baby unit. 10

59 Inform women with uncomplicated monochorionic twin pregnancies 10

* Specific recommendations about mode of delivery are outside the scope of this guideline.

	that elective birth from 36 weeks 0 days does not appear to be associated with an increased risk of serious adverse outcomes, and that continuing uncomplicated twin pregnancies beyond 38 weeks 0 days increases the risk of fetal death.	
60	Inform women with uncomplicated dichorionic twin pregnancies that elective birth from 37 weeks 0 days does not appear to be associated with an increased risk of serious adverse outcomes, and that continuing uncomplicated twin pregnancies beyond 38 weeks 0 days increases the risk of fetal death.	10
61	Inform women with triplet pregnancies that continuing uncomplicated triplet pregnancies beyond 36 weeks 0 days increases the risk of fetal death.	10
62	Offer 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.	10
63	For women who decline elective birth, offer weekly appointments with the specialist obstetrician. At each appointment offer an ultrasound scan, and perform weekly biophysical profile assessments and fortnightly fetal growth scans.	10

1.5 Key research recommendations

Number	Research recommendation	See section
	Information and emotional support	
RR 3	Does additional information and emotional support improve outcomes in twin and triplet pregnancies? Why this is important The guideline review identified insufficient evidence to determine the clinical and cost effectiveness of several specific aspects of information giving and emotional support in twin and triplet pregnancies. The evidence that was identified was generally of low quality. Outstanding research questions include: • What is the effectiveness of information and emotional support in improving maternal satisfaction and psychological wellbeing, and in increasing the uptake of breastfeeding? • Should different information and support be offered according to the chorionicity of the pregnancy? Well-designed prospective studies (including randomised controlled	5.1

* Specific recommendations about mode of delivery are outside the scope of this guideline.

trials or observational studies, and qualitative research to elicit views and experiences of women with twin and triplet pregnancies) should be conducted to inform future NICE guidance.

Specialist care

RR 6 Does specialist antenatal care for women with twin and triplet pregnancies improve outcomes for women and their babies? 5.4

Why this is important

Important issues for women with twin and triplet pregnancies in the antenatal period include access to care (including the implications of having to travel to a particular location to receive care) and the possibility of transfer to hospital during pregnancy or labour. Current evidence is limited, of low quality, and originates from a healthcare system that is different from the NHS (in particular, from a system where midwives are not involved in providing care). None of the studies identified in the guideline review made a direct comparison between specialist twin or triplet antenatal care and routine antenatal care (that is, care offered to women with singleton pregnancies).

Although health economic analysis conducted for the guideline demonstrated cost effectiveness of a range of models of specialist antenatal care, the recommendations reflect the clinical experience of the Guideline Development Group rather than strong evidence to support a particular model of care. Further research is, therefore, needed to evaluate the clinical and cost effectiveness of different models of specialist antenatal care for women with twin and triplet pregnancies. This includes evaluating the best mix of resources and skills in multidisciplinary antenatal care services, and identifying the most effective components of care.

Research should cover the roles of different healthcare professionals (including midwives, since their role is not addressed in any existing studies). It should also investigate maternal, perinatal and neonatal morbidity and mortality associated with different models of specialist care, and also long-term outcomes. Maternal outcomes to be considered include satisfaction with care and psychological wellbeing because the increased risks associated with twin and triplet pregnancies may lead to maternal anxiety or even depression. The chorionicity of the pregnancy should also be considered as a factor influencing components of specialist care. The outcomes of such research could identify particular models of care to be implemented in the NHS, which would affect service delivery and organisation (for example, by specifying a need for additional staff or further training for existing staff, both of which have cost implications).

In making this research recommendation the Guideline Development Group recognises that future research needs to provide data relevant to the current clinical context in England and Wales. The research should use cluster randomised trials or observational studies.

Monitoring for intrauterine growth restriction

RR 10 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? 6.4

Why this is important

Although the guideline review found some studies relating to the identification of intrauterine growth restriction in twin and triplet pregnancies, the larger existing studies are retrospective in design and, therefore, of low quality. No evidence-based growth charts specific to twin and triplet pregnancies are available for use in the diagnosis of intrauterine growth restriction. The evidence for the effectiveness of tests for diagnosis of intrauterine growth restriction according to chorionicity of the pregnancy is limited.

There is, therefore, a need for large, prospective cohort studies to develop fetal growth charts specific to twin and triplet pregnancies. This would allow definition and diagnosis of clinically significant intrauterine growth restriction using true growth velocity and trajectories, rather than estimated fetal weight and discrepancy. The charts should distinguish between growth patterns in monochorionic, dichorionic and trichorionic pregnancies, and the research should evaluate clinical outcomes associated with particular growth patterns.

Preventing preterm birth

RR 13 — What interventions are effective in preventing spontaneous preterm birth in women with twin and triplet pregnancies, especially in those at high risk of preterm birth? — 8.2

Why this is important

The guideline review considered several interventions aimed at preventing spontaneous preterm birth in women with twin and triplet pregnancies, including cervical cerclage, tocolytic drugs and sexual abstinence. The existing evidence for the effectiveness of cervical cerclage is of low quality (mostly originating from observational studies). The existing evidence in relation to tocolytics is also limited: there is evidence for the effectiveness of betamimetics, but no randomised controlled trials were identified for the effectiveness of ritodrine, magnesium sulphate or nifedipine. No evidence was identified for the effectiveness of sexual abstinence alone in preventing preterm birth.

Further research in the form of randomised controlled trials is, therefore, needed to evaluate the effectiveness of cervical cerclage, tocolytics other than betamimetics, and sexual abstinence. Future research should place particular emphasis on women at high risk of preterm birth in twin and triplet pregnancies. Some evidence suggested that a cervical length of less than 25 mm at 18–24 weeks of gestation in twin pregnancies or 14–20 weeks of gestation in triplet pregnancies, or a history of preterm labour in singleton pregnancies, increases the risk of spontaneous preterm birth in twin and triplet pregnancies. The evidence was limited in quality and additional research into the predictive accuracy of these factors would inform future NICE guidance. All research into the prevention of preterm birth should report spontaneous preterm birth separately from other preterm births. Data should also be reported separately for twin and triplet pregnancies, for different chorionicities, and for different gestational ages at birth (that is, less than 28 weeks, between 28 and less than 32 weeks, and 32–37 weeks).

Indications for referral to a tertiary level fetal medicine centre

RR 15 What is the incidence of monochorionic monoamniotic twin and triplet pregnancies, and what clinical management strategies are most effective in such pregnancies? 9

Why this is important

Monochorionic monoamniotic twin pregnancies occur rarely, as do all triplet pregnancies (fewer than 200 women give birth to triplets each year in England and Wales). Across the guideline, the evidence relating to such pregnancies was very limited in quantity and quality, with monochorionic monoamniotic pregnancy often listed as an exclusion criterion in studies reviewed for the guideline. Monochorionic monoamniotic pregnancies and triplet pregnancies are associated with greater complexity and risks to the woman and babies than other pregnancies considered in the guideline. The lack of evidence for effective clinical management of these pregnancies influenced the Guideline Development Group to recommend referral to a tertiary level fetal medicine centre for monochorionic monoamniotic twin pregnancies and complicated triplet pregnancies (including monochorionic and dichorionic triplet pregnancies).

Further research to determine the incidence of monochorionic monoamniotic pregnancies and triplet pregnancies of different chorionicities would inform future provision of NHS services, as would research into the most effective models for clinical management of such pregnancies. Studies could include national audits of clinical care and outcomes in such pregnancies before and after publication of the guideline. They should also include consideration of the impact of referral (or non-referral) to a tertiary level fetal medicine centre on perinatal psychological and emotional wellbeing of women and their partners.

Timing of birth

RR 17 What is the incidence of perinatal and neonatal morbidity and mortality in babies born by elective birth in twin and triplet pregnancies? 10

Why this is important

The existing evidence in relation to perinatal and neonatal outcomes associated with elective birth in twin and triplet pregnancies is limited in quantity and quality. Evidence suggests a consistently higher fetal death rate (at all gestational ages) in monochorionic twin pregnancies than in dichorionic twin pregnancies. It is uncertain whether elective birth in monochorionic twin pregnancies at 1 week earlier than recommended in the guideline (that is, from 35 weeks 0 days) would reduce fetal death rates significantly without increasing adverse neonatal outcomes significantly (for example, immaturity of the babies' respiratory systems). The research could be conducted through national audits of perinatal and neonatal morbidities in babies born by elective birth in twin and triplet pregnancies, taking account of the chorionicity of the pregnancy and gestational age at birth. If data from more than one study were available, then the technique of meta-regression might be useful for determining the optimal timing of birth precisely (according to gestational age).

1.6 Research recommendations

Number	Research recommendation	See section
	Determining gestational age and chorionicity	4
	Gestational age	4.1
RR 1	How should gestational age be estimated in twin and triplet pregnancies?	4.1
	Chorionicity	4.2
RR 2	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?	4.2
	General care	5
	Information and emotional support	5.1
RR 3	Does additional information and emotional support improve outcomes in twin and triplet pregnancies?	5.1
	Nutritional supplements	5.2
RR 4	Is dietary supplementation with vitamins or minerals, or dietary manipulation in terms of calorie intake, effective in twin and triplet pregnancies?	5.2
	Diet and lifestyle advice	5.3
RR 5	Is dietary advice specific to twin and triplet pregnancies effective in improving maternal and fetal health and wellbeing?	5.3
	Specialist care	5.4
RR 6	Does specialist antenatal care for women with twin and triplet pregnancies improve outcomes for women and their babies?	5.4
	Fetal complications	6
	Screening for chromosomal abnormalities	6.1
RR 7	When and how should screening for chromosomal abnormalities be conducted in twin and triplet pregnancies?	6.1
	Screening for structural abnormalities	6.2
RR 8	When and how should screening for structural abnormalities be conducted in twin and triplet pregnancies?	6.2
	Screening for feto-fetal transfusion syndrome	6.3
RR 9	When and how should screening for feto-fetal transfusion syndrome be conducted in twin and triplet pregnancies?	6.3
	Screening for intrauterine growth restriction	6.4
RR 10	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?	6.4
	Maternal complications	7
	Hypertension	7.1
RR 11	Which clinical factors, laboratory screening tests, and ultrasound	7.1

	tests are predictive of hypertensive disorders in twin and triplet pregnancies?	
	Preterm birth	8
	Predicting the risk of preterm birth	8.1
RR 12	Which clinical factors or laboratory tests are accurate predictors of spontaneous preterm birth in twin and triplet pregnancies?	8.1
	Preventing preterm birth	8.2
RR 13	What interventions are effective in preventing spontaneous preterm birth in women with twin and triplet pregnancies, especially in those at high risk of preterm birth?	8.2
	Untargeted corticosteroids	8.3
RR 14	What is the clinical and cost effectiveness, and safety, of routine antenatal administration of a single course of corticosteroids for women with twin and triplet pregnancies who are not in labour and in whom labour and birth are not imminent?	8.3
	Indications for referral to a tertiary level fetal medicine centre	9
RR 15	What is the incidence of monochorionic monoamniotic twin and triplet pregnancies, and what clinical management strategies are most effective in such pregnancies?	9
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?	9
	Timing of birth	10
RR 17	What is the incidence of perinatal and neonatal morbidity and mortality in babies born by elective birth in twin and triplet pregnancies?	10

1.7 Other versions of the guideline

A NICE guideline that contains only the recommendations from the full guideline is available from www.nice.org.uk/guidance.nice.org.uk/CG102/NICEGuidance.

A quick reference guide for healthcare professionals is available from www.nice.org.uk/guidance/CG129/QuickRefGuide.

A summary for patients and carers ('Understanding NICE guidance') is available from www.nice.org.uk/guidance/CG129/PublicInfo.

1.8 Schedule for updating the guideline

Clinical guidelines commissioned by NICE are published with a review date 3 years from the date of publication. Reviewing may begin before 3 years have elapsed if significant evidence that affects guideline recommendations is identified sooner.

2 Introduction

2.1 Multiple pregnancy

The incidence of multiple births has risen in the last 30 years. In 2009, 16 women per 1000 giving birth in England and Wales had multiple births compared with 10 per 1000 in 1980.[*] In total, 10,855 multiple births were recorded in 2008, of which 10,680 were twin births and 171 were triplet births.[†] This rising multiple birth rate is due mainly to increasing use of assisted reproduction techniques, including *in vitro* fertilisation (IVF). Up to 24% of successful IVF procedures result in multiple pregnancies.[‡] Increasing maternal age at conception and changes in population demographics (due to immigration) have also contributed to the rise. Multiple births currently account for 3% of live births.[§]

Multiple pregnancy is associated with higher risks for the mother and babies. Women with multiple pregnancies have an increased risk of miscarriage, anaemia, hypertensive disorders, haemorrhage, operative delivery and postnatal illness.[**] The risk of pre-eclampsia for women with twin pregnancies is almost three times that for singleton pregnancies, while the risk for triplet pregnancies is increased nine-fold.[††] In general, maternal mortality associated with multiple births is 2.5 times that for singleton births.[‡‡] Women with multiple pregnancies are also more likely to have more marked symptoms of minor ailments of pregnancy (such as nausea and vomiting) than women with singleton pregnancies.

The overall stillbirth rate in multiple pregnancies is higher than in singleton pregnancies: in 2009 the stillbirth rate was 12.3 per 1,000 twin births and 31.1 per 1,000 triplet and higher-order multiple births, compared with 5 per 1,000 singleton births.[1;2 §§]

The risk of preterm birth is also considerably higher in multiple pregnancies than in singleton pregnancies, occurring in 50% of twin pregnancies (10% of twin births take place before 32 weeks of gestation).[3-6] Duration of pregnancy becomes shorter with increasing numbers of fetuses. The higher incidence of preterm birth in multiple pregnancies is associated with an increased risk of neonatal mortality and long-term morbidity (especially neurodevelopmental disability and chronic lung disease).[***] Prematurity accounts for 65% of neonatal deaths among multiple births, compared with 43% in singleton births.[†††] The significantly higher preterm delivery rates in twin and triplet pregnancies mean there is increased demand for specialist neonatal resources.

Risks to the babies depend partly on the chorionicity and amniocity of the pregnancy.[7-11] Monochorionic twins share a placenta and have interconnected circulations, while dichorionic twins have separate placentas. Different combinations of shared and separate placentas occur in triplet pregnancies and other higher-order multiple pregnancies: monochorionic triplets share a single placenta; trichorionic triplets each have separate placentas; and dichorionic triplets occur when two fetuses share a placenta and the other has a separate placenta. Some risks to babies of multiple pregnancies are associated particularly with shared placentas. One condition associated with a shared placenta is feto-fetal transfusion syndrome (FFTS), which most commonly occurs in twin

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[*] See http://www.statistics.gov.uk/pdfdir/birth1110.pdf
[†] See Table 6.1b in http://www.statistics.gov.uk/downloads/theme_population/FM1-37/FM1_37_2008.pdf
[‡] See http://www.hfea.gov.uk/docs/MBSET_report.pdf
[§] See Table 4.3 in http://cemach.interface-test.com/getattachment/1d2c0ebc-d2aa-4131-98ed-56bf8269e529/Perinatal-Mortality-2007.aspx
[**] See http://www.mdeireland.com/pub/SML07_Executive_Summary.pdf
[††] See paragraph 6.2 in http://www.hfea.gov.uk/docs/MBSET_report.pdf
[‡‡] See Table 1.14 of http://cemach.interface-test.com/getattachment/927cf18a-735a-47a0-9200-cdea103781c7/Saving-Mothers--Lives-2003-2005_full.aspx
[§§] See Table 2 in Characteristics of birth 2 2009: 09/11/10 (366Kb - Xls) and table 1 in Characteristics of Mother 1 2009: 21/10/10 (251Kb - Xls)
[***] See Figures 4.5 and 4.6 http://cemach.interface-test.com/getattachment/1d2c0ebc-d2aa-4131-98ed-56bf8269e529/Perinatal-Mortality-2007.aspx
[†††] See Figures 4.5 and 4.6 in http://cemach.interface-test.com/getattachment/4cc984be-9460-4cc7-91f1-532c9424f76e/Perinatal-Mortality-2006.aspx

pregnancies (where it is termed twin-to-twin transfusion syndrome; TTTS). However, FFTS may also occur in monochorionic and dichorionic triplet pregnancies. FFTS affects 15% of monochorionic pregnancies and accounts for about 20% of stillbirths in multiple pregnancies. It is also associated with a significantly increased risk of neurodevelopmental morbidity. Additional complications can arise in monoamniotic pregnancies, in which two or more fetuses share a placenta and an amniotic sac. Although such pregnancies are very rare (1–2% of monochorionic pregnancies are monoamniotic), they are at risk of umbilical cord entanglement because there is no membrane separating the fetuses.[9-11]

Additional risks to the babies include intrauterine growth restriction (IUGR) and congenital abnormalities. In multiple pregnancies, 66% of unexplained stillbirths are associated with a birthweight of less than the tenth centile, compared with 39% for singleton births. Major congenital abnormalities are 4.9% more common in multiple pregnancies than in singleton pregnancies.[12]

Because of the increased risk of complications, women with multiple pregnancies need more monitoring and increased contact with healthcare professionals during their pregnancy than women with singleton pregnancies, and this will impact on National Health Service (NHS) resources. An awareness of the increased risks may also have a significant psychosocial and economic impact on women and their families because this might increase anxiety in the women, resulting in an increased need for psychological support.

There is considerable variation in the provision of antenatal care for women with multiple pregnancies in England and Wales. A survey in 2008[13] reported that limited expertise was focused on multiple births across the NHS. It also reported a lack of access to education about multiple pregnancy for healthcare professionals and inadequate continuity of antenatal care. This could have an impact on pregnancy outcomes. 'Antenatal care' (NICE clinical guideline 62)[14] did not cover the management of multiple pregnancies. There is therefore a need for high-quality, evidence-based guidance on the organisation and delivery of antenatal care for women with multiple pregnancies.

This guideline contains recommendations specific to twin and triplet pregnancies and covers the following clinical areas:

- optimal methods to determine gestational age and chorionicity
- maternal and fetal screening programmes to identify structural abnormalities, chromosomal abnormalities and FFTS, and to detect IUGR
- the effectiveness of interventions to prevent spontaneous preterm birth
- routine (elective) antenatal corticosteroid prophylaxis for reducing perinatal morbidity.

The guideline also advises how to give accurate, relevant and useful information to women with twin and triplet pregnancies and their families, and how best to support them.

2.2 For whom is this guideline intended

This guideline is of relevance to those who work in or use the NHS in England, Wales and Northern Ireland, in particular:

- healthcare professionals involved in the care of women with twin and triplet pregnancies (including general practitioners [GPs], midwives, obstetricians and ultrasonographers)
- those responsible for commissioning and planning healthcare services, including primary care trust commissioners, Health Commission Wales commissioners, and public health and trust managers
- women with twin and triplet pregnancies and their families.

A version of this guideline for women with twin and triplet pregnancies and the public is available from the NICE website (www.nice.org.uk/CG129).

2.3 Related NICE guidance

This guideline is intended to complement other existing and proposed works of relevance, including the following guidance published by NICE:

- Pregnancy and complex social factors. NICE clinical guideline 110 (2010).[16] Available from http://www.nice.org.uk/nicemedia/live/13167/50817/50817.pdf
- Hypertension in pregnancy. NICE clinical guideline 107 (2010).[20] Available from http://www.nice.org.uk/nicemedia/live/13098/50418/50418.pdf
- Induction of labour. NICE clinical guideline 70 (2008).[17] Available from http://www.nice.org.uk/nicemedia/pdf/CG070NICEGuideline.pdf
- Diabetes in pregnancy. NICE clinical guideline 63 (2008).[21] Available from http://www.nice.org.uk/nicemedia/pdf/CG063Guidance.pdf
- Antenatal care. NICE clinical guideline 62 (2008).[14] Available from http://www.nice.org.uk/nicemedia/pdf/CG062NICEguideline.pdf
- Maternal and child nutrition. NICE public health guidance 11 (2008).[25] Available from http://www.nice.org.uk/nicemedia/live/11943/40097/40097.pdf
- Antenatal and postnatal mental health. NICE clinical guideline 45 (2007).[15] Available from http://www.nice.org.uk/nicemedia/pdf/CG45fullguideline.pdf
- Laparoscopic cerclage for prevention of recurrent pregnancy loss due to cervical incompetence. NICE interventional procedure guidance 228 (2007).[24] Available from http://www.nice.org.uk/nicemedia/pdf/IPG228GuidanceFINAL.pdf
- Septostomy with or without amnioreduction for the treatment of twin-to-twin transfusion syndrome. NICE interventional procedure guidance 199 (2006).[23] Available from http://www.nice.org.uk/nicemedia/live/11276/31644/31644.pdf
- Intrauterine laser ablation of placental vessels for the treatment of twin-to-twin transfusion syndrome. NICE interventional procedure guidance 198 (2006).[22] Available from http://www.nice.org.uk/nicemedia/pdf/IPG198publicinfo.pdf
- Caesarean section. NICE clinical guideline 13 (2004; currently being updated).[18] Available from http://www.nice.org.uk/nicemedia/pdf/CG013NICEguideline.pdf
- Fertility. NICE clinical guideline 11 (2004; currently being updated).[19] Available from http://www.nice.org.uk/nicemedia/live/10936/29269/29269.pdf

3 Guideline development methodology

3.1 Introduction

This guideline was commissioned by NICE and developed in accordance with the process outlined in 'The guidelines manual' (see http://www.nice.org.uk/guidelinesmanual). Table 3.1 summarises the key stages of the process.

Table 3.1 Stages in the NICE guideline development process and edition of 'The guidelines manual' followed at each stage

Stage	2009 edition
Scoping the guideline (determining what the guideline would and would not cover)	✓
Preparing the work plan (agreeing timelines, milestones, guideline development group constitution, etc)	✓
Forming and running the guideline development group	✓
Developing review questions	✓
Identifying evidence	✓
Reviewing and synthesising evidence	✓
Incorporating health economics	✓
Making group decisions and reaching consensus	✓
Linking guidance to other NICE guidance	✓
Creating guideline recommendations	✓
Writing the guideline	✓
Stakeholder consultation on the draft guideline	✓
Finalising and publishing the guideline (including pre-publication check)	✓
Declaration of interests	✓

Information about the clinical areas covered by the guideline (and those that are excluded) is available in the scope of the guideline (reproduced in Appendix A). The guideline development group (GDG) was guided by NICE not to consider screening for gestational diabetes because 'Diabetes in pregnancy' (NICE clinical guideline 63)[21] had included a question on 'which women were at risk of gestational diabetes' and had not identified multiple pregnancy as a risk factor for gestational diabetes. The GDG recommended to NICE that the review of 'Diabetes in pregnancy' (started in March 2011) include specific consideration of multiple pregnancy as a risk factor for gestational diabetes.

All GDG members' potential and actual conflicts of interest were recorded on declaration forms provided by NICE (summarised in Appendix B). None of the interests declared by GDG members

constituted a material conflict of interest that would influence recommendations developed by the GDG.

Organisations with interests in the management of twin and triplet pregnancies in the antenatal period were encouraged to register as stakeholders for the guideline. Registered stakeholders were consulted throughout the guideline development process. A list of registered stakeholder organisations for the guideline is presented in Appendix C.

In accordance with NICE's Equality Scheme, ethnic and cultural considerations and factors relating to disabilities have been considered by the GDG throughout the development process and specifically addressed in individual recommendations where relevant. Further information is available from: www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp.

3.2 Developing review questions and protocols and identifying evidence

The GDG formulated review questions based on the scope (see Appendix D) and prepared a protocol for each review question (see Appendix E). These formed the starting point for systematic reviews of relevant evidence. Published evidence was identified by applying systematic search strategies (see Appendix F) to the following databases: Medline (1950 onwards), Embase (1980 onwards), Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 onwards) and three Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects). Searches to identify economic studies were undertaken using the above databases, the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database. None of the searches was limited by date or language of publication (although publications in languages other than English were not reviewed). Generic and specially developed search filters were used to identify particular study designs, such as randomised controlled trials (RCTs). There was no systematic attempt to search grey literature (conference abstracts, theses or unpublished trials), nor was hand searching of journals not indexed on the databases undertaken.

Towards the end of the guideline development process, the searches were updated and re-executed to include evidence published and indexed in the databases by 1 November 2010.

3.3 Reviewing and synthesising evidence

Evidence relating to clinical effectiveness was reviewed and synthesised according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (see http://www.gradeworkinggroup.org/index.htm). In the GRADE approach, the quality of the evidence identified for each outcome listed in the review protocol is assessed according to the factors listed below, and an overall quality rating (high, moderate, low or very low) is assigned by combining the ratings for the individual factors.

- Study design (as an indicator of intrinsic bias; this determines the initial quality rating)
- Limitations in the design or execution of the study (including concealment of allocation, blinding, loss to follow up; these can reduce the quality rating)
- Inconsistency of effects across studies (this can reduce the quality rating)
- Indirectness (the extent to which the available evidence fails to address the specific review question; this can reduce the quality rating)
- Imprecision (this relates to statistical or clinical significance of reported effects; uncertainty in effects can reduce the quality rating)
- Other considerations (including large magnitude of effect, evidence of a dose-response relationship, or confounding variables likely to have reduced the magnitude of an effect; these can increase the quality rating in observational studies, provided no downgrading for other features has occurred).

The type of review question determines the highest level of evidence that may be sought. For issues of therapy or treatment, the highest possible evidence level is a well-conducted systematic review or meta-analysis of RCTs, or an individual RCT. In the GRADE approach, a body of evidence based entirely on such studies has an initial quality rating of high, and this may be downgraded to moderate, low or very low if factors listed above are not addressed adequately. For issues of prognosis, the highest possible level of evidence is a controlled observational study (a cohort study or case–control study), and a body of evidence based on such studies would have an initial quality rating of low, which might be downgraded to very low or upgraded to moderate or high, depending on the factors listed above.

For each review question the highest available level of evidence was sought. Where appropriate, for example, if a systematic review, meta-analysis or RCT was identified to answer a question directly, studies of a weaker design were not considered. Where systematic reviews, meta-analyses and RCTs were not identified, other appropriate experimental or observational studies were sought. For diagnostic tests, test evaluation studies examining the performance of the test were used if the accuracy of the test was required, but where an evaluation of the effectiveness of the test in the clinical management of the condition was required, evidence from RCTs or cohort studies was optimal. For studies evaluating the accuracy of a diagnostic test, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratios for positive and negative test results (LR^+ and LR^-, respectively), were calculated or quoted where possible (see Table 3.2). If LR^+ is between 5 and 10 it is classified as 'strong'; if LR^+ is more than 10 it is classified as 'convincing'. If LR^- is between 0.1 and 0.2 it is classified as 'strong'; if LR^- is less than 0.1 it is classified as 'convincing'.[26]

Table 3.2 '2 x 2' table for calculation of diagnostic accuracy parameters

	Reference standard positive	**Reference standard negative**	**Total**
Index test result positive	a (true positive)	b (false positive)	a+b
Index test result negative	c (false negative)	d (true negative)	c+d
Total	a+c	b+d	a+b+c+d=N (total number of tests in study)

Sensitivity = a/(a+c), specificity = d/(b+d), PPV = a/(a+b), NPV = d/(c+d),
LR^+ = sensitivity/(1–specificity), LR^- = (1–sensitivity)/specificity

The GRADE system described above covers studies of treatment effectiveness. It is also being used increasingly for studies reporting diagnostic test accuracy measures, which is relevant to several of the review questions in this guideline. For such studies, NICE recommends using the Quality Assessment of Studies of Diagnostic Accuracy (QADAS) methodology checklist to assess the quality of individual studies (see the NICE guidelines manual). A body of evidence based on prospective cohort studies would have an initial quality rating of high, whereas a body of evidence based on retrospective cohort studies or case–control studies would have an initial quality rating of moderate.

Some studies were excluded from the guideline reviews after obtaining copies of the corresponding publications because they did not meet inclusion criteria specified by the GDG (see Appendix G). The characteristics of each included study were summarised in evidence tables for each review question (see Appendix H). Where possible, dichotomous outcomes were presented as relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs), and continuous outcomes were presented as mean differences (MDs) with 95% CIs or standard deviations (SDs). Absolute effects for dichotomous outcomes were calculated as the estimated relative effect (RR or OR) multiplied by an estimate of baseline risk (for a single study the baseline risk is the risk in the control group): absolute effects for continuous outcomes were estimated directly as the difference between outcomes in the different treatment groups.

The body of evidence identified for each review question (or part of a review question) was presented in the form of a GRADE findings table (evidence profile) summarising the quality of the evidence and the results (summary relative and absolute effect sizes and associated CIs). Where possible, the body of evidence corresponding to each outcome specified in the review protocol was subjected to quantitative meta-analysis. In such cases, summary effect sizes were presented as summary RRs, summary ORs or weighted mean differences (WMDs). Where summary RRs or summary ORs were estimated via meta-analysis the baseline risk was assumed to be the mean baseline risk in the studies included in the meta-analysis. By default, meta-analyses were conducted by fitting fixed effects models, but where unexplained heterogeneity was identified (I-squared statistic greater than 33%) random effects models were used. Where quantitative meta-analysis could not be undertaken (for example, because effect measures reported in the evidence were not accompanied by standard errors or data that would allow standard errors to be calculated), the range of effect sizes reported in the included studies was presented. Forest plots for all meta-analyses conducted for the guideline are presented in Appendix I. GRADE findings are presented in full in Appendix J and abbreviated versions (summary of findings without the individual components of the quality assessment) are presented in this document.

Various approaches may be used to assess imprecision in the GRADE framework. In this guideline, dichotomous outcomes in intervention studies were downgraded in terms of imprecision when the total number of events was less than 300 and continuous outcomes were downgraded when the total sample size was less than 400. These are default thresholds used in GRADE for intervention studies. For diagnostic test accuracy studies, evidence was downgraded in terms of imprecision when the width of the 95% CI for any of sensitivity, specificity, PPV or NPV was 40 percentage points or more, or if no CIs were reported. These thresholds or decision rules have been used in other NICE clinical guidelines (for example 'Non-invasive ventilation for motor neurone disease', NICE clinical guideline 105).[27]

3.4 Incorporating health economics

The aims of the health economic input to the guideline were to inform the GDG of potential economic issues relating to the management of twin and triplet pregnancies in the antenatal period, and to ensure that recommendations represented a cost-effective use of healthcare resources. Health economic evaluations aim to integrate data on benefits (ideally in terms of quality adjusted life years [QALYs]), harms and costs of different care options.

The GDG prioritised a number of review questions where it was thought that economic considerations would be particularly important in formulating recommendations. Systematic searches for published economic evidence were undertaken for these questions. For economic evaluations, no standard system of grading the quality of evidence exists and included papers were assessed using a quality assessment checklist based on good practice in economic evaluation.[28] Reviews of the (very limited) relevant published health economic literature are presented alongside the clinical effectiveness reviews.

Health economic considerations were aided by original economic analysis undertaken as part of the development process. For this guideline the areas prioritised for economic analysis were cost effectiveness of:

- specialist multiple pregnancy care (see Sections 5.3 and 11.2)
- screening for feto-fetal transfusion syndrome (FFTS) (see Section 6.3; no cost effectiveness analysis was actually conducted for this review question because no evidence of clinical effectiveness was identified)
- screening to predict intrauterine growth restriction (IUGR) (see Section 6.4; no cost effectiveness analysis was actually conducted for this review question because no evidence of clinical effectiveness was identified)
- screening to predict the risks of spontaneous preterm birth and interventions for preventing spontaneous preterm birth (see Sections 8.1 and 8.2; no cost effectiveness analysis was actually conducted for these review questions because no evidence of clinical effectiveness was identified)

- elective birth compared to expectant management (see Sections 10 and 11.3).

3.5 Evidence to recommendations

For each review question recommendations for clinical care were derived using, and linked explicitly to, the evidence that supported them. In the first instance, informal consensus methods were used by the GDG to agree short clinical and, where appropriate, cost effectiveness evidence statements which were presented alongside the evidence profiles. Statements summarising the GDG's interpretation of the evidence and any extrapolation from the evidence used to form recommendations were also prepared to ensure transparency in the decision-making process. The criteria used in moving from evidence to recommendations are summarised as:

- Relative value placed on the outcomes considered
- Trade-off between clinical benefits and harms
- Quality of the evidence
- Other considerations (including equalities issues)

In areas where no substantial clinical research evidence was identified, the GDG considered other evidence-based guidelines and consensus statements or used its members' collective experience to identify good practice. The health economics justification in areas of the guideline where the use of NHS resources (interventions or tests) was considered was based on GDG consensus in relation to the likely cost effectiveness implications of the recommendations. The GDG also identified areas where evidence to answer review questions was lacking and used this information to formulate recommendations for future research.

Towards the end of the guideline development process formal consensus methods were used to consider all the clinical care recommendations and research recommendations that had been drafted previously. The GDG identified ten 'key priorities for implementation' (key recommendations) and six high-priority research recommendations. The key priorities for implementation were those recommendations thought likely to have the biggest impact on pregnancy care and outcomes in the NHS as a whole; they were selected using a variant of the nominal group technique (see the NICE guidelines manual). The priority research recommendations were selected in a similar way.

3.6 Stakeholder involvement

Registered stakeholder organisations were invited to comment on the draft scope and the draft guideline. Stakeholder organisations were also invited to undertake a prepublication check of the final guideline to identify factual inaccuracies. The GDG carefully considered and responded to all comments received from stakeholder organisations. The comments and responses, which were reviewed independently for NICE by a Guidelines Review Panel, are published on the NICE website.

3.7 Specific considerations for this guideline

For this guideline, the effectiveness of interventions was assessed against the following main outcomes:

- maternal morbidity during pregnancy and after birth
- maternal mortality during pregnancy and after birth
- perinatal morbidity
- perinatal mortality
- *in utero* and postnatal transfer rates for specialist neonatal care
- maternal satisfaction relating to the provision of antenatal care.

Where the evidence supported it, the GDG made separate recommendations for women with twin and triplet pregnancies, for women with monochorionic and dichorionic twin pregnancies, and for women with monoamniotic and diamniotic twin pregnancies.

4 Determining gestational age and chorionicity

4.1 Gestational age

Introduction

Ultrasound is an established tool for dating singleton pregnancies to avoid unnecessary elective preterm delivery, to plan delivery or intervention (where appropriate) at an appropriate time, and to avoid post-term complications. Twin and triplet pregnancies are at higher risk of preterm delivery than are singleton pregnancies, making accurate dating essential. 'Antenatal care' (NICE clinical guideline 62)[14] recommends that healthy pregnant women with singleton pregnancies should be offered an early scan between 10 weeks and 13 weeks 6 days. However, it is not certain when dating by ultrasound should be performed or if ultrasound charts based on singleton pregnancies are applicable to twin and triplet pregnancies. The evidence considered for this review question is based on studies using *in vitro* fertilisation (IVF) or other assisted reproduction techniques where true gestational age could be established. Additional data were sought regarding which fetus should be used to date twin and triplet pregnancies; clinical practice currently varies between using the largest fetus, the smallest fetus or average fetal size to establish gestational age.

Review question

What are the optimal ultrasound measurements to determine gestational age in multiple pregnancy?

The following subquestions were considered by the GDG.

- 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?
- Which fetus should be used for estimating gestational age in multiple pregnancies?

Existing NICE guidance

'Antenatal care' (NICE clinical guideline 62)[14] includes the following recommendations for routine antenatal care of healthy pregnant women with singleton pregnancies.

- Offer pregnant women an early ultrasound scan between 10 weeks 0 days and 13 weeks 6 days to determine gestational age and to detect multiple pregnancies. This is to ensure consistency of gestational age assessment and reduce the incidence of induction of labour for prolonged pregnancy.
- Use crown–rump length measurement to determine gestational age. If the crown–rump length is above 84 mm, estimate gestational age using head circumference.

Fetal head circumference was considered in 'Antenatal care' (NICE clinical guideline 62)[14] to be more accurate in predicting gestational age than was biparietal diameter. This conclusion was based on one study involving singletons.[29] The evidence reviewed in 'Antenatal care' (NICE clinical guideline 62)[14] did not suggest that an upper limit should be placed on head circumference for predicting gestational age.

Description of included studies

Effectiveness of dating twin and triplet pregnancies using measurements and charts for singleton pregnancies

Six studies (reported in seven publications) were identified for inclusion in relation to effectiveness of measurements and charts used for dating singletons when applied to twins or triplets.[30-36]

The first study used data collected in the UK and compared biparietal diameter between twins and singletons, although details of the charts used were not reported.[30] This study used the day of fertilisation (or frozen embryo replacement) for dating pregnancies.

The second study (reported in two separate publications) was conducted in Brazil and prospectively compared crown–rump length between twins and singletons using published charts, although again details of the charts used were not provided.[31;32] Pregnancies were dated by day of oocyte retrieval, although embryo transfer was performed 2–3 days later.

The third study was conducted in the UK and used a retrospective cohort design.[33] Mean differences between the true gestational age and that estimated from first-trimester crown–rump length measurements were derived for singletons and twins and compared using three different formulae. In all pregnancies, gestational age was calculated using the date of embryo transfer.

The fourth study was also conducted in the UK and used a retrospective case–control design.[34] This study investigated whether there was a significant difference between second-trimester measurements of head circumference and femur length in twins when compared with measurements in singletons. In all pregnancies, gestational age was calculated using the date of embryo transfer. It is likely that this study involved the same population as the third study.

The fifth study used data collected in the USA to derive a prediction equation for gestational age in singleton pregnancies (using head circumference, femur length and abdominal circumference) and applied it to twins and triplets.[35] A 'best-fit' model for estimating gestational age in singletons was derived using the fetal biometric indices and then used to examine the accuracy of gestational age prediction in twin and triplet pregnancies (by comparing systematic and random errors). Data for this study came from birth records of women whose pregnancies were dated by day of oocyte retrieval and fertilisation.

The sixth study, conducted in Sweden, used a prediction equation for gestational age (using biparietal diameter with or without femur length) derived from maternity and ultrasound records of healthy women, and compared results between twins and singletons.[36] All pregnancies in this study were dated by day of oocyte retrieval and frozen–thawed embryos were transferred 2 days later.

With the exception of the sixth study, which involved Swedish women,[36] none of the studies provided information about ethnicity of the participants. The third and fourth studies excluded women with monochorionic twin pregnancies. None of the other studies provided information about chorionicity.[33;34]

Choosing which fetus to use to date twin and triplet pregnancies

Three studies were identified for inclusion to address the question of which fetus should be used to establish gestational age in twin and triplet pregnancies.[33;35;37]

The first study was a small prospective study, conducted in France, that compared gestational age predictions using crown–rump length measurements in twin pregnancies evaluated at 11–14 weeks of gestation.[37] The charts used in the study were not referenced and the method of dating the pregnancies was not reported.

The second study, which was conducted in the USA, was larger, although retrospective in design.[35] The gestational age range studied was later (second trimester) than in the first study. This study derived a 'best-fit' model for estimating gestational age in singletons using fetal biometric indices, which was then used to examine the accuracy of gestational age prediction using individual fetuses in twin and triplet pregnancies.

The third study was a retrospective cohort study conducted in the UK.[33] Crown–rump length measurements conducted routinely in the first trimester (at 11–14 weeks of gestation) were compared

using charts attributed to Robinson, Rossavik and Von Kaisenberg. In all pregnancies, gestational age was calculated from the date of embryo transfer.

Chorionicity was reported in the first and third studies,[33;37] but not the second study.[35] Ethnicity was not reported in any study.

Published health economic evidence

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

Evidence profile

Evidence profiles for the two subquestions are presented in Tables 4.1 and 4.2, respectively.

Table 4.1 GRADE summary of findings for effectiveness of dating twin and triplet pregnancies using measurements and charts for singleton pregnancies

Number of studies	Twins or triplets		Singletons		Effect	Quality
	Number	Mean or mean difference ± standard deviation	Number	Mean or mean difference ± standard deviation	Mean difference (95% confidence interval)	
Differences in size between twins or triplets and singletons						
Using crown–rump length measurement at 52 days of gestation						
1[31]	20 twins	11.48 mm ± 0.22	20	11.74 mm ± 0.27	NR; P = 0.45	Very low
Using crown–rump length measurement at 59 days of gestation						
1[31]	20 twins	19.36 mm ± 0.31	20	19.26 mm ± 0.43	NR; P = 0.85	Very low
Using crown–rump length measurement at 66 days of gestation						
1[31]	20 twins	26.51 mm ± 0.33	20	26.44 mm ± 0.57	NR; P = 0.91	Very low
Using crown–rump length measurement at 73 days of gestation						
1[31;32]	20 twins	35.87 mm ± 0.54	20	36.19 mm ± 0.90	NR; P = 0.76	Very low
Using crown–rump length measurement at 80 days of gestation						
1[32]	20 twins	50.8 mm ± 2.8	20	50.4 mm ± 3.0	NR; P = 0.62	Very low
Using crown–rump length measurement at 87 days of gestation						
1[32]	20 twins	63.4 mm ± 2.3	20	64.4 mm ± 2.3	NR; P = 0.19	Very low
Using crown–rump length measurement at 94 days of gestation						
1[32]	20 twins	75.4 mm ± 2.5	20	74.7 mm ± 2.7	NR; P = 0.41	Very low
Using crown–rump length measurement at 101 days of gestation						
1[32]	20 twins	85.2 mm ± 5.5	20	85.6 mm ± 5.5	NR; P = 0.83	Very low
Using mean difference between crown–rump length measurement and estimated crown–rump length based on Robinson's chart at 11–14 weeks of gestation						
1[33]	110 larger twins	4.7 mm (4.4 to 5.1)	266	2.72 mm (2.49 to 2.95)	1.98 mm	Very low
Using mean difference between crown–rump length measurement and estimated crown–rump length based on Rossavik's chart at 11–14 weeks of gestation						
1[33]	110 larger twins	2.1 mm (1.8 to 2.5)	266	0.24 mm (0.01 to 0.46)	1.86 mm	Very low

Number of studies	Twins or triplets		Singletons		Effect	Quality
	Number	Mean or mean difference ± standard deviation	Number	Mean or mean difference ± standard deviation	Mean difference (95% confidence interval)	
Using mean difference between crown–rump length measurement and estimated crown–rump length based on Von Kaisenberg's chart at 11–14 weeks of gestation						
1[33]	110 larger twins	−0.91 mm (−0.7 to −1.13)	266	0.98 mm (0.6 to 1.35	1.89 mm	Very low
Using biparietal diameter measurement at 111 and 173 days of gestation						
1[33]	20 twins	−0.12 mm ± 2.07	39	0.14 mm ± 2.21	0.26mm (−0.66 to 1.18)	Very low
1[34]	119 larger twins	NR	269	NR	NR; P < 0.05	Very low
1[34]	119 smaller twins	NR	269	NR	NR; P < 0.05	Very low
1[34]	119 twin pairs (using average from each pair)	NR	269	NR	NR; P = 1	Very low
Using femur length measurement at 16–26 weeks of gestation						
1[34]	119 larger twins	NR	269	NR	NR; P = 0.07	Very low
1[34]	119 smaller twins	NR	269	NR	NR; P < 0.005	Very low
1[34]	119 twin pairs (using average from each pair)	NR	269	NR	NR; P = 1	Very low
Differences in dating between twins or triplets and singletons						
Using formula based on mean head circumference , femur length and abdominal circumference measurements at 14–22 weeks of gestation						
1[35]	134 twins	NR	152	NR	–0.3 days	Very low
1[35]	67 triplets	NR	152	NR	–1.3 days	Very low
Using formula based on biparietal diameter measurements in the second trimester						
1[36]	168 twins	116.8 days ± 6.1	253	118.9 days ± 9.0	NS (P = NR)	Low
Using mean difference between true gestational age and estimated gestational age based on Robinson's crown–rump length formula at 11–14 weeks of gestation						
1[33]	110 larger twins	2.4 days (2.4 to 2.6)	266	1.41 days (1.15 to 1.68)	1.01 days	Very low
Using mean difference between true gestational age and estimated gestational age based on Rossavik's crown–rump length formula at 11–14 weeks of gestation						
1[33]	110 larger twins	1.27 days (1.05 to 1.5)	266	0.14 days (0.01 to 0.28)	1.13 days	Very low
Using mean difference between true gestational age and estimated gestational age based on Von Kaisenberg's crown–rump length formula at 11–14 weeks of gestation						
1[33]	110 larger twins	0.58 days (0.36 to 0.8)	266	–0.54 days (–0.41 to -0.67)	1.12 days	Very low
Using day of oocyte retrieval						
1[36]	168 twins	120.9 days ± 8.6	253	118.2 days ± 5.3	NS (P = NR)	Low

Table 4.2 GRADE summary of findings for choosing which fetus to use to date twin and triplet pregnancies

Number of studies	Number of twins or triplets	Mean difference ± standard deviation or accuracy (root mean square deviation; RMSD)	Quality
Prediction of growth discordance			
Between the larger and smaller twin based on crown–rump length measurement at 11–14 weeks of gestation			
1[37]	182 twins	3.4 days ± 3.18	Very low
Accuracy of dating			
Among twins in pregnancies resulting from assisted reproduction and based on comparison of crown–rump length measurement and true gestational age at 11–14 weeks of gestation in the larger fetus			
1[37]	47 twins	1.45 days ± 2.17	Very low
Among twins in pregnancies resulting from assisted reproduction and based on comparison of crown–rump length measurement and true gestational age at 11–14 weeks of gestation in the smaller fetus			
1[37]	47 twins	–0.06 days ± 2.21	Very low
Among twins using a formula based on mean head circumference, femur length and abdominal circumference at 14–22 weeks of gestation in the larger fetus			
1[35]	67 twins	RMSD 4.17 days	Very low
Among twins using a formula based on mean head circumference, femur length and abdominal circumference at 14–22 weeks of gestation in the smaller fetus			
1[35]	67 twins	RMSD 4.11 days	Very low
Among twins using a formula based on mean head circumference, femur length and abdominal circumference at 14–22 weeks of gestation averaged over both fetuses			
1[35]	67 twins	RMSD 3.91 days	Very low
Among triplets using a formula based on mean head circumference, femur length and abdominal circumference at 14–22 weeks of gestation in the larger fetus			
1[35]	19 triplets	RMSD 4.04 days	Very low
Among triplets using a formula based on mean head circumference, femur length and abdominal circumference at 14–22 weeks of gestation in the smallest fetus			
1[35]	19 triplets	RMSD 4.87 days	Very low
Among triplets using a formula based on mean head circumference, femur length and abdominal circumference at 14–22 weeks of gestation averaged over all fetuses			
1[35]	19 triplets	RMSD 3.73 days	Very low

Evidence statement

Evidence was identified for all fetal ultrasound parameters prioritised for consideration in terms of determining gestational age in twin and triplet pregnancies. All evidence came from observational studies which constitute low (or very low) quality evidence.

With regard to whether the measurements and charts used in singletons were accurate when applied to twins and triplets, no statistically significant differences in size were found between twin and singleton pregnancies using crown–rump length (very low quality evidence) or biparietal diameter (low quality evidence). Significant differences were reported in the head circumference of larger and smaller twins compared with singletons, although this difference did not remain significant when an average of each set of twins was used (very low quality evidence). There was a significant difference between smaller twins and singletons in femur length, but the difference was not significant when comparing the larger twin or the average of each set of twins with singletons (very low quality evidence). Gestational age estimation in twins was not statistically significantly different from singletons when dating was carried out by a formula based on femur length, head circumference and abdominal circumference (very low quality evidence), but the same formula systematically underestimated gestational age in triplets by 1 day (very low quality evidence). There was no statistically significant difference in dating by day of oocyte retrieval between twin and singleton pregnancies (low quality evidence).

Similarly, there was no evidence to suggest that any specific fetal measurement in multiple pregnancies was more effective than another in gestational age estimation.

The majority of the studies appeared to use date of oocyte retrieval to determine the true gestational age. However, the studies were limited, with bias from small sample sizes, operator bias and studies being retrospective. The impact of the use of the timing of oocyte retrieval versus the timing of embryo transfer on dating could not be evaluated from the searches conducted for the guideline (no additional searches for evidence relating to singleton pregnancies could be conducted within the timescale for developing the guideline).

With regard to which fetus should be used for estimating gestational age in twin and triplet pregnancies, the GDG was of the view that there was a possibility that in the first half of pregnancy, when gestational age is determined, the smaller twin could be pathologically undergrown in some cases. That would mean that use of the measurements from the smaller fetus could lead to an underestimate of gestational age. No evidence was available for prediction of fetal growth restriction as an outcome and whether use of the smaller fetus in twin pregnancies with impaired growth potential leads to this error in practice. Evidence was, however, available for growth discordance between twins, that resulted in an average discrepancy of 3.4 mm in crown–rump length between the larger and the smaller twin (very low quality evidence). No evidence was available for prediction of other twin complications or congenital anomalies. One study suggested that dating of twin pregnancies was more accurate when the smaller twin, rather than the larger twin, was used (very low quality evidence). However, two other studies showed evidence supporting the use of the average fetal size to determine gestational age in twins and triplets (very low quality evidence).

Health economics profile

No published health economics evidence was identified and no original health economic modelling was conducted for this review question. 'Antenatal care' (NICE clinical guideline 62)[14] recommends a routine scan at between 10 weeks 0 days and 13 weeks 6 days to determine gestational age and to detect multiple pregnancy. This review question focuses on what to measure when the scan is conducted in a women who is found to have a twin or triplet pregnancy; this has no additional resource implications and is, therefore, not relevant for further health economic analysis.

Evidence to recommendations

Relative value placed on the outcomes considered

There is a need to determine which fetus should be used as the reference for the dating process in twin and triplet pregnancies. Accurate estimation of gestational age in such pregnancies is important because it forms the basis for predicting, assessing and managing the potential complications of the pregnancy. All outcomes specific in the review protocol were considered critical in terms of informing recommendations for clinical practice.

Trade-off between clinical benefits and harms

'Antenatal care' (NICE clinical guideline 62)[14] already addresses estimation of gestational age using ultrasound and no additional benefits or harms were identified in relation to twin and triplet pregnancies. With regard to which fetus to use, the ultrasound measurements of all fetuses will be taken in the pregnancy in any case. The only issue is which measurement should be used to 'date' the pregnancy. Evidence shows limited differences between smallest, largest and mean measurements to predict gestational age. However, clinically it is 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 GDG therefore considered it more appropriate to date the pregnancy using the largest fetus.

Trade-off between net health benefits and resource use

The review question (including its subsidiary questions) was not identified as being of high priority for health economic evaluation. Only one ultrasound scan is needed to estimate gestational age, and such a scan is a standard requirement of routine antenatal care as recommended in 'Antenatal care' (NICE clinical guideline 62).[14] The GDG acknowledged that more time would be needed for scanning in twin and triplet pregnancies; however, the cost impact and opportunity costs of the additional time needed were thought to be negligible.

Quality of evidence

The available evidence was limited in quantity and quality. No randomised controlled trials (RCTs) were identified and most of the included studies were retrospective in design, using a variety of different methodologies (for example, categorical versus continuous representation of gestational age, smaller and larger twins analysed independently or combined, size of fetus used to date pregnancy, head circumference versus crown–rump length). The quality of evidence for differences in fetal size in twin and triplet pregnancies versus singleton pregnancies was mainly very low. The quality of evidence for differences in dating of twin and triplet pregnancies versus singleton pregnancies was also mainly very low, as was the quality of evidence for prediction of growth discordance and accuracy of dating.

Other considerations

The majority of the studies did not report chorionicity or ethnicity. Only one study considered triplets, with the other studies concentrating on twins. This review question addressed whether there are differences in dating or the size of singleton versus twin or triplet pregnancies that should be taken into account when calculating gestational age in clinical practice. In view of the limitations of the evidence, the GDG based its recommendation on consensus within the group and highlighted the need for further research in this area. The GDG was of the view that estimating gestational age by ultrasound using crown–rump length (between 10 weeks 0 days and 14 weeks 1 day) or head circumference (from 14 weeks 0 days) as recommended for singleton pregnancies in 'Antenatal care' (NICE clinical guideline 62),[14] and incorporating recent changes to the gestational age ranges appropriate for use of crown–rump length and head circumference (see NHS Fetal Anomaly Screening Programme [FASP] programme statement 2010/02[*]) would be appropriate in twin and triplet pregnancies.

Screening for Down's syndrome is best undertaken when crown–rump length is between 45 mm and 84 mm (11 weeks 2 days and 14 weeks 1 day; see the FASP programme statement and Section 6.1). From a practical point of view, if Down's syndrome screening is requested by the woman, it makes sense to perform it at the same first-trimester ultrasound scan as the estimation of gestational age and determination of chorionicity. The best interval for performing all three tests together is, therefore, when crown–rump length is between 45 mm and 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days). In practice, it may not be possible to schedule all three tests at the same appointment, and in such circumstances more than one appointment in a short period may be needed. Furthermore, it is important that adequate time is given to allow for the additional counselling required regarding Down's syndrome screening once a multiple pregnancy has been identified. Also, some women may have their first scan as early as 10 weeks 0 days (in accordance with 'Antenatal care' NICE clinical guideline 62),[14] in which case they would need a separate appointment for Down's syndrome screening, if requested. However, if the woman is known in advance to have a twin or triplet pregnancy (for example, if such a pregnancy results from IVF treatment) it may be possible to plan to schedule all three tests in a single appointment. The GDG emphasised the importance of ensuring timely referral to maternity services in the first trimester, so that women with twin and triplet pregnancies have the opportunity to access first-trimester screening for Down's syndrome (which is strongly preferred to second-trimester screening for Down's syndrome; see Sections 5.4 and 6.1).

Evidence suggests that the mean twin measurement best reflects gestational age, both in the first and second trimester, whether using crown–rump length in the first trimester or head circumference in the second trimester. The GDG recommends using the larger twin measurement to determine gestational age (in the first half of pregnancy) because using the mean twin measurement would lead to an underestimate of gestational age if the smaller twin were pathologically undergrown. Similarly, the largest triplet measurement should be used to date triplet pregnancies.

Recommendations

This guideline should be read in conjunction with 'Antenatal care' NICE clinical guideline 62 (www.nice.org.uk/guidance/CG62). This guideline specifies the care that women with twin and triplet pregnancies should receive that is additional or different from routine antenatal care for women with

[*] See http://www.perinatal.nhs.uk/ultrasound/RUG/Programme_statement_-_The_use_of_CRL_and_NT_measurements_in_screening_for_Down%92s_syndrome_Sept2010.pdf

singleton pregnancies. Table 5.8 shows a comparison of the schedule of appointments for women with singleton pregnancies and women with multiple pregnancies.

Note that for many women the twin or triplet pregnancy will be detected only after their routine booking appointment.

The following terms are used in the recommendations.

- Dichorionic twin pregnancies: each baby has a separate placenta.
- Monochorionic diamniotic twin pregnancies: both babies share a placenta but have separate amniotic sacs.
- Monochorionic monoamniotic twin pregnancies: both babies share a placenta and amniotic sac.
- Trichorionic triplet pregnancies: each baby has a separate placenta and amniotic sac.
- Dichorionic triamniotic triplet pregnancies: one baby has a separate placenta and two of the babies share a placenta; all three babies have separate amniotic sacs.
- Dichorionic diamniotic triplet pregnancies: one baby has a separate placenta and amniotic sac and two of the babies share a placenta and amniotic sac.
- Monochorionic triamniotic triplet pregnancies: all three babies share one placenta but each has its own amniotic sac.
- Monochorionic diamniotic triplet pregnancies: all three babies share one placenta; one baby has a separate amniotic sac and two babies share one sac.
- Monochorionic monoamniotic triplet pregnancies: all three babies share a placenta and amniotic sac.

Number	Recommendation
1	Offer women with twin and triplet pregnancies 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 (ideally, these should all be performed at the same scan; see 3 and 4).*
2	Use the largest baby to estimate gestational age in twin and triplet pregnancies to avoid the risk of estimating it from a baby with early growth pathology.

Number	Research recommendation
RR 1	How should gestational age be estimated in twin and triplet pregnancies? **Why this is important** Accurate documentation of gestational age in twin and triplet pregnancies is very important in ensuring that subsequent clinical management is timed appropriately. Addressing the proposed research question would improve methods used in clinical practice to determine appropriate timing of birth (for example, through elective birth). There was limited existing evidence and it was of low quality, with the evidence reviewed for the guideline showing that: there were no large studies on the use of singleton charts in twin and triplet pregnancies; there was conflicting evidence as to

* 'Antenatal care' (NICE clinical guideline 62) recommends determination of gestational age from 10 weeks 0 days. However, the aim in this recommendation is to keep to a minimum the number of scan appointments that women need to attend within a short time, especially if it is already known that a woman has a twin or triplet pregnancy.

which fetus should be used for dating twin and triplet pregnancies (the recommendation to use the larger or largest fetus was a consensus view rather than one supported by a strong evidence base); there were limited data on the impact of the use of the timing of oocyte retrieval versus the timing of embryo transfer on dating pregnancies resulting from in vitro fertilisation or other assisted reproduction techniques (although existing data suggested that date of oocyte retrieval date is used more frequently than date of embryo transfer); dating by crown–rump length may be accurate and simpler to use than other fetal biometric measurements; the potential confounding effects of chorionicity and ethnicity have seldom been addressed in research studies. There is, therefore, a need for larger prospective studies to examine: the use of singleton charts in twin and triplet pregnancies; which fetus to use for dating twin and triplet pregnancies; the impact of date of ultrasound versus date of oocyte retrieval versus date of embryo transfer on dating twin and triplet pregnancies resulting from in vitro fertilisation or other assisted reproduction techniques; the effects of chorionicity and ethnicity on all of the above (as in singleton pregnancies, growth charts should be relevant for the population and its ethnicity). The research would be of medium importance in that it would improve and refine existing clinical practices, rather than resulting in major changes to NICE guidance.

4.2 Chorionicity

Introduction

Pregnancy risks, clinical management and subsequent outcomes are very different for monochorionic and dichorionic twin pregnancies (and monochorionic, dichorionic and trichorionic triplet pregnancies). Currently, there appears to be considerable variation and uncertainty in the practice of assigning chorionicity for twin and triplet pregnancies, leading to the GDG prioritising this question for review. Diagnostic accuracy of various methods for determining chorionicity in twin and triplet pregnancies at different gestational ages was sought.

Review question

What is the optimal method to determine chorionicity in multiple pregnancies?

Existing NICE guidance

No existing NICE guidance was identified as being relevant to this review question.

Description of included studies

Fourteen studies investigating diagnostic accuracy of the following characteristics (as determined by an ultrasound scan) for determining chorionicity were identified for inclusion[38-51]:

- membrane thickness
- number of membrane layers
- number of placental sites and lambda/T-sign
- composite measures based on the above characteristics and others (number of placental masses, number of gestational sacs, concordant/discordant fetal sex and number of fetal poles).

Only two studies included triplets, and one of these included only one triplet pregnancy, meaning that sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs) and likelihood ratio statistics could not be calculated using the triplet data in the study.[50]

Six prospective cohort studies reported findings for using membrane thickness to determine chorionicity in twin pregnancies.[38;39;42;45-47] Thresholds for determining monochorionicity ranged from

1.0 mm to 2.0 mm, and some studies reported results for different thresholds within the same publication. One study was conducted in the UK,[39] one in Belgium[45] and four in the USA.[38;42;46;47]

Four prospective cohort studies reported on using the number of placental masses and a lambda or T-sign for determining chorionicity in twin pregnancies.[38;39;45;49] One study was conducted in the UK,[39] one in Belgium,[45] one in the USA[38] and one in Canada.[49]

One prospective cohort study reported on using the number of membrane layers to determine chorionicity in twin pregnancies.[48] This study was conducted in Canada.

One prospective cohort study conducted in the USA reported on using the number of placental sites to determine chorionicity in twin pregnancies.[43] .

Seven studies reported findings for a mixture of methods for determining chorionicity in twin and triplet pregnancies.[39-41;44;49-51] Five studies were prospective cohort studies of twin pregnancies,[39;41;49-51] one was a retrospective cohort study of twin pregnancies[40] and one was a prospective cohort study of triplet pregnancies.[44] Two studies were conducted in the UK,[39;41] one in France,[44] one in Canada[49] and three in the USA.[40;50;51]

Published health economic evidence

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

Evidence profiles

Evidence profiles for this question are presented in Tables 4.3 to 4.5.

Table 4.3 presents data from scans performed at 11–14 weeks of gestation, which is when the first ultrasound scan is performed in general UK practice. Table 4.4 presents data from scans performed after 14 weeks of gestation, which best represents the gestational age at which women would be scanned if they missed the scan at 11–14 weeks. Table 4.5 presents data from scans performed before 11 weeks of gestation, and from studies that reported data for a wide range of gestational ages without reporting the mean gestational age at the time of the scan; these data are less applicable to UK practice.

Results for twin pregnancies are expressed in terms of detection of monochorionicity. For example, diagnostic accuracy values for the lambda sign are reported as absence of the sign (which suggests monochorionicity) rather than presence of the sign (which suggests dichorionicity).

Results for triplet pregnancies are expressed in terms of detection of a monochorionic or dichorionic triplet pregnancy, rather than a trichorionic pregnancy.

Table 4.3 GRADE summary of findings for scans performed at 11–14 weeks of gestation

Number of studies	Number of twin pregnancies	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Membrane thickness						
1[38]	105	95 (75 to 100)	96 (90 to 99)	27 (9 to 82)	0.1 (0.0 to 0.4)	Moderate
1[38]	105	100 (83 to 100)	92 (84 to 97)	12 (6 to 25)	0.0 (NC)	Moderate
1[39]	140	100 (89 to 100)	94 (89 to 98)	15 (8 to 32)	0.0 (NC)	Low
Number of placental masses and Lambda or T-Sign						
3[38-40]	502	93 (87 to 97)	79 (75 to 83)	18 (0 to 1000)	0.2 (0.0 to 1.7)	Very low
Composite measures						
Membrane thickness and number of placental masses and Lambda or T-sign?						
1[39]	140	100 (89 to 100)	92 (85 to 96)	12 (6 to 22)	0.0 (NC)	Low
Lambda or T-sign and number of placental masses, and concordant/discordant fetal sex						
1[41]	96	100 (84 to 100)	99 (96 to 100)	75 (11 to 526	0.0 (NC)	Low

Table 4.4 GRADE summary of findings for scans performed at more than 14 weeks of gestation

Number of studies	Numbers of twin and triplet pregnancies	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Membrane thickness						
1[42]	44 twin 0 triplet	76 (29 to 96)	86 (71 to 95)	5 (2 to 14)	0.3 (0.1 to 1.1)	Very low
Number of placental sites						
1[43]	66 twin 0 triplet	100 (87 to 100)	33 (19 to 49)	1 (1 to 2)	0.0 (NC)	Moderate
Composite methods						
Number of placental masses and Lambda or T-sign and concordant or discordant fetal sex						
1[41]	42 twin 0 triplet	77 (54 to 100)	90 (79 to 100)	7 (2 to 23)	0.9 (0.8 to 1.0)	Very low
1[40]	163 twin 0 triplet	88 (79 to 97)	95 (91 to 99)	17 (8 to 36)	0.1 (0.1 to 0.3)	Very low
Membrane thickness, number of placental masses and Lambda or T-sign, and concordant or discordant fetal sex						
1[44]	0 twin 50 triplet	94 (73 to 100)	94 (79 to 99)	15 (4 to 58)	0.1 (0.0 to 0.2)	Moderate

Table 4.5 GRADE summary of findings for scans performed before 11 weeks of gestation or over a wide range of gestational ages with no mean age reported

Number of studies	Numbers of twin and triplet pregnancies	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Membrane thickness						
1[45]	82	100 (59 to 100)	94 (86 to 98)	17(7 to 45)	0.0 (NC)	Very low
1[46]	54	25 (5 to 57)	90 (77 to 97)	3 (1 to 10)	0.8 (0.6 to 1.2)	low
1[47]	75	74 (55 to 88)	89 (75 to 96)	7 (3 to 15)	0.3 (0.2 to 0.5)	Moderate
Number of membrane layers						
1[48]	69	100 (90 to 100)	98 (90 to100)	52 (7 to 362)	0.0 (NC)	Moderate
Number of placental masses and Lambda or T-sign						
1[45]	82	100 (69 to 100)	44 (32 to 55)	2 (1 to 2)	0.0 (NC)	Low
1[49]	45	89 (52 to 100)	94 (81 to 99)	16 (4 to 63)	0.1(0.0 to 0.8)	Low
Composite measures						
Membrane thickness and number of placental masses						
1[50]	33	100 (66 to 100)	100 (85 to 100)	500 (3 to 711)	0.0 (0 to 0.8)	Moderate
Membrane thickness, number of placental sites and Lambda or T-sign, number of gestational sacs and number of fetal poles						
1[51]	47	100 (29 to 100)	100 (92 to100)	1000 (5 to 1271)	0.0 (0.0 to 1.7)	Low

Evidence statement

Evidence was identified for a variety of methods used to determine chorionicity from ultrasound scans in twin and triplet pregnancies.

The sensitivity and specificity of the methods used to determine chorionicity from ultrasound scans is generally high. Over half of the reported methods achieved both a sensitivity and specificity over 90%.

At a mean or median gestational age of 11–14 weeks at the time of scan, diagnostic accuracy statistics were reported for membrane thickness (low and moderate quality evidence), the number of placental masses and lambda/T-sign (very low quality evidence), and two different composite methods (low quality evidence). The strongest likelihood ratios were reported for a composite method involving lambda/T-sign and number of placental masses with or without concordant/discordant fetal sex. The sensitivity for this test was also high.

For a mean or median gestational age of more than 14 weeks at the time of scan, results were reported for the use of membrane thickness (very low quality evidence), the number of placental sites (moderate quality evidence) and two different composite methods (very low and moderate quality evidence). Composite methods (number of placental masses and lambda/T-sign, and concordant/discordant fetal sex with or without membrane thickness) showed the strongest likelihood ratios. The highest sensitivity was reported when membrane thickness was included in the composite method.

Some studies reported findings for a gestational age of less than 11 weeks or over a wide range of gestational ages with no mean age reported. Results were reported for membrane thickness (very low to moderate quality evidence), number of membrane layers (moderate quality evidence), the number of placental masses and lambda/t-sign (low quality evidence), and composite methods (low to moderate quality evidence). The composite methods showed the strongest likelihood ratios and high sensitivity. These methods used membrane thickness and number of placental masses, with or without lambda/T-sign, number of gestational sacs and number of fetal poles.

The GDG is aware that the evidence presented may be biased due to analysis after the study concluded for patterns that were not specified before the study, particularly in studies that examined individual methods such as membrane thickness. In these studies, it is not clear how a clinician determining chorionicity on one measure alone (such as subjectively thin or thick membrane) would not be influenced by other aspects of the ultrasound scan (such as the number of gestational sacs).

Health economics profile

No published health economic analyses were identified and this question was not prioritised for health economic analysis as part of the development of the guideline. The various measures based on ultrasound scans which were evaluated in terms of diagnostic accuracy could all be obtained from a single scan, and so the costs associated with undertaking individual and composite measures are likely to be similar.

Evidence to recommendations

Relative value placed on the outcomes considered

Sensitivity is the percentage of pregnancies found to be monochorionic at placental examination that were predicted to be monochorionic at scan (true positive). One hundred minus sensitivity (100 – sensitivity) is the percentage of pregnancies found to be monochorionic at placental examination that were predicted to be dichorionic at scan (false negative).

Specificity is the percentage of pregnancies found to be dichorionic at placental examination that were predicted to be dichorionic at scan (true negative). One hundred minus specificity (100 – specificity) is the percentage of pregnancies found to be dichorionic at placental examination that were predicted to be monochorionic at scan (false positive).

PPV is the percentage of pregnancies predicted to be monochorionic by the scan that were confirmed at placental examination to be monochorionic. One hundred minus PPV (100 – PPV) is the percentage of pregnancies predicted to be monochorionic by the scan result that were confirmed at placental examination to be dichorionic.

NPV is the percentage of pregnancies predicted to be dichorionic by the scan that were confirmed at placental examination to be dichorionic. One hundred minus NPV (100 – NPV) is the percentage of pregnancies predicted to be dichorionic by the scan that were confirmed at placental examination to be monochorionic.

The positive likelihood ratio (LR^+) shows how much the odds of a pregnancy being monochorionic increase when a scan predicts monochorionicity. The negative likelihood ratio (LR^-) shows how much the odds of a pregnancy being monochorionic decrease when a scan predicts dichorionicity.

The GDG prioritised likelihood ratios and sensitivity when considering the evidence for different methods of predicting chorionicity. They considered a sensitivity of less than 75% to be an imprecise test, and this is reflected in the GRADE profiles for this review question.

Trade-off between clinical benefits and harms

Determination of chorionicity is required to correctly stratify perinatal risk according to the type of twin or triplet pregnancy. Since pregnancy risks, clinical management and subsequent outcomes are very different for monochorionic and dichorionic twin pregnancies (and monochorionic, dichorionic and trichorionic triplet pregnancies), accurately determining chorionicity is very important.

Monochorionic twin pregnancies have a higher risk of developing complications, including feto-fetal transfusion syndrome (FFTS), fetal growth problems, structural abnormalities and overall perinatal loss compared with dichorionic twin pregnancies. The assessment of chorionicity is easier in the first trimester than in later pregnancy and so it is important to assess and document chorionicity clearly at this gestational age. There is benefit in identifying true positives as women with monochorionic pregnancies will require additional fetal surveillance. Women can make decisions fully informed of risks and appropriate management of monochorionicity can be implemented.

Identification of true negatives (women with dichorionic pregnancies) will result in a saving of time and money by avoiding unnecessary additional interventions. False positives will result in additional and unnecessary monitoring, anxiety and cost in women with dichorionic pregnancies.

False negatives have the least desirable outcome, as monochorionic pregnancies will be monitored less, increasing the likelihood of missing serious complications. Furthermore women with false negative test results will not be informed about these potential risks and the consequences.

The trade-off between clinical benefits and harms is unaffected by the choice of methods for determining chorionicity since any measurements would be taken during a single ultrasound scan appointment.

Trade-off between net health benefits and resource use

There is no cost difference between the methods themselves (except that composite methods might take more time for measurements to be conducted) as they can be done at the same ultrasound scan. A method that is more accurate will be more cost effective than less accurate methods if it means fewer women with dichorionic pregnancies receive unnecessary extra monitoring. The GDG emphasised that these scans will tie in to the existing NICE guidance for dating pregnancy and screening, and so the extra costs will be minimal.

Quality of evidence

The quality of evidence was summarised separately for scans done at different times.

For scans at 11–14 weeks:

- membrane thickness: quality ranged from low to moderate and was mainly moderate
- number of placental masses and lambda or T-sign: quality was very low
- composite measures: quality was low.

For scans at more than 14 weeks:

- membrane thickness: quality was very low
- number of placental sites: quality was moderate
- composite methods: quality was very low and moderate.

For scans at less than 11 weeks or at a wide range of gestational ages:

- membrane thickness: quality was very low to moderate
- number of membrane layers: quality was moderate
- number of placental masses and lambda or T-sign: quality was low
- composite measures: quality was moderate to low.

Other considerations

Only one study reported on diagnosing chorionicity in triplet pregnancies and this study evaluated only one method. The GDG assumed that the diagnostic accuracy of methods for determining chorionicity were similar for twin and triplet pregnancies. The GDG is aware that current practice for determining chorionicity involves a composite of methods and there are differences across England and Wales in timing of ultrasound scans. If a twin or triplet pregnancy is diagnosed before 11 weeks of gestation, determining chorionicity immediately using a composite of the number of placental masses, the presence of a lambda or T-sign and membrane thickness is as effective as waiting for the 11 weeks 0 days to 13 weeks 6 days scan. There is no evidence that the use of three-dimensional scans improves the accuracy of chorionicity determination. From a practical point of view it makes sense to perform estimation of gestational age, chorionicity and fetal trisomy screening at the same first-trimester ultrasound scan and the best interval for all three is 11 weeks 0 days to 13 weeks 6 days.

The GDG recognised the importance of assigning nomenclature to fetuses (for example upper and lower, or left and right) and documenting this clearly to ensure consistency throughout pregnancy.

The GDG also recognised the importance of training and support from senior colleagues to ensure that ultrasonographers can identify the presence of a lambda or T-sign accurately and confidently. In view of the potential consequences of failure to determine chorionicity at the time of diagnosis of the twin or triplet pregnancy (especially failure to identify monochorionic pregnancies correctly) the GDG's recommendations include the possibility of seeking advice from a senior colleague or referral for specialist advice (from a healthcare professional who is competent in determining chorionicity by ultrasound scan).

The GDG's discussions highlighted that many women with twin and triplet pregnancies are told that the risks associated with such pregnancies depend on zygosity whereas in fact the risks are dependent on chorionicity, and so the GDG identified this as a specific issue to be covered in training.

The GDG also recognised the importance of maternity networks (proposed in the NHS White Paper 'Equity and excellence: liberating the NHS'[*]) in establishing appropriate care pathways for all twin and triplet pregnancies, regardless of chorionicity. Since maternity networks are not yet in place throughout England and Wales, the GDG has used the term 'networks' in its recommendations, in accordance with the Department of Health guidance.[†] The GDG considered that special consideration should be given to monochorionic monoamniotic pregnancies (see Chapter 9 for further details).

Recommendations

Number	Recommendation
3	Determine 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.
4	Assign nomenclature to babies (for example, upper and lower, or left and right) in twin and triplet pregnancies and document this clearly in the woman's notes to ensure consistency throughout pregnancy.

[*] Available at http://www.dh.gov.uk/en/Healthcare/LiberatingtheNHS/index.htm
[†] Available at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_107845

5 If a woman with a twin or triplet pregnancy presents after 14 weeks 0 days, determine chorionicity at the earliest opportunity by ultrasound using all of the following:

- the number of placental masses
- the lambda or T-sign
- membrane thickness
- discordant fetal sex.

6 If it is not possible to determine chorionicity by ultrasound at the time of detecting the twin or triplet pregnancy, seek a second opinion from a senior ultrasonographer or offer the woman referral to a healthcare professional who is competent in determining chorionicity by ultrasound scan as soon as possible.

7 If it is difficult to determine chorionicity, even after referral (for example, because the woman has booked late in pregnancy), manage the pregnancy as monochorionic until proved otherwise.

8 Provide regular training so that ultrasonographers can identify the lambda or T-sign accurately and confidently. Less experienced ultrasonographers should have support from senior colleagues.

9 Training should cover ultrasound scan measurements needed for women who book after 14 weeks 0 days and should emphasise that the risks associated with twin and triplet pregnancies are determined by chorionicity and not zygosity.

10 Conduct regular clinical audits to evaluate the accuracy of determining chorionicity.

11 If transabdominal ultrasound scan views are poor because of a retroverted uterus or a high body mass index (BMI), use a transvaginal ultrasound scan to determine chorionicity.

12 Do not use three-dimensional ultrasound scans to determine chorionicity.

13 Networks should agree care pathways for managing all twin and triplet pregnancies to ensure that each woman has a care plan in place that is appropriate for the chorionicity of her pregnancy.

Number — Research recommendation

RR 2 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?

Why this is important

Expected outcomes in twin and triplet pregnancies vary greatly depending on chorionicity. Thus, chorionicity needs to be determined accurately to guide the clinical management of twin and triplet pregnancies and to inform women and their partners about risks specific to their pregnancies. Existing evidence for the accuracy of methods of determining chorionicity in twin and triplet pregnancies is limited in quantity (particularly in the case of triplet pregnancies), and little of it is of high quality. Moreover, few studies have examined the effect of operator experience on the accuracy of methods for determining chorionicity. There might be direct implications for clinical staff and resources required for service provision if the conclusions from future research were different to current recommendations. The research question is of medium importance to the guideline since it is unlikely to change future updates substantially. The research is unlikely to alter the recommendations of the guideline, but would strengthen the existing evidence base.

5 General care

5.1 Information and emotional support

Introduction

Due to the significant risks associated with twin and triplet pregnancies, their management in the antenatal period represents a challenge for the healthcare professionals involved. The benefit of providing additional information and emotional support to women with twin and triplet pregnancies during the antenatal period has been emphasised in recent research. Moreover, the inconsistency and variability of services across the UK led the GDG to prioritise this as an area for providing guidance. In determining the prioritisation, the GDG noted the importance of antenatal risk factors for perinatal mental health problems.

Review question

Is there benefit in giving women with multiple pregnancy additional information and emotional support during the antenatal period?

Existing NICE guidance

'Antenatal care' (NICE clinical guideline 62)[14] contains no recommendations about the benefit in giving women with multiple pregnancy additional information and emotional support during the antenatal period.

'Antenatal and postnatal mental health' (NICE clinical guideline 45)[15] provides guidance on the recognition and management of mental health problems during pregnancy and in the first year after giving birth, but none of the recommendations is specific to multiple pregnancy.

Description of included studies

Three studies[52-54] investigating the benefit of giving women with twin pregnancies additional information and emotional support during the antenatal period were identified for inclusion.

Two studies[52;54] were prospective observational studies and the third[53] was a retrospective observational study. All of the studies were conducted in the USA.

The three studies[52-54] compared a specialist care programme with standard (routine) antenatal care. In all three studies, the study group received advice regarding diet and signs of preterm labour as part of the specialist programme. However, the contribution of education and emotional support in comparison to other additional input was not reported clearly. The control group in the three studies was standard (routine) antenatal care.

No studies reporting on the effects of additional information and support for women with triplet pregnancies were identified.

Published health economic evidence

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

Evidence profiles

The evidence profile for this question is presented in Table 5.1.

Table 5.1 GRADE summary of findings for effectiveness of giving women with twin pregnancies additional information and emotional support

Number of studies	Specialist clinics	Normal clinics	Relative effect (95% confidence interval)	Absolute effect	Quality
Maternal morbidity (including anxiety and depression)					
Anaemia (Hgb < 10mg/dl)					
1[52]	17/89 (19%)	11/51 (22%)	OR 0.85 (0.36 to 2.01)	25 fewer per 1000 (from 126 fewer to 140 more)	Very low
1[53]	5/30 (17%)	7/41 (17%)	OR 0.97 (0.27 to 3.4)	4 fewer per 1000 (from 118 fewer to 242 more)	Very low
Bleeding ≥ 20 weeks					
1[52]	2/89 (2%)	4/51 (8%)	OR 0.28 (0.05 to 1.47)	56 fewer per 1000 (from 74 fewer to 33 more)	Very low
1[54]	2/190 (1%)	2/339 (1%)	OR 1.78 (0.25 to 12.5)	5 more per 1000 (from 4 fewer to 63 more)	Very low
Caesarean section					
1[53]	12/30 (40%)	19/41 (46%)	OR 0.77 (0.29 to 2.00)	63 fewer per 1000 (from 263 fewer to 170 more)	Very low
1[52]	29/89 (33%)	15/51 (29%)	OR 1.16 (0.54 to 2.45)	32 more per 1000 (from 110 fewer to 217 more)	Very low
Gestational diabetes					
1[52]	6/89 (7%)	1/51 (2%)	OR 3.61 (0.42 to 30.9)	47 more per 1000 (from 11 fewer to 337 more)	Very low
1[53]	1/30 (3%)	0/41 (0%)	OR 1.12 (0.31 to 4.08)	1 more per 1000 (from 1 fewer to 1 more)	Very low
1[54]	8/190 (4%)	7/339 (2%)	OR 2.08 (0.74 to 5.8)	21 more per 1000 (from 5 fewer to 88 more)	Very low
Gestational hypertension					
1[53]	1/30 (3%)	0/41 (0%)	OR 1.12 (0.31 to 4.08)	1 more per 1000 (from 1 fewer to 1 more)	Very low
Pre-eclampsia					
1[52]	10/89 (11%)	4/51 (8%)	OR 1.16 (0.37 to 3.61)	34 more per 1000 (from 48 fewer to 157 more)	Very low
1[54]	15/190 (8%)	57/339 (17%)	OR 0.41 (0.23 to 0.75)	89 fewer per 1000 (from 37 fewer to 124 fewer)	Very low
Premature rupture of membranes					
1[52]	11/89 (12%)	13/51 (26%)	OR 0.40 (0.16 to 1.00)	131 fewer per 1000 (from 203 fewer to 0 more)	Very low

Number of studies	Specialist clinics	Normal clinics	Relative effect (95% confidence interval)	Absolute effect	Quality
1[54]	19/190 (10%)	84/339 (25%)	OR 0.35 (0.2 to 0.6)	148 fewer per 1000 (from 83 fewer to 186 fewer)	Very low
Preterm labour					
1[54]	44/190 (23%)	142/339 (42%)	OR 0.42 (0.28 to 0.62)	186 fewer per 1000 (from 110 fewer to 251 fewer)	Very low
Urinary tract infection					
1[52]	4/89 (5%)	3/51 (6%)	OR 0.75 (0.16 to 3.50)	14 fewer per 1000 (from 49 fewer to 121 more)	Very low
1[53]	2/30 (7%)	4/41 (10%)	OR 0.66 (0.11 to 3.86)	31 fewer per 1000 (from 86 fewer to 197 more)	Very low
Perinatal and neonatal mortality					
Perinatal mortality					
1[52]	1/178 (1%)	8/102 (8%)	OR 0.06 (0.009 to 0.53)	72 fewer per 1000 (from 33 fewer to 78 fewer)	Very low
1[53]	1/30 (3%)	2/41 (5%)	RR 0.68 (0.06 to 7.19)	16 fewer per 1000 (from 46 fewer to 236 more)	Very low
Perinatal and neonatal morbidity (including preterm birth)					
Anaemia					
1[54]	8/190 (4%)	44/339 (13%)	OR 0.31 (0.17 to 0.56)	90 fewer per 1000 (from 53 fewer to 105 fewer)	Very low
Antibiotics					
1[54]	80/190 (42%)	203/339 (60%)	OR 0.50 (0.37 to 0.67)	180 fewer per 1000 (from 99 fewer to 243 fewer)	Very low
Apnoea, bradycardia or cyanosis					
1[54]	13/190 (7%)	78/339 (23%)	OR 0.27 (0.17 to 0.44)	162 fewer per 1000 (from 114 fewer to 182 fewer)	Very low
Hyperbilirubinaemia					
1[54]	36/190 (19%)	98/339 (29%)	OR 0.56 (0.40 to 0.79)	100 fewer per 1000 (from 46 fewer to 149 fewer)	Very low
Intravenous fluids					
1[54]	72/190 (38%)	200/339 (59%)	OR 0.43 (0.32 to 0.57)	210 fewer per 1000 (from 139 fewer to 275 fewer)	Very low
Low birthweight					
1[54]	78/190 (41%)	217/339 (64%)	OR 0.39 (0.27 to 0.56)	231 fewer per 1000 (from 141 fewer to 316 fewer)	Very low

Number of studies	Specialist clinics	Normal clinics	Relative effect (95% confidence interval)	Absolute effect	Quality
Major neonatal morbidity (retinopathy of prematurity, necrotising enter-colitis, ventilator support, or intra-ventricular haemorrhage)					
1[54]	32/190 (17%)	108/339 (32%)	OR 0.44 (0.31 to 0.62)	151 fewer per 1000 (from 94 fewer to 192 fewer)	Very low
Mechanical ventilation					
1[54]	29/190 (15%)	102/339 (30%)	OR 0.41 (0.28 to 0.59)	150 fewer per 1000 (from 98 fewer to 193 fewer)	Very low
Necrotising enterocolitis					
1[54]	2/190 (1%)	10/339 (3%)	OR 0.21 (0.05 to 0.95)	20 fewer per 1000 (from 1 fewer to 28 fewer)	Very low
NICU admission					
1[52]	24/178 (14%)	39/102 (38%)	OR 0.35 (0.22 to 0.55)	247 fewer per 1000 (from 128 fewer to 262 fewer)	Very low
1[54]	82/190 (43%)	214/339 (63%)	OR 0.48 (0.36 to 0.64)	199 fewer per 1000 (from 108 fewer to 250 fewer)	Very low
Parenteral nutrition					
1[54]	25/190 (13%)	105/339 (31%)	OR 0.32 (0.22 to 0.46)	180 fewer per 1000 (from 139 fewer to 220 fewer)	Very low
Phototherapy					
1[54]	30/190 (16%)	125/339 (37%)	OR 0.34 (0.24 to 0.49)	210 fewer per 1000 (from 146 fewer to 246 fewer)	Very low
Patent ductus arteriosus					
1[54]	4/190 (2%)	17/339 (5%)	OR 0.37 (0.15 to 0.88)	30 fewer per 1000 (from 6 fewer to 42 fewer)	Very low
Preterm birth <37 weeks					
1[52]	69/89 (78%)	37/51 (73%)	OR 1.30 (0.59 to 2.87)	23 more per 1000 (from 116 fewer to 158 more)	Very low
1[54]	44/190 (23%)	142/339 (42%)	OR 0.45 (0.3 to 0.68)	187 fewer per 1000 (from 90 fewer to 241 fewer)	Very low
Preterm birth <36 weeks					
1[53]	38/60 (63%)	68/82 (83%)	OR 0.36 (0.16 to 0.77)	193 fewer per 1000 (from 40 fewer to 392 fewer)	Very low
1[54]	77/190 (41%)	180/339 (53%)	OR 0.62 (0.43 to 0.89)	126 fewer per 1000 (from 29 fewer to 204 fewer)	Very low
Preterm birth <32 weeks					
1[54]	14/190 (7%)	72/339 (21%)	OR 0.27 (0.15 to 0.51)	138 fewer per 1000	Very low

Number of studies	Specialist clinics	Normal clinics	Relative effect (95% confidence interval)	Absolute effect	Quality
				(from 91 fewer to 174 fewer)	
Preterm birth <30 weeks					
1[53]	0/30 (0%)	12/41 (29%)	Not calculable	Not calculable	Very low
1[52]	2/89 (2%)	9/51 (18%)	OR 0.29 (0.11 to 0.76)	154 fewer per 1000 (from 36 fewer to 153 fewer)	Very low
1[54]	6/190 (3%)	31/339 (9%)	OR 0.29 (0.11 to 0.76)	59 fewer per 1000 (from 20 fewer to 80 fewer)	Very low
Respiratory distress syndrome					
1[54]	34/190 (18%)	105/339 (31%)	OR 0.44 (0.31 to 0.62)	131 fewer per 1000 (from 92 fewer to 188 fewer)	Very low
Retinopathy of prematurity					
1[54]	2/190 (1%)	24/339 (7%)	OR 0.19 (0.07 to 0.50)	60 fewer per 1000 (from 34 fewer to 65 fewer)	Very low
Supplemental oxygen					
1[54]	53/190 (28%)	153/339 (45%)	OR 0.49 (0.36 to 0.67)	170 fewer per 1000 (from 96 fewer to 223 fewer)	Very low
Very low birthweight (<1500g)					
1[53]	5/30 (17%)	16/41 (39%)	OR 0.42 (0.17 to 1.03)	223 fewer per 1000 (from 292 fewer to 7 more)	Very low
1[52]	10/178 (6%)	27/102 (27%)	OR 0.21 (0.10 to 0.42)	209 fewer per 1000 (from 133 fewer to 230 fewer)	Very low
1[54]	9/190 (5%)	54/339 (16%)	OR 0.30 (0.15 to 0.61)	106 fewer per 1000 (from 56 fewer to 132 fewer)	Very low

Evidence statement

Evidence was identified from three studies that demonstrated benefit in giving women with twin pregnancies additional information and emotional support during the antenatal period. The evidence focused mainly on nutrition and awareness of preterm birth. It was not possible, however, to determine how much benefit was attributable to the additional information and support, as these interventions were given within specialist antenatal clinics. The quality of the evidence was low or very low for all included studies. No similar studies were identified for women with triplet pregnancies.

Maternal morbidity

There were significantly fewer women with preterm, prelabour rupture of membranes (two studies, very low quality) or preterm labour (one study, very low quality) in the group that received additional information and support compared with the group that received standard care.

There was no significant difference between the additional information and support group and the standard care group in the number of women with anaemia (two studies, very low quality), bleeding after 20 weeks of gestation (two studies, very low quality), gestational diabetes (three studies, very low quality), gestational hypertension (one study, very low quality) or urinary tract infection (two

studies, very low quality). There was also no significant difference in the caesarean section rate between the two groups (two studies, very low quality).

Mixed results were reported for pre-eclampsia (two studies, very low quality), with one study showing that significantly fewer women in the additional support and information group had pre-eclampsia compared with the control group (very low quality) and another study reporting no significant difference in the number of women with pre-eclampsia in each group (very low quality).

There was no evidence reported on affective disorders in women.

Perinatal and neonatal mortality

Mixed results were reported for perinatal mortality. One study reported that there were significantly fewer deaths in the information and support group (very low quality), while another study showed there was no significant difference between the groups in the number of deaths (very low quality).

The GDG believes that the significant results for mortality are likely to be consequences of the reduced rates of preterm birth associated with specialised care, rather than the measures representing independent outcomes.

No results were reported specifically for neonatal mortality.

Perinatal and neonatal morbidity

The number of preterm births was significantly lower in the additional information and support group in most studies (three studies, very low quality). This significant difference was present for preterm birth at 36 weeks of gestation (two studies, very low quality), 32 weeks of gestation (one study, very low quality) and 30 weeks of gestation (three studies, very low quality). For birth before 37 weeks, one study reported significantly fewer preterm births in the additional information and support group (very low quality evidence) while another reported that there was no significant difference between the groups in the number of births before 37 weeks (very low quality evidence).

There were several other measures of perinatal and neonatal morbidity reported in the studies to be significantly lower in the specialised care group than the standard care group. The GDG believes that the significant results for these measures are likely to be consequences of the reduced rates of preterm birth associated with specialised care, rather than the measures representing independent outcomes.

No studies were identified that reported on breastfeeding, maternal satisfaction or maternal mortality. No studies reported on the effects of additional information and emotional support during triplet pregnancies.

No evidence was found that reported on parental education in the antenatal period for looking after twins and triplets, or on social networking for women with twin and triplet pregnancies.

Health economics profile

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

Evidence to recommendations

Relative value placed on the outcomes considered

The priority outcomes as specified in the protocol for this review question were:

- maternal morbidity (including anxiety and depression)
- perinatal and neonatal mortality
- perinatal and neonatal morbidity including preterm delivery
- breastfeeding
- maternal satisfaction
- maternal mortality.

The GDG's view is that morbidity is more prevalent than mortality, and so morbidity was prioritised as an outcome for consideration.

Trade-off between clinical benefits and harms

Giving women with multiple pregnancy additional information has the potential harm of making women more anxious; for example, informing them that their pregnancy is monochorionic may lead them to believe that they are at high risk, even if they do not develop complications. There needs to be a balance of good quality, honest information that does not induce anxiety. Good emotional support is needed in antenatal care, with an appropriate mechanism for referral to specialist perinatal services that track holistically throughout the pregnancy and avoid unnecessary stigma or medicalisation of pregnancy. The GDG placed a high value on the 'normalisation' of twin and triplet pregnancies throughout the development process and this is reflected in its recommendations.

Trade-off between net health benefits and resource use

The cost of providing information and support is dependent on its quantity and method of delivery and the cost of providing extra professional input has resource implications. Potential harm caused by unnecessary contact with healthcare professionals could lead to unnecessary intervention and maternal anxiety. Benefits include improved outcomes, particularly perinatal morbidity.

Quality of evidence

The quality of the evidence was summarised as:

- maternal morbidity: quality was very low
- perinatal and neonatal mortality: quality was very low
- perinatal and neonatal morbidity: quality was very low.

Other considerations

It was not possible to determine whether there was a difference in the effect of additional information and support in twin and triplet pregnancies of different chorionicities. Currently, women with twin and triplet pregnancies are given extra information and support, but the content and quantity varies across England and Wales. There is potential for a positive effect of continuity of care, including establishing rapport through repeated contact with the same healthcare professionals throughout pregnancy. All of the reported evidence focused on avoiding negative outcomes rather than working towards positive ones.

No evidence was identified that allowed the GDG to address the benefits of information and emotional support on the mental health of women with twin or triplet pregnancies, although the GDG recognised the importance of identifying mental health problems antenatally, and so the GDG was unable to make specific recommendations in this area. Having a twin or triplet pregnancy is a risk factor for postnatal mental health problems for which early identification is desirable and plans for management in the postnatal period should be communicated to relevant healthcare professionals. Although postnatal care is outside the scope of this guideline, the GDG's view is that mental health problems can be identified antenatally and treatment can be started during pregnancy, and the GDG included a research recommendation highlighting the need for further research to determine exactly what information and support should be provided for women with twin and triplet pregnancies.

The GDG recognised that women can access information from various sources, including the Internet, and that they may find inaccurate information that could provoke anxiety. Healthcare professionals should be aware that women in their care may have access to poor information.

The scope of the guideline required the GDG to specify the schedule for antenatal appointments for women with twin and triplet pregnancies and its recommendations were based on consideration of the available evidence and pragmatism, seeking to avoid the need for women to attend several different appointments when visits for different purposes could be combined into a single appointment. The GDG recognised that women with triplet pregnancies tend to give birth even earlier than women with twin pregnancies, and so the recommended number of appointments for women with triplet pregnancies is less than for women with twin pregnancies (but apart from this, they would receive care similar to that received by women with monochorionic twin pregnancies). Provision for appropriate surveillance in twin and triplet pregnancies that extends beyond the expected number of

antenatal appointments (for example, if an offer of early elective delivery was declined) was also addressed in the GDG's recommendations. The recommendations relating to the schedule of antenatal appointments, the provision of information and support specific to twin and triplet pregnancies at the first contact with the woman, and ongoing opportunities for further discussion and advice (covering topics such as antenatal and postnatal mental health and wellbeing) are presented in Section 5.3. A recommendation for further research relating to information and emotional support is presented below.

Recommendations

Number	Recommendation
14	Explain sensitively the aims and possible outcomes of all screening and diagnostic tests to women with twin and triplet pregnancies to minimise their anxiety.

Number	Research recommendation
RR 3	Does additional information and emotional support improve outcomes in twin and triplet pregnancies? Why this is important The guideline review identified insufficient evidence to determine the clinical and cost effectiveness of several specific aspects of information giving and emotional support in twin and triplet pregnancies. The evidence that was identified was generally of low quality. Outstanding research questions include: • What is the effectiveness of information and emotional support in improving maternal satisfaction and psychological wellbeing, and in increasing the uptake of breastfeeding? • Should different information and support be offered according to the chorionicity of the pregnancy? Well-designed prospective studies (including randomised controlled trials or observational studies, and qualitative research to elicit views and experiences of women with twin and triplet pregnancies) should be conducted to inform future NICE guidance.

5.2 Nutritional supplements

Introduction

It is often assumed that women with twin or triplet pregnancies require additional dietary intake and supplements to reduce the additional risks associated with such pregnancies. Women are often advised to increase their dietary intake and aim for specific weekly weight gain to optimise pregnancy outcomes. In addition, nutritional supplements, particularly iron and folic acid, are often prescribed routinely to women with twin or triplet pregnancies to prevent anaemia. The rationale for this is that anaemia is more common in such pregnancies and, given the higher risk of operative delivery and postpartum haemorrhage, more emphasis is placed on optimising haemoglobin levels in preparation for this risk. Such practice may result in women experiencing unnecessary worry and pressure and unwanted side effects, and women and the NHS incurring additional cost.

Review question

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?

Existing NICE guidance

'Antenatal care' (NICE clinical guideline 62)[14] recommends daily supplementation with folic acid until 12 weeks of gestation for women planning to become pregnant, as this reduces the risk of neural tube defects. This clinical guideline also recommends daily supplementation with vitamin D during pregnancy and breastfeeding for all women, especially those at greatest risk of vitamin D deficiency.

'Antenatal care' (NICE clinical guideline 62)[14] recommends against routine supplementation with iron for healthy women with singleton pregnancies (because there is no benefit for the woman or baby and it can cause unpleasant side effects for the woman), and against supplementation with vitamin A (because of teratogenicity).

'Hypertension in pregnancy' (NICE clinical guideline 107)[20] recommends that supplementation with magnesium, folic acid, vitamins C and E, fish oils, algal oils or garlic is not used solely with the aim of preventing hypertensive disorders during pregnancy. This guideline does not contain any recommendations regarding calcium supplementation for preventing pre-eclampsia, but identified this as a priority for further research.

'Maternal and child nutrition' (NICE public health guidance 11)[25] provides guidance for midwives, health visitors, pharmacists and other primary care services to improve the nutrition of pregnant and breastfeeding mothers (and children in low income households). It recommends discussing the woman's diet and eating habits with her early in pregnancy, and identifying and addressing any concerns she may have about her diet. It also recommends providing information on the benefits of a healthy diet and practical advice on how to eat healthily throughout pregnancy. Information should be tailored to the woman's circumstances, and advice should include eating five portions of fruit and vegetables a day and one portion of oily fish a week. The guidance contains no recommendations that are specific to multiple pregnancy.

Description of included studies

Three studies assessing the effectiveness of dietary supplements were identified for inclusion.[55-57] All three studies reported on women with twin pregnancies. No study was identified which reported on women with triplet pregnancies. No subgroup analysis by chorionicity was reported.

One retrospective cohort study evaluated the impact of the Higgins Nutrition Intervention Program among women with twin pregnancies.[55] The programme involved a daily intake of an additional 1000 calories and an additional 50 g of protein for women with twin pregnancies after 20 weeks of gestation. The study was conducted in Canada.

One multicentre, placebo-controlled, double-blind randomised controlled trial (RCT) assessed the effectiveness of daily supplementation with vitamins C and E among women at risk of pre-eclampsia.[56] The trial was conducted in antenatal clinics and hospitals in India, Peru, South Africa and Vietnam. Twin pregnancies were included and data for twins were extracted for the guideline review.

One European multicentre RCT reported on the effectiveness of fish oil on reducing fetal growth restriction and maternal hypertension.[57] The trial was conducted in 19 centres in the UK, the Netherlands, Norway, Sweden, Denmark, Belgium, Italy and Russia. Twin pregnancies were included and data for twins were extracted for the guideline review.

No studies were identified that investigated the effectiveness of supplementation with iron, folic acid, calcium, magnesium or other supplements or vitamins, including homeopathic or herbal supplements, in improving maternal health and wellbeing in women with twin and triplet pregnancies.

Published health economic evidence

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

Evidence profiles

The evidence profiles for this question are presented in Tables 5.2 to 5.4.

Table 5.2 GRADE summary of findings for effectiveness of daily intake of additional calories and protein in women with twin pregnancies

Number of studies	Additional nutrition group	Normal antenatal care group	Relative effect (95% confidence interval)	Absolute effect	Quality
Pre-eclampsia					
1[55]	21/177 (12%)	52/343 (15%)	OR 0.75 (0.44 to 1.30)	38 fewer per 1000 (from 85 fewer to 45 more)	Very low
Maternal weight gain (measured in kg; better indicated by higher values)					
1[55]	mean 18 (standard deviation 7) N = 177	mean 16 (standard deviation 6) N = 343	-	mean difference 2.00 higher (0.79 higher to 3.21 higher)	Low
Preterm birth					
Preterm birth <37 weeks					
1[55]	142/354 (40%)	322/686 (47%)	OR 0.68 (0.51 to 0.92)	94 fewer per 1000 (from 21 fewer to 158 fewer)	Low
Preterm birth <34 weeks					
1[55]	64/354 (18%)	110/686 (16%)	OR 0.96 (0.64 to 1.44)	5 fewer per 1000 (from 51 fewer to 55 more)	Very low
Birthweight (measured in g; better indicated by higher values)					
1[55]	mean 2468 (standard deviation 559) N = 354	mean 2378 (standard deviation 620) N = 686	-	mean difference 80.00 higher (P < 0.06)	Low

Table 5.3 GRADE summary of findings for effectiveness of daily supplementation with vitamins C and E in women with twin pregnancies

Number of studies	Daily vitamins	Placebo	Relative effect (95% confidence interval)	Absolute effect	Quality
Pre-eclampsia					
1[56]	23/81 (28.4%)	23/100 (23.0%)	1.2 (0.7 to 2.0)	46 more per 1000 (from 69 fewer to 230 more)	Low

Table 5.4 GRADE summary of findings for effectiveness of daily supplementation with fish oil in women with twin pregnancies

Number of studies	Fish oil group	Placebo group	Relative effect (95% confidence interval)	Absolute effect	Quality
Pre-eclampsia					
1[57]	14/246 (5.7%)	6/251 (2.4%)	OR 2.46 (0.93 to 6.52)	33 more per 1000 (from 2 fewer to 114 more)	Moderate
Preterm birth					
Preterm birth <37 weeks					
1[57]	129/286 (45.1%)	127/283 (47%)	OR 1.01 (0.73 to 1.40)	2 more per 1000 (from 76 fewer to 84 more)	Moderate
Preterm birth <34 weeks					
1[57]	37/286 (12.9%)	44/283 (15.5%)	OR 0.81 (0.50 to 1.29)	26 fewer per 1000 (from 71 fewer to 36 more)	Moderate

Number of studies	Fish oil group	Placebo group	Relative effect (95% confidence interval)	Absolute effect	Quality
Birthweight (measured in g; better indicated by higher values)					
1[57]	mean 2512 (standard deviation 627) N = 556	mean 2498 (standard deviation 599) N = 556	-	mean difference 8.20 higher (52.8 lower to 36.4 higher)	High

Evidence statement

The evidence was limited to three studies and the quality was mostly low. The studies addressed three types of dietary supplementation or manipulation in women with twin pregnancies: daily intake of additional calories and protein; daily supplementation with vitamins C and E; and daily supplementation with fish oil.

Daily intake of additional calories and proteins

There was no significant reduction in risk of pre-eclampsia among women with twin pregnancies who increased their daily intake of calories and proteins compared with women who had normal antenatal care (very low quality evidence). Women who received additional calories and proteins, however, had significantly greater weight gain in pregnancy (low quality evidence). They also had a significant reduction in risk for preterm birth before 37 weeks of gestation (low quality evidence), but not preterm birth before 34 weeks (very low quality evidence), which the GDG considered to be a more clinically important outcome.

The population that these results came from suggests that the women were more likely to be undernourished. It was not possible to separate out the direct effects of diet, and some of the significant results may be due in part to better overall antenatal care.

No results were reported for the effect of additional calories and protein on maternal anaemia, nausea and vomiting, heartburn, constipation, maternal satisfaction, maternal stress levels, mood swings, anxiety or depression.

Daily supplementation with vitamins C and E

There was no significant reduction in risk of pre-eclampsia among women with twin pregnancies who had daily vitamin C and E supplements compared with women who had no such supplements (low quality evidence).

No results were reported for the effect of daily vitamin C and vitamin E supplementation on maternal anaemia, nausea and vomiting, heartburn, constipation, maternal weight gain or loss, maternal satisfaction, maternal stress levels, mood swings, anxiety or depression, nor for preterm delivery or birthweight centile.

Daily supplementation with fish oil

There was no significant difference in the incidence of pre-eclampsia among women with twin pregnancies who had daily fish oil supplements compared with women who had olive oil (moderate quality evidence). There was no significant difference in preterm birth between the two groups (moderate quality evidence). Babies of women who took daily fish oil supplements showed no significant difference in birthweight compared with babies whose women received placebo (high quality evidence).

No results were reported for the effect of daily fish oil supplementation on maternal anaemia, nausea and vomiting, heartburn, constipation, maternal weight gain or loss, maternal satisfaction, maternal stress levels, mood swings, anxiety or depression.

No evidence was identified to address dietary supplementation or manipulation to prevent anaemia in twin or triplet pregnancies.

Health economics profile

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

Evidence to recommendations

Relative value placed on the outcomes considered

The GDG considered birthweight centile, preterm delivery, maternal anaemia and preeclampsia to be the most important outcomes.

Trade-off between clinical benefits and harms

There is a trade-off to be made between potential benefits and unwanted side effects, maternal anxiety and the cost to the women of buying extra food and supplements.

While women who are underweight or significantly overweight may benefit from individual dietary advice and supplementation, in general changes in diet and supplementation are not necessarily risk free.

Trade-off between net health benefits and resource use

There is evidence that dietary intervention in socially disadvantaged groups may improve outcomes. However, the GDG believed the evidence to be limited by bias in patient selection and multiple interventions. Care may be required relating to access to information via the Internet, especially the quality of such information. Women may experience increased stress from perceived risk to their own health and/or that of the fetuses, and financial burden due to nutritional supplementation based on unfounded advice. Where possible, healthcare professionals should direct women to information from evidence-based sources. There is a resource implication of providing nutritional supplements to pregnant women.

Quality of evidence

The quality of evidence for pre-eclampsia ranged from very low to moderate, but was mainly low. The quality of evidence for maternal weight gain was low. The quality of evidence for preterm delivery ranged from very low to moderate, but was mainly low. The quality of evidence for birthweight ranged from low to high, but was mainly low.

Other considerations

The population included in one of the studies may not be representative of the UK population. There is no evidence to support routine use of iron and folic acid supplementation in twin and triplet pregnancies but healthcare professionals need to be aware of the increased risk of iron-deficiency anaemia in this group of women. The GDG therefore included a recommendation for full blood counts to be undertaken at 20–24 weeks in women with twin and triplet pregnancies to identify women requiring early iron or folic acid supplementation.

The GDG's recommendations for diet and lifestyle advice (see Section 5.3) are also covered by the recommendations below.

Recommendations

Number	Recommendation
15	Give women with twin and triplet pregnancies the same advice about diet, lifestyle and nutritional supplements as in routine antenatal care.*
16	Be aware of the higher incidence of anaemia in women with twin and triplet pregnancies compared with women with singleton pregnancies.
17	Perform a full blood count at 20–24 weeks to identify women with twin and triplet pregnancies who need early supplementation with iron or folic acid, and repeat at 28 weeks as in routine antenatal care.†

* See 'Antenatal care' (NICE clinical guideline 62). Available from www.nice.org.uk/guidance/CG62

† This is in addition to the test for anaemia at the routine booking appointment; see 'Antenatal care' (NICE clinical guideline 62). Available from www.nice.org.uk/guidance/CG62

Number	Research recommendation
RR 4	Is dietary supplementation with vitamins or minerals, or dietary manipulation in terms of calorie intake, effective in twin and triplet pregnancies? **Why this is important** The evidence reviewed in the guideline in relation to dietary supplementation and calorie intake was limited in quantity and low in quality. Large, prospective randomised controlled trials are needed to evaluate the effectiveness of such interventions in terms of birthweight centile and rates of preterm delivery, maternal anaemia and pre-eclampsia in twin and triplet pregnancies. There is also a lack of evidence regarding the natural history of iron deficiency anaemia in twin and triplet pregnancies, and whether routine iron supplementation or folic acid is required in such pregnancies. Future research should seek to resolve uncertainty in these areas. The research should include consideration of whether ethnicity or socio-economic status affects the prevalence of iron deficiency anaemia in twin and triplet pregnancies.

5.3 Diet and lifestyle advice

Introduction

Adequate nutrition is important during pregnancy, and particularly so in multiple pregnancies.[58] Any nutritional problems that a woman has before or during the pregnancy can result in life-long consequences for the woman and her babies. Moreover, the lack of evidence-based information that women might receive led the GDG to prioritise this issue as a review question for the guideline. The question recognises the importance of assessing the effectiveness of nutritional advice specific to twin and triplet pregnancies in improving maternal and fetal health and wellbeing, and reducing the risk of providing the women with erroneous information.

Review question

Is nutritional advice specific to multiple pregnancies effective in improving maternal and fetal health and wellbeing?

Existing NICE guidance

'Antenatal care' (NICE clinical guideline 62)[14] identified good-quality evidence showing that intensive antenatal dietary counselling and support is effective in increasing women's knowledge about healthy eating and can have an impact on eating behaviours, but no evidence of an association between this and improved pregnancy outcomes was identified.

'Hypertension in pregnancy' (NICE clinical guideline 107)[20] recommends against dietary salt restriction during pregnancy solely with the aim of preventing gestational hypertension or pre-eclampsia.

'Weight management before, during and after pregnancy' (NICE public health guidance 27)[59] includes the following recommendations.

- Advise pregnant women to eat a low-fat diet and avoid increasing fat and/or calorie intake.
- Discuss eating habits at the earliest opportunity to determine whether the woman has any concerns about diet, and address any concerns identified.
- Advise women to seek information and advice on diet from a reputable source.
- Do not advise weight loss programmes during pregnancy.

- Work to dispel myths about what, and how much, pregnant women should eat (for example, advise pregnant women that there is no need to 'eat for two' or to drink full-fat milk).
- Explain that energy needs do not change in the first 6 months of pregnancy and they increase by only 200 calories a day in the last 3 months.
- At the booking appointment, offer pregnant women with a BMI of 30 kg/m2 or more a referral to a dietitian or appropriately trained healthcare professional for assessment and personalised advice on healthy eating.

Description of included studies

One study assessing the effectiveness of nutritional advice in twin pregnancies was identified for inclusion.[54] The study was conducted in the USA and evaluated the effect of the University of Michigan Multiples Clinic on twin pregnancy, neonatal outcomes and early childhood outcomes. Women were either referred to the clinic by a healthcare professional or self-referred, with the programme group receiving more visits and scans than the non-programme group.

In addition to their regular physician-directed antenatal care visits, women with twin pregnancies who participated in the programme received dietary advice from a registered dietitian and nurse practitioner once a fortnight. Depending on pre-pregnancy body mass index (BMI), women were advised to consume a total of 3000–4000 kcal/day, composed of 20% protein, 40% carbohydrates and 40% fat, and divided into three meals and three snacks daily. Other nutritional modifications emphasised were daily supplementation with calcium, magnesium, zinc and a multivitamin.

Published health economic evidence

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

Evidence profiles

The evidence profile for this question is presented in Table 5.5.

Table 5.5 GRADE summary of findings for effectiveness of nutritional advice specific to twin pregnancies

Number of studies	Nutritional advice group	Normal antenatal care group	Relative effect (95% confidence interval)	Absolute effect	Quality
Birthweight					
Birthweight (measured in g; better indicated by higher values)					
1[54]	190	339	-	MD 220 higher (P < 0.0001)	Very low
Low birthweight					
1[54]	78/190 (41%)	217/339 (64%)	OR 0.42 (0.29 to 0.61)	213 fewer per 1000 (from 120 fewer to 300 fewer)	Very low
Very low birthweight					
1[54]	10/190 (5%)	54/339 (16%)	OR 0.30 (0.15 to 0.61)	106 fewer per 1000 (from 56 fewer to 132 fewer)	Very low
Pre-eclampsia					
1[54]	15/190 (8%)	58/339 (17%)	OR 0.41 (0.23 to 0.75)	93 fewer per 1000 (from 37 fewer to 126 fewer)	Very low
Preterm birth					
Preterm birth <36 weeks					
1[54]	78/190 (41%)	180/339 (53%)	OR 0.62 (0.43 to 0.89)	119 fewer per 1000 (from 29 fewer to 204 fewer)	Very low
Preterm birth <32 weeks					
1[54]	13/190 (7%)	71/339 (21%)	OR 0.27 (0.15 to 0.51)	143 fewer per 1000 (from 90 fewer to 171 fewer)	Very low
Preterm birth <30 weeks					

Number of studies	Nutritional advice group	Normal antenatal care group	Relative effect (95% confidence interval)	Absolute effect	Quality
1[54]	6/190 (3%)	31/339 (9%)	OR 0.29 (0.11 to 0.76)	63 fewer per 1000 (from 20 fewer to 80 fewer)	Very low

Evidence statement

Some evidence (from a single study) was identified for the effectiveness of nutritional advice in women with twin pregnancies. The study was of very low quality (because of significant bias and methodological flaws in the analyses). It was not possible to assess the effect of nutritional advice separately from the effects of other advice. The women in the study group received more frequent care from designated healthcare professionals, which may have had an effect on outcomes.

Significantly fewer women developed pre-eclampsia in the group that received nutritional advice compared with the women who did not (very low quality evidence).

There was evidence that there were significantly fewer preterm births among women with twin pregnancies who received nutritional advice during antenatal care (very low quality evidence). There were also significant reductions in the risk of low birthweight and very low birthweight babies in the group that received nutritional advice (very low quality evidence), although this is likely to be a result of fewer preterm births.

No results were reported for the effect of nutritional advice on maternal anaemia, nausea and vomiting, heartburn, constipation, maternal weight gain or loss, maternal satisfaction, maternal stress levels, mood swings, anxiety or depression.

No evidence was identified in relation to specific dietary advice to be given to women of different ethnicities.

Health economics profile

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

Evidence to recommendations

Relative value placed on the outcomes considered

The GDG considered birthweight centile, preterm delivery, maternal anaemia and pre-eclampsia to be the most important outcomes.

Trade-off between clinical benefits and harms

While women who are underweight or significantly overweight benefit from individual dietary advice and supplementation, changes in diet and supplementation are not, in general, necessarily risk free.

Trade-off between net health benefits and resource use

The evidence is poor that focused advice is beneficial in terms of twin and triplet pregnancy outcomes. Care may be required relating to access of information via the Internet, especially in terms of the quality of such information. Women may experience increased stress, from perceived risk to their own health and that of the fetuses, and financial burden due to nutritional supplementation based on unfounded advice. Providing additional nutritional advice on the NHS would require increased funding. Where possible, healthcare professionals should direct women to information from evidence-based sources.

Quality of evidence

The quality of evidence for birthweight, preterm delivery and pre-eclampsia was very low.

Other considerations

No evidence was identified in relation to the effects of different advice for monochorionic twins and triplets, nor the effects of dietary advice on maternal anaemia or specific dietary advice to be given to women of different ethnicities. Specifically, there was no evidence examining whether increasing

calorific intake was of value. Thus the GDG's view was that it could only recommend the use of the existing guidance about diet and lifestyle contained in 'Antenatal care' (NICE clinical guideline 62).[14]

The GDG's recommendations in relation to diet and lifestyle advice are covered by the recommendations for nutritional supplements (see Section 5.2), although the GDG's research recommendations are listed below.

Research recommendation

Number	Research recommendation
RR 5	Is dietary advice specific to twin and triplet pregnancies effective in improving maternal and fetal health and wellbeing? **Why this is important** Dietary advice for women with singleton pregnancies is provided in 'Antenatal care' (NICE clinical guideline 62).[14] There is, however, an absence of evidence-based advice specific to twin or triplet pregnancies, and diets that may be encouraged currently (e.g. eating for two) may be harmful. The evidence reviewed for the guideline was poor in quality, biased, and did not include subgroup analyses taking into account chorionicity. Large, prospective, randomised controlled trials involving twin and triplet pregnancies, and with subgroup analyses for different chorionicities, are therefore needed to inform future guidance. Important outcomes to be considered in such studies include birthweight and rates of preterm birth, maternal anaemia and pre-eclampsia. The research should also consider the relevance and feasibility of tailoring dietary advice for women with twin and triplet pregnancies to specific ethnic groups. Health economic analyses to evaluate the cost effectiveness of providing dietary advice, and qualitative studies exploring women's views and experiences in relation to dietary advice (including the timing, frequency and medium of information provision) would also inform future guidance.

5.4 Specialist care

Introduction

This section focuses on specialist clinics, which, for the purposes of the guideline recommendations, are referred to as specialist care (since the GDG's intended meaning of the word 'clinic' in this context refers to the organisation of services, including the composition of the multidisciplinary care team, rather than to the physical location or time at which antenatal contacts with the team take place). In this guideline, the terms specialist obstetrician and specialist midwife refer to obstetricians and midwifes with a special interest, experience and knowledge of managing multiple pregnancies, and who work regularly with women with multiple pregnancies.

Twin and triplet pregnancies are associated with higher risks of maternal, fetal and neonatal complications which may lead to short- or long-term morbidity or mortality. Since these risks are communicated to women with twin or triplet pregnancies and their families, such pregnancies may be associated with significant psychosocial and economic consequences for the women and their partners. Delivery of antenatal care in such pregnancies may, therefore, require specific modification over and above standard (routine) care to reduce the risks and manage concerns or complications appropriately, should they arise.

There is currently a wide variation in how obstetric and midwifery care is provided for women with twin and triplet pregnancies. This review question examines the provision of specialist care for twin and triplet pregnancies, including frequency and duration of contact, type and seniority of healthcare professionals involved in providing care, and the components of specialist care that are most effective. The components considered here include emotional support, peer support, nutrition, additional information on preterm birth, and common complications of twin and triplet pregnancies.

Review question

Do specialist multiple pregnancy clinics improve outcomes in twin and triplet pregnancies?

Existing NICE guidance

'Antenatal care' (NICE clinical guideline 62)[14] includes the following recommendations relating to provision of antenatal care.

- Offer women with uncomplicated singleton pregnancies midwife- or GP-led models of care.
- Provide care through a small group of healthcare professionals with whom the woman feels comfortable, and ensure continuity of care throughout the antenatal period.
- Establish a clear system of referral paths so that pregnant women who require additional care are managed and treated by appropriate specialist teams.

Description of included studies

Three observational studies[52-54] (including 529, 140 and 71 twin pregnancies, respectively) and one large epidemiological study[60] (1,479,862 twin pregnancies) were identified as focusing on potential effects of specialist antenatal care for women with twin pregnancies. The specialist antenatal care provided in the studies included more frequent care, greater continuity of caregivers and/or more specialist healthcare professionals delivering care. Each study considered a different package of interventions, making it difficult to determine which specific elements affected outcomes. All of the studies were conducted in the USA. A Cochrane review reporting on the use of specialist multiple pregnancy antenatal care compared to standard antenatal care found no relevant RCTs.[61]

The three observational studies compared specialist twin care to standard (routine) antenatal care.[52-54] In all three studies, the women in the specialist antenatal care group received advice regarding diet and signs of preterm labour. In one study,[54] the specialist care group in one study also took nutritional supplements. The control group in all three studies comprised women receiving standard (routine) antenatal care during a twin pregnancy.

The large epidemiological study compared outcomes across groups that received different frequencies of antenatal care.[60]

All of the studies focused on twin pregnancies, with no results reported for triplet pregnancies. None of the studies considered psychosocial outcomes, such as satisfaction with care or maternal/paternal anxiety, depression or wellbeing, and none of the studies considered additional emotional or practical support for women with twin and triplet pregnancies.

Two of the studies reported that there were no significant differences in demographic features between the standard and specialised care groups.[52;53] However, one study reported that there were significantly more smokers and fewer women with private health insurance in the standard care group than the specialised care group.[54] The remaining study did not report on the demographic characteristics of the groups.[60]

Published health economic evidence

No published health economic evidence was identified, although this question was prioritised for health economic analysis.

Evidence profiles

The evidence profiles for this question are presented in Tables 5.6 and 5.7.

Table 5.6 GRADE summary of findings for comparisons based on case numbers in study and control groups

Number of studies	Specialist clinics	Normal clinics	Relative effect (95% confidence interval)	Absolute effect	Quality
Maternal morbidity (including anxiety and depression)					
Anaemia (Hgb < 10mg/dl)					
1[52]	17/89	11/51	OR 0.85	25 fewer per	Very Low

Number of studies	Specialist clinics	Normal clinics	Relative effect (95% confidence interval)	Absolute effect	Quality
	(19%)	(22%)	(0.36 to 2.01)	1000 (from 126 fewer to 140 more)	
1[53]	5/30 (17%)	7/41 (17%)	OR 0.97 (0.27 to 3.4)	4 fewer per 1000 (from 118 fewer to 242 more)	Very Low
Bleeding ≥ 20 weeks					
1[52]	2/89 (2%)	4/51 (8%)	OR 0.28 (0.05 to 1.47)	56 fewer per 1000 (from 74 fewer to 33 more)	Very low
1[54]	2/190 (1%)	2/339 (1%)	OR 1.78 (0.25 to 12.5)	5 more per 1000 (from 4 fewer to 63 more)	Very low
Caesarean section					
1[53]	12/30 (40%)	19/41 (46%)	OR 0.77 (0.29 to 2.00)	63 fewer per 1000 (from 263 fewer to 170 more)	Very low
1[52]	29/89 (33%)	15/51 (29%)	OR 1.16 (0.54 to 2.45)	32 more per 1000 (from 110 fewer to 217 more)	Very low
Gestational diabetes					
1[52]	6/89 (7%)	1/51 (2%)	OR 3.61 (0.42 to 30.9)	47 more per 1000 (from 11 fewer to 337 more)	Very low
1[53]	1/30 (3%)	0/41 (0%)	OR 1.12 (0.31 to 4.08)	1 more per 1000 (from 1 fewer to 1 more)	Very low
1[54]	8/190 (4%)	7/339 (2%)	OR 2.08 (0.74 to 5.8)	21 more per 1000 (from 5 fewer to 88 more)	Very low
Gestational hypertension					
1[53]	1/30 (3%)	0/41 (0%)	OR 1.12 (0.31 to 4.08)	1 more per 1000 (from 1 fewer to 1 more)	Very low
Pre-eclampsia					
1[52]	10/89 (11%)	4/51 (8%)	OR 1.16 (0.37 to 3.61)	34 more per 1000 (from 48 fewer to 157 more)	Very low
1[54]	15/190 (8%)	57/339 (17%)	OR 0.41 (0.23 to 0.75)	89 fewer per 1000 (from 37 fewer to 124 fewer)	Very low
Prelabour rupture of membranes					
1[52]	11/89 (12%)	13/51 (26%)	OR 0.40 (0.16 to 1.00)	131 fewer per 1000 (from 203 fewer to 0 more)	Very low
1[54]	19/190 (10%)	84/339 (25%)	OR 0.35 (0.2 to 0.6)	148 fewer per 1000 (from 83 fewer to 186 fewer)	Very low
Preterm labour					

Number of studies	Specialist clinics	Normal clinics	Relative effect (95% confidence interval)	Absolute effect	Quality
1[54]	44/190 (23%)	142/339 (42%)	OR 0.42 (0.28 to 0.62)	186 fewer per 1000 (from 110 fewer to 251 fewer)	Very low
Urinary tract infection					
1[52]	4/89 (5%)	3/51 (6%)	OR 0.75 (0.16 to 3.50)	14 fewer per 1000 (from 49 fewer to 121 more)	Very low
1[53]	2/30 (7%)	4/41 (10%)	OR 0.66 (0.11 to 3.86)	31 fewer per 1000 (from 86 fewer to 197 more)	Very low
Perinatal and neonatal mortality					
Perinatal mortality					
1[52]	1/178 (1%)	8/102 (8%)	OR 0.06 (0.01 to 0.53)	72 fewer per 1000 (from 33 fewer to 78 fewer)	Very low
1[53]	1/30 (3%)	2/41 (5%)	RR 0.68 (0.06 to 7.19)	16 fewer per 1000 (from 46 fewer to 236 more)	Very low
Neonatal morbidity					
Preterm birth < 37 weeks					
1[52]	69/89 (78%)	37/51 (73%)	OR 1.30 (0.59 to 2.87)	23 more per 1000 (from 116 fewer to 158 more)	Very low
1[54]	44/190 (23%)	142/339 (42%)	OR 0.45 (0.3 to 0.68)	187 fewer per 1000 (from 90 fewer to 241 fewer)	Very low
Preterm birth < 36 weeks					
1[53]	38/60 (63%)	68/82 (83%)	OR 0.36 (0.16 to 0.77)	193 fewer per 1000 (from 40 fewer to 392 fewer)	Very low
1[54]	77/190 (41%)	180/339 (53%)	OR 0.62 (0.43 to 0.89)	126 fewer per 1000 (from 29 fewer to 204 fewer)	Very low
Preterm birth < 32 weeks					
1[54]	14/190 (7%)	72/339 (21%)	OR 0.27 (0.15 to 0.51)	138 fewer per 1000 (from 91 fewer to 174 fewer)	Very low
Preterm birth < 30 weeks					
1[53]	0/30 (0%)	12/41 (29.3%)	NC	293 fewer per 1000	Very low
1[54]	6/190 (3%)	31/339 (9%)	OR 0.29 (0.11 to 0.76)	59 fewer per 1000 (from 20 fewer to 80 fewer)	Very low
1[52]	2/89 (2%)	9/51 (18%)	OR 0.29 (0.11 to 0.76)	154 fewer per 1000 (from 36 fewer to 153 fewer)	Very low
Anaemia					
1[54]	8/190 (4%)	44/339 (13%)	OR 0.31 (0.17 to 0.56)	90 fewer per 1000 (from 53 fewer to 105 fewer)	Very low

Number of studies	Specialist clinics	Normal clinics	Relative effect (95% confidence interval)	Absolute effect	Quality
Antibiotics					
1[54]	80/190 (42%)	203/339 (60%)	OR 0.50 (0.37 to 0.67)	180 fewer per 1000 (from 99 fewer to 243 fewer)	Very low
Apnoea, bradycardia or cyanosis					
1[54]	13/190 (7%)	78/339 (23%)	OR 0.27 (0.17 to 0.44)	162 fewer per 1000 (from 114 fewer to 182 fewer)	Very low
Hyperbilirubinaemia					
1[54]	36/190 (19%)	98/339 (29%)	OR 0.56 (0.40 to 0.79)	100 fewer per 1000 (from 46 fewer to 149 fewer)	Very low
Intravenous fluids					
1[54]	72/190 (38%)	200/339 (59%)	OR 0.43 (0.32 to 0.57)	210 fewer per 1000 (from 139 fewer to 275 fewer)	Very low
Low birthweight					
1[54]	78/190 (41%)	217/339 (64%)	OR 0.39 (0.27 to 0.56)	231 fewer per 1000 (from 141 fewer to 316 fewer)	Very low
Major neonatal morbidity (retinopathy of prematurity, necrotising enterocolitis, ventilator support, or intraventricular haemorrhage)					
1[54]	32/190 (17%)	108/339 (32%)	OR 0.44 (0.31 to 0.62)	151 fewer per 1000 (from 94 fewer to 192 fewer)	Very low
Mechanical ventilation					
1[54]	29/190 (15%)	102/339 (30%)	OR 0.41 (0.28 to 0.59)	150 fewer per 1000 (from 98 fewer to 193 fewer)	Very low
Necrotising enterocolitis					
1[54]	2/190 (1%)	10/339 (3%)	OR 0.21 (0.05 to 0.95)	20 fewer per 1000 (from 1 fewer to 28 fewer)	Very low
NICU admission					
1[52]	24/178 (14%)	39/102 (38%)	OR 0.35 (0.22 to 0.55)	247 fewer per 1000 (from 128 fewer to 262 fewer)	Low
1[54]	82/190 (43%)	214/339 (63%)	OR 0.48 (0.36 to 0.64)	199 fewer per 1000 (from 108 fewer to 250 fewer)	Very low
Parenteral nutrition					
1[54]	25/190 (13%)	105/339 (31%)	OR 0.32 (0.22 to 0.46)	180 fewer per 1000 (from 139 fewer to 220 fewer)	Very low
Phototherapy					
1[54]	30/190 (16%)	125/339 (37%)	OR 0.34 (0.24 to 0.49)	210 fewer per 1000 (from 146 fewer to 246 fewer)	Very low
Patent ductus arteriosus					
1[54]	4/190	17/339	OR 0.37	30 fewer per	Very low

Number of studies	Specialist clinics	Normal clinics	Relative effect (95% confidence interval)	Absolute effect	Quality
	(2%)	(5%)	(0.15 to 0.88)	1000 (from 6 fewer to 42 fewer)	
Respiratory distress syndrome					
1[54]	34/190 (18%)	105/339 (31%)	OR 0.44 (0.31 to 0.62)	131 fewer per 1000 (from 92 fewer to 188 fewer)	Very low
Retinopathy of prematurity					
1[54]	2/190 (1%)	24/339 (7%)	OR 0.19 (0.07 to 0.50)	60 fewer per 1000 (from 34 fewer to 65 fewer)	Very low
Small for gestational age (resulting in preterm birth)					
1[60]	14,365/165,120 (9%)	57,067/425,876 (13%)	OR 0.62 (0.60 to 0.63)	46 fewer per 1000 (from 45 fewer to 49 fewer)	Low
1[60]	23,117/165,120 (14%)	62,178/425,876 (15%)	OR 0.95 (0.94 to 0.97)	6 fewer per 1000 (from 4 fewer to 8 fewer)	Low
Small for gestational age (birth at term)					
1[60]	47,720/165,120 (29%)	93,693/425,876 (22%)	OR 1.44 (1.42 to 1.46)	69 more per 1000 (from 66 more to 72 more)	Low
1[60]	31,537/165,120 (19%)	72,399/425,876 (17%)	OR 5.08 (5.00 to 5.16)	340 more per 1000 (from 336 more to 344 more)	Low
Supplemental oxygen					
1[54]	53/190 (28%)	153/339 (45%)	OR 0.49 (0.36 to 0.67)	170 fewer per 1000 (from 96 fewer to 223 fewer)	Very low
Very low birthweight (< 1500g)					
1[53]	5/30 (17%)	16/41 (39%)	OR 0.42 (0.17 to 1.03)	223 fewer per 1000 (from 292 fewer to 7 more)	Very Low
1[52]	10/178 (6%)	27/102 (27%)	OR 0.21 (0.10 to 0.42)	209 fewer per 1000 (from 133 fewer to 230 fewer)	Very Low
1[54]	9/190 (5%)	54/339 (16%)	OR 0.30 (0.15 to 0.61)	106 fewer per 1000 (from 56 fewer to 132 fewer)	Very low

Table 5.7 GRADE summary of findings for comparison of case rates per 1000 live births

Number of studies	Women with twin and/or triplet pregnancies		Rate per 1000 Live Births			Quality
	Study sub group	Study population	Rate in study sub group	Study sub group	Z score	
Perinatal and neonatal mortality						
1[60] (data for 1983 to 1984)	165,120 intensive care	811,505 all care	27.6 (24.6 to 30.5)	50.0 (48.7 to 51.3)	Significant (P value not reported)	Low
1[60] (data for 1989 to 1990)	165,120 intensive care	811,505 all care	22.1 (20.5 to 23.7)	41.1 (40.1 to 42.1)	Significant (P value not reported)	Low
1[60] (data for 1995 to 1996)	165,120 intensive care	811,505 all care	17.8 (16.5 to 19.1)	29.2 (28.4 to 30.0)	Significant (P value not reported)	Low
1[60] (data for 1983 to 1984)	425,876 adequate care	811,505 all care	53.8 (51.9 to 55.8)	50.0 (48.7 to 51.3)	Significant (P value not reported)	Low
1[60] (data for 1989 to 1990)	425,876 adequate care	811,505 all care	43.4 (42.0 to 44.8)	41.1 (40.1 to 42.1)	Significant (P value not reported)	Low
1[60] (data for 1995 to 1996)	425,876 adequate care	811,505 all care	33.0 (31.9 to 34.1)	29.2 (28.4 to 30.0)	Significant (P value not reported)	Low
Neonatal morbidity						
Preterm birth						
1[60] (data for 1981)	165,120 intensive care	425,876 adequate care	350	510	Not reported	Very low
1[60] (data for 1997)	165,120 intensive care	425,876 adequate care	550	600	Not reported	Very low

Evidence statement

There was no evidence reported from RCTs for the effectiveness of specialised antenatal care for twin and triplet pregnancies. Bias may have arisen from non-random allocation of women to each group in the included studies. In addition, the studies were all undertaken in the USA where some aspects of the healthcare system, including accessibility, may limit their applicability to the UK setting.

Evidence was reported in relation to the effectiveness of specialist antenatal care for improving maternal morbidity and perinatal and neonatal morbidity and mortality (including reduction in preterm birth rates). The specialist care described in the studies emphasised nutritional advice, but as there were a number of components, including more specific information and advice given, increased frequency of contact, continuity of caregivers and more specialist or senior caregivers, it is difficult to evaluate which individual components were effective when considering the outcomes. As all the specialised care groups received more frequent contact with caregivers, the observed differences in outcomes might be explained simply by the impact of more frequent professional support. There was insufficient information regarding the definition of standard care to determine whether there were other confounders relating to the differences between standard and specialist clinics (for example, it is possible that women attending specialist clinics saw professionals with greater competence and experience than did women who received standard care).

None of the included studies reported specifically on the effect of specialised care on maternal anxiety or depression. None of the studies included triplet pregnancies.

Maternal morbidity

There were no significant differences between the specialist and standard care groups for the number of women with anaemia (two studies, very low quality), bleeding at 20 weeks of gestation or later (two studies, very low quality), gestational diabetes (two studies, very low quality), gestational hypertension (one study, very low quality) or urinary tract infection (two studies, very low quality). The caesarean section rate was not significantly different between the specialist and standard care groups (two studies, very low quality).

Mixed results were found for pre-eclampsia (two studies, very low quality). One study reported no significant difference between the number of women with pre-eclampsia in a specialist unit compared to a standard care group (very low quality), while another study showed that there were significantly fewer women with pre-eclampsia in the specialist care group (very low quality).

Significantly fewer women experienced prelabour rupture of membranes (two studies, very low quality) or preterm labour (one study, very low quality) in the specialised antenatal care group compared with the standard care group.

Perinatal and neonatal mortality

Mixed results were reported for the effect of specialist antenatal clinics on perinatal mortality. One study showed there were significantly fewer perinatal deaths in a specialised care group (very low quality), while another study showed there was no significant difference in the number of perinatal deaths between the standard and specialised care groups (very low quality).

Neonatal morbidity

The number of preterm births was significantly lower in the specialist care groups than the standard care groups (three studies, very low quality). The significant difference was present for preterm birth at 36 weeks of gestation (two studies, very low quality), 32 weeks (one study, very low quality) and 30 weeks (two studies, very low quality). One study, however, reported significantly fewer preterm births at less than 37 weeks of gestation in the specialist care group (one study, very low quality), and another study reported that there was no significant difference between specialist and standard care groups (one study, very low quality). The significance level for the difference between the rate of preterm births per 1000 live births in the standard and specialised care groups was not reported (one study, very low quality).

It was not possible to determine from information provided in the studies whether the prevention of preterm birth was secondary to enhanced maternal and fetal wellbeing in the specialised clinic group or to differences in the level of experience and clinical decision-making between the groups. If, for example, there were less experienced professionals in the standard care group, there may have been a lower threshold for elective preterm birth rather than continued close observation.

There were several other measures of perinatal and neonatal morbidity reported in the studies to be significantly lower in the specialised care group than the standard care group. The GDG believes that the significant results for these measures are likely to be consequences of the reduced rates of preterm birth associated with specialised care, rather than the measures representing independent outcomes.

Mixed results were reported for very low birthweight, which is another outcome that is likely to arise from a difference in preterm birth rates: one study reported no significant difference between the number of very low birthweight babies in the standard and specialised care groups (very low quality), while two studies reported significantly fewer very low birthweight babies in the specialised care group (very low quality). Mixed results were also reported for the number of babies born small-for-gestational age (SGA). There were significantly fewer SGA babies born preterm in the specialist clinic group (one study, low quality). However, there were significantly more SGA babies born at term in the specialist clinic group compared with the standard care group (one study, low quality).

None of the studies reported evidence regarding maternal mortality, maternal satisfaction, psychopathology or breastfeeding. No studies reporting results for triplet pregnancies were identified.

Health economics profile

No published health economic evidence was identified, although this question was prioritised for health economic analysis. The GDG developed an original health economic model to evaluate the cost effectiveness of specialist care for women with twin and triplet pregnancies compared to routine antenatal care using published evidence of clinical effectiveness in settings outside the UK and information provided by GDG members in relation to staff configuration, frequency of surveillance for complications, criteria for admission to hospital and so on in four different settings (hospitals or groups of hospitals) in the UK (assuming that the clinical effectiveness of the non-UK settings would apply equally in the UK). The model also included consideration of specialist care staff configuration and protocol discussed in a published article,[62] which was excluded from the review of clinical effectiveness because it did not report effectiveness data. There was wide variation between the various protocols with regard to hospitalisation, specialist obstetrician appointments and frequency of ultrasound scanning. From this information, GDG consensus was used to define a 'typical' model of specialist care. The health economic model suggested that specialist care dominates routine antenatal care across a range of assumptions (that is, specialist care costs less and results in greater health benefits compared to routine antenatal care). The results of the model were demonstrated to be robust using sensitivity analysis and specialist care was shown to have a greater than 99.9% chance of being cost effective in a probabilistic sensitivity analysis (that is, specialist care costs less and results in better outcomes).

Further details of the health economic model are presented in Section 11.2.

Evidence to recommendations

Relative value placed on the outcomes considered

The priority outcomes specified in the review protocol were:

- maternal morbidity (including anxiety and depression)
- perinatal and neonatal mortality
- perinatal and neonatal morbidity including preterm delivery
- breastfeeding
- maternal satisfaction
- maternal mortality.

The GDG's view was that morbidity is more prevalent than mortality, and so morbidity was prioritised as an outcome.

Trade-off between clinical benefits and harms

Potential harm could be caused by unnecessary contact with healthcare professionals. This could lead to unnecessary intervention and maternal anxiety. However, frequent visits could also be reassuring and provide women with an opportunity to discuss potential anxieties. Contact with less experienced or competent healthcare professionals might increase anxiety and cause harm, hence the need for expertise locally. However, competent support and education can allay fears and inform women of potential complications at relevant times, as well as providing consistency, continuity and choice in relation to care. If the model of care specifies specialist care in a small number of locations, the practical and emotional impact for women of travel and needing to get to know two healthcare teams would need to be balanced. In the extreme, this may mean women giving birth in specialist centres when a local centre would have been appropriate and overloading the resources of specialist centres. However, the GDG's view is that it is paramount that antenatal care of twin and triplet pregnancies be delivered by multidisciplinary teams with specific expertise in such pregnancies. Benefits include improved outcomes, particularly perinatal morbidity arising from reduced preterm birth rates.

Trade-off between net health benefits and resource use

The current availability of equipment and healthcare professionals responsible for care of twin and triplet pregnancies at different hospitals varies greatly depending on the size and location of the

hospital. Implementing specialist care could be resource heavy if it requires establishing a specific team and equipment in all centres. However, the health economic model developed for the guideline demonstrated that specialist care is cost effective compared to routine antenatal care.

Quality of evidence

The quality of evidence for maternal morbidity was very low. The quality of evidence for perinatal and neonatal mortality was low. The quality of evidence for perinatal and neonatal morbidity (including preterm delivery) ranged from low to very low, and was mostly very low.

Other considerations

It was not possible to determine whether the effect of specialist care (clinics) differed according to the chorionicity of the pregnancy. It was not possible to determine whether the allocation process in the studies was biased: women may have been referred to twin clinics because they had signs of a more difficult pregnancy, or women who had access to such clinics due to financial, educational or other means may have been at lower risk or have had third-party funding for their care. There was a lack of evidence as to whether the components of specialist care are more important than continuity of care or the seniority or specialist knowledge of the healthcare professionals involved in care.

This review question focuses on the package of specialist antenatal care for twin and triplet pregnancies rather than the content of specialist clinics alone. All of the available evidence came from the USA, where the healthcare system does not include midwifery. There was, therefore, no evidence relating to interventions involving midwives as part of a specialist team. No study considered the impact of other healthcare professionals on women's wellbeing, such as clinical psychologists, health visitors or women's health physiotherapists.

The incidence of SGA babies did not differ between standard and specialist care groups and so specialist care does not appear to prevent SGA. However, the preterm SGA birth rate was lower in the specialist care groups. This could be the result of differences in experience and competence of healthcare professionals involved in the different settings, with more experienced personnel being less likely to intervene to deliver early in the case of an SGA baby. Alternatively, the severity of SGA may have been reduced in the specialised care groups. There is insufficient information regarding the nature of care in the two groups to determine the most likely explanation.

There is evidence that continuity and consistency of care by the same healthcare professionals throughout pregnancy contributes to improved outcomes in many settings. The GDG's view was, therefore, that care should be delivered by a nominated multidisciplinary specialist team. Since none of the clinical effectiveness studies reviewed for the guideline was undertaken in the UK, the health economic model constructed for the guideline considered a 'typical' model of specialist care, which is relevant to the UK. The health economic modelling also assumed that the effects of specialist care reported in the identified clinical effectiveness studies applied equally in the UK (NHS) setting.

GDG members provided information about specialist care operating in four settings (individual hospitals or groups of hospitals). An additional specialist care staff configuration and protocol discussed in a published article (which was excluded from the review of clinical effectiveness because it did not report effectiveness data) was also considered in the health economic modelling. There was wide variation between the various protocols with regard to hospitalisation, specialist obstetrician appointments and frequency of ultrasound scanning. From the results of the health economic model, the GDG was able to extrapolate the number of contacts with healthcare professionals needed for twin and triplet pregnancies, according to chorionicity. The number of contacts with the core team was agreed by the GDG members in accordance with their knowledge and expertise. Referral to selected members of the enhanced team would be made on the basis of the woman's individual need.

The overall schedule of appointments recommended for the different types of uncomplicated twin and triplet pregnancy is detailed in Table 5.8. The schedule includes the woman's first visit (booking appointment), as in routine antenatal care ('Antenatal care', NICE clinical guideline 62),[14] together with 'routine' screening recommended in that guideline. Table 5.8 also includes the recommended schedule of visits for singleton pregnancies ('Antenatal care', NICE clinical guideline 62)[14] for comparison.

The first (booking) appointment in routine antenatal care will often be identical to that in a singleton pregnancy because most women will not already know whether they have a singleton, twin or triplet

pregnancy. In such cases the first appointment will not be included in the total number of appointments with the specialist care core team specified in the recommendations. Where the woman already knows (or expects) that she has a twin or triplet pregnancy (for example, because the pregnancy results from an *in vitro* fertilisation [IVF] procedure) the first appointment may involve the specialist care team for twin and triplet pregnancies, and in this situation it would count towards the number of appointments with the core team. The GDG emphasised, however, that all women with twin and triplet pregnancies should be offered timely referral to maternity services once pregnancy is detected. Referral should occur sufficiently early in the first trimester to allow women with twin and triplet pregnancies the opportunity to access first-trimester screening for Down's syndrome (since this is strongly preferred to second-trimester screening for Down's syndrome; see Section 6.1).

Two appointments for nulliparous women that occur in routine antenatal care at 25 weeks and 31 weeks are not included in the schedule of appointments with the specialist care core team for uncomplicated twin and triplet pregnancies. The tests and discussions that normally apply to nulliparous women at those appointments are covered by the appointments for women with uncomplicated twin and triplet pregnancies that are scheduled for 24 and 32 weeks (that is, the tests and discussions take place as in routine antenatal care but at a different time to coincide with additional tests and discussions specific to women with twin and triplet pregnancies).

The total number of appointments in the schedules for uncomplicated twin and triplet pregnancies is lower than for women with singleton pregnancies because women with twin and triplet pregnancies usually give birth before 38 weeks: few women with twin and triplet pregnancies are likely to need antenatal appointments at 38, 40 or 41 weeks because they have already given birth. For women with uncomplicated twin and triplet pregnancies who have declined the offer of elective birth, weekly appointments with the specialist obstetrician should be offered, so that for uncomplicated twin and triplet pregnancies that continue beyond 37 weeks the frequency of appointments will be higher than in singleton pregnancies.

Variation in training and expertise of healthcare professionals requires local and regional coordination of services: coordination and continuity of care in hospitals, between hospitals and within the community should be paramount.

The GDG's consensus view was that at least two appointments should be with the specialist obstetrician (regardless of the chorionicity of the pregnancy). The purpose of these appointments is to assess and discuss the risks associated with the individual pregnancy, and to discuss timing and mode of birth.

The care provided by the core team does not routinely involve community midwife care antenatally, although the GDG recognised the contribution to postnatal care likely to be made by community midwives. Additional contacts with the community midwifery team may be arranged, depending on local circumstances (for example, for monitoring borderline proteinuria between visits to the core team). The GDG noted that, in addition to access to the core and enhanced multidisciplinary teams, those women with twin and triplet pregnancies who are socially disadvantaged may benefit from recommendations contained in 'Pregnancy and complex social factors' (NICE clinical guideline 110).[16]

The GDG recognised the importance to women with twin and triplet pregnancies of access to antenatal care (including the implications of having to travel to a particular location to receive care), and the possibility of transfer to hospital during pregnancy or labour. These issues are highlighted in the GDG's recommendations for clinical care (for example, they emphasised that care should be coordinated to minimise the number of hospital visits and to provide care as close to the woman's home as possible) and in their recommendation for further research to evaluate the clinical and cost effectiveness of particular models of specialist care.

Table 5.8 Comparison of care in singleton pregnancies ('Antenatal care', NICE clinical guideline 62)[14] and uncomplicated multiple pregnancies

Gestational age	Singleton pregnancy, routine antenatal care ('Antenatal care', NICE clinical guideline 62)[14]	Dichorionic diamniotic twin pregnancy	Monochorionic diamniotic twin pregnancy	Trichorionic triamniotic triplet pregnancy	Monochorionic triamniotic and dichorionic triamniotic triplet pregnancy
<11 weeks 0 days, first (booking) appointment; (ideally by 10 weeks; possibly two appointments)	Give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by written information (diet and lifestyle considerations, pregnancy care services available, maternity benefits and sufficient information to enable informed decision making about screening tests). Identify women who may need additional care and plan pattern of care for the pregnancy. Ask about mood to identify possible depression. Identify women who have had genital mutilation. Check blood group and rhesus D status. Offer screening for haemoglobinopathies, anaemia, red cell alloantibodies, hepatitis B virus, HIV, rubella susceptibility and syphilis. Inform women younger than 25 years about the high prevalence of chlamydia infection in their age group, and give details of their local National Chlamydia Screening Programme. Offer screening for asymptomatic	As for 'Antenatal care', NICE clinical guideline 62.[14] Some women will know they have a multiple pregnancy (previous scan for first trimester bleeding or assisted conception) but for many it will only be detected at the first scan. Thus, the first scan is best arranged for when crown–rump length is between 45 mm and 84 mm in multiple pregnancies (at approximately 11 weeks 0 days to 13 weeks 6 days). <u>General principles of care once a multiple pregnancy is detected</u> Clinical care for women with twin and triplet pregnancies should be provided by a nominated multidisciplinary team consisting of: • a core team of named specialist obstetricians, specialist midwives and ultrasonographers with experience and knowledge of managing twin and triplet pregnancies • an enhanced team for referrals (to include a perinatal mental health professional, a women's health physiotherapist, an infant feeding coordinator, and a dietitian). Members of the enhanced team should have experience and knowledge relevant to the management of twin and triplet pregnancies. Referral to a member of the enhanced team should be on the basis of the woman's individual needs, rather than as a routine. Coordinate clinical care for women with twin and triplet pregnancies to: • minimise the number of hospital visits • provide appropriate care as close to the woman's home as possible • provide continuity of care within and between hospitals and the community. The core team should offer information and emotional support specific to twin and triplet pregnancies at their first contact with the woman and provide ongoing opportunities for further discussion and advice			

	bacteriuria. Offer screening for Down's syndrome. Offer early ultrasound scan for gestational age assessment. Offer ultrasound screening for structural anomalies (18 weeks 0 days to 20 weeks 6 days). Measure BMI, blood pressure (BP) and test urine for proteinuria. Screen for gestational diabetes using risk factors. For women who choose to have screening, the following tests should be arranged as appropriate: • blood tests (for checking blood group and rhesus D status and screening for haemoglobinopathies, anaemia, red cell alloantibodies, hepatitis B virus, HIV, rubella susceptibility and syphilis) ideally before 10 weeks • urine tests (to check for proteinuria and screen for asymptomatic bacteriuria).	including: • antenatal and postnatal mental health and wellbeing • chorionicity and its meaning for the pregnancy • possible 'discordancy' of problems in multiple pregnancy • antenatal nutrition • the risks, symptoms and signs of preterm labour and the potential need for corticosteroids for fetal lung maturation • a generic discussion on the possible timing and modes of delivery[*] • breastfeeding • parenting.

[*] Specific recommendations about mode of delivery are outside the scope of this guideline.

11 weeks 0 days to 13 weeks 6 days	Ultrasound scan to determine gestational age using: – crown–rump measurement if performed at 10 weeks 0 days to 13 weeks 6 days – head circumference if crown–rump length above 84 mm. Down's syndrome screening using: – nuchal translucency at 11 weeks 0 days to 13 weeks 6 days – serum screening at 15 weeks 0 days to 20 weeks 0 days.	The following should occur when crown–rump length is between 45 mm and 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days): • detect multiple pregnancy • confirm viability • confirm gestational age • determine chorionicity • perform screening for Down's syndrome (if requested) • refer to core team (separate appointment may be necessary).			
16 weeks	The next appointment should be scheduled at 16 weeks to: • review, discuss and record the results of all screening tests undertaken; reassess planned pattern of care for the pregnancy and identify women who need additional care • investigate a haemoglobin level of less than 11 g/100 ml and consider iron supplementation if indicated • measure BP and test urine for proteinuria • give information, with an opportunity to discuss issues and ask questions including discussion of the routine anomaly scan; offer verbal information supported by antenatal classes and written information.	As for 'Antenatal care', NICE clinical guideline 62[14] plus a clinical review. Where first-trimester screening for Down's syndrome cannot be offered, consider second-trimester serum screening and explain to the woman the limitations of such screening.	As for 'Antenatal care', NICE clinical guideline 62[14] plus a clinical review. Scan for feto-fetal transfusion syndrome (FFTS). Where first-trimester screening for Down's syndrome cannot be offered, consider second-trimester serum screening and explain to the woman the limitations of such screening.	As for 'Antenatal care', NICE clinical guideline 62[14] plus a clinical review. Do not offer second-trimester serum screening for Down's syndrome.	As for 'Antenatal care', NICE clinical guideline 62)[14] plus a clinical review. Scan for FFTS. Do not offer second-trimester serum screening for Down's syndrome.
18 weeks	At 18–20 weeks, if the woman chooses, an ultrasound scan should be performed for the		Scan for FFTS plus a clinical review.		Scan for FFTS plus a clinical review.

20 weeks	detection of structural anomalies. For a woman whose placenta is found to extend across the internal cervical os at this time, another scan at 36 weeks should be offered and the results of this scan reviewed at the 36 week appointment.	Anomaly scan plus a clinical review.	Anomaly scan, scan for FFTS plus a clinical review.	Anomaly scan plus a clinical review.	Anomaly scan, scan for FFTS plus a clinical review.
22 weeks			Scan for FFTS, growth plus a clinical review.		Scan for FFTS, growth plus a clinical review.
24 weeks		Scan for growth plus a clinical review including: • measure BP and test urine for proteinuria • offer a second screening for anaemia and atypical red cell alloantibodies • investigate a haemoglobin level of less than 10.5 g/100 ml and consider iron supplementation, if indicated • give information, with an opportunity to discuss issues and ask questions.	Scan for FFTS, growth plus a clinical review including: • measure BP and test urine for proteinuria • offer a second screening for anaemia and atypical red cell alloantibodies • investigate a haemoglobin level of less than 10.5 g/100 ml and consider iron supplementation, if indicated • give information, with an opportunity to discuss issues and ask questions.	Scan for growth plus a clinical review including: • measure BP and test urine for proteinuria • offer a second screening for anaemia and atypical red cell alloantibodies • investigate a haemoglobin level of less than 10.5 g/100 ml and consider iron supplementation, if indicated • give information, with an opportunity to discuss issues and ask questions.	Scan for FFTS, growth plus a clinical review including: • measure BP and test urine for proteinuria • offer a second screening for anaemia and atypical red cell alloantibodies • investigate a haemoglobin level of less than 10.5 g/100 ml and consider iron supplementation, if indicated • give information, with an opportunity to discuss issues and ask questions.
25 weeks	At 25 weeks another appointment should be scheduled for nulliparous. At this appointment:				

	• measure and plot symphysis–fundal height • measure BP and test urine for proteinuria • give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information.				
28 weeks	The next appointment for all pregnant women should occur at 28 weeks. At this appointment: • offer a second screening for anaemia and atypical red cell alloantibodies • investigate a haemoglobin level of less than 10.5 g/100 ml and consider iron supplementation, if indicated • offer anti-D to rhesus-negative women • measure BP and test urine for proteinuria • measure and plot symphysis–fundal height • give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information.	Scan for growth plus a clinical review including: • offer anti-D to rhesus-negative women • measure BP and test urine for proteinuria • give information, with an opportunity to discuss issues and ask questions • discuss timing and mode of delivery.	Scan for FFTS, growth plus a clinical review including: • offer anti-D to rhesus-negative women • measure BP and test urine for proteinuria • give information, with an opportunity to discuss issues and ask questions • discuss timing and mode of delivery.	Scan for growth plus a clinical review including: • offer anti-D to rhesus-negative women • measure BP and test urine for proteinuria • give information, with an opportunity to discuss issues and ask questions • discuss timing and mode of delivery.	Scan for FFTS, growth plus a clinical review including: • offer anti-D to rhesus-negative women • measure BP and test urine for proteinuria • give information, with an opportunity to discuss issues and ask questions • discuss timing and mode of delivery.
31 weeks	For nulliparous women at 31 weeks: • measure BP and test urine for proteinuria • measure and plot symphysis–fundal height • give information, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information • review, discuss and record the results of screening tests undertaken at 28 weeks;				

	reassess planned pattern of care for the pregnancy and identify women who need additional care.				
32 weeks		Scan for growth plus a clinical review including: • measure BP and test urine for proteinuria • give information, with an opportunity to discuss issues and ask questions.	Scan for FFTS, growth plus a clinical review including: • measure BP and test urine for proteinuria • give information, with an opportunity to discuss issues and ask questions.	Scan for growth plus a clinical review including: • measure BP and test urine for proteinuria • give information, with an opportunity to discuss issues and ask questions.	Scan for FFTS, growth plus a clinical review including: • measure BP and test urine for proteinuria • give information, with an opportunity to discuss issues and ask questions.
34 weeks	At 34 weeks, all pregnant women should be seen in order to: • offer a second dose of anti-D to rhesus-negative women • measure BP and test urine for proteinuria • measure and plot symphysis–fundal height • give information, with an opportunity to discuss issues and ask questions on preparation for labour and birth, including the birth plan, recognising active labour and coping with pain; offer verbal information supported by antenatal classes and written information • review, discuss and record the results of screening tests undertaken at 28 weeks; reassess planned pattern of care for the pregnancy and identify women who need additional care.	Clinical review including: • offer a second dose of anti-D to rhesus-negative women • measure BP and test urine for proteinuria • review, discuss and record the results of tests undertaken at 28 weeks.	Scan for FFTS, growth plus a clinical review including: • measure BP and test urine for proteinuria. As for 'Antenatal care', NICE clinical guideline 62[14] at 36 weeks: • measure BP and test urine for proteinuria • discuss breastfeeding technique and good management practices, refer to the UNICEF Baby Friendly Initiative (www.babyfriendly.org.uk)	Scan for growth plus a clinical review including: • measure BP and test urine for proteinuria. As for 'Antenatal care', NICE clinical guideline 62[14] at 36 weeks: • measure BP and test urine for proteinuria • discuss breastfeeding technique and good management practices, refer to the UNICEF Baby Friendly Initiative (www.babyfriendly.org.uk) • give information, including care of the new baby, newborn screening tests	Scan for FFTS, growth plus a clinical review including: • measure BP and test urine for proteinuria. As for 'Antenatal care', NICE clinical guideline 62[14] at 36 weeks: • measure BP and test urine for proteinuria • discuss breastfeeding technique and good management practices, refer to the

			• give information, including care of the new baby, newborn screening tests and vitamin K prophylaxis, postnatal self-care and postnatal depression, with an opportunity to discuss issues and ask questions. Offer birth at 36 weeks.	and vitamin K prophylaxis, postnatal self-care and postnatal depression, with an opportunity to discuss issues and ask questions. Offer birth at 35 weeks.	UNICEF Baby Friendly Initiative (www.babyfriendly.org.uk) • give information, including care of the new baby, newborn screening tests and vitamin K prophylaxis, postnatal self-care and postnatal depression, with an opportunity to discuss issues and ask questions. Offer birth at 35 weeks.
36 weeks	At 36 weeks, all pregnant women should be seen again to: • measure BP and test urine for proteinuria • measure and plot symphysis–fundal height • check position of baby • for women whose babies are in the breech presentation, offer external cephalic version (ECV) • review ultrasound scan report if placenta extended over the internal cervical os at previous scan • discuss breastfeeding technique and good management practices, refer to the UNICEF	Scan for growth plus a clinical review including: • measure BP and test urine for proteinuria • discuss breastfeeding technique and good management practices, refer to the UNICEF Baby Friendly Initiative (www.babyfriendly.org.uk) • give information,	For women who decline the offer of elective birth offer weekly appointments with the specialist obstetrician. At each appointment offer an ultrasound scan, performing weekly biophysical profile assessments and fortnightly fetal growth scans.	For women who decline the offer of elective birth offer weekly appointments with the specialist obstetrician. At each appointment offer an ultrasound scan, performing weekly biophysical profile assessments and fortnightly fetal growth scans.	For women who decline the offer of elective birth offer weekly appointments with the specialist obstetrician. At each appointment offer an ultrasound scan, performing weekly biophysical profile assessments and fortnightly fetal growth scans.

	Baby Friendly Initiative (www.babyfriendly.org.uk) • give information, including care of the new baby, newborn screening tests and vitamin K prophylaxis, postnatal self-care and postnatal depression, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information.	including care of the new baby, newborn screening tests and vitamin K prophylaxis, postnatal self-care and postnatal depression, with an opportunity to discuss issues and ask questions. Offer birth at 37 weeks.			
38 weeks	At 38 weeks, all pregnant women should be seen again to: • measure BP and urine testing for proteinuria • measure and plot symphysis–fundal height • give information, including options for management of prolonged pregnancy, with an opportunity to discuss issues and ask questions; verbal information supported by antenatal classes and written information.	For women who decline the offer of elective birth offer weekly appointments with the specialist obstetrician. At each appointment offer an ultrasound scan, performing weekly biophysical profile assessments and fortnightly fetal growth scans.			
40 weeks	For nulliparous women, an appointment at 40 weeks should be scheduled to: • measure BP and test urine for proteinuria • measure and plot symphysis–fundal height • give information, including further discussion about management for prolonged pregnancy, with an opportunity to discuss issues and ask questions; offer verbal information supported by antenatal classes and written information.				

41 weeks	For women who have not given birth by 41 weeks: • a membrane sweep should be offered • induction of labour should be offered • BP should be measured and urine tested for proteinuria • symphysis–fundal height should be measured and plotted • information should be given, including further discussion about management for prolonged pregnancy, with an opportunity to discuss issues and ask questions; verbal information supported by written information.				

BMI body mass index, BP blood pressure, ECV external cephalic version, FFTS feto-fetal transfusion syndrome, HIV human immunodeficiency virus

Recommendations

Number	Recommendation
18	Clinical care for women with twin and triplet pregnancies should be provided by a nominated multidisciplinary team consisting of: • a core team of named specialist obstetricians, specialist midwives and ultrasonographers, all of whom have experience and knowledge of managing twin and triplet pregnancies • an enhanced team for referrals, which should include: – a perinatal mental health professional – a women's health physiotherapist – an infant feeding specialist – a dietitian. Members of the enhanced team should have experience and knowledge relevant to twin and triplet pregnancies.
19	Referrals to the enhanced team should not be made routinely for women with twin and triplet pregnancies but should be based on each woman's needs.
20	Coordinate clinical care for women with twin and triplet pregnancies to: • minimise the number of hospital visits • provide care as close to the woman's home as possible • provide continuity of care within and between hospitals and the community.
21	The core team should offer information and emotional support specific to twin and triplet pregnancies at their first contact with the woman and provide ongoing opportunities for further discussion and advice including: • antenatal and postnatal mental health and wellbeing • antenatal nutrition (see 15) • the risks, symptoms and signs of preterm labour and the potential need for corticosteroids for fetal lung maturation • likely timing and possible modes of delivery[I] • breastfeeding • parenting.
22	Offer women with uncomplicated monochorionic diamniotic twin pregnancies at least nine antenatal appointments with a healthcare professional from the core team. At least two of these appointments should be with the specialist obstetrician. • Combine appointments with scans when crown–rump length measures from 45 mm to 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days) and then at estimated gestations of 16, 18, 20, 22, 24, 28, 32 and 34 weeks (see 55).
23	Offer women with uncomplicated dichorionic twin pregnancies at least eight antenatal appointments with a healthcare professional from the core team. At least two of these appointments should be with the specialist obstetrician. • Combine appointments with scans when crown–rump length measures from 45 mm to 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days) and then at estimated gestations of 20, 24, 28, 32 and 36 weeks (see 55). • Offer additional appointments without scans at 16 and 34 weeks.
24	Offer women with uncomplicated monochorionic triamniotic and dichorionic triamniotic triplet pregnancies at least 11 antenatal appointments with a healthcare professional from the core team. At least two of these appointments should be with

[I] Specific recommendations about mode of delivery are outside the scope of this guideline.

the specialist obstetrician.

- Combine appointments with scans when crown–rump length measures from 45 mm to 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days) and then at estimated gestations of 16, 18, 20, 22, 24, 26, 28, 30, 32 and 34 weeks (see 55).

25 Offer women with uncomplicated trichorionic triamniotic triplet pregnancies at least seven antenatal appointments with a healthcare professional from the core team. At least two of these appointments should be with the specialist obstetrician.

- Combine appointments with scans when crown–rump length measures from 45 mm to 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days) and then at estimated gestations of 20, 24, 28, 32 and 34 weeks (see 55).
- Offer an additional appointment without a scan at 16 weeks.

26 Women with twin and triplet pregnancies involving a shared amnion should be offered individualised care from a consultant in a tertiary level fetal medicine centre (see 54).

Number	Research recommendation
RR 6	Does specialist antenatal care for women with twin and triplet pregnancies improve outcomes for women and their babies?

Why this is important

Important issues for women with twin and triplet pregnancies in the antenatal period include access to care (including the implications of having to travel to a particular location to receive care) and the possibility of transfer to hospital during pregnancy or labour. Current evidence is limited, of low quality, and originates from a healthcare system that is different from the NHS (in particular, from a system where midwives are not involved in providing care). None of the studies identified in the guideline review made a direct comparison between specialist twin or triplet antenatal care and routine antenatal care (that is, care offered to women with singleton pregnancies).

Although health economic analysis conducted for the guideline demonstrated cost effectiveness of a range of models of specialist antenatal care, the recommendations reflect the clinical experience of the Guideline Development Group rather than strong evidence to support a particular model of care. Further research is, therefore, needed to evaluate the clinical and cost effectiveness of different models of specialist antenatal care for women with twin and triplet pregnancies. This includes evaluating the best mix of resources and skills in multidisciplinary antenatal care services, and identifying the most effective components of care.

Research should cover the roles of different healthcare professionals (including midwives, since their role is not addressed in any existing studies). It should also investigate maternal, perinatal and neonatal morbidity and mortality associated with different models of specialist care, and also long-term outcomes. Maternal outcomes to be considered include satisfaction with care and psychological wellbeing because the increased risks associated with twin and triplet pregnancies may lead to maternal anxiety or even depression. The chorionicity of the pregnancy should also be considered as a factor influencing components of specialist care. The outcomes of such research could identify particular models of care to be implemented in the NHS, which would affect service delivery and organisation (for example, by specifying a need for additional staff or further training for existing staff,

both of which have cost implications).

In making this research recommendation the Guideline Development Group recognises that future research needs to provide data relevant to the current clinical context in England and Wales. The research should use cluster randomised trials or observational studies.

6 Fetal complications

6.1 Screening for chromosomal abnormalities

Introduction

The most common chromosomal abnormality at birth is Down's syndrome, also termed trisomy 21, which is a congenital syndrome that arises when the affected baby has an extra copy of chromosome 21. Other trisomies occur, including Edward's syndrome (trisomy 18) and Patau's syndrome (trisomy 13), but they are much less common. In the absence of antenatal screening, about 1 in 700 babies born would be affected by one of these trisomies.

Down's syndrome causes learning disabilities, which are often profound, but the majority of children with the condition learn to meet most developmental milestones, albeit later than other children. As well as delayed childhood neurodevelopment, there can be long-term societal, economic and personal issues associated with Down's syndrome in adults. Down's syndrome is also associated with increased incidence of congenital malformations (particularly cardiac and gastrointestinal anomalies) as well as an increased incidence of thyroid disorders. 'Antenatal care' (NICE clinical guideline 62)[14] recommends provision of unbiased, evidence-based information about Down's syndrome, enabling women to make autonomous, informed decisions about screening for the condition. This review question evaluates the evidence relating to when and how ultrasound screening for chromosomal abnormalities should be performed to aid in antenatal diagnosis of fetal chromosomal abnormalities in twin and triplet pregnancies.

Review question

When and how should screening be used to identify chromosomal abnormalities in multiple pregnancy?

Existing NICE guidance

'Antenatal care' (NICE clinical guideline 62),[14] which examined the diagnostic accuracy of existing first- and second-trimester tests to screen for Down's syndrome, contains the following recommendations.

- Offer all pregnant women screening for Down's syndrome. Women should understand that it is their decision to choose screening for Down's syndrome.
- Perform screening for Down's syndrome by the end of the first trimester (13 weeks 6 days), but make provision to screen later (up to 20 weeks 0 days) for women booking later in pregnancy.
- Offer the combined test (nuchal translucency, beta-human chorionic gonadotrophin [hCG] and pregnancy-associated plasma protein A [PAPP-A]) to screen for Down's syndrome between 11 weeks 0 days and 13 weeks 6 days. Offer women who book later in pregnancy the most clinically- and cost-effective serum screening method (triple or quadruple test) between 15 weeks 0 days and 20 weeks 0 days.
- Give women information about screening for Down's syndrome at their first contact with a healthcare professional. This will provide the opportunity for further discussion before embarking on screening.
- Offer women who screen positive for Down's syndrome rapid access to appropriate counselling by trained healthcare professionals.

Description of included studies

Nine studies were identified which examined the accuracy of the following screening methods to identify chromosomal anomalies in multiple pregnancy:[63-71]

- combined test (nuchal translucency, PAPP-A, free beta human chorionic gonadotrophin [f-beta-hCG]) and maternal age (three studies)[63;69;70]
- nuchal translucency combined with maternal age (three studies)[63-65]
- nuchal translucency alone (greater than 95th percentile; five studies)[64-66;68;71]
- nuchal translucency alone (greater than 99th percentile; one study).67

No evidence was reported for the use of nasal bone, tricuspid regurgitation, Doppler ultrasound, the quadruple test or the integrated test in predicting chromosomal abnormalities in twin or triplet pregnancies.

All studies appeared to use the test as the primary screening tool within the study setting. Two studies involved a mixture of twins and triplets,[66;68] however the data for triplets were not reported separately. One study population involved only monochorionic twins.[64] All other study populations comprised a mixture of monochorionic and dichorionic twins, and the accuracy of the screening method was calculated separately for these subgroups, where possible.[63-65;67-71]

One study reported the risk of chromosomal anomaly per pregnancy.[64] All other studies reported the risk or threshold per fetus.[63;65-71]

Of the studies that examined the accuracy of screening with the combined test, one was performed in the UK,[70] one in Spain[63] and one in China,[69] The gestational age at which the test was performed ranged from 10 weeks 3 days to 11 weeks 6 days. One study reported the crown–rump length range (38–84 mm), which was consistent with the gestational ages used in the other studies.[69]

Where nuchal translucency and maternal age were used for screening, two studies were conducted at one UK centre[64;65] and the other study was conducted in Spain.[63] The gestational age range at which the nuchal translucency ultrasound was performed ranged from 10 to 14 weeks.

Of the studies that reported the accuracy of nuchal translucency alone, two were conducted at one centre in the UK[64;65], one was conducted in the UK and Israel,[71] one in Italy,[68] one in Spain[67] and one in Chile.[66] The test was performed between 10 and 14 weeks of gestation.

There was suspected overlap between the populations in two studies conducted in the UK[64;65] and in two studies conducted in Spain.[63;67] Where meta-analyses were conducted for the guideline, care was taken to include only one of each pair of studies to avoid double counting of participants.

Published health economic evidence

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

Evidence profiles

The evidence profiles for this question are presented in Tables 6.1 to 6.3. Tables 6.1 and 6.2 present results for studies of twin pregnancies that allowed diagnostic accuracy statistics to be calculated separately for monochorionic and dichorionic twins, respectively. Table 6.3 presents results for studies of twin pregnancies with unreported or mixed chorionicity and studies of triplet pregnancies.

Table 6.1 GRADE summary of findings for studies evaluating screening tests for chromosomal abnormalities tests in monochorionic twins

Number of studies	Numbers of twin and triplet pregnancies	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Combined tests						
Nuchal translucency, maternal age, f-beta-hCG and PAPP-A - risk > 1:250 for trisomy 21						
1[63]	24	100 (16 to 100)	91 (79 to 100)	11 (3 to 41)	0.0 (0.0 to 2.4)	Very low
Nuchal translucency with maternal age						
Risk > 1:250 per fetus for trisomy 21						
1[63]	24	100 (16 to 100)	91 (79 to 100)	11 (3 to 41)	0.0 (0.0 to 2.4)	Very low
Risk > 1:300 per pregnancy for trisomy 21 (using fetus with highest nuchal translucency)						
1[64]	1538	100 (54 to 100)	81 (78 to 83)	5 (4 to 6)	0.1 (0.0 to 1.3)	Very low
Risk > 1:300 per pregnancy for trisomy 21 (using fetus with smallest nuchal translucency)						
1[64]	1538	67 (22 to 96)	93 (90 to 94)	9 (5 to 17)	0.4 (0.1 to 1.1)	Very low
Risk > 1:300 per pregnancy for trisomy 21 (using average of both fetuses' nuchal translucency)						
1[64]	1538	100 (54 to 100)	86 (83 to 89)	7 (5 to 9)	0.1 (0.0 to 1.2)	Very low
Nuchal translucency without maternal age						
>95th centile for trisomy 21 or trisomy 18						
1[64]	1538	86 (67 to 100)	90 (88 to 91)	8 (6 to 11)	0.2 (0.0 to 0.6)	Very low
>95th centile for trisomy 21						
1[64]	1538	83 (52 to 98)	89 (88 to 91)	8 (6 to 11)	0.2 (0.1 to 0.7)	Very low
>95th centile for trisomy 18						
1 [64]	1538	100 (16 to 100)	89 (87 to 91)	8 (4 to 13)	0.2 (0.0 to 2.4)	Very low

Table 6.2 GRADE summary of findings for studies evaluating screening tests for chromosomal abnormalities in dichorionic twins

Number of studies	Numbers of twin and triplet pregnancies	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Combined tests						
Nuchal translucency, maternal age, f-beta-hCG and PAPP-A – risk 1:250 for trisomy 21						
1[63]	176	100 (3 to 100)	97 (95 to 100)	35 (15 to 83)	0.0 (0.0 to 2.9)	Very low
Nuchal translucency with maternal age						
Risk > 1:250 per fetus for trisomy 21						
1[63]	88	100 (3 to 100)	91 (87 to 96)	12 (3 to 22)	0.0 (0.0 to 3.0)	Very low
Nuchal translucency alone						
>95th centile for trisomy 21, trisomy 18 or trisomy 13						
1[65]	706	91 (74 to 100)	96 (95 to 98)	23 (15 to 35)	0.1 (0.0 to 0.6)	Low
>95th centile for trisomy 21 or trisomy 18						
1[66]	350	100 (40 to 100)	98 (96 to 99)	48 (21 to 109)	0.1 (0.0 to 1.4)	Very low
>99th centile for trisomy 21						
1[67]	332	50 (1 to 99)	98 (96 to 99)	28 (6 to 136)	0.5 (0.1 to 2.0)	Very low
Nuchal translucency without maternal age						
>95th centile for trisomy 21						
1[68]	140	100 (3 to 100)	94 (89 to 98)	15 (8 to 29)	0.0 (0.0 to 3.0)	Very low
1[66]	350	100 (99 to 100)	98 (97 to 99)	50 (24 to 103)	0.0 (0.0 to 2.7)	Very low
>95th centile for trisomy 18						
1[66]	350	100 (3 to 100)	97 (96 to 99)	39 (20 to 74)	0.0 (0.0 to 2.8)	Very low

Table 6.3 GRADE summary of findings for studies evaluating screening tests for chromosomal abnormalities in twin pregnancies with unreported or mixed chorionicity or in triplet pregnancies

Number of studies	Numbers of twin and triplet pregnancies	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Combined tests						
Nuchal translucency, maternal age, f-beta-hCG and PAPP-A – risk > 1:250 per fetus for trisomy 21						
1[63]	200 twin 0 triplet	100 (29 to 100)	96 (93 to 99)	23 (10 to 51)	0.1 (0.0 to 1.7)	Very low
Nuchal translucency, maternal age, f-beta-hCG and PAPP-A – risk > 1:300 per fetus for trisomy 21						
1[69]	114 twin 0 triplet	100 (29 to 100)	95 (89 to 98)	13 (4 to 39)	0.3 (0.0 to 2.9)	Very low
1[70]	398 twin 0 triplet	100 (29 to 100)	99.8 (99 to 100)	395 (56 to 2797)	0.0 (0.0 to 1.7)	Very low
Nuchal translucency with maternal age						
Risk > 1:250 per fetus for trisomy 21						
1[63]	200 twin 0 triplet	100 (29 to 100)	91 (87 to 95)	11 (7 to 17)	0.0 (0.0 to 0.9)	Very low
Risk > 1:300 per fetus for trisomy 21						
1[65]	896 twin 0 triplet	100 (63 to 100)	81 (79 to 84)	5 (4 to 6)	0.1 (0.0 to 1.0)	Low
Nuchal translucency alone						
>95th centile for trisomy 21, trisomy 18 or trisomy 13						
1[65]	896 twin 0 triplet	91 (74 to 100)	95 (94 to 97)	19 (13 to 26)	0.1 (0.0 to 0.6)	Low
>95th centile for trisomy 21 or trisomy 18						
1[66]	412 twin 24 triplet	100 (40 to 100)	98 (97 to 99)	48 (25 to 91)	0.0 (0.0 to 1.4)	Very low
>99th centile for trisomy 21						
1[67]	412 twin 0 triplet	50 (1 to 99)	97 (95 to 99)	19 (4 to 84)	0.5 (0.1 to 2.1)	Very low
>95th centile for trisomy 21						
3[65;66;71]	828 twin 24 triplet	93 (66 to 100)	95 (94 to 96)	20 (12 to 35)	0.1 (0.0 to 0.5)	Very low
1[68]	200 twin 0 triplet	100 (3 to 100)	93 (89 to 96)	13 (8 to 21)	0.0(0.0 to 3.0)	Very low
>95th centile for trisomy 18						
1[66]	412 twin 24 triplet	100 (3 to 100)	97 (95 to 98)	24 (9 to 63)	0.3 (0.0 to 2.9)	Very low

Evidence statement

Monochorionic twins

Data were reported for the use of a combined test (nuchal translucency, maternal age, free beta-hCG and PAPP-A), nuchal translucency with maternal age, and nuchal translucency alone to predict trisomy 21 or trisomy 18 in monochorionic twin pregnancies.

For trisomy 21, using the combined test (risk greater than 1:250, very low quality evidence) and using nuchal translucency with maternal age (risk greater than 1:250, very low quality evidence) both showed stronger likelihood ratios and higher sensitivities than the other methods.

Dichorionic twins

Data were reported for the use of a combined test (nuchal translucency, maternal age, free beta-hCG and PAPP-A), nuchal translucency with maternal age, and nuchal translucency alone to predict trisomy 21, trisomy 18 or trisomy 13 in dichorionic twin pregnancies.

For predicting trisomy 21, the strongest likelihood ratios and highest sensitivity were reported when using nuchal translucency greater than the 95th centile alone (low to very low quality evidence), although using nuchal translucency above the 99th centile, the combined test or nuchal translucency with maternal age (all very low quality evidence) also showed strong likelihood ratios and high sensitivities.

Unreported or mixed chorionicity (including triplets)

Data were reported for the use of a combined test (nuchal translucency, maternal age, free beta-hCG and PAPP-A), nuchal translucency with maternal age, and nuchal translucency alone to predict trisomy 21, trisomy 18 or trisomy 13 in twin or triplet pregnancies with unreported or different chorionicities.

For predicting trisomy 21 in twin pregnancies, the strongest likelihood ratios were reported when using a combined test with a risk of greater than 1:300 per fetus (low quality evidence). This test also had a very high sensitivity.

Although no separate data were available for triplets, data were reported for the use of nuchal translucency greater than the 95th centile alone to predict trisomy 21 or 18 in populations that included twin and triplet pregnancies (low and very low quality evidence, but mainly very low). Strong positive likelihood ratio ($LR^{+)}$ and moderate to strong negative likelihood ratio (LR^{-}) statistics were obtained, and the sensitivities were high.

No evidence was reported for the use of nasal bone, tricuspid regurgitation, Doppler ultrasound, the quadruple test or the integrated test in predicting chromosomal abnormalities in twin or triplet pregnancies.

Health economics profile

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

Evidence to recommendations

Relative value placed on the outcomes considered

Sensitivity is the proportion of fetuses born with chromosomal abnormalities that were predicted to have an abnormality (true positive). One hundred minus sensitivity (100 – sensitivity) shows how many of these fetuses were predicted to be normal (false negative).

Specificity is the proportion of fetuses that had no abnormalities that were predicted to have no abnormalities (true negative). One hundred minus specificity (100 – specificity) shows how many of these fetuses were predicted to have an abnormality (false positive).

Positive predictive value (PPV) is the proportion of fetuses that were predicted to have abnormalities that had chromosomal abnormalities. One hundred minus PPV (100 – PPV) shows how many of these fetuses did not have chromosomal abnormalities.

Negative predictive value (NPV) is the proportion of fetuses that were predicted to not have chromosomal abnormalities that did not have chromosomal abnormalities. One hundred minus NPV (100 – NPV) shows how many of these fetuses had a chromosomal abnormality.

LR^{+} shows how much the odds of a fetus having chromosomal abnormalities increase when abnormalities are predicted. LR^{-} shows how much the odds of a fetus having chromosomal abnormalities decreases when a test predicts there will are no abnormalities.

The GDG prioritised likelihood ratios and sensitivity when considering the evidence for different methods of predicting chromosomal abnormalities.

Trade-off between clinical benefits and harms

Twin and triplet pregnancies are at greater risk of chromosomal and structural fetal abnormalities than are singleton pregnancies, and so the likelihood of being offered invasive testing (such as amniocentesis) is higher in twin and triplet pregnancies. The clinical benefits of screening for chromosomal abnormalities include the correct identification of the anomaly. This allows the woman to consider termination of pregnancy or selective termination of pregnancy, or to be prepared for the outcome after birth. Potential harms can arise from false positive test results, which could lead to unnecessary invasive testing with the associated risk of pregnancy loss, as well as unnecessary increase in anxiety for the woman. This is especially true in twin and triplet pregnancies, as two or more fetuses could be put at unnecessary risk. There is an added risk of miscarriage of the healthy co-twin if the woman chooses selective embryo reduction to manage the pregnancy. False negative

results are also harmful, as they would lead to inappropriate reassurance. This is particularly an issue with screening tests that provide 'average' risks for Down's syndrome in a dichorionic twin pregnancy. The main cost benefits are the correct identification of normal fetuses (the majority) and the few abnormal fetuses (the minority).

Quality of evidence

In each case, the quality of evidence for combined tests, for nuchal translucency with maternal age and for nuchal translucency alone ranged from very low to low, and was mostly very low.

Other considerations

Chorionicity will affect the accuracy of the tests. In monochorionic twin pregnancies, the specificity will be lower. Counselling in twin and triplet pregnancies should include the potential risks of selective termination of pregnancy (which presents an additional risk in twin and triplet pregnancies). As in 'Antenatal care' (NICE clinical guideline 62)[14], specific information should be given to women regarding:

- the screening pathway for positive and negative screening results
- the decisions that need to be made along the pathway and their consequences
- the fact that screening does not provide a definitive diagnosis and a full explanation of the risk score obtained following screening
- information about chorionic villus sampling and amniocentesis
- balanced and accurate information about Down's syndrome
- the additional risks of multiple pregnancy (as outlined above).

The triple/quadruple test and one version of the combined test provide an 'average' Down's syndrome risk in multiple pregnancies. Although this is entirely appropriate in monochorionic twin and monochorionic triplet pregnancies because the individual risk should be similar for all fetuses, it is likely to be misleading in dichorionic twin, dichorionic triplet and trichorionic triplet pregnancies where the individual risk can differ between fetuses. Furthermore, this sort of screening does not allow correct labelling or enable selective antenatal invasive diagnosis testing. The GDG's view was that offering first-trimester screening for Down's syndrome was the strongly preferred option for women with twin and triplet pregnancies, and that all women with twin and triplet pregnancies should be offered referral to maternity services sufficiently early in the first trimester to allow them the opportunity to access first-trimester screening for Down's syndrome (see Section 5.4). The GDG recommended that second-trimester serum screening for Down's syndrome should be considered for women with twin pregnancies only when first-trimester screening cannot be offered (for example, because the woman books too late in pregnancy) and as long the woman has been given information explaining the limitations of second-trimester serum screening in twin pregnancies.

The GDG noted the importance of assigning and clearly documenting nomenclature to fetuses (for example upper and lower, or left and right sac) to ensure consistency throughout the pregnancy; nomenclature assigned antenatally does not necessarily relate to the order of birth. The recommendations relating to nomenclature are presented in Section 4.2.

No evidence was identified regarding the accuracy of screening for trisomy 21 in triplet pregnancies. However, it is likely that the accuracy of nuchal translucency screening is similar to that in twin pregnancies. Women with triplet pregnancies may, therefore, be offered first-trimester screening with nuchal translucency combined with maternal age to calculate a risk for each fetus. This will require a change in practice in some settings where the computer software that is used to estimate risks reports risks per pregnancy. Second-trimester serum screening for trisomy 21 in triplet pregnancies is not recommended because of the lack of evidence to support its use.

Although the GDG recognised that screening tests for trisomy 21 also predict the much rarer chromosomal abnormalities, namely trisomies 13 and 18, the GDG restricted its recommendations to screening for Down's syndrome (trisomy 21), in line with 'Antenatal care' (NICE clinical guideline 62).[14]

In the light of the lack of evidence to the contrary, the GDG's view was that the threshold used to define high risk should be that recommended by the NHS Fetal Anomaly Screening Programme (FASP), which is 1:150 (see http://fetalanomaly.screening.nhs.uk/standardsandpolicies).

Recommendations

Number	Recommendation
27	A healthcare professional with experience of caring for women with twin and triplet pregnancies should offer information and counselling to women before and after every screening test.
28	Inform women with twin and triplet pregnancies about the complexity of decisions they may need to make depending on the outcomes of screening, including different options according to the chorionicity of the pregnancy.
29	Before screening for Down's syndrome offer women with twin and triplet pregnancies information about: • the greater likelihood of Down's syndrome in twin and triplet pregnancies • the different options for screening* • the false positive rate of screening tests, which is higher in twin and triplet pregnancies • the likelihood of being offered invasive testing, which is higher in twin and triplet pregnancies • the greater likelihood of complications of invasive testing • the physical risks and psychological implications in the short and long term relating to selective fetal reduction.
30	Healthcare professionals who screen for Down's syndrome in twin pregnancies should: • map the fetal positions • use 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 (at approximately 11 weeks 0 days to 13 weeks 6 days; see 1) • calculate the risk of Down's syndrome per pregnancy in monochorionic twin pregnancies • calculate the risk of Down's syndrome for each baby in dichorionic twin pregnancies.
31	Healthcare professionals who screen for Down's syndrome in triplet pregnancies should: • map the fetal positions • use nuchal translucency and maternal age to screen for Down's syndrome when crown–rump length measures from 45 mm to 84 mm (at approximately 11 weeks 0 days to 13 weeks 6 days; see 1) • calculate the risk of Down's syndrome per pregnancy in monochorionic triplet pregnancies • calculate the risk of Down's syndrome for each baby in dichorionic and trichorionic triplet pregnancies.
32	Where first trimester screening for Down's syndrome cannot be offered to a woman with a twin pregnancy (for example, if the woman books too late in pregnancy) consider second trimester serum screening and explain to the woman the potential problems of such screening. These include the increased likelihood of pregnancy

* See 'Antenatal care' (NICE clinical guideline 62). Available from www.nice.org.uk/guidance/CG62

	loss associated with double invasive testing because the risk of Down's syndrome cannot be calculated separately for each baby.
33	Do not use second trimester serum screening for Down's syndrome in triplet pregnancies.
34	Offer women with twin and triplet pregnancies who have a high risk of Down's syndrome (use a threshold of 1:150 as defined by the NHS Fetal Anomaly Screening Programme [FASP])* referral to a fetal medicine specialist in a tertiary level fetal medicine centre.

Number	Research recommendation
RR 7	When and how should screening for chromosomal abnormalities be conducted in twin and triplet pregnancies? Why this is important The evidence reviewed for the guideline in relation to screening for chromosomal abnormalities was limited in terms of predictive accuracy data for different thresholds of risk in twin and triplet pregnancies. The balance between the number of true positives (babies correctly identified as having Down's syndrome using a screening test) and the number of false positives (babies incorrectly identified as having Down's syndrome using a screening test), which may result in termination of pregnancy or selective fetocide, have not been reported widely for twin or triplet pregnancies, although it is likely to be different to that in singleton pregnancies. No evidence was identified in relation to the impact of screening on psychological health and wellbeing. Further research is, therefore, needed to determine the optimal (most accurate) threshold of risk in predicting chromosomal abnormalities in twin and triplet pregnancies. The research should consider the potential health economic impact in achieving a balance between the identification of Down's syndrome pregnancies and losses suffered from increased invasive testing and selective fetocide. It should also consider the maternal psychological impact of screening through qualitative studies.

6.2 Screening for structural abnormalities

Introduction

'Antenatal care' (NICE clinical guideline 62)[14] recommends that ultrasound screening for fetal anomalies is offered routinely between 18 and 21 weeks of gestation in singleton pregnancies. Timely diagnosis of fetal anomalies allows reproductive choice, time to prepare, planning for birth and access to intrauterine therapy, where appropriate. The presence of two or more fetuses in twin and triplet pregnancies may hinder full anatomical assessment of pregnancy by ultrasound. This review question aims to determine when and how ultrasound screening should be performed to aid in the antenatal diagnosis of fetal anomalies in twin and triplet pregnancies.

Structural anomalies (especially cardiac anomalies) occur more frequently in twin and triplet pregnancies than in singleton pregnancies, and the management of twin and triplet pregnancies found to be discordant for fetal anomalies (where only one fetus is abnormal) is more complicated as a consequence. Timely diagnosis of anomalies gives parents and healthcare professionals a wider range of options for management of the pregnancy. However, the presence of two or more fetuses can sometimes extend the time taken to undertake such scans and reduce their diagnostic accuracy.

* See http://fetalanomaly.screening.nhs.uk/standardsandpolicies

This review question aims to address ultrasound screening for structural anomalies in such circumstances.

Review question

When and how should screening be used to identify structural abnormalities in multiple pregnancy?

Existing NICE guidance

'Antenatal care' (NICE clinical guideline 62)[14] examined whether first- and second-trimester ultrasound scans, nuchal translucency measurement and serum screening for alpha-fetoprotein (AFP) were diagnostically accurate and effective in detecting structural anomalies in singleton pregnancies. Detection rates for second-trimester ultrasound scans were summarised according to specific anomalies, and overall detection rates were presented according to Royal College of Obstetricians and Gynaecologists (RCOG) categories. 'Antenatal care' (NICE clinical guideline 62)[14] includes the following recommendations:

- Offer ultrasound screening for fetal anomalies routinely, normally between 18 weeks 0 days and 20 weeks 6 days. Multiple pregnancy is identified as a consideration that may require a delay in the timing of the scan.
- At the first contact with a healthcare professional, give women information about the purpose and implications of the anomaly scan to enable them to make an informed choice as to whether or not to have the scan. The purpose of the scan is to identify fetal anomalies and allow:
    - reproductive choice (including the option of terminating the pregnancy)
    - parents to prepare for treatment, disability, palliative care or termination of pregnancy
    - managed birth in a specialist centre
    - intrauterine therapy.
- Inform women about the limitations of routine ultrasound screening and that detection rates vary by the type of fetal anomaly, the woman's BMI and the position of the unborn baby at the time of the scan.
- If an anomaly is detected during the anomaly scan, inform the woman of the findings to enable them to make an informed choice as to whether they wish to continue or terminate the pregnancy.
- Perform fetal echocardiography involving the four-chamber view of the fetal heart and outflow tracts as part of the routine anomaly scan.
- Do not offer routine screening for cardiac anomalies using nuchal translucency.
- When routine ultrasound screening is performed to detect neural tube defects, AFP testing is not required.
- Participation in regional congenital anomaly registers and/or UK National Screening Committee approved audit systems facilitates the audit of detection rates.

'Antenatal care' (NICE clinical guideline 62)[14] also recommends further research to be undertaken to elucidate the relationship between increased nuchal translucency and cardiac defects.

Description of included studies

Three studies investigating the diagnostic accuracy of the following methods to identify structural anomalies were identified for inclusion:

- ultrasound scan in the second or third trimester (one study)[72]
- fetal echocardiogram in the second or third trimester (one study)[73]
- a composite of ultrasound in the first trimester, ultrasound in the second trimester and fetal echocardiogram (one study).[74]

In the retrospective study that examined the accuracy of ultrasound scan,[72] the mean gestational age at the time of diagnosis of the anomaly was 21.3 weeks, with a range of 16–35 weeks. The study was conducted in Taiwan.

In the prospective study that examined the diagnostic accuracy of fetal echocardiogram,[73] the mean gestational age at the time of diagnosis of the anomaly was not reported, but ranged from 20 to 37 weeks. The study was conducted in China.

In the study which reported results of a composite test,[74] 68% of the study population had a first trimester ultrasound including nuchal translucency measurement performed before a gestational age of 13 weeks 6 days. All pregnancies then had an ultrasound scan performed at week 19 and fetal echocardiography performed at week 21. This study was conducted in Denmark and Sweden.

All of the studies included both monochorionic and dichorionic twin pregnancies. In one study, data were reported separately for monochorionic and dichorionic twins.[74] However, the numbers of abnormalities detected in monochorionic twin pregnancies were too small to allow diagnostic accuracy data to be calculated for this subgroup.

None of the studies included triplet pregnancies.

Published health economic evidence

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

Evidence profiles

The evidence profile for this question is presented in Table 6.4.

Table 6.4 GRADE summary of findings for studies evaluating screening tests for structural abnormalities

Number of studies	Numbers of twin and triplet pregnancies	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
All anomalies						
Ultrasound (second or third trimester anomaly scan)						
1[72]	1397 twin 0 triplet	78 (60 to 91)	100 (99 to 100)	2111 (131 to 33943)	0.2 (0.1 to 0.4)	Very low
Composite – nuchal translucency, ultrasound (second or third trimester anomaly scan) and fetal echocardiography						
1[74]	990 twin 0 triplet	28 (12 to 49)	100 (99 to 100)	557 (33 to 9502)	0.7 (0.6 to 0.9)	Very low
Composite – nuchal translucency, ultrasound (second or third trimester anomaly scan) and fetal echocardiography in dichorionic twin pregnancies						
1[74]	842 twin 0 triplet	33 (15 to 57)	100 (99 to 100)	560 (33 to 9509)	0.7 (0.5 to 0.9)	Very low
All cardiac anomalies						
Fetal echocardiography						
1[73]	1206 twin 0 triplet	88 (62 to 98)	100 (99 to 100)	2032 (126 to 32692)	0.2 (0.1 to 0.5)	Very low
Lethal anomalies						
Ultrasound (second or third trimester anomaly scan)						
1[72]	1397 twin 0 triplet	100 (29 to 100)	100 (99 to 100)	2436 (149 to 39898)	0.1 (0.0 to 1.7)	Very low
Fetal echocardiography						
1[73]	2204 twin 0 triplet	100 (3 to 100)	100 (99 to 100)	3306 (185 to 59171)	0.3 (0.0 to 2.8)	Very low
Composite – nuchal translucency, ultrasound (second or third trimester anomaly scan) and fetal echocardiography						
1[74]	990 twin 0 triplet	100 (48 to 100)	100 (99 to 100)	1808 (112 to 29184)	0.1 (0.0 to 1.2)	Very low
Possible survival and long-term morbidity						
Ultrasound (second or third trimester anomaly scan)						
1[72]	1394 twin	94	100	2526	0.1	Very low

	0 triplet	(71 to 99)	(99 to 100)	(158 to 40511)	(0.0 to 0.4)	
Fetal echocardiography						
1[73]	2204 twin 0 triplet	100 (69 to 100)	100 (99 to 100)	4191 (261 to 67176)	0.1 (0.0 to 0.7)	Very low
Anomalies amenable to intrauterine therapy						
Ultrasound (second or third trimester anomaly scan)						
1[72]	1394 twin 0 triplet	100 (16 to 100)	100 (99 to 100)	2091 (117 to 37418)	0.3 (0.0 to 2.8)	Very low
Anomalies associated with possible short-term/immediate morbidity						
Ultrasound (second or third trimester anomaly scan)						
1[72]	1394 twin 0 triplet	43 (10 to 82)	100 (99 to 100)	1215 (68 to 21647)	0.6 (0.3 to 1.0)	Very low
Fetal echocardiography						
1[73]	2005 twin 0 triplet	33 (1 to 91)	100 (99 to 100)	1652 (79 to 34754)	0.6 (0.3 to 1.3	Very low

Evidence statement

Evidence was identified for the use of the following methods for identifying structural abnormalities in twin pregnancies:

- second or third trimester ultrasound
- fetal echocardiogram
- a composite of second trimester ultrasound and fetal echocardiogram with or without first trimester ultrasound and nuchal translucency scan.

The overall quality of the evidence was very low.

Second or third trimester ultrasound (very low quality evidence) showed a higher sensitivity and stronger LR^- than did a composite of nuchal translucency, second or third trimester ultrasound and fetal echocardiography (very low quality evidence). The specificity and positive likelihood ratio was similar for both methods. Fetal echocardiography (very low quality evidence) had a low sensitivity but strong likelihood ratios and a high specificity.

Subgroup analysis was performed to determine the accuracy of the different methods to detect structural anomalies (especially cardiac anomalies) according to the categories of likely severity used by the RCOG and the NHS FASP (see http://fetalanomaly.screening.nhs.uk/standardsandpolicies).

For detecting all fetal structural abnormalities, diagnostic accuracy evidence was reported for second or third trimester ultrasound (very low quality evidence). All methods showed a very high specificity but low to moderate sensitivity with convincing likelihood ratios for detecting fetal structural abnormalities.

For detecting all fetal cardiac abnormalities, diagnostic accuracy evidence was reported for second or third trimester ultrasound (very low quality evidence). All methods showed very high sensitivity and specificity with convincing likelihood ratios for detecting fetal cardiac abnormalities.

For detecting lethal structural anomalies, diagnostic accuracy evidence was reported for second or third trimester ultrasound (very low quality evidence), fetal echocardiography (very low quality evidence) and a composite of nuchal translucency, second or third trimester ultrasound and fetal echocardiography (very low quality evidence). All methods showed a very high sensitivity and specificity with convincing likelihood ratios for detecting lethal structural anomalies.

For detecting structural anomalies that may lead to survival with long-term morbidity, diagnostic accuracy evidence was found for second or third trimester ultrasound (very low quality evidence) and fetal echocardiography (very low quality evidence). Both methods reported high sensitivity and specificity with very strong likelihood ratios.

For detecting anomalies amenable to intrauterine therapy, diagnostic accuracy evidence was found for second or third trimester ultrasound (very low quality evidence). Ultrasound was reported to have a very high sensitivity and specificity with strong likelihood ratios, although the quality of the evidence was low.

For detecting anomalies associated with possible short-term or immediate morbidity, evidence was found for second or third trimester ultrasound (very low quality evidence) and echocardiography (very low quality evidence). Both methods showed low sensitivities but high specificities and convincing likelihood ratios.

It was not possible to obtain diagnostic accuracy data for subgroups according to gestational age. In terms of subgroup analysis by chorionicity, only one set of data was reported. This showed that in detecting all anomalies, a composite of nuchal translucency, second or third trimester ultrasound and fetal echocardiography was slightly more sensitive in dichorionic twin pregnancies than in a group of mixed chorionicity. The likelihood ratios and specificity did not differ. No data were available for monochorionic twin pregnancies alone.

Health economics profile

No published health economic evidence was identified and this question was not prioritised for health economic analysis. The screening strategy for structural anomalies in twin and triplet pregnancies should be the same as that recommended in 'Antenatal care' (NICE clinical guideline 62)[14] for singleton pregnancies and in the NHS FASP. Consideration should be given to scheduling these scans at a later gestational age and to the increased amount of time that the scans will require. Those for twin and triplet pregnancies will last longer, as recommended by the NHS FASP*, and cost around £71 per scan.

Evidence to recommendations

Relative value placed on the outcomes considered

Sensitivity is the proportion of multiple pregnancies where at least one fetus developed a structural anomaly of the fetus that were predicted to develop a structural anomaly (true positive). One hundred minus sensitivity (100 – sensitivity) shows how many of these pregnancies were predicted to be normal (false negative).

Specificity is the proportion of multiple pregnancies where no fetus developed a structural anomaly during pregnancy and the prediction was that no fetuses would develop an anomaly during pregnancy (true negative). One hundred minus specificity (100 – specificity) shows how many of these pregnancies were predicted to have at least one fetus with a structural anomaly (false positive).

PPV is the proportion of multiple pregnancies predicted to have at least one fetus with a structural anomaly and that resulted in at least one fetus with a structural anomaly. One hundred minus PPV (100 – PPV) shows how many of these pregnancies had fetuses that were found to not to have a structural anomaly.

NPV is the proportion of the pregnancies that were predicted to be normal and none of the fetuses had structural anomalies. One hundred minus NPV (100– NPV) shows how many of these pregnancies did have at least one fetus that developed a structural anomaly.

LR^+ shows how much the odds of a pregnancy having at least one fetus with a structural anomaly increase when a structural anomaly is predicted. LR^- shows how much the odds of a pregnancy having at least one fetus with a structural anomaly decrease when a normal pregnancy is predicted.

The GDG's view was that focusing on likelihood ratios, sensitivity and specificity would allow it to make the most effective recommendations for this review question.

Trade-off between clinical benefits and harms

The trade-off between clinical benefits and harm are not dissimilar from those in routine ultrasound screening in singleton pregnancy. The parental anxiety generated from a presumed diagnosis of abnormality is considerable. This can be amplified further in twin or triplet pregnancy where invasive testing or therapeutic procedures carry a risk of harm to the healthy fetus(es). In contrast, there may be situations where failure to diagnose a fetal abnormality in a fetus may increase the risk of harm to

* See http://www.perinatal.nhs.uk/ultrasound/RUG/Programme_statement_-_The_use_of_CRL_and_NT_measurements_in_screening_for_Down%92s_syndrome_Sept2010.pdf

other fetuses that are healthy. However, the GDG did not consider that the potential harms outweighed the benefits of screening for fetal anomalies in twin and triplet pregnancies.

Trade-off between net health benefits and resource use

The NHS FASP identifies a resource implication for scanning in twin and triplet pregnancies, due to the increase in scanning time required for such pregnancies. Consideration should be given to scheduling scans nearer 20 weeks 6 days because of the increased complexity. Those for twin and triplet pregnancies will last longer and cost around £71 per scan.

Quality of evidence

There is very low quality evidence for the use of echocardiography and a composite method of ultrasound, echocardiography and nuchal translucency. There is very low quality evidence for the use of ultrasound.

Other considerations

The GDG noted that special consideration should be given to assigning nomenclature and position of the fetuses in twin and triplet pregnancies (see Sections 4.2 and 6.1). The relative infrequency of twin and triplet pregnancies compared to singleton pregnancies negatively affects the number and size of the studies in this area. Apart from the increased time required to undertake the ultrasound screening, there is little reason to expect mid-trimester ultrasound to be significantly less effective in twin and triplet pregnancies compared to singleton pregnancies. No evidence was identified to suggest that anomaly screening in twin or triplet pregnancies is more or less effective than in singleton pregnancies. There is a lack of evidence to support a different screening strategy for triplets or monochorionic twins.

Recommendations

Number	Recommendation
35	Offer screening for structural abnormalities (such as cardiac abnormalities) in twin and triplet pregnancies as in routine antenatal care.*
36	Consider scheduling ultrasound scans in twin and triplet pregnancies at a slightly later gestational age than in singleton pregnancies and be aware that the scans will take longer to perform.
37	Allow 45 minutes for the anomaly scan in twin and triplet pregnancies (as recommended by FASP).†
38	Allow 30 minutes for growth scans in twin and triplet pregnancies.

Number	Research recommendation
RR 8	When and how should screening for structural abnormalities be conducted in twin and triplet pregnancies? Why this is important The evidence reviewed for the guideline was limited in quantity and quality. The incidence of structural abnormalities may differ between monochorionic, dichorionic and trichorionic pregnancies, although there are currently no data to determine whether screening should be targeted in particular subpopulations (defined by chorionicity). Further research is, therefore, needed to evaluate screening tests for structural abnormalities in twin and triplet pregnancies. The research should address the optimal timing of the anomaly scan in twin and triplet pregnancies, the

* See 'Antenatal care' (NICE clinical guideline 62) and also FASP at http://fetalanomaly.screening.nhs.uk/standardsandpolicies
† See http://fetalanomaly.screening.nhs.uk/standardsandpolicies

effectiveness of mid-trimester ultrasound in the detection of structural abnormalities in such pregnancies, the impact of chorionicity on outcomes of twin and triplet pregnancies with structural abnormalities, and the psychological impact of screening for structural abnormalities in women with twin and triplet pregnancies. The last aspect could be addressed through qualitative studies.

6.3 Monitoring for feto-fetal transfusion syndrome

Introduction

About 20–25% of twin pregnancies are monochorionic and about 10–15% of monochorionic twin pregnancies are complicated by feto-fetal transfusion syndrome (FFTS) due to unequal placental sharing. This morbid condition may also affect monochorionic and dichorionic triplet pregnancies. FFTS is characterised by progressive growth discordance with hypovolaemia, oliguria and oligohydramnios in the donor fetus and volume overload, polyuria, polyhydramnios, high-output cardiac failure and hydrops in the recipient fetus. Outcomes associated with this chronic condition are very poor, with 60–90% of pregnancies resulting in stillbirth, neonatal death or disability. However, timely diagnosis, staging and fetoscopic laser ablation significantly improve perinatal outcomes, resulting in rates of 70–85% for being able to take at least one baby home with a low incidence of poor neurodevelopmental outcomes. Currently, there is no consensus regarding the optimal screening strategy to allow the early diagnosis of FFTS in monochorionic twin and triplet pregnancies.

Review question

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

Existing NICE guidance

No existing NICE guidance was identified as being relevant to screening for FFTS. 'Intrauterine laser ablation of placental vessels for the treatment of twin-to-twin transfusion syndrome' (NICE interventional procedure guidance 198)[22] and 'Septostomy with or without amnioreduction for the treatment of twin-to-twin transfusion syndrome' (NICE interventional procedure guidance 199)[23] address the management of FFTS, which is outside the scope of this guideline.

Description of included studies

Six studies that reported on predicting FFTS were identified for inclusion.[75-80] Three of the studies were conducted in the UK,[75;76;79] one in Portugal,[78] one in the Netherlands[77] and one in Spain.[80]

For screening in the first trimester, four studies reported findings for the use of nuchal translucency thickness to predict FFTS.[75-78] Two studies used crown–rump length[76;78] and two studies reported findings for using abnormal ductus venosus blood flow.[78;79]

For screening in the second trimester, one study reported findings for the use of intertwin membrane folding.[75] Another study reported findings for intertwin amniotic fluid discordancy.[80]

No studies were identified in relation to using femur length, abdominal circumference, estimated fetal weight, ultrasonography of placental anastomoses, tricuspid regurgitation or absent visualisation of a donor bladder to predict FFTS.

All of the included studies involved women with twin pregnancies. No studies were identified for predicting FFTS in triplet pregnancies.

Published health economic evidence

No published health economic evidence was identified, although this question was prioritised for health economic analysis.

Evidence profiles

Evidence profiles for this question are presented in Tables 6.5 and 6.6. Table 6.5 presents diagnostic accuracy statistics and Table 6.6 presents other outcome measures.

Table 6.5 GRADE summary of findings for studies reporting diagnostic accuracy measures for screening tests for feto-fetal transfusion syndrome

Number of studies	Numbers of twin pregnancies	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
First trimester methods						
Nuchal translucency – thickness > 95th centile for gestational age at 10–14 weeks (for fetuses)						
1[75]	574	38 (23 to 53)	94 (92 to 96)	6 (4 to 11)	0.7 (0.5 to 0.9)	Moderate
Nuchal translucency – thickness > 95th centile for gestational age in at least 1 fetus at 10–14 weeks (for pregnancies)						
1[75]	287	32 (17 to 48)	90 (86 to 94)	3 (2 to 6)	0.8 (0.6 to 0.9)	Moderate
Nuchal translucency – discordance ≥ 20% (as a percentage of larger measurement)						
2[76;77]	525	55 (43 to 67)	78 (74 to 82)	3 (2 to 4)	0.6 (0.4 to 0.7)	Low
Nuchal translucency – difference of ≥ 0.6mm at 11–14 weeks						
1[78]	99	50 (22 to 78)	92 (86 to 98)	6 (3 to 15)	0.5 (0.3 to 1.0)	Moderate
Crown–rump length (CRL) - discordance > 10% at 11–14 weeks (as a percentage of larger measurement)						
1[76]	480	19 (10 to 29)	92 (89 to 94)	2 (1 to 4)	0.9 (0.8 to 1.0)	Low
Ductus venosus blood flow – abnormal wave form in at least one fetus (at 11–14 weeks) (including absent, reversed or reversed a-wave)						
2[78;79]	278	45 (30 to 61)	89 (84 to 93)	6 (1 to 35)	0.6 (0.4 to 0.9)	Very low
Second trimester methods						
Intertwin membrane folding at 15–17 weeks						
1[75]	153	91 (80 to 103)	79 (71 to 86)	4 (3 to 6)	0.1 (0.0 to 0.5)	Moderate
Intertwin amniotic discordance of 3.1cm at 18–21 weeks						
1[80]	52	82 (59 to 100)	44 (29 to 59)	1 (1 to 2)	0.4 (0.1 to 1.5)	Moderate

Table 6.6 GRADE summary of findings for studies that did not report diagnostic accuracy measures for screening tests for feto-fetal transfusion syndrome

Number of studies	Number		Effect			Quality
	Number of twin pregnancies	Non FFTS group	FFTS group	Odds Ratio	P value	
Nuchal translucency						
Mean inter-twin discordance						
1[79]	179	19.6%	16.7%	Not reported	Not significant (P = 0.78)	Very low
Mean inter-twin discordance - multiple logistical regression analysis (discordancy in nuchal translucency, discordancy in crown–rump length, maternal age, ethnicity, IVF and smoking)						
1[79]	179	19.6%	16.7%	Not reported	Not significant (P = 0.16)	Very low

Evidence statement

First trimester methods

There is evidence that nuchal translucency thickness above the 95th centile for predicting FFTS has a high specificity. However, it has a low sensitivity and weak likelihood ratios (moderate quality evidence). Using the discordance between the twins' nuchal translucency thickness increased the sensitivity and PPV of the test, but did not improve the specificity or likelihood ratios (moderate quality evidence). There was additional evidence that showed the discordance of nuchal translucency thickness between fetuses in normal twin pregnancies was not significantly different from the discordance of nuchal translucency thickness in pregnancies affected by FFTS (low and moderate quality evidence).

Using the discordance in crown–rump length also had a low sensitivity and high specificity for predicting FFTS, with stronger LR^+ statistics than using nuchal translucency (low quality evidence).

An abnormal ductus venosus waveform showed similar results to nuchal translucency and crown–rump length when used to predict FFTS, with a low sensitivity but relatively high specificity. The LR^+ statistic was strong (very low quality evidence).

Second trimester methods

Intertwin membrane folding at 15–17 weeks of gestation had a convincing LR^- statistic and high sensitivity (moderate quality evidence). Intertwin amniotic discordance had less convincing likelihood ratios and lower sensitivity (moderate quality evidence). The specificity of both methods was lower than first trimester methods (moderate quality evidence).

No data were identified for using femur length, abdominal circumference, estimated fetal weight, placental anastomoses, tricuspid regurgitations or absent visualisation of donor bladder to predict FFTS.

No data were identified for predicting FFTS in triplet pregnancies.

Health economics profile

No published health economic evidence was identified, although this question was prioritised for health economic analysis. Since first trimester screening is not clinically effective, there was no need for the GDG to explore cost effectiveness.

Evidence to recommendations

Relative value placed on the outcomes considered

Therapeutic fetoscopic laser ablation to improve the outcome of FFTS (including TTTS in twin pregnancies) is predicated on the timely diagnosis of the condition in monochorionic twin and triplet pregnancies. Evidence for the optimal method and timing of screening was reviewed for this question.

Sensitivity is the proportion of pregnancies complicated by FFTS that were predicted correctly (true positive). One hundred minus sensitivity (100 – sensitivity) shows how many of these pregnancies were predicted to be normal (false negative).

Specificity is the proportion of pregnancies that did not develop FFTS that were predicted to be normal (true negative). One hundred minus specificity (100 – specificity) shows how many of these pregnancies were predicted to develop FFTS during pregnancy (false positive).

PPV is the proportion of pregnancies that were predicted to be complicated by FFTS and that developed FFTS. One hundred minus PPV (100 – PPV) shows how many of these pregnancies were actually found to be normal.

NPV is the proportion of pregnancies predicted to be normal that did not develop FFTS. One hundred minus NPV (100 – NPV) shows how many of these pregnancies actually developed FFTS.

LR^+ shows how much the odds of a pregnancy developing FFTS increase when FFTS is predicted. LR^- shows how much the odds of a pregnancy developing FFTS decrease when a normal pregnancy is predicted.

The GDG's view was that, since FFTS is associated with high fetal mortality and morbidity, the most appropriate predictive standard to be used to make recommendations for the condition is sensitivity. Sensitivity is also the most common predictor reported across the studies identified for this review question.

Trade-off between clinical benefits and harms

The clinical benefit of screening is the early diagnosis of FFTS which occurs in 10–15% of monochorionic multiple pregnancies. The latter would not only allow women to tailor their expectations for the pregnancy, but permit timely referral for fetoscopic laser ablation. Potential harms include the increased resources required for screening and the maternal anxiety generated from awareness of the condition and a presumed diagnosis of FFTS. The GDG's view is that the potential benefits outweigh the harms and screening for FFTS should be offered.

Trade-off between net health benefits and resource use

Although there is an additional resource implication from the increased monitoring recommended early in the second trimester, the GDG is aware that the majority of units already undertake these scans in monochorionic twin pregnancies. Furthermore, as there is no clear benefit in screening for FFTS in the first trimester, there may be a resource saving from reduced scanning time and unnecessary referral for FFTS.

Quality of evidence

The quality of the evidence ranged from very low to moderate, and was summarised as:

- nuchal translucency thickness low to moderate quality
- crown–rump length:low quality
- abnormal ductus venosus wave form: very low quality
- intertwin membrane folding in the second trimester: moderate quality
- intertwin amniotic discordance: moderate quality.

Other considerations

The GDG considered that there was insufficient evidence to support screening for FFTS in the first trimester. Regarding screening in the second trimester, the one small study examining intertwin amniotic discordance at 19–21 weeks did not demonstrate any predictive value. No evidence was identified that examined the value of other ultrasound features commonly used in clinical practice (such as femur length, abdominal circumference, estimated fetal weight, placental anastomoses, tricuspid regurgitations or absent visualisation of donor bladder) to predict FFTS. Thus, apart from membrane folding (which is a reflection of changing amniotic fluid volumes around each fetus which leads to the beginning of discordancy in fluid volumes), there was no evidence to recommend the use of ultrasound at a single point to predict FFTS in a monochorionic twin pregnancy. Nevertheless, the GDG was of the view that, in clinical practice, the best chance of identifying FFTS would be through the use of ultrasound assessment looking for features such as membrane folding, absence of bladder, abnormal umbilical artery Doppler recording or discordance of inter-twin amniotic volume. Fetal abdominal circumference or estimated weight can also be used to identify FFTS. Furthermore, the GDG agreed that, because of the speed of development of FFTS, these assessments should be undertaken weekly.

No evidence was identified in relation to triplet pregnancies. The GDG's view was that the recommendations for triplet pregnancies should be the same as those for twin pregnancies.

Recommendations

Number	Recommendation
39	Do not monitoring for feto-fetal transfusion syndrome in the first trimester.
40	Start diagnostic monitoring with ultrasound for feto-fetal transfusion syndrome (including to identify membrane folding) from 16 weeks. Repeat monitoring

	fortnightly until 24 weeks.
41	Carry out weekly monitoring of twin and triplet pregnancies with membrane folding or other possible early signs of feto-fetal transfusion syndrome (specifically, pregnancies with intertwin membrane infolding and amniotic fluid discordance) to allow time to intervene if needed.

Number	Research recommendation
RR 9	When and how should screening for feto-fetal transfusion syndrome be conducted in twin and triplet pregnancies? Why this is important Feto-fetal transfusion syndrome (including twin-to-twin transfusion syndrome in twin pregnancies) is associated with serious adverse outcomes, with 60-90% of affected pregnancies resulting in stillbirth, neonatal death or disability. An effective screening strategy would allow timely diagnosis and the potential for intervention to improve perinatal outcomes. The evidence reviewed for the guideline was obtained via retrospective observational studies involving twin pregnancies, most of which were of moderate or low quality. No studies were identified in relation to the optimal timing and frequency of screening for feto-fetal transfusion syndrome, the level of maternal satisfaction associated with available screening tests, or the accuracy of screening tests in triplet pregnancies. Moreover, no evidence was identified to determine whether or not to use femur length, abdominal circumference, estimated fetal weight, placental anastomoses, tricuspid regurgitation, or absent visualisation of a donor bladder to predict feto-fetal transfusion syndrome. Large randomised controlled trials or prospective cohort studies are, therefore, needed to determine the diagnostic or predictive accuracy of ultrasound and biochemical tests and the effects on clinical outcomes to establish the most effective first-trimester screening strategy for identifying feto-fetal transfusion syndrome in twin and triplet pregnancies. The trials should include consideration of the optimal timing and frequency of screening tests, and maternal satisfaction in relation to different tests. The research will inform future updates of this guideline, in an area where there is currently no consensus regarding an optimal screening strategy.

6.4 Monitoring for intrauterine growth restriction

Introduction

Women with twin and triplet pregnancies are at increased risk of intrauterine growth restriction (IUGR).This review question aims to determine the diagnostic accuracy of methods for detecting IUGR in such pregnancies.

Review question

What is the optimal screening programme to detect intrauterine growth restriction?

Existing NICE guidance

'Antenatal care' (NICE clinical guideline 62)[14] includes the following recommendations:

- Offer routine measurement and recording of symphysis-fundal height for women with healthy singleton pregnancies at every antenatal appointment from 24 weeks of gestation.

- Do not offer routine ultrasound examination after 24 weeks of gestation, and specifically ultrasound estimation of fetal size for suspected large-for-gestational age unborn babies, or routine use of Doppler ultrasound to determine fetal growth in low-risk pregnancies.

'Diabetes in pregnancy' (NICE clinical guideline 63)[21] recommends offering pregnant women with diabetes (who, like women with twin or triplet pregnancies, are at increased risk of IUGR) ultrasound monitoring of fetal growth and amniotic fluid volume every 4 weeks from 28 to 36 weeks. 'Hypertension in pregnancy' (NICE clinical guideline 107)[81] recommends the use of ultrasound screening of fetal growth in all women with hypertension disorders during pregnancy (who are also at increased risk of IUGR).

Detection of IUGR by ultrasound is considered to be an indication for induction of labour in 'Induction of labour' (NICE clinical guideline 70)[17] and an indication for continuous fetal heart rate monitoring in labour in 'Intrapartum care' (NICE clinical guideline 55)[82].

Description of included studies

Twenty-seven studies were identified for inclusion.[83-91;91-108]

The studies investigated the diagnostic accuracy of the following parameters as predictors of IUGR in twin and triplet pregnancies:

- symphysis-fundal height (SFH) measurement
- ultrasound scan (USS) measurement of fetal biometry
- estimated fetal weight (EFW) based on formulae using USS parameters
- Doppler ultrasound of the umbilical cord
- composite screening strategies.

All the studies involved women with twin pregnancies, except for one on the use of Doppler ultrasound[105] that also included triplets.

There were inconsistencies between studies in the criteria and definitions used by the study authors to define poor fetal growth, with some using small-for-gestational age (SGA) and others using IUGR. Two different definitions for SGA were reported, one being a 'late flattening' or 'low growth profile' on Campbell and Newman's charts,[109] and the other being birthweight at or below the fifth centile for gestational age based on Scottish birthweight data. Several different definitions were used for IUGR, falling into two categories. Some studies used fetal weight less than the tenth percentile using different data sets from singleton pregnancies and one used abnormal deviations from Rossavik, Deter and Harist's growth curves.[110] Varying definitions of IUGR and SGA in multiple pregnancy have been used interchangeably in the literature.

One study[83] reported on SFH measurement to detect intertwin birthweight discordance of 20% or more. This was a prospective study conducted in the USA.

One retrospective study[88] reported on the use of biparietal diameter (BPD) measurement to predict an SGA twin. This study was conducted in the UK.

Thirteen studies[89-101] reported on the use of estimated fetal weight (EFW), based on a variety of formulae combining two or more fetal biometric measurements, to predict IUGR (defined as an intertwin birthweight discordance of at least 15%). Overall, the studies examined various formulae, cut-offs and timing and frequency of ultrasound scanning. Three of the studies were prospective[93;96;100] and the others were retrospective. One study was conducted in Ireland,[94] six in the USA[93;95-97;99;101] and one each in France,[92] Belgium,[100] Norway,[89] Israel,[91] Brazil[98] and Taiwan.[90]

Five studies[84-87;106] reported on ultrasound measurements as well as the estimation of fetal weight. Again, the studies examined various parameters and cut-offs, including the timing of ultrasound scanning. Four of the studies were conducted in the USA[84-86;106] and one in Canada.[87] The Canadian study and one of the studies from the USA[85] were prospective; the other studies were retrospective.

Four studies[102-105] reported on the use of Doppler ultrasound to predict IUGR or birthweight discordance. Three examined the value of umbilical artery measurement and one studied Doppler

measurements of the umbilical vein. All four were prospective studies. One was carried out in the UK,[102] one in Switzerland,[104] one in the USA[105] and one in Thailand.[103]

Two studies[107;108] reported on the combination of Doppler ultrasound of the umbilical artery (systolic:diastolic ratio) with conventional ultrasound (EFW) in the prediction of intertwin birthweight discordance of more than 15%. Both were retrospective in design, with one carried out in the USA[108] and the other in Thailand.[107]

No studies were identified that reported data regarding abdominal palpation, amniotic fluid volume, middle cerebral artery Doppler ultrasound or timing and frequency of ultrasound scanning for predicting IUGR in twin or triplet pregnancies.

Published health economic evidence

No published health economic evidence was identified, although this question was prioritised for health economic analysis.

Evidence profiles

Evidence profiles for this question are presented in Tables 6.7 to 6.11.

Table 6.7 GRADE summary of findings of findings for symphysis-fundal height measurement

Number of studies	Numbers of women	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Symphysis-fundal height measurement in detecting intertwin birthweight difference (BWD) ≥ 20%						
1[83]	160	24 (3 to 44)	83 (76 to 89)	1 (1 to 3)	0.9 (0.7 to 1.2)	Moderate

Table 6.8 GRADE summary of findings for ultrasound scan measurement of fetal biometry

Number of studies	Numbers of women	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Abdominal circumference						
Intrapair difference in abdominal circumference > 5% in the prediction of BWD ≥ 20%						
1[84]	90	89 (74 to 100)	60 (48 to 72)	2 (2 to 3)	0.2 (0.1 to 0.7)	Moderate
Abdominal circumference to detect IUGR defined as <10th of expected neonatal birthweight percentile in the smaller weight twin (using logistic regression)						
1[85]	36	100 (NR)	85 (NR)	6 (NR)	0.0 (NR)	Moderate
Abdominal circumference based on ≥1 abnormal negative deviation to predict IUGR (defined according to third trimester growth patterns) in twins						
1[86]	17	100 (NR)	67 (NR)	3 (NR)	0.0 (NR)	Moderate
Abdominal circumference based on antenatal growth assessment score to predict IUGR (defined according to third trimester growth patterns) in twins						
1[86]	17	86 (NR)	88 (NR)	7 (NR)	0.2 (NR)	Moderate
Intertwin abdominal circumference ratio < 0.93 to predict BWD ≥ 25% between 11–38 weeks – all twins						
1[87]	503	61 (NR)	84 (NR)	4 (NR)	0.5 (NR)	Moderate
Intertwin abdominal circumference ratio < 0.93 to predict BWD ≥ 25% between 11–38 weeks – monochorionic twins						
1[87]	125	80 (NR)	73 (NR)	3 (NR)	0.3 (NR)	Moderate
Intertwin abdominal circumference ratio < 0.93 to predict BWD ≥ 25% between 11–38 weeks – dichorionic twins						
1[87]	378	48 (NR)	88 (NR)	4 (NR)	0.6 (NR)	Moderate
Head circumference						
Intrapair difference in head circumference > 5% in the prediction of birthweight difference (BWD) ≥ 20%						
1[84]	90	64 (35 to 92)	74 (61 to 88)	2 (1 to 5)	0.5 (0.2 to 1.1)	Low
Intrapair difference in head circumference > 10% in the prediction of BWD ≥ 20%						
1[84]	90	18 (0 to 41)	93 (85 to 100)	3 (1 to 14)	0.9 (0.7 to 1.2)	Low
Head circumference to detect IUGR defined as <10th of expected neonatal birthweight percentile in the smaller						

weight twin (using logistic regression)						
1[85]	36	38 (NR)	100 (NR)	999 (NR)	0.6 (NR)	Moderate
Head circumference ≥ 1 abnormal negative deviation to predict IUGR (defined according to third trimester growth patterns) in twins						
1[86]	17	57 (NR)	96 (NR)	14 (NR)	0.5 (NR)	Moderate
Head circumference based on antenatal growth assessment score to predict IUGR (defined according to third trimester growth patterns) in twins						
1[86]	17	57 (NR)	96 (NR)	14 (NR)	0.5 (NR)	Moderate
Femur length						
Intrapair difference in femur length > 5% in the prediction of BWD ≥ 20%						
1[84]	90	47 (23 to 71)	79 (69 to 89)	2 (1 to 5)	0.7 (0.4 to 1.1)	Low
Intrapair difference in femur length > 10% in the prediction of BWD ≥ 20%						
1[84]	90	18 (0 to 36)	94 (87 to 99.7)	3 (1 to 11)	0.9 (0.7 to 1.1)	Low
Femur length to detect IUGR defined as <10th expected neonatal birthweight percentile in the smaller weight twin (using logistic regression)						
1[85]	36	88 (NR)	85 (NR)	5 (NR)	0.2 (NR)	Moderate
Femur length ≥ 1 abnormal negative deviation to predict IUGR)						
1[86]	17	57 (NR)	75 (NR)	2 (NR)	0.6 (NR)	Moderate
Femur length based on prenatal growth assessment score to predict IUGR						
1[86]	17	57 (NR)	83 (NR)	3 (NR)	0.5 (NR)	Moderate
Biparietal diameter						
Intrapair difference in biparietal diameter > 5% in the prediction of BWD ≥ 20%						
1[84]	90	57 (31 to 83)	62 (49 to 76)	2 (1 to 3)	0.7 (0.4 to 1.3)	Low
Intrapair difference in biparietal diameter > 10% in the prediction of BWD ≥ 20%						
1[84]	90	36 (11 to 61)	94 (87 to 100)	6 (2 to 22)	0.7 (0.5 to 1.0)	Low
Biparietal diameter in the prediction of SGA twins						
1[88]	132	67 (51 to 82)	73 (63 to 82)	2 (2 to 4)	0.5 (0.3 to 0.7)	Moderate

Table 6.9 GRADE summary of findings for fetal weight or fetal weight difference estimation using formulae that incorporate two or more fetal biometric measurements

Number of studies	**Number of women**	**Sensitivity % (95% confidence interval)**	**Specificity % (95% confidence interval)**	**LR$^+$ (95% confidence interval)**	**LR$^-$ (95% confidence interval)**	**Quality**
EFW ≤ 10th percentile for prediction of IUGR defined as ≤10th birthweight percentile						
1[89]	73	85 (NR)	87 (NR)	7 (NR)	0.2 (NR)	Low
EFWD ≥ 15% for prediction of intertwin BWD ≥ 15%						
1[90]	575	64 (NR)	89 (NR)	6 (NR)	0.4 (NR)	Low
1[91]	90	65 (47 to 84)	72 (61 to 83)	2 (1 to 4)	0.5 (0.3 to 0.9)	Moderate
Using Warsof's formula (abdominal circumference, femur length)						
1[92]	283	66 (NR)	76 (NR)	3 (NR)	0.5 (NR)	Low
Using Ong's formula (abdominal circumference, femur length)						
1[92]	283	72 (NR)	75 (NR)	3 (NR)	0.4 (NR)	Low
Using Shepard's formula (abdominal circumference, femur length)						
1[92]	283	73 (NR)	71 (NR)	3 (NR)	0.4 (NR)	Low
Using Hadlock's three-parameter formula (based on biparietal diameter, abdominal circumference, femur length)						
1[92]	283	74 (NR)	76 (NR)	3 (NR)	0.3 (NR)	Low
Using Hadlock's four-parameter formula (based on based on biparietal diameter, abdominal circumference, femur length)						
1[92]	283	74 (NR)	75 (NR)	3 (NR)	0.4 (NR)	Low
EFWD ≥ 15% for prediction of intertwin BWD ≥ 20%						
USS within 7 days of birth						
1[90]	575	88 (NR)	84 (NR)	6 (NR)	0.1 (NR)	Low
USS within 14 days of birth						
1[90]	575	85 (NR)	86 (NR)	6 (NR)	0.2 (NR)	Low
USS within 28 days of birth						
1[90]	575	83 (NR)	86 (NR)	6 (NR)	1.2 (NR)	Low

Number of studies	Number of women	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Using Warsof's formula (abdominal circumference, femur length)						
1[92]	283	72 (NR)	72 (NR)	3 (NR)	0.4 (NR)	Low
Using Ong's formula (abdominal circumference, femur length)						
1[92]	283	78 (NR)	71 (NR)	3 (NR)	0.3 (NR)	Low
Using Shepard's formula (abdominal circumference, femur length)						
1[92]	283	83 (NR)	69 (NR)	3 (NR)	0.3 (NR)	Low
Using Hadlock's three-parameter formula (based on biparietal diameter, abdominal circumference, femur length)						
1[92]	283	85 (NR)	73 (NR)	3 (NR)	0.2 (NR)	Low
Using Hadlock's four-parameter formula (based on biparietal diameter, abdominal circumference, femur length)						
1[92]	283	84 (NR)	72 (NR)	3 (NR)	0.2 (NR)	Low
EFWD ≥ 15% for prediction of intertwin BWD ≥ 25%						
1[93]	78	77 (54 to 99.8)	92 (86 to 99)	10 (4 to 24)	0.3 (0.1 to 0.7)	Low
Using Warsof's formula (abdominal circumference, femur length)						
1[92]	283	77 (NR)	69 (NR)	2 (NR)	0.3 (NR)	Low
Using Ong's formula (abdominal circumference, femur length)						
1[92]	283	82 (NR)	67 (NR)	2 (NR)	0.3 (NR)	Low
Using Shepard's formula (abdominal circumference, femur length)						
1[92]	283	85 (NR)	64 (NR)	2 (NR)	0.2 (NR)	Low
Using Hadlock's three-parameter formula (based on biparietal diameter, abdominal circumference, femur length)						
1[92]	283	92 (NR)	69 (NR)	3 (NR)	0.1 (NR)	Low
Using Hadlock's four-parameter formula (based on biparietal diameter, abdominal circumference, femur length)						
1[92]	283	90 (NR)	67 (NR)	3 (NR)	0.2 (NR)	Low
EFWD ≥ 20% for prediction of intertwin BWD ≥ 20%						
6[89;91;94-97]	364 women	72 (61 to 81)	89 (85 to 92)	6 (4 to 9)	0.4 (0.2 to 0.6)	Low
USS 0–7 days before birth						
1[98]	221	94 (NR)	79 (NR)	5 (NR)	0.1 (NR)	Low
USS 7–14 days before birth						
1[98]	221	96 (NR)	56 (NR)	2 (NR)	0.1 (NR)	Low
USS 15–21 days before birth						
1[98]	221	96 (NR)	46 (NR)	2 (NR)	0.1 (NR)	Low
USS 21–28 days before birth						
1[98]	221	91 (NR)	67 (NR)	3 (NR)	0.1 (NR)	Low
USS within 7 days before birth						
1[99]	192	56 (NR)	97 (NR)	19 (NR)	0.5 (NR)	Low
USS within 10 days before birth						
1[99]	192	54 (NR)	97 (NR)	18 (NR)	0.5 (NR)	Low
USS within 16 days before birth						
1[99]	192	55 (NR)	97 (NR)	22 (NR)	0.5 (NR)	Moderate
1[90]	575	61 (NR)	95 (NR)	12 (NR)	0.4 (NR)	Low
Last USS within 14 days of birth						
1[94]	85	46 (19 to 73)	92 (85 to 99)	6 (2 to 16)	0.6 (0.4 to 0.9)	Low
Using Warsof's formula (abdominal circumference, femur length)						
1[92]	283	60 (NR)	86 (NR)	4 (NR)	0.5 (NR)	Low
Using Ong's formula (*abdominal circumference, femur length)*						
1[92]	283	69 (NR)	84 (NR)	4 (NR)	0.4 (NR)	Low
Using Shepard's formula (abdominal circumference, femur length)						
1[92]	283	70 (NR)	80 (NR)	4 (NR)	0.4 (NR)	Low
Using Shepard's formula (based on biparietal diameter, abdominal circumference)						
1[96]	25	86 (67 to 100)	80 (60 to 100)	4 (2 to 12)	0.2 (0.1 to 0.7)	Very low
Using Hadlock's three-parameter formula (based on biparietal diameter, abdominal circumference, femur length						
1[92]	283	72 (NR)	85 (NR)	5 (NR)	0.3 (NR)	Low
Using Hadlock's four-parameter formula (based on biparietal diameter, head circumference, abdominal circumference, femur length)						
1[92]	283	72 (NR)	84 (NR)	5 (NR)	0.3 (NR)	Low
EFWD ≥ 20% for prediction of intertwin BWD ≥ 25%						
1[93]	78	74 (NR)	90 (NR)	7 (NR)	0.3 (NR)	Moderate

Number of studies	Number of women	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
USS within 7 days of birth						
1[90]	575	85 (NR)	89 (NR)	8 (NR)	0.2 (NR)	Low
USS within 14 days of birth						
1[90]	575	84 (NR)	92 (NR)	11 (NR)	0.2 (NR)	Low
USS within 28 days of birth						
1[90]	575	78 (NR)	95 (NR)	16 (NR)	0.2 (NR)	Low
Using Warsof's formula (abdominal circumference, femur length)						
1[92]	283	70 (NR)	84 (NR)	4 (NR)	0.4 (NR)	Low
Using Ong's formula (abdominal circumference, femur length)						
1[92]	283	73 (NR)	80 (NR)	4 (NR)	0.3 (NR)	Low
Using Shepard's formula (abdominal circumference, femur length)						
1[92]	283	73 (NR)	76 (NR)	3 (NR)	0.4 (NR)	Low
Using Hadlock's three-parameter formula (based on biparietal diameter, abdominal circumference, femur length)						
1[92]	283	76 (NR)	80 (NR)	4 (NR)	0.3 (NR)	Low
Using Hadlock's four-parameter formula (based on biparietal diameter, head circumference, abdominal circumference, femur length)						
1[92]	283	76 (NR)	80 (NR)	4 (NR)	0.3 (NR)	Low
EFWD ≥ 25% for prediction of intertwin BWD ≥ 20%						
1[100]	60	86 (NR)	99.9 (NR)	86 (NR)	0.1 (NR)	Moderate
EFWD ≥ 25% for prediction of intertwin BWD ≥ 25%						
3[91;93;94]	242	59 (39 to 78)	93 (88 to 96)	8 (3 to 18)	0.5 (0.3 to 0.9)	Low
1[101]	242	33 (NR)	94 (NR)	5 (NR)	0.7 (NR)	Low
1[100]	60	88 (NR)	96 (NR)	23 (NR)	0.1 (NR)	Moderate
Using Warsof's formula (AC, FL)						
1[92]	283	60 (NR)	93 (NR)	9 (NR)	0.4 (NR)	Low
Using Ong's formula (AC, FL)						
1[92]	283	6 (NR)	90 (NR)	7 (NR)	0.4 (NR)	Low
Using Shepard's formula (AC, FL)						
1[92]	283	63 (NR)	86 (NR)	5 (NR)	0.4 (NR)	Low
Using Hadlock's three-parameter formula (based on biparietal diameter, abdominal circumference, femur length)						
1[92]	283	68 (NR)	91 (NR)	8 (NR)	0.4 (NR)	Low
Using Hadlock's four-parameter formula (based on biparietal diameter, head circumference, abdominal circumference, femur length)						
1[92]	283	68 (NR)	92 (NR)	9 (NR)	0.4 (NR)	Low
EFWD ≥ 25% for prediction of intertwin BWD ≥ 30%						
1[100]	60	99 (NR)	92 (NR)	2 (NR)	0.0 (NR)	Moderate
USS within 7 days of birth						
1[90]	575	86 (NR)	92 (NR)	11 (NR)	0.2 (NR)	Low
USS within 14 days of birth						
1[90]	575	85 (NR)	96 (NR)	21 (NR)	0.2 (NR)	Low
USS within 28 days of birth						
1[90]	575	78 (NR)	96 (NR)	20 (NR)	0.2 (NR)	Low
EFWD ≥ 30% for prediction of intertwin BWD ≥ 30%						
1[90]	575	56 (NR)	98 (NR)	28 (NR)	0.5 (NR)	Low

Table 6.10 GRADE summary of findings for Doppler ultrasound

Number of studies	Number of women/twins	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Umbilical artery systolic:diastolic (S:D) ratio >90th percentile for the prediction of small-for-gestational age (SGA) twin (defined as ≤5th birthweight centile for gestational age using Scottish birthweight data						
Scan at 20–23 weeks						
1[102]	178 twins	36 (8 to 65)	92 (86 to 99)	5 (2 to 15)	0.7 (0.4 to 1.1)	Moderate
Scan at 24–27 weeks						
1[102]	178 twins	5 (0 to 15)	94 (89 to 99)	1 (0 to 7)	1.0 (0.9 to 1.0)	Moderate

Number of studies	Number of women/twins	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Scan at 28–31 weeks						
1[102]	178 twins	17 (0 to 38)	87 (80 to 94)	1 (0 to 5)	1.0 (0.7 to 1.3)	High
Scan at 32–35 weeks						
1[102]	178 twins	39 (21 to 57)	79 (70 to 88)	2 (1 to 4)	0.8 (0.6 to 1.1)	High
Scan at 36–39 weeks						
1[102]	178 twins	50 (22 to 78)	86 (75 to 96)	4 (1 to 9)	0.6 (0.3 to 1.0)	Moderate
Intertwin umbilical artery S:D ratio difference >0.4 for the prediction of intertwin BWD > 25%						
1[103]	40 women	75 (45 to 100)	69 (53 to 85)	2 (1 to 5)	0.4 (0.1 to 1.2)	Moderate
Intertwin umbilical artery RI > 0.1 measured 2 weeks before birth for the prediction of intertwin BWD > 25%						
1[104]	31 women	75 (45 to 100)	96 (87 to 100)	17 (2 to 122)	0.3 (0.1 to 0.9)	Moderate
Combination of umbilical venous blood flow <10th percentile and abnormal S:D ratio for the prediction of intertwin BWD > 25% among twins and triplets						
1[105]	31 women	80 (55 to 100)	98 (94 to 100)	36 (5 to 256)	0.2 (0.1 to 0.7)	Moderate

Table 6.11 GRADE summary of findings for composite screening strategies

Number of studies	Number of women/twins	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Abdominal circumference (AC) <5th percentile or EFW <10th percentile or EFWD >20% for detection of IUGR defined as <10th birthweight percentile in twin pregnancies						
At 20–24 weeks						
1[106]	44	59 (35 to 82)	89 (77 to 100)	5 (2 to 17)	0.5 (0.3 to 0.8)	Low
At 25–28 weeks						
1[106]	44	0 (0 to 20)	78 (62 to 94)	0 (NC)	1.3 (1.1 to 1.6)	Low
At 29–32 weeks						
1[106]	44	35 (13 to 58)	67 (49 to 85)	1 (1 to 2)	0.97 (0.6 to 1.5)	Low
At 33–39 weeks						
1[106]	44	6 (0 to 17)	67 (49 to 85)	0 (0 to 1)	1.4 (1.1 to 1.9)	Moderate
AC <5th percentile or EFW < 10th percentile or EFWD > 20% for detection of intertwin discordance ≥ 20%						
At 20–24 weeks						
1[106]	44	50 (27 to 73)	85 (71 to 99)	3 (1 to 9)	0.6 (0.4 to 1.0)	Low
At 25–28 weeks						
1[106]	44	0 (0 to 19)	77 (61 to 93)	0 (NC)	1.3 (1.1 to 1.6)	Low
At 29–32 weeks						
1[106]	44	33 (12 to 55)	65 (47 to 84)	1 (0 to 2)	1.0 (0.7 to 1.6)	Low
At 33–39 weeks						
1[106]	44	17 (0 to 34)	73 (56 to 90)	1 (0 to 2)	1.1 (0.8 to 1.6)	Low
S:D ratio >15% combined with EFWD >15% for the prediction intertwin BWD > 15%						
1[107;108]	40	92 (NR)	70 (NR)	3 (NR)	0.1 (NR)	Low
1[108]	58	78 (59 to 97)	88 (77 to 98)	6 (3 to 15)	0.3 (0.1 to 0.6)	Low

Evidence statement

Evidence was identified for SFH, USS measurement of fetal biometry, EFW based on formulae using USS parameters, Doppler ultrasound for recording blood flow in the umbilical cord and composite screening strategies in predicting IUGR in twin and triplet pregnancies. The quality of the evidence was mostly low and data relating to triplets were reported in only one study.

There was evidence that symphysis-fundal height measurement does not predict intertwin discordance (moderate quality evidence).

The evidence for the value of fetal head and abdominal circumference measurements in predicting IUGR or birthweight discordance was variable and suggested that ultrasound measurement of any single fetal biometric parameter was a poor predictor of IUGR or birthweight discordance of 15% or more (low to moderate quality evidence).

There was evidence that estimated fetal weight at or less than the tenth percentile is a moderately useful predictor of IUGR defined as at or less than the tenth birthweight percentile (low quality evidence)

There was evidence that the best cut-off for intertwin birthweight discordance is an estimated fetal weight difference of 25%, especially when used to predict birthweight difference of 25% or more (low and moderate quality evidence, but mainly low)

There was evidence that the best estimate of fetal weight is derived when applying a formula that incorporates at least two fetal biometric parameters (moderate and low quality evidence).

There was evidence that the best predictor of IUGR or discordance between twins is an ultrasound scan carried out within 28 days of birth (low quality evidence).

There was no strong evidence supporting the routine use of Doppler ultrasound recording umbilical artery blood flow for the prediction of birthweight difference or IUGR in twins (moderate and high quality evidence). Doppler ultrasound of the umbilical vein was a better predictor of birthweight discordance in twins and a good predictor in triplets (moderate quality evidence). No evidence was reported for the use of Doppler ultrasound of the umbilical vein to predict IUGR.

There was no strong evidence that any composite screening strategy detects IUGR in twin pregnancies (low and moderate quality evidence). No studies were identified that reported the use of composite screening strategies in detecting IUGR in triplet pregnancies.

The only evidence with results reported separately for different chorionicities was for using an abdominal circumference ratio to predict birthweight discordance. The test had a higher sensitivity, higher predictive values and a stronger LR^- statistic in monochorionic twins than in dichorionic twins, but showed a higher specificity and stronger LR^+ statistic in dichorionic twins (moderate quality evidence).

No studies were identified that reported data regarding abdominal palpation, amniotic fluid volume, middle cerebral artery Doppler ultrasound or timing and frequency of ultrasound scanning for predicting IUGR in twin or triplet pregnancies.

Health economics profile

No published health economic evidence was identified, although this question was prioritised for health economic analysis. Routine scanning for IUGR is recommended in ‘Antenatal care’ (NICE clinical guideline 62)[14] and was found to be cost effective. However, in twin and triplet pregnancies there is a need for additional scanning, and this may increase the number of scans from two to eight, depending on the chorionicity of the pregnancy, costing an additional £200.

Evidence to recommendations

Relative value placed on the outcomes considered

Sensitivity is the proportion of pregnancies that went on to develop IUGR that were predicted to develop IUGR (true positive). One hundred minus sensitivity (100 – sensitivity) shows how many of these pregnancies were predicted to be normal (false negative).

Specificity is the proportion of pregnancies that did not develop IUGR that were predicted to be normal (true negative). One hundred minus specificity (100 – specificity) shows how many of these pregnancies were predicted to develop IUGR during pregnancy (false positive).

PPV is the proportion of pregnancies that were predicted to have IUGR that went on to develop IUGR. One hundred minus PPV (100 – PPV) shows how many of these pregnancies were actually found to be normal.

NPV is the proportion of pregnancies predicted to be normal that remained normal. One hundred minus NPV (100 – NPV) shows how many of these pregnancies actually developed IUGR.

LR^+ shows how much the odds of a pregnancy developing IUGR increase when IUGR is predicted. LR^- shows how much the odds of a pregnancy developing IUGR decrease when a normal pregnancy is predicted.

The GDG's view was that focusing on likelihood ratios would allow it to make the most effective recommendations for this review question.

Trade-off between clinical benefits and harms

There is a trade-off between missing a potential case of IUGR from not scanning often enough or using less predictive parameters, and increasing maternal anxiety through unnecessary additional or repeated scanning. However, there is also the potential for a strain on hospital resources due to more frequent scanning. An effective screening test will reduce the number of false positives and false negatives. This will prevent unnecessary anxiety associated with informing women with normal pregnancies that they will develop IUGR, and ensure that women who are told that they have a normal pregnancy do not develop IUGR later on.

Trade-off between net health benefits and resource use

Additional costs may arise from extra scanning (if additional scans were to be recommended) and from training ultrasonographers.

Quality of evidence

The quality of evidence for using symphysis-fundal height measurement, fetal abdominal circumference, fetal head circumference or biparietal diameter to detect IUGR is moderate in each case. The quality of evidence for using femur length is low to moderate; for estimated fetal weight is low to moderate (mainly low); for umbilical artery Doppler is moderate and high; and for composite strategies is low to moderate (mainly low).

Other considerations

Having considered all the evidence, the GDG's view was that ultrasound measurement of any single fetal biometric parameter alone was a poor predictor of IUGR or birthweight discordance of 15% or more. All the evidence of the value of a variety of ultrasound biometric measurements in predicting birthweight discordance was from studies in twin pregnancies. The GDG inferred that its recommendations regarding the use of ultrasound biometry in twin pregnancy also applied to triplets.

There was no strong evidence supporting the routine use of Doppler ultrasound of the umbilical artery for the prediction of birthweight difference or IUGR in twin or triplet pregnancies and this was reflected in the GDG's recommendation. The GDG's recommendation about the poor value of abdominal palpation and symphysis-fundal height measurements is based on the GDG members' clinical experience in the case of abdominal palpation and one study in twins in the case of symphysis-fundal height measurements. There was limited evidence as to whether the chorionicity of a pregnancy affected the accuracy of the test. The GDG concluded that a 25% or greater difference between twins should be regarded as a clinically significant indicator of IUGR and that the same criteria can be applied to triplets. Such cases should be offered referral to tertiary level fetal medicine centres (subspecialist services; see Chapter 9). However, the GDG also acknowledged that, in clinical practice, any degree of fetal growth restriction or discordance of less than 25% would lead to increased fetal surveillance.

Recommendations

Number	Recommendation
42	Do not use abdominal palpation or symphysis–fundal height measurements to predict intrauterine growth restriction in twin or triplet pregnancies.
43	Estimate fetal weight discordance using two or more biometric parameters at each ultrasound scan from 20 weeks. Aim to undertake scans at intervals of less than 28 days. Consider a 25% or greater difference in size between twins or triplets as a clinically important indicator of intrauterine growth restriction and offer referral to a tertiary level fetal medicine centre.
44	Do not use umbilical artery Doppler ultrasound to monitor for intrauterine growth restriction or birthweight differences in twin or triplet pregnancies.

Number	Research recommendation
RR 10	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? **Why this is important** Although the guideline review found some studies relating to the identification of intrauterine growth restriction in twin and triplet pregnancies, the larger existing studies are retrospective in design and, therefore, of low quality. No evidence-based growth charts specific to twin and triplet pregnancies are available for use in the diagnosis of intrauterine growth restriction. The evidence for the effectiveness of tests for diagnosis of intrauterine growth restriction according to chorionicity of the pregnancy is limited. There is, therefore, a need for large, prospective cohort studies to develop fetal growth charts specific to twin and triplet pregnancies. This would allow definition and diagnosis of clinically significant intrauterine growth restriction using true growth velocity and trajectories, rather than estimated fetal weight and discrepancy. The charts should distinguish between growth patterns in monochorionic, dichorionic and trichorionic pregnancies, and the research should evaluate clinical outcomes associated with particular growth patterns.

7 Maternal complications

7.1 Hypertension

Introduction

Pregnancy-induced hypertension is a significant cause of morbidity and mortality for women and their babies in the UK. Twin and triplet pregnancies are associated with an increased risk of pregnancy-induced hypertension: women with twin pregnancies have a two to three times higher risk of developing hypertension during pregnancy than women with singleton pregnancies.[111-114] The higher risk associated with twin and triplet pregnancies led the GDG to prioritise the need to determine the most accurate strategy for detecting hypertensive disorders in twin and triplet pregnancies.

Review question

What is the optimal screening programme to detect hypertension in multiple pregnancy in the antenatal period?

Existing NICE guidance

'Antenatal care' (NICE clinical guideline 62)[14] recommends blood pressure measurement and urinalysis for protein at each antenatal visit to screen for pre-eclampsia. Multiple pregnancy is recognised as a risk factor for pre-eclampsia and 'Antenatal care' (NICE clinical guideline 62)[14] recommends more frequent blood pressure measurements be considered for women with multiple pregnancy.

'Hypertension in pregnancy' (NICE clinical guideline 107)[20] addressed management of hypertensive disorders during pregnancy.

Description of included studies

Two studies were identified for inclusion for this question.[115;116] The studies reported diagnostic accuracy statistics for uterine artery Doppler investigation (using resistance index, notching, pulsatility index and combinations of these measures) in screening for pre-eclampsia in twin pregnancies. One study[116] used transvaginal scanning at 22–24 weeks of gestation: the other did not report the method of scanning used, but the test was undertaken at 18–24 weeks of gestation (median 21 weeks).[115] One study was conducted in England[116] and the other in Germany.[115]

No studies were identified which reported screening for gestational hypertension or for screening in triplet pregnancies. No studies were identified which reported on maternal history, blood pressure, maternal blood tests, maternal urine tests, integrated tests or composite screening strategies.

The prevalence rate of pre-eclampsia in the first study was 8.6% and in the second study 6.0%: these rates are higher than in general pregnant populations, supporting the finding that twin pregnancy is associated with an increased risk of pre-eclampsia.

Published health economic evidence

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

Evidence profiles

Evidence profiles for this question are presented in Table 7.1.

Table 7.1 GRADE summary of findings for screening tests to detect hypertension in twin pregnancies

Number of studies	Number of twin pregnancies	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Ultrasound						
Resistance index > 95th centile (according to singleton nonogram) for predicting pre-eclampsia						
1[115]	256	18 (2 to 34)	98 (96 to 100)	11 (3 to 40)	0.8 (0.7 to 1.0)	Very low
Resistance index > 95th centile (according to twin nonogram) for predicting pre-eclampsia						
1[115]	256	36 (16 to 56)	88 (84 to 92)	3 (2 to 6)	0.7 (0.5 to 0.9)	Very low
Resistance index > 95th centile (according to twin nonogram) for predicting pre-eclampsia						
1[115]	256	41 (20 to 61)	86 (81 to 90)	3 (2 to 5)	0.7 (0.5 to 0.9)	Very low
Bilateral notching for predicting pre-eclampsia						
1[115]	256	18 (2 to 34)	96 (94 to 99)	4 (2 to 13)	0.9 (0.9 to 0.9)	Very low
1[116]	351	19 (2 to 36)	98 (96 to 99)	8 (3 to 22)	0.8 (0.7 to 1.0)	Low
Pulsatility index > 95th centile for predicting pre-eclampsia						
1[116]	351	33 (13 to 54)	97 (95 to 99)	10 (4 to 22)	0.7 (0.5 to 0.9)	Low
Resistance index > 95th centile (according to twin nonogram) with unilateral or bilateral notching for predicting pre-eclampsia						
1[115]	256	32 (12 to 51)	93 (90 to 96)	4 (2 to 9)	0.9 (0.9 to 1.0)	Low
Pulsatility index > 95th centile with bilateral notching for predicting pre-eclampsia						
1[116]	351	19 (2 to 36)	99 (98 to 100)	21 (5 to 88)	0.8 (0.7 to 1.0)	Low

Evidence statement

Evidence was reported for uterine artery Doppler ultrasound for predicting the onset of pre-eclampsia in twin pregnancies. The evidence was mainly very low in quality.

The tests varied in terms of diagnostic accuracy. Using the pulsatility index with bilateral notching resulted in the strongest LR^+ statistic, highest specificity and highest predictive values (low quality evidence). The pulsatility index alone resulted in the strongest LR^- statistic (low quality evidence). The sensitivity of all tests was low.

No studies were identified that reported on screening for gestational hypertension in twin pregnancies or that reported on screening for any hypertensive disorders in triplet pregnancies. No studies were identified that used maternal history, blood pressure, maternal blood tests, maternal urine tests, integrated tests or composite screening strategies to predict hypertension in multiple pregnancy.

Health economics profile

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

Evidence to recommendations

Relative value placed on the outcomes considered

Screening for hypertensive disorders in pregnancy is important as they can result in maternal and neonatal morbidity or mortality.

Sensitivity is the proportion of women who went on to develop hypertension who were predicted to develop hypertension (true positive). One hundred minus sensitivity (100 – sensitivity) shows how many of these pregnancies were predicted to be normotensive (false negative).

Specificity is the proportion of women who remained normotensive during pregnancy who were predicted to be normotensive (true negative). One hundred minus specificity (100 – specificity) shows how many of these women were predicted to develop hypertension during pregnancy (false positive).

PPV is the proportion of women who were predicted to be hypertensive who went on to develop hypertension. One hundred minus PPV (100 – PPV) shows how many of these women were actually found to be normotensive.

NPV is the proportion of women who were predicted to be normotensive who remained normotensive. One hundred minus NPV (100 – NPV) shows how many of these women were actually found to be hypertensive.

The positive likelihood ratio (LR^+) shows how much the odds of a woman being hypertensive during pregnancy increase when hypertension is predicted. The negative likelihood ratio (LR^-) shows how much the odds of a pregnancy being hypertensive decrease when a normotensive pregnancy is predicted.

The GDG's view was that focusing on sensitivity and likelihood ratios would allow them to make the most effective recommendations for this review question.

Trade-off between clinical benefits and harms

It is important that a screening strategy allows women who will develop hypertension in pregnancy to be identified (high number of true positives). It is also important that women who are reassured that they will remain normotensive do not go on to develop hypertension in pregnancy (low number of false negatives). 'Antenatal care' (NICE clinical guideline 62)[14] states that blood pressure measurement and urinalysis for protein should be carried out at each antenatal visit to screen for pre-eclampsia. It also recommends that, because multiple pregnancy is a risk factor for pre-eclampsia, more frequent blood pressure measurements should be considered, and goes on to state that although there is a great deal of material published on alternative screening methods for pre-eclampsia (alternative to blood pressure monitoring, urinalysis for proteinuria and enquiring about symptoms such as severe headache, visual problems, epigastric pain, vomiting or sudden swelling of face, hands or feet), none of these has satisfactory sensitivity and specificity, and therefore they are not recommended.

Of the evidence reviewed for screening for hypertension in twin and triplet pregnancies, uterine artery Doppler shows promise (particularly pulsatility index more than the 95th centile), as its high NPV excludes risk (96% of women who were predicted to be normotensive remained normotensive). However, it is currently not a sensitive screening test, and therefore the GDG does not recommend its use in predicting hypertension in twin and triplet pregnancies.

Trade-off between net health benefits and resource use

All of the available evidence (which was limited to two studies) refers to ultrasound methods of screening. The GDG's view was that its recommendations would not lead to a change in practice, but the GDG acknowledges that women with twin or triplet pregnancies come into contact with healthcare professionals more often that those with singleton pregnancies. This extra contact will result in more frequent blood pressure monitoring, urine testing and so on, and this will lead to increased costs of antenatal care compared to a singleton pregnancy.

Quality of evidence

Very low quality evidence was found for using resistance index of more than 95th centile alone and very low to low quality evidence was found for using unilateral or bilateral notching alone. Low quality evidence was found for using resistance index of more than 95th centile with unilateral or bilateral notching and for using pulsatility index more than 95th centile alone and with bilateral notching.

Other considerations

No evidence was identified that allowed the GDG to consider different screening strategies for monochorionic and dichorionic pregnancies. No evidence was identified for screening in triplet pregnancies. The evidence for screening in twins is limited and heterogeneous. The evidence for uterine artery Doppler in twin and triplet pregnancies is limited. The NICE guidance for routine antenatal care recommends increased blood pressure testing and urinalysis at every contact with a healthcare professional from 24 weeks.

Multiple pregnancy is a moderate risk factor for the development of pre-eclampsia during pregnancy. Therefore, the GDG recommended that women with twin or triplet pregnancies, who have any of the other moderate risk factors for pre-eclampsia (first pregnancy, age 40 years or older, pregnancy interval of more than 10 years, BMI of 35 kg/m^2 or more at first visit, or family history of pre-eclampsia), should be offered a daily aspirin dose in accordance with 'Hypertension in pregnancy' (NICE clinical guideline 107).[20]

Recommendations

Number	Recommendation
45	Measure blood pressure and test urine for proteinuria to screen for hypertensive disorders at each antenatal appointment in twin and triplet pregnancies as in routine antenatal care.*
46	Advise women with twin and triplet pregnancies that they should take 75 mg of aspirin† daily from 12 weeks until the birth of the babies if they have one or more of the following risk factors for hypertension: • first pregnancy • age 40 years or older • pregnancy interval of more than 10 years • BMI of 35 kg/m^2 or more at first visit • family history of pre-eclampsia.

Number	Research recommendation
RR 11	Which clinical factors, laboratory screening tests, and ultrasound tests are predictive of hypertensive disorders in twin and triplet pregnancies? Why this is important The current evidence for screening tests for hypertensive disorders in twin and triplet pregnancies is limited and unconvincing. Emerging first-trimester tests may be good predictors of hypertensive disorders in twin and triplet pregnancies but they need further evaluation. There is, therefore, a need for further research using good quality, prospective cohort studies, with an emphasis on laboratory screening tests and first-trimester tests, and including subgroup analyses for different chorionicities.

* See 'Antenatal care' (NICE clinical guideline 62). Available from www.nice.org.uk/guidance/CG62

† At the time of publication (September 2011) this drug did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented. [This recommendation is adapted from recommendation 1.1.2.2 in 'Hypertension in Pregnancy' NICE clinical guideline 107.]

8 Preterm birth

8.1 Predicting the risk of preterm birth

Introduction

Spontaneous preterm birth (associated with preterm, prelabour rupture of the membranes or spontaneous preterm labour) and iatrogenic preterm birth (arising from a medical decision to deliver the baby or babies) occur more frequently in twin and triplet pregnancies than in singleton pregnancies. More than 50% of twins and almost all triplets are born before 37 weeks of gestation and about 15–20% of admissions to neonatal units are associated with preterm twins and triplets. Extreme prematurity (birth at less than 28 weeks of gestation) also occurs more frequently in twin and triplet pregnancies. Prematurity is the biggest cause of adverse neonatal and infant outcomes among twins and triplets compared to singletons, including higher levels of long-term neurodevelopmental problems. Predicting and preventing spontaneous preterm labour and birth are therefore important goals to optimise outcomes of twin and triplet pregnancies.

Review question

What is the optimal screening programme to predict the risks of spontaneous preterm delivery?

Existing NICE guidance

'Antenatal care' (NICE clinical guideline 62)[14] recommends that healthy women with singleton pregnancies should not be offered routine screening to predict preterm birth.

Description of included studies

Fifteen studies were identified for inclusion.[117-131] These investigated the diagnostic accuracy of a variety of measures as predictors of spontaneous preterm birth in twin and triplet pregnancies:

- cervical length
- fibronectin test
- additional antenatal care
- obstetric history
- composite measures based on the above approaches.

Eight studies reported on cervical length.[117-124] One of these was a systematic review of cohort studies,[119] four were prospective cohort studies[120-123] and three were retrospective cohort studies.[117;118;124] Three of the cohort studies were conducted in the UK,[120-122] two in the USA,[118;123] one in Brazil[117] and one in Israel.[124] The systematic review,[119] included two studies from the UK, five from the USA, one from Denmark and Sweden, and one each from France, Sweden, the Netherlands, Austria, Canada, Egypt and Israel.

Four of the studies (including the systematic review) involved twin pregnancies[117-119;122] and the other two involved triplet pregnancies.[123;124]

One study reported on using just the fetal fibronectin test.[126] This study involved twin pregnancies and was conducted in Sweden. One study reported on using the fetal fibronectin test as well as measuring cervical length.[125] The results for cervical length from this study were included in the published systematic review [119] and so only the results for fetal fibronectin are reported separately here. This study involved twin pregnancies and was conducted in the UK.

Two studies reported on a composite test of the fetal fibronectin test with cervical length measurement.[127;128] One was a prospective cohort study[128] while the other was a retrospective cohort study.[127] Both involved twin pregnancies and were conducted in the USA.

Two studies examined home uterine activity monitoring in women with twin pregnancies.[129;130] One was a meta-analysis of six randomised controlled trials (RCTs) that compared home monitoring with no monitoring as a predictor of preterm birth in twin pregnancies.[129] The other was a three-arm RCT that compared home monitoring of uterine activity and daily contact with a nurse with daily contact alone and with weekly contact.[130] The RCT was conducted in the USA but the meta-analysis did not report details of the countries where the individual trials were conducted.

One study examined obstetric history as a predictor of preterm birth.[131] This study involved women with twin pregnancies whose previous pregnancy had been a preterm singleton pregnancy. The study was a retrospective cohort study and was conducted in the USA.

Published health economic evidence

No published health economic evidence was identified, although this question was prioritised for health economic analysis.

Evidence profiles

Evidence profiles for this question are presented in Tables 8.1 to 8.8. One study[122] reported some results for the predictive value of cervical length measurements in the form of diagnostic test accuracy measures and other results in the form of relative risks (RRs). The evidence from this study is, therefore, presented in a separate evidence profile (Table 8.2). The RRs were considered by the GDG, but they did not influence its final recommendations and so Table 8.2 below does not include RRs (see the full evidence profile in Appendix J for these results).

Table 8.1 GRADE summary of findings for cervical length measurement in twin pregnancies (diagnostic accuracy studies reporting diagnostic accuracy measurements only)

Number of studies	Number	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Prediction of spontaneous birth before 28 weeks						
Measurement at 18–21 weeks; cut-off of <5th percentile for normal twin pregnancies based on gestational age						
1[117]	241	33 (3 to 64)	95 (93 to 98)	7 (2 to 20	0.7 (0.4 to 1.1)	Low
Measurement at 16–24 weeks; cut-off of 25 mm						
1[118]	97	100 (16 to 100)	88 (82 to 95)	9 (5 to 15)	0 (0 to 0.8)	Low
Measurement at 20–24 weeks; cut-off of 20 mm						
1[119]	591 (3 studies)	35(14 to 62)	93 (91 to 95)	5 (3 to 11)	0.7 (0.5 to 1.0)	Moderate
Measurement at 20–24 weeks; cut-off of 25 mm						
1[119]	637 (3 studies)	64 (41 to 83)	93 (91 to 95)	10 (6 to 15)	0.4 (0.2 to 0.7)	Moderate
Measurement at 20–24 weeks; cut-off of 35 mm						
1[119]	637 (3 studies)	82 (60 to 95)	66 (62 to 69)	2 (2 to 3)	0.3 (0.1 to 0.7)	High
Measurement at 22–24 weeks; cut-off of 15 mm						
1[120]	215	50 (15 to 85)	98 (95 to 99)	21 (7 to 63)	0.5 (0.3 to 1.0)	Moderate
Measurement at 22–24 weeks; cut-off of 25 mm						
1[120]	215	100 (63 to 100)	92 (87 to 96)	13 (8 to 21)	0.0 (0.0 to 0.9)	High
Measurement at 22–24 weeks; cut-off of 35 mm						
1[120]	215	100 (63 to 100)	62 (56 to 69)	3 (2 to 3)	0.0 (0.0 to 1.3)	High
Measurement at 22–24 weeks; cut-off of 45 mm						
1[120]	215	100 (63 to 100)	17 (12 to 22)	1 (1 to 1)	0.0 (0.0 to 4.9)	High
Measurement at 22–25 weeks; cut-off of <5th percentile for normal twin pregnancies based on gestational age						
1[117]	266	71 (38 to 100)	93 (90 to 97)	11 (6 to 21)	0.3 (0.1 to 1.0)	Low
Prediction of spontaneous birth before 30 weeks						
Measurement at 16–24 weeks; cut-off of 25 mm						
1[118]	97	60 (17 to 100)	89 (83 to 95)	6 (2 to 14)	0.5 (0.2 to 1.3)	Low

Number of studies	Number	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Measurement at 18–21 weeks; cut-off of <5th percentile for normal twin pregnancies based on gestational age						
1[117]	241	33 (10 to 57)	96 (94 to 99)	8 (3 to 22)	0.7 (0.5 to 1.0)	Low
Measurement at 22–24 weeks; cut-off of 15 mm						
1[120]	215	40 (10 to 70)	98 (95 to 99)	16 (5 to 52)	0.6 (0.4 to 1.0)	Moderate
Measurement at 22–24 weeks; cut-off of 25 mm						
1[120]	215	80 (55 to 100)	92 (89 to 96)	10 (6 to 18)	0.2 (0.1 to 0.8)	Moderate
Measurement at 22–24 weeks; cut-off of 35 mm						
1[120]	215	90 (71 to 100)	62 (56 to 69)	2 (2 to 3)	0.6 (0.6 to 0.7)	High
Measurement at 22–24 weeks; cut-off of 45 mm						
1[120]	215	100 (69 to 100)	17 (12 to 71)	1 (1 to 1)	0 (0 to 4)	Moderate
Measurement at 22–25 weeks; cut-off of <5th percentile for normal twin pregnancies based on gestational age						
1[117]	266	57 (32 to 83)	94 (92 to 97)	10 (5 to 20)	0.4 (0.2 to 0.8)	Low
Prediction of spontaneous birth before 32 weeks						
Measurement at 16–24 weeks; cut-off of 25 mm						
1[118]	97	43 (6 to 80)	89 (82 to 95)	4 (1 to 11)	0.6 (0.3 to 1.2)	Low
Measurement at 18–21 weeks; cut-off of <5th percentile for normal twin pregnancies based on gestational age						
1[117]	241	30 (10 to 50)	96 (94 to 99)	8 (3 to 22)	0.7 (0.5 to 0.9)	Low
Measurement at 20–24 weeks; cut-off of 20 mm						
1[119]	1955 (5 studies)	39 (31 to 48)	96 (95 to 97)	10 (7 to 14)	0.6 (0.6 to 0.7)	High
Measurement at 20–24 weeks; cut-off of 25 mm						
1[119]	2036 (6 studies)	54 (45 to 62)	91 (90 to 92)	6 (5 to 7)	0.5 (0.4 to 0.6)	High
Measurement at 20–24 weeks; cut-off of 30 mm						
1[119]	1812 (4 studies)	65 (56 to 74)	78 (76 to 80)	3 (3 to 4)	0.5 (0.4 to 0.6)	High
Measurement at 20–24 weeks; cut-off of 35 mm						
1[119]	1889 (5 studies)	81 (73 to 87)	58 (56 to 61)	2 (2 to 2)	0.3 (0.2 to 0.5)	High
Measurement at 22–24 weeks; cut-off of 15 mm						
1[120]	215	24 (3 to 44)	97 (95 to 99)	9 (3 to 32)	0.8 (0.6 to 1.0)	Moderate
Measurement at 22–24 weeks; cut-off of 25 mm						
1[120]	215	47 (23 to 71)	92 (88 to 96)	6 (3 to 12)	0.6 (0.4 to 0.9)	Moderate
Measurement at 22–24 weeks; cut-off of 35 mm						
1[120]	215	71 (49 to 92)	63 (56 to 69)	2 (1 to 3)	0.5 (0.2 to 1.0)	Moderate
Measurement at 22–24 weeks; cut-off of 45 mm						
1[120]	215	94 (83 to 100)	17 (12 to 22)	1 (1 to 1)	0.3 (0.1 to 2.4)	High
Measurement at 22–25 weeks; cut-off of <5th percentile for normal twin pregnancies based on gestational age						
1[117]	266	53 (30 to 75)	95 (93 to 98)	11 (5 to 22)	0.5 (0.3 to 0.8)	Low
Measurement at >24 weeks; cut-off of 25 mm						
1[119]	511 (3 studies)	65 (45 to 81)	76 (72 to 79)	3 (2 to 4)	0.5 (0.3 to 0.8)	High
Prediction of spontaneous birth before 33 weeks						
Measurement at 22–24 weeks; cut off of 15 mm						
1[121]	464	18 (5 to 31)	99 (98 to 99)	14 (5 to 44)	0.8 (0.7 to 1.0)	Moderate
Measurement at 22–24 weeks; cut off of 20 mm						
1[121]	464	26 (12 to 41)	97 (95 to 98)	8 (4 to 18)	0.8 (0.6 to 0.9)	Moderate
Measurement at 22–24 weeks; cut off of 25 mm						
1[121]	464	35 (19 to 51)	92 (89 to 94)	4 (2 to 8)	0.7 (0.6 to 0.9)	High
Prediction of spontaneous birth before 34 weeks						
Measurement at 18–21 weeks; cut-off of <5th percentile for normal twin pregnancies based on gestational age						
1[117]	241	23 (10 to 36)	98 (95 to 100)	9 (3 to 26)	0.8 (0.7 to 0.9)	Low
Measurement at 20–24 weeks; cut-off of 20 mm						
1[119]	1760 (5 studies)	29 (23 to 35)	97 (96 to 98)	9 (6 to 13)	0.7 (0.7 to 0.8)	High
Measurement at 20–24 weeks; cut-off of 25 mm						
1[119]	1987 (6 studies)	40 (38 to 46)	93 (92 to 94)	6 (5 to 7)	0.6 (0.6 to 0.7)	High

Number of studies	Number	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Measurement at 20–24 weeks; cut-off of 30 mm						
1[119]	2014 (5 studies)	56 (50 to 62)	81 (79 to 83)	3 (3 to 3)	0.6 (0.5 to 0.6)	High
Measurement at 20–24 weeks; cut-off of 35 mm						
1[119]	1884 (6 studies)	79 (74 to 84)	60 (57 to 62)	2 (2 to 2)	0.4 (0.3 to 0.4)	High
Measurement at 22–24 weeks; cut-off of 15 mm						
1[120]	215	11 (1 to 21)	97 (94 to 99)	4 (1 to 14)	0.9 (0.8 to 1.0)	Moderate
Measurement at 22–24 weeks; cut-off of 25 mm						
1[120]	215	35 (20 to 51)	94 (90 to 97)	6 (3 to 12)	0.7 (0.5 to 0.9)	Moderate
Measurement at 22–24 weeks; cut-off of 35 mm						
1[120]	215	57 (41 to 73)	63 (56 to 71)	2 (1 to 2)	0.7 (0.6 to 0.7)	High
Measurement at 22–24 weeks; cut-off of 45 mm						
1[120]	215	92 (83 to 100)	18 (12 to 24)	1 (1 to 1)	0.5 (0.2 to 1.4)	High
Measurement at 22–25 weeks; cut-off of <5th percentile for normal twin pregnancies based on gestational age						
1[117]	266	38 (22 to 55)	96 (94 to 99)	10 (5 to 21)	0.6 (0.5 to 0.8)	Low
Measurement at >24 weeks; cut-off of 25 mm						
1[119]	594 (4 studies)	44 (34 to 53)	81 (78 to 85)	2 (2 to 3)	0.7 (0.6 to 0.8)	High
Prediction of spontaneous birth before 37 weeks						
Measurement at 20–24 weeks; cut-off of 20 mm						
1[119]	434 (4 studies)	21 (15 to 27)	95 (92 to 98)	4 (2 to 8)	0.8 (0.8 to 0.9)	High
Measurement at 20–24 weeks; cut-off of 30 mm						
1[119]	218 (2 studies)	29 (18 to 43)	91 (86 to 95)	3 (2 to 7)	0.8 (0.7 to 0.9)	High
Measurement at 20-24 weeks; cut-off of 35 mm						
1[119]	134 (2 studies)	56 (43 to 68)	78 (50 to 74)	2 (1 to 2)	0.7 (0.5 to 1.0)	High
Measurement at >24 weeks; cut-off of 25 mm						
1[119]	276 (2 studies)	43 (35 to 51)	77 (68 to 84)	1 (1 to 3)	0.8 (0.6 to 0.9)	High

Table 8.2 GRADE summary of findings for cervical length measurement in twin pregnancies (diagnostic accuracy studies reporting relative risks and diagnostic accuracy measurements)

Number of studies	Number	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Prediction of spontaneous birth within one week of measurement of cervical length						
Measurement at 24–34 weeks; cut-off of 20 mm						
1[122]	46	65 (NC)	79 (NC)	3.06 (NC)	NR	Low
Measurement at 24–34 weeks; cut-off of 25 mm						
1[122]	46	77 (NC)	59 (NC)	1.86 (NC)	NR	Low
Measurement at 24–34 weeks; cut-off of 30 mm						
1[122]	46	88 (NC)	41 (NC)	1.51 (NC)	NR	Low
Measurement at 24–34 weeks; cut-off of 33 mm						
1[122]	46	92 (NC)	37 (NC)	1.47 (NC)	NR	Low

Table 8.3 GRADE summary of findings for cervical length measurement in triplet pregnancies

Number of studies	Number	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Prediction of spontaneous birth before 28 weeks						
Measurement at 15–20 weeks; cut-off of 25 mm						
1[123]	50	50 (15 to 85)	100 (92 to 100)	NC	0.5 (0.3 to 0.9)	Low
Measurement at 21–24 weeks; cut-off of 25 mm						
1[123]	50	86 (60 to 100)	79 (67 to 91)	4 (2 to 8)	0.2 (0.0 to 1.1)	Low
Measurement at 25–28 weeks; cut-off of 20 mm						
1[123]	46	100 (40 to 100)	57 (42 to 72)	2 (2 to 3)	0.0 (NC)	Low
Prediction of spontaneous birth before 30 weeks						
Measurement at 15–20 weeks; cut-off of 25 mm						
1[123]	49	36 (8 to 65)	100 (91 to 100)	NC	0.6 (0.4 to 0.9)	Low
Measurement at 21–24 weeks; cut-off of 25 mm						
1[123]	49	70 (42 to 98)	82 (70 to 94)	4 (2 to 9)	0.4 (0.1 to 0.9)	Low
Measurement at 25–28 weeks; cut-off of 20 mm						
1[123]	46	100 (59 to 100)	62 (46 to 77)	3 (2 to 4)	0 (NC)	Low
Prediction of spontaneous birth before 32 weeks						
Measurement at 14–20 weeks; cut-off of 25 mm						
1[124]	36	75 (54 to 96)	90 (77 to 100)	8 (2 to 29)	0.3 (0.1 to 0.7)	Low
Measurement at 15–20 weeks; cut-off of 25 mm						
1[123]	47	25 (3 to 46)	100 (89 to 100)	NC	0.8 (0.6 to 0.9)	Low
Measurement at 21–24 weeks; cut-off of 25 mm						
1[123]	47	60 (35 to 85)	84 (72 to 97)	4 (2 to 9)	0.5 (0.3 to 0.9)	Low
Measurement at 25–28 weeks; cut-off of 20 mm						
1[123]	44	83 (62 to 100)	66 (49 to 82)	2 (1 to 4)	0.3 (0.1 to 0.9)	Low

Table 8.4 GRADE summary of findings for fetal fibronectin test in twin pregnancies

Number of studies	Number of twin pregnancies	Sensitivity % (95% confidence interval)	Specificity % (95% confidence interval)	LR^+ (95% confidence interval)	LR^- (95% confidence interval)	Quality
Prediction of spontaneous preterm birth before 35 weeks						
Positive test at 24 weeks						
1[125]	73	50 (26 to 75)	49 (36 to 62)	1 (1 to 2)	1.0 (0.6 to 1.8)	Moderate
1[126]	101	37(15 to 59)	91(85 to 98)	4(2 to 11)	0.7(0.5 to 0.9)	Moderate
Positive test at 28 weeks						
1[125]	74	NR	NR	2 (NR)	0.9 (NR)	High
1[126]	101	50(28 to 71)	92 (86 to 98)	6 (3 to 15)	0.5 (0.4 to 0.9)	Moderate
Positive test at 24 and 28 weeks						
1[126]	101	24 (3 to 44)	99 (96 to 100)	16 (2 to 132)	0.8 (0.6 to 1.0)	Moderate
Positive test at 32 weeks						
1[125]	65	NR	NR	2 (NR)	0.5 (NR)	High
Positive test at 24, 26, 28, 30 or 32 weeks						
1[126]	101	59 (39 to 80)	71 (61 to 81)	2 (1 to 3)	0.6 (0.3 to 3.3)	Moderate
Positive test at 24, 26, 28, 30 and 32 weeks						
1[126]	101	23(5 to 40)	99 (96 to 100)	18 (2 to 146)	0.8 (0.6 to 0.9)	Moderate
Prediction of spontaneous preterm birth before 37 weeks						
Positive test at 24, 26, 28, 30 or 32 weeks						
1[126]	101	53 (36 to 69)	74 (63 to 85)	2 (1 to 3)	0.6 (0.4 to 0.9)	High
Positive test at 24, 26, 28, 30 and 32 weeks						
1[126]	101	14 (3 to 25)	99 (95 to 100)	9 (1 to 74)	0.9 (0.8 to 1.0)	Moderate

Table 8.5 GRADE summary of findings for combined cervical length measurement and fetal fibronectin test in twin pregnancies

Number of studies	Effect					Quality
	Number	Risk for spontaneous preterm birth (%)			P-value of difference between risks	
		Both tests positive	One test positive	Tests negative		
Prediction of spontaneous birth before 28 weeks						
Tests done at 22–32 weeks; cervical length threshold of 20 mm						
1[127]	155	50	13.3	1.6	< 0.001	Very low
Prediction of spontaneous birth before 28 to 30 weeks						
Tests done at 24–26 weeks; cervical length threshold of 25 mm						
1[128]	149	50.0	15.6	6.4	Significance not reported	Very low
Prediction of spontaneous birth before 30 weeks						
Tests done at 22–32 weeks; cervical length threshold of 20 mm						
1[127]	155	33.3	9.5	2.4	< 0.001	Very low
Prediction of spontaneous birth before 32 weeks						
Tests done at 22–32 weeks; cervical length threshold of 20 mm						
1[127]	155	54.5	8.3	4.2	< 0.001	Very low
Prediction of spontaneous birth before 34 weeks						
Tests done at 22–32 weeks; cervical length threshold of 20 mm						
1[127]	155	54.5	26.1	10.3	< 0.001	Very low
Prediction of spontaneous birth before 35 weeks						
Tests done at 22–32 weeks; cervical length threshold of 20 mm						
1[127]	155	54.5	39.1	18.3	< 0.001	Very low
Prediction of spontaneous birth before 37 weeks						
Tests done at 22–32 weeks; cervical length threshold of 20 mm						
1[127]	120/155	100	77.3	43.0	< 0.001	Very low

Table 8.6 GRADE summary of findings for home uterine activity monitoring (with or without nursing contact) versus no monitoring in twin pregnancies

Number of studies	Number of Preterm Births		Effect		Quality
	Home monitoring	No monitoring	Relative risk (95% confidence interval)	P-value	
Prediction of spontaneous preterm birth					
1[129]	72/165 (44%)	60/146 (41%)	1.01 (0.79 to 1.30)	0.95	Very low

Table 8.7 GRADE summary of findings for home uterine activity monitoring and daily contact with a nurse versus daily contact alone versus weekly contact in twin pregnancies

Number of studies	Number of Preterm Births		Effect		Quality
	Home monitoring	Daily contact only	Weekly contact only	Relative risk/ P-value	
Prediction of spontaneous preterm birth <32 weeks (monitoring and contact started at 24 week)					
1[130]	17/287 (6%)	25/277 (9%)	20/280 (7%)	No significant difference (p-value not reported)	Low
Prediction of spontaneous preterm birth <35 weeks (monitoring and contact started at 24 week)					
1[130]	69/287 (24%)	62/277 (24%)	62/280 (22%)	No significant difference (p-value not reported)	Low
Prediction of spontaneous preterm birth <37 weeks (monitoring and contact started at 24 week)					
1[130]	146/287 (51%)	150/277 (54%)	137/280 (49%)	No significant difference (p-value not reported)	Moderate

Table 8.8 GRADE summary of findings for obstetric history (preterm singleton birth in the previous pregnancy) in twin pregnancies

Number of studies	Number		Effect	Quality
	Number of preterm births to women with a previous preterm singleton birth	Number of preterm births to women with a previous term singleton birth	Odds Ratio (95% CI)	
Prediction of spontaneous preterm birth				
1[131]	17/23 (74%)	120/270 (44%)	3.5 (1.4 to 9.3)	Very low

Evidence statement

Evidence was identified for cervical length measurement, fibronectin testing, additional antenatal care and previous obstetric history in predicting preterm birth in twin and triplet pregnancies. The quality of the evidence ranged from very low to high.

There was evidence that a short cervical length, especially less than 25 mm, at 18–24 weeks of gestation in twin pregnancies is a good predictor of preterm birth at up to 35 weeks of gestation (high or moderate quality). A short cervix was, however, not predictive of birth before 37 weeks (high quality evidence).

There was evidence that a cervical length less than 25 mm measured at 14–20 weeks in triplet pregnancies was associated with spontaneous preterm birth before 32 weeks (low quality).

There was no association between a positive fetal fibronectin test result and the risk of spontaneous preterm birth in twin pregnancies (moderate to high quality). However, if used in conjunction with cervical length, the ability of the test to identify women who were at a significantly higher risk of preterm birth was improved (very low quality).

There was evidence that home uterine activity monitoring in twin pregnancies was not effective in predicting spontaneous preterm birth (very low to moderate quality).

There was evidence in twin pregnancies that the occurrence of a singleton preterm birth in the previous pregnancy significantly increased the risk of preterm birth in twin pregnancies (very low quality).

Health economics profile

No published health economic evidence was identified, although this question was prioritised for health economic analysis. This question is linked to the question considering effectiveness of interventions to prevent preterm birth once it has been predicted (see Section 7.2). There was evidence that a short cervical length, especially less than 25 mm, between 18 and 24 weeks of gestation in twin pregnancies is a good predictor of a preterm birth at up to 35 weeks; however, a short cervix was not predictive of delivery before 37 weeks. Also, the evidence identified in relation to interventions to prevent preterm birth showed that none of the interventions was clinically effective, and so the GDG did not proceed with the planned health economic analysis.

Evidence to recommendations

Relative value placed on the outcomes considered

Sensitivity is the proportion of pregnancies that resulted in preterm birth that were predicted to be preterm (true positive). One hundred minus sensitivity (100 – sensitivity) shows how many of these pregnancies were predicted to be term at scan (false negative).

Specificity is the proportion of pregnancies that resulted in a term birth that were predicted to be term (true negative). One hundred minus specificity (100 – specificity) shows how many of these pregnancies were predicted to be preterm at scan (false positive).

PPV is the proportion of pregnancies that were predicted to be preterm and that resulted in a preterm birth. One hundred minus PPV (100 – PPV) shows how many of these pregnancies resulted in a term birth.

NPV is the proportion of pregnancies that were predicted to be term that resulted in a term birth. One hundred minus NPV (100 – NPV) shows how many of these pregnancies resulted in a preterm birth.

The positive likelihood ratio (LR^+) shows how much the odds of a birth being preterm increase when preterm birth is predicted. The negative likelihood ratio (LR^-) shows how much the odds of a pregnancy being preterm decrease when a scan predicts term birth.

The GDG prioritised likelihood ratios and sensitivity when considering the evidence for different methods of predicting preterm birth.

Trade-off between clinical benefits and harms

Correctly identifying women who are at risk of preterm birth (true positives) potentially allows more careful monitoring. It allows decisions to be made in consultation with women who are fully aware of the risks involved, including planning for an earlier birth date. If women are predicted to be at risk of preterm birth but then deliver at term (false positives), this may result in unnecessary extra monitoring, which could cause maternal anxiety and unnecessary interventions from healthcare professionals. Correctly identifying women who are not at risk of preterm birth (true negatives) saves resources and prevents anxiety by avoiding unnecessary extra monitoring. It allows the woman and her healthcare team to plan for an accurate birth date. Failing to identify women who go on to miscarry or deliver extremely prematurely (false negatives) could result in the delivery of preterm fetuses in a setting where neonatal facilities are suboptimal: these women would also miss the opportunity for antenatal administration of corticosteroids.

Trade-off between net health benefits and resource use

A more accurate test may be worth an extra cost if there is a way to reduce preterm birth in women who are true positives. The treatments that have been investigated with the intention of preventing preterm birth were not clinically effective (see Section 8.2) and so the GDG did not proceed with the planned health economic analysis. Ultrasound scans cost about £71 and, assuming two scans are conducted for each woman, could cost the NHS around £140 per pregnant woman (no additional scanning appointments would be needed but the duration of these appointments would be increased by approximately 15 minutes per scan, compared with routine antenatal care). The GDG concluded that it could not recommend routine ultrasound scanning to predict preterm birth.

Quality of evidence

All the evidence in triplet pregnancies was low quality. For predicting preterm birth in twin pregnancies the quality of evidence varied, as follows:

- cervical length alone: low to high
- fetal fibronectin: moderate to high (mainly moderate)
- combined cervical length and fetal fibronectin tests: very low
- home uterine activity monitoring: moderate to very low
- obstetric history: very low.

Other considerations

Some evidence was identified regarding preterm birth in triplet pregnancies. However, there was not enough evidence to compare the effectiveness of all methods of preventing preterm birth in twin and triplet pregnancies. The 'Antenatal care' (NICE clinical guideline 62)[14] recommends against screening for preterm birth. The GDG believes that screening for preterm birth is an important consideration in twin and triplet pregnancies as there is a greater risk of preterm birth in such pregnancies. Cervical length measurement of less than 25 mm at 18–24 weeks of gestation in twin pregnancies and 14–20 weeks of gestation in triplet pregnancies predicts the risk of spontaneous preterm birth and the test may be improved further with the addition of fetal fibronectin. However, the GDG does not recommend that this test is undertaken routinely in twin or triplet pregnancies because no effective interventions to reduce this risk have been identified (see Section 8.2) and testing can create anxiety or offer false reassurance.

Recommendations

Number	Recommendation
47	Be aware that women with twin pregnancies have a higher risk of spontaneous preterm birth if they have had a spontaneous preterm birth in a previous singleton pregnancy.
48	Do not use fetal fibronectin testing alone to predict the risk of spontaneous preterm birth in twin or triplet pregnancies.
49	Do not use home uterine activity monitoring to predict the risk of spontaneous preterm birth in twin or triplet pregnancies.
50	Do not use cervical length (with or without fetal fibronectin) routinely to predict the risk of spontaneous preterm birth in twin or triplet pregnancies.

Number	Research recommendation
RR 12	Which clinical factors or laboratory tests are accurate predictors of spontaneous preterm birth in twin and triplet pregnancies? Why this is important Prematurity is the major contributor to increased adverse neonatal and infant outcomes in twin and triplet pregnancies (compared with singleton pregnancies), and being able to predict spontaneous preterm birth is an important goal to optimise outcomes of twin and triplet pregnancies for women and their babies. Several studies were identified in the guideline review in relation to accuracy of prediction of spontaneous preterm birth in twin and triplet pregnancies. The studies evaluated tests based on cervical length, fetal fibronectin, additional antenatal care, and obstetric history (preterm singleton birth in a previous pregnancy), and included composite measures based on the above tests. Most of the studies were observational in design (prospective or retrospective cohort studies), and few examined predictors of preterm birth in triplet pregnancies or the effects of chorionicity. Large, prospective studies are, therefore, needed to evaluate the accuracy of each of the tests as predictors of spontaneous preterm birth in twin and triplet pregnancies, with subgroup analysis by chorionicity.

8.2 Preventing preterm birth

Introduction

Spontaneous preterm birth and iatrogenic preterm birth that are secondary to other complications occur more frequently in twin and triplet pregnancies than in singleton pregnancies. Preterm birth (even near-term birth) is associated with considerable morbidity and use of healthcare resources, with many preterm babies being admitted to neonatal units. Extremely preterm birth (at less than 28 weeks of gestation) is associated with even greater morbidity and mortality and greater use of healthcare resources. It is, therefore, relevant to identify treatments which prevent spontaneous preterm birth without causing adverse effects in the woman or babies.

Review question

What interventions are effective in preventing spontaneous preterm delivery in multiple pregnancy, including bed rest, progesterone and cervical cerclage?

Existing NICE guidance

No existing NICE guidance was identified as being relevant to preventing spontaneous preterm birth, although 'Diabetes in pregnancy' (NICE clinical guideline 63)[21] recommends using an alternative to betamimetics when tocolysis (administration of drugs to inhibit uterine contractions) is indicated in women with diabetes.

Overview of the evidence

Eighteen studies were identified for inclusion.[132-149] The studies investigated the clinical effectiveness of the following interventions to prevent preterm birth in women with twin and triplet pregnancies:

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

Where evidence from systematic reviews of RCTs or individual RCTs was identified in relation to a particular intervention and associated outcomes prioritised for consideration by the GDG, evidence from study designs lower in the hierarchy of evidence (such as observational studies, including cohort studies and case–control studies) was excluded.

Women in two studies were advised to abstain from sexual intercourse. In one study that investigated hospital bed rest versus home bed rest, women in the intervention group only were advised to abstain from intercourse.[134] In another study that investigated the effectiveness of vaginal progesterone in twin pregnancies, both the intervention and control groups were advised to abstain from intercourse.[139]

Bed rest

A Cochrane review reported meta-analysis of evidence relating to the effectiveness of routine hospital bed rest compared to no bed rest for preventing preterm birth in women with twin and triplet pregnancies.[132] The review included six RCTs and one quasi-randomised controlled trial; five of the studies involved women with twin pregnancies and two involved women with triplet pregnancies. One of the RCTs was conducted in Finland, two in Australia and four in Zimbabwe.

One retrospective observational study, conducted in Denmark and involving women with twin pregnancies, compared hospital bed rest with bed rest at home or with no bed rest at all.[133] Another retrospective study, conducted in the USA, involved women with triplet pregnancies and also compared hospital bed rest with home bed rest but, in addition, all women in the study were advised to discontinue vaginal intercourse at 20 weeks of gestation.[134]

One RCT examined the effectiveness of hospital bed rest and prophylactic oral salbutamol (as a combined intervention) compared to hospitalisation for bed rest alone.[135] The study involved women with twin and triplet pregnancies and was conducted in Finland.

Progesterone

Seven RCTs evaluated the clinical effectiveness of progesterone compared to placebo in the prevention of preterm birth in women with twin or triplet pregnancies.[136-142]

Five of the studies reported data separately for spontaneous preterm birth.[136;137;139;140;142] One study did not specify whether or not the reported preterm birth data included iatrogenic preterm births,[138] and in another study, data for preterm birth and intrauterine death were reported together.[141] This last study reported clinical effectiveness data from the Study of Progesterone for the Prevention of Preterm Birth in Twins (STOPPIT; a double blind, randomised, placebo-controlled study; see https://www.charttrials.abdn.ac.uk/stoppit/). A published economic evaluation relating to STOPPIT was identified separately (see later).[150]

Two of the six studies reported on daily vaginal progesterone gel and they were conducted in the UK.[139;141] The other studies reported on weekly intramuscular progesterone:[136-138;140;142] one of these studies was conducted in Finland[136] and the other four in the USA.[137;138;140;142]

Two of the RCTs involved women with triplet pregnancies[140;142] and the other five involved women with twin pregnancies.[136-139;141]

Cervical cerclage

One RCT,[143] one prospective observational study[144] and four retrospective observational studies[145-148] evaluated the effectiveness of cervical cerclage in the prevention of preterm birth in women with twin or triplet pregnancies.

The RCT was conducted in Israel and involved women with twin pregnancies conceived after ovulation induction.[143] Women in the intervention group underwent elective cervical suture (McDonald) at 13 weeks of gestation and they were compared with a control group who received no cervical suture.

The prospective observational study involved women with a short cervix, all of whom rested at home or in the hospital.[144] The study was conducted in the USA. The other four studies used a retrospective cross-sectional review of medical records of women with triplet pregnancies who had undergone cervical cerclage compared to women who had not.[145-148] Three of the studies were conducted in the USA[145-147] and one in Israel.[148]

Tocolytic therapy

A Cochrane review involving women with twin pregnancies assessed the clinical effectiveness of prophylactic tocolytic therapy.[149] The review included five RCTs, each examining a different betamimetic agent (salbutamol, feneterol, isoxurpine, ritodrine or terbutaline). The trials were conducted in the UK, Ireland, Sweden, South Africa and Zimbabwe.

No studies examining the role of other tocolytic agents were identified for inclusion.

Sexual abstinence

No studies examining the effectiveness of sexual abstinence alone were identified for inclusion.

Published health economic evidence

One published health economic evaluation was identified in relation to this question,[150] which was prioritised for health economic analysis. The published economic evaluation related to STOPPIT, for which a separate publication reporting clinical effectiveness data only[141] was included in the review of clinical evidence (see above). The main outcomes of the STOPPIT trial were birth or fetal death before 34 weeks of gestation. The use of progesterone in this population of women did not reduce the incidence of preterm birth. There was a tendency towards increased neonatal stay in special care units in the progesterone group. The mean hospital costs for the progesterone group were about £28,000 compared to £25,000 in the placebo group.

Cost effectiveness acceptability curves reported in the economic evaluation showed the probability of prophylactic vaginal progesterone being cost effective as a function of the decision makers' willingness to pay to prevent a case of spontaneous preterm birth against the alternative of not providing prophylactic progesterone. In the health economic analysis, progesterone was 20% cost effective at a willingness to pay value of £30,000 per preterm birth prevented. The net benefit statistic confirmed the finding that progesterone was unlikely to be cost effective at £30,000 per preterm birth prevented, as the net benefit was negative (–£3,637, 95% CI –£3,853 to –£3,420), meaning that there would be a financial loss to the health service. The authors calculated the expected value of perfect information, which showed that using placebo consistently produced higher net health benefits.

The authors of the economic evaluation concluded that the probability of prophylactic vaginal progesterone being cost effective was low in women with twin pregnancies, and sensitivity analysis showed the findings to be robust. This was a well conducted and presented health economic analysis. The study did not consider quality adjusted life years (QALYs) as an outcome, although the QALY is NICE's preferred measure of outcome. However, the GDG believes the QALY approach would be unlikely to change the conclusions of the analysis, since preterm birth and fetal death are good proxies for the quality and quantity of life that would be needed to calculate QALYs.

Evidence profiles

Evidence profiles for this question are presented in Tables 8.9 to 8.18.

Table 8.9 GRADE summary of findings for routine hospitalisation for bed rest versus no bed rest for the prevention of spontaneous preterm birth in twin pregnancies

Number of studies	Number of women		Effect		Quality
	Routine hospitalisation	No bed rest	Relative (95% confidence interval)	Absolute	
Spontaneous preterm birth					
<37 weeks					
1[132]	117/264 (44%)	108/284 (38%)	RR 1.12 (0.89 to 1.42)	46 more per 1000 (from 42 fewer to 160 more)	Very low
34 weeks					
1[132]	33/127 (26%)	21/132 (16%)	RR 1.57 (0.72 to 3.43)	91 more per 1000 (from 45 fewer to 387 more)	Very low
1[133]	0/37 (0%)	14/34 (41%)	RR 0.03 (0 to 0.51)	399 fewer per 1000 (from 202 fewer to 412 fewer)	Very low
Gestational age at birth (measured in weeks; better indicated by higher values)					
1[132]	264 women in group	284 women in group	-	MD 0.39 lower (0.78 lower to 0.01 higher)	Moderate
Perinatal mortality					
1[132]	23/524 (4%)	19/568 (3%)	RR 1.64 (0.45 to 6.08)	21 more per 1000 (from 18 fewer to 170 more)	Very low
1[133]	0/37 (0%)	4/34 (12%)	RR 0.10 (0.01 to 1.83)	106 fewer per 1000 (from 116 fewer to 98 more)	Very low
Caesarean section					
1[132]	47/127 (37%)	49/132 (37%)	RR 1.04 (0.78 to 1.38)	15 more per 1000 (from 82 fewer to 141 more)	Moderate
Admission to neonatal care unit					
1[132]	72/254 (28%)	69/264 (26%)	RR 1.08 (0.82 to 1.42)	21 more per 1000 (from 47 fewer to 110 more)	Moderate
Low birthweight					
1[132]	240/528 (46%)	280/568 (49%)	RR 0.91 (0.81 to 1.03)	44 fewer per 1000 (from 94 fewer to 15 more)	Moderate
Very low birthweight					
1[132]	29/528 (6%)	17/568 (3%)	RR 1.82 (1.02 to 3.27)	25 more per 1000 (from 1 more to 68 more)	Low
Neonatal stay ≥ 7 days					
1[132]	14/116 (12%)	21/120 (18%)	RR 0.69 (0.37 to 1.29)	54 fewer per 1000 (from 110 fewer to 51more)	Moderate

Table 8.10 GRADE summary of findings for routine hospitalisation for bed rest versus no bed rest for the prevention of spontaneous preterm birth in triplet pregnancies

Number of studies	Number of women		Effect		Quality
	Routine hospitalisation	No bed rest	Relative (95% confidence interval)	Absolute	
Spontaneous preterm birth					
<37 weeks					
1[132]	11/13 (85%)	13/13 (100%)	RR 0.88 (0.66 to 1.16)	120 fewer per 1000 (from 340 fewer to 160 more)	Low
34 weeks					
1[132]	6/13 (46%)	6/13 (46%)	RR 1.17 (0.46 to 2.94)	78 more per 1000 (from 249 fewer to 895 more)	Low
Gestational age at birth (measured in weeks; better indicated by higher values)					
1[132]	13 babies in group	13 babies in group	-	Mean difference 0.58 (–1.35 to 2.51)	Moderate
Perinatal mortality					
1[132]	1/39 (3%)	5/39 (13%)	RR 0.28 (0.05 to 1.65)	92 fewer per 1000 (from 122 fewer to 83 more)	Moderate
Caesarean section					
1[132]	4/19 (21%)	4/21 (19%)	RR 0.98 (0.27 to 3.62)	4 fewer per 1000 (from 139 fewer to 499 more)	Moderate
Admission to neonatal care unit					
1[132]	25/30 (83%)	25/27 (93%)	RR 0.90 (0.74 to 1.09)	93 fewer per 1000 (from 241 fewer to 83 more)	Moderate
Low birthweight					
1[132]	35/39 (90%)	35/39 (90%)	RR 1.08 (0.66 to 1.78)	72 more per 1000 (from 305 fewer to 700 more)	Moderate
Very low birthweight					
1[132]	5/39 (13%)	9/39 (23%)	RR 0.56 (0.20 to 1.54)	102 fewer per 1000 (from 185 fewer to 125 more)	Moderate
Neonatal stay ≥ 7 days					
1[132]	17/30 (57%)	11/27 (41%)	RR 1.39 (0.80 to 2.42)	159 more per 1000 (from 81 fewer to 579 more)	Moderate

Table 8.11 GRADE summary of findings for hospital bed rest versus home bed rest for the prevention of spontaneous preterm birth in twin pregnancies

Number of studies	Number of women		Effect		Quality
	Hospital bed rest	Home bed rest	Relative (95% confidence interval)	Absolute	
Spontaneous preterm birth <34 weeks					
1[133]	0/37 (0%)	4/31 (13%)	RR 0.09 (0.01 to 1.67)	117 fewer per 1000 (from 128 fewer to 86 more)	Very low
Perinatal mortality					
1[133]	0/37 (0%)	1/31 (3%)	RR 0.28 (0.01 to 6.66)	23 fewer per 1000 (from 32 fewer to 183 more)	Very low

Table 8.12 GRADE summary of findings for hospital bed rest versus home bed rest (with advice for women in both groups to discontinue vaginal intercourse at 20 weeks of gestation for the prevention of spontaneous preterm birth in triplet pregnancies

Number of studies	Number of women		Effect		Quality
	Hospital bed rest	Home bed rest	Relative (95% confidence interval)	Absolute	
Gestational age at birth (measured in weeks; better indicated by higher values)					
1[134]	102 women in group	96 women in group	-	MD 1.00 higher (0.22 to 1.78 higher)	Very low
Perinatal mortality					
1[134]	1/102 (1%)	1/96 (1%)	OR 0.94 (0.06 to 15.25)	1 fewer per 1000 (from 10 fewer to 128 more)	Very low
Caesarean section					
1[134]	31/34 (91%)	26/32 (81%)	OR 2.38 (0.54 to 10.48)	99 more per 1000 (from 112 fewer to 166 more)	Very low
Respiratory distress syndrome					
1[134]	0/102 (0%)	1/96 (1%)	OR 0.31 (0.01 to 7.72)	7 fewer per 1000 (from 10 fewer to 65 more)	Very low
Intraventricular haemorrhage					
Grades 1 to 4					
1[134]	1/102 (1%)	10/96 (10%)	OR 0.09 (0.01 to 0.68)	94 fewer per 1000 (from 31 fewer to 103 fewer)	Very low
Grades 3 to 4					
1[134]	0/102 (0%)	1/96 (1%)	OR 0.31 (0.01 to 7.72)	7 fewer per 1000 (from 10 fewer to 65 more)	Very low
Necrotising enterocolitis					
1[134]	0/102 (0%)	0/96 (0%)	Not calculable	Not calculable	Very low
Neonatal length of stay					
Measured in days of stay in neonatal special care unit (better indicated by lower values)					
1[134]	102 women in group	96 women in group	-	MD 0.10 lower (9.64 lower to 9.44 higher)	Very low
Measured in days of stay in nursery (better indicated by lower values)					
1[134]	102 women in group	96 women in group	-	MD 0.30 higher (0.54 lower to 1.14 higher)	Very low
Maternal length of stay (measured in days of hospital stay; better indicated by lower values)					
1[134]	102 women in group	96 women in group	-	MD 26.7 higher (17.59 to 35.81 higher)	Very low

Table 8.13 GRADE summary of findings for hospital bed rest and oral salbutamol versus hospital bed rest only for the prevention of spontaneous preterm birth in twin and triplet pregnancies

Number of studies	Number of women		Effect		Quality
	Hospital bed rest and oral salbutamol	Hospital bed rest only	Relative (95% confidence interval)	Absolute	
Spontaneous preterm birth					
<37 weeks					
1[135]	37/101 (37%)	37/99 (37%)	RR 0.98 (0.68 to 1.41)	7 fewer per 1000 (from 120 fewer to 153 more)	Low
<33 weeks					
1[135]	10/101 (10%)	9/99 (9%)	RR 1.09 (0.46 to 2.57)	8 more per 1000 (from 49 fewer to 143	Low

Number of studies	Number of women		Effect		Quality
	Hospital bed rest and oral salbutamol	Hospital bed rest only	Relative (95% confidence interval)	Absolute	
				more)	
Perinatal mortality					
1[135]	9/101 (9%)	11/99 (11%)	RR 0.80 (0.34 to 1.88)	22 fewer per 1000 (from 73 fewer to 98 more)	Moderate
Low birthweight					
1[135]	88/204 (43%)	84/199 (42%)	RR 1.03 (0.82 to 1.29)	13 more per 1000 (from 76 fewer to 122 more)	Moderate
Very low birthweight					
1[135]	10/204 (5%)	14/199 (7%)	RR 0.70 (0.32 to 1.53)	21 fewer per 1000 (from 48 fewer to 37 more)	Moderate
Respiratory distress syndrome					
1[135]	2/204 (1%)	4/199 (2%)	RR 0.49 (0.09 to 2.56)	10 fewer per 1000 (from 18 fewer to 31 more)	Low

Table 8.14 GRADE summary of findings for intramuscular or vaginal progesterone versus placebo for the prevention of spontaneous preterm birth in twin pregnancies

Number of studies	Number of women		Effect		Quality
	Progesterone (intramuscular or vaginal)	Placebo	Relative (95% confidence interval)	Absolute	
Spontaneous preterm birth					
<37 weeks – intramuscular progesterone					
2[136;138]	19/55 (35%)	14/52 (27%)	OR 1.42 (0.62 to 3.27)	74 more per 1000 (from 83 fewer to 277 more)	Very low
<35 weeks – intramuscular progesterone					
1[137]	101/325 (31%)	86/330 (26%)	OR 1.28 (0.91 to 1.8)	50 more per 1000 (from 18 fewer to 128 more)	Moderate
<34 weeks – vaginal progesterone					
1[139]	4/11 (36%)	7/13 (54%)	OR 0.49 (0.09 to 2.53)	175 fewer per 1000 (from 443 fewer to 208 more)	Very low
Spontaneous or iatrogenic preterm birth or intrauterine death < 34 weeks					
1[141]	61/247 (25%)	48/247 (19%)	OR 1.36 (0.89 to 2.09)	53 more per 1000 (from 18 fewer to 141 more)	Very low
Gestational age at birth (measured in weeks of gestation; better indicated by higher values)					
2[136;137]	366 women in group	372 women in group	-	MD 0.32 lower (0.83 lower to 0.19 higher)	Moderate
Perinatal mortality					
2[136;141]	18/572 (3%)	12/570 (2%)	OR 1.51 (0.72 to 3.16)	10 more per 1000 (from 6 fewer to 43 more)	Very low
Caesarean section					
2[136;141]	348/574 (61%)	365/578 (63%)	OR 0.90 (0.71 to 1.14)	25 fewer per 1000 (from 83 fewer to 30 more)	Moderate
Maternal side effects (any of urticaria, nausea, injection site, fatigue, dizziness and headache)					
1[137]	211/320 (66%)	210/326 (64%)	OR 1.0 (0.9 to 1.1)	0 fewer per 1000 (from 24 fewer to 22 more)	High

Number of studies	Number of women		Effect		Quality
	Progesterone (intramuscular or vaginal)	Placebo	Relative (95% confidence interval)	Absolute	
Admission to neonatal unit					
1[141]	167/494 (34%)	158/494 (32%)	OR 1.08 (0.76 to 1.54)	17 more per 1000 (from 57 fewer to 100 more)	Low
Low birthweight (<2500 g)					
1[137]	377/628 (60%)	415/648 (64%)	OR 0.9 (0.8 to 1.0)	25 fewer per 1000 (from 53 fewer to 0 more)	High
Very low birthweight (<1500 g)					
1[137]	81/628 (13%)	64/648 (10%)	OR 2.0 (1.0 to 3.39)	81 more per 1000 (from 1 more to 172 more)	Moderate
Respiratory distress syndrome					
2[137;138]	106/664 (16%)	96/676 (14%)	OR 1.14 (0.84 to 1.54)	17 more per 1000 (from 20 fewer to 61 more)	Low
Intraventricular haemorrhage					
2[137;138]	10/664 (2%)	10/674 (2%)	OR 0.97 (0.40 to 2.37)	1 fewer per 1000 (from 9 fewer to 20 more)	Low
Necrotising enterocolitis					
2[137;138]	4/664 (1%)	4/676 (1%)	OR 0.99 (0.26 to 3.70)	1 fewer per 1000 (from 4 fewer to 16 more)	Low
Neonatal length of stay in intensive care unit (measured in days; better indicated by lower values)					
1[138]	36 women in group	28 women in group	-	MD 1.10 higher (24.23 lower to 26.43 higher)	Low
Maternal quality of life					
1[141]	1/247 (0.4%)	0/247 (0%)	OR 3.01 (0.12 to 74.30)	1 more per 1000 (from 1 fewer to 1 more)	Low
Maternal satisfaction (measured with Likert-type questionnaire; better indicated by lower values)					
1[141]	250 women in group	250 women in group	-	MD 0.0 higher (0.5 lower to 0.4 higher)	Moderate

Table 8.15 GRADE summary of findings for intramuscular progesterone versus placebo for the prevention of spontaneous preterm birth in triplet pregnancies

Number of studies	Number of women		Effect		Quality
	Progesterone (intramuscular)	Placebo	Relative (95% confidence interval)	Absolute	
Spontaneous preterm birth					
<35 weeks					
1[142]	34/71 (48%)	27/63 (43%)	RR 1.1 (0.8 to 1.6)	43 more per 1000 (from 86 fewer to 257 more)	Low
<32 weeks					
1[140]	17/56 (30%)	7/25 (28%)	RR 1.1 (0.5 to 2.3)	28 more per 1000 (from 140 fewer to 364 more)	Low
Gestational age at birth (measured in weeks; better indicated by higher values)					
1[142]	71 women in group	63 women in group	-	Median difference 0.6 (P = 0.527)	Low
1[140]	56 women in group	25 women in group	-	Median difference NR (P = 0.36)	Low
Perinatal mortality					
1[142]	5/212 (2%)	2/183 (1%)	RR 2.2	13 more per 1000	Very low

Number of studies	Number of women		Effect		Quality
	Progesterone (intramuscular)	Placebo	Relative (95% confidence interval)	Absolute	
			(0.4 to 12.4)	(from 7 fewer to 125 more)	
1[140]	19/168 (11%)	2/75 (3%)	OR 4.7 (1.0 to 22.0)	87 more per 1000 (from 1 fewer to 349 more)	Low
Caesarean section					
2[140;142]	123/127 (97%)	87/88 (99%)	RR 0.99 (0.91 to 1.07)	10 fewer per 1000 (from 89 fewer to 69 more)	Very low
Low birthweight					
1[142]	191/212 (90%)	175/183 (96%)	RR 0.9 (0.9 to 1.0)	96 fewer per 1000 (from 96 fewer to 1 more)	Moderate
Very low birthweight					
1[142]	91/212 (43%)	46/183 (25%)	RR 1.7 (1.1 to 2.7)	176 more per 1000 (from 25 more to 427 more)	Low
Respiratory distress syndrome					
2[140;142]	109/367 (30%)	78/258 (30%)	RR 0.94 (0.64 to 1.37)	18 fewer more per 1000 (from 109 fewer to 112 more)	Very low
Intraventricular haemorrhage (grades 3 and 4)					
2[140;142]	6/362 (2%)	7/258 (3%)	RR 0.54 (0.18 to 1.64)	12 fewer per 1000 (from 22 fewer to 17 more)	Low
Necrotising enterocolitis (stage 2 and 3)					
1[140]	8/154 (5%)	3/75 (4%)	OR 1.4 (0.2 to 7.6)	15 more per 1000 (from 32 fewer to 201 more)	Low
Necrotising enterocolitis					
1[142]	2/212 (1%)	5/183 (3%)	RR 0.3 (0 to 3.1)	19 fewer per 1000 (from 27 fewer to 57 more)	Low
Neonatal length of stay (measured in days; better indicated by lower values)					
1[140]	168 babies in group	75 babies in group	-	MD 11.50 lower (from 24.49 lower to 2.51 higher)	Low

Table 8.16 GRADE summary of findings for cervical cerclage versus no cerclage for the prevention of spontaneous preterm birth in twin pregnancies

Number of studies	Number of women		Effect		Quality
	Progesterone (intramuscular)	Placebo	Relative (95% confidence interval)	Absolute	
Spontaneous preterm birth					
<37 weeks					
1[143]	10/22 (46%)	11/23 (48%)	OR 0.83 (0.25 to 2.72)	46 fewer per 1000 (from 292 fewer to 235 more)	Very low
<34 weeks					
1[144]	9/21 (43%)	6/12 (50%)	OR 0.75 (0.18 to 3.12)	71 fewer per 1000 (from 347 fewer to 257 more)	Very low
Gestational age at birth (measured in weeks; better indicated by higher values)					
1[144]	33.5 weeks (SD 3.6)	32.8 weeks (SD 3.9)	-	MD 0.70 higher (0.99 lower to 3.39 higher)	Very low
Perinatal mortality					

Number of studies	Number of women		Effect		Quality
	Progesterone (intramuscular)	Placebo	Relative (95% confidence interval)	Absolute	
1[143]	8/44 (18%)	7/46 (15%)	OR 1.24 (0.41 to 3.76)	30 more per 1000 (from 84 fewer to 251 more)	Very low
Caesarean section					
1[143]	9/22 (41%)	7/23 (30%)	OR 1.58 (0.46 to 5.41)	104 more per 1000 (from 137 fewer to 399 more)	Low
Very low birthweight (<1500 g)					
1[144]	9/42 (21%)	7/24 (29%)	OR 0.66 (0.21 to 2.09)	78 fewer per 1000 (from 212 fewer to 171 more)	Very low

Table 8.17 GRADE summary of findings for cervical cerclage versus no cerclage for the prevention of spontaneous preterm birth in triplet pregnancies

Number of studies	Number of women		Effect		Quality
	Cervical cerclage	No cerclage	Relative (95% confidence interval)	Absolute	
Spontaneous preterm birth					
<32 weeks					
3[145-147]	83/323 (26%)	860/3109 (28%)	OR 0.78 (0.44 to 1.42)	47 fewer per 1000 (from 133 fewer to 75 more)	Very low
<31 weeks					
1[145]	2/20 (10%)	15/39 (39%)	OR 0.18 (0.04 to 0.89)	283 fewer per 1000 (from 27 fewer to 360 fewer)	Very low
<28 weeks					
2[146;147]	11/303 (4%)	136/3070 (4%)	OR 0.93 (0.49 to 1.76)	3 fewer per 1000 (from 22 fewer to 31 more)	Very low
Gestational age at birth (measured in weeks; better indicated by higher values)					
4[145-148]	320 women in group	3147 women in group	-	MD 0.11 higher (0.20 lower to 0.42 higher)	Low
Perinatal mortality					
2[145;148]	3/96 (3%)	11/186 (6%)	OR 0.56 (0.16 to 1.94)	25 fewer per 1000 (from 49 fewer to 50 more)	Very low
Admission to neonatal intensive care unit					
1[146]	594/737 (81%)	7376/9028 (82%)	OR 0.93 (0.77 to 1.13)	11 fewer per 1000 (from 42 fewer to 18 more)	Low
Very low birthweight (<1500 g)					
2[145;146]	202/804 (25%)	2362/9207 (26%)	OR 0.80 (0.46 to 1.38)	40 fewer per 1000 (from 120 fewer to 66 more)	Very low
Extremely low birthweight (<1000 g)					
1[145]	1/60 (2%)	18/117 (15%)	OR 0.09 (0.01 to 0.72)	138 fewer per 1000 (from 38 fewer to 152 fewer)	Very low
Respiratory distress syndrome					
1[145]	11/60 (18%)	32/117 (27%)	OR 0.60 (0.23 to 1.29)	89 fewer per 1000 (from 194 fewer to 53 more)	Very low
Intraventricular haemorrhage					
1[145]	6/35 (17%)	19/57 (33%)	OR 0.44 (0.15 to 01.23)	153 fewer per 1000 (from 264 fewer to 47 more)	Very low
Neonatal length of stay in the hospital (better indicated by lower values)					
1[146]	248 women in group	3030 women in group	-	MD 1.6 lower	Low

Table 8.18 GRADE summary of findings for oral betamimetics versus placebo for the prevention of spontaneous preterm birth in twin pregnancies

Number of studies	Number of women		Effect		Quality
	Oral betamimetics	Placebo	Relative (95% confidence interval)	Absolute	
Spontaneous preterm birth					
<37 weeks					
1[149]	57/140 (41%)	65/136 (48%)	RR 0.85 (0.65 to 1.10)	72 fewer per 1000 (from 167 fewer to 48 more)	Very low
<34 weeks					
1[149]	4/74 (5%)	8/70 (11%)	RR 0.47 (0.15 to 1.50)	61 fewer per 1000 (from 97 fewer to 57 more)	Low
Perinatal mortality					
1[149]	9/230 (4%)	11/220 (5%)	RR 0.80 (0.35 to 1.82)	10 fewer per 1000 (from 33 fewer to 41 more)	Very low
Low birthweight (<2500 g)					
1[149]	99/188 (53%)	85/178 (48%)	RR 1.19 (0.77 to 1.85)	91 more per 1000 (from 110 fewer to 406 more)	Low
Respiratory distress syndrome					
1[149]	5/198 (3%)	17/190 (9%)	RR 0.30 (0.12 to 0.77)	63 fewer per 1000 (from 21 fewer to 79 fewer)	Low

Evidence statement

Evidence was identified for all outcomes prioritised in relation to the interventions used to prevent preterm birth in twin and triplet pregnancies, although the studies varied in the number of outcomes reported. The quality of the evidence was mostly low or very low, with some being of moderate or high quality.

Bed rest

In twin pregnancies, routine hospitalisation for bed rest had no significant effect on the following compared with no bed rest:

- spontaneous preterm birth before 37 weeks of gestation (very low quality evidence)
- gestational age at birth (moderate quality evidence)
- perinatal mortality (very low quality evidence)
- caesarean section rates (moderate quality evidence)
- admission to neonatal care unit (moderate quality evidence)
- low birthweight (moderate quality evidence)
- very low birthweight (low quality evidence)
- neonatal stay of 7 days or more (moderate quality evidence).

The hospital bed rest group showed significantly fewer spontaneous births before 34 weeks of gestation in one study (very low quality evidence), but not in another (very low quality evidence). Compared to bed rest at home, hospital bed rest also had no significant effect on spontaneous preterm birth or perinatal mortality (very low quality evidence).

In triplet pregnancies, routine hospitalisation for bed rest had no significant effect on the following compared with no bed rest:

- spontaneous preterm birth (low quality evidence)

- gestational age at birth (moderate quality evidence
- perinatal mortality (moderate quality evidence)
- caesarean section rates (moderate quality evidence)
- admission to neonatal care unit (moderate quality evidence)
- low birthweight (moderate quality evidence)
- very low birthweight (moderate quality evidence)
- neonatal stay of 7 days or more (moderate quality evidence).

Compared with bed rest at home, hospital bed rest had no significant effect on:

- gestational age at birth (very low quality evidence)
- perinatal mortality (very low quality evidence)
- maternal length of stay (very low quality evidence)
- caesarean section rates (very low quality evidence)
- neonatal respiratory distress syndrome rates (very low quality evidence)
- necrotising enterocolitis (very low quality evidence)
- neonatal length of stay (very low quality of evidence).

The hospital bed rest group had a lower incidence of neonatal intraventricular haemorrhage than the home bed rest group when intraventricular haemorrhage grades 1 to 4 were pooled (very low quality evidence). There was, however, no effect on the incidence of the more severe grades (grades 3 and 4) when these were considered alone (very low quality evidence). Both bed rest groups also had advice to discontinue vaginal intercourse at 20 weeks of gestation.

For twin and triplet pregnancies, routine hospitalisation for bed rest combined with maternal oral salbutamol had no significant effect on spontaneous preterm birth (low quality evidence), perinatal mortality (moderate quality evidence), low or very low birthweight (moderate quality evidence) or neonatal respiratory distress syndrome (low quality evidence) compared to hospital bed rest alone.

Progesterone

In twin pregnancies, when compared with placebo, progesterone (intramuscular or vaginal) had no significant effect on:

- spontaneous preterm birth (very low or moderate quality evidence)
- gestational age at birth (moderate quality evidence)
- perinatal mortality (very low quality evidence)
- caesarean section rates (moderate quality evidence)
- maternal side effects (high quality evidence)
- maternal satisfaction (moderate quality evidence)
- maternal quality of life (moderate quality evidence)
- admission to neonatal care unit (low quality evidence)
- low birthweight (high quality evidence)
- very low birthweight (moderate quality evidence)
- neonatal respiratory distress syndrome (low quality evidence)
- neonatal intraventricular haemorrhage (low quality evidence)
- neonatal necrotising enterocolitis (low quality evidence)
- neonatal stay (low quality evidence).

In triplet pregnancies, when compared with placebo, intramuscular progesterone had no significant effect on:

- spontaneous preterm birth (low quality evidence)
- gestational age at birth (low quality evidence)
- perinatal mortality (low and very low quality evidence)
- caesarean section rates (very low quality evidence)
- low birthweight (moderate quality evidence)
- very low birthweight (low quality evidence)
- neonatal respiratory distress syndrome (very low quality evidence)
- neonatal intraventricular haemorrhage (low quality evidence)
- neonatal necrotising enterocolitis (low quality evidence)
- neonatal length of stay in hospital (low quality evidence).

Cervical cerclage

In twin pregnancies, cervical cerclage had no significant effect on caesarean section rate (low quality evidence) or spontaneous preterm birth, gestational age at birth, perinatal mortality or very low birthweight (all very low quality evidence) compared with no cerclage.

In triplet pregnancies, cervical cerclage had no significant effect on the following when compared to no cerclage:

- spontaneous preterm birth (very low quality evidence)
- gestational age at birth (low quality evidence)
- perinatal mortality (very low quality evidence)
- admission to neonatal intensive care unit (low quality evidence)
- very low birthweight (very low quality evidence)
- extremely low birthweight (very low quality evidence)
- neonatal respiratory distress syndrome (very low quality evidence)
- neonatal intraventricular haemorrhage (very low quality evidence)
- or neonatal length of stay (low quality evidence).

Tocolytic therapy

In twin pregnancies, oral betamimetics had no significant effect on spontaneous preterm birth (low and very low quality evidence), perinatal mortality (very low quality evidence) or low birthweight (low quality evidence) compared to placebo. However, there was a significantly lower incidence of neonatal respiratory distress syndrome in the group receiving tocolytic therapy compared to the placebo group (low quality evidence).

No studies were identified that examined the role of other tocolytic agents in twin pregnancies.

No studies were identified that examined the role of tocolytic agents in preventing preterm birth in triplet pregnancies.

Sexual abstinence

No studies were identified that examined sexual abstinence alone.

Health economics profile

One well-conducted health economic analysis was identified for inclusion and this concluded that the probability of prophylactic vaginal progesterone being cost effective in women with twin pregnancies is low. The findings were shown to be robust in sensitivity analysis.

This question was prioritised for further health economic evaluation. The question is linked to the question considering tests to predict preterm birth (see Section 8.1), in that this question addresses the cost effectiveness of interventions to prevent preterm birth once it has been predicted. None of the interventions considered for preventing preterm birth, including bed rest, cervical cerclage, progesterone and tocolytic drugs, was found to be clinically effective and so a formal health economic analysis was not required. Data from NHS reference costs show that a cervical cerclage procedure will cost the NHS about £320, while the British National Formulary (BNF) 59 shows that tocolytic drugs will cost £56 on average and progesterone £90 per pregnant woman. Given that the interventions are not clinically effective, these resources could be used for other more clinically effective and, therefore, cost-effective interventions.

Evidence to recommendations

Relative value placed on the outcomes considered

Primary outcomes:

- neonatal:
    - spontaneous preterm birth
    - gestational age at delivery
    - perinatal mortality and morbidity
- maternal:
    - length of stay
    - maternal side effects (infection, haemorrhage, drug effects, tachycardia, caesarean section).

Secondary outcomes:

- neonatal unit admission
- low birthweight and very low birthweight
- respiratory distress syndrome
- intraventricular haemorrhage
- necrotising enterocolitis
- neonatal length of stay
- maternal quality of life
- maternal satisfaction.

The GDG considered all outcomes to be important but believed perinatal mortality to be the most critical.

Trade-off between clinical benefits and harms

Preventing preterm birth can lead to better short- and long-term outcomes for the baby. This will also result in less use of healthcare resources. The clinical harms associated with preventing preterm birth include keeping a woman in an environment she does not wish to be in (for example, hospitalisation for bed rest), which may not be beneficial in the long term. Interventions may have unexpected adverse side effects for women and babies, and may result in higher preterm labour rates.

Trade-off between net health benefits and resource use

This review question was prioritised for health economic analysis but there was no evidence of clinical effectiveness for any of the interventions considered by the GDG (bed rest at home or in hospital, intramuscular or vaginal progesterone, cervical cerclage, oral tocolytics or sexual abstinence) and so no formal health economic analysis was conducted because the GDG was not going to recommend use of any of the interventions. NHS reference costs show that cervical cerclage will cost the NHS about £320 while BNF 59 shows that tocolytic drugs will cost on average £56 and progesterone £90

per pregnant woman. These cost data illustrate that these are expensive interventions that should not be used. Given that the interventions are not clinically effective, these resources could be freed for more clinically effective, and hence cost-effective, interventions.

Quality of evidence

Evidence for bed rest ranged from very low to moderate quality (mainly low); for progesterone from very low to high quality (mainly low); for cervical cerclage it was very low or low quality; and for tocolytics (oral betamimetics) it was low or very low quality.

Other considerations

Although the GDG recommended that bed rest (at home or in hospital), intramuscular or vaginal progesterone, cervical cerclage and oral tocolytics should not be used routinely to prevent spontaneous preterm birth in twin or triplet pregnancies, this does not preclude their use when clinically indicated (that is, targeted use appropriate to individual circumstances).

It was not possible to determine whether chorionicity affected the effectiveness of the methods used to prevent preterm birth.

Since the GDG had identified some evidence to suggest that the risk of spontaneous preterm birth could be predicted accurately (see Section 8.1), the group included a recommendation for further research to evaluate interventions for preventing spontaneous preterm birth in women with twin and triplet pregnancies, including those at high risk.

Recommendations

Number	Recommendation
51	Do not use the following interventions (alone or in combination) routinely to prevent spontaneous preterm birth in twin or triplet pregnancies: • bed rest at home or in hospital • intramuscular or vaginal progesterone • cervical cerclage • oral tocolytics.

Number	Research recommendation
RR 13	What interventions are effective in preventing spontaneous preterm birth in women with twin and triplet pregnancies, especially in those at high risk of preterm birth? Why this is important The guideline review considered several interventions aimed at preventing spontaneous preterm birth in women with twin and triplet pregnancies, including cervical cerclage, tocolytic drugs and sexual abstinence. The existing evidence for the effectiveness of cervical cerclage is of low quality (mostly originating from observational studies). The existing evidence in relation to tocolytics is also limited: there is evidence for the effectiveness of betamimetics, but no randomised controlled trials were identified for the effectiveness of ritodrine, magnesium sulphate or nifedipine. No evidence was identified for the effectiveness of sexual abstinence alone in preventing preterm birth. Further research in the form of randomised controlled trials is, therefore, needed to evaluate the effectiveness of cervical cerclage, tocolytics other than betamimetics, and sexual abstinence. Future research should place particular emphasis on women at high risk of preterm birth in twin and triplet pregnancies. Some evidence suggested that a cervical length of less than 25 mm at 18–24 weeks of gestation in twin pregnancies or 14–20 weeks of gestation in triplet pregnancies, or a history of

preterm labour in singleton pregnancies, increases the risk of spontaneous preterm birth in twin and triplet pregnancies. The evidence was limited in quality and additional research into the predictive accuracy of these factors would inform future NICE guidance. All research into the prevention of preterm birth should report spontaneous preterm birth separately from other preterm births. Data should also be reported separately for twin and triplet pregnancies, for different chorionicities, and for different gestational ages at birth (that is, less than 28 weeks, between 28 and less than 32 weeks, and 32–37 weeks).

8.3 Untargeted corticosteroids

Introduction

It is well established that antenatal administration of corticosteroids reduces neonatal complications in preterm babies resulting from singleton pregnancies. Since the risk of preterm birth is increased in twin and triplet pregnancies, consideration should be given to whether routine antenatal administration of corticosteroids (when preterm birth is not expected imminently) is effective in reducing neonatal complications in twin and triplet pregnancies. Since the interval between antenatal administration of corticosteroids and birth reduces their effectiveness, and recognising the difficulty in predicting time of birth in twin and triplet pregnancies, consideration should also be given to the effectiveness of multiple courses of corticosteroids in high-risk twin and triplet pregnancies, including those at higher risk of preterm birth.

However, a Cochrane review of studies involving singleton pregnancies showed a reduction in birthweight and head circumference in babies of women who received multiple courses of corticosteroids compared to those who received single courses.[151] Furthermore, there is a lack of evidence about the long-term benefits and risks[152] and there is evidence from retrospective studies that corticosteroids are less effective in multiple pregnancies than in singleton pregnancies.

This review question aims to establish whether routine (untargeted) courses of corticosteroids are effective in reducing perinatal morbidity in twin and triplet pregnancies.

Review question

Is routine/elective antenatal corticosteroid prophylaxis effective in reducing perinatal morbidity, including neonatal respiratory distress syndrome, necrotising colitis and intravenous haemorrhage, in multiple pregnancy?

Existing NICE guidance

No existing NICE guidance was identified as being relevant to this review question.

Overview of the evidence

Four studies were identified for inclusion for this question.[153-156] The studies comprised one RCT[155] and three observational studies.[153;154;156]

The RCT was a multicentre trial conducted at 80 centres in 20 countries (Argentina, Bolivia, Brazil, Canada, Chile, China, Colombia, Denmark, Germany, Hungary, Israel, Jordan, Peru, Poland, Russia, Spain, Switzerland, Netherlands, UK and the USA).[155] The study of 1858 pregnant women included 320 women with twin pregnancies and 70 women with triplet pregnancies. All of the pregnancies were at 25–32 weeks of gestation and the women had already completed a course of antenatal corticosteroids. If birth did not take place 14–21 days after the initial course, the women were randomly assigned to repeated courses of intramuscular betamethasone or to a placebo every 2 weeks until 33 weeks of gestation or birth. The ethnicity of the women and the chorionicity of the pregnancies were not reported.

Two of the observational studies were conducted in the UK.[153;156] One was a retrospective cohort study of 1038 twin pregnancies (including 137 monochorionic twin pregnancies), comparing women who received repeated courses of dexamethasone prophylaxis (route of administration not reported)

every 2 weeks from 24 to 32 weeks of gestation with those who received corticosteroids as rescue therapy when there was an immediate risk of preterm birth.[156] The ethnicity of the women involved in the study was not reported. The other study was a retrospective case note review of 173 triplets, comparing three groups:[153]

- those who were exposed to a single course of corticosteroids (dexamethasone or betamethasone, route of administration not reported) after 24 weeks of gestation and before birth
- those who were exposed to repeated courses of corticosteroids after 24 weeks of gestation and before birth
- those whose mothers received no corticosteroids or corticosteroids less than 24 hours before birth (the ethnicity of the women and the chorionicity of the pregnancies were not reported).

The fourth study was a prospective cohort study conducted in Kuwait.[154] The study involved twin, triplet and quadruplet pregnancies. For some outcomes, data were not reported separately for triplet and quadruplet pregnancies and so triplet data could not be extracted for the guideline for every outcome reported in the study. Half of the 44 twin pregnancies received routine dexamethasone (route of administration not reported) and half received no drug. The gestational age at which corticosteroid treatment started was not reported. The ethnicity of the women and the chorionicity of the pregnancies were not reported.

Published health economic evidence

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

Evidence profiles

Evidence profiles for this question are presented in Tables 8.19 to 8.22.

Table 8.19 GRADE summary of findings for routine single course of corticosteroids versus no routine corticosteroids

Number of studies	Number of women		Effect		Quality
	Routine prophylactic corticosteroids	No corticosteroids	Relative (95% confidence interval)	Absolute	
Perinatal and neonatal mortality in twins					
1[153]	2/91 (2%)	15/82 (18%)	OR 0.10 (0.02 to 0.45)	161 fewer per 1000 (from 91 fewer to 178 fewer)	Very low
Respiratory distress syndrome					
All severities of respiratory distress syndrome in twins					
1[154]	20/44 (46%)	30/44 (68%)	OR 0.39 (0.16 to 0.93)	227 fewer per 1000 (from 16 fewer to 426 fewer)	Very low
Mild respiratory distress syndrome in twins					
1[154]	11/44 (25%)	12/44 (27%)	OR 0.89 (0.34 to 2.30)	22 fewer per 1000 (from 160 fewer to 190 more)	Very low
Moderate or severe respiratory distress syndrome in twins					
1[154]	9/44 (21%)	18/44 (41%)	OR 0.37 (0.14 to 0.96)	205 fewer per 1000 (from 10 fewer to 321 fewer)	Very low
Neonatal length of stay					
In neonatal intensive care unit for twins					
1[154]	Median 3.5 days	Median 6 days	-	P-value reported as not significant	Very low
Birthweight by gestational age					
24 to 27 weeks in twins					
1[154]	725 g ± 35 g	715 g ± 92 g	-	P-value reported as	Very low

Number of studies	Number of women		Effect		Quality
	Routine prophylactic corticosteroids	No corticosteroids	Relative (95% confidence interval)	Absolute	
				not significant	
24 to 27 weeks in triplets					
	798 g ± 215 g	878 g ± 26 g	-	P < 0.016	Very low
28 to 32 weeks in twins					
1[154]	1201 g ± 412 g	1569g ±142 g	-	P < 0.0001	Very low
28 to 32 weeks in triplets					
1[154]	1379 g ± 216 g	1522 g ± 376g	-	P < 0.032	Very low
33 to 34 weeks in twins					
1[154]	2054 g ± 517 g	2043 g ± 367 g	-	P-value reported as not significant	Very low
33 to 34 weeks in triplets					
1[154]	1696g ± 515g	1469g ± 271g	-	P < 0.011	Very low

Table 8.20 GRADE summary of findings for routine multiple courses of corticosteroids versus no routine corticosteroids

Number of studies	Number of women		Effect		Quality
	Routine prophylactic corticosteroids	No corticosteroids	Relative (95% confidence interval)	Absolute	
Perinatal and neonatal mortality in triplets					
1[153]	2/76 (3%)	15/82 (18%)	OR 0.12 (0.03 to 0.55)	157 fewer per 1000 (from 73 fewer to 176 fewer)	Very low
Long-term neurodevelopmental outcomes					
At 1 year in triplets					
1[153]	1/76 (1%)	4/82 (5%)	OR 0.26 (0.03 to 2.38)	36 fewer per 1000 (from 47 fewer to 60 more)	Very low
Intraventricular haemorrhage in triplets					
1[153]	1/76 (1%)	10/82 (12%)	OR 0.10 (0.01 to 0.77)	108 fewer per 1000 (from 25 fewer to 121 fewer)	Very low

Table 8.21 GRADE summary of findings for routine multiple courses of corticosteroids versus routine single course of corticosteroids

Number of studies	Number of women		Effect		Quality
	Routine prophylactic corticosteroids	No corticosteroids	Relative (95% CI)	Absolute	
Composite outcomes					
Composite of neonatal mortality and morbidity in twins					
1[155]	62/427 (15%)	60/414 (15%)	OR 1.00 (0.68 to 1.47)	0 fewer per 1000 (from 42 fewer to 55 more)	Low

Table 8.22 GRADE summary of findings for routine multiple courses of corticosteroids versus targeted (rescue) corticosteroids

Number of studies	Number of women		Effect		Quality
	Routine prophylactic corticosteroids	Rescue corticosteroids	Relative (95% confidence interval)	Absolute	
Perinatal and neonatal mortality in twins					
1[156]	2/136 (2%)	30/902 (3%)	OR 0.43 (0.10 to 1.84)	19 fewer per 1000 (from 30 fewer to 26 more)	Very low
Respiratory distress syndrome in twins					
1[156]	17/136 (13%)	96/902 (11%)	OR 1.20 (0.69 to 2.08)	19 more per 1000 (from 30 fewer to 92 more)	Very low
Intraventricular haemorrhage in twins					
1[156]	1/136 (1%)	7/902 (1%)	OR 0.95 (0.12 to 7.76)	1 fewer per 1000 (from 7 fewer to 49 more)	Very low
Necrotising enterocolitis in twins					
1[156]	2/136 (2%)	2/902 (0.2%)	OR 6.71 (0.94 to 48.1)	12 more per 1000 (from 1 fewer to 94 more)	Very low
Neonatal length of stay					
In special care baby unit for twins					
1[156]	Not reported	Not reported	-	Adjusted MD –1.5 days (–5.3 days to +2.4 days)	Low
Birthweight in twins					
1[156]	Not reported	Not reported	-	Adjusted MD –129g (–218g to –33g)	Low

Evidence statement

Limited evidence was identified for the effectiveness of routine (elective) corticosteroids for reducing perinatal morbidity in twin and triplet pregnancies. The evidence compared different aspects of treatment and was mostly very low in quality.

The evidence that was reported addressed neonatal mortality, neurodevelopmental outcomes at 1 year, respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis, neonatal length of stay, birthweight and composites of these outcomes.

No studies were identified that examined development of gestational diabetes, development of gestational hypertension, maternal satisfaction or neurodevelopmental outcomes after 1 year in twin or triplet pregnancies treated with corticosteroids.

The corticosteroids for which data were reported were betamethasone and dexamethasone. No data were reported that allowed a direct comparison between the two corticosteroids, between different routes of administration for the same corticosteroid or between different doses of the same corticosteroid. There were limited data comparing the number of courses of dexamethasone or betamethasone, with a single course showing a lower mortality rate than multiple courses (very low quality evidence). However, the significance of the difference was not reported.

Routine single course of corticosteroids compared to no corticosteroids (or suboptimal course)

There were significantly fewer perinatal and neonatal deaths and significantly fewer babies with respiratory distress syndrome among twins in the corticosteroid group (very low quality evidence). There was inconsistent evidence that corticosteroids may be associated with differences in birthweight at different gestational ages, but this did not impact on the improved outcome as a result of the use of corticosteroids.

In twins, there was no significant difference between the groups in length of stay in the neonatal intensive care unit (very low quality evidence).

Routine multiple courses of corticosteroids compared to no corticosteroids (or suboptimal course)

There were significantly fewer perinatal and neonatal deaths in triplet pregnancies in the group that received multiple courses of corticosteroids, but gestational age at birth was the only independent predictor of survival (very low quality evidence).

No evidence was identified for effectiveness of multiple courses of corticosteroids by themselves in twin pregnancies.

Routine multiple courses of corticosteroids compared to routine single course

There was no significant difference in a composite score of neonatal mortality and morbidity in twin and triplet pregnancies (low quality evidence).

Routine multiple courses of corticosteroids compared to targeted (rescue) corticosteroids

There were no significant differences in perinatal and neonatal mortality or neonatal length of stay between twins in the group that received multiple courses of routine corticosteroids and those that received targeted (rescue) corticosteroids (low and very low quality evidence). There was no significant difference in the incidence of respiratory distress syndrome, intraventicular haemorrhage or necrotising enterocolitis (very low quality evidence).

The birthweights of twins whose mothers received multiple courses of corticosteroids were significantly higher than those of babies whose mothers received a targeted course (low quality evidence), but this may have been due to the later gestational age at delivery in the group that received multiple courses.

Routine single course of corticosteroids compared to targeted (rescue) corticosteroids

No evidence was identified for the effectiveness of a single course of corticosteroids compared to targeted corticosteroids in twin or triplet pregnancies.

Health economics profile

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

Evidence to recommendations

Relative value placed on the outcomes considered

All outcomes specified in the review protocol, including neonatal mortality and morbidity (respiratory distress syndrome, necrotising enterocolitis, intraventricular haemorrhage) and long-term neurodevelopmental outcomes, were considered by the GDG to be critical to the formulation of recommendations for clinical practice. Birthweight was considered a particularly important outcome given the potential harm of multiple courses of corticosteroids.

Trade-off between clinical benefits and harms

No clear evidence of benefit in giving routine single or multiple courses of antenatal corticosteroids in twin or triplet pregnancies was identified and there is limited evidence of harm from multiple courses compared to no treatment or targeted (rescue) treatment. However, the effect of corticosteroids on long-term neurodevelopmental outcomes is unknown.

Trade-off between net health benefits and resource use

The cost impact and opportunity costs of using corticosteroids prophylactically can be significant. Intramuscular corticosteroids cost up to £4.70 per dose and oral corticosteroids cost up to £1.40 per dose. If multiple doses were to be used (in one of the included studies up to eight doses were used) a course of treatment could cost almost £40 per pregnant woman. A recommendation not to use routine antenatal corticosteroid prophylaxis in twin and triplet pregnancies will save the NHS money because routine antenatal corticosteroid prophylaxis is sometimes used in current practice.

Quality of evidence

Few studies were identified for inclusion, with only one being an RCT. The resulting body of evidence considered by the GDG was generally of very low quality. The evidence for perinatal and neonatal mortality was very low in quality, as was the evidence for long-term neurodevelopmental outcomes,

respiratory distress syndrome, intraventricular haemorrhage and necrotising enterocolitis. The evidence for a composite of mortality and morbidity was low in quality. Evidence for birthweight and neonatal length of stay was low quality.

Other considerations

The majority of the studies identified did not report chorionicity and no studies reported ethnicity. Some evidence specific to triplet pregnancies was identified, although most studies focused on twin pregnancies. It is not possible to extrapolate twin data to triplets because triplets have a higher preterm birth rate. There was very little evidence in relation to choice of corticosteroids (for example betamethasone or dexamethasone), dosages or route of administration, or gestational age at administration or delivery. The studies identified were of poor quality and significant differences in birthweight between corticosteroid and no corticosteroid groups may be due to corticosteroid exposure.

It is unclear whether antenatal corticosteroids should be given routinely or targeted. There is no strong evidence of the benefit or harm of a single course of corticosteroids compared to multiple courses in twin and triplet pregnancies. A recommendation not to use antenatal corticosteroids 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 GDG considered reporting of gestational age at birth to be very important as differences in gestational age may account for some observed differences in outcomes: in one study, logistic regression showed that gestational age was the best predictor of survival.[153] The incidence of respiratory distress syndrome was very high in the control and experimental groups in another study,[154] and no explanation was provided by the study authors.

Recommendations

Number	Recommendation
52	Inform women with twin and triplet pregnancies of their increased risk of preterm birth and about the benefits of targeted corticosteroids.
53	Do not use single or multiple untargeted (routine) courses of corticosteroids in twin or triplet pregnancies. Inform women that there is no benefit in using untargeted administration of corticosteroids.

Number	Research recommendation
RR 14	What is the clinical and cost effectiveness, and safety, of routine antenatal administration of a single course of corticosteroids for women with twin and triplet pregnancies who are not in labour and in whom labour and birth are not imminent? **Why this is important** The evidence reviewed for the guideline is limited and of poor quality. The only evidence from randomised controlled trials relates to twin pregnancies investigated through subgroup analysis in a trial comparing a routine (prophylactic) single course of corticosteroids to routine multiple courses. No evidence was identified in relation to chorionicity, ethnicity, or acceptability of corticosteroid administration in women with twin or triplet pregnancies, or incidence of gestational hypertension or gestational diabetes following administration of corticosteroids. Further research in the form of large, prospective randomised controlled trials is, therefore, needed to evaluate the effectiveness of routine antenatal administration of a single course of corticosteroids compared to no (routine) corticosteroids for women with twin and triplet pregnancies. The research should address each of the following factors: acceptability of corticosteroid administration to women with twin or triplet

pregnancies; effectiveness in terms of reducing perinatal mortality and morbidity and long-term physical and neurodevelopmental outcomes; subgroup analyses for twin and triplet pregnancies and for different chorionicities; whether a short cervix is an indication for receiving routine (prophylactic) corticosteroids; timing of corticosteroid administration (in terms of gestational age) if it is to be offered.

9 Indications for referral to a tertiary level fetal medicine centre

Introduction

This chapter focuses on indications for referral to subspecialist services, which for the purposes of the guideline recommendations are referred to as tertiary level fetal medicine centres (regionally commissioned centres with the experience and expertise for management of complicated twin and triplet pregnancies).

Feto-fetal transfusion syndrome

Feto-fetal transfusion syndrome (FFTS), including twin-to-twin transfusion syndrome (TTTS), results in highly complicated pregnancies that should be referred to subspecialist services. Since FFTS is specified in the guideline scope as an indication for referral, the GDG did not search for evidence of the effectiveness of referral for this condition.

Discordant fetal growth, fetal anomaly and single fetal death in twin and triplet pregnancies

Discordant fetal growth, fetal anomaly and single fetal death are associated with poor perinatal outcomes in twin and triplet pregnancies.[157-159] Discordant fetal growth in twins with estimated fetal weight differences of more than 25% is associated with increased perinatal mortality and morbidity, which can lead to difficult clinical situations that require decisions to be made relating to investigation and potential delivery with risks to one or both fetuses. Twin and triplet pregnancies with fetal anomaly present options for healthcare professionals and parents which are clinically and emotionally complex, and also require difficult decisions to be made. Single fetal death increases perinatal morbidity and mortality in the surviving fetus or fetuses in all twin and triplet pregnancies, irrespective of chorionicity.

However, single fetal death in monochorionic twin pregnancies poses some of the most difficult decisions in the first 24 to 48 hours for the surviving twin. The risk of co-twin death in this period is 12% in monochorionic twin pregnancies and 4% in dichorionic twin pregnancies.[160] Informed and expert management of single fetal death is vital because inappropriate intervention may lead to the live birth of a twin (or triplet) at very high risk of neurodevelopmental damage, which may be compounded by the effects of prematurity. A twin who survives after a monochorionic twin single fetal death has a significant risk of neurodevelopmental morbidity from the effects of transfusional haemodynamic fluctuations. This may lead to (significant) neurodevelopmental morbidity in up to 20% of surviving twins.[160]

Careful ultrasound examination, investigation and discussion (including the involvement of paediatricians) are required to give women accurate information, where available, about the prognosis for these conditions. Termination of monochorionic and dichorionic twin pregnancies may be considered by the parents and their clinicians. If selective feticide is an option, accurate risks of miscarriage and other outcomes for the surviving twin, and the timing of such a procedure, need careful discussion.

Monochorionic monoamniotic pregnancies

Monochorionic, monoamniotic pregnancies are very rare (1–2% of monochorionic pregnancies are monoamniotic). They are associated with severe adverse perinatal outcomes resulting from complications secondary to cord entanglement (which is unique to monoamniotic pregnancies), in

addition to the complications associated with other high-risk twin and triplet pregnancies (discordant fetal growth, fetal anomaly, single fetal death, preterm birth and FFTS).[9-11]

Triplet pregnancies in general

Triplet pregnancies are relatively rare, with fewer than 200 maternities each year being associated with triplet births in England and Wales*. Triplet pregnancies carry greater risks of maternal and infant mortality and morbidity, which are further increased in monochorionic and dichorionic triplet pregnancies. Monitoring and planning clinical management of these complicated pregnancies in collaboration with teams with subspecialist training in fetal medicine should result in optimum care because subspecialist teams have additional experience and expertise in assessing clinical risks and possible outcomes. Subspecialist teams should also be able to give women with triplet pregnancies information about options and likely outcomes of interventions and non-interventions, and counselling and support required when faced with difficult decisions and potential ongoing psychological and emotional stress.

Collaborative care between local and subspecialist services facilitates access to tertiary level neonatal and paediatric services as required, while maintaining the focus on delivery of care locally, where possible, with expedient transfer back from regional services to local services. Referral of women with triplet pregnancies to specialist services will have significant resource implications, is likely to be inconvenient for the woman and her partner, and may cause additional anxiety for the woman. It could, however, be reassuring and helpful for some women who are experiencing these complications (discordant fetal growth, fetal anomaly, single fetal death, preterm birth and FFTS), and so this review question aims to evaluate the benefits of referral against economic and personal costs.

Review question

What are the clinical indications for referral to subspecialist services?

Existing NICE guidance

'Antenatal care' (NICE clinical guideline 62)[14] recognises the need for additional care for women with a history of stillbirth, a small-for-gestational age (SGA) baby, or a baby with structural or chromosomal abnormalities. Recommendations include the following:

- establish a system of clear referral paths so that pregnant women who require additional care are managed and treated by the appropriate specialist teams when problems are identified
- refer women in whom two or more 'soft markers' for Down's syndrome are found on second-trimester ultrasound (18–23 weeks) promptly for fetal medicine opinion
- offer a referral to a fetal medicine specialist or an appropriate healthcare professional with a special interest in fetal medicine if an increased nuchal fold (6 mm or above) or two or more soft markers are found on the routine anomaly scan.

Description of included studies

No studies were identified for inclusion in relation to direct evidence of the effectiveness of referral to subspecialist services in women with twin or triplet pregnancies complicated by discordant fetal growth, discordant fetal anomaly or single fetal death, nor in monochorionic, monoamniotic pregnancies or triplet pregnancies generally.

Two retrospective observational studies[161;162] conducted at tertiary care centres (in Japan and France, respectively) examined perinatal outcomes in women referred to subspecialist care from their usual care settings and compared them with women who had booked and received care at the same centre throughout pregnancy. The women had various conditions, including some of the above-mentioned conditions.

Published health economic evidence

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

* See Table 6.1b in http://www.statistics.gov.uk/downloads/theme_population/FM1-37/FM1_37_2008.pdf

Evidence profiles

Evidence profiles for this question are presented in Tables 9.1 and 9.2.

Table 9.1 GRADE summary of findings for indications for referral to subspecialist services (comparison of case numbers between study and control groups)

Number of studies	Referred for specialist care	Usual care	Relative risk (95% confidence interval)	Absolute risk reduction	Quality
Comparison of late referral to early followed up at tertiary care centre					
Fetal mortality rate					
1[162]	13/108	9/1220	16.32 (7.14 to 37.30)	113 more per 1000 (from 45 more to 268 more)	Very low
Infant mortality (before 1 year of age)					
1[161]	6/64	11/474	4.04 (1.55 to 10.55)*	71 more per 1000 (from 13 more to 222 more)	Very low
Infant mortality (before 1 year of age) – monochorionic					
1[161]	9/30	4/94	47.05 (2.34 to 21.26)*	1960 more per 1000 (from 57 more to 862 more)	Very low
Infant mortality (before 1 year of age) – dichorionic					
1[161]	1/30	7/364	1.73 (0.22 to 13.63)*	14 more per 1000 (from 15 fewer to 243 more)	Very low
Number of babies with disabilities at 1 year of age					
1[161]	10/64	13/474	5.70 (2.61 to 12.45)*	129 more per 1000 (from 44 more to 314 more)	Very low
Number of babies with disabilities at 1 year of age – monochorionic					
1[161]	9/30	7/94	4.03 (1.64 to 9.89)*	226 more per 1000 (from 48 more to 662 more)	Very low
Number of babies with disabilities at 1 year of age – dichorionic					
1[161]	1/30	6/364	2.02 (0.25 to 16.25)*	17 more per 1000 (from 12 fewer to 251 more)	Very low

* Calculated by NCC technical team

Table 9.2 GRADE summary of findings for indications for referral for subspecialist advice (continuous outcome measures)

Number of studies	Mean (SD)		Mean Difference		Quality
	Referred for specialist care	Usual care	Difference	P value	
Comparison of late referral to early followed up at tertiary care centre					
Birthweight in grams – larger twins (all)					
1[161]	1778 (611)	2278 (443)	–500	P < 0.001	Very low
Birthweight in grams – larger twins (monochorionic)					
1[161]	1580(570)	2158(501)	–578	P < 0.01*	Very low
Birthweight in grams – larger twins (dichorionic)					
1[161]	1922(598)	2302(409)	–380	P < 0.01*	Very low
Birthweight in grams – smaller twins (all)					
1[161]	1504(628)	2003(433)	–499	P < 0.001	Very low
Birthweight in grams – smaller twins (monochorionic)					
1[161]	1304(671)	1869(495)	–565	P < 0.01*	Very low
Birthweight in grams – smaller twins (dichorionic)					
1[161]	1632(530)	2030(401)	–398	P < 0.01*	Very low

* Calculated by NCC technical team

Evidence statement

No studies were identified which directly examined the effectiveness of referral to subspecialist care in twin or triplet pregnancies complicated by discordant fetal growth, discordant fetal anomaly or single fetal death, nor in monochorionic, monoamniotic pregnancies or triplet pregnancies generally.

Two studies conducted at tertiary care centres examined perinatal outcomes in women with complicated twin pregnancies (the complications included, but were not limited to, discordant fetal

growth, discordant fetal anomaly and single fetal death; neither of the studies reported inclusion of monochorionic, monoamniotic pregnancies) (very low quality evidence). These studies reported worse perinatal outcomes in referred women than in women who booked and received care at the same centre throughout pregnancy, although the results may simply reflect the risks associated with complicated twin pregnancies rather than direct effects of receiving subspecialist care.

Health economics profile

No published health economic evidence was identified and this question was not prioritised for health economic analysis.

Evidence to recommendations

Relative value placed on the outcomes considered

The priority outcomes identified in the protocol for this review question were:

- stillbirth
- neonatal mortality
- neonatal morbidity (especially respiratory and neurological morbidity)
- admission to a neonatal unit
- maternal satisfaction and the impact of travelling to receive care at tertiary level fetal medicine centres
- maternal morbidity
- emergency caesarean section
- Apgar score
- birthweight
- maternal anxiety, depression and quality of life
- breastfeeding.

Trade-off between clinical benefits and harms

The potential clinical benefits of referral to tertiary level fetal medicine centres are:

- reduction of infant and maternal mortality and morbidity in twin pregnancies complicated by discordant fetal growth, single fetal death, discordant fetal anomaly, pregnancies complicated by FFTS, monochorionic, monoamniotic pregnancies and triplet pregnancies in general
- women may experience less anxiety during pregnancy and short- and long-term psychopathology may be reduced
- delivery and neonatal care will be offered in the most appropriate setting
- development of specialist clinical expertise and experience for managing pregnancies which are relatively rare, with audit and monitoring of outcomes and research being facilitated
- potentially easier access to, and close collaboration with, neonatal and other specialist services giving better continuity of care (for example, preparation for admission to a neonatal intensive care unit).

The potential harms are:

- unnecessary monitoring and interventions
- increased maternal anxiety
- increased financial and practical costs for service providers and women (for example, time needed to travel and arranging childcare)
- reduced maternal confidence in local maternity and neonatal services

- women receiving care at a level that is not necessary.

Trade-off between net health benefits and resource use

Referral to tertiary level fetal medicine centres may have greater initial resource implications but long-term savings may occur if maternal, neonatal and long-term morbidity are reduced. Tertiary level services may be used inappropriately and transfer back to local care when appropriate may be delayed or not achieved at all.

Quality of evidence

The quality of evidence was very low for all outcomes considered. The difficulty in conducting RCTs to evaluate effectiveness of referral to tertiary level fetal medicine centres for the conditions investigated is reflected in the paucity of literature on the topic. The GDG based its recommendations on the collective experience of the group.

Other considerations

Monochorionic, monoamniotic pregnancies were recognised by the GDG as requiring special consideration. All pregnancies complicated by FFTS were identified in the guideline scope as requiring referral to tertiary level fetal medicine centres.

Discordant fetal growth with estimated fetal weight differences of more than 25% in twins is associated with increased perinatal loss and morbidity. This can lead to difficult clinical decisions relating to both investigation and potentially decisions about preterm delivery with risks to one or both fetuses.

Any pregnancy complicated by a fetal anomaly (a structural or chromosomal abnormality) requires careful ultrasound examination, investigation and discussion between the woman and healthcare professionals, including specialist paediatricians, with accurate information about prognosis. Women with a discordant fetal anomaly may consider selective termination of pregnancy and accurate risks for surviving fetuses and the timing of the procedure need careful discussion. In monochorionic twins, transfusional and haemodynamic fluctuation in intertwin blood flow during selective termination procedures should be discussed. Such procedures (intrafetal laser, radio frequency thermal ablation and diathermy cord occlusion) are highly specialised and should be offered only in supraregional centres. If selective termination of pregnancy is not an option or is declined by the woman, then there may be risks to the whole pregnancy (for example, when oesophageal atresia and polyhydramnios in one fetus increases the risk of preterm birth). Such scenarios require specialist ultrasound examination, investigation and counselling and carefully planned management, including the woman's local multidisciplinary team if necessary.

Discordant (single) fetal death increases perinatal morbidity and mortality in surviving fetuses, irrespective of chorionicity. Informed and expert management is vital, as inappropriate intervention may lead to the live birth of a baby at very high risk of neurodevelopmental damage that may be compounded by the effects of prematurity. Surviving twins in monochorionic discordant fetal death have a significant risk of neurodevelopmental morbidity from the effects of transfusional haemodynamic fluctuations, which may lead to (significant) neurodevelopmental morbidity in up to 20% of cases. Specialist counselling, investigation and triage of these pregnancies is vital to minimise long-term morbidity.

The GDG's view is that uncomplicated triplet pregnancies can be managed in the same antenatal setting as twin pregnancies, although the woman may need to give birth in a different unit to access appropriate neonatal care, and information about the likely need for neonatal care should be provided (see Section 5.1). The GDG placed a high value on the 'normalisation' of twin and triplet pregnancies throughout the development process and this is reflected in its recommendations.

Recommendations

Number	Recommendation
54	Seek a consultant opinion from a tertiary level fetal medicine centre for: • monochorionic monoamniotic twin pregnancies

- monochorionic monoamniotic triplet pregnancies
- monochorionic diamniotic triplet pregnancies
- dichorionic diamniotic triplet pregnancies
- pregnancies complicated by any of the following:
  - discordant fetal growth
  - fetal anomaly
  - discordant fetal death
  - feto-fetal transfusion syndrome.

Number	Research recommendation
RR 15	What is the incidence of monochorionic monoamniotic twin and triplet pregnancies, and what clinical management strategies are most effective in such pregnancies? **Why this is important** Monochorionic monoamniotic twin pregnancies occur rarely, as do all triplet pregnancies (fewer than 200 women give birth to triplets each year in England and Wales). Across the guideline, the evidence relating to such pregnancies was very limited in quantity and quality, with monochorionic monoamniotic pregnancy often listed as an exclusion criterion in studies reviewed for the guideline. Monochorionic monoamniotic pregnancies and triplet pregnancies are associated with greater complexity and risks to the woman and babies than other pregnancies considered in the guideline. The lack of evidence for effective clinical management of these pregnancies influenced the Guideline Development Group to recommend referral to a tertiary level fetal medicine centre for monochorionic monoamniotic twin pregnancies and complicated triplet pregnancies (including monochorionic and dichorionic triplet pregnancies). Further research to determine the incidence of monochorionic monoamniotic pregnancies and triplet pregnancies of different chorionicities would inform future provision of NHS services, as would research into the most effective models for clinical management of such pregnancies. Studies could include national audits of clinical care and outcomes in such pregnancies before and after publication of the guideline. They should also include consideration of the impact of referral (or non-referral) to a tertiary level fetal medicine centre on perinatal psychological and emotional wellbeing of women and their partners.
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? **Why this is important** The guideline review identified no randomised studies comparing models of care for twin or triplet pregnancies, and no evidence was identified in relation to the impact of referral to tertiary level fetal medicine centres compared with routine care for women with twin or triplet pregnancies. There is currently great variation in terms of clinical monitoring and management of twin and triplet pregnancies, and in criteria used for referral to tertiary level fetal medicine centres. Implementation of the guideline recommendations should result in consistent approaches to clinical management and referral to subspecialist services throughout the NHS, and women with twin and triplet pregnancies should be confident that they and their babies are receiving the level of care appropriate to their circumstances. Nevertheless, there remains uncertainty about the effectiveness of referral to tertiary level fetal medicine centres in twin and triplet pregnancies complicated by discordant fetal growth, discordant

fetal anomaly or discordant fetal death, and in determining the level of care appropriate to the complexity of the pregnancy. This research recommendation focuses on pregnancies that need special consideration because they are associated with risks to the woman and babies (for example, in terms of maternal and neonatal mortality and morbidity and potential lifelong disability for the children). Further research is needed to determine how and where to provide services to improve outcomes for women and babies most effectively. The research is relevant to the possible establishment of maternity networks proposed in 'Equity and excellence: liberating the NHS' (NHS White Paper, available at http://www.dh.gov.uk/en/Healthcare/LiberatingtheNHS/index.htm), since the guideline recommends that care be provided at the level required according to the complexity of the pregnancy. The research would support the development of care pathways within maternity networks (or networks more generally), and it would improve service delivery and continuity of multidisciplinary care. There are potential ethical issues with randomising care to referral or no referral in such complex pregnancies, and so the research may need to take the form of prospective observational studies rather than randomised controlled trials. The research should include consideration of the impact of referral (or non-referral) to tertiary level fetal medicine centres on perinatal psychological and emotional wellbeing of women and their partners.

10 Timing of birth

Introduction

It is commonly acknowledged by healthcare professionals that twin and triplet pregnancies tend to come to an end earlier than singleton pregnancies. It is also a widely held, although often contested, view among clinicians that perinatal outcomes in twin and triplet pregnancies worsen with increasing gestational age after 37 weeks. As a result, women with twin and triplet pregnancies are often advised to undergo elective birth without any obvious indication. This review question aims to examine the optimal gestational age for uncomplicated twin and triplet pregnancies.

Review question

What is the optimal timing of delivery in women with uncomplicated multiple pregnancies?

The following subquestions were considered by the GDG:

- What is the gestational age profile for spontaneous delivery in twin/triplet pregnancies?
- What is the perinatal mortality and morbidity in spontaneous or uncomplicated delivery in twin/triplet pregnancies at different gestational ages?
- What is the effectiveness of elective delivery in multiple pregnancies?

Existing NICE guidance

Neither 'Antenatal care' (NICE clinical guideline 62)[14] nor 'Intrapartum care' (NICE clinical guideline 55)[82] nor 'Induction of labour' (NICE clinical guideline 70)[17] covered the management of multiple pregnancies. The last of these ('Induction of labour', NICE clinical guideline 70)[17] recommends offering induction to women with uncomplicated singleton pregnancies between 41 weeks 0 days and 42 weeks 0 days to avoid the risks associated with prolonged pregnancy, with the exact timing decided according to woman's preference and local circumstances. It also recommends offering induction of labour, elective caesarean section or expectant management on an individual basis to women with previous caesarean section, and offering information on risks associated with emergency caesarean section and uterine rupture with induction of labour. Maternal request should not be considered as the sole reason for induction of labour, but may be considered after 40 weeks of gestation under exceptional circumstances.

'Caesarean section' (NICE clinical guideline 13, currently being updated)[18] does not recommend offering routine elective caesarean section in uncomplicated twin pregnancies at term except under research circumstances.

Description of included studies

Gestational age profile for spontaneous birth in twin and triplet pregnancies

One study[163] was identified for inclusion in relation to incidence of spontaneous birth in twin and triplet pregnancies by gestational age. This study reported data from all twin births in New South Wales, Australia, for a period of 10 years (1990–1999). No study reporting similar data for spontaneous birth in triplet pregnancies was identified.

Perinatal mortality and morbidity in spontaneous or uncomplicated birth at different gestational ages

No studies were identified for inclusion in relation to perinatal outcomes of spontaneous birth in uncomplicated twin and triplet pregnancies according to gestational age at birth. Two large, population-based studies from Japan and the UK, [164;165] reported data on fetal death rates according to gestational age in multiple (predominantly twin) pregnancies. These studies did not make any distinction between monochorionic and dichorionic twin pregnancies.

To explore the effect of chorionicity on fetal death rates at different gestational ages, six smaller studies reporting data for monochorionic twin pregnancies were identified.[166-171] Three of the studies reported data for dichorionic twin pregnancies in the same population.[166-168]

Neonatal mortality among twins born at different gestational ages was reported in three studies.[164;166;170] A Japanese study reported neonatal morbidity according to gestational age at birth in dichorionic twins.[172]

Two small studies reported fetal death rates at different gestational ages in triplet pregnancies.[173;174] In addition, one large study examined US data over 4 years and compared twin and triplet pregnancies to singleton pregnancies for stillbirth and neonatal mortality rates specific to gestational age.[159]

Effectiveness of elective delivery in twin and triplet pregnancies

Three studies, including one RCT,[175] one quasi-randomised trial[176] and one retrospective observational study[177] were identified that compared elective delivery with expectant management in twin pregnancies. No studies were identified that compared elective delivery with expectant management in triplet pregnancies.

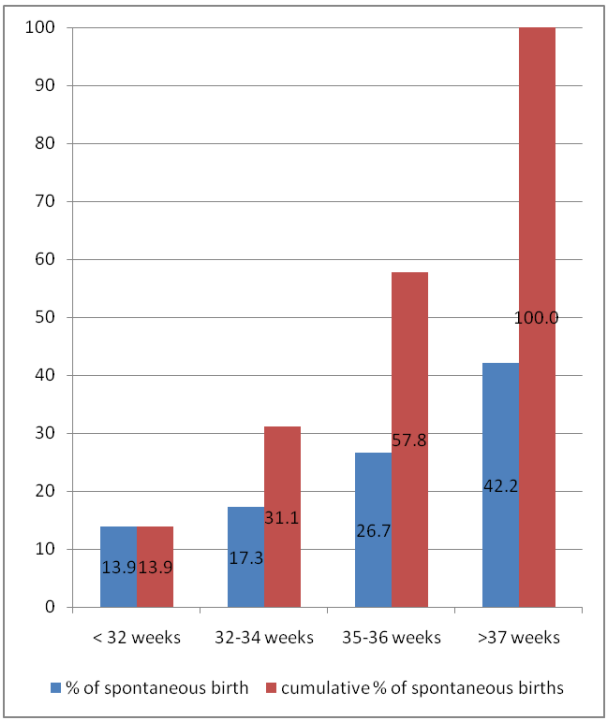
Published health economic evidence

No published health economic evidence was identified, although this question was prioritised for health economic analysis.

Evidence profiles

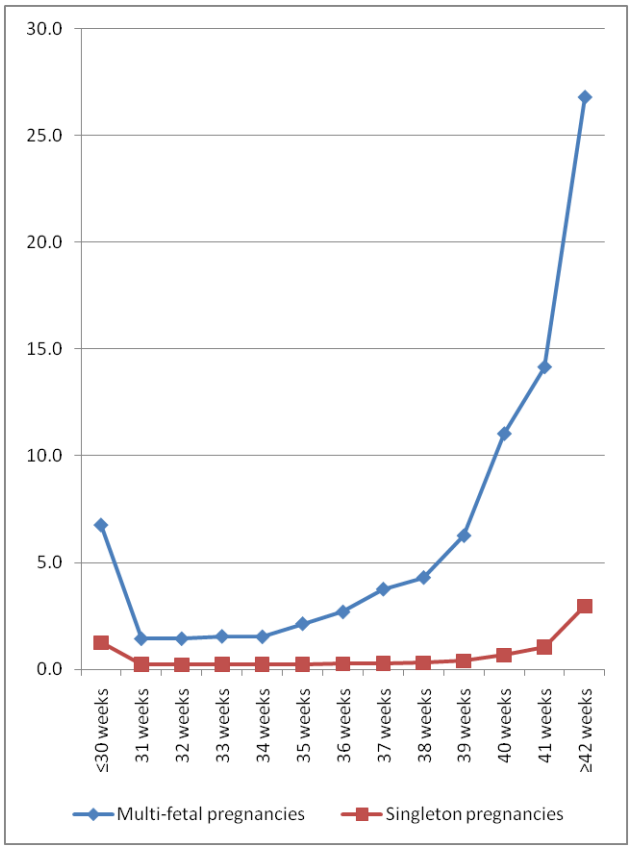
Evidence profiles for this question are presented in Figures 10.1 to 10.8 and Tables 10.4 to 10.12. Figure 10.1 presents evidence relating to the gestational age profile for spontaneous births in twin pregnancies. Figures 10.2 to 10.8 and Tables 10.4 to 10.9 present evidence relating to fetal deaths and neonatal mortality and morbidity in spontaneous or uncomplicated births at different gestational ages. Tables 10.11 and 10.12 present evidence relating to effectiveness of elective delivery in twin and triplet pregnancies.

Figure 10.1 Evidence profile for timing of birth in spontaneous labour and delivery in uncomplicated twin pregnancies



Source: Roberts, 2002[163] (n=5930, low quality evidence)

Figure 10.2 Evidence profile for the risk of fetal death in spontaneous or uncomplicated birth at different gestational ages (studies reporting results for twin pregnancies or predominantly twin pregnancies): a) fetal deaths per 1000 fetuses at the start of the given gestational week



Source: Minakami, 1996[164] (low quality evidence)

a) Twin pregnancies accounted for 96% of births in multiple pregnancies

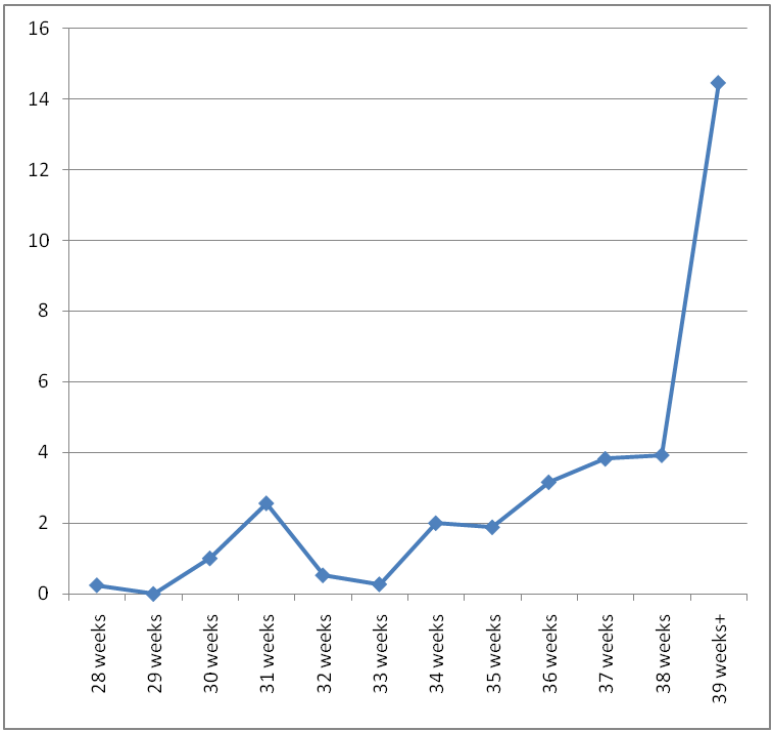
b) The data cover all of Japan over a 5 year period, but they do not distinguish between complicated and uncomplicated twin pregnancies

c) See Table 10.1 for data on relative risk of fetal death in predominately twin pregnancies compared with fetal death at 42 weeks of gestation or more in singleton pregnancies in the same population

Table 10.1 Relative risk of fetal death in predominately twin pregnancies compared with fetal death at 42 weeks of gestation or more in singleton pregnancies in the same population

Gestational age	RR	95% CI
33 weeks	0.523	(0.424 to 0.645)
34 weeks	0.516	(0.417 to 0.639)
35 weeks	0.723	(0.596 to 0.878)
36 weeks	0.909	(0.755 to 1.095)
37 weeks	1.270	(1.062 to 1.518)
38 weeks	1.454	(1.193 to 1.771)
39 weeks	2.116	(1.693 to 2.646)
40 weeks	3.729	(2.852 to 4.876)
41 weeks	4.786	(2.902 to 7.891)
42 weeks	9.053	(2.947 to 27.813)

Figure 10.3 Evidence profile for the risk of fetal death in spontaneous or uncomplicated birth at different gestational ages (studies reporting results for twin pregnancies or predominantly twin pregnancies): b) fetal deaths per 1000 fetuses at the start of the given gestational week



Source: Sairam, 2002[165] (very low quality evidence)

a) Data for all multiple births (n=4193) occurring in the North-East Thames region of London during 1989 to 1991

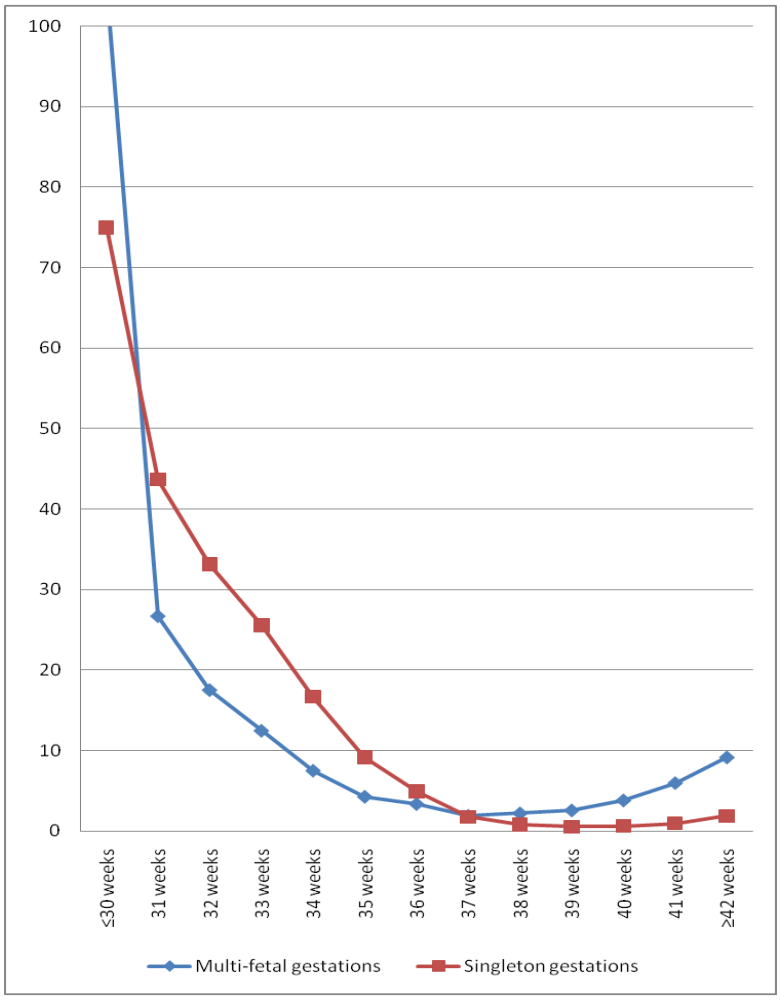
b) Twin pregnancies accounted for 99.8% of included multiple pregnancies

c) See Table 10.2 for data on relative risk of fetal death in predominately twin pregnancies compared with fetal death at 42 weeks of gestation or more in singleton pregnancies in the same population

Table 10.2 Relative risk of fetal death in predominately twin pregnancies compared with fetal death at 42 weeks of gestation or more in singleton pregnancies in the same population

Gestational age	RR	95% CI
33 weeks	0.144	(0.02 to 1.07)
34 weeks	1.05	(0.44 to 2.51)
35 weeks	0.993	(0.4 to 2.49)
36 weeks	1.66	(0.75 to 3.68)
37 weeks	2.01	(0.91 to 4.45)
38 weeks	2.07	(0.82 to 5.18)
≥39 weeks	7.61	(3.52 to 16.4)

Figure 10.4 Evidence profile for the risk of neonatal death in spontaneous or uncomplicated birth at different gestational ages (studies reporting results for twin pregnancies or predominantly twin pregnancies): a) early neonatal deaths per 1000 fetuses at the start of the given gestational week



Source (first author, year): Minakami, 1996[164] (low quality evidence)

a) Early neonatal death defined as death occurring within 7 days of live birth

b) Twin pregnancies accounted for 96% of births in multiple pregnancies

c) The data cover all of Japan over a 5-year period, but they do not distinguish between complicated and uncomplicated twin pregnancies

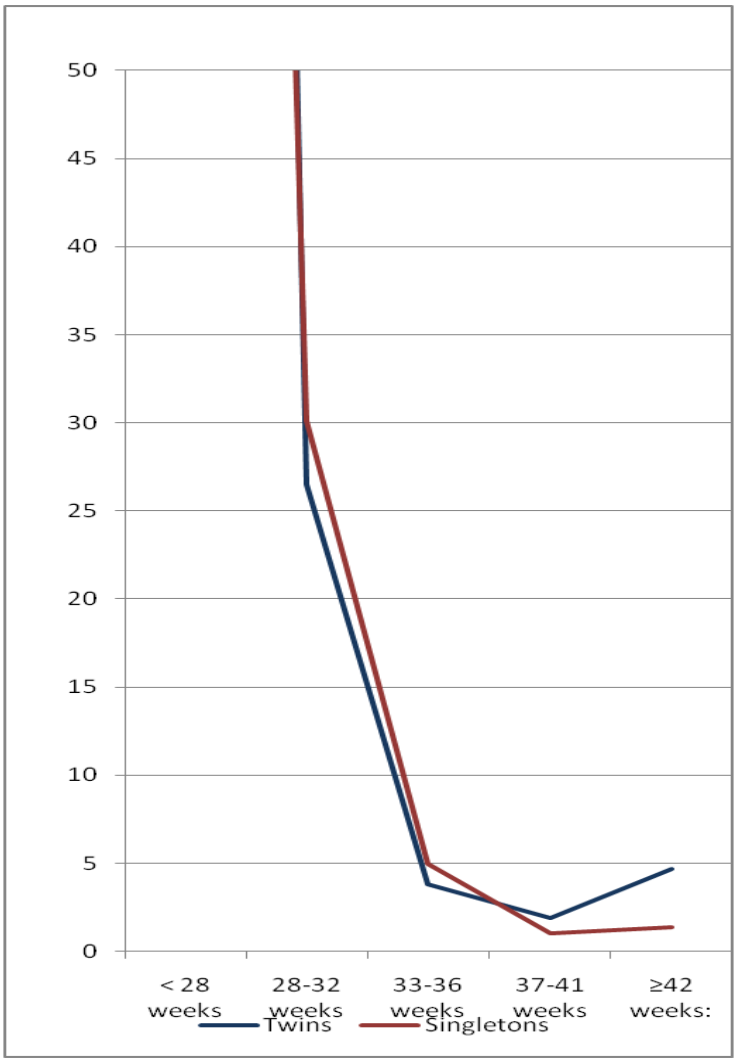
d) See Table 10.3 for data on relative risk of early neonatal death in predominately twin pregnancies compared with early neonatal death at 37 weeks of gestation in the same population

Table 10.3 Relative risk of early neonatal death in predominately twin pregnancies compared with early neonatal death at 37 weeks of gestation in the same population

Gestational age	RR	95% CI
≤30 weeks	54.495	(39.245 to 75.669)
31 weeks	13.888	(8.829 to 21.844)
32 weeks	9.114	(5.747 to 14.455)
33 weeks	6.488	(4.103 to 10.258)
34 weeks	3.914	(2.445 to 6.265)
35 weeks	2.230	(1.373 to 3.621)

Gestational age	RR	95% CI
36 weeks	1.761	(1.137 to 2.729)
37 weeks	1.000	–
38 weeks	1.158	(0.745 to 1.799)
39 weeks	1.351	(0.832 to 2.194)
40 weeks	1.992	(1.141 to 3.480)
41 weeks	3.113	(1.321 to 7.335)
42 weeks	4.769	(0.661 to 34.402)

Figure 10.5 Evidence profile for the risk of neonatal death in spontaneous or uncomplicated birth at different gestational ages (studies reporting results for twin pregnancies or predominantly twin pregnancies): b) neonatal deaths per 1000 live births



Source (first author, year): Alexander, 2005[159] (low quality evidence)

a) US data from 1995 to 1998

b) Neonatal death defined as death occurring within 27 days of live birth

Table 10.4 Evidence profile for neonatal morbidity in spontaneous or uncomplicated birth at different gestational ages (studies reporting results for dichorionic twin pregnancies): neonatal morbidity in dichorionic twin pregnancies versus singleton pregnancies

Gestational age (weeks)	Respiratory morbidity (transient tachypnoea of the newborn or respiratory distress syndrome)		Intraventricular haemorrhage	
	Twins (dichorionic)	Singletons	Twins (dichorionic)	Singletons
34	10/36 (27.8%)	47/121 (38.8%)	0/36 (0%)	2/121 (1.7%)
35	10/64 (15.6%)	38/120 (31.7%)	0/64 (0%)	0/120 (0%)
36	15/126 (11.9%)	44/248 (17.7%)	0/126 (0%)	0/248 (0%)
37	11/210 (5.2%)	59/893 (6.6%)	0/210 (0%)	0/893 (0%)
38	6/62 (9.7%)	81/1696 (4.8%)	0/62 (0%)	0/1696 (0%)
39	8/44 (18.2%)	91 /2323 (3.9%)	0/44 (0%)	0/2323 (0%)
40	0/6 (0%)	67/2320 (2.9%)	0/6 (0%)	0/2320 (0%)

Source (first author, year): Suzuki, 2010[172] (very low quality evidence)

Table 10.5 Evidence profile for the risk of fetal death by chorionicity at different gestational ages (studies reporting results for monochorionic and dichorionic twin pregnancies)

Number of studies	Monochorionic twins (fetal deaths/total number of fetuses)	Dichorionic twins (fetal deaths/total number of fetuses)	Relative risk (95% confidence interval)	Absolute risk reduction	Quality
Risk of fetal death at given gestational age					
At 26–27 weeks					
3[166-168]	4/847	3/3942	5.63 (0.61 to 52.14)*	4 more per 1000 (from 1 fewer to 39 more)	Very low
At 28–29 weeks					
3[166-168]	3/812	4/3840	4.53 (1.08 to 18.88)*	4 more per 1000 (from 1 more to 19 more)	Very low
At 30–31 weeks					
3[166-168]	4/768	7/3679	2.89 (0.89 to 9.39)*	4 more per 1000 (from 1 fewer to 16 more)	Very low
At 32–33 weeks					
3[166-168]	3/618	2/3389	6.75 (1.27 to 35.79)*	2 more per 1000 (from 1 more to 21 more)	Very low
At 34–35 weeks					
3[166-168]	2/599	3/3077	3.36 (0.65 to 17.37)*	3 more per 1000 (from 1 fewer to 16 more)	Very low
At ≥36 weeks					
3[166-168]	5/283	3/2031	10.86 (2.82 to 41.89)*	15 more per 1000 (from 3 more to 60 more)	Very low

*Calculated by NCC technical team

Table 10.6 Evidence profile for the risk of fetal death at different gestational ages (studies reporting results for monochorionic twin pregnancies)

Number of studies	Given gestational age (fetal deaths/total number of fetuses)	≥36 weeks (fetal deaths/total number of fetuses)	Relative risk (95% confidence interval)	Absolute risk reduction	Quality
Risk of fetal death at given gestational age					
At 26–27 weeks					
6[166-171]	10/2287	11/1098	0.49 (0.21 to 1.12)*	5 fewer per 1000 (from 8 fewer to 1 more)	Very low
At 28–29 weeks					
6[166-171]	10/2233	11/1098	0.52 (0.22 to 1.22)*	5 fewer per 1000 (from 8 fewer to 2 more)	Very low
At 30–31 weeks					
6[166-171]	6/2135	11/1098	0.30 (0.11 to 0.84)*	7 fewer per 1000 (from 8 fewer to 3 more	Very low
At 32–33 weeks					
6[166-171]	10/1965	11/1098	0.54 (0.22 to 1.30)*	5 fewer per 1000 (from 2 fewer to 9 fewer)	Very low
At 34–35 weeks					
6[166-171]	13/1662	11/1098	0.84 (0.29 to 2.42)*	2 fewer per 1000 (from 7 fewer to 14 more)	Very low

*Calculated by NCC technical team

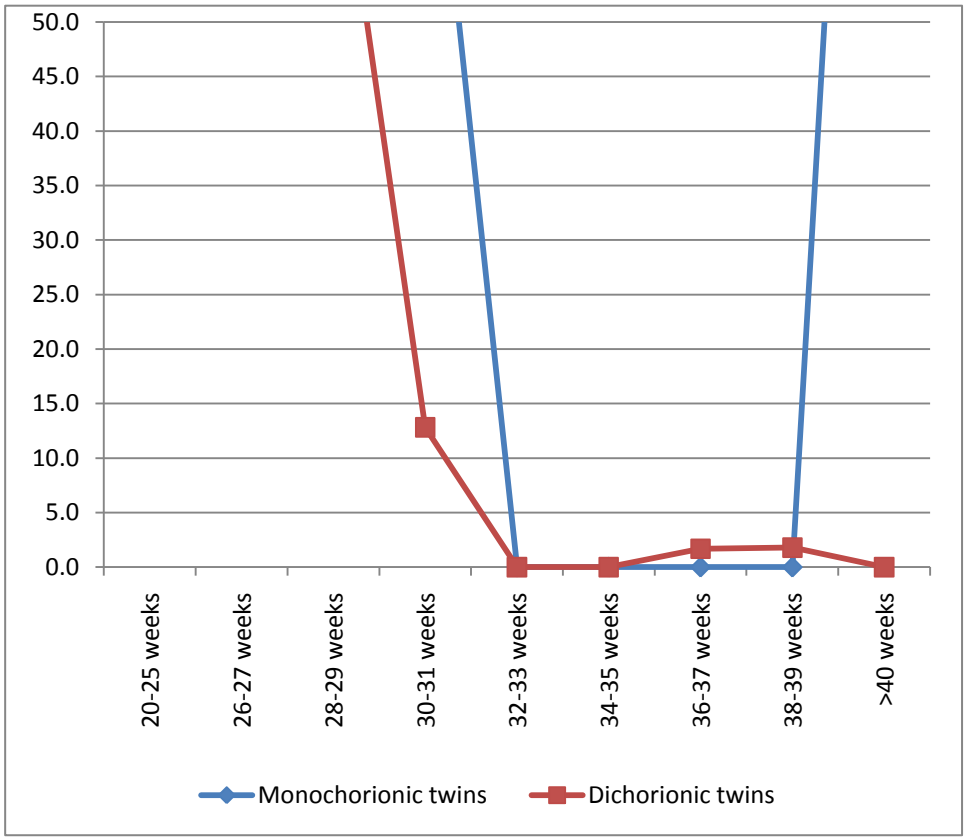
Table 10.7 Evidence profile for the risk of fetal death at different gestational ages (studies reporting results for dichorionic twin pregnancies)

Number of studies	Given gestational age (fetal deaths/total number of fetuses)	≥36 weeks (fetal deaths/total number of fetuses)	Relative risk (95% confidence interval)	Absolute risk reduction	Quality
Risk of fetal death at given gestational age					
At 26–27 weeks					
3[166-168]	3/3942	3/2031	0.20 (0.02 to 1.94)*	1 fewer per 1000 (from 1 fewer to 1 more)	Very low
At 28–29 weeks					
3[166-168]	4/3840	3/2031	0.77 (0.19 to 3.23)*	1 fewer per 1000 (from 1 fewer to 3 more)	Very low
At 30–31 weeks					
3[166-168]	7/3679	3/2031	1.00	0 fewer	Very

Number of studies	Given gestational age (fetal deaths/total number of fetuses)	≥36 weeks (fetal deaths/total number of fetuses)	Relative risk (95% confidence interval)	Absolute risk reduction	Quality
			(0.26 to 3.87)*	per 1000 (from 1 fewer to 4 more)	low
At 32–33 weeks					
3[166-168]	3/3389	3/2031	0.47 (0.08 to 2.82)*	1 fewer per 1000 (from 1 fewer to 3 more)	Very low
At 34–35 weeks					
3[166-168]	5/2961	3/2031	0.82 (0.06 to 10.99)*	1 fewer per 1000 (from 1 fewer to 15 more)	Very low

*Calculated by NCC technical team

Figure 10.6 Evidence profile for the risk of neonatal death at different gestational ages (studies reporting results for monochorionic and dichorionic twin pregnancies): early neonatal deaths per 1000 live births in monochorionic and dichorionic twin pregnancies



Source (first author, year): Hack, 2007[166] (very low quality evidence)

a) Early neonatal death defined as death occurring within 7 days of live birth

Table 10.8 Evidence profile for the risk of neonatal death at different gestational ages (studies reporting results for monochorionic twin pregnancies)

Number of studies	Given gestational age (neonatal deaths/total live births)	≥38 weeks (neonatal deaths/total live births)	Relative risk (95% confidence interval)	Absolute risk reduction	Quality
Risk of neonatal death at given gestational age					
At 26–27 weeks					
2[166;170]	8/27	2/242	31.83 (6.91 to 146.66)*	255 more per 1000 (from 49 more to 1000 more)	Very low
At 28–29 weeks					
2[166;170]	7/44	2/242	18.22 (3.91 to 84.83)*	142 more per 1000 (from 24 more to 693 more)	Very low
At 30–31 weeks					
2[166;170]	4/75	2/242	5.38 (0.95 to 30.37)*	36 more per 1000 (from 1 fewer to 243 more)	Very low
At 32–33 weeks					
2[166;170]	1/112	2/242	1.31 (0.16 to 10.51)*	3 more per 1000 (from 7 fewer to 79 more)	Very low
At 34–35 weeks					
2[166;170]	0/199	2/242	0.41 (0.04 to 3.95)*	5 fewer per 1000 (from 8 fewer to 24 more)	Very low
At 36–37 weeks					
2[166;170]	2/392	2/242	0.66 (0.10 to 4.47)*	3 fewer per 1000 (from 7 fewer to 29 more)	Very low

*Calculated by NCC technical team

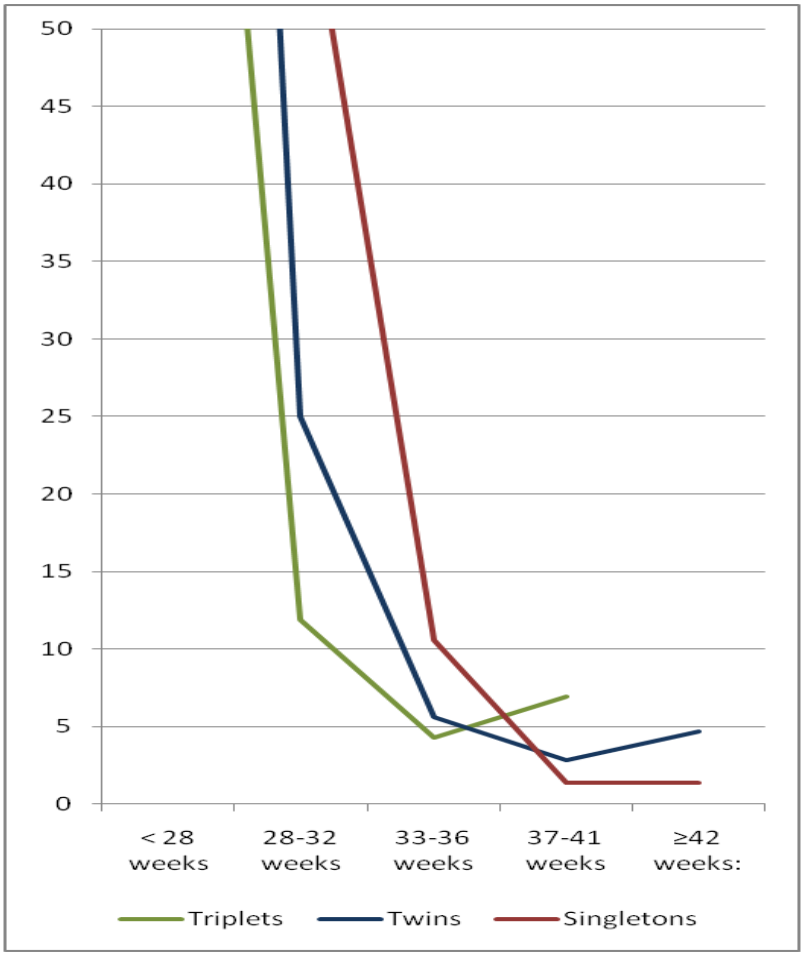
Table 10.9 Evidence profile for the risk of fetal death at different gestational ages (studies reporting results for triplet pregnancies)

Number of studies	Given gestational age (fetal deaths/total number of fetuses)	≥37 weeks (fetal deaths/total number of fetuses)	Relative risk (95% confidence interval)	Absolute risk reduction	Quality
Risk of fetal death at given gestational age					
At 33 weeks					
2[173;174]	24/111	6/18	0.18 (0.01 to 3.54)*	273 fewer per 1000 (from 330 fewer to 847 more) fewer)	Very low
At 34 weeks					
2[173;174]	6/78	6/18	0.14 (0.07 to 0.31)*	287 fewer per 1000 (from 230 fewer to 310 fewer)	Very low

Number of studies	Given gestational age (fetal deaths/total number of fetuses)	≥37 weeks (fetal deaths/total number of fetuses)	Relative risk (95% confidence interval)	Absolute risk reduction	Quality
At 35 weeks					
2[173;174]	21/60	6/18	0.34 (0.04 to 3.32)*	220 fewer per 1000 (from 320 fewer to 773 more)	Very low
At 36 weeks					
2[173;174]	19/39	6/18	0.64 (0.12 to 3.44)*	120 fewer per 1000 (from 293 fewer to 813 more)	Very low

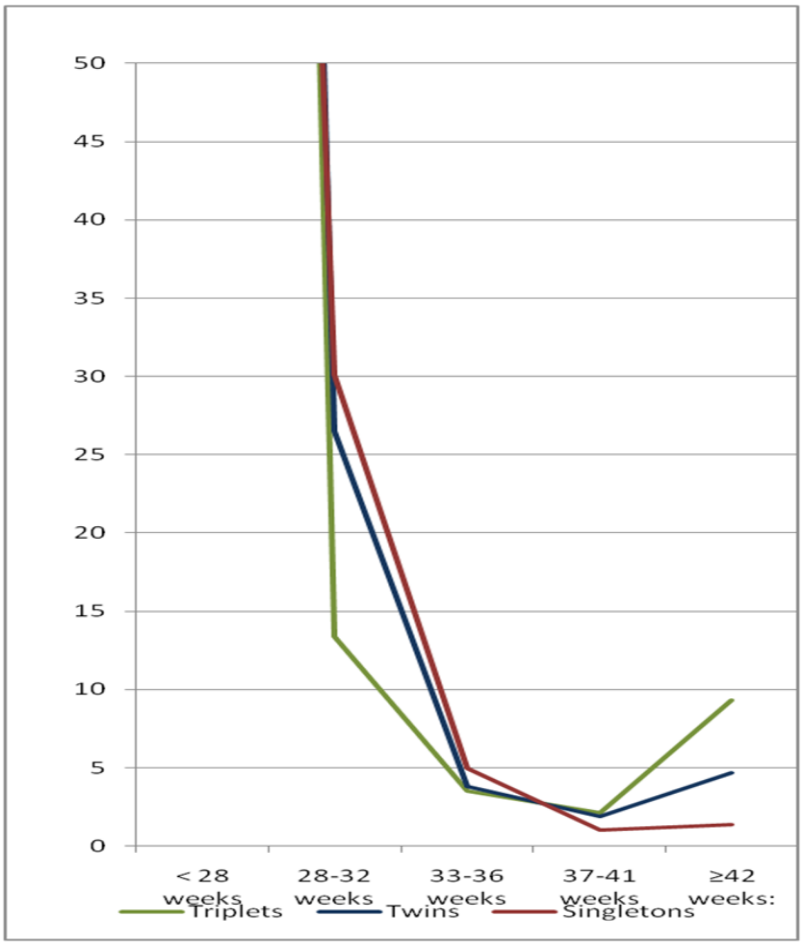
*Calculated by NCC technical team

Figure 10.7 Evidence profile for the risk of fetal or neonatal death at different gestational ages (twins versus triplets versus singletons): a) fetal deaths per 1000 births



Source (first author, year): Alexander, 2005[159] (all live births in the USA, 1995–1998, low quality evidence)

Figure 10.8 Evidence profile for the risk of fetal or neonatal death at different gestational ages (twins versus triplets versus singletons): b) neonatal deaths per 1000 live births



Source (first author, year): Alexander, 2005[159] (all live births in the USA, 1995–1998, low quality evidence)

Table 10.10 Evidence profile for neonatal morbidity in spontaneous or uncomplicated birth at different gestational ages (studies reporting results for triplet pregnancies): neonatal morbidity in triplet pregnancies according to gestational age at birth

Gestational age at birth (weeks)	Respiratory distress syndrome	Chronic lung disease	Intraventricular haemorrhage (grade 3 or 4)	Necrotising enterocolitis	Proliferative retinopathy of prematurity
32	1/21 (5%)	0/21 (0%)	0/21 (0%)	0/21 (0%)	0/21 (0%)
33	5/51 (10%)	0/51 (0%)	0/51 (0%)	1/51 (2%)	0/51 (0%)
34	0/24 (0%)	0/24 (0%)	0/24 (0%)	0/24 (0%)	0/24 (0%)
35	0/39 (0%)	0/39 (0%)	0/39 (0%)	1/39 (3%)	0/39 (0%)
36	0/27 (0%)	0/27 (0%)	0/27 (0%)	0/27 (0%)	0/27 (0%)
37	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)

Source : Devine, 2001[178] (n=100 pregnancies, very low quality evidence)

Table 10.11 GRADE summary of findings for comparison between elective birth and expectant management based on dichotomous outcome measures

Number of studies	Elective birth	Expectant management	Relative risk (95% confidence interval)	Absolute risk reduction	Quality
Perinatal mortality					
Induction of labour at 37 weeks in twin pregnancies					
1[175]	0/34	0/38	NC	NC	Moderate
Induction of labour at 36 weeks in twin pregnancies					
1[176]	0/72	0/90	NC	NC	Very low
Birthweight <2500 g					
Induction of labour at 37 weeks in twin pregnancies					
1[175]	11/34	13/38	0.95 (0.49 to 1.82)*	17 fewer per 1000 (from 174 fewer to 281 more)	Moderate
Induction of labour at 36 weeks in twin pregnancies					
1[176]	23/72	54/90	0.53 (0.37 to 0.78)*	282 fewer per 1000 (from 132 fewer to 378 fewer)	Very low
Birthweight <2000 g					
Induction of labour at 37 weeks in twin pregnancies					
1[175]	0/34	2/38	NC	NC	Moderate
Induction of labour at 36 weeks in twin pregnancies					
1[176]	3/72	6/90	0.63 (0.16 to 2.41)*	25 fewer per 1000 (from 56 fewer to 94 more)	Very low
Apgar score <7 at 1 minute					
Induction of labour at 37 weeks in twin pregnancies					
1[175]	0/34	0/38	NC	NC	Moderate
Induction of labour at 36 weeks in twin pregnancies					
1[176]	9/72	12/90	0.94 (0.42 to 2.1)*	8 fewer per 1000 (from 77 fewer to 147 more)	Very low
Apgar score <7 at 5 minutes					
Induction of labour at 37 weeks in twin pregnancies					
1[175]	0/34	0/38	NC	NC	Moderate
Induction of labour at 36 weeks in twin pregnancies					
	0/72	3/90	NC	NC	Very low
Neonatal morbidity					
Admission to neonatal intensive care unit (NICU) – induction of labour at 36 weeks in twin pregnancies					
1[176]	22/72	24/90	1.15 (0.70 to 1.87)*	40 more per 1000 (from 80 fewer to 232 more)	Very low
Admission to NICU – precise time of induction not reported (≥36 weeks)					
1[177]	3/91	13/178	0.45 (0.13 to 1.54)*	8 fewer per 1000 (from 77 fewer to 147 more)	Very low
Immediate admission to NICU – induction of labour at 36 weeks in twin pregnancies					
1[176]	15/72	21/90	0.89 (0.50 to 1.60)*	26 fewer per 1000 (from 117 fewer to 140 more)	Very low
Delayed admission to NICU – induction of labour at 36 weeks in twin pregnancies					
1[176]	7/72	3/90	2.92 (0.79 to 10.88)*	43 more per 1000 (from 5 fewer to 220 more)	Very low
Neonatal sepsis – precise time of induction not reported (≥36 weeks)					
1[177]	3/91	9/178	0.65 (0.18 to 2.35) *	18 fewer per 1000 (from 41 fewer to 68 more)	Very low

Number of studies	Elective birth	Expectant management	Relative risk (95% confidence interval)	Absolute risk reduction	Quality
Maternal outcomes					
Caesarean section - induction of labour at 37 weeks in twin pregnancies					
1[175]	3/17	6/19	0.56 (0.16 to 1.90)	139 fewer per 1000 (from 265 fewer to 284 more)	Moderate
Caesarean section – induction of labour at 36 weeks in twin pregnancies					
1[176]	3/36	6/45	0.63 (0.17 to 2.33)	49 fewer per 1000 (from 111 fewer to 177 more)	Very low
Instrumental delivery – Induction of labour at 36 weeks in twin pregnancies					
1[176]	19/36	21/45	1.13 (0.73 to 1.76)*	61 more per 1000 (from 126 fewer to 355 more)	Very low
Need for blood transfusion – Induction of labour at 37 weeks in twin pregnancies					
1[175]	0/17	1/19	NC	NC	Moderate
Maternal infection					
Need for blood transfusion – Induction of labour at 36 weeks in twin pregnancies					
1[176]	2/36	3/45	0.85 (0.15 to 4.83)*	10 fewer per 1000 (from 57 fewer to 255 more)	Very low

*Calculated by NCC technical team

Table 10.12 GRADE summary of findings for comparison between elective birth and expectant management based on continuous outcome measures

Number of studies	Mean (standard deviation)		Mean difference		Quality
	Referred for specialist care	Usual care	Difference	P value	
Birthweight in g					
Induction of labour at 37 weeks in twin pregnancies					
1[175]	2700 (330)	2672 (392)	28	Not significant	Moderate
Induction of labour at 36 weeks in twin pregnancies					
1[176]	2639 (352)	2463 (298)	176	P < 0.001	Very low
Duration of maternal hospital stay in days					
Induction of labour at 36 weeks in twin pregnancies					
1[176]	7.3 (2.0)	7.5 (2.3)	–0.2	Not significant	Very low

Evidence statement

Gestational age profile for spontaneous birth in twin and triplet pregnancies

One cross-sectional study (low quality evidence) suggested that the majority (58%) of women with uncomplicated twin pregnancies give birth spontaneously before 37 weeks 0 days. No robust data were identified for the gestational age profile in spontaneous triplet births.

Perinatal mortality and morbidity in spontaneous or uncomplicated birth at different gestational ages

No evidence was identified for perinatal outcomes at different gestational ages in uncomplicated twin or triplet pregnancies with spontaneous onset of labour.

Indirect evidence from studies reporting all multiple pregnancies together (uncomplicated, spontaneous onset of labour or otherwise) demonstrated an increase in the risk of fetal death per week towards the end of pregnancy. In the largest study of multiple pregnancies (predominantly dichorionic twin pregnancies), the relative risk of fetal death per week of gestation compared to the risk in singleton pregnancies at 42 or more weeks of gestation rose significantly from 37 weeks (low quality evidence). In the same study, early neonatal mortality (death within 7 days of live birth) showed similar trends, with the lowest death rate being reported in twins born at 37 weeks of gestation (low quality evidence).

Most studies that reported fetal or neonatal death rates separately for different types of multiple pregnancy (monochorionic twin, dichorionic twin or triplet pregnancies) were underpowered to detect differences in death rates between clinically important gestational ages (for example between fetal death rates at a given gestational age and those at 37 weeks 0 days to 37 weeks 6 days). The fetal death rate in monochorionic twin pregnancies was significantly higher than that in dichorionic twin pregnancies at 36 weeks or more, and point estimates of relative risk of fetal death were greater than one at all gestational ages (very low quality evidence). In monochorionic twin pregnancies and dichorionic twin pregnancies, fetal death rates were consistently lower at gestational ages between 26 weeks and 35 weeks compared to 36 weeks or more, although not significantly lower (very low quality evidence). In triplet pregnancies, fetal death rates were consistently lower at 33 weeks to 36 weeks compared with 37 weeks or more, and significantly lower at 34 weeks (very low quality evidence). In monochorionic twin pregnancies, neonatal death rates were significantly higher at gestational ages up to 29 weeks compared with 37 weeks or more, and the rates declined further from 30 to 35 weeks (very low quality evidence). In one study involving triplet pregnancies, no serious neonatal morbidity (respiratory distress syndrome, chronic lung disease, intraventricular haemorrhage grades 3 or 4, necrotising enterocolitis or proliferative retinopathy of prematurity) was reported after 34 weeks (very low quality evidence).

Effectiveness of elective delivery in twin and triplet pregnancies

Three studies showed no clinically significant difference in neonatal or maternal outcomes between women with twin pregnancies who underwent elective delivery and those who underwent expectant management (low to high quality evidence).

No studies were identified that examined effectiveness of elective delivery in women with triplet pregnancies.

Health economics profile

No published health economic evidence was identified, although this question was prioritised for health economic analysis. The analysis undertaken for this guideline evaluated the cost effectiveness of offering birth at 37 weeks 0 days for multiple pregnancies compared to delaying birth (expectant management). The economic evaluation suggested that there would be QALY (quality adjusted life year) losses associated with increased fetal mortality and increased neonatal morbidity if multiple pregnancies were managed expectantly beyond 37 weeks 0 days. Expectant management beyond 37 weeks 0 days would also be likely to increase costs, with any decrease in costs of elective birth (via induction of labour or caesarean section) being offset by further monitoring costs in addition to 'downstream' costs associated with worse outcomes. Thus, the strategy of offering birth at 37 weeks 0 days is likely to be less costly as well as producing greater health benefits. Elective birth is therefore deemed to be cost effective, dominating a strategy of expectant management.

The health economic analysis was based on a study which included all types of multiple pregnancy,[164] although the majority were dichorionic twin pregnancies. There were no sufficiently robust data to conduct separate health economic analyses for monochorionic twin pregnancies or triplet pregnancies. The GDG decided to recommend elective birth before 37 weeks 0 days for these types of multiple pregnancy. The increasing risk of fetal death towards the end of pregnancy seems to be even more pronounced in monochorionic twin pregnancies than in dichorionic twin pregnancies, and the GDG's view was, therefore, that women with monochorionic twin pregnancies should be offered elective birth at 36 weeks 0 days.

In triplet pregnancies there is a high risk of spontaneous preterm labour and birth occurring in an adverse setting if a pregnancy is managed expectantly towards the end of the third trimester. Furthermore, the clinical evidence suggests that there is a higher risk of fetal death after 34 weeks in triplet pregnancies, and the GDG's view was, therefore, that women with triplet pregnancies should be offered elective birth at 35 weeks 0 days. While not formally assessed in health economic analysis, these clinical risks would tend to make an earlier timing of elective birth more cost effective, providing that some of the benefits of earlier birth were not completely offset by a higher risk of respiratory morbidity.

Further details of the health economic model are presented in Section 11.3.

Evidence to recommendations

Relative value placed on the outcomes considered

The following were considered to be critical outcomes for this review question:

- perinatal mortality, neonatal mortality or stillbirth
- neonatal respiratory problems
- admission to a neonatal unit
- neonatal encephalopathy
- maternal morbidity (such as postpartum haemorrhage requiring blood transfusion, hypertension)
- operative delivery (instrumental delivery or caesarean section)
- Apgar score
- birthweight.

Trade-off between clinical benefits and harms

The evidence reviewed by the GDG indicated that 58% of women with twin pregnancies give birth spontaneously before 37 weeks 0 days. No comparable evidence was identified for triplet pregnancies; however, the GDG is aware of literature suggesting that about 75% of women with triplet pregnancies give birth spontaneously before 35 weeks 0 days.[179] The baseline risks of spontaneous preterm birth and its consequences, especially for babies, and the comparative risks of fetal death at increasing gestational ages are the main focus of attention in this review question, which seeks to identify the optimal timing of birth for women with twin and triplet pregnancies. For twin pregnancies the main clinical harm is the increasing risk of fetal death towards the end of pregnancy; this appears to be disproportionately greater in monochorionic twin pregnancies. Hence the GDG's view was that women with dichorionic twin pregnancies should be offered elective birth at 37 weeks 0 days, whereas those with monochorionic twins should be offered elective birth at 36 weeks 0 days.

For triplets there are two clinical risks with continuing pregnancy towards the end of the third trimester. One is the risk of spontaneous preterm labour and delivery occurring in an adverse setting, the other is a significantly higher risk of fetal death after 34 weeks 6 days. Thus, the GDG's view was that women with triplet pregnancies should be offered birth at 35 weeks 0 days.

The main trade-offs between clinical benefits and harms for women with twin and triplet pregnancies who have not given birth spontaneously at a given gestational age are the risks of neonatal mortality and morbidity or maternal operative delivery associated with elective delivery versus the risks of fetal death (stillbirth) from continued pregnancy. The GDG acknowledged that the evidence regarding neonatal morbidity associated with elective birth in twin and triplet pregnancies was limited and further research is needed.

It would be helpful in clinical practice to inform women of the absolute risks of fetal death in twin and triplet pregnancies. While this is possible for twin pregnancies (using the fetal death rate per 1000 fetuses for a given gestational period), it is not possible for triplet pregnancies (because the rates are available only as fetal deaths per 1000 live births). The GDG's view is that it would be confusing to quote absolute fetal death rates for twin and triplet pregnancies in different units. This is why the GDG's recommendations do not include absolute fetal death rates.

Trade-off between net health benefits and resource use

The health economic analysis conducted for this review question showed that prolonging twin pregnancies beyond 37 weeks 0 days and triplet pregnancies beyond 35 weeks 0 days would incur the loss of health benefits (QALYs), albeit at an increasing cost, and this would not represent value for money. To maximise health benefits in uncomplicated twin and triplet pregnancies, birth should be at 36 weeks 0 days in dichorionic pregnancies, 37 weeks 0 days in monochorionic twin pregnancies and 35 weeks 0 days in triplet pregnancies. This is expected to result in cost savings to the NHS. The GDG recognised that it may be appropriate to offer birth even earlier than 37 weeks 0 days, 36 weeks 0 days, or 35 weeks 0 days if clinically indicated.

Quality of evidence

The evidence ranged in quality from very low to moderate. The best available evidence was sufficient to demonstrate that elective birth by 37 weeks 0 days would be cost effective for all types of multiple pregnancy. Observational studies that reported fetal or neonatal death rates separately for different types of multiple pregnancy were underpowered to detect differences in death rates between clinically important gestational ages (for example, between fetal death rates at a given gestational age and those at 37 weeks 0 days to 37 weeks 6 days), and so recommendations for elective birth at 36 weeks 0 days in monochorionic twin pregnancies and 35 weeks 0 days in triplet pregnancies incorporated consideration of current practice in addition to the available evidence. Further research is needed to determine precisely the optimal timing of birth according to chorionicity and multiplicity of the pregnancy.

Other considerations

The GDG recognised the importance of offering antenatal administration of corticosteroids for elective preterm birth in monochorionic twin pregnancies and triplet pregnancies. The specialist team should discuss with all women with twin and triplet pregnancies the possibility of their babies being admitted to a special care unit if they have a spontaneous preterm birth or if the offer of elective preterm birth is accepted. The GDG also recognised the importance of ensuring that ongoing care is provided for women with twin and triplet pregnancies who decline the offer of elective early birth. No evidence was identified in relation to the optimal surveillance strategy for pregnancies that continue beyond 37 weeks 0 days, 36 weeks 0 days or 35 weeks 0 days in dichorionic twins, monochorionic twins and triplets, respectively. The GDG's recommendation for weekly appointments with the specialist obstetrician, with weekly biophysical profile testing of all fetuses and fortnightly growth scans, was based on the GDG members' collective experience.

The possibilities for elective birth are induction of labour or caesarean section. Consideration of mode of delivery is outside the scope of this guideline (because it relates to intrapartum care, not antenatal care), although the GDG was aware that in triplet pregnancies, for example, caesarean section is currently used more frequently than induction of labour. The footnotes to the recommendations relating to timing of birth emphasise that mode of delivery is outside the scope of the guideline.

The GDG highlighted the importance of a member of the core team starting discussions and planning regarding timing of birth and mode of delivery before the time at which elective birth would occur if the offer was accepted.

Recommendations

Number	Recommendation
55	Discuss with women with twin and triplet pregnancies the timing of birth and possible modes of delivery[**] early in the third trimester.
56	Inform women with twin pregnancies that about 60% of twin pregnancies result in spontaneous birth before 37 weeks 0 days.
57	Inform women with triplet pregnancies that about 75% of triplet pregnancies result in spontaneous birth before 35 weeks 0 days.
58	Inform women with twin and triplet pregnancies that spontaneous preterm birth and elective preterm birth are associated with an increased risk of admission to a special care baby unit.
59	Inform women with uncomplicated monochorionic twin pregnancies that elective birth from 36 weeks 0 days does not appear to be associated with an increased risk of serious adverse outcomes, and that continuing uncomplicated twin pregnancies beyond 38 weeks 0 days increases the risk of fetal death.
60	Inform women with uncomplicated dichorionic twin pregnancies that elective birth from 37 weeks 0 days does not appear to be associated with an increased risk of

[**] Specific recommendations about mode of delivery are outside the scope of this guideline.

serious adverse outcomes, and that continuing uncomplicated twin pregnancies beyond 38 weeks 0 days increases the risk of fetal death.

61 Inform women with triplet pregnancies that continuing uncomplicated triplet pregnancies beyond 36 weeks 0 days increases the risk of fetal death.

62 Offer 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.

63 For women who decline elective birth, offer weekly appointments with the specialist obstetrician. At each appointment offer an ultrasound scan, and perform weekly biophysical profile assessments and fortnightly fetal growth scans.

Number	Research recommendation
RR 17	What is the incidence of perinatal and neonatal morbidity and mortality in babies born by elective birth in twin and triplet pregnancies?

Why this is important

The existing evidence in relation to perinatal and neonatal outcomes associated with elective birth in twin and triplet pregnancies is limited in quantity and quality. Evidence suggests a consistently higher fetal death rate (at all gestational ages) in monochorionic twin pregnancies than in dichorionic twin pregnancies. It is uncertain whether elective birth in monochorionic twin pregnancies at 1 week earlier than recommended in the guideline (that is, from 35 weeks 0 days) would reduce fetal death rates significantly without increasing adverse neonatal outcomes significantly (for example, immaturity of the babies' respiratory systems). The research could be conducted through national audits of perinatal and neonatal morbidities in babies born by elective birth in twin and triplet pregnancies, taking account of the chorionicity of the pregnancy and gestational age at birth. If data from more than one study were available, then the technique of meta-regression might be useful for determining the optimal timing of birth precisely (according to gestational age).

* Specific recommendations about mode of delivery are outside the scope of this guideline.

11 Cost effectiveness analyses

11.1 Introduction

Health economic analysis in a clinical guideline can support and strengthen recommendations by making explicit comparisons between different healthcare alternatives in terms of their costs and effects. For example, where an alternative or additional service costs more but is associated with better outcomes, economic evaluation can provide guidance as to whether the additional cost represents good value to the NHS compared with the best alternative use of those same resources.

This guideline focuses on interventions to improve outcomes for women with twin and triplet pregnancies. For this guideline, the areas originally prioritised for economic analysis were:

- cost effectiveness of specialist multiple pregnancy care
- cost effectiveness of screening for feto-fetal transfusion syndrome (FFTS)
- cost effectiveness of screening to predict intrauterine growth restriction (IUGR)
- cost effectiveness of screening to predict the risks of spontaneous preterm birth and interventions for preventing spontaneous preterm birth
- cost effectiveness of elective birth compared to expectant management.

Due to lack of clinical effectiveness evidence, health economic analyses were conducted only for cost effectiveness of specialist multiple pregnancy care compared to usual care (see Section 11.2) and cost effectiveness of elective birth (at 37 weeks 0 days for multiple pregnancies) compared to expectant management (see Section 11.3). No relevant published economic evaluations were identified from literature searches.

11.2 Cost effectiveness of specialist care compared to usual care for women with twin or triplet pregnancies

Introduction

Twin pregnancies make up around 1% of pregnancies in the UK,[180] with the increase in assisted conception thought to be a contributing factor in the increase in multiple pregnancies.[181] Such pregnancies are high risk for both the woman and the fetuses: the woman is at risk of maternal complications such as pre-eclampsia, gestational diabetes and preterm labour,[60] while the fetuses are at increased risk of morbidity and mortality.[164] A systematic search of the literature did not identify any published health economic evaluations assessing the cost effectiveness of specialist clinics for the antenatal care of women with multiple pregnancies. Therefore, the GDG requested an original health economic analysis to assist with the development of guideline recommendations.

Description of alternative strategies

Usual care

'Usual care' is the level of care offered in routine antenatal care, as defined in 'Antenatal care' (NICE clinical guideline 62).[14] The model assumes that twin and triplet pregnancies will be managed in the same way as singleton pregnancies, including the schedule of appointments and scanning for each

visit. There is no need for specialist healthcare professional involvement unless there are complications.

Specialist twin and triplet pregnancy care

For the purposes of this guideline, the term 'specialist clinic' refers to a team of specialists rather than a particular setting where care is provided. None of the studies reviewed for the guideline was undertaken in the UK (see Section 5.3). The model assumes that NHS specialist care would achieve the same level of effectiveness as that found in the identified studies.

There is no standard model for specialist care within the NHS. To estimate the costs of providing a 'typical' specialist service, service information and protocols for specialist care were provided by GDG members from their various hospitals (Liverpool Women's Hospital, St Georges Hospital, Royal Victoria Infirmary and Guy's and St Thomas' Hospitals). An additional protocol was obtained from the Birmingham Women's Hospital.[62] There was wide variation between the various protocols with regard to hospitalisation, specialist obstetrician appointments and frequency of scanning. The protocols from the different hospitals were presented to the GDG members, who then reached a consensus on what they considered the best and most practical model of care for women in an NHS setting. The implications for this in terms of resource use are shown in Table 11.1. The GDG assumed that all scans would be performed by an ultrasonographer since all pregnancies were assumed to be uncomplicated (only complicated cases would have scans performed by a specialist obstetrician).

Table 11.1 Specialist care and usual antenatal care resource use (numbers of different individuals involved during pregnancy)

Activity	Usual care	Monochorionic diamniotic twin pregnancy	Dichorionic twin pregnancy	Monochorionic triamniotic or dichorionic triamniotic triplet pregnancy
Ultrasonographer	2	9	6	11
Specialist midwife	1	1	1	1
Specialist midwife follow-up	9	6	5	8
Specialist obstetrician	0	1	1	1
Specialist obstetrician follow-up	0	1	1	1

Table 11.2 shows the estimated amount of time needed for an average appointment for an uncomplicated multiple pregnancy. Early pregnancy classes, parenting sessions and breastfeeding classes are delivered by a midwife as outlined in 'Antenatal care' (NICE clinical guideline 62).[14]

Table 11.2 Estimated staff time in delivering care

Healthcare professional	Time in minutes*
Midwife first specialist booking appointment	60
Specialist midwife follow up	30
Midwife appointment usual care	30
Specialist obstetrician first appointment	45
Specialist obstetrician follow up	30

*Time estimates were provided by the GDG

Methods

Model structure

A decision analytic model was developed in Microsoft Excel® for a population of pregnant women to evaluate the cost effectiveness of specialist care for twin and triplet pregnancies compared with usual care. Schematic representations of this model are shown in Figures 11.1 and 11.2. The decision analytic approach is used to evaluate the differences in costs and effects of each strategy, based on the costs of the intervention and the costs and outcomes of various events weighted by the probability of their occurrence.

The model incorporated maternal and neonatal outcomes using the outcomes reported in the clinical review undertaken for this guideline (see Section 5.3), with baseline data derived from the review of outcomes with 'normal care'. The effect size of specialist care was determined by the relative risk reported in the clinical review of 'normal' and 'specialist clinics' (see Table 5.6). The maternal outcomes considered were pre-eclampsia, gestational hypertension, gestational diabetes, preterm labour, maternal satisfaction and quality of life. The neonatal outcomes considered were perinatal mortality, intraventricular haemorrhage (IVH), respiratory distress syndrome (RDS), necrotising enterocolitis (NEC) and prematurity. In this analysis, outcome data for mortality and RDS were evaluated by gestational age, while IVH and NEC were assumed to be the same for all gestational ages. Prematurity affected costs through its impact on length of stay in hospital and mortality.

The analysis is presented separately for monochorionic diamniotic twin pregnancies, dichorionic twin pregnancies, and monochorionic triamniotic and dichorionic triamniotic triplet pregnancies, as these have different resource implications in terms of pregnancy management (see Table 11.1).

Figure 11.1 Model structure for the cost effectiveness of specialist care (clinics) compared with usual care in women with twin and triplet pregnancies (neonatal outcomes)

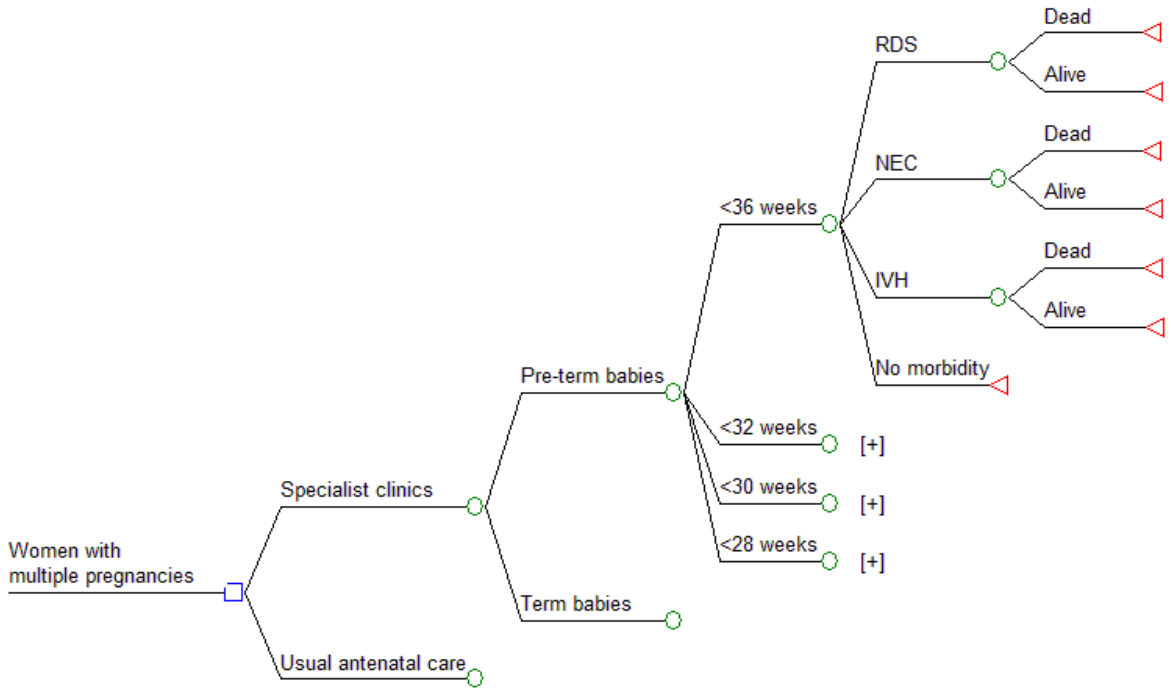
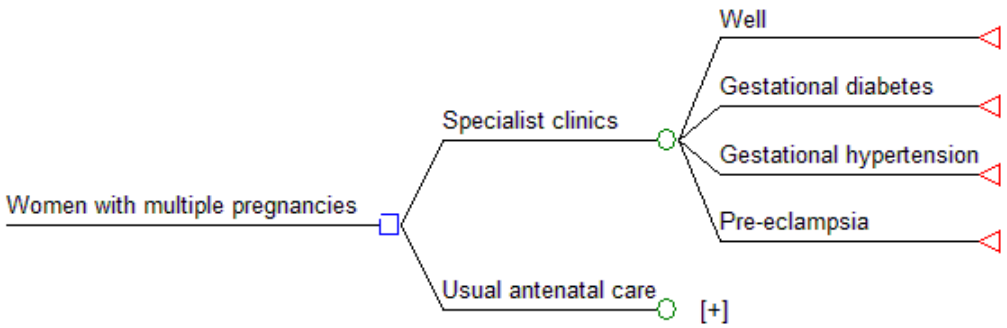


Figure 11.2 Model structure for the cost effectiveness of specialist care (clinics) compared with usual care in women with twin and triplet pregnancies (maternal outcomes)



Three studies reported the proportion of babies that were born preterm: before 30 weeks, before 32 weeks and before 36 weeks.[52-54] Morbidity data by gestational age at birth were taken from a study which showed that there was no statistically significant difference in IVH in twins and that the risk of RDS fell from 28% at 34 weeks to 5% at 37 weeks 0 days, increasing again to 9% from 38 weeks 0 days.[175] A further study showed that there was no difference in neonatal morbidity from 32 weeks (RDS, NEC and IVH).[178]

Table 11.3 Clinical data for usual care taken from the guideline review (see Table 5.6)

Outcome	Point estimate	Distribution*	alpha*	beta*	Number
Gestational diabetes	1.86%	Beta	8	423	431
Gestational hypertension	0.00%	Beta	0.5	41.5	42
Pre-eclampsia	15.64%	Beta	61	329	390
Preterm labour	41.89%	Beta	142	197	339
Perinatal mortality	6.99%	Beta	10	133	143
Intraventricular haemorrhage	4.17%	Beta	1	23	24
Necrotising enterocolitis	2.95%	Beta	10	329	339
Respiratory distress syndrome	33.33%	Beta	121	242	363
Preterm birth before 36 weeks	58.91%	Beta	248	173	421
Preterm birth before 32 weeks	21.24%	Beta	72	267	339
Preterm birth before 30 weeks	12.35%	Beta	52	369	421

*The last four columns relate to probabilistic sensitivity analysis; alpha = number of events; beta = number of non-events; number = alpha + beta

Table 11.4 Clinical data for specialist twin and triplet pregnancy care taken from the guideline review (see Table 5.6)

Outcome	Point estimate	Distribution*	alpha*	beta*	Number
Gestational diabetes	4.9%	Beta	15	294	309
Gestational hypertension	3.3%	Beta	1.5	29	30.5
Pre-eclampsia	9.0%	Beta	25	254	279
Preterm labour	23.2%	Beta	44	146	190
Perinatal mortality	1.0%	Beta	2	206	208
Intraventricular haemorrhage	13.6%	Beta	3	19	22
Necrotising enterocolitis	1.1%	Beta	2	188	190
Respiratory distress syndrome	21.2%	Beta	45	167	212
Preterm birth before 36 weeks	46.0%	Beta	115	135	250
Preterm birth before 32 weeks	7.4%	Beta	14	176	190
Preterm birth before 30 weeks	2.6%	Beta	8	301	309

*The last four columns relate to probabilistic sensitivity analysis; alpha = number of events; beta = number of non-events; number = alpha + beta

Cost data

Costing was undertaken from an NHS and personal social services perspective, in accordance with NICE methodology,[182] at 2009–10 prices. The relevant costs for this model were the cost of the intervention (that is, the cost of providing the specialist twin or triplet pregnancy care), maternal morbidity costs and neonatal complication costs. The costs of the intervention were calculated by using the costs of the incremental schedule of appointments for specialist care (that is, the costs over and above those of the routine antenatal care schedule). In this model, costs relating to the mode of delivery are assumed to be the same because the clinical evidence did not show any difference in caesarean section rates between specialist care and usual care.

The cost of preterm birth was estimated using GDG assumptions about length of stay in hospital and the level of care provided. The length of stay was determined by the gestational age at birth. The following assumptions were made about length of stay and level of care provided:

- For babies born at 36 weeks of gestation: 1 week in a special care baby unit.
- For babies born at 32 weeks of gestation: such babies will stay in hospital for up to 6 weeks, with 2 weeks in neonatal intensive care level 2, 2 weeks in neonatal care level 1 and 2 weeks in a special care baby unit.
- For babies born at 30 weeks of gestation: such babies will stay in hospital for up to 9 weeks, with 2 weeks in neonatal intensive care level 1, 2 weeks in a high-dependency unit and 5 weeks in a special care baby unit.

The cost of the total length of stay for each gestational age was calculated as the cost per baby per day (determined by level of care given) multiplied by the number of days and weighted according to the proportion of babies born at that gestational age. To simplify costing, it was assumed that none of the twins or triplets would be sicker than the others for the duration of their stay in hospital.

It was assumed that RDS and IVH would both be managed in neonatal intensive care level 1 and that NEC would be managed in a high dependency unit. Total neonatal complication costs were calculated as a weighted average of the cost of these morbidities (estimated by the level of care provided for that morbidity), with the weight determined by their frequency (see Tables 11.3 and 11.4).

The cost parameters used in the model are shown in Table 11.5. These include the cost of ultrasound monitoring and the cost of consultation by specialist midwives and specialist obstetricians.

Table 11.5 Cost data used in the model

Procedure	Unit cost	Notes	Source
Ultrasound scan lasting > 20 min	£71	HRG Currency Code RA24Z	NHS Reference Costs 2009–10[183]
Special care baby unit	£468	HRG Currency Code XA03Z	NHS Reference Costs 2009–10[183]
Neonatal intensive care level 2	£792	HRG Currency Code XA02Z	NHS Reference Costs 2009–10[183]
Neonatal intensive Care level 1	£1087	HRG Currency Code XA01Z	NHS Reference Costs 2009–10[183]
Hospital admission	£629	HRG Currency Code NZ08C	NHS Reference Costs 2009–10[183]
Specialist obstetrician	£171	Per hour of patient contact	Unit costs of health and social care[184]
Specialist midwife	£70	Per hour of patient contact	Unit costs of health and social care[184]
Gestational hypertension	£3000		'Hypertension in pregnancy', NICE clinical guideline 107[20]
Pre-eclampsia	£4300		'Hypertension in pregnancy', NICE clinical guideline 107[20]
Gestational diabetes	£3000	Assumed to be the same as gestational hypertension	
Term twins	£1882	Calculated[a]	
Preterm birth at 36 weeks	£6552	Calculated[b]	
Preterm birth at 32 weeks	£65,716	Calculated[c]	
Preterm birth at 30 weeks	£85,372	Calculated[d]	

[a]Calculated as cost of singleton multiplied by two

[b]Calculated as cost per baby staying for 1 week in a special baby unit ([7 days *£468]*2)

[c]Calculated as cost per baby staying for 2 weeks in a special baby unit + 2 weeks in Neonatal Intensive Care level 2 + 2 weeks in Neonatal Intensive Care level 1 ([14 days *£468]*2) + ([14*£792]*2) + ([14*£1087]*2)

[d]Calculated as cost per baby staying for 9 weeks in a special baby unit + 2 weeks in Neonatal Intensive Care level 2 ([35 days *£468]*2) + ([14*792]*2) + ([14*1087]*2)

Quality adjusted life years (QALYs)

Economic evaluation requires an assessment of whether the benefits of a particular course of action are justified by the opportunity costs of that action; that is, the sacrifice of other benefits that would have been obtained had the resources been used in their next best alternative use. In health care, quality adjusted life years (QALYs) are frequently used as a generic measure of health and are NICE's preferred outcome measure for economic analysis. To calculate QALYs, a health state utility is assigned to the various maternal and neonatal outcomes in the model to capture the impact that state has on quality of life. This is then multiplied by the number of years spent in that state to derive the QALY associated with being in that state. A QALY loss can be calculated by subtracting this from

the QALY that would be achieved in a state of 'perfect health'. A weighted QALY for these outcomes is then calculated by multiplying the QALY associated with that state by its relative frequency for each type of pregnancy care (Tables 11.3 and 11.4). The weighted QALYs for all outcomes (neonatal and maternal) are then summed to find the expected QALY associated with usual pregnancy care and specialist pregnancy care, respectively. All QALYs are discounted at an annual rate of 3.5% in accordance with NICE methodology.[182]

QALY loss from maternal morbidity was taken from 'Hypertension in pregnancy', NICE clinical guideline 107.[20] The QALY loss from gestational hypertension and pre-eclampsia was 0.04 and 0.07, respectively (see Table 11.6). Quality of life loss due to gestational diabetes and preterm birth was assumed to be the same as that of a singleton pregnancy without any complications. One study[185] evaluated the cost effectiveness of contraceptive methods in women of average health and fertility aged 15–50 years compared with non-use of contraception. The authors found that short-term loss of quality of life due to pregnancy was 0.0375 throughout the pregnancy. We converted this utility loss to QALY loss by dividing 0.0375 by 52 to get a weekly utility loss, and then multiplied by 37 and 35 weeks for twin and triplet pregnancies, respectively. Thus for twin pregnancies the estimated utility loss due to gestational diabetes was 0.0267 and for triplet pregnancies it was 0.0252.

We assumed that the total discounted QALYs of an otherwise healthy baby would be 27 QALYs over the individual's lifetime. This is based on a life expectancy of 80 years at birth[186] and assumes remaining years are lived in full health. We acknowledge the fact that all years of life are not necessarily lived in full health and explored this in sensitivity analysis. No quality of life data were available for morbidity relating to neonatal outcomes. QALY loss was estimated using excess mortality due to NEC, RDS and IVH. For instance, it was estimated that IVH would result in excess mortality of about 5%.[187] The resulting QALY loss was calculated to be 1.35 QALYs. Table 11.6 shows the excess mortality due to morbidity and the associated QALY loss.

Table 11.6 Loss of quality adjusted life years (QALYs)

Morbidity	Excess mortality	QALY loss	Source
Gestational diabetes	-	0.0267	
Gestational hypertension	-	0.04	'Hypertension in pregnancy', NICE clinical guideline 107[20]
Pre-eclampsia	-	0.07	'Hypertension in pregnancy', NICE clinical guideline 107[20]
Preterm labour	-	0.0267	
Neonatal death	-	27	Calculated
Intraventricular haemorrhage	5.0%	1.35*	Ment et al. (2004)[188]
Necrotising enterocolitis	4.7%	1.27*	Wiswell at al. (1988)[189;189]
Preterm birth before 36 weeks	0.5%	0.14*	Luke et al. (2003)[54]; Ellings et al. (1993)[52]; Ruiz et al. (2010)[53]
Preterm birth before 32 weeks	5.0%	1.35*	Luke et al. (2003)[54]
Preterm birth before 30 weeks	8.0%	2.16*	Luke et al. (2003)[54]; Ellings et al. (1993)[52]; Ruiz et al. (2010)[53]
Respiratory distress syndrome	0.0%	0.00*	Luke et al. (2003)[54]

*QALY loss was calculated

Sensitivity analysis

Probabilistic sensitivity analysis was used to estimate the probability that specialist clinics or alternative care would be cost effective at a willingness to pay of £20,000 per QALY, the advisory threshold suggested by NICE.[182] A number of model parameters were assigned a distribution reflecting the uncertainty around the point estimate due to sampling variation (see Tables 11.3 and 11.4). Costs and effects are determined after simultaneously sampling random values from each distribution. The process was repeated 2000 times in a Monte Carlo simulation. No standard errors were available for the utility values and so these were treated deterministically within the probabilistic sensitivity analysis, as were cost inputs.

One-way sensitivity analysis was restricted to inputs relating to length of stay and QALY loss from neonatal death. The GDG's view was that uncertainty with respect to these inputs could have an important bearing on the result.

Results

Specialist care compared with usual care for monochorionic diamniotic twin pregnancies

Overall, specialist care costs less than usual care per monochorionic diamniotic twin pregnancy and results in more health benefits, and is said to dominate usual care (see Table 11.7).

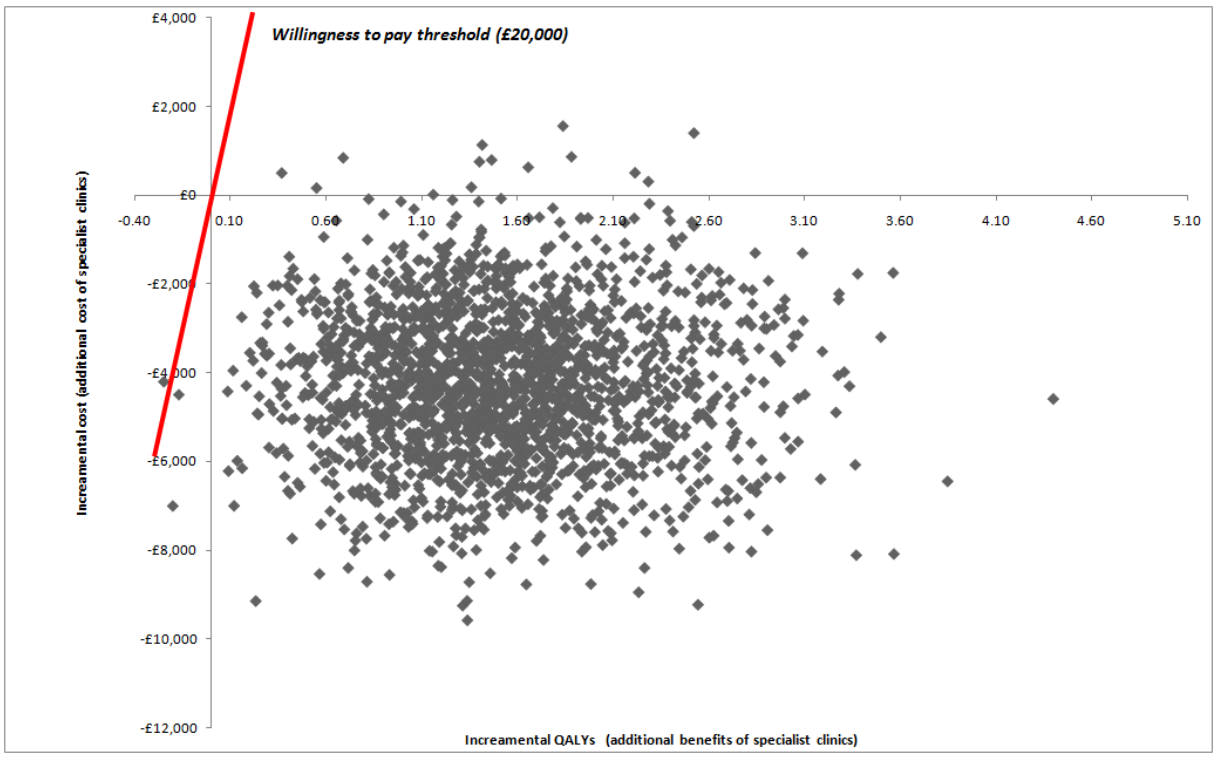
Table 11.7 Specialist care compared with usual care for monochorionic diamniotic twin pregnancies

	Specialist care (£)	Usual care (£)	Specialist care QALY loss	Usual care QALY loss	Incremental costs	Incremental QALY	Cost/QALY
Maternal	£1,872	£1,673	0.02	0.02			
Neonatal	£11,619	£15,977	1.00	2.52			
Total	£13,491	£17,650	1.01	2.55	-£4,159	1.53	Dominant

Probabilistic results for specialist care compared with usual care for monochorionic diamniotic twin pregnancies

The results of 2000 iterations of the model are illustrated on the cost effectiveness/decision plane in Figure 11.3. Each point represents the incremental cost and incremental QALY for specialist care compared to usual care derived from a single iteration of the model. In 99.95% of the iterations, specialist care remained cost effective, as shown by the clustering of points below the £20,000 per QALY willingness-to-pay threshold (shown in red).

Figure 11.3 Cost effectiveness plane comparing specialist care (clinics) with usual care for monochorionic diamniotic twin pregnancies



Specialist care compared with usual care for dichorionic twin pregnancies

For dichorionic twins the results also suggested that specialist clinics dominate usual care as shown in Table 11.8 (that is, specialist clinics are both cheaper and more effective).

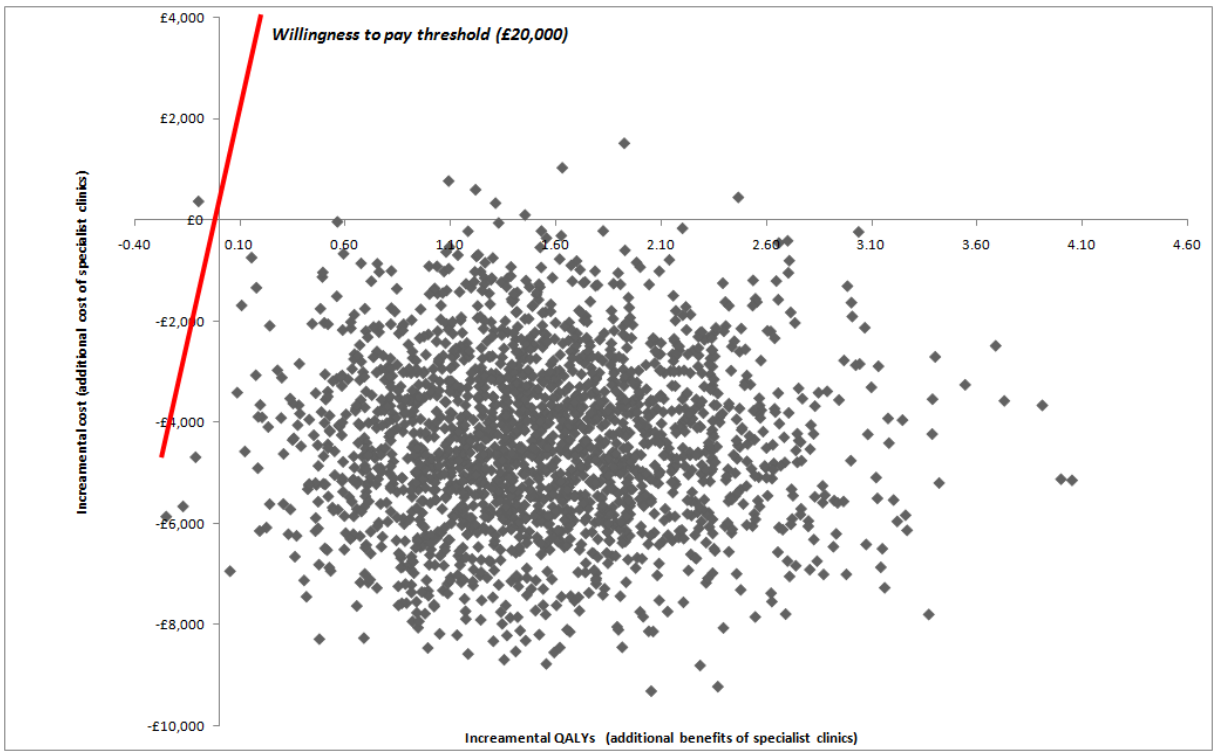
Table 11.8 Specialist care compared with usual care for dichorionic twin pregnancies

	Specialist care (£)	Usual care (£)	Specialist care QALY loss	Usual care QALY loss	Incremental costs	Incremental QALY	Cost/QALY
Maternal	£1627	£1675	0.02	0.02			
Neonatal	£11,619	£15,977	1.00	2.52			
Total overall	£13,246	£17,652	1.01	2.55	–£4406	1.53	Dominant

Probabilistic results for specialist care compared with usual care for dichorionic twin pregnancies

Figure 11.4 shows that in an overwhelming majority of iterations, specialist care saves costs and increases QALYs, as demonstrated by the number of simulations occurring in the south-east quadrant.

Figure 11.4 Cost effectiveness plane comparing specialist care (clinics) with usual care for dichorionic twin pregnancies



Specialist care compared with usual care for monochorionic triamniotic and dichorionic triamniotic triplet pregnancies

The results for monochorionic triamniotic and dichorionic triamniotic triplet pregnancies (shown in Table 11.9) show specialist care to be cheaper than usual care while generating a gain in QALYs.

Table 11.9 Specialist care compared with usual care for monochorionic triamniotic and dichorionic triamniotic triplet pregnancies

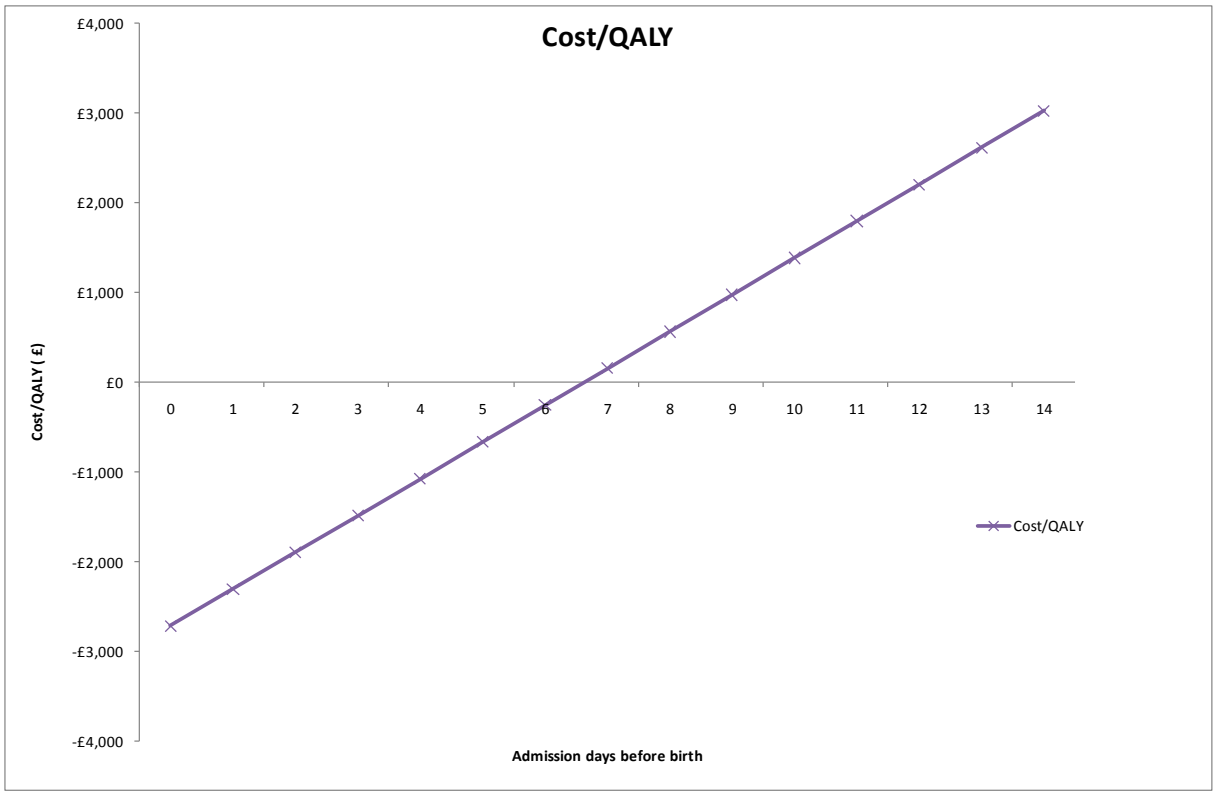
	Specialist care	Usual care	Specialist care	Usual care	Incremental costs	Incremental QALY	Cost/QALY
Maternal	£2 093	£1 675	0.02	0.02			
Neonatal	£11,619	£15,977	1.00	2.52			
Total	£13,712	£17,652	1.01	2.55	-£3 940	1.533	Dominant

One-way sensitivity analysis

Varying the number of admission days for monochorionic diamniotic twin pregnancies

In the base-case analysis it was assumed that women would not be admitted for observation and monitoring. In sensitivity analysis this assumption was relaxed, with admission varied between 0 and 2 weeks. Specialist care still saved costs for admission of up to 6 days and was cost effective thereafter (see Figure 11.5). The incremental cost effectiveness ratio (ICER) for specialist care was about £3000 per QALY when women were assumed to be admitted for 2 weeks. Varying the assumptions about hospitalisation did not change the GDG's conclusion that specialist care is the preferred management strategy for women with monochorionic diamniotic twin pregnancies.

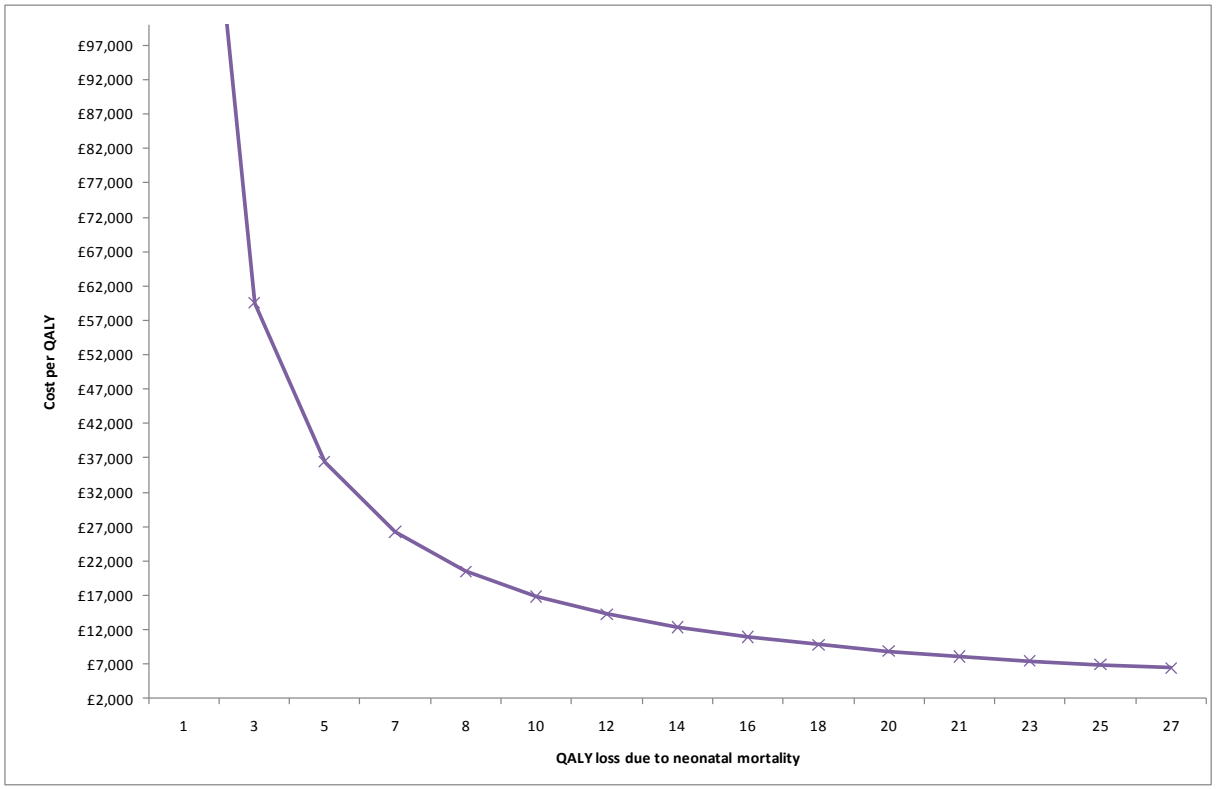
Figure 11.5 Cost effectiveness of specialist care compared with usual care varying the admission days for monochorionic diamniotic twin pregnancy



Varying neonatal QALY loss due to neonatal mortality

In the model we assumed that the total discounted health gain of an otherwise healthy baby was 27 QALYs over the individual's lifetime. This assumption works in favour of interventions that reduce neonatal mortality. In sensitivity analysis the QALY loss was varied between 1 and 27 QALYs (see Figure 11.6). Specialist clinics remained cost effective across this range for all twin and triplet pregnancies since the specialist clinics remained cheaper and still had a small but positive health benefit ranging from a gain of 0.064–1.53 QALY . The model conclusions are not sensitive to assumptions made about the QALY loss from neonatal mortality.

Figure 11.6 Cost effectiveness of specialist care compared with usual care varying QALY loss due to neonatal mortality for monochorionic diamniotic twin pregnancy



Discussion

The model demonstrated that, in a wide range of scenarios, specialist care for women with twin and triplet pregnancies saves costs compared to usual care (routine antenatal care). The savings were driven primarily by reduced costs due to a lower risk of adverse neonatal events requiring hospitalisation in the specialist care group. Probabilistic sensitivity analysis showed that the probability of specialist care being cost effective was greater than 99% for monochorionic diamniotic twin pregnancies, dichorionic twin pregnancies and triplet pregnancies when compared with usual care.

A major strength of this analysis is that the model considered the potential improvement in health outcomes for both the woman and the babies. To our knowledge this is the first economic analysis of its kind. However, the clinical effectiveness data were taken from medium-quality studies which were mainly undertaken in the USA. Extrapolating from these studies to an NHS setting is clearly an important limitation of this model. Data were not reported separately by chorionicity, and we therefore assumed reported outcomes would apply equally to monochorionic and dichorionic twin pregnancies, which may not be the case. This may overestimate the impact of specialist care for dichorionic twin pregnancies and probably underestimates the impact for monochorionic twin pregnancies which have a much higher risk of adverse outcomes.

11.3 Cost effectiveness of elective birth compared to expectant management for multiple pregnancies

Introduction

Twin and triplet pregnancies tend to end earlier than singleton pregnancies.[190] It is also a widely held view among clinicians that perinatal outcomes in multiple pregnancies worsen with advancing gestational age beyond 37 weeks. The GDG's experience suggests that women with twin and triplet pregnancies are often advised to undergo elective birth without any other indication. The review

question aimed to determine the optimal gestational age for birth in uncomplicated twin and triplet pregnancies.

A systematic search of the literature did not identify any published health economic evaluations assessing the cost effectiveness of elective birth at a predetermined gestational age for twin or triplet pregnancies compared to delaying birth (expectant management). Therefore, the GDG requested an original health economic analysis to assist with the development of guideline recommendations.

Methods

A simple decision tree model was constructed in Microsoft Excel® depicting the two different strategies for caring for women with multiple pregnancies. The model focuses on neonatal outcomes as there were no statistically significant differences in maternal outcomes found in the studies of clinical effectiveness that were reviewed for the guideline (see Chapter 10). A schematic of the model structure is shown in Figure 11.7.

Description of alternatives

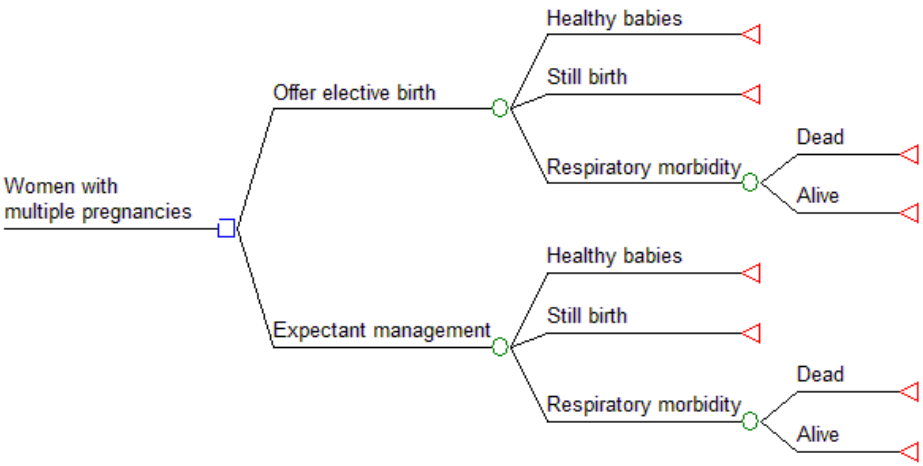
Elective birth

Elective birth occurs when a woman accepts an offer from her healthcare professionals of birth at 37 weeks 0 days. In the model, the GDG assumed that about one-third of women would have their babies delivered by elective caesarean section, one-third by emergency caesarean section because of failed induction of labour and one-third would have a successful induction and vaginal delivery. In the event that a woman chooses to have induction of labour, the choice of induction drug for cervical ripening is assumed to be intravaginal prostaglandin as recommended in 'Induction of labour' (NICE clinical guideline 70).[17]

Expectant management

In this strategy it is assumed that women will give birth 1 week later than the 37 weeks 0 days at which elective birth occurs. Monitoring beyond 37 weeks 0 days would be conducted by the specialist obstetrician due to the risks of fetal mortality. The mode of delivery was assumed to be the same whether the women had elective birth or the birth was managed expectantly because there were no data showing any difference.

Figure 11.7 Model structure for cost effectiveness of elective birth compared with expectant management in women with twin and triplet pregnancies



Clinical evidence

Five studies showed there were no significant differences in neonatal or maternal outcomes between women undergoing elective birth and women undergoing expectant management.[164-166;168;191]

Neonatal outcomes considered were stillbirth, IVH, RDS and NEC. There was evidence suggesting an increasing risk of intrauterine fetal death (indicated by the stillbirth rate) with increasing gestational age at birth, with the lowest risk observed at 37 weeks 0 days in twin pregnancies and 35 weeks 0 days in triplet pregnancies. Two further studies examined the effect of chorionicity on risk of fetal death.[166;168] Both studies showed higher risks of stillbirth in monochorionic pregnancies at all gestational ages compared to dichorionic pregnancies (see Chapter 10).

For the purposes of the health economic analysis, stillbirth rates reported in a large Japanese study[164] (see Table 11.10) and respiratory morbidity data from another study[175] (see Table 11.11) were used in the model. Other neonatal outcomes were not explicitly modelled as the clinical evidence reviewed for the guideline showed that there were no statistically significant differences between these outcomes by gestational age in twin pregnancies after 34 weeks[175] and in triplet pregnancies after 33 weeks.[178]

Table 11.10 Stillbirth rate by gestational age [164]

Gestational age	Stillbirths	Fetuses at risk	Stillbirth rate at each gestational age
<30 weeks	601	88,916	0.68%
31 weeks	122	84,843	0.14%
32 weeks	723	173,759	0.42%
32 weeks	120	83,411	0.14%
33 weeks	126	81,409	0.15%
34 weeks	120	78,559	0.15%
35 weeks	159	74,322	0.21%
36 weeks	182	67,636	0.27%
37 weeks	208	55,355	0.38%
38 weeks	150	34,875	0.43%
39 weeks	105	16,768	0.63%
40 weeks	65	5891	1.10%
41 weeks	16	1130	1.42%
42 weeks	3	112	2.68%

Table 11.11 Incidence of respiratory morbidity (transient tachypnoea of the newborn or respiratory distress syndrome)[175]

Gestational age	Incidence
34 weeks	10 out of 36 (27.8%)
35 weeks	10 out of 64 (15.6%)
36 weeks	15 out of 126 (11.9%)
37 weeks	11 out of 210 (5.2%)
38 weeks	6 out of 62 (9.7%)
39 weeks	8 out of 44 (18.2%)
40 weeks	1 out of 6 (16.7%)

QALYs

We assumed that the total discounted QALYs of an otherwise healthy baby would be 27 QALYs over the individual's lifetime. This is based on a life expectancy at birth of 80 years[186] and assumes remaining years are lived in full health. QALYs are discounted at a rate of 3.5% per annum in accordance with NICE methodology.[182]

QALY loss for birth at each gestational age is calculated from the stillbirth rate and an excess mortality due to respiratory morbidity of 22%.[192] For example, for birth at a gestational age of 36 weeks, the stillbirth rate was 0.27% (see Table 11.10) and the incidence of respiratory morbidity was 11.9% (see Table 11.11). The expected QALY loss for birth at a gestational age of 36 weeks is estimated as:

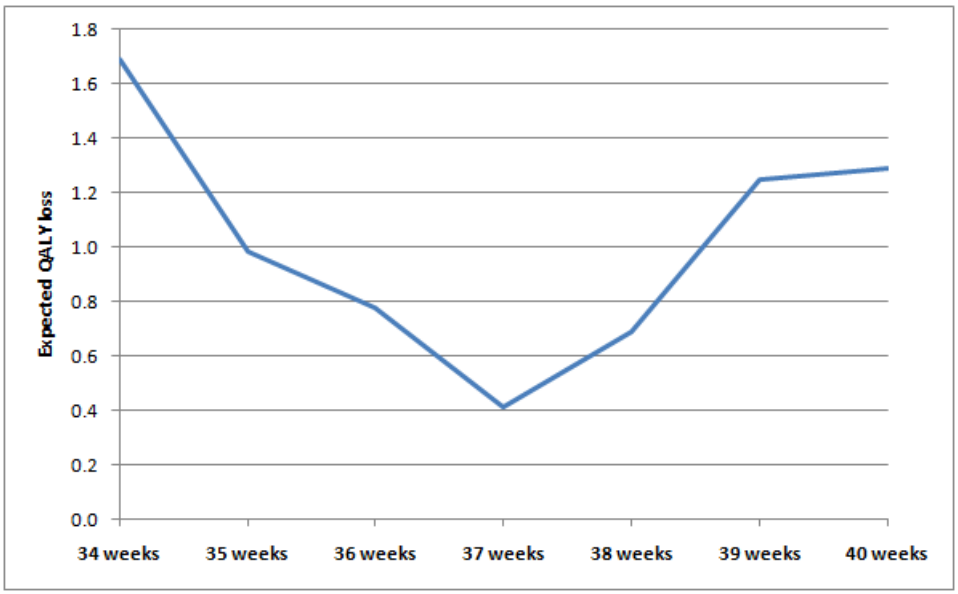
$$(27 \times 0.0027) + (27 \times 0.119 \times 0.22) = 0.78 \text{ QALYs}$$

The relationship between QALY loss and births by gestational age is shown in Table 11.12 and Figure 11.8.

Table 11.12 Expected QALY loss per pregnancy in multiple pregnancies by gestational age at birth

Gestational age	QALY loss per pregnancy
34 weeks	1.691
35 weeks	0.986
36 weeks	0.780
37 weeks	0.413
38 weeks	0.691
39 weeks	1.249
40 weeks	1.288

Figure 11.8 Graph showing QALY loss for birth at different gestational ages



Results

The data used in this model suggest that prolonging multiple pregnancies beyond 37 weeks 0 days increases the QALY loss (see Table 11.13). If 37 weeks 0 days, as per the elective birth strategy, is the optimal timing in terms of clinical outcomes, then expectant management can only be preferred if it produces significant savings relative to elective birth. If that were the case, the better outcomes of elective birth would not be worth the opportunity cost, as the savings could produce greater benefit by being used in an alternative way.

This model did not explicitly cost the different strategies. Instead, in Table 11.13 a threshold analysis is presented to show the incremental saving that would be necessary, using the advisory willingness to pay threshold of £20,000 per QALY suggested in the NICE guidelines manual,[182] to make each additional week of expectant management cost effective relative to elective birth 1 week earlier.

Table 11.13 Incremental QALY loss for waiting an additional week beyond 37 weeks 0 days and cost savings needed for expectant management to be cost effective compared to elective birth at 37 weeks 0 days in twin pregnancies

Gestational age	Incremental QALY loss by waiting an additional week	Incremental cost savings needed
38 versus 37 weeks	0.278	£5567
39 versus 38 weeks	0.558	£11,162
40 versus 39 weeks	0.039	£777

Sensitivity analysis

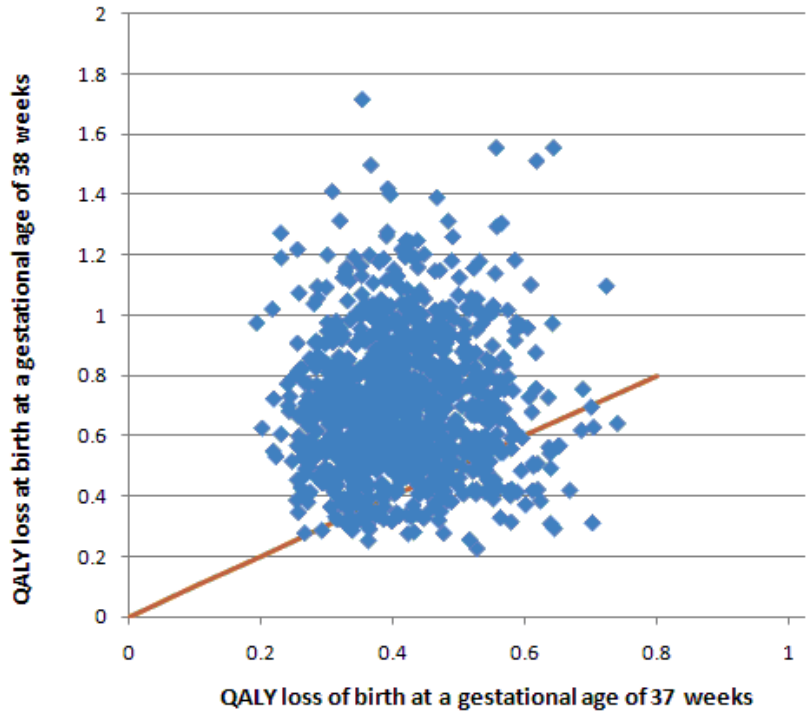
A Monte Carlo probabilistic simulation was undertaken to assess how likely it was that the QALY loss with elective birth at 37 weeks 0 days would be less than with a strategy of expectant management (with birth at 38 weeks 0 days). The probability distribution data on which this simulation was based are shown in Table 11.14. The alpha and beta parameters were derived from the same studies which were used to obtain the point estimates.

Table 11.14 Parameter values used for probabilistic analysis

Variable	Alpha	Beta	Distribution
Stillbirth at 37 weeks	208	55,147	Beta
Stillbirth at 38 weeks	150	34,725	Beta
Respiratory morbidity at 37 weeks	11	199	Beta
Respiratory morbidity at 38 weeks	6	56	Beta

The simulation sampled from these probability distributions 1000 times and the results are shown below in Figure 11.9. The red line denotes where the QALY loss of the strategies is identical.

Figure 11.9 Graph showing QALY loss for birth at different gestational ages



Above the red line, the QALY loss is greater with expectant management. Below the red line the QALY loss is greater with elective birth. In 89.6% of the simulations a lower QALY loss resulted with elective birth at 37 weeks 0 days compared to expectant management with birth at 38 weeks 0 days.

Discussion

In the review of clinical effectiveness evidence undertaken for this guideline no statistically significant difference was found for any reported outcomes, with the exception of fetal mortality and respiratory morbidity, both of which increase with increasing gestational age beyond 37 weeks 0 days for multiple pregnancies. The results from the UK study[165] were consistent with those from the (bigger) Japanese study.[164] There was a tendency in the UK study for increasing stillbirth rates from 38 weeks 0 days.

Increasing mortality and morbidity from 37 weeks 0 days for multiple pregnancies will inevitably lead to a greater QALY loss with increasing gestational age (see Table 11.12). It follows, therefore, as a necessary but not sufficient condition, that for expectant management to be cost effective it would have to generate cost savings relative to elective birth. The health economic analysis demonstrated the minimum incremental savings per additional week of gestational age at birth that would be needed to make expectant management cost effective. However, it is not likely that a strategy of expectant management would yield these savings; indeed, the opposite may be the case. Elective birth may increase the costs of birth with induction of labour, adding approximately £500 to the cost of birth where it is used.[183] On the other hand, expectant management requires additional monitoring costs as well as higher 'downstream' costs arising from worsening neonatal morbidity associated with increasing gestational age.

The Japanese study[164] included a very small number of triplet pregnancies as well as twin pregnancies. Most of the study population was women with dichorionic twin pregnancies. Therefore, this analysis suggests that expectant management beyond 37 weeks 0 days is not cost effective in multiple pregnancies and that elective birth is the preferred strategy. The composition of the Japanese study population supports the GDG recommendation for timing of birth for dichorionic twin pregnancies.

There were, however, no sufficiently robust data to conduct a separate analysis for monochorionic twin pregnancies or triplet pregnancies. The GDG decided to recommend earlier birth for these groups for the reasons described in Chapter 10. The increasing risk of fetal death towards the end of

pregnancy seems to be even higher in monochorionic twin pregnancies than in dichorionic twin pregnancies, and the GDG's view was that women with monochorionic twin pregnancies should be offered elective birth at 36 weeks 0 days. For triplet pregnancies there is a risk of spontaneous preterm labour and delivery occurring in an adverse setting if a pregnancy is continued towards the end of the third trimester. Furthermore, the evidence suggests there is a higher risk of fetal death after 34 weeks, and the GDG's view was that women with triplet pregnancies should be offered birth at 35 weeks 0 days. While not formally assessed in health economic analysis, these clinical risks would tend to make an earlier timing of elective birth more cost effective, as long as some of the benefits of earlier birth were not completely offset by a higher risk of respiratory morbidity.

Conclusions

This model using the available clinical evidence suggests that elective birth at 37 weeks 0 days for multiple pregnancies, and dichorionic twin pregnancies in particular, is cost effective relative to a strategy of expectant management beyond this gestational age.

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13 Abbreviations and glossary

Abbreviations

AGA	appropriate-for-gestational age
BMI	body mass index
BP	blood pressure
BPD	biparietal diameter
BWD	birthweight discordance
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CRL	crown–rump length
CT	computed tomography
CTG	cardiotocography
ECV	external cephalic version
EFW	estimated fetal weight
EFWD	estimated fetal weight discordance
FASP	Fetal Anomaly Screening Programme
f-beta-hCG	free beta human chorionic gonadotrophin
FFTS	feto-fetal transfusion syndrome
FMF	Fetal Medicine Foundation
GDG	guideline development group
GP	general practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
hCG	human chorionic gonadotrophin
Hgb	haemoglobin
HIV	human immunodeficiency virus
HTA	Health Technology Assessment
ICER	incremental cost effectiveness ratio
IUGR	intrauterine growth restriction
IVF	*in vitro* fertilisation
IVH	intraventricular haemorrhage
LR^+	positive likelihood ratio
LR^-	negative likelihood ratio

Max	maximum
MD	mean difference
NC	not calculable
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NEC	necrotising enterocolitis
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NHS FASP	NHS Fetal Anomaly Screening Programme
NICE	National Institute for Health and Clinical Excellence
NICU	neonatal intensive care unit
NPV	negative predictive value
NT	nuchal translucency
OR	odds ratio
PAPP-A	pregnancy-associated plasma protein A
PCT	primary care trust
PPV	positive predictive value
PTP^{+}	post-test probability (of a positive test)
PTP^{-}	post-test probability (of a negative test)
QADAS	Quality Assessment of Studies of Diagnostic Accuracy
QALY	quality adjusted life year
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomised controlled trial
RDS	respiratory distress syndrome
RMSD	root mean square deviation
RI	resistance index
RR	relative risk (or risk ratio)
ROC	receiver operator characteristic
SCBU	special care baby unit
S:D	systolic:diastolic
SD	standard deviation
Sens	sensitivity
SFH	symphysis-fundal height
SGA	small-for-gestational age
Spec	specificity
STOPPIT	Study of Progesterone for the Prevention of Preterm Birth in Twins
TAPS	twin anaemia-polycythaemia sequence
TOP	termination of pregnancy
TRAP	twin reversed arterial perfusion
TTTS	twin-to-twin transfusion syndrome

UK	United Kingdom
USA	United States of America
USS	ultrasound scan

Glossary

Abdominal circumference	The ultrasound measurement of the outer circumference of a developing baby's abdomen (an ultrasound transverse section of the fetal abdomen taken through the stomach, vertebrae and fetal liver)
Abdominal palpation	Part of the clinical examination of the abdomen in pregnant women. It comprises an assessment of uterine size, confirmation of the number of babies, their lie and presentation and the amount of amniotic fluid
Absolute effect (absolute risk reduction or risk difference)	The difference between the risk in the intervention group (or another group of interest, for example a group with a particular exposure in an observational study) and the risk in the comparison group. Absolute effect, absolute risk reduction and risk difference are synonyms
Anaemia	A deficiency in haemoglobin (the iron-containing oxygen-carrying component of red blood cells)
Anomaly	In the context of pregnancy, this refers to a congenital malformation in the fetus
Assisted reproduction	Treatments designed to lead to conception by means other than sexual intercourse. Assisted reproduction techniques include intrauterine insemination, *in vitro* fertilisation (IVF), intracytoplasmic sperm injection and donor insemination (see 'Fertility', NICE clinical guideline 11)[19]
Audit	A systematic review of a practice, process or performance to establish how well it meets predetermined criteria
Antenatal day unit	A unit established to undertake a variety of pregnancy assessments, reducing the need for admission to hospital
Biometric	A measure of certain aspects of an individual's anatomy or physiology (for example height or weight) or behaviour, or a combination of such characteristics
Biophysical profile assessment	An antenatal ultrasound evaluation of fetal wellbeing based on fetal movement, fetal tone, fetal breathing, amniotic fluid volume and the nonstress test of the fetal heart rate (or cardiotocography)
Body mass index	A measure of body build calculated as weight in kilograms divided by height in metres squared
Care pathway	A multidisciplinary outline of predicted care for a particular condition in the context of a specific timeframe
Cervical cerclage	A surgical procedure used to treat cervical weakness (or insufficiency) associated with a risk of miscarriage or preterm birth. Cervical cerclage consists of the insertion of stitches with the aim of preventing a miscarriage or preterm. Also referred to as cervical stitch or suture
Cervical length	The length of the cervix identified by a transvaginal ultrasound measurement

Chorionicity	The number of chorionic membranes that surround the fetuses in a multiple pregnancy. If there is only one membrane the pregnancy is described as monochorionic; if there are two, the pregnancy is described as dichorionic; and if there are three, the pregnancy is described as trichorionic. Monochorionic twin pregnancies and dichorionic triplet pregnancies carry higher risks because fetuses share a placenta
Chromosomal abnormality	An abnormality of chromosome structure or number, usually arising before or during conception
Combined test	A group of screening tests used together to determine the risk of an unborn baby having Down's syndrome. The tests are a nuchal translucency ultrasound scan and blood tests to measure levels of beta human chorionic gonadotrophin and pregnancy-associated plasma protein-A. The test should be performed between 11 weeks 0 days and 13 weeks 6 days
Combined screening test	The use of more than one test in combination for screening
Complicated pregnancy	A twin or triplet pregnancy that is associated with maternal or fetal complications (see also Uncomplicated)
Congenital malformation	An abnormality (genetic, chromosomal or structural) of the baby that is present during fetal life or at birth
Corticosteroids	Pharmacological agents (drugs) used to help mature a baby's lungs
Crown–rump length	The length of a human fetus from the top of the head (crown) to the bottom of the buttocks (rump)
Diagnosis	Confirmation of the presence of a condition
Dichorionic (diamniotic)	Twins that have separate placentas. Different combinations of shared and separate placentas occur in triplet pregnancies and other higher-order multiple pregnancies and dichorionic triplets occur when two fetuses share a placenta and the other has a separate placenta
Discordance	A significant discrepancy between fetuses in terms of size, structure or condition
Discordant fetal death	This refers to the situation in a multiple pregnancy where one fetus is dead and the other(s) are alive. Also referred to as single twin demise
Doppler ultrasound	An ultrasound method of recording and evaluating fetal blood flow in real time, including measurement of the direction and speed of blood flow
Doppler velocimetry	A term used to describe the process of recording and measuring fetal blood flow using Doppler ultrasound
Embryo–fetal adverse outcome	Loss of or damage to an embryo (usually ending in a miscarriage) or a fetus (usually ending in a stillbirth, fetal abnormality or growth restriction)
Elective delivery	A birth that is planned, rather than occurring naturally
Estimated fetal weight	Estimation of the weight of the fetus using one or more ultrasound biometric measures

False negative	Where a negative screening test result is obtained in an individual who has the target condition
False positive	Where a positive screening test result is obtained in an individual who does not have the target condition
Fetal fibronectin	A protein found in amniotic fluid and placental tissue
Femur length	The ultrasound measurement of the length of fetal femur
Fetal biometry	Measurement of anatomical structures in the fetus by ultrasound (for example biparietal diameter, head circumference, abdominal circumference and femur length)
Fetal death	Death of a fetus. The term fetus is used to refer to the unborn baby from 9 weeks 0 days of pregnancy whereas the term embryo is used before that time, so fetal death implies that the fetus has reached 9 weeks 0 days. When a dead fetus is delivered before 24 weeks the process is termed miscarriage and when it occurs at 24 weeks or later it is termed stillbirth
Feto-fetal transfusion syndrome	Feto-fetal transfusion syndrome occurs when blood moves from one fetus to another. The fetus that loses the blood is called the donor and the fetus receiving the blood is called the recipient. Feto-fetal transfusion syndrome is a complication of monochorionic multiple pregnancies arising from shared placental circulation. It is also referred to as twin-to-twin transfusion syndrome in twin pregnancies
Fetal growth restriction or intra-uterine growth restriction	A condition in which the fetus fails to meet its genetic growth potential. It is diagnosed using ultrasound biometry (often on more than one occasion)
Fetal medicine	The healthcare discipline which deals with diseases of the fetus
Fetal weight discordance	A significant discrepancy between the estimated fetal weights of fetuses in a multiple pregnancy
Folic acid	A water-soluble vitamin in the B-complex group that helps to prevent fetal malformations when taken before conception and up to 12 weeks afterwards
Full blood count	A laboratory measure of specific haematological parameters in a blood sample. It usually comprises haemoglobin concentration, certain features of the red blood cells, the white blood cell count (concentration) and platelet count
Gestation	The time from conception to birth. Traditionally, the duration of gestation is measured from the first day of the last normal menstrual period, assuming that conception occurs 14 days after the first day of menstruation. Ultrasound biometric measurements in the first half of pregnancy are used to determine gestational age
Head circumference	The ultrasound measurement of the outer circumference of the fetal head (used as part of the assessment of fetal growth)
Home uterine activity monitoring	A procedure for early detection of uterine contractions involving a belt worn around the pregnant woman's abdomen and transmission of recordings by telephone modem to a remote site where expert assessment and advice can be provided

Hypertension	High blood pressure. The following definitions apply in pregnancy (see 'Hypertension in pregnancy', NICE clinical guideline 107[20]): • mild hypertension: diastolic blood pressure 90–99 mmHg, systolic blood pressure 140–149 mmHg • moderate hypertension: diastolic blood pressure 100–109 mmHg, systolic blood pressure 150–159 mmHg • severe hypertension: diastolic blood pressure 110 mmHg or greater, systolic blood pressure 160 mmHg or greater
Intrauterine growth restriction	A 25% or more difference in size between twins or triplets is a clinically significant indicator of intrauterine growth restriction. In clinical practice any degree of fetal growth restriction or discordance of less than 25% would lead to increased fetal surveillance
Iron deficiency anaemia	Iron deficiency is the most common cause of anaemia in pregnancy. It is caused by iron loss in the body or insufficient dietary intake or absorption of iron
Iron supplementation	Iron supplements help to increase levels of iron in the body; they are typically prescribed to prevent or treat iron deficiency anaemia
In vitro fertilisation	A technique whereby eggs are collected from a woman and fertilised with a man's sperm outside the body. Usually one or two resulting embryos are transferred to the womb with the aim of starting a pregnancy (see 'Fertility', NICE clinical guideline 11[19])
Lambda sign	In a diamniotic pregnancy, the ultrasound appearance of the dividing membrane (comprising two amnions and two chorions) where it is attached to the uterine wall
Lethal anomalies	Fetal abnormalities that carry a risk of the baby dying before birth or a shorter than normal life expectancy
Low birthweight	A birthweight of less than 2.5 kg
Membrane folding	The term used to describe the appearance of the dividing amnion (comprising two amnion layers) in a monochorionic pregnancy resulting from a discrepancy in the intra-amniotic pressure between the two amniotic sacs
Monochorionic	Twins or triplets that share a placenta and have the potential for shared circulations
Monochorionic monoamniotic	Twins or triplets that share a placenta and have interconnected circulations and are in the same amniotic sac
Monochorionic diamniotic	Twins that share a placenta and a single chorionic sac but have separate amniotic sacs
Morbidity rate	The number of cases of a nonfatal condition within a specific time (usually a year). It can also refer to the percentage of people with a particular condition in a defined population
Mortality rate	The proportion of a population that dies within a particular period of time (often expressed as a certain number per 1000 people)
Multiple pregnancy	A pregnancy with more than one fetus

Multi-gravid	An adjective indicating that a woman is pregnant for the second or subsequent occasion
Neonate	A baby aged up to 28 days
Neurodevelopment	The development of the nervous system
Nuchal translucency	The fluid-filled space at the back of the unborn baby's neck (between the spine and skin). Its thickness is measured by ultrasound: the larger the measurement, the greater the risk of certain congenital abnormalities, especially Down's syndrome
Obesity	A body mass index of 30 mg/kg^2 or more
Offer birth	The process of offering a woman elective early birth (through induction of labour or caesarean section)
Perinatal	Usually defined as a period from 24 weeks of gestation to 7 days after birth
Placental abruption	Partial or complete separation of the placenta before the baby is born
Pre-eclampsia	New hypertension presenting after 20 weeks of pregnancy with significant proteinuria (more than 300 mg in a 24-hour urine collection or more than 30 mg/mmol in a spot urinary protein:creatinine ratio sample (see 'Hypertension in pregnancy', NICE clinical guideline 107[20])
Prematurity	A term relating to birth of a baby before 37 weeks of gestation. Also referred to as preterm
Preterm birth or delivery	A birth occurring before 37 weeks of gestation
Primary care	Care in the community
Progesterone	A steroid hormone involved in the female menstrual cycle
Prognosis	Likely eventual outcome before it has occurred
Prophylaxis	A measure taken to prevent health problems
Psychological wellbeing	Good mental health
Proteinuria	Protein in the urine
Pulsatility index	A measure of the variability of blood velocity in a vessel
Quadruple screening test	Second trimester test to calculate the risk of Down's syndrome using four tests in combination together with the woman's age; usually based on the measurement of alpha-fetoprotein (AFP), unconjugated oestriol (uE3), free beta human chorionic gonadotrophin (f-beta-hCG; or total hCG) and inhibin-A. From the Fetal Anomaly Screening Programme (FASP) glossary (http://www.screening.nhs.uk/glossary)
Resistance index	Used in the assessment of doppler velocity waveforms. Also known as the Pourcelot index
Respiratory distress syndrome	A condition of newborn babies associated with immature lungs
Retroverted uterus	A uterus that is angled backwards towards the sacrum in the pelvis (instead of forwards towards the symphysis pubis)

Routine (untargeted)	A practice that is offered to all (rather than to a selected or targeted subpopulation)
Secondary care	Hospital-based care
Screening test	A test applied to a population (for example all pregnant women) to identify those at greater risk of having a particular condition
Selective fetal reduction	Reduction of the number of living fetuses in a multiple pregnancy by pharmacologically inducing cardiac arrest in a selected fetus or fetuses
Single fetal death	Spontaneous death of one fetus in a multiple pregnancy. Also known as single fetal demise
Singleton pregnancy	A pregnancy with one fetus or baby
Small for gestational age	A baby's size being below a specific threshold (for example 5th or 10th centile) for a given biometric parameter (such as ultrasound measurements or birthweight) for a given gestational age
Spontaneous preterm birth	Nonoperative vaginal birth before 37 weeks of gestation
Spontaneous vaginal birth	Nonoperative vaginal birth
Stillbirth	A baby born dead at 24 weeks of gestation or later
Subspecialist services	See Tertiary level fetal medicine centre
Specialist obstetrician	An obstetrician with a special interest, experience and knowledge of managing multiple pregnancies, and who works regularly with women with multiple pregnancies
Specialist midwife	A midwife with a special interest, experience and knowledge of managing multiple pregnancies, and who works regularly with women with multiple pregnancies
Symphysis–fundal height	The distance in centimetres from the top of the pregnant woman's symphysis pubis (the front part of the pelvis) to the top of the pregnant uterus (fundus). Assessed clinically as part of abdominal palpation
Term	The gestational age at which a baby is normally due. Defined as 37 weeks 0 days to 42 weeks 6 days
Tertiary level fetal medicine centre	A regionally commissioned tertiary fetal medicine centre (a centre with the experience and expertise for management of complicated twin and triplet pregnancies). Also referred to as subspecialist services
Tocolytic	A drug used to suppress preterm labour
T sign	In a monochorionic pregnancy, the ultrasound appearance of the dividing membrane (comprising two amnions) where it is attached to the uterine wall
Transabdominal	Used in connection with ultrasound examination in pregnancy where scanning takes place through the woman's abdomen
Transvaginal	Used in connection with ultrasound examination in pregnancy where scanning takes place through the woman's vagina
Trichorionic	Triplets that each have a separate placenta
Triamniotic	Triplets that each have a separate amniotic sac

Trimester	One of the three periods lasting approximately 3 months into which pregnancy is conventionally divided. The first trimester lasts up to 13 weeks 6 days, the second trimester is from 14 weeks 0 days to 27 weeks 6 days and the third trimester is from 28 weeks 0 days until birth
Triple test	Second trimester test taken between 15 and 20 weeks of pregnancy to calculate the risk of Down's syndrome in the fetus. Uses three tests in combination together with the woman's age and gestation of pregnancy; usually based on the measurement of alpha-fetoprotein (AFP), unconjugated oestriol (uE3) and human chorionic gonadotrophin (hCG). From the Fetal Anomoly Screening Programme (FASP) glossary (http://www.screening.nhs.uk/glossary)
Trisomy 21	A genetic condition in which an individual has 47 chromosomes in the nucleus of cells instead of the usual 46. Also referred to as Down's syndrome
True negative	Where a negative screening test result is obtained in an individual who does not have the target condition
True positive	Where a positive screening test result is obtained in an individual who has the target condition
Twin-to-twin transfusion syndrome	See Feto-fetal transfusion syndrome
Uncomplicated pregnancy	A pregnancy in the absence of maternal and fetal complications that are associated with twin and triplet pregnancies (see also Complicated pregnancy)
Ultrasonographer	A healthcare professional trained to perform and interpret ultrasound examinations
Ultrasound	The use of ultrasonic waves to produce an image of the fetus or fetuses in the womb
Umbilical artery Doppler scan	An ultrasound examination technique to estimate blood flow in the umbilical artery
Urinalysis	A series of tests performed on urine in a clinical setting (rather than in a laboratory), usually comprising testing for protein, glucose, red blood cells and white blood cells
Zygosity	The number of fertilised eggs that resulted in a multiple pregnancy. If one egg is fertilised and divides into two embryos the pregnancy is described as monozygous, whereas if two eggs are fertilised and result in separate embryos the pregnancy is described as dizygous

Health economics terms

Cost consequence analysis	A form of economic evaluation where the costs and consequences of two or more interventions are compared and the consequences are reported separately from costs
Cost effectiveness analysis	A form of economic evaluation in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (for example life-years gained, deaths avoided, heart attacks avoided or cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness

Cost minimisation analysis	A form of economic evaluation that compares the costs of alternative interventions that have equal effects
Cost of illness study	A study that measures the economic burden of a disease or diseases and estimates the maximum amount that could potentially be saved or gained if a disease was eradicated
Cost utility analysis	A form of cost-effectiveness analysis in which the units of effectiveness are quality adjusted life years (QALYs)
Decision(-analytic) model or technique	A model of how decisions are or should be made. This could be one of several models or techniques used to help people to make better decisions (for example when considering the trade-off between costs, benefits and harms of diagnostic tests or interventions)
Decision tree	A method for helping people to make better decisions in situations of uncertainty. It illustrates the decision as a succession of possible actions and outcomes. It consists of the probabilities, costs and health consequences associated with each option. The overall effectiveness or cost effectiveness of different actions can then be compared
Discounting	Costs, and perhaps benefits, incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present
Dominate (in cost effectiveness analysis)	A term used in health economics when a treatment option is both more clinically effective and less costly than an alternative option. This treatment is said to 'dominate' the less effective and more costly option
Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and their consequences
Equity	Fair distribution of resources or benefits
Health-related quality of life	A combination of a person's physical, mental and social wellbeing; not merely the absence of disease
Incremental cost-effectiveness ratio	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest
Markov modelling	A decision-analytic technique that characterises the prognosis of a cohort of patients by assigning them to a fixed number of health states and then models transitions among health states
Model input	Information required for economic modelling. For clinical guidelines, this may include information about prognosis, adverse effects, quality of life, resource use or costs
Net benefit estimate	An estimate of the amount of money remaining after all payments made are subtracted from all payments received. This is a source of information used in the economic evidence profile for a clinical guideline
Opportunity cost	The opportunity cost of investing in a healthcare intervention is the other healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention

Quality adjusted life year	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost–utility analysis
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations
One-way sensitivity analysis (univariate analysis)	Each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study
Probabilistic sensitivity analysis	Probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example Monte Carlo simulation)

A general glossary, including technical terms related to guideline development, is available on the NICE website (see http://www.nice.org.uk/website/glossary/).

Appendix A Scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Multiple pregnancy: the management of twin and triplet pregnancies in the antenatal period

1.1 Short title

Multiple pregnancy

2 The remit

The Department of Health has asked NICE: 'to prepare a clinical guideline on the management of multiple pregnancy'.

3 Clinical need for the guideline

3.1 Epidemiology

a) In England and Wales, multiple births were recorded in 15.3 per 1000 maternities in 2007 compared with 9.8 in 1980. The increased incidence of multiple births is mainly due to the introduction of assisted reproduction techniques (including in vitro fertilisation [IVF]), but increased maternal age at conception is also a contributing factor. Multiple births currently account for 3% of all live births; 24% of all IVF pregnancies are multiple pregnancies.

b) Multiple pregnancy is associated with increased risks for the mother and babies. The mother is at increased risk of hypertensive disorders, anaemia, gestational diabetes, haemorrhage, preterm labour and operative delivery (including caesarean section). The risk of pre-eclampsia for women with twin pregnancies is almost three times that for singleton pregnancies. The risk for triplet pregnancies is increased nine times. The maternal death rate associated with multiple births is 2.5 times that for singleton births.

c) Risks to babies include low birthweight and immaturity needing admission to a neonatal intensive care unit, congenital malformations, cerebral palsy, and impaired physical and cognitive development. The stillbirth rate for twin births is 2.5 times that for singleton births, and the stillbirth rate for triplet and higher-order births is 3.1 times that for singleton births. The neonatal death rate for twin births is 6.7 times that for singleton births, and the neonatal death rate for triplet and higher-order births is 14.8 times that for singleton births.

d) Among babies of multiple pregnancies, 66% percent of unexplained stillbirths are associated with a birthweight of less than the tenth centile (based on gestational age); the corresponding figure for singleton births is 39%. Immaturity accounts for 65% of neonatal deaths among babies of multiple pregnancies compared with 43% for singleton births.

e) Risks to babies of multiple pregnancies vary according to the zygosity and chorionicity of the pregnancy. Monozygotic (identical) twins (arising from a single embryo which has split into two) can share a placenta (monochorionic twins) or have separate placentas (dichorionic twins). Dizygotic (non-identical) twins (arising from the fertilisation of two separate eggs) always have separate placentas. Combinations of shared and separate placentas can occur in higher-order multiple pregnancies. Some risks associated with multiple pregnancy (for example, congenital malformations and cerebral palsy) occur more frequently when babies share a placenta. Twin-to-twin transfusion syndrome (also known as TTTS) is a complication that occurs only if babies share a placenta. Twin-to-twin transfusion syndrome accounts for about 21% of stillbirths among babies of multiple pregnancies. IVF usually results in dizygotic twins. IVF pregnancies may have a slightly increased risk of monochorionicity than found in spontaneous pregnancies.

3.2 Current practice

a) The number of fetuses in a multiple pregnancy and whether or not a placenta is shared (judged by how many placentae are seen at the first trimester ultrasound) affects the level of risk for a mother and her babies. Therefore the quality and timing of ultrasound used to establish the number of fetuses present and their chorionicity is crucial. Variations in practice have an important influence on how a woman is cared for during pregnancy and hence on its outcome.

b) Screening for chromosomal and structural abnormalities takes longer and is more complex for multiple pregnancies so adequate time and skills are needed to do this effectively. The specialist knowledge and time needed for effective screening is not always available in routine NHS antenatal care settings.

c) Because they have an increased risk of complications, women with multiple pregnancies need more monitoring and more frequent antenatal visits than women with singleton pregnancies. Women with quadruplet and higher-order pregnancies need subspecialist care by a maternal–fetal medicine specialist. Pregnancies in which babies share a placenta (monochorionic) may be associated with complications, including twin-to-twin transfusion syndrome, that necessitate referral to a specialist fetal medicine unit. There is recent clinical guidance from the Royal College of Obstetricians and Gynaecologists for the management of monochorionic twin pregnancies[1]. Multiple pregnancies in which babies have separate placentas may also be associated with serious complications, but are usually managed in non-specialist hospital antenatal clinics.

d) 'Antenatal care' (NICE clinical guideline 62) does not cover the frequency and timing of antenatal care visits for women with multiple pregnancies, what should be done at each visit (that is, frequency of maternal blood pressure measurement, urinalysis and, most importantly, ultrasound scans), and what additional risk factors need to be monitored. These need to be addressed.

e) There is variation in the availability of specialist services throughout England and Wales. Not all women with multiple pregnancies are cared for in dedicated settings such as `twin clinics' or by multidisciplinary teams of healthcare professionals and this may lead to higher than necessary rates of assisted birth and caesarean section and the possible lack of appropriate neonatal risk assessment prior to birth.

4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

- All women confirmed as having a twin or triplet pregnancy (dichorionic or monochorionic) by routine ultrasound.
- All women confirmed as having monochorionic pregnancy unless the development of twin-to-twin transfusion syndrome is suspected.

1 'Management of monochorionic twin pregnancy' Royal College of Obstetricians and Gynaecologists Green-top Guideline 51 (December 2008).

4.1.2 Groups that will not be covered

a) Women with confirmed monochorionicity and suspected twin-to-twin transfusion syndrome. Such women require subspecialist maternal–fetal medicine care available in tertiary care

b) Women with a quadruplet or higher-order pregnancy. Such women need subspecialist care usually available in tertiary care.

4.2 Healthcare setting

a) All settings that routinely provide NHS antenatal care.

4.3 Clinical management

4.3.1 Key clinical issues that will be covered

The guideline will cover additional care for twin and triplet pregnancies above that routinely offered to all women during pregnancy. This will cover:

a) The determination of gestational age and chorionicity.

b) Timing and additional requirements for structural and chromosomal abnormality screening, including the use of nuchal translucency (and other tests) in the identification of monochorionic pregnancies at risk of twin-to-twin transfusion syndrome.

c) Schedule of antenatal care visits (when they should take place and what should be done at each visit) and additional factors to be monitored, including risk of spontaneous preterm labour (such as cervical length screening), discordant fetal growth and co-twin death.

d) The clinical effectiveness and cost effectiveness of any additional tests and interventions (for example, bed rest and routine antenatal steroids) over and above those routinely offered to pregnant women.

e) Indications for referral to subspecialist services, for example development of twin-to-twin transfusion syndrome.

f) Timing of birth for dichorionic and monochorionic pregnancy (excluding twin-to-twin transfusion syndrome).

g) Information that should be offered to women with twin and triplet pregnancies during the antenatal period for both their current care and for postnatal preparation, for example advice about diet and supplements.

4.3.2 Clinical issues that will not be covered

a) Embryo reduction and fetal implantation, including counselling for multiple conception.

b) Management of monochorionic (shared placenta) twin or triplet pregnancies in the presence of twin-to-twin transfusion syndrome.

c) Management of specific conditions associated with twin and triplet pregnancies once these conditions have been diagnosed (for example, hypertension in pregnancy and diabetes in pregnancy).

d) Intrapartum care for twin and triplet pregnancies, including mode of delivery and place of birth.

e) Postnatal care for twin and triplet births.

4.4 Main outcomes

a) Maternal morbidity during pregnancy and after birth (with assessment to include quality of life measures).

b) Maternal mortality during pregnancy and after birth (with assessment to include quality of life measures).

c) Perinatal morbidity (with assessment to include quality of life measures).

d) Perinatal mortality.

e) In utero and postnatal transfer rates for specialist neonatal care

f) Maternal satisfaction relating to the provision of antenatal care.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions related to aspects of care not covered in ‘Antenatal care’ (NICE clinical guideline 62). A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually only be from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see ‘Further information’).

Specific issues for this guideline may cover place of care as well as the specific interventions of an enhanced service for multiple pregnancy.

4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing

The development of the guideline recommendations will begin in October 2009.

5 Related NICE guidance

5.1.1 NICE guidance to be updated

None.

5.1.2 NICE guidance to be incorporated

None.

5.1.3 Other related NICE guidance

- Induction of labour. NICE clinical guideline 70 (2008). Available from www.nice.org.uk/CG70
- Diabetes in pregnancy. NICE clinical guideline 63 (2008). Available from www.nice.org.uk/CG63
- Antenatal care. NICE clinical guideline 62 (2008). Available from www.nice.org.uk/CG62
- Maternal and child nutrition. NICE public health guidance 11 (2008). www.nice.org.uk/PH11
- Intrapartum care. NICE clinical guideline 55 (2007). Available from www.nice.org.uk/CG55
- Antenatal and postnatal mental health. NICE clinical guideline 45 (2007). www.nice.org.uk/CG45
- Postnatal care. NICE clinical guideline 37 (2006). Available from www.nice.org.uk/CG37
- Caesarean section. NICE clinical guideline 13 (2004). Available from www.nice.org.uk/CG13
- Fertility. NICE clinical guideline 11 (2004). Available from www.nice.org.uk/CG11

6 Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS'
- 'The guidelines manual'

These are available from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Appendix B Declarations of interest

All GDG members' interests were recorded on declaration forms provided by NICE. The form covered consultancies, fee-paid work, shareholdings, fellowships and support from the healthcare industry. GDG members' interests are listed in this appendix. No material conflicts of interest were identified.

This appendix includes all interests declared on or before 20 September 2011.

Table B.1 GDG members' declarations of interest

GDG member	Interest
Jane Anderson	No interests declared
Abhijit Bhattacharyya	**Personal pecuniary interests**: previously held shares in GlaxoSmithKline (sold before the first GDG meeting)
	Personal non-pecuniary interests: edits 'Emma's Diary' for the Royal College of General Practitioners (published by TNT Post)
Sandra Bosman	**Personal non-pecuniary interests**: honorary consultant for the Twins and Multiple Births Association (TAMBA); founder of More Than One
Leanne Bricker	**Personal non-pecuniary interests**: member of and reviewer for Cochrane Pregnancy and Childbirth Group; co-lead for multiple pregnancy service, Liverpool Women's NHS Foundation Trust; site investigator for The Twin Birth Study (international multicentre randomised controlled trial (RCT) of planned vaginal birth versus planned caesarean section for twin pregnancies at 32–38 weeks of gestation) funded by the Canadian Institutes of Health Research, and for the First-Trimester Screening for TTTS Study (multicentre prospective observational study) funded by Wellbeing of Women and the National Institute of Health Research
Jane Denton	**Personal non-pecuniary interests**: director of the Multiple Births Foundation (MBF) with interests in developing and implementing high-standard care for multiple births and improving professional understanding of the best management for multiple pregnancy and provision of care for women; seconded to the Royal College of Nursing as adviser for women's health and midwifery from October 2010; elected to the Board of the International Society for Twin Studies with effect from January 2011; co-investigator on an application submitted to the National Institute for Health Research for research on multiple birth families; in discussion with Quadrille Publishing about co-authoring a book on multiple pregnancy
Jane Hawdon	**Personal non-pecuniary interests**: chair of the Breast Feeding Manifesto Coalition; member of the board of trustees, Bliss
Mark Kilby	**Personal pecuniary interests**: medicolegal expert witness giving opinions for claimants and defendants (sometimes in relation to management of monochorionic twin pregnancies); funded by the Buenos Aires Society of Obstetrics and Gynaecology, Argentina, to attend meetings relating to management of multiple pregnancies
	Non-personal pecuniary interests: hospital department sponsored by

GDG member	Interest
	Siemens' ultrasound Europe to act as a reference centre and test new software/hardware; principal investigator on a project funded by Wellbeing of Women to investigate screening tests for the detection of twin-to-twin transfusion syndrome (TTTS)
	Personal non-pecuniary interests: asked by TAMBA to produce a patient-friendly version of the RCOG guideline on the management of monochorionic twin pregnancy; Visiting Aw Boon professor at University of Hong Kong (giving a series of seminars and lectures, including the scientific basis and management of feto-fetal transfusion syndrome [FFTS]); adviser to Multiple Birth Foundation and TAMBA; in discussion with Quadrille Publishing about co-authoring a book on multiple pregnancy; editor of Journal of Ultrasound in Obstetrics and Gynaecology; president elect of the British Maternal and Fetal Medicine Society
Frances Martin	No interests declared
Kirstie McKenzie-McHarg	**Personal non-pecuniary interests**: encouraged to apply to join GDG by the Birth Trauma Association; asked to provide psychological support to a multiple pregnancy clinic within South Warwickshire General Hospitals NHS Foundation Trust
Manjit Randhawa	**Personal non-pecuniary interests**: matron for antenatal ward and high-risk midwifery teams; involved in antenatal classes for twin pregnancies; involved in updating guidelines at Guy's and St Thomas' Foundation Trust Hospital
Baskaran Thilaganathan	**Personal pecuniary interests**: holds a patent relating to first-trimester screening tests for pre-eclampsia; previously held a patent for computer-assisted nuchal translucency measurement by ultrasound (patent withdrawn in 2008)
	Personal non-pecuniary interests: chair of the RCOG meetings committee; member of scientific and education boards of the International Society of Ultrasound in Obstetrics and Gynaecology; editor in chief of Ultrasound in Obstetrics and Gynaecology

Table B.2 NCC-WCH staff members' declarations of interest

NCC-WCH staff	Interest
Khalid Ashfaq	No interests declared
Ella Fields	No interests declared
Maryam Gholitabar	No interests declared
David James	No interests declared
Paul Jacklin	No interests declared
Anwar Jilani	No interests declared
Rosalind Lai	No interests declared
Gemma Malin	No interests declared
Moira Mugglestone	No interests declared
Leo Nherera	No interests declared
Cristina Visintin	No interests declared
Martin Whittle	No interests declared

Appendix C Registered stakeholder organisations

A Little Wish

Antenatal Screening Wales

Association for Improvements in Maternity Services (AIMS)

Association of Breastfeeding Mothers

Association of British Health-Care Industries

Association of Catholic Nurses of England and Wales

Barnsley Hospital NHS Foundation Trust

Birmingham Women's NHS Trust

Birth Trauma Association

BLISS - the premature baby charity

Breastfeeding Network, The

Brighton and Sussex University Hospitals Trust

British Association for Counselling and Psychotherapy

British Medical Association (BMA)

British Maternal and Fetal Medicine Society (BMFMS)

BMJ

British National Formulary (BNF)

British Psychological Society

Brook London

Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)

Care Quality Commission (CQC)

Central Area of North Wales NHS Trust

Central Lancashire PCT

Centre For Fetal Care

Chartered Physiotherapists Promoting Continence (CPPC)

Chesterfield Royal Hospital NHS Trust

City Hospitals NHS Trust

Cleft Lip and Palate Association

Cochrane Pregnancy & Childbirth Group

Confidential Enquiry into Maternal & Child Health (CEMACH)

Connecting for Health

Cytyc UK Limited

Department for Communities and Local Government

Department of Health

Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)

Department of Health, Social Services & Public Safety, Northern Ireland (DHSSPSNI)

Derbyshire Mental Health Services NHS Trust

Evidence based Midwifery Network

Ferring Pharmaceuticals Ltd

Foundation for the Study of Infant Deaths

GE Healthcare

George Eliot Hospital Trust

Gloucestershire Hospitals NHS Trust

Gloucestershire LINk

Gloucestershire PCT

Great Western Hospitals NHS Foundation Trust

Guys and St Thomas NHS Foundation Trust

Gwent Healthcare NHS Trust

Harrogate and District NHS Foundation Trust

Healthcare Improvement Scotland

Healthcare Quality Improvement Partnership

Hologic

Homerton University Hospital NHS Foundation Trust

Human Fertilisation and Embryology Authority (HFEA)

Huntleigh

Imperial College Healthcare NHS Trust

Independent Midwives UK

Innermost Secrets Ltd

Institute of Biomedical Science

King's College London

Kingston Hospital NHS Trust

La Leche League GB

Leeds PCT

Liverpool Women's NHS Foundation Trust

Liverpool Community Health

Lothian University Hospitals Trust

Luton & Dunstable Hospital NHS Foundation Trust

Maternal Health and Reproduction Research Group

Maternity Health Links

Medicines and Healthcare Products Regulatory Agency (MHRA)

Mid and West Regional Maternity Service Liaison Committee (MSLC)

MIDIRS (Midwives Information & Resource Service)

Ministry of Defence (MoD)

Miscarriage Association, The

Mother and Infant Research Unit

Multiple Births Foundation

National Childbirth Trust (NCT)

National Forum of LSA Midwifery Officers (UK)

National Maternity Support Foundation

National Patient Safety Agency (NPSA)

National Perinatal Epidemiology Unit

National Treatment Agency for Substance Misuse

National Collaborating Centre - Cancer

National Collaborating Centre – Mental Health

National Collaborating Centre – National Clinical Guideline Centre (NCGC)

National Collaborating Centre - Women's and Children's Health

NETSCC (NIHR Evaluation, Trials and Studies Coordinating Centre), Health Technology Assessment

Newcastle Upon Tyne Hospitals NHS Foundation Trust

NHS Bedfordshire

NHS Clinical Knowledge Summaries Service (SCHIN)

NHS Direct

NHS Fetal Anomaly Screening Programme

NHS Forth Valley

NHS Islington

NHS Kirklees

NHS Plus

NHS Sheffield

North Somerset PCT

North Tees and Hartlepool Acute Trust

North Tees & Hartlepool NHS Foundation Trust

NHS Western Cheshire

North West London Perinatal Network

North Yorkshire and York PCT

Northumbria Healthcare NHS Foundation Trust

Nottingham University Hospitals NHS Trust

Obstetric Anaesthetists Association

Oxfordshire Maternity Services Liaison Committee

Patients Council

PERIGON Healthcare Ltd

Perinatal Institute

Picker Institute Europe

Poole and Bournemouth PCT

Positively Pregnant

Programme Development Group in Maternal and Child Nutrition

Public Health Wales

Queen Mary's Hospital NHS Trust (Sidcup)

Regional Maternity Survey Office

Rotherham NHS Foundation Trust

Royal College of Anaesthetists

Royal College of General Practitioners

Royal College of General Practitioners Wales

Royal College of Midwives

Royal College of Nursing

Royal College of Obstetricians and Gynaecologists

Royal College of Paediatrics and Child Health

Royal College of Pathologists

Royal College of Physicians London

Royal College of Psychiatrists

Royal College of Radiologists

Royal College of Surgeons of England

Royal Cornwall Hospitals Trust

Royal Pharmaceutical Society of Great Britain

Royal Society of Medicine

Royal United Hospital

Sands, the Stillbirth & neonatal death charity

Sandwell PCT

Scottish Intercollegiate Guidelines Network (SIGN)

Sheffield PCT

Sheffield Teaching Hospitals NHS Foundation Trust

Social Care Institute for Excellence (SCIE)

Society for Endocrinology

South Devon Acute Trust

South Tees Hospitals NHS Trust

Southampton University Hospitals NHS Trust

St Marys Hospital

Tenscare Ltd

The Society and College of Radiographers

Tiny Tickers

Twins & Multiple Births Association (TAMBA)

UCLH NHS Foundation Trust

UK Clinical Pharmacy Association (UKCPA)

UK National Screening Committee

United Leeds Teaching Hospitals NHS Trust

United Lincolnshire Hospitals NHS Trust

University of Leicester (The Infant Mortality & Morbidity Studies)

University of Liverpool

University of Nottingham

VBAC Information and Support

Verity - The PCOS Self Help Group

Vifor Pharma UK Ltd

Walsall PCT

Wellbeing of Women

Welsh Assembly Government

Welsh Scientific Advisory Committee (WSAC)

West Hertfordshire PCT & East and North Hertfordshire PCT

West Midlands SHA

Western Cheshire Primary Care Trust

Western Health and Social Care Trust

Women’s Health and Reproduction Research Group at King's College London

York Teaching Hospital NHS Foundation Trust

Appendix D Review questions

Chapter 4 Determining gestational age and chorionicity

- What are the optimal ultrasound measurements to determine gestational age in multiple pregnancy?
- What is the optimal method to determine chorionicity in multiple pregnancies?

Chapter 5 General care

- Is there benefit in giving women with multiple pregnancy additional information and emotional support during the antenatal period?
- 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?
- Is nutritional advice specific to multiple pregnancies effective in improving maternal and fetal health and wellbeing?
- Do specialist multiple pregnancy clinics improve outcomes in twin and triplet pregnancies?

Chapter 6 Fetal complications

- When and how should screening be used to identify chromosomal abnormalities in multiple pregnancy?
- When and how should screening be used to identify structural abnormalities in multiple pregnancy?
- When and how should screening be used to identify feto-fetal transfusion syndrome in multiple pregnancy?
- What is the optimal screening programme to detect intrauterine growth restriction?

Chapter 7 Maternal complications

- What is the optimal screening programme to detect hypertension in multiple pregnancy in the antenatal period?

Chapter 8 Preterm birth

- What is the optimal screening programme to predict the risks of spontaneous preterm delivery?
- What interventions are effective in preventing spontaneous preterm delivery in multiple pregnancy, including bed rest, progesterone and cervical cerclage?
- Is routine/elective antenatal corticosteroid prophylaxis effective in reducing perinatal morbidity, including neonatal respiratory distress syndrome, necrotising colitis and intravenous haemorrhage, in multiple pregnancy?

Chapter 9 Indications for referral to a tertiary level fetal medicine centre

- What are the clinical indications for referral to subspecialist services?

Chapter 10 Timing of birth

- What is the optimal timing of delivery in women with uncomplicated multiple pregnancies?

Appendices E to J

The following appendices are presented as separate files:

- Appendix E – Review protocols
- Appendix F – Search strategies
- Appendix G – Excluded studies
- Appendix H – Evidence tables
- Appendix I – Forest plots
- Appendix J – GRADE findings