Management of preterm labour

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Abstract

Preterm birth is defined as birth before 37 weeks of gestation and is the single biggest cause of neonatal morbidity and mortality. The UK preterm birth rate is 7.9%, therefore approximately 1 in 13 babies are born prematurely. This is despite advances in prediction of those at risk, prevention strategies and treatment. Transvaginal ultrasound and fetal fibronectin have been the major advances in the prediction of preterm labour, and with the use of both of these tests it may be possible to predict up to 75% of those who will deliver prematurely. At best, tocolytics are able to delay preterm labour long enough for the administration of corticosteroids. Labour involves complex and co-ordinated events, greater knowledge of which is necessary to understand processes involved in premature labour and advance healthcare in this field.

Keywords high-risk; obstetric labour; pregnancy; premature; progesterone/therapeutic use; tocolysis

Introduction

Preterm birth, defined as birth before the 37th week, can be further subdivided according to gestational age as shown in Table 1. Preterm birth contributes to substantial neuro-cognitive, pulmonary and ophthalmologic morbidity and globally accounts for 28% of neonatal deaths. However, over the past decade, survival rates have dramatically improved due to improvements in neonatal care rather than improvements in obstetric care. Babies born at 26 weeks of gestation and above now have a survival rate of approximately 75%. However, approximately 40% will suffer from some form of disability. It has been shown that prolonging a pregnancy from 30 weeks to 34 weeks gestation decreases the neonatal mortality from 9.6% to 0.9%.

Incidence of preterm birth

The incidence of preterm birth is increasing in both the UK and USA. The UK preterm birth is around 7.9%, compared to approximately 12% in the USA. This rate has not altered despite advancing knowledge of risk factors related to preterm labour and the introduction of many public health and medical interventions, such as tocolysis, e.g. Atosiban and Nifedipine, designed to delay preterm birth.

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Causes of preterm birth

The principal pathways leading to preterm birth are spontaneous preterm labour (PTL), preterm prelabour rupture of the membranes (PPROM) and iatrogenic causes. Approximately 45% of births occur following spontaneous PTL, 30% are iatrogenic and 15% follow PPROM. PPROM is defined as preterm spontaneous rupture of membranes, at least 1 hour before the onset of contractions. In addition to prematurity, PPROM is particularly associated with maternal sepsis and chorioamnionitis. Iatrogenic causes are deliveries (labour induction or Caesarean section) for maternal or fetal indications, such as pre-eclampsia and fetal growth restriction.

There are several maternal characteristics associated with preterm labour (Table 2). Maternal ethnicity has a significant impact on risk of preterm delivery. In the USA in 2003, the preterm birth rate for African-American women was 17.8%, compared to 10.5% in Asian and Pacific Islanders and 11.5% for Caucasian women. Previous preterm delivery increases the risk of a subsequent preterm delivery 2.5 fold, with those women with a previous preterm delivery at the lowest gestations at highest risk.

PTL is a complex process and is likely the endpoint of multiple influencing factors (Figure 1). It is useful to consider the management of PTL in three sections: the detection of those women at high risk, prevention of PTL in high risk women and finally diagnosis and treatment of those women in PTL.

Prediction – in the general population and those at increased risk

There are several studies that have been carried out to investigate methods of predicting PTL in women at high risk. In addition to the identification of risk factors (Table 2), the main methods used are transvaginal ultrasound and fetal fibronectin (FFN).

Transvaginal ultrasound

Transvaginal ultrasound to measure cervical length and funnelling has been studied as a screening test for preterm labour. It has been shown to be safe, acceptable, and reproducible. Cervical length at 24 weeks has been shown to be normally distributed with a mean length of 35.2 mm +/− 8.3 mm. In normal pregnancies delivered at term, the cervical length stays relatively constant until the third trimester.

There is an inverse relationship between cervical length and incidence of preterm delivery. Iams (1996) showed that relative risks could be assigned to a particular cervical length. For example, a lady with a cervical length of 22 mm has a relative risk of PTL of nine-fold while a women with a cervical length of <13 mm has a relative risk of fourteen-fold, when compared with longer cervical length. In the general population, only 1.7% of women have a cervical length less that 15 mm and these women account for 100% of births prior to 26 weeks, 80% of births prior to 30 weeks of gestation and 60% of births prior to 32 weeks of

Definition of preterm deliveries gestation

	Gestation (weeks)	% Of premature deliveries
Extreme prematurity	<28	5
Severe prematurity	28 to 31 + 6	15
Premature	32 to 33 + 6	20
Near term	34 to 36 + 6	60

Table 1

gestation. Therefore, a cervical length less than 15 mm is a sensitive predictor of severe prematurity, as it is associated with a 50% risk of delivery prior to 32 weeks' gestation.

Funnelling, which is opening of the internal os with closed cervix below, has also been shown in some studies to be associated with an independent risk factor for PTL, while other studies have contradicted this. It is likely that the length of the closed cervix below the funnel is more important. The RCOG have advised that funnelling of the cervix should not be used as an independent factor for the insertion of a cervical suture without shortening of the cervix below.

In order for a screening test to be effective, there needs to be an effective available treatment. At present there is no conclusive evidence that any one intervention helps to prevent preterm labour following the identification of cervical shortening or funnelling. Therefore the main benefit of transvaginal ultrasound screening may be its high negative predictive value of 90% for cervical length over 3 cm at 24 weeks. Women may be reassured, avoiding further clinic visits and intervention.

The guidance from the RCOG is to offer serial sonographic surveillance of cervical length for women with a history of spontaneous second-trimester loss or preterm delivery, as there is evidence to suggest that those who experience cervical shortening are at an increased risk of subsequent early delivery and may benefit from ultrasound-indicated cerclage. However, as this area is still lacking in evidence, women should be informed that expectant management is a suitable alternative to serial cervical length measurements, as most women who have suffered a previous spontaneous preterm birth will deliver after 33 weeks.

Fetal fibronectin

Fetal fibronectin (FFN) is an extracellular matrix glycoprotein localized at the maternal–fetal interface of the amniotic membranes, between chorion and decidua. Thus, it is found in the cervico-vaginal secretions prior to labour in both preterm and term labours. In a normal pregnancy, FFN should not be present in cervico-vaginal secretions between 20 and 36 weeks gestation. Only 3–4% of cervico-vaginal secretions between 21 and 37 weeks are positive for fetal fibronectin, suggesting disruption between the membranes and the decidua has occurred. FFN levels greater than or equal to 50 ng/mL at 22 weeks have been associated with a 40% increased risk of spontaneous preterm birth.

In order to be accurate, the swab for FFN must be taken correctly. The swab should be taken from the posterior fornix or ectocervix. False positive results can occur with the use of lubricant gel, recent sexual intercourse, vaginal bleeding, and rupture of membranes.

At present available FFN kits are non-quantitative, giving positive or negative results only. However, it has been shown that there is a correlation between preterm birth and quantitative assessment of fetal fibronectin. The higher the level of fetal fibronectin, the higher the relative risk of delivery prior to 28 weeks. A randomized controlled study is currently in progress to identify whether quantitative measurement of FFN gives improved predictive value in asymptomatic women.

Therapeutic interventions to prevent PTL in those at high risk

Cervical suture

Cervical suture or cerclage has been widely used in the management of pregnancies at high risk of preterm delivery. It was initially introduced as a treatment for 'cervical incompetence' where the cervix was believed to have some form of inherent weakness. However, true cervical incompetence is very difficult to diagnose, therefore it is not recommended as an indication for a cervical suture. The current uses of cervical cerclage are as an elective or preventative procedure, conducted on the basis of previous history or ultrasound findings, or as an emergency, when the cervix is found to be effacing and dilating at a pre-viable gestation (a 'rescue cerclage' as discussed below). Current recommendations are that a history-indicated cervical cerclage should only be offered to women with a history of three spontaneous preterm births or mid-trimester losses. Such sutures should be placed at around 14 weeks gestation. Women with a history of fewer preterm births or second trimester losses should be offered ultrasound surveillance.

There are three main forms of cervical suture, the Shirodkar suture described in 1954, the Macdonald suture described in

Risk factors for spontaneous preterm labour

Maternal characteristics	Pregnancy complications	Obstetric history
Race	Multiple pregnancy	Shortened cervix
Low BMI	Infection	Cervical surgery e.g. cone biopsy/multiple LLETZ procedures
Age less than 18 and over 40	Bleeding <24 weeks	One previous preterm labour = 13–21% risk
Poor nutrition		Two previous preterm labours = 42% risk
Smoking		Previous 2nd trimester miscarriage
Low socioeconomic status		Previous history of repeat TOP

Table 2

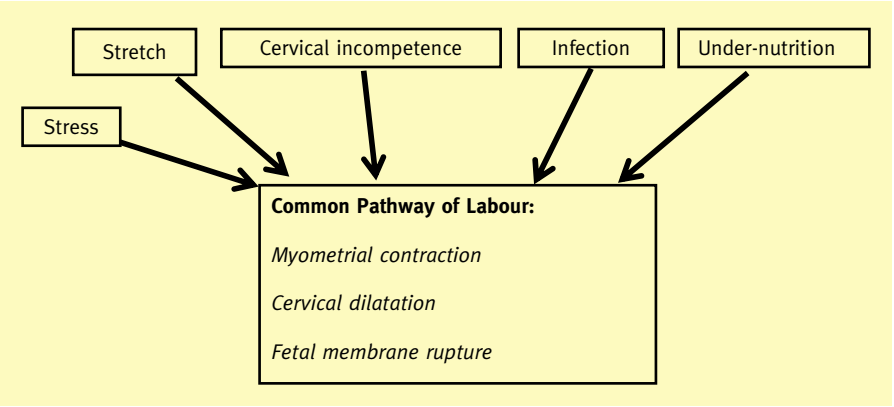

Figure 1 Mechanisms of preterm labour.

1957 and abdominal cervical cerclage. The most common method of cerclage used is the Macdonald suture, which is a purse string suture around the cervix. A Shirodkar suture is placed at the level of the internal os and requires dissection of the vaginal mucosa and bladder, with the vaginal mucosa then closed over the suture. A meta-analysis of Shirodkar vs Macdonald cervical cerclage was performed in women at high risk of preterm birth and no differences were seen in the rates of preterm birth. Further analysis was carried out for those women with short cervices diagnosed on ultrasound scan and again no difference was seen in outcome between the two types of suture. Abdominal sutures are used less often as they require more specialist expertise, and tend to be used in women with an extremely short, lacerated or scarred cervix or when transvaginal cerclage has previously failed. They are usually inserted around 11–12 weeks gestation, but can also be inserted preconceptually. Approximately 80–90% of those women who have an abdominal suture will deliver at term and they are currently the focus of a randomized trial. All types of cervical cerclage have associated complications, such as rupture of membranes, bleeding, pregnancy loss, bladder injury and anaesthetic risks. Abdominal sutures remain in situ and are not removed, and the baby is delivered by Caesarean section. Macdonald and Shirodkar sutures should be removed as soon as possible if labour occurs (to prevent cervical laceration), or electively before spontaneous labour, usually around 36 + 1–37 + 0 weeks gestation. A Macdonald suture can often be removed without the need for anaesthetic, whereas a Shirdokar suture will need an anaesthetic for removal.

Studies have suggested that ultrasound indicated cerclage may reduce the risk of preterm labour. A meta-analysis of 607 pregnancies from four randomized controlled trials suggested cerclage was associated with relative risk of 0.61 (95% confidence interval 0.40–0.92) for delivery less than 35 weeks compared with expectant management. This was similar to the largest randomized control trial which suggested that cerclage in women less than 22 weeks gestation when the cervix measured less than 25 mm reduced the rate of previable delivery from 14% to 6.1%. A recent (2012) Cochrane review has also suggested that cervical sutures reduce the risk of PTL in women at risk, although there was no reduction in perinatal death or neonatal morbidity. Therefore, women with singleton pregnancies and a history of PTL or second trimester loss should be offered a cervical suture if the cervical length on ultrasound scan is less than 25 mm at less than 24 weeks gestation. Studies have not shown any benefit for cervical cerclage in women without any history of PTL or second trimester loss, who have incidentally been found to have a shortened cervix on ultrasound scan. Similarly, cervical suture based on ultrasound or history should not currently be recommended to women with multiple pregnancy as there is evidence that they may be harmful. All available studies of multiple pregnancy are small and suggest either no benefit to cervical sutures, or report increased premature delivery rates or losses in association with suture use.

Progesterone

Progesterone has been of interest for the prevention of preterm labour for many years. Progesterone is an anti-inflammatory agent, which acts by inhibiting myometrial contractions and cervical ripening, down regulating gap junctions and inhibiting chemokine production. Progesterone has been studied extensively to assess whether it is effective at preventing preterm labour. A recent meta-analysis has shown that progesterone reduces the risk of PTL in women with a singleton pregnancy and a previous history of a preterm delivery when compared with placebo, with the number needed to treat to prevent one PTL being 16. Progesterone has also been shown to reduce preterm birth when administered to women with a short cervix. A recent meta-analysis of 775 women found that administration of vaginal progesterone to asymptomatic women with a cervical length less than 25 mm in the midtrimester was associated with a reduction in preterm delivery and composite neonatal morbidity and mortality. For this latter reason, progesterone is probably used over cervical suture in the USA.

In the UK, concerns over neonatal outcomes have limited its widespread use prior to the completion of an ongoing clinical trial, OPTIMMUM (see below). A Cochrane review carried out in 2009, concluded that the use of progesterone in women with a past history of spontaneous preterm labour was associated with a reduction in delivery prior to 34 weeks' gestation and 37 weeks' gestation. However, it also concluded that further information was needed on the optimal route of administration and dose of progesterone, as well as long term follow up data on the infants health outcomes.

Although it may be beneficial in reducing the risks of preterm labour in women at high risk, there is currently little evidence to indicate an improvement in neonatal outcomes. One randomized control trial, which included neonatal factors as secondary outcomes, suggested that treatment with progesterone significantly reduced the rates of necrotizing enterocolitis and intraventricular haemorrhage, and the need for supplemental oxygen. Only one study has attempted longer term follow up of children whose mothers were administered progesterone. This study showed no effect of progesterone on either physical examination or development. However, there was significant loss to follow up and the study was underpowered.

In contrast to singleton pregnancy, there is no evidence of benefit from the use of progesterone in multiple pregnancies. The largest double blinded randomized control trial of progesterone in twin pregnancy was the STOPPIT trial. The primary outcome was delivery or intrauterine death prior to 34 weeks gestation. The results demonstrated that 24.7% of women in the progesterone group had either a delivery or fetal death in utero prior to 34 weeks compared to 19.4% in the placebo group, showing that progesterone does not reduce the combined risk. Other studies in twin pregnancies using different progesterone regimes have had similar results. Therefore, progesterone is of no benefit in multiple pregnancy, and may confer some harm.

Given the lack of evidence for long term benefit of progesterone treatment, and the hypothesis that maintaining a fetus in adverse environment may be harmful, the RCOG Preterm Birth Study Group issued a statement that progesterone use should be restricted to randomized controlled trials. A UK multicentre randomized controlled trial is currently ongoing to investigate both the effect on PTL and long term neonatal outcome (OPTIMMUM). There is also currently limited evidence to guide the best dosing regimes and routes of administration. The dosage being used by OPTIMMUM is a 200 mg vaginal pessary daily.

Genital swabs and use of antibiotics

Several organisms have been linked with PTL such as *Ureaplasma urealyticum*, *Mycoplasma hominis* (those typically associated with bacterial vaginosis), *Trichomonas vaginalis*, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae*. Antenatal screening and treatment of asymptomatic vaginal infection has shown conflicting results. One randomized control trial showed that treatment of bacterial vaginosis found on routine screening prior to 22 weeks' gestation can reduce the rate of PTL by 10%. Furthermore a large study with 2058 women in the intervention group has shown that infection screening and treatment in early second trimester, between 15 weeks and 19 weeks and 6 days, for bacterial vaginosis, *T. vaginalis* and candidiasis can significantly reduce the preterm birth rate when compared with control group (3% versus 5.3%). Furthermore, screening and treatment of those women with infection was found to be cost effective due to its reduction in neonatal care. Other studies disagree although most of these have looked at treating bacterial vaginosis up to 26 weeks of gestation. The RCOG therefore suggest that treatment of BV prior to 20 weeks' gestation maybe beneficial in reducing PTL.

A more recent study has been carried out using prophylactic azithromycin at 16 weeks and again at 24 weeks in a population at high risk of preterm labour. This study has shown no significant reduction in PTL in these women when compared with no treatment.

Diagnosis of PTL

The presentation of women to the labour ward with symptoms suggestive of threatened PTL is common, but diagnosis is hampered with inaccuracy. Only a small proportion, 8%–24%, of those who present with symptoms will go on to deliver prematurely. The diagnosis is usually made on the clinical basis of regular uterine contractions associated with cervical change, as assessed on vaginal examination. The poor association between clinical symptoms and the likelihood of delivery means that a large number of women receive treatment unnecessarily, and this also causes significant problems for trials of potential treatments. Therefore, a better means of diagnosis is needed to prevent women receiving steroids, tocolysis and possible transfer to a tertiary centre unnecessarily, all of which represent a significant financial cost to NHS resources.

FFN has been shown in some studies to be of predictive value in women presenting with symptoms of preterm labour with intact fetal membranes. A recent meta-analysis of 32 studies suggested that FFN is a good short term predictor of preterm birth with a sensitivity of 76% and specificity of 81% for delivery within the next 7 days. A positive fetal fibronectin test has been shown to be a better predictor of PTL than clinical assessments alone. However, the main benefit of FFN is the high negative predictive value of 99%, which can allow clinicians the ability to avoid unnecessary interventions such as tocolysis and to reassure women.

Transvaginal ultrasound can also be used in the diagnosis of PTL, although this requires expensive equipment and expertise. A study performed by Gomez et al looked at the use of FFN and transvaginal ultrasound in the diagnosis of preterm labour. The results of the study are shown below (Table 3). They showed that combining the use of these two diagnostic tests can identify 75% of those women who will deliver within 7 days.

Treatment of PTL

Tocolysis

Several drugs have been investigated for their tocolytic properties, but, to date, no study has shown that tocolysis reduces rates of preterm delivery or improves neonatal outcome. However, pregnancy can be prolonged for up to 48 hours in approximately

Rates of diagnosis of PTL with FFN and transvaginal scanning

Test	Delivery in 48 hours %	Delivery in 7 days %
Transvaginal ultrasound cervix <15 mm	36.7	56.7
Fetal fibronectin FFN +ve	19.2	34.6
Both test used in conjunction	48.3	75

Table 3

80% of cases, which beneficial in allowing time for administration of corticosteroids and in-utero transfer. The main tocolytics used in the United Kingdom are COX inhibitors (e.g. Indomethacin), calcium channel blockers (e.g. Nifedipine) and oxytocin antagonists (e.g. Atosiban). It should be noted, however, that the only licensed drugs in the UK for this indication are Ritodrine and Atosiban. Ritodrine, a β-2 adrenergic receptor agonists, which induced uterine relaxation, was previously used but is no longer recommended due to significant adverse maternal side effects.

Nifedipine: is not licensed for use in threatened preterm labour and there have been no randomized control trials of nifedipine versus placebo in the treatment of threatened preterm labour. However, in comparison to other tocolytic drugs (usually beta-agonists), nifedipine appears to reduce the risk of delivery with 1 week of administration and before 34 weeks gestation. Nifedipine is the only tocolytic drug for which there are any reports of neonatal benefit, in that it was associated with less respiratory distress, less necrotizing enterocolitis and less risk of intraventricular haemorrhage. Nifedipine is also associated with maternal side effects including flushing, headache, palpitations and hypotension. In particular, nifedipine should be avoided in women with cardiac disease and care should be taken in women with diabetes or multiple pregnancy, as there are reports of pulmonary oedema in the literature.

Advantages of nifedipine over other tocolytics are that it is cheap and can be given orally. There is no standard protocol for the administration of nifedipine but the suggested dose is currently an initial oral dose of 20 mg, followed by 10–20 mg 3–4 times per day for up to 48 hours. This can be adjusted in response to observed uterine activity. Total doses higher than 60 mg are associated with an increased risk of side effects.

Atosiban: is the only drug licensed for treatment of threatened preterm labour in common use in the UK. It is a competitive oxytocin antagonist that acts at the uterine oxytocin receptors. It is given as an initial bolus of 6.75 mg over 1 minute, followed by an infusion of 18 mg/hour for 3 hours then reduced to 6 mg/hour for up to 45 hours. Similar to nifedipine, it should only be continued for 48 hours.

Atosiban has not been shown to reduce the preterm labour rate when compared with beta-agonists or to improve neonatal outcomes. There is a report of a higher number of neonatal deaths in the atosiban compared with placebo group, but this could have been due to a higher number of women at less than 26 weeks gestation randomized to the atosiban group. Atosiban has also been compared with betamimetics, such as salbutamol, terbutaline and ritodrine. In these studies, atosiban efficacy was similar to betamimetics, in that it did not significantly alter delivery before 48 hours. However, atosiban was better tolerated than betamimetics. Reported side effects for atosiban include nausea, vomiting, chest pain and dyspnoea. Importantly, atosiban is not contraindicated in cardiac disease or diabetes. There has been no direct comparison of atosiban and nifedipine in clinical trials.

COX inhibitors: there are several cyclo-oxygenase inhibitors used for tocolysis, such as Ketorolac, Celecoxib, Indomethacin and Sulindac. The one most commonly used in the UK is Indomethacin. When COX inhibitors have been compared with other tocolytics such as ritodrine they have equal efficacy at prolonging gestation for 48 hours. COX inhibitors inhibit uterine contractions, are easily administered and have few maternal side-effects. However, adverse effects have been reported in the newborn following exposure to COX inhibitors, including premature closure of the ductus arteriosus, renal and cerebral vasoconstriction, and necrotizing enterocolitis. For these reasons, indomethacin is usually used in the UK at only very early gestations.

In summary, there is no good evidence that tocolysis is of clinical benefit. It therefore is reasonable not to administer any tocolytic drug. At best, tocolysis delays delivery by between 48 hours and 7 days, giving enough time for corticosteroids to be administered, or for in-utero transfer to occur. Choice of drug varies with unit policy but first line agents are usually atosiban or nifedipine, with indomethacin only being administered at less than 32 weeks' gestation. Nifedipine and atosiban are probably of similar effectiveness and both have an acceptable side effect profile. There are no studies of cost effectiveness, but atosiban costs substantially more than nifedipine. There is insufficient evidence for the use of tocolysis in multiple pregnancy, but case reports associating nifedipine with pulmonary oedema suggests that atosiban should be first line in these women.

Emergency cervical sutures ('Rescue sutures')

Emergency cervical sutures are performed when the cervix is objectively open and the membranes are at or below the external os prior to 26 weeks' gestation. In a retrospective study over an 8 year period, 46 emergency cervical cerclages were inserted with a 44% success rate for delivery after 36 weeks; this is similar to other studies quoting a 50% success rate. There is limited availability of prospective data, with only one randomized control trial that included 23 women. Compared to expectant management, a rescue suture may increase the length of the pregnancy by 4–5 weeks. Indicators of poor outcome are membranes below the external os, dilatation over 4 cm, signs of infection (raised C-reactive protein or white blood cell count) and continued vaginal bleeding. Failure of the suture was also closely associated with post delivery chorioamnionitis.

Antibiotics

Extreme preterm birth is usually associated with infection, most commonly ascending infection from the vagina and several studies have assessed antibiotic use in the prevention of preterm labour. The largest study performed to date was the ORACLE II study which investigated women presenting with symptoms of spontaneous preterm labour with intact membranes. The primary outcome was a reduction in neonatal death with the use of antibiotics. The routine prescribing of antibiotics to women in spontaneous preterm labour did not reduce neonatal death, but did reduce the risk of maternal infection. Further follow up of the participants of the ORACLE II study at 7 years found an increased risk of cerebral palsy in the children who received antibiotics (odds ratio 1.93 (95% confidence interval 1.21–3.09) for erythromycin and 1.69 (1.07–2.67) for co-amoxiclav). When antibiotics were combined, risks were higher still than with erythromycin alone (4.55% vs 2.29%). It has been suggested that the use of antibiotics could be masking a subclinical infection

and keeping a baby within a hostile environment longer, thus increasing the risk of cerebral palsy. Therefore, routine prescription of antibiotics is not recommended in the presence of intact membranes and should be restricted to specific clinical indications such as chorioamnionitis, group B streptococcus and prelabour premature rupture of membranes.

Corticosteroids

Corticosteroids are used in PTL to increase fetal surfactant and accelerate fetal lung maturity. They have been shown to be beneficial in reducing neonatal death, respiratory distress syndrome (RDS), necrotizing enterocolitis, cerebrovascular haemorrhage and neonatal intensive care admissions. For maximum benefit, the optimum time between administration of steroids and delivery is from 24 hours to 7 days, though there has been a trend towards benefit following 7 days. In addition, studies have shown a reduction in risk of neonatal death where there has been less than 24 hours between steroid administration and birth, therefore steroids should still be used if delivery is likely within this time period. A single course of corticosteroids, two intramuscular injections of 12 mg betamethasone 24 hours apart or 4 doses of 6 mg dexamethasone 12 hours apart, has been shown to confer no harm to the fetus in long term follow up studies and every effort should be given to administer steroids to all women at risk of preterm labour between 24—34 + 6 weeks gestation. It has also been shown that there is benefit in treating women up to 36 weeks gestation, though the number needed to treat to prevent one case of RDS is considerably increased. Steroids can be considered between 23 + 0 and 23 + 6 weeks gestation as they may confer benefit. However, the RCOG suggest that it should be a senior decision to administer at this extreme gestation, with careful consideration of the whole clinical picture.

There has been considerable debate about the use of repeat doses of corticosteroids in women who have not delivered within 7 days but remain at risk of delivery. Studies have shown (including a recent Cochrane review) that repeated doses probably reduce the risks of neonatal lung disease and other short term outcomes. However, there is also evidence from human and animal studies showing that repeated courses of steroids may be associated with reduced growth and smaller head size. Animal studies have suggested adverse effects on brain function. Therefore, current RCOG recommendations is that repeat doses are not advised but cautious use of a single 'rescue' course can be considered where the initial dose was given at less than 26 weeks gestation.

Magnesium sulphate

Risks of cerebral palsy are significant in preterm infants, with rates of 14.6% being reported at less than 28 weeks gestation and 6.2% between 28 and 31 weeks. Although magnesium sulphate is not recommended as a tocolytic agent, there is evidence from several studies suggesting that maternal administration of magnesium sulphate may reduce the risks of cerebral palsy in the preterm neonate. A Cochrane review reported that magnesium sulphate was associated with a lower relative risk of cerebral palsy of 0.68 (95% confidence interval 0.54—0.87) and lower relative risk of gross motor dysfunction of 0.61 (95% confidence interval 0.44—0.85). Whilst the dose regimen remains unclear, consideration of magnesium sulphate for neuroprotection at the same doses given for the prevention of eclampsia should be a consideration for women at risk of severe preterm delivery (less than 32 weeks).

Delayed cord clamping

It has been suggested that delayed cord clamping after pre-term delivery may be associated with improved neonatal outcomes. Delaying clamping for between 30 and 120 seconds improves placental perfusion and increases the infant's blood volume at birth by around 30%. A recent Cochrane review (2012) suggested that it reduced the need for blood transfusion and reduced the risks of necrotizing enterocolitis and intraventricular haemorrhage. However, it was also associated with higher serum bilirubin level (and therefore increased need for phototherapy). There was insufficient data to conclude on the effects on severe brain injury and neonatal mortality.

Consequences of preterm birth

Preterm birth contributes to substantial neuro-cognitive, pulmonary, and ophthalmologic morbidity and globally accounts for 28% of neonatal deaths. In the US, preterm birth is the most frequent cause of infant death, accounting for one third of infant mortality in 2002. Prolonging a pregnancy from 30 weeks to 34 weeks gestation decreases the in-hospital mortality from 8.1% to 0.4%. Respiratory distress syndrome also reduces from 43.8% at 30 weeks' gestation to 2.6% at 34 weeks, even with steroid use in both groups. Therefore, the ability to prolong a pregnancy has the potential to have a huge impact on the health of the child. Understanding more about the mechanisms of term and preterm labour is essential to identify targets for novel therapies to prevent PTL.

Despite significant advances in neonatal care, preterm delivery is still the largest cause of neonatal morbidity and mortality. The UK multicentre study EPICure collected data on 2327 births in 2006 between 22 weeks and 25 weeks 6 days. Of these births, 72% of babies survived to be admitted to neonatal units and of these 61% survived to be discharged. The survival rates at discharge from hospital show a great improvement from the previous EPICure study in 1995, in which only 39% of those admitted to neonatal units were discharged home. There is also improvement of those children being disability free at the age of 3 years of age. With approximately 49% being disability free at 2.5 years, while in 2006, 69% of the surviving children were disability free. Despite these advances in neonatal care, the morbidity and mortality of premature delivery remains high.

The Nuffield Council on Bioethics has developed guidelines on the critical care in fetal and neonatal decisions. In this report it is stated that normal practice of full intensive care and support should be offered to all neonates from 24 weeks gestation, unless the patient or clinicians decide it is not in the baby's best interests due to her/his condition. They also state that between 23 weeks, 0 days and 23 weeks, 6 days, precedence should be given to the wishes of the parents as to whether they wish for full intensive care for the child. However, this should not be completely against clinical judgement, if treatment would be futile. Prior to 23 weeks, it suggested that resuscitation should not be offered.

In conclusion, PTL remains poorly understood. Treatment and diagnostic strategies continue to be limited in their success.

Further research is needed within this area to improve preventative strategies and treatment of PTL. ◆

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Practice points

- The aetiology of PTL is multifactorial
- Antenatal corticosteroids are the only drug proven to improve neonatal outcome in PTL
- Tocolysis can at best delay PTL for long enough for the maximum benefit of steroids
- Diagnosis of PTL is difficult but can be improved with use of FFN and cervical scanning
- Cervical cerclage in selected patients may prolong pregnancy but there is limited evidence of neonatal benefit
- Further research is needed to investigate the use of progesterone for the prevention of PTL in women at risk prior to its widespread use
- Magnesium sulphate and delayed cord clamping have potential to improve some neonatal outcomes