GUIDELINES

Evidence-based labour ward guidelines for the diagnosis, management and treatment of spontaneous preterm labour

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Summary
Currently, there is considerable variation in the way spontaneous preterm labour is diagnosed and managed internationally. As a result, 12 international leading experts from 10 countries met to establish consensus on clinical recommendations and guidelines regarding the diagnosis, management and treatment of spontaneous preterm labour. The consensus was supported by evidence from quality literature published during the last 15 years and graded using the National Health Service Executive classification system (Grades A – C), endorsed by the Royal College of Obstetricians and Gynaecologists. The Council found enough evidence of a lack of a consensus across nations to recommend guidelines. It is hoped that these international guidelines, while not meant to be prescriptive, will initiate discussion and correspondence for a basis for implementation on a national level and be adapted for local clinical practice, leading to further meetings around the world, to discuss other areas including infection, mode of delivery and in-utero transfer.

Introduction
Preterm birth, defined as delivery < 37 completed weeks of pregnancy (World Health Organisation, 1993) has a worldwide incidence estimated to be 13 million, occurring in 5–10% of all pregnancies (Hall et al., 1997). Preterm birth is not only one of the more common obstetric complications, but also one of the most serious causes of perinatal mortality and morbidity. Early preterm birth (< 32 weeks' gestation) is associated with a high perinatal mortality rate (Lopez-Bernal and Tamby-Raja, 2000).

The second and third trimesters of pregnancy are vital for maturation of the fetal lungs and other organs in preparation for extrauterine life. If this is interrupted by very early delivery, the chances of survival of the newborn are markedly diminished. Preterm birth is also the leading cause of long-term morbidity, including neurodevelopmental handicap, cerebral palsy, seizure disorders, blindness, deafness and non-neurological disorders, such as bronchopulmonary dysplasia and retinopathy of prematurity (Hole and Tessler, 2001). Delaying delivery may reduce the rate of long-term morbidity by facilitating the growth and maturation of developing organs and system. The benefits of administration of antepartum glucocorticoids (Crowley et al., 1990) to reduce the incidence and severity of respiratory distress syndrome may be exploited by delay. Delay may also permit transfer of the fetus in utero to a centre with neonatal intensive care unit facilities (Lamont et al., 1983).

The economic burden of preterm birth includes the immediate neonatal intensive care unit costs together with the longer-term costs for residential care or support of infants born preterm with residual disabilities. In the United States, the weekly cost of caring for a baby in the neonatal intensive care unit is estimated to be approximately US$10 000 per baby (Keirse, 1995). Annually this amounts to approximately US$5 000 000 000. If, as a result of disability, an infant needs long-term residential care, the lifelong cost may be as high as US$450 000 each.

There is considerable variation in the way that spontaneous preterm labour is diagnosed, managed and treated internationally and this variation is outlined in Table I. The existence of national guidelines varies from country to country with little or no agreement on the use of tocolytics.

In this review, the guidelines for diagnosis concentrated on whether the woman was in true labour and whether it was at a gestational age that required intervention. The diagnostic criteria were based on contractions, cervical dilatation and cervical effacement, and consideration was given to the role of oncofetal fibronectin and vaginal ultrasound measurements of cervical length. The issues surrounding the choice of tocolytic focused on licensed drugs including the oxytocin antagonist, atosiban, and β-agonists, as well as unlicensed drugs. The relative efficacy and safety of each class were compared, contrasted and graded with respect to quality of evidence, according to
recognised definitions. The absolute and relative contra-
indications for prolongation of pregnancy were also
discussed.

The development of clinical guidelines requires an
evidence-based approach to improve patient outcome and
allow more efficient use of resources (Woolf et al.,
1999).

With recent advances in our understanding of the aetiology
and mechanisms of spontaneous preterm labour and the
availability of safer, more specific tocolytics, it was felt that
guidelines should be developed to achieve, if possible, an
international consensus in patient diagnosis, management
and treatment. The aim of this report is to provide evidence-
based practical guidelines for the diagnosis, management
and treatment of spontaneous preterm labour within a
labour ward environment. It is hoped that these guidelines
will stimulate thought and debate internationally with
respect to the management of spontaneous preterm labour
and be used as a basis for the development of national and
local guidelines.

Methods

In June 2001, a group of 10 obstetricians with a special
interest in the management of preterm labour convened
under the auspices of the ‘International Preterm Labour
Council’ to discuss clinical guidelines for the diagnosis,
treatment and management of spontaneous preterm
labour.

Their objective was: ‘to reduce the fetomaternal mortality
and morbidity associated with spontaneous preterm labour
and preterm birth’. Their discussions focused on the
diagnosis and management of spontaneous preterm labour
within the labour ward. The recommendations were
supported by data collected from a systematic review of
the literature that supplied evidence of an appropriate
quality published during the last 15 years.

To ensure that the evidence used to support the
statements was based on current research, the evidence for
diagnosis and treatment of spontaneous preterm labour was
graded following the United Kingdom National Health
System Executive classification system (which is endorsed
by the Royal College of Obstetricians and Gynaecologists.
These are as follows:

- Grade A evidence is derived from randomised controlled
trials or systematic reviews of randomised trials. Meta-
analyses/systematic reviews had to include 50% or more
randomised controlled studies.
- Grade B evidence is from non-randomised controlled
trials, other robust experimental or good observational
studies and meta-analyses/systematic reviews with
450% randomised controlled studies.
- Grade C evidence is more limited and refers to
observational studies with poorer methodology or case
reports or the advice relies on consensus among
professional groups.

Within each literature search only certain papers were
selected for grading. Evidence for oncofetal fibronectin and
transvaginal ultrasound scanning concentrated on papers
that investigated these markers for the prediction of preterm
birth rather than predicting infection. Evidence for
corticosteroid recommendations concentrated on papers
that examined single and/or repeated doses of therapy and
those papers whose outcome measures concentrated on the
evidence for decreasing fetal mortality and respiratory
distress syndrome. Evidence for the benefits of tocolytic
therapy came from those papers that looked at placebo-
controlled trials or comparisons between tocolytics.
Data sources

The following databases were used to ensure that the recommendations were supported in the literature: MEDLINE (1986–present), EMBASE (1986–present), BIOSIS (1986–present), Current Contents (1995–present), Derwent Drugfile (1986–present), Reactions Database (1986–present). The search terms were: 'steroid'/corticosteroid', 'preterm labour'/labour premature', 'randomised', 'meta-analysis', 'controlled trial', 'utero AND transfer AND guideline', 'fetal fibronectin AND ultrasound', 'tocolytics'/tocolytic AND efficacy', 'safety AND maternal/fetal'.

Results

The discussion and data from the systematic literature review are presented in the form of the following subheadings: the diagnosis of spontaneous preterm labour, the management and treatment of spontaneous preterm labour (tocolytic therapy, the administration of antepartum glucocorticoids, the role of infection and preterm labour and other measures) and finally the contraindications for the intervention of spontaneous preterm labour.

The diagnosis of spontaneous preterm labour

On admission with suspected spontaneous preterm labour, the accuracy of the expected date of confinement should be re-checked scrupulously because the best estimate will influence whether or not intervention should take place. If the mother is sure of the last day of her last menstrual period, had a regular monthly cycle and an early ultrasound scan confirmed the date then menstrual dates should be used. If the dates are uncertain, or the cycle irregular, or there is a discrepancy of > 10 days between the scan and the menstrual dates, then the scan dates should be used.

The diagnosis of spontaneous preterm labour on clinical grounds should include the following:

1. contractions that are painful, palpable, last longer than 30 seconds duration and occur at least four times every 30 minutes;
2. there should be evidence of change in the position, consistency, length and/or dilatation of the cervix

Where there is doubt using clinical parameters, then in centres where the technique is available, oncotefal fibronectin may be considered in addition to clinical assessment.

Fetal fibronectin is an extracellular matrix glycoprotein produced by the chorion and concentrated in the amniotic fluid. It is normally present in cervicovaginal secretions until about 20 weeks and then disappears to reappear before the onset of labour at term. If the adhesive fibronectin interface between the chorion and the decidua is disturbed, fetal fibronectin may reappear in the vaginal secretions at an earlier gestation. As a result, the detection of fetal fibronectin in cervicovaginal secretion after 22 weeks' gestation has been proposed as an indicator of spontaneous preterm labour (Lockwood et al., 1991).

Systematic review for the use of fetal fibronectin and vaginal ultrasound

The systematic review produced six of 30 references that studied the predictive value of fetal fibronectin and cervical length for preterm delivery. The detection of fetal fibronectin has a high negative predictive value of 86.6% for preterm delivery before 37 weeks' gestation so may prevent unnecessary intervention but has a low positive predictive value of 45.2% for delivery (Grade A) (Rozenberg et al., 1997).

When compared with digital examination and transabdominal scanning, transvaginal ultrasound has a high sensitivity for the detection of cervical shortening and the risk of preterm birth (Vause and Johnston, 2000). Grade A evidence indicates that ultrasound measurement of cervical length is more valuable than the Bishop score for predicting the onset of spontaneous labour within 7 days, when measured close to term (Rozenberg et al., 1999). There is still debate with respect to the length of the cervix below which the risk of preterm birth is increased and by how much this risk is increased, if at all, with shorter cervical measurements.

It was concluded that fetal fibronectin and transvaginal ultrasound used for the diagnosis of spontaneous preterm labour as an adjuvant to clinical parameters but without further research should not be recommended for routine use. It was resolved to consider the use of fetal fibronectin and transvaginal ultrasound in the diagnosis of spontaneous preterm labour and their place in the prediction and prevention of preterm birth, as part of future guidelines. An algorithm describing the diagnosis of preterm labour is shown in Figure 1.

The management and treatment of spontaneous preterm labour

These guidelines are based on the acute management of spontaneous preterm labour < 34 weeks' gestation. As a consequence, the main management focus is centred on the inhibition of preterm labour and therefore the administration of tocolytics forms the majority of the recommendations obtained from the systematic literature review.

Tocolytic therapy

The primary aims of tocolytic therapy are to delay delivery to allow the administration of a complete course of antepartum glucocorticoids in order to reduce the incidence and severity of idiopathic respiratory distress syndrome and to arrange in-utero transfer to a centre with neonatal intensive care unit facilities.

The secondary aim of tocolytic therapy is to delay delivery to permit significant growth and maturity of the fetus and to reduce the perinatal mortality and morbidity associated with preterm birth.

Because some of the currently used tocolytic agents have the potential to cause serious fetomaternal adverse effects, informed consent from the patient, and/or partner should be sought.

Licensed tocolytic agents: β-agonists. Beta-agonists are related structurally to adrenalin and noradrenalin and include such drugs as ritodrine, terbutaline, albuterol, fenoterol, hexoprenaline and salbutamol. These β2-agonists act on receptors in the uterus to increase cAMP in smooth muscle cells, which decreases intracellular free calcium and phosphorylation of myosin light chain kinase, which in turn inhibits myometrial contraction (Hearne and Nagy, 2000). Within 48 hours
of administration, the β-agonists are able to reduce the number of women who deliver preterm (King et al., 1998), but have not been found to produce a reduction in perinatal mortality or morbidity (Rozenberg et al., 2001) (Grade A).

Several randomised clinical studies have shown the most widely used β-agonist, ritodrine, is equally as active as the calcium channel blocker, nifedipine, but with poorer tolerability (Kupfermine et al., 1993; Papatsonis et al., 1997; Garcia-Velasco and Gonzalez-Gonzalez, 1998; Koks et al., 1998; Al-Qattan et al., 2000; Papatsonis et al., 2000) (Grade A, Table II).

The maternal adverse events of β-agonists include palpitations, tremor, nausea, vomiting, headache and restlessness (RCOG, 1997). Pulmonary oedema occurs with an incidence of approximately one in 400 (Black et al., 1999; Lamont, 2000) (Grade A).

The risk of these adverse events associated with β-agonists in the management of spontaneous preterm labour requires close monitoring of the mother in a high dependency unit. These have been addressed by the Royal College of Obstetrics and Gynaecology (RCOG, 1997) and their recommendations for monitoring are shown in Table III.

**Licensed tocolytics: oxytocin antagonists.** Oxytocin is believed to initiate myometrial contractility by a direct effect on membrane-bound receptors that leads to an increase in intracellular calcium. It is also understood to act indirectly by stimulating the release of prostaglandins in decidual and fetal membranes, contributing further to myometrial contractions and cervical ripening (Bossmar, 1998).

Compared with β-agonists, in randomised double-blind placebo-controlled trials atosiban (oxytocin antagonist, partial vasopressin antagonist) offers comparable effectiveness (i.e. the proportion of women remaining undelivered at 48 hours and 7 days) as well as comparable efficacy and tolerability (non-delivery and no alternative tocolysis) at 48 hours (European Atosiban Study Group, 2001) (Grade A, Table II). Due to more favourable safety and tolerability atosiban, assessed at 7 days, is significantly superior to β-agonists. The likelihood of prolongation of pregnancy is increased (Worldwide Atosiban versus Beta-agonists Study Group, 2001) (Grade A, Table II). In addition, atosiban had a significantly lower rate of cardiovascular side effects and a reduced need to discontinue therapy due to unacceptable side effects. Significantly fewer patients required alternative tocolytic therapy following allocation to atosiban due to the superior tolerability profile (Romero et al., 2000; Moutquin et al., 2000) (Grade A, Table II). Atosiban represents an advance in currently available tocolytics, and should be considered a first-line tocolytic for the management of spontaneous preterm labour (Worldwide Atosiban versus Beta-agonists Study Group, 2001) (Grade A, Table II).

**Unlicensed tocolytic therapy: calcium channel blockers.** Calcium channel blockers, such as nifedi-
Table II. Grade A evidence for the efficacy and tolerability of the \( \beta \)-agonists in comparison with other tocolytics. NB: in terms of efficacy, > implies a greater efficacy and in terms of tolerability, > implies a greater tolerability

<table>
<thead>
<tr>
<th>( \beta )-agonists versus other tocolytics</th>
<th>Tocolytic efficacy</th>
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<tr>
<td>Ritodrine and glyceryl trinitrate</td>
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<td>Atosiban and terbutaline</td>
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<td>Atosiban &gt; terbutaline</td>
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<td>Atosiban &gt; ritodrine</td>
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<td>Atosiban and salbutamol</td>
<td>Atosiban &gt; salbutamol</td>
<td>Atosiban &gt; salbutamol</td>
<td>French/Australian Atosiban Investigators Group, 2001</td>
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<td>Atosiban, ritodrine, salbutamol and terbutaline</td>
<td>Atosiban &gt; ritodrine and salbutamol Atosiban = terbutaline</td>
<td>Atosiban &gt; ritodrine, salbutamol and terbutaline</td>
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<td>Nifedipine and ritodrine</td>
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<td>Terbutaline and magnesium sulphate</td>
<td>Magnesium sulphate &gt; terbutaline</td>
<td>Magnesium sulphate = terbutaline</td>
<td>Jannet et al., 1997</td>
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Table III. The recommended guidelines for monitoring IV administration with \( \beta \)-agonists produced by the Guidelines from the Royal College of Obstetricians and Gynaecologists (Rozenberg, 2001)

Recommended monitoring

- Maternal pulse and BP should be monitored every 15 minutes
- Chest auscultation should be performed every 4 hours
- Strict input/output charts should be measured for fluid balance
- Urea and electrolytes and haematocrit should be measured every 24 hours
- Maternal blood glucose should be measured 4-hourly.

Magnesium sulphate, terbutaline and nifedipine are more effective than other tocolytics (mainly \( \beta \)-agonists) in terms of fewer patients who have to discontinue treatment due to drug-associated side effects (Grade A). Since the International Preterm Labour Council meeting, the recent Cochrane meta-analysis (King et al., 2003) also suggested that calcium antagonists (mainly nifedipine) were more effective than other tocolytics (mainly \( \beta \)-agonists) in terms of fewer births within 7 days of initiation of treatment and before 34 days’ gestation, with improvement in some neonatal outcomes and a reduction in adverse maternal side effects (Grade A). Side effects commonly associated with nifedipine include flushing, headache and rarely hypotension in the hypovolaemic patient (Childress and Katz, 1994).

Recent reviews of the evidence pertaining to the use of nicardipine suggest that the safety profiles of these drugs are incomplete and should lead to careful consideration before use. It has been recommended that nicardipine should only be used in a clinical trial setting (King, 2001).

Prostaglandin synthetase inhibitors. Prostaglandin synthetase inhibitors (e.g. indomethacin, sulindac and ketorolac) decrease prostaglandin synthetase and block conversion of free arachidonic acid to prostaglandin. As the prostaglandin E and F series are mediators of uterine contractions, a decrease in production results in decreased contractile activity (Hearne and Nagey, 2000).

Indomethacin is a potent inhibitor of prostaglandin synthesis and has been used as a tocolytic agent since the
early 1970s. Indomethacin is effective in delaying preterm labour and increases birth weight, results in shorter stays in neonatal intensive care units and shorter intervals of mechanical ventilation (Grades A or B, depending on study quoted) (Table IV). Conversely, contradictory evidence shows that indomethacin fails to prolong gestation and infants are delivered prematurely (Merrill et al., 1994) (Grade A).

In one study, indomethacin was associated with a reduced risk of neonatal complications in infants born between 24 and 31 weeks’ gestation (Gardner et al., 1996) (Grade B). Morales and Madhav (1993) reported that indomethacin used to treat spontaneous preterm labour, caused oligohydramnios and was associated with maternal side effects such as chest pain, shortness of breath, malaise and pulmonary oedema (Grade A). Potential fetal adverse effects include premature closure of the ductus arteriosus, necrotising enterocolitis, respiratory distress syndrome and bronchopulmonary dysplasia (Highby and Suiter, 1999) (Grade A).

Magnesium sulphate. The mode of action of magnesium sulphate is believed to be via competitive antagonism to calcium for entry into myometrial cells. Decreased intracellular free calcium results in decreased myometrial contractility (Hearne and Nagey, 2000).

In a study by Mittendorf et al. (1997), the Magnesium and Neurologic Endpoints Trial (MagNET) showed that magnesium sulphate was as effective, but no more effective as a tocolytic agent than ritodrine, terbutaline, indomethacin or nifedipine (Grade A). This finding appears to reflect other evidence (see Table IV) that magnesium sulphate is comparable to β-agonists and prostaglandin synthetase inhibitors in prolonging gestation. The authors state that safety and efficacy has not been demonstrated sufficiently with magnesium sulphate. High doses (exceeding a total dose of 48 g) have been associated significantly with increased perinatal mortality (Scudiero et al., 2000) (Grade A).

Since the International Preterm Labour Council, the Cochrane Database has also investigated the use of magnesium sulphate (Crowther et al., 2003). They concluded that magnesium sulphate is ineffective at delaying birth or preventing preterm birth after preterm labour, and its use is associated with an increased mortality for the infant (Grade A). They suggested that any further trials should be of high quality, large enough to assess serious morbidity and mortality, compare different dose regimens and provide information about the neurodevelopmental status of the child.

The administration of antepartum glucocorticoids
Prolonging gestation with tocolytic therapy allows for the administration of antepartum glucocorticoids to reduce the incidence and severity of respiratory distress syndrome and hence reduce neonatal morbidity and mortality. The systematic literature review concentrated on those papers that studied the single and multiple administrations of antepartum glucocorticoids.

Ten of 63 references in the literature search provided Grade A evidence for the use of single rather than multiple courses of antepartum glucocorticoids. The administration of a single course of antepartum glucocorticoids to pregnant women, between 24 – 34 weeks’ gestation, at risk of preterm delivery within 7 days, reduces the risk of death, respiratory distress syndrome and intraventricular haemorrhage in the preterm infant (Schmitz et al., 2000; Crowley 2001). This has been reflected in the National Institutes of Health Consensus Statement, 1994. The treatment should consist of two doses of 12 mg betamethasone given intramuscularly 24 hours apart or four doses of 6 mg dexamethasone given intramuscularly 12 hours apart.

There is still debate about the use of repeated doses of antepartum glucocorticoids. Multiple doses of antepartum glucocorticoids may be associated with early-onset neonatal sepsis and death (Vermillion et al., 2000) (Grade B) or have no effect on these outcomes or others such as intraventricular haemorrhage, bronchopulmonary dysplasia, necrotising enterocolitis and birth weight (Aghajafari et al., 2001) (Grade B). A recent consensus panel (National Institutes of Health Consensus Development Panel, 2001) concluded that data from currently available studies assessing the benefits and risks of the use of repeated courses of antepartum glucocorticoids remains unanswered at this stage.

Furthermore, there is evidence that delaying the use of antepartum glucocorticoids in women with preterm premature rupture of the membranes (PPROM) may significantly increase the risk of fetomaternal infection (Crowley, 2001).

Table IV. Grade A and B evidence for the efficacy and tolerability for prostaglandin synthetase inhibitors and magnesium sulphate in spontaneous preterm labour

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<thead>
<tr>
<th>Clinical trial</th>
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<td>Sibony et al., 1994</td>
<td>Indomethacin (Grade B)</td>
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<tr>
<td>Gardner et al., 1996</td>
<td>Indomethacin (Grade B)</td>
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<td>Scudiero et al., 2000</td>
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<td>Spisso et al., 1982</td>
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<tr>
<td>Schorr et al., 1998</td>
<td>Ketorolac and magnesium sulphate (Grade A)</td>
</tr>
<tr>
<td>Morales and Madhav, 1993</td>
<td>Indomethacin and magnesium sulphate (Grade A)</td>
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(Grade A). At earlier gestation, the benefits may outweigh the risks but at later gestations, the risk–benefit analysis may change.

The role of infection and preterm labour

The Council agreed that the following investigations would be routine in most units:

1. Full blood count and group and save serum;
2. Midstream specimen of urine examined for bacteruria;
3. High vaginal swab for culture microscopy and sensitivities; and
4. Low vaginal swab and rectal swab to be cultured in selective broth medium for screening for Group B streptococci.

The role of infection in the aetiology of preterm labour and the implication this has on the choice of investigation on admission will be the subject of a separate set of guidelines.

Other measures

As soon as possible after the diagnosis of spontaneous preterm labour, it is recommended that neonatal paediatricians involved in management decisions are informed to ensure that a neonatal intensive care cot is available on site or that an in-utero transfer to a centre with neonatal intensive care unit facilities needs to be arranged.

Finnström et al. (1997) have shown that the level of care at birth and the level of subsequent neonatal care in the neonatal intensive care unit are related directly to a lower rate of neonatal morbidity and mortality when compared with babies born in hospitals without specialised staff and equipment (Finnström et al., 1997) (Grade B). Hospitals that had full resources for obstetric and neonatal intensive care had significantly lower infant mortality than those without. In-utero transfer is safer for the baby and significantly reduces mortality and morbidity when compared with neonatal transfer (Lamont et al., 1983) (Grade B).

If time permits, an ultrasound scan should be arranged to check for fetal viability, fetal morphology, fetal number, fetal presentation, placental site, an estimate of fetal weight and amniotic fluid volume index, all of which might affect management. Appropriate analgesia following discussion with an anaesthetist should be arranged and opiates should be avoided, if possible, to prevent central fetal and neonatal respiratory depression.

If intervention is contraindicated or unsuccessful, then the mode of delivery of a preterm infant should be individualised according to the gestational age, the fetal presentation, the number of fetuses and the presence or absence of non-reassuring fetal heart tracing on cardiotocograph. The debate with respect to the mode of delivery of the preterm infant will be the subject of further Council discussion.

Contraindications to intervention in the management of spontaneous preterm labour

When considering intervention to prolong gestation, certain absolute and relative contraindications should be considered in order to minimise maternal and fetal morbidity and mortality.

The expected benefit in survival and reduced disability from prolonging gestation comes from three recent sources. Magowan et al. (1999), showed that mortality fell from 80% at 24 weeks’ gestation to 10% at 30 weeks’ gestation and that while 50% of preterm births occur after 35 weeks’ gestation, almost all the mortality occurs before this time (Magowan et al., 1999). Secondly, between the gestational ages of 23 and 27 weeks, neonatal survival increases in a linear fashion at a rate of 3% per day with a concomitant reduction in neonatal morbidity from 31% at 23 weeks to 7% at 27 weeks (Finnström et al., 1997). Thirdly, the contribution of preterm birth to morbidity was highlighted in the recently reported Epicure study (Costeloe et al., 2000). This study was designed to describe the survival and health problems for all infants born before 26 weeks’ completed gestation in the United Kingdom and the Republic of Ireland. A total of 276 maternity hospitals provided information showing that 65% of these babies died in the delivery suite or in the neonatal intensive care unit, before discharge from hospital.

The most frequently cited cause of death was pulmonary hypoplasia. Data from the babies that survived showed that failure to administer antenatal steroids and failure for postnatal transfer for intensive care within 24 hours of birth were predictive of major abnormalities based on cerebral ultrasound scanning.

Follow-up data at 30 months from the Epicure study showed that 49% of survivors had some form of disability (mental and psychomotor development, neuromotor function, sensory and communication function) and nearly 50% of these met the criteria for severe disability using neurological and developmental assessment (Wood et al., 2000). Only 13% of infants survived to 30 months without disabilities.

Absolute contraindications are those in which prolongation of pregnancy is contraindicated per se, e.g. clinically apparent intrauterine infection, known lethal fetal congenital malformation, fulminating proteinuric pre-eclampsia and any other urgent fetomaternal indication for delivery. Relative contraindications are those in which there is a debate about the risks and benefits of intervention such as antepartum haemorrhage, ruptured membranes, non-reassuring fetal heart rate pattern on the cardiotocograph, intrauterine growth restriction, insulin-dependent diabetes and multiple pregnancy.

Tocolytics should not be used if there is a significant antepartum haemorrhage, especially if there are signs and symptoms of abruptio placentae. Following a mild bleed due to placenta praevia, it is acceptable to use tocolytics because they may help to stop uterine contraction and the stretch they induce, leading to further separation of the placenta and haemorrhage.

Tocolytics are rarely indicated after 32 weeks’ gestation in the presence of ruptured membranes. At an earlier gestation, they may be administered when the risk–benefit analysis is in favour of delaying delivery to allow a full course of glucocorticoids to be administered or arrangements to transfer a woman to a centre with neonatal intensive care unit facilities.

Tocolytics to delay delivery of the preterm infant are contraindicated where non-reassuring fetal heart rate patterns on the cardiotocograph occur in association with a significant haemorrhage or with signs of fetomaternal infection or where the cardiotocograph trace is suggestive of fetal compromise.
Severe intrauterine growth restriction may be associated with congenital malformation, and consideration should be given to this possibility before intervention. Severe placental insufficiency where continued intrauterine existence puts the fetus at risk, is a contraindication to intervention although minor degrees of intrauterine growth restriction where further fetal growth might be anticipated would not be a contraindication to the use of a tocolytic. In cases where the fetus is thought to be clinically or ultrasonographically small for the dates, the calculation of the estimated date of confinement and the dates should be re-checked.

Well-controlled insulin-dependent diabetic women with spontaneous preterm labour can safely be treated with tocolytics. Close monitoring is required because both glucocorticoids and particularly β-agonists are likely to potentiate the risk of pulmonary oedema. Beta-agonists are known to increase both aldosterone and renin levels in twin pregnancies (Lammintausta and Erkkola, 1979), which may potentiate the risk of pulmonary oedema. Beta-agonists are therefore relatively contraindicated in multiple pregnancies, and alternative tocolytics should be used where available.

Twins and higher-order births are associated with a greater maternal plasma volume expansion (Cambell and MacGillivray, 1997) and secondary hyperaldosteronism when compared with single pregnancies. Beta-agonists are known to increase both aldosterone and renin levels in twin pregnancies (Lammintausta and Erkkola, 1979), which may potentiate the risk of pulmonary oedema. Beta-agonists are therefore relatively contraindicated in multiple pregnancies, and alternative tocolytics should be used.

**References**


