



Royal College of
Obstetricians &
Gynaecologists

Amniocentesis and Chorionic Villus Sampling

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Amniocentesis and Chorionic Villus Sampling

This is the fourth edition of this guideline, which was previously published in October 1996, February 2000 and January 2005.

1. Aim

It is estimated that around 5% of the pregnant population (approximately 30 000 women per annum in the UK) are offered a choice of invasive prenatal diagnostic tests (most commonly amniocentesis or chorionic villus sampling). The type of diagnostic test available and offered is likely to vary depending upon the timing of any initial screening test that is performed. The aim of this guideline is to set a series of evidence-based standards to ensure a high level and consistency of practice in the provision and performance of amniocentesis and chorionic villus sampling.

2. Background and introduction

Amniocentesis is the most common invasive prenatal diagnostic procedure undertaken in the UK. Most amniocenteses are performed to obtain amniotic fluid for karyotyping from 15 weeks (15⁺⁰) onwards. Amniocentesis performed before 15 completed weeks of gestation is referred to as 'early amniocentesis'.

Chorionic villus sampling (CVS) is usually performed between 11 (11⁺⁰) and 13 (13⁺⁶) weeks of gestation and involves aspiration or biopsy of placental villi. CVS can be performed using either a transabdominal or a transcervical approach.

3. Identification and assessment of evidence

This RCOG guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines. The Cochrane Library (including the Cochrane Database of Systematic Reviews), DARE, EMBASE, TRIP, Medline and PubMed electronic databases were searched for relevant randomised controlled trials, systematic reviews, meta-analyses and cohort studies. The search was restricted to articles published from 2000 to July 2008. The databases were searched using the relevant MeSH terms, including all subheadings, and this was combined with a keyword search. Search words included 'amniocentesis', 'chorionic villus sampling', 'standards', 'adverse effects' and 'audit' and the search was limited to humans and the English language. The National Library for Health and the National Guidelines Clearing House were also searched for relevant guidelines and reviews.

4. Rates of miscarriage

Women should be informed that the additional risk of miscarriage following amniocentesis is around 1%.

B
B

Women should be informed that the additional risk of miscarriage following CVS may be slightly higher than that of amniocentesis carried out after 15 weeks gestation.

The best estimate of miscarriage risk associated with amniocentesis comes from a randomised trial from Denmark reported in 1986.¹ This study randomised 4606 women at low risk of miscarriage aged 24–35 years to have (or not to have) an amniocentesis carried out using a 20-gauge needle under continuous real-time ultrasound guidance. Most procedures were performed between 16 and 18 weeks of gestation. The amniocentesis group had a loss rate which exceeded the control group by 1%. More than 50% of the amniocenteses were performed by one operator and the remainder by four other operators who were less experienced. The placenta was avoided whenever possible but a transplacental approach was recorded in 15% of cases. Bloodstained amniotic fluid was obtained in 0.5% of cases overall.

Evidence
level 1+

More recently, several large cohort studies have suggested significantly lower procedure-related loss rates after amniocentesis.^{2,3} There is a debate, however, on what should constitute an appropriate control group and what constitutes a true procedure-related loss, particularly in relation to the time interval after the procedure. A recent systematic review estimated total post-amniocentesis pregnancy loss (background and procedure related loss combined) to be 1.9% (95% CI 1.4–2.5).⁴ Practitioners should be aware of these issues and, if quoting procedure-related loss rates lower than 1%, they should carefully evaluate the adequacy of their own follow-up data. There is also increasing evidence that operators who perform procedures frequently have lower miscarriage rates.⁵

Evidence level 1+

There are no published studies comparing CVS with ‘no testing’. Meta-analyses of all randomised trials comparing CVS by any route with second-trimester amniocentesis showed an excess pregnancy loss following CVS.⁶ However, there was only one direct randomised comparison of transabdominal CVS with second-trimester amniocentesis reporting similar total pregnancy loss in the two groups (6.3% compared with 7%).⁷

As previously mentioned, recent uncontrolled cohort series report significantly lower pregnancy losses after CVS as well as after amniocentesis.⁸ However, the potential for bias is considerable in all of these studies and these data may have limited utility in counselling.

Evidence level 2-

Several randomised trials show almost identical miscarriage rates after transcervical CVS compared with the transabdominal approach.^{9,10} Only one trial demonstrated the transabdominal approach to be significantly safer; however, it should be noted that operator experience in the two techniques in this study differed.⁷ Interestingly, meta-analysis comparing transcervical CVS with second-trimester amniocentesis showed amniocentesis to be significantly safer.⁶ Women should be informed that the additional risk of miscarriage following CVS may be higher than that of amniocentesis carried out after 15 weeks of gestation.

Evidence level 1+

5. At what gestation should amniocentesis and CVS be carried out?

Amniocentesis should be performed after 15 (15⁺⁰) weeks of gestation.

A

Amniocentesis before 14 (14⁺⁰) weeks of gestation (early amniocentesis) has a higher fetal loss rate and increased incidence of fetal talipes and respiratory morbidity compared with other procedures.

A

CVS should not be performed before 10 (10⁺⁰) completed weeks of gestation.

D

Early amniocentesis is not a safe alternative to second-trimester amniocentesis because of increased pregnancy loss (7.6% compared with 5.9%; RR 1.29; 95% CI 1.03–1.61). Early amniocentesis has a higher incidence of talipes when compared with CVS (RR 4.61; 95% CI 1.82–11.66).⁶ Early amniocentesis is not recommended.

Evidence level 1+

The association between CVS, oromandibular limb hypoplasia and isolated limb disruption defects has been debated since the issue was first raised in 1991 when a cluster of five babies with limb reduction defects was reported among a series of 289 women undergoing transabdominal CVS between 8 and 9 (9⁺³) weeks.¹¹ A subsequent analysis showed no difference in the rate of this abnormality compared with the population incidence, although the vast majority of procedures were performed after 10 weeks of gestation.¹² Although a few publications subsequently appeared to support this association, most found few, if any, cases of oromandibular limb hypogenesis syndrome and an incidence of limb reduction defects no higher than the background incidence. Despite reassuring reports, most units stopped performing CVS before 10 weeks of gestation and thus most subsequent analyses include later procedures only. Furthermore, CVS before 11 (11⁺⁰) weeks can be technically difficult to perform, owing to a smaller uterus and thinner placenta.

Evidence level 3

6. What consent is required prior to performing amniocentesis or CVS?

Written consent should be obtained prior to performing amniocentesis or CVS.



It is good clinical practice to obtain formal written consent for amniocentesis or CVS before the procedure. Practice should conform to recommendations on consent from the General Medical Council and the RCOG. Use of the Department of Health Consent Form 3 is recommended. Written or oral information should include the reason for offering the invasive procedure, the explanation of the type of cytogenetic results which will become available, processes for any long-term sample storage and quality control. Information should also be provided in relation to:

- national and locally estimated risks of procedure related pregnancy loss
- accuracy and limitations of the particular laboratory test(s) being performed, with information noted on culture failure rates and reporting times
- method of communication of results
- indications for seeking medical advice following the test
- the need for anti-D post procedure if the woman is RhD negative.

A record of the counselling process, including consent, should be clearly recorded in the patient notes.

7. What technique should be used to perform amniocentesis or CVS?

Needle insertion during amniocentesis and transabdominal CVS should be carried out under simultaneous ultrasound visualisation by the practitioner performing the ultrasound guidance.



Transplacental passage of the amniocentesis needle should be avoided unless it provides the only safe access to an adequate pool of liquor.



Maximum outer needle gauge size of 0.9 mm (20-gauge) should be used to perform amniocentesis.



Clinicians should use the CVS technique with which they are competent, using local anaesthesia for transabdominal CVS.



Methods of amniocentesis have been variously described in the literature. A 'blind' procedure involving palpating the outline of the uterus and inserting a needle into a selected spot is no longer an acceptable technique. With 'ultrasound guidance', the contents of the uterus, particularly the position of the placenta and the umbilical cord insertion, are visualised prior to amniocentesis and a suitable entry point on the mother's abdomen noted. The use of real-time ultrasound allows the insertion of the needle under 'continuous ultrasound control' and is the technique of choice.

Evidence level 2+

Continuous visualisation of the needle with ultrasound reduces bloodstaining from 2.4% to 0.8%.¹³ Similar evidence for adopting continuous ultrasound guidance is drawn from other studies^{14,15} and, although most studies used historical controls, the trend of improved outcome, reduced bloodstaining of the amniotic fluid and greater success in obtaining amniotic fluid is apparent.

There are case reports documenting serious fetal trauma caused by an amniocentesis needle, although continuous ultrasound guidance minimises the risk.¹⁶ Continuous guidance is more likely to avoid maternal bowel injury at needle insertion. The current recommendation for 'continuous ultrasound control' rests on the need to avoid 'dry' and 'bloody taps' principally because the presence of blood may interfere with amniocyte culture.

Traditionally, amniocentesis techniques aimed at avoiding the placenta have been adopted; Tabor *et al.* suggested an increased miscarriage rate following placental puncture.¹ However, recent evidence suggests that penetration of the placenta may not be associated with increased complications where continuous ultrasound guidance is used. Three large studies involving over 2000 cases have not demonstrated increased miscarriage rates where the transplacental approach

Evidence level 2+

was used.¹⁷⁻¹⁹ Unfortunately, needle size is only mentioned in one of the studies.¹⁷ In fact, if a clear pool of amniotic fluid can be reached **only** by passage through the placenta then this is the approach of choice. Under these circumstances, placing the needle through the thinnest available part of the placenta is recommended. It is also important to ensure that the placental cord insertion is avoided.

Evidence level 2+

Needle diameter is likely to be important but there are few clinical data upon which to base choice. The study of Tabor *et al.* used a 20-gauge needle (note that in the original report the size of the needle was reported as 18-gauge by mistake).¹ One experimental model comparing 18-, 20- and 22-gauge needles suggested that there was less amniotic fluid flow from the puncture site with smaller gauge needles.²⁰

Some experts recommend particular angles at which the needle should enter the uterus but the data are not robust enough to guide practice.²¹

Amniocentesis generates considerable parental anxiety but most women rate the discomfort as equivalent to that of venepuncture.²² A randomised trial by van Schonbrock *et al.* showed that injection of local anesthetic did not reduce pain scores reported by women undergoing amniocentesis.²²

Evidence level 1+

A recent survey of practice revealed that only 4% of the specialists in the UK use local anesthesia for amniocentesis compared with 98% when transabdominal CVS is performed.²³

Evidence level 3

There is a consensus that CVS, both transabdominal and transcervical, must be performed under continuous ultrasound control. Techniques for transabdominal CVS vary significantly both in the size of the needle used (18-gauge, 20-gauge, double needle 17/19-gauge, double needle 18/21-gauge) and method of aspiration (negative pressure by syringe, negative pressure by vacuum aspirator, biopsy forceps). As there are no published studies comparing clinical outcomes using different techniques, clinicians are advised to use the technique with which they are familiar. The same applies to transcervical CVS; although there is some evidence to support use of small forceps as opposed to aspiration cannulae, the evidence is not strong enough to support change in practice for clinicians familiar with aspiration cannulae.²⁴

Evidence level 1-

8. What is required for training and maintaining good practice in amniocentesis or CVS?

Operators carrying out unsupervised amniocentesis and CVS should be trained to the competencies expected of subspecialty training in maternal and fetal medicine, the RCOG Fetal Medicine Advanced Training Skills Module (ATSM) or other international equivalent.



Clinical skills models, assessment of interaction with patients and supervised procedures should be an integral part of training.



Competency should be maintained by carrying out at least 30 ultrasound guided invasive procedures per annum.



Units and operators should carry out continuous audit of frequencies of multiple insertions, failures, bloody taps and post procedure losses.



Very experienced operators (more than 100 per annum) may have a higher success rate and a lower procedure-related loss rate. Occasional operators who perform a low number of procedures per annum may have increased rates of procedure-related loss.



Further opinion should be sought from a more experienced operator if difficulties are anticipated or encountered.



Expert opinion suggests that an operator's competence should be reviewed where loss rates appear high and audit should certainly occur where they exceed 4/100 consecutive amniocenteses or 8/100 CVS.



Evidence level 2+

Operator experience, as well as technique, may be important. Results from a study in which the majority of amniocenteses were undertaken by a single operator were compared with those of an occasional operator. With the former, success at the first attempt occurred in 94% of amniocenteses, with 3% of bloody taps, compared with 69% and 16%, respectively, for the latter.²⁵ Maternal contamination rates are lower when practitioners perform greater numbers of amniocentesis.²⁶ Studies comparing very experienced practitioners (more than 100 procedures per annum) with less experienced practitioners have shown substantial differences in outcome, with a six- to eight-fold increase in loss rates associated with less experience.^{27,28}

A Medical Research Council (MRC) trial found no clear evidence that over the course of the trial (4 years) increased operator experience improved safety of CVS.²⁹ However, each operator was required to perform at least 30 procedures before participation.

Adequate training and maintenance of skills are important. Ultrasound skills for performing invasive prenatal procedures are greater than those required for the completion of the RCOG specialist training logbook. Specific training in invasive diagnostic procedures will include ultrasound training beyond this level. Best practice requires ultrasound training to the level of the current RCOG subspecialty training in maternal and fetal medicine, ATSM in fetal medicine or equivalent.

Before undertaking procedures on women, consideration should be given to initial training using a clinical skills model. Several suitable models have been constructed and some of these validated.³⁰ Pittini *et al.* used a well-validated educational approach that included examination of patient interactive skills.³¹ They demonstrated improved performance among all levels of trainees but particularly those with the least experience before the training, suggesting an ability to shorten the learning curve. Nizard *et al.* suggest that between 50 and 100 procedures are required to be undertaken before there is no further improvement.³²

Evidence level 2+

Postgraduate training is moving to competence-based assessments rather than adherence to a particular numerical goal and no concrete data exist on the number of supervised prenatal invasive procedures necessary before competence is gained. Amniocentesis and CVS procedures are practical skills and trainees will achieve competence at different rates. Individual centres should agree to a training and assessment process that is open and transparent, and with a clearly responsible trainer. Local deaneries and NHS trust clinical governance systems should have a role in ensuring quality training.

Although it is not currently possible to make evidence-based recommendations on the annual number of procedures required to maintain competency, an arbitrary number of at least 30 ultrasound-guided invasive procedures per annum is reasonable. This number should be feasible in most clinical settings in the UK. Operators performing less than this number should ensure that they have audit processes in place to provide robust evidence of safety.

Competence is best assessed through continuous audit of complications such as 'need for second insertion' and 'miscarriage rate'. The 95% confidence intervals for complications from experienced operators^{1,33} indicate that 'second insertion' may be acceptable in, at most, 7/100 consecutive amniocentesis cases. Pregnancy loss should not exceed 4/100 amniocenteses. Higher numbers of complications may be an unfortunate 'cluster' or consequence of high background risk of miscarriage. Nevertheless, where loss rates exceed these limits, an independent review of the operator's skills should be carried out.

Comparable numbers for CVS are different because of the higher background risk of miscarriage. Also, CVS is often performed in the presence of increased nuchal translucency, cystic hygroma, fetal anomalies or genetic

conditions, most of which are associated with a higher spontaneous miscarriage rate. The Cochrane Review quotes CVS sampling failure between 2.5% and 4.8% and spontaneous miscarriage rate of 3% after trans-abdominal CVS in the Danish trial and 7.9% in the MRC trial.²⁴ If one accepts a 3% sampling failure rate and a 3% pregnancy loss as the 'gold standard', an audit of practice should be carried out when either five sampling failures or eight miscarriages occur in 100 consecutive cases.⁶

Obviously, any such audit should take into account the background risk of miscarriage, which is likely to be significantly higher in the presence of fetal anomaly or subsequently diagnosed abnormal karyotype. All organisations where prenatal invasive procedures are carried out should have robust mechanisms for collecting and monitoring these data. The mechanisms of review should be agreed locally, though national or regional guidance should be developed.

For either procedure, a more experienced operator should be consulted if two attempts at uterine insertion have failed to produce an adequate sample for analysis.

9. What are the clinical considerations when performing amniocentesis or CVS for multiple pregnancy?

It is recommended that, in the case of multiple pregnancies, a CVS or amniocentesis is performed by a specialist who has the expertise to subsequently perform a selective termination of pregnancy if required.



A high level of expertise in ultrasound scanning is essential for operators undertaking amniocentesis or CVS in multiple, dichorionic pregnancies, because uterine contents have to be 'mapped' with great care. This is essential to ensure that separate samples are taken for each fetus and clearly labelled as such.

Labelling is greatly assisted by the presence of obvious fetal abnormality (such as hydrocephalus or heart defect) or discordant fetal gender. However, to minimise the risk of chromosomal abnormality being assigned to the wrong twin, invasive procedures in multiple pregnancy should only be performed by a specialist who is able to proceed to selective termination of pregnancy. It is very unlikely that a specialist would be prepared to carry out a selective termination of pregnancy relying on information provided by a referring doctor, particularly in the absence of clearly identifiable ultrasound appearances.

Most clinicians will use two separate puncture sites when performing amniocentesis or CVS in multiple pregnancies, although there are series using single-entry techniques with low rates of complications.³⁴ Either way, the miscarriage rate is likely to be higher than in singleton pregnancies.³⁵ A recent single-centre study of 311 twin, mid-trimester amniocenteses estimated the attributable pregnancy loss rate at 1/56 (1.8%).³⁶

The role of CVS in dichorionic placentas remains controversial because of a relatively high risk of cross-contamination of chorionic tissue, which may lead to false positive or false negative results. This risk may be minimised if two separate needles are used. Such procedures should be performed only after detailed counselling.

10. What information should women be given about third-trimester amniocentesis?

Women should be informed that third-trimester amniocentesis does not appear to be associated with a significant risk of emergency delivery.



Women should be informed that, compared with mid-trimester procedures, complications including multiple attempts and bloodstained fluid are more common in third-trimester procedures.



Amniocentesis in the third trimester is carried out for a number of indications, most commonly, for late karyotyping and detection of suspected fetal infection in prelabour preterm rupture of the membranes

Evidence level 2+

(PPROM). Much of the literature on the risks of late amniocentesis predates the use of continuous ultrasound-guided amniocentesis. More recent series report more than one attempt in over 5% of samplings and bloodstained fluid in 5–10% of cases.^{37,38} When amniocentesis is carried out in the presence of PPROM, failure rates are higher.³⁹ Serious complications are rare. Two series with 194 and 562 procedures did not describe any emergency deliveries as a result of amniocentesis, while Stark *et al.* suggested a rate of 0.7% for procedure-related delivery.^{37,38,40} A case-control study of 167 matched pairs reported a composite poor outcome (urgent birth, abruption, premature rupture of the membranes and 5-minute Apgar score less than 7) among women undergoing amniocentesis after 32 weeks for lung maturity studies; late amniocentesis resulted in no adverse outcomes compared with one adverse outcome in controls.⁴¹ There is a suggestion that culture failure rates may be higher following third-trimester amniocentesis with a rate of 9.7% reported in the series of O'Donoghue *et al.*⁴²

Evidence
level 2+

11. What are the risks of transmission of infection?

The ultrasound probe should be enclosed in a sterile bag during any invasive prenatal procedure unless suitably audited processes for probe decontamination and gel microbiological surveillance are in place.



Separate sterile gel should be used.



Invasive prenatal procedures should not be carried out without reviewing available bloodborne virus screening tests.



Where women decline screening for bloodborne viruses and are being counselled for prenatal diagnostic procedures, inform and document the potential risk of vertical transmission of infection to the fetus.



Review viral load and treatment regimens prior to invasive prenatal testing in women with HIV and consider delaying the procedure until there is no detectable viral load if the woman is already on treatment.



Consider antiretroviral therapy prior to prenatal invasive procedures in women not yet on treatment for HIV.



Invasive prenatal testing in the first or second trimester can be carried out in women who carry hepatitis B or C. The limitations of the available data should be explained.



Severe sepsis, including maternal death, has been reported following invasive prenatal procedures. The level of risk cannot be quantified as case report literature does not provide denominator information but the risk of severe sepsis is likely to be less than 1/1000 procedures. Infection can be caused by inadvertent puncture of the bowel, skin contaminants or organisms present on the ultrasound probe or gel. The first two sources should be avoidable by standard practices. Decontamination of ultrasound probes between patients is variable and there are practical difficulties in balancing the need for cleaning with prevention of degradation of the probe.⁴³ Ultrasound gel may contain organisms and many departments have mechanisms to minimise the risks including the use of sterile ultrasound gel when performing invasive procedures. Standards for control of infection should conform to those for any invasive diagnostic radiological procedure and are commented on by the Health Care Commission.

Bloodborne viruses constitute both an infection-control risk and a possible risk factor for maternal–fetal transmission. For hepatitis B, individual studies are small but show no evidence of a transmission risk.⁴⁴ Davies *et al.* concluded that the risk of transmission of hepatitis B was very low.⁴⁵ It has been suggested that ‘e’ antigen status may be important and recent evidence shows that maternal viral load is more important for determining the risk of transmission.⁴⁵ There are fewer data on transmission of hepatitis C but, to date, there is currently no evidence that transmission is increased following amniocentesis.^{41,46}

Evidence
level 2+

Most studies examining HIV suggest that invasive testing may be a risk factor in transmission to the fetus and recommend avoidance, although most studies predate the use of antiretroviral drugs.^{47,48} The data are most robust for third-trimester procedures where the relative risk is 4.⁴⁸ Others have suggested that testing earlier in pregnancy is safe provided that retroviral therapy is being used and the maternal viral load is low.⁴⁹ Specialists need to be aware and inform women that the vast majority of evidence is based on amniocentesis and that data on CVS are very limited. Where antiretroviral therapy is used, an Italian study demonstrated no difference in transmission rates between HIV positive women undergoing amniocentesis and those who did not.⁵⁰ A small French study involving women where triple retroviral therapy was instituted did not show an increase in transmissions following amniocentesis.⁵¹ Of 166 procedures in the 81 women receiving highly active antiretroviral therapy, there were no cases of transmission; however, there were significant rates of transmission where no treatment was in place (25%) and where mono or double therapy was used (6.1%).⁵² Whenever possible, procedures should be delayed until treatment has optimised the maternal viral load.

Evidence
level 2+

Where the results of screening for maternal infection are not yet known or the woman has declined such testing then informed consent should include discussion of the risks of vertical transmission of infection. If no HIV test result is available, advise delaying the invasive test and perform a rapid HIV test. If results indicate maternal infection then the risk of transmission should be discussed and consideration given to starting antiretroviral therapy to reduce the viral load prior to the procedure.

11.1 *Rhesus status*

Maternal RhD status should be available or obtained in every case. Prophylaxis with anti-D immunoglobulin must be offered following each procedure in line with national recommendations.⁵³

Evidence
level 1+

12. How should care be organised in providing amniocentesis and CVS?

The scope of this guideline is confined to technical aspects of the two procedures. For the woman and her family, good care in these circumstances encompasses more than the simple performance of a technique. Women facing either procedure are usually anxious and clinicians should bear this in mind.

Hospital trusts and organisations should ensure that the equipment, environment, staff training, arrangements for follow-up and links with related services carrying out pregnancy termination or support for women with diagnosed chromosomal or genetic disease are of sufficient standard. The National Screening Committee provides advice and direction on service organisation for prenatal diagnosis.

13. Auditable standards

- Rate of pregnancy loss at any gestation after a procedure.
- Rate of pregnancy loss less than 24⁺⁰ weeks after a procedure.
- Rate of pregnancy loss within 14 days of procedure.
- Local cytogenetic laboratory culture failure rates for amniocentesis and CVS.
- Proportion of procedures requiring more than one needle insertion.
- Proportion of procedures with failure to obtain an adequate sample.
- Complication rates ('bloody' tap, amniotic fluid leakage).
- Maintenance of a register of invasive diagnostic procedures to facilitate audit. Audit should be performed annually and the results made accessible to patients.
- Rate of anti-D prophylaxis for women who are RhD-negative undergoing amniocentesis or CVS.

14. Areas for further research

- Comparison of safety of different techniques for transabdominal CVS.
- Transmission rates of bloodborne virus following invasive prenatal testing.

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APPENDIX

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Development of RCOG Green-top Guidelines* (available on the RCOG website at www.rcog.org.uk/womens-health/clinical-guidance/development-rcog-green-top-guidelines-policies-and-processes). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated within the appropriate health services.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme. Once adapted for local use, these guidelines are no longer representative of the RCOG.

Classification of evidence levels	Grades of recommendations
1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias	A At least one meta-analysis, systematic reviews or randomised controlled trial rated as 1++ and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias	B A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
1- Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias	C A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
2++ High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal	D Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal	Good practice point
2- Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	<input checked="" type="checkbox"/> Recommended best practice based on the clinical experience of the guideline development group
3 Non-analytical studies; e.g. case reports, case series	
4 Expert opinion	

The first two versions of this guideline were produced by Professor MJ Whittle FRCOG. This guideline was produced on behalf of the Guidelines Committee of the Royal College of Obstetricians and Gynaecologists by **Professor Z Alfirevic FRCOG, Liverpool; Mr SA Walkinshaw FRCOG, Liverpool; and Professor MD Kilby FRCOG, Birmingham.**

It was peer reviewed by the British Medical Ultrasound Society; British Maternal and Fetal Medicine Society; NHS Infectious Diseases in Pregnancy Screening Programme; Antenatal Results and Choices; Mr DT Liu FRCOG, Nottingham; RCOG Consumers' Forum; Genetic Interest Group; Antenatal Screening Wales; Professor CH Rodeck FRCOG, London; Professor AD Cameron FRCOG, Glasgow.

The Guidelines Committee lead reviewers were Dr P Owen MRCOG and Dr SK Surendran FRCOG.

The final version is the responsibility of the Guidelines Committee of the RCOG.

The guideline review process will commence in 2013
unless otherwise indicated

DISCLAIMER

The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available within the appropriate health services.

This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.