1 Introduction

Preterm birth remains the major cause of mortality and of both short- and long-term morbidity in normally formed babies. Prevention and
treatment of preterm labor is important, not as an end in itself, but as a
means of preventing preterm birth and its consequences (see Chapter 37).
Preterm labor, by definition labor beginning before 37 completed
weeks of gestation, is a continuum, with the more serious consequences
of preterm birth occurring before 34 weeks of gestation.

Prevention of preterm birth is not always wise; many preterm
births occur as a result of conditions such as prelabor rupture of
the membranes with its inherent risk of amnionitis, or as a planned
intervention to end a pregnancy because of serious maternal illness or
problems with fetal well-being or growth. These situations are
discussed in other chapters.

Physiologically, preterm labor differs little from labor at term, except
that it occurs too early. It will, however, be accompanied by increased
anxiety for the women and her partner. It is not always easy to tell
whether preterm labor really has or has not commenced. In many
instances, apparently progressive preterm labor stops, irrespective of
whether any treatment is instituted. An overly expectant attitude while
watching for signs of progress can be dangerous, as more advanced
preterm labor is more difficult to stop.

Successful suppression of uterine contractions does not necessarily
improve the outcome for the infant. Birth may not be postponed to a
clinically useful extent, while any treatment that is powerful enough to
suppress uterine contractions may have other effects on the women or
the baby, some of which may be undesirable or dangerous.

2 Prevention of preterm labor

2.1 Social interventions
There is a strong association between a woman’s social and economic
circumstances, and her risk of preterm birth. This association has
prompted a number of social programs with the aim of reducing
that risk. However well-intentioned these interventions are, controlled
evaluation (discussed in Chapter 3) has not detected any effects on the
rate of preterm birth.

2.2 Physical measures

2.2.1 Home uterine-activity monitoring
Several trials have addressed the question of whether electronic
monitoring of uterine activity at home, with daily transmission to a
monitoring center by telephone, can reduce the frequency of preterm birth by early identification of women at risk for preterm labor. Unfortunately, there was enormous potential for bias in the initial reports. More recent, better-quality trials in pregnancies at higher risk of preterm labor, failed to show that home uterine-activity monitoring resulted in earlier diagnosis of preterm labor or in reduced rates of preterm birth or neonatal morbidity.

2.2.2 Bed-rest
Bed-rest, in the hope of reducing the incidence of preterm birth, has been used predominantly in multiple pregnancies. The intervention has not been demonstrated to be effective for this purpose (see also Chapter 17.)

2.2.3 Cervical cerclage
Cervical cerclage may be useful for preventing preterm birth in a small proportion of women but, unfortunately, there are no satisfactory methods of identifying the women who are likely to benefit from this intervention. Benefits are more likely to occur in women who have had two or more past pregnancies that ended preterm.

The intervention should be avoided in women who are unlikely to benefit, because of potential hazards associated with the surgery and the additional risk of stimulating uterine contractions.

2.2.4 Cervical assessment
A few small trials, and one large multicenter trial, have addressed the question of whether vaginal examination or ultrasound assessment of cervical length may help to recognize women who are likely to give birth too early, in time to institute useful preventive measures. No benefits have been demonstrated. While some of these approaches may be promising, there are also distinct disadvantages both to the procedures themselves and to the interventions that may be precipitated by their results.

2.3 Prophylactic pharmacological approaches

2.3.1 Betamimetic drugs
Many clinicians prescribe betamimetic drugs to prevent uterine contractions in women who, for one reason or another, are considered to be at increased risk of preterm labor. Trials of prophylactic beta-mimetics, both in multiple pregnancy and in singleton pregnancies
believed to be at high risk of preterm birth, have failed to detect any reduction in the risk of preterm birth, low birthweight, or perinatal mortality.

2.3.2 Magnesium
The effects of routine magnesium supplementation on a number of adverse pregnancy outcomes, including preterm labor, have been addressed in a few trials. Overall they are of too poor quality to provide a reliable assessment of magnesium supplementation.

2.3.3 Calcium
Calcium supplementation of at least 1 g daily during pregnancy reduces the risk of women developing hypertension and pre-eclampsia. The effect is greatest for women at high risk of hypertension and women with a low baseline dietary calcium intake. Whether lower doses of calcium may have similar benefits needs assessment. Overall, no reduction in the risk of preterm birth is evident.

2.3.4 Progestogens
Regular intramuscular injections of 17α-hydroxyprogesterone caproate may reduce the incidence of preterm labor and preterm birth in women considered to be at high risk of preterm labor, but they have not been shown to decrease perinatal mortality or morbidity. The findings may warrant further evaluation, preferably with less invasive forms of administration.

2.3.5 Other agents
Prophylactic dietary supplementation with fish oils, and with zinc compounds, have both been evaluated in randomized trials. The use of fish oils shows a promising increase in the length of gestation and birthweight (see Chapter 6).

3 Tocolytic treatment for active preterm labor

3.1 Betamimetic drugs
Betamimetics to suppress uterine contractions preterm are used more extensively than any of the other labor-inhibiting agents that are employed. A variety of betamimetics have been introduced in the hope of developing agents that would have a maximal effect on uterine relaxation, with minimal effect on the heart or other body organs.
Only three of the many betamimetic agents available have ever been compared with a placebo or a no-treatment control group for inhibition of preterm labor. Some of the drugs that are widely used, such as salbutamol or fenoterol, have never been so tested. The majority of the controlled trials relate to ritodrine.

Data from these trials show that betamimetics reduce the proportion of births that occur within the first 24 hours and within 48 hours after beginning treatment. Betamimetics also reduce the incidence of preterm birth. No decrease in perinatal mortality or serious morbidity, such as respiratory distress syndrome, has been detected.

At least three factors may contribute to this lack of effect on important adverse outcomes. First, the trials may have included too many women who were already sufficiently advanced in gestation, so that postponement of birth and prolongation of pregnancy were unlikely to confer any substantial benefit to the baby. Second, the time gained by betamimetic drug treatment may not have been used to implement measures with direct beneficial effects, such as promoting fetal lung maturity or transfer to a center with adequate perinatal care facilities (see Chapter 37). Third, there may be direct or indirect adverse effects of the drug treatment (including prolongation of pregnancy when this is contrary to the best interests of the baby), which counteract their potential gain.

The placebo-controlled trials do not suggest that betamimetic drug treatment frequently poses great hazards to either the woman or her baby, but other data in the literature show that these drugs are not harmless. The most frequently observed symptoms associated with betamimetic use are palpitations, tremor, nausea, and vomiting. Headache, vague uneasiness, thirst, nervousness, and restlessness may occur.

The most common, and dose-related, side-effect observed in all betamimetic treated women is an increase in heart rate. Only rarely will effective labor inhibition be achieved with maternal heart rates below 100 beats per minute. Heart rates of 130–140 beats per minute, on the other hand, should preclude further increases in the dose of betamimetics administered. Chest discomfort and shortness of breath should alert those providing care to the possibility of pulmonary congestion.

Pulmonary edema is a well-recognized complication of betamimetics. Most cases are associated with aggressive intravenous hydration and neglecting signs of fluid accumulation. It is safer to administer betamimetic drugs in a small volume of fluid with the use of an
infusion pump than to rely on intravenous infusion of dilute solutions of the drug. Pulmonary edema is more likely in women with twin pregnancies. Plasma volume expansion is larger in women with multiple pregnancies, and these women are at greater risk of developing pulmonary edema during treatment with betamimetics than women with singleton pregnancies.

Myocardial ischemia has been described as the other serious, albeit rare, complication of betamimetic drug treatment. Betamimetic drug administration in pregnancy results in a marked increase in cardiac output, of the same order as that observed in moderate exercise. The additional work imposed on the myocardium may be too much for women with pre-existing cardiac disease. These women should not be given betamimetic drug treatment, as the hazards for them are likely to be greater than any possible benefits that might be derived.

All betamimetic agents show a clear tendency to lower diastolic blood pressure. This is usually accompanied by an increase in systolic blood pressure, with the effect of a net increase in pulse pressure. Clinically significant hypotension is less frequently encountered with currently used betamimetic drugs, such as ritodrine and terbutaline, than with earlier agents, such as isoxsuprine, but the problem has not been eliminated.

Other drugs, including calcium antagonists (verapamil) and beta-1 blockers (atenolol, metoprolol), have been tried as adjuncts to betamimetics in attempts to reduce the cardiovascular side-effects. The use of these agents has not been shown to achieve the desired effects, and the available data do not justify their use.

All betamimetic agents influence carbohydrate metabolism: blood sugar levels increase by about 40% and there is an increase in insulin secretion. In women with diabetes the rise in glucose levels is even more pronounced. Thus a woman with well-controlled diabetes is likely to become deregulated when betamimetics are administered. This applies even more forcibly when betamimetics are combined with corticosteroids, which also have diabetogenic effects.

There is no doubt that betamimetic agents cross the placenta. Stimulation of beta receptors in the fetus evokes roughly the same effects as it does in the mother. The cardiovascular effects result in fetal tachycardia, although this is usually less pronounced than in the mother. Since the metabolic effects in mother and fetus may result in hypoglycemia and hyperinsulinism after birth, assessment of blood sugar levels is advisable in infants born during or shortly after use of betamimetics to inhibit labor.
A few studies have compared long-term outcomes between infants whose mothers had received betamimetic drugs and infants whose mothers had not received such treatment. All of these studies have been small, and the control groups have been variously constructed. No long-term ill effects have as yet been observed.

None of the studies comparing one betamimetic drug with another has been large enough to have had a chance of detecting or excluding important differences in the outcomes that really matter. Nor have any of the trials shown any clear differences in serious maternal outcomes, such as pulmonary edema. Taken together, the trials comparing different betamimetic agents show no reason to prefer one agent over another.

3.2 Inhibitors of prostaglandin synthesis

As prostaglandins are of crucial importance in the initiation and maintenance of human labor, suppression of prostaglandin synthesis is a logical approach to the inhibition of preterm labor. Several agents with widely different chemical structures inhibit prostaglandin synthesis. Those that have been used to treat preterm labor include naproxen, flufenamic acid, aspirin, and sulindac, but the most widely used has been indomethacin.

These drugs all act by inhibiting the activity of the cyclooxygenase enzyme necessary for the synthesis of prostaglandins, prostacyclin and thromboxane, but the mechanisms of inhibition may be different. Aspirin, for example, causes an irreversible inhibition of the enzyme, whereas indomethacin results in a competitive and reversible inhibition.

Prostaglandin synthesis inhibitors are effective inhibitors of myometrial contractility, both during and outside pregnancy. They are more effective in this respect than any of the betamimetic drugs. No case has been reported in which a betamimetic drug resulted in suppression of uterine contractility after inhibition of prostaglandin synthesis had failed; the reverse has been observed repeatedly. Trials of indomethacin, although of a heterogeneous nature, show that this drug reduces the frequency of delivery within 48 hours, and within 7–10 days, of beginning treatment. The incidence of preterm birth and low birthweight are reduced. There is a trend, towards a reduction in the incidence of perinatal death and respiratory distress syndrome.

Only a few reports on the use of naproxen, flufenamic acid, and aspirin have appeared in the literature. These drugs have not been as widely used as indomethacin, and there have been no controlled trials of their use.
Inhibitors of prostaglandin synthesis are not innocuous. The most serious potential maternal side-effects are peptic ulceration, gastrointestinal and other bleeding, thrombocytopenia and allergic reactions. Nausea, vomiting, dyspepsia, diarrhea, and allergic rashes have all been observed in women treated, even briefly, with prostaglandin synthesis inhibitors in preterm labor. Headache and dizziness may occur at the very start of treatment.

Gastro-intestinal irritation is common with the use of prostaglandin synthesis inhibitors, and it can occur irrespective of the route of administration. With indomethacin, it is less frequent with rectal than with oral administration; as the drug is equally well absorbed with both routes of administration, the rectal route offers some advantage.

Signs of infection may be masked by administration of prostaglandin synthesis inhibitors and this could hamper or postpone the diagnosis of incipient intra-uterine infection. The prolongation of bleeding time seen with prostaglandin synthesis inhibitors may be important, especially when epidural anesthesia is considered.

Prostaglandin synthesis inhibitors, including indomethacin and sulindac, cross from the mother to the fetus, and influence several fetal functions. The areas of major concern relate to the cardiopulmonary circulation, renal function, gastro-intestinal function, and coagulation. Constriction of the ductus arteriosus has been identified as a serious concern. This probably has little effect on fetal oxygenation in the short term, but with prolonged treatment, may result in changes similar to those seen in persistent pulmonary hypertension in the newborn. Several reports have linked persistent pulmonary hypertension in the neonate to the prenatal use of prostaglandin synthesis inhibitors.

Indomethacin treatment may reduce both fetal and neonatal renal function. The effect is dose-related and appears to be transient. Several reports have noted impaired renal function in fetuses and in the neonates at birth following administration of prostaglandin synthesis inhibitors to the mother. Long-term maternal treatment may influence fetal urine output enough to alter amniotic fluid volume, although other mechanisms may be involved in the reduction of amniotic fluid volume that can be seen during indomethacin treatment. There is no evidence, however, that the use of this drug in preterm labor leads to permanent impairment of renal function in the infant.

Several reports have linked the prenatal use of prostaglandin-synthesis inhibitors to the development of necrotizing enterocolitis.

Inhibitors of prostaglandin synthesis all inhibit platelet aggregation and prolong bleeding time. They do so in the mother, in the fetus, and
in the neonate at birth. Since neonates, and particularly preterm neonates, eliminate these drugs far less efficiently than their mothers, these effects will last longer in the baby than in the mother.

Indomethacin, like betamimetics, may prove to be a useful drug for obtaining sufficient delay of delivery to improve infant outcome. More and better controlled data will be needed before an adequate assessment of its usefulness in care for preterm labor can be made.

The lasting effect of salicylates on platelet function and the large doses required to arrest uterine contractions preclude the use of these drugs for preterm labor.

3.3 Ethanol
Ethanol, for a long time one of the main labor-inhibiting drugs, is now only of historical interest. It is less efficacious than other drug treatments and has serious side-effects in both mothers and babies.

3.4 Progestogens
The small amount of controlled research on the use of progesterone in established preterm labor has not demonstrated any useful labor-inhibiting effects.

3.5 Magnesium sulphate
Magnesium sulphate has been used for inhibition of preterm labor, although the placebo-controlled trials have not shown it to be effective in reducing the frequency of any adverse outcomes. It can have serious side-effects. Pulmonary edema has been reported in association with magnesium sulphate and corticosteroid administration in preterm labor. As magnesium is primarily excreted by the kidney, hypermagnesemia can occur if renal function is impaired. This may lead to impaired reflexes, respiratory depression, alteration in myocardial conduction, cardiac arrest, and death. Regular examination of the tendon reflexes is said to offer protection against such complications, since these reflexes disappear at less elevated magnesium levels than those that cause respiratory depression and cardiac conduction defects.

Magnesium levels in the fetus closely parallel those in the mother. Infants born during or shortly after treatment are reported to be drowsy; they have reduced muscle tone, low calcium levels and may take 3 or 4 days to eliminate the excess magnesium.
3.6 Calcium antagonists

‘Calcium channel blockers’ or ‘calcium antagonists’ include a wide range of different and apparently unrelated compounds, some of which, such as verapamil and nifedipine, have been used in the treatment of ischemic heart disease and arterial hypertension, and have also been used for the treatment of hypertension in pregnancy.

In the few small trials to evaluate these agents in preterm labor, fewer maternal side-effects, longer postponement of delivery, and fewer admissions to the neonatal intensive care unit, have been reported. Further well-designed, randomized trials are needed to establish whether these effects lead to improved neonatal and infant outcome.

3.7 Oxytocin antagonists

Several oxytocin analog antagonists are currently under investigation. Results to date suggest that maternal side-effects may be fewer compared with betamimetics, while effects on uterine activity are similar.

3.8 Diazoxide

Diazoxide is a powerful antihypertensive agent, which also inhibits uterine contractions. It shares many of the properties of the beta-mimetic drugs, both on the cardiovascular system and on carbohydrate metabolism. No controlled trials of this drug in preterm labor have been reported, although it is said to be the principal tocolytic agent in at least a few centers in North America. The available evidence does not justify its use in pregnancy and certainly not for the inhibition of preterm labor.

4 Other treatments for active preterm labor

4.1 Hydration

Hydration with intravenous fluid, with or without sedation, is frequently used as a primary approach to stop preterm labor, particularly in North America. This approach has not been well evaluated and the available data show that hydration is not more useful than no treatment at all. There is an increased risk of pulmonary edema if labor inhibiting-drugs are subsequently used. This practice should be abandoned unless evidence is brought forward to substantiate it.
4.2 Antimicrobial agents
Subclinical infection and bacterial colonization may cause preterm labor with or without prior rupture of the membranes. A wealth of data in support of these suggestions has, for many years, been described in various epidemiological, microbiological, and histological associations between preterm birth and infections of the reproductive tract. The hypothesis that antibiotic therapy might be of benefit in the care of women in preterm labor is thus attractive.

The evidence from the few trials that have been conducted is conflicting. When membranes are intact, the data demonstrate no significant benefit from antibiotic treatment on the rate of preterm birth, prolongation of pregnancy, respiratory distress syndrome, or neonatal sepsis, although maternal infection (chorioamnionitis/endometritis) and neonatal necrotizing enterocolitis were reduced. Overall there appears to be a slight increase in perinatal related mortality associated with the use of antibiotics. A large pragmatic multicenter trial is underway and should help to clarify some of these uncertainties.

Antibiotic treatment following preterm prelabor rupture of the membranes is associated with prolonging pregnancy, reduced chorioamnionitis, and reduced neonatal infectious morbidity. No difference on other measures of neonatal morbidity or mortality in the short or long term could be detected from the trials that have been reported.

4.3 Magnesium sulphate
Infants born very, or extremely, preterm are at increased risk of cerebral palsy; the earlier the gestational age at birth the greater the risk. From case-controlled studies there is a strong association between prenatal exposure to magnesium sulphate before very preterm birth and a reduced risk of cerebral palsy, but there are also concerns about a potential increase in perinatal mortality with the use of magnesium sulphate. Several multicenter international controlled trials are currently in progress to assess whether prenatal administration of magnesium sulphate to women immediately prior to very preterm birth reduces the risk of cerebral palsy for the infant.

5 Maintenance of preterm labor inhibition
Successful arrest of preterm labor does not imply that the problem may not reoccur before adequate fetal maturity has been achieved. Thus,
attention has been devoted to detecting recurrences and to maintaining labor inhibition for as long as necessary.

Home uterine-activity monitoring has been used for early detection of recurrences in women in whom contractions were said to have been effectively stopped by treatment of preterm labor.

Betamimetics given orally to maintain labor inhibition after uterine contractions had been arrested by intravenous therapy will reduce the risk of recurrent preterm labor, but they have not been shown to reduce the incidence of preterm birth. The few reported trials of oral maintenance of labor inhibition failed to detect any effect on the incidence of respiratory distress syndrome or perinatal death.

Oral magnesium maintenance treatment has not been shown to reduce the risk of preterm birth or perinatal mortality, although the few trials have been of poor quality.

6 Conclusions

Social and physical interventions have proved to be disappointing in their lack of effect in preventing preterm labor. Enhanced social support, despite its promise, has not been shown to be effective in reducing the risk of preterm labor and birth. Home uterine-activity monitoring is an expensive and invasive intervention, which has not been demonstrated to result in any substantive benefit. Bed-rest, which has been evaluated mainly in multiple pregnancy, does not reduce the risk of preterm birth. No benefits (or hazards) have been shown for repeated vaginal examinations or ultrasound assessment of cervical length.

There is no evidence that the prophylactic use of oral betamimetic agents does more good than harm. Because long term-treatment with these agents cannot be assumed to be free from adverse effects on the baby, they should not be used outside the context of controlled trials. There is reasonable evidence, however, that oral maintenance treatment after inhibition of active preterm labor with intravenous betamimetics, reduces the frequency of recurrent preterm labor and the need for repeated hospitalization, and intravenous treatment with betamimetic agents, although no reduction in the risk of preterm birth or in substantive neonatal outcomes have been demonstrated.

At present, only two categories of drugs merit consideration for the inhibition of preterm labor: betamimetic agents and inhibitors of prostaglandin synthesis. All the others are either obsolete, excessively
hazardous, or still in an experimental stage. There is no longer a place for ethanol or progesterone in the treatment of preterm labor. Oxytocin analogs and calcium antagonists have been insufficiently studied to assess whether they are beneficial. Magnesium sulphate, although widely used in some centers, has never been adequately evaluated. Other drugs, such as diazoxide, should not be used in attempts to inhibit preterm labor because of their potential for serious side effects.

The rejection of other agents does not imply strong endorsement of either betamimetic agents or the inhibitors of prostaglandin synthesis. Although both are effective in temporarily postponing delivery, there is no evidence that the use of these drugs per se reduces infant morbidity. They can be useful when the time that is gained before delivery is used to implement effective measures, such as transfer of the mother to a center with adequate facilities for intensive perinatal and neonatal care, the administration of prenatal corticosteroids to reduce neonatal morbidity, or judicious use of 'expectant management' in the period of gestation in which the infants chances of intact survival are very poor. Treatment with these powerful drugs may be dangerous for the women and can occasionally result in maternal death.

The potential benefits of betamimetics, weighed against the risk of adverse effects, does not justify their use in women with heart disease, hyperthyroidism, or diabetes. If labor needs to be inhibited in these women, prostaglandin synthesis inhibitors are the logical choice. For other women who require labor inhibition, betamimetic drugs are currently the drugs of choice.

Oral maintenance therapy with betamimetics or magnesium after inhibition of active preterm labor does not reduce the risk of preterm birth.

The roles of antimicrobial agents in active preterm labor, and magnesium sulphate administered immediately before preterm birth for the prevention of cerebral palsy, are under evaluation.

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