ARCHIVES OF DISEASE IN CHILDHOOD

This issue live and online www.archdischild.com

REVIEW

Management of preterm labour

Sarah Vause, Tracey Johnston

"The aetiology of preterm labour remains unknown, prediction lacks specificity, prophylaxis is unhelpful, diagnosis is difficult and the benefits and risks of tocolytic therapy are still being debated"[1]

Fetomaternal Medicine, St Mary's Hospital, Hathersage Road, Manchester M13 0JH, UK
S Vause
T Johnston

Correspondence to:
Dr Vause
email: adavies@care.cmht.nwest.nhs.uk

Accepted 17 May 2000

The above quote testifies to the complexity of preterm labour, a process that ultimately results in considerable neonatal morbidity and mortality. It is difficult to quantify the incidence of spontaneous preterm labour, as many studies relating to preterm birth do not discriminate between spontaneous preterm labour and iatrogenic/therapeutic preterm delivery. The picture is further complicated as many studies report their results by birth weight rather than gestation. However, it has been estimated that the incidence of preterm delivery varies from 5% to 10% of all births in developed countries, and that spontaneous preterm labour in otherwise uncomplicated singleton pregnancies accounts for between one third and one half of all preterm deliveries.[2 3] In 1997, in England and Wales, 50.3% of all neonatal deaths were due to immaturity.[4] The costs of neonatal intensive care in the short term and the resources needed to support children with long term morbidity as a result of preterm birth are considerable.

The underlying physiology and molecular biology of preterm labour is complex and not yet fully understood. A full discussion of the processes involved is outside the scope of this paper but is covered in a recent review article.[5] The causes are also diverse and multifactorial. Figure 1[1] summarises some of the factors that may contribute to preterm labour. This paper will concentrate on the prediction, prevention, and treatment of preterm labour, and discuss the ways in which antenatal interventions can optimise the outcome for the fetus.

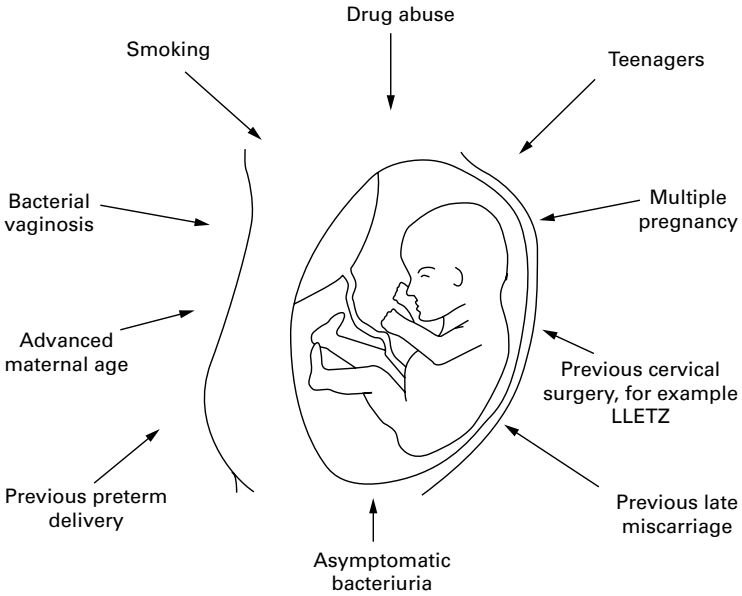

Figure 1 Risk factors for preterm labour.

Prediction

CLINICAL RISK SCORING

Preterm labour is more common in smokers, teenagers, drug abusers, women with bacterial vaginosis, multiple pregnancy, and women who have previously delivered preterm. Some of these observations would suggest that low grade cervical infection may contribute to preterm labour. Understanding the epidemiology may help in the development of health promotion programmes and guide research into aetiology and treatment. Several clinical risk scoring systems to predict preterm labour have been devised based on these epidemiological observations.[6] The risk scoring systems often place emphasis on the woman's past obstetric history and are therefore not helpful in the prediction of preterm labour in the primiparous woman. It has also been found that scoring

systems perform less well once they are applied to a population other than that from which they were derived. Although various risk scoring systems have been suggested, they have low positive predictive values,[7] and are therefore of limited value in identifying women with a significant risk of preterm labour.

CERVICAL LENGTH

Before the onset of labour, the cervix shortens and softens. Various methods have been tried to detect these changes, such as manual vaginal examination, transabdominal ultrasound, and transvaginal ultrasound. Of these modalities, transvaginal scanning appears to have the highest sensitivity, whereas transabdominal scanning was not predictive. There is, however, no clear cut gestation at which the test should be performed or what length is discriminatory.[8] Although digital cervical assessment has poor predictive value in singleton pregnancy,[9 10] it appears to be more useful in multiple pregnancy.[11 12]

FIBRONECTIN

Fetal fibronectin is an extracellular matrix glycoprotein produced by the chorionic cells. It is normally present in vaginal secretions until 22 weeks, and then disappears from the cervicovaginal secretions, only to reappear before the onset of labour at term. If the adhesive fibronectin interface between the chorion and the decidua is damaged by mechanical factors or infection, fibronectin may reappear in the vaginal secretions earlier, and its detection has therefore been proposed as a predictor of preterm labour.[13] However, the low positive predictive value limits its use as a screening test (positive predictive value for delivery within 14 days is 36%). Its value may lie in its high negative predictive value and prevent overtreatment (negative predictive value for delivery within 14 days is 97%).[14]

SALIVARY OESTRIOL

As parturition approaches, levels of plasma progesterone and oestradiol change. Although measurement of serum levels of these hormones is not predictive for the onset of preterm labour,[15] there is evidence that measurement of salivary oestriol may be.[16] This is currently being investigated further in the PREMET study. This study is comparing fetal fibronectin, bacterial vaginosis, interleukin (IL)-6, IL-8, and salivary oestriol as predictive tests for preterm labour. It also aims to test the hypothesis that metronidazole is of benefit to women identified in this way.

HOME UTERINE ACTIVITY MONITORING

A multicentre randomised controlled trial showed a reduced risk of preterm labour with a home uterine activity monitoring device,[17] but whether this was due to the gadget or increased awareness of uterine activity is difficult to ascertain. In another multicentre trial in which an active device was compared with a sham device, there was no difference between the two groups.[18]

EDUCATION

A meta-analysis of randomised trials that aimed to increase a woman's awareness of preterm labour showed no difference in outcome with regard to gestation at delivery, but it did show an increase in the false positive diagnosis rate of preterm labour.[19]

Prevention

In the population as a whole, various social factors, such as poverty and smoking, are associated with preterm delivery (fig 1). The development of health promotion programmes to reduce the prevalence of adverse lifestyle and health activities in certain populations may lead to a reduction in the incidence of preterm birth. Achieving such change is slow and difficult, and the introduction of such programmes has met with only limited success.[5]

Interventions to prevent preterm labour can be divided into those that aim to prevent cervical dilatation (cervical cerclage) and those that aim to prevent the initiation of myometrial contractility (mainly detection and treatment of asymptomatic infection).

CERVICAL CERCLAGE

A proportion of preterm deliveries are thought to be due to cervical incompetence. These cases are usually characterised by silent dilatation of the cervix with or without spontaneous rupture of the membranes in the late second trimester, in the absence of uterine contractions. Some women present with membranes bulging through the cervix, again in the absence of contractions. Often there is a history of cervical surgery such as cone biopsy or large loop excision of the transformation zone (LLETZ) for cervical dyskaryosis. The diagnosis of cervical incompetence is often made retrospectively from the history, after a late miscarriage or an extremely premature delivery. The diagnosis can be confirmed by measuring cervical resistance to dilatation outside of pregnancy.[20] In subsequent pregnancies, the insertion of a cervical suture in early pregnancy may help to maintain cervical competence, and hence prevent premature delivery. The multicentre cervical cerclage study of the Medical Research Council/Royal College of Obstetricians and Gynaecologists published in 1993 showed a modest, but statistically significant, reduction in delivery before 33 weeks from 17% to 13% (odds ratio 0.72; 95% confidence interval 0.53 to 0.97) after cervical cerclage. In the group in which cerclage had been performed, there were increased rates of emergency lower segment caesarean section (9.2% compared with 7.5%) and an increased incidence of puerperal pyrexia (6% compared to 3%). Only women deemed to be high risk by their obstetrician were included in the study. The authors concluded that "the use of cervical cerclage should be considered when there was a high likelihood of benefit e.g. for women with three or more second trimester miscarriages or preterm deliveries".[21]

DETECTION AND TREATMENT OF ASYMPTOMATIC INFECTION

There is strong evidence that infection is a cause of preterm labour.[22] This may be mediated through an inflammatory response

and cytokine release. Treating the infection when a woman presents in preterm labour is analogous to closing the stable door after the horse has bolted. Two conditions have been identified in which detection and treatment of asymptomatic or subclinical infection can prevent preterm labour. These are bacterial vaginosis and asymptomatic bacteriuria.

There is evidence that bacterial vaginosis predisposes women to preterm labour.[23–26] These women need to be identified and treated while asymptomatic and before preterm labour occurs. Although treatment with antibiotics does not seem to be of benefit in women at low risk of preterm labour, there is a statistically significant reduction in preterm birth, preterm prelabour rupture of membranes, and low birthweight babies in women at high risk of preterm labour who receive treatment.[27] None of the trials has reported on neonatal wellbeing or long term paediatric follow up. There is therefore no evidence to support a routine screening programme of all women for bacterial vaginosis, but there is evidence that a programme targeted at high risk women may be of value.

About 10% of pregnant women have asymptomatic bacteriuria. These women are at risk of developing a symptomatic urinary tract infection during pregnancy and of preterm delivery. Screening all pregnant women for asymptomatic bacteriuria, and treating those who screen positive has been suggested as an intervention to prevent such complications. Although there are still questions about when the most appropriate time to screen is, and the optimal duration of treatment, meta-analysis of 13 randomised controlled trials suggests that this is an effective intervention which leads to a reduction in preterm delivery rates.[28]

Nimesulide and atosiban, which are discussed more fully below, may also have a role in the prevention of preterm labour by maintaining uterine quiescence.

Treatment

Should we treat? As with any pregnant woman, the obstetrician should always balance the risks to both mother and fetus of delivering the baby prematurely against the risks of trying to prolong the pregnancy. It is interesting that in some trials no benefit in terms of neonatal morbidity and mortality has been shown, despite prolongation of the pregnancy. There is also evidence to suggest a link between maternal infection and cerebral palsy, possibly mediated by cytokine damage to the fetal brain.[29] Further research needs to be directed towards determining the best management strategy when faced with a preterm fetus and a risk of maternal infection, as it may be that prompt delivery is better despite the gestational age.

When discussing prevention of preterm labour, cervical and myometrial factors were considered. The same factors can be considered when discussing treatment.

EMERGENCY CERVICAL CERCLAGE

Cervical dilatation is usually the result of uterine contractions. In some women, the cervix appears to dilate in the absence of uterine contractions, and these women are thought to have an incompetent cervix. Such women may attend with relatively little in the way of symptoms, but, on vaginal examination, membranes are seen to be bulging through a partially dilated cervix. Under such circumstances, emergency cervical cerclage is a treatment option. The procedure is not suitable for women who are actively contracting, as the suture may tear through the cervix as it dilates, nor is it suitable if the membranes are ruptured, as vaginal surgery would promote ascending infection. A recent review of 23 cases of emergency cervical cerclage carried out in a tertiary referral centre showed a mean duration of prolongation of pregnancy of 17 days.[30] The mean gestation at suture insertion was 23.2 weeks. Around this gestation, prolonging the pregnancy by 17 days not only allows time for administration of steroids but can make the difference between delivery at a non-viable gestation and delivery at a gestation where survival is possible.

TREATMENT OF MYOMETRIAL CONTRACTILITY

The concentration of calcium in the myometrial cell dictates the degree of contractility. Levels of intracellular calcium and calcium flux are regulated by a variety of mechanisms. Levels of intracellular calcium can rise either because calcium enters the cell from outside through voltage gated calcium channels, or because it is released from the sarcoplasmic reticulum. Despite the central role of calcium channels, there is no evidence to suggest that their numbers or their function change as parturition approaches. Tocolytics exert their effect by reducing the level of intracellular calcium.

CALCIUM CHANNEL BLOCKERS

There are two types of calcium channels in the myometrial cell, the L type and the T type. Nifedipine binds to the inside of myometrial L type voltage dependent calcium channels causing them to remain closed, and hence inhibits contractility.[31] However, these L type channels are present in other types of smooth muscle cells such as vascular smooth muscle. The T type calcium channel is peculiar to myometrium. The drug mibefradil is a specific T type calcium channel blocker, and therefore has the potential to inhibit myometrium specifically without having side effects on vascular smooth muscle.

A multicentre randomised controlled trial comparing the calcium channel blocker nifedipine with the β agonist ritodrine showed that there were fewer maternal side effects with nifedipine. In women with intact membranes, there was a significant reduction in delivery within 24 hours, 48 hours, one week, and two weeks. In the women with intact membranes, the mean delay from randomisation to delivery was 39.2 days in the nifedipine group and 22.1 days in the ritodrine group ($p = 0.003$).[32]

PROSTAGLANDIN INHIBITORS

Prostaglandins directly stimulate calcium channels on the myometrial cell membrane to open and allow an influx of extracellular

calcium. They are produced from arachidonic acid by cyclooxygenases (COXs). Prostaglandin production is stimulated by cytokines such as IL-1α, IL-1β, and tumour necrosis factor α. Particularly in preterm labour, these may be stimulated by an infective process.[33 34] They in turn stimulate production of IL-6 and hence prostaglandin production. In addition to the effect on calcium, prostaglandins have for a long time been known to cause cervical ripening. IL-8 is involved in neutrophil mediated cervical ripening, and its production may be influenced by steroid hormones.[35] IL-6 may also have a direct effect on collagen formation and catabolism, acting in a paracrine fashion on the cervix to cause ripening.

Production of COX I is relatively constant throughout pregnancy, whereas COX II production increases towards term and is very high in labour. COX II predominates in the fetal membranes and the myometrium.[36] COX I is more common in fetal cardiovascular tissue. This enzyme is usually stimulated by infection and cytokines.

Indomethacin is a potent COX inhibitor and can therefore be used in the treatment of preterm labour. However, it inhibits both COX I and COX II and therefore poses a cardiovascular risk to the fetus and neonate.[37] Trials of indomethacin versus ritodrine show that both treatments are equally effective in postponing delivery.[38 39] There are fewer maternal side effects with indomethacin, but in 11% of trial participants oligohydramnios was noted. An increased rate of intraventricular haemorrhage and necrotising enterocolitis has been found in association with antenatal indomethacin use.[40] There are also worries with regard to the effect of indomethacin on the ductus arteriosus and isolated reports of premature closure. However, Doppler studies of the ductus arteriosus suggest that there is less effect at earlier gestations,[41] and before 30 weeks gestation any effect on the ductus is unlikely to be of clinical significance. Fortunately, this is the gestation at which the treatment is most likely to be of value as a tocolytic.

Sulindac, another COX inhibitor, may deliver the same beneficial effects as indomethacin with respect to inhibiting uterine activity but may have fewer adverse fetal effects, as it does not cross the placenta as readily and is not associated with changes in amniotic fluid volume or ductal flow velocities.[42] It inhibits both forms of COX and is therefore not free of fetal effects. Sulindac is a prodrug that is converted into the active form in the liver. This is a slower process in the fetus than in the mother, and therefore concentrations of the active drug are lower in the fetus than in the mother.

Nimesulide is a specific inhibitor of COX II and may therefore be an effective tocolytic which does not have any adverse effects on fetal ductal flow, but does cause oligohydramnios.[43] This drug also directly inhibits T type and L type calcium channels. It is currently being investigated as a prophylactic tocolytic—that is, one that will be effective in preventing the onset of preterm labour—and at present is only available in the context of a clinical trial.

OXYTOCIN ANTAGONISTS

Second messenger systems are regulated by hormones, such as oxytocin, and neurotransmitters. These second messenger systems modify the activity of ion channels. One such enzyme, phospholipase C, hydrolyses phosphatidylinositol, which releases calcium from the sarcoplasmic reticulum and causes the release of arachidonic acid, the obligate precursor of prostaglandins.

In preterm labour, oxytocin has been found to stimulate uterine smooth muscle by increasing intracellular calcium flow from the sarcoplasmic reticulum,[44] by inhibiting its reuptake,[45] and through receptor mediated L type calcium channels.[46] Atosiban is a specific oxytocin antagonist which competitively inhibits oxytocin from binding to its receptors. Preliminary studies have reported successful tocolysis.[47] The results of randomised controlled clinical trials of these agents are awaited. Atosiban is not entirely specific in its binding and can also bind to arginine vasopressin receptors. Alternative more specific oxytocin antagonists are now being developed.

NITRIC OXIDE (NO) DONORS

NO is a highly active free radical that has a powerful inhibitory effect on smooth muscle contraction. It is synthesised from L-arginine by nitric oxide synthetase. Animal studies have shown that nitric oxide synthetase activity and hence NO synthesis in the myometrium decreases with the onset of labour. The role of NO in the maintenance of pregnancy and the initiation of labour remains speculative. In rats, inhibition of NO leads to increased myometrial tone; in the human it leads to an increase in frequency of contraction but not in tone. There is high expression of endothelial nitric oxide synthetase in term and preterm labouring myometrium.

NO donors, such as glyceryl trinitrate, activate cGMP which promotes the uptake of intracellular calcium into the sarcoplasmic reticulum. In this way, glyceryl trinitrate acts as a myometrial relaxant.[48] In comparison with vascular smooth muscle, the myometrium is relatively insensitive to glyceryl trinitrate. It also ripens the cervix and is therefore not the ideal tocolytic.[49]

MAGNESIUM

Magnesium sulphate is used as a tocolytic agent because it inhibits voltage gated calcium channels from opening in response to action potentials. However, as a maintenance treatment, magnesium does not appear to have any advantage over other treatments with which it has been compared,[50] and the problems of magnesium toxicity limit its use.

PROGESTERONE

Progesterone, which is present in high concentrations during pregnancy, increases cAMP production. cAMP and cGMP maintain uterine quiescence by promoting the uptake of intracellular calcium into the sarcoplasmic reticulum and thereby reducing intracellular calcium concentrations and reducing contractility.[51] They also lower the amount of phosphorylated myosin and promote myometrial relaxation. Progesterone therefore exerts a relaxant effect on the

uterus,[52] and has been used in the treatment of preterm labour. Unfortunately, exogenous progesterone has been shown not to have a clinically significant tocolytic effect in humans, although it does in some animal models.

β AGONISTS

β Agonists act through a similar mechanism to progesterone, increasing cAMP production and promoting the uptake of intracellular calcium into the sarcoplasmic reticulum. However, downregulation of this mechanism occurs with continuous stimulation,[53] leading to tachyphylaxis. β Agonists do not appear to be useful as prophylactics to prevent the onset of preterm labour.[54] They have been shown to postpone delivery by 24–48 hours, but with no significant reduction in preterm birth, perinatal morbidity, or mortality.[55 56] Their use is associated with a high incidence of maternal side effects which at times can be life threatening.[57] β Agonists are an effective treatment which can be used to "buy time" for the administration of steroids, or to allow transfer of the woman to a more appropriate centre for delivery.

POTENTIAL THERAPEUTIC AVENUES

Potassium channel openers, such as levcromakalim, act by hyperpolarising the smooth muscle cell and are therefore potent smooth muscle relaxants.[58] There is evidence that the properties of potassium channels in human pregnant myometrium are considerably altered with the onset of parturition, suggesting that they have an important role in the regulation of uterine excitability. In smooth muscle, there are a large number of different types of potassium channels with different gating mechanisms. This offers the possibility that a potassium channel opener that acts specifically on the myometrium and not on any other smooth muscle may be developed.[59]

Gap junctions are membrane spanning proteins (connexins). They provide a low resistance pathway between myometrial cells along which action potentials can spread. There is a pronounced increase in the density and size of gap junctions just before parturition.[60] This may be due to the influence of oestrogens. Prostaglandins enhance production of myometrial gap junctions. Understanding the factors that modify the numbers or properties of gap junctions may open avenues for treatment.

The role of prostaglandins in cervical ripening has already been mentioned. Collagen is the main structural molecule in the extracellular matrix of the cervix. Its synthesis and metabolism are altered during pregnancy. Metalloproteinases (collagenases, gelatinases, and stromelysins) degrade the extracellular matrix. Collagenase activity and levels of tissue inhibitor of metalloproteinases are altered in term and preterm delivery.[61] Testing for activity of these enzymes or inhibiting their action may be explored in the future.

It can therefore be seen that multiple mechanisms are involved in the maintenance of uterine quiescence and in the initiation of uterine contractility. Many of these mechanisms are also involved in the contractility of other types of smooth muscle. Although the interplay of the various modulatory factors presents various therapeutic options, it can be difficult to find a uterospecific treatment, and side effects of tocolytic treatment are common.

Optimising outcome

It can be seen from the above that there is no ideal tocolytic at present, and it is unfortunately inevitable that some women will deliver prematurely. It is therefore important that interventions that have been proved to optimise the outcome are used.

STEROIDS

The use of steroids in women in whom preterm delivery is expected has been extensively studied (18 trials, 3700 babies). The evidence in favour of their use now seems incontrovertible as they reduce the incidence of respiratory distress syndrome, neonatal death, and intraventricular haemorrhage.[62] They also appear to act synergistically with postnatal surfactant treatment.[63] Whether one course is sufficient or whether the steroids should be repeated at weekly intervals is currently the subject of a multicentre trial (TEAMS).

THYROTROPHIN RELEASING HORMONE

Both triiodothyronine and thyroxine can stimulate the rate of precursor incorporation into the major components of surfactant lipids in organ cultures of fetal rat, rabbit, and human lung. Triiodothyronine also increases the synthesis of atrial natriuretic peptide (the principal mediator of the perinatal shift in lung fluid and ion transport) by the alveolar type II cells. It has therefore been postulated that thyroid hormones may stimulate fetal lung maturation. However, they do not readily reach the fetal circulation because of metabolism by the placenta and membranes, and therefore an alternative approach to produce increased levels in the fetus is to administer intravenous thyrotrophin releasing hormone to the mother. Meta-analysis of the earlier trials suggested a reduction in severe respiratory distress but no difference in mortality. Further trials were undertaken, but stopped after publication of further work, which, when incorporated into the meta-analysis, suggested that any clinical benefit from thyrotrophin releasing hormone was unlikely, and if it did exist would be too small to be clinically meaningful.[64 65] As extremely large numbers of women would have been needed to show such a small difference in outcome, further clinical trials were not feasible.

PHENOBARBITOL, ANTENATAL VITAMIN K

With both of these drugs, early trials showed a benefit in the prevention of periventricular haemorrhage. However, the methodology in the early trials was not robust, and the later trials showed no difference.[66 67] Unfortunately one of the later trials with sound randomisation procedures tested both phenobarbitol and vitamin K as cotreatments.[68] No difference in outcome was found but it was not possible to separate the effects of the two drugs.

ANTIBIOTICS

Infection can be a cause of preterm labour. It therefore seems logical to suggest that antibiotics may have a role in the treatment or preterm

labour. A meta-analysis of eight trials of the use of antibiotics in women with intact membranes in threatened preterm labour showed that treatment with antibiotics did not seem to reduce the rate of preterm birth or prolong the pregnancy. No difference was found in the incidence of respiratory distress syndrome or neonatal sepsis. There appeared to be a reduction in the rate of maternal infection and necrotising enterocolitis.[69]

In women with preterm rupture of membranes, treatment with antibiotics led to a significant prolongation of the pregnancy and in reduction in the incidence of chorioamnionitis and neonatal infection, but there was no difference in perinatal mortality or necrotising enterocolitis.[70]

A large multicentre study which should answer this question conclusively is being carried out (ORACLE).

MODE OF DELIVERY

There have only been five trials of mode of delivery in preterm labour, with 104 women in total. It is therefore impossible to draw any conclusions from these studies, particularly when subgroup analysis is performed for different gestational ages or different presentations of the fetus.[71]

Conclusions

Spontaneous preterm labour is an important and challenging problem. Although much progress is being made in understanding the underlying mechanisms of preterm labour, the incidence of preterm delivery has changed little in the last 20 years. It would be easy to become despondent. However, various predictive tests have been developed, and their relative merits are currently being evaluated in the context of the PREMET study. Treatment of asymptomatic infection appears to be effective in preventing preterm labour in some women. The results of the ORACLE study should clarify the role of antibiotics for women with premature rupture of membranes and for women in preterm labour. New tocolytic treatments, such as atosiban and nimesulide, are being subjected to clinical trials. Evidence based reviews have proved beyond doubt the role of steroids in optimising the outcome for the fetus.

Although there are still many unanswered questions, current research may provide some if not all of the answers. It could be suggested that the outlook is not quite as bleak as the opening quote suggests.

1 Lamont RF, Elder MG. The prevention of preterm birth. In: Studd JWW, ed. *The yearbook of the RCOG.* London: RCOG Press in association with Parthenon Publishing Group, 1996:369–382.
2 Rush RW, Keirse MJNC, Howat P, Baum JD, Anderson AB, Turnbull AC. Contribution of preterm delivery to perinatal mortality. *BMJ* 1987;**294**:594–5.
3 Meis PJ, Ernest JM, Moore ML. Causes of low birth weight in public and private patients. *Am J Obstet Gynecol* 1985;**156**:1165–8.
4 Confidential Enquiry into Stillbirths and Deaths in Infancy. *Sixth Annual Report of the Maternal and Child Health Research Consortium*. London: Maternal and Child Health Research Consortium, 1999.
5 Bocking AD. Preterm labour: recent advances in understanding of pathophysiology, diagnosis and management. *Curr Opin Obstet Gynecol* 1998;**10**:151–6.
6 Creasy RK, Gummer GA, Liggins GC. System for predicting spontaneous preterm birth. *Obstet Gynecol* 1980;**55**:692–5.
7 Owen J, Goldenberg RL, Davis RO, Kirk KA, Copper RL. Evaluation of a risk scoring system as a predictor of preterm birth in an indigent population. *Am J Obstet Gynecol* 1990;**163**:873–9.
8 Andersen HF, Nugent CE, Wanty SD Hayashi RH. Prediction of risk for preterm delivery by ultrasonographic measurement of cervical length. *Am J Obstet Gynecol* 1990;**163**:859–67.
9 Leveno JJ, Cox K Roark ML. Cervical dilatation and prematurity revisited. *Obstet Gynecol* 1986;**68**:434–5.
10 Stubbs TM, van Dorsten P, Miller MC. The preterm cervix and preterm labor: relative risks, predictive values and change over time. *Am J Obstet Gynecol* 1986;**155**:829–34.
11 Nelson JP, Verkuyl DAA, Crowther CA, *et al.* Preterm labor in twin pregnancies: prediction by cervical assessment. *Obstet Gynecol* 1988;**72**:719–23.
12 Newman RB, Godsey RK, Ellings JM, *et al.* Quantification of cervical change: relationship to preterm delivery in multifetal gestation *Am J Obstet Gynecol* 1991;**165**:264–71.
13 Lockwood CJ, Senyel AE, Renate Disch M, *et al.* Fetal fibronectin in cervical and vaginal secretions as a predictor of preterm delivery. *N Engl J Med* 1991;**325**:669–74.
14 Leeson S, Maresh M. Fibronectin: a predictor of preterm delivery *Br J Obstet Gynaecol* 1993;**100**:304–6.
15 Hanssens MCAJA, Selby C, Symmonds EM. Sex steroid concentrations in preterm labour and the outcome with ritodrine. *Br J Obstet Gynaecol* 1982;**92**:698–702.
16 Jackson GM, McGregor JA Lachelin GCL, Goodwin TM, Artal R, Dullien V. Salivary estriol rise predicts preterm labour. *Am J Obstet Gynecol* 1995;**172**:406.
17 Corwin MJ, Mou SM, Sunderji SG, *et al.* Multicenter randomized clinical trial of home uterine activity monitoring: pregnancy outcomes for all women randomized. *Am J Obstet Gynecol* 1996;**175**:1281–5.
18 The Collaborative Home Uterine Monitoring Study (CHUMS) Group. A multicenter randomized controlled trial of home uterine monitoring: active versus sham device. *Am J Obstet Gynecol* 1995;**173**:1120–7.
19 Hueston WJ, Knox MA, Eilers G, Powels J, Lansdorf D. The effectiveness of preterm birth prevention educational programs for high risk women: a meta analysis. *Obstet Gynecol* 1995;**86**:705–12.
20 Anthony GS, Calder AA, Macnaughton MC. Cervical resistance in patients with previous spontaneous midtrimester abortion. *Br J Obstet Gynaecol* 1982;**89**:1046–9.
21 The Medical Research Council/Royal College of Obstetricians and Gynaecologists Working Party on Cervical Cerclage. Final Report of the MRC/RCOG multicentre randomised trial of cervical cerclage. *Br J Obstet Gynaecol* 1993;**100**:516–23.
22 McGregor JA, French JI, Lawellin D, Todd JK. Preterm birth and infection: pathogenic possibilities. *Am J Reprod Immunol* 1998;**16**:123–32.
23 Minkoff H, Grunebaum AN, Schwarz RH, *et al.* Risk factors for prematurity and premature rupture of the membranes: a prospective study of the vaginal flora in pregnancy. *Am J Obstet Gynecol* 1984;**150**:965–72.
24 Lamont RF, Taylor Robinson D, Newman M, *et al.* Spontaneous early preterm labour associated with abnormal genital bacterial colonisation. *Br J Obstet Gynaecol* 1986;**93**:804–10.
25 Kurki T, Sivonen A, Renkonen OV, Savia E, Ylikorkala O. Bacterial vaginosis in early pregnancy and pregnancy outcome. *Obstet Gynecol* 1992;**80**:173–7.
26 Hay PE, Lamont RR, Taylor Robinson D, *et al.* Abnormal bacterial colonisation of the genital tract and subsequent preterm delivery and late miscarriage. *BMJ* 1994;**308**:295–8.
27 Brocklehurst R, Hannah M, McDonald H. Interventions for treating bacterial vaginosis in pregnancy (Cochrane Review). In: *The Cochrane library*. Oxford: Update Software, 1999:issue 1.
28 Smaill F. Antibiotics for asymptomatic bacteriuria in pregnancy. (Cochrane Review). In: *The Cochrane library*. Oxford: Update Software, 1999:issue 1.
29 Dammonn O, Leviton A. Maternal intrauterine infection, cytokines and brain damage. *Pediatr Res* 1997;**42**:1–8.
30 Abu-Bakar HZ, Johnston TA, Seif MW. Outcomes of emergency cervical cerclage: a retrospective study. *J Obstet Gynaecol* 1999;**19**(supp 1):55.
31 Triggle DJ, Janis RA. Calcium channel ligands. *Annu Rev Pharmacol Toxicol* 1987;**27**:369–74.
32 Papatsonis DNM, van Geijn HP, Ader HJ, Lange FM, Bleker OP, Dekker GA. Nifedipine and ritodrine in the management of preterm labor: a randomised multicenter trial. *Obstet Gynecol* 1997;**90**:230–4.
33 Bejar R, Curbelo V, Davis C, Gluck L. Premature labour bacterial sources of phospholipase. *Obstet Gynecol* 1981;**57**:479.
34 Lamont RF, Taylor Robinson D, Wigglesworth JS, *et al.* The role of mycoplasmas, ureaplasmas and chlamydia in the genital tract of women presenting in spontaneous early preterm labour. *J Med Microbiol* 1987;**24**:253–7.
35 Barclay CG, Brennand JE Kelly RW, Calder AA. Interleukin-8 production by the human cervix. *Am J Obstet Gynecol* 1993;**169**:625–32.
36 Slater DM, Berger LC, Newton R, Moore GE, Bennett PR. Expression of cyclooxygenase types 1 and 2 in human fetal membranes at term. *Am J Obstet Gynecol* 1995;**172**:77–82.
37 Bennett PR, Slater D, Sullivan M, Elder MG, Moore GE. Changes in amniotic arachidonic acid metabolism associated with increased cyclo oxygenase gene expression. *Br J Obstet Gynaecol* 1993;**100**:1037–42.
38 Morales WJ, Smith SG, Angel JL, O'Brien WF, Knuppel RA. Efficacy and safety of indomethacin versus ritodrine in the management of preterm labor. *Obstet Gynecol* 1989;**74**:567–72.

39 Besinger RE, Niebyl JR, Keyes WG, Johnson TR. Randomised comparative trial of indomethacin and ritodrine for the long term treatment of preterm labor. *Am J Obstet Gynecol* 1991;**164**:981–8.
40 Norton ME, Merrill J, Cooper BAB, Kuller JA, Clayman RI. Neonatal complications after the administration of indomethacin for preterm labor. *N Engl J Med* 1993;**329**:1602–7.
41 Vemillion ST, Scardo JA, Lashus AG, Wiles HB. The effect of indomethacin tocolysis on fetal ductus arteriosus constriction with advancing gestational age. *Am J Obstet Gynecol* 1997;**177**:256–9.
42 Carlan SJ, O'Brien WF, O'Leary TD, Mastrogiannis D. Randomised comparative trial of indomethacin and sulindac for the treatment of refractile preterm labour. *Obstet Gynecol* 1992;**79**:223–8.
43 Groom K, Sawdy R, Elliott C, Louden J, Shennan AH, Bennett PR. Experience of the use of nimesulide, a COX2 selective non steroidal anti inflammatory drug, in the prevention of preterm delivery in high risk cases. *J Obstet Gynecol* 2000;**20**(supp1):61–2.
44 Schrey MP, Read AM, Steer PJ. Oxytocin and vasopressin stimulate inositol phosphate production in human gestational myometrium and decidua cells. *Biosci Rep* 1986;**6**:613–19.
45 Magocsi M, Penniston JT. Oxytocin pretreatment of pregnancy rat uterus inhibits calcium uptake in plasma membrane and sarcoplasmic reticulum. *Biochim Biophys Acta* 1991;**1063**:7–14.
46 Tasaka K, Masumoto N, Miyake A, Tanizawa O. Direct measurement of intracellular free calcium in cultured human puerperal myometrial cells stimulated by oxytocin: effects of extracellular calcium and calcium channel blockers. *Obstet Gynecol* 1991;**77**:101–6.
47 Akerlund M, Stromberg P, Hauksson A, *et al*. Inhibition of uterine contractions of premature labour with an oxytocin analogue. Results from a pilot study. *Br J Obstet Gynaecol* 1987;**94**:1040–4.
48 Cole RM, Lamont RF. Current perspectives on drug treatment for preterm labour. *J Obstet Gynaecol* 1998;**18**:309–14.
49 Thomson AJ, Lunan CB, Cameron AD, Cameron IT, Greer IA, Norman JE. Nitric oxide donors induce ripening of the cervix: a randomised controlled trial. *Br J Obstet Gynaecol* 1997;**104**:1054–7.
50 Higby K, Xenakis EMJ, Pauerstein CJ. Do tocolytic agents stop preterm labor? A critical and comprehensive review of efficacy and safety. *Am J Obstet Gynecol* 1993;**168**:1247–59.
51 Thornton S, Gillespie JI. Biochemistry of uterine contractions. *Contemporary Reviews in Obstetrics and Gynaecology* 1992;**4**:121–6.
52 Egarter CA, Husslein P. Biochemistry of myometrial contractility. *Clin Obstet Gynecol* 1992;**6**:755–69.
53 Caritis SN, Chiar JP, Kridgen P. Comparison of pulsatile and continuous ritodrine administration: effects on uterine contractility and beta adrenergic cascade. *Am J Obstet Gynecol* 1991;**164**:1005–12.
54 Hemminki E, Starfield B. Prevention and treatment of premature labour by drugs: review of controlled clinical trial. *Br J Obstet Gynaecol* 1978;**85**:411–17.
55 King JF, Grant A, Keirse MJNC, Chalmers I. Betamimetics in preterm labour: an overview of the randomised controlled trials. *Br J Obstet Gynaecol* 1988;**95**:211–22.
56 Canadian Preterm Labor Investigators Group. Treatment of preterm labor with the beta adrenergic agonist ritodrine. *N Engl J Med* 1992;**327**:308–12.
57 Royal College of Obstetricians and Gynaecologists. *RCOG guideline no 1(A): beta agonists for the care of women in preterm labour*. London: Royal College of Obstetricians and Gynaecologists, Jan 1997.
58 Duty S, Weston AH. Potassium channel openers: pharmacological effects and future uses. *Drugs* 1990;**40**:785–91.
59 Weston AH, Edwards G. Recent progress in potassium channel opener pharmacology. *Biochem Pharmacol* 1992;**43**:47–54.
60 Garfield RE, Sims SM, Daniel EE. Gap junctions: their presence and necessity in myometrium during parturition. *Science* 1977;**198**:958–60.
61 Rajabi M, Dean DD, Woessner Jr JF. High levels of serum collagenase in premature labor: a potential biochemical marker. *Obstet Gynecol* 1987;**69**:179–86.
62 Crowley P. Prophylactic corticosteroids for preterm delivery (Cochrane Review). In: *The Cochrane library*. Oxford: Update Software, 1999:issue 1.
63 Jobe A. Beneficial interactions of antenatal corticosteroids and postnatal surfactant. In: *Report of the Consensus Development Conference on the Effect of corticosteroids for fetal maturation on perinatal outcomes*. Bethesda, MD: National Institutes of Child Health and Human Development. NIH publication no 95-3784:39–41.
64 Crowther CA, Alfirevic Z, Haslam RR. Prophylactic prenatal thyrotrophin releasing hormone for preterm delivery (Cochrane Review). In: *The Cochrane library*. Oxford: Update Software, 1999:issue 1.
65 Alferevic Z, Boer K, Brocklehurst P, *et al*. Two trials of antenatal thyrotrophin-releasing hormone for fetal maturation: stopping before the due date. *Br J Obstet Gynaecol* 1999;**106**:898–906.
66 Crowther CA, Henderson-Smart DJ. Prophylactic prenatal vitamin K for preterm birth (Cochrane Review). In: *The Cochrane library*. Oxford: Update Software, 1999:issue 1.
67 Crowther CA, Henderson-Smart DJ. Prophylactic prenatal phenobarbitol for preterm birth (Cochrane Review). In: *The Cochrane library*. Oxford: Update Software, 1999:issue 1.
68 Thorp JA, Ferrette-Smith D, Gaston L, Johnson J, Yeast J, Myer B. Combined antenatal vitamin K and phenobarbitol therapy for preventing intracranial haemorrhage in newborns less than 34 weeks' gestation. *Obstet Gynecol* 1995;**86**:1–8.
69 King J, Flenady V. Antibiotics for preterm labour with intact membranes (Cochrane Review). In: *The Cochrane library*. Oxford: Update Software, 1999:issue 1.
70 Kenyon S, Boulvain M. Antibiotics for preterm premature rupture of membranes (Cochrane Review). In: *The Cochrane library*. Oxford: Update Software, 1999:issue 1.
71 Grant A. Elective versus selective Caesarean section for delivery of the small baby (Cochrane Review). In:*The Cochrane library*. Oxford: Update Software, 1999:issue 1.

STAMPS IN NEONATOLOGY

Incubators

Very seldom has an incubator been part of any stamp design. This Nepalese stamp was issued on 8th April 1988 to commemorate the Silver Jubilee of the Kanti Children's Hospital in Kathmandu. The stamp issuing details from the Postal Services Department describes the hospital as having 150 beds and the only children's hospital in the country catering "to the health needs of the children of the Kathmandu valley and other parts of the Kingdom as well". The stamp also bears the hospital logo. Four million stamps in sheets of 50 were printed by the Austrian Government Printing Office in Vienna.

M K DAVIES
A J MAYNE