



Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

Green-top Guideline No. 44

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Preterm Prelabour Rupture of Membranes

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This is the first edition of this guideline, which was reviewed in 2010 and has received minor amendments to section 4 and section 5.

1. Aim

The aim of this guideline is to make recommendations relating to the diagnosis, investigation and management of preterm prelabour rupture of membranes (PPROM). The guideline evaluates various antenatal tests in helping to predict the fetus at risk from intrauterine infection. The role of prophylactic antibiotics, steroids and tocolytic agents and the optimum gestation to deliver women with pregnancies complicated by PPRM is examined and recommendations are provided based on published evidence.

2. Background

PPROM complicates only 2% of pregnancies but is associated with 40% of preterm deliveries and can result in significant neonatal morbidity and mortality.¹⁻³ The three causes of neonatal death associated with PPRM are prematurity, sepsis and pulmonary hypoplasia. Women with intrauterine infection deliver earlier than non-infected women and infants born with sepsis have a mortality four times higher than those without sepsis.⁴ In addition, there are maternal risks associated with chorioamnionitis.

There is evidence demonstrating an association between ascending infection from the lower genital tract and PPRM. In patients with PPRM, about one-third of pregnancies have positive amniotic fluid cultures^{5,6} and studies have shown that bacteria have the ability to cross intact membranes.^{7,8}

3. Identification and assessment of evidence

This guideline was developed using the standard methodology for producing RCOG Green-top Guidelines. The Cochrane Library and Medline were searched for the following terms in the title or abstract: 'preterm prelabour rupture of membranes', 'amnioinfusion', 'sealing amniotic membranes', 'intraamniotic infection', 'Nitrazine', 'amniocentesis', 'antenatal corticosteroids' and 'tocolytics'. Previous guidelines on this subject were obtained using the sites recommended in the RCOG Clinical Governance Advice No. 1c.⁹

The recommendations given in this guideline have been graded according to the guidance for the development of RCOG Green-top Guidelines.

4. How is the diagnosis of PPRM best achieved?

The diagnosis of spontaneous rupture of the membranes is best achieved by maternal history followed by a sterile speculum examination.

B

Ultrasound examination is useful in some cases to help confirm the diagnosis.

B

The presence of a pool of fluid in the vagina at sterile speculum examination is highly suggestive of amniorrhexis. A range of tests have been used to confirm membrane rupture; the most widely used has been the Nitrazine test, which detects pH change.^{10,11} Other tests which have been used include microscopic examination of the vaginal fluid for the characteristic ferning of the crystalline pattern of dried amniotic fluid owing to its sodium chloride and protein content,^{12,13} examination for lanugo hair¹² and fetal epithelial cells stained with Nile blue.¹⁴

A study evaluating the various tests in the diagnosis of membrane rupture examined 100 consecutive women in labour with either intact or ruptured membranes.¹⁵ The best results were obtained with the Nitrazine and ferning tests, with a sensitivity of 90%. The false-positive rate was 17% for the Nitrazine test, owing to contamination with urine, blood or semen, and 6% for the ferning test, owing to contamination with cervical mucus. A similar sensitivity and false-positive rate was achieved by obtaining a history of rapid passage of fluid from the vagina. Ultrasound examination demonstrating oligohydramnios is also used to help confirm the diagnosis of spontaneous rupture of the membranes.¹⁶⁻¹⁹ AmniSure® (AmniSure® International LLC, Boston, MA, USA), a rapid immunoassay, has been shown to be accurate in the diagnosis of ruptured membranes with a sensitivity and specificity of 98.9% and 100%, respectively.²⁰

Evidence level IIb

The diagnosis is made by a history suggestive of spontaneous rupture of membranes followed by a sterile speculum examination demonstrating pooling of fluid in the posterior vaginal fornix; a Nitrazine test is not necessary. Digital vaginal examination is best avoided unless there is a strong suspicion that the woman may be in labour. This is because micro-organisms may be transported from the vagina into the cervix leading to intrauterine infection, prostaglandin release and preterm labour. Indeed, a retrospective study reported that the latency interval between spontaneous rupture of membranes and delivery in those who had a digital vaginal examination was significantly shorter than if a sterile speculum examination only was performed.²¹

Evidence level IIb

4.1 What antenatal tests should be performed?

Women should be observed for signs of clinical chorioamnionitis.



Weekly high vaginal swab need not be performed.



It is not necessary to carry out weekly maternal full blood count or C-reactive protein because the sensitivity of these tests in the detection of intrauterine infection is low.



Cardiotography is useful and indeed fetal tachycardia is used in the definition of clinical chorioamnionitis. Biophysical profile score and Doppler velocimetry can be carried out, but women should be informed that these tests are of limited value in predicting fetal infection.



The criteria for the diagnosis of clinical chorioamnionitis include maternal pyrexia, tachycardia, leucocytosis, uterine tenderness, offensive vaginal discharge and fetal tachycardia. During observation, the woman should be regularly examined for such signs of intrauterine infection and an abnormal parameter or a combination of them may indicate intrauterine infection. The frequency of maternal temperature, pulse and fetal heart rate auscultation should be between every 4 and 8 hours.^{16,17,22}

Maternal pyrexia, offensive vaginal discharge and fetal tachycardia indicate clinical chorioamnionitis. There is variation in the literature regarding the accuracy of the laboratory tests of leucocytosis and raised C-reactive protein in the prediction of chorioamnionitis. The sensitivities and false-positive rates for leucocytosis in the detection of clinical chorioamnionitis range from 29% to 47% and from 5% to 18%, respectively.^{16,22} The specificity of C-reactive protein is 38-55%.^{16,23,24} Although weekly culture of swabs from the vagina is often performed as part of the clinical management of women with PPRM, the data evaluating this practice do not show conclusively that it is beneficial. It has been shown that positive genital tract cultures predict 53% of positive amniotic fluid cultures with a false-positive rate of 25%.²⁵

Evidence level IIa

There have also been publications describing non-invasive antenatal fetal assessments with the aim of differentiating fetuses that are not infected and will benefit from remaining in utero from those who are

at risk of infection or infected and need to be delivered. Several studies have examined the value of the biophysical profile score, fetal tachycardia, non-reactive non-stress test and Doppler studies of the placental and fetal circulation in the prediction of intrauterine infection. As with maternal assessment, there is a wide range of true and false-positive results, which may partly be a consequence of the different endpoints used for the diagnosis of intrauterine infection such as clinical chorioamnionitis, histological chorioamnionitis or positive amniotic fluid cultures.

Abnormal biophysical profile scores and increased systolic/diastolic ratios in the umbilical artery have been shown to be markers of intrauterine infection.²⁶ The true and false-positive rates for an abnormal biophysical profile score in the prediction of clinical chorioamnionitis range from 30% to 80% and from 2% to 9%, respectively.²⁷⁻³¹ Another data set using positive amniotic fluid and positive fetal blood cultures as endpoints for infection found that the biophysical profile score or Doppler studies of the placental or fetal circulation did not provide accurate distinction between infected and non-infected cases.^{18,32} Fetal tachycardia predicts 20-40% of cases of intrauterine infection with a false-positive rate of about 3%.^{16,18,33} Cardiotocography is useful because a fetal tachycardia, if present, may represent a late sign of infection and is frequently used in the clinical definition of chorioamnionitis in studies.

Evidence
level IIa

There are no randomised controlled trials to support the premise that pregnancy outcome is improved by the use of frequent biophysical or Doppler assessment. The disparity in the literature evaluating these non-invasive tests of fetal wellbeing suggests that, although some studies have shown benefit, overall the tests are of limited value in differentiating between fetuses with and without infection.

4.2 *What is the role of amniocentesis?*

Although there are data documenting an association between subclinical intrauterine infection and adverse neonatal outcome, the role of amniocentesis in improving outcome remains to be determined. There is insufficient evidence to recommend the use of amniocentesis in the diagnosis of intrauterine infection.

B

Intrauterine infection, as defined by positive amniotic fluid cultures, is found in 36% of women with PPRM. Most infections are subclinical without obvious signs of chorioamnionitis.⁵ Positive amniotic fluid cultures increase the risks of preterm delivery, neonatal sepsis, respiratory distress syndrome, chronic lung disease, periventricular leukomalacia, intraventricular haemorrhage and cerebral palsy.³⁴⁻³⁶

Evidence
level IIa

Current evidence suggests that infection is a cause rather than a consequence of amniorrhexis.³⁷ Amniocentesis has the potential to detect subclinical infection before the onset of maternal signs of chorioamnionitis and before the onset of fetal sepsis, allowing appropriate intervention such as administration of antibiotics in infected cases and/or delivery depending on the gestation, and expectant management for patients with negative amniotic fluid cultures. Rapid tests on amniotic fluid such as Gram stain and assay of cytokines such as interleukins 6 and 18,^{36,38,39} which indicate intrauterine infection, may be performed.

Evidence
level IIa

Although prophylactic antibiotic therapy in cases of PPRM has been shown to have benefits, proponents for clinical management using amniocentesis argue that treatment should be targeted to appropriate women because a potential adverse effect of prolonged antibiotic therapy in PPRM includes superinfection with virulent organisms.⁴⁰ It remains to be determined in future studies whether amniocentesis improves outcomes. Amniocentesis should be performed in specialised units.

5. Management

5.1 Treatment

5.1.1 Are prophylactic antibiotics recommended?

Erythromycin should be given for 10 days following the diagnosis of PPROM.

A

Twenty-two trials involving over 6000 women with PPROM before 37 weeks of gestation were included in a meta-analysis.⁴¹ The use of antibiotics following PPROM is associated with a statistically significant reduction in chorioamnionitis (RR 0.57; 95% CI 0.37–0.86). There was a significant reduction in the numbers of babies born within 48 hours (RR 0.71; 95% CI 0.58–0.87) and 7 days (RR 0.80; 95% CI 0.71–0.90). Neonatal infection was significantly reduced in the babies whose mothers received antibiotics (RR 0.68; 95% CI 0.53–0.87). There was also a significant reduction in the number of babies with an abnormal cerebral ultrasound scan prior to discharge from hospital (RR 0.82; 95% CI 0.68–0.98). There was no significant reduction in perinatal mortality, although there was a trend for reduction in the treatment group.

Evidence level Ia

There was variation in the choice of antibiotics used and the duration of therapy in the studies examined in the meta-analysis.⁴¹ Ten trials tested broad-spectrum penicillin, either alone or in combination, five tested macrolide antibiotics (erythromycin) either alone or in combination and one trial tested clindamycin and gentamycin. The duration of treatment varied between two doses and 10 days. Any penicillin (except co-amoxiclav) or erythromycin versus placebo was associated with a significant reduction in the numbers of babies born within 48 hours and who had positive blood cultures. Co-amoxiclav versus placebo was associated with an increase in the numbers of babies born with necrotising enterocolitis.

This review shows that routine antibiotic administration reduces maternal and neonatal morbidity. Antibiotic therapy also delays delivery, thereby allowing sufficient time for prophylactic prenatal corticosteroids to take effect. The data also showed that prenatal co-amoxiclav increased the risk of neonatal necrotising enterocolitis and this antibiotic is best avoided. Erythromycin or penicillin appears the antibiotic of choice. Erythromycin may be used in women who are allergic to penicillin.

Evidence level Ia

If group B streptococcus is isolated in cases of PPROM, antibiotics should be given in line with the recommendation for routine intrapartum prophylaxis. As indicated in the RCOG Green-top Guideline No. 36: *Prevention of early onset neonatal group B streptococcal disease*,⁴² penicillin should be administered, or clindamycin in women who are allergic to penicillin.

Evidence level IV

5.1.2 What is the role of antenatal corticosteroids?

Antenatal corticosteroids should be administered in women with PPROM.

A

A meta-analysis of 15 randomised controlled trials involving more than 1400 women with preterm rupture of the membranes demonstrated that antenatal corticosteroids reduce the risk of respiratory distress syndrome (RR 0.56; 95% CI 0.46–0.70), intraventricular haemorrhage (RR 0.47; 95% CI 0.31–0.70) and necrotising enterocolitis (RR 0.21; 95% CI 0.05–0.82). They may also reduce the risk of neonatal death (RR 0.68; 95% CI 0.43–1.07). They do not appear to increase the risk of infection in either mother (RR 0.86; 95% CI 0.61–1.20) or baby (RR 1.05; 95% CI 0.66–1.68).⁴³

Evidence level Ia

As stated in the RCOG Green-top Guideline No. 7: *Antenatal corticosteroids to reduce neonatal morbidity*,⁴⁴ indications for antenatal corticosteroid therapy include women with PPROM between 24 and 34 weeks of gestation.

5.1.3 Should tocolytic agents be used?

Tocolysis in women with PPROM is not recommended because this treatment does not significantly improve perinatal outcome.

A

5.1.4 Prophylactic tocolysis

Three randomised studies on a total of 235 patients with PPROM reported that the proportion of women remaining undelivered 10 days after membrane rupture were not significantly higher in those receiving tocolysis compared with those receiving none.⁴⁵⁻⁴⁷

Evidence level Ib

A retrospective case-control study showed that tocolysis after PPROM did not increase the interval between membrane rupture and delivery or reduce neonatal morbidity.⁴⁸

Evidence level IIa

5.1.5 Therapeutic tocolysis

A randomised trial involving 30 women demonstrated that delivery can be inhibited for 24 hours by intravenous ritodrine.⁴⁹ After 24 hours there was no difference in the duration of pregnancy in either group. A randomised study involving 109 women showed that, for premature labour associated with premature rupture of the membranes after 28 weeks of gestation, there were no significant differences between treatment groups in intrauterine time after the onset of regular contractions.⁵⁰ The results of another randomised study of 79 patients with contractions following PPROM did not suggest that there is benefit of tocolysis in terms of prolonging the interval to delivery or in reducing perinatal morbidity or mortality.⁵¹ A case-control study involving 193 women found that aggressive tocolysis after PPROM did not increase latency or decrease neonatal morbidity compared with either limited tocolysis or no tocolysis at all.¹⁹

Tocolytic treatment for women in preterm labour is the subject of RCOG Green-top Guideline No. 1(B): *Tocolytic drugs for women in preterm labour*.⁵²

In the absence of clear evidence that tocolysis improves neonatal outcome following PPROM, it is reasonable not to use it. Additionally, with PPROM in the presence of uterine contractions, it is possible that tocolysis could have adverse effects, such as delaying delivery from an infected environment, since there is an association between intrauterine infection, prostaglandin and cytokine release and delivery.

5.2 When is the appropriate time to deliver the baby?

Delivery should be considered at 34 weeks of gestation. Where expectant management is considered beyond this gestation, women should be informed of the increased risk of chorioamnionitis and the decreased risk of respiratory problems in the neonate.

B

The decision to deliver or manage expectantly in cases of PPROM requires an assessment of the risks related to the development of intrauterine infection in those pregnancies managed expectantly compared with the gestational age-related risks of prematurity in pregnancies delivered earlier.

A retrospective study examining 430 women with PPROM demonstrated that composite neonatal minor morbidity such as hyperbilirubinaemia and transient tachypnoea of the newborn was significantly higher among pregnancies delivered at 34 weeks of gestation or less compared with those delivered at 36 weeks.⁵³ Composite major neonatal morbidity including respiratory distress syndrome and intraventricular haemorrhage was not significantly different.

Evidence level III

A randomised trial assigning 93 women with PPROM between 32 and 36 weeks and 6 days of gestation to either immediate or delayed delivery showed that the incidence of respiratory distress syndrome, intraventricular haemorrhage and confirmed neonatal sepsis was not signif-

Evidence level Ib

icantly different in the two groups.⁵⁴ Although in the expectantly managed group the 27.7% incidence of chorioamnionitis was higher than the 10.9% in the induced group, this difference did not reach statistical significance.

Evidence
level Ib

In another report, 129 women with PPROM between 30 and 34 weeks of gestation were randomly assigned to either immediate delivery or expectant management.⁵⁵ The mean gestational age at delivery was 31.7 weeks in the immediate delivery group and 32 weeks in the group managed expectantly. Although the incidence of chorioamnionitis was significantly less in the immediate delivery group (2%) compared with the expectant management group (15%; $P < 0.05$), there were no significant differences between the groups with regard to neonatal morbidity.

Evidence
level Ib

In a prospective randomised study of 120 women with PPROM between 34 and 37 weeks of gestation, the expectantly managed group had a higher incidence of chorioamnionitis (16%) compared with the immediate delivery group (2%; $P < 0.05$). The incidence of sepsis was 5% in the expectantly managed group and 0% in the immediate delivery group, but this was not statistically significant. There was no difference in the risk of respiratory distress syndrome.⁵⁶

Evidence
level Ib

A retrospective series examining neonatal outcome following cases with PPROM between 32 and 36 weeks showed that the specific gestation for reduced morbidity was 34 weeks.⁵⁷ The incidence of respiratory distress syndrome and the length of hospital stay were reduced in infants delivered after 34 weeks of gestation. The incidence of respiratory distress syndrome was 22.5% and 5.8% at 33 and 34 weeks, respectively. Although the incidence of RDS beyond 34 weeks was relatively low, the condition affected infants into the 36th week, with incidences of 10.4% and 1.5% at 35 and 36 weeks, respectively.

Many studies have demonstrated benefits of conservative management for gestations of less than 34 weeks, whereas the management of pregnancies complicated by PPROM between 34 and 37 weeks continues to be a contentious issue.⁵⁶ Proponents of delivery at 34 weeks argue that, because of the lack of significant neonatal benefit with prolongation of the pregnancy until 37 weeks, early delivery is justified to reduce the risk of chorioamnionitis. Data from existing studies call for further research to elucidate the optimal gestational age at delivery for women with PPROM between 34 and 37 weeks of gestation. A large randomised trial of induction compared with expectant management of women with PPROM between these gestations is needed. There are currently two randomised controlled trials comparing intentional delivery versus conservative management in women with PPROM between 32 and 35 weeks of gestation.^{58,59}

Until the results of these trials become available, published data question the benefit of continued expectant management beyond 34 weeks of gestation. There is little evidence that intentional delivery after 34 weeks adversely affects neonatal outcome. There is a suggestion from these studies that expectant management beyond 34 weeks is associated with an increased risk of chorioamnionitis. A longer latency interval with expectant management may allow time for clinical chorioamnionitis, which either is subclinical at the time of membrane rupture or develops with ascending bacterial infection subsequent to membrane rupture.

A Cochrane review of planned early birth versus expectant management for women with PPROM before 37 weeks of gestation was published in 2010. The conclusions were that there is insufficient evidence to guide clinical practice on the benefits and harms of immediate delivery compared with expectant management.⁶⁰

5.3 *Can women be monitored at home?*

In a randomised study of home versus hospital management, outcomes were comparable in the two groups with a similar latency period and gestational age at delivery.¹⁶ There were no significant differences in the

frequencies of chorioamnionitis, respiratory distress syndrome or neonatal sepsis. However, only 18% of the patients were eligible and agreed to randomisation. The patients were randomised after 72 hours in hospital and 57% and 74% of those in the home and hospital groups, respectively, had an amniocentesis for Gram stain and culture. This study does not support routine home management in patients with PPROM but supports rigorous individual selection of women for this treatment.

There are insufficient data to make recommendations for home and outpatient monitoring rather than continued hospital admission in women with PPROM. The decision to allow the woman home should incorporate the finding that women presenting with PPROM and subclinical intrauterine infection deliver earlier than non-infected patients. It would be considered reasonable to keep the woman in hospital for at least 48 hours before a decision is made to allow her to go home. This method of management should be individualised and restricted to certain women. Women should be instructed to take regular temperature recordings at home every 4–8 hours.

Evidence
level III

5.4. *Should amnioinfusion in labour be carried out?*

Amnioinfusion during labour is not recommended in women with preterm rupture of membranes.

A

PPROM places the fetus at risk of umbilical cord compression. Amnioinfusion has been described as a method of preventing this complication. Amnioinfusion during labour has been the subject of a Cochrane review,⁶¹ which examined one randomised controlled trial involving 66 women with spontaneous rupture of membranes between 26 and 35 weeks of gestation who received amnioinfusion during labour.⁶² The results showed no significant differences between amnioinfusion and no amnioinfusion for caesarean section, low Apgar scores and neonatal death. The implication is that there is insufficient evidence to guide clinical practice concerning the use of amnioinfusion.

Evidence
level Ib

5.5 *What is the role of transabdominal amnioinfusion in the prevention of pulmonary hypoplasia?*

There is insufficient evidence to recommend amnioinfusion in very preterm PPROM as a method to prevent pulmonary hypoplasia.

B

A published trial of 65 women with PPROM between 24 and 33 weeks of gestation who were randomised to amnioinfusion or expectant management showed that the risk of postnatal death from pulmonary hypoplasia was similar in both groups.⁶³

Evidence
level Ib

Another case-control study involving 24 women reported no difference in the incidence of pulmonary hypoplasia between controls and treated women.⁶⁴

Evidence
level IIa

Another study involving 71 women with PPROM before 26 weeks of gestation demonstrated that the percentage of intrauterine fetal survival was higher in the treated group than in the control group (64.8% versus 32.3%; $P < 0.01$).⁶⁵

Evidence
level IIa

A randomised controlled trial is under way comparing expectant management with serial amnioinfusions in women with early second-trimester PPROM.⁶⁶

5.6 *What is the role of fibrin glue in the sealing of chorioamniotic membranes to prevent pulmonary hypoplasia?*

There is insufficient evidence to recommend fibrin sealants as routine treatment for second-trimester oligohydramnios caused by PPROM.

B

There are publications involving small numbers of women with midtrimester PPROM describing transvaginal or transabdominal injection of fibrin into the amniotic fluid with the aim of sealing the membranes.⁶⁷⁻⁶⁹ The ‘amniopatch’ resulted in an increase in amniotic fluid volume in some cases. Larger studies are needed examining neonatal outcome before this treatment can be recommended as routine practice.

6. Possible audit topics

- Proportion of women with PPROM receiving erythromycin for 10 days.
- Proportion of women with PPROM receiving a complete course of antenatal corticosteroids.
- Proportion of women with PPROM being delivered at 34 weeks of gestation.
- Proportion of women with PPROM delivered after 34 weeks of gestation with documented advice of increased risk of chorioamnionitis and decreased risk of neonatal respiratory problems.

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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: Guidance for the development of RCOG green-top guidelines' (available on the RCOG website at www.rcog.org.uk/guidelines). 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.

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.

Classification of evidence levels	Grades of recommendations
Ia Evidence obtained from meta-analysis of randomised controlled trials.	A Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
Ib Evidence obtained from at least one randomised controlled trial.	
IIa Evidence obtained from at least one well-designed controlled study without randomisation.	B Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.	
III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.	C Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)
IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.	
	Good practice point
	 Recommended best practice based on the clinical experience of the guideline development group.

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

The guideline review process will commence in 2013 unless evidence requires earlier review.

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.

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.